



# Prevention of Infectious Complications in Patients With Chronic Granulomatous Disease

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Chronic granulomatous disease (CGD) is a primary immunodeficiency that confers a markedly increased risk of bacterial and fungal infections caused by certain opportunistic pathogens. Current evidence supports the use of prophylactic antibacterial, antifungal, and immunomodulatory therapies designed to prevent serious or life-threatening infections in patients with CGD. In this review, we discuss current strategies for the prevention of infections in children and adults with CGD and the evidence that supports those strategies. In addition, we address current challenges and opportunities for future research in this important area.

Chronic granulomatous disease (CGD), a primary immunodeficiency caused by a mutation in any of the components of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex, which leads to frequent and severe infections by a specific group of pathogens [1]. These organisms are united largely (although not exclusively) by production of the enzyme catalase, and the majority of serious infections in North American patients with CGD are caused by 5 pathogens, *Staphylococcus aureus*, *Aspergillus* spp, *Nocardia* spp., *Burkholderia* spp, and *Serratia* spp.

Therefore, the prevention of infectious complications in patients with CGD involves targeted prophylaxis against these organisms. Optimal avoidance of infection in patients with CGD involves a combination strategy that typically involves prophylactic antibacterial agents, antifungal agents, and immunomodulation via interferon-gamma (IFN- $\gamma$ ) therapy.

## PROPHYLACTIC ANTIBIOTIC THERAPY

Although the list of bacteria that are strongly associated with serious infections in patients with CGD is relatively short, it is also remarkably diverse; it includes Gram-positive (*S aureus*), Gram-negative (*Burkholderia* and *Serratia* spp), and partially acid-fast (*Nocardia*) species [1]. (Other less common pathogens

that infect children and adults with CGD are reviewed by Rider N et al, and Yu J et al, elsewhere in this Supplement.) An ideal antibacterial prophylactic regimen for patients with CGD, therefore, would include bactericidal activity against all 5 of the pathogens that most commonly infect them and would be available orally. Trimethoprim-sulfamethoxazole (TMP-SMX) remarkably exhibits all of these properties and has been used routinely for the prevention of bacterial infections in patients with CGD for more than 40 years. Along with its antimicrobial spectrum, TMP-SMX confers additional benefits for infection prevention in patients with CGD in that it concentrates in polymorphonuclear cells and does not eradicate anaerobic gut microbes unnecessarily [2].

Without antimicrobial prophylaxis, patients with CGD suffer, on average, approximately 1 life-threatening infectious episode every 10 months [3]. With TMP-SMX prophylaxis, the infection rate was reduced to 1 life-threatening episode every 40 months in 1 randomized trial [3]. A similar study found that the proportion of patients that remained infection free for at least 1 year increased from 5% to >40% with TMP-SMX prophylaxis [4]. Prophylaxis with TMP-SMX is effective in preventing infectious complications in patients with either X-linked or autosomal recessive (AR) CGD. Prophylaxis decreased the incidence of bacterial infections by 66% (from 7.1 to 2.4 per 100 patient-months) in patients with AR CGD and 56% (from 15.8 to 6.9 infections per 100 patient-months) in patients with X-linked CGD [4]. Important to note is that no evidence exists for a concomitant increase in the incidence of fungal infections in patients with CGD while on TMP-SMX prophylaxis [5]. As a consequence of infection prevention, TMP-SMX prophylaxis also is associated with decreased rates of hospitalization and surgical interventions [6].

TMP-SMX for the prevention of infections in patients with CGD is typically dosed at 5 mg/kg per day (based on the TMP component) up to 1 double-strength tablet daily [7]. Although TMP-SMX therapy is generally well tolerated,

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it does have a variety of potential toxicities. Serious adverse effects are rare but include hematologic (eg, agranulocytosis, hemolysis, thrombocytopenia), renal (interstitial nephritis), and metabolic (hyperkalemia) complications. More frequent adverse effects, which are important because they can interfere with medication adherence, include gastrointestinal (abdominal pain, diarrhea, and, rarely, pancreatitis) and dermatologic (rash, photosensitivity, and, rarely, Stevens-Johnson syndrome) symptoms [8]. Complete blood counts and monitoring of serum potassium and creatinine are indicated for patients after the initiation of chronic therapy until they are proven stable.

Antibacterial prophylaxis in the presence of TMP-SMX intolerance is difficult, because few oral agents with reliable activity against both *S aureus* (including methicillin-resistant strains, especially while the rates of clindamycin resistance are rising progressively [9]) and Gram-negative pathogens are available. The first step of antibacterial prophylaxis in a patient with CGD and an apparent sulfa allergy is determining whether true hypersensitivity in fact exists, because antibiotic allergy rates are often overreported. The most common reaction to TMP-SMX is a morbilliform rash and associated fever that occurs 7 to 12 days after the initiation of therapy [10]. Although no formal testing for immunoglobulin E (IgE)-mediated hypersensitivity reactions exist, there is extensive literature providing regimens for successful induction of drug tolerance. These regimens have been adapted for individuals with IgE- or non-IgE-mediated hypersensitivity reactions, with the exception of severe cutaneous drug eruptions (toxic epidermal necrolysis, Stevens-Johnson syndrome, or drug reaction with eosinophilia and systemic symptoms), in which case the medication is contraindicated [10]. In patients with a true IgE-mediated sulfa allergy in whom drug tolerance cannot be induced, TMP alone can be a consideration. Other options in cases of TMP-SMX intolerance include using a fluoroquinolone or second- or third-generation cephalosporin. The addition of clindamycin or another agent with activity against methicillin-resistant *S aureus* could be considered if needed.

## PROPHYLACTIC ANTIFUNGAL THERAPY

Patients with CGD have long been plagued by not only bacterial infections but also a predominance of fungal infections that lead to significant morbidity and death. In fact, invasive fungal infection is a major risk factor for death in patients with CGD [11]. In the United States, *Aspergillus* spp (most commonly *Aspergillus fumigatus* or *Aspergillus nidulans*) account for >35% of all deaths attributable to infection in patients with CGD, which often involves dissemination to the lung, liver, or brain [12]. Aspergillosis is the leading cause of invasive fungal infection in patients with CGD; 26% to 43% of these patients experience at least 1 invasive fungal infection in their lifetime,

particularly pneumonia or brain abscesses. Other prevalent fungal infections include those caused by yeast and various dematiaceous and nondematiaceous fungi (eg, *Paecilomyces*, *Rasamsonia argillacea* [formerly *Geosmithia argillacea*], and *Candida* spp) [13–16]. Invasive candidal infections (not mucocutaneous candidiasis) occur far less frequently (3 of 268 in the US cohort, 1 of whom had concurrent human immunodeficiency virus infection) but are the next most common invasive fungal disease seen [11]. Infection with the filamentous fungus *R argillacea* is an emerging problem in patients with CGD and causes both disseminated and locally invasive disease [17]. Mucormycosis has also been described in several patients with CGD in whom an immunosuppressive regimen was being administered for inflammatory complications (eg, pneumonitis, colitis) [18]. Overall, fungal disease continues to have a major negative effect on survival in patients with CGD [16].

CGD was termed “fatal granulomatous disease of childhood” when it was first characterized in 1959. With the initiation of prophylactic antimicrobial agents (and antifungal therapy, in particular), an altered landscape has emerged for those with CGD [19, 20]. The results of 2 relatively small case series suggested that antifungal prophylaxis reduces the incidence of fungal infections in patients with CGD [21, 22]. A recent analysis that involved a larger cohort (n = 155) from the French national registry revealed that patients with CGD on itraconazole had a significantly lower incidence of invasive fungal infection than those who were not receiving prophylaxis (0.027 vs 0.053 invasive fungal diseases per patient-year, respectively;  $P < .01$ ). Overall, any antifungal prophylaxis conferred a lower incidence of invasive fungal disease than previously reported (0.04 vs 0.1 invasive fungal diseases per patient-year, respectively) [14]. The results from this larger cohort provide compelling evidence for a decreased incidence of invasive fungal infection in patients who receive prophylaxis [13]. Although fungal infection remains the leading cause of death, patients with CGD have experienced overall fewer invasive fungal infections and lived longer since the initiation of antimicrobial prophylaxis (median ages at death, 15.53 years [before 1991] vs 28.12 years [in 2012];  $P$  value  $< .01$ ) [11].

Before the initiation of antifungal therapy, superficial and invasive fungal infections were more prevalent and occurred earlier in life. Now that the majority of patients with CGD receive antifungal prophylaxis, concerns regarding drug resistance are emerging. An ongoing shift seems to be occurring in fungal susceptibility within patients with CGD; although *A fumigatus* remains the most prevalent organism, a growing number of locally invasive or disseminated infections caused by *A nidulans* and other fungal organisms are found in patients taking antifungal prophylaxis ( $P < .05$ ) [23]. Breakthrough infections by *Aspergillus viridinutans*, *Neosartorya udagawae*, *R argillacea*, and *Sporothrix schenckii* in patients with CGD also have been reported [23–25]. Advances in genomic sequencing

of microbial species have revealed *R argillacea* as an emerging pathogen with a susceptibility to therapy with azole antifungal agents that varies, which contributes to the concern regarding choice of prophylactic agent, dose, and bioavailability of the triazole antifungal agents [15]. Patients taking itraconazole prophylaxis experience a longer time interval before they encounter an invasive fungal infection (median time to invasive mold infection, 10 vs 4 years, respectively;  $P < .1$ ), but an ongoing need for optimization of therapy remains, as evidenced by the small proportion (25%) of patients who remain infection free by the age of 30 years [23]. Although the benefits of antifungal prophylaxis are clear and their use can prolong the interval between invasive fungal infections, resistant and invasive organisms are a growing problem in patients with CGD.

Itraconazole traditionally has been the azole of choice for the prevention of fungal infection in patients with CGD, but because of the emergence of resistant organisms and occasional medication intolerance, the use of voriconazole and posaconazole has increased. The use of itraconazole therapy as prophylaxis in patients with CGD did not become widespread until after 1994, but it has proven to be well tolerated and effective. Up to 70% of patients with CGD (and closer to 95% at some centers) use itraconazole prophylaxis, but the use of posaconazole and voriconazole is increasing [11]. Voriconazole bioavailability is somewhat superior to that of itraconazole, and it confers a broader spectrum of fungal coverage with enhanced activity against *Aspergillus* spp. However, long-term voriconazole use is associated with dermatotoxicity, including photodermatitis and increased susceptibility to skin cancer. Posaconazole also provides broad-spectrum activity, and oral administration is more palatable than that of itraconazole. However, pharmacokinetic data from children are sparse, which recently prompted a small pediatric study in which posaconazole was found to be safe and well tolerated in the short term in children with CGD [26]. To date, only itraconazole has been studied adequately for the efficacy of prophylaxis in patients with CGD; further investigation is needed.

Dosing regimens for the azole antifungal agents have emerged from both prospective studies in patients with CGD and from their use in patients with another immunocompromising

condition. Recommended regimens for itraconazole in the United States differ from the accepted European dosing recommendations, which are based on the 1994 French studies [21, 22, 27] (Table 1). Doses for voriconazole and posaconazole are primarily extrapolated from their use in patients with cancer and those who have undergone hematopoietic stem cell transplantation [28]. Many experts recommend routine monitoring of serum drug levels, because variability in absorption remains a challenge with chronic itraconazole and voriconazole therapy, although whether serial drug monitoring affects the outcomes of therapy remains unknown [27]. Azole absorption can vary as a result of factors such as patient age, gastrointestinal inflammation, and differences in the gastric acidity. Voriconazole bioavailability, for example, is variable in pediatric patients and is overall lower than that in adults (73% vs 96% bioavailability, respectively) [29]. By contrast, posaconazole reaches similar plasma levels in children and adults, and its liquid formulation's cherry flavor might lend itself more readily to palatability in the pediatric population [30–34]. Last, the burden of cost should be considered for each patient. The newer azoles are considerably costlier; voriconazole costs 2 to 3 times more than itraconazole, and posaconazole costs >5 times more than itraconazole [Data as of 2017 via Lexicomp Online, Pediatric & Neonatal Lexi-Drugs, Hudson, Ohio: Lexi-Comp, Inc.]. With prescription insurance, the cost of these medications decreases depending on specific coverage and qualifications. Thus, when choosing a triazole for antifungal prophylaxis in patients with CGD, the prescriber must consider not only the dosing regimen but also factors that influence medication adherence and delivery.

Adverse effects of the triazoles vary widely despite their commonalities, although overall, they are a relatively safe class of medication. Medication intolerance is a common reason for discontinuation, although drug hypersensitivity to this class of medications is quite rare. Itraconazole is known to cause elevated transaminase levels, headache, nausea, and vomiting. IgE-mediated symptoms (ie, immediate onset of hives, angioedema, and breathing difficulty) that lead to discontinuation are reported rarely. However, as with many medications that result in an IgE-mediated hypersensitivity reaction, drug tolerance can be achieved successfully and should be pursued in the case

**Table 1. Antifungal Agents Commonly Used for Prevention of Invasive Fungal Infection in Patients With CGD**

Azole	Formulations Available in the United States	US Dosing Regimens
Itraconazole	100-mg capsule; 10 mg/mL oral solution; 200-mg tablet	100 mg/day (<13 y or <50 kg); 200 mg/day (>13 y or >50 kg) [21]
Voriconazole	200-mg IV solution; 40 mg/mL oral suspension; 50- and 200-mg oral tablets	Oral suspension dose, 9 mg/kg per dose every 12 h (maximum 350 mg/dose) (2–12 y and <40 kg); 200 mg every 12 h (>40 kg) [28–32]
Posaconazole	300 mg/16.7 mL IV solution; 40 mg/mL oral suspension; 100-mg delayed-release tablet	Oral suspension dose, every 12 h, 120 mg (10–14 kg), 160 mg (15–19 kg), 200 mg (20–24 kg), 220 mg (25–29 kg), 260 mg (30–34 kg), 280 mg (35–39 kg); oral suspension, 200 mg 3 times daily (>40 kg); delayed-release tablet, 300 mg 2 times daily on day 1 followed by 300 mg daily thereafter [26, 27]

Abbreviation: IV, intravenous.

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of such reactions to itraconazole [35]. Although photosensitivity is typically the limiting factor in long-term treatment with voriconazole, a recent case of hypersensitivity to voriconazole treated successfully with a rapid induction of tolerance highlighted a viable option in the rare instance of IgE-mediated voriconazole hypersensitivity [36]. Photosensitive eruptions with voriconazole use are more common than IgE-mediated hypersensitivity, and because severe cutaneous adverse reactions also have occurred with voriconazole (including precancerous lesions), the drug should be stopped if photosensitivity is observed. Posaconazole seems to have an adverse-effect profile most similar to that of itraconazole, and the successful induction of drug tolerance has been performed for this medication also [37]. However, the potential for hypersensitivity cross-reactivity between itraconazole, voriconazole, and posaconazole remains largely unknown, but cases of patients able to tolerate other agents within the group of triazoles have been reported. Azoles also affect cytochrome P450 metabolism and might significantly alter steroid metabolism and lead to iatrogenic Cushing syndrome when coadministered with steroids (including inhaled or gut-directed therapy) [38]. Therefore, caution must be used when prescribing azoles to patients with CGD who also are receiving treatment for an inflammatory complication. In the case of complete azole intolerance, medications such as caspofungin and amphotericin B are potential alternatives, but they require intravenous administration and have a more difficult adverse-effect profile.

Granulocyte transfusions have been reported to be helpful when given in the setting of invasive fungal infection, but they can lead to alloimmunization and complicate future stem cell transplantation, and they have little if any role as a prophylactic modality [39]. In general, prophylactic regimens with the triazole antifungal agents are well tolerated and the most viable current option for controlling invasive fungal disease in patients with CGD.

## **IFN- $\gamma$**

The final component of a standard prophylactic regimen for patients with CGD, in addition to antibacterial and antifungal agents, is the use of IFN- $\gamma$  for immunomodulation. The use of IFN- $\gamma$  for prophylactic therapy in patients with CGD stems largely from substantial data generated in the late 1980s, which showed the augmentation of phagocyte-mediated bacterial killing with the use of IFN- $\gamma$  *in vitro* [40]. In subjects with X-linked CGD and some residual baseline respiratory burst activity, IFN- $\gamma$  stimulated the oxidative burst up to 8-fold. It was subsequently shown that IFN- $\gamma$  stimulated the oxidative burst in approximately two-thirds of patients with CGD, regardless of genetic defect, and that IFN- $\gamma$  seemed to enhance bactericidal activity independent of the oxidative-burst pathway [41, 42].

On the basis of these *in vitro* data, and results from a small study that indicated restoration of the oxidative burst in 2 patients with CGD who received subcutaneous IFN- $\gamma$  [41], a randomized double-blind placebo-controlled study was conducted in the early 1990s to determine the efficacy of IFN- $\gamma$  in patients with CGD [43]. In that trial, 128 patients with CGD were randomly assigned to receive IFN- $\gamma$  or placebo 3 times per week. IFN- $\gamma$  was found to reduce the number of serious infections in patients with CGD by 67%. A reduction in the frequency and length of hospitalizations was observed also. Subgroup analyses revealed potential distinctions in the efficacy of IFN- $\gamma$  based on the recipient populations. Although the administration of IFN- $\gamma$  therapy was found to be effective in patients with either X-linked or AR CGD, the effect was more substantial in those with X-linked disease, particularly younger patients with X-linked CGD. In addition, IFN- $\gamma$  was well tolerated in all populations, and the adverse-effect rate was minimal [43].

A phase IV study of the long-term efficacy and toxicity of IFN- $\gamma$  in patients for up to 9 years found that no patients experienced a life-threatening adverse event related to interferon therapy. Compared to a baseline rate of 1.1 serious infections per patient-year, IFN- $\gamma$  therapy reduced the rate of serious infections to 0.30 per patient-year and reduced the mortality rate to 6.6% over 9 years (1.5% per patient-year) [44]. These data clearly support the use of IFN- $\gamma$  therapy in the prevention of severe infections in patients with CGD. It must be noted, however, that this study was conducted before the introduction of fungal prophylaxis as a component of routine care for patients with CGD. Thus, the specific contribution of IFN- $\gamma$  in preventing serious infections in patients with CGD on otherwise optimal preventive therapy remains undefined.

IFN- $\gamma$  can be initiated at a dose of 50  $\mu\text{g}/\text{m}^2$  in a subcutaneous injection 3 times per week. One barrier to the use of IFN- $\gamma$  therapy in some patients is the potential for adverse medication effects, most commonly flu-like symptoms (fever, chills, fatigue), rash, and local injection-site reactions (erythema or tenderness) [43]. Stepwise dose escalation over a 2-week interval can reduce the likelihood of these adverse effects [45]. Additional dose adjustments can be beneficial if flu-like symptoms are prohibitive, and these symptoms often diminish with consistent use of the medication or premedication with acetaminophen. Hypersensitivity reactions are uncommon, and a recent study found that rapid induction of drug tolerance is possible for 3-times-weekly dosing [46]. In general, many experts consider the risk/benefit ratio to be favorable for the use of IFN- $\gamma$  to prevent invasive infectious complications in patients with CGD, particularly for young patients with X-linked disease and those with a history of invasive infections [47].

One challenge to the optimal use of IFN- $\gamma$ , including selection of which patients are ideal candidates for therapy, is the

fact that the specific mechanisms of immune modulation in the setting of CGD remain unclear. Data from a murine model of CGD, in which IFN- $\gamma$  was shown to be efficacious in preventing infection, suggest that restoration of the neutrophil oxidative burst is not the mechanism of action [48]. Recent data indicate that IFN- $\gamma$  therapy strongly increases nitric oxide (NO) production by phagocytes and circulating NO levels [49]. Because NO is a known component of phagocyte-mediated innate immunity against bacterial and fungal pathogens [50], these data might suggest a mechanism for interferon-mediated reduction of infections in patients with CGD. In addition, IFN- $\gamma$  therapy was shown recently to enhance the bactericidal activity of macrophages against *S aureus*, which suggests that augmenting the nonneutrophil arms of the innate host response might be another mechanism of this molecule through which serious infections are reduced [51]. Because interferon modulates numerous downstream effects, including the stimulation of leukocyte migration, natural killer cell activity, and antigen presentation [52], it is possible that the mechanisms of action of IFN- $\gamma$  in patients with CGD are multifactorial, and further work to elucidate these effects is warranted.

## CONCLUSIONS: 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. Nonadherence is a result of a variety of 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 the prophylactic measure. 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 many other people with the condition. The role of educating patients and their families about the seriousness of this condition typically rests on the healthcare provider. Last, the role of bone marrow transplantation as a curative modality for patients with CGD is increasingly being explored, particularly in patients for whom a well-matched donor can be identified, and is reviewed elsewhere in this Supplement.

With the advent of appropriate therapeutic and prophylactic therapies, fatal granulomatous disease evolved to become CGD, and it is now the norm for patients with CGD to survive well beyond childhood and early adulthood [12, 53]. Future studies, particularly to investigate the mechanism of IFN- $\gamma$  and its role in the setting of additional prophylactic therapy, and evaluations of the efficacy of newer antifungal agents for the prevention of invasive fungal infections are needed.

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