Treating Patients with Chronic Granulomatous Disease for Over 35 Years

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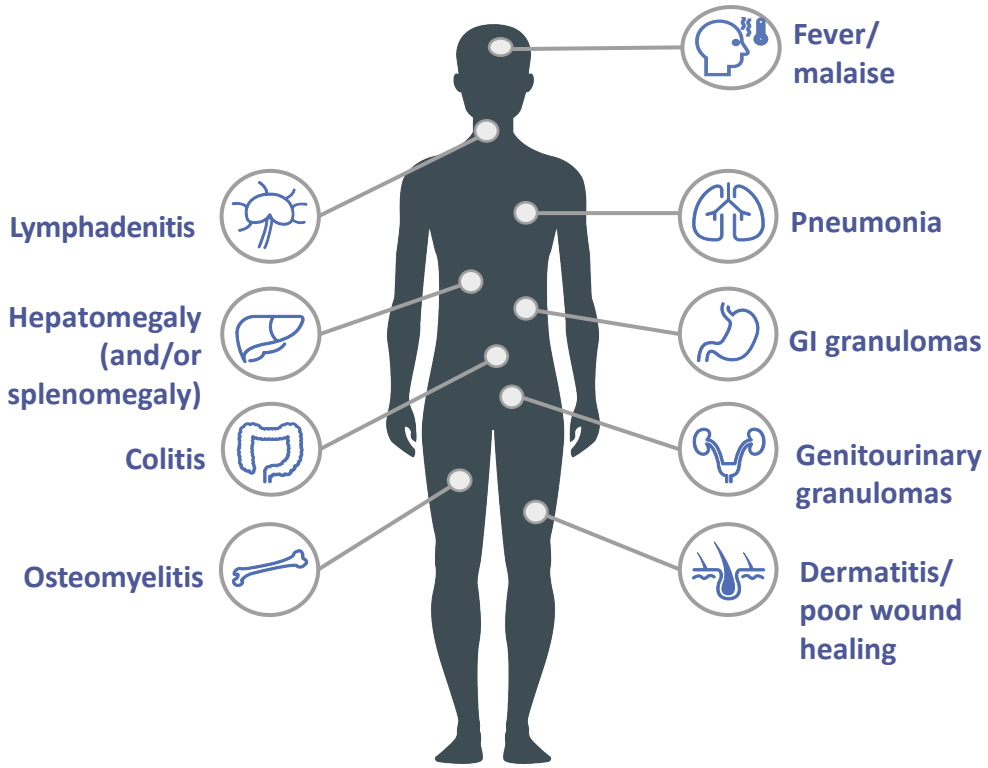
What Is CGD?

- Rare, inherited, primary immunodeficiency disorder of phagocytes that results from impaired killing of fungi and bacteria and is characterized by[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[1]
- **Types of Chronic Granulomatous Disease (CGD)[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.

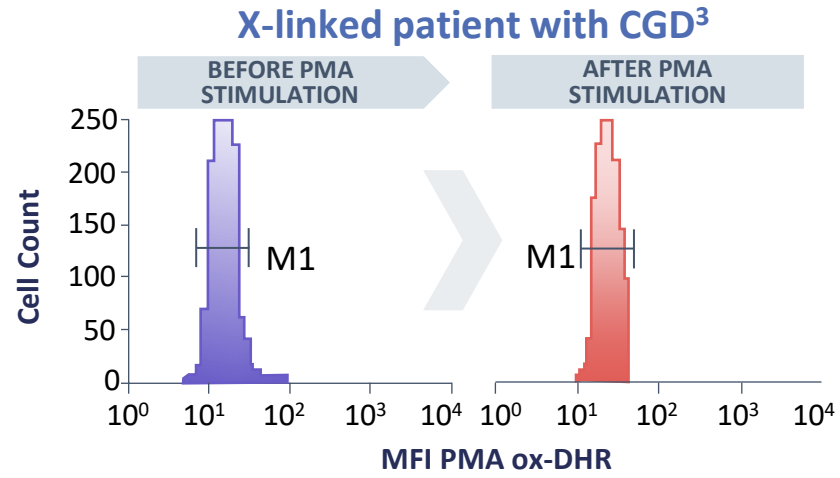
References: 1. Leiding JW, Holland SM. 2012 Aug 9 [Updated 2016 Feb 11]. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews®* [Internet]. University of Washington, Seattle; 1993-2020. 2. Thomsen IP, et al. *J Allergy Clin Immunol Pract*. 2016;4(6):1082-1088. 3. NORD. Chronic granulomatous disease. Accessed September 14, 2022. https://rarediseases.org/rare-diseases/chronic-granulomatous-disease/ 4. Battersby AC, et al. *J Allergy Clin Immunol*. 2017;140(2):628-630e6.

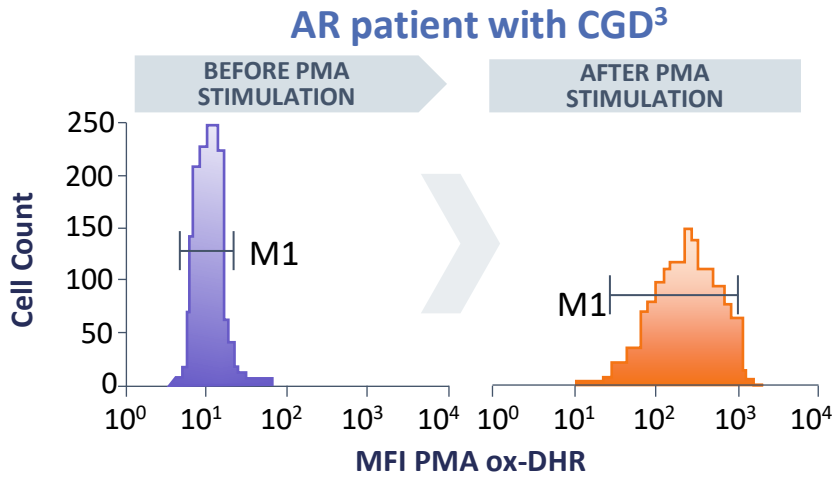
How to Test for CGD?

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** to order a DHR testing kit





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

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

References: 1. Leiding JW, Holland SM. 2012 Aug 9 [Updated 2016 Feb 11]. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews®* [Internet]. University of Washington, Seattle; 1993-2020. 2. Jirapongsananuruk O, et al. *J Allergy Clin Immunol*. 2003;111(2):374-379. 3. Yu JE, et al. *J Pediatric Infect Dis Soc*. 2018;7(suppl 1):S6-S11.

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‡ from[1,3]
  - *Staphylococcus aureus*
  - *Burkholderia cepacia* complex
  - *Klebsiella* species
  - *Nocardia* species
  - *Serratia marcescens*

Antifungal therapy

- Reduces the rate of serious infections‡ from environmental fungi, such as[1,2,6]
  - *Aspergillus* species, the leading cause of fungal infections in patients with CGD
  - Various yeast species (ie, *Trichophyton, Trichosporon, Candida*)

Recommended By:

American Academy of Allergy Asthma & Immunology www.aaaai.org

American College of Allergy, Asthma & Immunology

JCAAI Joint Council of Allergy, Asthma & Immunology

Immune Deficiency Foundation

IDSA Infectious Diseases Society of America

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]

References: 1. Bonilla FA, et al. *J Allergy Clin Immunol*. 2015;136(5):1186-1205.e1-78. 2. Gallin JI, et al. *N Engl J Med*. 2003;348(24):2416-2422. 3. Thomsen IP, et al. *J Allergy Clin Immunol Pract*. 2016;4(6):1082-1088. 4. Patterson TF, et al. *Clin Infect Dis*. 2016;63(4):e1-e60. 5. ACTIMMUNE (Interferon gamma-1b) [prescribing information] Horizon. 6. Slack MA, Thomsen IP. *J Pediatric Infect Dis Soc*. 2018;7(suppl 1):S25-S30.

Patient CASE #1

CGD Patient Treatment and Journey Have Evolved Over Time

1960

BIRTH
1962
Male with X-linked CGD

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

1966
- Calcaneus osteomyelitis with *Klebsiella*

1970

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

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*

1990

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

1993
- Pneumococcal pneumonia
- **Started on antifungal prophylaxis with itraconazole**

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

DEATH
1995
Age 33 due to a motor vehicle accident

Note: This case study is the experience of one individual, and results may vary.
TMP-SMX, trimethoprim-sulfamethoxazole; WBC, white blood cell.

Patient CASE #2

CGD Patient Treatment and Journey Have Evolved Over Time

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
- This presentation is sponsored by Horizon Therapeutics

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