*Clinical Reviews*

# Haematological Emergencies on the Acute Medical Take

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## Abstract

*As haematological emergencies are uncommon in daily clinical practice, enhanced awareness and high index of suspicion is required to ensure that the potentially lifesaving measures are offered. This article discusses some of the haematological conditions which may present on the acute medical take.*

## Keywords

*Bleeding, sepsis, thrombosis, transfusion reaction.*

## Neutropenic Sepsis

Neutropenia(defined as Neutrophil count <1500/mm$^3$) has many causes (Table 1). The commonest causes are viral infection or myelosuppression due to a disease process (i.e Leukemia) or drug therapy.

Early involvement of the specialist haematology team is essential in the management of these patients. Depending on the underlying cause, a significant proportion will already be under the care of a haematologist, who should be informed of their patient's admission at the earliest opportunity.

### *Risk of Neutropaenic Sepsis*

Cytotoxic-induced neutropenia carries higher risk of infection than that occurring after transient viral infection, aplastic anaemia or congenital neutropenia.[1]

Increased susceptibility to infection can be expected as the neutrophil count falls below 1000 cells/mm$^3$. The risk increases markedly with a reduction in neutrophil count to <500 cells/mm$^3$ and especially with a count of <100 cells/mm.$^3$ Similarly, the risk of infection rises steeply with increasing duration of neutropenia.[5]

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| **Bone marrow disorders** |
| • Aplastic anaemia |
| • Infiltrative disease: Leukaemia, lymphoma |
| • Myelodysplasia |
| • Cyclical neutropenia |
| • Drugs: Chemotherapeutic agents, carbimazole; antiretroviral drugs, other immunosuppressants (e.g. azathioprine, sulphasalazine) |
| **Peripheral Disorders** |
| • Hypersplenism |
| • Sepsis |
| • Viral infection |
| • Autoimmune neutropenia |

**Table 1.** Causes of Neutropenia.

### *Causative Organisms and sites of infection*

At least half of the infections in neutropenic patients are endogenous. Cellulitis, pneumonia, urinary tract and gastrointestinal tract infections are the most common infections. Special consideration should be given to the possibility of vascular line and urinary catheter associated infection.

Initial infections are usually bacterial.[1,3] No pathogen is isolated in more than half of the cases while initial evaluation fails to identify a focus of infection in nearly two-thirds of cases.[3,4]

Gram-positive cocci (*Staphylococci* and *Streptococci*) and Gram-negative bacilli (*Escherichia coli, Klebsiella, Pseudomonas*) are most frequently isolated. Gram-negative organisms are isolated more frequently from the urinary tract, GI tract and lung, while bacteraemia is more commonly due to Gram-positive organisms especially if a central venous cannula is in place. Anaerobic organisms are rarely isolated.[3]

Fungal, viral and protozoal infections present less commonly as initial infections. Fungi more commonly cause secondary infections in patients who have been on broad-spectrum antibiotics.

### *Clinical Features and Initial Assessment*

Fever must always be taken very seriously in such patients even if they look well initially. Although fever may be due to other causes including mucositis, drugs and underlying malignancy, fever in neutropenic patients should always be initially assumed to be of infective origin. At least 50% of febrile patients with neutropaenia have an infection and many of them develop bacteraemia. However, patients with neutropaenia and infections may be afebrile or even hypothermic, therefore infection must be considered in any unwell neutropenic patient.[1]

Initial evaluation starting with a detailed history and Clinical examination aims at finding the cause of neutropenia, source or site of infection, co morbidities, drug history and other.[1]

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***Investigations***

Blood (two 15 ml blood cultures)[2] and mid-stream urine sample should be sent for culture and sensitivity. Full blood count, liver and renal function tests should be sent at admission and monitored at least every 3 days afterwards.[5]

Chest radiography is commonly performed even though consolidation is not usually seen in severe neutropenia. More than half of febrile neutropenic patients with normal chest radiographs will have evidence of pneumonia on high-resolution CT.[7]

Cultures of cerebrospinal fluid, synovial fluid, stool and drainage sites should be undertaken if specific symptoms are present. Biopsy of suspicious lesions, sinus radiographs and nasal endoscopy may be needed in some cases along with CT of chest and abdomen.[5]

***Treatment***

The patient should be isolated in a side room and barrier nursing is advised. Empirical antibiotic therapy must be administered promptly.[1]

*(a) Empirical antibiotic therapy*

There are three general principles when faced with the choice of appropriate initial antimicrobial therapy.

1. Local trust guidelines based on local epidemiology and drug-susceptibility patterns should be consulted.
2. The chosen antimicrobial agent should have activity against gram-negative organisms, including Pseudomonas.
3. The chosen treatment needs to take in consideration individual patient factors (i.e. allergies or unsuitability for any particular therapy).

Initial Antibiotic therapy is guided by assessment of a patient's relative risk of developing serious complications. In general, younger patients with no significant co-morbidities, recovering phagocyte counts, no focus of bacterial infection or symptoms and signs suggestive of systemic infection (e.g. rigors, hypotension) other than fever are considered at "lower risk" and can be suitable for oral antibiotic therapy, in some cases as outpatient. Commonly used regimens are quinolone-based combinations (ciprofloxacin plus amoxicillin-clavulanate).[5]

Patients considered to be at higher risk should be treated with in-patient parenteral therapy. Two general regimens include monotherapy with an antipseudomonal beta-lactam alone such as Cefipime or Meropenem, or combination therapy that does or does not contain glycopeptides (vancomycin or teicoplanin).

Glycopeptides are considered for patients with suspected catheter related infections, significant mucosal damage, hypotension and history of >1 week of quinolone prophylaxis. If Glycopeptides are considered unnecessary a combination regimen including an aminoglycoside (gentamicin) plus an extended-spectrum cephalosporin (cefipime or ceftazidime), an antipseudomonal penicillin (piperacillin-tazobactam) or a carbapenem (meropenem) can be considered.

Glycopeptides can be combined with of the agents mentioned above, with or without an aminoglycoside.[5] As a general rule it may be safer to administer monotherapy to patients with no obvious focus or simple infections and combination therapy to complex, tissue-based infections and those with pneumonia or enterocolitis, which are more likely to be polymicrobial.[3]

*(b) Antifungal therapy*

Patients who remain febrile after 3–5 days of antibiotic therapy may have fungal infection, drug resistance or a new site of infection and should therefore be empirically started on broad spectrum lipid based anti-fungal therapy[3] (e.g. liposomal amphoteracin). Up to one-third of neutropenic patients who remain febrile after 1 week of empirical antibiotic therapy have been found to have systemic fungal infections.

*(c) Other treatments*

Colony stimulating factors and granulocyte infusions are not recommended routinely but may be useful in refractory cases, especially when associated with severe and protracted neutropenia.

Human activated protein C, although not fully studied in neutropenic patients, may be considered in severe neutropaenic sepsis associated with multiple organ dysfunctions.[6]

## Hyperviscosity Syndrome

Hyperviscosity syndrome (HVS) refers to the clinical manifestations of increased blood viscosity. Symptomatic hyperviscosity usually results from a marked increase in circulating serum proteins and can be seen in Waldenström's macroglobulinaemia, multiple myeloma[14] and occasionally dysgammaglobulinaemias. It can also result from increased cellular constituents (typically white or red blood cells) in hyperproliferative states such as the leukaemias and polycythaemias. The overall rise in blood viscosity leads to impaired microvascular flow and a variety of clinical symptoms and signs (Table 2).[14,15] Complications may occur as consequence of bleeding, thrombosis or sepsis and may result in neurological deficit, heart failure, and renal failure. In some cases this may prove fatal. The overall prognosis will depend on the underlying cause.

***Diagnosis***

Measurement of plasma viscosity is diagnostic in evaluating hyperviscosity syndrome when the elevated viscosity is concomitant with characteristic symptoms. As different patients will have symptoms at different values of viscosity, there is no exact diagnostic value for hyperviscosity. In general, blood viscosity will often be more than four times the normal level before symptoms appear.[14,15] Other useful tests include FBC and differential cell count, LFT for total protein, blood film (may show Rouleaux formation) and clotting screen. Investigations to determine the underlying cause may include bone

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| **Central Nervous System** |
| • Headache |
| • Nystagmus, ataxia |
| • Seizures |
| • Stroke |
| • Coma |
| **Haematological** |
| • Coagulopathy |
| • Bleeding, |
| • Thrombosis |
| • Leukocyte dysfunction-sepsis |
| **Visual** |
| • Papilloedema |
| • Fundal haemorrhages |
| • Hemorrhagic retinal veins (appear 'sausage like')[14,15] |
| • Visual loss |
| **Cardiovascular** |
| • Hypervolaemia |
| • Congestive cardiac failure |
| **Renal** |
| • Renal failure |

**Table 2.** Clinical manifestations of HVS.

marrow aspiration, urine electrophoresis and paraprotein levels.

### *Management*

The management of HVS should be primarily directed at the reduction of blood viscosity (removal of the abnormal component). At the same time, it should be accompanied by measures that can control the underlying disease and prevent the production of the causative element.[14,16]

Plasmapheresis is the effective treatment of the hyperviscosity syndrome caused by the paraproteinemias (the majority of cases),[14,15] while venesection is indicated for patients with polycythemia. Intravenous hydration and intensive chemotherapy often results in a rapid reduction in the white cell count in patients with acute leukemias. Until the chemotherapy exerts its full effect, other measures like leukapheresis and plateletpheresis may be used in cases of leukostasis, and symptomatic thrombocythaemia, respectively.[17]

## Acute Blood Transfusion Reactions

The complications of blood transfusion consist of a diverse group of non-immune and immune-mediated transfusion reactions that range from immediate life-threatening to subclinical reactions.

### *Febrile non-haemolytic transfusion reaction*

This is a relatively common complication affecting up to 1% of RBC transfusions and 20% of platelet transfusions.[21] It occurs in recipients of multiple transfusions who have developed antibodies against the HLA antigens present on the surface of the transfused leukocytes.

The reaction which usually begins 30–60 minutes after starting transfusion is usually mild and self-limiting; symptoms include pyrexia, rigors, nausea, aches and high blood pressure.

In mild cases and where an acute haemolytic reaction is excluded, transfusion can continue with paracetamol and possibly antihistamine or steroid cover. Future recurrences of similar febrile reactions can be limited by the use of leukocyte-reduction filters, which is the usual practice in the UK.

### *Acute haemolytic transfusion reaction*

This is the most serious form of transfusion reaction. The commonest cause for a major haemolytic transfusion reaction is a clerical error attributable to misidentification of patient or blood units.

The reaction can occur after infusion of as little as 0.7 mL of mismatched blood, though marked symptoms and signs typically arise after transfusion of 5 to 20 mL.

The clinical manifestations include fever, rigors, nausea, loin pain and hypotension followed by haemodynamic compromise and the consequences of shock, acute renal failure and DIC.

Management starts with immediate discontinuation of transfusion, maintaining venous access, and provision for haemodynamic and renal support. In addition to repeating the cross-matching on a post-transfusion sample, the laboratory workup may include a direct antiglobulin (coombs') test and testing for the haemoglobinemia and haemoglobinuria.

### *Other forms of reaction*

Rare acute transfusion reactions include anaphylaxis and transfusion-related acute lung injury (TRALI). The latter is a potentially fatal reaction occurring within 6 hours of transfusion.[21] It is usually caused by the presence of antibodies in the donor plasma reacting against the recipient white cells. The clinical and radiological picture is that of noncardiogenic pulmonary oedema and the treatment is usually supportive with oxygen and mechanical ventilation if needed.

## Disseminated Intravascular Coagulation

Disseminated Intravascular Coagulation (DIC) is associated with a number of clinical conditions which are listed in Table 3. Sepsis is the most common cause which is likely to present to the acute medical team. As DIC increases the risk of organ failure and mortality beyond that expected of the underlying condition itself, rapid diagnosis and treatment can make a significant difference to the outcome.[9]

The key to management of patients with suspected DIC is close co-operation between the primary speciality team, intensive care team and senior haematologist. In some larger hospitals, one haematologist may take a specific interest in haemostasis, in which case their expertise will be invaluable.

### *Clinical Presentation*

DIC has an acute and sub acute presentations. Both are manifestations of the same disease process and simply reflect different ends of a disease spectrum.[8] A patient with DIC can present with thrombosis, bleeding or both. As a consequence of the rapid consumption and depletion of platelets and coagulation factors, bleeding is the usual presentation in acute fulminant DIC. Bleeeding may occur at any site, but oozing from venipuncture sites or wounds and spontaneous bleeding should alert to the possibility of DIC. In fact bleeding from 3 unrelated sites is not unusual in an average patient with DIC.[8]

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| **Sepsis** |
| • Gram-negative(endotoxin) |
| • Gram-positive (mucopolysaccharides) |
| **Malignancy** |
| • Solid Tumors |
| • Disseminated malignancy |
| • Haematological (e.g.Acute promyelocytic Leukaemia) |
| **Obstetric conditions** |
| • Placental abruption |
| • Amniotic fluid embolism |
| • Retained products of conception |
| • Eclampsia |
| **Trauma** |
| • Head injury |
| • Fat embolism |
| **Burns** |
| **Hepatic failure** |
| **Acute pancreatitis** |
| **Vascular abnormalities** |
| **Acute allergies** |
| • Insect stings/bites |
| • Drug reactions |

**Table 3.** Conditions associated with DIC.

In the sub-acute variety, the liver is able to compensate for these coagulation factors and thrombosis is a more common presentation. Thrombosis commonly manifests as digital ischemia and gangrene. Renal, cardiac, pulmonary and cerebral vascular thrombosis resulting in organ dysfunction is also common. Sub acute DIC is commonly associated with malignancy.

Although patients with DIC commonly present with bleeding, it is in fact the small-and large-vessel thrombosis that is mainly responsible for organ failure and the increased morbidity or mortality.[8]

### *Diagnosis*

No single laboratory investigation can reliably diagnose or rule out the diagnosis of DIC.[11] Most of the commonly used laboratory tests lack the high specificity needed although they have a relatively high sensitivity. Use of a combination of such tests is therefore more helpful in reaching a diagnosis of DIC in the appropriate clinical context.[11] Classically coagulopathy of DIC shows evidence of fibrinolytic activation and consumption of platelets and coagulation factors resulting in elevated fibrin degradation products (FDP), especially D-Dimer, hypofibrinogenemin, prolonged Prothrombin time (PT), activated partial thromboplastin time (APTT) and thrombocytopenia.[11] D-Dimer, PT and APTT are abnormal in 93%, 50%-75% and 50%-60% of patients respectively. Low platelet count or significant and progressive drop in platelet count is a highly suggestive of DIC in patients at risk of the condition. Also as a part of the acute phase response, elevated levels of fibrinogen and shortening of APTT are expected and therefore even with the onset of DIC initial levels can still show minimal or no abnormality.[9]

A diagnostic algorithm for the diagnosis of overt DIC suggested by International society on Thrombosis and Haemostasis therefore takes into account not only abnormal results but also abnormal trends in platelets, fibrinogen, PT and FDPs.[11,13] Sub acute DIC causes mild thrombocytopenia and elevated D-dimer although PT, APTT and Fibrinogen levels are usually normal.

Liver disease and sepsis can mimic some of the abnormalities seen in DIC. Liver disease may prolong both PT and PTT although fibrinogen levels are expected to be normal except in severe liver disease. Platelet count is usually only mildly reduced and other features of liver disease should be evident. Sepsis may produce low platelet count, vitamin K induced coagulopathy and digital ischemia but fibrinogen levels are usually high or normal.

### *Treatment*

Treatment should be aimed at both the primary cause and the manifestations of DIC.[10] Replacement therapy with platelets should be considered to keep platelets count >20,000/ul, Cryoprecipitate is administered if fibrinogen levels are <100 mg/dl and Fresh Frozen Plasma (FFP) is recommended in patients who are actively bleeding.[9,10] The underlying condition should be treated aggressively.[9,10] Recombinant activated protein C (rAPC) has anticoagulant activity and has been effective in treating severe sepsis and should therefore be considered for sepsis related DIC. Caution is advised in patients with severe thrombocytopenia being considered for rACP because of concern for an increased incidence of intracerebral haemorrhage.[6,9]

The role of heparin remains unclear. Although traditionally used for thrombotic manifestations,[10,12] it is now less commonly used. It may be used in low doses when, platelet count and fibrinogen level fails to increase despite replacement indicating ongoing consumption. In this scenario heparin may prove helpful by blocking activation of the coagulation system and excess thrombin generation.

## Tumour Lysis Syndrome

Tumour lysis syndrome (TLS) is a set of metabolic complications observed in neoplasms with rapid cell turnover. There is a high incidence of TLS in tumours with rapid growth rate, high chemosensitivity, and a relatively large tumour burden such as high-grade NHL and Burkitt's lymphoma.[18,19]

While TLS may occur spontaneously prior to administration of chemotherapy, it is usually caused by response to treatment. TLS is characterized by the increased release of intracellular molecules and metabolic by-products (uric acid, potassium, phosphate) into the systemic circulation. These metabolites can overwhelm the body's capacity for clearance and lead to hyperuricemia, hyperkalemia, and hyperphosphatemia with accompanying hypocalcaemia and uraemia.[18,19] Acute renal failure may be multifactorial during acute TLS. Causes include uric acid or calcium phosphate deposition, ureteric obstruction, sepsis and nephrotoxic drugs.[18,19] Patients with pre-existing renal impairment, dehydration or reduced urinary flow are more likely to develop acute renal failure after rapid tumour lysis.

### *Clinical Features*

Clinical manifestations usually develop 12–72 hours after chemotherapy.[18] Patients often describe nausea, vomiting, lethargy and anorexia. In addition there may be clinical

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manifestations of electrolyte disturbances, including paraesthesia, muscle cramps, tetany, confusion, seizures, arrhythmias, and occasionally sudden cardiac arrest.[18,19]

***Management***

The key principle in the management of TLS is to identify patients at risk of developing the condition and introduce proactive measures to prevent or reduce the severity of its manifestations. Cardiac monitoring is essential with regular measurement of serum electrolyte levels. Patients should ideally be managed in a high dependency unit with close liaison with the haematology team.[18]

Treatment approaches can be summarised as follows:

- **Aggressive hydration and diuresis** enhances renal blood flow and promotes the urinary excretion of uric acid and phosphate.[18,19]
- **Therapy to reduce serum potassium level** should be started promptly in patients with hyperkalaemia Acute treatment approaches including calcium gluconate, rapid acting insulin and hypertonic dextrose infusions.
- **Phosphate reduction** may be needed to correct hyperphosphatemia and hypocalcemia. Besides the avoidance of phosphate administration through intravenous solutions, the use of an oral phosphate binder such as aluminium hydroxide is a useful measure. Generally, calcium administration is not recommended in the treatment of asymptomatic hypocalcemia because it may cause metastatic calcification.[18,19]
- **Decreasing uric acid production with allopurinol** and facilitating its excretion by urinary alkalinization has been the standard treatment of hyperuricaemia for many years. An alkaline urine (>= urine pH 6.5) reduces urate crystal deposition in renal tubules and promotes the urinary excretion of uric acid. As urinary alkalization may have adverse consequences such as metabolic alkalosis and/or xanthine obstructive uropathies, the administration of sodium bicarbonate to increase the urinary pH is controversial.[18]

By inhibiting the enzyme xanthine oxidase, allopurinol blocks the conversion of hypoxanthine and xanthine into uric acid. As allopurinol only prevents the formation of new uric acid and does not reduce the level of the pre-existing uric acid, it may take several days after allopurinol therapy initiation before actual reduction in urate level is observed.[18-20] An alternative treatment is urate oxidase which oxidates uric acid into allantoin. Allantoin is far more soluble than uric acid and is therefore excreted easily. In several clinical trials rasburicase ( the recombinant form of urate oxidase) has been shown to be safe and effective in preventing and treating hyperuricemia.[18,19] Rasburicase is much more expensive than allopurinol, but has faster action (4 hours), fewer drug interactions and does not require dose adjustment in renal or hepatic impairment.[20]

In some instances and when other treatment approaches are exhausted, patients with increasing renal dysfunction may require more aggressive measures, including haemodialysis or haemofiltration. [19]

## Conclusion

Although haematological emergencies are uncommon in daily clinical practice, failure to recognise these emergencies and rapidly begin the appropriate therapy may have fatal consequences. A high level of suspicion of these emergency situations, early recognition of patients at risk and rapid initiation of treatment can be life saving.

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