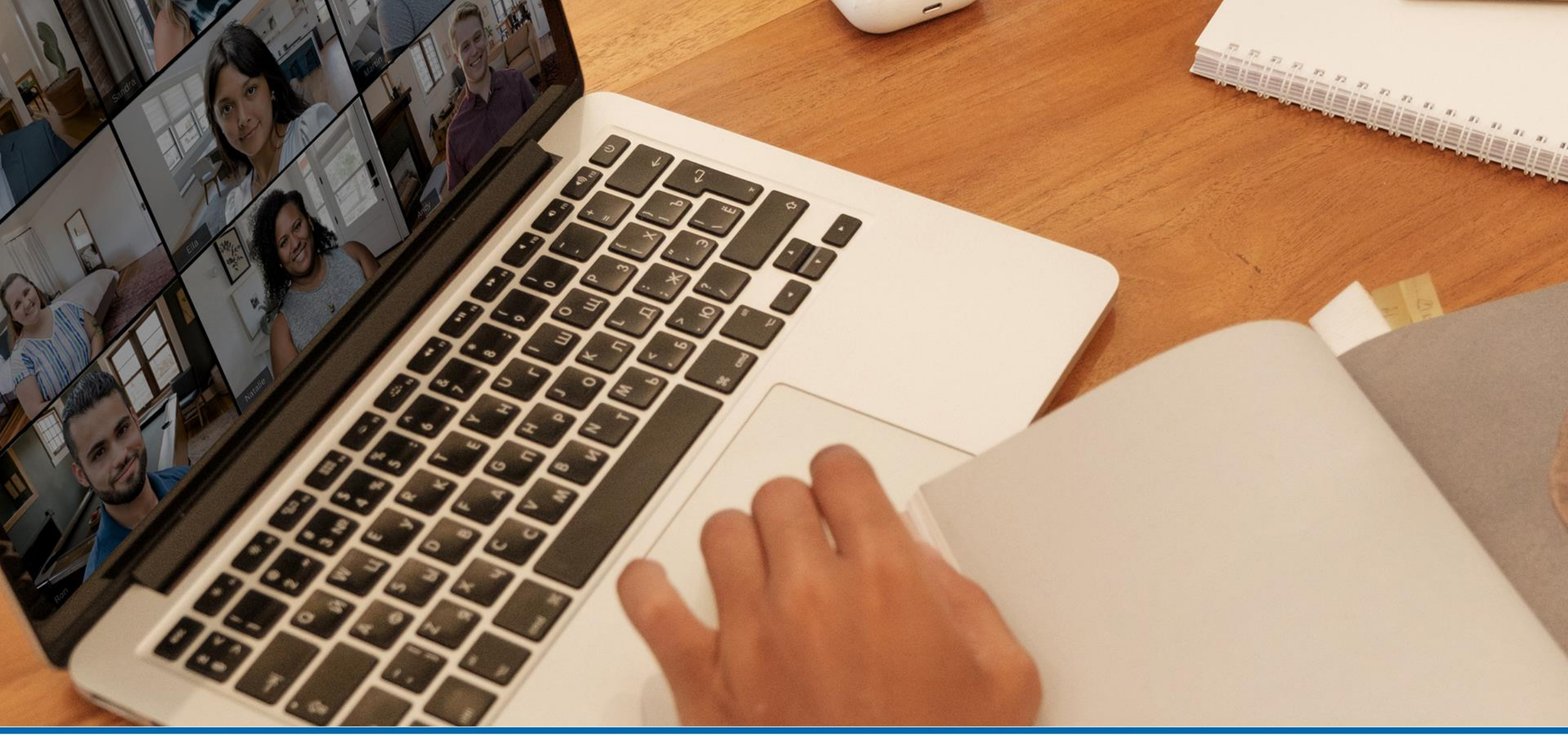
Welcome!

Thank you for joining us!
The webinar will begin shortly.

Immune Deficiency Foundation



Immune Deficiency Foundation

Lunch & Learn: Chronic Neutropenia 101

February 8th, 2023

IDF's Mission

Improving the diagnosis, treatment and quality of life of people affected by primary immunodeficiency through a community empowered by advocacy, education and research.

Immune Deficiency Foundation

Thank you to our Sponsor!

Housekeeping

Zoom Webinars

Attendees will not have access to their mic or webcam throughout the event.

Slides

To see the full slides, select "side-by-side" in the dropdown menu at the top of your Zoom screen.

Questions

Submit your questions throughout the session via the Q&A Box.

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Immune Deficiency (IDF) education events offer a wide array of educational presentations, including presentations developed by healthcare and life management professionals invited to serve as presenters. The views and opinions expressed by guest speakers do not necessarily reflect the views and opinions of IDF.

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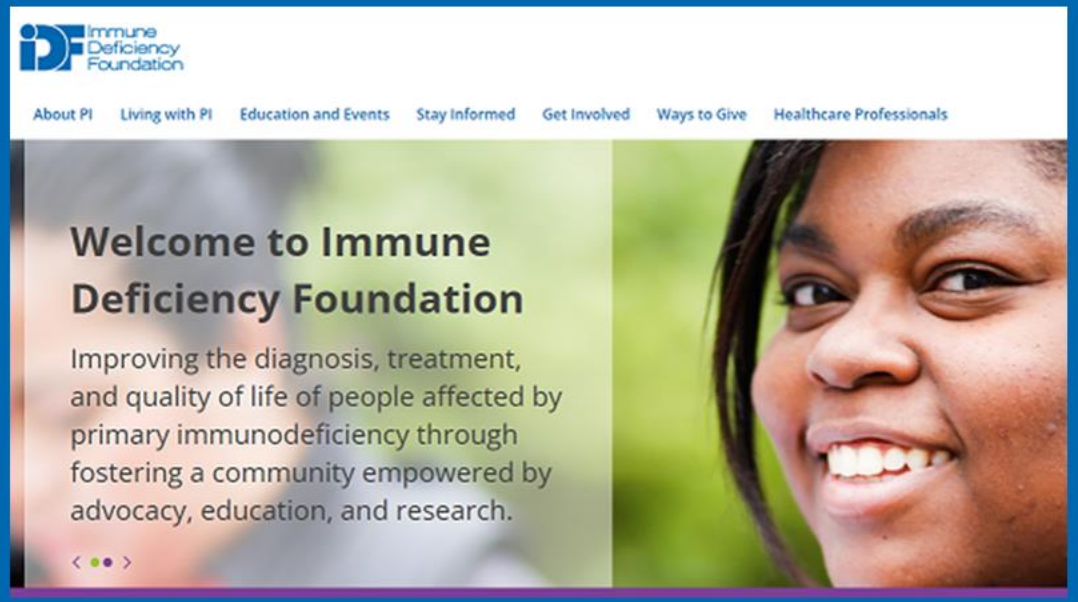
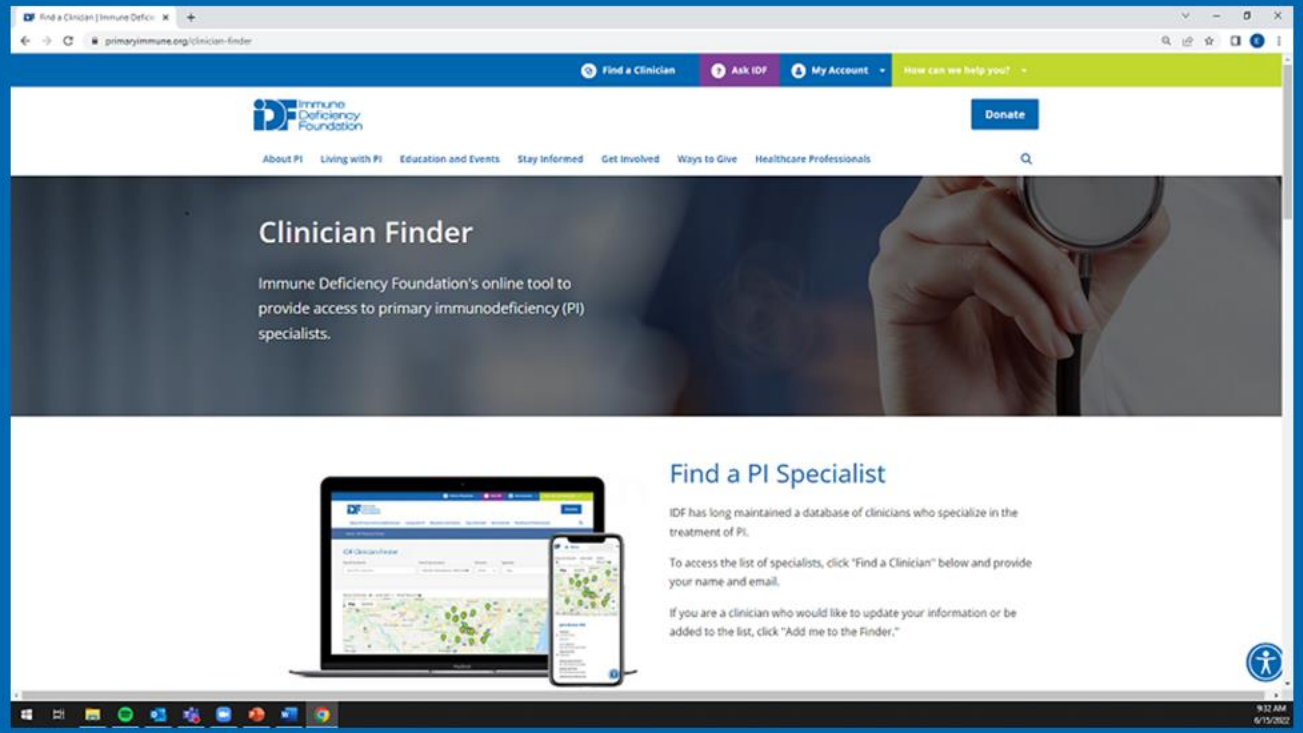
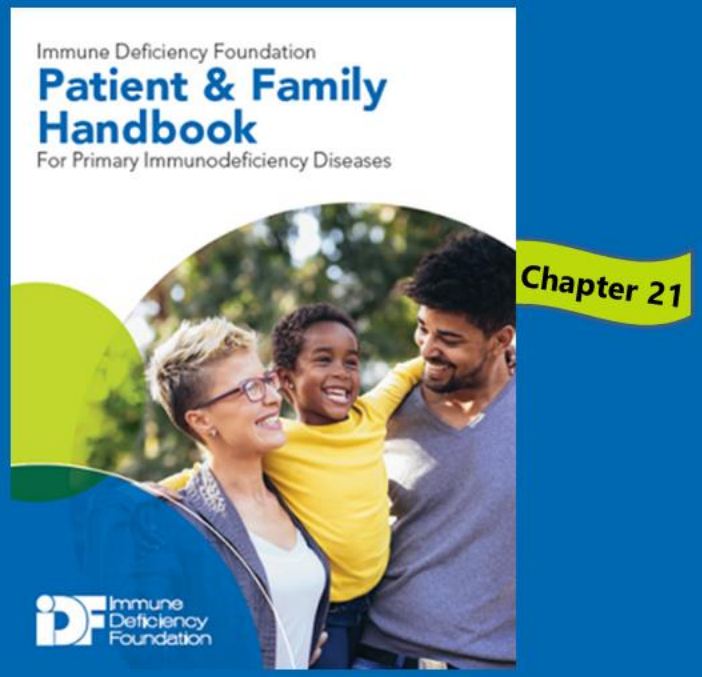


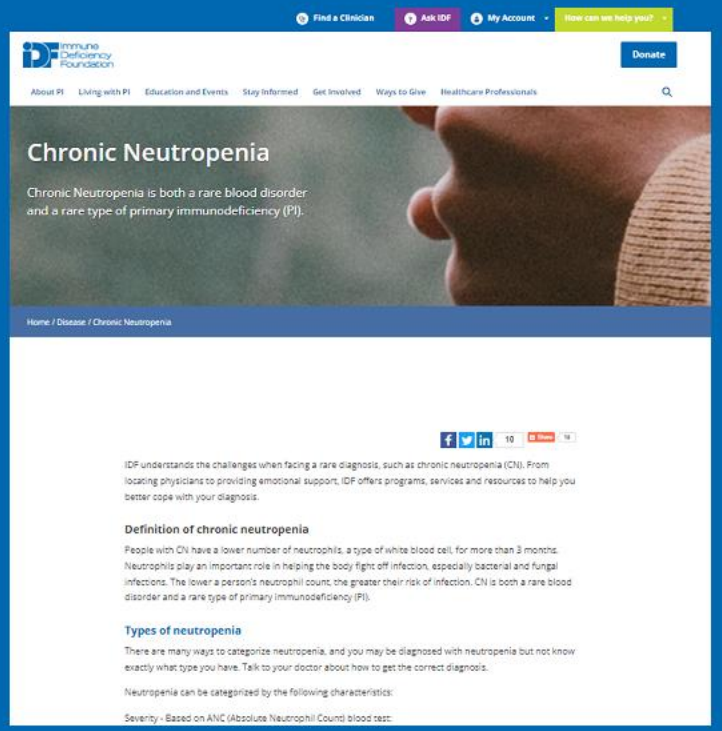


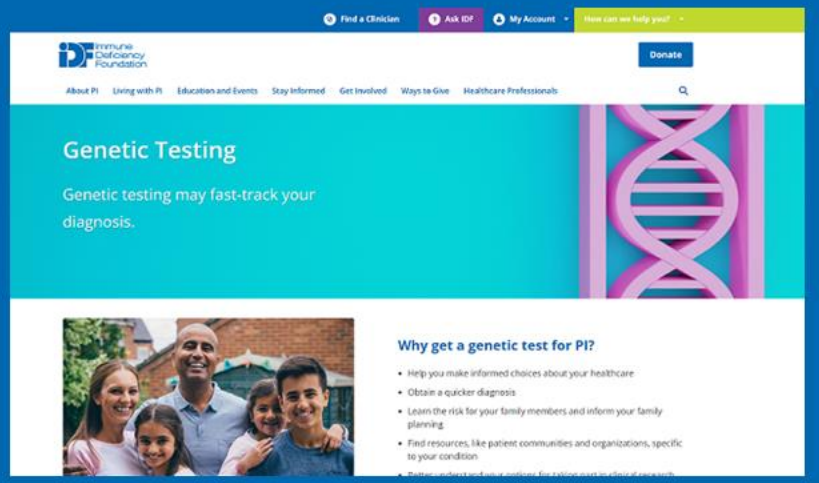
Ask IDF

Resources for CN

https://primaryimmune.org/disease/chronic-neutropenia







Click to learn more about PATH4WARD
Patient Access To Hope
for Rare Primary Immunodeficiencies

https://primaryimmune.org/resource-center

Immune Deficiency Foundation

Connect & Collaborate

Monthly Lunch & Learns

Medical experts provide education on various diagnosis-specific topics.

IDF Webinars

Top Clinicians present on medical and lifestyle topics most pressing to the PI Community.

Get Connected Groups

Individuals and families living with PI can connect with others in their local community or online.

ASK IDF

Submit your questions about insurance, treatment options and more!

Annual PI Conference

Attend presentations from top immunology experts and engage with others in the PI Community.

WELCOME!

James Connelly, MD
Assistant Professor of Pediatrics, Hematology & Oncology
Vanderbilt University Medical Center

Immune Deficiency Foundation

VANDERBILT UNIVERSITY

Monroe Carell Jr. Children's Hospital at Vanderbilt®

Chronic Neutropenia 101

Jim Connelly, MD
Assistant Professor of Pediatrics, Vanderbilt University Medical Center
Director, Comprehensive Hematology, Immunology, and Infectious Disease Program

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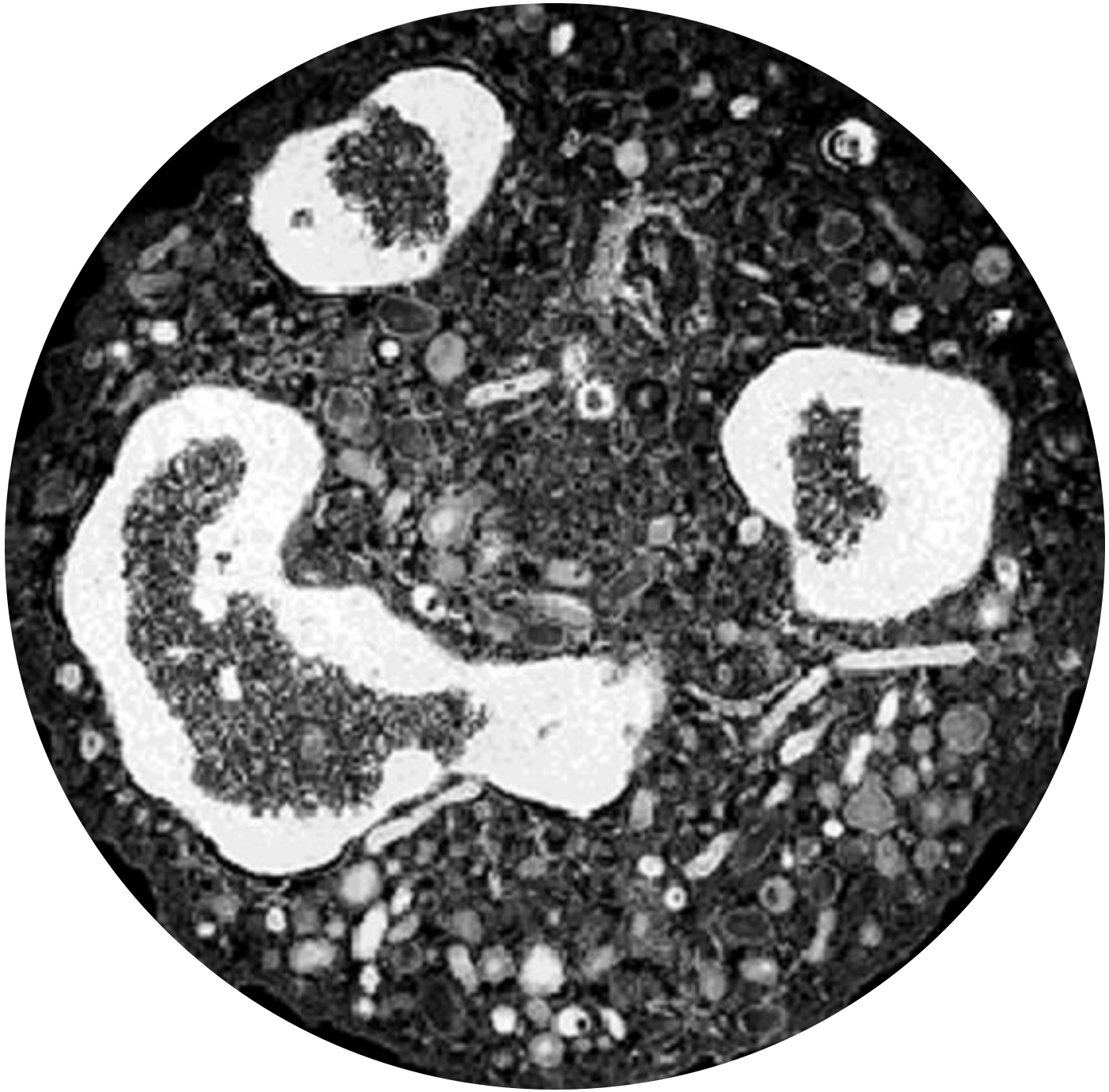
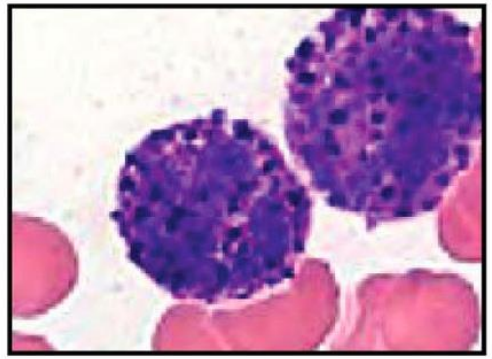


Outline for Chronic Neutropenia 101

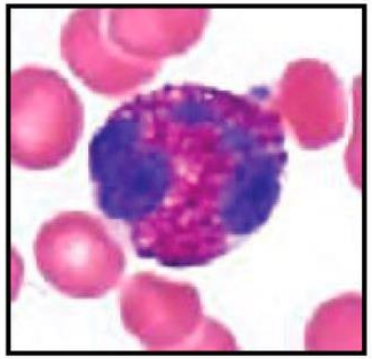
- Neutrophils: Terminology, where do they come from, and what do they do
- Neutropenia: Definition and Classifications
- Causes of Chronic Neutropenia
- Complications of Chronic Neutropenia (Infection, Leukemia)
- Supportive Care for Chronic Neutropenia
- Definitive treatment (G-CSF, Bone Marrow Transplant)

Neutrophil Terminology

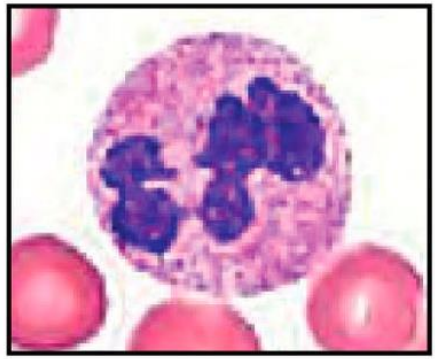
Granulocytes



Basophil

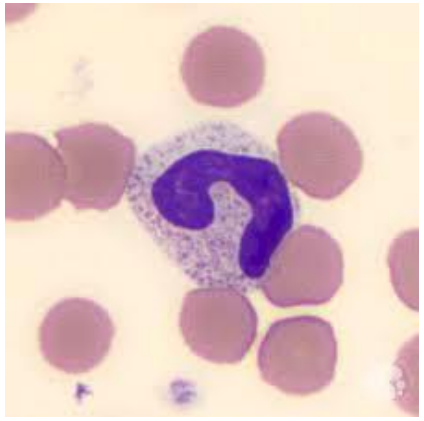


Eosinophil



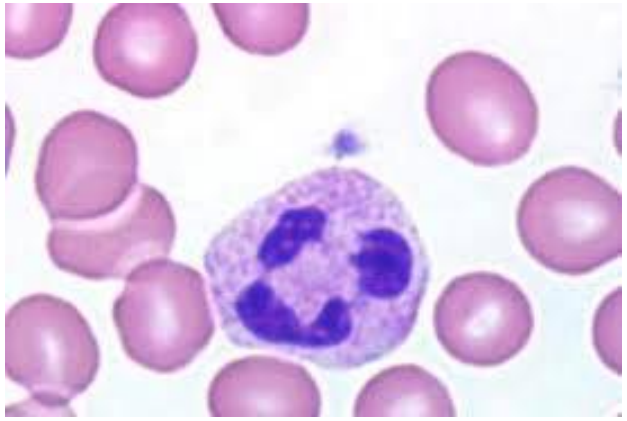
Neutrophil

Neutrophils



Band Neutrophil

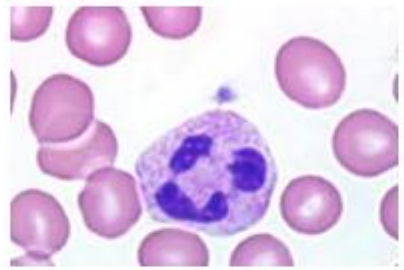
+



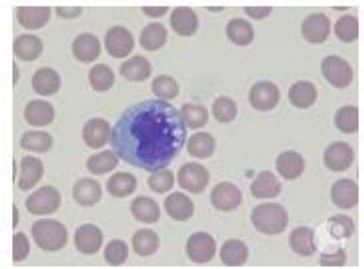
Polymorphonuclear Neutrophil (PMN) or Segmented Neutrophil

Neutrophil Terminology

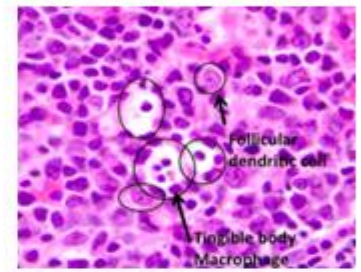
Phagocytes
(Professional)



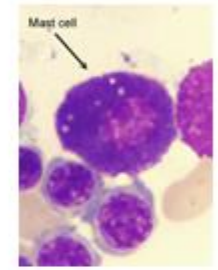
Neutrophil



Monocyte/
Macrophage



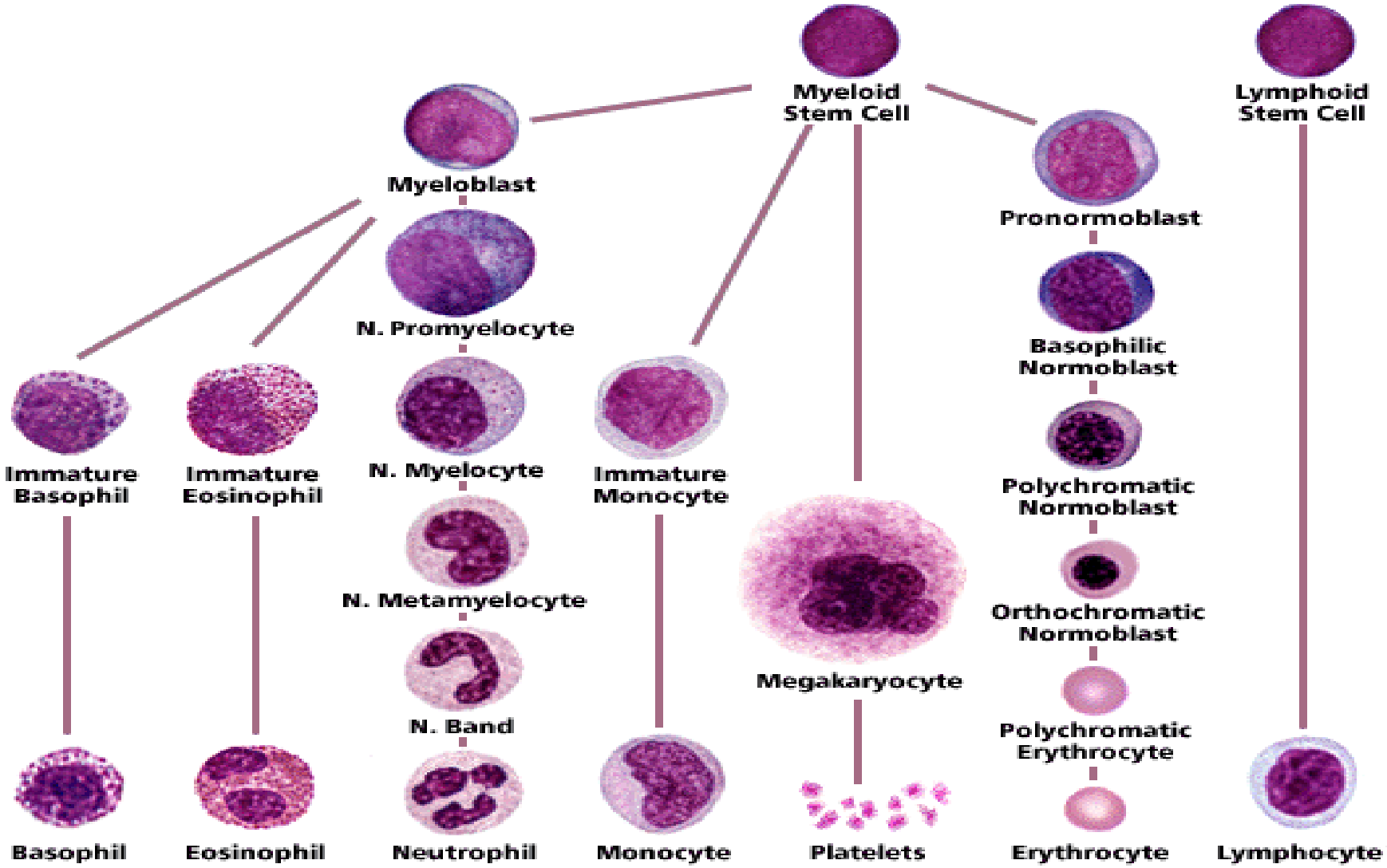
Dendritic Cell



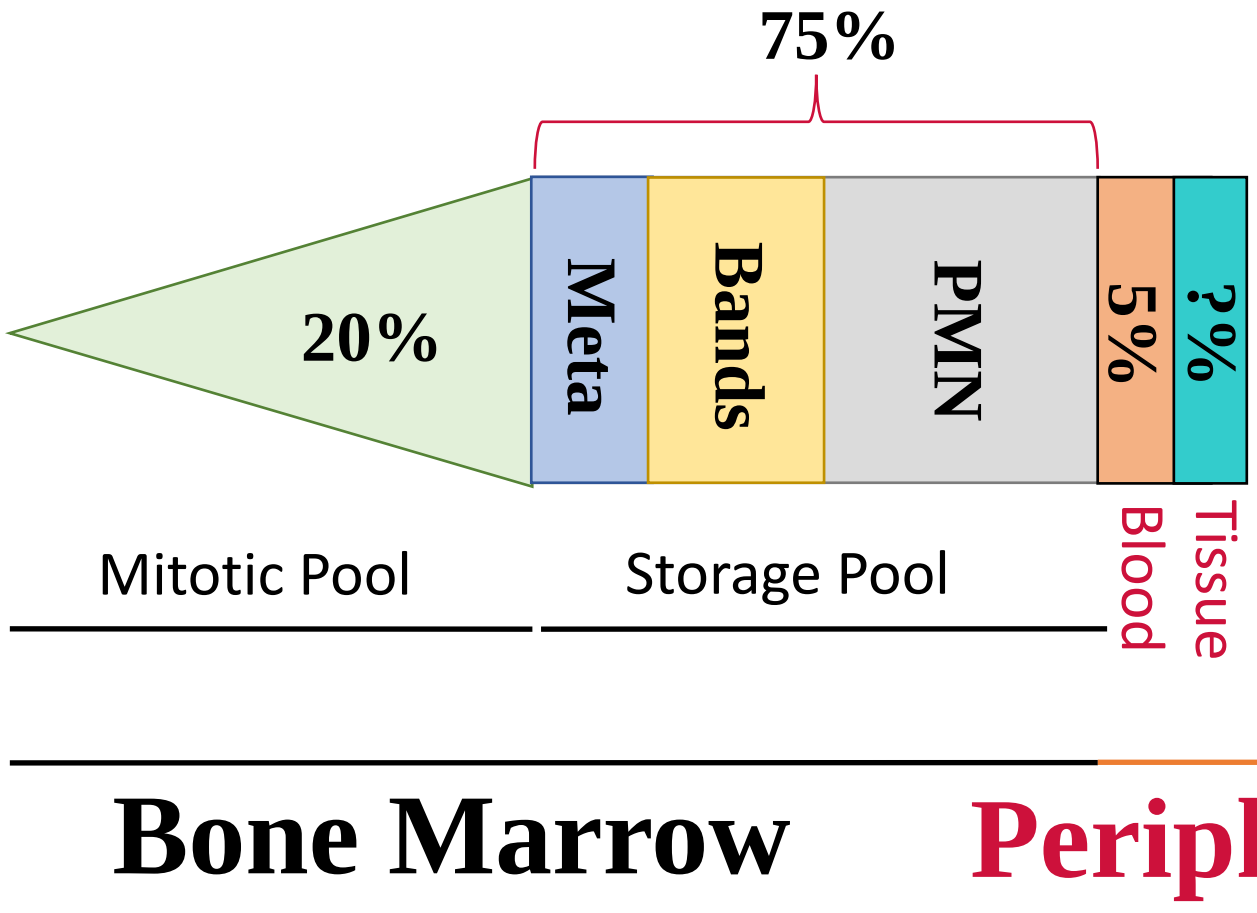
Mast Cell

Neutrophils ≠ PMN ≠ Phagocyte ≠ Granulocyte

Production of Neutrophils



The Different Pools of Neutrophils



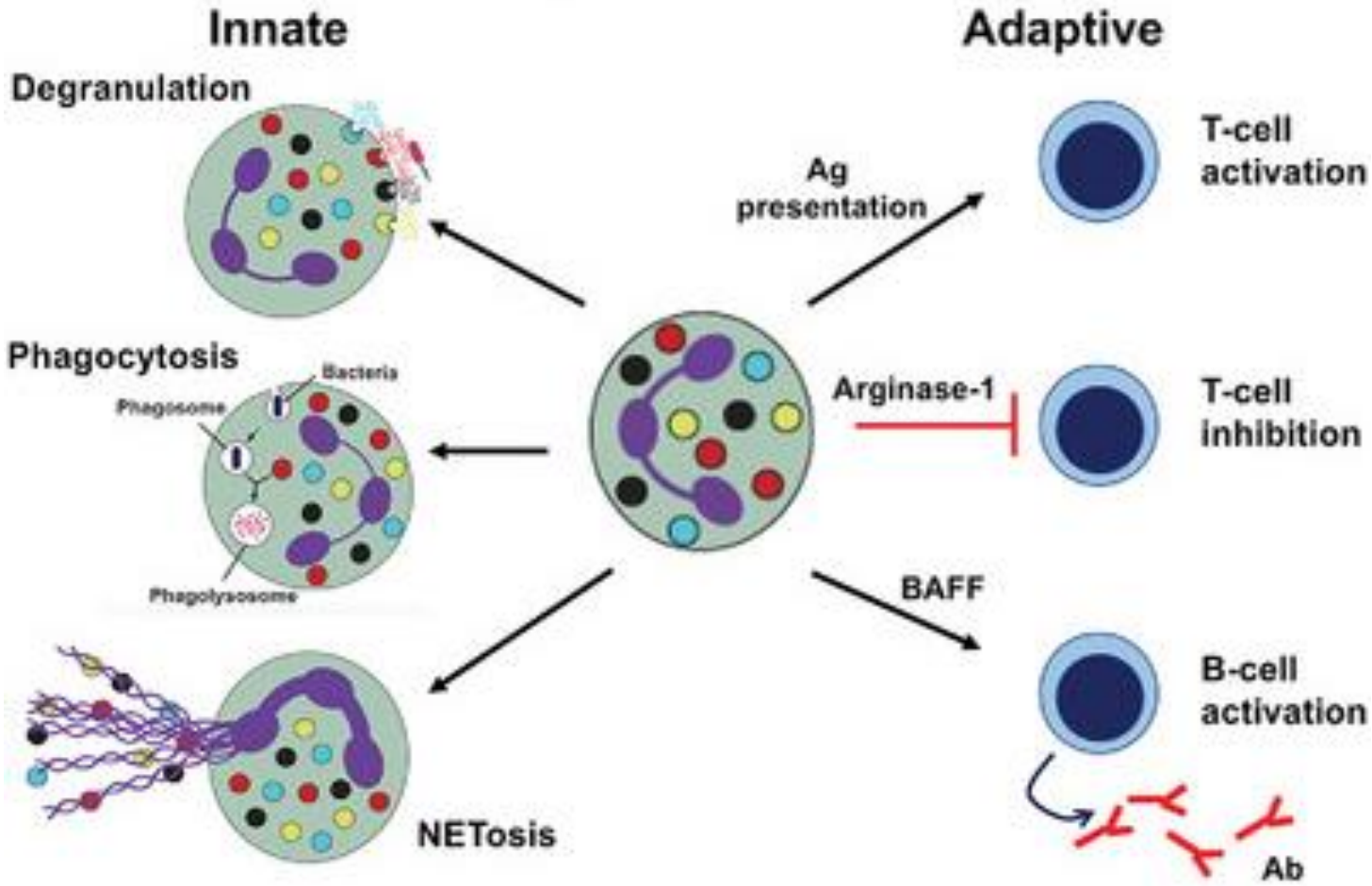
- Mitotic/Proliferating Pool: Myeloblasts, promyelocytes, myelocytes
- Storage pool/Non-proliferating: Metamyelocytes, bands, polymorphic neutrophil (PMN)
- Peripheral blood
  - 2% circulating pool (the measured absolute neutrophil count, ANC)
  - 3% marginating pool

"Mature neutrophils emerge from the bone marrow intent on pursuing one simple, yet essential, question: **Has host integrity been compromised by potentially harmful invaders**?...At its disposal is an impressive arsenal of **antimicrobial weapons** that are **deadly, indiscriminate, and brutish** in their application….[T]hese weapons can prove to be just as **dangerous to the host cells** as to their intended targets, the microbial invaders. Therefore, their deployment must be executed with **exquisite precision and timing**…"

Amulic et al. *AnnRevImmunol* 2012, 30:459-489

Neutrophil Killing Mechanisms

- Degranulation: Release of toxic granules across the cell membrane
- Phagocytosis: Engulfment of foreign material such as bacteria
- Production of reactive oxygen species that are toxic to infectious intruders
- Neutrophil extracellular traps (NETs)

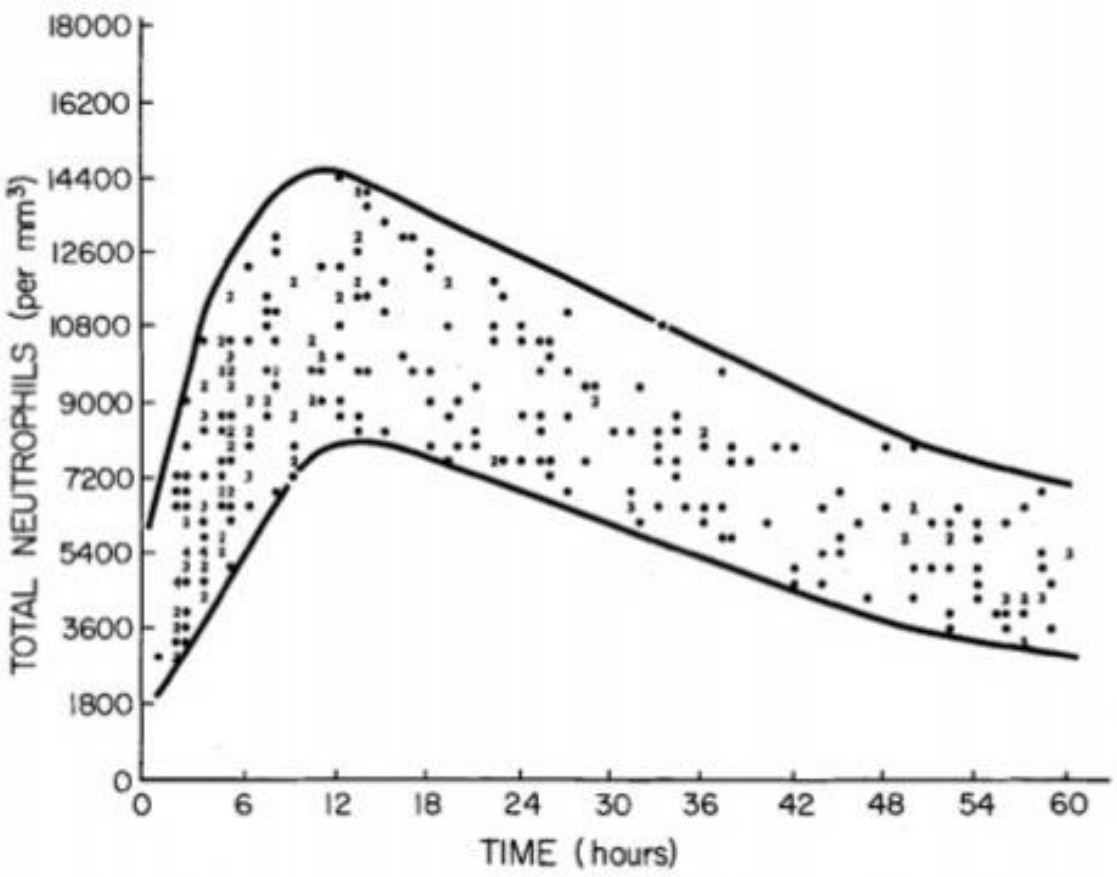


Rosales C. J Leukoc Biol 2020 Jul; 108(1): 377-396

Classic Definitions of Neutropenia

- Term infant (< 1 week)
  - ANC < 3,000 cells/µL
- Infant (1 week to 2 years)
  - ANC < 1,100 cells/µL
- Child, adolescent and adult
  - ANC 1000-1500 cells/µL (mild)
  - ANC 500-999 cells/µL (moderate)
  - ANC < 500 cells/ µL (severe)

Neutrophil Reference Range (First 60 Hours of Life)



Manroe et al .*J Pediatr*. 1979; 95(1): 89-98.

Race/Ethnicity Impact Normal ANC Values

When non-Whiteness becomes a condition

Lauren E. Merz[1] and Maureen Achebe[2,3]

[1]Department of Internal Medicine, Brigham and Women's Hospital, Boston, MA; [2]Division of Hematology, Department of Internal Medicine, Brigham and Women's Hospital, Boston, MA; and [3]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

The term "benign ethnic neutropenia" describes the phenotype of having an absolute neutrophil count (ANC) <1500 cells/μL with no increased risk of infection. It is most commonly seen in those of African ancestry. In addition, ANC reference ranges from countries in Africa emphasize that ANC levels <1500 cells/μL are common and harmless. The lower ANC levels are driven by the Duffy null [Fy(a-b-)] phenotype, which is protective against malaria and seen in 80% to 100% of those of sub-Saharan African ancestry and <1% of those of European descent. Benign ethnic neutropenia is clinically insignificant, but the average ANC values differ from what are typically seen in those of European descent. Thus, the predominantly White American medical system has described this as a condition. This labeling implicitly indicates that common phenotypes in non-White populations are abnormal or wrong. We believe that it is important to examine and rectify practices in hematology that contribute to systemic racism. (*Blood*. 2021; 137(1):13-15)

Alternative Classification

Decreased Production

Increased Peripheral Consumption or Destruction

Ineffective Trafficking

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Genetic Causes of Congenital Neutropenia

Unfolded Protein Response

- *ELANE* (45-60% of SCN)

Mitochondrial Dysfunction

- *HAX1*
- *STK4*
- *TAZ*
- *AK2*
- *EIF2AK3*
- *CLPB*
- Pearson's

RNA Processing

- *SBDS*
- *USB1*
- *SRP54*
- *DNAJC21*

Endosome Trafficking

- *TCIRG1*
- *AP3B1*
- *LAMTOR2*
- *LYST*
- *RAB27A*
- *VPS45*

Glucose Metabolism

- *G6PC3*
- *SLC37A4*

Glycosylation

- *JAGN1*
- *VPS13B*

Transcription Factor

- *GFI1*
- *GATA2*

Cellular Signaling

- *CSF3R*
- *CD40LG*
- *CXCR4*
- *CXCR2*

Cytoskeleton

- *WAS*

Vitamin Transport

- *TCN2*

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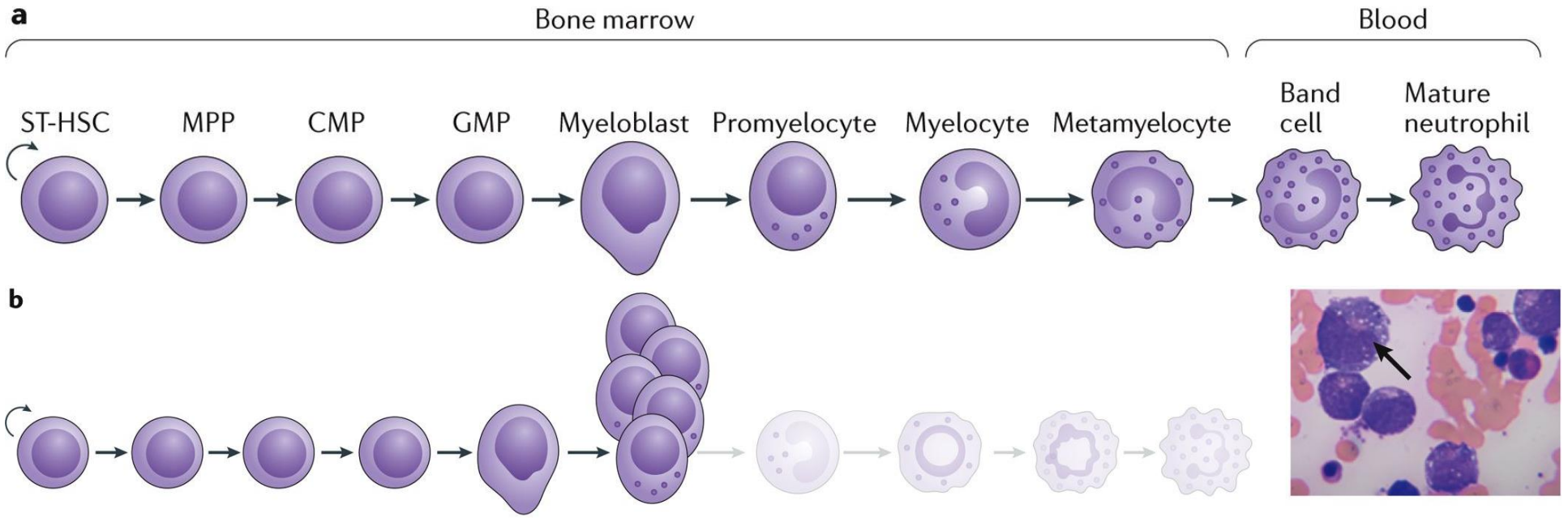
Severe Congenital Neutropenia

- Defined as ANC below 500 cells/µL (and often less than 200 cells/µL)
- High risk for severe bacterial and fungal infections
- Often associated with maturation arrest in the bone marrow

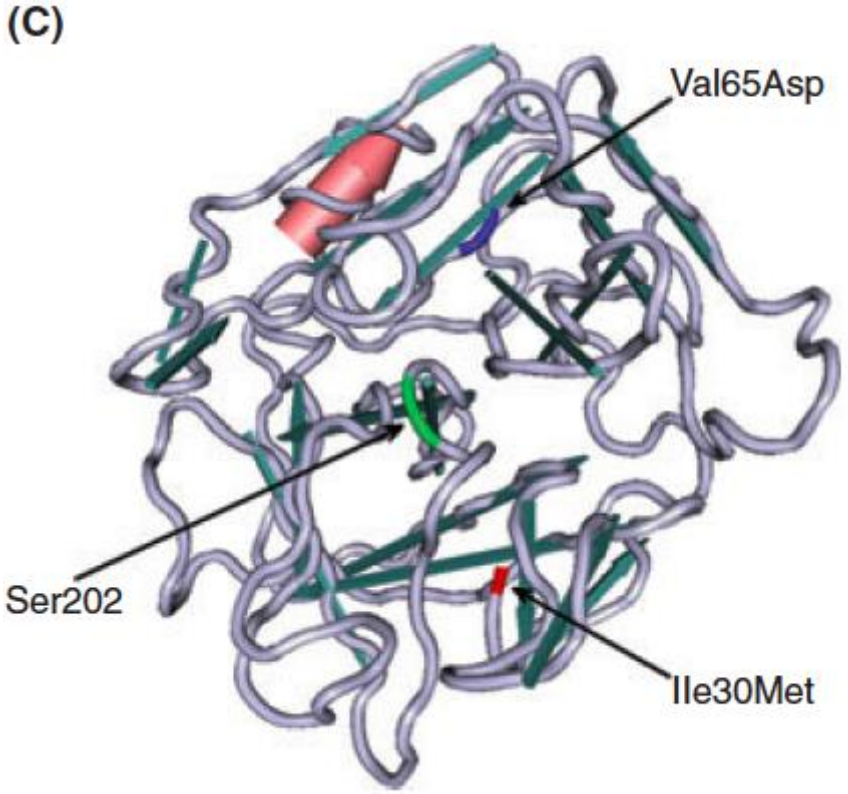


Skokowa et al. *NatRevDisPrim* 2017

ELANE-associated neutropenia

- *ELANE* codes for neutrophil elastase
- Mutant protein results in improper folding, processing, degradation or localization resulting in cellular accumulation
- Stress in the cell causes a process known as the “unfolded protein response (UPR)” resulting in cellular death

Neutrophil Elastase Protein Structure



ELANE-associated neutropenia

- Autosomal dominant mutations in *ELANE* can result in severe congenital neutropenia or cyclic neutropenia
- Cyclic neutropenia is characterized by regular, periodic oscillations in the ANC.
  - Mean oscillatory period is 21 +/- 4 days with 7-10 days of profound neutropenia
  - Historical diagnosis required CBCPDs 2-3 times/week for 6 weeks to document the oscillation in ANC
  - Modern diagnosis is *ELANE* genetic sequencing (mutation found in 90% of patients)

Shwachman-Diamond Syndrome (SDS)

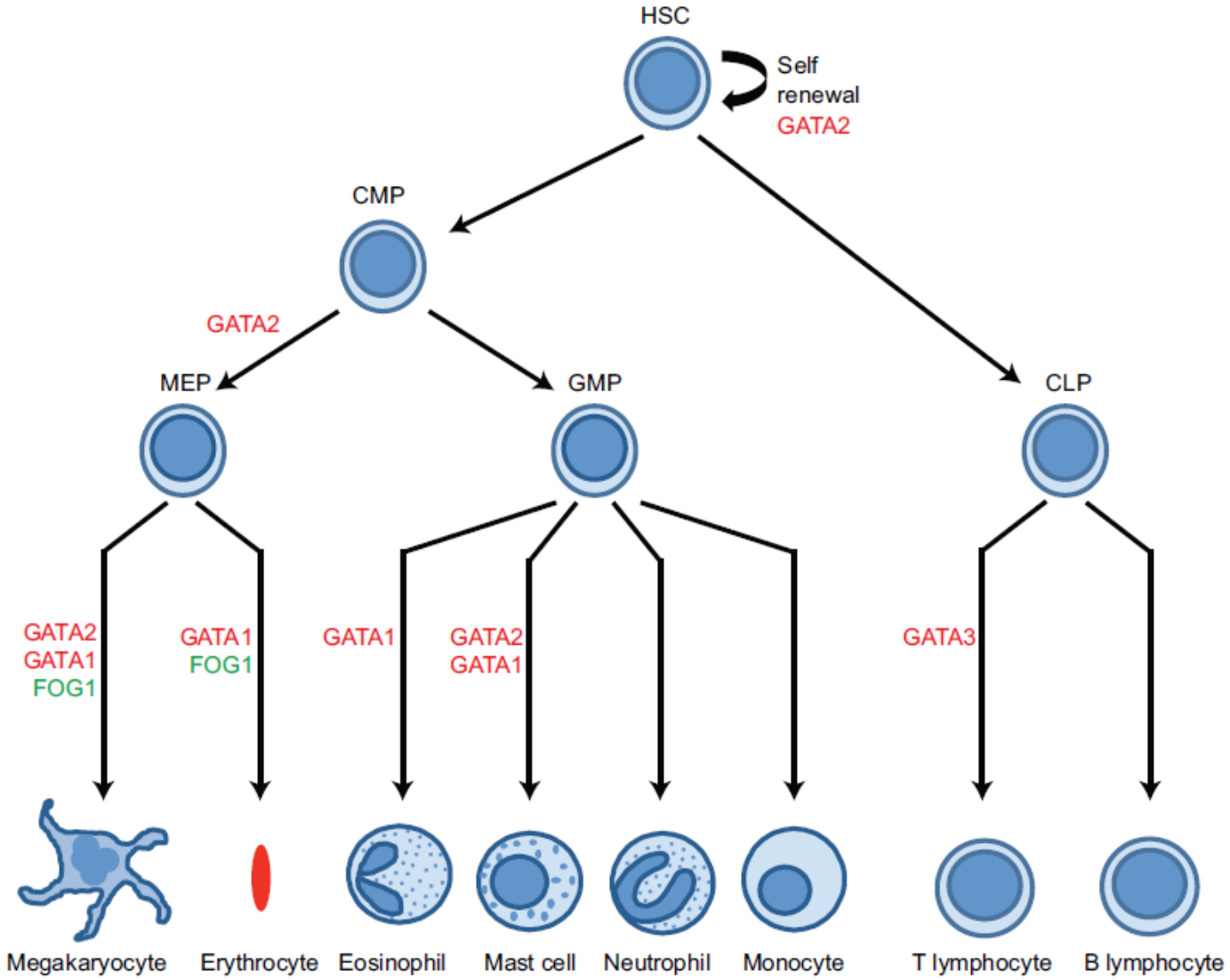
- Autosomal recessive disorders in the *SBDS* gene resulting in abnormal protein production
- Neutropenia very common (80%), but can also affect other blood cell types
- Commonly associated with pancreatic exocrine (digestive) function
- May also be associated with other congenital defects

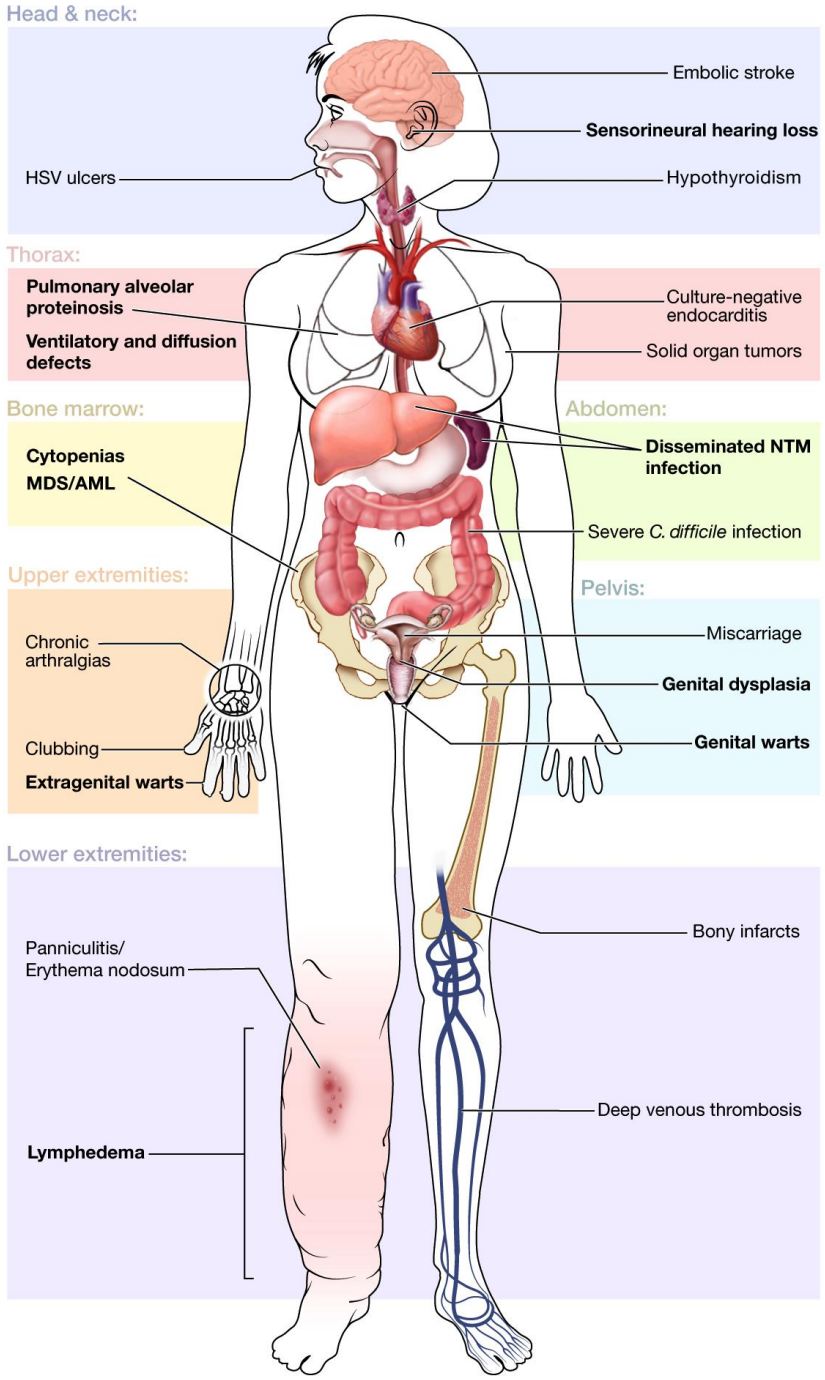
Table III. Congenital anomalies and medical comorbidities identified in patients with SDS

	Number of patients (n = 37)
Congenital anomalies	
Cardiac	7 (19%)
Ventricular septal defect	3
Patent foramen ovale/atrial septal defect	5
Patent ductus arteriosus	5
Gastrointestinal	3 (8%)
Malrotation	1
Bilateral inguinal hernia	1
Imperforate anus	1
Musculoskeletal	14 (38%)
Thoracic dystrophy (rib abnormalities)	9
Short arms/legs	2
Metaphyseal dysplasia	4
Other legs (knock knees, bowing legs)	2
Pelvic dysostosis - absent pubic ramus	1
Scoliosis	3
Neurologic	2 (5%)
Chiari malformation, type I	1
Cerebellar tonsillar ectopia	1
Myopathy/hypotonia	1
Urologic	2 (5%)
Testicular atrophy	2
Hypospadias	1
Other	5 (14%)
Subglottic stenosis	1
Eye anomaly	1
Ear anomalies/hearing loss	4
Medical comorbidities	
Eczema	11
Elevated liver function tests	15
Adrenal insufficiency	1
Hypopituitarism	1
Type I diabetes	1
Pulmonary hypertension	1
Hypothyroid	1

Myers et al., *J Pediatrics* 164(4):866-70, 2014

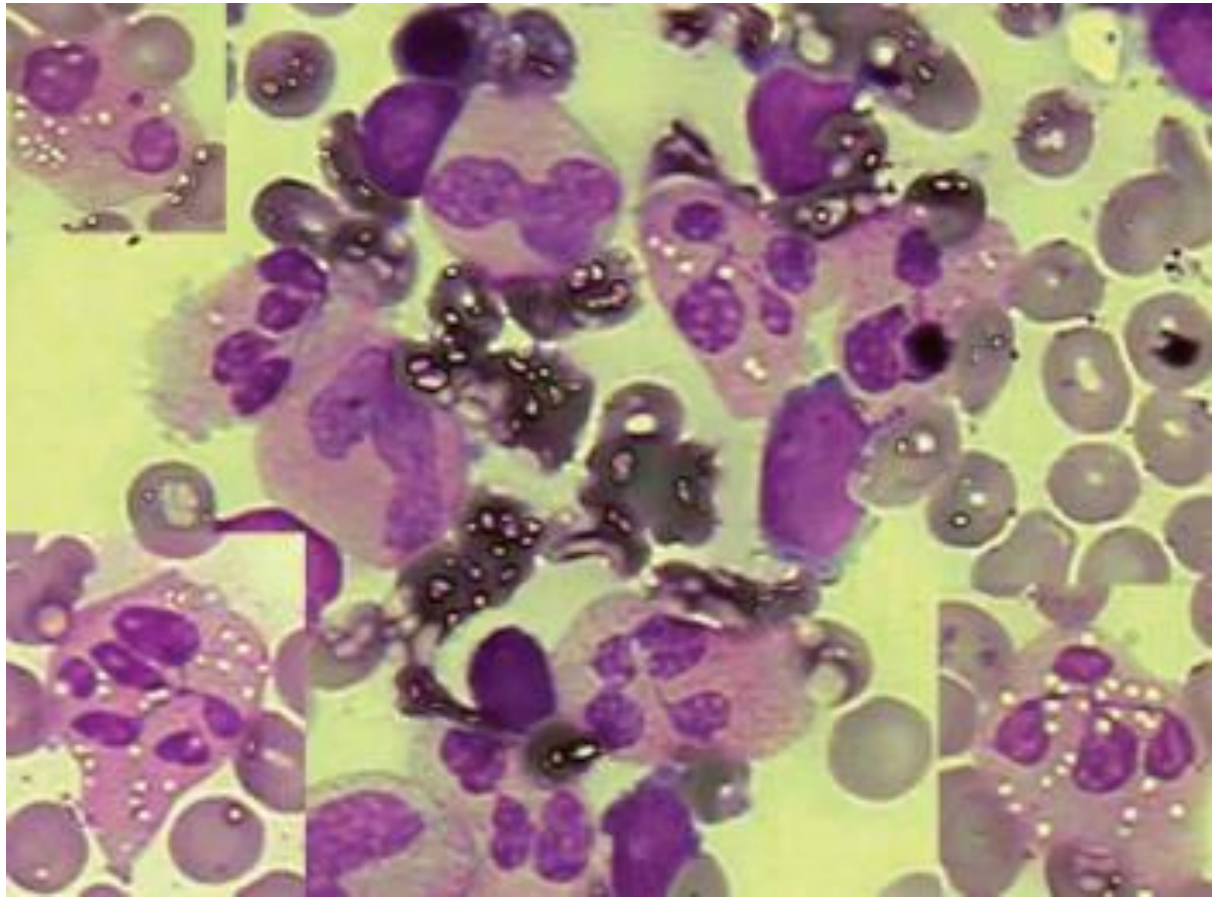
GATA2 Haploinsufficiency





WHIM Syndrome

- Term coined in 1990 to describe the combined clinical manifestations in a family with **W**arts, **H**ypogammaglobulinemia, bacterial **I**nfections, and **M**yelokathexis
- Secondary to autosomal mutations in *CXCR4* which causes retention of neutrophils in the bone marrow and myelokathexis
- Low immunoglobulins and warts variable, but bacterial infections can result in chronic lung disease for older patients




Drug-Induced Neutropenia (DIN)

- Most case occur within 1 week to 6 months of starting the offending agent.
  - Can present with fever and/or oral ulcers or frank sepsis
  - Significantly more common in adults, especially in woman after age 50 years. Only 10% of cases occur in children/young adults
- Etiology is immune mediated (drug or metabolite attaches to neutrophil and creates an immune target) or direct toxicity
- Often will improve with withdrawal of the offending agent(s)
  - If not, can trial G-CSF

Common Agents Causing DIN

Antibiotics	Anti-Thyroid Drugs	Anti-Convulsant & Anti-Psychotic Agents
Cephalosporins	Propylthiouracil (PTU)	Carbamazapine
Penicillins	Carbamizole	Valproic Acid
Sulfonamides	Methimazole	Clozapine
Vancyomycin		
Levamisole		
Choramphenicol		

- Other common classes of drugs associated with DIN include: analgesics, anti-arrhythmic agents and anti-malarial drugs
- Rituximab and cocaine are well associated with neutropenia

Immune-Mediated Neutropenia

- Autoimmune neutropenia of infancy
  - Classically appears around 12 month of life
  - Prophylactic antibiotics or G-CSF is generally not indicated (90-95% are asymptomatic)
  - Most patients undergo spontaneous remission
- Autoimmune neutropenia in children and adults can occurs as part of broader immune dysregulation syndromes, e.g. Evan's syndrome, lupus, ALPS, common variable immunodeficiency
  - Typically termed "secondary autoimmune neutropenia" when a co-existing immune disorder is present

Chronic Idiopathic Neutropenia

- Usually presents as an incidental finding on routine blood work in asymptomatic patients.
  - No evidence of nutritional deficiency, neutrophil antibody, or myelodysplasia
  - Unknown underlying pathophysiology but likely related to immune chemicals (cytokines) causing neutropenia
  - Bone marrow normal with normal cytogenetics
- Clinical course is mostly benign with a variable need for G-CSF

Complications of Neutropenia: Infections

- Congenital neutropenia disorders
  - High risk for ANC < 500 cells/ µL; low risk for persistent ANC > 1000 cells/µL
- Primary autoimmune and chronic idiopathic neutropenia are in general low risk for bacterial infection
  - Secondary autoimmune neutropenia has an increased frequency of severe bacterial infections compared to primary autoimmune neutropenia

Study Location	Number and Category of Patients	Severe Bacterial Infections (SBIs)
Texas Children's Cancer and Hematology Center[1]	Pediatric 43 autoimmune or idiopathic neutropenia	133 ER visits for fever but no patients with SBI
Italian Neutropenia Registry[2]	Pediatric 38 autoimmune and 23 idiopathic neutropenia	3 total blood stream infections over 9.5 years
French SCNIR[3]	Adult 108 primary autoimmune or idiopathic neutropenia	3.85 SBIs per 100 patient years
Italian Neutropenia Registry[4]	Pediatric 263 primary and 26 secondary autoimmune neutropenia	11% vs 40% SBI in primary vs secondary over 15 years

1 Kirk et al. *Pediatr Blood Cancer*. 2020; 67(4): e.28146.
2 Fioredda et al. *Pediatr Infect Dis J*. 2013; 32(4): 410-412.
3 Sicre de Fontbrune et al. *Blood*. 2015; 126(14): 1643-1650.
4 Farruggia et al. *Hematol*. 2017; 92(9): E546-E549.

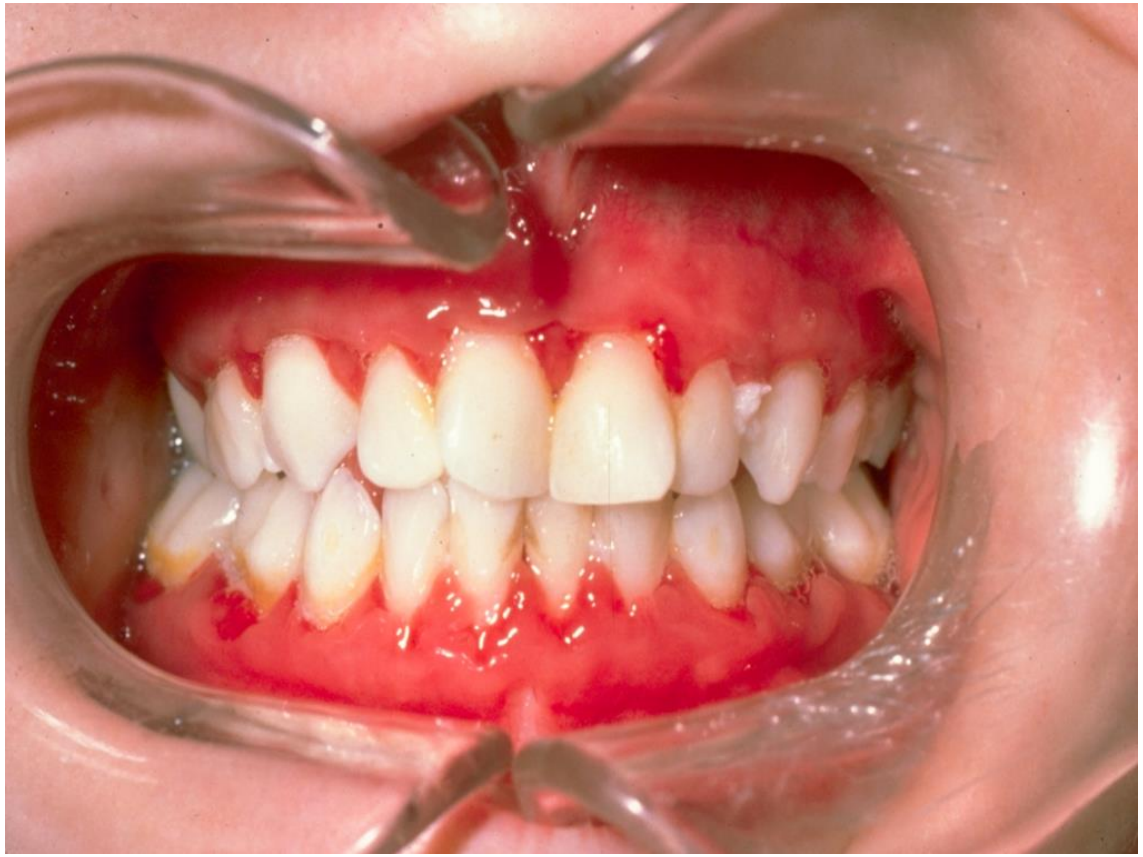
COVID-19 and Congenital Neutropenia

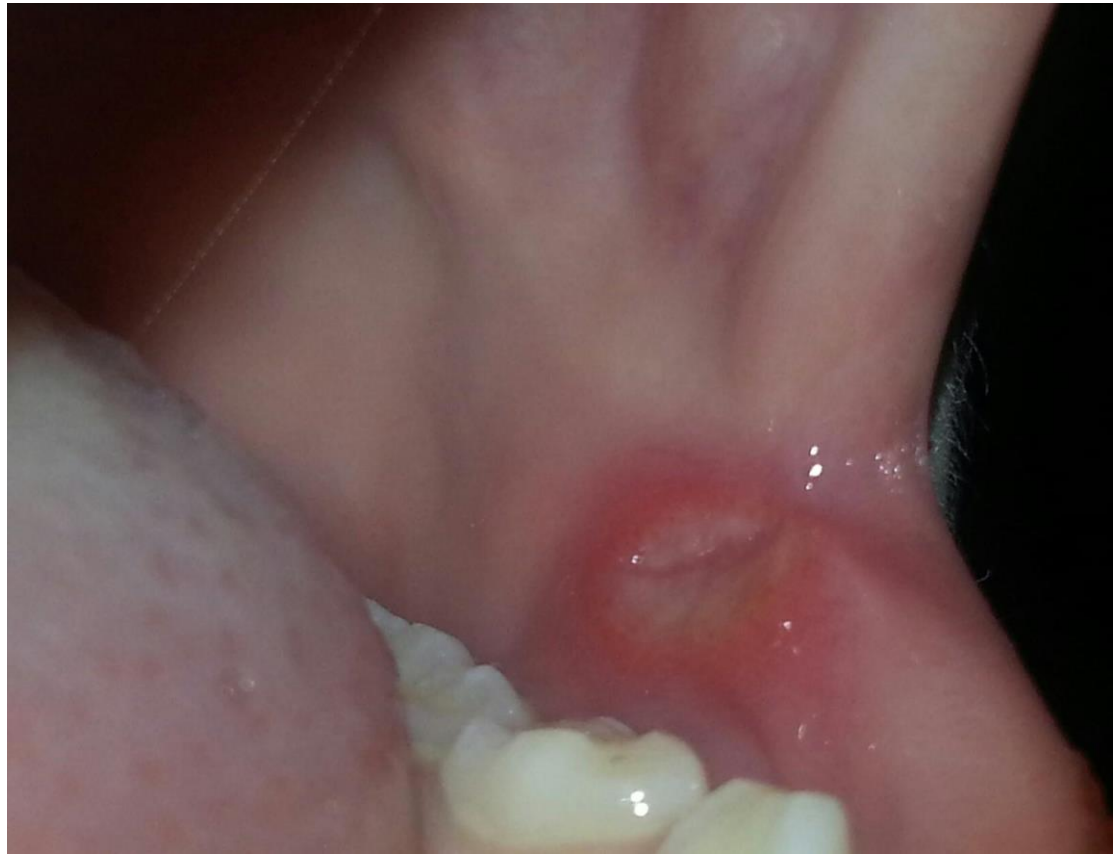
- Severe Chronic Neutropenia International Registry has received some reports on patient reported outcomes with SARS-CoV-2
- Most patients have similar symptoms and disease courses as patients without chronic neutropenia, although a small number of deaths have been reported
- Patients should take protective measures to prevent infection (vaccination, social distancing/masking where appropriate, hand washing)
- Patients should continue G-CSF in the setting of SARS-CoV-2 infection

Vaccinations in Chronic Neutropenia

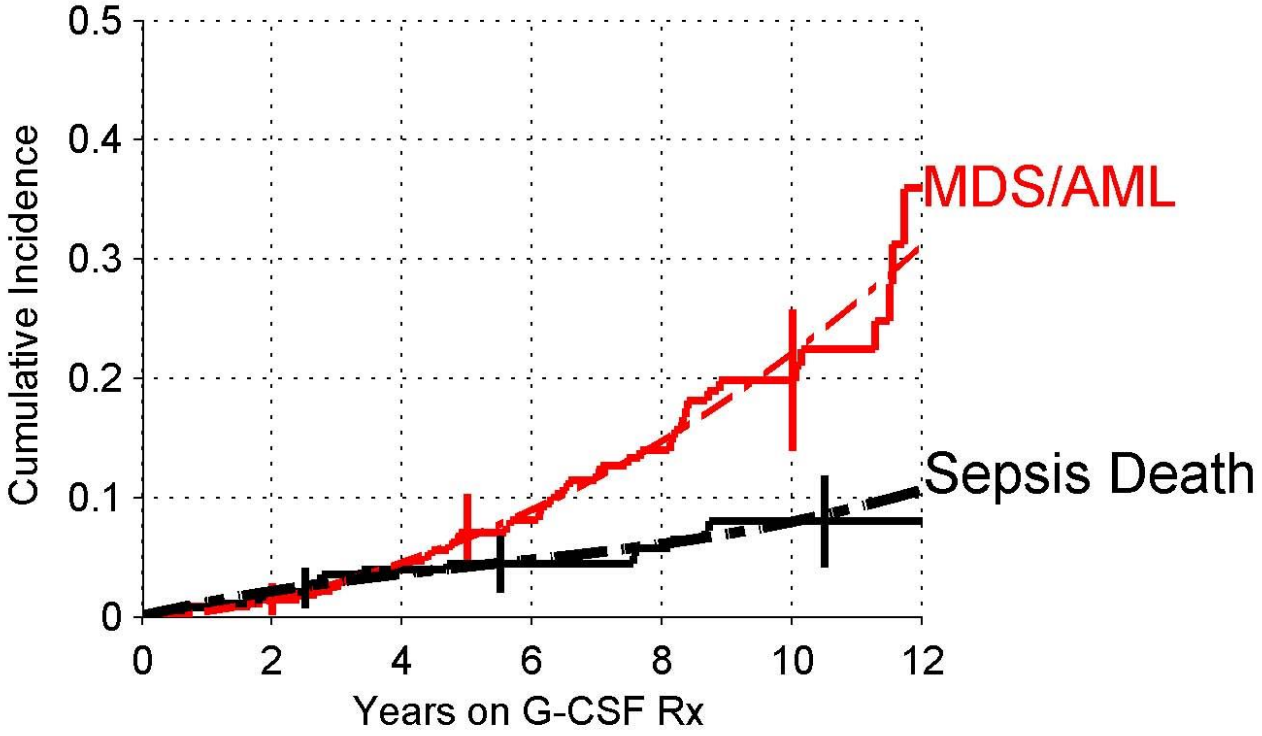
- Neutrophils are not critical for vaccine response and patients with isolated neutropenia should have normal vaccine responses
- Vaccinations should be part of routine care for patients with neutropenia
- Patients with neutropenia as part of a combined immune disorder should discuss vaccinations with their physicians as live vaccines may not be safe

Oral Care in Neutropenic Patients





Development of MDS/AML in Congenital Neutropenia

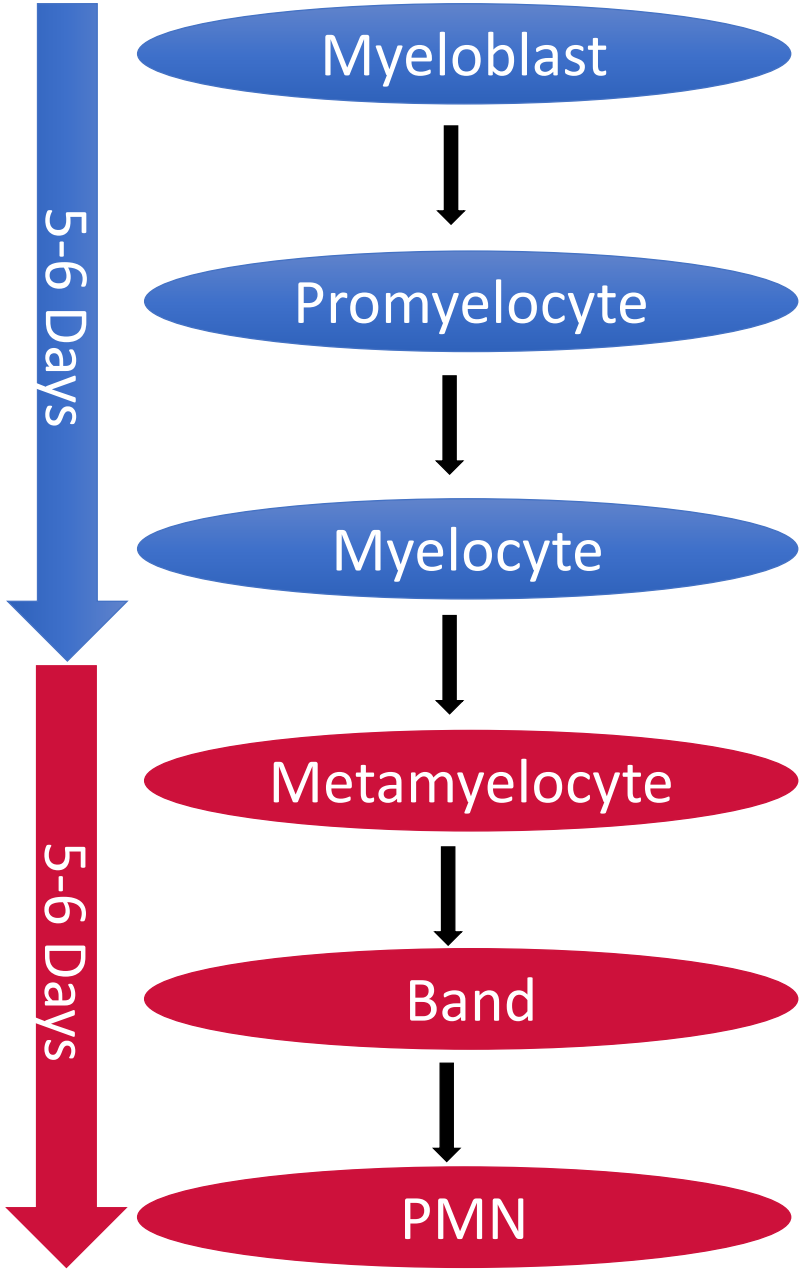


- After 10 years on G-CSF, 21% of patients developed myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML)
- Death related to MDS/AML remains the number one cause of mortality in congenital neutropenia
- Patients with congenital neutropenia typically undergo regular CBCs and bone marrow biopsies to detect early signs of leukemia

Rosenberg et al. *BJH* 2010; 140:210

Definitive Treatment of Congenital Neutropenia

- Primary treatment of congenital neutropenia is G-CSF with response in the majority (~95%) of patients
- G-CSF has dramatically reduced the risk of severe bacterial infection (sepsis)
  - Death from severe infection is rare and has been reported in patients with poor response to G-CSF or in patient's not taking G-CSF as prescribed
- Patients with congenital neutropenia are at risk of AML/MDS
  - Development of AML/MDS requires a bone marrow transplant for cure



G-CSF

- Produced by immune cells, bone marrow cells, and cells lining blood vessels
- Enhances proliferation of all mitotic granulocytic lineages
- Accelerates the maturation time at the metamyelocyte stage
- Principal cytokine stimulating release of neutrophils from the bone marrow
- Activates mature neutrophils and extends lifespan in the tissue

Indications for G-CSF

- Congenital Neutropenia
  - Severe congenital neutropenia: 5 µg/kg/day with escalation to 10 µg/kg/day and then by increments of 10 µg/kg/day every 14 days for goal ANC 1000-1500 cells/µL
  - Cyclic neutropenia: 1-3 µg/kg/day given every 1-3 days

- Primary and Chronic Idiopathic Neutropenia
  - No established association of G-CSF with cancer in this population
  - Recommended for recurrent infections or stomatitis in severe neutropenia
  - Small doses 0.5-3 µg/kg/day given every 1-3 days for a goal ANC 1000-1500 cells/µL

Changing Landscape of G-CSF: Biosimilars

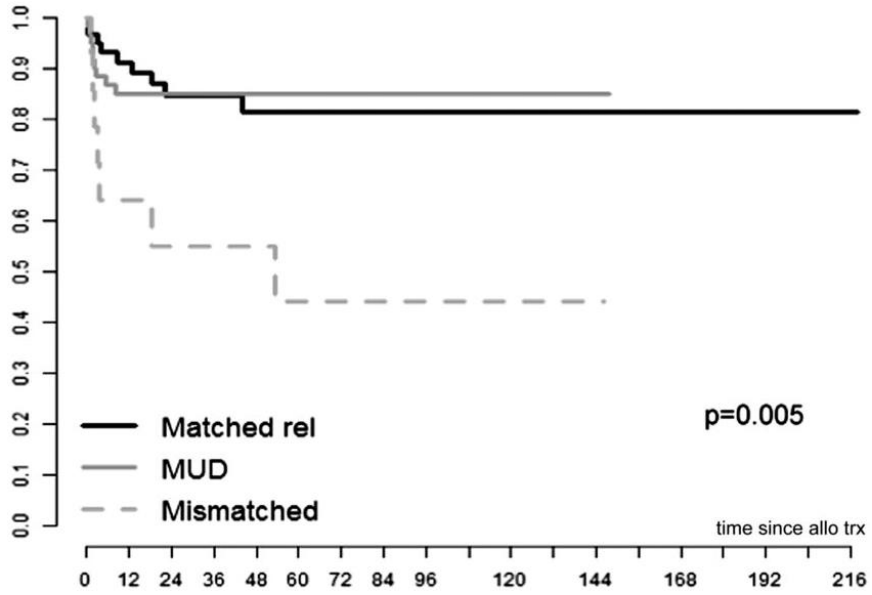
- Biosimilars offer options for G-CSF dosing
  - Neupogen®
  - Granix ®
  - Zarxio®
  - Nivestym ®
  - Releuko®
  - Zarxio®
- No significant differences in reported adverse reactions
- Differences may exist in how the drug is supplied (pre-filled syringes, multi-use vials) and concentration

Bone Marrow Transplant Indications in Congenital Neutropenia

Absolute Indication	Possible Indication	Not Likely Indication
MDS/AML	High doses of G-CSF (>15 µg/kg/day) (SCN)	Acquisition of *CSF3R* (SCN) or *TP53* mutation (SDS) alone
MDS-associated cytogenetic abnormality	*ELANE* mutation with high risk of MDS/AML (SCN)	
Bone marrow failure (SDS)	Intolerable side effects of G-CSF	

What Determines a Successful Transplant for Severe Congenital Neutropenia?

Transplant Outcomes Based on Donor Type



Fioredda et al. Blood 2015; 126(16): 1885-92

Transplant Outcomes Based on Disease Status

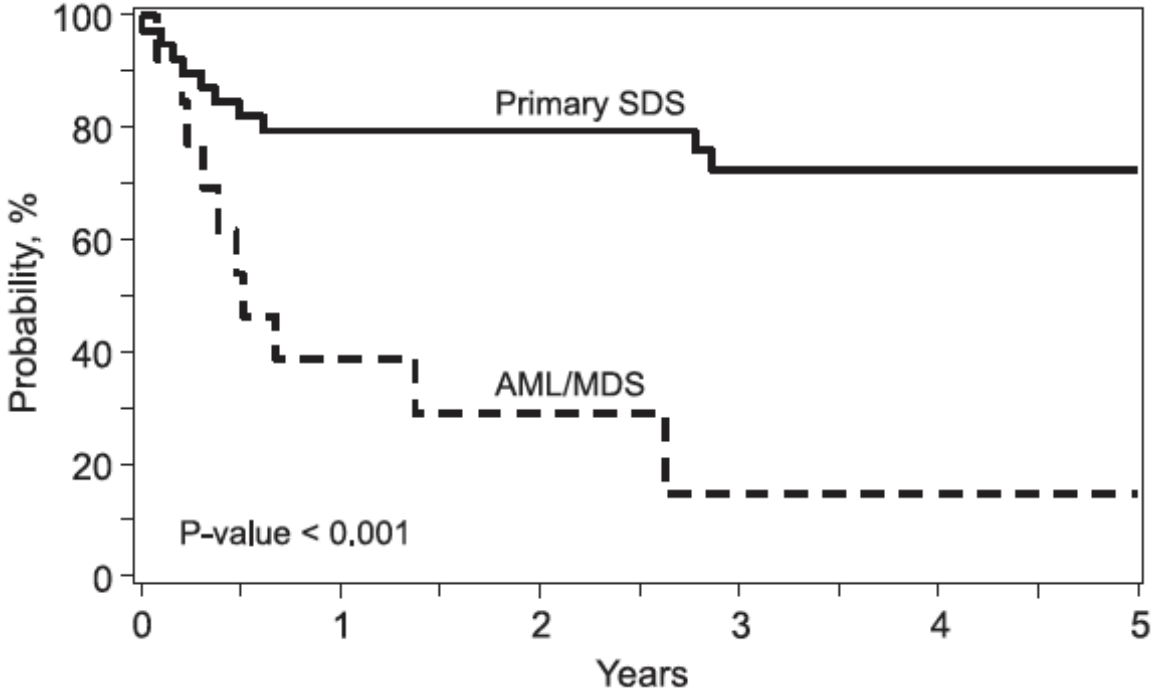
	Without MDS/AML	With MDS/AML
Literature Summary[1]	80%	39%
SCNIR[2]	78%	83%
EBMT[3]	87%	79%

1. Connelly et al. COH 2013
2. Zeidler et al. ASH 2014
3. Fioredda et al. Blood 2015

Monroe Carell Jr. Children's Hospital at Vanderbilt

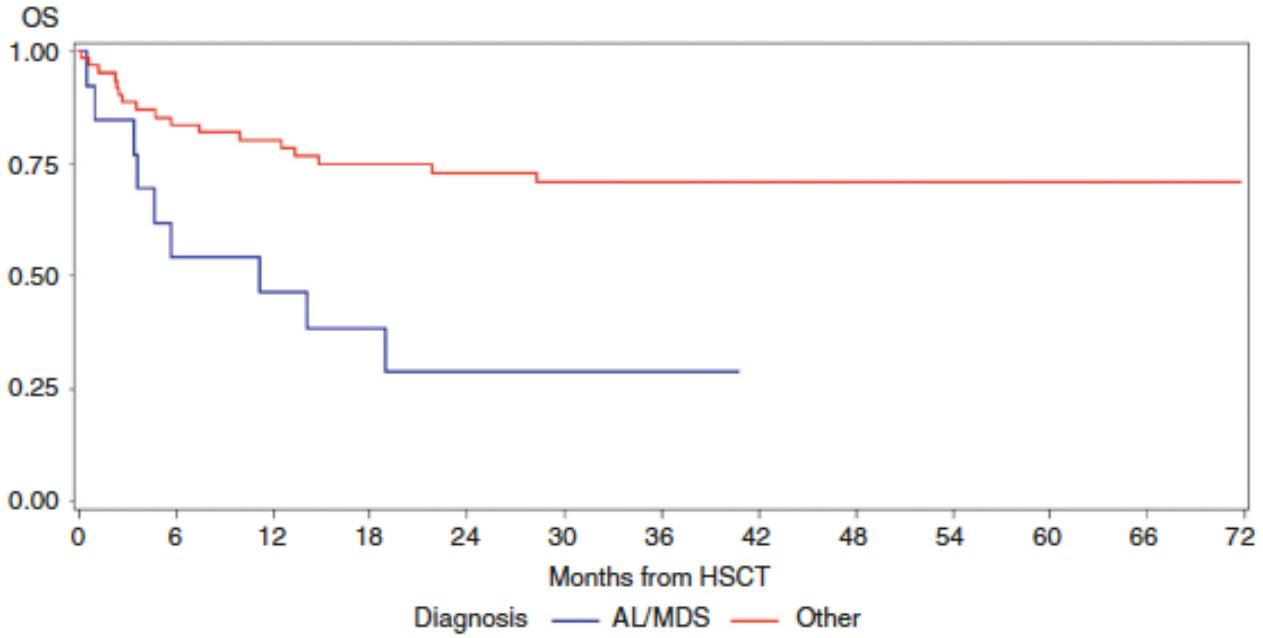
What Determines a Successful Transplant for SDS?

BMT Outcomes in CIBMTR Cohort of SDS Patients



Myers et al. *BBMT* 2020; 1446-1809.

BMT Outcomes in European Cohort of SDS Patients



Cesaro et al. *BMT* 2020; 55: 1796-1809.

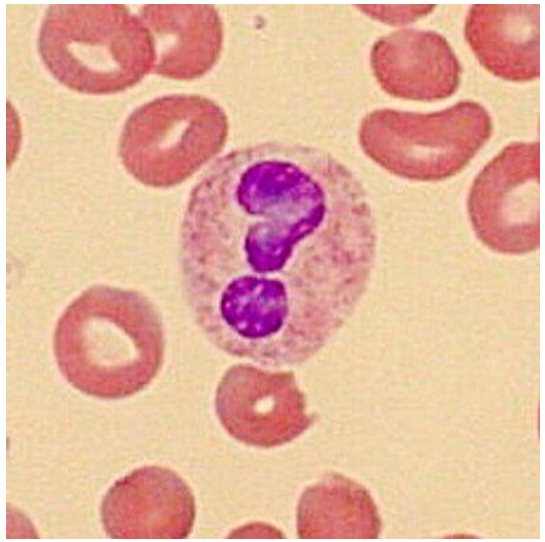
What about new therapies for congenital neutropenia?

- New therapies are currently being investigated to treat congenital neutropenia, but a lot of “pre-clinical” research must be completed first before moving the therapy to a clinical trial
- For patients with ELANE severe congenital neutropenia, treatment options under pre-clinical investigation include:
  - Elastase (the protein made by the gene *ELANE*) inhibitors
  - Genetic editing to remove the *ELANE* gene
  - Genetic editing to repair the *ELANE* gene
- For patients with specific mutations in SDS, pre-clinical investigations include treatments to improve SBDS expression and function

Summary

- Chronic neutropenia has many causes (congenital and acquired)
- Complications of chronic neutropenia include infection, the risk of which is dependent on the etiology and availability of stored neutrophils in the bone marrow
- Treatment includes supportive care to reduce infection and G-CSF in some patients (mainly congenital neutropenia) to increase the peripheral blood neutrophil count and significantly reduce the risk of infection
- Bone marrow transplant is curative of congenital neutropenia but is reserved for patients who have developed or are at high risk of severe complications such as leukemia

Questions



And Discussion

THANK YOU!

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Hematology & Oncology
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Immune Deficiency Foundation


Immune
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Q & A
alt

Additional Resources

- ASK IDF: www.Primaryimmune.org/ask-idf
  - 800-296-4433
- IDF Resource Center:
  •https://primaryimmune.org/resource-center

- IDF Support Services:
  https://primaryimmune.org/support-services

- IDF's YouTube Channel
  - We record and upload all IDF Education sessions
  - https://www.youtube.com/user/IDFvideos

Immune Deficiency Foundation

Upcoming Events

IDF Webinar: The Use of Prophylactic Antibiotics in Antibody Deficiencies
Ken Paris, MD, MPH
Thursday, 2/16/23
7:00-8:30PM ET

SCID Compass Lunch & Learn: What is Chimerism?
Kenneth Weinberg, MD
Wednesday, 3/22/23
11:00AM-12:00PM ET

For a list of all upcoming IDF Events, visit:
https://community.primaryimmune.org/s/events?language=en_US

No previous advocacy experience is necessary - this interactive workshop gives participants the tools to become an informed, skilled advocate for the PI community.
Participants will receive online training prior to the day on February 16th at 6:00 PM CT.

On February 22 in Austin, participants will use their newly fostered advocacy skills to meet with elected representatives

https://community.primaryimmune.org/s/events?language=en_US

Thank you for your support!

From all of us at IDF

Thank You!

Abe Frances CHRIS Lorraine Jorey ANGELA Katherine Rachel
Lynn Elizabeth Chuck Fri Stephanie Karen Zach
Cheryl Sarah Christopher
Emma Kathy Alissa Jennifer Brian Kat Tawny Aimee Doreen Jamie
Amy Julieann Adam Wanda STEPHANIE Colleen Becca Maura Kim

You make the IDF community stronger

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