Neutropenia

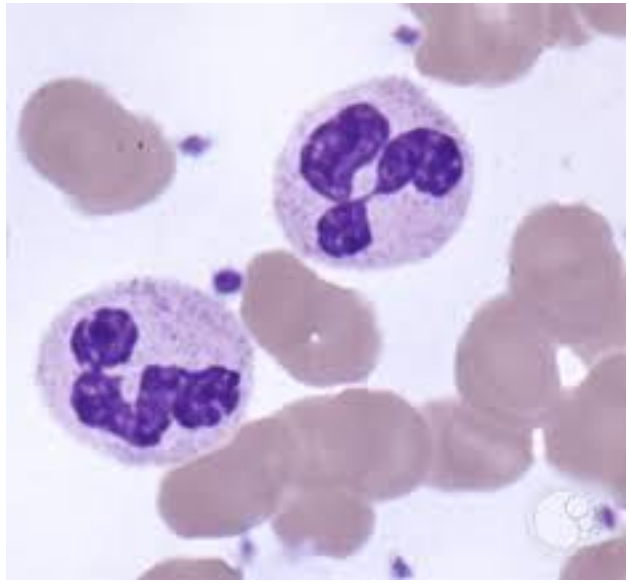
Investigation and management

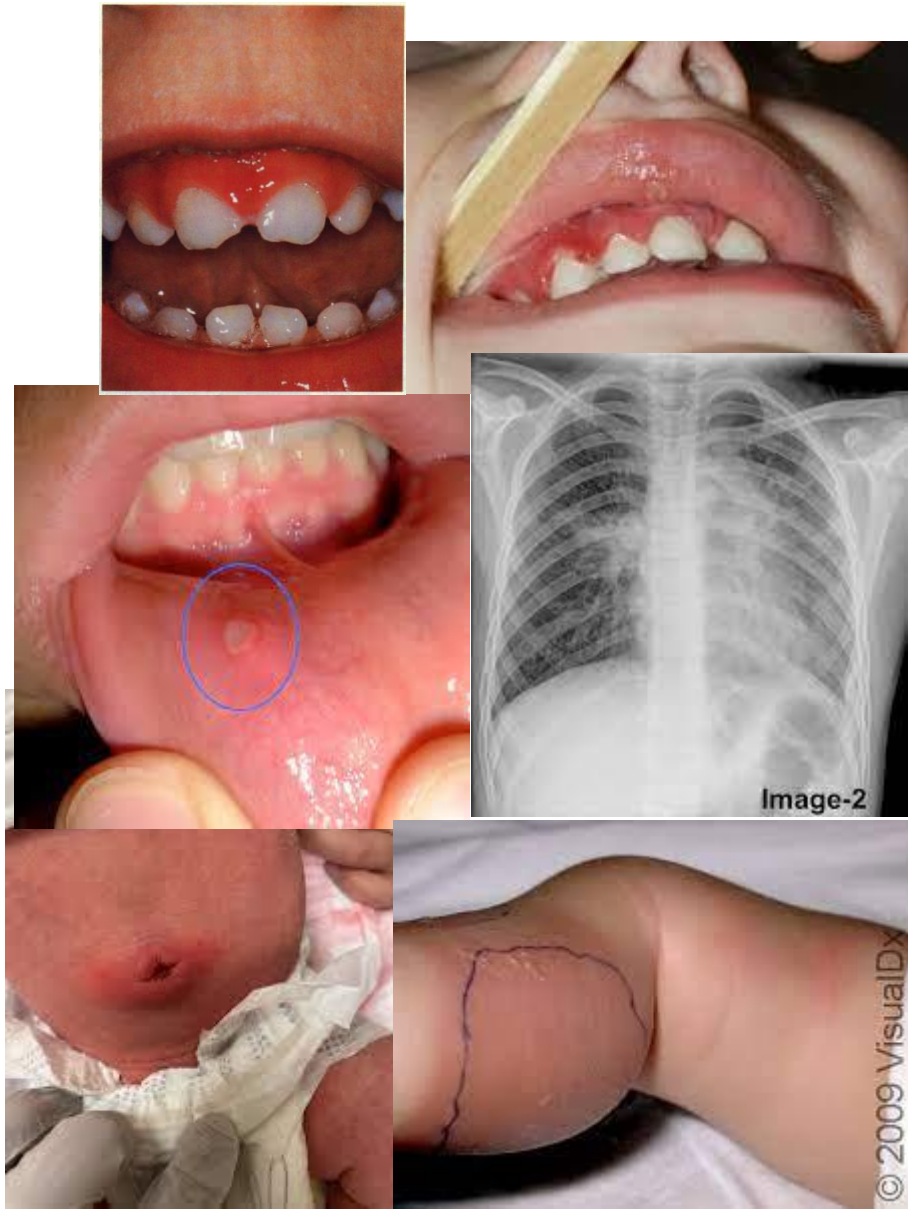
B Kaya

Consultant in Paediatric Haematology

Barts Health NHS Trust

Neutropenia can lead to life threatening infection





Neutropenic sepsis is a paediatric emergency!

Neutropenia classification

Normal ranges vary with age and ethnicity

Only 2-5% enter circulation (pooled in BM)

Reduced circulating or absolute neutrophil count to < 1.5 x $10^{9/L}$*

Mild: 1-1.5 x $10^{9/L}$

Moderate: 0.5-1 x $10^{9/L}$

Severe: 0.2-0.5 x $10^{9/L}$

Very Severe < 0.2 x $10^{9/L}$

Chronic if > 3 months

*Lower limit of 1.0 acceptable in infants, neonates < 2 weeks 5.0, racial normal (Duffy null associated neutropenia)<1.5

Causes of neutropenia

Decreased production	Impaired migration	Increased margination-sequestration	Increased destruction	Complex
Congenital neutropenia	Congenital neutropenia	Hypersplenism	Allo or auto-immune neutropenia	Immune dysfunction disorder
Bone marrow failure disorder		Pseudoneutropenia		Drugs (immune or non immune)
Infiltration				Viral infections
Cytotoxic drugs / radiotherapy				Congenital neutropenia
Storage disorders				
Nutritional				

Clinical assessment

- History of symptoms, age of onset, pattern of infection and episodes of hospitalisation, family history, medication, vaccination history
- Examination, dysmorphic features, growth and development, oral health, skeletal, hair & nails, lymphadenopathy and organomegaly

- If acute presentation with febrile illness – examine for signs of bacterial infection

- Don’t delay treatment with broad spectrum antibiotics!

Laboratory investigations
Determined by clinical features

1.

- Repeat FBC and blood film microscopy (interval dependent on clinical picture)
- Virology screen: Hepatitis A, B and C, EBV, CMV, HIV

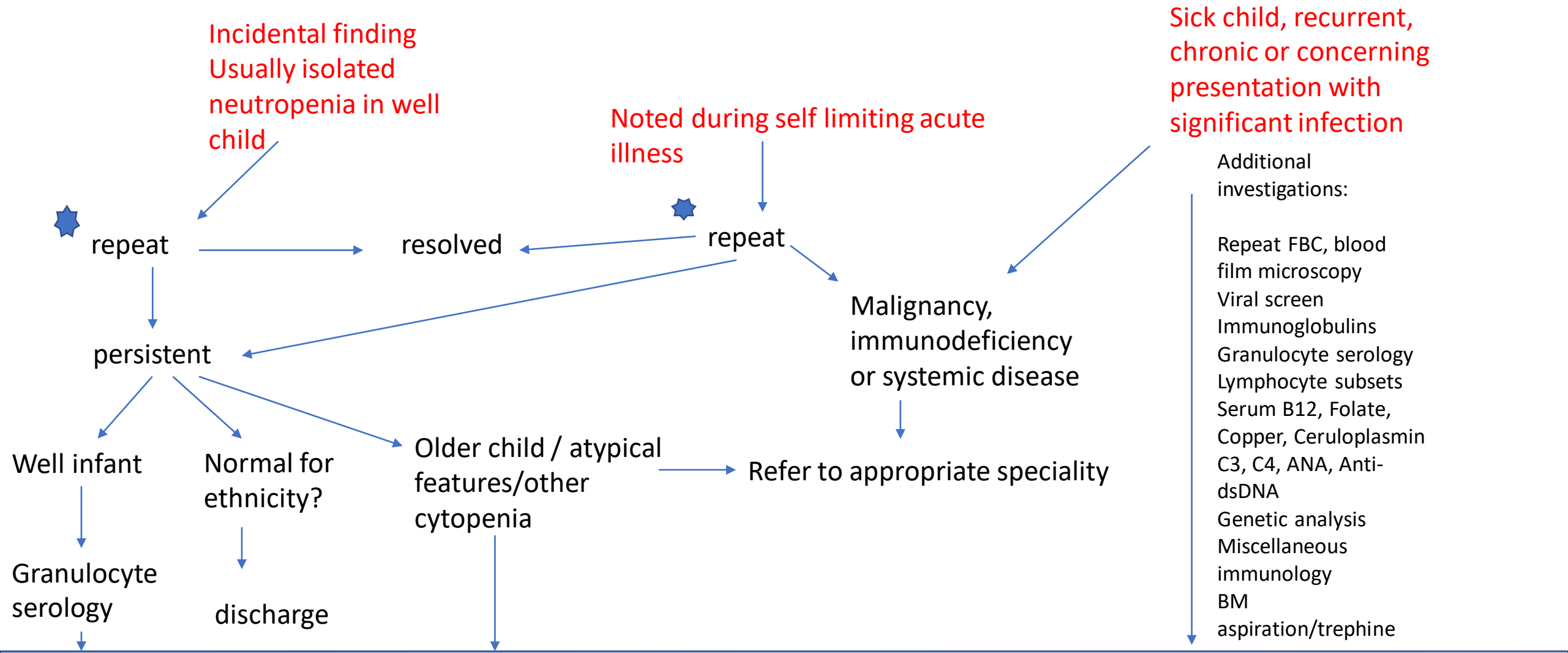
2.

- Serum immunoglobulin profile
- Granulocyte serology

3.

- Lymphocyte sub-sets
- Miscellaneous immunology
- Serum B12, Folate, Copper, Ceruloplasmin
- C3, C4, ANA, Anti-dsDNA
- Genetic analysis
- BM aspirate and trephine

Neutropenia



Transient viral mediated

- Very common and mostly transient with resolution in 6-8 weeks
- Many viral pathogens implicated
- Can suppress BM granulopoeisis directly or via immune mediated process
- Repeat in 6-8 weeks (can ask GP to f/u)
- If persistent or atypical features refer for haematology consultation (or A+G)

Autoimmune neutropenia of infancy (AIN)

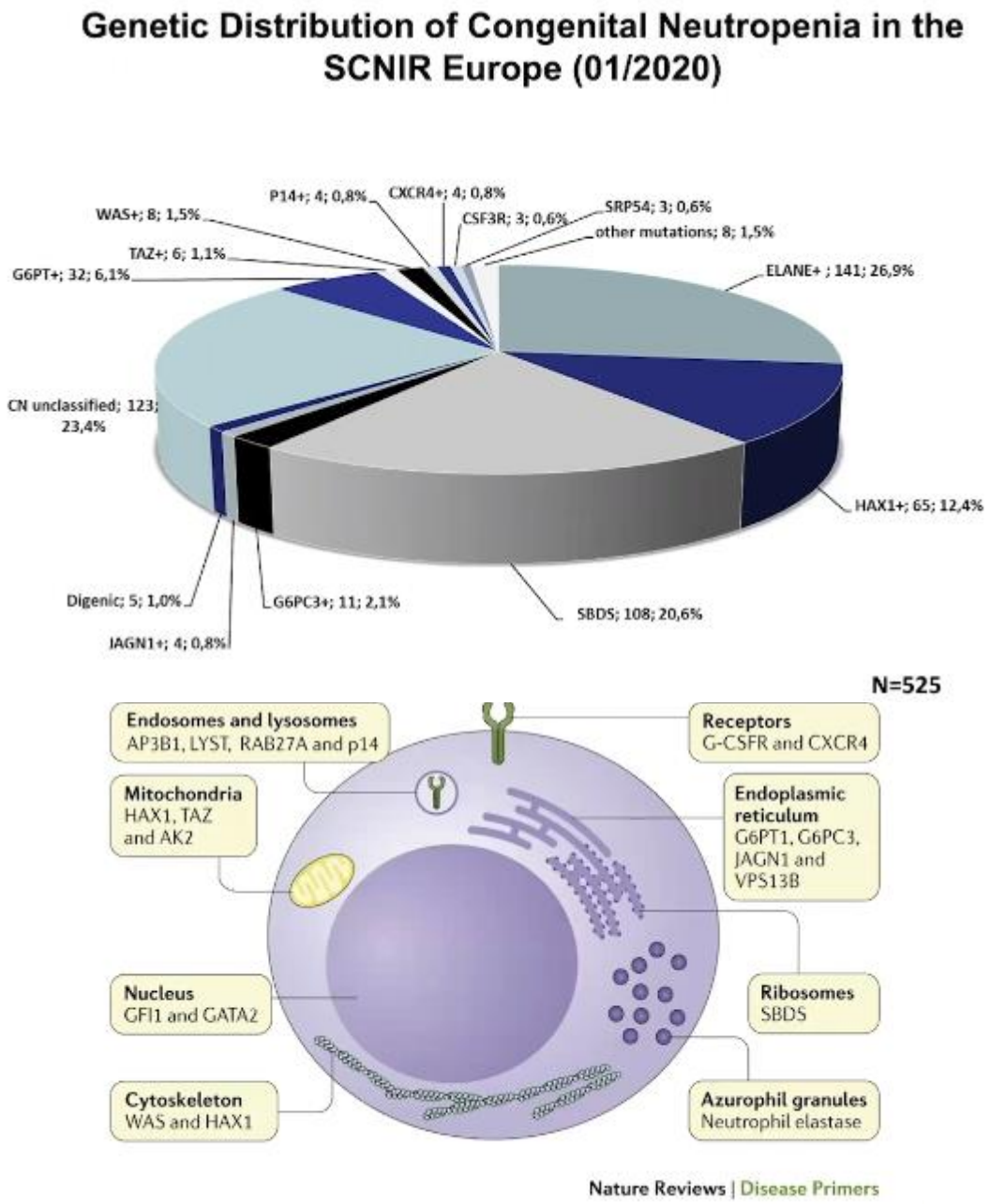
- Prevalence probably under reported
- Typically well infant / incidental finding (e.g., prolonged jaundice screen) with severe neutropenia
- Median age 7-9 months
- Auto antibodies directed at neutrophil membrane antigens = peripheral destruction
- Neutrophil function not impaired and able to mobilise neutrophils during infection
- Recovery usual within 2 years
- F/U in clinic:
  - Expectant management
  - Safety netting
  - No contra indication to live vaccines
  - Prophylactic antibiotics (e.g. azithromycin M/W/F)
  - Rarely need GCSF

Low neutrophil count in keeping with ethnicity

- Polygenic inheritance
- Duffy null phenotype (Fy(a-b-)) – protective against malaria (80-100% individuals of sub-Saharan African ancestry)
- Polymorphisms in Duff Antigen/Receptor gene ‘DARC’ – Duffy Null Associated Neutrophil Count ‘DANC’
- Not a medical condition
- Can screen indirectly with genotyping
- In practice mostly diagnosis of exclusion

Severe congenital neutropenia (SCN)

Diagnosis	Gene	recessive	dominant	Neutropenia plus
ELANE-CN	*ELANE*	-	+	Pre-leukemic Syndrome
Kostmann Syndrome	*HAX1*	+	-	Pre-leukemic Syndrome, CNS convulsions
JAGN1-CN	*JAGN1*	+	-	Osteoporosis, Heart Malformations, Exocrine Pancreatic Insufficiency
G6PC3-CN	*G6PC3*	+	-	Short Stature, Cardiac- and Urogenital Malformations, Translucent Subcutaneous Veins
Congenital Neutropenia with GFI1 Mutation	*GFI1*	-	+	B-/T-Cell defect
WHIM Syndrome	*CXCR4*	-	+	Myelokathexis, IgG Reduction Warts
Shwachman Diamond Syndrome	*SDBS*	+	-	Exocrine Pancreatic Insufficiency, Short Stature, Skeletal Abnormalities, Anemia, Thrombocytopenia
Barth Syndrome	*TAZ1*	X-linked	-	Dilated Cardiomyopathy, Skeletal Myopathy, Short Stature, 3-Methylglutaconic Aciduria
Neutronenia with WAS Mutation	*WAS*	X-linked	-	Monocytopenia, Normal Platelet Count
Glycogen Type 1b	*SLC37A4*	+	-	Hepatosplenomegaly, Hypoglycemia, Lactic Acidosis
Hermansky-Pudlack Syndrome	*AP3B1*	+	-	Partial Albinism, Short Stature, IgG Reduction, Hemorrhagic Diathesis
Hermansky-Pudlack-like Syndrome	multiple	+	-	Partial Albinism, Short Stature, IgG Reduction
Griscelli Syndrome	*RAB27A*	+	-	Hemophagocytosis
Chediak-Higashi Syndrome	*LYST*	+	-	Albinism, T-/NK-Cell and Chemotaxis defective
Hyper IgM	*CD40LG*	X-linked	-	IgG, IgA, IgE Reduction
Congenital Neutropenia with VPS45 Mutation	*VPS45*	+	-	Nephromegaly, Splenomegaly, Osteosclerosis, and Neurological Abnormalities
Congenital Neutropenia (unclassified)	unknown	?	?	Increased IgG Levels



Skokowa, J. et al. (2017) Severe congenital neutropenias. *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2017.32

Management

- Presentations with pyrexial illness – treat for neutropenic sepsis as per local practice
- Known patients with low risk conditions e.g., autoimmune neutropenia may have individualised care plans
- Chronic neutropenia – multi-disciplinary care, support for child and family, care plans for nursery & school, long term surveillance

Questions?