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Review Article

National Consensus Guideline on Diagnosis and Management of Chronic Granulomatous Disease

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Abstract

Currently, a national consensus or guideline for diagnosing and managing patients suspected of having chronic granulomatous disease (CGD) is lacking. This consensus is written based on a combination of scientific literature and comments from the expert panel of Iranian immunologists. A group of clinical immunologists reviewed the current consensus, presented their comments at a meeting titled "First Meeting on the Diagnosis of Inborn Errors of Immunity (IEI) by IEI Experts" and agreed on this consensus. This consensus guideline provides recommendations on the diagnosis, antimicrobial prophylaxis, management of clinical manifestations, administration of interferon gamma (IFN-γ) and hematopoietic stem cell transplantation (HSCT) for patients with CGD.

Keywords: National Consensus; Inborn Errors of Immunity; Chronic Granulomatous Disease; Management; IFN-γ; HSCT

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Introduction

Inborn errors of immunity (IEI), formerly known as primary immunodeficiency disorders (PIDs), are a heterogeneous group of disorders, caused by mutations in genes associated with immunoregulation and immune host defense, which result in increased susceptibility to allergy, infections, autoimmunity, autoinflammatory, and nonmalignant lymphoproliferative (1, 2). To date, more than 500 IEI have been described and many are life-threatening and require curative therapy (3).

Chronic granulomatous disease (CGD) is a heterogenous group of inborn errors of immunity (IEI) classified under phagocytic defects by the International Union of Immunological Societies (IUIS)(4). It is characterized by key features such as severe, recurring bacterial and fungal infections, along with abnormal inflammatory responses that lead to granuloma formation and other inflammatory conditions (5, 6). The prevalence of CGD is estimated to be approximately 1 in 200,000–300,000 live births worldwide (7, 8). Infections typically involve the lungs (pneumonia), skin (abscesses or cellulitis), lymph nodes (lymphadenitis), bone (osteomyelitis), and liver (abscess)(8).

CGD is caused by mutations in the genes that code for components of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex. These mutations impair the respiratory burst in phagocytes, leaving patients more vulnerable to frequent and severe infections from a specific group of pathogens (9-11). Inheritance of CGD is X-linked (XL) or autosomal recessive (AR)(12). The XL-CGD is caused by mutations in the cytochrome B-245 beta chain (*CYBB*)/gp-91phox that account for 65% of CGD patients, while the AR-CGD is caused by mutations in *neutrophil cytosolic factor 1* (*NCF1*)/p47phox (25%), cytochrome B-245 alpha chain (*CYBA*)/p22phox (5–10%), (*NCF2*)/p67phox (5–10%), (*NCF4*)/p40phox (rare), or cytochrome B-245 chaperone 1 (*CYBC1*)(rare)(13-15).

Invasive fungal and bacterial infections are the main risk factor for mortality in CGD patients (16, 17). The mainstay of therapy for CGD is prevention of infections through antibacterial and antifungal prophylaxis and administration of immunomodulatory therapy with interferon gamma (IFN-γ) and HSCT in unresponsive or severe cases (18, 19).

The aim of the current national consensus is to provide a comprehensive review for diagnosis, management and therapeutic challenges of CGD patients according to a combination of scientific literature and the comments of the expert panel of Iranian clinical immunologists.

Consensus on Diagnosis of CGD

Diagnosis of CGD is made according to the diagnostic criteria for IEI recommended by European Society for Immunodeficiencies (ESID) consisting of at least one of the following: deep seated infection due to bacteria and/or fungi (abscesses, osteomyelitis, lymphadenitis), recurrent pneumonia, lymphadenopathy and/or hepatomegaly and/or splenomegaly, obstructing/diffuse granulomata (gastrointestinal or urogenital tract), chronic inflammatory manifestations (colitis, liver abscess and fistula formation), failure to thrive, affected family member and absent/significantly decreased respiratory burst (NBT or DHR, measured at least 2 occasions)(https://esid.org/Working-Parties/Registry-Working-Party/Diagnosis-criteria).

Consensus Recommendations and Discussion on Management of Clinical Manifestations in CGD

In the following sections, we have briefly discussed management of the most important clinical complications in CGD patients.

Acute Infectious Episodes

Patients with CGD are more susceptible to severe bacterial and fungal infections. Symptoms typically begin in infancy, with the average age of diagnosis being around 2.5 to 3 years. However, some individuals may not be diagnosed until their teenage years or even adulthood (20). Major sites of infection are lungs (66%), skin/subcutis (53%), lymph nodes (50%), gastrointestinal tract (48%), liver (32%), kidney/urinary tract (22%), septicaemia (20%), ears (14%), bone (13%), eyes (11%), joints (7%) and brain (7%)(21).

Invasive Aspergillosis (IA)

CGD patients face the highest lifetime risk of de-

veloping invasive aspergillosis. The lungs are the most frequently affected site, followed by infections in the skin, lymph nodes, liver, and gastrointestinal tract (22, 23).

Even with antifungal prophylaxis, *aspergillus* infections remain the leading cause of death in patients with CGD (24). Itraconazole prophylaxis has been proven to significantly lower the risk of invasive fungal infections in patients with CGD (25). Posaconazole, a newer mold-active azole with a broader spectrum of activity and increased tolerability, seems to be a favorable alternative (26).

Mulch Pneumonitis

Mulch pneumonitis as a medical emergency occurs within one week of exposure to organic material such as mulch, hay, or leaves (27). Treatment for these patients includes high-dose corticosteroids and antifungal and antibacterial agents (18).

Liver Abscesses

These abscesses develop in roughly one-third of CGD patients and are often caused by *Staphylococcus aureus*. These abscesses are typically multi-loculated and surrounded by a thickened pseudocapsule (28). In patients with CGD, surgical resection of liver abscesses, when combined with antibiotic therapy, is considered safe. It is also linked to lower recurrence rates and shorter hospital stays (29).

Treating CGD-related liver abscesses with corticosteroids (at a median dose of 1 mg/kg/day for about five months) alongside targeted antimicrobial therapy has been shown to lead to better outcomes and fewer follow-up liver procedures compared to invasive approaches like interventional radiology or open surgery. Steroids may help by reducing systemic inflammation, improving local immune response in the liver, and enhancing the effectiveness of antibiotics by allowing better tissue penetration in a less inflamed environment (28).

Lung Abscesses

These abscesses are relatively less common but potentially severe (30). Treatment for the condition often involves lifelong antibiotics, antifungals and INF-γ (31).

Mycobacterial Infections Caused by *Bacillus Calmette–Guérin* and *Mycobacterium tuberculosis*

Mycobacterial infections are a significant concern for patients with CGD, particularly in regions where the BCG vaccine is commonly given, tuberculosis is widespread, or both (32). Long-term remission can be reached with a combination of three or four antibiotics, such as rifampicin, ethambutol, isoniazid, and/or streptomycin (33). BCG vaccination should be officially avoided in individuals diagnosed with or suspected of having CGD, as well as in their newborn siblings. This recommendation aligns with guidelines for children with other inborn errors of immunity (IEI) that affect T cells, phagocytes, or IFN-gamma immunity (34).

Suppurative or Necrotising Lymphadenitis

It can affect at least 50% of these patients. CGD Patients are predisposed to lymphadenitis after receiving BCG vaccination. In addition to antimicrobial therapy, lymphadenitis often requires excisional surgery (31).

Osteomyelitis

Surgical debridement is not routinely advised as first-line treatment for osteomyelitis but may be considered in certain situations, such as when infection persists or other complications arise (35).

Autoimmunity

About half of CGD patients experience not only frequent infections but also autoinflammation or immune system dysregulation such as inflammatory bowel disease (IBD)(36). For mild cases of IBD in CGD, treatments like sulfasalazine or other aminosalicylates are typically used initially (13). Recently, monoclonal antibodies targeting pro-inflammatory cytokines, such as infliximab, anakinra, adalimumab, and ustekinumab, have been studied, though evidence is limited (38, 39). Of these, ustekinumab has shown somewhat better outcomes. Despite known side effects, many patients continue to rely on corticosteroids to manage their IBD (40). Immunomodulators for CGD-related inflammatory manifestations are under investigation, including pioglitazone, tamoxifen, and rapamycin (41).

Hemophagocytic Lymphohistiocytosis (HLH)

Children with CGD can develop HLH, a condition marked by excessive and harmful inflammation often triggered by infections. When diagnosing HLH in children, it's essential to consider underlying conditions like CGD, as HLH may sometimes point to its presence. However, managing HLH in children with CGD remains a challenge, and there is still no established best approach for treatment. Early recognition and proper management of infectious triggers and HLH are crucial to reducing mortality (42).

Children with CGD often face challenges with growth, with growth delays being a common issue. In young children, difficulty thriving is often one of the first noticeable signs of the condition. Approximately 75% are below the population mean for height and weight at the time of diagnosis and 35% require nasogastric and/or parenteral nutritional supplementation. Growth often improves in late adolescence, and many patients with CGD attain their expected growth potential by adulthood (43).

McLeod Syndrome

The *Kell metallo-endopeptidase* (*KEL*) gene, located on chromosome 7q33, encodes the Kell blood group proteins, which consist of over 25 different antigens. The Kell blood group system is made up of two proteins, Kell and Kx, which are connected by disulfide bonds. Kx is encoded by the X-linked *XK* gene, located near *CYBB* on chromosome Xp21. In patients with deletions on the X chromosome, portions of both *CYBB* and *XK* may be missing, resulting in a contiguous gene disorder that causes X-linked CGD and McLeod syndrome (44).

Consensus Recommendations and Discussion on Antimicrobial and Antifungal Prophylaxis

Bacterial infections in patients with CGD include gram-positive (*S. aureus*), gram-negative (*Burkholderia* and *Serratia spp*), and partially acid-fast (*Nocardia*) species. Trimethoprim-sulfamethoxazole (TMP-SMX) has been used routinely to prevent bacterial infections in patients with CGD (45). TMP-SMX prophylaxis has significantly increased the proportion of infection-free patients from 5% to over 40% (46). It is effective for both X-linked and autosomal recessive CGD and is typically dosed at 5 mg/kg/day (based on the TMP component) up to one double-strength tablet daily (47).

Invasive fungal infections pose a significant mortality risk in CGD patients. *Aspergillus* species, particularly *Aspergillus fumigatus* and *Aspergillus nidulans*, account for over 35% of these deaths. Other notable pathogens include *Paecilomyces*, *Rasamsonia Argillacea*, and *Candida species* (47). Traditionally, itraconazole has been the preferred azole for preventing fungal infections in CGD patients. However, due to the emergence of resistant organisms and occasional intolerance to medication, there has been an increase in the use of voriconazole and posaconazole. These newer azoles offer broader antifungal coverage and, in some cases, better patient tolerability. This shift underscores the ongoing need to evaluate and optimize prophylactic strategies in CGD management (48). Itraconazole is typically dosed at 100 mg up to 200 mg daily based on age and weight (49). Due to resistant organisms and intolerance, the use of voriconazole and posaconazole has been recommended (50). **Table 1** shows the antifungal agents commonly used for prevention of fungal infection in CGD patients.

Consensus Recommendations and Discussion on IFN-γ Treatment

A key part of the standard preventive care for patients with CGD includes immunomodulation with IFN-γ, alongside antibacterial and antifungal medications. The use of IFN-γ as a preventive treatment in CGD is supported by research from the late 1980s, which demonstrated its ability to enhance phagocytes' bacterial-killing activity in laboratory studies (51). In individuals with X-linked CGD who have some residual respiratory burst activity, IFN-γ has been shown to boost this activity by up to eight times. Further studies revealed that IFN-γ enhances the oxidative burst in about two-thirds of CGD patients, regardless of their specific genetic mutation. Additionally, IFN-γ appears to improve the ability to fight bacteria through mechanisms beyond the oxidative burst pathway (52, 53).

A phase IV study examining the long-term use

of IFN-γ in patients with CGD over a period of up to nine years found it to be both effective and safe. None of the patients experienced life-threatening side effects from the therapy. IFN-γ significantly lowered the rate of serious infections, from an initial average of 1.1 per patient per year to just 0.30 per patient per year. Additionally, it reduced the overall mortality rate to 6.6% over nine years, or 1.5% per year (54).

This evidence strongly supports the use of IFN-γ therapy to help prevent severe infections in patients with CGD. However, it's important to note that this study was conducted before fungal prophylaxis became a standard part of routine care for CGD patients. As a result, the exact role of IFN-γ in preventing serious infections in patients already receiving optimal preventive therapy is still unclear (54).

Common side effects of IFN-γ include flu-like symptoms (fever, fatigue, muscle aches), rash, and local reactions at the injection site (such as redness or tenderness). Many experts believe that the benefits of using IFN-γ to prevent invasive fungal infections outweigh the risks, especially for young patients with X-linked CGD or those with a history of such infections (55).

Consensus Recommendations and Discussion on HSCT

Hematopoietic stem cell transplantation (HSCT) is increasingly seen as the standard treatment for CGD and should be considered early after diagnosis. All genetic forms of CGD, including the rare *CYBC1* mutation, respond well to transplantation. While the best conditioning regimen is still under study, reduced-toxicity approaches, particularly using treosulfan or targeted busulfan, have shown promise. These regimens help achieve stable myeloid engraftment, correcting the disease while minimizing chemotherapy's harmful side effects. While a fully matched donor remains the preferred option, mismatched donors, especially when T-lymphocyte-depleted, can also be successful, though more research is needed to find the optimal method. Traditional indications for allogeneic hematopoietic stem cell transplant (HSCT) include greater than or equal to one life-threatening infection, steroid-dependent or refractory granulomatous disease, organ dysfunction due to hyperinflammation, and prophylaxis non-adherence (56).

The best outcomes are seen when transplantation occurs early, ideally before irreversible organ damage, but successful transplants can still happen in adults. For adults, HSCT remains a potential cure, and it should not be dismissed. Early transplantation helps patients reach their full growth potential, eliminates infection risks, and prevents inflammatory complications (57). Many patients who undergo successful transplantation experience normal life quality, unlike those who rely on ongoing medical treatment, and can stop taking prophylactic medications. Many even go on to have families and lead typical lives.

There are still open questions, such as the best age for transplantation, the most effective conditioning regimen, and the required donor chimerism level. Ideally, donor myeloid chimerism should be over 80%, but in practice, stable chimerism of 15-20% can be sufficient. We do not recommend re-transplantation solely based on chimerism levels but rather consider the patient's symptoms and history. For some patients, HSCT may not be an option due to their severe condition. In these cases, gene therapy may be a potential alternative, with clinical trials now available for patients with *CYBB* and *NCF1* mutations. Whichever approach is considered, much prog-

Table 1. Antifungal agents commonly used for prevention of fungal infection in CGD patients.

Antifungal Agents	Dosing Regimens
Itraconazole	100 mg/day (<13 y or <50 kg); 200 mg/day (>13 y or >50 kg)
Voriconazole	Oral suspension dose 9 mg/kg per dose every 12 hours (2–12 y and <40 kg) 200 mg every 12 hours (>40 kg)
Posaconazole	Oral suspension dose 100-300 mg every 12 hours (<40 kg) 200 mg 3 times daily (>40 kg) Delayed-release tablet, 300 mg daily on day 1, followed by 300 mg daily thereafter

ress has been made since the first description of the disease, and patients should now expect to lead a normal life (57).

HSCT in patients with CGD is a complex procedure with significant morbidity and mortality, especially in patients who receive grafts from unrelated donors. These factors should be carefully considered when making decisions about treatment and when discussing conditioning regimens and graft-versus-host disease (GVHD) prevention (58).

Consensus Recommendations and Discussion on Other Medications and Managements

In CGD, gastrointestinal obstructions and liver abscesses are typically caused by Staphylococcus infections. These abscesses often contain dense, caseous material and may require excisional surgery. Using tumor necrosis factor (TNF)-alpha inhibitors in CGD patients could help improve outcomes for those dealing with severe inflammatory complications, although the potential risks need to be carefully considered. This treatment could offer short-term benefits for selected patients with severe inflammation, while they await HSCT. However, there is conflicting evidence about the effectiveness of infliximab, a TNF-alpha inhibitor, in causing rapid improvement. While it may show some benefit, it is also linked to a higher risk of serious infections and death in CGD patients, so it should be avoided (59). Corticosteroids have been shown to be helpful in treating CGD colitis, although they are usually avoided in patients with active infections. When combined with the right antibiotics, steroids can effectively manage excessive inflammatory responses. Despite their benefits, corticosteroids can cause long-term side effects like growth delays, osteoporosis, and a higher risk of infections. For treating inflammatory conditions, steroids paired with immunosuppressants, such as anti-TNF agents, can work well as a second-line treatment, as they show some effectiveness. However, the use of immunosuppressants like anti-TNF agents, thalidomide, and anakinra is still debated, as their potential risks need to be weighed against their benefits (60). Considering that patients with X-linked CGD who have a KELL-negative minor blood group may encounter severe transfusion reactions, it is recommended that they should not be transfused with KELL-positive blood.

Consensus Recommendations and Discussion on Daily Life of CGD Patients

CGD patients should avoide exposure to molds (13). CGD patients should wear a FFP3 mask to prevent molds from entering their airways (61).
Regarding vaccination, CGD patients should not be given the live bacterial vaccines such as BCG and oral typhoid vaccine (62).
CGD patients should avoid exposure to mulch, hay, wood chips, decaying plants and activities such as gardening and agricultural works (13). It is not recommended for CGD patients to keep pets, although the risk may be manageable with careful hygiene (13).

Conclusions

Herein, we have provided the first national consensus guideline on the diagnosis and management of CGD patients in Iran in light of scientific literature and comments from the expert panel of Iranian clinical immunologists. This national consensus guideline could be used as a reference for increasing the awareness of clinicians and improving diagnosis and management of patients with CGD.

Conflict of Interests

There is no conflict of interest.

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