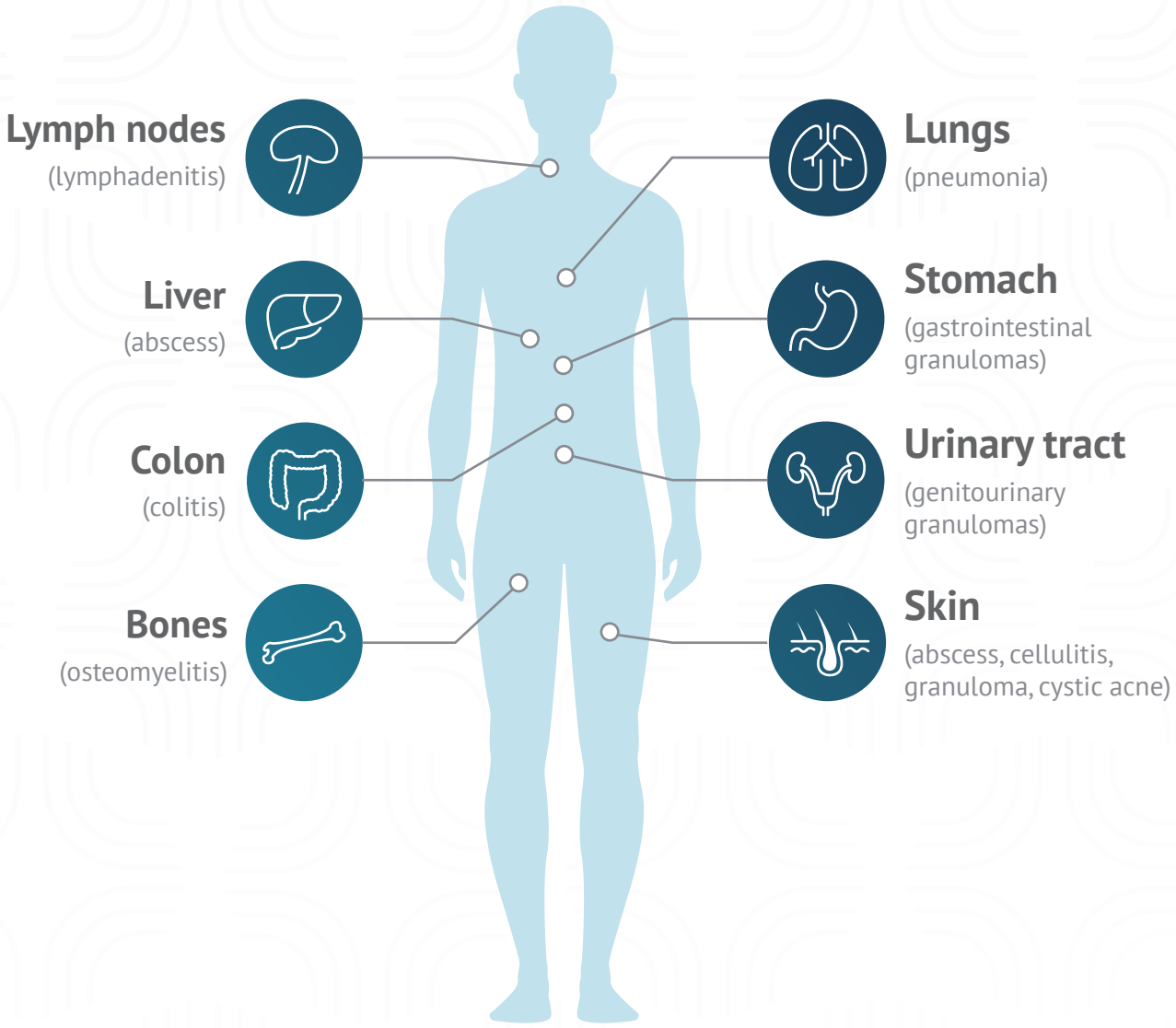
CGD pathways

# CHRONIC GRANULOMATOUS DISEASE (CGD)

Disease Overview, Testing, and Management

**CGD is a primary immunodeficiency disorder** of phagocytes that results from the impaired killing of fungi and bacteria and can lead to severe, recurrent, and **life-threatening infections**. CGD may become apparent at any time from infancy to late adulthood.[1]

## Most frequent sites of infection, common infectious complications, and common inflammatory complications[1]



# Look for the pathogens that may indicate CGD

Patients with primary immunodeficiencies present frequently with chronic and/or recurrent infections caused by a broad array of pathogens, and do so early in life. Many severe infections in patients with CGD in North America are caused by a select group of organisms, both bacterial and fungal.[1-7]

## Most frequent pathogens and common presentations associated with CGD

This is not a complete list of pathogens. Infections may also be caused by other species of bacteria and fungi not listed here.

### FUNGAL

***Aspergillus* species**

*Pneumonia, lymphadenitis, osteomyelitis, brain abscess*

***Candida* species**

*Sepsis, soft tissue infection, liver abscess*

### BACTERIAL

***Nocardia* species**

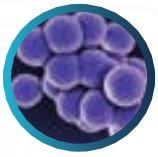
*Pneumonia, osteomyelitis, brain abscess*

***Klebsiella* species**

*Pneumonia, skin infections, lymphadenitis*

***Serratia marcescens***

*Osteomyelitis, soft tissue infections, pneumonia, sepsis*



***Staphylococcus aureus***

*Soft tissue infections, lymphadenitis, liver abscess, perirectal abscess, osteomyelitis, pneumonia, sepsis*

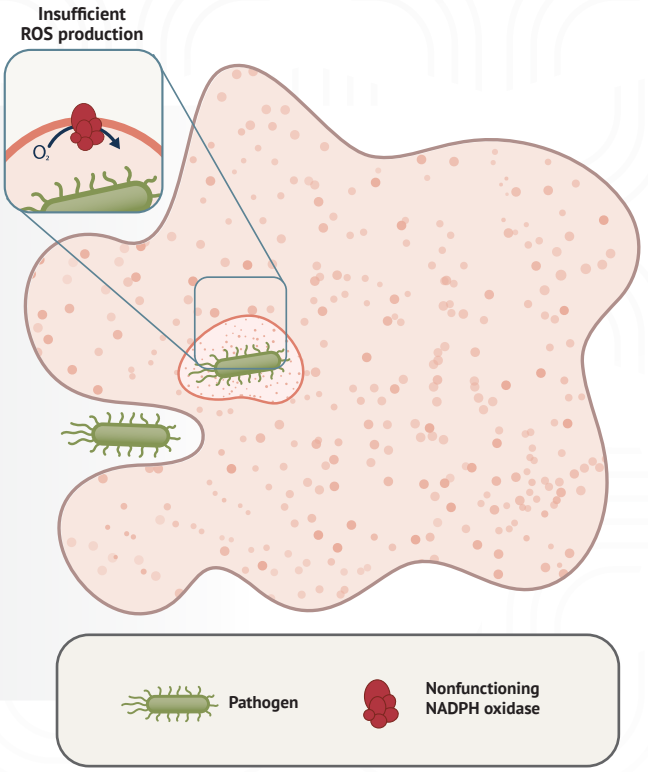
***Burkholderia (pseudomonas) cepacia* complex**

*Pneumonia, sepsis*

# The impact of CGD on immune response goes beyond the innate immune system

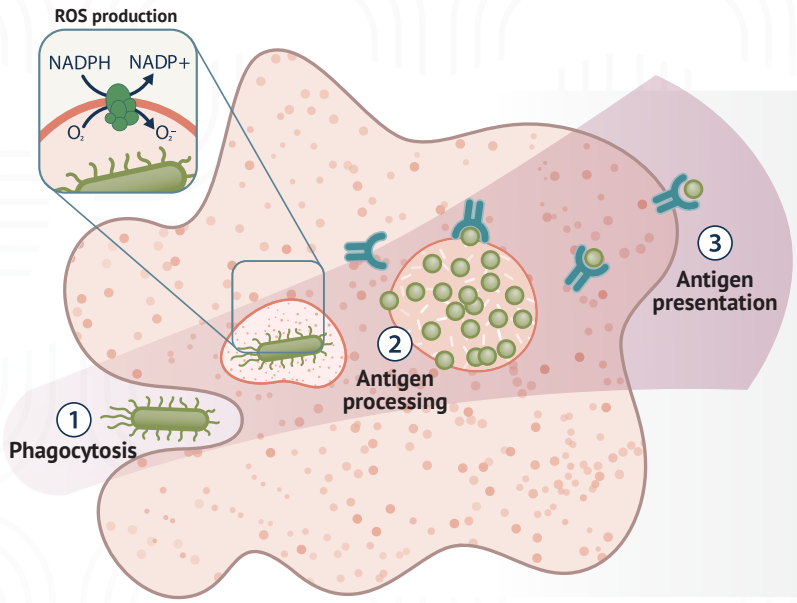
## In patients with CGD, oxidative burst in phagocytes is inhibited due to a defect in the enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase[1]

Phagocytes' failure to produce an adequate respiratory burst results in **NOT ONLY** failed microbial killing, but also delayed induction of the secondary immune response, worsening outcomes of infections in individuals with CGD.[1,8]

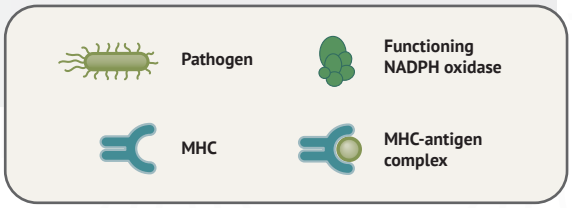



Patients with CGD suffer from severe recurrent bacterial and fungal infections due to insufficient reactive oxygen species (ROS) production. **Presentation can be insidious, making recognition difficult when early treatment is critical.[1]**

## In a normal patient, Reactive Oxygen Species (ROS) play an important role in the immune system, engaging in both microbicidal effects and in signaling as a messenger in certain cell pathways[9]




There is evidence that ROS play a role in signaling pathways related to antigen processing and major histocompatibility complex (MHC) modulation.[9]




**1 Phagocytosis:** Following phagocytosis, the destroyed microbes are used as antigens[9,10]

**2 Antigen processing:** Antigens are processed and presented on the cell surface to activate the adaptive immune system[10]

**3 Antigen presentation:** Critical for initiation of the **antigen-specific adaptive immune response**[9]

## By aiding cells of the innate immune system, cytokine replacement therapy can help activate the adaptive immune response in CGD[8,11]

# Infectious and inflammatory complications of CGD

## The following images depict complications associated with pathogens in patients with CGD

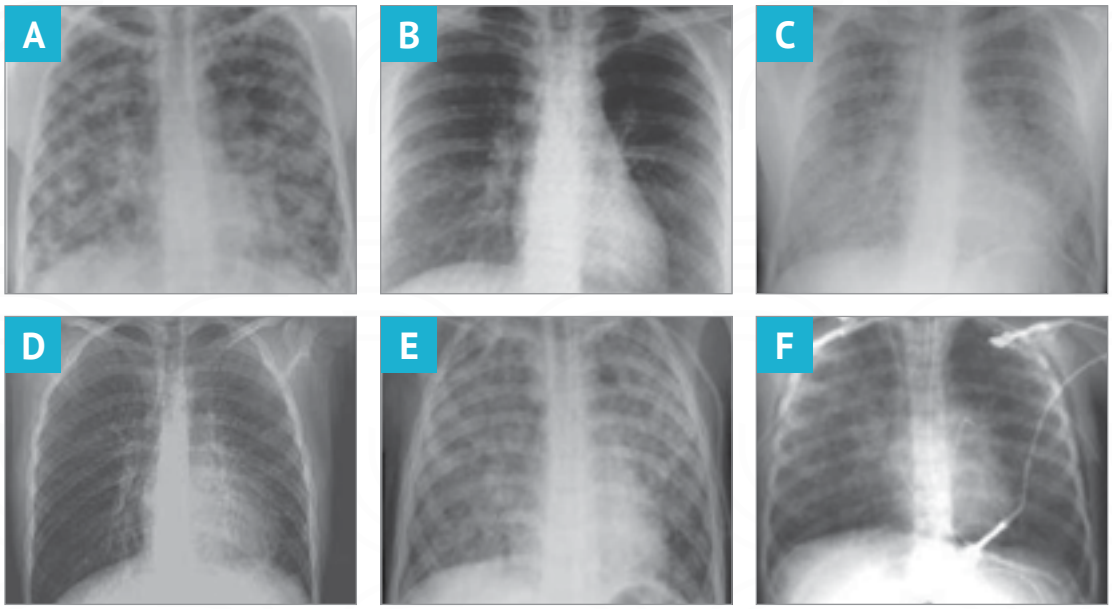
This is not a complete list of the complications of CGD nor of infectious pathogens.

## Pneumonia

Radiographic images of multiple patients with CGD with invasive fulminant mulch pneumonia caused by (A) *Absidia corymbifera* and *Aspergillus* species; (B) *Aspergillus* species and *Rhizopus* species; (C) *Aspergillus* species, *Penicillium* species, *Rhizopus* species, and *Streptomyces thermoviolaceous*; (D) *Aspergillus* species; (E) unknown; (F) *Aspergillus* species and *Streptomyces* species.

### Common infectious pathogens:

*Aspergillus* species, *Burkholderia cepacia* complex, *Klebsiella* species, *Nocardia* species, *Staphylococcus aureus*



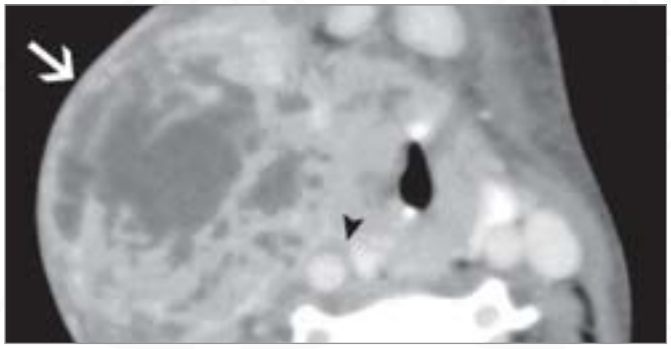

Adapted with permission from Siddiqui S, et al (2007).[12]

## Lymphadenitis

Lymphadenitis caused by a *Haemophilus aphrophilus* infection in a boy aged 10 years with known CGD. Contrast-enhanced computed tomography scan shows a large abscess with enhancing septa in the right side of the neck (white arrow).

**Common infectious pathogens:**

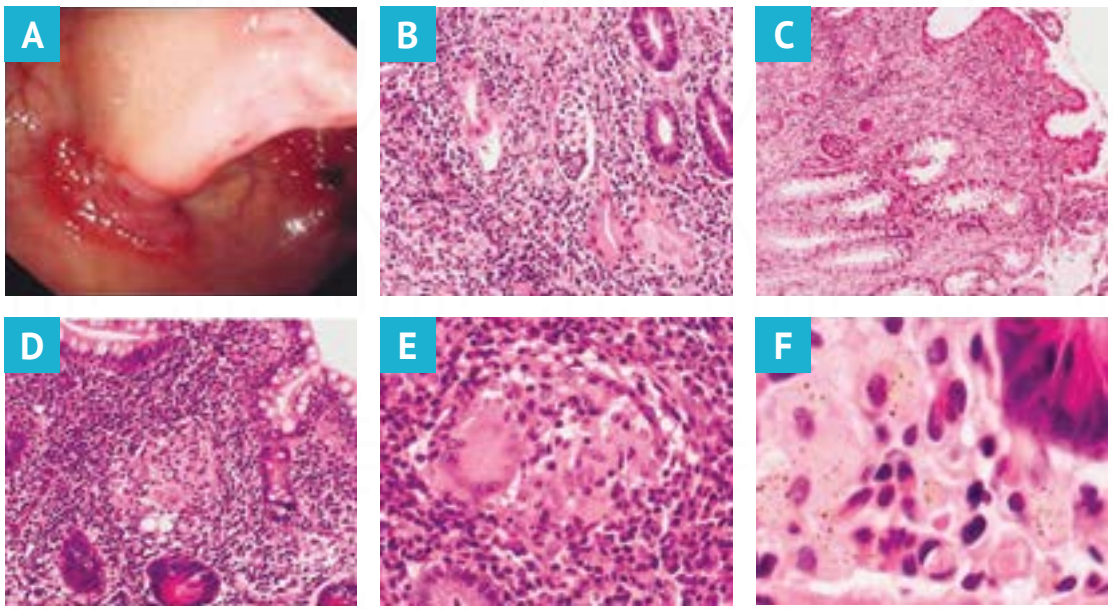
*Aspergillus* species, *Klebsiella* species, *Staphylococcus aureus*



Adapted with permission from Khanna G, et al (2005).[13]

## Inflammatory bowel disease

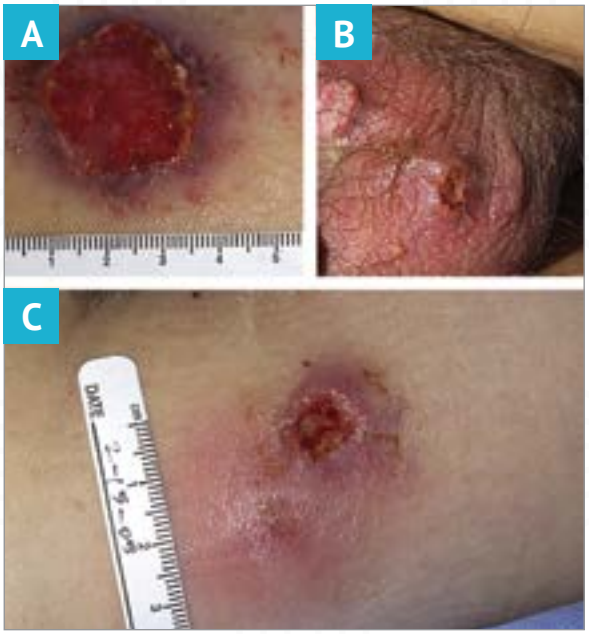
Endoscopic and histologic appearances of inflammatory bowel disease in CGD. (A) Colonoscopic view with well-demarcated area of inflammation and ulceration. (B) Colonic mucosa with active inflammation with withered crypts. (C) Active chronic colitis. (D, E) Well-formed epithelioid granuloma with Langhans-type giant cells. (F) Pigment-laden macrophages in noninflamed regions of bowel.




Adapted with permission from Marks DJ, et al (2009).[14]

## Skin and soft tissue abscesses

Skin ulcers resulting from *Serratia marcescens* infection in a patient aged 20 years with CGD. (A) Ulcerating lesion on the inner right thigh. (B) Ulcerating lesions on the left scrotum. (C) Lesions on the inner aspect of the right upper arm.




**Common infectious pathogens:**

*Candida* species, *Klebsiella* species, *Serratia marcescens*, *Staphylococcus aureus*

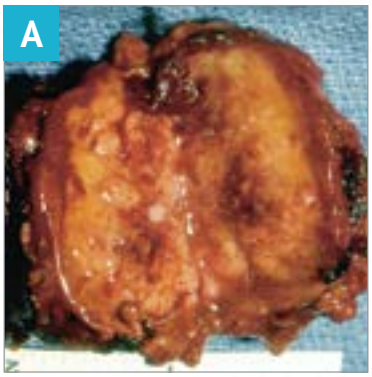
Adapted with permission from Friend JC, et al (2009).[15]

## Hepatic abscess

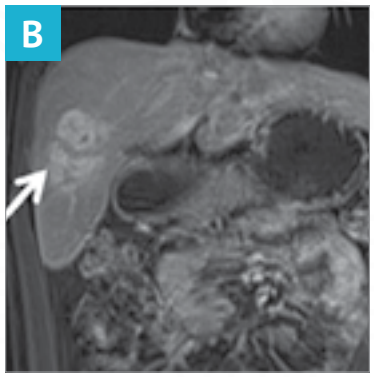
Hepatic abscesses in patients with CGD. (A) Typical appearance of an excised hepatic abscess in a patient with CGD. (B) Coronal postgadolinium magnetic resonance imaging of a hepatic abscess in a patient aged 18 years with CGD.

**Common infectious pathogens:**

*Aspergillus* species, *Klebsiella* species, *Staphylococcus aureus*



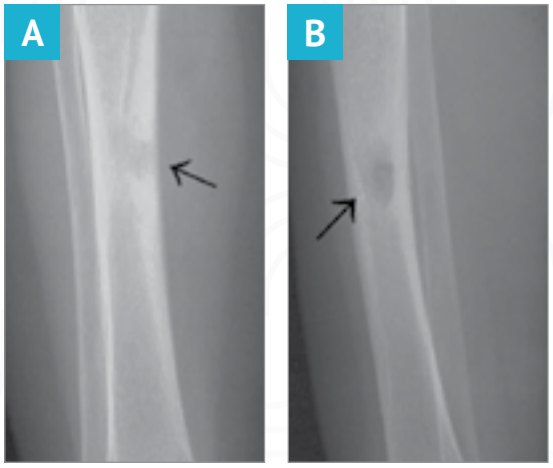

(A) Adapted with permission from Lublin M, et al (2002).[16]




(B) Adapted with permission from Leiding JW, et al (2012).[17]

## Osteomyelitis

Osteomyelitis in a patient aged 4 years with CGD who presented with a limp. Anteroposterior (A) and lateral (B) radiographs of the lower leg show a lytic lesion with surrounding sclerosis in the tibial diaphysis.



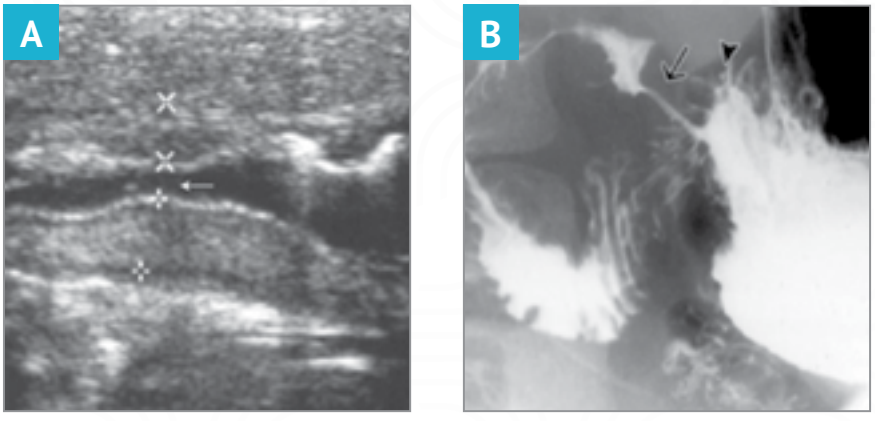

**Common infectious pathogens:**

*Aspergillus* species, *Nocardia* species, *Serratia marcescens*, *Staphylococcus aureus*

Adapted with permission from Khanna G, et al (2005).[13]

## Gastric outlet obstruction

Gastric outlet obstruction in a symptomatic boy aged 9 years with CGD. (A) Ultrasonographic scan with thickening of the antral wall and narrowing of the lumen. (B) Image from a barium study showing marked narrowing and elongation of the pyloric channel and thickening of the gastric folds.



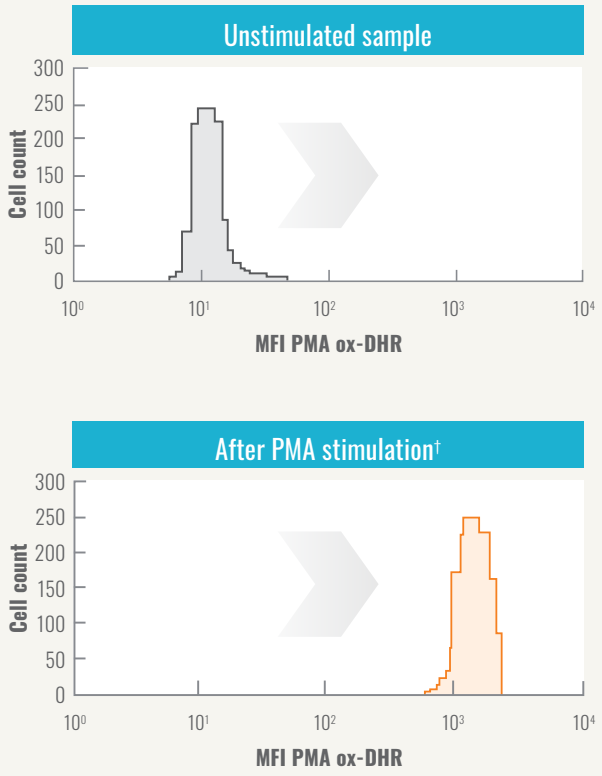

Adapted with permission from Khanna G, et al (2005).[13]

# The DHR test is the preferred test for CGD

## What to look for when reading dihydrorhodamine (DHR)* histogram test results

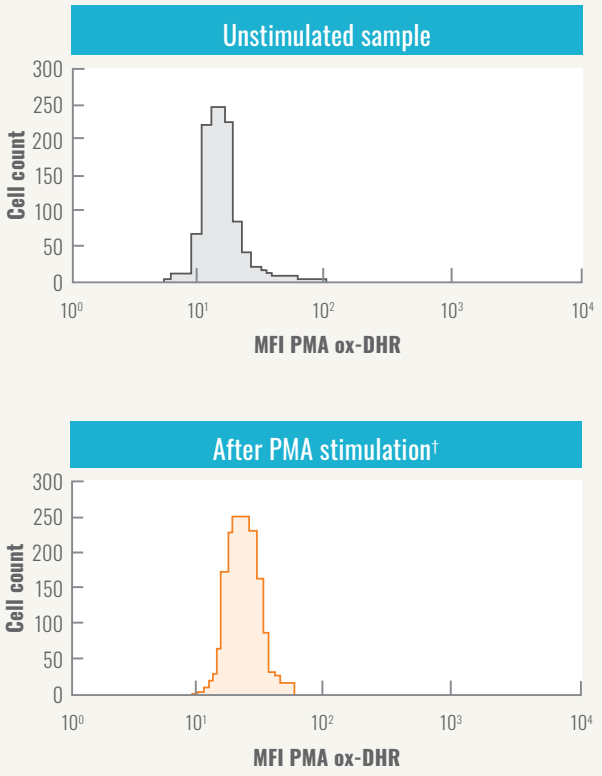
### INDIVIDUAL WITHOUT CGD

The histograms below show the difference in neutrophil NADPH oxidase activity in both an unstimulated sample and a sample that has been stimulated with PMA. There is a strong shift on the x-axis after PMA stimulation, indicating normal, robust neutrophil NADPH oxidase activity.




### PATIENT WITH X-LINKED CGD

The histogram for the stimulated sample shows almost no shift along the x-axis, indicating an absence of neutrophil oxidative burst due to defective NADPH oxidase function.

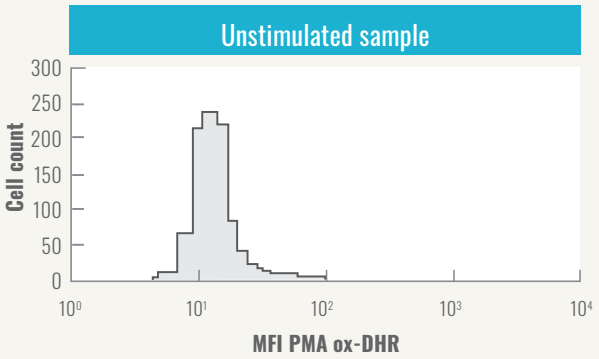


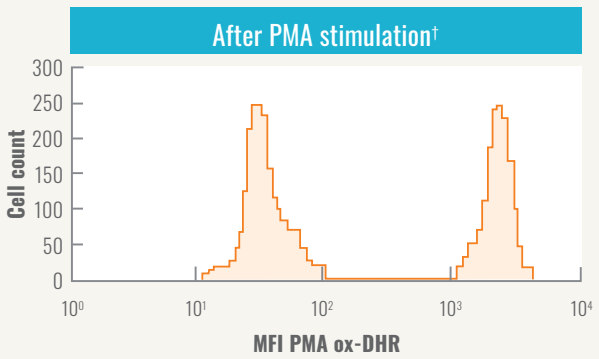

Abbreviations: MFI, mean fluorescence intensity; PMA, phorbol myristate acetate.
Adapted from Leiding JW, et al (2013)[6] and Jirapongsananuruk O, et al (2003).[18]
*The DHR test is also referred to as the neutrophil oxidative burst assay for assessing neutrophil superoxide production.
†PMA is an activator used to stimulate neutrophil NADPH oxidase activity.
‡Usually a female with a healthy and a mutated allele for gp91$^{phox}$.

**Lab results typically include percentage (%) of residual oxidative burst values.**

## X-LINKED FEMALE CGD CARRIER‡

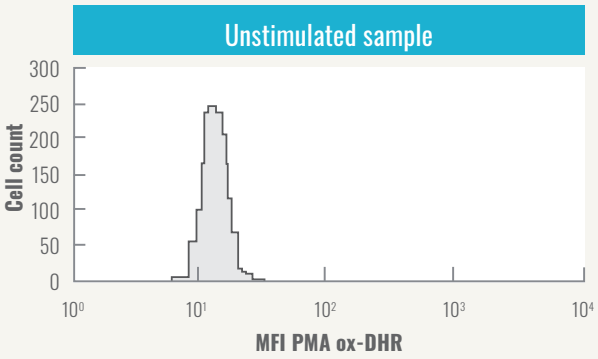
The stimulated sample shows 2 populations of cells. In one population, there is minimal shift along the x-axis because of the absence of NADPH oxidase activity. The other population does have NADPH oxidase activity, as indicated by the shift along the x-axis to the right.

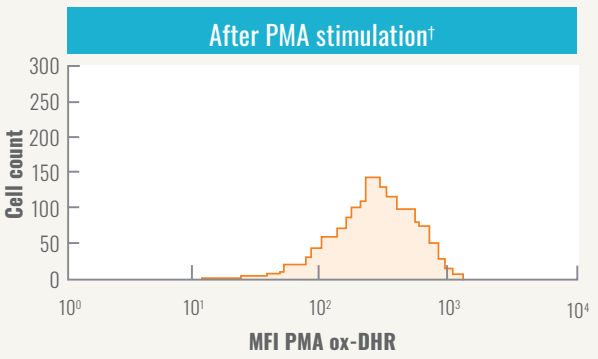



## PATIENT WITH AUTOSOMAL RECESSIVE CGD

The stimulated sample shows a low degree of neutrophil NADPH oxidase activity, as demonstrated by a shift to the right along the x-axis that is much less dramatic than in histograms of patients with X-linked CGD. Both males and females can present with autosomal recessive CGD.




These values are representations of possible DHR outcomes. Because of heterogeneity in disease severity and genotype, outcomes will vary.

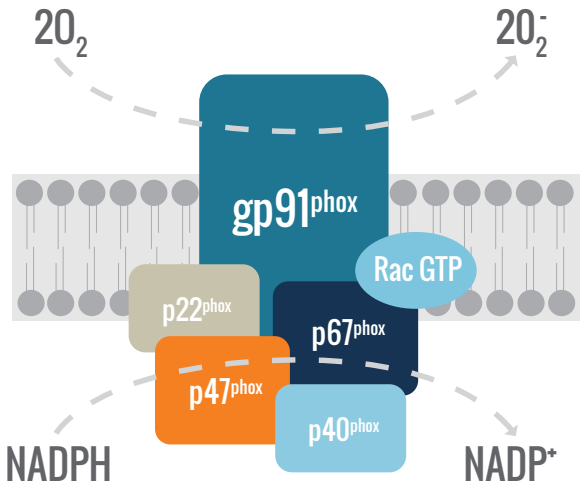
# Identifying the genetic subtypes of CGD

## NADPH oxidase system generates ROI involved in killing bacteria[19-23]

In healthy phagocytes, the NADPH oxidase system catalyzes the formation of superoxide, which can be converted into other reactive oxygen intermediates (ROI).[21-23]

**Any pathologic mutation within the 5 genes that code for the subunits of the NADPH oxidase system can cause CGD.[1]**

Normal NADPH Oxidase System



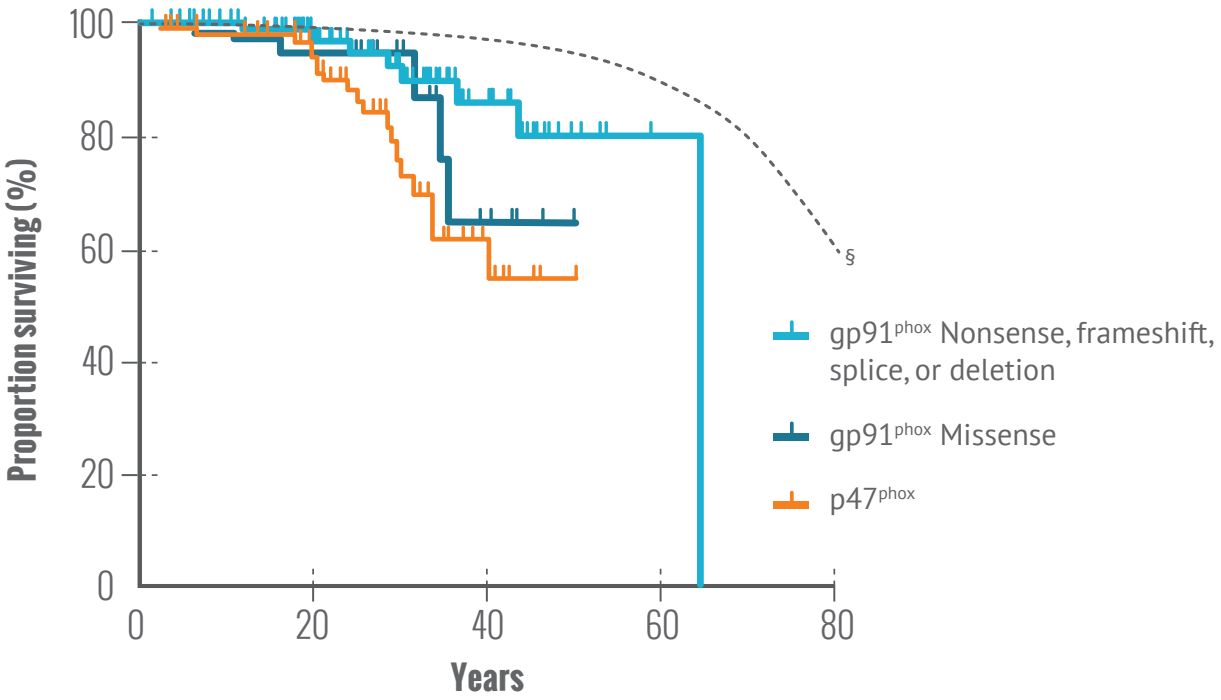

The gp91phox mutation results in X-linked CGD, and the p47phox mutation is the most common mutation in autosomal recessive CGD.[1,20,23-25]

### FREQUENCY OF NADPH OXIDASE SYSTEM GENE MUTATIONS

| Subunit (gene) | Mode of inheritance | Frequency | Sex affected |
|---|---|---|---|
| gp91phox (CYBB) | X-linked | 65%–70%[1,19,20] | Male/rarely female |
| p47phox (NCF1) | Autosomal recessive | 20%–25%[1,19,20] | Male/female |
| p67phox (NCF2) | Autosomal recessive | 5%–6%[1,19,20] | Male/female |
| p22phox (CYBA) | Autosomal recessive | 3%–6%[1,19,20] | Male/female |
| p40phox (NCF4) | Autosomal recessive | 25 cases[1,20,24,25] | Not specified |

# Residual ROI production is more predictive of survival than the specific NADPH oxidase gene mutation[19]

## Even in cohorts where there is significant residual Reactive Oxygen Intermediate (ROI) production, survival is still far below that of the general population[19,22]




§For comparison, the survival curve of the general US population has been included.
Adapted from supplement to Kuhns DB, et al (2010).[19]

**While there are differences in mortality between X-linked and autosomal recessive CGD, the gene mutations alone do not account for the substantial variation in survival rates[19]**

# Combination immunomodulatory and antimicrobial prophylaxis therapy

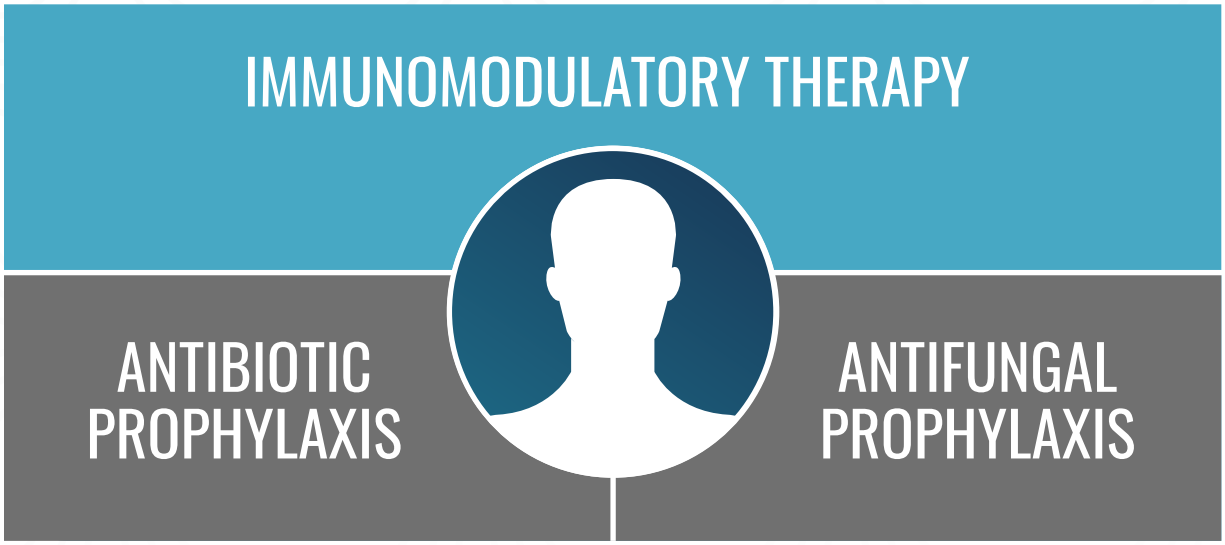
For the chronic medical management of CGD, immunomodulatory therapy in combination with prophylactic antimicrobials is recommended by the[2,6]:

- **American Academy of Allergy, Asthma & Immunology (AAAAI)**
- **American College of Allergy, Asthma & Immunology (ACAAI)**
- **Immune Deficiency Foundation (IDF)**

For the treatment of active infections, using appropriate antimicrobials based on pathogen likelihood or identification is recommended.[1]

This does not include all options for managing CGD.

## Recommended chronic treatment paradigm[26,27]



# DHR testing services are being offered by Horizon at no cost

To order a DHR Collection Kit to test for CGD, visit DHRTestKit.com or contact your Horizon Clinical Science Associate


Testing services are provided by ARUP Laboratories, SLC, Utah, a national reference laboratory for esoteric diagnostic testing.

## The DHR test is known for its ability to[1,19]:

- Quantitatively assess residual superoxide production
- Distinguish between X-linked and autosomal recessive forms of CGD
- Detect low levels of NADPH oxidase activity

# Suspect CGD in a patient with:

**FREQUENT, REPEAT INFECTIONS**

**UNUSUALLY SEVERE INFECTIONS**

**INFECTIONS FROM A SPECIFIC GROUP OF PATHOGENS**

For more information about the clinical manifestations of, testing for, and management of CGD, visit [CGDPathways.com](CGDPathways.com)


References:

**1.** Leiding JW, Holland SM. Chronic granulomatous disease. In: Pagon RA, Adam MP, Ardinger HH, et al, eds. *GeneReviews*. Seattle, WA: University of Washington, Seattle; 1993-2018. **2.** Bonilla FA, Khan DA, Ballas ZK, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. *J Allergy Clin Immunol*. 2015;136(5):1186-1205. **3.** Marciano BE, Spalding C, Fitzgerald A, et al. Common severe infections in chronic granulomatous disease. *Clin Infect Dis.* 2015;60(8):1176-1183. **4.** Bortoletto P, Lyman K, Camacho A, Fricchione M, Khanolkar A, Katz BZ. Chronic granulomatous disease: a large, single-center US experience. *Pediatr Infect Dis J*. 2015;34(10):1110-1114. **5.** van den Berg JM, van Koppen E, Ahlin A, et al. Chronic granulomatous disease: the European experience. *PLoS ONE*. 2009;4(4):e5234. **6.** Leiding JW, Malech HL, Holland SM. Chronic granulomatous disease. *Clinical Focus on Primary Immunodeficiencies*. 2013;15:1-9. **7.** Song E, Jaishankar GB, Saleh H, Jithpratuck W, Sahni R, Krishnaswamy G. Chronic granulomatous disease: a review of the infectious and inflammatory complications. *Clin Mol Allergy*. 2011;9(1):10. **8.** McCusker C, Upton J, Warrington R. Primary immunodeficiency. *Allergy Asthma Clin Immunol.* 2018;14(suppl 2):61. **9.** Cachat J, Deffert C, Hugues S, Krause KH. Phagocyte NADPH oxidase and specific immunity. *Clin Sci (Lond)*. 2015;128(10):635-648. **10.** Gardiner GJ, Deffit SN, McLetchie S, Pérez L, Walline CC, Blum JS. A role for NADPH oxidase in antigen presentation. *Front Immunol.* 2013;4(295). **11.** Kak G, Raza M, Tiwari BK. *Biomol Concepts*. 2018;9(1):64-79. **12.** Siddiqui S, Anderson VL, Hilligoss DM, et al. Fulminant mulch pneumonitis: an emergency presentation of chronic granulomatous disease. *Clin Infect Dis.* 2007;45(6):673-681. **13.** Khanna G, Kao SC, Kirby P, Sato Y. Imaging of chronic granulomatous disease in children. *Radiographics*. 2005;25(5):1183-1195. **14.** Marks DJ, Miyagi K, Rahman FZ, Novelli M, Bloom SL, Segal AW. Inflammatory bowel disease in CGD reproduces the clinicopathological features of Crohn's disease. *Am J Gastroenterol*. 2009;104(1):117-124. **15.** Friend JC, Hilligoss DM, Marquesen M, et al. Skin ulcers and disseminated abscesses are characteristic of Serratia marcescens infection in older patients with chronic granulomatous disease. *J Allergy Clin Immunol*. 2009;124(1):164-166. **16.** Lublin M, Bartlett DL, Danforth DN, et al. Hepatic abscess in patients with chronic granulomatous disease. *Ann Surg.* 2002;235(3):383-391. **17.** 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. **18.** Jirapongsananuruk O, Malech HL, Kuhns DB, et al. Diagnostic paradigm for evaluation of male patients with chronic granulomatous disease, based on the dihydrorhodamine 123 assay. *J Allergy Clin Immunol*. 2003;111(2):374-379. **19.** Kuhns DB, Alvord WG, Heller T, et al. Residual NADPH oxidase and survival in chronic granulomatous disease. *N Engl J Med.* 2010;363(27):2600-2610. **20.** Holland SM. Chronic granulomatous disease. *Clin Rev Allergy Immunol.* 2010;38(1):3-10. **21.** El-Benna J, Dang PM, Gougerot-Pocidalo MA, Elbim C. Phagocyte NADPH oxidase: a multicomponent enzyme essential for host defenses. *Arch Immunol Ther Exp (Warsz).* 2005;53(3):199-206. **22.** Chronic granulomatous disorder: A guide for medical professionals. CGD Society website. cgdsociety.org/wp-content/uploads/2019/05/CGDS-Medical-Guide.pdf. Accessed September 16, 2019. **23.** Thomsen IP, Smith MA, Holland SM, Creech CB. A comprehensive approach to the management of children and adults with chronic granulomatous disease. *J Allergy Clin Immunol Pract.* 2016;4(6):1082-1088. **24.** Matute JD, Arias AA, Wright NA, 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(15):3309-3315. **25.** 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):3957-3975. **26.** Gallin JI, Alling DW, Malech HL, et al. Itraconazole to prevent fungal infections in chronic granulomatous disease. *N Engl J Med*. 2003;348(24):2416-2422. **27.** Holland SM. Chronic granulomatous disease. *Hematol Oncol Clin North Am*. 2013;27(1):89-99.


CGD pathways

HORIZON