Issues of thrombosis, bleeding, and transfusion are extremely common, and often complex, in critically ill patients. Haematology in Critical Care: A Practical Handbook provides a dependable source of expert guidance on how to handle common haematological problems seen in the critical care setting, as well as the acute care of patients with a primary haematological disorder.

Full-time clinical haematologists, regularly attending on intensive care, the Editors begin with an approach to abnormal laboratory tests, following with a disease-orientated approach to topics such as coagulation and haematological malignancy. Other key topics include paediatric and neonatal care, transfusion, point of care testing and the emergency presentation of haematological disease.

This title brings together two of the most highly scientific specialties in clinical practice, delivering a practical approach to these problems, and guiding the clinician through the diagnosis and management of common scenarios encountered in the ICU.

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List of Contributors

Shubha Allard, MD, FRCP, FRCPath
Consultant Haematologist and Honorary Clinical Senior Lecturer
Clinical Haematology
Barts and the London NHS Trust
NHS Blood and Transplant
London, UK

Arvind Arumainathan, MBChB (Hons), MRCP, FRCPath
Consultant Haematologist
Department of Haematology
Royal Liverpool University Hospital
Liverpool, UK

Roopen Arya, MA, PhD, FRCP, FRCPath
Professor of Thrombosis and Haemostasis
King's Thrombosis Centre
Department of Haematological Medicine
King's College Hospital NHS Foundation Trust
London, UK

Jon Bailey
Academic Clinical Fellow in Emergency Medicine
Oxford University Hospitals
John Radcliffe Hospital
Oxford, UK

Sarah A. Bennett, MRCP
Clinical Research Fellow in Coagulation
King's Thrombosis Centre
Department of Haematological Medicine
King's College Hospital NHS Foundation Trust
London, UK

Andrew Breen, MBChB, FRCA, FFICM
Consultant in Critical Care Medicine
Adult Critical Care
St James's University Hospital
Leeds, UK

Therese A. Callaghan, BSc (Hons), MB ChB, FRCP, FRCPath
Consultant Haematologist
NHS Blood and Transplant
Liverpool, UK

Medical Department
Royal Liverpool University Hospital
Liverpool, UK

Joydeep Chakrabartty, MBBS, MRCP, FRCPath
Consultant Haematologist
MIOT Hospital
Chennai, India

Leon Cloherty, MB ChB, FRCA, FFICM
Consultant in Anaesthesia and Intensive Care Medicine
Department of Critical Care
Royal Liverpool University Hospital
Liverpool, UK

Daniel Collins, BPharm (Hons), PGDipClinPharm, MRPharmS, IP
Haematology Pharmacist
Department of Pharmacy
Royal Liverpool University Hospital
Liverpool, UK

Tim Collyns, MA, MB, BCHir, FRCPath
Consultant Microbiologist
Leeds Teaching Hospitals Trust
St James's University Hospital
Leeds, UK
Nicola S. Curry, MA, MRCP, FRCPath
Consultant Haematologist
Oxford Haemophilia and Thrombosis Centre
Oxford University Hospitals
Oxford, UK

Department of Haematology
Oxford University Hospitals
Oxford University
Oxford, UK

Khaled El-Ghariani, MA, FRCP, FRCPath
Consultant in Haematology and Transfusion Medicine & Clinical Director
Department of Stem Cells and Therapeutic Apheresis Services
NHS Blood and Transplant and Sheffield Teaching Hospitals
NHS Trust
Sheffield, UK

Honorary Senior Lecturer
University of Sheffield
Sheffield, UK

Peter A. Hampshire, FRCA, FFICM
Consultant in Intensive Care and Anaesthesia
Department of Critical Care
Royal Liverpool and Broadgreen University Hospitals
NHS Trust
Liverpool, UK

Fran Hartley, RGN, BSc, PG Cert (Clinical Education)
Transfusion Practitioner
Hospital Transfusion Team
Leeds Teaching Hospitals NHS Trust
Leeds, UK

Catharina Hartman, MB ChB, MCEM
Speciality Registrar
Intensive Care Unit
Aberdeen Royal Infirmary
Aberdeen, UK

Stephen F. Hawkins, MB ChB (Hons), MRCP, FRCPath, PhD
Consultant Haematologist
Department of Haematology
Royal Liverpool University Hospital
Liverpool, UK

Quentin A. Hill, MRCP, FRCPath
Consultant Haematologist
Department of Haematology
Leeds Teaching Hospitals NHS Trust
Leeds, UK

Jo Howard, MB BChir, MRCP, FRCPath
Consultant Haematologist
Department of Haematology
Guy's and St Thomas' NHS Foundation Trust
London, UK

Charlotte Kallmeyer, MD, MRCP, FRCPath
Consultant Haematologist
Department of Haematology
St James's University Hospital
Leeds Teaching Hospitals NHS Trust
Leeds, UK

Anne Kelly, MA, MB, Bchir, MRCPCH
Clinical Research Fellow
Department of Haematology
Division of Transfusion Medicine
University of Cambridge/NHS Blood and Transplant
Cambridge
Cambridge, UK

Suzanne Kite, MA, FRCP
Consultant in Palliative Medicine
Palliative Care Team
St James's University Hospital
Leeds, UK

Jerrold H. Levy, MD, FAHA, FCCM
Professor of Anesthesiology
Department of Anesthesiology and Critical Care
Duke University School of Medicine
Durham, NC, USA

Vanessa Martlew, MA, MB ChB, FRCP, FRCPath, FRCPEdin
Consultant Haematologist
Department of Haematology
Royal Liverpool Hospital
Liverpool, UK

Helen V. New, PhD, FRCP, FRCPath
Honorary Senior Lecturer
Consultant in Paediatric Haematology and Transfusion Medicine
Department of Paediatrics
Imperial College Healthcare NHS Trust/NHS Blood and Transplant
London, UK

Derek R. Norfolk, MB, BS, FRCP, FRCPath
Consultant in Haematology and Transfusion Medicine
NHS Blood and Transplant
Leeds Teaching Hospitals NHS Trust
Leeds, UK
Elankumaran Paramasivam, MBBS, MD, MRCP, EDICM, FICM
Consultant in Respiratory and Intensive Care Medicine
St James's University Hospital
Leeds, UK

Amrana Qureshi, MB BChir, MRCPCH, FRCPath
Consultant Paediatric Haematologist
Paediatric Haematology and Oncology Children's Hospital
John Radcliffe Hospital
Oxford, UK

Amin Rahemtulla, PhD, FRCP
Consultant Haematologist
Department of Haematology
Imperial College Healthcare NHS Trust
Hammersmith Hospital
London, UK

Andrew Retter, MBBS, BSc, MRCP, DICM
Haematology Registrar
Department of Haematology
Guy’s and St Thomas’ NHS Foundation Trust
London, UK

Intensive Care Department
Guy’s and St Thomas’ NHS Foundation Trust
London, UK

Michael Richards, MA, BM, BCh, DM, MRCP, FRCPath
Department of Paediatric Haematology
Consultant Paediatric Haematologist
Leeds Children’s Hospital
Leeds, UK

Marie Scully, BSc (Hons), MD, MRCP, FRCPath
Consultant Haematologist
Department of Haematology
University College Hospital London
London, UK

John Snowden, BSc (Hons), MB ChB, MD, FRCP, FRCPath
Consultant Haematologist and Director of BMT
Department of Haematology
Sheffield Teaching Hospitals NHS Foundation Trust
South Yorkshire, UK

Honorary Professor
Department of Oncology
University of Sheffield
Sheffield, UK

Simon J. Stanworth,
FRCP, FRCPath, DPhil
Consultant Haematologist
NHS Blood and Transplant/Oxford University Hospitals NHS Trust
John Radcliffe Hospital
Oxford, UK

Honorary Senior Clinical Lecturer
Department of Haematology
University of Oxford
Oxford, UK

Jecko Thachil, MRCP, FRCPath
Consultant Haematologist
Department of Haematology
Central Manchester University Hospitals NHS Foundation Trust
Manchester, UK

Mari Thomas, MA (Cantab), MRCP, FRCPath
Clinical Research Fellow
Haemostasis Research Unit
University College London
London, UK

Joost J. van Veen,
FRCP, FRCPath, MD
Consultant Haematologist
Department of Haematology
Sheffield Haemophilia and Thrombosis Centre
Sheffield Teaching Hospitals NHS Foundation Trust
Sheffield, UK

Jonathan Wallis,
BA, MB BS, FRCP, FRCPath
Consultant Haematologist
Department of Haematology
Newcastle upon Tyne NHS Acute Hospitals Trust
Newcastle upon Tyne, UK
Stephen Webber, MBChB, FRCA, FFICM
Critical Care Consultant
Department of Anaesthesia and Critical Care
Sheffield Teaching Hospitals NHS Foundation Trust
South Yorkshire, UK

Nigel Webster, MBChB, PhD, FRCA,
FRCP, FRCS, FFICM
Professor of Anaesthesia and Intensive Care
Anaesthesia and Intensive Care
Institute of Medical Sciences
University of Aberdeen
Aberdeen, UK

Richard Wenstone, MBChB,
FRCA, FFICM
Consultant Intensivist
Department of Critical Care
Royal Liverpool University Hospital
Liverpool, UK

Anne M. Winkler, MD
Assistant Professor
Department of Pathology and Laboratory Medicine
Emory University School of Medicine
Atlanta, GA, USA
Medical Director
Grady Health System Transfusion Service
Atlanta, GA, USA
Assistant Medical Directory
Emory Special Coagulation Laboratory
Atlanta, GA, USA

Stephen Wright, MRCP, FRCA, FFICM
Consultant in Intensive Care and Anaesthesia
Department of Perioperative and Critical Care
Freeman Hospital
Newcastle upon Tyne, UK
Preface

Patients with a primary haematological disorder account for 1–2% of admissions to intensive care units. In the UK, patients are usually managed on a mixed medical and surgical unit where low patient numbers may limit the degree of expertise that can be developed. In contrast, almost all critically ill patients require a full blood count and coagulation screen. These tests are frequently abnormal and require interpretation. Issues of thrombosis, bleeding, and transfusion are also extremely common in critically ill patients.

This book is a practical guide to the investigation and management of these common problems as well as the acute aspects of care in patients with a primary haematological disorder. We are full-time clinical haematologists, and both regularly attend on intensive care. We have started with an approach to abnormal laboratory tests and then taken a disease-orientated approach to topics such as coagulation and haematological malignancy. Other key topics include paediatric and neonatal care, transfusion, point-of-care testing and the emergency presentation of haematological disease.

Quentin A. Hill
Jecko Thachil
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QAH

I would like to thank my parents for their continued blessings, my wife Gail for her patience and support and my children Nimue, Neah and Izahak for the tremendous bliss.

JT
SECTION 1
Approach to Abnormal Blood Tests
Anaemia was defined by the World Health Organization as a haemoglobin (Hb) concentration less than 120 g/L (Hb < 36%) in females and less than 130 g/L (Hb < 39%) in males, but the lower level of the reference range for Hb may vary between laboratories. It is common in critically ill patients, occurring in up to 80% of those in intensive care units (ICUs) [1] with 50–70% having a Hb less than 90 g/L during their admission. By reducing oxygen delivery to the tissues, this may be tolerated poorly in those with cardiorespiratory compromise. In critical care, anaemia is commonly due to multiple factors such as inflammation, blood loss, renal impairment and nutritional deficiencies [2, 3] (see Table 17.1), but it is important to consider treatable causes and identify when more detailed investigation is needed. The role of transfusional support is considered in Chapter 17.

Tissue hypoxia exerts physiological control of Hb by triggering the release of erythropoietin (EPO) by the kidneys, which stimulates bone marrow (BM) erythropoiesis. Hb will increase so long as there are no underlying BM disorders (e.g. myelodysplasia) and there are adequate supplies of iron, vitamin B12 and folic acid.

When a rapid marrow response occurs (e.g. following haemorrhage or replacement of a deficient vitamin), reticulocytes (young erythrocytes) enter the blood in large numbers and can be identified on the blood film (polychromasia) or by an elevated reticulocyte count. The normal lifespan for erythrocytes is 120 days, before being removed by the reticuloendothelial system (predominantly in the spleen and liver), but their lifespan may be shortened by inflammation, haemorrhage or haemolysis.

**Diagnostic approach to anaemia in critical care**

In the history, note pre-existing co-morbidities including renal and cardiac impairment. Also note medications, diet and symptoms suggestive of blood loss. Examine for jaundice, lymphadenopathy or organomegaly.

- If there is a sudden unexpected drop in Hb, this may be a sampling error; consider repeating the full blood count (FBC).
- Is the anaemia acute or chronic? This may inform the diagnosis, likely tolerance of anaemia and treatment strategy. Only 10–15% of ICU patients have chronic anaemia prior to admission [4].
- Is the anaemia isolated or are there other cytopenias? Thrombocytopenia (Chapter 3) is also a common finding (~40% of ICU patients) and will therefore often coexist with anaemia in critically ill patients. Common causes of both include sepsis, organ failure and acute blood loss, but important differentials include disseminated intravascular coagulation (DIC) (Chapter 9) and thrombotic microangiopathies (TMAs) (Chapter 11). Review the
clotting and blood film. Haemophagocytic lymphohistiocytosis (HLH) is an important cause of fever and cytopenias that can present with single or multiple organ failure (see succeeding text under extrinsic causes of extravascular haemolysis).

- Pancytopenia may be an artefact (i.e. dilution during sampling) or result from BM failure or infiltration, infection, HLH, hypersplenism, drugs, autoimmune disease or megaloblastic anaemia. If pancytopenia is present, examine for splenomegaly and request a blood film and haematinics. If the cause remains unclear, the advice of a haematologist should be sought as a BM examination may be required.

If the cause of an isolated anaemia remains unclear, it is worth classifying on the basis of the mean cell volume (MCV) as this helps to direct further investigation (Figure 1.1).

### Normocytic anaemia (MCV within the normal range)

Anaemia is most commonly normocytic in critically ill patients and usually multifactorial [4]. Iatrogenic reasons include frequent blood sampling and haemodilution (intravenous fluid administration). Occult blood loss can occur as a result of gastrointestinal mucosal inflammation and contributed to by coagulation defects, thrombocytopenia and uraemia. Another important reason is secondary anaemia, also termed anaemia of chronic disease (AoCD) or anaemia of inflammation. This is the most common cause of anaemia in hospitalized patients and can be caused by infection, cancer, autoimmune disease or chronic kidney disease [5]. This results in a functional iron deficiency, whereby adequate iron stores are present but the availability of iron for erythropoiesis is reduced. Hepcidin, a peptide produced by the liver in

**Figure 1.1** Investigation of anaemia in critical care. MCV, mean cell volume; DIC, disseminated intravascular coagulation; TMAs, thrombotic microangiopathies; HLH, haemophagocytic lymphohistiocytosis; BM, bone marrow; AoCD, anaemia of chronic disease; PNH, paroxysmal nocturnal haemoglobinuria.
response to inflammatory cytokines, may be at least in part responsible for this phenomenon. Typically, ferritin is elevated and serum iron and transferrin saturation are low. Iron supplementation usually produces no improvement (in contrast to true iron deficiency). In addition to functional iron deficiency, inflammation results in reduced EPO production, reduced marrow sensitivity to EPO and shortened red cell survival.

Check haematinics as combined deficiencies can result in a normal MCV. Additionally, due to the acute phase response, a normal ferritin does not exclude iron deficiency. Consideration should be given to the possibility of occult or recent bleeding. The anaemia is likely to resolve with improvement of the underlying conditions. Meanwhile, supportive management (including transfusion when required; see Chapter 17) is the mainstay of therapy, and blood sampling should be kept to a minimum.

**Microcytic anaemia (MCV below the normal range)**

This is often a result of iron deficiency (blood loss, malabsorption or dietary deficiency). It can also occur during prolonged and severe illness as an extreme form of AoCD. Less commonly, microcytosis can be due to a haemoglobinopathy (e.g. thalassaemia trait), acaeruloplasminaemia, myelodysplasia, hyperthyroidism, lead poisoning and some rare congenital conditions (e.g. congenital sideroblastic anaemia).

Iron deficiency can be associated with a thrombocytosis, especially with bleeding. Less frequently, severe iron deficiency may also result in a leukopenia and thrombocytopenia. The blood film may show hypocromic, microcytic red cells, polychromasia and pencil cell poikilocytes. The usual tests of iron status (ferritin and iron studies) are less likely to be informative in the critically ill patient. A reliable measure of iron storage is specially stained BM aspirate slides, but this may not identify acute blood loss and is not usually justifiable solely for this purpose. Instead, if the clinical picture and blood film are compatible, consider a trial of iron replacement and appropriate investigations to identify a cause.

Consider additional testing:
- Lead level if prominent basophilic stippling on film or clinical suspicion
- Thyroid function if relevant clinical symptoms/signs
- BM if dysplastic blood film (haematology referral)
- Hb electrophoresis if target cells, long-standing microcytosis, iron replete or not of northern European ethnicity

**Macrocystic anaemia (MCV above the normal range)**

The leading causes of macrocytic anaemia are alcohol abuse, megaloblastic anaemia (deficiency of vitamin B12 and/or folic acid) and accelerated erythropoiesis (e.g. in response to bleeding or haemolysis).

Other causes include medications (e.g. some chemotherapy agents, hydroxycarbamide, methotrexate, azathioprine, zidovudine, phenytoin), liver dysfunction, hypothyroidism, aplastic anaemia and myelodysplasia. Macrocytosis can occur in pregnancy, in Down syndrome and in smokers.

Spurious causes of macrocytosis include cold agglutinins (red cells agglutinate due to an autoantibody; this will correct by warming a repeat FBC sample), high white cell counts (e.g. acute leukaemia), severe hyperglycaemia (in patient or by sampling close to an intravenous dextrose infusion causing osmotic swelling) or an under-filled tube at venepuncture (increased concentration of EDTA anticoagulant).

- Initial investigations would include liver and thyroid function, B12/folate levels and screening tests for haemolysis (lactate dehydrogenase [LDH], reticulocyte count, haptoglobin, direct Coombs’ test [DCT], bilirubin and blood film examination).

Alcohol excess may be suggested by the history, examination or other blood results (e.g. raised gamma glutamyl transferase). The resulting anaemia and macrocytosis are usually mild, in contrast to megaloblastic anaemia where the MCV may be as high as 120fl. The blood film may show typical megaloblastic features such as oval macrocytosis and neutrophil hypersegmentation. Folic acid replacement should not be given unless the vitamin B12 level is known as by stimulating erythropoiesis, folic acid may aggravate B12 deficiency thereby precipitating subacute combined degeneration of the cord. In B12 deficiency, heart failure may arise through overenthusiastic blood transfusion, and B12 replacement is usually sufficient. If transfusion is judged essential, transfuse one unit slowly, consider diuretic cover, and then reassess.

Myelodysplasia is a clonal BM disorder characterized by ineffective erythropoiesis. There may be dysplastic changes on blood film or additional cytopenias. Although onset is usually insidious, patients may present acutely
with infection or transformation to acute myeloid leukaemia and, if suspected, require a haematology referral.

Haemolysis causes anaemia when increased red cell destruction exceeds the marrow’s capacity to compensate. Typical findings include a reduced haptoglobin, raised LDH and raised unconjugated bilirubin, but these are not fully sensitive or specific. For example, haptoglobin rises as an acute phase response and may fall in liver disease and megaloblastic anaemia and can be congenitally low. The reticulocyte count will only rise if the marrow is healthy. A positive DCT suggests autoimmune haemolysis but can also be positive in other circumstances such as following therapeutic immunoglobulin infusion, recent stem cell or organ transplantation or alloimmunization following recent blood transfusion. Results must therefore be taken in clinical context before diagnosing haemolysis.

Haemolysis can be intravascular or extravascular. Acute intravascular haemolysis can be life-threatening and may require renal or cardiovascular support. Patients may develop chills, fever, rigors, flank or back pain, dyspnoea, dizziness, tachycardia, hypotension, dark urine, oliguria and shock. Red cell fragments may be present on the blood film; LDH is more markedly elevated compared with extravascular haemolysis. Urine and plasma may become red or brown due to the presence of free Hb. Some Hb is taken up by renal cells and iron stored as haemosiderin is subsequently shed into the urine where it can be detected 1–2 weeks after the onset of haemolysis.

In patients where severe intravascular haemolysis is a major presenting feature, consider:
• Was there recent blood transfusion? Most immediate haemolytic transfusion reactions are due to ABO mismatch. Bacterial contamination can present with a similar picture. Investigation and management of transfusion reactions are discussed in Chapter 14.
• Is there a history of fever and foreign travel or splenectomy? Investigate for falciparum malaria with thin and thick films (also antigen testing if available). Bartonellosis and babesiosis can also invade the red cell, cause haemolysis and be visible on the blood film (see Chapter 6). Severe babesiosis often occurs in patients with a history of prior splenectomy.
• Always consider Clostridium perfringens sepsis. Massive intravascular haemolysis due to alpha-toxin occurs in approximately 10% of cases and is associated with shock and mortality of up to 80%, usually within hours of presentation. Risk factors include diabetes, malignancy or following abdominal surgery. The primary focus is usually hepatobiliary, intestinal or uterine. Infection of a traumatic injury (gas gangrene) can also lead to sepsis. Spherocytes and ghost cells (depigmented red cells) feature on the blood film. Tissue or blood cultures confirm diagnosis. Treatment involves early high-dose antibiotics (e.g. penicillin and clindamycin) and surgical debridement of devitalized tissue.
• Review medications (including peri-operative antibiotics and over-the-counter medication). An important differential is drug (or drug metabolite)-induced immune haemolytic anaemia (e.g. second- or third-generation cephalosporins or diclofenac). The DCT may be negative if haemolysis is massive. Further exposure to the causative drug can be fatal.
• Has there been accidental (or intentional) ingestion/inhalation of toxic substances? Haemolysis is caused by oxidative damage with the formation of physiologically useless methaemoglobin and denatured Hb, which precipitates (Heinz bodies), damaging the red cell membrane and leading to extravascular and, if severe, intravascular haemolysis. Symptoms of methaemoglobinemia may also be prominent including cyanosis, headache and fatigue, leading to arrhythmias, seizures and coma in severe cases. Blood is characteristically a chocolate brown colour.
  ◦ Nitrates. Present in fertilizer and can result in methaemoglobinemia in infants exposed to well water or vegetable juice. Inhaled amyl nitrite (poppers, liquid gold) used recreationally can cause fatal oxidant injury.
  ◦ Copper sulphate poisoning. Rare in the UK but in some countries is sold over the counter for pesticide and home-made glue and is burnt in houses for religious purposes by Buddhists and Hindus. Hydrated crystals are marine blue and attractive to children. Ingestion is also associated with erosive gastropathy, hepatitis, acute renal failure and rhabdomyolysis.
  ◦ Arsine gas. Produced in industrial processes.
• Are symptoms associated with cold exposure? In paroxysmal cold haemoglobinuria (PCH), haemolysis is provoked by the cold, resulting in haematuria, back or abdominal pain and fever. It usually follows a viral
infection in children and, although often transient, can be severe. The DCT is positive and PCH is confirmed by the Donath–Landsteiner test.

- Also consider glucose-6-phosphate dehydrogenase (G6PD) deficiency. There may be a personal or family history and a recent trigger for haemolysis. It is an inherited, X-linked red cell enzyme defect resulting in susceptibility to oxidative damage. It affects an estimated 400 million people worldwide and is most prevalent in sub-Saharan African countries. As well as a variably severe chronic extravascular haemolysis, oxidative stress such as infection, ingestion of fava (broad) beans and various medications (e.g. dapsone, primaquine, nitrofurantoin) leads to acute intravascular haemolysis and bite cells on the blood film. Blood tests are readily available but false-negative results can occur in the presence of a reticulocytosis (higher G6PD levels).

- Are there additional cytopenias or a history of venous thrombosis? Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired stem cell disorder that renders blood cells susceptible to complement-mediated injury. It is readily diagnosed with peripheral blood flow cytometry. See Chapter 32 for further details.

Intravascular haemolysis may not be the major clinical feature of a disorder and is not always fulminant. Examples are listed:

- Renal failure – red cell fragments may be present due to uraemia, complications of haemodialysis or the underlying cause of renal failure (e.g. lupus nephritis).
- Other extracorporeal circuits (e.g. ventricular assist devices, cardiopulmonary bypass circuits) or following placement of an indwelling transjugular intrahepatic portosystemic shunt (TIPS).
- Severe burns.
- Drowning.
- TMAs. Associations include HIV, autoimmune disease, malignancy, pregnancy, diarrhoeal illness, hypertension and certain drugs (e.g. ciclosporin).
- DIC.
- Cardiac periprosthetic or perivalvular leaks.
- Cold agglutinin disease (CAD). Autoimmune haemolytic anaemia (AIHA) is caused by a cold reactive IgM antibody. The DCT is usually positive to complement only and agglutination is seen on the blood film. The patient and blood products for transfusion should be kept warm.
- March haemoglobinuria. Caused by intensive exercise, e.g. long-distance running.
- Oxidant drugs (e.g. dapsone, salazopyrin) and inherited unstable haemoglobins can give rise to chronic intravascular haemolysis.
- Zieve’s syndrome. Rarely, intravascular haemolysis has been described associated with cirrhosis and alcohol excess.
- Wilson’s disease. Usually presents with liver or neurological disease, or through family screening, but can occasionally present with acute intravascular haemolysis. Haemolysis that is mainly extravascular can be caused by intrinsic red cell defects or extrinsic factors.

Intrinsic defects: inherited conditions give rise to a long-term haemolytic state, but compensated anaemia can occur with additional stress such as haematinic deficiency, pregnancy or infection. Aplastic crisis, classically by parvovirus B19, results in transient interruption of red cell production and reticulocytopenia, which can cause a life-threatening anaemia. Intrinsic defects are reviewed in more depth in Chapter 32.

- Disorders of Hb. In thalassaemia, an imbalance of globin chains leads to their precipitation and reduced red cell survival. Structural Hb variants can give rise to sickle cell disease (see Chapter 18).
- Red cell membrane defects (e.g. hereditary spherocytosis) usually give rise to a chronic non-spherocytic haemolytic anaemia.

Extrinsic factors:

- Liver disease. Mild effect due to alteration of the red cell membrane (e.g. acanthocytes, stomatocytes).
- Splenomegaly. Results in increased red cell sequestration and destruction.
- Delayed haemolytic transfusion reaction – typically seen 1–2 weeks after transfusion, caused by an anamnestic immune response due to an antibody undetectable during routine pre-transfusion testing.
- Warm AIHA. Spherocytes are seen on the blood film. DCT is positive.
- Immune haemolysis can also be drug induced or follow solid organ and BM transplantation.
- HLH. May be primary or secondary to infection or malignancy. Phagocytosis in the marrow, liver, spleen or lymph nodes leads to cytopenia, organomegaly, fever, deranged liver function and coagulopathy. There may also be
neurological symptoms and lymphadenopathy. Fibrinogen may be low and fasting triglycerides and ferritin high.

In conclusion, anaemia is common and usually multifactorial. The cause may be clear from the clinical context, but, if not, classification according to the MCV is helpful in directing investigations. Anaemia is most often normocytic and contributed to by blood loss, haemodilution, impaired EPO release and functional iron deficiency. Consider a haematology referral: where anaemia is prominent and the cause unclear despite investigation and where haemolysis, haemoglobinopathy, TMA or myelodysplasia are suspected or in cases of an unexplained pancytopenia.

References

Leukopenia is defined as a total white blood count (WBC) or leukocyte count below the lower limit of the reference range for the laboratory in question (e.g. <3.5 × 10^9/L). Leukopenia on admission to intensive care occurs in approximately 7% of admissions and is associated with increased mortality [1]. It can be a result of a reduction in any of the major subtypes of WBC (neutrophils, lymphocytes, monocytes, eosinophils or basophils), but most frequently neutrophils and/or lymphocytes, which contribute most to the total WBC count. The differential diagnosis of neutropenia and lymphopenia can be seen in Table 2.1.

Neutropenia

The severity of neutropenia may be divided into mild (1.5 – 2 × 10^9/L), moderate (0.6 – 1.4 × 10^9/L) or severe (≤0.5 × 10^9/L). Persistent and severe neutropenia is more likely to be clinically significant and lead to complications. The pathogenesis of neutropenia can include decreased production from the bone marrow, increased destruction in the blood circulation, increased margination to the vascular endothelium, neutrophil aggregation and splenic pooling.

In the ICU setting, neutropenia is usually secondary, most commonly to drugs or infection. A primary haematological cause such as leukaemia or another malignancy will rarely develop in a patient who arrived in the ICU with a normal neutrophil count. A drug-induced cause for neutropenia can easily be overlooked due to the multiple agents the patients may receive. A temporal relationship between the commencement of any drug and the development of neutropenia is usually the only clue and may not be considered. A sudden drop in the count can also suggest drug-induced neutropenia, and often, the neutropenia resolves soon after the discontinuation of the drug.

Any infection can lead to neutropenia, most often viral infections such as influenza, cytomegalovirus (CMV) and respiratory syncytial virus. The most likely bacterial cause for neutropenia is a chronic infection like tuberculosis, brucellosis or typhoid rather than streptococcal or staphylococcal infections. The pathogenesis for this neutropenia includes margination and sequestration in the spleen and in the lungs. HIV infection can frequently cause neutropenia, with over two-thirds of patients being neutropenic sometime during their illness. The mechanisms for this include antibody formation, bone marrow suppression and cytokine-mediated neutrophil destruction, while certain antiretroviral agents may decrease neutrophil counts.

Immunological causes like vasculitis and systemic lupus erythematosus can lead to neutropenia through antibody-mediated destruction. Disease control often leads to resolution of the neutropenia. Haemophagocytic
syndrome can cause cytopenias due to macrophage overactivity, consuming blood cells and their precursors. This is can be primary or associated with rheumatological diseases, malignancy and viral infections. Presenting features are discussed in Chapter 1.

Vitamin B12 or folate deficiency can present with neutropenia, with folic acid deficiency developing relatively quickly in patients not supplemented. Associated macrocytic anaemia may provide a clue to this diagnosis and can easily be treated with replacement. Copper deficiency may also be associated with neutropenia due to maturation arrest in the bone marrow or antibody formation. This can occur in patients receiving total parenteral nutrition without adequate copper supplementation, typically with a normocytic anaemia and a normal platelet count. Bone marrow examination can support the diagnosis. Some rarer causes of neutropenia include patients with ketoacidosis and hyperglycaemia, haemodialysis (activation of complement by dialyser membranes, which causes neutrophil aggregation) and cardiopulmonary bypass surgery.

When neutropenia is identified, determine whether it is isolated or associated with other cytopenias. Pancytopenia usually suggests the presence of bone marrow failure (from any cause including drugs) or hypersplenism, usually merits a haematology referral and is discussed in more detail in Chapter 1. The risk of severe, potentially life-threatening infection increases as the neutrophil count drops and is highest for those with severe neutropenia (<=0.5 x 10⁹/L) [2], especially when the mechanism is marrow failure since there is no reserve capacity to produce neutrophils. Also review the trend in the WBC count to ascertain whether the problem is new or potentially long standing and to correlate its development with any changes in medication. Neutropenia developing in a septic patient is most likely to be a result of the sepsis, and little specific testing is required other than examination of the blood film which may show characteristic features in the remaining neutrophils (e.g. toxic granulation and left shift). The count should improve as the sepsis resolves, but if not, alternative diagnoses should be considered. If the cause remains unclear, or if the neutropenia is severe, a haematology opinion should be requested as a bone marrow aspirate and trephine biopsy may be required.

**Lymphopenia**

Lymphopenia can be a pre-existing problem or can develop during the course of an illness. The approach is similar to neutropenia in terms of reviewing the history and previous results. Long-standing lymphopenia is most likely a result of chronic viral infection (such as HIV) but can occur due to generalized marrow failure diseases or (rarely) congenital immunodeficiency syndromes. A sudden-onset lymphopenia may be a result of an acute viral infection (including HIV, EBV and CMV) or due to marrow suppression by drugs (again numerous causes).

**Management**

In addition to identifying and treating the root cause of leukopenia where possible, it is important to recognize that patients are susceptible to infection and that infections can progress more rapidly than in those with normal WBC counts. Consequently, patients with leukopenia should ideally be managed in a side room (i.e. protective isolation), and if infection is suspected (due to fever or other clinical features such as hypotension), urgent treatment is required. Cultures should be taken and antibiotics started without delay (approach to neutropenic fever in haematology patients is discussed in Chapter 20). The choice of antibiotics should take into account local policy. In some centres, initial empirical therapy for neutropenic sepsis is with intravenous piperacillin–tazobactam, but in others, this is combined with an aminoglycoside (most commonly gentamicin) if renal function has previously been satisfactory. In patients who are allergic to penicillin, options may include meropenem or aztreonam with gentamicin. This will depend on the severity of the penicillin allergy and on local policy, which is influenced by
CHAPTER 2 Leukopenia

regional variations in microbiological data. Figure 2.1 shows a suggested pathway for neutropenic fever though it is advisable to consult local guidelines.

In some cases, granulocyte colony-stimulating factor (G-CSF) may be given to facilitate neutrophil recovery, but this can make bone marrow interpretation difficult. Studies looking at G-CSF in the setting of chemotherapy-induced febrile neutropenia have shown that its use reduces the duration of neutropenia and shortens hospital stays but does not improve overall survival [3]. As a result, its use is generally limited to selected groups of patients such as those with severe neutropenia (<0.1 × 10⁹/L) expected to last for more than 10 days and patients with severe hypotensive sepsis. The use of G-CSF remains controversial in the setting of intensive care, and discussion with a haematologist is advisable.

In summary, leukopenia is not uncommon in critical care and is usually due to neutropenia. In the setting of critical illness, infection and sepsis are the predominant causes of leukopenia, though drug-induced reductions are also common. Laboratory investigations should include a blood film and assays of B12 and folate. A haematology referral may be appropriate when the leukopenia is severe or persistent and if advice is needed regarding the management.

References

CHAPTER 3
Thrombocytopenia in the Intensive Care Unit

Jecko Thachil
Department of Haematology, Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK

Introduction

Thrombocytopenia is the most common haemostatic abnormality seen in the intensive care unit (ICU). The reported incidence of thrombocytopenia in this setting ranges from 15% to 60% and is more frequently seen in surgical and trauma patients (35–41%) compared to medical patients (20–25%). Approximately half of the patients with thrombocytopenia already have this on arrival at the ICU, while the remainder usually develops it in the first 4 days of being in the ICU.

Prognostic significance

The degree of thrombocytopenia has been regarded as a marker of illness severity in critically ill patients. A lower platelet count on admission to ICU correlates with higher Simplified Acute Physiology Scores (SAPS), Multiple Organ Dysfunction Scores (MODS) and Acute Physiology and Chronic Health Evaluation (APACHE) scores than those with normal platelet counts. It is also an independent predictor of mortality in ICU with the severity of thrombocytopenia being inversely related to survival. A four- to sixfold increase in mortality has been reported if the platelet count is reduced by more than 50% during ICU admission or if the thrombocytopenia is sustained for more than 4 days. Thrombocytopenia has also been associated with longer hospital and ICU stays.

Clinical presentation

Although the well-recognized clinical manifestations of thrombocytopenia are purpura, petechiae and bleeding, it is more common for these symptoms to be absent when the low platelet count is detected. Although the classical definition of thrombocytopenia is a platelet count less than $150 \times 10^9/L$, significant or spontaneous bleeding rarely occurs with a platelet count above $50 \times 10^9/L$ (unless there are coexistent reasons for platelet dysfunction). Diffuse bleeding and haemorrhage from venepuncture sites may accompany thrombocytopenia and often due to increased vascular permeability and poor vasoconstriction rather than the low platelet count per se. At the same time, the risk of bleeding increases four- to fivefold with a count less than $50 \times 10^9/L$. Spontaneous intracerebral haemorrhage is rare in ICU patients with low platelet count (frequency of 0.3–0.5%) and is most commonly seen when the platelet count is less than $10 \times 10^9/L$.

In contrast to bleeding, thrombocytopenia in ICU may be the result of increased platelet aggregation in the different vasculature. Often, thrombocytopenia is an accompaniment of organ failure, especially renal impairment and respiratory distress syndrome. Platelet aggregation in the organs has been described as a contributory factor in these clinical states. In this regard, a dropping platelet count may be considered as a predictor of impending organ failure, and the aetiological causes may be sought.
and treated early. In addition to microvascular thrombosis, low platelet count can also be associated with an increased risk of thrombosis in disorders such as microangiopathic haemolytic anaemia or heparin-induced thrombocytopenia, where once again platelet aggregation is the underlying pathophysiological mechanism.

Another consequence of thrombocytopenia is the increased vascular permeability, which occurs with the very low platelet count. Platelets are integral constituents of the mechanisms necessary for the maintenance of the vascular integrity. Hence, in cases of thrombocytopenia, there are increased capillary leakage and consequent vascular oedema, clinically evident as generalized oedema, and adult respiratory distress syndrome.

**Specific characteristics of thrombocytopenia in the ICU**

- The cause of thrombocytopenia in ICU patients is usually multifactorial.
- Although an easily recognizable cause of drop in platelet count may be identified, several other reasons may coexist.
- Different reasons for thrombocytopenia may develop over the course of time – for example, drug-induced thrombocytopenia may not improve since sepsis has set in, causing thrombocytopenia due to a different mechanism.
- Unsuccessful management of thrombocytopenia may mean all the underlying reasons have not been adequately managed.
- As discussed earlier, low platelet count can present as organ failure, thrombosis and, less often, bleeding.

**Causes of thrombocytopenia in the ICU**

For practical purposes, five different mechanisms for thrombocytopenia may be considered:

- Decreased platelet production
- Increased destruction
- Increased aggregation
- Dilution
- Sequestration

**Decreased platelet production**

Bone marrow suppression leading to thrombocytopenia can occur in response to drugs, infections and nutritional deficiencies (vitamin B₁₂, folate, copper) and as a consequence of bone marrow infiltration with metastases and haematological disorders such as leukaemia.

Drug-induced thrombocytopenia is extremely common in ICU and can be due to myelosuppression, e.g. chemotherapy agents, or via immune-mediated mechanisms, e.g. heparin. Many antibiotics like teicoplanin, penicillin derivatives and meropenem can cause low platelet count and are often overlooked. Proton pump inhibitors and diuretics are the other common, but not often considered, culprits. Temporal relationship with the commencement of the drug and the drop in platelet count is the only way to suspect drug-induced thrombocytopenia, while confirmation requires their discontinuation and recovery of the platelet count over the next few days. Definitive laboratory investigations to confirm the implicated drug are often difficult.

Acute viral infections such as rubella, mumps, varicella, cytomegalovirus (CMV) and Epstein–Barr virus (EBV) can cause thrombocytopenia as well as more chronic infections such as hepatitis C and human immunodeficiency virus (HIV). Bacterial infections and fungal diseases often cause thrombocytosis initially and then cause thrombocytopenia due to platelet aggregation rather than a problem of platelet production. In this context, it is useful to note that platelets actively participate in the immune effector function of the body by secreting granules, which are microbicidal. It also works alongside the different white cells including neutrophils and monocytes to destroy the invading microorganisms. In the case of viral infections, thrombocytopenia is often a consequence of the phenomenon *molecular mimicry* where the virus resides inside a protective barrier created by the platelets, which then become immunogenic and are destroyed by the body’s defence system.

Excessive alcohol intake can also have a direct toxic effect on megakaryocytes, resulting in decreased platelet production. This can be exacerbated further by coexisting nutritional deficiencies such as vitamin B₁₂ or folate deficiency. In addition to the effect on bone marrow, alcohol excess affects the platelets through the development of liver cirrhosis. The liver produces the platelet hormone thrombopoietin, which becomes deficient in liver cirrhosis, leading to low platelet count.
Portal hypertension, which can accompany liver cirrhosis, can also cause thrombocytopenia.

Bone marrow disorders like leukaemia and lymphoma are not common presentations in the ICU. It may be argued for this reason that bone marrow examination may not be an ideal test in the ICU patient for the diagnosis of cause for thrombocytopenia, although one reason for performing this procedure is to obtain specimens for microbiological culture in some chronic infections like tuberculosis.

**Increased platelet destruction**

Thrombocytopenia due to increased platelet destruction occurs via immune- or nonimmune-mediated mechanisms. Immune-mediated thrombocytopenia results from the production of antibodies against platelets, which can occur in response to viral infections (EBV, CMV), drugs (heparin-induced thrombocytopenia) or following transfusion of blood products (post-transfusion purpura (PTP)). Nonimmune thrombocytopenia arises from the physical destruction of platelets by extracorporeal circuits used in cardiopulmonary bypass and haemofiltration machines and by intravascular devices such as intra-aortic balloon pumps. Increased platelet destruction can also occur in vasculitides, where immune-mediated destruction is the cause.

**Increased platelet aggregation**

Increased platelet aggregation is probably the main cause of thrombocytopenia in bacterial sepsis. Platelets can aggregate with each other and also with other cells including monocytes and neutrophils, decreasing the number of total circulating individual platelets. In addition, there is also an increased binding of platelets to activated endothelium, which leads to platelet sequestration and destruction in micro-vessels. Bacterial lipopolysaccharide and inflammatory cytokines also induce platelet aggregation.

Increased platelet consumption also occurs in acute and chronic disseminated intravascular coagulation (DIC) and in the thrombotic microangiopathic disorders, thrombotic thrombocytopenic purpura (TTP), haemolytic uremic syndrome (HUS) and HELLP syndrome in pregnant women (characterized by haemolysis, elevated liver enzymes and low platelets). Platelet aggregation can also be a manifestation of massive pulmonary embolism. Recently, acute drop in platelet count has been described as a phenomenon in thrombotic storm where widespread thrombosis occurs in different organs and leads to thrombocytopenia due to increased consumption.

**Dilution**

Patients with massive blood loss develop thrombocytopenia via the direct loss of platelets in the blood from the site of bleeding and through the consumption of platelets utilized in clot formation in response to the haemorrhage. Dilutional thrombocytopenia may also arise in this setting if large volumes of crystalloid or colloid solutions are infused into the patient or if inadequate replacement of platelets occurs in relation to the transfusion of red cells and plasma blood products.

**Sequestration**

Platelet sequestration secondary to splenomegaly can occur in cirrhosis, congestive heart failure, portal hypertension, infection and myeloproliferative disorders. Approximately one-third of the total platelet mass is sequestered in the spleen normally, and this can increase to 90% in massive splenomegaly. These patients are less likely to bleed from their thrombocytopenia as the platelets are able to enter the circulation in response to bleeding and have a normal lifespan.

**Diagnostic approach to thrombocytopenia in the ICU setting**

- In order to establish the cause of thrombocytopenia in critically ill patients, it is important to obtain an accurate history of their current illness and past medical history.
- Drug history is one of the most important checks in a thrombocytopenic ITU patient. A review of all the medications which the patient has recently received (including non-prescription and recreational drugs) should be done. The timing of onset of each medication in relation to the development of thrombocytopenia should be considered.
- Exposure to heparin in the ICU setting as a result of central catheter flushes or haemofiltration/dialysis should also be excluded as a potential cause of thrombocytopenia.
- A review of the timing of all transfusions of blood products received by the patient should also occur in order to consider PTP as a possible diagnosis.
- Clinical examination should focus on any evidence of bleeding or microthrombosis. Splenomegaly may be a relevant finding in this context.
Investigations
1 Previous laboratory results can be used to determine the rate of thrombocytopenia development and if the thrombocytopenia is an acute or a chronic problem. A gradual decrease in platelet count over 5–7 days is more in keeping with decreased platelet production or a consumptive cause of thrombocytopenia, while a more abrupt drop in platelet count occurring within 2 weeks of transfusion or commencement of a new drug points towards an immunological cause such as drug-induced thrombocytopenia or PTP.
2 Valuable diagnostic information can be gained from examining a blood film, and this should be requested in all patients with thrombocytopenia:
   a. The presence of platelet clumping on the blood film indicates that the thrombocytopenia maybe spurious and that the full blood count should be repeated in a heparin- or citrate-containing blood collection tube.
   b. The presence of schistocytes (red blood cell fragments) indicates a microangiopathic process.
   c. A leukoerythroblastic blood film with teardrop cells, nucleated red blood cells and immature granulocyte precursors present is suggestive of an underlying bone marrow abnormality.
   d. Macrocytosis of red cells is seen in patients with folate or vitamin B12 deficiency, hypothyroidism or alcohol toxicity.
   e. For those with history of foreign travel, the blood film can also be examined for the presence of parasites such as malaria.
3 Clotting screen abnormalities may suggest sepsis or DIC.
4 Liver function tests.
5 Haemolysis screen to include lactate dehydrogenase (LDH) and reticulocyte count, bilirubin and haptoglobin.
6 HIT screen if appropriate.
7 Vasculitic screen.
8 Nutritional deficiencies – serum vitamin B12 and folate levels.
9 Blood cultures.
10 Viral screen including HIV, EBV, CMV and hepatitis C.
Although the aforementioned is a rough guide to the investigations which may be considered for an ITU patient with thrombocytopenia, all these tests may not be required in every patient.

Management
In general, the management of thrombocytopenia is to treat the underlying cause. However, platelet transfusions may be considered if there is active bleeding or if a procedure with bleeding risk is required. The following guidance may be followed for practical purposes:
• If platelet count is below $10 \times 10^9$/L, one adult dose of platelets may be transfused.
• If the platelet count is below $20 \times 10^9$/L and patient is septic or very ill, one adult dose of platelets may be transfused (in these clinical situations, increased platelet consumption can occur).
• If the platelet count is below $30 \times 10^9$/L and the patient is bleeding, one adult dose of platelets may be transfused.
• If the platelet count is over $30 \times 10^9$/L, platelet transfusion is avoided unless:
   ◦ Patient requires an interventional procedure (threshold is most often $50 \times 10^9$/L).
   ◦ Patient requires anti-platelet agent (threshold is $50 \times 10^9$/L).

In certain conditions like TTP and heparin-induced thrombocytopenia, platelet transfusions are best avoided unless active and life-threatening bleeding occurs.

Further reading