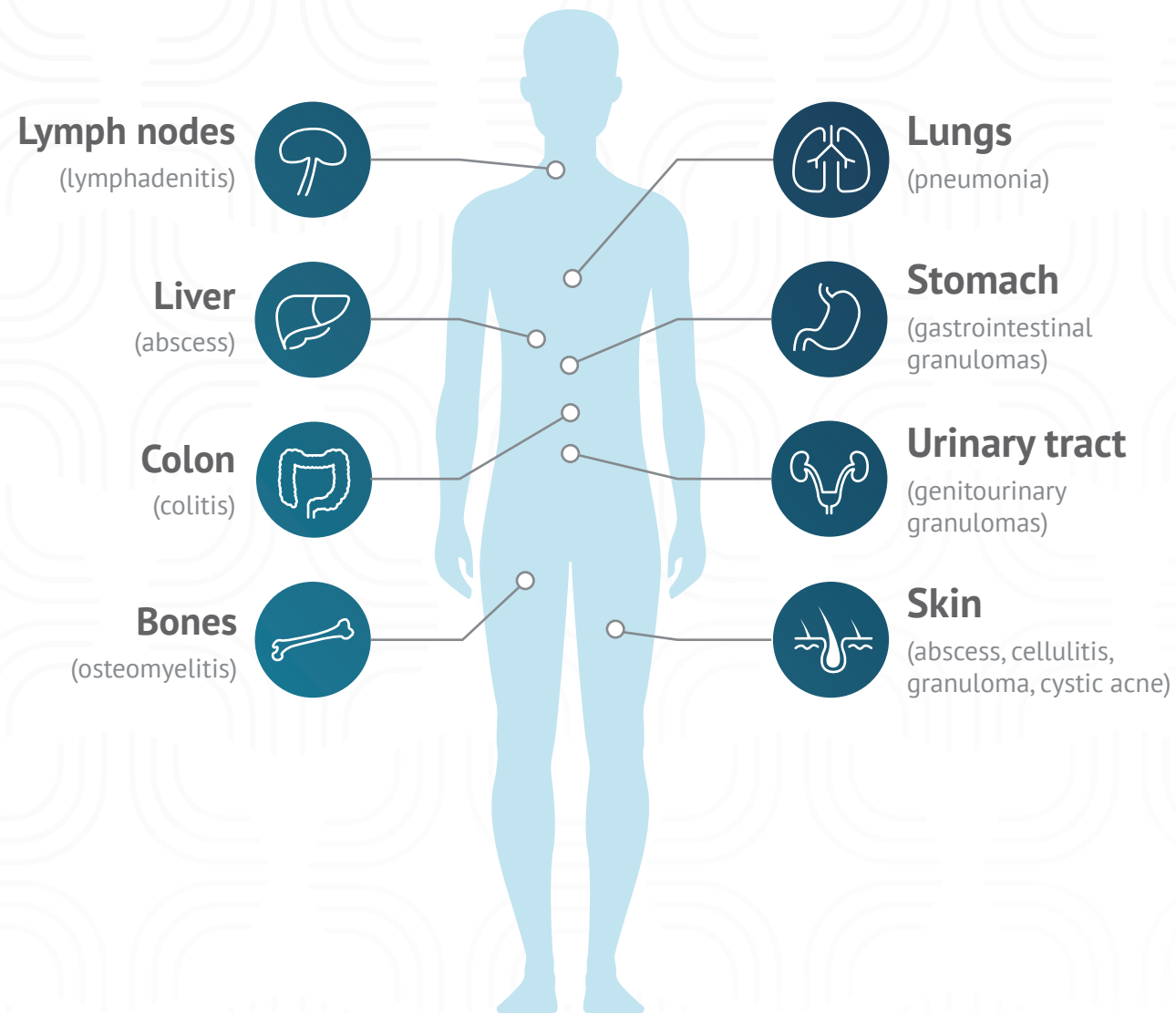


CHRONIC GRANULOMATOUS DISEASE (CGD)

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 complications¹



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

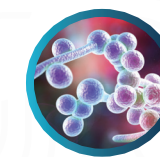
This is not a complete list of pathogens. Infections may also be caused by other species of bacteria and fungi not listed here.

FUNGAL



Aspergillus species

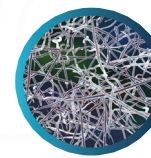
Pneumonia, lymphadenitis, osteomyelitis, brain abscess



Candida species

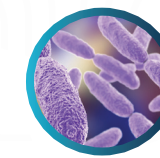
Sepsis, soft tissue infection, liver abscess

BACTERIAL



Nocardia species

Pneumonia, osteomyelitis, brain abscess



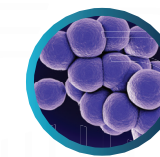
Klebsiella species

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



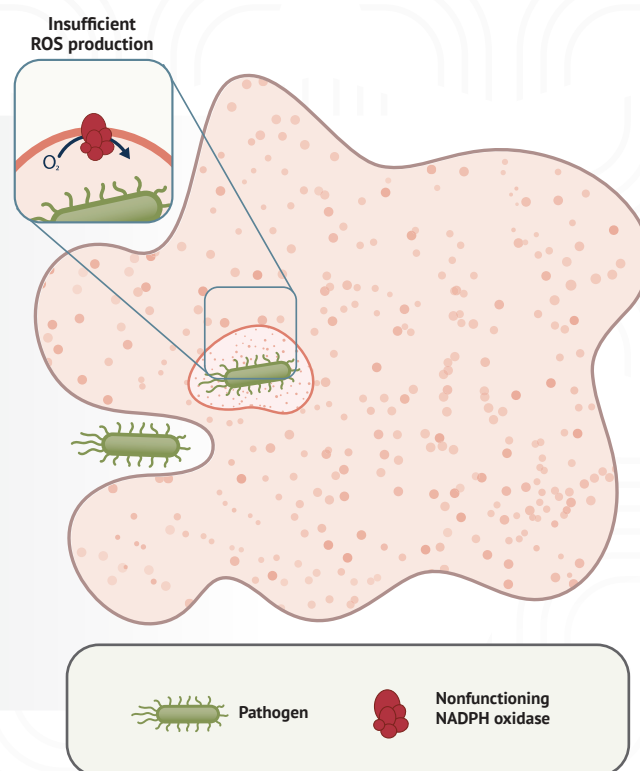
Burkholderia (pseudomonas) cepacia complex

Pneumonia, sepsis

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

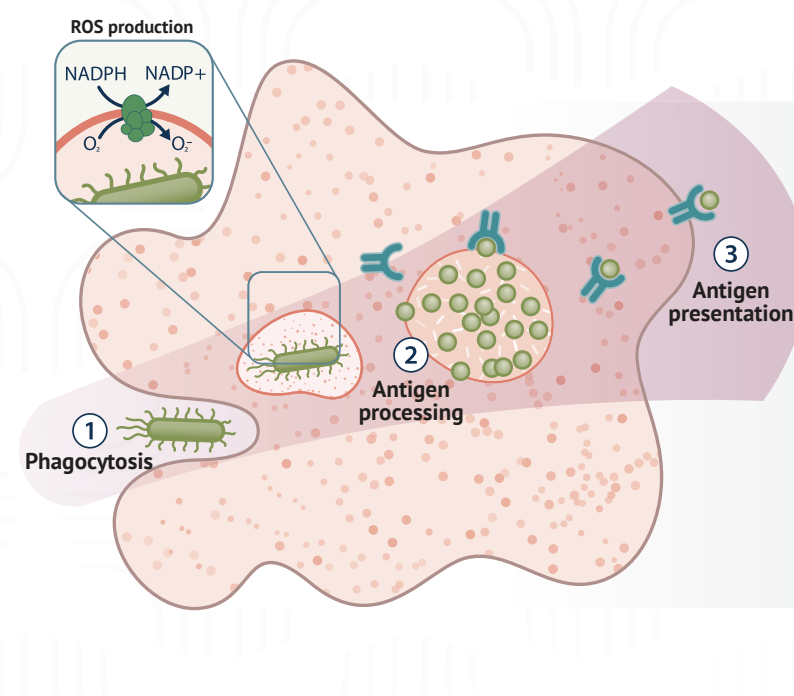
In patients with CGD, oxidative burst in phagocytes is inhibited due to a defect in the enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase¹

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 pathways⁹



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 system¹⁰
- 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.

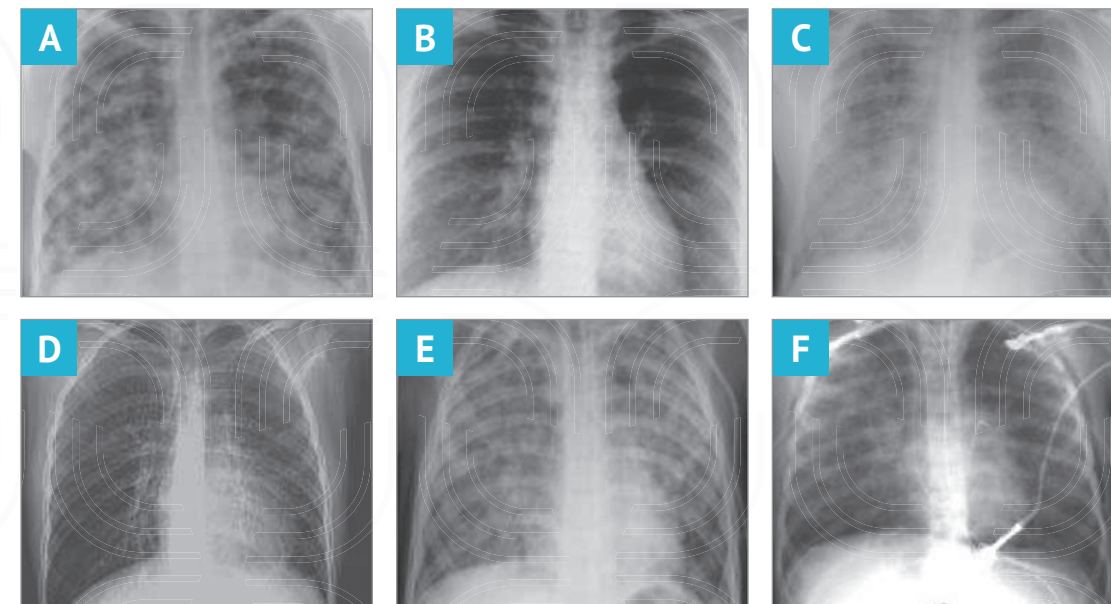


Pneumonia

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 thermoviolaceus*; (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

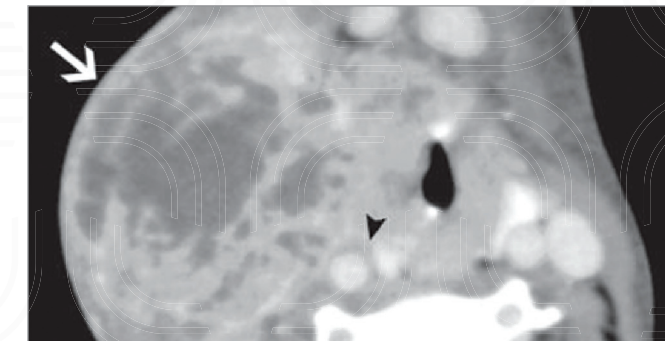


Lymphadenitis

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*



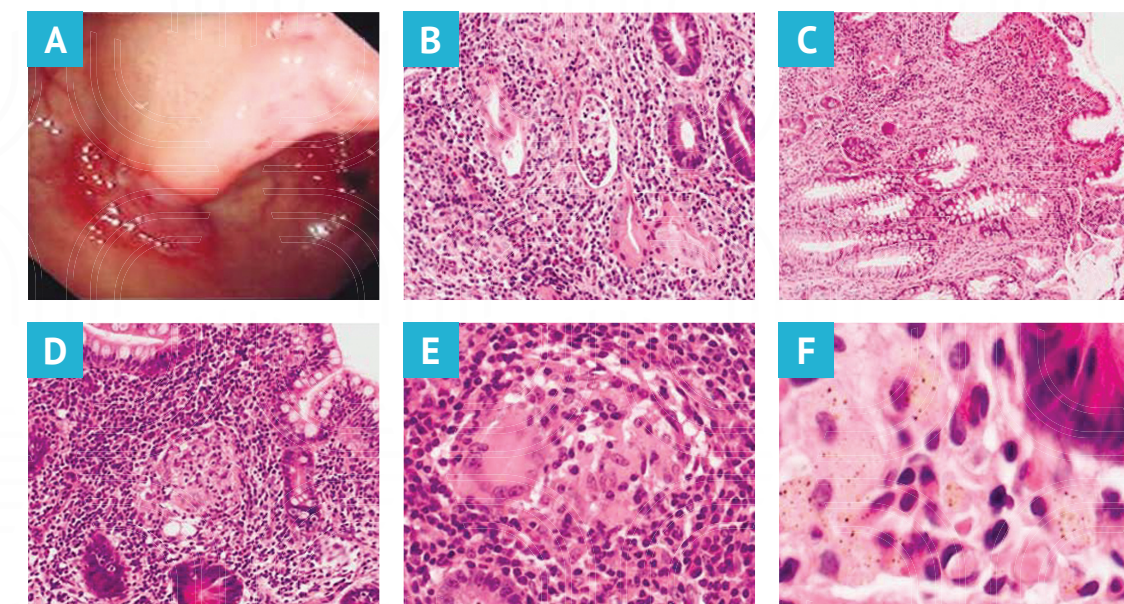
Adapted with permission from Khanna G, et al (2005).¹³



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.

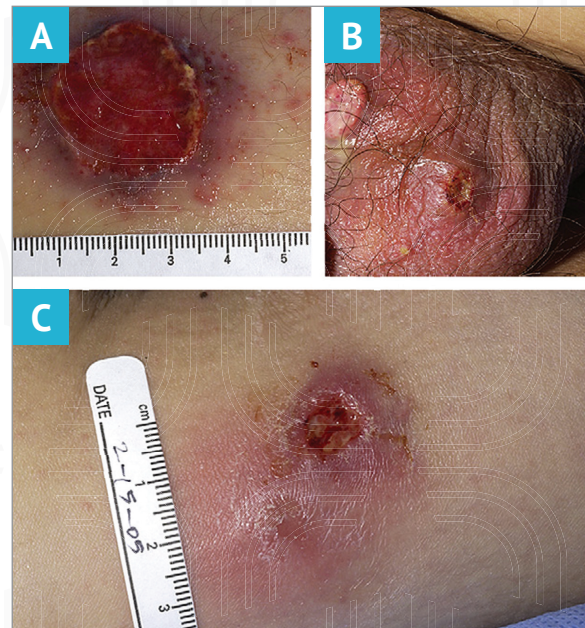


Adapted with permission from Marks DJ, et al (2009).¹⁴



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

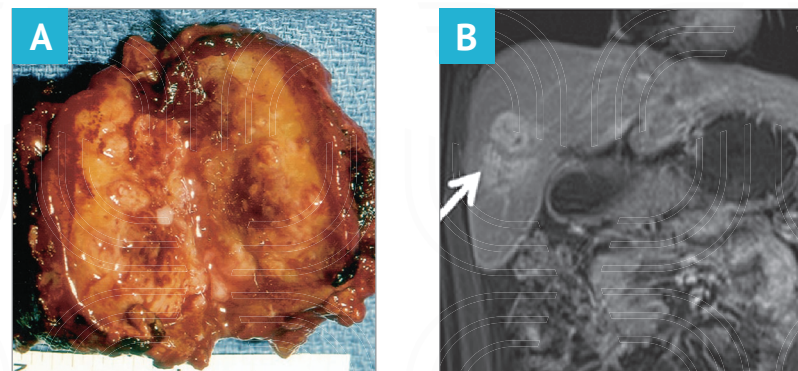


Hepatic abscess

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*



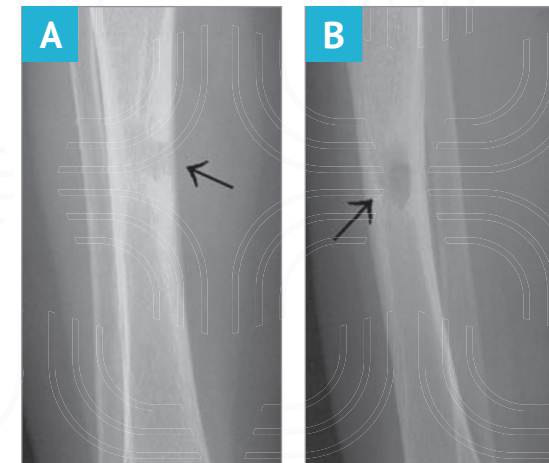
(A) Adapted with permission from Lublin M, et al (2002).¹⁶

(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:

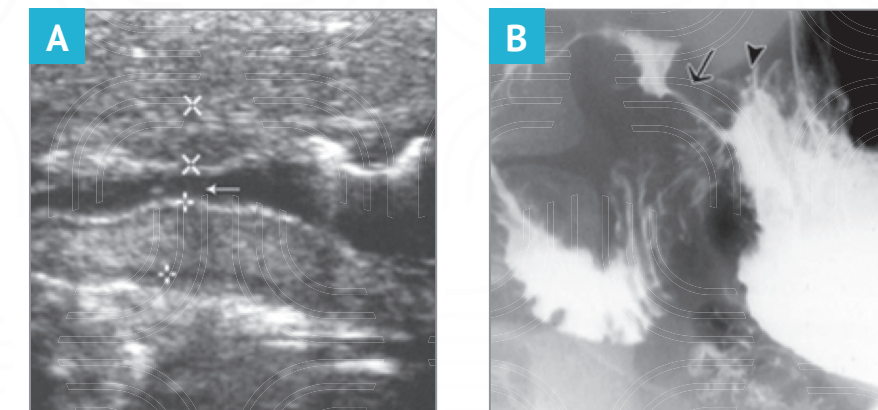
Aspergillus species, *Nocardia* species, *Serratia marcescens*, *Staphylococcus aureus*

Adapted with permission from Khanna G, et al (2005).¹⁵



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.



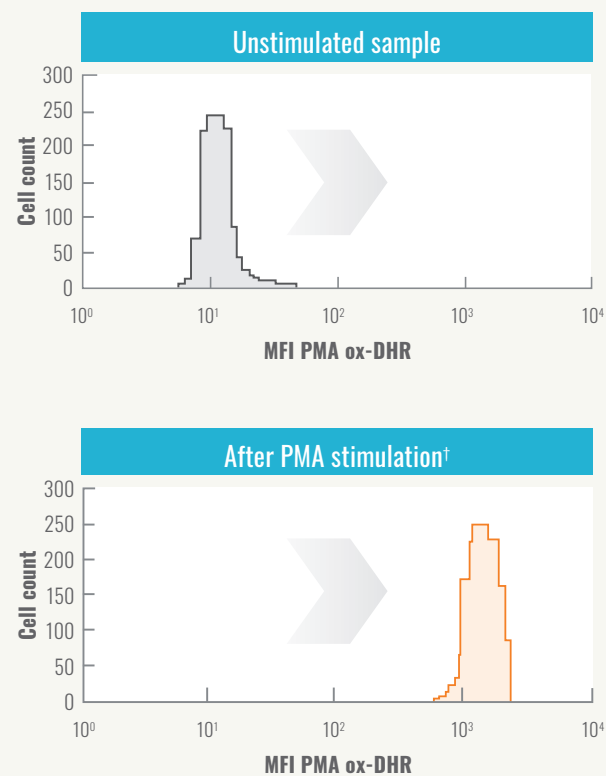
Adapted with permission from Khanna G, et al (2005).¹⁵

The DHR test is the preferred test for CGD

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

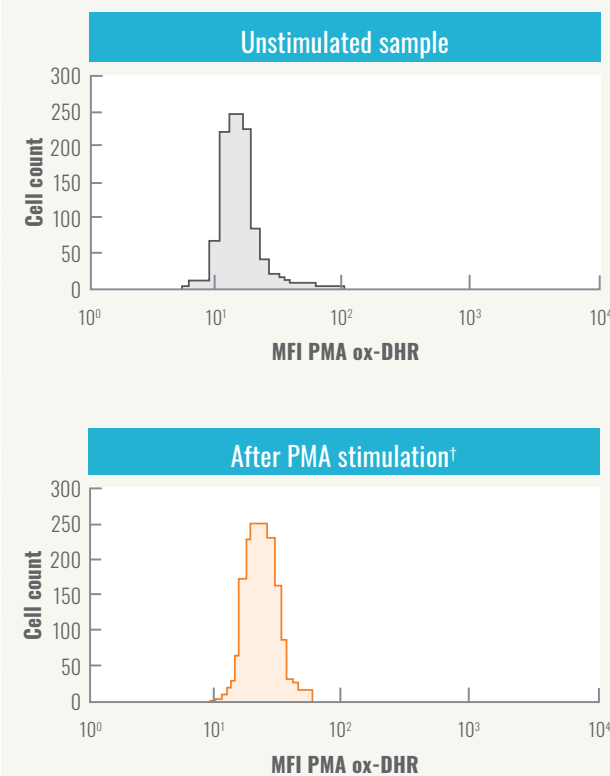
INDIVIDUAL WITHOUT CGD

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

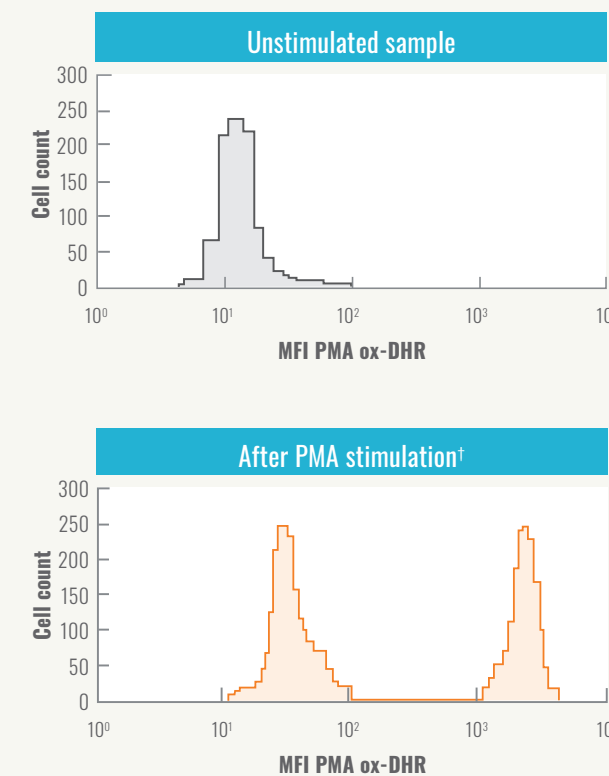
The histogram for the stimulated sample shows almost no shift along the x-axis, indicating an absence of neutrophil oxidative burst due to defective NADPH oxidase function.



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

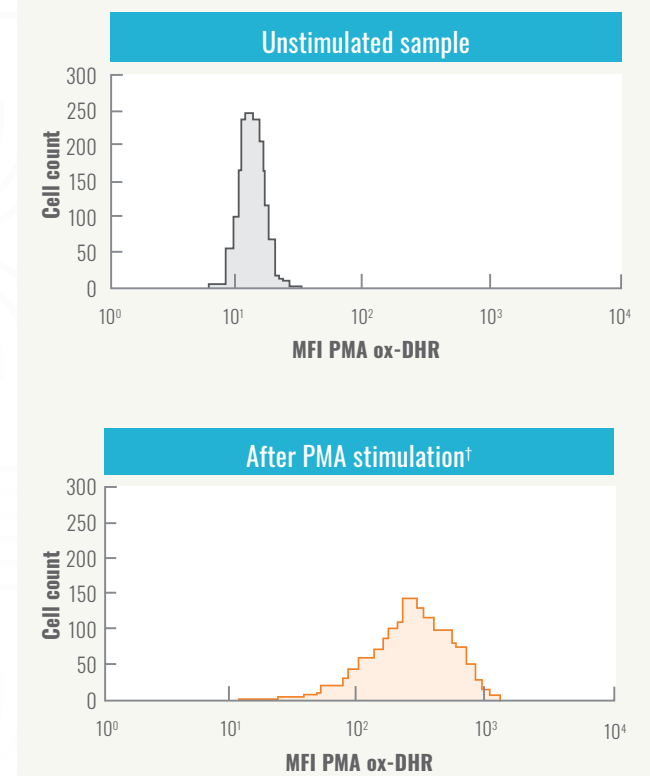
X-LINKED FEMALE CGD CARRIER‡

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.



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}.

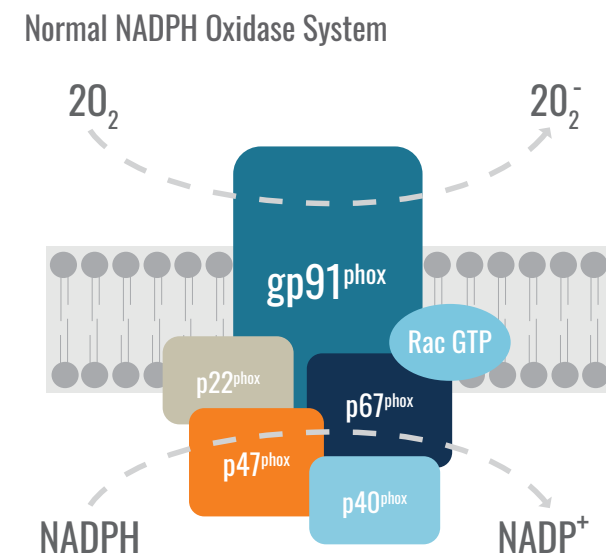
These values are representations of possible DHR outcomes. Because of heterogeneity in disease severity and genotype, outcomes will vary.

Identifying the genetic subtypes of CGD

NADPH oxidase system generates ROI involved in killing bacteria¹⁹⁻²³

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



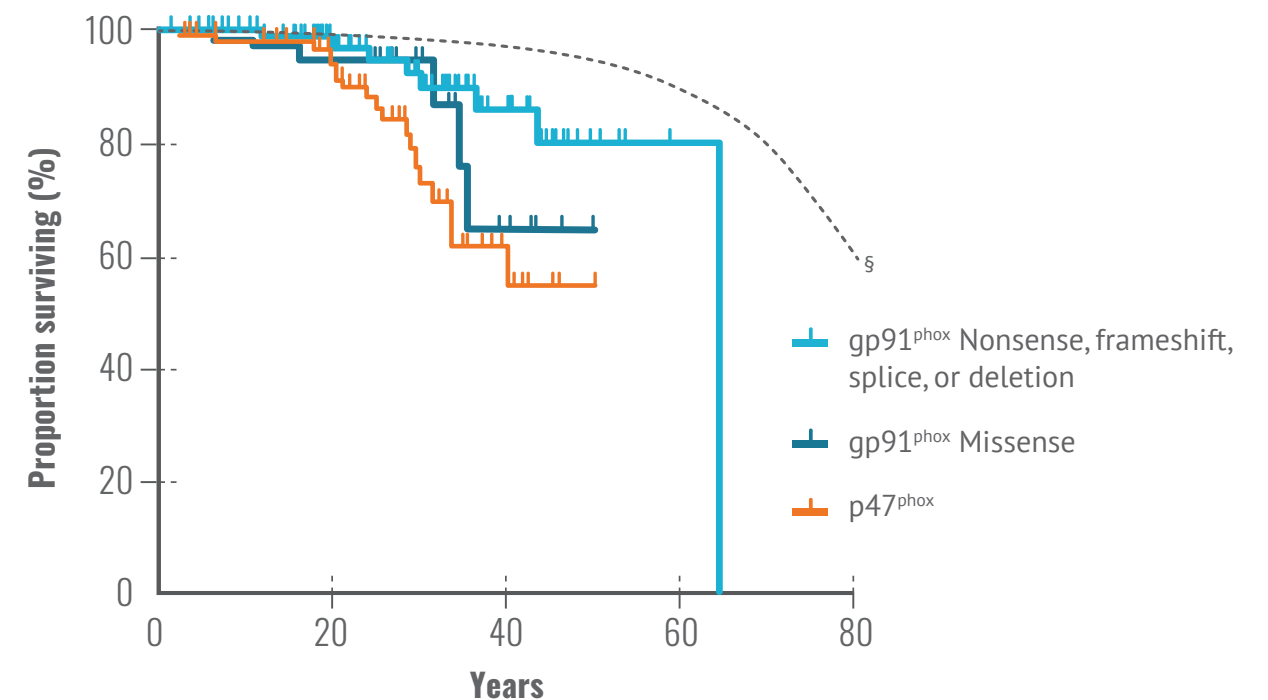
The gp91^{phox} mutation results in X-linked CGD, and the p47^{phox} mutation is the most common mutation in autosomal recessive CGD.^{1,20,23-25}

FREQUENCY OF NADPH OXIDASE SYSTEM GENE MUTATIONS

Subunit (gene)	Mode of inheritance	Frequency	Sex affected
gp91 ^{phox} (CYBB)	X-linked	65%–70% ^{1,19,20}	Male/rarely female
p47 ^{phox} (NCF1)	Autosomal recessive	20%–25% ^{1,19,20}	Male/female
p67 ^{phox} (NCF2)	Autosomal recessive	5%–6% ^{1,19,20}	Male/female
p22 ^{phox} (CYBA)	Autosomal recessive	3%–6% ^{1,19,20}	Male/female
p40 ^{phox} (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 mutation¹⁹

Even in cohorts where there is significant Residual Oxidative Intermediaries (ROI) production, survival is still far below that of the general population^{19,22}



¹⁹For 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 rates¹⁹

Combination immunomodulatory and antimicrobial prophylaxis therapy

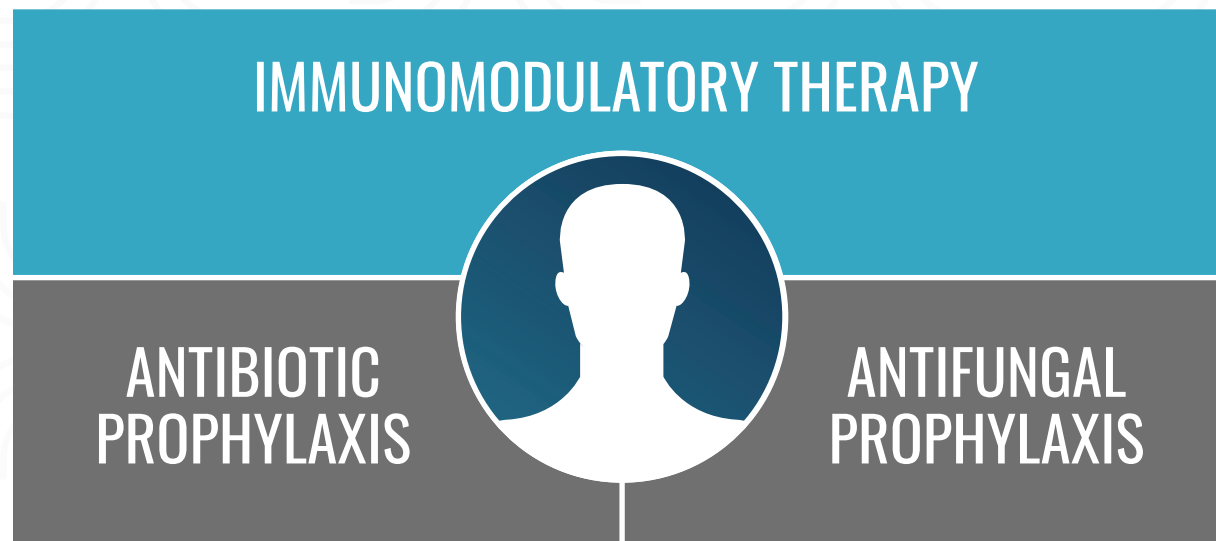
For the chronic medical management of CGD, immunomodulatory therapy in combination with prophylactic antimicrobials is recommended by the^{2,6}:

- 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

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