



Neutropenia

Insight - January 2019

Neutrophil granulocytes are the most abundant leukocytes in humans.

Approximately 70 billion neutrophils leave the bone marrow per day in a healthy adult, 50% of these will have undergone apoptosis (programmed cellular death) by 7-10 hours¹.

Physiological changes in neutrophil count can occur in an individual patient due to changes in neutrophil margination (exercise, stress) or total neutrophil numbers (steroid therapy, infection). The neutrophil count is also higher in pregnant women.

Neutrophil granulocytes (named for their staining characteristics "neutral"= pink with standard peripheral blood stain, as opposed to "eosinophilic"= red or "basophilic"= blue) are the most abundant leukocyte in humans. Approximately 70 billion neutrophils leave the bone marrow per day in a healthy adult, 50% of these will have undergone apoptosis (programmed cellular death) by 7-10 hours¹.

The key molecule involved in neutrophil proliferation and survival is the cytokine granulocyte-colony stimulating factor (G-CSF), isolated by Professor Don Metcalf from Melbourne's Walter and Eliza Hall Institute in the 1980s and subsequently used successfully in more than four million patients with defects in neutrophil numbers and function².

Reference Range

Neutropenia is currently defined as a neutrophil count less than $2.0 \times 10^9/L$, however a recent statistical analysis of 1.5×10^6 episodes across Sonic laboratories nationally, suggests that a lower limit of 1.7 or $1.8 \times 10^9/L$ may be appropriate^{3,4}. Physiological changes in neutrophil count can occur in an individual patient due to changes in neutrophil margination (exercise, stress) or total neutrophil numbers (steroid therapy, infection). The neutrophil count is also higher in pregnant women.

Congenital Neutropenia

Congenital causes of neutropenia include severe congenital neutropenia (SCN), cyclic neutropenia (CN), neutropenia associated with bone marrow failure syndromes, as well as benign ethnic neutropenia. Population studies show that approximately 5% of African Americans have a neutrophil count less than $1.5 \times 10^9/L$. Recent work has demonstrated that the cause of the neutropenia is due to an inherited polymorphism in the Duffy antigen⁵ on the red cell surface, common in African populations and protective against the *P. Vivax* malaria strain (see Figure 1).

The same polymorphism is present in the Yemenite Jewish population, although at lower frequency. Benign ethnic neutropenia is not thought to be associated with an increased risk of infections and is important to recognise to prevent repeated testing and unnecessary further investigation of the patient.

SCN and CN are rare disorders with mutations in the neutrophil elastase gene (ELANE). The former leads to severe neutropenia ($<0.5 \times 10^9/L$) from birth and recurrent infections and the latter cyclical oscillation in the neutrophil count (usually on a 21-day cycle and associated with mouth ulceration at neutrophil nadir). SCN can also be due to mutations in other genes (eg. HAX1, G6PC3). Patients with SCN (and patients with symptomatic severe acquired neutropenia) may require regular therapy with G-CSF to prevent infections and mouth ulceration.

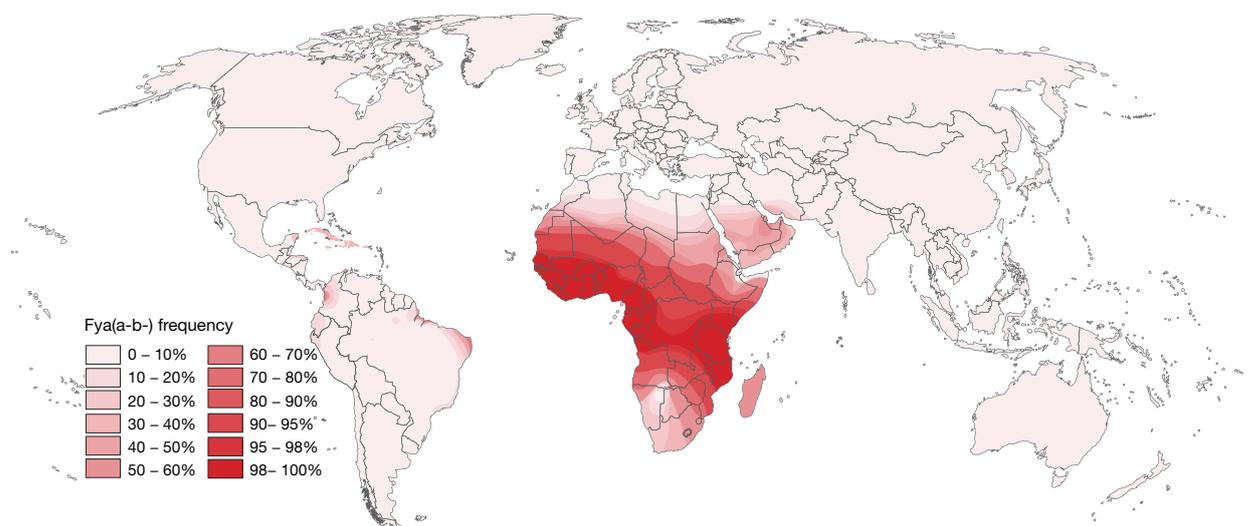


Figure 1. Global distribution of the Duffy null/Fy(a-b-) phenotype associated with benign ethnic neutropenia

Acquired Neutropenia

Acquired causes of neutropenia include drug-induced neutropenia, which may be a dose dependant effect such as from chemotherapy, or idiosyncratic such as from clozapine, carbimazole or sulfasalazine. Many other drugs can cause neutropenia less commonly and reviewing the patient's current medications and their temporal relation to the development of neutropenia is an important part of the evaluation. All non-essential medications should be ceased as part of the investigation of significant neutropenia.

Other common causes include:

- viral infections (acute and chronic), including EBV, CMV, viral hepatitis and HIV
- autoimmune disorders and cytotoxic T cell proliferations (large granular lymphocyte or LGL proliferations) as seen in SLE and Felty's syndrome in rheumatoid arthritis
- B12/ folate deficiency
- anorexia nervosa
- underlying bone marrow disorder eg. myelodysplasia, aplasia, leukaemia, lymphoma

Patients with significant splenomegaly and hypersplenism associated with portal hypertension also have sequestration of neutrophils in the spleen leading to lower counts, commonly in association with thrombocytopenia.

	Common	Rare
Congenital	<ul style="list-style-type: none"> • Benign ethnic neutropenia 	<ul style="list-style-type: none"> • Cyclic neutropenia • Severe congenital neutropenia • Multi-system inherited disorders associated with neutropenia
Acquired	<ul style="list-style-type: none"> • Viral infection eg. EBV, CMV, hepatitis, HIV • Drug toxicity eg. clozapine, carbimazole, chemotherapy • Severe bacterial infection • Autoimmune neutropenia • B12 or folate deficiency 	<ul style="list-style-type: none"> • Copper deficiency • LGL proliferation/ Felty's syndrome • Bone marrow disorders eg. Myelodysplasia, aplasia, leukaemia, lymphoma

Table 1. Causes of Neutropenia

Investigation

Assessment of a patient with neutropenia should include clinical history looking for potential aetiological agents (ethnic origin, family history, drug history), and clinical outcomes (history of infections or mouth ulceration), as well as examination for features of mouth ulceration, splenomegaly, systemic autoimmune disorders or complex congenital syndromes.

Initial pathology testing should include FBE and blood film review, B12/folate assay, viral serology for hepatitis B, C and HIV and Anti-Nuclear Antibodies (ANA).

The blood film is a most important investigation in initial assessment and is reviewed for features suggestive of bone marrow infiltration, dysplasia or viral infection.

When to Act and What to Do

Where neutropenia can be anticipated, the patient should be educated with appropriate precautions and clinical directives discussed and documented. This may include availability of a thermometer and antibiotics if indicated in select patients.

When neutropenia is an incidental finding the patient should be managed based on both clinical history and historic results.

Patients with severe neutropenia ($<0.5 \times 10^9/L$) and associated fever (temperature $\geq 38^\circ C$) should be sent immediately to hospital for assessment and antibiotics as indicated.

A patient with chronic moderate neutropenia ($<1.0 \times 10^9/L$), progressive neutropenia even before the counts reach critical levels, or neutropenia of any level associated with recurrent infections or mouth ulceration, should be referred to a clinical haematologist for assessment regarding possible diagnoses. This may include bone marrow biopsy.

For patients with chronic mild/moderate neutropenia ($1.0 - 1.9 \times 10^9/L$), with no clinical evidence of recurrent infections, and in whom benign ethnic neutropenia, drug-induced neutropenia and other secondary causes of neutropenia have been excluded by initial pathology testing, clinical observation may be appropriate. Monitoring of the patient for infections and a periodic neutrophil count (dependant on the time course of neutropenia development and clinical assessment of the patient) is recommended.

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Dr Maxwell is a University of Melbourne graduate who completed combined fellowships with the College of Physicians and the College of Pathologists in 1997.

She trained initially at the Austin and Repatriation Medical Centres

and later the Alfred Hospital where she developed a keen interest in coagulation and transfusion medicine.

Dr Maxwell is a current member of the Victorian Blood User Group, the National Blood Transfusion Committee, The Australian Red Cross Blood Service Advisory Committee and the Serious Transfusion Incident Reporting Working Group (DHS Victoria). She has been an active member of many committees for the RCPA and ANZSBT.

Dr Maxwell was appointed Medical Director at Melbourne Pathology in September 2009.

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