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Interpretation of the full blood count in systemic disease – a guide for the physician

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ABSTRACT The full blood count (FBC) is perhaps the single most common investigation performed in medical patients. It has the potential, when interpreted carefully and in relation to the clinical history, to provide very useful information to assist in diagnosis and management. Clinicians are often alerted to the presence of a primary haematological disorder by abnormalities in the FBC. For the purpose of this review these diseases will not be discussed in detail but the reader will be alerted to pointers which might indicate primary blood disorders throughout the text. The haematology laboratory in large teaching hospitals will often provide up to 1,500 automated FBC analyses each day. These are individually checked for 'flags' provided by the analyser which indicate values outside the normal range. It is clearly essential that clinical information is provided with the request as this will influence how the result is handled by scientific and medical staff. Furthermore, significant abnormalities will generate a blood film request and the report will be most useful when interpreted in light of the patient's working diagnosis. In cases where a diagnosis is not yet known, even brief information on presentation, for example 'collapse with hypotension', 'fever on return to UK', 'weight loss and anorexia', can all be important and help the lab provide clinicians with guidance.

This short review aims to provide physicians with a workable guide to the interpretation of some of the commoner findings in the full blood count. Some of these will be very familiar to you but some will not. This review is not meant to be exhaustive as the rare minutiae will obscure the essential core material. Your haematology colleagues are always happy to help and available for assistance in difficult or problematic cases. I have not specified normal ranges in relation to each entity as these will be defined by your local laboratory.

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OVERVIEW

Haemoglobin

Anaemia is a common finding in medical patients. It is best characterised in relation to the mean cell volume (MCV). The important causes of microcytic anaemia (MCV <80 fl) are outlined below in order of frequency. In the presence of microcytosis with hypochromia (low mean cell haemoglobin [MCH]) it is essential to check a serum ferritin assay. A low serum ferritin is diagnostic of iron deficiency. Ferritin levels, however, can be elevated in the acute phase response often in parallel to the erythrocyte sedimentation rate (ESR) so a normal ferritin does not exclude iron deficiency. A ferritin level over 100 ng/ml virtually excludes iron deficiency regardless of circumstances. A mild microcytosis may be seen in anaemia of chronic disease (discussed below) but the MCV is rarely less than 70 fl and the serum ferritin is normal. The thalassaemias and thalassaemia traits frequently cause microcytosis and hypochromia but the serum ferritin is normal. If thalassaemia trait is suspected in the presence of a low ferritin it is important to correct the iron deficiency before requesting a haemoglobinopathy screen.

The finding of a macrocytic anaemia/macrocytosis is also of diagnostic importance. The differential diagnosis is summarised in Table 2.

A normochromic normocytic anaemia (MCV 80–100 fl) is frequently present in hospitalised patients. It can result from blood loss or may be a reflection of the effects of ongoing systemic infective, inflammatory, and neoplastic disorders and chronic organ failure, when it is known as anaemia of chronic disease (ACD) or anaemia of

TABLE 1 Causes of microcytic anaemia

	Mean cell volume (fl)	Mean cell haemoglobin (pg/ml)	Ferritin (ng/ml)	Red blood cell count ($x10^{12}$/L)	Blood film	History
Iron deficiency	<80, occasionally normal	Low	Low (normal if acute phase response)	Low	Target cells Pencil cells	Bleeding
Anaemia chronic disease	70–80, often normal	Normal	Normal or high	Low	No specific features	Medical disease
Thalassaemia/ trait	Low, often 50–60	Low	Normal	High	Target cells Poikilocytes Tear drop cells Nucleated red blood cells	Ethnic origin
Lead poisoning	Low or normal	Normal	Normal	Normal	Basophilic stippling	History of exposure
Rare red cell disorders, e.g. sideroblastic anaemia, pyro-poikilocytosis	Low	Normal	Normal	Low/Normal	According to condition	Congenital

TABLE 2 Causes of macrocytic anaemia

	Full blood count	Blood film	History	Investigation
Vitamin B12 deficiency	May cause pancytopenia	Oval macrocytes	Pernicious anaemia Ileal surgery	B12 assay Intrinsic factor Ab
Folate deficiency	May cause pancytopenia	Oval macrocytes	Diet Coeliac disease	Serum folate TTG Ab Duodenal Bx
Liver disease	Thrombocytopenia	Regular macrocytes Target cells	Alcohol Hep B, C, etc.	According to history
Hypothyroidism	Normal WBC and platelets	Unhelpful	Thyroiditis Radiotherapy	According to history
Hereditary haemochromatosis	Normal Hb	Unhelpful Mild macrocytosis	Family history	HFE gene studies Ferritin Transferrin saturation
Drug therapy	Variable	Unhelpful	Azathioprine Mercaptopurine Folate antagonists Hydroxycarbamide	According to history
Haemolysis with reticulocytosis	Anaemia	Spherocytes Bite cells polychromasia	Drugs Systemic lupus erythematosus (SLE) Lymphoma	Retic count Direct Coombs test Bilirubin Haptoglobin
Myelodysplastic syndrome	May cause pancytopenia	Dysplastic neutrophils	Exclude other causes	Bone marrow (BM) biopsy Marrow cytogenetics
Plasma cell dyscrasias	Anaemia	Rouleaux	Bone pain Fractures Renal failure	Immunoglobulins Serum electrophoresis Serum free light chains BM biopsy

TABLE 3 Causes of polycythaemia

Type	Red cell mass	Plasma volume	Erythropoietin level*	Causes
Myeloproliferative disease (MPD) (primary polycythaemia)	Raised	Normal	Low	Janus kinase 2 gene (JAK2) mutation
Secondary polycythaemia with hypoxia	Raised	Normal	Normal	Chronic hypoxia due to cardiopulmonary diseases, smoking, high altitude
Secondary polycythaemia without hypoxia	Raised	Normal	High	Ectopic erythropoietin (Renal tumours/cysts, hepatic tumours, fibroids, cerebellar tumours)
Spurious or apparent polycythaemia	Normal	Reduced	Normal	Dehydration Diuretics Alcohol Stress

*Erythropoietin levels are mainly of use in secondary polycythaemia due to ectopic production. In routine practice, levels in the other groups are often normal.

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inflammation (AI). These patients have a normal or raised serum ferritin and normal reticulocyte count and do not respond to iron replacement therapy. In parallel, it is common to find elevated polyclonal gammaglobulins and raised ESR or C-reactive protein (CRP) in inflammatory and infective disorders, respectively. In any patient with such an anaemia and raised ESR it is clearly important to perform serum electrophoresis to exclude a paraprotein and possible plasma cell dyscrasia. The anaemia in ACD will only respond to effective management of the underlying disorder though in renal anaemia with erythropoietin deficiency it will often respond to erythropoietin replacement. Anaemia of chronic disease is a secondary anaemia that results from cytokine-mediated suppression of bone marrow erythroid activity and shortened red cell lifespan. When present, it should always lead the physician to consider its cause. It is an important anaemia to recognise as in some patients it can be the first manifestation of an occult tumour. The anaemia resolves when the tumour is excised.

Polycythaemia (abnormal high haemoglobin and haematocrit) may be the result of a primary myeloproliferative disorder (MPD), particularly if associated with neutrophilia, thrombocytosis, and splenomegaly. Over 90% of patients with primary polycythaemia and approximately 50% of those with myelofibrosis and essential thrombocythaemia harbour a mutation (V617F) in the Janus kinase 2 gene (JAK2) which renders haemopoietic cells more sensitive to growth factors. This mutation can be detected by polymerase chain reaction (PCR) studies on peripheral blood and shows high specificity for myeloproliferative diseases so is very helpful in diagnosis. The presence of this mutation will often mean that investigations such as blood volume studies and erythropoietin levels are not necessary. Polycythaemia is relatively frequently seen as a sole abnormality of the full blood count in medical patients in the circumstances outlined in Table 3 (compared with primary polycythaemia). In many patients the cause will be obvious but in others the finding may be unexpected.

Leucocytes

Changes in peripheral leucocyte count can be highly informative in medical practice and the cell line involved can be specific to certain scenarios.

Neutrophilia is commonly seen in patients with bacterial infection. The most severe infections are associated with more marked neutrophilia and often a degree of myeloid left shift (the presence of immature myeloid cells in peripheral blood) with 'toxic' neutrophil granulation. Neutrophilia may also be seen in non-infective disorders. It is a common response to steroid therapy, severe exercise, and following surgery or splenectomy, but can also occur in systemic vasculitis, in the presence of tissue necrosis/burns, and as a response to certain tumours (summarised below).

- Bacterial infection
- Steroid therapy
- Post-surgery
- Extreme exercise
- Tissue necrosis
- Burns
- Systemic vasculitis
- Carcinoma

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Isolated neutropenia can be seen in connective tissue disorders, particularly rheumatoid arthritis and Sjogren's disease. It can be a result of drug therapy, e.g. clozapine, azathioprine, carbimazole, such that patients need careful regular monitoring when treated with these agents. It is of course seen following cytotoxic chemotherapy. It is commonly seen following viral infection e.g. Epstein-Barr virus infection, when it tends to be mild and self-limiting. A sudden onset neutropenia can be seen in patients with overwhelming bacterial infection and appears to be a poor prognostic sign. A significant persisting neutropenia requires the opinion of a haematologist particularly in patients with cytopenias in other lineages. Mild chronic neutropenias not associated with infection are reasonably common and are sometimes referred to as benign idiopathic neutropenia. Finally, Afro-Caribbean patients commonly show mild neutropenia below the normal range seen in Caucasians: this racial neutropenia should be recognised as such and not generate unnecessary investigations.

Eosinophilia is a much less common finding in clinical practice but the search for a likely cause is often rewarding. Mild eosinophilia is common in patients with asthma, hayfever, and eczema but rarely exceeds 1.0 x 10^9/L. Some of the more common causes are listed in Table 4.

TABLE 4 Causes of eosinophilia

Cause	Condition
Connective tissue diseases	Churg-Strauss syndrome Idiopathic eosinophilic pneumonia
Parasitic infections	
Neoplastic	Carcinoma T cell lymphoma Hodgkin lymphoma Myeloproliferative disorders Myeloid and eosinophilic leukaemias
Allergy	Asthma, hayfever, eczema Drug hypersensitivity Food allergy

A few cases remain unexplained and were previously known as hypereosinophilic syndrome but these patients are increasingly rare now that molecular diagnostics are able to characterise many of these as clonal eosinophilic leukaemias.

Lymphocytosis is commonly seen as a result of viral infection often with a mild self-limiting neutropenia as noted above. Stress lymphocytosis is a relatively common phenomenon in hospital patients and is precipitated by acute onset illnesses such as myocardial infarction, major trauma, and status epilepticus. The lymphocytosis appears abruptly and resolves within a few days of the insult. Mild lymphocytosis is also seen post-splenectomy and can also be a result of smoking. A persistent significant lymphocytosis (lymphocyte count >6 x 10^9/L) requires a haematology opinion and exclusion of a chronic lymphoproliferative disorder.

Lymphopenia is a common result of therapy with steroids and other immunosuppressive agents, e.g. azathioprine. It is seen in advanced HIV infection, can be a presenting feature in patients with Hodgkin lymphoma, and is associated with rheumatoid arthritis, systemic lupus, and sarcoidosis. Mild lymphopenia is a relatively common finding in a routine FBC and in the absence of any other specific symptoms should not trigger extensive investigations. In my experience, the investigation of mild isolated lymphopenia is rarely rewarding.

Monocytosis can be a feature in chronic infection with tuberculosis and syphilis, as part of the inflammatory reaction in Crohn's disease and ulcerative colitis and as a response to certain carcinomas. A persistent monocytosis that is unexplained, particularly if associated with anaemia or thrombocytopenia, may be a feature of myelodysplastic and myeloproliferative disorders, so a haematology assessment is advised in these cases.

Platelets

Thrombocytosis is commonly seen as a reactive phenomenon in patients with active chronic infection, inflammation, and malignancy. The longer the duration of these disease processes, the more likely is thrombocytosis to become evident. These patients will often show an elevation in other inflammatory markers in parallel and the blood film tends to show small relatively uniform platelets with little variation in size. Chronic bleeding and iron deficiency anaemia is frequently associated with thrombocytosis and it will resolve when the bleeding source and iron deficiency is corrected. Reactive thrombocytosis, and the thrombocytosis seen after splenectomy, accounts for the majority of cases seen in general medical practice. Thrombocytosis is also a feature of a number of myeloproliferative disorders, often in association with abnormalities in the haemoglobin or platelet count. These cases will not show elevation of inflammatory markers and the blood film typically shows large platelets with wide variation in individual size. As noted above, testing for the JAK2 mutation can be very helpful in diagnosis. These patients are at increased risk of vascular occlusive events so it is important they are identified.

Thrombocytopenia is seen in a myriad of medical scenarios but it is important to establish that the thrombocytopenia is real and confirmed on a blood film. Spurious thrombocytopenia can result from *in vitro* platelet clumping in ethylenediaminetetraacetic acid

(EDTA)-anticoagulated specimens.This is an idiosyncratic phenomenon seen in some patients and is not associated with disease. The two main groups of conditions causing true thrombocytopenia are firstly those associated with increased platelet consumption and secondly those causing bone marrow failure, as a result of primary haematological diseases, bone marrow infiltration, or fibrosis. The causes of consumptive thrombocytopenia are summarised in Table 5 and more than one mechanism can be active in any individual patient so careful sequential investigation, in light of the clinical history, is essential.

TABLE 5 Causes of consumptive thrombocytopenia

Immune	Idiopathic Connective tissue disorders Drugs HIV infection
Systemic sepsis	
Viral infection	
Heparin	
Alcohol	Acute intoxication
Hypersplenism	Portal hypertension Splenomegaly
Massive transfusion	
Cardiac bypass procedures	
Post transfusion purpura	
Multiorgan failure	
Microangiopathy	Haemolytic uraemic syndrome Thrombotic thrombocytopenic purpura Haemolysis, elevated liver enzymes and low platelet (HELLP) syndrome Disseminated intravascular coagulation

SUMMARY

The FBC can provide a wealth of important information which can assist the physician in patient diagnosis and management. It is essential to assess not only the current lab values but also to establish potential trends over time and in relation to known diagnoses, surgical interventions and drug treatment. The cause of many abnormalities will be obvious but any unexpected findings need explanation. Not only will this assist in achieving a prompt diagnosis in many patients but awareness of the common causes for each abnormality might prevent unnecessary investigations in others.

Highlights

- Abnormalities in the full blood count may be informative in all fields of medicine.
- Anaemia is a common finding in medical patients: assessment of the cause of anaemia is essential in patient management.
- It is important to recognise common reactive full blood count changes in patients presenting with active systemic disease.
- Certain reactive phenomena, e.g. eosinophilia may help direct investigations to achieve a specific diagnosis
- Persisting abnormalities in the full blood count that remain unexplained should prompt an opinion from a haematologist.

Further reading

1 Hoffbrand AV, Pettit J, Moss P. *Essential haematology*. London: John Wiley and sons; 2011.
2 Hoffbrand AV, Tuddenham EGD, Catovsky D et al. editors. *Postgraduate haematology*. London: John Wiley and Sons; 2011.

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SELF-ASSESSMENT QUESTIONS

1. Which ONE of the following is not associated with thrombocytopenia?

A. Massive transfusion.
B. Haemolytic uraemic syndrome.
C. Secondary antiphospholipid syndrome.
D. Essential thrombocythaemia.
E. Portal hypertension.

2. Which ONE of the following is not characteristic in a patient presenting with a collapse due to an overwhelming bacterial infection?

A. Lymphocytosis.
B. Neutrophilia.
C. Neutropenia.
D. Thrombocytopenia.
E. Eosinophilia.

3. A 65-year-old male patient presents with a six-week history of anorexia, weight loss, and lethargy. He is noted to have a low grade fever. The physical examination showed no specific findings. The full blood count showed Hb 90 g/L, MCV 72 fl, WBC 9 x 10^9/L, platelets 600 x 10^9/L. Serum ferritin was 120 ng/ml, ESR was 50 mm/hr. Gammaglobulins were diffusely increased. The chest X-ray was normal.

Which ONE of the following would be an appropriate management plan?

A. Perform endoscopy and colonoscopy then give iron replacement.
B. Request a myeloma screen and skeletal survey.
C. Obtain urine, blood, and sputum for culture then commence empirical antibiotic therapy.
D. Request a bone marrow biopsy for morphology and culture.
E. Consider investigations for a systemic inflammatory/connective tissue disorder or occult neoplasm.

4. A 45-year-old fireman presents with progressive numbness in his feet and some unsteadiness of gait. He was noted to be mildly icteric. The full blood count showed Hb 110 g/L, MCV 131 fl, WBC 4 x 10^9/L, platelets 120 x 10^9/L. Serum LDH was 800 U/ml.

Which ONE of the following would be an appropriate first line of management?

A. Arrange imaging of the liver and biliary tree.
B. Arrange outpatient EMG studies and a neurology opinion.
C. Check a serum B12 assay and commence intramuscular B12 therapy.
D. Request an outpatient haematology opinion.
E. Arrange MRI imaging of the brain and spinal cord.

5. A 25-year-old man with a history of childhood asthma presented with a six-week history of fever and night sweats. Physical examination was unremarkable. The full blood count showed Hb 120 g/L, MCV 91 fl, WBC 11 x 10^9/L, neutrophils 5 x 10^9/L, lymphocytes 0.6 x 10^9/L, eosinophils 4 x 10^9/L, platelets 450 x 10^9/L.

Which ONE of the following is a priority investigation?

A. Chest X-ray.
B. Blood, urine and sputum cultures including investigations for TB.
C. Serology and blood films for helminths.
D. HIV serology.
E. Spirometry with reversibility.

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