Goals of Therapy for WHIM Syndrome (a Chronic Neutropenic Disorder)

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Resource Information

About This Resource

These slides are one component of a continuing education program available online at MedEd On The Go titled WHIM Syndrome (A Chronic Neutropenic Disorder): Uncouple the Complex for HCPs and Patients

Program Learning Objectives:

- Gain an understanding of WHIM syndrome as a rare PID/ chronic neutropenic disorder with diverse clinical presentations
- Implement strategic measures to improve the early identification of WHIM syndrome patients for prompt assessment and diagnosis to avoid potential complications and long-term sequelae
- Understand the CXCR4 pathway dysregulation and how it relates to the underlying causes of WHIM syndrome
- Garner an understanding of the limitations of current approaches for WHIM syndrome and potential new approaches for patients

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Why Are Neutrophils Important?

A: Neutrophils are one of the first cells that respond to infectious pathogens like bacteria

- Rapid mobilization and migration from the bone marrow
- Release cytotoxic granules to kill bacteria
- Phagocytosis of opsonized bacteria
- NADPH oxidase-derived ROS for intracellular killing
- NETosis - extracellular traps formed by DNA fibers and proteins from the granules

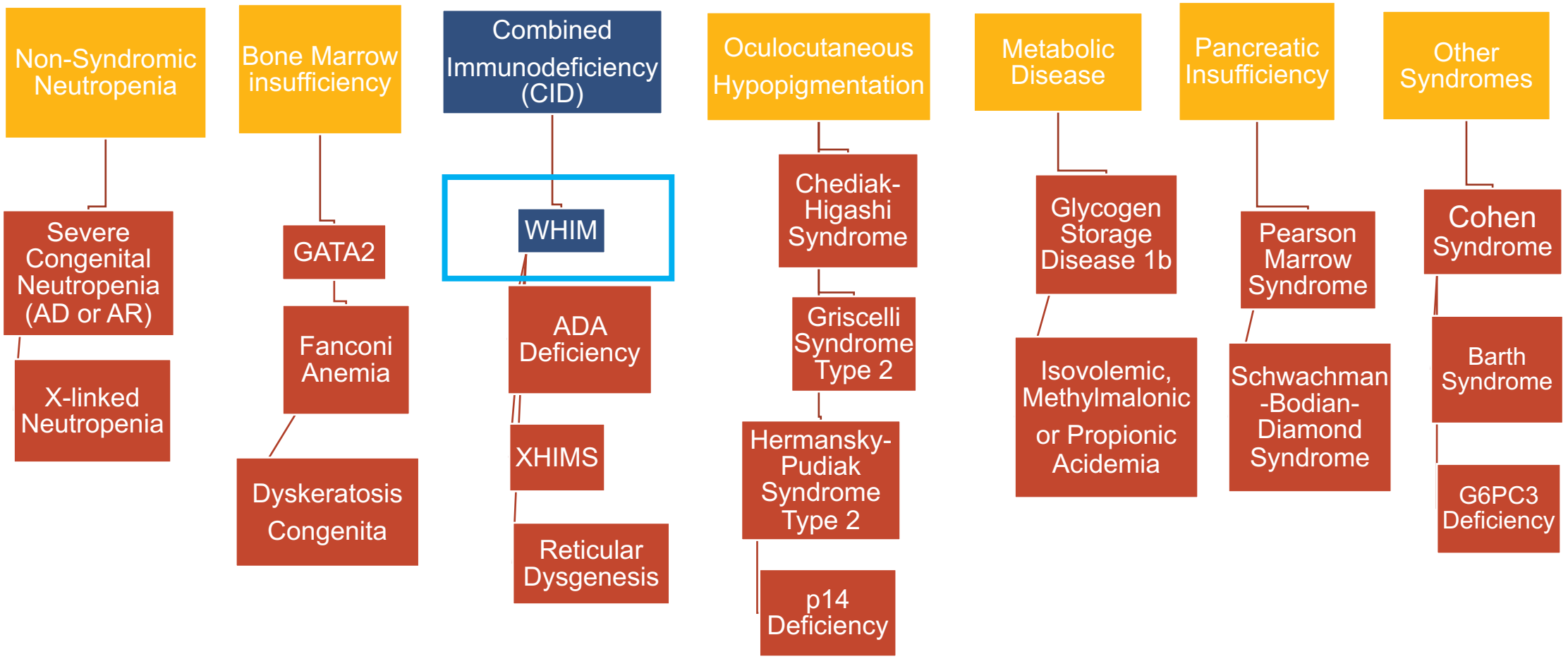
ROS, reactive oxygen species.

What is Congential Neutropenia?

A: Typically due to a bone marrow maturation arrest in the myeloid lineage

- **Multiple etiologies:**
  - Inborn errors of immunity
  - Complex inherited syndromic diseases
  - Metabolic
  - Idiopathic

Congenital Neutropenia



WHIM, Warts, Hypogammaglobulinemia, Infections, and Myelokathexis.

WHIM Syndrome Is an Inborn IEI Autosomal Dominant Gain of Function in *CXCR4*

WHIM Syndrome Clinical Hallmarks

Warts

- Increase in susceptibility to HPV infections
- Manifestations include cutaneous and anogenital warts

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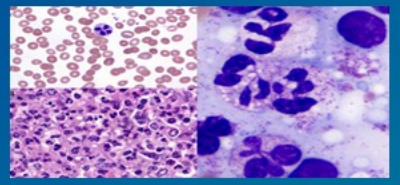
Hypogammaglobulinemia

- May present with low levels of IgG, IgA, and/or IgM
- Associated with impaired isotype switching and defects in B-cell maturation and function
- Immunoglobulin replacement therapy is used in approximately 45% of patients with WHIM syndrome

Myelokathexis

- Retention of neutrophils in the bone marrow
- Clinical features include neutropenia, lymphopenia, and monocytopenia[6,7]



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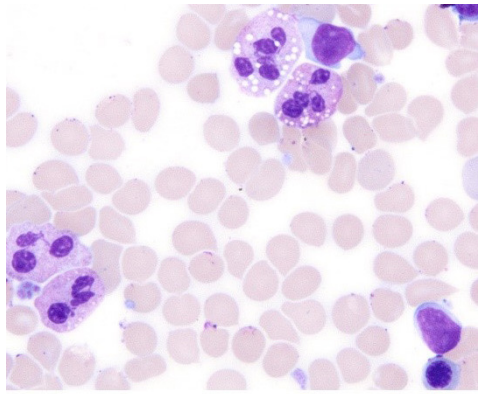
Infections

- Increase in infections owing to dysfunctional or low levels of circulating B-cells, T cells, or neutrophils
- Infections of the ear, skin, oral cavity, and sinopulmonary tract are common

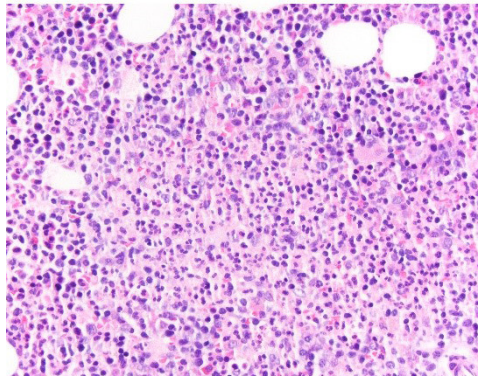
- Not all patients present with the 4 characteristics of WHIM syndrome at any given time
- Many patients experience additional manifestations of disease

EIE, error of immunity.

WHIM Syndrome – Myelokathexis and Neutropenia

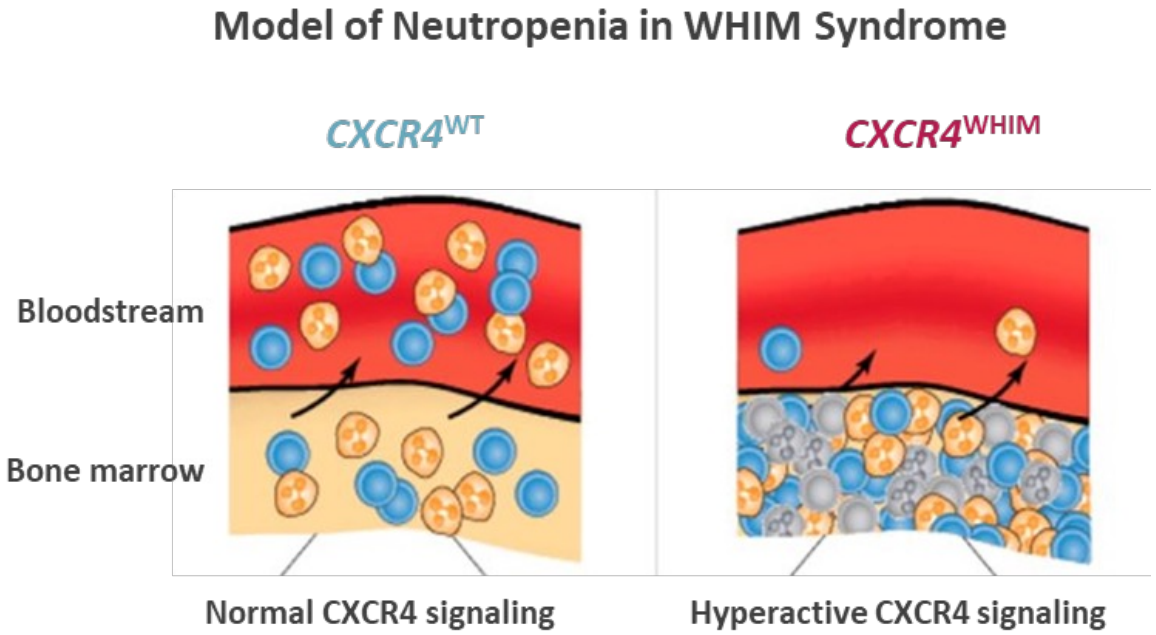


Thin chromatin strands connecting abnormal lobes and vacuoles



Hypercellular marrow

Permission by Jacob Bledsoe



There Are No FDA-Approved Medications for WHIM Syndrome

Current treatments:

- Symptomatic, not targeted
- Preventive treatment for HPV-associated infections and cancers

Symptomatic Management of WHIM Syndrome	
Category of therapeutics	**Role in the management of WHIM syndrome**
Antibiotics	• May attenuate the risk of exacerbations • Low-dose macrolides and inhaled aminoglycosides may reduce risk of bronchiectasis exacerbations
Antivirals	• Effective against recurrent herpes infections
Immunoglobulins	• May reduce incidence of recurrent infections • No well-controlled studies documenting efficacy in WHIM syndrome • Not approved by FDA specifically for WHIM syndrome
G-CSFs	• Used to increase levels of circulating neutrophils • No well-controlled studies documenting efficacy in WHIM syndrome • Not approved by FDA specifically for WHIM syndrome
Vaccine	• Early vaccination with HPV vaccine may prevent certain HPV infections and reduce HPV related cancers • Require periodic revaccination • More research is needed to determine the role of HPV vaccination in the treatment for WHIM syndrome

FDA, Food and Drug Administration; G-CSFs, granulocyte colony-stimulating factors; HPV, human papillomavirus; Ig, immunoglobulin.

Heusinkveld LE, et al. *Expert Opin Orphan Drugs*. 2017;5(10):813-825; McDermott DH & Murphy PM. *Immunol Rev*. 2019;287(1):91-102; Wabiko H, et al. *J Bacteriol*. 1988;170(6):2705-10; Badolato R & Donadieu J. *Blood*. 2017;130(23):2491-2498; National Organization for Rare Disorders. WHIM syndrome. 2024; Bonilla FA, et al. *J Allergy Clin Immunol*. 2015;136(5):1186-205.

Summary

- Help treat symptomatic infections as they arise
- Prevent HPV infections when possible
- Use immunoglobulin replacement therapy to protect patients from infectious complications

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