CHRONIC GRANULOMATOUS DISEASE (CGD)

Clinical Manifestations, Testing, and Management
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Chronic Granulomatous Disease

Frequent sites of infection
Pathogens that may indicate CGD
Infectious and inflammatory complications of CGD
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  Lymphadenitis
  Inflammatory bowel disease
  Skin and soft tissue abscesses
  Hepatic abscess
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Frequent, repeat infections
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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 potentially life-threatening infections. CGD may become apparent at any time from infancy to late adulthood; however, most affected individuals are diagnosed before age 5 years.¹

**CLINICAL MANIFESTATIONS**

Fungal infections associated with CGD:

- Aspergillus species
  - Pneumonia, lymphadenitis, osteomyelitis, brain abscess
- Candida species
  - Sepsis, soft tissue infection, liver abscess

Bacterial infections associated with CGD:

- 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

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

**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.¹⁷

**Most frequent pathogens and common presentations associated with CGD**

**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
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

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

Inflammatary 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 et al.
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 et al.11

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*

Adapted with permission from Lublin et al.12

Adapted with permission from Leiding et al.13

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 et al.9

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*

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 et al.9
Clinical Manifestations, Testing, and Management

Chronic Granulomatous Disease

Test for CGD with the preferred method

Historically, the nitroblue tetrazolium (NBT) test has been the recognized diagnostic test for CGD. Relying on light microscopy, the NBT test provides only a qualitative determination of phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity.

*The DHR test is also referred to as the neutrophil oxidative burst assay for assessing neutrophil superoxide production.1

The DHR test* produces fewer false-negative test results than the NBT test and is known for its:1,14

- Relative ease of use
- Ability to distinguish between X-linked (gp91phox) and autosomal recessive forms of CGD
- Ability to detect carrier status
- High sensitivity that can detect low levels of NADPH oxidase activity
- Ability to quantitatively assess residual superoxide production

DHR Collection Kits are being offered by Horizon at no cost

ABOUT THE DHR COLLECTION KIT

- Includes lab forms, labels, and shipping materials
- Blood samples for patient and healthy donor must be shipped within 24 to 36 hours of blood draw
- Test results will be sent by the testing facility to the ordering healthcare professional via fax within 2 to 3 days (including weekends) after being analyzed and processed
- Results will be provided along with an enhanced report and histogram

Information about DHR histograms can be found on pages 12 to 13.

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

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Examples and explanations of pre- and postactivation DHR histograms

What to look for when reading DHR histograms

**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.

**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.

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

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

Abbreviations: MFI, mean fluorescence intensity; PMA, phorbol myristate acetate.

Adapted from Leiding et al (2013) and Jirapongsananuruk et al.

PMA is an activator used to stimulate neutrophil NADPH oxidase activity.

Usually a female with a healthy and a mutated allele for gp91phox.

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Clinical Manifestations, Testing, and Management
**Combination immunomodulatory and antimicrobial prophylaxis therapy**

For the chronic medical management of CGD, immunomodulatory therapy in combination with prophylactic antimicrobials is recommended by the

- 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.

**MANAGEMENT**

†These steps do not include all the options for managing CGD.

For the chronic medical management of CGD, immunomodulatory therapy in combination with prophylactic antimicrobials is recommended by the

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

Without proper treatment, patients tend to have a higher rate of hospitalizations and potentially fatal infections.

**Help patients with CGD navigate their journey**

**DIAGNOSE**

When frequent, repeat, and severe infections from a specific group of pathogens present, order the DHR test to confirm a diagnosis of CGD.

**TREAT**

Use the triple therapy combination of immunomodulatory therapy and prophylactic antimicrobials recommended by the AAAAI, ACAAI, and IDF for the medical management of CGD.

**EDUCATE**

The risks are real. Inform patients about avoiding activities and areas with bacteria and fungi that could put them at risk for life-threatening infection. Schedule routine checkups to:

- Encourage compliance with medications
- Facilitate early detection and intervention of infections
- Continue educating your patients and their families

**ANTIBIOTIC PROPHYLAXIS**

Eg, trimethoprim/sulfamethoxazole

**ANTIFUNGAL PROPHYLAXIS**

Eg, itraconazole

**IMMUNOMODULATORY THERAPY**

Recommended chronic treatment paradigm

Adapted from Gallin et al.†

†These steps do not include all the options for managing CGD.

DHR testing for CGD is being offered at no cost. To order a DHR Collection Kit, visit DHRTestKit.com
References: