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Clinical Haematology

Patients in the intensive care unit frequently report haematological issues. These issues are often a result of critical illness. The most common haematological complications seen in the ICU include thrombocytopenia, anaemia, leukocytosis, thrombocytosis, and coagulopathies. In addition, emergencies in malignant haematology are commonly seen in the ICU and can cause significant mortality and morbidity in critically ill patients.

It is important to assess and understand factors that affect mortality and outcomes in patients admitted to the ICU with a diagnosis of haematological disease. Whether it's identifying the cause of anaemia or determining the right approach to coagulation problems, managing transfusion patients, determining appropriate haemoglobin concentrations in critically ill patients, or managing and improving outcomes for patients with haematological malignancies, there are many challenges for ICU teams to address when it comes to patients with haematological issues.

In our latest cover story, **Clinical Haematology**, our contributors discuss topics such as coagulation, anaemia, pulmonary embolism, haematological malignancy, and other important presentations of haematological disease in critical care. They provide a practical approach to addressing clinical issues related to haematology and outline effective strategies for diagnosis and management of scenarios that are commonly encountered in the ICU.

Charles Marc Samama provides an overview of different techniques to reverse direct oral anticoagulants with specific or non-specific agents, while Flavio Nacul, Valentina Torre and Kaushik Bhowmick discuss anaemia, highlight its multifactorial causes and explore whether high hepcidin levels and a blunted response to erythropoietin may play a role.

Eder Zamarrón-López, Orlando Pérez-Nieto, Jorge Miño-Bernal and co-authors talk about pulmonary embolism in the intensive care unit, how this complication in hospitalised patients is associated with high morbidity and mortality and why it is important to effectively identify and manage it.

Jenna Spring and Laveen Munshi provide an overview of emergencies commonly seen in malignant haematology, discuss the side effects of novel therapies, and highlight complications of allogeneic haematologic stem cell transplant.

Victoria Metaxa, Tasneem Pirani, Neeraj Singh and Rohit Saha discuss chimeric antigen receptor T-cell therapy and its associated toxicities and highlight the importance of monitoring recognition and prompt management in the ICU for good outcomes.

In our Matrix section, Jean-Charles Preiser, Lee-Anne Chapple and Emma Ridley discuss nutritional care for patients with COVID-19 who require intensive care, and Emmanuel Pardo and Jean-Michel Constantin provide an overview of the physiological aspects of indirect calorimetry, its limitations in use and future prospects for tailored nutrition.

Handling haematological problems in the ICU and providing acute care to patients with a primary haematological disorder can be challenging for critical care doctors. In this issue, our contributors have shared their experience in critical care practice and have presented practical approaches to managing haematology issues in the ICU.

As always, if you would like to get in touch, please email JLVincent@icu-management.org.

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283 Clinical Haematology Digital Conference

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Join our panellists on November 30 at 16:00 CET as they discuss coagulation, anaemia, haematological malignancy, and other important presentations of haematological disease in critical care.



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Reversal of Direct Oral Anticoagulants

This review focuses on different techniques to reverse direct oral anticoagulants, either with specific or non-specific agents.

Direct oral anticoagulants (DOACs) are now standing for Vitamin K antagonists in many clinical settings. They are recognised as a major step forward for our patients. Their efficacy has been confirmed in venous thromboembolism prophylaxis and treatment, in atrial fibrillation and even in acute coronary syndromes (Stensballe and Møller 2018). The biological monitoring is now widely available, and the interactions and contraindications are well known. The ratio of efficacy/safety is widely positive. Unfortunately, the global picture is still fuzzy as far as the reversion of these agents is concerned (Jaspers et al. 2021). Only two specific antidotes are approved, but the compound which is mostly used (prothrombin complex concentrate), is a non-specific reversal agent. This review will focus on different techniques to reverse DOACs.

There are several ways to control the anticoagulant activity of these agents while acting either on absorption, on the mechanism of action, or on elimination (Crowther and Crowther 2015).

Only activated charcoal deals with absorption. Wang et al. (2014) have given 50 grammes of activated charcoal to healthy volunteers who had been previously treated with apixaban either two hours or six hours before charcoal was given. Activated charcoal was able to decrease the apixaban elimination half-life from 13 hours down to five hours. The limit of this compound is that it has to be given in a rather short time slot i.e. six hours max.

Another way to decrease DOAC concentration is to act on elimination with haemodialysis. This technique has been shown to be effective in decreasing the plasma

concentration of dabigatran by 50% after a four-hour procedure (Khadzhynov et al. 2013). Of note, after the interruption of the dialysis, a rebound of the dabigatran concentration has been observed. It has to be understood that this technique is only available for dabigatran which binding to the proteins is weak. Even if it is usually implemented in an intensive care environment, it may be difficult and dangerous to insert a very large catheter in an old patient overdosed with dabigatran.

Prothrombin Complex Concentrates (PCC) and activated Prothrombin Complex Concentrates (FEIBA®) interfere with the mechanism of action. They have been tested with various doses and have shown conflicting results in different animal models (Godier et al. 2012) and healthy volunteers. They are now being used by clinicians in bleeding patients on a non-evidence basis. Several series, especially in neurology/neurosurgery patients have shown a better outcome in patients treated with four factor-PCC (4F-PCC as compared with nothing) (Grandhi et al. 2015). In the GIHP-NACO registry, 4F-PCC and aPCC have been shown to partially or totally control bleeding in patients treated with DOACs (Albaladejo et al. 2017). Majeed et al. (2017) and Schulman and colleagues (2018) have published two short series of bleeding patients treated with 4F-PCC with interesting results. Ten case series with 340 patients as a total have been reviewed by Piran et al. (2019). The pooled percentage of patients with effective management of major bleeding was 69% (95% confidence interval [CI], 61-76) in two studies using the International Society on Thrombosis

and Haemostasis (ISTH) criteria and 77% (95% CI, 63-92) in eight studies that did not use the ISTH criteria; all-cause mortality was 16% (95% CI, 7-26), and thromboembolism rate was 4% (95% CI, 1-8). The obvious limit of such observational series is that it is difficult to determine whether 4F-PCC in addition to cessation of direct oral FXa inhibitor is more effective than cessation of direct oral FXa inhibitor alone in patients with direct FXa inhibitor-related major bleeding.

The same group has studied the efficacy/safety ratio of 4F-PCC (26 U/Kg) in 21 non-bleeding anti-Xa-treated patients who were about to undergo an emergent surgery or an invasive procedure (Piran et al. 2018). The efficacy of PCC was good in 18 patients, allowing a normal haemostasis with no thromboembolic events. Barzilai et al. (2019) have reported the results of a slightly larger study performed in two tertiary hospitals. Sixty-two apixaban or rivaroxaban patients were treated with 4F-PCC (26U/Kg) and assessed retrospectively. Bleeding during surgery was reported in three patients (5%), no patient required additional PCC, and 16 patients (26%) were transfused. The 30-day mortality and thrombosis rates were 21% and 3%, respectively.

Today, PCC is the most widely used agent for the reversal of xabans (anti-Xa agents). The median initial dose is close to 25 IU/Kg. A reinfusion might be necessary.

Activated PCC has also been used in some patients (Albaladejo et al. 2017). FEIBA® is a kind of haemostatic bomb which was initially dedicated to haemophiliacs with an inhibitor. It has been tested in vitro

(Martin et al. 2015) and in small series of patients. Low doses (< 20 U/kg) to moderate (20–30 U/kg) doses appear to be effective, but with no follow-up for the side effects (Dager et al. 2018). Of note, this compound is very expensive.

Specific antidotes are also being developed. Three of them have already completed phase II and/or phase III studies:

- Idarucizumab (Praxbind®) is a fully humanised antibody fragment (Fab) which binds to the thrombin binding site of dabigatran hence inactivating the molecule. In healthy young and older volunteers, idarucizumab was associated with immediate, complete, and sustained reversal of dabigatran-induced anticoagulation (Glund et al. 2015). It was well tolerated with no unexpected or clinically relevant safety concerns. The global reversal duration lasted about 24 hours. The phase III study (REVERSE-AD) has included bleeding patients who have developed a serious bleeding event, or patients who require an urgent procedure (Pollack et al. 2017). The results including 503 patients show a complete reversal of the anticoagulant effect of dabigatran within minutes and 18% mortality (mainly unrelated to the antibody). The European (EMA) and U.S. (FDA) regulators have granted an approval for this compound, but further studies and a much larger number of patients are needed to be fully reassured. Nevertheless, this antibody may save lives. Some reinjections may be needed as a rebound in dabigatran concentration has been reported (Hegemann et al. 2018).
- Andexanet alpha is a recombinant modified human factor Xa protein that binds factor Xa inhibitors. This specific reversal agent is designed to neutralise the anticoagulant effects of both direct and indirect factor Xa inhibitors. Its half-life is short (less than 90 minutes) and the bolus has

to be combined with a continuous IV infusion. Up to now, no data are available after a 6-hour administration. Andexanet has been shown to be effective in 101 healthy volunteers on a biological standpoint (Siegal et al. 2015). The ANNEXA-4 study has evaluated 352 patients who had acute major bleeding within 18 hours after administration of a factor Xa inhibitor (either apixaban or rivaroxaban) (Connolly et al. 2019). The patients

the global picture regarding the reversion of direct oral anticoagulants is still fuzzy

received a bolus of andexanet, followed by a 2-hour infusion. Excellent or good haemostasis occurred in 204 of 249 patients (82%) who could be evaluated. Within 30 days, death occurred in 49 patients (14%) and a thrombotic event in 34 (10%). However, it has to be emphasised that the definition of an excellent or good haemostasis was debatable and that the very high thrombotic event rate was worrying. Furthermore, no data are available with a longer infusion period. Andexanet is effective, no doubt, but many undesirable side effects have led the FDA to issue a black box warning on thromboembolic risks, ischaemic risks, cardiac arrest, and sudden death: “Treatment with the agent has been associated with serious and life-threatening adverse events, including arterial and venous thromboembolic events, cardiac arrest, sudden deaths, and ischaemic events, such as myocardial infarction and ischaemic stroke.” Is this what we expect from a specific reversal agent? Since, a study with a small number of patients has shown a lack

of benefit of andexanet (Nederpelt et al. 2020) and a meta-analysis of studies on PCC, idarucizumab and andexanet has shown that the three agents developed the same efficacy for a comparable death toll but with a much higher thrombotic rate for andexanet (10.7% as compared to 4.3% for PCC and 3.8% for idarucizumab) (Gómez-Outes et al. 2021). A large study is ongoing, comparing andexanet to standard of care (mainly PCC). Results are awaited in 2023.

- Ciraparantag (PER977) is a small, synthetic, water-soluble, cationic molecule that is designed to bind specifically to unfractionated heparin, low-molecular-weight heparin, and to the new oral factor Xa inhibitors (xabans) (Chan and Weitz 2021). Ciraparantag directly binds to DOACs and to enoxaparin through non-covalent hydrogen bonds and charge–charge interactions. Only phase 2 data are available for the moment. Ciraparantag provides a dose-related reversal of anticoagulation induced by steady-state dosing of apixaban or rivaroxaban. All doses of ciraparantag were well tolerated. The slow development of this compound probably relates to the almost impossibility to quantify its effect with conventional biological tests (aPTT, PT, antiXa level) because ciraparantag binds to the sodium citrate used for blood collection and to the reagents used to trigger clotting in these tests. In the reported studies, the anticoagulant effect of apixaban and rivaroxaban at steady state was assessed with the whole blood clot time (WBCT) (Ansell et al. 2021). Therefore, the quality of data is still weak and further studies with patients are needed.
- Other specific antidotes for xabans are being developed by several research groups and will be available in the near future, hopefully (Jourdi et al. 2018).

	Idarucizumab	Andexanet alpha	Ciraparantag	4F-PCC
Target	Dabigatran	Xabans (tested on rivaroxaban and apixaban)	Xabans, LMWH, UFH	Xabans, VKA
Effective haemostasis (Gómez-Outes et al. 2021)	76.7%	80.7%	Unknown	80.1%
Thrombotic risk (Gómez-Outes et al. 2021)	3.8%	10.7%	Unknown	4.3%
Cost	Medium to high	Very high	Unknown	Low

Table 1. Comparison of specific antidotes with 4F-PCC

Conclusion

As DOACs are very effective and increasingly popular, more and more patients are shifting from VKA treatments to DOACs. As a result, the number of DOACs treated

patients undergoing an emergency procedure, a trauma or an overdose is increasing steadily and the need for long lasting, safe, user-friendly and cheap antidotes will increase. Physicians are keen to work with

potent specific antidotes with a long half-life and low rates of thrombotic side effects.

Conflict of Interest

None. ■

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Anaemia is defined by haemoglobin (Hb) < 12 g/dL for women and Hb below 13 g/dL for men, according to the WHO (1968). Anaemia is a prevalent condition that affects nearly all critically ill patients. Approximately two-thirds of patients are anaemic at admission in Intensive Care Units (ICU) (Vincent et al. 2002); nearly 100% of the remainder become anaemic during their ICU stay (Napolitano et al. 2017), 77% of patients are still anaemic at hospital discharge (Walsh et al. 2006), and many persist to be anaemic for several months after leaving the hospital. Warner et al. (2020) showed that the prevalence of anaemia post hospitalisation was 56% at 3 months, 52% at 6 months, and 45% at 12 months among those alive and with available haemoglobin (Hb) measurements. In addition, there is scientific evidence that lower mean Hb levels are associated with higher SOFA scores, a longer length of stay, and higher mortality rates (Vincent et al. 2002). Anaemia becomes an issue when it

Anaemia in the Critically Ill: What is the Major Culprit?

Anaemia is commonly encountered in the critically ill and is associated with poor outcomes. The cause is multifactorial and includes high hepcidin levels and a blunted response to erythropoietin.

is linked with insufficient oxygen supply to vital organs.

The cause of anaemia in critical illness is complex and multifactorial and has been a topic of debate in critical care medicine for many years. Primary mechanisms of anaemia may include haemodilution, blood loss, increased hepcidin levels, reduced erythropoietin levels, neocytolysis, drug reactions, and nutrient deficiency (Astin and Puthuchery 2014).

Haemodilution

Fluid administration may cause a relative reduction in Hb concentration, producing a secondary decrease in oxygen delivery (DO_2). This phenomenon was observed by Perel et al. (2017) in patients who received more colloids as part of perioperative goal-directed therapy (GDT); moreover Otto et al. (2017) reported that in approximately half of cases, anaemia could be explained as a result of increased plasma volume (PV) rather than by a reduction in red cell mass (RCM). Drevon et al. (2021) retrospectively analysed RCM and PV of normal, anaemic and polycythemic patients using direct measurements of red cell and plasma volumes and demonstrated that Hb is a good surrogate marker of decreased RCM for severely anaemic patients but not for moderately or mildly anaemic patients. Finally, Yan et al. (2011) analysed blood volume in patients admitted to the ICU and showed that anaemia is over diagnosed in hypervolaemic patients, potentially producing unnecessary interventions. An accurate measurement of intravascular

status, coupled with fluid balance might be useful to differentiate hypovolaemic real anaemic patients from haemodiluted ones.

Blood Loss

Although blood loss is considered a significant cause of anaemia in critically ill patients, it is not the only explanation for the high prevalence of anaemia. A study reported that bleeding was the reason for transfusion in 46% of patients (Westbrook et al. 2010). Another study showed that 18% percent of critically ill patients received transfusion associated with haemorrhage, while 26% received transfusion not associated with haemorrhage (Walsh et al. 2004). Potential causes of blood loss are trauma, surgery, gastrointestinal, vascular, and obstetric bleeding. Moreover, coagulopathies, thrombocytopenia, and phlebotomy can cause blood loss. Phlebotomy is highly associated with changes in Hb and haematocrit levels, can contribute to anaemia and is an underrecognised cause of anaemia in critically ill patients. A prospective blood sampling study of 1136 patients being cared for in 145 intensive care units across Europe revealed that the mean number of blood samples taken per day was 4.6, and the mean total volume of blood sampled per day was 41.1 mL (Vincent et al. 2002). Strategies to reduce anaemia due to blood sampling procedures include switching to small-volume phlebotomy tubes and replacing routine multiple daily phlebotomies for blood sampling with phlebotomy only when essential (McEvoy and Shander 2013).

Hepcidin

Hepcidin is the main regulator of plasma iron concentrations. It is a small 25-amino acid peptide mainly synthesised by the liver. Hepcidin is produced from a pre-pro-peptide of 84 amino acids that is biologically inactive. After an inflammatory stimulus, cytokines released by activated leukocytes induce hepcidin synthesis, and hepcidin binds to ferroportin, the pore that allows egress of iron from intestinal epithelial cells and reticuloendothelial macrophages. Ferroportin is predominantly expressed in duodenal cells and macrophages, allowing iron absorption from the digestive lumen (**Figure 1**) and iron recycling after erythrophagocytosis. Inflammation and iron overload induce hepcidin synthesis, whereas iron deficiency, hypoxia, and erythroid expansion inhibit hepcidin synthesis (Lasocki et al. 2011). Therefore, high hepcidin levels block intestinal iron absorption and macrophage iron recycling, inhibiting iron entry into

plasma and causing decreased iron delivery for erythropoiesis and functional iron deficiency anaemia (Heming et al. 2011; Pagani et al. 2019).

Reduced Levels of Erythropoietin

Human erythropoietin (EPO) is a 30.4 kDalton glycoprotein hormone composed of a single 165 amino acid residue chain to which four glycans are attached. It is produced mainly by peritubular cells in the kidneys of adults and by hepatocytes in the foetus. EPO is essential for the survival, proliferation, and differentiation of erythrocyte progenitors in the bone marrow, and its level is continuously adjusted to regulate erythrocytes production and to optimise tissue oxygenation. Systemic hypoxia activates hypoxia-inducible factor (HIF), which stimulates EPO production and iron uptake and utilisation in the bone marrow to facilitate erythroid progenitor maturation and proliferation. EPO needs a receptor (EPO-R) that is

expressed on erythroid cell progenitors and in a variety of tissues and cell types, such as the brain, retina, heart, kidneys, vascular smooth muscle cells, myoblasts, and vascular endothelium (McCook et al. 2012). While absolute EPO levels are not necessarily decreased in critically ill patients, there is evidence for a blunted EPO response to anaemia secondary to increased levels of cytokines such as IL-1, IL-6 and TNF-alpha (Rogiers et al. 1997; von Ahsen et al. 1999), reinforcing that a blunted EPO response is a factor contributing to anaemia in critical illness. Mainly IL-1 and TNF-alpha seem to be responsible for the defect in EPO production in severe systemic inflammatory diseases (Jelkemann 1998).

Neocytolysis

Neocytolysis is the selective destruction of erythrocytes that have been formed during stress erythropoiesis in conditions of hypoxia, with the objective of decreasing the excess number of erythrocytes that are no longer required (Mairbäurl et al. 2018). This phenomenon was first described in astronauts after returning from space and people descending from high altitude. Upon entering microgravity, astronauts' blood volume in the extremities pools centrally. The body adapts by transudating approximately 20% of the plasma volume into the soft tissues and suppressing EPO production (Rice and Alfrej 2005). Similar processes seem to occur in descent from high altitude. Rice et al. (2001) studied polycythaemic residents of high altitude upon travel to sea level and found a rapid decrease in erythrocyte mass within 3–7 days after descent. They also demonstrated a rapid decrease in EPO levels, and increased bilirubin levels. In both situations, there is a rapid reduction in erythrocyte levels upon return to normoxia that cannot be accounted for by cessation of cell production despite a reduced EPO level. Therefore, EPO insufficiency, a known mechanism of decreased RBC production, cannot elucidate the reduction in Hb in critically ill patients

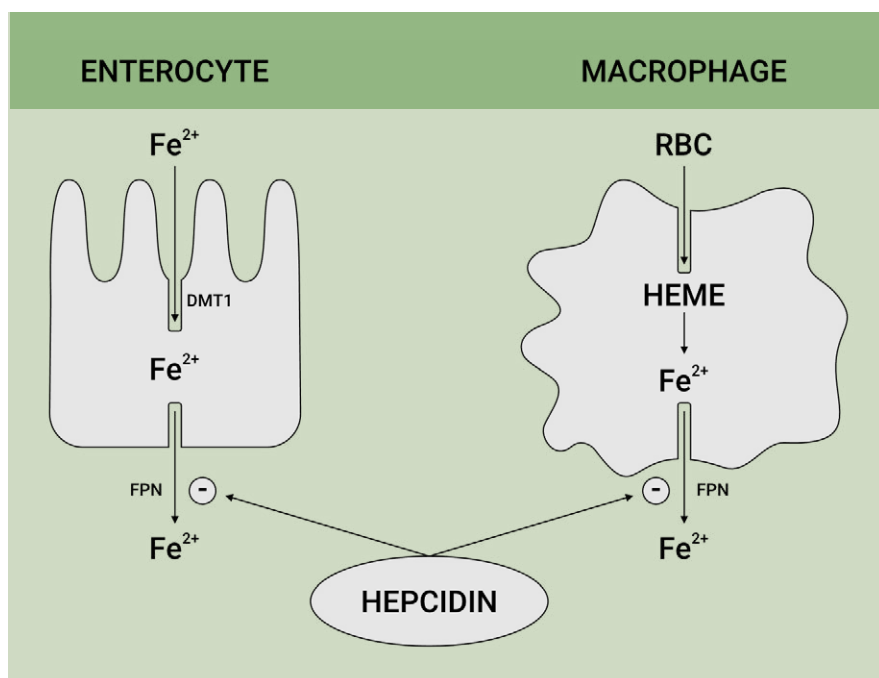


Figure 1. Iron obtained from the diet is passed through the intestinal enterocyte apical membrane via divalent metal transporter 1 (DMT1), either stored as ferritin or moved into the plasma by ferroportin (FPN) as an exporter. Macrophages play important roles in recycling iron derived from the clearance of red blood cells (RBCs). The senescent erythrocytes are recognised and phagocytosed by macrophages. After heme catabolism, iron can be stored in ferritin molecules or recycled towards the circulation via the ferroportin. High hepcidin levels reduce ferroportin expression, blocking intestinal iron absorption and decreasing iron release from macrophages.

over the first few days. Neocytolysis can explain how red cell mass can be reduced over a short time frame of a few days, leading to rapid development of anaemia. Although the mechanism of neocytolysis has not been clearly defined, it is likely dependent on decreased EPO serum levels.

Nutrient Deficiency

Due to inadequate nutritional support and increased demands, vitamin B12 and folate deficiency may worsen in critically ill patients, potentially producing anaemia. Deficiency of iron, vitamin B12, folate, or copper can result in acquired microcytic or macrocytic anaemia. Rodriguez et al. (2001) studied 184 critically ill patients and demonstrated that 4 (2%) were B12 deficient and 4 (2%) were folate deficient. Thus, these deficiencies probably do not play an important role in the pathogenesis of anaemia. Serum vitamin B12 level should be measured in all patients with unevaluated macrocytosis. All individuals

who are nutritionally compromised or who have had gastric surgery should also have serum folate measured (McEvoy and Shander 2013).

the cause of anaemia in critical illness is complex and multifactorial and has been a topic of debate in critical care medicine for many years

Drug Reactions

Drugs administered in ICU can have adverse effects that can lead to anaemia by two distinct pathways, one by causing haemolysis and the other way by suppressing normal renal release of erythropoietin. Drug induced haemolytic anaemia, although rare, is a serious adverse effect. Few antimicrobials like piperacillin and ceftriaxone can cause

it, whereas suppression of erythropoietin can be caused by commonly used drugs like angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers, calcium channel blockers, theophylline and β -adrenergic blockers.

Conclusion

Anaemia is a common occurrence in critically ill patients, and it is associated with poor outcomes. The cause of anaemia is complex and often multifactorial, and in many cases, it can be due to inflammation. Humans, as rationalising beings, generally trust that they are accurately perceiving where the problem is, and they like to find a culprit to blame. In the case of anaemia in the critically ill, we can blame, in most cases, high hepcidin levels and a blunted response to EPO.

Conflict of Interest

None. ■

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Critically ill patients are not found just in intensive care units, but throughout the hospital: emergency departments, post-anaesthesia care units, operating rooms, and many other environments now care for the critically ill. These patients require specialised, timely, and individualised care to achieve the best outcomes.

Glycaemic control is a component of care in many, if not most critically ill patients, and the foundation of proper glycaemic control is accurate and timely measurement of blood glucose. Point-of-care testing (POCT) would seem to be a logical solution, but it is not as simple as it appears. Many POC blood glucose monitoring systems (BGMS) simply do not perform adequately in these patients. In fact, only one BGMS has been approved by the U.S. FDA for use in critically ill patients. A major reason for poor performance in some BGMS is from interfering agents. These can be endogenous (anaemia, hypotension), or exogenous such as medications. Drugs which are commonly used in the ICU such as dopamine, acetylcysteine, icodextrin, and ascorbic acid are known to cause falsely elevated glucose readings in most meters.

Anaemia is present in over 70% of ICU patients, and often worsens over time due to phlebotomy (Thavendiranathan et al. 2005). It is also known to cause factitious hyperglycaemia with certain BGMS. While glycaemic control has long been known to play a role in the ICU, it is also being increasingly recognised as important in COVID-19 patients. Diabetes is a comorbidity which increases morbidity and mortality in COVID-19 patients, and well

The Importance of Accurate Glucose Monitoring in Critically Ill Patients

The complexity of glucose testing, the limitations of point-of-care blood glucose monitoring systems and the need for accuracy and reliability to ensure optimised patient outcomes.

controlled blood glucose in this population is associated with improved outcomes (Zhu et al. 2020). Even in non-diabetic patients with COVID-19, those with uncontrolled hyperglycaemia had a mortality rate of over 40% (Bode et al. 2020).

Clinicians caring for these patients therefore face a difficult situation: send all glucose specimens to the central lab, with its inherent drawbacks (delay in results, preanalytical errors, etc.), or use a BGMS which may give inaccurate results.

Erroneously elevated glucose, regardless

of the cause, can lead to overtreatment with insulin, resulting in hypoglycaemia. In fact, at least one death [has been reported](#) due to insulin administration in a patient on high dose ascorbic acid who had a falsely high glucose level measured on a BGMS, and there are also numerous case reports of significant and permanent neurologic damage due to inappropriate insulin administration in the setting of other interfering agents (Disque et al. 2013; Jadhav et al. 2013). So, this is not just a theoretical concern. The Italian point-of-care study group recently issued

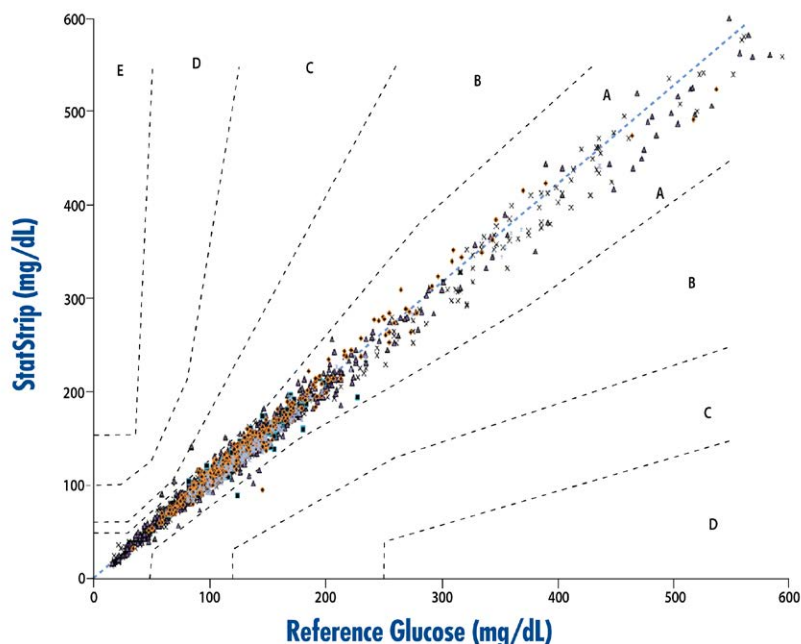


Figure 1.: Parkes Error Grid showing correlation between Nova StatStrip and Hospital Core Lab Glucose Measurements. 99.3% of the results fall into Zone A, meaning there is no clinical significance [Jadhav et al. 2013].

a recommendation not to use BGMS in critical care settings unless the meter is certified for use in critically ill patients (Rampoldi et al. 2021).

One interfering agent that is being utilised more is ascorbic acid (vitamin C). A recent search on clinicaltrials.gov shows over 100 active or recently completed studies using high dose ascorbic acid for COVID-19, sepsis, and burns, among others. One such trial, the LOVIT study (which looks at vitamin C to lessen organ dysfunction) states in its protocol that “Blood glucose can only be measured by one of the following three methods: hospital core laboratory instruments; a point-of-care arterial blood gas machine whose glucose measurement has been validated in the setting of high blood concentration of ascorbic acid; and point-of-care StatStrip glucometers (Nova Biomedical, Waltham, MA, USA), whose measurements have been shown to be accurate in the presence of high blood concentration of ascorbic acid.” (Masse et al. 2020).

In one large study done in five ICUs in three countries, involving nearly 1700 patients, one BGMS was compared to the

hospital central laboratory analyser (DuBois et al. 2017). Using a Parkes Error Grid, 99.3% of results were in Zone A, which means there was no clinical significance in the results between the BGMS and the central

■ while glycaemic control has long been known to play a role in the ICU, it is also being increasingly recognised as important in COVID-19 patients ■

lab (Figure 1). The remaining results were in Zone B, representing minimal clinical significance. In addition, the performance of the BGMS met the most current standard for glucose measurement as defined by [CLSI POCT12-A3](#) with 95.4% of results <100mg/dL and 96.5% of the results >100 mg/dL falling within 12 mg/dL of the core lab. No significant interferences were identified in any patient.

Given the complexity of glucose testing it is imperative for clinicians and labora-

torians to be aware of the limitations of any BGMS that is being used in settings where critically ill patients are cared for. In a high-risk environment, where accuracy and reliability can directly impact patient outcomes, not all BGMS devices are created equally. ■

Key Points

- Glycaemic control is a component of care in many, if not most critically ill patients.
- Point-of-care testing would seem to be a logical solution, but many POC blood glucose monitoring systems do not perform adequately in these patients.
- Erroneously elevated glucose, regardless of the cause, can lead to over-treatment with insulin, resulting in hypoglycaemia.
- Given the complexity of glucose testing it is imperative for clinicians and laboratorians to be aware of the limitations of any BGMS that is being used in settings where critically ill patients are cared for.

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Management of Pulmonary Embolism in the Intensive Care Unit

Pulmonary Embolism (PE) is a reason for admission to the Intensive Care Unit (ICU) and this complication in hospitalised patients is associated with high morbidity and mortality. The identification and management of PE is a challenge for doctors.

Introduction

Pulmonary Embolism (PE) is the third cardiovascular cause of death since its clinical expressions in critical patients may go unnoticed or present themselves as sudden respiratory arrest or failure, which could lead to death. The approach in the ICU is focused on timely identification, haemodynamic and respiratory support, and reperfusion therapy, either with thrombolysis or thrombectomy (Essien et al. 2019).

Epidemiology

PE affects 900,000 people per year in United States and Europe, out of which 100,000 die (Torres and Haut 2020). Its incidence has a range of 70 to 183 per 100,000 people per year (Essien et al. 2019; Ashrani and Heit 2008; Spencer et al. 2006). From 10 to 30% of these patients die within 30 days and 25% are expressed as sudden death (White 2003). The patients' quality of life is reduced when complications such as post-thrombotic syndrome and chronic pulmonary hypertension appear. PE is seen more frequently in patients of >40 years. Between 25 and 50% of cases do not have a clear aetiology, 20% are associated with a recent surgery and between 15 and 25% are associated with cancer. Factors associated mainly with mortality are old age, cancer, and previous heart or pulmonary diseases, which happened 30 days after a deep vein thrombosis (DVT) in 6% of

the patients and after a PE in 12% (White 2003). Patients with PE who are not treated show a mortality of 25%, decreasing up to 1% in patients who received appropriate treatment (Essien et al. 2019). Depending on PE seriousness, patients with normal blood pressure show a mortality of 2%, 30% in patients with right ventricular failure, and 65% in patients who go into cardiopulmonary arrest (White 2003).

PE has a mortality risk 18 times higher in comparison with patients with equal demographic conditions and those who do not have the disease (Essien 2019). The main factors of poor prognosis are presentation with syncope, shock and hypotension, right ventricular dysfunction, elevated troponins, and B-type natriuretic peptide (Vacca and Jehle 2013). Mortality is independent of the thrombus location in the pulmonary vasculitis, being higher in proximal involvement (10.7%) than in subsegmental involvement (6.5%) (Den Exter et al. 2013).

Pathophysiology

The cause of venous thromboembolism is multifactorial, commonly requiring a predisposing risk factor (e.g., thrombophilia) and/or a triggering one (e.g., surgery). A prothrombotic and proinflammatory aetiology in which coagulation factors interrelate extensively with immune cells is proposed (Khan et al. 2021). Venous thrombosis triggering mechanisms are related to

Virchow's Triad, characterised by venous stasis, vascular endothelial injury, and hypercoagulability, favoured by hypoxia and constant inflammation. Tissue damage leads to the activation of von Willebrand factor, E-selectin and P-selectin receptors. Tissue factor (TF), erythrocytes, and leukocytes bind to these receptors; this binding causes activation of the direct coagulation cascade, which is exacerbated by the action of neutrophil extracellular traps (NETs). NETs activate factor XII which initiates the intrinsic coagulation pathway producing factor X and thrombin. Finally, the thrombus is formed which is composed of fibrin, NETs, platelets, and red blood cells.

Right Ventricular Failure in PE

There are anatomical and functional differences between the right and left ventricles. The right ventricle (RV) is part of the pulmonary circulation, a system of low pressures, with low vascular resistances and greater distensibility compared to the left ventricle (LV) and the systemic circulation. When a thrombotic event occurs in the pulmonary artery or arteries (**Figure 1**), there is a large increase in RV afterload, which is exacerbated by a vasoconstrictor effect triggered by hypoxaemia and caused by increased serotonin and thromboxane (Weinstein et al. 2021). This results in a

reduction of RV stroke volume, which limits antegrade blood flow and causes dilatation of said cavity (Bryce et al. 2019). RV dilatation causes displacement of the interventricular septum in the direction of the LV causing a reduction in its SV, which in turn decreases cardiac output (CO) and is accompanied by coronary hypoperfusion. This phenomenon is known as ventricular interdependence. The increase in transmural pressure of the RV wall leads to occlusion of its corresponding coronary arteries and

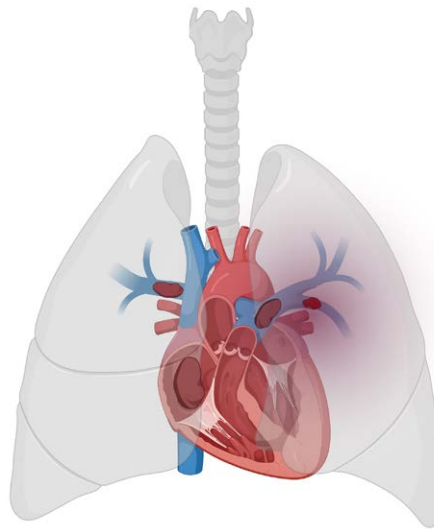


Figure 1. Massive pulmonary embolism with thrombi in both proximal and distal pulmonary arteries and mobile thrombus in the right atrium. Created by BioRender.com

generation of ischaemia (Mahmood 2018). Another characteristic is tricuspid annular dilation that causes tricuspid regurgitation with reduced RV volume. In short, the sum of these events results in reduced cardiac output with reduced blood pressure, increased coronary hypoperfusion with obstructive shock and death.

High- and Intermediate-Risk PE

A diagnosed PE that does not cause RV dysfunction is classified as mild or low-risk PE, and these patients can usually be managed on an outpatient basis. When PE is accompanied by RV dysfunction indicated by cardiac biomarkers and/or imaging studies, it is classified as intermediate-risk or submassive PE. If there is sustained hypotension (systolic blood pressure <90 mmHg for >15 minutes or a decrease of >40 mmHg) and clinical data of obstructive shock or cardiac arrest, it is categorised as high-risk or massive PE (**Table 1**). Massive PE occurs in 5% of patients with a mortality of 18–65% of cases; on the other hand, submassive PE occurs in 40% of patients with a mortality of 5–25% (Bryce et al. 2019). The Pulmonary Embolism Severity Index (PESI) and simplified PESI (s-PESI) (**Table 2**) can also be used to categorise PE into mild, intermediate, or high risk (Konstantinides et al. 2019).

Early mortality risk		Indicators of risk			
		Haemodynamic instability ^a	Clinical parameters of PE severity and/or comorbidity: PESI class III–V or sPESI ≥ 1	RV dysfunction on TTE or CTPA ^{bw}	Elevated cardiac troponin levels ^c
High		+	(+) ^d	+	(+)
Intermediate	Intermediate–high	-	+ ^e	+	+
	Intermediate–low	-	+ ^e	One (or none) positive	
Low		-	-	-	Assessment optional; if assessed, negative

Table 1. Classification of pulmonary embolism severity and the risk of early (in-hospital or 30 day) death (Konstantinides et al. 2019)

Abbreviations: BP = blood pressure; CTPA = computed tomography pulmonary angiography; H-FABP = heart-type fatty acid-binding protein; NT-proBNP = N-terminal pro B-type natriuretic peptide; PE = pulmonary embolism; PESI = Pulmonary Embolism Severity Index; RV = right ventricular; sPESI = simplified Pulmonary Embolism Severity Index; TTE = transthoracic echocardiogram.

a One of the following clinical presentations: cardiac arrest, obstructive shock (systolic BP \leq 90 mmHg despite an adequate filling status, in combination with end-organ hypoperfusion), or persistent hypotension (systolic BP \leq 40 mmHg for $>$ 15 min, not caused by new-onset arrhythmia, hypovolaemia, or sepsis).

b Prognostically relevant imaging (TTE or CTPA) findings in patients with acute PE, and the corresponding cut-off levels, are graphically presented in Figure 3, and their prognostic value is summarised in Supplementary Data Table 3.

c Elevation of further laboratory biomarkers, such as NT-proBNP $>$ 600 ng/L, H-FABP $>$ 6 ng/mL, or copeptin $>$ 24 pmol/L, may provide additional prognostic information. These markers have been validated in cohort studies but they have not yet been used to guide treatment decisions in randomised controlled trials.

d Haemodynamic instability, combined with PE confirmation on CTPA and/or evidence of RV dysfunction on TTE, is sufficient to classify a patient into the high-risk PE category. In these cases, neither calculation of the PESI nor measurement of troponins or other cardiac biomarkers is necessary.

e Signs of RV dysfunction on TTE (or CTPA) or elevated cardiac biomarker levels may be present, despite a calculated PESI of III or an sPESI of 0.234. Until the implications of such discrepancies for the management of PE are fully understood, these patients should be classified into the intermediate-risk category.

Parameter	Original version	Simplified version
Age	Age in years	1 point (if age $>$ 80 years)
Male sex	+10 points	-
Cancer	+30 points	1 point
Chronic heart failure	+10 points	1 point
Chronic pulmonary disease	+10 points	
Pulse rate \geq 110 bpm	+20 points	1 point
Systolic BP $<$ 100 mmHg	+30 points	1 point
Respiratory rate $>$ 30 breaths per min	+20 points	-
Temperature $<$ 36°C	+20 points	-
Altered mental status	+60 points	-
Arterial oxyhaemoglobin saturation $<$ 90%	+20 points	1 point
Risk stratification		
	<ul style="list-style-type: none"> • Class I: \leq 65 points • very low 30 day mortality risk (0–1.6%) • Class II: 66–85 points • low mortality risk (1.7–3.5%) • Class III: 86–105 points • moderate mortality risk (3.2–7.1%) • Class IV: 106–125 points • high mortality risk (4.0–11.4%) • Class V: $>$ 125 points • very high mortality risk (10.0–24.5%) 	<ul style="list-style-type: none"> • 0 points = 30 day mortality risk 1.0% • (95% CI 0.0–2.1%) • \geq 1 point(s) = 30 day mortality risk 10.9% (95% CI 8.5–13.2%) <p>\geq 1 point(s) = 30 day mortality risk 10.9% (95% CI 8.5–13.2%)</p>

Table 2. Original and simplified Pulmonary Embolism Severity Index.

Abbreviations: BP = blood pressure; b.p.m. = beats per minute; CI = confidence interval. aBased on the sum of points.

Cardiac troponin elevation as a marker of cardiac necrosis is associated with higher short-term mortality and more adverse events (Becattini et al. 2007). Increased values of other cardiac biomarkers such as heart-type fatty acid-binding protein (H-FABP), N-terminal pro B-type natriuretic peptide (NT-proBNP) and brain natriuretic peptide (BNP) are associated with RV involvement.

The echocardiographic findings associated with RV dysfunction are (Figure 2):

- RV size increase in the parasternal long axis
- RV/LV relationship increase $>0,9$
- Flattening of the intraventricular septum in the parasternal short axis
- Absence of the inferior vena cava

collapsibility

- 60/60 sign
- Mobile thrombus in the right atrium or RV
- TAPSE <16 mm
- Decreased tricuspid annular peak systolic velocity $<9,5$ cm/s

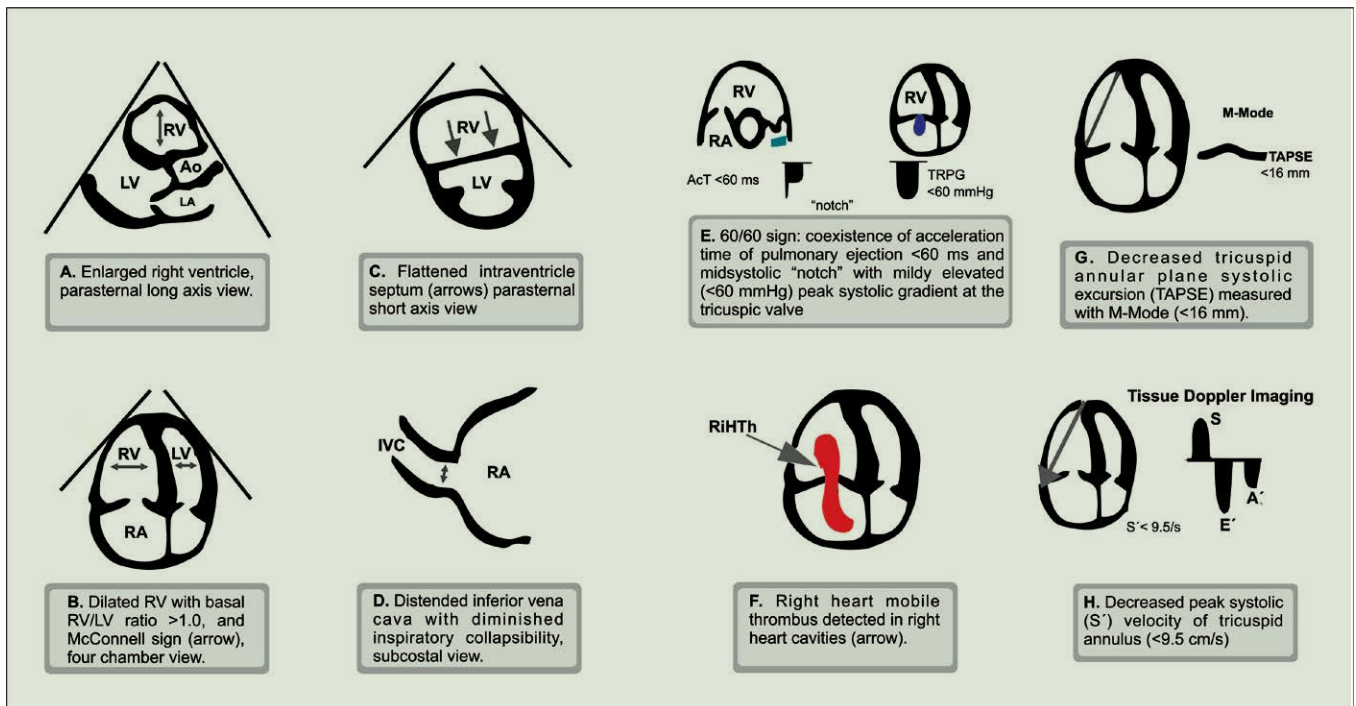


Figure 2. Graphic representation of transthoracic echocardiographic parameters in the assessment of right ventricular pressure overload (Adapted from Konstantinides et al. 2019). A0 = peak late diastolic (during atrial contraction) velocity of tricuspid annulus by tissue Doppler imaging; AcT = right ventricular outflow Doppler acceleration time; Ao = aorta; E0 = peak early diastolic velocity of tricuspid annulus by tissue Doppler imaging; IVC = inferior vena cava; LA = left atrium; LV = left ventricle; RA = right atrium; RIHTh = right heart thrombus (or thrombi); RV = right ventricle/ventricular; S0 = peak systolic velocity of tricuspid annulus by tissue Doppler imaging; TAPSE = tricuspid annular plane systolic excursion; TRPG = tricuspid valve peak systolic gradient.

Evaluation of a Critical Patient With PE

The main symptoms of patients with PE are commonly sudden onset dyspnoea and tachypnoea; tachycardia, chest pain, pelvic limb pain, fever, haemoptysis or syncope may also be experienced. Electrocardiographic changes such as sinus tachycardia, complete right bundle branch block and S wave pattern in DI, Q wave in DIII, and inverted T wave in DIII may be seen in laboratory tests although these are

relatively infrequent. However, diagnosing a severely hospitalised patient under sedation and mechanical ventilation who gets complicated with PE is challenging; thus, it should be considered when patients develop sudden respiratory and haemodynamic deterioration, as tachycardia and pain may be suppressed by painkillers and sedatives. The increase in physiological dead space due to pulmonary hypoperfusion disorder may generate an increase in arterial pressure (PaCO_2) and hypoxaemia,

without modifications to the respiratory system compliance or resistance and, therefore, without evident modifications to the respiratory mechanics during mechanical ventilation. Electrocardiographic changes and swelling of the pelvic limbs may also be present, which may complement the diagnostic suspicion.

In a hospitalised patient with suspected or diagnosed PE, continuous monitoring of blood pressure (BP), respiratory rate (RR), heart rate (HR), peripheral partial blood

oxygen saturation (SpO₂), consciousness and tissue perfusion data such as capillary filling, skin colouration and temperature and uresis is recommended, intentionally looking for clinical data of shock due to haemodynamic instability. Bedside ultrasound is recommended to detect: 1) RV dysfunction data, 2) thrombi detection in the right ventricle, and 3) thrombi detection in femoral veins proximal segment. Haemodynamic management should be established immediately and, if possible, diagnostic confirmation with pulmonary angiography or ventilation/perfusion scan after stabilisation.

Specific Management

Anticoagulation

Anticoagulation therapy decreases mortality in patients with PE (Weinstein et al. 2021). Anticoagulants may be used enterally or parenterally. The group of direct oral

anticoagulants (DOACs) and Vitamin K antagonists (VKAs) are included in enteral feeding; the most commonly used DOACs are rivaroxaban and apixaban, whereas VKAs include warfarin and acenocoumarin. Parenteral anticoagulants include unfractionated Heparin (UFH) and low-molecular-weight heparins (LMWHs), of which the most commonly used are enoxaparin and fondaparinux (**Table 3**).

DOACs are recommended over VKAs because they have fewer pharmacological interactions and have been shown to have a lower incidence of adverse effects, including clinically relevant bleeding; moreover, they do not require biochemical monitoring with serial laboratory tests which are necessary for monitoring the effectiveness of VKAs since an International Normalised Ratio (INR) of 2 to 3 must be kept. In addition, DOACs may be administered as soon as the diagnosis

is confirmed and do not require prior parenteral anticoagulation, unlike VKAs. If VKAs are used, parenteral anticoagulation should be started at the same time and kept for at least 5 days and the INR value of 2 to 3 should be corroborated for at least 2 consecutive days.

As for parenteral anticoagulation, comparative studies have shown that LMWHs are associated with a decrease in thrombotic events, greater decrease in thrombus size, and less bleeding when compared to UFH; besides they are the anticoagulation treatment of choice for pregnant patients. However, some indications that might suggest using UFH are patients with haemodynamic instability and the need for surgical reperfusion therapy or other urgent major surgery (Leentjens et al. 2017).

Direct Oral Anticoagulants		
	Regimen	Contraindications
Rivaroxaban	15 mg twice a day for 21 days Extended phase: 20 mg once daily with food	CrCl <30 ml/min Moderate or severe hepatic impairment (Child Pugh B and C), or hepatic disease associated with coagulopathy Concomitant use of combined P-GP and strong CYP3a4 inhibitors or inducers
Dabigatran	150 mg twice a day	CrCl <30 ml/min Concomitant treatment with P-GP inhibitors in patients with crcl <50ml/min Concomitant treatment with P-GP inducers
Apixaban	10 mg twice a day for 7 days Long-term phase: 5mg twice daily Extended: 2.5mg twice a day after at least 6 months of treatment	CrCl < 15ml/min Severe hepatic impairment (Child Pugh C), or hepatic disease associated with coagulopathy Strong dual inhibitors or inducers of CYP3A4 and P-GP
Edoxaban	Initial therapy with parenteral anticoagulation for 5-10 days should precede administration of Edoxaban long-term: 60 mg/day 30 mg/day can be considered in patients with ≥1 of the following factors: CrCl 15-50ml/min; body weight ≤60 kg; cyclosporin, dronedarone, erythromycin, or ketoconazole	CrCl <15ml/min Moderate or severe hepatic impairment (Child Pugh B and C), or hepatic disease associated with coagulopathy Concomitant treatment with rifampin

Low-Molecular Weight Heparins		
	Regimen	Adjust kidney function (CrCl<30ml/min)
Bemiparin	115 Ui/kg/day S.C.	3500 ui
Dalteparin	100 UI/kg/12h S.C. 200 UI/kg/day S.C.	Not recommended (control anti-Xa)
Enoxaparin	1mg/kg/12h S.C.	40mg/12h CrCl <15 ml/min: contraindicated
Nadroparin	86 Ui/kg/12h S.C.	CrCl >50 and >30 ml/min: reduce between 25 and 33% CrCl <30 ml/min: not recommended
Tinzaparin	175 ui/kg/day S.C.	Anti-Xa control
Fondaparinux	7.5 mg/day S.C.	Cr Cl between 30-50 ml/min: use with caution, same dosage of 5 to 7.5 mg SQ q daily. CrCl <30 ml/min: contraindicated
Unfractionated Heparin		
	Bolus dose	Immediate infusion to follow
Initial dose	80 U/kg	18 U/kg/h
Adjustment according to control of ttpa		
<35 s	80 U/kg	4 U/kg/h
35-45 s	40 U/kg	2 U/kg/h
46-70 s	Without modifications	
71-90 s		Decrease infusion to 2 U/kg/h
>90 s		Stop infusion one hour, then resume at 3 U/kg/h
Thrombolytics		
	Regimen	Contraindications to fibrinolysis
Alteplase	100 mg over 2h 0.6 mg/kg over 15min (max. dose 50 mg)	Absolute History of haemorrhagic stroke or stroke of unknown originw Ischaemic stroke in previous 6 months
Streptokinase	250 000 U as a loading dose over 30 min, followed by 100 000 U/h over 12-24h	Central nervous system neoplasm Major trauma, surgery, or head injury in previous 3 weeks
	Accelerated regimen: 1.5 million U over 2h	Bleeding diathesis Active bleeding
Urokinase	4400 U/kg as a loading dose over 10 min, followed by 4400 U/kg/h over 12-24h Accelerated regimen: 3 million U over 2h	Relative Transient ischaemic attack in previous 6 months Oral anticoagulation Pregnancy or first post-partum week
Tenecteplase	30-50 mg IV bolus over 5 sec once (based on weight) <60 kg: 30 mg 60-70 kg: 35 mg 70-80 kg: 40 mg 80-90 kg: 45 mg >90 kg: 50 mg	Non-compressible puncture sites Traumatic resuscitation Refractory hypertension (systolic bp >180 mmHg) Advanced liver disease Infective endocarditis Active peptic ulcer

Table 3. Anticoagulants and thrombolytics

Thrombolysis

Thrombolysis used in patients with massive PE has been successful in reducing mortality up to 50%. It is associated with faster clot dissolution but there is a risk of haemorrhage. As for thrombolysis in intermediate-risk PE, significant decrease in RV dysfunction, decreased need for escalating interventions and improved quality of life (Marti et al. 2015; Becattini et al. 2014; Kline et al. 2014), lower mortality or escalation in treatment but with a higher chance of haemorrhage (Weinstein 2021) have been reported. Thus, thrombolysis is only fully justified in case of PE with haemodynamic instability (Konstantinides et al. 2019).

Surgical Treatment

Surgical treatment of PE includes open pulmonary embolectomy or catheter-directed thrombolysis. To date, studies supporting the efficacy of surgical management are few; however, patients with high-risk PE or in cardiorespiratory arrest may benefit from this intervention. Compared to the use of a second dose of thrombolytic when there is no improvement with the initial dose, surgical management has been reported to have better results. Preoperative thrombolysis is associated with an increased risk of surgical bleeding but is not an absolute contraindication. Therefore, thrombectomy is indicated when thrombolysis is contraindicated, fails, or when cardiopulmonary resuscitation is needed; the perioperative mortality rate in these cases is <6% (Yamamoto 2018). Anticoagulation is required following surgical resolution; however, there is no consensus on when the best time is to start it and it should be indicated according to the doctor's judgment. A regimen of anticoagulation with heparin for at least 5 days before switching to DOACs might be recommended (Konstantinides et al. 2019).

Haemodynamic and Respiratory Management in the ICU Patient With PE

Respiratory Support

Appropriate tissue oxygenation must be

guaranteed in order to avoid organ failure; furthermore, it contributes to reduce pressure in pulmonary circulation and RV afterload by avoiding vasoconstriction due to a decrease in pulmonary vascular resistance mediated by hypoxaemia (Lyhne 2021). Oxygen therapy also contributes to alleviate dyspnoea and decrease work of breathing and respiratory rate. To increase the fraction of inspired oxygen (FiO_2), conventional devices such as low-flow nasal cannulas, face mask or mask with oxygen reservoir with non-rebreathing valve may be used. These devices should be scaled according to the clinical situation, a goal of SpO_2 from 90 to 96% or PaO_2 from 60 to 90 mmHg may be recommended for most cases (Erol 2018). High-flow nasal cannula (HFNC) can deliver a FiO_2 close to 1, generating a rapid increase in SpO_2 and PaO_2 . Thermal regulation of inhaled oxygen preserves mucociliary function and contributes to device tolerance and increased flow that can reach up to 50 to 70 L/min. It could favour ventilation by increasing end-expiratory lung volume, increasing functional residual capacity, and decreasing respiratory drive and work of breathing. This benefit has been shown to be effective in retrospective studies and case reports (Aguilar-Piedras 2021; Vikas 2021; Messika 2017).

Regarding patients in whom adequate oxygenation cannot be guaranteed and who persist having tachypnoea and increased respiratory effort, noninvasive ventilation (NIV) may be used to support ventilation by releasing the load on the inspiratory muscles, conserving the negativity exerted by them and favouring venous return, unlike invasive ventilation.

In patients with high-risk PE, it is recommended to avoid intubation and invasive mechanical ventilation (IMV) when possible and to exhaust respiratory support strategies mentioned above; if these fail and there is one or more indications to start IMV, it should be carried out in the safest possible way. Using cardio-stable drugs during the rapid intubation sequence (etomidate, ketamine) may be recommended unless

contraindicated. The use of propofol or midazolam for induction could decrease cardiac rate and contractility and worsen the haemodynamic status (Zamarron 2019). When starting IMV, it is recommended not to place positive end-expiratory pressure (PEEP) and to limit plateau pressure in order not to further increase intrathoracic positive pressure and afterload to the RV (Meyer 2016). There is no consensus on sedative management in this pathology but avoiding unnecessary and prolonged sedation may be associated with a better prognosis.

Fluid therapy and Diuretics

Intravenous fluids should be used with caution because the increase in RV end-diastolic pressure at the expense of preload will contribute to a decrease in LV end-diastolic volume, decrease in LV systolic volume and, thus, cardiac output, paradoxically worsening the haemodynamic status (Meyer 2016). On the other hand, the use of diuretics in normotensive patients with PE is associated with a decrease in the severity of PE without affecting renal function; theoretically, this may be due to a decrease in RV congestion and secondary venous congestion (Lim 2021).

Vasopressors, Inotropes, and Vasodilators

Norepinephrine (NE) is the vasopressor of first choice for patients in shock. In the case of PE accompanied by haemodynamic instability, NE can improve RV performance by enhancing coronary perfusion pressure (Meyer 2016). Vasopressin, methylene blue, and other vasopressors could increase BP in case of refractory shock; however, there is not enough information to issue recommendations on their use in this pathology. Dobutamine is an inodilator that can be used to improve cardiac contractility in cardiogenic shock and PE; its use can be considered under BP strict monitoring because using it could cause a decrease in BP. The combination of both drugs could also be considered if the doctor deems it appropriate and only under dynamic monitoring that may include transthoracic

or transesophageal ultrasound. Inhaled nitric oxide has been shown to improve pulmonary function, but without achieving a benefit in mortality numbers.

Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) may be considered in critically ill patients with PE. Successful cases have been reported when it has been used in

an arteriovenous modality in patients with high-risk PE or cardiac arrest, in order to provide cardiac and respiratory support; however, studies on this subject are few as they require a trained team and there is

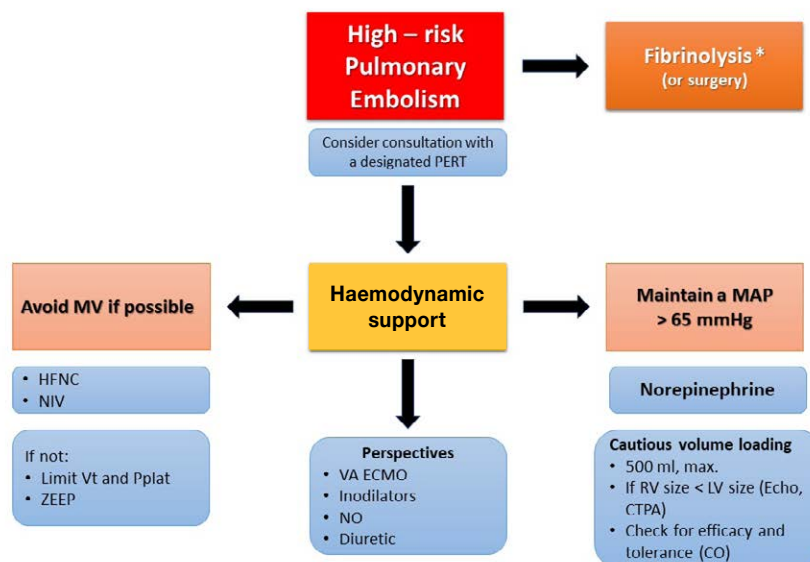


Figure 3. Proposal for haemodynamic management in high-risk pulmonary embolism *in the absence of contraindication.

PERT: Pulmonary Embolism Response Team, HFNC: high flow nasal cannula, NIV: noninvasive ventilation, ZEEP: 0 cmH₂O of end-expiratory pressure, Vt tidal volume, Pplat plateau pressure, RV: right ventricle, LV: left ventricle, CTPA: computed tomography pulmonary angiography, CO: cardiac output, MV: mechanical ventilation, NO: nitric oxide inhalation, VA ECMO: veno-arterial extracorporeal membrane oxygenation.

no consensus on when to initiate therapy (Murray 2021).

The summary of specific management and multiorgan support is presented in **Figure 3**.

Recurrence Prevention

Recurrent PE occurs in 7 to 30% of cases over 10 years, being more frequent in the first 12 months despite the use of oral anticoagulation and is more frequent in patients with cancer. The risk factors associated with recurrence are age, body mass index (BMI), male gender, active cancer, immobility of lower extremities, lupus anticoagulant, antiphospholipid antibodies, and protein S, C and antithrombin deficiencies (Heit et al. 2002).

Duration of Anticoagulation

Therapeutic anticoagulation should suffice with only 3 months if a provoked or tran-

sient risk factor has been identified (e.g. surgery, trauma, prolonged immobilisation, etc). The recurrence rate in these patients is 3%; however, in those patients at high risk of recurrence (e.g. active cancer, prolonged immobilisation), anticoagulation should be extended indefinitely and monitored for new thrombotic events, which can occur in up to 8% of cases. active cancer, prolonged immobilisation) should extend anticoagulation indefinitely and monitor for new thrombotic events, which can occur in up to 8% of cases, in addition to complications of anticoagulants such as haemorrhage (Konstantinides et al. 2019).

Inferior Vena Cava Filter

When there is a contraindication to pharmacological anticoagulation, an inferior vena cava filter may be indicated. This strategy has been associated with lower mortality

despite associated complications such as an increased possibility of thrombotic events (like filter thrombosis), which can occur in up to 10% of cases, and DVT in up to 40% of cases. Its use in high-risk PE or combined with oral or parenteral anticoagulants is not recommended since it does not generate an added benefit (Yamamoto 2018).

Conclusion

PE is a serious disease associated with a high morbidity and mortality, which can occur in critically ill patients during hospitalisation. The recognition of this disease, its timely diagnosis and establishing an adequate treatment with multidisciplinary support can improve its prognosis.

Conflict of Interest

None. ■

References

For full references, please email editorial@icu-management.org or visit <https://iii.hm/1d3b>



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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, hyper-

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.

viscosity 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	<p>Signs and symptoms of end-organ hypoperfusion (Rollig et al. 2015; Porcu et al. 2000):</p> <ul style="list-style-type: none"> Respiratory failure (tachypnoea, hypoxaemia, pulmonary haemorrhage) Neurologic symptoms (decreased level of consciousness, delirium, visual disturbances, headache, and tinnitus) Bowel or limb ischaemia Myocardial infarction <p>Imaging features (Stefanski et al. 2016):</p> <ul style="list-style-type: none"> CXR: focal or diffuse opacities, pleural effusion. Chest CT: interlobular septal thickening, consolidation, ground glass opacities. 	<p>Emergent cytoreduction should be arranged in consultation with a haematologist. Options include the following:</p> <ul style="list-style-type: none"> Hydroxyurea: <ul style="list-style-type: none"> Oral medication that inhibits DNA synthesis Used as a temporising measure prior to induction chemotherapy (Mamez et al. 2016) Chemotherapy: <ul style="list-style-type: none"> Intensive chemotherapy is the definitive management Low-dose cytarabine may also be used to temporise at some institutions Leukapheresis: <ul style="list-style-type: none"> WBCs removed from the circulation with an apheresis 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 <p>Supportive care:</p> <ul style="list-style-type: none"> Avoid RBC transfusions unless symptomatic anaemia Hydration with IV crystalloids, avoid diuretics unless clinical evidence of volume-overload
Tumour Lysis Syndrome	<p>TLS has both clinical and laboratory diagnostic criteria (Cairo and Bishop 2004):</p> <p>Clinical criteria (one or more):</p> <ul style="list-style-type: none"> Acute kidney injury: Creatinine $\geq 1.5 \times$ ULN Seizure Arrhythmia or sudden cardiac death <p>Laboratory criteria (two or more):</p> <ul style="list-style-type: none"> Uric acid $\geq 476 \mu\text{mol/l}$ or 25% Potassium $\geq 6.0 \text{ mmol/l}$ or 25% Phosphate $\geq 1.45 \text{ mmol/l}$ or 25% Calcium $\leq 1.75 \text{ mmol/l}$ or 25% 	<p>Uric acid lowering therapies:</p> <ul style="list-style-type: none"> All high-risk patients, which includes hyperleukocytosis, should receive rasburicase regardless of the uric acid level on presentation <ul style="list-style-type: none"> 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. <p>Supportive care (Jones et al. 2015; Matuskiewics-Rowinska and Malyszko 2020):</p> <ul style="list-style-type: none"> 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	<p>Patients may present with a bleeding diathesis and/or thrombosis.</p> <p>DIC is characterised by the following abnormalities (Levi et al. 2009):</p> <ul style="list-style-type: none"> Elevated PT/PTT and d-dimer Low fibrinogen Schistocytes on peripheral smear 	<p>Coagulation parameters should be monitored frequently with administration of blood products to maintain the following:</p> <ul style="list-style-type: none"> Platelets $> 20\text{-}30 \times 10^9/\text{L}$ ($50 \times 10^9/\text{L}$ in bleeding patients) Fibrinogen greater $> 1\text{-}1.5\text{g/dL}$ INR $< 1.5\text{-}2.0$ <p>Particular caution must be taken to monitor and aggressively treat coagulopathy in patients with APL.</p>

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/RAR α 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 $10 \times 10^9/L$). 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 $30 \times 10^9/L$ ($50 \times 10^9/L$ 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 $\geq 38.3^\circ\text{C}$ or a temperature $\geq 38.0^\circ\text{C}$ lasting more than 1 hour with an absolute neutrophil count (ANC) $< 0.5 \times 10^9/L$ (Freifeld et al. 2011). Following induction chemotherapy, patients with acute leukaemia may develop profound, prolonged neutropenia with an ANC $< 0.1 \times 10^9/L$ 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 (G-CSF) 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 G-CSF 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,

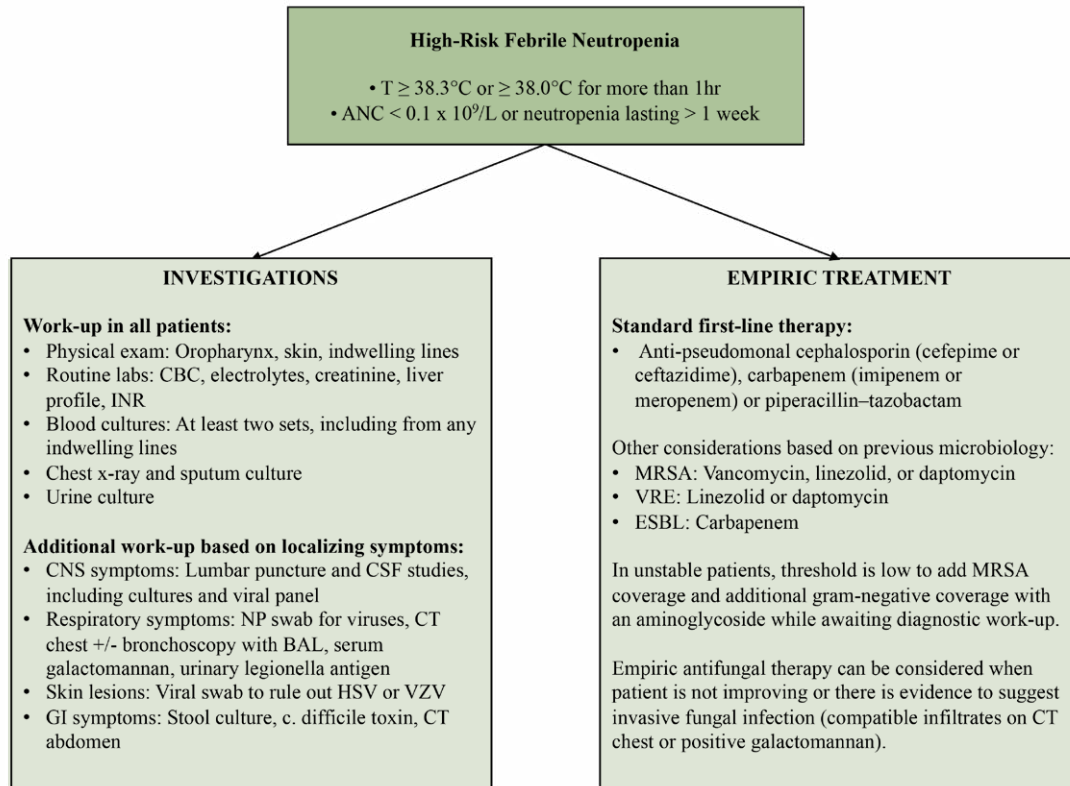


Figure 1 : Diagnostic work-up and empiric treatment for patients with high-risk febrile neutropenia [Freifeld et al. 2011; Klastersky et al. 2016; Taplitz et al. 2018]

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 = gastrointestinal; HSV = herpes simplex virus; INR = international normalised ratio; MRSA = methicillin-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 manage-

ment 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)	<p>Any organ may be involved but the most relevant presentations for critical care include the following:</p> <ul style="list-style-type: none"> • Pneumonitis, myocarditis, encephalitis, hepatitis, colitis <p>Severity: Graded on a scale of 1-4 with specific criteria for each organ system.</p> <p>Timing: Weeks to months after starting an immune checkpoint inhibitor.</p>	<p>For grade 3 or 4 reactions, the immune checkpoint inhibitor is held and might be permanently discontinued.</p> <p>First-line treatment = steroids with some conditions requiring pulse-dosing.</p> <p>Need for additional immunosuppression depends on underlying organ involvement and steroid response but may include infliximab, IVIG, MMF, azathioprine, and cyclophosphamide.</p>
Cytokine Release Syndrome (CRS)	<p>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.</p> <p>Severity: Graded on a scale of 1-4</p> <p>Timing: Highest risk in first week following infusion</p>	<p>Tocilizumab, an IL-6 monoclonal antibody, is the first line treatment.</p> <ul style="list-style-type: none"> • Should be administered in all Grade 3 or 4 CRS • May be considered in Grade 1 or 2 CRS <p>Steroids may be administered in conjunction with tocilizumab in higher grades of CRS or when it does not respond to tocilizumab.</p>
Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)	<p>Symptoms include fatigue, aphasia, tremor, and apraxia with altered level of consciousness and coma in severe cases. Dysgraphia is also a prominent feature.</p> <p>Timing: Onset is typically around the same time as CRS</p>	<p>Steroids are first line therapy for ICANS.</p> <p>When both CRS and ICANS are present, tocilizumab and steroids are given together.</p>

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)
<ul style="list-style-type: none"> • Risks: <ul style="list-style-type: none"> • Primary immunodeficiency = severe neutropenia • Mucositis, indwelling lines • Types of Infection: <ul style="list-style-type: none"> • Bacterial infections are most common (gram positive or gram negative) • Fungal infections may also be seen (aspergillus, candida) as well as HSV 	<ul style="list-style-type: none"> • Risks: <ul style="list-style-type: none"> • Primary immunodeficiency = cell-mediated immunity • Acute GVHD and related immunosuppression • Types of Infection: <ul style="list-style-type: none"> • Bacterial infections still occur • HSV, CMV, PJP and aspergillus are commonly described • HHV6 may also be seen 	<ul style="list-style-type: none"> • Risks: <ul style="list-style-type: none"> • Ongoing impairment in cell-mediated immunity • Chronic GVHD and related immunosuppression • Types of Infection: <ul style="list-style-type: none"> • Risk for encapsulated bacteria is increased: <i>S. pneumo</i>, <i>H. flu</i>, <i>N. meningitidis</i>, etc. • VZV is common • Risk of HSV, CMV, PJP, aspergillus, and HHV6 remains

Figure 2 : Infectious risks post-allogeneic 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 leukoencephalopathy, among others (Pruitt et al. 2013).

Typical Timing	Complication	Presentation and Treatment
Early	Peri-Engraftment Respiratory Distress Syndrome (PERDS)	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> Fever, cough, shortness of breath with patchy infiltrates, ground glass or nodular opacities. May require lung biopsy for diagnosis. Treatment: Steroids
Late	Bronchiolitis obliterans	<ul style="list-style-type: none"> 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 Allogeneic 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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Introduction

Chimeric antigen receptor (CAR) T-cell therapy has been hailed as a much-awaited treatment for patients with relapsed/ refractory (r/r) haematological malignancies. CARs are synthetic receptors consisting of an extracellular domain that can bind specifically to a target molecule expressed on the surface of tumour cells, a transmembrane domain, and an intracellular signalling and costimulatory domain that provides an activation signal to T cells, when the extracellular domain is engaged with its target.

CAR-T Cell Therapy – What An Intensivist Should Know

CAR-T therapy is a promising treatment for B-cell malignancies but is also associated with toxicities such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Frequent monitoring, timely recognition and prompt management in ICU are paramount to ensure good outcomes.

CD19 was selected as an attractive therapeutic target as it is a transmembrane glycoprotein required for normal B-cell development in humans and it is expressed in over 95% of B-cell malignancies. Addition of a costimulatory domain to the CAR T construct (second-generation CAR) promoted T-cell proliferation and persistence, but also increased the risk of cytotoxicity. Several CAR T products are approved in Europe and the United States for acute lymphoblastic leukaemia (ALL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma and most recently multiple myeloma (Berdeja et al. 2021).

After leukapheresis of autologous T lymphocytes, genetic information for the CAR is transduced into the cells normally by means of viral vectors. The patients then receive lymphocyte-depleting chemotherapy as preparation. Once infused, CAR T cells recognise tumour cells expressing the target antigen. They expand locally and eliminate tumour cells by contact-dependent cytotoxicity (June and Sadelain 2018). Each activated CAR T cell releases cytokines and activates other components of the immune system, preventing tumour recurrence by promoting immune surveillance. Time from CAR T collection to patient infusion is approximately 3 weeks but often closer to 4 weeks. The leukapheresed cells are transferred to a manufacturing facility, sometimes abroad, for T cell engineer-

ing and expansion. The manufactured CAR T cells are transferred back to the centre for infusion, which typically happens as a single infusion, with varying infusion protocols depending on centre, sponsor and product.

Clinical trial data report overall response rate (ORR) between 54-83% and complete response (CR) rate between 40-58% for aggressive B-cell lymphoma, depending on the CAR product used (Tang and Nastoupil 2021). 'Real-world' outcomes of CD19 CAR T cell therapy for aggressive r/r non-Hodgkin lymphoma have response and survival rates that are comparable to the impressive results from pivotal trials. These results become even more pertinent since they demonstrate the efficacy of CAR T therapy in patients who would have been excluded from clinical trials.

Common Toxicities

As CAR T cell therapies become more widely used, recognition of their unique toxicities, distinct from those seen with other immune effector therapies, is of utmost importance. The two most common toxicities after CAR T cell infusion are the cytokine-release syndrome (CRS) and neurotoxicity, recently renamed immune effector cell-associated neurotoxicity syndrome (ICANS) (Lee et al. 2019). Their true incidence, severity and need for support are unclear, as published studies have used different CAR products and

different grading systems. Direct comparison of toxicities has been made easier after the publication of a consensus paper by the American Society for Transplantation and Cellular Therapy (ASTCT) in 2019 (Lee et al. 2019). The ASTCT consensus grading for CRS and ICANS is presented in **Table 1**.

Cytokine Release Syndrome

Activation and proliferation of T cells after engagement with the CAR ligand result in secretion of cytokines and proinflammatory signals from the activated lymphocytes but also other immune cells. In particular, Interleukin (IL) -6 and interferon- γ (IFN- γ) play a decisive role in initiation of this systemic inflammatory response that in extreme cases can result in fluid-refractory hypotension and other organ damage. The range of symptoms varies but the pres-

ence of fever is essential for the diagnosis (**Table 1**). In clinical trials, CRS of any grade was observed between 58-93%, with 13-22% developing grade 3 or higher CRS. Despite differences in the baseline characteristics among patients, similar rates of toxicities were observed in the real-world data (Tang and Nastoupil 2021). Risk of CRS is influenced by pre-treatment factors, such as tumour burden and ALL as the underlying disease, and treatment-related factors such as the costimulatory domain of the CAR, dose of CAR T cells infused and regimen of lymphodepletion.

Treatment of CRS varies between institutions and is mainly supportive. Enhanced monitoring, regular antipyretics, fluids and broad-spectrum antibiotics are suggested for grade 1 CRS. When grade 1 symptoms persist or progress to grade 2, treatment with

tocilizumab, an IL-6 receptor antagonist, is recommended (8mg/kg; maximum of 3 doses and 800mg/dose). Corticosteroids are considered if symptoms do not subside after tocilizumab administration or if there is progression to grade 3. We advocate the use of intravenous dexamethasone (up to 10mg QDS), as the corticosteroid of choice. In our institution, all patients with grade 2 CRS and/or ICANS are followed up with our critical care outreach team (CCOT). Severe cases of CRS (\geq grade 3) are admitted to the intensive care unit (ICU) and may require additional supportive measures, such as vasopressor agents for hypotension and supplemental oxygen or intubation for hypoxaemia. Refractory CRS can be treated empirically with further immunosuppression (methylprednisolone 1g/day, anakinra, siltuximab).

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$
With				
Hypotension	None	Not requiring vasopressors	Requiring one vasopressor with/without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or†				
Hypoxia	None	Requiring low-flow nasal cannula‡ or blow-by	Requiring high-flow nasal cannula, facemask, nonrebreather mask or Venturi mask	Requiring positive pressure (e.g. CPAP, BiPAP, intubation and mechanical ventilation)

Table 1: Consensus grading for Cytokine Release Syndrome

* Fever is defined as temperature $\geq 38^{\circ}\text{C}$ not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C , hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

‡ Low-flow nasal cannula is defined as oxygen delivered at $\leq 6\text{L}/\text{minute}$. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at $>6\text{L}/\text{minute}$. Source: Lee et al 2019.

Immune Effector Cell–Associated Neurotoxicity Syndrome

The exact pathophysiology behind the neurotoxicity observed after CAR T cell therapy is not fully understood. Systemic inflammation appears to also be important

in ICANS but less so than in CRS, with IL-1 playing a more significant role than IL-6. The presence of pro-inflammatory cytokines has been demonstrated in the cerebrospinal fluid (CSF) and is linked with increased endothelial activation. It is

unclear whether elevated levels of cytokines in CSF are a consequence of the blood-brain barrier disruption or a result of CAR T cell engagement with CD19-expressing cerebral endothelial cells. ICANS symptoms often occur a few days follow-

ing CRS but can manifest independently. They range from mild word-finding difficulties, aphasia, toxic encephalopathy, impaired

cognitive skills, altered consciousness, or hallucinations to more devastating symptoms including seizures, motor weakness,

and cerebral oedema (**Table 2**) (Tang and Nastoupil 2021).

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7 to 9	3 to 6	0 to 2	0 (patient is unrousable and unable to perform ICE)
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unrousable or requires vigorous or repetitive tactile stimulus to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalised that resolves rapidly; or nonconvulsive seizures on EEG that resolve with intervention	Life threatening prolonged seizure (> 5 mins); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral oedema	N/A	N/A	Focal/local oedema on neuroimaging§	Diffuse cerebral oedema on neuroimaging; decorticate or decerebrate posturing; or cranial nerve VI palsy; or papilloedema; or Cushing's triad

Table 2: Consensus grading for Immune Effector Cell-Associated Neurotoxicity Syndrome

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral oedema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

N/A indicates not applicable.

* A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

† Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

‡ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

§ Intracranial haemorrhage with or without associated oedema is not considered a neurotoxicity feature and is excluded from ICANS grading. Source: Lee et al 2019.

Management of low grade ICANS is based on increased frequency of neurological observations using the Immune Effector Cell-Associated Encephalopathy (ICE) score (**Table 3**) and administration of antiepileptics in case of seizures. Tocilizumab is ineffective, unless there is concurrent CRS, whereas corticosteroids

are the immunomodulator of choice. In our institution, we use intravenous dexamethasone (up to 10mg QDS), followed by methylprednisolone 1g/day for refractory symptoms. Close monitoring by the CCOT, admission to ICU when ICANS \geq grade 3 and close collaboration with neurology and neurosurgery in severe cases are standard

practice. When managing neurotoxicity, it is important to exclude alternative causes, such as infection, stroke or haemorrhage. The choice of diagnostic modalities (e.g., magnetic resonance vs. computer tomography imaging, electroencephalogram, cerebrospinal fluid analysis) is tailored to the severity and nature of symptoms.

Domain	Assessment	Point(s)
Orientation*	Orientation to year, month, city, hospital	4
Naming	Ability to name 3 objects e.g. point to clock, pen, button	3
Following commands	Ability to follow simple commands e.g. "Show me 2 fingers" or "Close your eyes and stick out your tongue"	1
Writing	Ability to write a standard sentence e.g. "Our national bird is the bald eagle"	1
Attention	Ability to count backwards from 100 by 10	1

Table 3: Immune Effector Cell-Associated Encephalopathy score

Scoring: 10, no impairment; 7-9, grade 1 ICANS; 3-6, grade 2 ICANS; 0-2, grade 3 ICANS; 0 due to patient unarousable and unable to perform ICE assessment, grade 4 ICANS.

Source: Lee et al. 2019.

Tips for the Intensivist

Consensus grading system

The new classification aimed to simplify and streamline the grading system, and has enabled comparison of outcomes and adverse events between CAR T products. Its use is not without caveats, which become very important when assessing the severity of CRS/ ICANS and hence the appropriate response.

For patients to be graded as level 3 of CRS, vasopressor use, with or without vasopressin is required. However, there is significant difference between patients that receive vasopressin and those that don't, as in many institutions use of vasopressin signifies catecholamine-resistant/ refractory shock. These patients will be at risk of significant mortality and expedited ICU admission and initiation of rescue therapies should be escalated rapidly. Furthermore, the lack of differentiation in the consensus grading system between patients on low-dose single vasopressor vs high dose noradrenaline plus high dose vasopressin should be noted. Currently, both patients are classified as grade 3 and their treatment includes varying doses of steroids. Early identification of deteriorating patients (irrespective of the grade) should lead to timely escalation of treatment and hopefully prevent further deterioration.

The same caveats need to be considered regarding oxygen requirements for patients with grade 3 and 4 CRS. Those requiring high-flow nasal cannula, which is defined as oxygen delivered at > 6 L/min, are classified as grade 3, whereas patients in need of positive pressure ventilation (whether invasive or not) are grade 4. However, no mention is made of high flow nasal cannula oxygen (HFNCO) therapy, the relatively novel strategy of respiratory support that can supply high flow (up to 60 L/min) of heated and humidified gas with an adjustable inspiratory fraction of

oxygen up to 100%, through a dedicated nasal cannula. Under the consensus classification, a patient requiring 100% via HFNCO is considered less critical than one on 40% CPAP, with the potential delays in escalating interventions mentioned above.

Differential diagnosis

Patients treated with anti CD19 CAR T for B-cell haematologic malignancies are at high risk of infection due to prior cytotoxic treatments, development of CRS, the risk for prolonged cytopenia and B-cell aplasia with associated hypogammaglobulinemia. Approximately 20–40% of patients develop infections within the first month after CAR T therapy despite antimicrobial prophylaxis, with bacterial and viral microorganisms being the most common culprit, followed by fungal infections (Hill et al. 2018). Since microbiologically documented infection at admission to ICU has been associated with increased mortality (Azoulay et al. 2021), diagnosing infection is critical and extensive diagnostic workup should be carried out during ICU admission. Despite that, differentiating CRS from sepsis can be very challenging and empirical antibiotics should always be started, especially since laboratory tests like CRP become uninterpretable after administration of tocilizumab.

Limitation of life-sustaining treatment

CAR T therapy has significantly improved the prognosis of patients with r/r lymphomas, without which their median survival would not exceed 6 months. The ICU and hospital mortality of patients treated with CAR T were reported as 5.8% and 14.9% respectively (Azoulay et al. 2021), lower than those quoted for patients with haematological malignancies admitted in ICU without having received CAR T cells. Nonetheless, and with the expected extension of the therapy in other types of haematological but also solid tumours, the

number of patients being treated and hence developing toxicities and requiring ICU will increase. A number of these patients will be critically ill, with a proportion not responding to CAR T therapy, and continuing to have limited life expectancy despite aggressive treatment. Deciding who will benefit from continuation of ICU treatment is difficult, as response cannot be assessed until 3–4 weeks post infusion whereas the toxicities appear hours or days post therapy. Close collaboration between intensivists and haematologists, as well as open communication with and expectation management of patients and their families are paramount to ensure that treatment is administered appropriately and in accordance with patient wishes.

Take-Away Messages

- CAR T therapy prolongs survival in patients with end-stage B-cell malignancies.
- Common toxicities include Cytokine Release Syndrome (CRS) and Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS).
- Treatment for CRS includes the IL-6 receptor antagonist, tocilizumab and corticosteroids.
- Tocilizumab is not the treatment for ICANS; corticosteroids are first-line treatment
- Higher grade toxicities should be managed in ICU.
- Close collaboration between intensivists and haematologists is necessary to ensure that treatments are administered according to patient wishes.

Conflict of Interest

Victoria Metaxa and Tasneem Pirani have received speaker fees from Kite/Gilead. Neeraj Singh and Rohit Saha have no conflict of interest. ■

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🐦 ICUnutrition

The worldwide pandemic of COVID-19 continues to impact all aspects of intensive care unit (ICU) management, including nutritional care (Minnelli et al. 2020). Nutritional guidelines based on expert opinions have been rapidly released and endorsed by professional societies of nutritionists or dietitians. These recommendations were formulated in the absence of interventional studies specifically dedicated to patients admitted in an ICU with COVID-19 and are largely based on existing guidelines for nutrition care in critically ill patients without COVID-19 as well as expert consensus based on clinical characteristics of COVID-19. Many different aspects of nutrition care are addressed (**Figure 1**). A recent summary review of the guidelines available in English was published in August 2021 which discusses the following issues (Chapple et al. 2021):

Nutritional Care For Patients With COVID-19 Requiring Intensive Care

Recommendations for the management of nutrition of COVID-19 patients provide guidelines for nutrition risk screening, requirements, timing, route and mode of feeding, monitoring, equipment and workforce requirements.

Nutrition Risk Screening

An assessment of nutrition risk is recommended by most guidelines, using validated tools combining anthropometric, clinical and lab data. The recommended tools to assess nutrition risk vary between guidelines, as a reflection of the differences of local practices.

In addition to the scores given by nutrition risk tools, extreme values of body mass index (BMI) are associated with increased morbidity and mortality. A J-shaped curve linking BMI with in-hospital mortality rate have been reported (Huang et al. 2020). Obesity is associated with a respiratory insufficiency likely exacerbated by a COVID-19 pneumonitis or respiratory

complication that may increase the need for ventilatory support and hospital stay (Chetboun et al. 2021). The association between obesity and higher mortality has been reported by some (Gao et al. 2021; Du et al. 2021; Hendren et al. 2021), but not all investigators (Ullah et al. 2021; Deng et al. 2021). Interestingly, the abundance of ACE (angiotensin converting enzyme)-2 receptors in the adipose tissue can explain the high prevalence of severe forms of COVID-19 in obese patients, as a result of the prolonged residence of SARS-CoV-2. In particular, the amount of visceral fat has been reported as a risk factor for poor outcome (Huang et al. 2020; Földi et al. 2021). From a nutritional perspective,

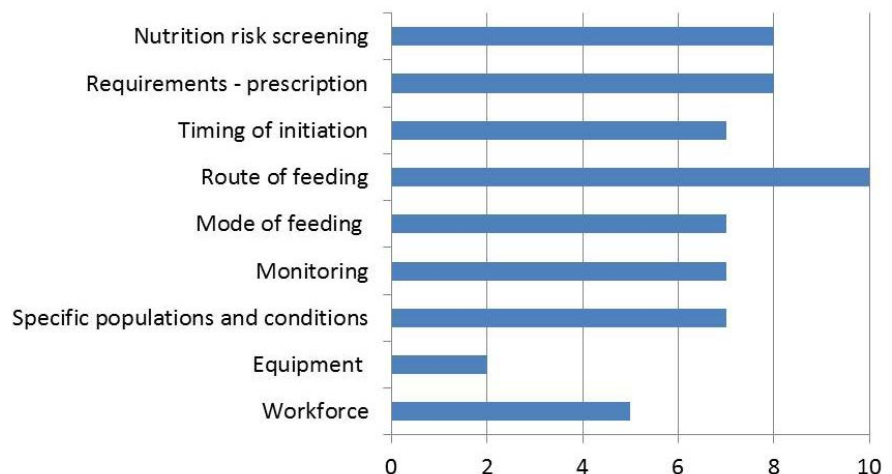


Figure 1: Aspects of nutrition care

there is no reason to manage obese patients differently than non-obese. The adjusted weight is recommended to calculate the nutritional intakes (Singer et al. 2019).

A potential association between a low BMI and mortality of patients hospitalised for COVID-19 has been less extensively scrutinised (Caccialanza et al. 2021; Ochoa et al. 2020). Underweight and especially malnourished patients facing an acute inflammation such as COVID-19 can experience more frequent complications related to refeeding syndrome, muscle weakness and immune deficiency. Older age, male gender and chronic diseases (with or without inflammatory component) are known risk factors for both malnutrition (Cederholm et al. 2019), and poor outcome after a COVID-19 infection. Furthermore, a greater muscle mass is associated with successful extubation, shorter ICU length of stay and decreased hospital mortality (Damanti et al. 2021).

Nutrition Requirements and Prescriptions

The **slow and progressive delivery** of energy and protein is recommended by all guidelines, implying that the target should be achieved by 5-7 days after admission. A typical course of energy intake recorded during the ICU stay of a cohort of patients is displayed in **Figure 2** (Hoyois et al. 2021).

Energy

Persistent hypermetabolism reflected by high energy expenditure has been reported (Whittle et al. 2020; Niederer et al. 2021) during prolonged stays in an ICU, except during the period of muscle paralysis (Karayannis et al. 2021).

However, the measurement of energy expenditure by indirect calorimetry carries a risk of staff exposure to the virus, potential spread of disease, and/or workforce related demands. Hence, only one set of guidelines recommends that indirect calorimetry is used where safely available (Barazzoni et al. 2020), whereas three other sets of guidelines recommend against the use of indirect calorimetry (Martindale et al. 2020; Chapple et al. 2020; Campos et al. 2020). Most guidelines provide recommendations on the prescription of energy using a predictive equation. As high doses of sedative agents can be required in ventilated patients, the amount of non-nutritional calories from propofol and glucose administration can be high and these calories need to be considered in the calculation of energy balance, understanding that this is likely to negatively impact protein and micronutrient provision.

Proteins

Most guidelines recommend using a high protein formula to achieve protein doses

of 1.2-1.5 g/kg/day based on expert consensus and small observational studies in critically ill patients without COVID-19 (**Figure 3**) (Fadour et al. 2020).

Micronutrients

Although not discussed in the available guidelines, there is a major enthusiasm for the use of vitamins and trace elements in patients with COVID-19 following the association of low vitamin C, D and zinc levels and poor outcomes. Interventional trials assessed the effects of high doses of these micronutrients. Overall, vitamin C and zinc supplementation did not improve the outcome, while oral vitamin D supplementation decreased the need for ICU admission, induced a faster negativity of SARS-CoV-2 tests and even mortality in one study (Speakman et al. 2021). This requires further investigation. At a minimum, micronutrients to the recommended dietary intakes should be provided and supplementation considered in patients who stay for extended periods or who have considerable nutrition inadequacy.

Timing of Initiation

Most guidelines recommend an early initiation of enteral nutrition within 48 h of admission, at least at a minimal trophic rate including in patients receiving low or decreasing doses of vasopressors.

Route of Feeding

Most guidelines recommend the enteral route (oral or enteral nutrition (EN)) in preference of parenteral nutrition (PN) for nutrition therapy, via the nasogastric (NG) route.

The delivery of EN can be impaired by gastrointestinal (GI) dysfunction during the ICU stay (Hoyois et al. 2021). The limited tolerance to EN can be related to a dysfunction of GI tract, reflected by the high prevalence of GI symptoms upon admission or during the ICU stay in COVID-19 patients (Kariyawasam et al. 2021; Blaser et al. 2021a; Drake et al. 2021) and frequent

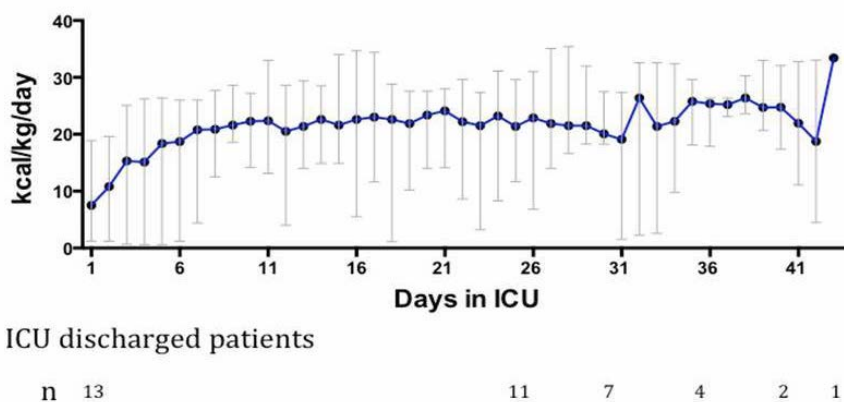


Figure 2: Nutritional intake in ICU during phases of critical illness. Source: Hoyois et al. 2021

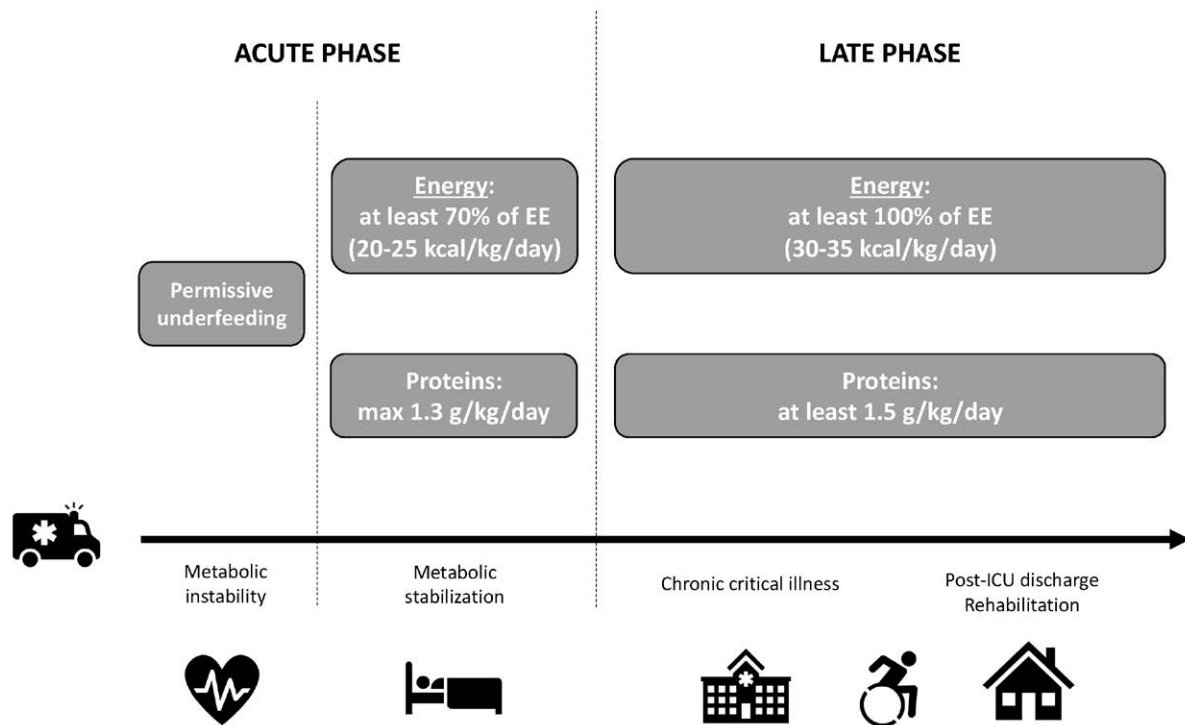


Figure 3: Calories and proteins provision by oral route. Source: Fadeur et al. 2020.

GI complications reported. Moreover, the significant need for NMB agents and prone positioning to aid ventilation can also impair GI intolerance. Notably, the presence of GI symptoms has been associated with higher illness severity, reflected in a higher need for hospital admission, ICU admission and intubation, even after adjustment for demographics, comorbidities, and other clinical symptoms (Bishehsari et al. 2021). Cytotoxic enterocyte injury and microvascular injury and thromboinflammation have been incriminated (Blaser et al. 2021a). Hence, EN should be withheld and gradually recommenced upon patient stabilisation in the case of uncontrolled shock and haemodynamic instability.

Mode of Feeding

Six guidelines recommend continuous EN, as this mode is easier to manage and could be associated with a lower risk of diarrhoea and less frequent patient interaction for staff with continuous EN, decreasing

exposure of healthcare professionals to COVID-19.

Monitoring

Gastric residual volumes

Seven guidelines make recommendations around the use of gastric residual volumes (GRVs) to monitor EN tolerance using cut-off values of 300-500 ml. However, as acknowledged in most guidelines, the routine monitoring of GRVs may be unreliable to detect delayed gastric emptying, can impact nutrition delivery if EN is stopped or reduced unnecessarily, and may be a risk of viral transmission to the healthcare provider. In the absence of GRV measurement, other clinical features of EN intolerance including abdominal distension and regurgitation should be closely monitored (Blaser et al. 2021b).

Electrolytes

Four guidelines mention that re-feeding syndrome risk should be considered in criti-

cally ill patients admitted with COVID-19, as poor appetite and intake and GI symptoms are common prior to and during hospital admission. These guidelines recommend close monitoring and replacement of potassium, phosphate, and magnesium when commencing nutrition support (Boot et al. 2018).

Nutrition adequacy

To prevent under- or over-feeding, the majority of guidelines recommend close monitoring of nutrition adequacy (energy and protein delivery compared to estimated or measured requirements). This is particularly true in the setting of a pandemic where normal models of care are disrupted and the risk for nutrition failure is significant.

Specific Patient Populations and Conditions

Prone positioning

Early and continuous EN is recommended,

while patients are in the prone position. Patients in the prone position may have increased GI intolerance, and prokinetics and insertion of post-pyloric tubes should be considered as necessary. PN may be needed in cases of significant EN intolerance and nutrition deficit.

Extracorporeal membrane oxygenation

Three guidelines make specific recommendations for patients receiving extracorporeal membrane oxygenation (ECMO) including early EN in this patient group. Patients on ECMO are likely to have high metabolic needs (e.g. after ICU day 5 up to 30 kcal/kg and 1.5–2 g protein/kg day in normal-weight individuals).

Non-intubated critically ill patients

Seven guidelines make recommendations for non-intubated patients. The overarching theme is that these patients are at high nutrition risk and that a high energy and high protein diet and oral nutrition supplements should be provided. Escalation to EN should

occur if energy and protein intakes are inadequate (e.g. meeting <50–65% targets after 5 days). Some guidelines specifically recommend avoiding early removal of NG tubes post extubation.

Equipment Considerations

Two guidelines recommend assessment of equipment needs early and development of plans in the event of equipment (e.g. feeding pumps and delivery lines) and nutrition formula shortages.

Workforce Recommendations

Two guidelines make specific recommendations regarding dietetic workforce capacity during the COVID-19 pandemic. This includes rapidly identifying additional staff who could be upskilled in the case of significant admission numbers or staff sickness (such as the use of appropriately trained allied health assistant staff, or training of dietetic staff who have transferable skills in specific ICU nutrition processes).

It is also recommended that training be commenced early with an appropriate education package that has been developed by an experienced critical care dietitian, and that the most experienced critical care dietitians see the sickest patients. Five guidelines mention the use of remote working processes to protect staff from infection risk of COVID-19.

In summary, most available recommendations do not differ from guidelines for the management of general ICU patients although the risk of contamination supports the avoidance of unnecessary invasive manipulation. The level of evidence supporting these guidelines is very low in the absence of large-scale prospective studies and the appropriateness of the recommendations needs to be considered in the context it is being applied.

Conflict of Interest

None. ■

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Indirect Calorimetry in Mechanically Ventilated Patients to Assess Nutritional Targets

An overview of the physiological aspects of indirect calorimetry, its limitations in use, the available literature and future prospects for tailored nutrition.

Introduction

Medical nutrition therapy (MNT) is an essential part of patient care in the intensive care unit (ICU) setting. Similar to mechanical ventilation and haemodynamic management, nutritional intake should be individualised for each patient. Achieving energy and protein targets should be a daily concern for the ICU physician. Indeed, it is currently established that the accumulation of an energy debt is associated with an increase in morbidity and mortality in the ICU (Villet et al. 2005). In addition, insufficient protein intake may contribute to the development of ICU-acquired muscle weakness (De Janghe et al. 2009). These disabling functional sequelae may persist over the long term (Herridge et al. 2011). On the other hand, the provision of excessive artificial nutrition or 'overfeeding' may lead to infectious or metabolic complications (Elke et al. 2014; Weinsier et al. 1981).

It therefore seems pragmatic to tailor the daily intake of patients to their precise nutritional needs. These can vary significantly over the course of a stay, according to the patient's age, pre-existing comorbidities and the severity of their condition. Historically, the assessment of the energy expenditure in the ICU was based on equations that included clinical and anthropometric

data. Most of these were developed for healthy subjects to which a stress factor was applied. These assessments turned out to be highly inaccurate when compared to actual measurements in a study published in 2003. In this work, Harris and Benedict equation developed in 1918 was providing only 60% of actual energy requirements in critically ill patients (MacDonald and Hildebrandt 2003; Harris and Benedict 1918). Another strategy recommended by international guidelines was the use of fixed energy targets around 25 kcal/kg/day for ICU patients (Lefrant et al. 2014; McClave et al. 2015). However, this simplistic solution, which is supposed to suit everyone, does not take into account the individuality of patients and their specific characteristics. Given these inaccuracies, the ESPEN recommendations, published in 2018, have reshuffled the deck (Singer et al. 2019). The recommended technique for assessing nutritional requirements has evolved into the measurement of energy expenditure based on indirect calorimetry. This recommendation was made possible by technological advances allowing the development of more reliable and ergonomic tools available to the ICU physician (Oshima et al. 2020; Rehal et al. 2016). In this review we will discuss the physiological aspects of the technique, its limitations in use, the available literature and the future prospects for tailored nutrition.

Physiological Principles

The energy target is determined by the energy expenditure which can be assessed in several ways. Direct calorimetry measures heat production but require an insulated chamber which makes it unsuitable for daily patient care. Indirect calorimetry is the gold standard method for estimating energy metabolism based on gas exchange analysis. Indeed, the oxidation of substrates results in the production of energy, in the form of adenosine triphosphate, nitrogen and water. Estimating resting energy expenditure (REE) through indirect calorimetry relies on the measurements of oxygen consumption (VO_2) and carbon dioxide production (VCO_2). The use of the Weir formula can therefore be applied with the help of urinary nitrogen that reflects protein oxidation.

$$\text{EE (kcal/day)} = 1.44 \times [3.94 \times \text{VO}_2 (\text{ml/min}) + 1.11 \times \text{VCO}_2 (\text{ml/min})] - \text{urinary nitrogen (g/day)} \times 2.17$$

According to the Haldane transformation principle, nitrogen is inert and its concentration is the same in the gas inspired and exhaled by the patient. This observation eliminates the need for urine sampling which can be unreliable in ICU patients. This customisation raises the error level to less than one percent (Wilmore and Costill 1973; Weir 1949).

$$\text{EE (kcal/day)} = 1.44 \times [3.94 \times \text{VO}_2 (\text{ml/min}) + 1.11 \times \text{VCO}_2 (\text{ml/min})]$$

Indirect calorimetry also allows the measurement of the respiratory quotient (RQ) which estimates the type of substrate consumed such as carbohydrates, proteins and lipids. This ratio is measured between 0.67 and 1.3 in humans. The ratio is close to 1 for carbohydrate metabolism, 0.8 for protein and 0.7 for lipids.

$$RQ = VCO_2 / VO_2$$

By assigning the respiratory quotient to an average of 0.86 or estimating it from the nutritional intake (food quotient or nutritional quotient), energy expenditure can be estimated based on the production of carbon dioxide alone. This method, derived from indirect calorimetry, is a fair compromise that is more accurate than predictive equations but less than exhaustive indirect calorimetry (Stapel et al. 2015; Oshima et al. 2017; Kagan et al. 2018).

$$FQ = \%_{\text{protein}} \times 0.8 + \%_{\text{carbohydrates}} \times 1 + \%_{\text{lipids}} \times 0.7$$

$$EE (FQ) (\text{kcal/day}) = 1.44 \times [3.94 \times VCO_2 (\text{ml/min}) / FQ + 1.11 \times VCO_2 (\text{ml/min})]$$

$$EE_{(RQ=0.86)} (\text{kcal/day}) = VCO_2 (\text{ml/min}) \times 8.19$$

Even if the process is fully automated, the knowledge of these formulas allows a better understanding of the functioning of the indirect calorimetry machines but also of their limitations.

Indication, Repetition and Limitation

The 15th recommendation of 2019 ESPEN guidelines, which was accepted with strong consensus, states that in critically ill mechanically ventilated patients, energy expenditure should be determined by using indirect calorimetry. This decision has greatly expanded the scope of calorimeters in the ICU and has led to an evolution in our nutritional practices towards tailored prescriptions and goal-oriented therapy (Singer et al. 2019).

Nevertheless, this technique has several limitations linked with all situations that can disturb the measurement of gas exchange. The first prerequisite for reliable measure-

ments is the stability of the patient's clinical condition. This implies the absence of sudden haemodynamic or respiratory parameters variations. The second limit relies on respiratory parameters that may interfere with the gas analyser including an inspired oxygen fraction (FiO_2) higher than 70%, a respiratory rate higher than 35/min or a positive end expiratory pressure higher than 10 cmH₂O. Furthermore, the presence of any type of air leaks in the ventilator circuit or within the patient respiratory tree (bronchopleural fistula or

ESPEN guidelines state that in critically ill mechanically ventilated patients, energy expenditure should be determined by using indirect calorimetry

chest drainage) may result in an underestimation of the energy expenditure.

Finally, any variation of CO₂ stock may impair IC functioning. Continuous renal replacement therapy (CRRT) is a known factor that may cause CO₂ extraction or metabolic shift via fluid dynamics or citrate use. A recent clinical trial published by Jonckheer et al. (2020) have questioned this relative contraindication. They measured CO₂ content in the CRRT effluent liquid to estimate and correct the 'true VCO₂' used in the Weir equation. Surprisingly, the use of CRRT accounted for less than 2-3% of REE measurement error. The use of a correcting factor was then considered irrelevant (Jonckheer et al. 2020). In the same field, in critically ill patient benefiting from an extracorporeal membrane oxygenation (ECMO) therapy, Wollersheim's team suggested in a recent paper the use of the MEEP protocol to correct energy expenditure measurements based on pre- and post-membrane blood gas (Wollersheim et al. 2018).

Despite these few precautions and adjustments, use of IC remains possible in the majority of ICU patients. However, it is important to note that the measurement of energy expenditure is a reflection of energy metabolism at a given time. This value can vary significantly from one hour or one day to the next. Therefore, longitudinal assessment is advised during the ICU stay and when significant changes in clinical status occurs (Vermeij et al. 1989). For example, the incidence of sepsis was associated with a 30% increase in metabolic rate in a landmark study published in 1993 (Kreymann et al. 1993). The degree of hypermetabolism in the acute phase of severe sepsis was even associated with 28-day mortality in the ICU setting (Wu et al. 2015). This observation seems plausible given that energy expenditure is a direct reflection of the systemic inflammatory exacerbation associated with the secretion of proinflammatory cytokines and neurohormonal response. Moreover, in a study published in 2020, Li et al. demonstrated the feasibility of using indirect calorimetry to assess the metabolic capacity of nutrient assimilation in septic critically ill patients. The ability of the organism to metabolise carbohydrates after the introduction of enteral nutrition was associated with better survival in the ICU (Li and Mukhopadhyay 2020).

In addition to sepsis, other known factors have been identified for their impact on the measures (Mtaweh et al. 2019). Apart from clinical constants such as temperature, minute ventilation and heart rate, therapies inherent to organ failure management may affect calorimetric measurements. The administration of neuromuscular blocking agents is a known influencing factor. A recent cohort study observed a significant decrease in energy expenditure in mechanically ventilated patients treated with continuous infusion of cisatracurium (Koekkoek et al. 2020). The same findings were observed with the use of deep sedation such as midazolam or analgesia with opiates in ICU patients (Swinamer et

al. 1988; Terao et al. 2003). Furthermore, obese patients have very heterogeneous energy requirements, even with identical body mass index. The use of adjusted body weight, recommended by various experts groups, can regularly be associated with an overestimation of actual needs (Ridley et al. 2020). This justifies conducting repeated measurements of energy expenditure and paying particular attention to the prevention of skeletal muscle loss.

The value of longitudinal measurement has been highlighted recently by the LEEP-COVID project coordinated by Paul Wischmeyer's team, whose preliminary results have been published. In 22 patients with severe COVID, repeated measurements of energy expenditure showed high, rising and persistent hypermetabolism for up to three weeks after intubation (Whittle et al. 2020). This prolonged metabolic exacerbation could explain the muscle damage and the severity of functional sequelae in COVID survivors (Van Aerde et al. 2020). The underestimation of actual energy expenditure was already known in other pathologies associated with marked systemic inflammation such as acute pancreatitis or peritonitis (Valainathan et al. 2019; Plank et al. 1998). These measured values, sometimes far above the expert recommendations for caloric provision, raise concerns and may justify broader use of indirect calorimetry. Furthermore, this great variability in daily values goes against the pattern historically described by Cuthbertson in 1942 of an initial 'ebb phase' followed by a 'flow phase' supposed to describe the majority of intensive care stays (Cuthbertson et al. 1942). The day-to-day use of calorimetry not only allows us to adapt nutritional intake to the real needs of critically ill patients, but also to understand more accurately their metabolic patterns resulting from the progression of their condition.

From Energy Expenditure to Caloric Target

ESPEN guidelines state that if indirect

calorimetry is used, isocaloric nutrition rather than hypocaloric nutrition can be progressively implemented after the early phase of acute illness. During the early phase, it is suggested to administer hypocaloric nutrition not exceeding 70% of EE and slowly increase up to 80-100% after day 3 (Singer et al. 2019).

This recommendation is based on a recent study by Zusman et al. (2016) analysing data from 1171 patients who benefitted from energy expenditure measurements by indirect calorimetry. A ratio of administered

the measurement of energy expenditure via indirect calorimetry constitutes a major advance in the era of individualised evidence-based medicine

calories to energy expenditure between 60% and 80% was associated with the lowest mortality, length of stay and duration of mechanical ventilation. This result is consistent with the findings of Arabi et al. (2015) who demonstrated the non-inferiority of a permissive, normo-protein hypocaloric strategy in the first week of the ICU stay.

The gradual increase in energy target during the acute phase makes sense since the initial caloric intake adds to the endogenous production of energy from proteolysis, lipogenesis and gluconeogenesis. Excessive initial intake would be considered as overfeeding, which is known to be associated with metabolic and infectious complications.

Benefit on ICU Outcomes

The main focus in the last few years has been to determine whether monitoring energy expenditure and providing individualised nutritional prescriptions can improve the outcome of intensive care patients.

In 2011, Singer et al. published one of the landmark studies investing indirect calorimetry. This randomised controlled trial included 130 mechanically ventilated patients with a length of stay greater than 3 days. Daily caloric intake was prescribed according to energy expenditure assessed by indirect calorimetry or based on a fixed dose of 25 kcal/kg/day. Regarding in-hospital mortality, the primary endpoint, a trend in favour of indirect calorimetry guided strategy was observed ($p=0.058$). Nevertheless, there was a significant reduction of the length of stay and duration of mechanical ventilation (Singer et al. 2011). The TICACOS international follow-up study was published in 2021 and included 7 sites and 417 patients. The use of energy expenditure measurement compared to a fixed target significantly increased caloric and protein intakes without significantly influencing morbidity and mortality in participants (Singer et al. 2021).

The EAT-ICU study published in 2017 aimed to demonstrate the superiority of 'early goal' approach management with an early achievement of caloric targets estimated by indirect calorimetry. Unfortunately, this strategy was not associated with any benefit on the mental or physical outcome of the participants (Allingstrup et al. 2017).

A recent meta-analysis published in 2021 by Duan et al. included eight randomised controlled trials evaluating the clinical impact of energy prescription based on expenditure measurement by indirect calorimetry. A significant beneficial effect on short-term mortality was found in the 991 critically ill patients included. However, no significant effect was observed regarding duration of mechanical ventilation and length of stay (Duan et al. 2021).

Several reasons may be suggested to explain the lack of clear evidence of the benefit of indirect calorimetry guided nutrition in the literature. On one hand, an individualised assessment of nutritional needs is maybe not necessary for all critically ill patients including short stays and

illnesses associated with low nutritional risk. Heyland et al. (2011) developed the NUTRIC score in order to distinguish the patients who would benefit most from optimising their nutritional intake. One line of research could be to assess the impact of individualised nutrition based on indirect calorimetry in at-risk patients with a NUTRIC score strictly higher than 4.

On the other hand, individualised energy target alone may not be sufficient to influence patient outcome. The answer may lie in the importance of the proportion of calories related to protein intake. Several methods are available to the ICU physician for estimating anabolic/catabolic balance and skeletal muscle loss. The most frequently cited technique in the literature is the measurement of the nitrogen balance calculated from the difference between excreted (urinary and non-measurable) and ingested nitrogen; the result is obtained from the analysis of 24-hour urine (Danielis et al. 2019). Nevertheless, its measurement may be affected by the occurrence of renal failure or major fluid movements. Bioimpedance and radiological measurements by ultrasound or tomography are paths of research to explore in the longitudinal follow-up of our critically ill and post-ICU

patients (Thibault et al. 2016; Pardo et al. 2018; Dusseaux et al. 2019). None of these techniques have yet shown clear benefit in guiding the prescription of tailored protein intakes. Until a reliable, repeatable, non-invasive technique is available, ESPEN advises progressive prescription of protein intake with a target of 1.3 g/kg/day (Singer et al. 2019). This progressive approach seems crucial in view of a study published in 2019 which demonstrated better survival in patients receiving less than 0.8g/kg/day before D3 and more than 0.8g/kg/day after 3 days (Koekkoek et al. 2019).

Finally, the choice of endpoints considered to be sufficiently hard, such as mortality and length of stay, may not be the most appropriate for the evaluation of nutritional practices. In this field, the selection of a functional primary endpoint was very rare in a recent pragmatic study (Taverny et al. 2019). However, this observation seems to be challenged in recent studies such as EAT-ICU where the primary endpoint was the physical component of the SF-36 quality of life score (Allingstrup et al. 2017). Similarly, in an ongoing trial evaluating the combination of physical exercise and high-protein intake, the primary endpoint is physical functioning at hospital discharge

(Heyland et al. 2019).

Conclusion

The spread of the measurement of energy expenditure via indirect calorimetry constitutes a major advance in the era of individualised evidence-based medicine for each patient. The development of longitudinal monitoring of metabolic activity and the evaluation of substrate consumption via the analysis of the respiratory quotient are promising aspects that should be the subject of future clinical trials. Large-scale trials evaluating the impact of indirect calorimetry on functional endpoints would certainly contribute to the debate. Moreover, the conduct of medico-economic studies justifying the purchase of these expensive machines would constitute a strong signal for the future of critically ill patient nutrition care (Arabi et al. 2017). In the meantime, given its ease of use when available, bedside use of indirect calorimetry should be encouraged to move towards personalised medicine in the intensive care unit.

Conflict of Interest

None. ■

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- 1-3** DIVI 2021 - German Interdisciplinary Association for Intensive Care and Emergency Medicine Congress
Virtual event
<https://iii.hm/1dcs>
- 5-8** Critical Care Canada Forum 2021
Virtual event
<https://iii.hm/1dct>
- 6-8** ICS State of the Art 2021
Virtual event
<https://iii.hm/1dcu>
- 17-19** Euroanaesthesia 2021
Virtual event
<https://iii.hm/1dcv>

2022 JANUARY

- 3-7** Blood Diseases in the ICU: Advance Training 2022
Paris, France
<https://iii.hm/1dcw>
- 13-15** Society for Technology in Anesthesia Annual Meeting 2022
Virtual event
<https://iii.hm/1dcx>
- 28-30** ASA® ADVANCE 2022: The Anesthesiology Business Event!
Dallas, Texas, USA
<https://iii.hm/1dcy>

FEBRUARY

- 6-9** SCCM - 51st Critical Care Congress
San Juan, Puerto Rico
<https://iii.hm/1dcz>
- 17-19** 6th International Trauma Congress ITC 2022
Dubai, UAE
<https://iii.hm/1dd0>

MARCH

- 22-25** 41st ISICEM
Brussels, Belgium
<https://iii.hm/1dd1>

APRIL

- 23-26** 32nd ECCMID
Lisbon, Portugal
<https://iii.hm/1dd2>
- 27-30** 12th Congress of the European Pain Federation (EFIC 2022)
Dublin, Ireland
<https://iii.hm/1dd3>
- 28-29** 18th Annual Critical Care Symposium
Manchester, UK
<https://iii.hm/1dd4>

ICU

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