

A Comprehensive Approach to the Management of Children and Adults with Chronic Granulomatous Disease



Isaac P. Thomsen, MD, MSCI^a, Meaghan A. Smith, MPH^a, Steven M. Holland, MD^b, and C. Buddy Creech, MD, MPH^a
Nashville, Tenn; and Bethesda, Md

Chronic granulomatous disease (CGD), a disease characterized by inadequate neutrophil killing of microbial pathogens, affects 4 to 5 per million live births. For many decades following its description, CGD was a fatal disease in childhood. With the development of effective preventive therapies and the early recognition of infectious complications, 90% of children with CGD now survive into adulthood. The management of CGD in adults includes unique challenges and potential disease manifestations. In this article, the authors discuss the current approach to the management of CGD in both children and adults. This includes a focus on the importance of a comprehensive multidisciplinary approach in the care of CGD and its potential complications. In addition, a novel approach to improving education about CGD, and subsequently improving adherence to preventive therapies, is discussed. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;4:1082-8)

Key words: Chronic granulomatous disease; Multidisciplinary care; IFN- γ

Chronic granulomatous disease (CGD) was first identified as a distinct immunodeficiency in the 1950s.^{1,2} The disease was initially termed “fatal granulomatous disease of childhood” and was characterized by chronic suppurative lymphadenitis, hepatosplenomegaly, pneumonia and diffuse pulmonary infiltrates, and eczema. The disease was initially described in boys (and therefore considered to be exclusively X-linked inheritance) and was characterized by hypergammaglobulinemia (as opposed to Bruton’s agammaglobulinemia) and granulomatous involvement

of affected tissue. Since its original description, and due in part to successful antimicrobial prophylaxis, fatal granulomatous disease has now become a disease in which careful management leads to survival well into adulthood. Therefore, the purpose of this review was to highlight the challenges in the management of not only children with CGD but also adults with CGD.

CGD PATHOGENESIS, INHERITANCE, AND DIAGNOSIS

The genetic basis for CGD lies in any of the 5 structural genes encoding the phagocytic oxidase (*phox*) subunits of the nicotinamide adenine dinucleotide phosphate oxidase complex. When CGD was initially discovered, the disease was observed only in males and was believed to be exclusively an X-linked disease. In 1968, CGD was identified in a female patient, leading to the discovery of autosomal-recessive forms of the disease.³ Approximately two-third of CGD cases in the United States are caused by mutations in *CYBB*, which is present on the X chromosome and encodes the heme-containing Nox2 subunit (also known as gp91^{phox}). Biallelic mutations in the other 4 genes (*CYBA*, neutrophil cytosolic factor 1 [*NCF1*], *NCF2*, and *NCF4*) are associated with autosomal-recessive CGD.⁴ Mutations in *NCF1* are the second most common cause of CGD.⁵ Table I presents the genetic defects of CGD and the relative frequency of each mutation in North America.

The incidence of CGD in the United States is estimated at approximately 4 to 5 cases per million live births.⁶ Before the introduction of oral antifungals, mortality rates ranged from 2% per year among those with autosomal-recessive CGD to 5% per year among those with X-linked CGD.⁷ Further understanding of CGD along with utilization of a more comprehensive treatment regimen allows the vast majority of individuals with CGD to live into adulthood. Although long-term survival is dependent on several factors, overall survival into adulthood with CGD is now around 90%, although significant morbidity due to frequent infectious and inflammatory complications remains common.⁷

Female *CYBB* mutation carriers are often phenotypically normal. Nearly half, however, report various symptoms including aphthous ulcers, cutaneous photosensitivity, or arthralgias.^{8,9} In addition, there are reports of women with heterozygous mutations who have the X-linked CGD phenotype due to skewed inactivation of the normal X chromosome by lyonization. This highlights the fact that the population of normal neutrophils required for immune function is not 100%; however, when the number of neutrophils capable of a normal oxidative burst falls below approximately 15%, classic CGD symptoms may be seen.⁴

^aDivision of Pediatric Infectious Diseases, Department of Pediatrics, Vanderbilt Vaccine Research Program, Vanderbilt University School of Medicine, Nashville, Tenn

^bLaboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md

This work was supported in part by an educational grant from Horizon Pharma, plc. Conflicts of interest: I. P. Thomsen has received research support from Horizon Pharmaceuticals. C. B. Creech has received research support from Horizon Pharmaceuticals, Novartis, and Pfizer and has provided expert witness testimony for various entities unrelated to chronic granulomatous disease. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication October 14, 2015; revised March 11, 2016; accepted for publication March 24, 2016.

Available online May 10, 2016.

Corresponding author: Isaac P. Thomsen, MD, MSCI, D-7235 MCN, 1161 21st Ave South, Nashville, TN 37232. E-mail: isaac.thomsen@vanderbilt.edu. 2213-2198

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<http://dx.doi.org/10.1016/j.jaip.2016.03.021>

Abbreviations used

CGD- chronic granulomatous disease
CT- computed tomography
MRI- magnetic resonance imaging
NCF- neutrophil cytosolic factor
SCT- stem cell transplantation
TMP-SMX- trimethoprim-sulfamethoxazole

Chronic granulomatous disease is phenotypically diagnosed by measurement of the neutrophil oxidative burst, which in the current era is done most commonly via the dihydrorhodamine assay. Dihydrorhodamine is a nonfluorescent compound that is oxidized by activated neutrophils into the fluorescent compound rhodamine. The detection of fluorescence by flow cytometry provides a reliable indicator of normal neutrophil activation; inadequate fluorescence is most consistent with CGD, but can also be seen in myeloperoxidase deficiency. Other diagnostic modalities may be used, such as nitroblue tetrazolium reduction, but the dihydrorhodamine assay's ability to distinguish X-linked from autosomal patterns of CGD, as well as its ease of use, makes it the preferred modality at most centers.

INFECTIOUS COMPLICATIONS OF CGD

Common pathogens: "The big 5"

Early clinical manifestations of CGD include recurrent upper and lower respiratory tract infections, failure to thrive, visceral abscesses, cellulitis, lymphadenitis, and granulomatous lesions in hollow viscera without apparent organisms. Sites of infection most often include the lungs, lymph nodes, skin, and liver.⁵ Most infections in patients with CGD living in North America are caused by 5 organisms: *Staphylococcus aureus*, *Burkholderia cepacia* complex, *Serratia marcescens*, *Nocardia* species, and *Aspergillus* species.¹⁰ The pathogenicity of organisms was once thought to be due to their production of catalase, an enzyme that degrades the organism's own hydrogen peroxide, thus depriving the phagocyte of additional reactive oxygen species.⁸ Although the precise mechanisms underlying the pathogenicity of these organisms are unclear, deletion of bacterial or fungal catalase production does not affect virulence, indicating that catalase is not an important virulence factor. Tuberculosis and *Salmonella* species are important causes of infections in regions of the world where these organisms are prevalent.¹¹ Similarly, in regions of the world where BCG is routinely administered, severe local or regional BCG disease may be the initial CGD presentation.

Infection with *Actinomyces* species (catalase-negative organisms) was previously thought to be unlikely in CGD. However, a series of 10 patients with CGD with chronic *Actinomyces* indicated that this is an important pathogen. Patients with CGD with actinomycosis did not present with typical signs and symptoms of infection, making it more difficult to diagnose.¹² A recently identified organism, *Granulibacter bethesdensis*, causes necrotizing lymphadenitis in patients with CGD, and the patients can have a relapse after initial symptoms resolve.¹³ Other pathogens are likely to emerge in patients with CGD as molecular genetic testing improves.

EVIDENCE-BASED APPROACH TO PREVENTION

The prevention of infectious complications of CGD involves an evidence-based, 3-pronged approach that consists of

TABLE I. Genetic defects of CGD

Protein	Characteristic	Subunit	Gene locus	Frequency (%)
Cytochrome b558	Membrane-bound components	gp91 ^{phox}	CYBB, Xp21.1	65
		p22 ^{phox}	CYBA, 16q24.3	5-10
	Cytosolic components	p47 ^{phox}	NCF1, 7q11.23	25
		p67 ^{phox}	NCF2, 1q25.3	5-10
		p40 ^{phox}	NCF4, 22q13.1	Rare

prophylactic antibacterial agents, antifungal agents, and IFN-γ therapy.

Antibiotic therapy

Trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis has been used routinely for the prevention of infections in patients with CGD since the 1970s. Gallin et al¹⁴ showed that patients with CGD, on average, suffered 1 life-threatening episode every 10 months; however, with TMP-SMX prophylaxis, this was reduced to 1 life-threatening episode every 40 months. Similarly, Regelman et al¹⁵ reported that only 5% of patients with CGD remained infection-free for more than 1 year without TMP-SMX prophylaxis, but more than 40% were infection-free for more than 1 year while taking TMP-SMX prophylaxis. Further evidence to support the use of TMP-SMX prophylaxis was reported in 1990 by Margolis et al,¹⁶ who demonstrated that prophylaxis decreased the incidence of nonfungal infections from 7.1 to 2.4 per 100 patient-months in patients with autosomal-recessive CGD and from 15.8 to 6.9 infections per 100 patient-months in patients with X-linked CGD. Importantly, there was no concomitant increase in the incidence of fungal infections in patients with CGD while on TMP-SMX prophylaxis.

Although TMP-SMX therapy is generally well tolerated, it does have various potential toxicities. Hematologic (eg, agranulocytosis, hemolysis, and thrombocytopenia), renal (interstitial nephritis), metabolic (hyperkalemia), gastrointestinal (abdominal pain, diarrhea, and pancreatitis), and dermatologic (photosensitivity, Stevens-Johnson syndrome) adverse effects are well described. Monitoring of a complete blood cell count and serum potassium and creatinine is indicated after initiation of therapy until proven stable.

Antibacterial prophylaxis in the presence of TMP-SMX intolerance is difficult because there are few orally available agents with reliable activity against both *S aureus* (including methicillin-resistant strains) and gram-negative pathogens. In the case of sulfa allergy, trimethoprim alone can be used. Other options include a fluoroquinolone (likely with the addition of clindamycin or another agent with activity against methicillin-resistant *S aureus* in areas where these strains are prevalent).

Antifungal therapy

The current standard of care for preventive therapy in patients with CGD includes daily prophylactic itraconazole therapy to prevent superficial and invasive fungal infections. This recommendation stems, in part, from a randomized, double-blinded, placebo-controlled trial of 39 patients with CGD.¹³ Among patients receiving itraconazole, none developed a superficial fungal infection, whereas 5 patients receiving placebo developed superficial fungal infections. Moreover, 7 placebo recipients

developed invasive fungal disease compared with only 1 receiving itraconazole therapy. Although the numbers in the trial are small, resulting in findings that were not statistically significant, long-term use of itraconazole was found to be well tolerated, with minimal side effects.¹⁷ Therefore, the risk-benefit ratio strongly favors the use of prophylactic itraconazole in all patients with CGD.

Adverse effects of itraconazole include hepatitis (~5% of patients) and drug-drug interactions (due to CYP3A4 inhibition). Monitoring of liver tests every 6 months while on therapy is recommended. Voriconazole, another highly active azole compound, is an alternative agent for antifungal prophylaxis. Although not considered the first-line prophylactic agent by most experts, because of a higher cost and unnecessarily broad spectrum against many mold species, voriconazole has a different side-effect profile and may represent an appropriate option in patients who cannot tolerate itraconazole.

IFN- γ

A randomized, double-blinded, placebo-controlled study conducted in the early 1990s demonstrated that subcutaneous injections of recombinant IFN- γ administered 3 times per week reduced the number of serious infections in patients with CGD by 67%.¹¹ A reduction in frequency and length of hospitalizations was also observed. Administration of IFN- γ therapy was found to be effective in both X-linked and autosomal-recessive CGD with minimal side effects.¹⁸ A phase IV study of long-term efficacy and toxicity of IFN- γ in patients for up to 9 years found that no patients experienced a life-threatening adverse event related to IFN- γ therapy. Compared with baseline rates of disease and mortality, IFN- γ therapy reduced the rate of serious infections to 0.30 per patient-year and reduced mortality rate to 6.6% over 9 years (1.5% per patient-year).¹⁹ These data clearly supported the use of IFN- γ therapy in the prevention of severe infection in patients with CGD. It must be noted that this study was conducted before the introduction of fungal prophylaxis and that European groups are less prone to use IFN- γ than those in the United States.

One barrier to the use of IFN- γ therapy in some patients is the potential for adverse medication effects. This most commonly involves “flu-like symptoms” (fever, chills, fatigue), rash, and local injection site reactions (erythema or tenderness). Dose adjustments may be beneficial if flu-like symptoms are prohibitive, and these often diminish with consistent use of the medication. In general, many experts consider the risk-benefit ratio to be favorable for the use of IFN- γ to prevent invasive infectious complications of CGD, particularly for patients with X-linked disease and those with a history of invasive infections.

Optimizing preventive care

The medications involved in the 3-pronged prophylactic approach to the care of patients with CGD are effective only to the extent that they are taken. Medication nonadherence is a major barrier to the optimal preventive management of patients with CGD. This is due to various factors, including concern over adverse effects of the medications, logistical difficulties of dosing multiple medications on different schedules, and (particularly in the adolescent population) denial of the importance of prophylactic measures. One critical aspect to improving adherence is education about the condition. CGD is a rare and complex disease, and patients and their families are unlikely to know of

anyone else with the condition. The role of educating patients and their families about the seriousness of this condition rests on the provider. To address this, we developed a short educational video designed to explain this complex condition (and the importance of preventive management) in a straightforward and easily understandable way (see [Video](#) in this article’s Online Repository at www.jaci-inpractice.org).

PRACTICAL APPROACH TO CGD MANAGEMENT

Given the rarity of CGD in the general population, opportunities for evidence-based approaches are limited for many of the potential complications of CGD. In this section, we will highlight common treatment dilemmas in patients with CGD and offer experiential guidance where possible ([Figure 1](#)).

Acute infection

A patient with CGD who develops new fever or other acute symptom is challenging. Frequently, symptoms are vague (eg, malaise, fatigue, and nonspecific musculoskeletal complaints), and even a thorough history and physical examination often do not reveal a specific diagnosis. Moreover, symptoms such as headache, cough, or abdominal pain are commonly seen with benign conditions, yet in CGD may represent indolent bacterial, fungal, or inflammatory processes. For these reasons, securing a microbiologic diagnosis is of the highest priority for any new process that does not appear to be a self-limited illness, such as a viral upper respiratory tract syndrome.

First is determination whether the presentation is most consistent with a self-limited process or a complication of CGD. The presence of nasal congestion, rhinorrhea, or sore throat is often reassuring and typically warrant only watchful waiting. Other common symptoms such as cough, abdominal pain, or diarrhea, while often associated with viral syndromes, are more problematic. The threshold to obtain chest or abdominal radiographs should be substantially lower than for patients without CGD. Seemingly innocuous symptoms such as myalgia or musculoskeletal point tenderness may be a harbinger of deep-seated infection such as an abscess or osteomyelitis, and symptom evaluation requires vigilance on the part of the provider. Similarly, gastrointestinal symptoms such as persistent diarrhea, tenesmus, or painful defecation warrant a focused workup given the increased prevalence of inflammatory bowel disease in this population (see “Inflammatory complications”).

Laboratory markers of inflammation such as the erythrocyte sedimentation rate and C-reactive protein can be very useful in the evaluation of new symptoms. Although many patients with CGD maintain mild elevations in erythrocyte sedimentation rate and C-reactive protein, a significant and sustained rise is often a hallmark of occult infection that may require imaging even if localizing symptoms are not present.

Imaging

Given the broad differential and high risk of indolent disease in children and adults with CGD, imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) are often critical in the evaluation of new or persistent symptoms. A persistent cough without a clearly identified source typically warrants a chest CT, both to define the disease process and to determine whether a lesion is amenable to biopsy. Persistent bone or joint pain is often an indication for MRI of the affected region, due to its excellent positive and negative

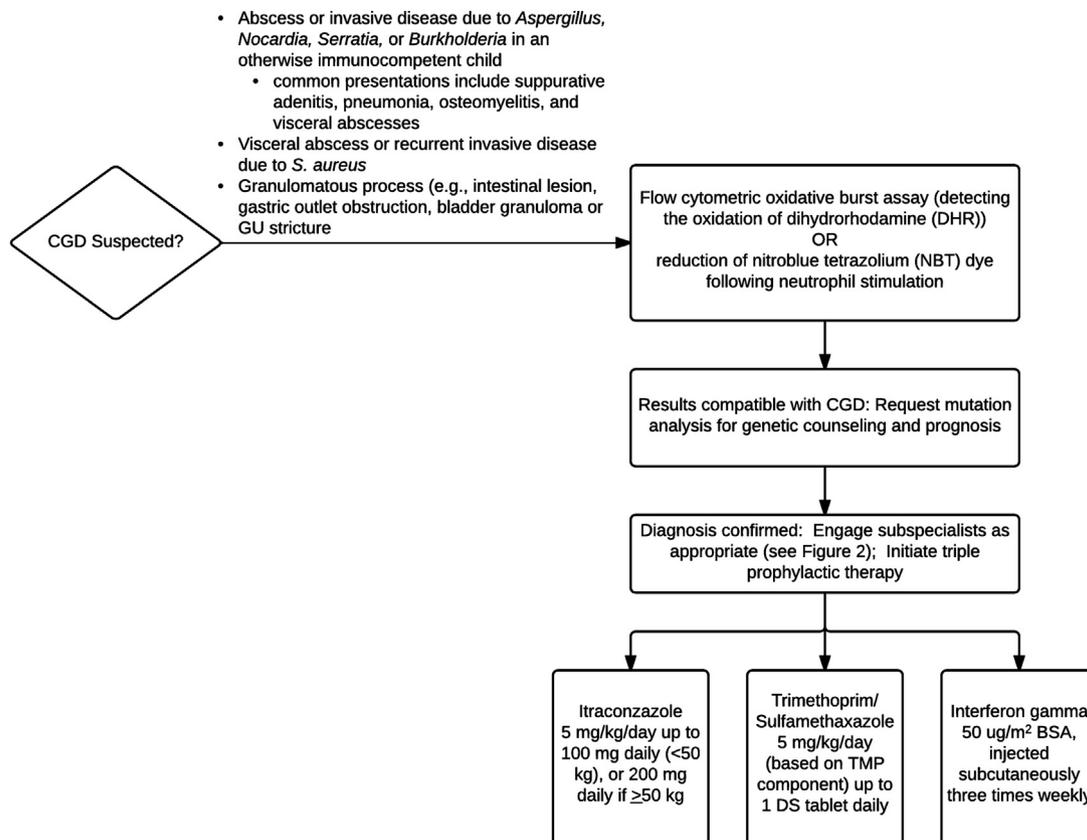


FIGURE 1. Flowsheet for diagnosis and therapy. *Notes.* Gastrointestinal intolerance with TMP/SMX is common and may limit adherence. Itraconazole absorption is impaired by simultaneous use of antacids. The liquid formulation is better absorbed but less well tolerated than the capsules. Measurement of levels may be appropriate but has not been shown to affect prophylactic benefit. While on itraconazole therapy, transaminases should be monitored (at least every 6 months) as hepatitis occurs in approximately 5%. Drug interactions are also common (strong inhibitor of CYP3A4). Common IFN- γ side effects include fever and myalgia; acetaminophen may be beneficial. Local reactions (erythema, pain, or pruritis) at the injection site may occur. Rotating the site of injection (upper and lower extremities, trunk) may alleviate this. *BSA*, Body surface area; *DS*, double strength.

predictive value for osteomyelitis. Both *Nocardia* and *Aspergillus* species have a propensity for central nervous system involvement in patients with CGD; therefore, we favor imaging of the central nervous system (preferably with MRI) early in the course of treatment for disseminated *Nocardia* or *Aspergillus* disease.

Mild, diffuse nodular lung disease or hilar adenopathy in a patient with CGD who otherwise feels well is a common occurrence. In these cases, tissue examination is the first-line evaluation if the lesion is amenable to biopsy. If a biopsy cannot be easily obtained without an open surgical procedure, serial imaging (eg, CT every 3 or 6 months) can be useful. Cumulative radiation exposure is a significant concern in subjects with CGD. Low-radiation CT scans offset this risk, however, and the benefits of diagnosis and directed therapy enabled by CT outweigh the risks of radiation-induced malignancy. Care should be taken to follow disease resolution with lower-radiation techniques such as ultrasound, MRI, or plain radiograph when possible.

EMPIRIC ANTIMICROBIALS

One of the most difficult aspects of the care of children and adults with CGD is that the 5 most common pathogens are vastly different organisms with variable susceptibilities. For this

reason, securing a microbiologic diagnosis when feasible (which may require surgically obtaining a tissue specimen) is especially important in the care of patients with CGD.

Certain aspects of the patient's history may aid in guiding the choice of empiric agents. If inhalational exposure to mold, such as mulching, yard work, or construction, is suspected in the presence of fever, dyspnea, and/or hypoxia, voriconazole or posaconazole should be empirically used after diagnostic procedures (eg, bronchoscopy) are performed. Coinfection with bacteria is common following exposures of this nature, and empiric antibacterials directed at the CGD gram negatives (*Burkholderia*, *Serratia*) and *Nocardia* are advised, as well. Invasive fungal infections remain the most common cause of mortality in CGD.¹⁰ Liver abscesses occur in approximately one-third of patients and are most commonly caused by *S aureus*; however, coverage for gram-negative bacilli is usually included until cultures (usually by needle aspiration) return. Carbapenems are the most reliable antibacterials for empiric coverage in patients with CGD because they cover all the relevant bacterial species, including *Nocardia*. In areas with a high prevalence of methicillin-resistant *S aureus*, agents with activity against methicillin-resistant *S aureus* such as clindamycin or vancomycin are advised until sensitivities return.

Importantly, adherence to prophylactic CGD therapy is rarely optimal, especially as patients enter teenage years. Thus, infections with TMP/SMX or itraconazole-susceptible pathogens are common. Empiric regimens must take into account the severity of disease, location, and likely causes. For instance, severe acute localized pneumonia is well covered by empiric meropenem and voriconazole or posaconazole, whereas acute liver abscess does not typically need empiric antifungal coverage. Conversely, lymphadenitis is most commonly due to *S aureus*, though other pathogens may be present. The importance of a secure microbiologic diagnosis is paramount.

Curative options

Despite the aforementioned advances in the prevention and treatment of the infectious complications of CGD, refractory disease remains a problem. Invasive mold infections, chronic bacterial infections, and multiply resistant organisms (compounded by frequent incomplete adherence to complex medical regimens) may result in the need for alternative forms of therapy.

Stem cell transplantation (SCT) is well described as potentially curative in CGD (>90% in the largest series).²⁰ Overall survival appears to be equivalent between SCT and conventional therapy.^{20,21} Although certain complications, such as growth impairment and inflammatory bowel disease, are overcome by SCT, very long-term post-SCT survival data in CGD are not yet available. However, extrapolating from the few cases of CGD who had undergone a transplant decades ago and with cases who had a transplant for other immunodeficiencies, it is likely that SCT is quite durable. SCT has also been shown to be curative for cases of refractory invasive fungal disease, both in our experience and in the published literature,²⁰ but transplantation in the setting of active fungal disease requires a comprehensive transplant and management team.

Transplantation as an early treatment option (eg, soon after the diagnosis is made) is gaining favor as rates of success have improved, particularly if an excellent HLA match exists. Early SCT has the potential not only to prevent infections and inflammatory complications but also to reduce exposure to prophylactic medications and related adverse effects. One recent series compared 30 children who underwent SCT for CGD to 32 patients treated with standard prophylaxis. They found equivalent survival at age 15 years (90%), with fewer hospitalizations per year in the SCT group.²² Some experts now recommend strong consideration of SCT in all boys with X-linked CGD if an HLA-identical donor is available.²³

CGD is theoretically an ideal candidate disease for gene replacement therapy because the defect is a single gene mutation and only partial restoration of nicotinamide adenine dinucleotide phosphate oxidase function can result in a complete clinical cure (as evidenced by the normal phenotype of the lyonized X-linked female carrier state).²⁴ Approximately 15% to 20% normal neutrophil oxidative burst function appears to be sufficient to avoid the CGD phenotype. However, CGD gene therapy has been complicated by poor levels of persistent gene correction and several cases of retroviral insertional myeloproliferation,²⁵ but new trials with improved vectors are underway.

Inflammatory complications

The seemingly paradoxical association between primary immunodeficiencies and autoimmune disease is well described,²⁶ and CGD is a prototypical example of this relationship.²⁷

Granulomatous colitis appears to be the most common inflammatory complication of CGD, and more than 40% of patients with X-linked CGD develop some form of inflammatory bowel disease.²⁸ Granulomatous lesions and strictures of the genitourinary tract are also much more common in patients with CGD than in the general population.²⁹ Many other inflammatory conditions have been reported, including discoid lupus, polyarthritis, noninfectious granulomatous disease, and aphthous ulcers with cutaneous lesions mimicking Behçet disease.³⁰

The treatment of inflammatory disease in patients with CGD poses a difficult balance between therapeutic immunosuppression and the augmented risk of severe infection. CGD-associated enteritis or colitis management often requires a combination of luminal anti-inflammatory therapy (eg, mesalamine) and low-dose corticosteroids. Antimetabolites such as methotrexate or azathioprine are also helpful for recurrent cases. TNF-blocking biologics have been associated with severe infections and death.³¹ Collaboration with gastroenterology for enteric monitoring and to help minimize symptom breakthrough and prolonged systemic immunosuppression is ideal.

TRANSITION TO ADULT CARE

As both therapeutic and preventive options have improved for the care of patients with CGD over the past several decades, the condition is rarely fatal during childhood. Patients with CGD now routinely survive well into adulthood, and therefore require a transition of medical care to adult providers.

The basic tenets of prophylaxis (antibacterial, antifungal, and immunomodulatory agents) remain the same in adult patients with CGD. Disease manifestations, however, may differ substantially. Inflammatory complications may be more frequent in adults with CGD than in children, similar to what is seen in the general population.

A recent study of 67 adults with CGD showed that pulmonary manifestations are common in this population (67% of patients), and 25% of respiratory events were inflammatory rather than proven to be infectious.³² These inflammatory pulmonary manifestations were clinically indistinct from pulmonary infections but were treated with immunosuppressive therapy (eg, corticosteroids) rather than antimicrobials. Inflammatory respiratory events typically presented radiographically as nodules, parenchymal consolidation, or diffuse interstitial infiltrates, often with associated ground glass opacities and/or bronchiectasis. Biopsies revealed granulomata-lacking organisms, eosinophilic microabscesses, or diffuse granulocytic infiltration. Further complicating this issue was that 40% of cases developed inflammatory pathology associated with concomitant fungal infections. These data strongly justify procedures such as bronchoscopy with endobronchial biopsy, percutaneous needle biopsy, or open lung biopsy to secure a microbiologic and tissue diagnosis when clinically feasible. It is important to keep in mind that the failure to isolate an organism does not prove the lack of an infectious etiology. Low-grade pathogens can cause immunopathology in CGD that may improve with immune modulation, leading to “inflammatory” states with a possible infectious trigger.

Close interaction between the CGD provider—ideally someone with significant experience in caring for patients with CGD—and the patient’s primary care provider facilitates effective comanagement of acute issues as well as general health

Allergy and Immunology	Infectious Diseases	Hematology and Oncology	Multidisciplinary Partners
Evaluation of Suspected Primary Immunodeficiency	Diagnosis and Management of Sentinel Infection	Evaluation for hematopoietic stem cell transplantation (HSCT)	Gastroenterology: Diagnosis and Management of CGD-associated colitis
Genetic Counseling and Family Planning	Evaluation of Suspected Primary Immunodeficiency	Optimal timing and type of HSCT, as applicable	Dermatology: Management of cutaneous manifestations of CGD
Management of Drug Hypersensitivity	Diagnosis and Management of Infectious Complications		Pulmonary Medicine: Diagnosis and Management of Infectious and Noninfectious Pulmonary Manifestations of CGD
<i>In various medical centers, each of these specialties may serve as the primary coordinator of care. In our experience, optimal care is achieved when each of these specialties are working together to provide comprehensive care plans for their patients and families.</i>			Surgical specialists: Acquisition of tissue samples to aid diagnosis; surgical management of CGD complications
			Psychology / Psychiatry: Management of psychosocial issues including medication nonadherence and depression, especially common in adolescence
			Primary Care Provider: First-line evaluation of symptoms that may (or may not) be due to CGD; coordination of multidisciplinary teams.

FIGURE 2. Multidisciplinary approach to the care of CGD.

maintenance as patients with CGD transition to adulthood. Adult primary care providers may be less comfortable dealing with the complex medication regimens and diagnostic dilemmas occasionally posed by CGD, making the CGD provider a default medical home for these patients. This requires the CGD provider to be vigilant in identifying common adult-onset medical conditions (eg, hypertension or hyperlipidemia) as well as adverse medication events that may become more common with increasing age (eg, hyperkalemia associated with TMP/SMX or medication interactions with itraconazole). Genetic counseling also becomes relevant as patients and their siblings reach adulthood, including discussions of the probability that children will inherit the gene mutation; referral to a genetic counselor may be appropriate.

THE IMPORTANCE OF A MULTIDISCIPLINARY APPROACH

Paramount to the optimal care of children, adolescents, and adults with CGD is the engagement of a multidisciplinary team. At different medical centers across the country, different types of medical specialists coordinate the care of these patients. Infectious diseases, allergy/immunology, and hematology/oncology specialists all play critical roles in the care of these subjects, with key support by gastroenterology, pulmonology, general surgery, dermatology, and primary care colleagues (Figure 2).

Infectious diseases

CGD is first and foremost a primary immunodeficiency, and the acute complications of this disorder are infections. As discussed above, many pathogens seen in patients with CGD may be rare in other conditions, and the antimicrobial regimens needed to combat them may be complex. In addition to securing the proper microbiological diagnosis, an experienced infectious diseases specialist and ancillary staff can help manage the dosing, administration, and potential adverse effects of regimens needed to care for this condition.

Allergy and immunology

Specialists in allergy and immunology are key in CGD in all phases of care, beginning with diagnosis. Astute primary care physicians will often refer patients to an immunologist following an unusual infectious presentation (eg, invasion by a typical pathogen or an unusually high number of infections). The immunologist is frequently the provider securing the diagnosis of CGD and coordinating management moving forward. In addition, medication intolerance (including true hypersensitivity) is a significant problem in patients with CGD, particularly as beta-lactam antibiotics and sulfa drugs (eg, TMP/SMX) are mainstays of therapy. Testing for drug hypersensitivity (and even desensitization) may be necessary for optimal therapeutic regimens.

Hematology/oncology

At many centers in the United States, the hematologist/oncologist coordinates the care of patients with CGD. Even at centers where care is led by infectious diseases or allergy/immunology specialists, frequent engagement with hematology/oncology colleagues is highly important. SCT currently represents the only method for cure of CGD; proper patient selection and timing of this procedure require a multidisciplinary approach.

Additional specialties

The inflammatory complications of CGD can occur at any age, and are especially common as patients grow into adolescence/adulthood. As discussed above, these conditions are especially difficult to manage because immunosuppressive treatments are challenging in patients with a severe immunodeficiency. Furthermore, a lifetime of frequent infections often results in significant end-organ damage (eg, chronic lung disease following frequent episodes of pneumonia, or the need for wedge resections of the lung or liver to treat refractory disease). Close collaboration with gastroenterology and pulmonology colleagues in the management of CGD-associated colitis or pulmonary disease,

respectively, provides tremendous benefit in the management of these difficult cases. Similarly, patients with CGD are prone to atypical dermatologic presentations and often suffer from cutaneous damage due to chronic inflammation/frequent superficial infections, and a dermatologist with experience caring for subjects with CGD is highly valuable.

As patients with CGD age into adolescence and young adulthood, new challenges arise. Symptoms of depression are common, and often secondary to issues related to having a chronic illness, including frequent hospitalizations, long-term antibiotic therapies requiring indwelling catheters, and so on. Furthermore, medication nonadherence is very common in adolescence. Involving a skilled psychologist or psychiatrist in the long-term management of these patients is often highly beneficial. Finally, the role of the primary care physician in subjects with CGD should not be understated. Patients with CGD also develop common illnesses not related to their underlying condition. The primary care provider who is comfortable with initial assessment and is willing to maintain close communication with the CGD specialists is essential to a successful multidisciplinary team and a healthy patient.

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