CHRONIC GRANULOMATOUS DISEASE (CGD)

Clinical Manifestations, Testing, and Management
Chronic granulomatous disease (CGD) is a primary immunodeficiency disorder of phagocytes that results from impaired killing of fungi and bacteria, which can lead to severe and recurrent infections. CGD may become apparent at any time from infancy to late adulthood; however, most affected individuals are diagnosed before age 5 years.¹ Approximately 1 out of every 200,000 people in the United States has CGD.²

**Most frequent sites of infection, common infectious complications, and common inflammatory complications¹**

- **Lymph nodes** (lymphadenitis)
- **Liver** (abscess)
- **Colon** (colitis)
- **Bone** (osteomyelitis)
- **Lung** (pneumonia)
- **Stomach** (gastrointestinal granulomas)
- **Urinary tract** (genitourinary granulomas)
- **Skin** (abscess or cellulitis)
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. Most severe infections in patients with CGD in North America are caused by a select group of organisms, both bacterial and fungal.1,3-8

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

<table>
<thead>
<tr>
<th><strong>FUNGAL</strong></th>
<th><strong>BACTERIAL</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspergillus species</strong>&lt;br&gt; <strong>COMMON PRESENTATION</strong>&lt;br&gt; Pneumonia, lymphadenitis, osteomyelitis, brain abscess</td>
<td><strong>Candida species</strong>&lt;br&gt; <strong>COMMON PRESENTATION</strong>&lt;br&gt; Sepsis, soft tissue infection, liver abscess</td>
</tr>
<tr>
<td><strong>Nocardia species</strong>&lt;br&gt; <strong>COMMON PRESENTATION</strong>&lt;br&gt; Pneumonia, osteomyelitis, brain abscess</td>
<td><strong>Klebsiella species</strong>&lt;br&gt; <strong>COMMON PRESENTATION</strong>&lt;br&gt; Pneumonia, skin infections, lymphadenitis</td>
</tr>
<tr>
<td><strong>Serratia marcescens</strong>&lt;br&gt; <strong>COMMON PRESENTATION</strong>&lt;br&gt; More common: osteomyelitis, soft tissue infection&lt;br&gt; Less common: pneumonia, sepsis</td>
<td><strong>Staphylococcus aureus</strong>&lt;br&gt; <strong>COMMON PRESENTATION</strong>&lt;br&gt; Soft tissue infections, lymphadenitis, liver abscess, perirectal abscess, osteomyelitis, pneumonia, sepsis</td>
</tr>
<tr>
<td><strong>Burkholderia (pseudomonas) cepacia complex</strong>&lt;br&gt; <strong>COMMON PRESENTATION</strong>&lt;br&gt; Pneumonia, sepsis</td>
<td></td>
</tr>
</tbody>
</table>

*This is not a complete list of pathogens. Infections may also be caused by other species of bacteria and fungi not listed here.*
**THE DHR TEST IS THE PREFERRED TEST FOR CGD**

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 NBT test is also open to operator subjectivity and can produce false-negative results.

The dihydrorhodamine (DHR) test* is the preferred method for diagnosing CGD because it produces fewer false-negative test results than the NBT method. The DHR test is known for its:1-9:

- Relative ease of use
- Objectivity without requiring significant operator experience
- Ability to distinguish between X-linked and autosomal recessive forms of CGD
- Ability to detect gp91phox carriers
- High sensitivity
- Ability to quantitatively assess residual superoxide production

*The DHR test is also referred to as the neutrophil oxidative burst (NOXB1) assay for assessing neutrophil superoxide production.10

**Examples of pre- and postactivation DHR histograms**

**NORMAL**

In a normal individual, neutrophils respond to the stimulus, meaning the cells are functioning.

**TYPICAL X-LINKED CGD CARRIER**

In an X-linked patient with CGD, cells do not respond to the stimulus, meaning they are not functioning as they should. If they do not respond to the stimulus, then they also don’t respond to specific bacteria and fungi, suggesting an immune deficiency.

**AUTOSOMAL RECESSIVE PATIENT WITH CGD**

An autosomal recessive patient with CGD demonstrates a reduced response to the stimulus. Both males and females can present with autosomal recessive CGD.

| Abbreviations:  |
| MFI, mean fluorescence intensity; PMA, phorbol myristate acetate. |
| Adapted from Leiding et al (2013)7 and Jirapongsananuruk et al.11 |
| *PMA is an activator used to stimulate neutrophil NADPH oxidase activity. |
| *Usually a female with a healthy and a mutated allele for gp91phox. |
| *The DHR test is also referred to as the neutrophil oxidative burst (NOXB1) assay for assessing neutrophil superoxide production.10 |

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**X-linked CGD patient**

Before stimulation

![Cell count graph before stimulation](image)

After PMA stimulation

![Cell count graph after PMA stimulation](image)

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>VALUE (PATIENT)</th>
<th>UNIT</th>
<th>NORMAL CUTOFF</th>
<th>VALUE (UNRELATED HEALTHY DONOR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC</td>
<td>4,235</td>
<td>Cell/μL</td>
<td>1,700-7,000*</td>
<td>5,987</td>
</tr>
<tr>
<td>% PMA ox-DHR+</td>
<td>4.1</td>
<td>%</td>
<td>≥ 95%</td>
<td>100.0</td>
</tr>
<tr>
<td>MFI PMA ox-DHR+</td>
<td>6.73</td>
<td>MFI</td>
<td>≥ 60</td>
<td>78.25</td>
</tr>
</tbody>
</table>

Abbreviations: ANC, absolute neutrophil count; FITC, fluorescein isothiocyanate; MFI, mean fluorescence intensity; PMA, phorbol myristate acetate.

**Results:** Result is consistent with associated X-linked CGD in a male patient.

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**Autosomal recessive CGD patient**

Before stimulation

![Cell count graph before stimulation](image)

After PMA stimulation

![Cell count graph after PMA stimulation](image)

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>VALUE (PATIENT)</th>
<th>UNIT</th>
<th>NORMAL CUTOFF</th>
<th>VALUE (UNRELATED HEALTHY DONOR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC</td>
<td>2,743</td>
<td>Cell/μL</td>
<td>1,700-7,000*</td>
<td>5,987</td>
</tr>
<tr>
<td>% PMA ox-DHR+</td>
<td>53.8</td>
<td>%</td>
<td>≥ 95%</td>
<td>100.0</td>
</tr>
<tr>
<td>MFI PMA ox-DHR+</td>
<td>31.54</td>
<td>MFI</td>
<td>≥ 60</td>
<td>78.25</td>
</tr>
</tbody>
</table>

Abbreviations: ANC, absolute neutrophil count; FITC, fluorescein isothiocyanate; MFI, mean fluorescence intensity; PMA, phorbol myristate acetate.

**Results:** Result is consistent with associated autosomal recessive CGD in a female patient.

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*The appropriate age-related reference values for absolute neutrophil count will be provided on the report.

These values are representations of possible DHR outcomes. Because of heterogeneity in disease severity and genotype, outcomes will vary.
REQUEST INFORMATION ABOUT THE DHR COLLECTION KIT

To help ensure appropriate patients are diagnosed, Horizon Pharma is sponsoring the DHR Collection Kit. The kit is:

- Easy to use: It includes labeling and shipping materials for the sample
- Easy to process: Comprehensive test results will be sent via fax, including a link to an enhanced report and histogram

The DHR Collection Kit includes:

- LABORATORY REQUISITION FORM
- SAMPLE VIALS AND LABELS
- SHIPPING MATERIALS

To learn more about the DHR test, visit CGDPathways.com or contact your Horizon Clinical Science Associate.
Combination Immunomodulatory and Antimicrobial Prophylaxis Therapy*

For the chronic medical management of CGD, the American Academy of Allergy, Asthma & Immunology; the American College of Allergy, Asthma & Immunology; and the Immune Deficiency Foundation recommend immunomodulatory therapy in combination with prophylactic antimicrobials. For the treatment of active infections, they recommend using appropriate antimicrobials based on pathogen likelihood or identification.3,7

Recommended chronic treatment paradigm12,13

*This does not include all options for managing CGD. Adapted from Gallin et al.11
TEST AND DIAGNOSE

Test patients presenting with unusual infections in unusual places to help diagnose a possible immune deficiency, including CGD.

ADVOCATE COMBINATION THERAPY

Reinforce to your CGD patients the importance of adherence to prescribed medications to reduce the frequency and severity of serious infections.

COUNSEL CAUTION

Educate patients about making careful lifestyle choices to avoid activities and areas with bacteria, fungi, or yeasts that could put them at risk for serious infection. Encourage patients to schedule routine checkups to facilitate early intervention when necessary.

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

References: