Chapter 17
Chronic Granulomatous Disease

Danielle E. Arnold and Jennifer R. Heimall

Introduction

Chronic granulomatous disease (CGD) is a rare inherited primary immunodeficiency due to mutations in any of the critical subunits of the phagocyte NADPH oxidase complex, resulting in impaired oxidase activity of neutrophils, monocytes, and tissue macrophages. It is characterized by increased susceptibility to recurrent and severe infections with a subset of microorganisms, granuloma formation, and inflammatory disease. CGD was first described by Janeway et al. in 1954 [1] and was dubbed "fatal granulomatous disease of childhood" in 1959 [2], with most patients historically succumbing to infection or other complications of disease by 10 years of age. However, with increasing awareness of disease, widespread use of prophylactic antimicrobials, and advancements in hematopoietic stem cell transplantation (HSCT), outcomes have improved dramatically and many patients now live well into adulthood.

Mechanism of Neutrophil Dysfunction

Neutrophils play a key role in the defense against invading pathogens primarily by engulfing and rapidly killing microbes within phagocytic vacuoles via activation of the NADPH oxidase complex and the resultant "respiratory burst" during which

D. E. Arnold (✉) · J. R. Heimall
Immune Deficiency – Cellular Therapy Program, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA
e-mail: danielle.arnold@nih.gov

J. A. Bernstein (ed.), *Primary and Secondary Immunodeficiency*,
https://doi.org/10.1007/978-3-030-57157-3_17

reactive oxygen species (ROS) are generated and microbicidal proteases are activated. The NADPH oxidase complex is assembled from both membrane-bound proteins embedded in the walls of secondary granules and distinct cytosolic proteins (Fig. 17.1). The membrane-bound heterodimer cytochrome b558 is composed of the catalytic glycoprotein gp91phox and the non-glycosylated protein p22phox. Upon phagocyte activation, the cytosolic proteins p47phox, p67phox, and p40phox translocate to cytochrome b558 and recruit Rac1/2 to form the activated NADPH oxidase complex. Upon formation of the activated NADPH oxidase complex, gp91phox undergoes a conformational change to expose the protein's catalytic component, which then shuttles electrons from cytosolic NADPH to molecular oxygen in the phagolysosome, leading to the formation of superoxide ions. Superoxide ions are used to generate reactive oxygen species (ROS) such as hydrogen peroxide, hypochlorous acid, hydroxyl radicals, and secondary amines that participate in the direct killing of phagocytosed microorganisms. The creation of the hydroxyl radical also results in an overall negative charge within the phagolysosome, triggering the rapid influx of potassium,

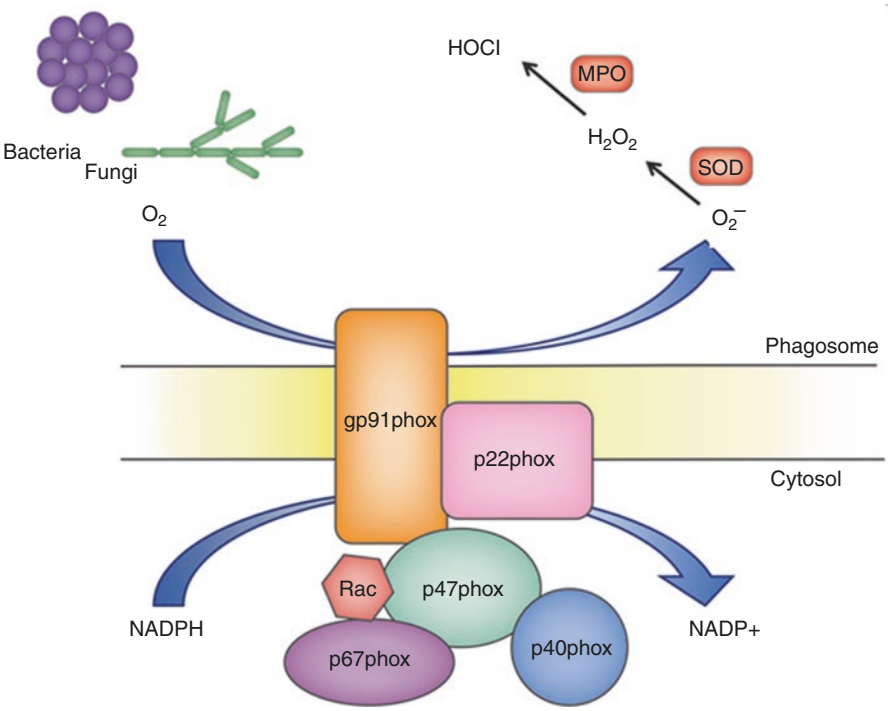

Fig. 17.1 The activated NADPH oxidase complex. Upon phagocyte activation, the various components of NADPH oxidase come together to form the activated NADPH oxidase complex. Gp91phox shuttles electrons from cytosolic NADPH to molecular oxygen in the phagolysosome, resulting in the formation of superoxide ion (O_2^-). Superoxide ion is converted to hydrogen peroxide (H_2O_2) either spontaneously or by superoxide dismutase (SOD), and hydrogen peroxide is converted to hypochlorous acid (HOCl, bleach) by myeloperoxidase. Bleach is then able to directly kill engulfed pathogens

which in turns leads to activation of intraphagosomal proteases that further contribute to microbial clearance [3]. Additionally, the NADPH oxidase complex is required for the activation of neutrophil extracellular traps (NETs) [4], which are webs of chromatin filaments and antimicrobial peptides that are released from apoptotic neutrophils and entrap extracellular pathogens to facilitate clearance by the immune system.

Of note, neutrophils are essential for the elimination of a wide spectrum of microorganisms; however, patients with CGD are at increased risk of infection almost exclusively with catalase-positive pathogens. This is thought to be because the distal mechanisms of the bactericidal pathway, including myeloperoxidase, remain intact in patients with CGD. Catalase-positive organisms, however, can degrade host-produced hydrogen peroxide before it is converted to hypochlorous acid by myeloperoxidase, thus escaping this mechanism of killing. That being said, only a subset of catalase-positive microorganisms is responsible for the majority of infections seen in CGD, the reasons for which remain unclear.

Epidemiology

The incidence of CGD varies significantly worldwide. A large retrospective review of a national registry reported an incidence of about 1:200,000–250,000 live births in the United States [5]. Interestingly, the incidence of CGD is quite variable across Europe, ranging from 1:133,000 in the United Kingdom to 1:100,000 in Italy [6, 7]. Published rates of CGD by country are shown in Table 17.1 [5–11].

Genetics

Mutations in any of the five structural subunits of the NADPH oxidase complex result in defective ROS production and the clinical presentation of CGD (Table 17.2). Mutations in the *CYBB* gene, which encodes the transmembrane glycoprotein gp91phox and is the located on the X chromosome, is the most common cause of

Table 17.1 Reported rates of CGD worldwide

Country	Rate of CGD
United States [5]	1:200,000–250,000
United Kingdom [6]	1:133,000
Italy [7]	1:1,000,000
Sweden [8]	1:450,000
Greece [9]	1:45,450
Japan [10]	1:300,000
Israel [11]	
Jews	1:100,000
Arabs	1:67,000

Table 17.2 Genetic etiology of CGD in the United States and Western Europe

Gene	Protein	Mode of inheritance	Proportion of CGD
CYBB	gp91phox	X-linked	67%
CYBA	p22phox	AR	5%
NCF1	p47phox	AR	20–25%
NCF2	p67phox	AR	5%
NCF4	p40phox	AR	26 cases
CYBC1	CYBC1/Eros	AR	9 cases

AR autosomal recessive

CGD worldwide and accounts for approximately two-thirds of cases of CGD in North America and Europe [5–7, 12–14]. Biallelic pathogenic mutation in *NCF1* (p47phox) is the most common cause of autosomal recessive CGD and accounts for between 20% and 25% of CGD, and mutations in *CYBA* (p22phox) and *NCF2* (p67phox) each account for about 5% of cases. There have been 26 reported cases of CGD due to *NCF4* (p40phox) mutations [15, 16]. Interestingly, these patients suffered from significant autoinflammatory disease but none of the patients had the recurrent infections characteristic of the other genetic forms of CGD. Of note, in countries with high rates of consanguinity, the incidence of autosomal recessive CGD often exceeds that of X-linked CGD.

Recently, biallelic loss-of-function mutations in *CYBC1* were identified as the genetic cause of CGD in a cohort of eight patients from Iceland and in one patient from Saudi Arabia [17, 18]. Most of the patients suffered from recurrent infections and several had autoinflammatory disease, including colitis and histopathological evidence of granuloma formation. *CYBC1* is not directly involved in the respiratory burst but was found to be essential for the expression of the gp91phox/p22phox heterodimer and formation of the NADPH oxidase complex. All patients had an impaired neutrophil oxidative burst on whom testing was performed.

Finally, *CYBB* is located at Xp21.1, and patients with large deletions in the X chromosome may have other monogenic disorders in addition to CGD. The *XK* gene, which encodes the Kx blood group, is immediately telomeric to *CYBB*, and the loss of *XK* results in McLeod syndrome, the most common syndrome seen with CGD. Patients with McLeod syndrome are severely restricted for receiving transfusions, which may have implications for those patients under consideration for HSCT. Larger deletions may also result in loss of *RPGR* (retinitis pigmentosa), *DMD* (Duchenne muscular dystrophy), and *OTC* (ornithine transcarbamylase deficiency).

Case Presentation 1

A 6-year-old boy with a history of recurrent cutaneous abscesses and one prior episode of *Aspergillus fumigatus* pneumonia at 4 years of age presents to the ED with 3 days of low-grade fever and vague abdominal pain. The boy appeared tired, and physical exam was notable for slight guarding on palpation of the right upper

quadrant and a liver edge palpable 2 cm below the right costal margin. Labs were remarkable for an elevated white blood cell count at 12.6 × 10^3/μL and an elevated C-reactive protein level at 9.8 mg/dL (normal < 1.0). Transaminases, bilirubin, and albumin levels were all normal. A right upper quadrant ultrasound demonstrated a loculated collection of fluid 6.2 cm in diameter in the right hepatic lobe, and the patient was empirically started on piperacillin-tazobactam plus metronidazole. He underwent percutaneous drainage of the abscess, and cultures returned positive for methicillin-sensitive *Staphylococcus aureus* at 9 h. Antibiotics were transitioned to oxacillin monotherapy at that time. Immunology was consulted given the patient's infectious history, and the new unusual diagnosis of a *Staphylococcal* liver abscess. Immune workup demonstrated normal quantitative immunoglobulin levels and lymphocyte subset counts with protective vaccine titers. Dihydrorhodamine assay demonstrated a broad-based histogram peak with a modest shift of the fluorescence signal in stimulated neutrophils characteristic of autosomal recessive CGD. After 9 days on antibiotic therapy, the patient continued to spike intermittent fevers, and his CRP remained elevated despite broadening antibiotics to vancomycin and meropenem. Repeat ultrasound demonstrated that the abscess had increased in size to 8.4 cm in diameter, and so methylprednisolone 1 mg/kg/day was initiated given the patient's new diagnosis of CGD. The patient defervesced, and repeat ultrasound 3 days later demonstrated shrinking of the abscess. The liver abscess resolved over the next 6 weeks, and glucocorticoids were weaned off over a period of 5 months. Genetic testing ultimately demonstrated a deleterious mutation in the *NCF1* gene, and the patient was started on trimethoprim-sulfamethoxazole and itraconazole prophylaxis.

Diagnosis/Assessment

This patient's clinical presentation is characteristic for CGD with onset of symptoms at an early age and a history of recurrent often unusual infections. In general, patients with X-linked CGD have a more severe disease course with earlier age of onset (9–14 months) and diagnosis (2.1–4.9 years) compared to patients with autosomal recessive disease (mean age of onset 30–41 months and diagnosis 5.8–8.8 years) [5–7, 11, 12]. Most patients present with infection, as this patient did, and infection remains the leading cause of death in patients with CGD despite the use of appropriate antimicrobial prophylaxis [5, 19].

Infections in CGD

Infections are primarily with a subset of catalase-positive microorganisms, and the most common sites of infection are the lungs, skin, lymph nodes, and liver (Table 17.3). Osteomyelitis and bacteremia/fungemia are also common. In North America, the majority of infections are due to *Aspergillus* spp., *Staphylococcus*

Table 17.3 Most common infections in CGD

Infection	Percent of patients affected
Pneumonia	79–87%
Aspergillus species	
Staphylococcus aureus	
Burkholderia cepacia	
Nocardia species	
Subcutaneous abscess	42%
Staphylococcus aureus	
Serratia marcescens	
Liver abscess	27–32%
Staphylococcus aureus	
Lymphadenitis	25–53%
Staphylococcus aureus	
Serratia marcescens	
Osteomyelitis	25%
Serratia marcescens	
Aspergillus	
Bacteremia/fungemia	18%
Burkholderia cepacia	
Lung abscess	16%
Aspergillus species	
Staphylococcus aureus	
Nocardia species	
Brain abscess	3%
Aspergillus species	

aureus, *Burkholderia* spp., *Serratia marcescens*, and *Nocardia* spp. About 80% of patients have at least one episode of pneumonia, and *Aspergillus*, *Staphylococcus*, *Burkholderia*, and *Nocardia* are the pathogens most commonly identified in cases of pneumonia [5, 19]. *Staphylococcus* and *Serratia* are the most common causes of lymphadenitis and skin abscesses, and *Staphylococcus* is the most common cause of liver abscesses [5, 19]. Liver abscesses ultimately affect about one-third of patients with CGD and are often recurrent and difficult to treat [5, 19]. *Burkholderia* is the most common cause of sepsis and is associated with a high fatality rate [19, 20]. Europe and Israel also have high rates of infection with *Salmonella* spp. and *Salmonella* spp., which are frequent causes of septicemia in these regions [11, 12, 21]. In addition to the aforementioned pathogens, local or disseminated infections due to bacille Calmette-Guerin (BCG) have been reported at rates of 16.6–59.2% in CGD patients in countries where the BCG vaccine is routinely administered [22–25]. *Mycobacterium tuberculosis* infections are also reported at higher rates than what is considered usual for people living in areas endemic for tuberculosis [26, 27].

There are a number of unusual and virtually pathognomonic bacterial infections that have been identified in CGD patients in recent years. *Chromobacterium violaceum* and *Francisella philomiragia* are both gram-negative bacteria found in

brackish water (i.e., water resulting from the mixing of seawater with freshwater, as in estuaries) and have been reported to cause skin and deep tissue abscesses as well as sepsis in CGD [28–30]. *Granulibacter bethesdensis* is a ubiquitous gram-negative rod found in soil and organic decay that has been isolated from patients with chronic necrotizing lymphadenitis, sepsis, and meningitis [31].

Patients with CGD have one of the highest rates of invasive fungal infection among all primary immunodeficiencies, with *Aspergillus* spp. being isolated at some point in about 40% of patients [5, 19]. The lungs and chest wall are the most common sites of *Aspergillus* infection. *Aspergillus* is also a major cause of osteomyelitis and brain abscesses [5, 32]. *A. fumigatus* followed by *A. nidulans* are the most frequently identified Aspergillus species [19, 33–35]. Of note, *A. fumigatus* was previously the leading cause of mortality in CGD, but with the advent of azole antifungal treatment, death from *A. fumigatus* is now uncommon [35]. However, the incidence of infection with *A. nidulans* and other *Aspergillus* species (e.g., *A. viridinutans*, *A. tanneri*, *A. niger*, and *A. terreus*) has increased with widespread use of azole antifungal prophylaxis. Unfortunately, these *Aspergillus* species generally cause more severe, refractory, and invasive disease that are difficult to treat and associated with high mortality rates [32–39]. Other fungi frequently seen in CGD include *Rhizopus* spp., *Trichosporon* spp., *Paecilomyces* spp., *Phellinus tropicalis*, *Geosmithia argillacea*, and *Neosartorya udagawae*, among others [40–46]. *Candida* infections are also common [5, 19]. Of note, dimorphic mold infections such as histoplasmosis and blastomycosis as well as the yeast infection cryptococcosis are not seen at increased rates in CGD, and mucormycosis is typically seen only in the setting of significant iatrogenic immunosuppression [47].

Diagnostic Testing

CGD should be in the differential diagnosis for all patients with severe or recurrent cutaneous abscesses, lymphadenitis, and pneumonia and any instance of deep tissue abscess, especially in the lungs or liver. Infections with organisms such as *Aspergillus* spp., *B. cepacia*, *Nocardia* spp., and *Serratia marcescens* should also prompt evaluation for CGD, and infection with any of the other rare or pathognomonic pathogens referenced above should be considered CGD until proven otherwise.

Dihydrorhodamine Assay

There are a number of diagnostic tests available to assess NADPH oxidase function in stimulated neutrophils. The nitroblue tetrazolium (NBT) reduction test was used historically, and the ferricytochrome c oxidase assay has been used on a research basis; however, the dihydrorhodamine (DHR) assay is currently considered the gold standard for diagnosis given the ease, wide availability, and high sensitivity of the

assay. In the DHR assay, neutrophils are incubated with DHR-123 and stimulated with phorbol 12-myristate 13-acetate (PMA). Functional neutrophils produce superoxide radicals that oxidize DHR-123 to rhodamine, which fluoresces green and can be detected by flow cytometry. This allows for the enumeration of the proportion of rhodamine-positive (i.e., oxidase-positive) neutrophils (Fig. 17.2). In addition to diagnosing CGD, the DHR assay can also distinguish between those with absent and those with residual NADPH oxidase activity. Mechanistically, the survival of patients with CGD is strongly associated with residual superoxide production independent of the specific gene affected [14]. In general, patients with X-linked CGD have absent and those with AR CGD have residual NADPH oxidase activity. Carriers of X-linked CGD typically have two distinct populations of neutrophils on the DHR assay: a rhodamine-positive and a rhodamine-negative subset. The relative proportions of these populations can be used to evaluate degree of lyonization (i.e., X chromosome inactivation). Of note, there are a number of medical conditions that can result in a false-positive DHR assay, including severe G6PD deficiency, myeloperoxidase deficiency, and the syndrome of synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO). Granulocytic ehrlichiosis, an infection

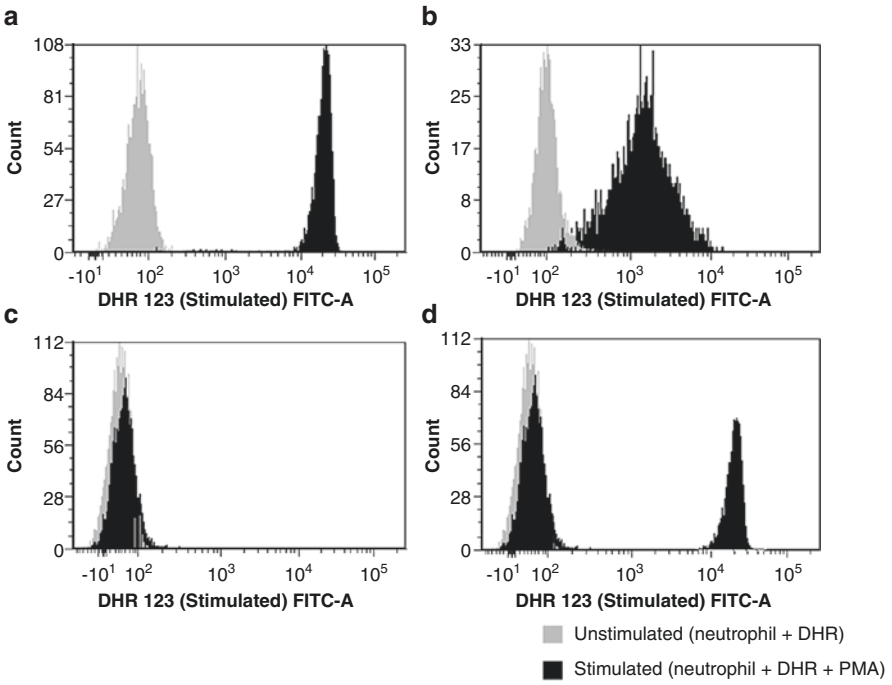

Fig. 17.2 The DHR-123 assay. Typical DHR histograms from a (**a**) healthy donor, patients with (**b**) autosomal recessive and (**c**) X-linked CGD, and a (**d**) carrier of X-linked CGD. Patients with autosomal recessive CGD classically have residual oxidase activity while patients with X-linked CGD are typically oxidase null. Carriers of X-linked CGD have two distinct populations of neutrophils – a rhodamine-negative and a rhodamine-positive population

caused the *Ehrlichia* bacterium primarily transported by the lone star tick, has also been reported to decrease neutrophil oxidase activity and may be associated an abnormal DHR assay [48–51].

Genetic Testing

Patients with an abnormal neutrophil function test should undergo confirmatory genetic testing. In general, patients with nonsense, frameshift, and splice site variants or deletions are more likely to be associated with absent or severely decreased residual NADPH oxidase activity and worse clinical outcomes than patients with missense mutations. Of note, the *NCF1* gene is flanked by highly homologous (>98%) pseudogenes, which may complicate genetic testing in patients with suspected p47phox deficiency. Western blot assays and flow cytometry have both been used on a research basis to evaluate for p47phox protein expression in patients with inconclusive genetic testing as a confirmatory diagnostic measure [52, 53].

Management/Outcome

Prophylaxis

All patients diagnosed with CGD should be promptly started on trimethoprim-sulfamethoxazole (5 mg/kg/d div BID up to 320 mg trimethoprim a day) and itraconazole (5 mg/kg/d up to 200 mg daily) prophylaxis, and prophylaxis should be continued lifelong or until the patient has successfully undergone definitive curative therapy. Trimethoprim-sulfamethoxazole has been shown to markedly reduce the incidence of bacterial infections in patients with CGD [54–58]; in one large retrospective study, trimethoprim-sulfamethoxazole prophylaxis decreased the rate of bacterial infection from 15.8 to 6.9 per 100 patient-months in patients with X-linked disease and from 7.1 to 2.4 per 100 patient-months in those with autosomal recessive disease [58]. Trimethoprim alone, dicloxacillin, ciprofloxacin, and quinolones are alternative options for patients with sulfamethoxazole allergy or G6PD deficiency.

The advent of azole antifungals and the widespread adoption of itraconazole prophylaxis have led to improved overall survival rates for patients with CGD around the world. In a seminal trial of 39 patients with CGD randomized to receive either placebo or itraconazole, only one patient receiving itraconazole had a serious fungal infection compared to seven in the placebo group over a follow-up period of approximately 113 patient-years [59]. For those unable to tolerate itraconazole, posaconazole has been shown to be safe and effective [60]. Of note, azole antifungal therapy may be complicated by transaminitis, and as such, liver function tests should be periodically monitored. Azole absorption is also quite variable, so many clinicians choose to monitor drug levels, especially in patients with gastrointestinal disease.

IFN-gamma has been shown to stimulate superoxide production and bactericidal activity of neutrophils in vitro, and in one large randomized, double-blind, placebo-controlled trial of 128 patients with CGD from the National Institutes of Health (NIH), IFN-gamma prophylaxis was associated with a decrease in both the number and severity of infections compared to controls [61]. Furthermore, long-term follow-up of 9 years demonstrated sustained benefit [62]. However, a large prospective Italian study found that long-term IFN-gamma prophylaxis did not significantly decrease the rate of infection [7], and there was no significant difference in the number of fungal infections between patients receiving IFN-gamma and those not receiving it in the itraconazole study discussed above [59]. Additionally, side effects are common, including fever, malaise, chills, fatigue, and injection site swelling and/or tenderness, and as such, many patients do not tolerate IFN-gamma injections. For these reasons, the use of IFN-gamma prophylaxis remains variable. However, when used, IFN-gamma is started at a dose of 50 μg/m^2 (or 1.5 μg/kg if BSA is <0.5 m^2) administered subcutaneously three times weekly.

In addition to antimicrobial prophylaxis, patients with CGD should receive all routine childhood immunizations except for the BCG vaccine. They should also be counseled to avoid decaying organic matter (e.g., mulch, hay, dead leaves), where fungal spores are often found, and brackish water as described above. CGD patients may otherwise participate in all normal activities without restriction.

Management of Acute Infections

Patients with CGD have reported rates of significant infection of around 0.3 per year despite appropriate antimicrobial prophylaxis [7, 19]. As such, all CGD patients with fever or any other signs or symptoms concerning for infection should be promptly evaluated with a thorough physical and laboratory evaluation. It should be noted that some patients with CGD, particularly young children, may not present with classic signs and symptoms of infection, and laboratory values may be falsely reassuring. Therefore, there should be a low threshold for imaging, particularly of the chest and/or abdomen, and when in doubt, one should err on the side of treating empirically with antimicrobials. Initial antibiotic therapy should provide good coverage for both *S. aureus* and gram-negative bacteria, including *B. cepacia* (e.g., combination of vancomycin/clindamycin/oxacillin and ceftazidime/carbapenem depending on local resistance patterns). The addition of treatment strength dosing of trimethoprim-sulfamethoxazole to cover ceftazidime-resistant *B. cepacia* and *Nocardia* spp. and voriconazole to cover *Aspergillus* spp. may also be considered as part of initial empiric therapy. If patients do not improve within 24–48 h, and an infectious agent has not been identified, voriconazole should be started if not already done so, and more aggressive diagnostic procedures should be considered. Of note, *Aspergillus* serological tests (e.g., *Aspergillus* galactomannan), the (1-3)-beta-D-glucan assay, and bronchoalveolar lavage all have low sensitivity in patients with CGD, and therefore, invasive sampling of involved tissues is often needed [35]. However, even with invasive sampling, a causative pathogen is only identified about

50% of the time [19, 20]. Surgical intervention is often necessary, and patients frequently require prolonged treatment courses extending for several months.

Granulocyte transfusions have also been used successfully for patients with severe and/or refractory infections unresponsive to antimicrobials [63]. The number of infused granulocytes is typically about 10^9–10^10 per transfusion with variable dosing schedules, ranging from daily to a few times per week which are sometimes limited by granulocyte availability. Adverse events are common, most frequently manifested as chills and fever but hypotension, respiratory distress, and transfusion-related acute lung injury have also been reported. Many patients develop alloimmunization [64–66], and as such, granulocyte transfusions should be used cautiously for those patients being considered for HSCT. Some centers have used sirolimus with granulocyte transfusions to decrease the risk of alloimmunization, and rituximab has been used to treat alloimmunization, although the effectiveness of these measures has not been well described.

In general, glucocorticoids are typically avoided in patients with active infection; however, one of the hallmarks of CGD is an exuberant and aberrant inflammatory response to infection. As such, glucocorticoids are sometimes used for CGD patients with severe and/or refractory infections [67, 68]. In particular, glucocorticoids in addition to appropriate antimicrobial agents are recommended for the treatment of liver abscesses [69, 70], as was done for the patient described in the case above. Liver abscesses are dense, caseous, and often difficult to drain, and traditionally, CGD patients often required surgical resection. However, in a case series from the NIH, nine patients who received glucocorticoids for the treatment of *Staphylococcal* liver abscesses refractory to conventional therapy all experienced resolution of the liver abscesses without the need for surgical intervention [69]. Glucocorticoids are typically dosed at 1 mg/kg/day for 2–3 weeks, followed by a taper over several months (on average 5 months).

Case Presentation 2

An otherwise healthy boy developed abdominal pain; bloody, mucousy stools; and failure to thrive at 18 months of age and was diagnosed at age 24 months with very early-onset inflammatory bowel disease based on results from an endoscopy and flexible sigmoidoscopy. Inflammatory bowel disease was complicated by recurrent perirectal abscesses and multiple enterocutaneous fistulae requiring surgical intervention. Colitis was poorly responsive to multiple therapies, including azathioprine, methotrexate, infliximab (anti-TNF-alpha), anakinra (anti-IL-1), and vedolizumab (anti-alpha 4 beta 7 integrin), and the patient ultimately underwent partial colectomy with diverting ileostomy at 8 years of age. The patient was referred to immunology for evaluation at 12 years of age given the early onset and severe nature of his inflammatory bowel disease. At time of evaluation, he was on methotrexate, ustekinumab (anti-IL-12/IL-23), and prednisone 10 mg daily with moderate control of disease. His height and weight were both at the third percentile. Infectious history

was not significant. The patient's mother had systemic lupus erythematous, but family history was otherwise unremarkable. A DHR assay demonstrated absent neutrophil oxidative burst consistent with X-linked CGD, and genetic testing identified a pathogenic mutation in *CYBB*. The decision was made at that time to pursue curative HSCT. Fortunately, the patient's younger brother was found to be a full 10/10 HLA-identical match, and the patient underwent HSCT at 13 years of age with reduced-toxicity myeloablative conditioning. His posttransplant course was overall unremarkable, and the patient had full resolution of CGD colitis by 3 months posttransplant. Growth also improved, and the patient is now at the tenth percentile for height and weight 2 years posttransplant.

Diagnosis/Assessment

Inflammatory Complications of CGD

In addition to recurrent and severe infections, CGD is characterized by immune dysregulation with high rates of autoinflammation, particularly of the GI tract, lungs, and liver. Importantly, patients may present with inflammatory disease as their only disease manifestation in the absence of a significant infectious history, as was the case for the patient described above. Autoinflammation is seen with all genotypes, but in general, severe inflammatory disease occurs more commonly in patients with X-linked CGD than in those with autosomal recessive disease [71]. Furthermore, up to 18% of CGD patients reaching adulthood develop autoimmune disease, including lupus-like symptoms, sarcoidosis, IgA nephropathy, and rheumatoid arthritis, among others [5, 12, 72].

Inflammatory bowel disease or colitis is the most common inflammatory disease seen in patients with CGD. In a series of 140 pediatric patients with CGD at the NIH, 32.8% had colitis [73], and rates as high as 60% have been reported in other series [71]. The median age of onset of GI disease was 5 years in the NIH cohort, although symptoms may develop at any point. Furthermore, the GI symptoms may be nonspecific, including abdominal pain, noninfectious diarrhea, nausea and vomiting, and failure to thrive. Any portion of the GI tract may be involved, but the colon is the most common site affected, and colitis is often fistulizing [73, 74]. Perirectal disease, frequently with recurrent and/or severe perirectal abscesses, is also particularly common. Many patients develop failure to thrive due to poorly controlled disease; in the aforementioned NIH study, 32% of patients had delayed growth [73]. In addition to colitis, about 50% of patients also develop gastrointestinal granulomas, which may be obstructive [71, 73, 75].

Other common sites of inflammatory disease include the lungs, liver, genitourinary tract, eyes and skin. About 20–30% of patients surviving into adulthood develop inflammatory lung disease [71, 76], and granulomatous disease, with or without lymphocyte infiltration, interstitial lung disease, pulmonary nodules, pleural thickening and/or effusions, and chronic obstructive pulmonary disease have all

been reported [71, 76, 77]. Of note, inflammatory lung disease may occur independently from or simultaneously with infection, and infection may be the trigger for onset of inflammatory disease. Inflammatory liver disease is also common in CGD patients. In one review from the NIH, granulomas, venopathy of the portal vein, and nodular regenerative hyperplasia were all reported [78]. Poorly controlled liver disease may progress to non-cirrhotic pulmonary hypertension; the development of thrombocytopenia in this setting is associated with especially poor outcomes [79]. Inflammatory genitourinary symptoms are not uncommon, and granuloma formation in the genitourinary tract may result in ureteral or bladder outlet obstruction [71, 80]. Eosinophilic cystitis is also a rare complication that has also been reported [81, 82]. Ocular manifestations of CGD include chorioretinitis, uveitis, and ocular granulomas [71]. Common dermatologic manifestations include severe and/or granulomatous acne, inflammatory nodular lesions, and cutaneous lymphocytic infiltration [71, 72]. Poor wound healing with increased risk of wound dehiscence has also been described [83, 84]. Furthermore, macrophage activation syndrome or hemophagocytic lymphohistiocytosis has been reported in CGD patients and may be life-threatening [85–88].

Finally, patients with CGD may develop an entity known as mulch pneumonitis, which is due to an exuberant inflammatory response to inhalation of fungal elements in decaying organic matter (e.g., mulch, hay, and dead leaves) [89–91]. Symptoms typically occur 1–10 days after exposure to fungal elements, and symptoms tend to progress rapidly. Chest x-ray characteristically demonstrates diffuse interstitial infiltrates. Mulch pneumonitis is associated with a high mortality rate if not identified early and should be considered for all CGD patients who present with acute onset of fever, dyspnea, and hypoxia.

X-Linked Carriers

The patient's mother in the case above reported a history of systemic lupus erythematosus, which may be related to her presumed status as a carrier of X-linked CGD. Female carriers of X-linked CGD have a dual phagocyte population due to lyonization, and in some cases, severe skewing of X chromosome inactivation may lead to the clinical syndrome of CGD. Furthermore, female carriers may have progressive skewing with age and may develop manifestations of CGD later in life. However, recent studies from the United Kingdom and the NIH also indicate that female carriers are at increased risk of medical complications, particularly autoimmune disease, regardless of degree of lyonization.

In a UK survey of 94 female carriers of X-linked CGD [92], cutaneous symptoms, most frequently photosensitivity but also malar-like lupus rash and eczema, were reported by 63 (79%) women. Skin abscesses were reported by 14 (17%), and gastrointestinal symptoms were reported by 40 (42%) women. Twenty-four (26%) women also met criteria for systemic lupus erythematosus. The NIH study [93], which included 162 female carriers of X-linked CGD, also found high rates of cutaneous symptoms and autoimmune disease, at 25% and 19%, respectively. Fifteen

percent of women also had a history of severe CGD-related infections. There was a clear correlation between history of infection and neutrophil oxidative capacity in the NIH study; women with less than 10–20% oxidase-positive neutrophils were at increased risk of infection. Interestingly, in both studies, there was no relationship between autoimmune disease and neutrophil respiratory oxidative burst.

In addition to an increased rate of the medical complications described above, a recent publication, also from the United Kingdom, reported impaired emotional health with high rates of anxiety and significantly reduced quality of life scores in female carriers of X-liked CGD [94]. Taken together, these studies suggest that female carriers should be monitored long term, and in general, experts recommend antimicrobial prophylaxis for those with less than 10% oxidase-positive neutrophils. Furthermore, based on the increased risk of autoimmune disease and potential skewing of X inactivation with time, many centers prefer not to use female carriers as donors for HSCT in their affected family members, although HSCT outcomes using female carrier donors have not been published.

Diagnostic Testing

Patients with granulomatous inflammation, early-onset inflammatory bowel disease, or any of the unusual inflammatory complications described above should be screened for CGD regardless of infectious history. In particular, all patients with early-onset inflammatory bowel disease should receive a DHR assay at presentation, as a diagnosis of CGD may influence treatment decisions.

Management/Outcome

Treatment of Autoinflammation

Glucocorticoids are the mainstay of treatment of inflammatory disease in patients with CGD, and they are often effective for the treatment of granulomatous lesions. However, CGD colitis, interstitial lung disease, and other inflammatory manifestations of CGD are often difficult to treat, and additional immunomodulators are often necessary. This raises a dilemma for CGD patients, as iatrogenic immunosuppression increases their already high risk of infection and may be associated with significant morbidity and mortality.

Patients with CGD colitis typically respond to glucocorticoids, but relapse is common, and many patients become glucocorticoid dependent [71, 73]. Infliximab may be effective at treating colitis, but has been associated with increased risk of infection and death in patients with CGD, and as such, infliximab and other TNF-alpha inhibitors are generally strictly avoided [94]. Patients have variable response to the typical glucocorticoid-sparing agents used for the treatment of inflammatory

bowel disease, including salicylic acid derivatives, antimetabolites such as azathioprine, and 6-mercaptopurine. Anakinra, ustekinumab, and vedolizumab have all been used in small numbers of patients with CGD colitis with varying degrees of success [95–98]. Ultimately, many patients remain refractory to treatment and fail multiple therapies as described in the case above, and their only curative option is hematopoietic stem cell transplantation and possibly gene therapy.

Hematopoietic Cell Transplantation

Allogeneic HSCT is the only widely available definitive treatment for CGD with the potential for resolution of both infectious and inflammatory complications. Initial studies showed that HSCT for CGD was possible, but rates of graft failure were high and overall survival outcomes were poor [100–102]. However, with optimization of clinical status pre-HSCT, fine-tuning of conditioning regimens, and improved supportive care peri- and post-HSCT, outcomes have improved significantly over the last two decades (Table 17.4). Overall survival rates are now consistently near or >90% for pediatric patients less than 14 years regardless of donor source [103–109], and pediatric patients who undergo HSCT have fewer infections, improved growth parameters and performance scores, and higher quality of life measures compared to those treated conventionally [110–112]. Adolescents and adults have traditionally been difficult to transplant; however, there have been several studies in recent years reporting high disease-free survival rates in adolescents and adult patients, including those with severe infection and/or uncontrolled inflammatory disease at time of transplantation [66, 113–117].

There remains debate as to the optimal conditioning regimen for CGD, and practice varies significantly from center to center. Many centers throughout the world have adopted a highly successful reduced-toxicity myeloablative conditioning regimen reported by Güngör and others in 2014 [113] that includes customized busulfan dosing with pharmacokinetic analysis, fludarabine, and antithymocyte globulin. However, some centers have subsequently reported an increased incidence of graft rejection, late graft failure, and mixed myeloid chimerism [119]. This is notable, as data on female carriers of X-linked CGD suggests the level of neutrophil oxidase activity that protects a CGD patient from infection may be different than that which protects against autoinflammation [92, 93], and the degree of myeloid chimerism needed to protect against new-onset inflammatory and autoimmune disease post-transplant is unknown.

Furthermore, the role of autoinflammation on HSCT outcomes also remains incompletely understood. Encouragingly, one recent study report from the Primary Immunodeficiency Treatment Consortium that included 49 CGD patients with IBD and 96 patients without IBD who underwent allogeneic HSCT reported a 5-year overall survival was equivalent for patients with and without colitis at 80% and 83%, respectively [120]. Furthermore, colitis was not associated with an increased risk of graft-versus-host disease and all surviving patients with a history of colitis had resolution of disease posttransplant. However, further studies are needed to fully elucidate how the presence of autoinflammation and accompanying organ

Table 17.4 Published HSCT outcomes in patients with CGD

Reference	*N*	Age in years, median (range)	Donor source	Conditioning regimen	Overall survival (%)	Disease-free survival (%)	Median follow-up (years)
Horowitz et al. [99]	10	15 (5–36)	MRD	RIC	70	60	1.4
Seger et al. [101]	27	8.5 (0.8–38.7)	MRD (25) URD (2)	MAC (23) RIC (4)	85	81	2
Soncini et al. [103]	20	6.25 (1.25–21)	MRD (9) URD (9) UCB (2)	MAC (16) RIC (4)	90	90	5
Schuetz et al. [102]	12	9.5 (4–20)	MRD (3) URD (9)	MAC (9) RIC (3)	75	58	4.4
Martinez et al. [105]	11	3.8 (1–13)	MRD (4) URD (7)	MAC	100	100	4
Tewari et al. [106]	12	4.95 (0.67–11.6)	MRD (5) UCB (7)	MAC	100	83.3	5.8
Gungor et al. [113]	56	12.7 (0.8–40)	MRD (21) URD (35)	RTC	93	89	1.75
Khandelwal et al. [114]	18	3.18 (0.45–19.39)	MRD (3) URD (15)	MAC (14) RIC (4)	83	83	1.65
Morillo-Gutierrez et al. [107]	70	8.9 (3.8–19.3)	MRD (13) URD (55) UCB (1) Haplo (1)	RTC	91.4	84	2.8
Fox et al. [115]	11	19 (17–28)	MRD (3) URD (8)	RIC	81.8	81.8	2.69
Parta et al. [116]	40	16 (4–32)	MRD (4) URD (36)	RIC	82.5	80	3.4
Genenry et al. [118]	55	5.3 (0.6–18)	MRD (20) URD (31) Haplo (4)	MAC (25) RTC (30)	89	77	6.5

MRD matched related donor, *URD* unrelated donor, *UCB* umbilical cord blood, *Haplo* haploidentical donor, *MAC* myeloablative conditioning, *RIC* reduced-intensity conditioning, *RTC* reduced-toxicity myeloablative conditioning

dysfunction at time of HSCT impacts overall survival, engraftment, immune reconstitution, and risk of post-HSCT complications.

Gene Therapy

As with all monogenic diseases, gene therapy is an appealing alternative to HSCT, providing an option for patients without an HLA-identical donor and eliminating the risk of graft-versus-host disease. The first gene therapy trials for CGD took place at

the NIH in the 1990s [121], and several small trials have subsequently been conducted to treat gp91phox deficiency using gamma-retroviral vectors and reduced-intensity conditioning [122–126]. Notably, many of the patients had active and refractory severe infection at time of gene therapy. All trials demonstrated initial engraftment of transduced neutrophils at 10–30% of circulating neutrophils, and most patients experienced full or partial resolution of infection. However, cell engraftment progressively decreased with time, and several patients developed myelodysplastic syndrome (MDS) due to insertional activation of proto-oncogenes [123, 125].

In response to the high incidence of MDS seen with γ-retroviral vectors, gene therapy trials are currently underway using self-inactivating (SIN) lentiviral vectors. Encouragingly, a recent report from a multicenter trial using a SIN lentiviral vector and near-myeloablative conditioning demonstrated sustained persistence of 12–46% oxidase positive neutrophils and no new infections in six of seven patients (aged at 7–27 years) at 1–2.5-year follow-up [127]. Furthermore, one of these patients had a history of colitis that resolved completely following gene therapy.

Ultimately, long-term outcomes with gene therapy are unknown, and as with HSCT, it is unclear what level of oxidase-positive neutrophils is necessary for resolution of preexisting autoinflammation and to prevent new-onset inflammatory and autoimmune disease.

Conclusion

Overall, CGD outcomes have improved markedly over the past few decades. In 2000, Winkelstein et al. reported a mortality rate for 5% per year for X-linked CGD and 2% per year for autosomal recessive CGD[5]. However, several large registries have subsequently reported survival rates approaching 90% by age 10 years, largely attributed to the widespread adoption of itraconazole prophylaxis [6, 7, 14]. Current long-term survival rates are unknown, however, as recognition and management of disease and transplant outcomes continue to improve with time. Furthermore, there remain no standard long-term treatment guidelines for patients with CGD. Indications for HSCT remain controversial, particularly for patients with residual oxidase activity, and transplant procedures for CGD patients vary markedly from center to center. Thus, additional large, multicenter studies are needed to further optimize HSCT procedures, and long-term follow-up is needed to clarify the role of gene therapy for CGD.

Clinical Pearls and Pitfalls

- All patients with severe or recurrent cutaneous abscesses, lymphadenitis, and/or pneumonia, any instance of deep tissue abscess, and infection with *Aspergillus* spp., *B. cepacia*, *Nocardia* spp., and *Serratia marcescens* should be evaluated for CGD.

- All patients with early-onset inflammatory bowel disease (<10 years of age), particularly those with perirectal and/or difficult to control disease, should be screened for CGD, particularly before starting infliximab or other anti-TNF-alpha agents.
- CGD patients should be counseled to avoid decaying organic matter (e.g., hay, mulch, dead leaves) and brackish water (i.e., water resulting from the mixing of seawater with freshwater, as in estuaries).
- CGD patients with fever or any signs or symptoms of infection should be evaluated promptly with a thorough physical and laboratory evaluation even if symptoms are mild and guardians/patients report that they are overall well appearing.
- *Aspergillus galactomannan*, (1-3)-beta-D-glucan, and bronchoalveolar lavage all have poor sensitivity in CGD, and negative results do not exclude fungal infection.
- CGD patients often require prolonged antimicrobial courses with courses 4–6 months or longer in duration common.
- Glucocorticoids may be necessary in addition to antimicrobial therapy for the treatment of the hyperactive inflammatory response frequently seen in CGD patients with infection.
- Female relatives of patients with X-linked CGD should be screened for carrier status and, if positive, followed long term. Those with <10% oxidase-positive neutrophils on DHR assay should be started on antimicrobial prophylaxis.
- Definitive therapy with allogeneic hematopoietic cell transplantation should be considered for all patients with CGD. Transplant should not be delayed, as outcomes are better for younger patients before they develop severe infection or autoinflammation with resultant organ dysfunction.

References

1. Janeway CA, Craig J, Davison M, et al. Hypergammaglobulinemia associated with severe, recurrent, and chronic non-specific infection. Am J Dis Child. 1954;88:388–92.
2. Bridges RA, Berendes H, Good RA. A fatal granulomatous disease of childhood; the clinical, pathological, and laboratory features of a new syndrome. AMA J Dis Child. 1959;97(4):387–408.
3. Reeves EP, Lu H, Jacobs HL, et al. Killing activity of neutrophils is mediated through activation of proteases by K+ flux. Nature. 2002;416(6878):291–7.
4. Fuchs TA, Abed U, Goosmann C, et al. Novel cell death program leads to neutrophil extracellular traps. J Cell Biol. 2007;176(2):231–41.
5. Winkelstein JA, Marino MC, Johnston RB, et al. Chronic granulomatous disease: report on a national registry of 368 patients. Medicine. 2000;79(3):155–69.
6. Jones LB, McGrogan P, Flood TJ, et al. Special article: chronic granulomatous disease in the United Kingdom and Ireland: a comprehensive national patient-based registry. Clin Exp Immunol. 2008;152(2):211–8.

7. Martire B, Rondelli R, Soresina A, et al. Clinical features, long-term follow-up and outcome of a large cohort of patients with chronic granulomatous disease: an Italian multicenter study. Clin Immunol. 2008;126(2):155–64.
8. Åhlin A, de Boer M, Roos D, et al. Prevalence, genetics and clinical presentation of chronic granulomatous disease in Sweden. Acta Paediatr. 1995;84(2):1386–94.
9. Raptaki M, Varela I, Spanou K, et al. Chronic granulomatous disease: a 25-year patient registry based on a multistep diagnostic procedure, from the referral center for primary immunodeficiencies in Greece. J Clin Immunol. 2013;33(8):1302–9.
10. Hasui M, Hayakawa H, Kanegasaki S, et al. Chronic granulomatous disease in Japan: incidence and natural history. Pediatr Int. 1999;41(5):589–93.
11. Wolach B, Gavrieli R, de Boer M, et al. Chronic granulomatous disease: clinical, functional, molecular, and genetic studies. The Israeli experience with 84 patients. Am J Hematol. 2017;92(1):28–36.
12. van den Berg J, van Koppen E, Ahlin A, et al. Chronic granulomatous disease: the European experience. PLoS ONE. 2009;4(4):e5234.
13. Roos D, Kuhns DB, Maddalena A, et al. Hematologically important mutations: the autosomal recessive forms of chronic granulomatous disease (second update). Blood Cell Mol Dis. 2010;44(4):291–9.
14. Kuhns DB, Alvord WG, Heller T, et al. Residual NADPH oxidase and survival in chronic granulomatous disease. N Engl J Med. 2010;363(27):2600–10.
15. Matute JD, Arias AA, Wright NAM, et al. A new genetic subgroup of chronic granulomatous disease with autosomal recessive mutations in p40 phox and selective defects in neutrophil NADPH oxidase activity. Blood. 2009;114(5):3309–15.
16. van de Geer A, Nieto-Patlán A, Kuhns DB, et al. Inherited p40 phox deficiency differs from classic chronic granulomatous disease. J Clin Invest. 2018;128(9):3957–75.
17. Thomas DC, Charbonnier LM, Schejtman A, et al. EROS/CYBC1 mutations: decreased NADPH oxidase function and chronic granulomatous disease. J Allergy Clin Immunol. 2019;143(2):782–5.
18. Arnadottir GA, Norddahl GL, Gudmundsdottir S, et al. A homozygous loss-of-function mutation leading to CYBC1 deficiency causes chronic granulomatous disease. Nat Commun. 2018;9(1):4447.
19. Marciano BE, Spalding C, Fitzgerald A, et al. Common severe infections in chronic granulomatous disease. Clin Infect Dis. 2015;60(8):1176–83.
20. Bortoletto P, Lyman K, Camacho A, et al. Chronic granulomatous disease: a large, single-center US experience. Pediatr Infect Dis J. 2015;34(10):1110–4.
21. Wolach B, Gavrieli R, de Boer M, et al. Chronic granulomatous disease in Israel: clinical, functional and molecular studies of 38 patients. Clin Immunol. 2008;129(1):103–14.
22. Baba LA, Ailal F, el Hafidi N, et al. Chronic granulomatous disease in Morocco: genetic, immunological, and clinical features of 12 patients from 10 kindreds. J Clin Immunol. 2014;34(4):452–8.
23. de Oliveira-Junior EB, Zurro NB, Prando C, et al. Clinical and genotypic spectrum of chronic granulomatous disease in 71 Latin American patients: first report from the LASID registry. Pediatr Blood Cancer. 2015;62(12):2102–7.
24. Fattahi F, Badalzadeh M, Sedighipour L, et al. Inheritance pattern and clinical aspects of 93 Iranian patients with chronic granulomatous disease. J Clin Immunol. 2011;31(5):792–801.
25. Zhou Q, Hui X, Ying W, et al. A cohort of 169 chronic granulomatous disease patients exposed to BCG vaccination: a retrospective study from a single center in Shanghai, China (2004–2017). J Clin Immunol. 2018;38(3):260–72.
26. Lee PPW, Chan KW, Jiang L, et al. Susceptibility to mycobacterial infections in children with x-linked chronic granulomatous disease: a review of 17 patients living in a region endemic for tuberculosis. Pediatr Infect Dis J. 2008;27(3):224–30.
27. Conti F, Lugo-Reyes SO, Blancas Galicia L, et al. Mycobacterial disease in patients with chronic granulomatous disease: a retrospective analysis of 71 cases. J Allergy Clin Immunol. 2016;138(1):241–8.

28. Sirinavin S, Techasaensiri C, Benjaponpitak S, Pornkul R, Vorachit M. Invasive Chromobacterium violaceum infection in children: case report and review. Pediatr Infect Dis J. 2005;24(6):559–61.
29. Meher-Homji Z, Mangalore RP, D R Johnson P, Y L Chua K. Chromobacterium violaceum infection in chronic granulomatous disease: a case report and review of the literature. JMM Case Rep. 2017;4(1):e005084.
30. Mailman TL, Schmidt MH. Francisella philomiragia adenitis and pulmonary nodules in a child with chronic granulomatous disease. Can J Infect Dis Med Microbiol. 2005;16(4):245–8.
31. Greenberg DE, Shoffner AR, Zelazny AM, et al. Recurrent granulibacter bethesdensis infections and chronic granulomatous disease. Emerg Infect Dis. 2010;16(9):1341–8.
32. Dotis J, Roilides E. Osteomyelitis due to Aspergillus species in chronic granulomatous disease: an update of the literature. Mycoses. 2011;54(6):e686–96.
33. Falcone EL, Holland SM. Invasive fungal infection in chronic granulomatous disease: insights into pathogenesis and management. Curr Opin Infect Dis. 2012;25(6):658–69.
34. Beauté J, Obenga G, le Mignot L, et al. Epidemiology and outcome of invasive fungal diseases in patients with chronic granulomatous disease: a multicenter study in France. Pediatr Infect Dis J. 2011;30(1):57–62.
35. Blumental S, Mouy R, Mahlaoui N, et al. Invasive mold infections in chronic granulomatous disease: a 25-year retrospective survey. Clin Infect Dis. 2011;53(12):e159–69.
36. Vinh DC, Shea YR, Jones PA, et al. Chronic invasive aspergillosis caused by Aspergillus viridinutans. Emerg Infect Dis. 2009;15(8):1292–4.
37. Sugui JA, Peterson SW, Clark LP, et al. Aspergillus tanneri sp. nov., a new pathogen that causes invasive disease refractory to antifungal therapy. J Clin Microbiol. 2012;50(10):3309–17.
38. Kaltenis P, Mudänienė V, Maknavičius S, Šeinin D. Renal amyloidosis in a child with chronic granulomatous disease and invasive aspergillosis. Pediatr Nephrol. 2008;23(5):831–4.
39. Mortaz E, Sarhifynia S, Marjani M, et al. An adult autosomal recessive chronic granulomatous disease patient with pulmonary Aspergillus terreus infection. BMC Infect Dis. 2018;18(1):552.
40. Dotis J, Pana ZD, Roilides E. Non-Aspergillus fungal infections in chronic granulomatous disease. Mycoses. 2013;56(4):449–62.
41. Silliman CC, Lawellin DW, Lohr JA, Rodgers BM, Donowitz LG. Paecilomyces lilacinus infection in a child with chronic granulomatous disease. J Infect. 1992;24(2):191–5.
42. Wang SM, Shieh CC, Liu CC. Successful treatment of Paecilomyces variotii splenic abscesses: a rare complication in a previously unrecognized chronic granulomatous disease child. Diagn Microbiol Infect Dis. 2005;53(2):149–52.
43. Ramesh M, Resnick E, Hui Y, et al. Phellinus tropicalis abscesses in a patient with chronic granulomatous disease. J Clin Immunol. 2014;34(2):130–3.
44. Haidar G, Zerbe CS, Cheng M, et al. Phellinus species: an emerging cause of refractory fungal infections in patients with X-linked chronic granulomatous disease. Mycoses. 2017;60(3):155–60.
45. de Ravin SS, Challipalli M, Anderson V, et al. Geosmithia argillacea: an emerging cause of invasive mycosis in human chronic granulomatous disease. Clin Infect Dis. 2011;52(6):e136–43.
46. Vinh DC, Shea YR, Sugui JA, et al. Invasive Aspergillosis due to Neosartorya udagawae. Clin Infect Dis. 2009;49(1):102–11.
47. Vinh DC, Freeman AF, Shea YR, et al. Mucormycosis in chronic granulomatous disease: association with iatrogenic immunosuppression. J Allergy Clin Immunol. 2009;123(6):1411–3.
48. Siler U, Romao S, Tejera E, et al. Severe glucose-6-phosphate dehydrogenase deficiency leads to susceptibility to infection and absent NETosis. J Allergy Clin Immunol. 2017;139(1):212–9.
49. Mauch L, Lun A, O'Gorman MRG, et al. Chronic granulomatous disease (CGD) and complete myeloperoxidase deficiency both yield strongly reduced dihydrorhodamine 123 test signals but can be easily discerned in routine testing for CGD. Clin Chem. 2007;53(5):890–6.

50. Ferguson PJ, Lokuta MA, El-Shanti HI, et al. Neutrophil dysfunction in a family with a SAPHO syndrome-like phenotype. Arthritis Rheum. 2008;58(10):3264–9.
51. Banerjee R, Anguita J, Roos D, Fikrig E. Cutting edge: infection by the agent of human granulocytic ehrlichiosis prevents the respiratory burst by down-regulating gp91phox. J Immunol. 2000;164(8):3946–9.
52. Kuhns DB, Wu X, Hsu AP, et al. Characterization of patients and carriers of p47phox chronic granulomatous disease by flow cytometric analysis of p47phox expression and droplet digital PCR analysis of NCF1. J Clin Immunol. 2018;38(3):349.
53. Kuhns DB, Hsu AP, Sun D, et al. NCF1 (p47 phox)-deficient chronic granulomatous disease: comprehensive genetic and flow cytometric analysis. Blood Adv. 2019;3(2):136–47.
54. Gallin JI, Buescher ES, Seligmann BE, et al. NIH conference. Recent advances in chronic granulomatous disease. Ann Intern Med. 1983;99(5):657–74.
55. Forrest CB, Forehand JR, Axtell RA, Roberts RL, Johnston RB. Clinical features and current management of chronic granulomatous disease. Hematol Oncol Clin N Am. 1988;2(2):253–66.
56. Weening RS, Kabel P, Pijman P, Roos D. Continuous therapy with sulfamethoxazole-trimethoprim in patients with chronic granulomatous disease. J Pediatr. 1983;103(1):127–30.
57. Mouy R. Chronic septic granulomatosis. Clinical and therapeutic aspects. Ann Pediatr. 1989;36(6):374–8.
58. Margolis DM, Melnick DA, Alling DW, Gallin JI. Trimethoprim-sulfamethoxazole prophylaxis in the management of chronic granulomatous disease. J Infect Dis. 1990;162(3):723–6.
59. Gallin JI, Alling DW, Malech HL, et al. Itraconazole to prevent fungal infections in chronic granulomatous disease. N Engl J Med. 2003;348(24):2416–22.
60. Segal BH, Barnhart LA, Anderson VL, et al. Posaconazole as salvage therapy in patients with chronic granulomatous disease and invasive filamentous fungal infection. Clin Infect Dis. 2005;40(11):1684–8.
61. Gallin JI, Malech HL, Weening RS, et al. A controlled trial of interferon gamma to prevent infection in chronic granulomatous disease: the international chronic granulomatous disease cooperative study group. N Engl J Med. 1991;324(8):509–16.
62. Marciano BE, Wesley R, de Carlo ES, et al. Long-term interferon-therapy for patients with chronic granulomatous disease. Clin Infect Dis. 2004;39(5):692–9.
63. Marciano BE, Allen ES, Conry-Cantilena C, et al. Granulocyte transfusions in patients with chronic granulomatous disease and refractory infections: the NIH experience. J Allergy Clin Immunol. 2017;140(2):622–5.
64. Stroncek DF, Leonard K, Eiber G, et al. Alloimmunization after granulocyte transfusions. Transfusion. 1996;75(3):744–55.
65. Heim KF, Fleisher TA, Stroncek DF, et al. The relationship between alloimmunization and posttransfusion granulocyte survival: experience in a chronic granulomatous disease cohort. Transfusion. 2011;51(6):1154–62.
66. Parta M, Kelly C, Kwatemaa N, et al. Allogeneic reduced-intensity hematopoietic stem cell transplantation for chronic granulomatous disease: a single-center prospective trial. J Clin Immunol. 2017;37(6):548–58.
67. Yamazaki-Nakashimada MA, Stiehm ER, Pietropaolo-Cienfuegos D, Hernandez-Bautista V, Espinosa-Rosales F. Corticosteroid therapy for refractory infections in chronic granulomatous disease: case reports and review of the literature. Ann Allergy Asthma Immunol. 2006;97(2):257–61.
68. Freeman AF, Marciano BE, Anderson VL, et al. Corticosteroids in the treatment of severe nocardia pneumonia in chronic granulomatous disease. Pediatr Infect Dis J. 2011;30(9):806–8.
69. Leiding JW, Freeman AF, Marciano BE, et al. Corticosteroid therapy for liver abscess in chronic granulomatous disease. Clin Infect Dis. 2012;54(5):694–700.
70. Straughan DM, McLoughlin KC, Mullinax JE, et al. The changing paradigm of management of liver abscesses in chronic granulomatous disease. Clin Infect Dis. 2018;66(9):1427–34.

71. Magnani A, Brosselin P, Beauté J, et al. Inflammatory manifestations in a single-center cohort of patients with chronic granulomatous disease. J Allergy Clin Immunol. 2014;134(3):655–62.
72. Dunogué B, Pilmis B, Mahlaoui N, et al. Chronic granulomatous disease in patients reaching adulthood: a nationwide study in France. Clin Infect Dis. 2017;64(6):767–75.
73. Marciano BE, Rosenzweig SD, Kleiner DE, et al. Gastrointestinal involvement in chronic granulomatous disease. Pediatrics. 2004;114(2):462–8.
74. Alimchandani M, Lai JP, Aung PP, et al. Gastrointestinal histopathology in chronic granulomatous disease a study of 87 patients. Am J Surg Pathol. 2013;37(9):1365–72.
75. Johnson FE, Humbert JR, Kuzela DC, Todd JK, Lilly JR. Gastric outlet obstruction due to X-linked chronic granulomatous disease. Surgery. 1975;78(2):217–23.
76. Salvator H, Mahlaoui N, Catherinot E, et al. Pulmonary manifestations in adult patients with chronic granulomatous disease. Eur Respir J. 2015;45(6):1613–23.
77. Mahdaviani SA, Mohajerani SA, Rezaei N, et al. Pulmonary manifestations of chronic granulomatous disease. Expert Rev Clin Immunol. 2013;9(2):153–60.
78. Hussain N, Feld JJ, Kleiner DE, et al. Hepatic abnormalities in patients with chronic granulomatous disease. Hepatology. 2007;45(3):675–83.
79. Feld JJ, Hussain N, Wright EC, et al. Hepatic involvement and portal hypertension predict mortality in chronic granulomatous disease. Gastroenterology. 2008;134(7):1917–26.
80. Walther MM, Malech H, Berman A, et al. The urological manifestations of chronic granulomatous disease. J Urol. 1992;147(5):1314–8.
81. Barese CN, Podestá M, Litvak E, Villa M, Rivas EM. Recurrent eosinophilic cystitis in a child with chronic granulomatous disease. J Pediatr Hematol Oncol. 2004;26(3):209–12.
82. Claps A, della Corte M, Gerocarni Nappo S, et al. How should eosinophilic cystitis be treated in patients with chronic granulomatous disease? Pediatr Nephrol. 2014;29(11):2229–33.
83. Eckert JW, Abramson SL, Starke J, Brandt ML. The surgical implications of chronic granulomatous disease. Am J Surg. 1995;169(3):320–3.
84. Feingold PL, Quadri HS, Steinberg SM, et al. Thoracic surgery in chronic granulomatous disease: a 25-year single-institution experience. J Clin Immunol. 2016;36(7):677–83.
85. Akagi K, Kawai T, Watanabe N, et al. A case of macrophage activation syndrome developing in a patient with chronic granulomatous disease-associated colitis. J Pediatr Hematol Oncol. 2014;36(3):e169–72.
86. Valentine G, Thomas TA, Nguyen T, Lai YC. Chronic granulomatous disease presenting as hemophagocytic lymphohistiocytosis: a case report. Pediatrics. 2014;134(6):e1727–30.
87. Parekh C, Hofstra T, Church JA, Coates TD. Hemophagocytic lymphohistiocytosis in children with chronic granulomatous disease. Pediatr Blood Cancer. 2011;56(3):460–2.
88. Bode SFN, Ammann S, Al-Herz W, et al. The syndrome of hemophagocytic lymphohistiocytosis in primary immunodeficiencies: implications for differential diagnosis and pathogenesis. Haematologica. 2015;100(7):978–88.
89. Siddiqui S, Anderson VL, Hilligoss DM, et al. Fulminant mulch pneumonitis: an emergency presentation of chronic granulomatous disease. Clin Infect Dis. 2007;45(6):673–81.
90. Ameratunga R, Woon ST, Vyas J, Roberts S. Fulminant mulch pneumonitis in undiagnosed chronic granulomatous disease: a medical emergency. Clin Pediatr. 2010;49(12):1143–6.
91. Maaloul I, Ben Ameur S, Chabchoub I, et al. Fulminant mulch pneumonitis in a previously healthy child. Arch Pediatr. 2018;25(8):495–6.
92. Battersby AC, Braggins H, Pearce MS, et al. Inflammatory and autoimmune manifestations in X-linked carriers of chronic granulomatous disease in the United Kingdom. J Allergy Clin Immunol. 2017;140(2):628–30.
93. Marciano BE, Zerbe CS, Falcone EL, et al. X-linked carriers of chronic granulomatous disease: illness, lyonization, and stability. J Allergy Clin Immunol. 2018;141(1):365–71.
94. Battersby A, Braggins H, Pearce M, et al. Health-related quality of life and emotional health in X-linked carriers of chronic granulomatous disease in the United Kingdom. J Clin Immunol. 2019;39(2):195–9.
95. de Luca A, Smeekens SP, Casagrande A, et al. IL-1 receptor blockade restores autophagy and reduces inflammation in chronic granulomatous disease in mice and in humans. Proc Natl Acad Sci U S A. 2014;111(9):3526–31.

96. Hahn KJ, Ho N, Yockey L, et al. Treatment with Anakinra, a recombinant IL-1 receptor antagonist, unlikely to induce lasting remission in patients with CGD colitis. Am J Gastroenterol. 2015;110(6):938–9.
97. Butte MJ, Park KT, Lewis DB. Treatment of CGD-associated colitis with the IL-23 blocker ustekinumab. J Clin Immunol. 2016;36(7):619–20.
98. Campbell N, Chapdelaine H. Treatment of chronic granulomatous disease–associated fistulising colitis with vedolizumab. J Allergy Clin Immunol Pract. 2017;5(6):1748–9.
99. Horwitz ME. Stem-cell transplantation for inherited immunodeficiency disorders. Pediatr Clin North Am. 2000;47(6):1371–87. https://doi.org/10.1016/s0031-3955(05)70276-5. Pediatr Clin North Am. 2000. PMID: 11131001.
100. Horwitz ME, Barrett AJ, Brown MR, et al. Treatment of chronic granulomatous disease with nonmyeloablative conditioning and a T-cell-depleted hematopoietic allograft. N Engl J Med. 2001;344(12):881–8.
101. Seger RA, Gungor T, Belohradsky BH, et al. Treatment of chronic granulomatous disease with myeloablative conditioning and an unmodified hemopoietic allograft: a survey of the European experience, 1985–2000. Blood. 2002;100(13):4344–50.
102. Schuetz C, Hoenig M, Gatz S, et al. Hematopoietic stem cell transplantation from matched unrelated donors in chronic granulomatous disease. Immunol Res. 2009;44(1–3):35–41.
103. Soncini E, Slatter MA, Jones LBKR, et al. Unrelated donor and HLA-identical sibling haematopoietic stem cell transplantation cure chronic granulomatous disease with good long-term outcome and growth. Br J Haematol. 2009;145(1):73–83.
104. Goździk J, Pituch-Noworolska A, Skoczeń S, et al. Allogeneic haematopoietic stem cell transplantation as therapy for chronic granulomatous disease-single centre experience. J Clin Immunol. 2011;31(3):322–7.
105. Martinez CA, Shah S, Shearer WT, et al. Excellent survival after sibling or unrelated donor stem cell transplantation for chronic granulomatous disease. J Allergy Clin Immunol. 2012;129(1):176–83.
106. Tewari P, Martin PL, Mendizabal A, et al. Myeloablative transplantation using either cord blood or bone marrow leads to immune recovery, high long-term donor chimerism and excellent survival in chronic granulomatous disease. Biol Blood Marrow Transplant. 2012;18(9):1368–77.
107. Morillo-Gutierrez B, Beier R, Rao K, et al. Treosulfan-based conditioning for allogeneic HSCT in children with chronic granulomatous disease: a multicenter experience. Blood. 2016;128(21):2585.
108. Mehta B, Mahadeo K, Kapoor N, Abdel-Azim H. Low-dose total-body irradiation and alemtuzumab-based reduced-intensity conditioning regimen results in durable engraftment and correction of clinical disease among children with chronic granulomatous disease. Pediatr Transplant. 2015;19(4):408–12.
109. Lum SH, Flood T, Hambleton S, et al. Two decades of excellent transplant survival for chronic granulomatous disease: a supraregional immunology transplant center report. Blood. 2019;133(23):2547–9.
110. Cole T, Pearce MS, Cant AJ, et al. Clinical outcome in children with chronic granulomatous disease managed conservatively or with hematopoietic stem cell transplantation. J Allergy Clin Immunol. 2013;132(5):1150–5.
111. Cole T, McKendrick F, Titman P, et al. Health related quality of life and emotional health in children with chronic granulomatous disease: a comparison of those managed conservatively with those that have undergone haematopoietic stem cell transplant. J Clin Immunol. 2013;33(1):8–13.
112. Yonkof JR, Gupta A, Fu P, Garabedian E, Dalal J. Role of allogeneic hematopoietic stem cell transplant for chronic granulomatous disease (CGD): a report of the United States Immunodeficiency Network. J Clin Immunol. 2019;39:448–58.
113. Güngör T, Teira P, Slatter M, et al. Reduced-intensity conditioning and HLA-matched haemopoietic stem-cell transplantation in patients with chronic granulomatous disease: a prospective multicentre study. Lancet. 2014;383(9915):436–48.

114. Khandelwal P, Bleesing JJ, Davies SM, et al. A Single-Center Experience Comparing Alemtuzumab, Fludarabine, and Melphalan Reduced-Intensity Conditioning with Myeloablative Busulfan, Cyclophosphamide, and Antithymocyte Globulin for Chronic Granulomatous Disease. Biol Blood Marrow Transplant. 2016;22(11):2011–8. https://doi.org/10.1016/j.bbmt.2016.08.013. Epub 2016. Biol Blood Marrow Transplant. 2016. PMID: 27543157.
115. Fox TA, Chakraverty R, Burns S, et al. Successful outcome following allogeneic hematopoietic stem cell transplantation in adults with primary immunodeficiency. Blood. 2018;131(8):917–31.
116. Parta M, Kelly C, Kwatemaa N, et al. Allogeneic Reduced-Intensity Hematopoietic Stem Cell Transplantation for Chronic Granulomatous Disease: a Single-Center Prospective Trial. J Clin Immunol. 2017;37(6):548–58. https://doi.org/10.1007/s10875-017-0422-6. Epub 2017 Jul 28. J Clin Immunol. 2017. PMID: 28752258.
117. Arnold DE, Sullivan KE, Jyonouchi S, et al. Immune reconstitution in six adolescents with chronic granulomatous disease following hematopoietic stem cell transplant. J Allergy Clin Immunol Pract. 2017;7(3):1052–4.
118. Lum SH, Flood T, Hambleton S, et al. Two decades of excellent transplant survival for chronic granulomatous disease: a supraregional immunology transplant center report. Blood. 2019;133(23):2546–9. https://doi.org/10.1182/blood.2019000021. Epub 2019 Apr 5. Blood. 2019. PMID: 30952673.
119. Oshrine B, Morsheimer M, Heimall J, Bunin N. Reduced-intensity conditioning for hematopoietic cell transplantation of chronic granulomatous disease. Pediatr Blood Cancer. 2015;62(2):359–61.
120. Marsh RA, Leiding JW, Logan BR, et al. Chronic granulomatous disease-associated IBD resolves and does not adversely impact survival following allogeneic HCT. J Clin Immunol. 2019;39(7):653–67.
121. Malech HL, Maples PB, Whiting-Theobald N, et al. Prolonged production of NADPH oxidase-corrected granulocytes after gene therapy of chronic granulomatous disease. Proc Natl Acad Sci U S A. 1997;94(22):12133–8.
122. Ott MG, Schmidt M, Schwarzwaelder K, et al. Correction of X-linked chronic granulomatous disease by gene therapy, augmented by insertional activation of MDS1-EVI1, PRDM16 or SETBP1. Nat Med. 2006;12(4):401–9.
123. Stein S, Ott MG, Schultze-Strasser S, et al. Genomic instability and myelodysplasia with monosomy 7 consequent to EVI1 activation after gene therapy for chronic granulomatous disease. Nat Med. 2010;16(2):198–204.
124. Bianchi M, Hakkim A, Brinkmann V, et al. Restoration of NET formation by gene therapy in CGD controls aspergillosis. Blood. 2009;114(13):2619–22.
125. Siler U, Paruzynski A, Holtgreve-Grez H, et al. Successful combination of sequential gene therapy and rescue allo-HSCT in two children with X-CGD – importance of timing. Curr Gene Ther. 2015;15(4):416–27.
126. Kang HJ, Bartholomae CC, Paruzynski A, et al. Retroviral gene therapy for X-linked chronic granulomatous disease: results from phase I/II trial. Mol Ther. 2011;19(11):2092–101.
127. Malech HL, Booth C, Kang EM, et al. Lentiviral vector gene therapy for X-linked chronic granulomatous disease corrects neutrophil function. J Clin Immunol. 2019;39(Suppl 1):S45.