



Complete Blood Count

in Primary Care

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All information is intended for use by competent health care professionals and should be utilised in conjunction with pertinent clinical data.

Contents

Key points/purpose	2
Introduction	2
Background	
▪ Haematopoiesis - Cell development	3
▪ Limitations of reference ranges for the CBC	4
▪ Borderline abnormal results must be interpreted in clinical context	4
▪ History and clinical examination	4
White Cells	
▪ Neutrophils	5
▪ Lymphocytes	9
▪ Monocytes	11
▪ Basophils	12
▪ Eosinophils	12
▪ Platelets	13
Haemoglobin and red cell indices	
▪ Low haemoglobin	15
▪ Microcytic anaemia	15
▪ Normocytic anaemia	16
▪ Macrocytic anaemia	17
▪ High haemoglobin	17
▪ Other red cell indices	18
Summary Table	19
Glossary	20

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Key points/purpose

To provide an overview of the use of the complete blood count in primary care and to provide advice on appropriate follow-up for abnormal results.

Introduction

The complete blood count (CBC) is the most frequently requested blood test in New Zealand. The primary points of interest in the CBC are often whether a patient is anaemic, whether the white count shows evidence of infection and whether the platelets are at a level that may affect haemostasis.

GPs have told us they are reasonably comfortable interpreting CBC results with marked abnormalities, but would like guidance when the results show only subtle abnormalities or when the clinical picture is not clear.

THIS IS A CONSENSUS DOCUMENT

This is not a comprehensive document covering all causes of abnormal results; it is a consensus document produced in conjunction with specialist haematologists, providing an overview for some scenarios encountered in primary care.

Background

HAEMATOPOIESIS – CELL DEVELOPMENT

All blood cells are produced within the bone marrow from a small population of stem cells. Less than one in 5000 of the marrow cells is a stem cell. These cells represent a self-renewing population.

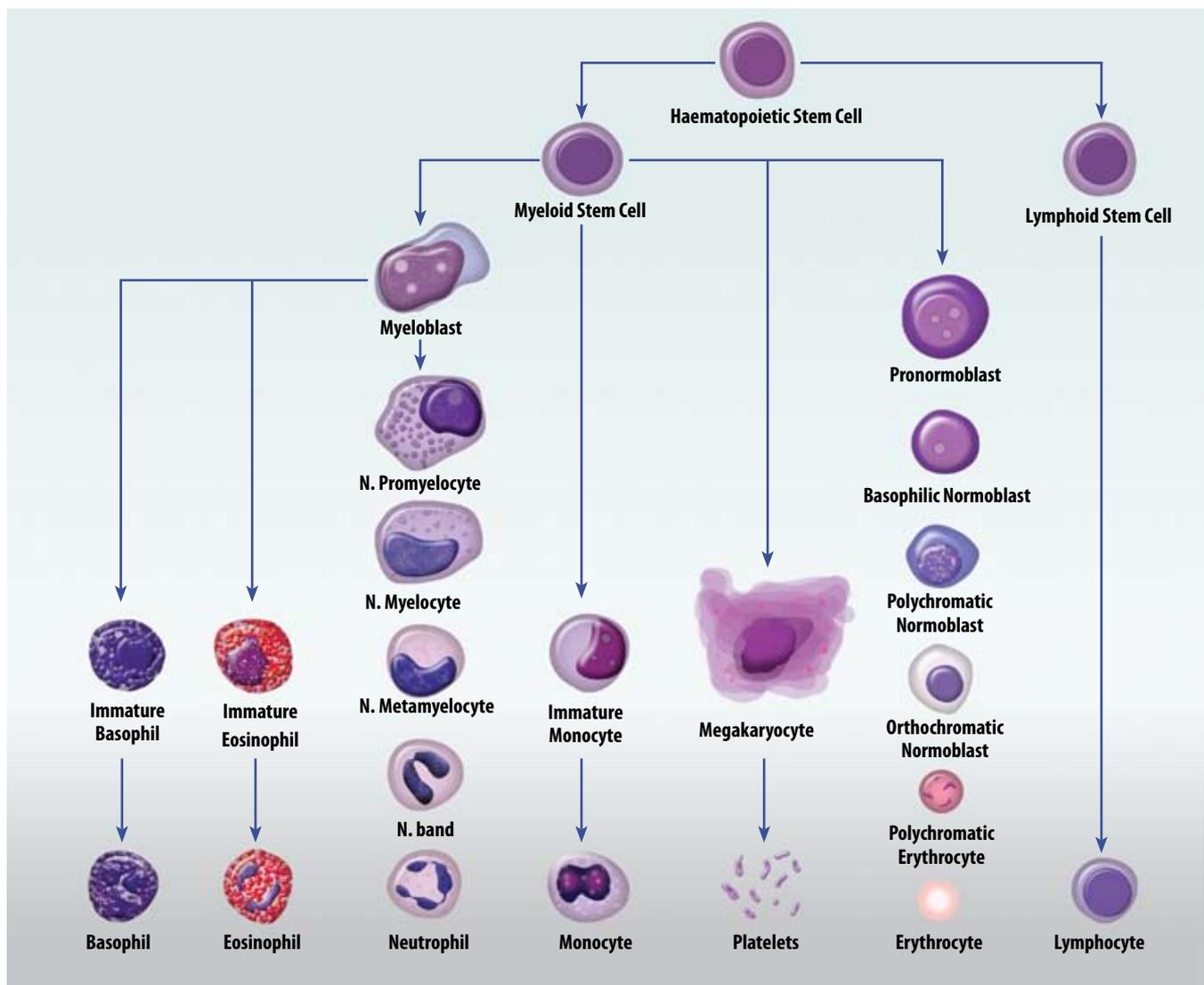
The term haematopoiesis refers to the formation and development of the blood cells (Figure 1). In humans the bone marrow is the major site of haematopoiesis for the life of the individual.

Initial differentiation of haemopoietic stem cells involves one of two pathways, lymphoid or myeloid. Stem cells then become progenitor cells for each type of mature blood cell and are committed to a given cell lineage.

Myeloid stem cells eventually give rise to erythrocytes, megakaryocytes (platelets), neutrophils, monocytes, eosinophils and basophils.

Lymphoid stem cells give rise to T and B lymphocytes and plasma cells.

Figure 1: Haematopoiesis cell development pathways.



Limitations of reference ranges for the CBC

For most people conventional reference ranges will be adequate for diagnostic purposes, but a number of pitfalls may make interpretation more difficult in some cases.

Deriving blood count reference ranges is difficult due to the number of factors that may affect blood count parameters and their frequency in the community. These include iron deficiency, thalassaemias, medication, alcohol and minor infections. In addition there are ethnic differences in some parameters, differences between males and females and differences in pregnancy. Some of these factors are taken into account in published ranges (gender, pregnancy) others are not. Finally, there are differences between different haematology analysers that may affect some blood count parameters.

In view of the above, the approach taken to blood count reference intervals has been different to that seen with many biochemical parameters, where reference intervals usually encompass the 2.5th to 97.5th percentiles. Blood count reference intervals have been derived using a mixture of local and published data, together with a degree of pragmatism. This means that many of the reference intervals encompass more than 95%

of “normal” individuals and marginal results must be considered in context. Likewise, a normal blood count does not preclude the possibility of early disease states (e.g. iron deficiency).

Borderline abnormalities must be interpreted in clinical context

All haematology results need to be interpreted in the context of a thorough history and physical examination, as well as previous results. Follow-up counts are often helpful to assess marginal results as many significant clinical conditions will show progressive abnormalities.

The CBC is often included as part of a “well-person” check, or as part of a series of screening tests for life or health insurance applicants. While a number of organisations are advocating “well-person” checks, others argue that blood tests are not indicated for well people. In asymptomatic people, the pre-test probability for tests is low, leading to a high rate of false positives. In addition, undertaking investigations in people who do not have a clear clinical need will use resources (time and money) that could be better applied to those with unmet health care needs.

History and clinical examination

There are a number of features which may be revealed by history and clinical examination. These can provide clues for diagnosis and allow the results of the complete blood count to be interpreted in context.

Signs and symptoms relevant to the CBC:

- Pallor, jaundice
- Fever, lymphadenopathy
- Bleeding/bruising
- Hepatomegaly, splenomegaly
- Frequency and severity of infections, mouth ulcers, recent viral illness
- Exposure to drugs and toxins including herbal remedies
- Fatigue/weight loss

White Cells

TOTAL WHITE BLOOD CELL COUNT MAY BE MISLEADING

Although the total white count may provide a useful summary, the absolute count of each of the cell types is more useful than the total.

The total white count may be misleading; e.g. abnormally low neutrophils with an elevated lymphocyte count may produce a total white count that falls within the reference range. As a result the total white count should not be considered in isolation.

Neutrophils

For most adults neutrophils account for approximately 70% of all white blood cells. The normal concentration range of neutrophils is $2.0 - 8.0 \times 10^9/L$ (range can be different for different labs).

The average half-life of a non-activated neutrophil in the circulation is about 4–10 hours. Upon migration, outside the circulation, neutrophils will survive for 1–2 days.

NEUTROPENIA (LOW NEUTROPHIL COUNT)

Neutropenia is potentially associated with life threatening infection. It is most significant when the total neutrophil count is less than $0.5 \times 10^9/L$, particularly when the neutropenia is due to impaired production (e.g. after chemotherapy). When the neutropenia is due to increased peripheral destruction or margination (e.g. with viral infection), it is less certain what constitutes a significant level. These patients rarely have problems with significant bacterial infection despite quite low neutrophil counts.

Neutropenia can be classified as:

Classification	Neutrophil count
Mild	$1.0 - 2.0 \times 10^9/L$
Moderate	$0.5 - 1.0 \times 10^9/L$
Severe	$< 0.5 \times 10^9/L$

Neutrophils – Low

Significant levels

- $< 1.0 \times 10^9/L$ (high risk infection)

Most common causes

- Viral (overt or occult)
- Autoimmune/idiopathic
- Drugs

Red flags

- Person particularly unwell
- Severity of neutropenia
- Rate of change of neutropenia
- Lymphadenopathy, hepatosplenomegaly

APPROACH TO PATIENTS WITH NEUTROPENIA

Neutrophils $<1.0 \times 10^9/L$: The risk of significant bacterial infection rises as the neutrophil count drops below $1.0 \times 10^9/L$, but is most marked as the count falls below $0.5 \times 10^9/L$. Careful assessment of the patient's condition is critical, and patients who are unwell and/or febrile with a count below $1.0 \times 10^9/L$ generally need urgent referral. Patients who are febrile but otherwise well should at least be discussed with a Haematologist. If the patient is well and afebrile, they need to be advised to seek medical attention promptly if their condition deteriorates or they become febrile. Well patients should have follow up blood counts within 48 hours, and if the neutropenia persists at this level or progresses they should be discussed with a Haematologist.

Neutrophils $1.0 - 2.0 \times 10^9/L$: If an isolated abnormality follow up blood counts are indicated, with frequency dependent on the severity of the neutropenia but usually within 1-2 weeks. If the neutropenia persists for more than 6 weeks further investigation is indicated. If it is progressive or other abnormalities develop a haematology referral, or discussion with a Haematologist, is indicated.

Drug induced neutropenias: There are specific protocols for management of clozapine induced neutropenia. Otherwise, if a drug cause is suspected and the neutropenia is moderate or severe, Haematology referral, or discussion with a Haematologist is indicated.

Causes

In routine clinical practice the most frequent cause of a low neutrophil count is overt or occult viral infection, including viral hepatitis. Acute changes are often noted within one to two days of infection and may persist for several weeks. The neutrophil count seldom decreases enough to pose a risk of infection.

A low neutrophil count is often discovered in some people as an incidental finding in the CBC result. The patient is generally asymptomatic and the clinical examination is unremarkable. The count is usually stable on follow-up. This is likely to be idiopathic although in some cases a neutropenia may be associated with splenomegaly or an autoimmune disease such as lupus.

The presentation of a haematological malignancy with only an isolated neutropenia is a rare finding.

Drugs causing neutropenia

Although relatively rare, drug therapy may cause an acquired neutropenia in some people. The drugs most likely to be associated with moderate neutropenia are chemotherapy and immunosuppressive drugs, antithyroid

medications, antibiotics, antirheumatics, antipsychotics and anticonvulsants. For a more comprehensive list see Neutropenia, drug induced on Page 20.

Many drugs may cause a chronic mild neutropenia e.g. nonsteroidal anti-inflammatory drugs, valproic acid.

Investigations

The history and clinical features are important for providing the clues for diagnosis and allowing the results to be interpreted in context.

- History: frequency and severity of infections, mouth ulcers, recent viral illness, exposure to drugs and toxins, symptoms of malabsorption, symptoms suggesting reduced immunity
- Drugs (see Neutropenia, drug induced on Page 20).
- Examination: mouth ulcers, fever, signs of infection, jaundice, lymphadenopathy, hepatomegaly, splenomegaly, signs of autoimmune/connective tissue disorders
- CBC: is the CBC otherwise normal (particularly haemoglobin and platelets)

- In persistent moderate neutropenia, without an infection or drug related cause, testing might include ANA (anti-nuclear antibodies), B12, folate, SPE (serum protein electrophoresis), HIV, liver enzymes, Hepatitis B and rheumatoid factor. Look for changes on physical examination.

Significant red flags

- Patient unwell
- Persistence/duration of neutropenia, rate of change
- Severity
- Significant findings on physical examination

NEUTROPHILIA (HIGH NEUTROPHIL COUNT)

Neutrophils are the primary white blood cells that respond to a bacterial infection. The most common cause of marked neutrophilia is a bacterial infection.

Neutrophils react within an hour of tissue injury and are the hallmark of acute inflammation. An excessive increase in neutrophils ($>50 \times 10^9/L$) as a reactive phenomenon is known as a leukaemoid reaction.

Neutrophils generally exhibit characteristic changes in response to infection. The neutrophils tend to be more immature, as they are being released earlier. This is called a left shift (Figure 2). In a severe infection the neutrophils may show toxic granulation and other toxic changes such as vacuolation and the presence of Döhle bodies.

Neutrophils will frequently be increased in any acute inflammation, therefore will often be raised after a heart attack, or other infarct and necrosis. Any stressor, from heavy exercise to cigarette smoking, can elevate the neutrophil count.

A number of drugs have been demonstrated to increase the neutrophil count, including steroids, lithium, clozapine and adrenalin. Even nervousness may very slightly raise the neutrophil count because of the effect of steroid release.

Pregnancy is associated with a slight increase in total neutrophil count demonstrating a left shift. Most laboratories provide pregnancy specific reference ranges.

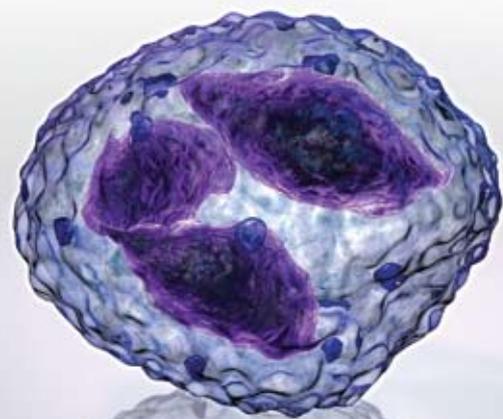
Neutrophils – High

Most likely cause

- Infection/inflammation
- Necrosis
- Any stressor/heavy exercise
- Drugs
- Pregnancy
- Smoking
- CML

Red flags

- Person particularly unwell
- Severity of neutrophilia
- Rate of change of neutrophilia
- Presence of left shift



Persistent elevation of neutrophils may be a sign of chronic myeloid leukaemia (CML). Characteristic changes are a moderate increase in neutrophil count (usually $>50 \times 10^9/L$), with a left shift and a prominence of myelocytes. Basophilia and/or eosinophilia may also be present. Chronic mild neutrophilia without left shift is very unlikely to be due to CML.

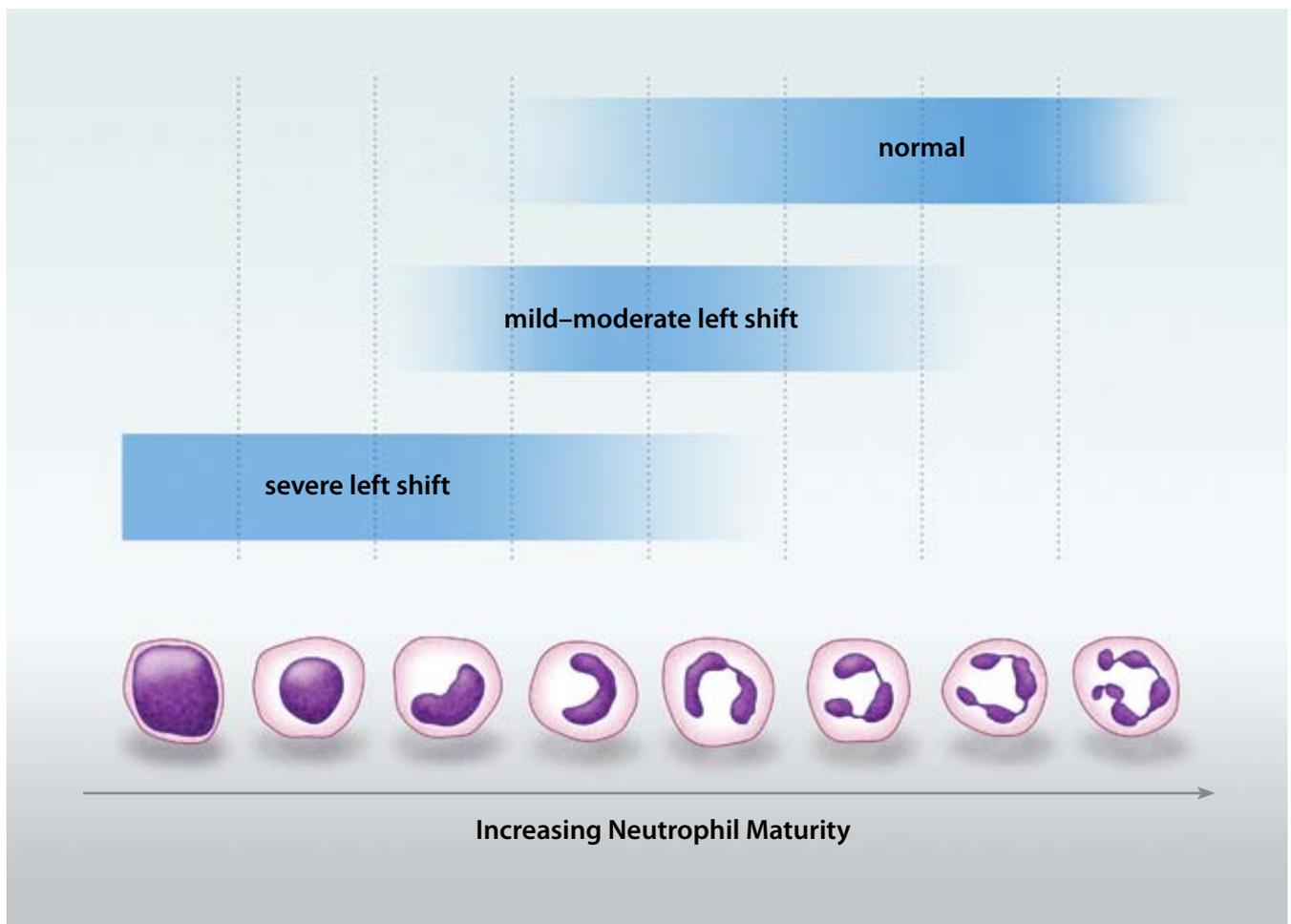
CML occurs in all age groups but most commonly in the middle aged and elderly. The annual incidence is estimated at 1 – 2 cases per 100,000.

Follow-up for high neutrophil count

For essentially well people:

- Repeat in 1 – 2 months, then
- Continue to follow (3 monthly for 12 months, then occasionally thereafter)
- Stop monitoring when normal

Figure 2: Diagram of left shift



Lymphocytes

Lymphocytes normally represent 20 – 40% of circulating white blood cells. The normal concentration of lymphocytes is between $1.0 - 4.0 \times 10^9/L$.

There are two broad morphologic categories of lymphocytes which can be distinguished under the light microscope, large granular lymphocytes and small lymphocytes.

Functionally distinct subsets of lymphocytes do not correlate with their appearance.

LYMPHOCYTOPENIA (LOW LYMPHOCYTE COUNT)

Low lymphocyte counts are not usually significant.

Characteristic decreases in the lymphocyte count are usually seen late in HIV infection, as T lymphocytes (CD4+ T cells) are destroyed.

Steroid administration may reduce lymphocyte counts. More rarely lymphocytopenia may be caused by some types of chemotherapy or malignancies. People exposed to large doses of radiation, such as those involved with situations like Chernobyl, can have severe lymphocytopenia.

LYMPHOCYTOSIS (HIGH LYMPHOCYTE COUNT)

Increases in the absolute lymphocyte count are usually due to acute infections, such as Epstein-Barr virus infection and viral hepatitis. Less commonly, increased lymphocytes may be the result of pertussis and toxoplasmosis or (rarely) chronic intracellular bacterial infections such as tuberculosis or brucellosis.

The lymphocyte count may also be elevated in:

- Smoking (reactive)
- Hyposplenism (usually following splenectomy)

Lymphocyte – Low

- Not usually clinically significant

Lymphocyte – High

Causes

- Acute infection (viral, bacterial)
- Smoking
- Hyposplenism
- Acute stress response
- Autoimmune thyroiditis
- CLL

- Acute stress response – usually seen in hospital setting, uncommon in community, usually resolves within 24 hours
 - Acute cardiac event
 - Trauma
- Autoimmune thyroiditis

Chronic lymphocytic leukaemia (CLL) and other lymphoproliferative disorders should be considered in patients with a persistent lymphocytosis.

- CLL is rarely encountered in people under the age of 40 but increases in incidence with age. It is often discovered as an incidental finding on a blood count, but may be associated with lymphadenopathy, hepatomegaly and splenomegaly.

In some cases lymphocyte surface markers may be recommended for differentiating between reactive lymphocytosis and lymphoproliferative disorders. Because they do not affect management of asymptomatic patients with early stage disease, they are usually only indicated

when the lymphocyte count is persistently $>6 - 7 \times 10^9/L$; the lymphocytes demonstrate abnormal features; other blood count parameters are abnormal; or there are signs or symptoms suggestive of lymphoma (fever, sweats, weight loss, lymphadenopathy, hepatosplenomegaly).

Inappropriate use should be avoided because the test is particularly expensive around \$500.

Follow-up

Follow-up for clinically unexplained lymphocytosis:

- In a patient who appears to be essentially well and has no alarming features, check in one to two months.
- In a patient with mild symptoms of a transient condition, rechecking when the patient is well is appropriate.
- Patients with persistently elevated lymphocyte count, accompanied by lymphadenopathy, hepatomegaly and splenomegaly should be referred for haematology assessment.

Monocytes

Monocytes constitute between 3 – 8% of all white cells in the blood. They circulate in the bloodstream for about one to three days and then typically move into tissues (approx 8 – 12 hours) to sites of infection. The normal concentration of monocytes is between $0 - 1.0 \times 10^9/L$.

Monocytes which migrate from the bloodstream to other tissues are called macrophages. Macrophages have a role in specific immunity and phagocytosis.

MONOCYTOPENIA (LOW MONOCYTE COUNT)

An isolated decrease in the total monocyte count is an unusual finding. Occasionally monocytes become depleted in overwhelming bacterial infections, but this is more an incidental finding than a defining clinical indicator. Hairy cell leukaemia, a rare indolent lymphoproliferative disorder, may occasionally be associated with monocytopenia, although other abnormalities (especially neutropenia and lymphocytosis) would generally be present.

MONOCYTOSIS (HIGH MONOCYTE COUNT)

Most often, elevated monocyte counts are associated with infection and inflammatory processes and will be seen in conjunction with other blood count changes.

Isolated increases in the monocyte count, not accompanied by other changes in the blood count, are uncommon but may be associated with:

- Chronic infection including tuberculosis
- Chronic inflammatory conditions (e.g. Crohn's disease, ulcerative colitis, rheumatoid arthritis, SLE)
- Dialysis
- Early sign of chronic myelomonocytic leukaemia (rare)

Monocytes – Low

- Not clinically significant if other cell counts are normal

Monocytes – High

- Usually not significant
- Watch levels $> 1.5 \times 10^9/L$ more closely, consider chronic infection or inflammation.

If levels are persistently elevated (i.e. $> 1.5 \times 10^9/L$), particularly in association with suspicious symptoms, a haematology referral may be prudent.

A mild elevation of monocytes is relatively common and does not usually require follow-up.

Basophils

Basophils are the least common of the white cells, representing about 0.01 – 0.3% of all white blood cells. The normal concentration of basophils is $0 - 0.2 \times 10^9/L$

The function of basophils is not fully understood, but it is known that they are capable of phagocytosis and producing histamine.

BASOPENIA (LOW BASOPHIL COUNT)

Basopenia is difficult to demonstrate as the normal basophil count is so low.

BASOPHILIA (HIGH BASOPHIL COUNT)

The basophil count will only very rarely be significantly raised. When present, it may indicate a myeloproliferative disorder, or other more obscure causes. A repeat CBC a week or two later may help.

Basophils – Low

- Difficult to demonstrate

Basophils – High

Associated with:

- Myeloproliferative disorders
- Other rare causes

Eosinophils

In most people eosinophils make up about 1–6% of white blood cells. The normal concentration of eosinophils is $0 - 0.5 \times 10^9/L$. Eosinophils persist in the circulation for 8 – 12 hours, and can survive in tissue for an additional 8 – 12 days in the absence of stimulation.

EOSINOPENIA (LOW EOSINOPHIL COUNT)

Eosinopenia is difficult to demonstrate in practice because of the low frequency of eosinophils in most healthy people. As a result a low eosinophil count should not be a cause for concern.

EOSINOPHILIA (HIGH EOSINOPHIL COUNT)

In developed countries the most common causes are allergic diseases such as asthma and hay fever, but

Eosinophils – Low

- No real cause for concern

Eosinophils – High

Most common causes:

- Allergy/atopy: asthma/hayfever
- Parasites (less common in developed countries)

Rarer causes:

- Hodgkins disease
- Myeloproliferative disorders
- Churg-Strauss syndrome

worldwide the main cause of increased eosinophils is parasitic infection.

Follow-up

Total eosinophil count	Follow-up
$< 1.0 \times 10^9/L$	Trivial, ignore
Up to $1.5 \times 10^9/L$	Probably, ignore
$> 1.5 \times 10^9/L$	Consider possible causes

Haematology assessment is appropriate for patients with persistent (more than six months) moderate eosinophilia, or marked or increasing eosinophilia.

Platelets

Platelets are produced by budding off from megakaryocytes in the bone marrow. Each megakaryocyte produces between 5,000 to 10,000 platelets. Platelets circulate for approximately one to two weeks and are destroyed by the spleen and liver.

A normal platelet count ranges from $150 - 450 \times 10^9/L$.

THROMBOCYTOPENIA (LOW PLATELET COUNT)

Interpretation of a low platelet count involves consideration of the clinical context. Severe thrombocytopenia is associated with an increased risk of bleeding and requires urgent assessment. It is particularly significant if accompanied by other changes in the CBC or the platelet count is falling. Bleeding is unusual at platelet counts of $>50 \times 10^9/L$ unless there is an associated platelet function defect (which is uncommon).

Causes

Thrombocytopenia may be artefactual due to a variety of causes, which are worth excluding before looking for clinical causes, including:

- Partially clotted sample.
- Platelet clumping in the blood collection tube.

Platelets – Low

Significant levels

- $< 100 \times 10^9/L$

Most common causes

- Viral infection
- Idiopathic thrombocytopenic purpura
- Liver disease
- Medications
- Hypersplenism
- Autoimmune disease
- Pregnancy

Red flags

- Bruising
- Petechiae
- Signs of bleeding

The laboratory will usually look for evidence of these, but if the platelet count is not consistent with the clinical picture, a repeat sample may be warranted.

Causes of isolated thrombocytopenia include:

- Viral infection
- Idiopathic thrombocytopenic purpura (ITP)
- Medications
- Liver disease
- Autoimmune disease
- Hypersplenism
- HIV infection
- Pregnancy
- Bone marrow causes

Thrombocytopenia may also occur in conjunction with microangiopathic haemolysis (usually apparent on blood film examination) in haemolytic uraemic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP) and chronic or acute disseminated intravascular coagulation (DIC). TTP should be considered if the patient is febrile, unwell or has neurological symptoms.

Follow-up

Low platelets are reasonably common, but it is important that results be interpreted in context, looking for clues to

help. Further testing that should be considered in patients with persistently low platelets includes a blood film, ANA (anti-nuclear antibodies), HIV, Hepatitis B and C and liver enzymes. In some cases of chronic thrombocytopenia, *Helicobacter pylori* serology and anticardiolipin antibodies may be indicated. Splenomegaly and lymph nodes should be checked on examination.

Recommended follow up for thrombocytopenia:

Platelet count	Referral
< 30 × 10 ⁹ /L	Requires urgent referral
30 – 100 × 10 ⁹ /L	Judgment depending on context. Urgent referral if bleeding. Needs further investigation if persistent/progressive. Refer if no cause found.
100 – 145 × 10 ⁹ /L	Follow up counts. Investigate if persistent. Refer if progressive without obvious cause.

THROMBOCYTOSIS (HIGH PLATELET COUNT)

Elevated platelet levels may be a reactive change and will not necessarily signal any clinical problem. Generally, a reactive thrombocytosis is not associated with an increased thrombotic risk. Rarely will a thrombocytosis reflect a myeloproliferative disorder such as essential thrombocythaemia or myelofibrosis. These should particularly be considered if there is a chronic persistent elevation in platelet counts (more than six months) or a very high platelet count without an obvious reactive cause. They may also be associated with splenomegaly and the platelet count is usually >600 × 10⁹/L (and often much higher).

Platelets – High

Significant levels

- >500 × 10⁹/L

Most likely causes

- Reactive conditions e.g. infection, inflammation
- Pregnancy
- Iron deficiency
- Post splenectomy
- Essential thrombocythaemia

Haemoglobin and red cell indices

LOW HAEMOGLOBIN

Low haemoglobin levels are generally indicative of anaemia. Most laboratories report a haemoglobin level of less than 130 g/L for men as low. The lower limit of the reference range for women is usually presented as 115 g/L but some laboratories use a value of 120 g/L.

Anaemia requires careful consideration. The wide differential diagnosis can be narrowed considerably by checking the mean cell volume (MCV) and the reticulocyte count and initially classifying the anaemia as:

- Microcytic, MCV < 80 fl
- Normocytic, MCV 80 – 100 fl
- Macrocytic, MCV > 100 fl

Microcytic Anaemia

The three most common causes for microcytic anaemia are:

- Iron deficiency
- Thalassaemia
- Anaemia of Chronic disease

A suggested approach to laboratory testing is shown in Figure 3.

Iron deficiency is the most common cause of microcytic anaemia, therefore measurement of serum ferritin is the appropriate first step. A low ferritin in the presence of a microcytic anaemia is diagnostic of iron deficiency. Patients with low normal ferritin levels (<30 µg/L) may well have a latent iron deficient state. Iron deficiency can not be excluded in a person with concurrent inflammation, despite a normal ferritin, and requesting a CRP may be useful to exclude inflammation.



Microcytic anaemia not related to iron deficiency

When microcytic anaemia is not due to iron deficiency it is most likely related to thalassaemia or an underlying chronic disease.

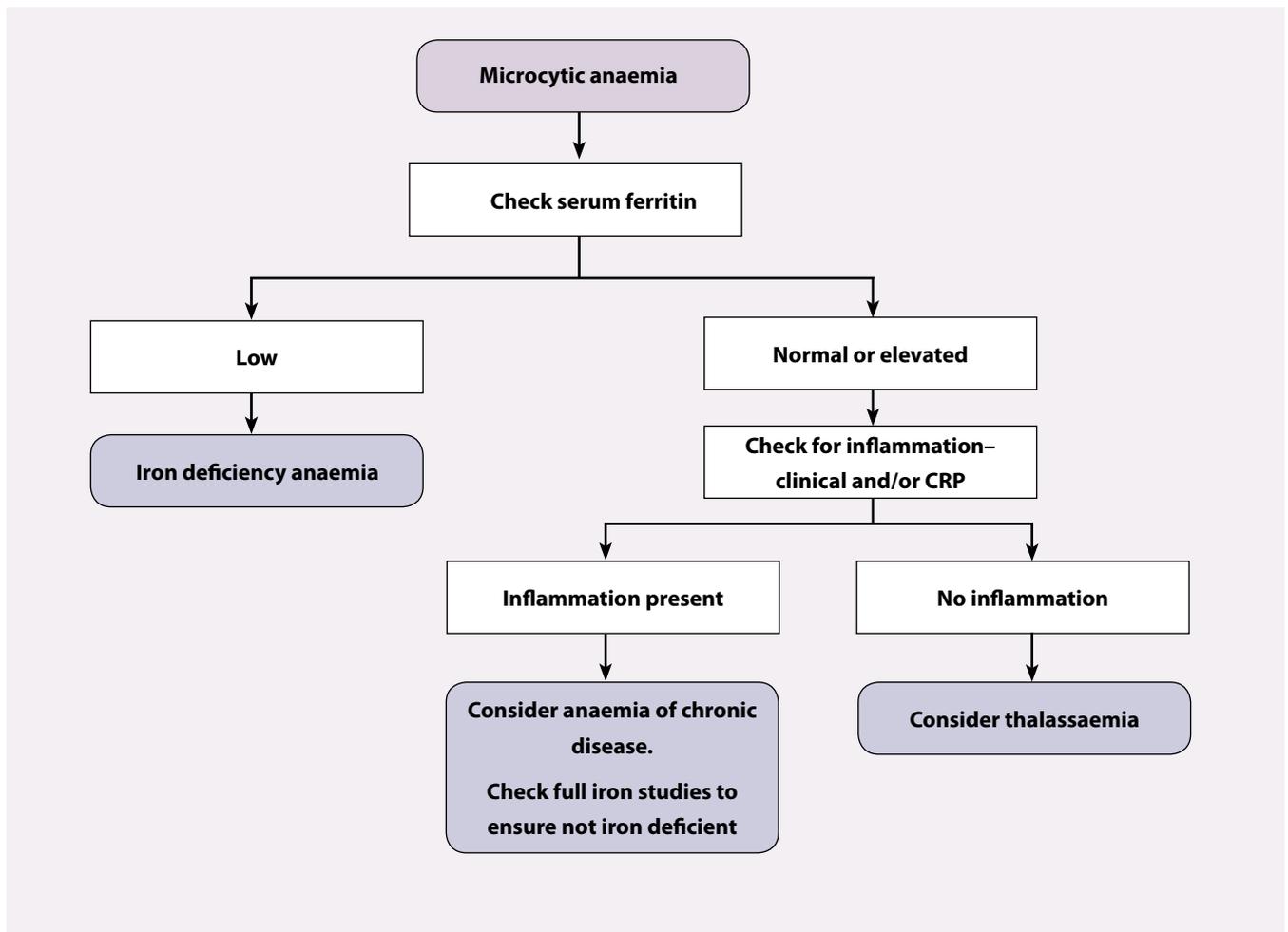
Thalassaemias are associated with chronic microcytosis with no or mild anaemia. They are seen with high frequency in a number of ethnic groups, including Māori and Pacific Peoples, Asians and those of Mediterranean or Middle Eastern origin. Appropriate investigation includes ferritin and a haemoglobinopathy screen. For some patients with milder forms of alpha thalassaemia the haemoglobinopathy screen may be negative.

Microcytic anaemia of chronic disease is most frequently associated with:

- Chronic inflammation
- Chronic infection

The microcytosis is usually only mild and many patients with anaemia of chronic disease are normocytic.

Figure 3: A suggested approach to laboratory testing for microcytic anemia.



Normocytic anaemia

The causes of normocytic anaemia include:

- Bleeding
- Early nutritional anaemia (iron, B12, folate deficiencies)
- Anaemia of renal insufficiency
- Anaemia of chronic disease/chronic inflammation
- Haemolysis
- Primary bone marrow disorder

Initial investigation in primary care generally focuses on the tests listed below. These will depend on history and examination, potential sources of bleeding, diet and general health status.

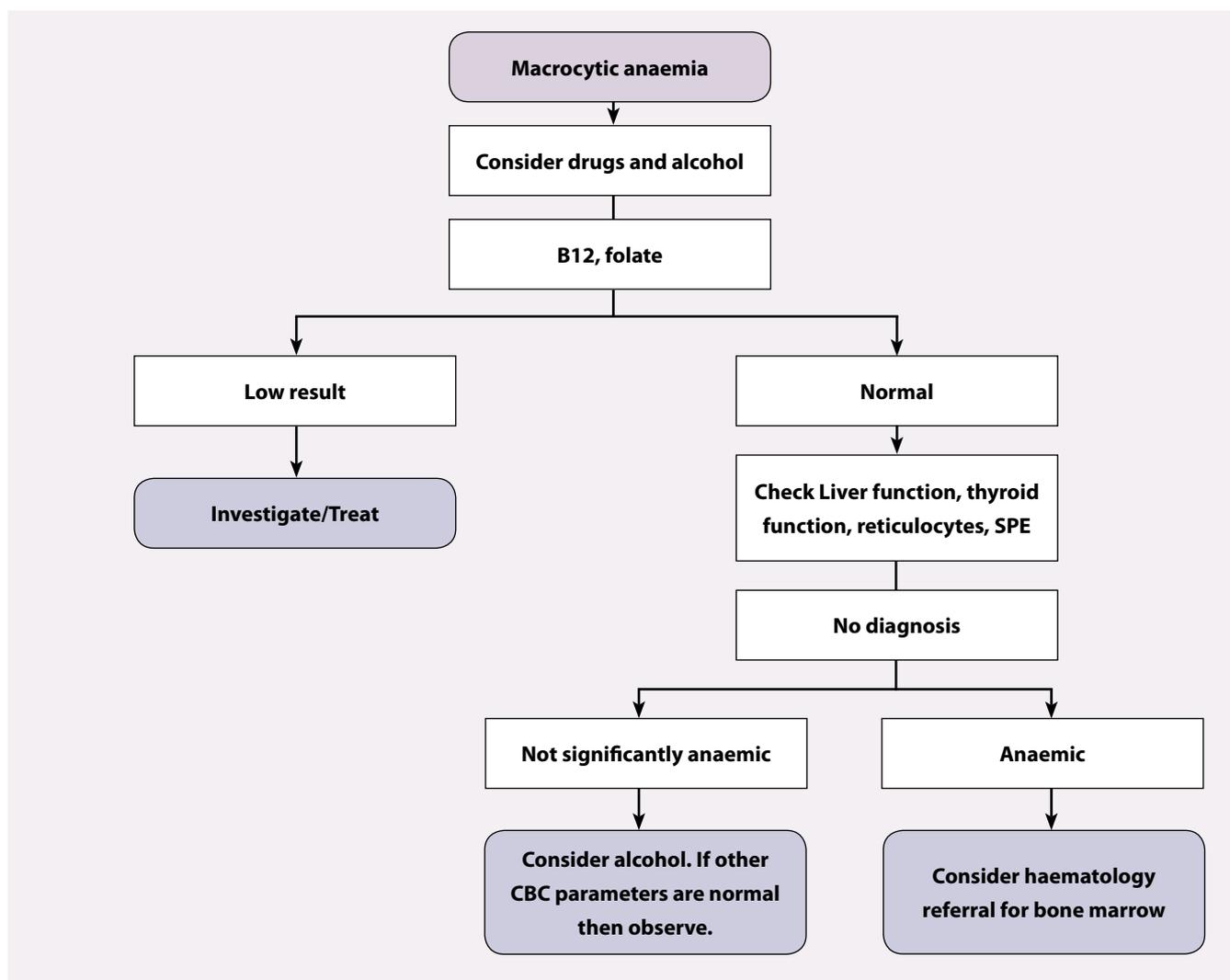
Testing may include:

- Ferritin, B12, folate
- Creatinine
- Reticulocyte count
- CRP
- Liver enzymes
- Serum Protein Electrophoresis

If the reticulocyte count is elevated the differential is small and includes blood loss, haemolysis and hypersplenism.

If the clinical features and results of these tests are inconclusive a haematological opinion may be appropriate.

Figure 4: A suggested approach to laboratory testing for macrocytic anaemia.



Macrocytic anaemia

Common causes of macrocytosis include alcohol, liver disease, B12 or folate deficiency, thyroid disease and some drugs (especially hydroxyurea). Macrocytosis may be present without anaemia. A reticulocytosis may also elevate the MCV and a reticulocyte count should be checked. Severe hypothyroidism may cause a macrocytosis, but is usually clinically apparent.

Investigation in primary care includes history and examination, and laboratory testing. A suggested diagnostic approach to macrocytosis is shown in Figure 4. The frequently requested tests include:

- B12 and folate
- A blood film

- Reticulocyte count
- Liver enzymes
- TSH

RAPS4 Alcohol Screening Test for dependent drinking may be useful (see over page).

When these investigations are normal, and the anaemia is significant, bone marrow disorders may need to be excluded.

HIGH HAEMOGLOBIN

Elevated haemoglobin and PCV (packed cell volume or “haemocrit”) levels can reflect decreased plasma

volume (due to dehydration, alcohol, cigarette smoking, diuretics) or increased red cell mass (polycythaemia). Polycythaemia may be secondary (usually to chronic hypoxia, but occasionally to erythropoietin-secreting tumours, especially renal tumours, fibroids) or primary (polycythaemia vera). Unless the haemoglobin/PCV is very high it is usually advisable to repeat the blood count ensuring adequate hydration.

A PCV of > 0.52 in men and > 0.47 in women needs to be confirmed in a specimen taken without venous occlusion. A confirmed PCV above these levels, in the absence of an obvious secondary cause, is an indication for a haematological opinion because of the high risk of stroke and other adverse events for people with polycythaemia vera.

Other Red cell indices (Red cell count, RDW, MCH, MCHC)

These red cell indices are useful for building a “picture” of many patterns suggested by the haemoglobin. There are limited situations in which isolated abnormalities of these indices are useful and not all of the indices are reported by all laboratories.

The RAPS4 Alcohol Screening Test for dependent drinking

Ask the patient the following four questions:

- During the last year have you had a feeling of guilt or remorse after drinking?
- During the last year has a friend or a family member ever told you about things you said or did while you were drinking that you could not remember?
- During the last year have you failed to do what was normally expected from you because of drinking?
- Do you sometime take a drink when you first get up in the morning?

A positive response to any of these questions warrants further investigation.

From: Cherpitel, C. J. (2000) A brief screening instrument for problem drinking in the emergency room: the RAPS4. *Journal of Studies on Alcohol* 61, 447-449

SUMMARY TABLE

Cell	High	Low
Neutrophil	<p>Most common causes:</p> <ul style="list-style-type: none"> ▪ Infection/inflammation ▪ Necrosis ▪ Any stressor/heavy exercise ▪ Drugs ▪ Pregnancy ▪ CML ▪ Smoking ▪ Malignancy <p>Red flags:</p> <ul style="list-style-type: none"> ▪ Person particularly unwell ▪ Severity of neutrophilia ▪ Rate of change of neutrophilia ▪ Presence of left shift 	<p>Significant levels:</p> <ul style="list-style-type: none"> ▪ $< 1.0 \times 10^9/L$ (high risk infection) <p>Most common causes:</p> <ul style="list-style-type: none"> ▪ Viral (overt or occult) ▪ Autoimmune/idiopathic ▪ Medications <p>Red flags:</p> <ul style="list-style-type: none"> ▪ Person particularly unwell ▪ Severity of neutropenia ▪ Rate of change of neutropenia ▪ Lymphadenopathy, hepatosplenomegaly
Lymphocyte	<p>Causes:</p> <ul style="list-style-type: none"> ▪ Acute infection (viral, bacterial) ▪ Smoking ▪ Hyposplenism ▪ Acute stress response ▪ Autoimmune thyroiditis ▪ CLL 	Not usually clinically significant
Eosinophils	<p>Most common causes:</p> <ul style="list-style-type: none"> ▪ Allergy/atopy, asthma/hayfever ▪ Parasites (less common in developed countries) <p>Rarer causes:</p> <ul style="list-style-type: none"> ▪ Hodgkins ▪ Myeloproliferative disorders ▪ Churg-Strauss syndrome 	No real cause for concern
Monocytes	<ul style="list-style-type: none"> ▪ Usually not significant ▪ Watch levels $> 1.5 \times 10^9/L$ more closely 	Not clinically significant
Basophils	<p>Associated with:</p> <ul style="list-style-type: none"> ▪ Myeloproliferative disorders ▪ Other rare causes 	Difficult to demonstrate
Platelets	<p>Significant levels:</p> <ul style="list-style-type: none"> ▪ $> 500 \times 10^9/L$ <p>Most likely causes:</p> <ul style="list-style-type: none"> ▪ Reactive conditions e.g. infection, inflammation ▪ Pregnancy ▪ Iron deficiency ▪ Post splenectomy ▪ Essential thrombocythaemia 	<p>Significant levels:</p> <ul style="list-style-type: none"> ▪ $< 100 \times 10^9/L$ <p>Most common causes:</p> <ul style="list-style-type: none"> ▪ Viral infection ▪ Idiopathic thrombocytopenic purpura ▪ Liver disease ▪ Drugs ▪ Hypersplenism ▪ Autoimmune disease ▪ Pregnancy <p>Red flags:</p> <ul style="list-style-type: none"> ▪ bruising ▪ petechiae ▪ signs of bleeding

Glossary

CELLULAR ABNORMALITIES SEEN ON THE PERIPHERAL BLOOD FILM

Acanthocytes are irregularly spiculated (spikey) red cells. Found in liver disease, hyposplenism, anorexia, myelodysplasia and abetalipoproteinaemia (very rare).

Anisocytosis is variation in red cell size. May occur in many different situations and is a non-specific finding.

Variant Lymphocytes (reactive lymphocytes) are lymphocytes that, as a result of antigen stimulation, have become larger than usual. Usually the result of infection, especially viral.

Basophilic stippling the presence of small granular bodies within the red cell cytoplasm. This occurs when there is accelerated red cell production and cells with immature cytoplasm are released into the circulation or else with dyserythropoiesis (abnormal production of red cells). May be found in lead poisoning, thalassaemia or other causes of significant anaemia.

Blast cells are very immature precursor cells which are not usually seen outside the bone marrow. Their presence in the peripheral blood most commonly indicates acute leukaemia, myelodysplasia or myelofibrosis.

Burr cells (echinocyte or crenated cell) are irregularly shaped red cells that may be found in patients with uraemia or as an artefact in older samples.

Dimorphic picture/appearance describes heterogeneity in the size of red blood cells, usually with two distinct populations. It can be found in partially treated iron deficiency, mixed deficiency anaemias (e.g. folate/B12 and iron together), following transfusion, or in cases of sideroblastic anaemia.

Döhle bodies appear as a small, light blue-grey staining area in the cytoplasm of the neutrophil. They are most commonly found in severe infections, but may also be seen with poisoning, burns and following chemotherapy.

Elliptocytes are red blood cells that are oval or cigar-shaped. They may be found in various anaemias, but are found in large numbers in hereditary elliptocytosis. Which is a reasonably common but usually clinically insignificant red cell membrane disorder.

Howell-Jolly bodies are nuclear remnants found in red cells after splenectomy, in cases of megaloblastic anaemia and occasionally in cases of myelodysplasia.

Hypersegmented neutrophils. See “Right shift”

Hypochromia is reduced staining of red cells seen commonly in iron deficiency anaemia and also in thalassaemia and sideroblastic anaemias. Usually associated with microcytosis.

Left shift describes immature white blood cells that are released from the marrow when there is a cause of marrow outpouring, typically due to infection.

Leucoerythroblastic anaemia/picture describes a combination of nucleated red cells and a left shift of granulocytes. It may be seen with severe infection, blood loss, hypoxia, haemolysis or else with bone marrow infiltration, fibrosis or dysplasia.

Leukaemoid reaction is an excessive marked reactive leucocytosis, usually consisting of granulocytes. It is seen after burns, in cases of severe infection, following an acute haemolysis or prolonged hypoxia.

Macrocytosis is the presence of abnormally large red cells found when erythropoiesis is disordered or when red cells are released prematurely from the marrow. See Page 17 for causes.

Microcytosis is the presence of abnormally small red cells often found in association with hypochromia. See Page 15 for causes.

Metamyelocytes, myelocytes and promyelocytes are increasingly immature white cells with a “left shift”.

Neutropenia, drug induced. Many drugs have been implicated including:

Analgesics and anti-inflammatory agents

include phenylbutazone, indomethacin, ibuprofen, acetylsalicylic acid, barbiturates, mesalazine, and quinine.

Antimicrobials include penicillin, cephalosporins, vancomycin, chloramphenicol, gentamicin, clindamycin, doxycycline, flucytosine, nitrofurantoin, minocycline, metronidazole, rifampin, isoniazid, streptomycin,

mebendazole, pyrimethamine, levamisole, sulfonamides, chloroquine, hydroxychloroquine, dapsone, ciprofloxacin, trimethoprim, imipenem/cilastatin, zidovudine, acyclovir and terbinafine.

Antipsychotics, antidepressants and neuropharmacologics include phenothiazines (chlorpromazine, thioridazine, prochlorperazine, trifluoperazine, trimeprazine), clozapine, risperidone, imipramine, desipramine, diazepam, chlordiazepoxide, thiothixene and haloperidol.

Anticonvulsants include valproic acid, phenytoin and carbamazepine.

Antithyroid drugs include thiouracil, propylthiouracil, methimazole and carbimazole.

Cardiovascular system drugs include procainamide, captopril, propranolol, methyl dopa, quinidine, nifedipine and ticlopidine.

Other drugs include cimetidine, ranitidine, allopurinol, colchicine, famotidine, bezafibrate, flutamide, tamoxifen, penicillamine, retinoic acid, metoclopramide, ethanol, chlorpropamide, tolbutamide, thiazides, spironolactone, acetazolamide, IVIG and levodopa. Some herbal remedies.

Nucleated red blood cells are immature red blood cells. These are usually seen in newborn infants and in patients with severe bone marrow stress. Other causes are similar to those for a leucoerythroblastic blood picture (see above).

Pappenheimer bodies are the granules seen in siderocytes found after splenectomy and in association with iron overload and dyserythropoiesis.

Poikilocytosis is the variation in cell shape usually seen in iron deficiency anaemia.

Polychromasia is the heterogeneous staining of RBCs of different ages, and reflects an increase in younger cells (reticulocytes), which appear blue. It may occur after haemorrhage, haemolysis, dyserythropoiesis and treatment with haematinics such as iron and vitamin B12.

Reticulocytosis is the presence of >0.8–2% of total red cell count in the form of reticulocytes. They are young, oversized red cells that are present when the marrow is actively producing red cells. They are increased after haemorrhage, haemolysis or following treatment of deficient patients with haematinics.

Right shift is characterised by the presence of hypersegmented neutrophils (five or more lobes to their nucleus), seen most commonly in B12 and folate deficiency. Other rarer causes include infection, uraemia, and myelodysplastic syndrome. Confusingly a right shift can also be seen in iron deficiency.

Rouleaux are stacked/clumped groups of red cells caused by the presence of high levels of circulating acute-phase proteins which increase red cell “stickiness”. They are often an indicator that a patient has a high ESR and are seen in infections, autoimmune conditions and myeloma.

Schistocytes are red cells fragmented by their passage through intravascular strands of fibrin, found in cases of microangiopathic haemolysis.

Spherocytes are overly-round or spheroid red cells that usually indicate active haemolysis. They are seen more rarely in cases of hereditary spherocytosis.

Stomatocytes are red blood cells with an oval or rectangular area of central pallor, sometimes referred to as a “mouth”. These cells have lost the indentation on one side and may be found in liver disease, electrolyte imbalance and hereditary stomatocytosis.

Target cells are red cells with a central area of increased staining, surrounded by a ring of lighter staining and then a further ring of dense staining at the edge of the cell, giving an appearance similar to an archery target. They may be found in liver disease, thalassaemia, and other haemoglobinopathies. They occur occasionally in small numbers in iron deficiency anaemia.

Teardrop cells (dacrocytes) are teardrop shaped red blood cells found in: iron deficiency, megaloblastic anaemia, thalassaemia, some haemolytic anaemias, marrow infiltration and myelofibrosis and other myeloproliferative disorders.



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