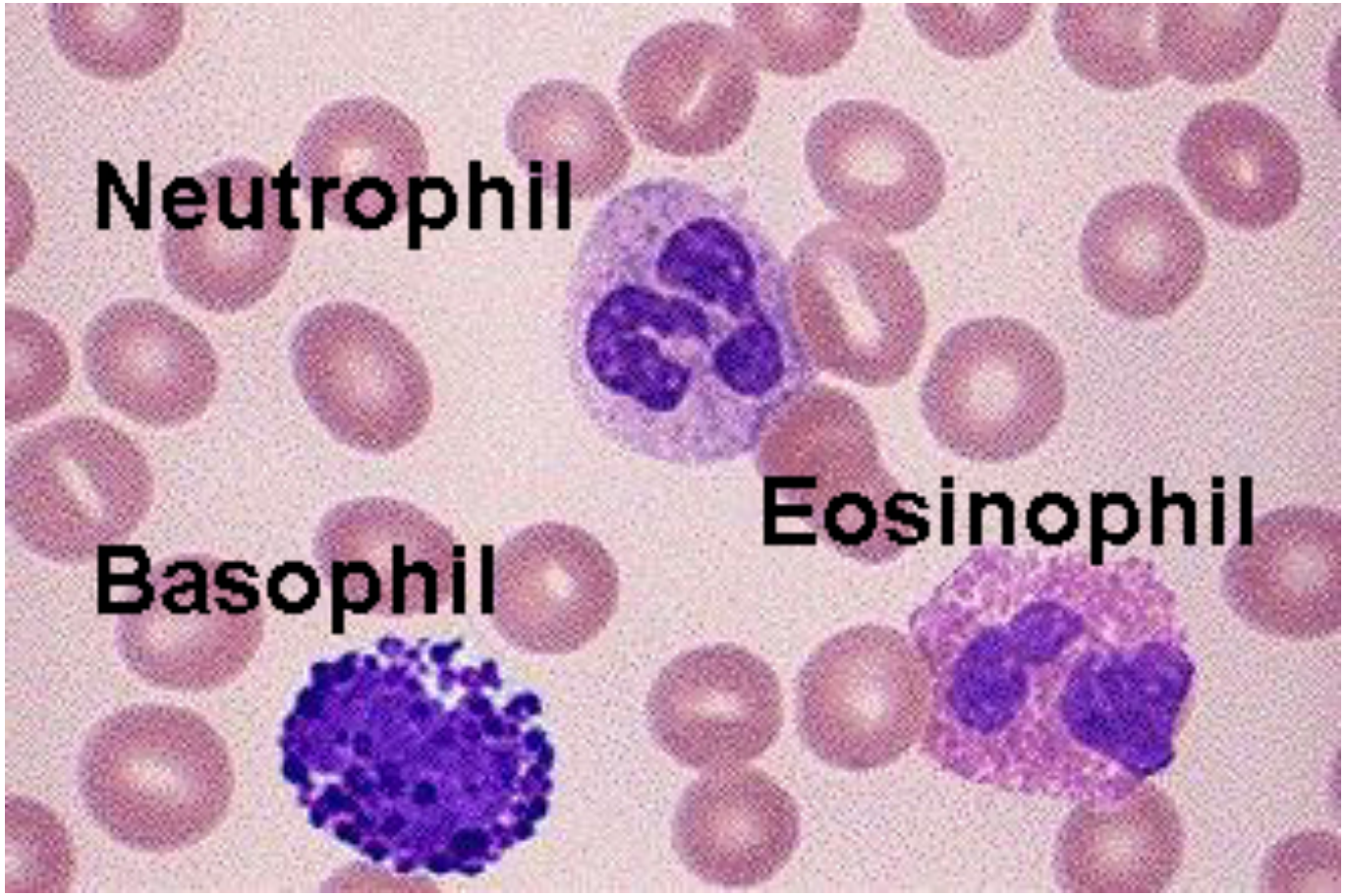
General overview of neutropenia

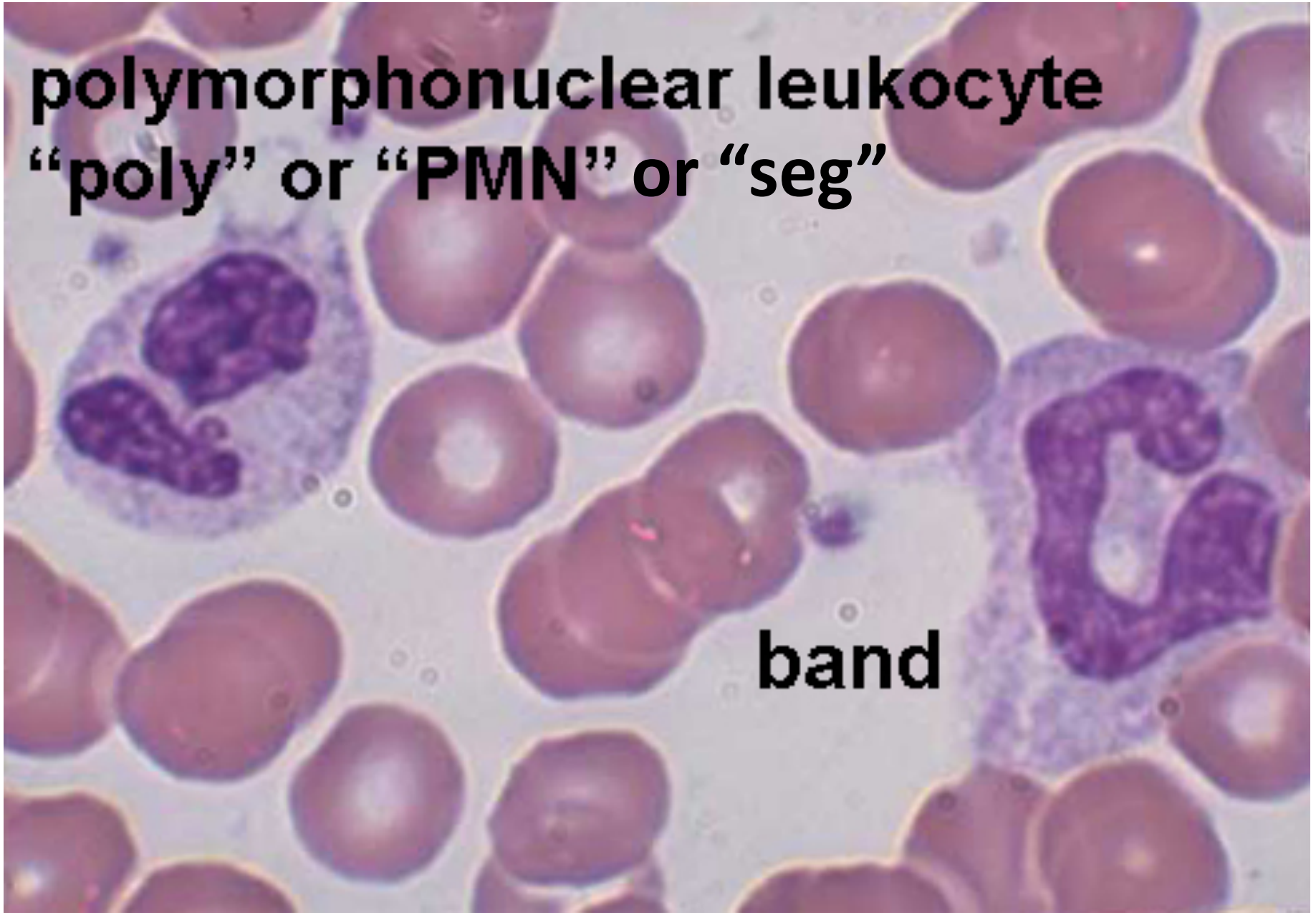
Peter Newburger, MD

First, a few words about neutrophils

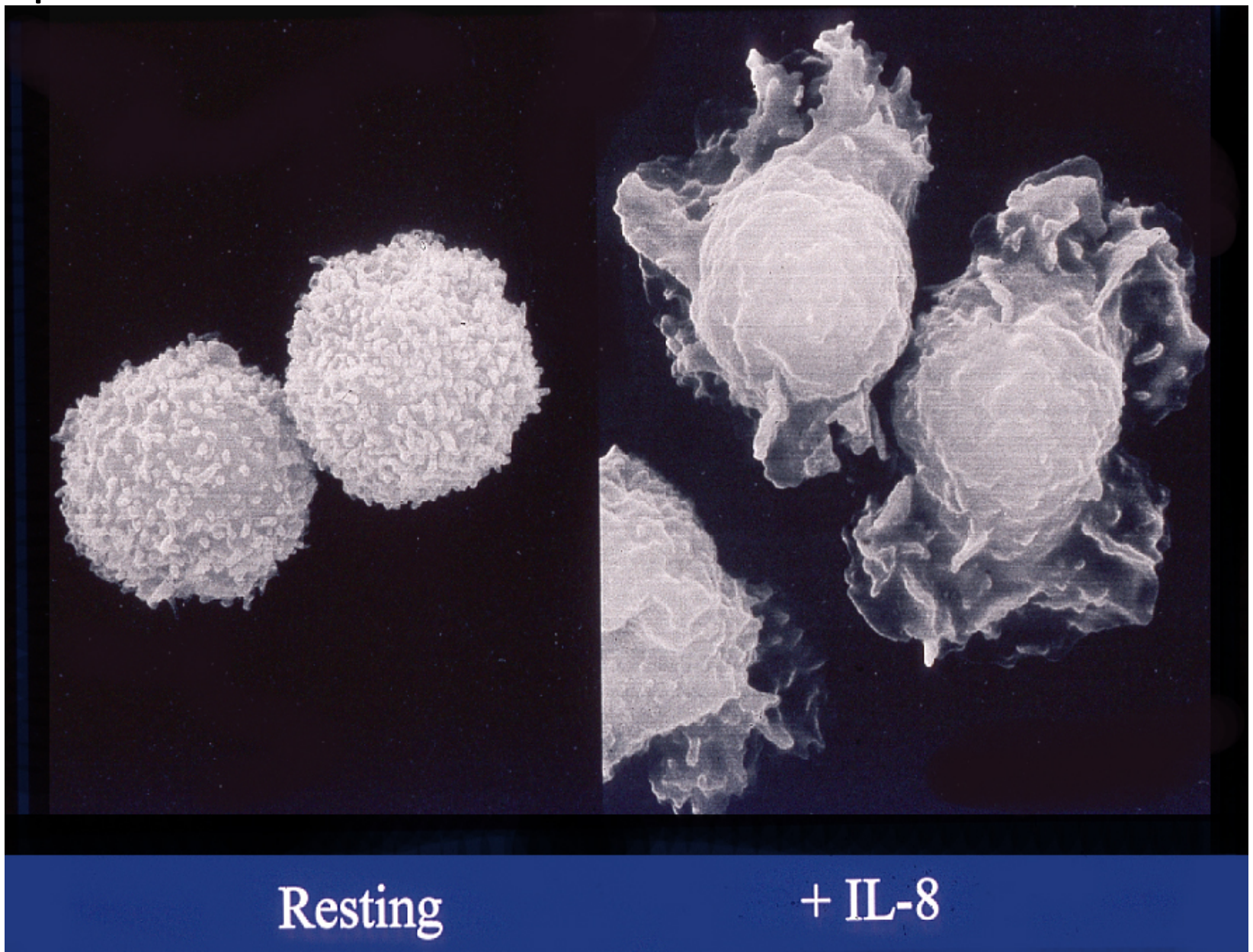
and their family of granulocytes



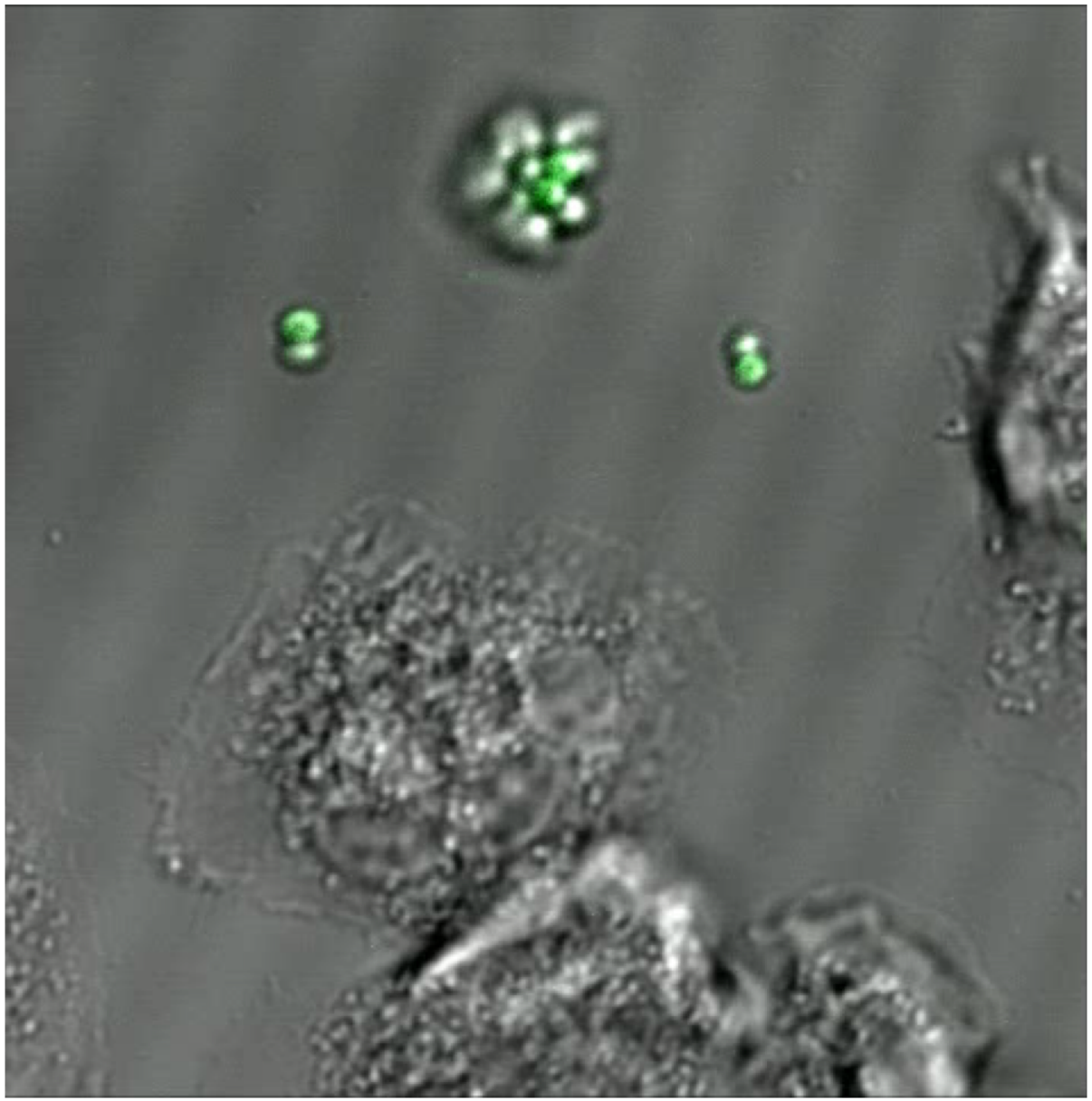
Neutrophils have many aliases:



Neutrophils in 3-d

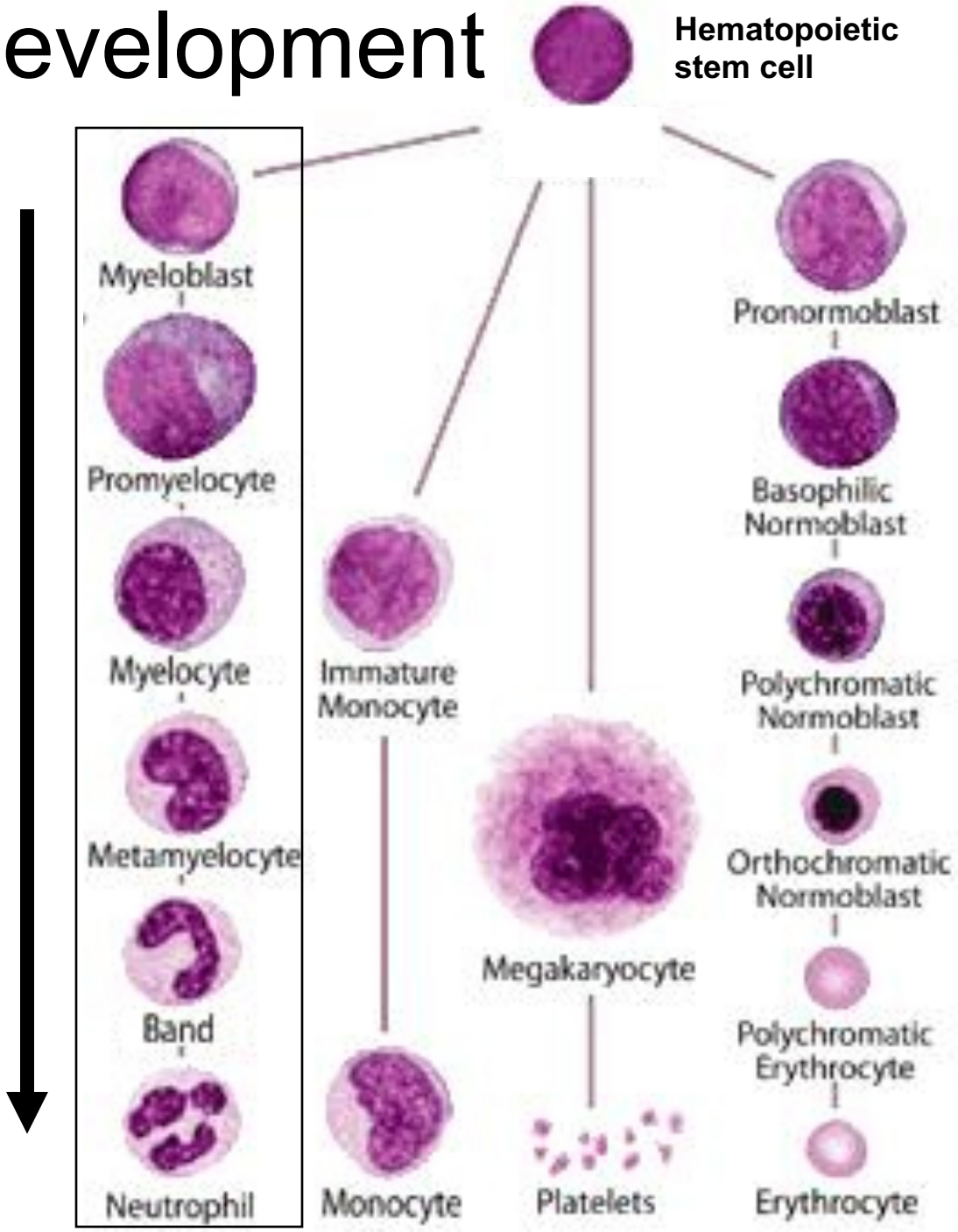


Neutrophil in real time

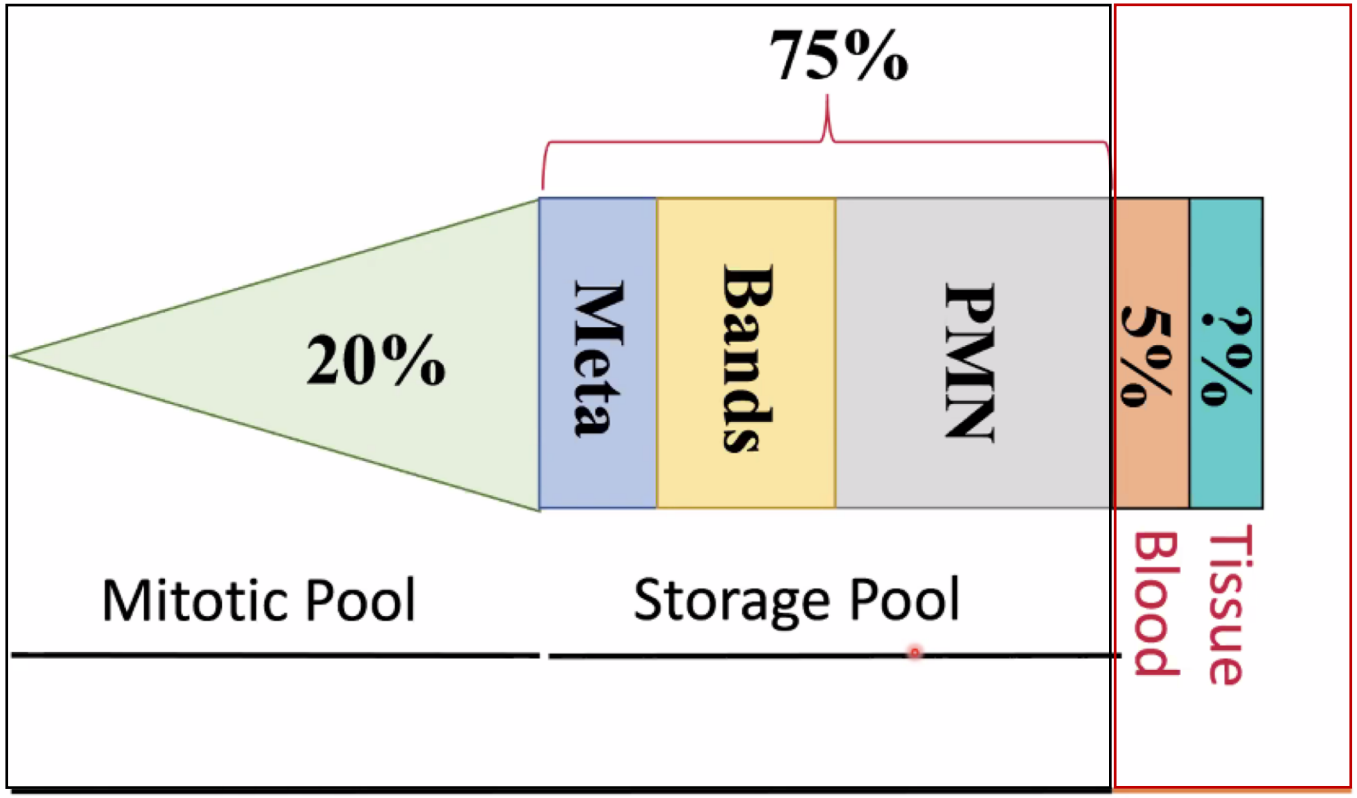


Neutrophil development

G-CSF
(Neupogen)



The Different Pools of Neutrophils



- Mitotic/Proliferating Pool:
  Starts from myeloblast and produces billions of cells daily
- Storage pool/Non-proliferating:
  Final maturation and pool of neutrophils to mobilize
- Peripheral blood
  - 2% circulating pool (the measured absolute neutrophil count, ANC)
  - 3% marginating pool

Neutropenia
“Standard” Definition of Risk

ANC	Clinical Severity
1000-1500	No increased risk of infection
500-1000	Little or no increased risk of infection
200-500	Increased risk of infection
<200	Very high risk of infection

Modifiers of Risk

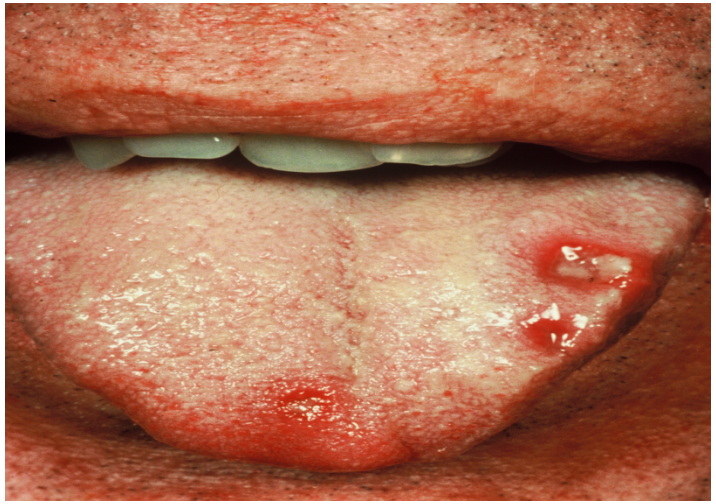
Risk also depends on

- Duration of neutropenia: long-term is higher risk
- Mechanism of neutropenia: destruction (e.g. autoimmune) is lower risk than lack of production (e.g. congenital)
- Bone marrow reserves
- Barrier function (e.g. mucositis)

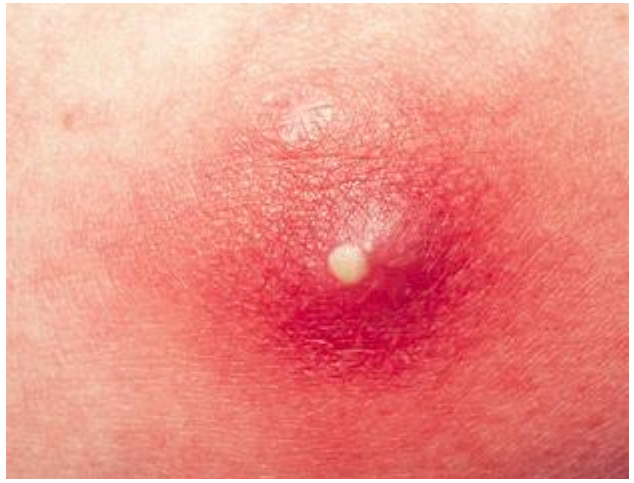
The standard classification was based largely on cancer patients receiving chemotherapy. They have additional risk from immune suppression, poor nutrition, central venous catheters, organ damage, etc.

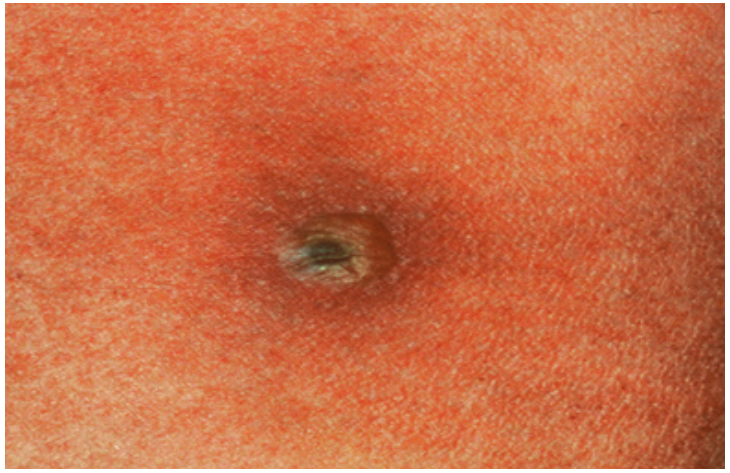
Clinical Indicators of Risk

- Severe or recurrent infections
- Mouth ulcers



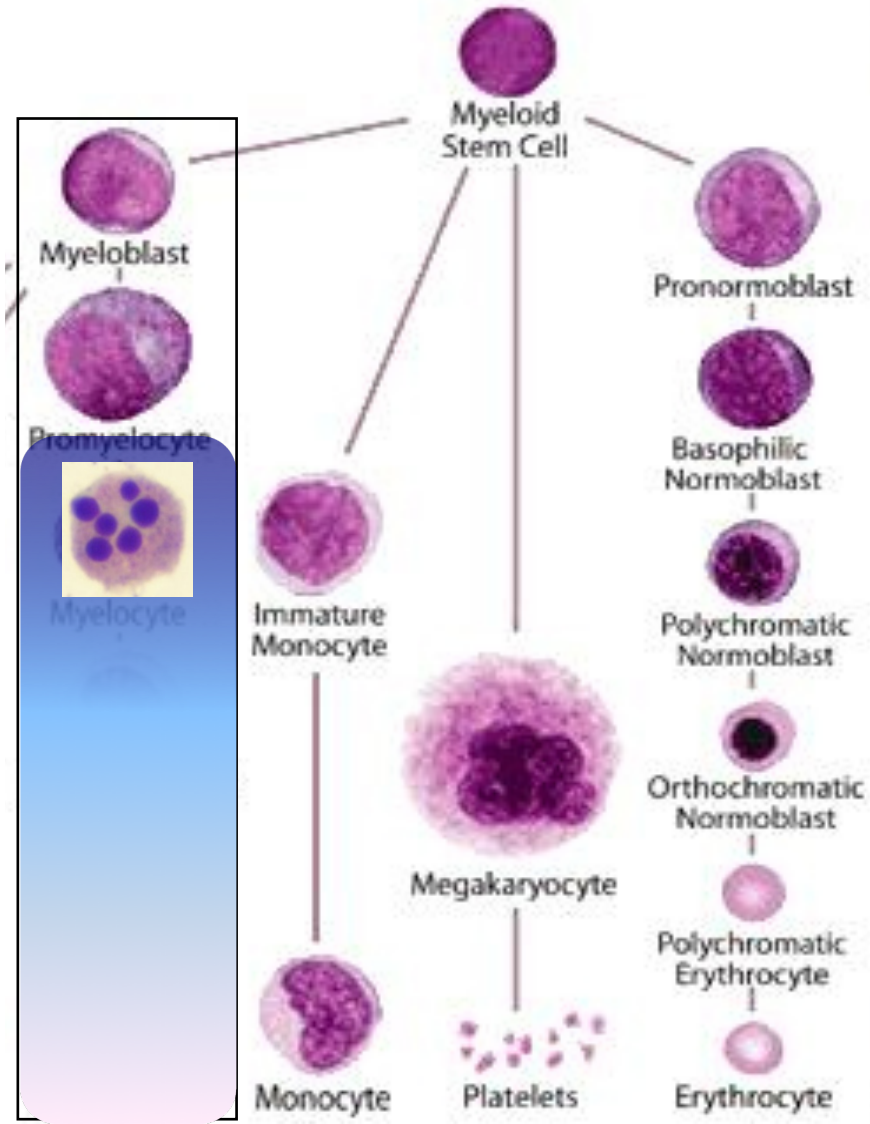
- Abscesses: pus vs. “cold”





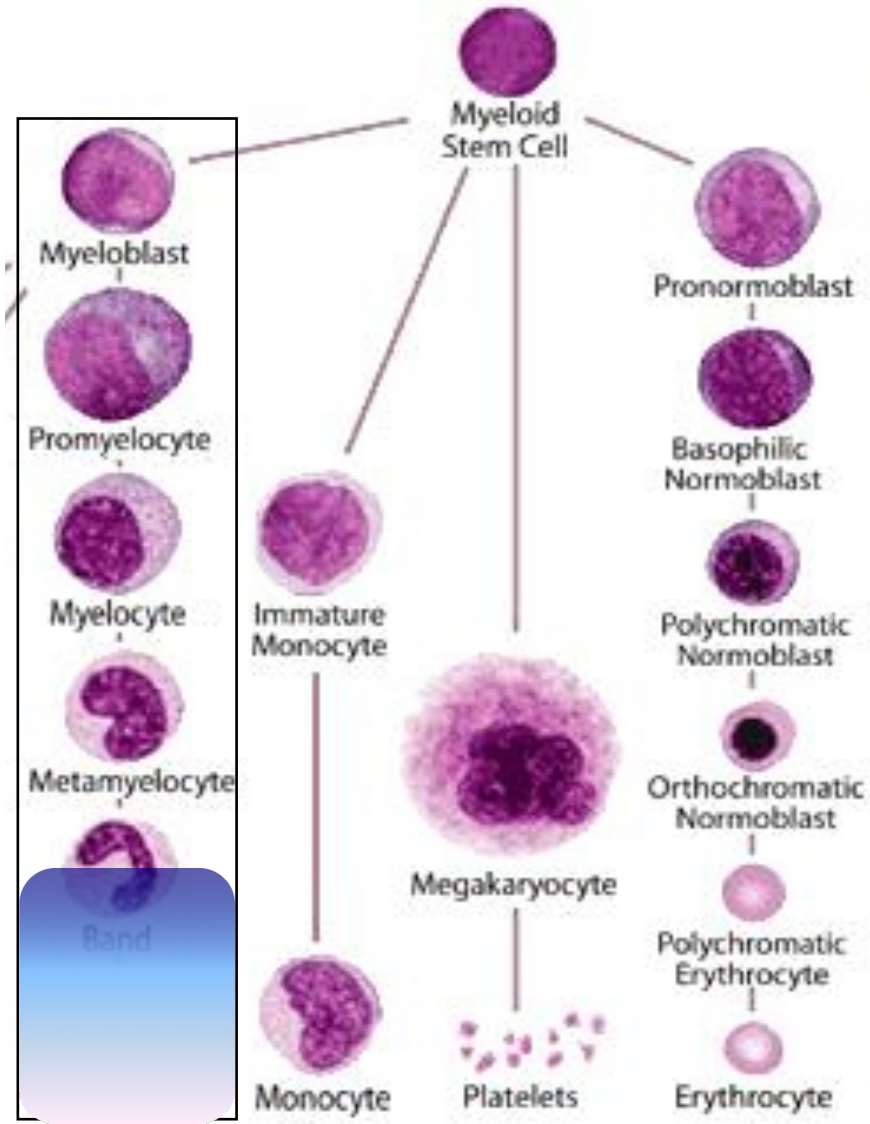
Mechanisms of Neutropenia: Lack of production

- Severe congenital



Mechanisms of Neutropenia: Lack of production

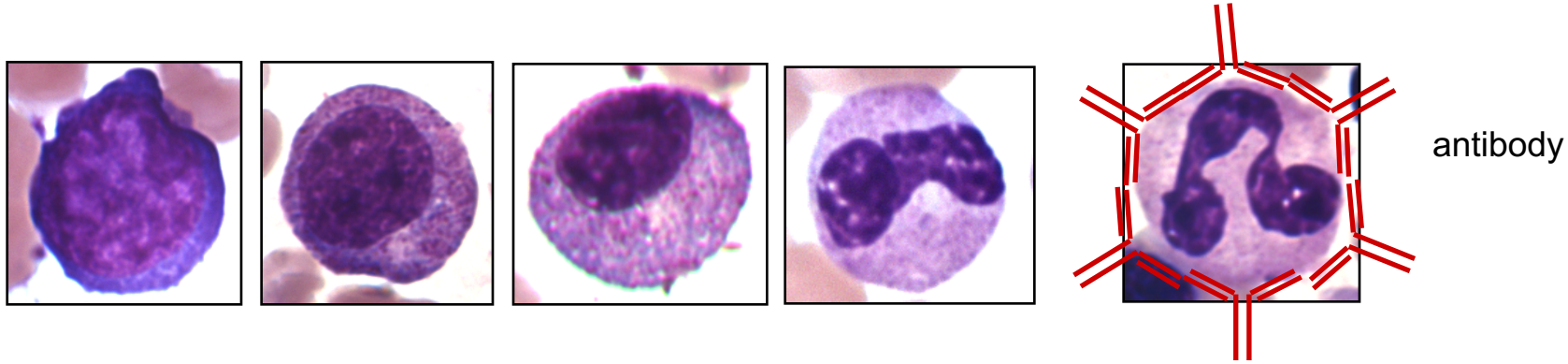
- Cyclic



Mechanisms of Neutropenia:

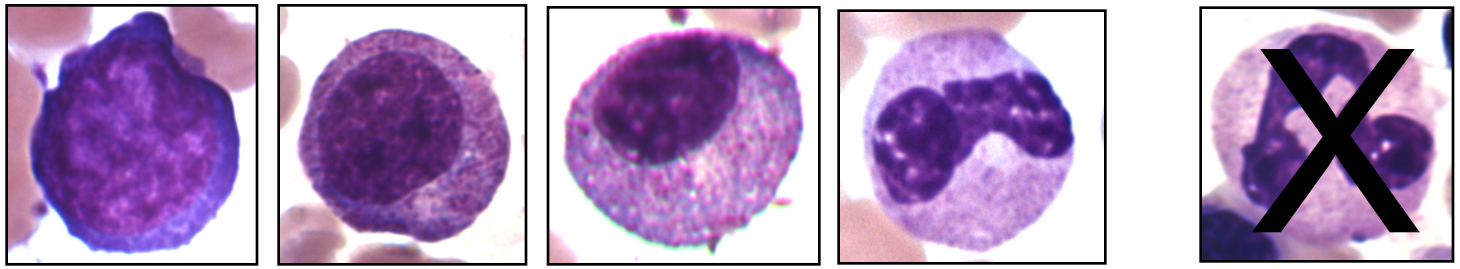
Antibody-mediated destruction

- autoimmune



Mechanisms of Neutropenia:

Idiopathic: medicalese for
"we don't know"

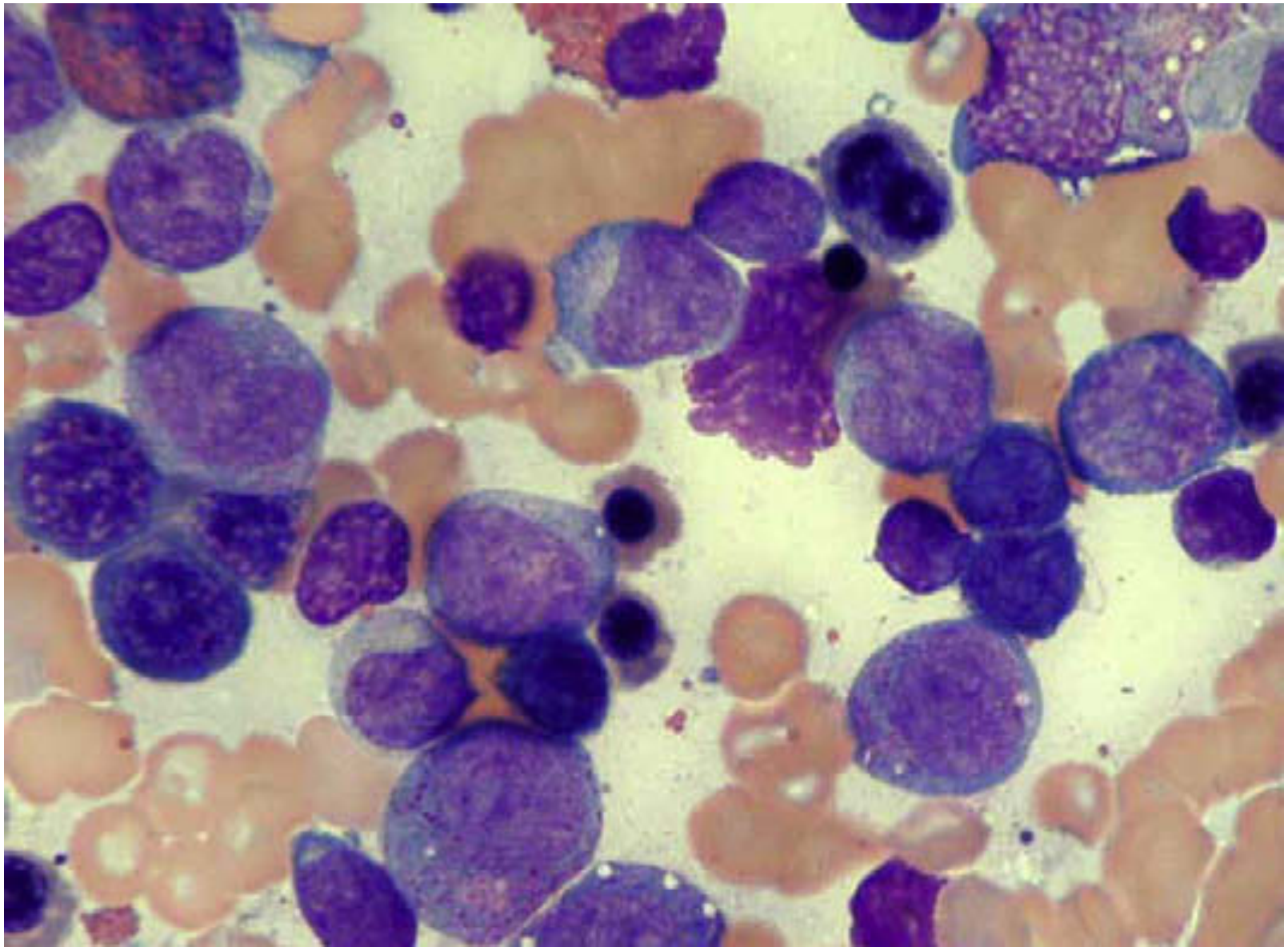


Bone marrow

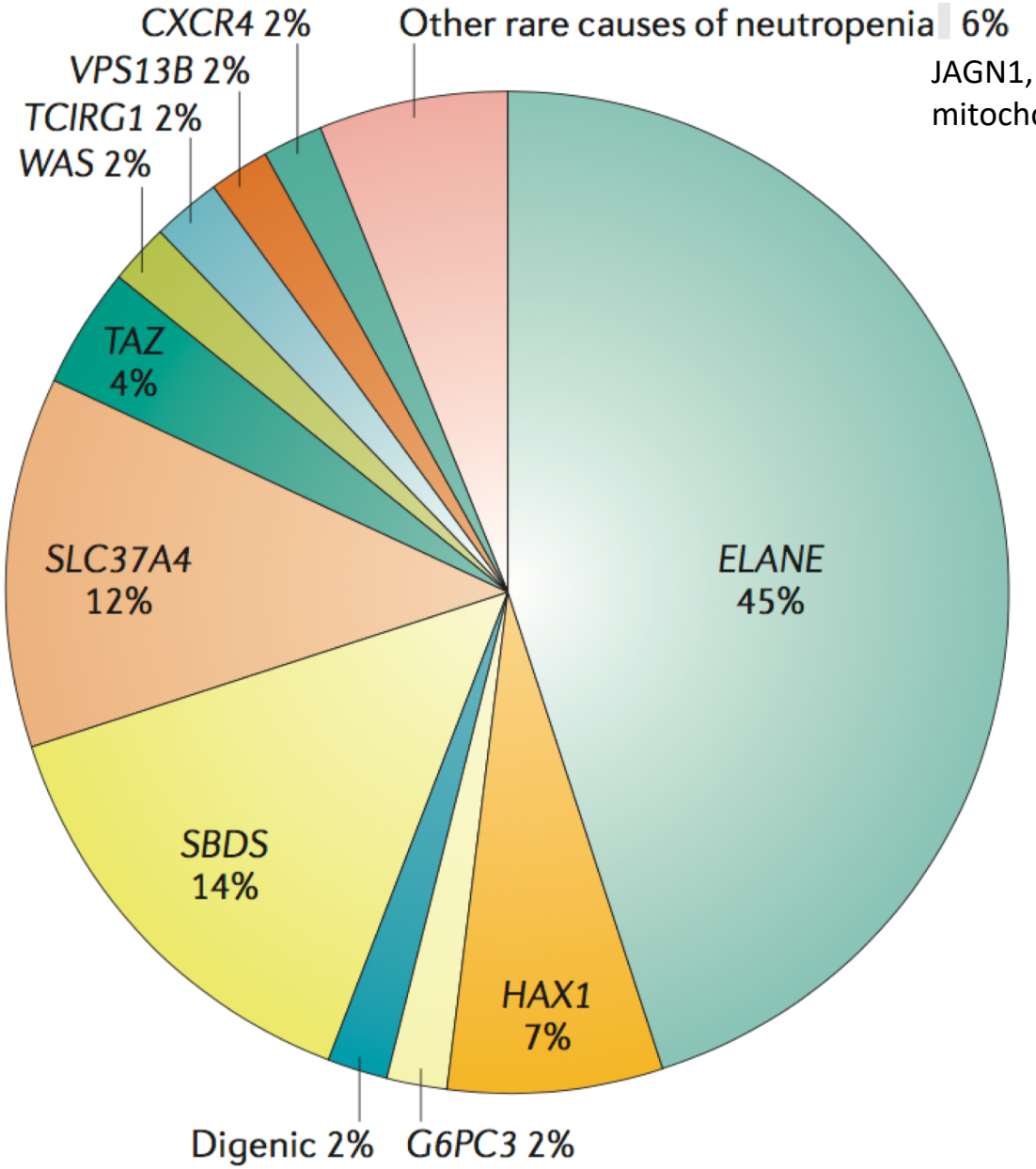
Blood

- ?autoimmune – most, especially in childhood
- ?lack of production
- ?failure to release cells from bone marrow

Congenital Neutropenias



Genetic causes of severe congenital neutropenia



JAGN1, LAMTOR2, GFI1, LYST, USB1, mitochondrial DNA deletions

Skokowa et al. *Nat Rev Primer Dis*. 2017; 3:1

Free 527-gene SCN/IEI panel from Invitae

https://www.invitae.com/en/path4ward/

Sponsored, no-charge genetic testing and counseling for individuals who may carry a genetic mutation known to be associated with chronic neutropenia or primary immunodeficiency disorders (PID).

CLINICIANS: GET STARTED

PATIENTS: GET STARTED

PATH4WARD

Patient Access To Hope

for Rare Primary Immunodeficiencies

This program is available to patients in the U.S. and Canada who meet the criteria below:

- Suspicion of chronic neutropenia or primary immunodeficiency disorders (PID)

Can't see your patients in-office? Have Invitae ship buccal or saliva collection kits directly to them.

HOWEVER:

***SBDS* not included in the panel**

(nor *DARC/ACKR1*)

Treatment of Severe Congenital Neutropenia

- G-CSF (filgrastim, Neupogen®)
  - Does G-CSF cause MDS/AML or does treatment permit patients to live long enough to develop it?
    - ANSWER: YES
  - Few or no cases of MDS/AML in cyclic, idiopathic, or autoimmune neutropenia treated with G-CSF
- Hematopoietic stem cell transplantation
  - Who should be transplanted?
- Gene therapy
- Novel drug therapies

Severe Congenital Neutropenia: Treatment

G-CSF (filgrastim, Neupogen®, biosimilars)

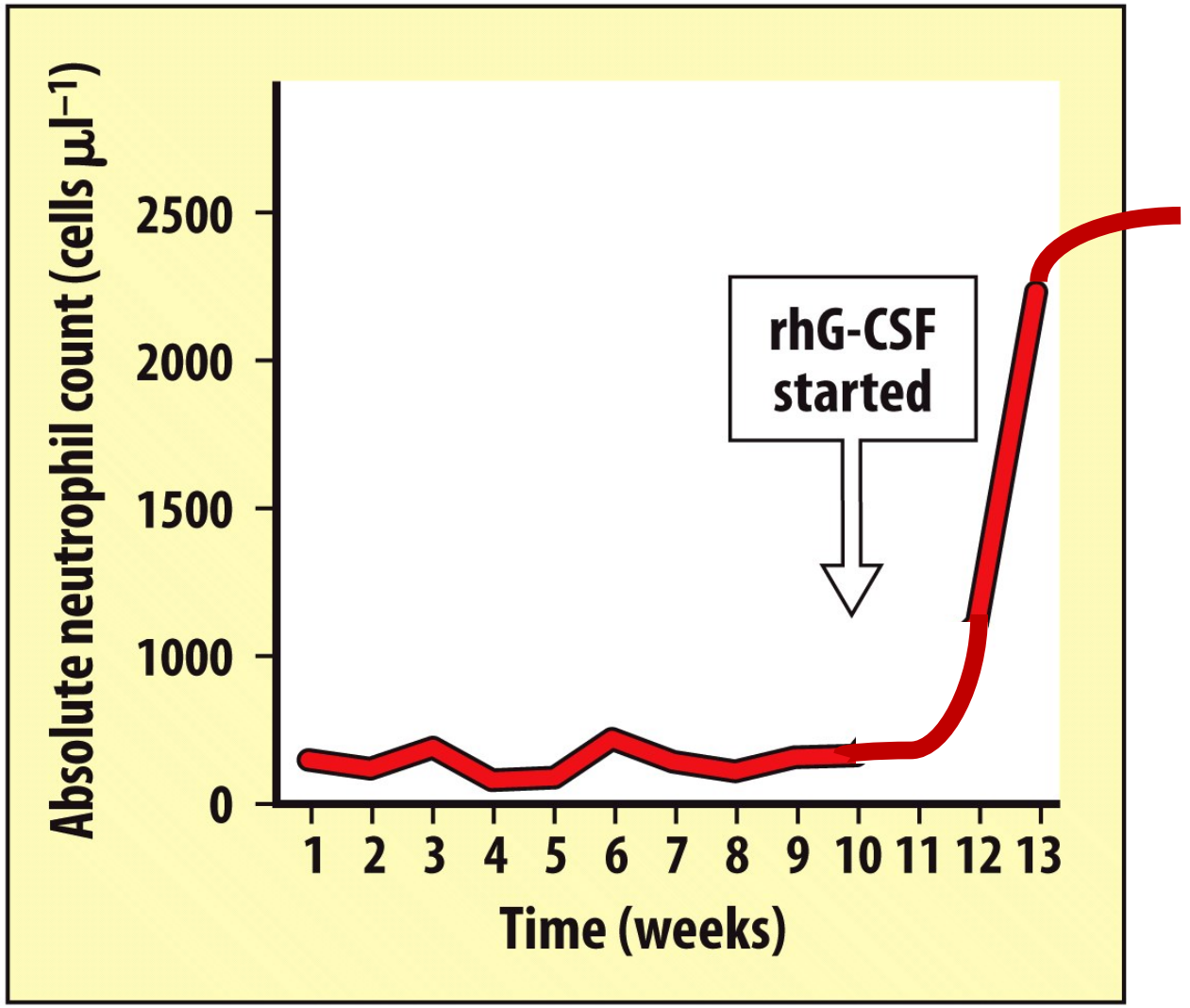


Figure 25.2 Case Studies in Immunology, 6ed. (© Garland Science 2012)

Benefits of G-CSF in SCN

- Before the cytokine era (pre-1993):
  - Severe recurrent bacterial and fungal infections
  - Sepsis mortality 50% in the first year of life
  - 3 case reports of acute myeloid leukemia (AML)
- Currently:
  - G-CSF is now the standard of care for SCN (also severe cyclic) and some forms of idiopathic/autoimmune
  - Dramatic reduction in infections and deaths
  - Increased risk of myelodysplasia (MDS) and AML

Indications for transplant in SCN

Absolute indication	Probable indication	Possible indication
Myelodysplasia/leukemia (MDS/AML)	Requirement for high doses of G-CSF (e.g. >15 mcg/kd/day)	Acquisition of bone marrow stem cell mutations predictive of MDS/AML *
Cytogenetic changes predictive of MDS/AML	ELANE mutation with high risk of MDS/AML	Matched sibling donor available
No response to G-CSF	Intolerable side effects of G-CSF	

Donor availability may influence “probable” vs “possible”

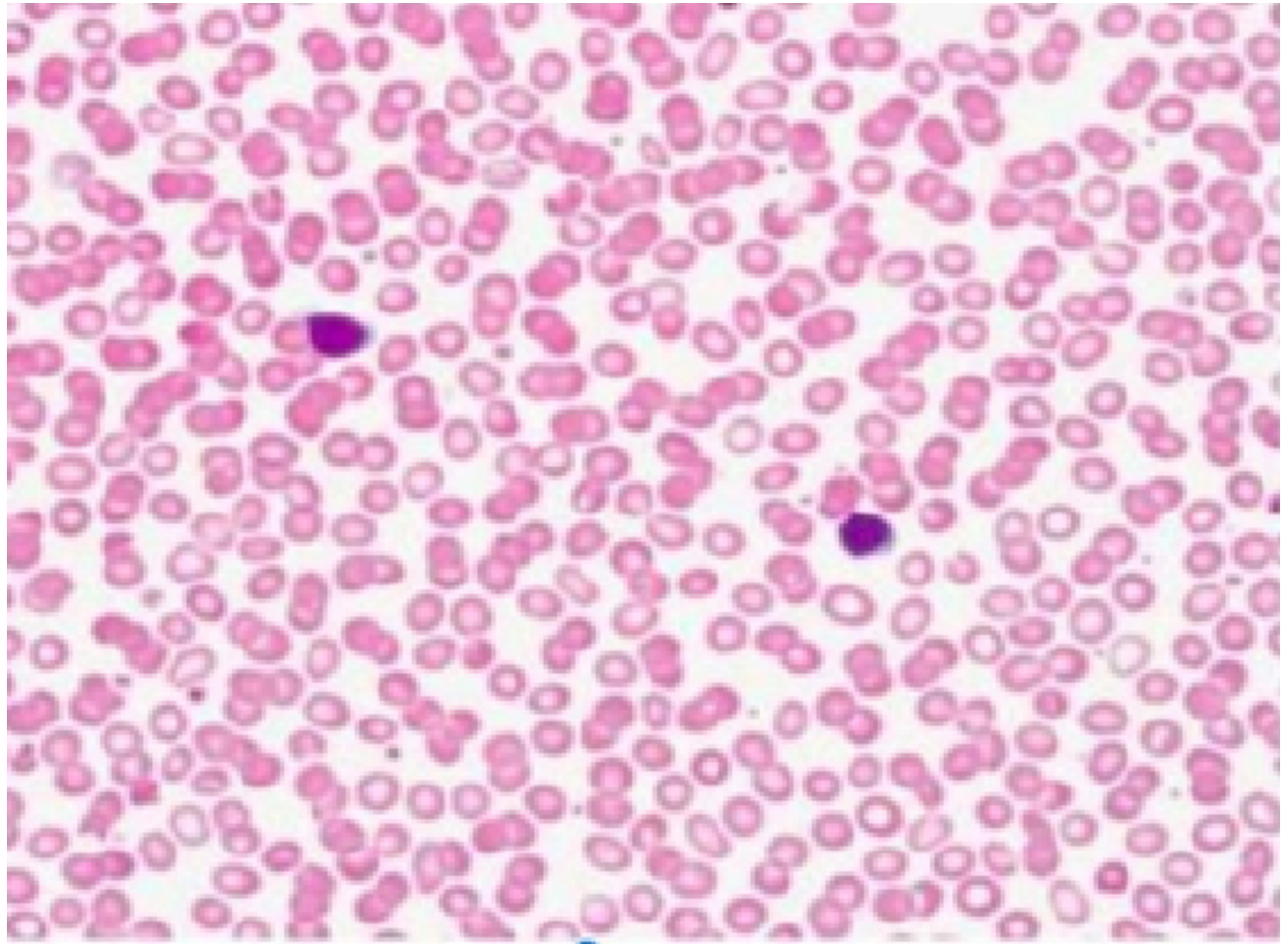
* This may become a “probable” indication as we gather more data

Bone marrow transplant

aka hematopoietic stem cell transplant

- Donor types:
  - Matched related (usually a sibling)
  - Matched unrelated
  - Mismatched unrelated – many different degrees of mismatch
  - Haplo-identical (half-matched, usually a parent)
  - Autologous (self – i.e. gene therapy)
- Conditioning: preparing the recipient for the transplant
  - Reduced intensity: intense chemo
  - Myeloablative: very intense chemo/radiation
- Success rates, survival, immediate and long-term side effects: discuss with transplant team
- More to come, later this morning

Acquired Neutropenia



Acquired Isolated Neutropenia: Etiologies

Transient

- Infections
- Drugs
- Nutritional (rarely isolated neutropenia)
- Alloimmune

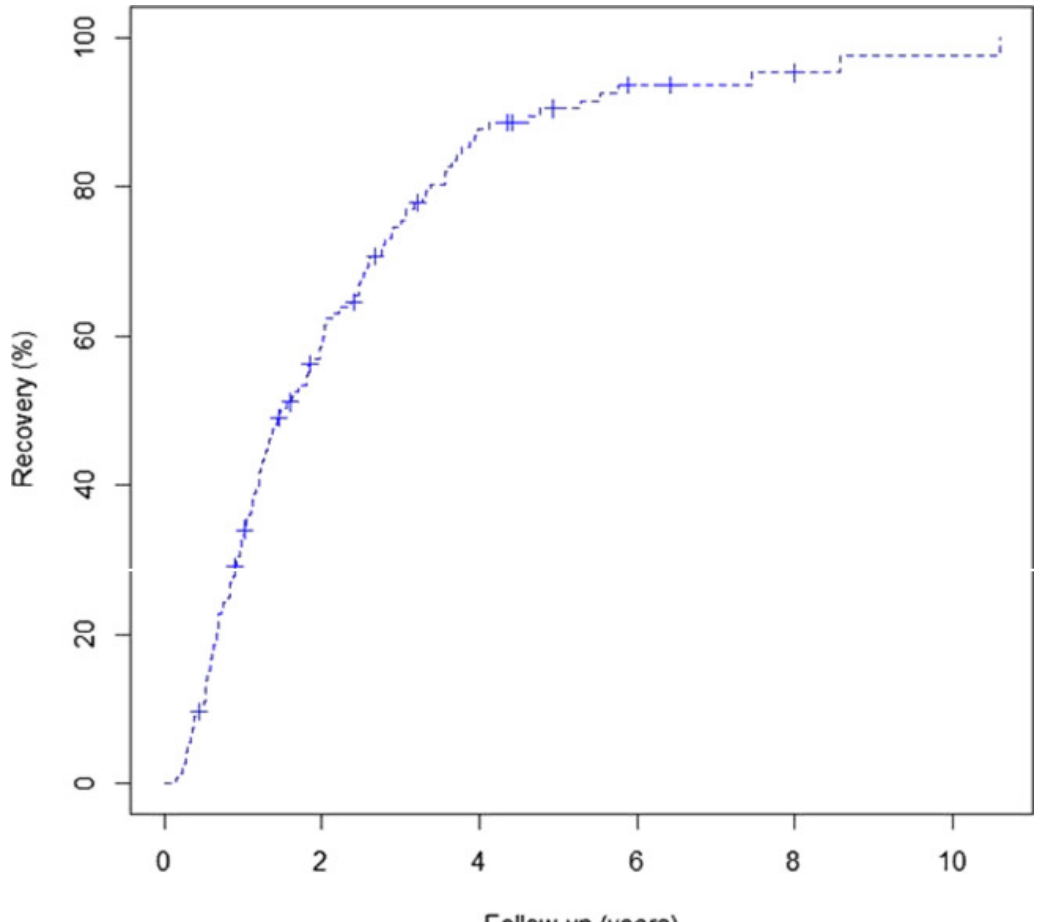
Chronic

- Immune/Idiopathic
- (Single lineage bone marrow failure)

Chronic Autoimmune/Benign/Idiopathic Neutropenia of Childhood

Clinical features

- Median age of diagnosis 8-11 months (range 3 - 38 months)
- Few and minor infections (mostly upper respiratory)
- Occasional gingivitis
- Rarely any serious or invasive infections
- Usually resolves spontaneously by age 5-10



Chronic Autoimmune/Benign/Idiopathic Neutropenia of Childhood

Laboratory features

- Median ANC at time of diagnosis ≈200 cells/µL
- ANC rises at times of stress or bacterial infection, or with glucocorticoid stimulation
- Bone marrow (if performed) shows normal to increased neutrophils and precursors
- Anti-neutrophil antibodies sometimes detected, but not sensitive or specific

Predictive Value of Anti-Neutrophil Antibody Test

	Positive	Negative
Patients	22	14
Male/Female	9/13	6/8
Age at onset - years mean (range)	1.1 (0.01 – 1.4)	0.7 (0.07 – 1.2)
ANC median (range)	167 (0 – 784)	255 (41 – 692)
Age at recovery - years mean (range)	3.0 (1.1 – 6.9)	4.0 (0.8 – 9.6)
Duration of G-CSF - years median (range)	1.6 (0.4 – 3.6)	2.7 (0.5 – 8.0)

100% recovered

Boxer LA, Bolyard AA, Marrero TM et al. Is there a role for anti-neutrophil antibody testing in predicting spontaneous resolution of neutropenia in young children? [abstract]. Blood 2015;126:2211

Management of Acquired Neutropenia

Whom to observe?	**Mild/Moderate, asymptomatic** **But R/O severe causes such as GATA2**
When to evaluate further?	**ANC<1000 for > 4 weeks; serious infections; more than 1 lineage; syndromic features**
How to manage fever?	**Mild/Mod Neutropenia: depends on age, vitals** **Severe: IV antibiotics**
Whom to treat with G-CSF?	**Severe or refractory infection** **Quality of life – avoid ER visits** **Treat for symptoms or quality of life, not ANC**

No prophylactic antibiotics or steroids

General measures

- Good dental hygiene and dental care
- Discourage excessive precautions (social isolation, “neutropenic diet,” antibacterial skin cleaners, household disinfection)
- Encourage PCP to continue all immunizations
  - Neutropenia does not increase the risk of vaccines, including live virus vaccines
  - Neutropenia does not diminish the response to vaccines
  - Patients with neutropenia as part of a more generalized immune deficiency disorder should discuss vaccines with their immunologists

Questions