Treating Patients with Chronic Granulomatous Disease for Over 35 Years

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What Is CGD?

• Rare, inherited, primary immunodeficiency disorder of phagocytes that results from impaired killing of fungi and bacteria and is characterized by\textsuperscript{1,2}:
  – **Severe, recurrent, and life-threatening** infections
  – Formation of granulomas in tissue
  – Inflammatory diseases (eg, colitis, inflammatory lung disease)

• **Caused by mutations in the NADPH oxidase system**, which delays immune response\textsuperscript{1}

• **Types of Chronic Granulomatous Disease (CGD)**\textsuperscript{1,3,4}
  – **X-linked CGD**: Most common type of the disease involving a mutation of the CYBB gene and almost always affects males
  – **Autosomal recessive CGD**: Mutations in the CYBA, NCF1, NCF2, CYBC1, or NCF4 genes
  – **X-linked carriers**: Mothers of boys with X-linked CGD, with up to 23% of carriers experiencing significant infections


**Common signs/symptoms of CGD**

GI, gastrointestinal; NADPH, nicotinamide adenine dinucleotide phosphate.
How to Test for CGD?

**DHR Is the Preferred Test to Confirm CGD Diagnosis**

- **Dihydrorhodamine (DHR)** is the standard diagnostic test, which relies on the measurement of neutrophil superoxide production via the NADPH oxidase complex\(^1\)\(^-\)\(^3\)
  - Can distinguish X-linked and autosomal recessive forms of CGD and carriers
- **Diagnosis** can also be established with **genetic testing**\(^1\)
  - Can help with managing disease and confirming abnormal or inconclusive DHR results
- **Genetic testing for family members is important** in order to help identify carriers and patients with CGD before a serious infection* occurs\(^3\)

Visit [www.dhrtestkit.com](http://www.dhrtestkit.com) to order a DHR testing kit

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

*Serious infection is defined as a clinical event requiring hospitalization and intravenous antibiotics.

How to Treat CGD?

Triple Prophylaxis Is the Recommended Approach to Reduce the Rate of Infections*1-4

Interferon gamma-1b

- In healthy cells, interferon gamma was observed to enhance innate immunity and secondary immune responses through†,5
  - Enhancing other mechanisms of macrophages
  - Augmenting antibody-dependent cellular cytotoxicity and promoting expression of Fc receptors and MHC antigens
  - Activating NK cells
- Does not increase phagocyte superoxide production, even in treatment responders

Antibiotic therapy

- Reduces the rate of serious bacterial infections‡ from1,3
  - Staphylococcus aureus
  - Burkholderia cepacia complex
  - Klebsiella species
  - Nocardia species
  - Serratia marcescens

Antifungal therapy

- Reduces the rate of serious infections‡ from environmental fungi, such as1,2,6
  - Aspergillus species, the leading cause of fungal infections in patients with CGD
  - Various yeast species (i.e., Trichophyton, Trichosporon, Candida)

Recommended By:

MHC, major histocompatibility complex; NK, natural killer.

*Not all options for managing CGD are shown.
†The exact mechanism of action of interferon gamma-1b in CGD is unknown.5
‡Serious infection is defined as a clinical event requiring hospitalization and intravenous antibiotics.5

1965
- First hospital admission for multiple *Staphylococcus aureus* abscesses
- Metacarpal osteomyelitis with paracolon *Hafnia*

1966
- Calcaneus osteomyelitis with *Klebsiella*

1966
- Calcaneus osteomyelitis with *Klebsiella*

1971-1972
- Surgeries for two *Staphylococcus epidermidis* liver abscesses
- Started on antibacterial prophylaxis with TMP-SMX

1975-1976
- Lymphadenitis with *Enterobacter agglomerans*
- Pulmonary aspergillosis due to hay exposure

1977-1979
- Surgical drainage for two liver abscesses
- Aphthous oral ulceration

1980-1981
- Inguinal epididymitis with *Staphylococcus aureus*
- Perirectal fistula and pyelonephritis after ureteropelvic junction obstruction/ureteral granuloma

1983-1987
- Multiple lymphadenitis with *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Streptococcus intermedius*
- Severe nodulocystic acne
- Nephrectomy for hydronephrosis and liver abscess with WBC transfusions
- Perianal abscess with *Streptococcus intermedius*

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1990
- Coombs-positive hemolytic anemia
- Neck lymph node *Aspergillus terreus*

1993
- Pneumococcal pneumonia
- Started on antifungal prophylaxis with itraconazole

1994
- *Propionibacterium acnes* submandibular abscess
- Had suffered hearing loss and tinnitus from aminoglycoside medications

Note: This case study is the experience of one individual, and results may vary.

TMP-SMX, trimethoprim-sulfamethoxazole; WBC, white blood cell.
Relevant medical and family history

• Seemingly normal, healthy 2-week-old male
  – No infections or other signs/symptoms of CGD
• Parents requested testing for CGD, given family history
  – Patient’s mother was diagnosed as an X-linked carrier of CGD
• X-linked CGD diagnosis was confirmed via DHR and genetic testing results
  – Histogram and quantitative measurement of oxidative burst were unavailable

Treatment plan and outcomes

• Patient was prescribed TMP-SMX at 4 weeks of age and itraconazole at 3 months of age
  – Interferon gamma-1b was later added to the treatment regimen
  – Assessed every 6 months for signs of inflammation (ESR, CBC, liver panel) per the label for patients <1 year of age
  – Within the 8 years following CGD diagnosis, he experienced minor infections, but none required hospitalization

Today, patient has continued triple prophylaxis and has had normal growth and development, and is co-managed by primary pediatrician and pediatric infectious disease specialist.

Note: This case study is the experience of one individual, and results may vary.

CBC, complete blood count; ESR, erythrocyte sedimentation rate.
Key Points

- CGD is a chronic, rare disorder that is characterized by **severe, recurrent, and life-threatening infections**
- **DHR and genetic testing** can help diagnose CGD before a patient experiences repeated life-threatening infections
  - Family genetic testing can identify potentially undiagnosed or misdiagnosed relatives
- **Triple prophylaxis with interferon gamma-1b, an antibiotic, and an antifungal is recommended** to reduce the serious infections* related to CGD
  - Interferon gamma-1b enhances the microbicidal potential of innate immune response and promotes induction of secondary immune response

*Serious infection is defined as a clinical event requiring hospitalization and intravenous antibiotics.
Thank You for Your Attention. Any Questions?
Disclosure

• This speaker is being compensated for this presentation as a member of the Horizon Therapeutics Speaker Bureau
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Objectives

• Understand how to identify and diagnose CGD
• Discuss the role of triple prophylaxis in the management of patients with CGD
• Explore how family testing supports early diagnosis of X-linked CGD