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Emergencies in Malignant Haematology for the Intensivist

An overview of emergencies that are commonly seen in malignant haematology, side effects of novel therapies, and complications of allogeneic haematologic stem cell transplant.

Introduction

Critical illness is common in patients with haematologic malignancies. Recent data demonstrate that 14% of patients will require ICU admission within one year of their initial diagnosis, with the highest risk in acute leukaemia (Ferreyro et al. 2021). As cancer care, infectious disease practices and critical care management have evolved, ICU outcomes in this population have improved. Furthermore, critical illness is increasingly being recognised as part of the treatment pathway for a subset of patients receiving intensive therapies to achieve cure or sustained disease control. Given this, the current and future states of Oncologic Critical Care management for this population will require increased collaboration between intensivists and haemato-oncologists. While sepsis and respiratory failure are the most common admitting diagnoses, there are a range of disease- and treatment-specific complications that intensivists must be aware of to provide optimal care for these complex patients. This review will provide an overview of emergencies that are commonly seen in malignant haematology including hyperleukocytosis, leukostasis, tumour lysis syndrome, disseminated intravascular coagulation, neutropenic sepsis, hyperviscosity syndrome, side effects of novel therapies, and complications of allogeneic haematologic stem cell transplant.

Epidemiology

The modern 1-year incidence of ICU admission after diagnosis of haematologic malignancies is 14% ranging from 7% for indolent lymphoma to 23% for acute myeloid leukaemia (AML) followed by aggressive non-Hodgkin's lymphoma (18%) (Ferreyro et al. 2021). Half of this cohort are admitted within 30 days of diagnosis and the median time from diagnosis to admission in a large population based cohort study is 35 days (Ferreyro et al. 2021). As novel therapies increase as part of the standard of care, an increase in the incidence of critical illness will likely be seen.

Acute Myeloid Leukaemia with Hyperleukocytosis

Up to 20% of patients with acute myeloid leukaemia (AML) will present with an extreme elevation in their white blood cell count (WBC) known as hyperleukocytosis (Rollig et al. 2015; Ali et al. 2016). Generally defined by a WBC > 50-100 x 109/L, hyperleukocytosis is a medical emergency. Without rapid recognition and treatment, early mortality rates are high, with intracranial haemorrhage and respiratory failure as frequent causes of death (Marbello et al. 2008). Cytoreduction is the definitive treatment but excellent supportive care and prompt recognition of complications are essential. For patients who do not receive intensive chemotherapy, the mortality rate may exceed 50% at 30 days (Shallis et al. 2020).

The most concerning complications of hyperleukocytosis include leukostasis, tumour lysis syndrome (TLS) and disseminated intravascular coagulation (DIC) with the diagnostic features and management considerations outlined in **Table 1**. Leukostasis is a clinical diagnosis based on evidence of end-organ hypoperfusion in a patient with hyperleukocytosis. It results from occlusion of the microcirculation with endothelial damage and is much more common in AML than ALL due to the large size of the myeloid blasts (Porcu et al. 2000). Respiratory or neurologic symptoms are the most common clinical manifestations of leukostasis and may be the reason for ICU admission (Stahl et al. 2020).

Tumour Lysis Syndrome

Tumour lysis syndrome (TLS) results from the rapid breakdown of cancer cells and release of intracellular contents. It can occur either spontaneously or after initiation of cytoreductive therapies and may present clinically as acute kidney injury (AKI), arrhythmias, seizures, or sudden death. TLS can present in 25% of patients with AML and hyperleukocytosis, with similarly high incidence reported in the paediatric literature for ALL (Shallis et al. 2020; Stahl et al. 2020; Bewersdorf et al. 2020a; Truong et al. 2007). Patients with aggressive lymphomas or significant disease burden such as Burkitt lymphoma, lymphoblastic lymphoma, and DLBCL, T-cell lymphoma with elevated LDH, or bulky disease on CT are also at high risk (Jones et al. 2015). Risk

for death from TLS is highest in AML, with mortality rates that may approach 30% for patients hospitalised (Durani et al. 2017).

The approach to diagnosis and management are outlined in **Table 1.** In addition to administering uric acid lowering therapies and addressing the sequelae of acute kidney injury, the primary management is supportive with frequent monitoring. All high-risk patients, or those that have already progressed to TLS, should receive rasburicase. Rasburicase is recombinant urate oxidase that leads to the breakdown of uric acid. This is in contrast to allopurinol which reduces uric acid formation and is appropriate when the TLS risk is low to moderate. IV fluids should be given to maintain adequate urine output, routine electrolyte replacement protocols should be avoided, and nephrology should be consulted for consideration of dialysis in the event of progressive AKI, acidosis, or electrolyte disturbances. Contrary to historical practices, there is no evidence for urinary alkalinisation, and diuretics should generally be avoided unless there is concern for volume overload.

Complication	Diagnostic Features	Management
Leukostasis	Signs and symptoms of end-organ hypoperfusion (Rollig et al. 2015; Porcu et al. 2000): • Respiratory failure (tachypnoea, hypoxaemia, pulmonary haemor rhage) • Neurologic symptoms (decreased level of consciousness, delirium, visual disturbances, headache, and tinnitus • Bowel or limb ischaemia • Myocardial infarction Imaging features (Stefanski et al. 2016): • CXR: focal or diffuse opacities, pleural effusion. • Chest CT: interlobular septal thickening, consolidation, ground glass opacities.	Emergent cytoreduction should be arranged in consultation with a haematologist. Options include the following: • Hydroxyurea: - Oral medication that inhibits DNA synthesis - Used as a temporising measure prior to induction chemotherapy (Mamez et al. 2016) • Chemotherapy: - Intensive chemotherapy is the definitive management - Low-dose cytarabine may also be used to temporise at some institutions • Leukapheresis: - WBCs removed from the circulation with an a pheresis machine, requires haemodialysis catheter - Rapid reduction in WBC but no proven benefit with regard to complications or morality (Bewersdorf et al. 2020b) - Avoid in APL due to risks associated with coagulopathy Supportive care: • Avoid RBC transfusions unless symptomatic anaemia • Hydration with IV crystalloids, avoid diuretics unless clinical evidence of volume-overload
Tumour Lysis Syndrome	TLS has both clinical and laboratory diagnostic criteria (Cairo and Bishop 2004): Clinical criteria (one or more): • Acute kidney injury: Creatinine ≥ 1.5x ULN • Seizure • Arrhythmia or sudden cardiac death Laboratory criteria (two or more): • Uric acid ≥476 µmol/l or 25% • Potassium ≥6.0 mmol/l or 25% • Phosphate ≥1.45 mmol/l or 25% • Calcium ≤ 1.75 mmol/l or 25%	Uric acid lowering therapies: • All high-risk patients, which includes hyperleukocytosis, should receive rasburicase regardless of the uric acid level on presentation - A fixed dose of 4.5g IV x 1 can be given with need for additional doses based on clinical response (Patel et al. 2017) - G6PD deficiency is a contraindication to rasburicase should be screened for prior to administration. Supportive care (Jones et al. 2015; Matuskiewics-Rowinska and Malyszko 2020): • Monitor electrolytes closely (i.e., Q6H to Q8H) • Administer IV crystalloids to maintain adequate urine output and avoid routine electrolyte replacement protocols. • Consult Nephrology early in the setting of hyperkalaemia, refractory fluid overload, severe acidosis, or severe hyperphosphatemia for consideration of renal replacement therapy.
Disseminated Intravascular Coagulation	Patients may present with a bleeding diathesis and/or thrombosis. DIC is characterised by the following abnormalities (Levi et al. 2009): • Elevated PT/PTT and d-dimer • Low fibrinogen • Schistocytes on peripheral smear	Coagulation parameters should be monitored frequently with administration of blood products to maintain the following: • Platelets > 20-30 × 10^9/L (50 × 10^9/L in bleeding patients) • Fibrinogen greater > 1-1.5g/dL • INR < 1.5-2.0 Particular caution must be taken to monitor and aggressively treat coagulopathy in patients with APL.

Abbreviations: APL = acute promyelocytic leukaemia; CXR. = chest x-ray; CT = computed tomography; INR = international normalised ratio; IV = intravenous; PT = prothrombin time; PTT = partial thromboplastin time; ULN = upper limit of normal

Acute Promyelocytic Leukaemia

Acute promyelocytic leukaemia (APL) is a variant of AML that is seen in approximately 10-15% of cases (Tallman and Altman 2009). While APL is uncommon, it is important to be aware of it due to its unique complications and prognostic considerations. The molecular hallmark of APL is a translocation between chromosome 15 and 17 leading to the production of a the PML/RARα fusion gene. Clinically, patients present with cytopenia, coagulopathy, and bleeding and are considered to have high risk disease if the WBC is elevated (greater than $10x10^9$/L). While the overall outcomes for APL are excellent, 20-25% of patients may die in the first 30 days largely due to haemorrhagic complications with a significant portion of these deaths in the first week (Lehmann et al. 2017; Micol et al. 2014). For patients who survive this initial period, long-term survival approaches 90%, underscoring the importance of excellent supportive care (Coombs et al. 2015; Yilmaz et al. 2021).

When APL is suspected, treatment with all-trans retinoic acid (ATRA) should be started emergently as per the treating haematologist even if the diagnosis is not confirmed. Treatments administered for APL in addition to ATRA include arsenic trioxide (ATO) and chemotherapy. The primary consideration for the intensivist is monitoring for and aggressively treating coagulopathy. Coagulation parameters should be checked frequently, and blood products should be administered to keep platelets greater than 30×10^9/L (50×10^9/L in bleeding patients), fibrinogen greater than 1-1.5g/dL, and INR less than 1.5 (Sanz et al. 2019). After treatment is initiated, approximately 25% of patients may develop ATRA differentiation syndrome which manifests as fever, hypotension, respiratory failure with interstitial infiltrates, AKI, pleural or pericardial effusions, and peripheral oedema (Montesinos et al. 2009). The treatment is dexamethasone 10mg IV Q12H which should be started at the first sign of any symptoms (Sanz et al. 2019). Prophylactic steroids may also be considered in patients being started on ATRA, particularly in the setting of an elevated WBC. This decision should be discussed with the malignant haematology team.

Febrile Neutropenia and Neutropenic Sepsis

Febrile neutropenia (FN) is defined as a temperature ≥ 38.3°C or a temperature ≥ 38.0°C lasting more than 1 hour with an absolute neutrophil count (ANC) < 0.5×10^9/L (Freifeld et al. 2011). Following induction chemotherapy, patients with acute leukaemia may develop profound, prolonged neutropenia with an ANC < 0.1×10^9/L lasting over 1 week. This places them at high risk for infection and neutropenic sepsis. Patients with leukaemia are at the highest risk of death from FN among all patients with cancer with invasive fungal infections, candidaemia, bacteraemia, pneumonia, and the presence of comorbidities associated with a further increase in mortality (Kuderer et al. 2006). While patients with lymphoma may develop FN, the degree and duration of neutropenia are typically less than that seen in acute leukaemia, decreasing the overall risk of severe infection. However, it is important to discuss the anticipated course based on the underlying malignancy and therapy received with the patient's haemato-oncologist.

The core management principles for sepsis apply to neutropenic patients including early recognition, urgent administration of antibiotics, source control, fluid resuscitation as needed, and haemodynamic support to maintain end-organ perfusion (Kochanek et al. 2019). However, the diagnostic work-up to determine the source is frequently more extensive and empiric antibiotic coverage is broader due to different risk factors in the setting of profound immunosuppression (**Figure 1**). Bacteraemia from central lines, gut translocation of organisms, and pneumonia are common causes of infection in the setting of neutropenia. Granulocyte colony stimulating factor (GCS-F) may be considered as an adjunctive treatment to reduce the duration and severity of neutropenia and can be discussed with oncology (Mhaskar et al. 2014). However, there is also concern that GCS-F may precipitate or worsen respiratory failure during neutrophil recovery (Mignard et al. 2019).

One specific aetiology of FN that is important to consider in any patient with gastrointestinal symptoms is neutropenic enterocolitis (NE). The diagnosis is based on the presence of abdominal pain and bowel wall thickening of more than 4mm on CT in a patient with FN (Gorschluter et al. 2005). The initial management is supportive with bowel rest, fluid resuscitation, and broad-spectrum antibiotics. C. difficile infection should also be ruled out. Consideration should be given to empiric antifungal coverage as high rates of fungal infection have been reported in critically ill patients with NE, particularly when there is small bowel involvement on CT (Duceau et al. 2019). Surgical management is generally reserved for complications such as bowel perforation or necrosis, uncontrolled bleeding, or abscess formation (Rodrigues et al. 2017). Early surgery consultation is warranted in critically ill patients (Saillard et al. 2018).

Superior Vena Cava Syndrome

Patients with lymphoma and bulky mediastinal disease or lymph node involvement are at risk for developing superior vena cava (SVC) syndrome. Progressive SVC obstruction from exterior compression, infiltration, or thrombosis leads to decreased venous drainage into the right atrium and corresponding symptoms of increased venous pressure including oedema of the face and arms, dyspnoea, cough, and development of vascular collaterals in the upper chest. In severe cases,

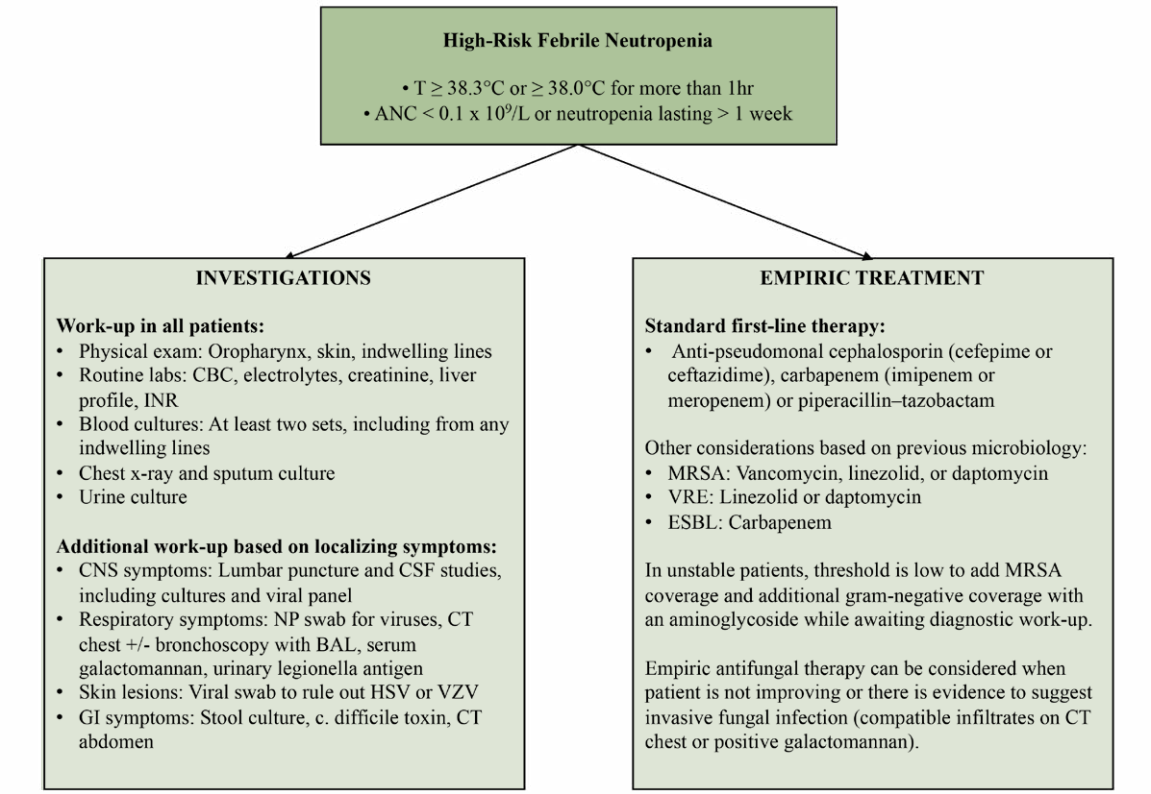

Figure 1 : Diagnostic work-up and empiric treatment for patients with high-risk febrile neutropenia (Freifeld et al. 2011; Klastersky et al. 2016; Taplitz et al. 2018)
Abbreviations: ANC = absolute neutrophil count; BAL = bronchoalveolar lavage; CBC = complete blood count; CNS = central nervous system; CT = computed tomography; ESBL = extended spectrum beta-lactamase; GI = gastrointenstinal; HSV = herpes simplex virus; INR = international normalised ratio; MRSA = methacillin-resistant staph aureus; NP = nasopharyngeal; VRE = vancomycin-resistant enterococci; VZV = varicella zoster virus.

symptoms of airway or cerebral oedema may develop, and rarely, patients may have haemodynamic collapse. The best test to confirm the diagnosis is CT venogram, with MRI as another option (Friedman et al. 2017). However, care must be taken to ensure patients are able to safely lay flat as compressive symptoms may significantly worsen in the supine position.

The major considerations for the intensivist surround airway management and haemodynamic support. Due to the risk of airway collapse from mediastinal compression on induction of anaesthesia and airway oedema from venous engorgement, an airway expert should be involved during intubation. Awake fiberoptic intubation should be performed by an experienced provider with the head of the bed in an upright position (Chaudhary et al. 2012). To maintain preload, IV fluids should be given via lower extremity access with vasopressors as needed to achieve an adequate mean arterial pressure. In cases of severe airway compromise where intubation is not possible, extracorporeal life support (ECLS) as a bridge to therapy can be considered (Leow et al. 2021).

In the case of life-threatening symptoms, endovascular stenting is an effective first-line treatment associated with minimal complications (Lanciego et al. 2009). Catheter-directed thrombolysis can also be performed if thrombosis is contributing to the obstruction (Rachapalli and Boucher 2014). If the diagnosis is not previously known, urgent biopsy should also be arranged. However, if safe to do so, decisions regarding stenting should be deferred until a definitive management plan is discussed with the malignant haematology team as chemotherapy and/or radiation may also be effective therapy.

Hyperviscosity Syndrome

Hyperviscosity syndrome is an emergency that results from elevated levels of monoclonal protein in the blood and can be life-threatening if not promptly recognised and treated. It is most commonly seen in Waldenstrom's macroglobulinaemia (WM) which is a rare subtype of non-Hodgkin lymphoma (NHL). In WM, there is abnormal production of monoclonal IgM protein leading to a rise in serum viscosity which is the primary indication for treatment in 17% of patients (Dimopoulos and Kastritis 2019). Hyperviscosity syndrome can also be seen in a small proportion of patients with multiple myeloma (Weaver et al. 2020).

Once serum viscosity rises above 4 centipoise with the presence of a monoclonal protein, patients may become symptomatic with mucocutaneous bleeding, neurologic symptoms, visual disturbances, fatigue, and generalised malaise (Crawford et al. 1985; Castillo et al. 2016). In severe cases, permanent vision loss, coma, and seizures may occur. Fundoscopic exam is helpfully diagnostically with the presence of dilated and tortuous veins, haemorrhages, papilledema, and exudates supportive of the diagnosis (Stone and Bogen 2012). If serum viscosity testing is not available, the immunoglobulin level can be used as a substitute. Concern for hyperviscosity is increased with IgM greater than 3 g/dL, IgG greater than 4 g/dL, or IgA greater 6 g/dL (Mehta and Singhal 2003).

Therapeutic plasma exchange (TPE) to reduce IgM levels is the primary treatment and should be instituted when clinical suspicion is high, even in the absence of serum viscosity testing. While this is being arranged, care should be taken to avoid any treatments that may increase plasma viscosity such as RBC transfusions. Plasmapheresis is generally continued to maintain serum viscosity below the level that results in symptoms, which may vary between individuals (Stone and Bogen 2012). Chemotherapy to treat the underlying disease is the definitive management. However, caution must be maintained in patients receiving rituximab for WM as it may result in an increase in IgM levels in a proportion of patients requiring consideration for pre-emptive TPE (Weaver et al. 2006).

Side-Effects of Novel Therapies

Treatment of haematologic malignancies is rapidly changing with increasing use of novel therapies which leverage the immune system to eliminate cancer cells. Two of these immuno-therapies: immune checkpoint inhibitors (ICIs) and chimeric antigen receptor (CAR) T-cells, may lead to severe and reversible side effects that can result in critical illness.

ICIs are primarily used in solid tumours but pembrolizumab, which is a monoclonal antibody against the programmed death-1 (PD-1) receptor, is approved for Hodgkin lymphoma and primary mediastinal large B-cell lymphoma (Twomey et al. 2021). ICIs allow the patient's T-cells to target cancer by blocking checkpoints in the immune response. However, this upregulation of the immune system may result in side-effects known as immune-related adverse events (irAEs), which can affect any organ system and may lead to death in severe cases (Wang et al. 2018).

Complication	Presentation	Treatment
Immune-mediated adverse events (iRAEs)	Any organ may be involved but the most relevant presentations for critical care include the following: • Pneumonitis, myocarditis, encephalitis, hepatitis, colitis Severity: Graded on a scale of 1-4 with specific criteria for each organ system. Timing: Weeks to months after starting an immune checkpoint inhibitor.	For grade 3 or 4 reactions, the immune checkpoint inhibitor is held and might be permanently discontinued. First-line treatment = steroids with some conditions requiring pulse-dosing. Need for additional immunosuppression depends on underlying organ involvement and steroid response but may include infliximab, IVIG, MMF, azathioprine, and cyclophosphamide.
Cytokine Release Syndrome (CRS)	Presentation may range from non-specific symptoms such as fever, shortness of breath, tachycardia, rash, headache and generalised malaise with shock, multi-organ failure, ARDS, and DIC in severe cases. Severity: Graded on a scale of 1-4 Timing: Highest risk in first week following infusion	Tocilizumab, an IL-6 monoclonal antibody, is the first line treatment. • Should be administered in all Grade 3 or 4 CRS • May be considered in Grade 1 or 2 CRS Steroids may be administered in conjunction with tocilizumab in higher grades of CRS or when it does not respond to tocilizumab.
Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)	Symptoms include fatigue, aphasia, tremor, and apraxia with altered level of consciousness and coma in severe cases. Dysgraphia is also a prominent feature. Timing: Onset is typically around the same time as CRS	Steroids are first line therapy for ICANS. When both CRS and ICANS are present, tocilizumab and steroids are given together.

Table 2 : Presentation and Treatment of iRAEs, CRS, and ICANS (Brahmer et al. 2018; Lee et al. 2019; Riegler et al. 2019)
Abbreviations: ARDS = acute respiratory distress syndrome; CNS = central nervous system; DIC = disseminated intravascular coagulation; IVIG = intravenous immunoglobulin; MMF = mycophenolate mofetil

In CAR T-cell therapy, the patient's T-cells are collected and genetically modified to recognise and target antigens on cancer cells. This therapy has been approved for use in a variety of haematologic malignancies including several types of lymphoma, ALL, and multiple myeloma. Leveraging the immune response in this way can lead to an inflammatory cascade known as cytokine release syndrome (CRS), which may lead to shock and multiorgan failure in severe presentations. Neurologic sequelae known as immune effector cell-associated neurotoxicity syndrome (ICANS) may also occur either in conjunction with or independently from CRS.

An overview of the presentation and treatment of iRAEs, CRS, and ICANS is outlined in **Table 2**. Severity grades of CRS and ICANS have been defined in the literature and many centres with CART programmes have established guidelines surrounding thresholds for initiation of pharmacologic treatments to blunt inflammation (eg. corticosteroids) and thresholds for ICU admission. Decisions surrounding treatment should be made following a multidisciplinary discussion with the oncology team. It is also important to have a low threshold to treat empirically for sepsis, and to rule out other mimickers of CRS such as haemophagocytic lymphohistiocytosis (HLH), and TLS.

Complications Following Allogeneic Haematopoietic Stem Cell Transplantation

Although outcomes have improved overall in recent decades for critically ill patients with haematologic malignancy, ICU mortality among patients who have undergone an allogeneic haematopoietic stem cell transplant (HSCT) remains high (Darmon et al. 2019). There are a range of complications that may result in critical illness and are important to have in the differential diagnosis with respiratory failure as the most common reason for ICU admission (Bayraktar et al. 2013; Kew et al. 2006). The post-transplant course is generally divided into the pre-engraftment stage (day 0-30), early post-engraftment stage (day 31-100) and late post-engraftment stage (after 100 days) with variable risks in each time frame. If a patient presents with critical illness after having undergone transplantation, understanding these three distinct timepoints is critical to understanding the mechanism of immunosuppression they are exposed to. This will inform which potential infectious organisms they are susceptible to as well as help develop the non-infectious differential. The major infectious considerations in each of these periods are outlined in **Figure 2**. Although patients may develop respiratory failure related to these infectious causes, there are a range of non-infectious aetiologies for respiratory failure in this population (**Table 3**). Close communication with the haemato-oncology team and oncologic- infectious disease services can help guide identifying cause and empiric management.

Pre-Engraftment (Day 0-30)	Early Post-Engraftment (Day 31-100)	Late Post-Engraftment (After 100 days)

• Risks:
  • Primary immunodeficiency = severe neutropenia
  • Mucositis, indwelling lines
• Types of Infection:
  • Bacterial infections are most common (gram positive or gram negative)
  • Fungal infections may also be seen (aspergillus, candida) as well as HSV
	• Risks:
	  • Primary immunodeficiency = cell-mediated immunity
	  • Acute GVHD and related immunosuppression
	• Types of Infection:
	  • Bacterial infections still occur
	  • HSV, CMV, PJP and aspergillus are commonly described
	  • HHV6 may also be seen
		• Risks:
		  • Ongoing impairment in cell-mediated immunity
		  • Chronic GVHD and related immunosuppression
		• Types of Infection:
		  • Risk for encapsulated bacteria is increased: S. pneumo, H. flu, N. meningitidis, etc.
		  • VZV is common
		  • Risk of HSV, CMV, PJP, aspergillus, and HHV6 remains

Figure 2 : Infectious risks post-allogenic stem cell transplant stratified by time from transplant (Tomblyn et al. 2009; Sahin et al. 2016; Hiemenz et al. 2009)
Abbreviations: CMV = cytomegalovirus GVHD = graft versus host disease; HHV6 = human herpes virus 6; HSV = herpes simplex virus;; PJP = pneumocystis jiroveci.

In addition to infectious and respiratory complications, other post-transplant complications to be aware of include acute graft versus host disease (GVHD), veno-occlusive disease (VOD), and neurologic complications. Acute GVHD traditionally occurs in the first 100 days post-transplant and most commonly manifests with skin involvement, gastrointestinal symptoms, and hyperbilirubinaemia although other organs may be involved. The mainstay of treatment is steroids with the potential addition of other immunosuppressive agents or the kinase inhibitor ruxolitinib in refractory disease (DiMaggio 2020). VOD, also called sinusoidal obstructive syndrome (SOS) is caused by obstruction of the hepatic venules and sinusoids in the liver. The aetiology is felt to be due to hepatic endothelial damage from transplant conditioning medications. VOD presents with abdominal pain, hepatomegaly, jaundice, ascites, weight gain and thrombocytopenia that typically presents in the pre-engraftment phase. Definitive diagnosis is often made by biopsy as imaging techniques are not sufficient. Treatment includes supportive care (paracentesis, monitoring fluid balance) with the addition of defibrotide in severe cases. For refractory disease which carries a significant mortality risk, steroids, transhepatic portosystemic shunt (TIPS), and liver transplantation may be considered and should involve the gastroenterology or hepatology team at an early stage (Senzolo et al. 2007). Finally, patients may also develop altered level of consciousness which can be related to infectious encephalities, drug toxicity (e.g., fludarabine neurotoxicity), intracranial haemorrhage, posterior reversible encephalopathy syndrome, neuro-GVHD, post-transplant lymphoproliferative disorder, or progressive multifocal leukencephalopathy, among others (Pruitt et al. 2013).

Typical Timing	Complication	Presentation and Treatment
Early	Peri-Engraftment Respiratory Distress Syndrome (PERDS)	• Bilateral infiltrates and hypoxaemia that develops during neutrophil recovery. It can manifest as hypoxaemia with pulmonary infiltrates, fever, rash, diarrhoea, hepatic or renal impairment. • Treatment: Steroids
	Diffuse Alveolar Haemorrhage	• Infiltrates on chest x-ray, cough, and hypoxaemia with no identifiable infection. Haemoptysis may be absent. • Diagnosed based on serial BALs demonstrating increasing RBC count. • Treatment: Supportive with consideration for steroids.
Subacute	Idiopathic Pneumonia Syndrome	• Diffuse alveolar injury with no identifiable infectious source. Can be rapidly progressive and may require lung biopsy for diagnosis. • Treatment: Largely supportive. Steroids are frequently used although strong evidence is lacking. TNF-alpha inhibitors may also be considered.
	Bronchiolitis Obliterans Organising Pneumonia (BOOP)	• Fever, cough, shortness of breath with patchy infiltrates, ground glass or nodular opacities. • May require lung biopsy for diagnosis. • Treatment: Steroids
Late	Bronchiolitis obliterans	• Progressive respiratory symptoms (cough, shortness of breath, wheeze) with airflow obstruction on spirometry. • Treatment: Steroids and immunosuppression but typically follows progressive course.

Table 3: Pulmonary Complications Following Allogenic Hematopoietic Stem Cell Transplantation (Haider et al. 2020; Soubani and Pandya 2010; Chi et al. 2013).
Abbreviations: BAL = bronchoalveolar lavage

Conclusion

Patients with haematologic malignancies presenting with critical illness represent a unique population with specific syndromes. Early identification of aetiologies of critical illness and prompt initiation of appropriate critical care support is essential to their improved outcomes. Given their complexity, a multidisciplinary approach to their management with close collaboration between haemato-oncology and critical care is needed.

Conflict of Interest

None. ■

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