Neutropenia in Children

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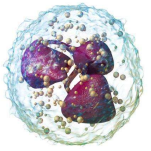
Objectives

1. Review function and life cycle of a neutrophil
2. Develop a structured approach for neutropenia in a child
3. Discuss practical considerations in managing a child with neutropenia



Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". WikiJournal of Medicine 1 (2). DOI:10.15347/wjm/2014.010.

Disclosures

- No relevant conflicts of interest

Hematology Referrals for Triage

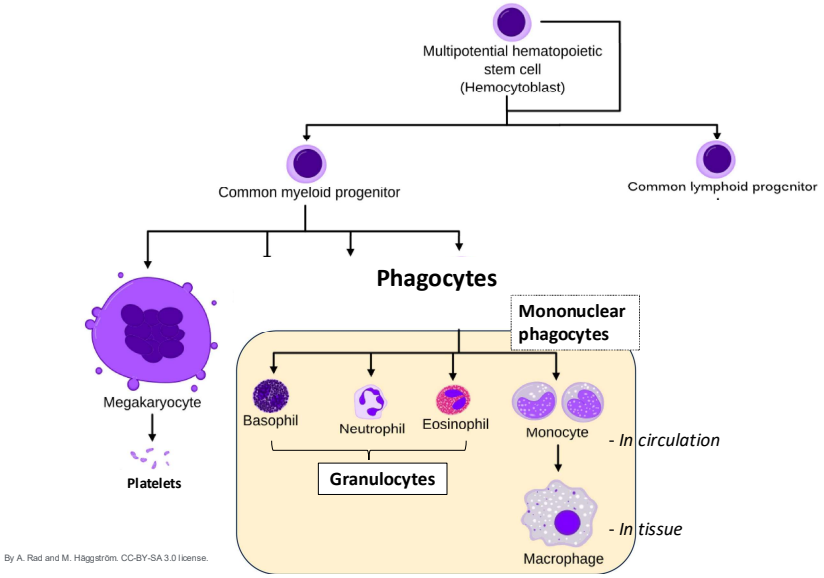
- 7 yo admitted with clostridial necrotizing enterocolitis. Longstanding history of 'gum boils' and poor dentition. Multiple CBCs since birth, **neutrophils 0.1 – 1.0**.
- 4 month old, in ER with fever, **neutrophils 0.2**. No previous bloodwork.
- 3 yo, severe failure to thrive, multiple CBCs, **neutrophils 0.9 - 1.0**, Platelets 90.
- 14 yo, with restrictive eating disorder, anxiety, **neutrophils 0.9**, Hb 90, MCV 68.

Pattern Recognition:
Whose neutropenia are you most worried about?

What Are Neutrophils?

Hematology Profile, Differential and Blood Film Review

CBC & Differential			Ref Range	Units
WBC	7.7		3.9-10.2	10*9/L
RBC	**5.34**	**H**	4.05-5.15	10*12/L
Hemoglobin	133		118-146	g/L
Hematocrit	0.42		0.35-0.43	
MCV	78		77-92	fL
MCH	**25**	**L**	26-32	pg
RDW	12.6		11.6-14.8	%
Platelets	339		180-440	10*9/L
MPV	10.6		8.6-11.1	fL
Neutrophils	3.2		1.5-7.4	10*9/L
Lymphocytes	3.9		1.5-4.2	10*9/L
Monocytes	0.5		0.1-0.7	10*9/L
Eosinophils	0.1		0.0-0.7	10*9/L
Basophils	0.0		0.0-0.1	10*9/L



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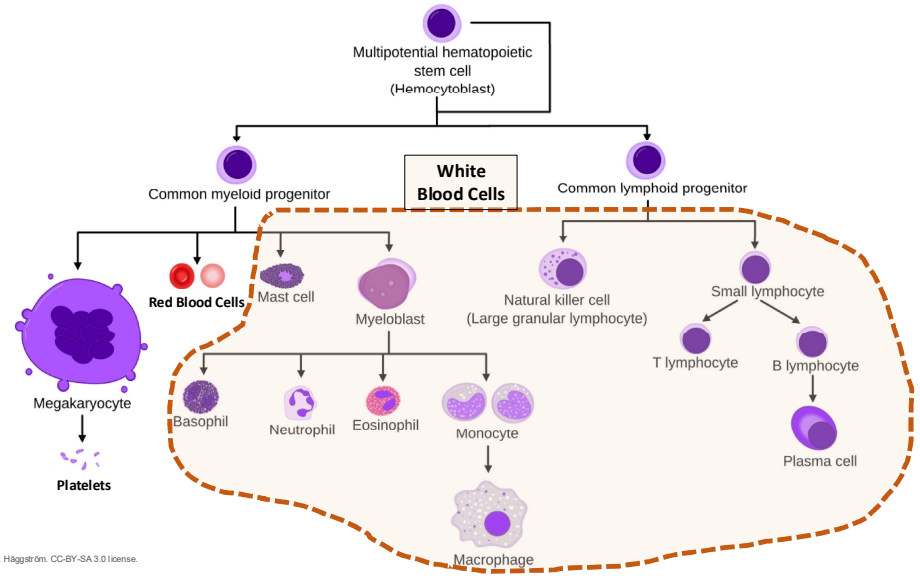

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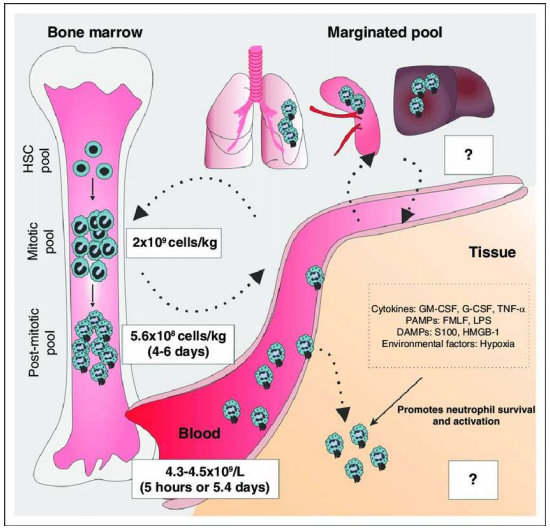
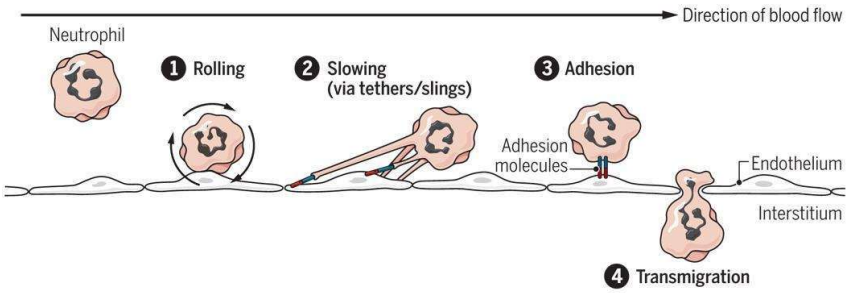


Neutrophil heterogeneity: Implications for homeostasis and pathogenesis - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Integration-of-factors-determining-neutrophil-lifespan-The-bone-marrow-neutrophil_fig1_299343590 [accessed 21 Oct 2024]

Neutrophil Migration



Klaus Ley *et al*, Neutrophils: New insights and open questions. *Sci. Immunol.* 3, (2018)

Disorders of Neutrophils

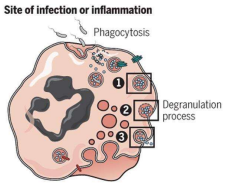
Function

- ❑ Abnormal chemotaxis (adhesion, migration)
  - e.g. Leukocyte Adhesion Deficiency, actin deficiency
- ❑ Abnormal degranulation
  - e.g. Chronic Granulomatous Disease, Chediak-Higashi Syndrome

Number

- ❑ Neutropenia
  - Increased destruction/sequestration
  - Decreased production

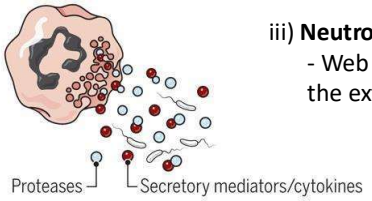
Neutrophil Killing



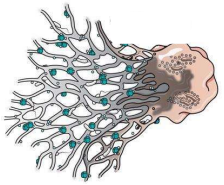
i) **Phagocytosis**
- Engulfing pathogen

www.itechpost.com/articles/109889/20220406/entertainmenttech-fascinating-tech-behind-spider-mans-web-shooters.htm

ii) **Degranulation**
- Release of cytotoxic enzymes from granules



iii) **Neutrophil Extracellular Trap (NET)**
- Web of chromatin expelled into the extracellular space



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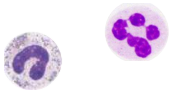
Absolute Neutrophil Count (ANC)



Differential				
Neutrophils	56.01	H	1.70-5.00	10*9/L
Band Neutrophils	26.79	H	0.00-0.80	10*9/L
Lymphocytes	14.61	H	1.90-4.30	10*9/L
Monocytes	7.31	H	0.10-0.70	10*9/L
Eosinophils	12.18	H	0.00-0.70	10*9/L
Basophils	9.74	H	0.00-0.10	10*9/L
Metamyelocytes	14.61	H	<0.01	10*9/L
Myelocytes	9.74	H	<0.01	10*9/L
Promyelocytes	2.44	H	<0.01	10*9/L
Nucleated RBC	2.44	H	<0.01	10*9/L
RBC Morphology				

Neutropenia (x 10^9/L)

Normal: ≥1.5

Mild: 1.0 – 1.4

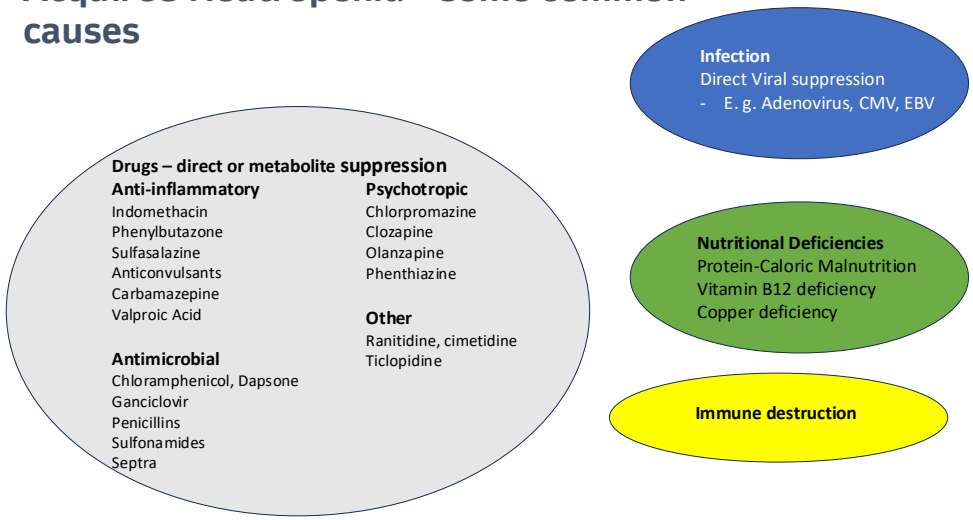
Moderate: 0.5 – 0.9

Severe: <0.5

Manifestations of Neutropenia

1. **Infection**
   - Fungal, candidal
   - Bacterial (staph aureus, gram-negative)
   - Opportunistic, Nosocomial infection
   - Otitis media, pneumonia, sepsis, CNS, and gastrointestinal (clostridial)
2. **Gastrointestinal Tract Integrity**
   - Oral mucosal ulcers, angular chelitis, gingivitis, periodontitis
   - Mucositis, typhlitis, neutropenic enterocolitis, peri-rectal abscesses
3. **Integumentary Integrity**
   - Poor healing
   - Cellulitis, furunculosis, superficial or deep abscesses
   - May form sterile abscess – lack of pus

Acquired Neutropenia – some common causes



An Approach to Neutropenia

Acquired
- Infection
- Drug
- (Auto) immune
- Nutritional Deficiencies

Immune Deficiency
- Immunoglobulins
- Lymphocytes, Thymus
- Neutrophil function, granule morphology

Rheumatological/Autoimmunity
- ANA, C3, C4, ESR
- HLH screening

Isolated Neutropenia
- Decreased marrow production
  - Congenital neutropenias

Acquired, Transient, or Fixed?

Fixed

Part of Systemic Condition?

Primary Bone Marrow Etiology?

Transient
- Post-infectious
- Marrow stress

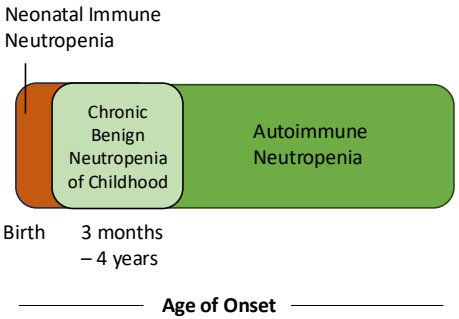
Visceral /Syndromic Features
- Musculoskeletal, Facial Dysmorphisms
- Cardiac, Genitourinary, Hepato-splenic abnormalities

Metabolic
- Abnormal glycogen metabolism

Abnormal Marrow Function / Broad Hematological Abnormalities
- Increased Destruction/Sequestration
- Bone Marrow Failure syndromes
- Bone Marrow infiltration

Immune Neutropenia

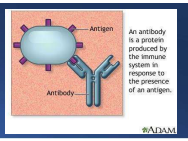
- **Anti-neutrophil antibody**
  - Neutrophils rapidly cleared from circulation by immune system
- **Neonatal:** isoimmunization with transplacental maternal IgG antibody, analogous to Rh disease
  - Can take up to 6 months to clear IgG from circulation
  - Risk of infection



Chronic Benign Neutropenia of Childhood

Demographics	▪ Most common cause of chronic neutropenia in infancy & childhood ▪ **Age of presentation:** 3 months – 4 yrs (typically 1st year of life)
Neutrophil Count	▪ Often severe neutropenia (median 0.2 x 10^9/L).

Autoimmune Neutropenia



Etiology	• **Variable** ▫ Isolated or idiopathic ▫ Manifestation of generalized autoimmune process ▫ Secondary complication of infection, drugs, or malignancy

Autoimmune Disorders
- **Autoimmune cytopenias (Evan's Syndrome)**
- Autoimmune lymphoproliferative syndrome (ALPS)
- Felty syndrome (arthritis, splenomegaly, leukopenia)
- Primary biliary cirrhosis
- Sjogren syndrome
- Scleroderma
- **Systemic Lupus Erythematosus**

Malignancy - lymphoma
Castleman Disease

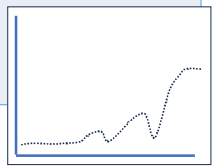
Infections
- Infectious mononucleosis
- HIV

Immunoglobulin Defects
- **Common Variable Immunodeficiency (CVID)**
- Hyper IgM Syndrome (CD40L deficiency)
- IgA deficiency
- X-linked agammaglobulinemia

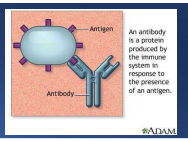
Drugs
- Anti-inflammatory - Aminopyrine, Ibuprofen, IVIg
- Anticonvulsants - Phenytoin
- Antimicrobials - Penicillins
- Anti-thyroid - Methimazole, propylthiouracil
- Cardiovascular - Hydralazine, procainamide, quinidine
- Other – Chlorpropramide, Gold, Levamisole

Chronic Benign Neutropenia of Childhood

Demographics	▪ Most common cause of chronic neutropenia in infancy & childhood ▪ **Age of presentation:** 3 months – 4 yrs (typically 1st year of life)
Neutrophil Count	▪ Often severe neutropenia (median 0.2 x 10^9/L).
Infectious Complications	▪ Minor infections, increased frequency – otitis media, gingivitis, URTI, skin/soft tissue - Rarely (in infants) – pneumonia, sepsis
Outcome:	▪ Spontaneous resolution occurs in nearly all patients ▪ **Duration of severe neutropenia**: Median 20 months, but can persist up to 5 years



Autoimmune Neutropenia



Etiology	• **Variable** ▫ Isolated or idiopathic ▫ Manifestation of generalized autoimmune process ▫ Secondary complication of infection, drugs, or malignancy
Median Neutrophil Count	• **Variable** - Can show reactive rise with infection, inflammation, steroids - Mild splenomegaly and elevated monocytes can be present
Infectious Complications	• Cutaneous and respiratory tract infections - Serious infections generally uncommon
Outcome:	• Depends on etiology • Older children – often a secondary manifestation of generalized autoimmunity

How I Manage Benign Neutropenia of Childhood / Autoimmune Neutropenia

Making the Diagnosis

- ❑ **History, Family History, Physical Exam, Bloodwork**
  - Exclude alternative diagnosis
  - Bone Marrow biopsy (select patients) – wait until child is >1 year of age
  - Genetic panel (select patients) - exclude congenital bone marrow failure syndromes or immune deficiencies

→ **Currently, no reliable lab testing available for anti-neutrophil antibody**

Follow Up

- **Trend ANC** - bloodwork 1-3 times per year
- **Education** – reassurance, re-iteration of febrile neutropenia precautions
- **Surveillance** – any emergence of other autoimmune or syndromic manifestations
  - **Resolution**: 2x normal CBC (outside of periods of illness), separated by at least 1 month
    – will discharge from my clinic

Febrile Neutropenia Precautions

Does this apply to every neutropenic patient?

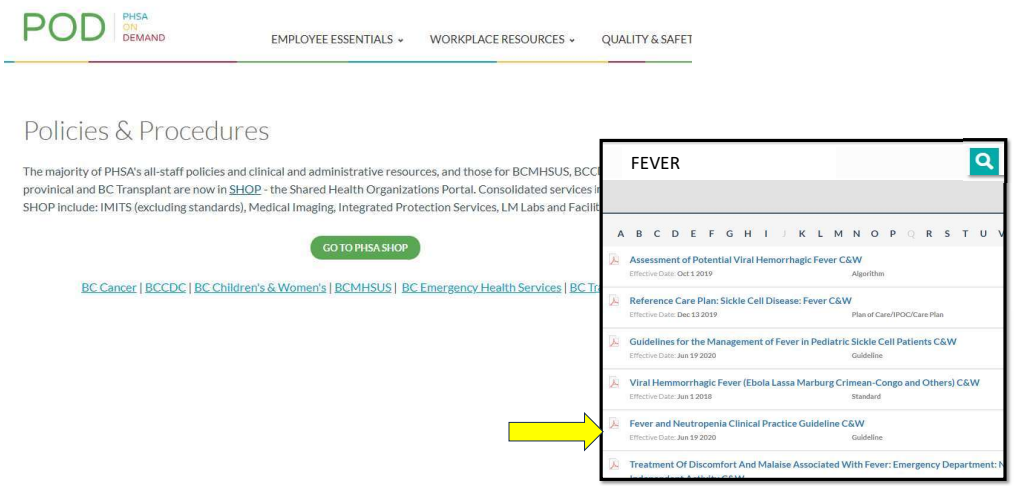
- ❑ Select group of hematology/oncology patients <u>with known diagnoses</u> are considered low risk for invasive bacterial infections, despite neutropenia
  - → If patient appears unwell, treat accordingly
  - → If ANC is very low (e.g. <0.1) or history of prolonged sustained neutropenia, will treat conservatively regardless of diagnosis
- ❑ BCCH POD Febrile Neutropenia Guidelines

Febrile Neutropenia Precautions

In a neutropenic patient, assume their ability to fight bacterial infection is impaired

- ❑ **Urgent clinical assessment**
- ❑ **CBC and blood culture**
  - consider CRP, lactate, creatinine, blood gas
  - other investigations as indicated (e.g. chest xray, NP swab, urine culture, etc.)
- ❑ **Consider broad-spectrum empiric antibiotics until bacterial infection is excluded**
  - piperacillin-tazobactam, 3rd or 4th generation cephalosporines, meropenem, levofloxacin
- ❑ **Low threshold to admit to hospital for observation**

<u>BCCH POD Febrile Neutropenia Guidelines</u>



Granulocyte Colony Stimulating Factor

G-CSF (Filgrastim, Nivestym)

- Mobilizes neutrophils from bone marrow into circulation
- Severely neutropenic patients with serious infections or congenital neutropenias
  - *Rarely* used in AIN to prevent infectious complications
- Daily subcutaneous injection, short duration of action
- Expensive

An Approach to Neutropenia

Acquired, Transient, or Fixed?

Fixed

Immune Deficiency
- Immunoglobulins
- Lymphocytes, Thymus
- Neutrophil function, granule morphology

Rheumatological/Autoimmunity
- ANA, C3, C4, ESR
- HLH screening

Part of Systemic Condition?

Visceral /Syndromic Features
- Musculoskeletal, Facial Dysmorphisms
- Cardiac, Genitourinary, Hepato-splenic abnormalities

Metabolic
- Abnormal glycogen metabolism

Isolated Neutropenia
- Decreased marrow production
  - Congenital neutropenias

Primary Bone Marrow Etiology?

Abnormal Marrow Function / Broad Hematological Abnormalities
- Increased Destruction/Sequestration
- Bone Marrow Failure syndromes
- Bone Marrow infiltration

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- Marrow stress

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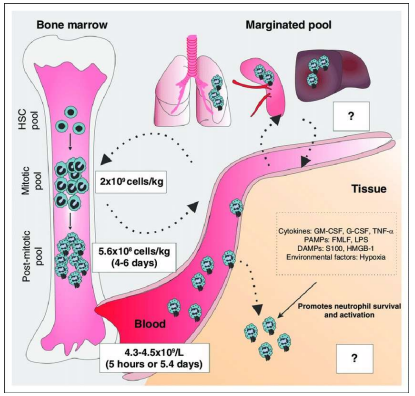
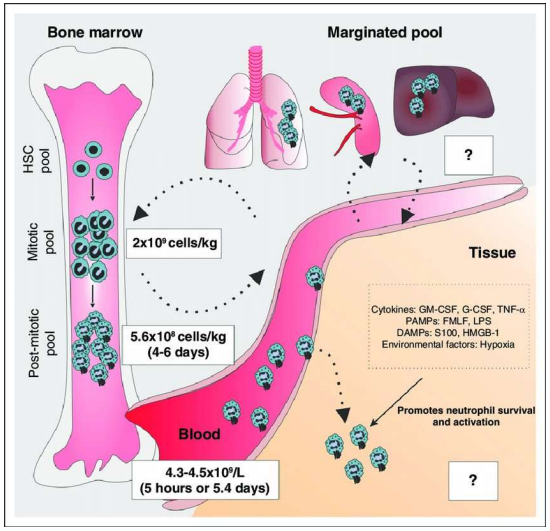
Congenital Neutropenias

Isolated Neutropenia
- Decreased marrow production

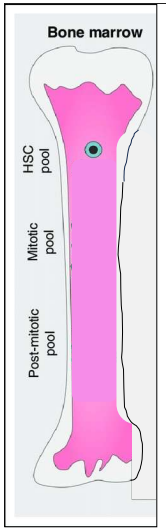
Some congenital entities:
- **Severe Congenital Neutropenia**
- **Cyclic Neutropenia**
- Reticular Dysgenesis
- Myelokathexis/WHIM syndrome
- Albinism/neutropenia syndromes (e.g. Chediak-Higashi)
- Familial benign neutropenia
- Neutropenia as a first isolated presentation of Bone Marrow Failure syndromes



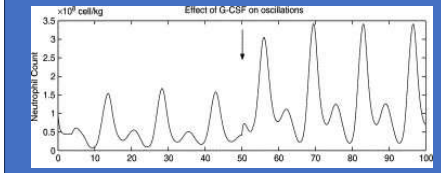


Cyclic Neutropenia

- Cyclical "Maturation Arrest" – failure to progress through myelocyte stage of development
- Incidence: 1 case per million
- Phenotype lessens with age
- Autosomal Dominant or sporadic
  - ***ELANE*** gene mutation (up to 80% of cases)



- **3-week cycles of severe neutropenia**
  - Secondary monocytosis, eosinophilia, thrombocytosis
- Periodontal Disease
- Clostridial infections - necrotizing enterocolitis, myofaciitis

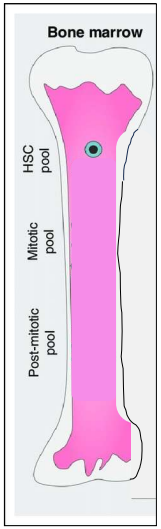


G-CSF
- Does not stop oscillations, but shortens cycle

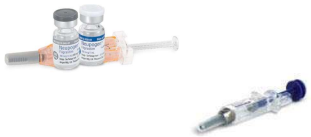
Neutrophil heterogeneity: Implications for homeostasis and pathogenesis - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Integration-of-factors-determining-neutrophil-lifespan-The-bone-marrow-neutrophil_fig1_299343590 [accessed 21 Oct 2024]

Severe Congenital Neutropenia (Kostmann Syndrome)

- "Maturation Arrest" – failure to progress through myelocyte stage of development
- Incidence: 2 cases per million
- Autosomal Dominant, Recessive, X-linked, or sporadic
  - ***ELANE*** gene mutation (up to 80% of cases)



- **ANC consistently <0.2 x 10^9/L**
  - Secondary monocytosis, eosinophilia, thrombocytosis
- G-CSF used to decrease risk of serious infection



Risks
- **Infection**
- **Malignancy**
  - 2-3% lifetime risk of evolving to Acute Myeloid Leukemia
  - Long-term GCSF use may increase risk

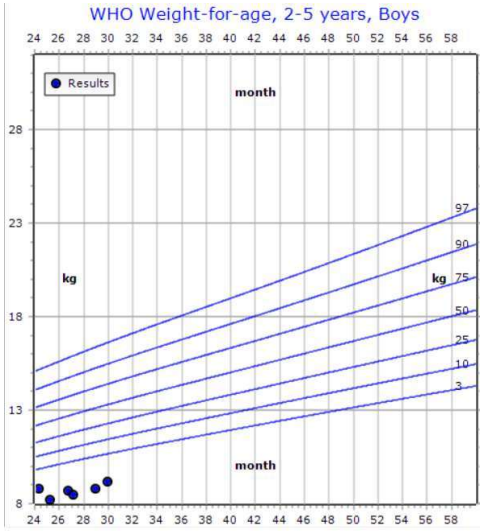
Neutrophil heterogeneity: Implications for homeostasis and pathogenesis - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Integration-of-factors-determining-neutrophil-lifespan-The-bone-marrow-neutrophil_fig1_299343590 [accessed 21 Oct 2024]

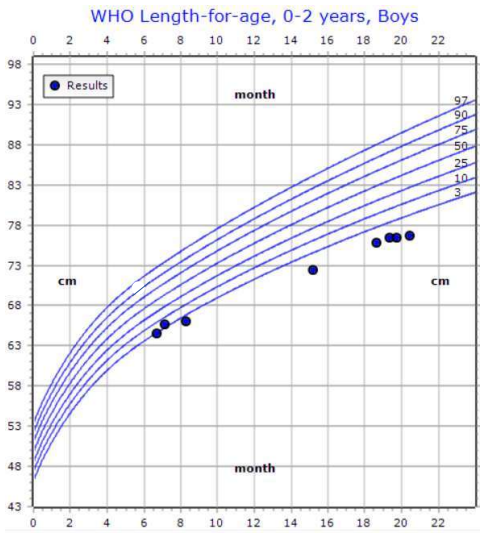
Bone Marrow Failure Syndromes (BMFS)

- **Congenital syndromes involving failure of the hematopoietic system**
  - Poor growth, congenital abnormalities, developmental delay
- **Pre-disposition to Cancer**
  - Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML)
  - Some solid tumours (life-long risk)
- **Single or multiple cytopenias - abnormalities can evolve with time**

	Type of Bone Marrow Abnormality
Severe Aplastic Anemia (sporadic)	Autoimmune destruction of hematopoietic progenitor cell
Fanconi Anemia (AR, X-linked, sporadic)	Bone marrow failure evolving to MDS/AML
Dyskeratosis Congenita (AD, AR, X-linked, sporadic)	Bone marrow failure evolving to MDS/AML
Shwachman-Diamond Syndrome (AR, sporadic)	Cytopenias, BMF, MDS/AML
Diamond Blackfan Anemia (AD, sporadic)	Isolated red cell aplasia; MDS/AML.

	Type of Bone Marrow Abnormality	Congenital Abnormalities	Treatment of Bone Marrow Failure
Severe Aplastic Anemia (sporadic)	Autoimmune destruction of hematopoietic progenitor cell	No. May have overlap presentation with **autoimmune hepatitis**	Immunosuppresive Therapy or BMT
Fanconi Anemia (AR, X-linked, sporadic)	Bone marrow failure evolving to MDS/AML	Yes. Failure to thrive, developmental delay, **abnormal thumbs**, cardiac, skeletal, renal/GU, Cafe-au-lait spots, craniofacial abnormalities, microcephaly. **Risk of solid tumours, particularly head and neck carcinomas.**	BMT
Dyskeratosis Congenita (AD, AR, X-linked, sporadic)	Bone marrow failure evolving to MDS/AML	Yes. **Leukoplakia, dystrophic nails, alopecia, pulmonary and liver fibrosis**, hypogonadism	BMT
Shwachman-Diamond Syndrome (AR, sporadic)	Cytopenias, BMF, MDS/AML	Possible. **Pancreatic exocrine insufficiency**, malabsorption, skeletal abnormalities, poor growth, mild development delay, behavioural challenges	BMT
Diamond Blackfan Anemia (AD, sporadic)	Isolated red cell aplasia; MDS/AML.	Yes. Failure to thrive, developmental delay, craniofacial abnormalities, cleft palate, **abnormal thumbs, cardiac,** skeletal, renal/GU. **Risk of osteosarcoma.**	Steroids, BMT if non-responsive





Bone Marrow Failure Syndromes – Care of the Patient

- **Hematology**: Bone Marrow Evaluation, regular surveillance bloodwork
  - Determination if/when transfusions, bone marrow transplant is indicated
- **<u>Multi-Disciplinary Care</u>**
  - General Pediatrics - quarterback
  - Nutrition, General Surgery - Gastrostomy Tube
  - Cardiology/Cardiac Surgery
  - Plastic Surgery – hypoplastic thumbs
  - ENT/Dental/Sleep Medicine/audiology – palate, midline abnormalities, hearing loss
  - Orthopedics, PT, OT – skeletal abnormalities
  - Ophthalmology
  - Gastroenterology – pancreatic and hepatic abnormalities
  - Respirology
  - Dermatology
  - Developmental Peds, Psychology, Psychiatry – developmental, learning, behavioural challenges

Hematology Referrals for Triage

- 7 yo admitted with clostridial necrotizing enterocolitis. Longstanding history of 'gum boils' and poor dentition. Multiple CBCs since birth, **neutrophils 0.1 – 1.0**.

Cyclic Neutropenia

- 4 month old, in ER with fever, **neutrophils 0.2**. No previous bloodwork.

Benign Autoimmune Neutropenia

- 3 yo, severe failure to thrive, multiple CBCs, **neutrophils 0.9 - 1.0**, Platelets 90.

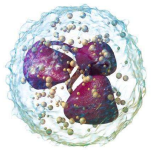
Fanconi Anemia

- 14 yo, with restrictive eating disorder, anxiety, **neutrophils 0.9**, Hb 90, MCV 68.

Neutropenia associated with malnutrition

Objectives

1. Review function and life cycle of a neutrophil
2. Develop a structured approach for neutropenia in a child
3. Discuss practical considerations in managing a child with neutropenia



Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". WikiJournal of Medicine 1 (2). DOI:10.15347/wjm/2014.010.

Summary

1. Neutropenia can be acquired, transient, or chronic
2. Associated lab or congenital abnormalities can point to underlying etiology
3. Fever in children with neutropenia is a medical emergency and should follow febrile neutropenia guidelines