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Jean-Louis Vincent

Editor-in-Chief
ICU Management & Practice
Professor
Department of Intensive Care
Erasme Hospital
Université libre de Bruxelles
Brussels, Belgium
JLVincent@icu-management.org
[@ICU_Management](#)

Organ Support

When patients are critically ill, one or more organs may not function optimally or even fail, so organ support is an important component of ICU management.

However, organ support can be associated with complications such as infections, bleeding, and damage to surrounding tissue or organs. These complications can alter the patient's condition, leading to additional interventions or treatments. Critical care teams need to manage these challenges. Other factors also need to be considered, for example, the financial burden on patients, families and healthcare systems, limited availability of the necessary equipment or trained personnel, patient comfort when using the interventions and the ethical considerations when organ support can only prolong the dying process or result in a very poor quality of life.

Addressing these challenges requires a multidisciplinary approach. Clear communication, shared decision-making, and ongoing assessment and monitoring of the patient's condition are essential to providing effective and appropriate organ support to critically ill patients.

In this issue, our contributors discuss progress in the management of multiorgan failure and different forms of **organ support** and treatment strategies for acute kidney injury, respiratory failure, cardiac failure and liver failure. As always, if you would like to get in touch, please email JLVincent@icu-management.org.

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Biomarkers as Prognostic Predictors and Guide in Critically Ill Patients

An overview of promising biomarkers in critical care, characteristics a biomarker should have and how to ensure their usefulness in clinical practice.

Introduction

Precision medicine is a medical approach that tailors treatments based on individual patient characteristics and their unique response to therapies for a particular disease. The goal of precision medicine is to achieve accuracy in both diagnosis and treatment using innovative clinical and laboratory tools (Collins and Varmus 2015).

Biomarkers play a crucial role in precision medicine as they enable personalised treatment based on a patient's specific needs (von Groote and Meersch-Dini 2022). Biomarkers can be objectively, systematically, and accurately measured in a biological sample. Their levels can indicate whether a biological process is normal or pathological. An ideal biomarker should be easy and cost-effective to measure while having high sensitivity and specificity. Additionally, it should provide clinical assessments with supplementary information (Moons 2010).

Six steps have been proposed to progressively evaluate new biomarkers before their integration into clinical practice (Hlatky et al. 2009). These include:

1. Proof of concept: Is there a significant difference in levels of the new biomarker between subjects with different perioperative outcomes?
2. Prospective validation: Can the new biomarker predict the likelihood of certain outcomes in prospective studies?
3. Incremental value demonstration: Does the new biomarker provide additional predictive information to standard risk markers?
4. Clinical utility: Can modifying the levels of the new biomarker predict risk when changing the

recommended therapy?

5. Improved clinical outcome: Does the new biomarker lead to improved clinical outcomes?
6. Cost-effectiveness: Is the use of the new biomarker cost-effective, given the improvement in clinical outcomes?

Promising Biomarkers in Intensive Care

Many biomarkers are potentially interesting, some already integrated into clinical practice, while others require more validation.

C-Reactive Protein (CRP) is a widely used clinical marker to detect infection and sepsis. It is used to diagnose intra-abdominal infections (Kørner et al. 2009), pneumonia, and tracheal infections. It can also aid in differentiating bacterial infection from viral. Elevated CRP levels have been linked to an increased risk of organ failure and mortality in critical patients (Travlos et al. 2022). CRP concentrations have been used as a biomarker of infection in septic patients with community-acquired pneumonia or ventilator-associated pneumonia and to monitor bacterial load and appropriate antibiotic therapy. However, compared to other biomarkers, CRP rises late, takes time to recover normal values and can also increase in non-infectious processes.

Interleukins are cytokines that modulate and originate an immune response by carrying signals to neighbouring cells. Interleukin-6 (IL-6) is a biomarker with pro-inflammatory and anti-inflammatory activity, and its levels rise after surgery, trauma, or critical illness. Elevated IL-6 levels have been linked to adverse outcomes, and thresholds vary between systemic

inflammatory response syndrome, sepsis, and septic shock. In addition, IL-6 levels can be used to stratify patients for therapeutic intervention (Jawa et al. 2011). IL-6 is also used as a biomarker of COVID-19 severity, and its levels have been used to decide on the administration of immunosuppressive treatment for cytokine storms (Kavanaugh 2008).

The urokinase-like soluble plasminogen activator receptor (suPAR) is a biomarker associated with cancer and infections, and its level reflects the degree of immune activation in the patient. Studies have shown that suPAR levels are associated with higher mortality in critical patients with sepsis and serious infectious pathology. However, suPAR is elevated in patients with other diseases and cannot discriminate sepsis from other pathologies, making its interpretation nonspecific (Huang et al. 2020).

Presepsin is a soluble subtype of the CD14 glycoprotein expressed on the surface of monocytes and macrophages. CD14 is the receptor of protein-bound lipopolysaccharide complexes, which translates signals of endotoxins released by gram-negative bacteria, leading to the release of cytokines (Zou et al. 2014). Its elevation implies the activation of monocytes and macrophages by an inflammatory or infectious stimulus, with elevated levels in the early stages of sepsis. Elevated presepsin has also been associated with major cardiovascular and perioperative cerebrovascular complications in high-risk patients undergoing noncardiac surgery (Handke et al. 2019) and proposed as a biomarker for predicting mortality in cardiac surgery (Clementi et al. 2019).

Dipeptidyl peptidases (DPPs) are a class of enzymes involved in various cellular activities and physiological functions. DPP3 is an enzyme that inactivates angiotensin II, a hormone crucial in haemodynamic balance and heart function. The release of DPP3 into the blood leads to haemodynamic instability and cardiac dysfunction. High levels of circulating DPP3 are associated with reduced cardiac output, multi-organ failure, and circulatory shock (Ye et al. 2022). Elevated blood levels of DPP3 are observed in septic shock, and low or decreasing levels of DPP3 in the first 24 hours of ICU admission predict improved organ function and better outcomes. DPP3 is considered a promising biomarker for shock diagnosis and stratification and for guiding haemodynamic and shock therapy (Takagi et al. 2020).

Pancreatic Stone Protein

Pancreatic stone protein (PSP) was initially identified as a molecule that inhibits the growth of calcium carbonate crystals in pancreatic juice. PSP has also been associated with pathological changes in the pancreas during inflammation (Eggimann et al. 2019). In experiments with rats, PSP was found to be an indicator of systemic stress, which numerous studies have since confirmed. The pancreas responds to remote organ damage and systemic stress by secreting PSP, particularly in cases of serious infectious complications and sepsis, as PSP may activate neutrophils and promote bacterial aggregation (Reding et al. 2017). The normal levels of PSP in healthy individuals are 10.4 ng/mL (7.5–12.3). PSP is a promising biomarker for early diagnosis of infections in hospitalised patients, using a cut-off value of 44.18 ng/L (Prazak et al. 2021). PSP values can be obtained through the point-of-care Platform Abioscope®. Elevated PSP levels have predicted the onset of sepsis before

clinical manifestation in several scenarios, including trauma and cardiac surgery (Pugin et al. 2021). Additionally, PSP can aid in patient stratification based on severity (Lopes et al. 2022).

Future Outlook

The positioning of numerous biomarkers will require validation (Pierrakos et al. 2020; Vincent et al. 2020). In critical and perioperative medicine, as in oncology, precision medicine aims to personalise and improve the precision of treatments to enhance outcomes (Ware 2017). To achieve this goal, panels of biomarkers, biomarker scaling, point-of-care biomarker testing, therapies tailored to control biomarkers with specific biological effects that impact outcomes, and the development of systems biology and genomics will all improve the accuracy, speed, and efficiency of patient care.

Point of Care (PoC) devices are becoming increasingly common in perioperative and ICU settings. These devices typically include equipment for blood gas, haematimetry, basic biochemistry, and coagulation tests. There is growing interest in developing cost-effective biomarkers in PoC that can provide quick results and can be easily obtained by clinicians when needed. A successful PoC biomarker should be affordable, sensitive, specific, easy to use, fast, robust, and effective (Rhee and Kahn 2010). A reliable PoC biomarker in surgical and ICU settings would provide valuable information about high-risk patients and could supplement the information provided by standard clinical, monitoring, and analytical variables (Vincent et al. 2020).

Biomarkers play a key role in implementing precision medicine in the ICU, but their precise role may be more fully defined in the coming years (Póvoa et al. 2023). Developing biomarkers alongside clinical phenotyping, systems biology, arti-

ficial intelligence, and big data analysis are future challenges that must be addressed to advance precision medicine (Seymour et al. 2017). It is important to acknowledge that biomarkers are useful in infection and congestion in critically ill patients and perioperative risk stratification. In the future, therapies associated with deficits of specific biomarkers will be available, and biomarkers will describe phenotypes associated with prognosis and the usefulness of specific therapies. Clinicians must understand the advantages and limitations of biomarkers for rational and effective use. The development of more specific biomarkers, point-of-care biomarkers, and panels of biomarkers, along with clinical or genetic data, will shape prognosis in intensive and perioperative care in the future (Méndez Hernández and Ramasco Rueda 2023).

Key Points

- Biomarkers play a crucial role in precision medicine as they enable personalised treatment based on a patient's specific need.
- Six steps have been proposed to progressively evaluate new biomarkers: proof of concept, prospective validation, incremental value demonstration, clinical utility, improved clinical outcome and cost-effectiveness.
- Pancreatic Stone Protein (PSP) is a promising biomarker for early diagnosis of infections in hospitalised patients.
- Elevated PSP levels have predicted the onset of sepsis before clinical manifestation in several scenarios, including trauma and cardiac surgery.
- PSP values can be obtained through the point-of-care Platform Abioscope®.

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References

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Silvia De Rosa

Centre for Medical Sciences
- CISMED
University of Trento
Trento, Italy

Anaesthesia and Intensive
Care
Santa Chiara Regional Hospital
APSS Trento, Italy
silvia.derosa@unitn.it



Etrusca Brogi

Department of Anaesthesia
and Intensive Care
University of Pisa
Pisa, Italy

etruscabrogi@gmail.com



Francesco Forfori

Department of Anaesthesia
and Intensive Care
University of Pisa
Pisa, Italy

francesco.forfori@unipi.it

Introduction

Extracorporeal membrane oxygenation (ECMO) is a widely recognised lifesaving support strategy for the management of patients with severe heart or/and lung failure of various aetiologies. ECMO finds its place when other conventional therapeutic strategies fail (Eckman et al. 2019). Providing support of the lung and/or the heart function, ECMO is a heart and/or lung bridge therapy for resting or replacing organ functioning.

According to the Extracorporeal Life Support Organisation (ELSO) Registry, ECMO patients are at high risk of Acute Kidney injury (AKI); the incidence ranges from 20% to as high as 85% in specific populations (i.e., neonates with congenital diaphragmatic hernia or congenital heart disease). This high variation in reported incidences is based on differences in patients' characteristics, clinical settings and the use of diverse methods to outline AKI (Ostermann and Lumlertgul 2021).

During artificial organ support, the

Combined Extracorporeal Lung and Kidney Support in Fluid Overload

During artificial organ support, kidney injury is multifactorial and related to the high severity of patients treated with extracorporeal membrane oxygenation (ECMO). The successful delivery of continuous renal replacement therapy (CRRT) during ECMO requires a clear prescription of the target solute clearance and fluid removal rate based on the cumulative fluid balance and physiological variables. The role of CRRT and the optimal time, modality, and dose still need clarification.

kidney injury is multifactorial and particularly related to the high severity of patients treated with ECMO and the lung-kidney (Gu et al. 2021). Indeed, additional circuit-related risk factors for AKI during ECMO system are represented by non-pulsatile blood flow, blood exposure to the artificial surfaces of ECMO circuit, red cell stress, haemolysis, bleeding, coagulopathy, limb ischaemia, and infection. Even more, patients requiring ECMO with high blood flows are particularly prone to develop fluid overload (FO) that is associated with prolonged use of ECMO and AKI (Patil and Salunke 2020).

Fluid balance (FB) is a fundamental aspect of critical care practice and the association between FO and worse outcome is widely recognised in intensive care (Samoni et al. 2016). For this reason, the assessment of the hydration status, for a tailored FB, represents a central and critical aspect of patients' management (Kalantari et al. 2013). Although volume resuscitation strategy is indispensable for the intravascular volume preservation and organ perfusion, salt and water intake excess can lead to tissue oedema, increasing venous pressure with consequent altered renal blood flow, contributing to ongoing organ dysfunction (Ostermann et al. 2014). Nevertheless, FO plays a well-known negative impact on lung function and recovery. A tight FB evaluation may allow the administration of adequate nutrition and blood produc-

tion avoiding further fluid accumulation with less diuretic intake. Consequently, conservative fluid administration and strategy to prevent or treat FO are essential in critically ill patients, likewise, in ECMO patients (Silversides et al. 2017).

Major indications for renal replacement therapy (RRT) during ECMO are represented by prevention of FO (16%), treatment of FO (43%), AKI (35%) and electrolyte imbalance (4%) (Fleming et al. 2012). RRT during ECMO is usually provided as a continuous modality (CRRT) because of the haemodynamic instability characteristic of such patients. CRRT allows a more constant and reliable fluid elimination and electrolyte adjustment over a longer period of time. ECMO and CRRT can be combined in two main modalities; parallel approach vs integrated application (Martins-Costa et al. 2022). The choice of the modalities is influenced, generally, by local experience and technical availability. Both techniques present advantages and disadvantages and it is vital to know the drawback and the potential of such technologies before CRRT initiation (Ostermann et al. 2018).

Central aspect of effective delivery of CRRT during ECMO is represented by a clear prescription of the target solute clearance and fluid removal rate with regular reassessment and re-adjustment of the prescription based on the changing needs of the patient (Tandukar and Palesvsky

2019). Finally, while the deleterious impact of AKI and FO on outcomes for ECMO patients is clear, critical questions that warrant further study remain regarding the device, the modality, and the optimal timing of initiation.

Fluid Balance in Critical Care

In ECMO patients, fluid management is critical to prevent complications such as fluid overload, which can lead to oedema, hypoxaemia, and increased mortality. Particularly, positive fluid balance is associated with increased mortality, especially in patients with underlying cardiorespiratory and renal disease (Malbrain et al. 2014; Neyra et al. 2016). Several factors are responsible for fluid overload and the consequences are multisystemic. Therefore, the restoration of euvolaemia is an essential goal in intensive care settings (Kim et al. 2022). FO is also proven to increase the length of mechanical ventilation, the incidence of AKI, the need of CRRT, and the risk of infection and of intra-abdominal hypertension (Salahuddin et al. 2017). AKI, oligo-anuria, positive pressure mechanical ventilation, stress response retention of sodium and water, abdominal compartment syndrome, and iatrogenic simultaneous fluid loading are potential risk factors of FO (Wang et al. 2015). Concurrently, an inadequate fluid balance evaluation and an insufficient fluid unloading strategy may even worsen fluid retention.

The consequence of excessive fluid administration and retention leads to an expansion of interstitial space and increased venous congestion. The resulting elevated mean circulatory filling pressure, and the altered transmural pressure of the circulatory system leads to tissue oedema, severe hypoalbuminaemia, inflammatory capillary leakage and impaired lymphatic drainage that in turn may impair intra-abdominal pressure, cardiac function and pulmonary gas exchange, and also reduce lung compliance, increases the work of breathing, potentially leading to a multiorgan failure (Monnet and Teboul 2018). Additionally, venous congestion and increased intraabdominal pressure are well recognised risk factors of AKI

development, with a huge impact of fluid removal. Increased venous pressure alters renal blood flow with consequent inadequate glomerular filtration rate (Doty et al. 1999).

In order to tailor fluid balance to the needs of patients, it is also crucial to set specific treatment strategies in different clinical situations (e.g., resuscitative vs. post-resuscitative phase) to prevent or treat FO (Ramesh et al. 2019). In an intensive care setting, specific patient demands can vary quickly, and sometimes conflicting requirements may coexist (Malbrain et al. 2018). Indeed, in the acute “resuscitative” phase, fluid administration is mandatory to reach haemodynamic goals. Even more, large amounts of fluid are often required in order to meet nutrition demand or drug dosage targets. In all these situations, CRRT may represent an important aid, allowing the continuous manipulation of net fluid removal. Even if there is not a solid conclusion about the optimal timing of initiation and CRRT modality, CRRT may allow clinicians to meet the dynamic changes in a patient’s fluid requirement (Prowle and Mehta 2021). Clinicians have to evaluate at fixed intervals, the total volume of fluid that is essential to be removed, in the light of fluid administration required to meet specific needs, and of haemodynamic and volume status (Neyra et al. 2022). In order to provide precise fluid management therapy, CRRT can regulate, not only the total volume of fluid removal, but also the rate of fluid removal (Murugan et al. 2016). This is particularly important in haemodynamic unstable critical care patients, also to maintain a physiological plasma refilling rate.

Finally, another important aspect to consider is the fact that fluid administration is important for the maintenance of the patency of the CRRT circuit itself. Fluids administered before the filter (pre-dilution) can maintain circuit integrity and prevent clotting formation. Fluid balance can be achieved modifying the ultrafiltration rate and the replacement fluid, keeping in mind that the variation of the effluent volume will affect solute clearance (dose) (Claire-Del Granado and Clark 2021).

Continuous monitoring of circuit integrity is essential for optimal delivery of CRRT and patient safety.

Fluid Status Assessment in ECMO Patients

Fluid status assessment is an essential part of the management of patients undergoing ECMO therapy (Freitag et al. 2010). Although the clinical examination includes a physical examination of the patient for signs of fluid overload, precise fluid assessment and recording is extremely challenging in a critically ill setting. Daily weights could be an essential tool for fluid status assessment in patients with extracorporeal multiorgan support, but it is necessary to record the “dry body weight” (i.e., weight before fluid resuscitation) with a goal to return from the extracellular volume to normal (dry weight).

There are several formulas that can be used to assess fluid status in ECMO patients. Fluid balance can be calculated by subtracting total fluid output (urine output, insensible losses, drainage) from total fluid input (oral, intravenous, enteral). Net fluid balance could be calculated by subtracting the amount of fluid removed by ultrafiltration or haemofiltration from total fluid input. This formula can help assess the effectiveness of fluid removal therapy. In addition, cumulative fluid balance could be assessed as the sum of daily fluid balance over a defined period, such as 24 hours or 48 hours. This formula can help assess trends in fluid status over time. Extracellular fluid volume (ECFV) could be also determined by $\text{body weight} \times (1 - \text{haematocrit}) \times 0.9$. This formula assumes that the haematocrit is a good estimate of the intravascular volume. It is important to note that these formulas should be used in conjunction with clinical examination and other monitoring methods to assess fluid status accurately in ECMO patients. However, haemodynamic monitoring can help determine fluid status and guide fluid management.

Indeed, predicting fluid responsiveness is important in avoiding unnecessary fluid administration, reducing the risk of renal failure, and improving outcomes for criti-

cally ill patients. Although pulse pressure variations and stroke volume variations accurately predict fluid responsiveness during mechanical ventilation, unfortunately there is scarce evidence on fluid responsiveness assessments in patients with ECMO (Yang and Du 2014; Jozwiak et al. 2018). Luo et al. (2021) found that changes in left ventricular outflow tract velocity-time integral (ΔVTI) induced by the Trendelenburg manoeuvres could effectively predict fluid responsiveness in VA-ECMO patients.

Bedside ultrasound can be used to evaluate fluid status in ECMO patients. Non-invasive ultrasonographic assessment of skin tissue thickness seems to give further information to identify fluid shifts to the extravascular space and to guide fluid management (Sarvazyan et al. 2005; Wagner and Cotter 2021). The evaluation of the interstitial thickness measuring the distance between superficial dermis surface and the bone tissue interface in the calcaneus area with a linear array transducer is one of the proposed methods to determine hydration status. The measurement of subcutaneous tissue depth between the skin surface to the adipose-muscle boundary in four different body areas (i.e., upper anterior chest, lateral chest, lateral abdomen and anterior thigh) could be another tool to estimate FB. These methods, even if particularly

interesting, still require further evaluation.

Obviously, point of care ultrasound (POCUS) to assess volume status have gained a huge role in fluid management for intensive care specialists in the last years (Argaiz et al. 2021). However, despite the assessment of inferior vena cava collapsibility and the presence of pleural effusions that can help identify fluid overload, the use of VV-ECMO and VA-ECMO always entails presence of semi-rigid central venous cannula(s) occupying the inferior vena cava (IVC) to a variable extent, thereby limiting its collapsibility (Via et al. 2016).

In addition, the negative venous pressure that can interfere with the IVC size and respiratory dynamics, the masses compressing/occupying the vessel, vena cava filters or IVC thrombosis can equally affect physiological IVC patency and size. However, a deep description of the role of LUS and ultrasonographic haemodynamic evaluation (i.e., inferior vena cava collapsibility index – IVC CI) for fluid management is beyond the scope of this paper.

Bioelectrical impedance vector analysis (BIVA) may represent a viable promising tool that involves the measurement of electrical resistance to assess body composition, including extracellular fluid volume (Samoni et al. 2016; Basso et al. 2013). Although BIVA can reflect the fluid overload state earlier and bypass errors due

to fluid balance accounting, it is not well investigated in both ECMO and integrated systems settings (Wang et al. 2021).

Fluid Overload in ECMO Patients

Due to the severity of the underlying disease and to the intrinsic characteristic of the circuit, patients on ECMO may receive a large volume of crystalloids and blood products (Chiu et al. 2021). In order to maintain a sufficient rate of vascular blood drainage for ECMO flow, clinicians often administered large volumes of fluid especially during the initial phases of ECMO. Even more, due to the several complications that may arise during the treatment (e.g., bleeding, anaemia, coagulopathies), patients also receive an important amount of blood products. Fluid administration is important for the maintenance of the patency of the ECMO circuit and to prevent premature circuit changes. This liberal approach of fluid infusion during ECMO exacerbated the underlying disease, often characterised by systemic hypovolaemic status. Even more, blood exposure to the artificial surfaces of ECMO circuit, can worsen systemic capillary leakage, with consequent increase in interstitial and tissue oedema. To make things worse, the high concomitant prevalence of AKI in ECMO patients, reducing fluid output, aggravates fluid overload (Cheng et al. 2014).

Fluid overload can exacerbate the underlying cardiopulmonary disease and prolong cardiorespiratory recovery and time to ECMO weaning. FO during ECMO has been associated with prolonged ECMO duration and mortality (Selewski et al. 2017). Another important aspect that emerges from the existing literature is that a percentage of ECMO patients (up to 50%) present FO before ECMO cannulation and that higher level of FO at CRRT beginning is associated with increased mortality and ECMO duration. Consequently, pre-ECMO fluid balance represents an important target intervention. Even more, He et al. (2018) found that fluid balance on the third day of ECMO initiation and lactate level at CRRT beginning both represent prognosis independent risk factors for patients undergoing CRRT while on ECMO. Therefore,

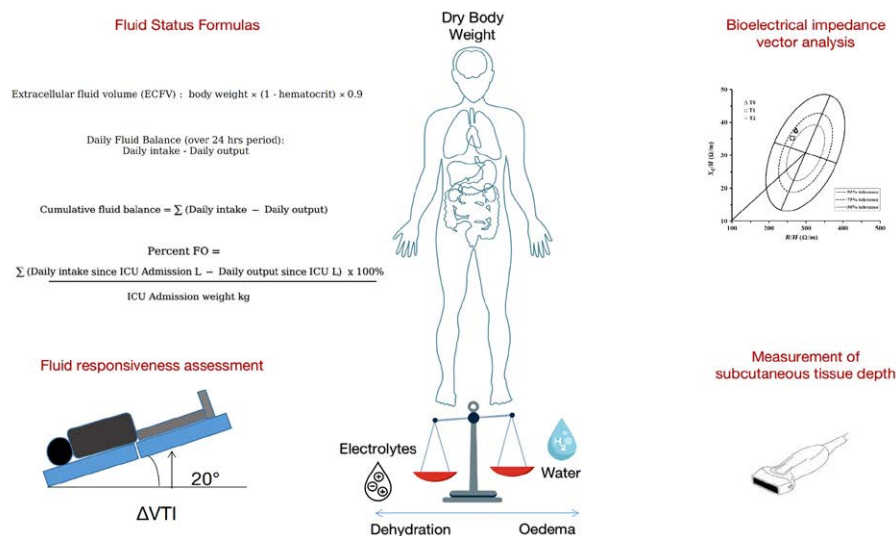


Figure 1. Methods to evaluate the determination of fluid balance and fluid overload

even if volume resuscitating strategy is fundamental especially during initiation of ECMO treatment, excessive volume overload impacts survival and outcome (Schmidt et al. 2014). However, to find a specific threshold is still challenging. From this perspective, the possible correlation between specific threshold of fluid balance (mL/kg) and mortality warrants further studies (Kim et al. 2018). Even more, it will be interesting to evaluate if the threshold diverges according to the indication for ECMO treatment (i.e., cardiovascular versus respiratory disease).

The prevention or the treatment of FO in these kinds of patients can require aggressive use of diuretics with potential collateral effects or fluid restriction with consequent reducing ideal caloric intake.

Consequently, the addition of CRRT during ECMO can diminish the administration of diuretics and allow a precise nutritional target. However, also in this group of patients, open questions still exist on the optimal timing, dose prescription target, and ideal modality technique (Paek et al. 2018).

However, FO is a common complication in paediatric patients receiving ECMO therapy, and it can have serious consequences such as pulmonary oedema, decreased oxygen delivery, and increased mortality. Over 75% of patients had a positive fluid balance while on ECMO, suggesting that FO and the ability to achieve a negative fluid balance are potentially important therapeutic targets (Selewski et al. 2017; Sakurai and Singhal 2022). The ability to

achieve a negative fluid balance on ECMO is associated with improved survival. CRRT provides flexibility and control in fluid management and has been shown to enhance the ability to achieve dry weight and negative fluid balance during ECMO (Rajapreyar et al. 2021).

Taken together with the epidemiology of FO and its independent association with adverse outcomes in this study, these results suggest that a trial utilising CRRT to manage fluids in children on ECMO may be warranted and probably as a need for earlier intervention. While these studies provide some evidence for the use of ECMO-CRRT integrated systems in managing fluid overload in the paediatric population, larger, randomised controlled trials are needed to establish the safety and

Authors/Year	Study Design	Participants	Method of Fluid Overload Assessment	AKI, RRT and Modality	Integrated Systems	Findings
Hoover et al. 2008	Retrospective case-matched study (patients receiving CRRT +ECMO vs. ECMO alone)	52 paediatric patients with respiratory failure receiving ECMO with CRRT	Fluid balance was calculated as the difference between fluids (ml) in and out over total ECMO course divided by weight (kg) divided by total ECMO days (ml kg ⁻¹ day ⁻¹). Fluid overload was not defined.	No AKI classification used. 26 (30% of respiratory failure ECMO) required RRT CVVH modality for all patients.	CRRT combined (in-line) with ECMO.	Use of CVVH in ECMO was associated with improved fluid balance and caloric intake and less diuretics than in case matched ECMO controls.
Blijdorp et al. 2009	Retrospective single centre, case-comparison study	61 new-borns (less than 28 days postpartum) on ECMO treated with RRT	Fluid balance was assessed as mean net fluid balance per ECMO day, by measuring total fluid input and output and dividing the difference by the time on ECMO. The difference between predilution and filtration flow rate was included.	No AKI classification used. Ultrafiltration was targeted to achieve a normal or negative fluid balance depending on the clinical condition of the patient while maintaining normal haemodynamic parameters.	Haemofilter placed parallel to the ECMO circuit, distal to the ECMO roller pump.	Haemofiltration during ECMO improves clinical outcome. This is expressed by a shorter duration of ECMO treatment, and of mechanical ventilation after ECMO. Moreover, the use of haemofiltration resulted in fewer blood transfusions in this group.
Schmidt et al. 2014	Retrospective single centre study	172 adult critically ill patients receiving VA-ECMO or VV-ECMO	Daily FB was calculated as the difference between fluid administered and fluid loss (dialysis effluent-dialysate from CRRT, urine output, enteral losses, drain losses) in a 24-h period. Negative daily FB was present when fluid loss was greater than fluid administered per day.	Incidence of RIFLE-defined AKI. 46 (27%) required RRT. RRT modality not specified.	CRRT combined (in-line) with ECMO.	Patients who had positive fluid balance on ECMO day 3, regardless of RRT status, were more likely to experience 90-day mortality. In their adjusted analyses, day-3 fluid balance was an independent predictor of long-term mortality. In addition, 60% (n=103) of patients received RRT in the setting of ECMO and receipt of CRRT did not guarantee negative fluid balance.
Selewski et al. 2015	Retrospective single centre study	53 paediatric critically ill patients receiving VA-ECMO or VV-ECMO	The change in FO while on CRRT was determined as follows: Change in FO = Initiation FO – Discontinuation FO FO was also examined as a categorical variable using a cut-off of 10% (<=10% versus >10%) and 20% (<=20% versus >20%).	No AKI classification used. 57 (28%) required RRT. RRT modality was CVVHD (until 2008) and CVVHDF.	Haemofilter placed parallel to the ECMO circuit (until 2008) and CRRT combined (in-line) with ECMO.	The association between FO at CRRT initiation and mortality was found. The degree of FO at CRRT discontinuation is also associated with mortality but appears to reflect the effect of fluid overload at initiation. The correction of FO to ≤ 10% was not associated with improved survival.
Selewski et al. 2017	Retrospective multicentre study	753 children < 18 years of age receiving VA-ECMO or VV-ECMO	Daily cumulative percent FO Cumulative percent FO Change in FO on ECMO = Discontinuation FO% - Initiation FO %	Incidence of KDIGO-defined AKI. 380 (50.4%) required RRT. RRT modality not specified.	Integrated system not specified.	Severe FO commonly occurs in children on ECMO and that worse FO during ECMO is associated with mortality and ECMO duration, independent of other factors, including the presence of AKI.
McCanny et al. 2019	Retrospective single centre study	24 adult patients supported by VV-ECMO and concomitant continuous renal replacement therapy.	Daily fluid balance was calculated as the difference between all fluids in and out per day, and cumulative fluid balance was the sum of daily fluid balances for all ECMO days.	Incidence of KDIGO-defined AKI. All patients were in acute kidney failure. RRT modality not specified.	CRRT combined (in-line) with ECMO.	Negative cumulative daily fluid balance was strongly associated with improved pulmonary compliance. 79% placed on CRRT day 1 of ECMO. Early CRRT with fluid removal is associated with trend to survival. Fluid removal associated with increased pulmonary compliance.
Gorga et al. 2020	Retrospective multicentre study	357 children < 18 years of age concurrently treated with ECMO and CRRT.	Daily cumulative percent FO was determined using daily intake and output for the 28 days prior to ECMO cannulation and the first 21 days following cannulation. Fluid overload was calculated at multiple time-points (CRRT initiation, CRRT discontinuation). Change in FO on CRRT = FO% at CRRT Discontinuation - FO % at CRRT Initiation.	Incidence of KDIGO-defined AKI. All patients were in acute kidney failure. RRT modality not specified.	Haemofilter placed parallel to the ECMO circuit and CRRT combined (in-line) with ECMO.	Severe FO occurs commonly in children supported by ECMO prior to CRRT initiation and that worse FO at CRRT initiation and at discontinuation is associated with increased mortality and duration of ECMO.

Mallory et al. 2020	Retrospective single centre study	424 paediatric critically ill patients receiving VA -ECMO or VV-ECMO 261 (63.9%) of those patients were neonatal, and 153 (36.1%) patients were paediatric.	Daily cumulative FO was calculated using the daily total fluid intake and total fluid output recorded from ICU admission up to 28 days before ECMO cannulation and up to 21 days after cannulation. Cumulative FO was also calculated. The change in FO between ECMO initiation and discontinuation was calculated using the cumulative FO at those times.	Incidence of KDIGO-defined AKI. All patients were in acute kidney failure. RRT modality not specified.	Renal support therapy was defined as peritoneal dialysis, continuous renal replacement therapy using a commercially available device, intermittent haemodialysis, or the use of haemofilter in line with the ECMO circuit.	Volume overload was associated with longer duration of mechanical ventilation and increased morbidity and mortality. In their cohort, 44% of patients received RRT and, as with our cohort, patients remained in positive fluid balance despite ECMO and RRT support.
Fong et al. 2020	Retrospective single centre study	123 adult critically ill patients receiving VA -ECMO or VV-ECMO.	Daily Fluid Balance (Fluid intake - Fluid output) Cumulative Fluid Balance (the sum of the fluid balance on the preceding days). Fluid overload was defined as positive fluid balance.	Incidence of RIFLE-defined AKI. 63 (51.2 %) required RRT. RRT modality not specified.	CRRT combined (in-line) with ECMO.	A more positive fluid balance was found in non-survivors; non-survivors had lower urine and fluid outputs; and fluid intake was not associated with hospital mortality. After adjusting for potential confounders, the cumulative fluid balance on day 7, but not on day 3, was independently associated with hospital mortality.
Gunning et al. 2020	Retrospective single centre study	98 adult critically ill patients receiving VA -ECMO or VV-ECMO.	Cumulative fluid balance was categorised into three groups: negative (negative cumulative fluid balance), no volume overload (positive cumulative fluid balance but not >10% of admission weight), and volume overload (defined as achieving a positive fluid balance of 10% above admission weight over the first 72 hours after ECMO cannulation).	Incidence of KDIGO-defined AKI. 48 (58%) required RRT. CVVHD modality for all patients.	CRRT combined (in-line) with ECMO.	Patients with volume overload had an increased risk of death at 90 days compared with those without volume overload. Patients with AKI requiring RRT had an increased risk of death at 90 days compared with those without. Volume overload remained an independent predictor of 90-day mortality when adjusting for RRT, APACHE score, weight, diabetes, and heart failure.
Besnier et al. 2020	Retrospective single centre study	101 Adult Critically Ill Patients receiving VA -ECMO.	The cumulative fluid balance was obtained by the addition of each daily fluid balance from the starting of VA-ECMO therapy until the day of evaluation.	Incidence of KDIGO-defined AKI. 48 (58%) required RRT. RRT modality not specified.	Integrated system not specified.	Early and positive fluid balance was associated with worse outcomes in patients treated with VA-ECMO.
Dado et al. 2020	Retrospective single centre study	92 adult critically ill patients receiving VA -ECMO.	Fluid balance but not specified if daily and cumulative were considered.	Incidence of KDIGO-defined AKI. 48 (53.3%) required RRT. CVVH modality for all patients.	CRRT combined (in-line) with ECMO.	The use of CRRT is prevalent among patients undergoing ECMO. Fluid balance appears to be an important variable associated with outcomes in this cohort. Rates of renal recovery and overall survival were higher compared to previously published reports among those requiring combined ECMO/CRRT.
Murphy et al. 2021	Retrospective multicentre study	446 neonates receiving VA -ECMO.	Percent FO (%FO) was determined using daily fluid intakes and outputs. Cumulative %FO was calculated using the following equation: %FO = $\frac{\{[\text{Sum of Daily (Fluid in - Fluid out) (L)]/[\text{ICU Admission weight (kilograms)}]\}}{A} \times 100$. Cumulative % FO was determined at ECMO and RRT initiation and discontinuation; peak % FO during ECMO was also determined.	Incidence of KDIGO-defined AKI . 195 (44%) required RRT. PD: 3 (2%). RRT (not better specified): 24 (12%). Inline haemofilter: 165 (86%).	RRT included peritoneal or intermittent haemodialysis, continuous RRT, or slow continuous haemofiltration.	96% of neonates with cardiac disease and AKI received VA ECMO. Physiologically distinct. ECMO diagnoses warrant individualised treatment strategies given variable incidence and effects of AKI, FO, and RRT by category on mortality.

Table 1. Studies evaluating fluid overload and integrated systems in critically ill patients in the last years.

AKI, Acute Kidney Injury; APACHE II score, The Acute Physiology and Chronic Health Evaluation; CRRT, Continuous renal replacement therapy; CVVH, Continuous Veno- venous hemofiltration; CVVHD, Continuous venovenous haemodialysis; FO, Fluid Overload; KDIGO, Kidney Disease Improving Global Outcomes; RIFLE, Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; RRT, Renal replacement therapy; VA-ECMO, Veno-arterial extracorporeal membrane oxygenation; VV-ECMO, Veno-venous extracorporeal membrane oxygenation

efficacy of this approach. In the meantime, fluid management should be closely monitored in paediatric patients on ECMO, and a multidisciplinary team approach should be taken to optimise patient outcomes. **Table 1** shows studies evaluating fluid overload and integrated systems in critically ill patients.

Indications and Modality for Integrated Systems

Indications for ECMO-CRRT integrated systems are represented by severe acute respiratory distress syndrome (ARDS) and AKI who require both respiratory and renal support, sepsis or multi-organ failure who require simultaneous ECMO and CRRT therapy, cardiac arrest who require ECMO and CRRT for haemodynamic and

metabolic stabilisation.

During ECMO, RRT can be provided by introducing a haemofilter or RRT circuit into the ECMO circuit (integrated system) or independently via a separate catheter and circuit (parallel system) (Chen et al. 2014; Kielstein et al. 2013). Parallel systems are not the objective of the present paper.

The ECMO-CRRT integrated systems are typically configured in three different ways as following:

1. In-line haemofilter (**Figure 2, Panel A**): In this modality, the CRRT circuit is connected in-line with the ECMO circuit, allowing for continuous ultrafiltration and dialysis. The filter inlet is typically connected after the oxygenator in the ECMO circuit to avoid interference with gas exchange and the outlet

is reconnected to the ECMO circuit to allow the return of the blood before it enters the oxygenator. The blood from ECMO circuit is shunted through in-line haemofilter. The intravenous pump allows the control of fluid removal. The fluid replacement or dialysis fluid can allow an additional solute clearance.

2. Side-by-side (**Figure 2, Panel B and C**): In this modality, the ECMO and CRRT circuits are arranged side-by-side, with a common venous access and a common arterial return, also possible via existing Luer locks on the inlet and outlet ports of the oxygenator. It requires a larger footprint and more complex tubing arrangement. There is no need for separate vascular access and anticoagulation.

This modality allows the control of pressures inside the circuit but also for higher ultrafiltration rates without the need of an external pump with better clearance of solutes (Chen et al. 2014). However, not all devices are able to recognise pressure changes leading to iterative stops and interruptions in treatment. In addition, the integration after ECMO motor pump could evoke high pressure alarms (de Tymowski et al. 2017). Therefore, since the two integrated circuits have two different pressure levels, the pressure differences can cause extremely risky situations with a shunt effect inside the ECMO circuit. The integration could be possible, and it is strongly suggested that the blood return to the ECMO circuit before the oxygenator.

The modality chosen should depend on the patient's specific needs and the available resources. The use of ECMO-CRRT integrated systems requires expertise in both ECMO and CRRT therapies and should only be performed by trained healthcare professionals.

Effects of Integrated Systems on Outcome

There is no strong recommendation on the optimal RRT modality during ECMO and the decision depends on local expertise and availability. The role of CRRT in modifying the outcome in ECMO patients is still uncertain.

Several published articles found that the mortality was high in patients receiving ECMO and CRRT in comparison with ECMO alone (Chen et al. 2014; Mitra et al. 2021; Han et al. 2015). However, it is important to stress that this data has to be interpreted with caution. First, the impact of the severity of AKI itself may contribute to the increased mortality in such fragile patients. Even more, AKI requiring RRT is associated with other life-treating complications (e.g., sepsis, immunodeficiency, hepatic failure, bleeding, neurological complications), increasing the severity of the underlying disease of ECMO patients. Nevertheless, the high heterogeneity of initiation, FO evaluation modalities and the differences in AKI definitions may have to be considered. Furthermore, there is no clear evidence

that the different strategies (i.e., parallel, integrated) may impact mortality or ECMO duration. Noteworthy, the aetiology of AKI in patients on ECMO is multifactorial, consequently, even if the studies are matched for severity of illness, it is difficult to come to any solid conclusions (Martins Costa et al. 2022). Central risk factors for mortality in ECMO patients with AKI are represented and not limited to age, AKI stage, RRT duration, hypercapnia, multiorgan failure syndrome, blood loss, transfusion requirement, haemodynamic instability, liver failure, and fluid overload (Ostermann and Lumlertgul 2021).

Not only the short-term outcome but also long-term outcomes and renal recovery are other important aspects that warrant major attention. Up to now, the renal recovery, the rate of liberation from dialysis, chronic kidney disease rate and quality of life is still indeterminate and require major evaluation in future trials. What seems to emerge from the existing literature is that lower GFR at baseline, higher AKI stage prior ECMO cannulation, transfusion requirement represents risk factor for 1-year major adverse kidney events. Consequently, the risk of kidney events in ECMO survivors has to be precisely evaluated (Ostermann and Lumlertgul 2021).

Complications related to CRRT during ECMO may arise during vascular placement of the cannula (e.g., bleeding, pneumothorax, haemothorax, retroperitoneal haemorrhage, vascular injury, arterial puncture, fistula formation) and during the treatment itself (e.g., infection, thrombosis, arrhythmias, hypokalaemia, hypophosphataemia, hypothermia, nutrient losses, haemolysis, intracranial haemorrhage and gastrointestinal bleeding). Special attention has to be put on the prevention of air embolism that can arise in several procedures during the treatment (e.g., central line insertion, connecting/disconnecting CRRT or infusions and flow variations due to the interaction of pressure and flow of ECMO and CRRT system). Another vital aspect is represented by a tight control of the anticoagulation regimen (e.g., systemic, regional) in order to prevent thrombosis,

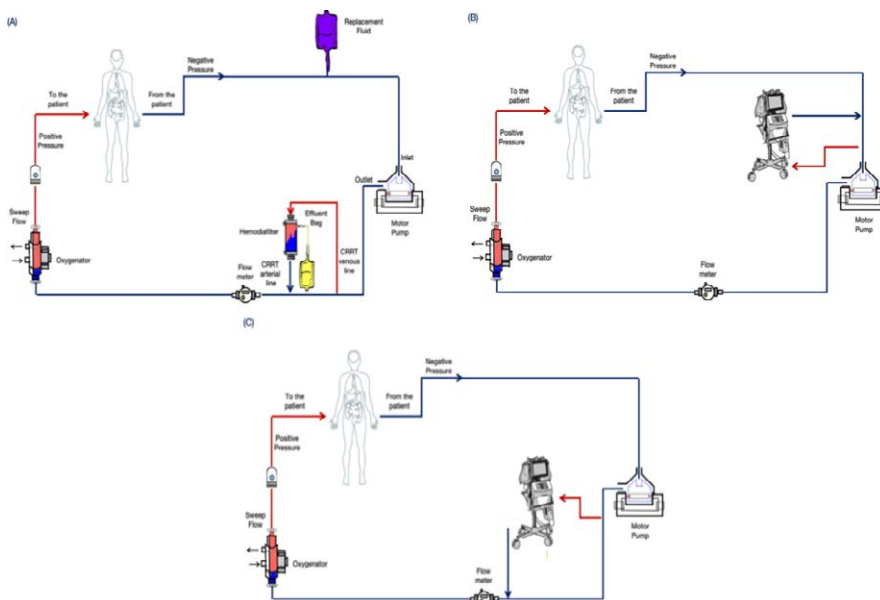


Figure 2. Methods for integrated approach of renal replacement therapy with extracorporeal membrane oxygenation. Panel A shows the in-line haemofilter configuration while Panel B and Panel C show side by side configuration. CRRT - continuous renal replacement therapy.

bleeding, premature circuit clotting and to increase circuit patency (Selewski and Wille 2021). However, in a 2014 systematic review, the authors found that the integration of ECMO and CRRT systems appear to be safe and effective with improvement in fluid removal and electrolyte disturbances (Chen et al. 2014).

Technical Issues

Each specific modality system to perform CRRT during ECMO presents specific advantages and drawbacks that need to be known before initiation of the treatment. A deep understanding of intra-circuit pressure and flow is essential to guarantee safety during the treatment (Ostermann et al. 2018; Wu et al. 2023; Na et al. 2018).

An integrated system is characterised by the introduction of an in-line haemofilter or a CRRT machine into the ECMO circuit. The introduction of a haemofilter requires a smaller priming volume compared to a parallel approach. However, ECMO circuit is characterised to work with negative pressure in the drainage part of the circuit (e.g., -20 to -100mmHg) and with positive pressure between the pump and oxygenator and between the oxygenator and the patients (Kashani and Ostermann 2019). Conversely, the CRRT machine generally works with venous pressure (from and to the patients) from about 0 to 30 mmHg. Furthermore, the flow within ECMO circuits is higher (3500-5000ml/min) than those working on a CRRT system (100-200mL/min). Possible complications of pressure and flows differences are represented by air entrapment, turbulences, haemolysis,

increasing shear stress and alarms out of range. Another important implication of an in-line system is represented by the difficulty of the net ultrafiltration evaluation due to the fact that part in-line system required an external infusion pump and the presence of tube ramification within the circuits (Askenazi et al. 2012). This led to an important difference between prescribed and actual ultrafiltration rate. Using a CRRT machine within the ECMO circuit can obviate of this issue (de Tymowski et al. 2017). A CRRT circuit allows to control pressure, ultrafiltration without an external pump with a more precise control of effluent volume (Santiago et al. 2009). However, also in this setting, problems with pressure alarms and connection lines may arise with consequent interruption in the treatment or complications such as air embolism and flow turbulence. Not to be underestimated, the introduction of an integrated system within the ECMO system with tube ramification is responsible of blood shunt off ECMO circuit with consequent potential alteration in oxygenation and blood flow.

Of course, such technical aspects and possible complications are not encountered in parallel systems, characterised by an independent circuit to deliver either ECMO or CRRT modalities (Martins Costa et al. 2022). In the parallel approach, no interferences are encountered between ECMO and CRRT techniques (Seczyńska et al. 2014). CRRT can be prescribed and monitored independently from ECMO and not to be underestimated, CRRT changing can be accomplished with less

risk and without the contribution of an ECMO expert. However, a separate vascular access is required, with possible consequent bleeding, infection and thrombosis risk (Subbarayan et al. 2021). Even more, the use of a vascular site for CRRT may diminish the choice of access site in case of the necessity of an additional cannula for a higher output of ECMO treatment. Furthermore, the usage of an independent circuit increases the artificial surface with increased risk of activation of coagulation cascade, systemic inflammation, shear stress and haemolysis.

In order to obviate the aforementioned issue, novel extracorporeal devices are currently under development, with particular attention on fibre arrangement, filtration mode, artificial surface characteristics and connections (Tang et al. 2022).

Conclusions

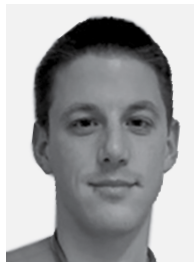
The successful delivery of CRRT during ECMO requires a clear prescription of the target solute clearance and fluid removal rate based on the cumulative fluid balance and physiological variables (haemodynamic, oxygenation). Treatment monitoring and re-adjustment are necessary and are based on patients need. While the deleterious impact of AKI and FO on outcomes for ECMO patients is clear, critical questions warranting further study remain regarding the role of CRRT in patient management, including device, modality, and optimal timing of initiation.

Conflict of interest

None. ■

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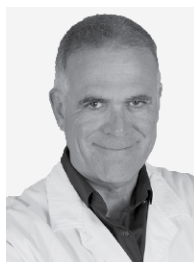
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Alessandro Belletti
Department of Anesthesia and
Intensive Care
IRCCS San Raffaele Scientific
Institute
Milan, Italy
belletti.alessandro@hsr.it



Giovanni Landoni
Department of Anesthesia and
Intensive Care
IRCCS San Raffaele Scientific
Institute
School of Medicine
Vita-Salute San Raffaele
University
Milan, Italy
landoni.giovanni@hsr.it



Alberto Zangrillo
Department of Anesthesia and
Intensive Care
IRCCS San Raffaele Scientific
Institute
School of Medicine
Vita-Salute San Raffaele
University
Milan, Italy
zangrillo.alberto@hsr.it

Introduction

Cardiac output (CO) is a key determinant of oxygen delivery. Low cardiac output syndrome (LCOS) causes organ dysfunction, prolonged hospital stay, and reduces survival in perioperative settings and in critical illness (Algarni et al. 2011; Maganti et al. 2010; Maganti et al. 2005; Lomivorotov et al. 2017; Zangrillo et al. 2020). Ultimately, the inability of the circulatory system to match oxygen demand is considered the main pathophysiological cause underlying the development of multi-organ failure and death (Schoemaker et al. 1988; Vincent et al. 2012). When heart function is incapable of providing enough CO to support tissues metabolic demands, inotropes can be administered with the goal of improving cardiac contractility and, therefore, restore and maintain an adequate oxygen delivery (Fellahi et al. 2013; Francis et al. 2014).

Similarly, maintenance of an adequate mean arterial pressure (MAP) is widely accepted as fundamental to ensure end-organ perfusion, and most professional

Which Vasopressors and Inotropes to Use in the Intensive Care Unit

Vasopressors and inotropes are frequently used in intensive care units. With a special focus on recent studies, this article summarises the key messages in the management of patients requiring inotropes and vasopressors.

guidelines recommend starting vasopressor administration when fluid resuscitation alone is unable to restore MAP (Evans et al. 2021; Van Diepen et al. 2017; Chioncel et al. 2020; Møller et al. 2018; Møller et al. 2016).

As a consequence, every clinician caring for patients with cardiovascular dysfunction is familiar with inotropes and vasopressors. Vasoactive medications are typically used in cardiogenic shock, septic shock, acute heart failure, and patients undergoing cardiac or high-risk non-cardiac surgery. In general, every critically ill patient may require some degree of haemodynamic support.

Inotropes and vasopressors have been administered for decades to patients with cardiovascular failure, and, as many other interventions (e.g. blood products transfusion, intra-aortic balloon pump), entered in routine clinical practice well before development of the evidence-based medicine concept. Accordingly, their safety and efficacy have never been formally tested. We will summarise recent evidence regarding use of inotropes and vasopressors in critically ill patients.

Haemodynamic and Side Effects of Vasoactive Agents

Every available inotropic agent increases cardiac contractility to a variable degree. Some agents such as epinephrine and dobutamine also have chronotropic effect, with the increase in heart rate further contributing to CO increase. Effect on vascular tone is variable, with some agents

also having vasoconstrictor effect (inocostrictors or inopressors) and others having a vasodilator effect (inodilators). As a result, the net effect of the different molecules on blood pressure depends on relative and absolute patient volume status and might be difficult to be predicted.

Pure vasoconstrictors (Table 1) (Francis et al. 2014; Gillies et al. 2005; Overgaard and Dzavik 2008; Bangash et al. 2012; Jentzer et al. 2015; Annane et al. 2018; Maack et al. 2019; Belletti et al. 2022) such as phenylephrine or vasopressin generally increase MAP, and often reduce CO even if their effect on CO depends on cardiac function, subsequent effects on heart rate and stressed and unstressed volume (Funk et al. 2013a; Funk et al. 2013b; Hamzaoui et al. 2018; Thiele et al. 2011a; Thiele et al. 2011b).

Despite the proven positive haemodynamic effects, inotropes and vasopressors are not free from side effects. The most frequently described are tachycardia, ventricular and supraventricular arrhythmias, and [with the possible exception of levosimendan (Papp et al. 2012; Nieminen et al. 2013)] increase in myocardial oxygen consumption (Fellahi et al. 2013; Arrigo and Mebazaa 2015; Schmittinger et al. 2012). In addition, inodilator agents may also cause severe hypotension (Nieminen et al. 2013; Arrigo et al. 2015), while inoconstrictors and pure vasoconstrictors may cause limb and mesenteric ischaemia (Anantasit et al. 2014).

Catecholamines, the most frequently used vasoactive agents, also have a wide

range of effects on respiratory, endocrine, immunological, gastrointestinal, and coagulation system that could be detrimental when adrenergic stimulation becomes excessive (Andreis and Singer 2016; Dünser and Hasibeder 2009; Belletti et al. 2020; Freestone et al. 2012). Increase in cardiomyocytes apoptosis has been described and may be particularly important in patients with a limited cardiovascular reserve (Rona 1985; Singh et al. 2001; Felker et al. 2003). Cardiac side effects have been reported in almost half of patients receiving catecholamine therapy (Schmittinger et al. 2012).

Between the end of the 80s and the early 90s, several large RCTs demonstrated reduction in survival in patients with chronic, stable heart failure treated with daily administration of inotropes, regardless of molecule tested (Packer et al. 1991; Xamoterol in Severe Heart Failure Study Group 1990; Cohn et al. 1998). Since then, side effects of inotropes are supposed to outweigh the positive haemodynamic effect of these drugs in patients in a stable clinical condition.

More recently, several authors have raised concerns regarding safety of inotropes also in acute clinical settings. Several observational trials reported an association between inotropes administration and poor survival in acute heart failure (Abraham

et al. 2005; Mebazaa et al. 2011; Mortara et al. 2014; O'Connor et al. 1999; Costanza et al. 2007; Rossinen et al. 2008; Kalogeropoulos et al. 2014), cardiac surgery (Fellahi et al. 2009; Shahin et al. 2011; Nielsen et al. 2014) and septic shock (Wilkman et al. 2013), although other observational trials did not find a similar association (Williams et al. 2011). In addition, some meta-analyses also highlighted a trend towards increased mortality when catecholamines are administered in patients with heart failure (Thackray et al. 2002; Tacon et al. 2012).

Despite evidence from observational trials, there is currently no randomised clinical trial demonstrating that inotropes administration increase mortality in settings other than chronic stable heart failure (Belletti et al. 2015). However, it should be acknowledged that there are no trials randomising haemodynamically unstable patients to inotropes/vasopressors versus no vasoactives.

Some indirect evidence may derive from trials investigating timing and intensity of vasoactive treatment, for example liberal (or higher) versus restrictive (or lower) haemodynamic targets (e.g. high vs low MAP, high vs low CO). Indeed, mRCTs comparing higher versus lower MAP targets (and hence greater versus lower

exposure to exogenous vasopressors) for septic shock patients showed no difference in mortality, although trends towards lower mortality but higher rate of AKI were generally observed in the low-MAP groups (Asfar et al. 2014; Lamontagne et al. 2020). Similarly, a recent large mRCT compared restrictive (prioritising lower intravenous fluid volumes and vasopressors) versus a liberal (prioritising higher volumes of intravenous fluids before vasopressor use) fluid strategy did not show mortality or serious adverse events difference between the two groups (NHLBI Prevention and Early Treatment of Acute Lung Injury Clinical Trials Network 2023). Few, small RCTs assessing different timing of norepinephrine administration (early versus delayed) in patients with septic shock have been performed, suggesting greater benefit with early norepinephrine administration (Permpikul et al. 2019; Elbouhy et al. 2019). Trials comparing suprathreshold CO or oxygen delivery targets versus standard treatment in critically ill patients showed no additional benefit (Gattinoni et al. 1995), or even harm (Hayes et al. 1994) associated with higher intensity treatment.

Collectively, these studies suggested that, in critically ill patients, higher targets (and hence greater use of interventions including fluids, vasopressors, and inotropes) are generally not necessary and sometimes may be harmful (Asfar et al. 2014; Lamontagne et al. 2020; Gattinoni et al. 1995; Hayes et al. 1994; Hernández et al. 2019).

A large number of RCTs investigated the effect of perioperative goal-directed haemodynamic therapy in various types of surgery (Jessen et al. 2022; Brienza et al. 2019; Giglio et al. 2021). There is agreement that goal-directed haemodynamic therapy (a bundle of vasopressors/inotropes, fluids, and blood products, to target tissue perfusion or haemodynamic targets) in the first hours after surgical procedures reduces complications in high-risk surgery patients, while improvement in survival remains debated (Giglio et al. 2021; Hamilton et al. 2011; Cecconi et al. 2013; Pearse et al. 2014; Osawa et al. 2016). Of note, goal-directed haemodynamic therapy may also reduce cardiac complications, which,

Drug	Pharmacology	Main theoretical haemodynamic effects				
		CO/CI	SVR	PCWP	MAP	HR
Inoconstrictors						
Dopamine (>4µg/kg/min)	Catecholamine (β ₁ -agonist ≈ α-agonist > β ₂ agonist)	↑	↑	↑	↑	↑↑
Norepinephrine	Catecholamine (α-agonist > β ₁ -agonist >> β ₂ agonist)	↑↓	↑↑	↑	↑↑	↑↔
Epinephrine	Catecholamine (β ₁ -agonist ≥ α-agonist ≥ β ₂ agonist)	↑↑	↑	↑	↑↑	↑↑
Inodilators						
Dobutamine	Catecholamine (β ₁ -agonist > β ₂ agonist >> α-agonist)	↑↑	↔↓	↔↓	↑↔↓	↑
Milrinone/Enoximone	PDE-3 inhibitor	↑↑	↓↓	↓↓	↔↓	↑↔
Levosimendan	Calcium-sensitiser + PDE-3 inhibitor	↑↑	↓↓	↓↓	↔↓	↑↔
Vasoconstrictors						
Vasopressin	V ₁ + V ₂ vasopressin receptor agonist	↓	↑↑	↑	↑↑	↔↓
Terlipressin	Long-acting V ₁ -vasopressin receptor agonist	↓	↑↑	↑	↑↑	↔↓
Angiotensin II	Angiotensin receptor agonist	↓	↑↑	↑	↑↑	↔↓

Table 1. Haemodynamic effects of commonly used inotropes/vasopressors. Modified from Jentzer et al. 2015 and Belletti et al. 2022.

CI: cardiac index; CO: cardiac output; HR: heart rate; MAP: mean arterial pressure; PCWP: pulmonary capillary wedge pressure; PDE-3: phosphodiesterase-3; SVR: systemic vascular resistance

theoretically, can increase when administering catecholamines (Arulkumaran et al. 2014). Nevertheless, the question of whether inotropes in addition to fluids provide increasing benefit remains open according to some authors (Nielsen and Algotsson 2015).

Specific Molecules

In this section, we will review the latest evidence on specific inotropes/vasopressors, with a focus on most recent or largest RCTs and meta-analyses. A detailed review of pharmacology of inotropes and vasopressors is available elsewhere (Fellahi et al. 2013; Francis et al. 2014; Overgaard and Dzavik 2008; Bangash et al. 2012; Jentzer et al. 2015; Annane et al. 2018; Maack et al. 2019; Belletti et al. 2022) and summarised in **Table 2**.

Catecholamines

First-line vasoactive agents are usually represented by catecholamines which are infused to patients who are unstable under the haemodynamic point of view, with guidelines and experts consensus suggesting their use in different settings (Evans et al. 2021; Van Diepen et al. 2017; Chioncel et al. 2020; McDonagh et al. 2021; Mebazaa et al. 2010; Mebazaa et al. 2016; Mebazaa et al. 2018; Scheeren et al. 2021) and with epinephrine, dobutamine, dopamine, and norepinephrine being the most frequently used (Jentzer et al. 2015).

Noradrenaline is the first-line vasopressor recommended to rise MAP in all clinical contexts by most available guidelines (Evans et al. 2021; Chioncel et al. 2020; McDonagh et al. 2021). An interesting observational study performed in the United States assessed patient outcome during a period of norepinephrine shortage and documented that unavailability of noradrenaline resulted in reduced survival despite use of alternative agents such as vasopressin, dopamine and phenylephrine (Vail et al. 2017). Norepinephrine has been studied in several multicentre RCTs against dopamine, vasopressin, and epinephrine (De Backer et al. 2010; Annane et al. 2007; Myburgh et al. 2008; Levy et al. 2018; Russell et al. 2008; Gordon et al.

2016). Collectively, these studies showed no clear improvement in survival when using norepinephrine over other agents. In the Sepsis Occurrence in Acutely Ill Patients II (SOAP-II) trial, 1679 patients requiring vasopressors were randomised to receive norepinephrine or dopamine (De Backer et al. 2010). In the overall study population, there was no difference in 28-days or 1-year survival. Norepinephrine was associated with lower rate of arrhythmias in the overall population, and a higher survival rate in the subgroup of cardiogenic shock patients. Mortality reduction associated with norepinephrine use as compared with dopamine has been confirmed in meta-analyses of RCTs mostly including septic shock trials (Vasu et al. 2012; De Backer et al. 2012).

Of note, there is little awareness overall that norepinephrine is marketed under different salt preparations (e.g. tartrate, hydrochloride) with different equivalent potency to the referral product (norepinephrine base) (Leone et al. 2022; Mongardon et al. 2023; Bitton et al. 2022), while the referral product is not marketed at all. Clinical scientists and experts should be aware of this and overtly state whether they refer to norepinephrine base or other formulations when presenting trial results or recommendations.

Epinephrine is commonly used in critically ill patients as second-line agent or alternative vasopressor, especially in low-resource settings (Evans et al. 2021). In clinical practice, epinephrine is generally considered more an inotrope than a vasoconstrictor, while the opposite is true for norepinephrine. Accordingly, several clinicians prefer to use epinephrine in patients with myocardial dysfunction and are scared of noradrenaline which might increase afterload and decrease CO. However, recent observational studies noted that epinephrine is used in cardiogenic shock patients with high mortality (Léopold et al. 2018; Tarvasmäki et al. 2016). On the contrary, when pooling RCTs only no evidence of increased mortality was noted in patients randomised to receive epinephrine (Belletti et al. 2020). The study, however, also underlined the

very limited number of RCTs performed in the setting of cardiogenic shock, and the overall limited numbers of RCTs investigating epinephrine as vasopressor outside the context of cardiopulmonary resuscitation (Belletti et al. 2020; Belletti et al. 2018).

In a recent RCT by Levy et al. (2018), epinephrine was compared against norepinephrine in patients (n=57) with cardiogenic shock due to acute myocardial infarction. The trial was interrupted early for safety issues due to a higher rate of refractory shock and a trend towards increased mortality in the epinephrine group. Haemodynamic data collected in the trial showed that epinephrine increased CO more than norepinephrine. However, this was driven by an increase in heart rate, while measured stroke volume remained similar between the two groups. This might be relevant in the context of myocardial ischaemia, as heart rate is a major determinant of myocardial oxygen consumption. It should be noted that very high dose of catecholamines (0.6-0.7 µg/kg/min) were used in this trial. Subtle haemodynamic effects may become more relevant at lower doses (e.g. 0.1-0.2 µg/kg/min). The trial has some limitations, such as higher baseline lactate levels in the epinephrine group and including lactate as a component of a safety outcome of refractory shock (despite the well-known effect of epinephrine on lactate). Nevertheless, these results challenge the notion that norepinephrine is detrimental in patients with myocardial dysfunction and provide a background for its use and further studies in this clinical setting (van Diepen 2018).

Vasopressin and terlipressin

Vasopressin is a pure vasoconstrictor and has been increasingly used in recent years as an alternative or an adjunct to norepinephrine.

The Vasopressin and Septic Shock Trial (VASST) trial, published in 2008, was the first, large RCT comparing vasopressin versus norepinephrine in septic shock (Russell et al. 2008). In this study, 778 patients with septic shock requiring 5 µg/min of norepinephrine were randomised

to receive vasopressin or norepinephrine on top of open-label vasopressors.

The study showed that vasopressin improves MAP and reduces requirements of concomitant vasopressors but does not improve survival. However, subgroup and post-hoc analyses suggested that vasopressin, especially in combination with steroids, may reduce mortality and rate of acute kidney injury in patients with less severe shock (Gordon et al. 2010; Russell et al. 2009). This hypothesis was subsequently tested in a 2×2 factorial trial investigating the effect of vasopressin and hydrocortisone in early septic shock (Vasopressin vs Norepinephrine as Initial Therapy in Septic Shock [VANISH]) (Gordon et al. 2014).

This RCT, enrolling 409 patients with early septic shock (Gordon et al. 2016), showed no difference in survival, a lower rate of renal-replacement therapy (RRT) in the vasopressin group (although driven by reduction in RRT only in non-survivors), and a higher rate of digital and myocardial ischaemia in the vasopressin group. Taken together, these data suggest that vasopressin effectively reduces norepinephrine requirements and increases MAP, but with no significant effects on major outcomes. The only potential benefit may be on renal outcomes, as also suggested by a recent single-centre RCT performed in the setting of post-cardiotomy vasoplegic shock (Hajjar et al. 2017). This study (Vasopressin versus Norepinephrine in Patients with Vasoplegic Shock after Cardiac Surgery [VANCS]) showed a lower rate of AKI and atrial fibrillation in the vasopressin group, with no difference in survival or rate of adverse events.

Similarly, terlipressin (a long-acting analogue of vasopressin), despite some promising early results (Belletti et al. 2015; Serpa Neto et al. 2012; Avni et al. 2015; Kochkin et al. 2021), failed to show improvement in outcomes in a recent mRCT of 617 patients (Liu et al. 2018). On the contrary, terlipressin use increased rate of serious adverse events, and in particular rate of digital ischaemia.

Phosphodiesterase 3-inhibitors

Phosphodiesterase-3 inhibitors are inodilators frequently used as inotropic agents in patients with LCOS, especially in acute heart failure, of cardiac surgery, and in patients receiving chronic beta-blocker therapy (McDonagh et al. 2021; Bignami et al. 2016; Kastrup et al. 2007; Lowes et al. 2001; Metra et al. 2002). They are generally considered as an alternative to catecholamines, or as a synergic agent in patients requiring high-dose inotropic support.

In the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study, patients with acutely decompensated heart failure but without shock were randomised to receive milrinone or placebo (Cuffe et al. 2002; Cuffe et al. 2000). Patients randomised to milrinone had a higher rate of hypotension and arrhythmias, while rate of mortality and other major outcomes remained comparable. In addition, an interesting post-hoc analysis suggested that milrinone may be beneficial in patients with non-ischaemic heart failure, while it may worsen outcome in patients with ischaemic heart failure (Felker et al. 2003).

Another multicentre RCT performed in the setting of cardiac surgery compared milrinone versus dobutamine in patients with perioperative LCOS (Feneck et al. 2001). The study focused on haemodynamic parameters and was not powered to assess clinical endpoints. It showed that dobutamine administration was associated with higher cardiac index (driven by a greater increase in heart rate), higher MAP, and higher incidence of atrial fibrillation, while milrinone was associated with greater decrease in pulmonary capillary wedge pressure (PCWP).

A single-centre study published in 2021 randomised 192 patients with cardiogenic shock {Society of Cardiovascular Angiography and Interventions [SCAI]-stage B or higher (Baran et al. 2019)} to receive dobutamine or milrinone as primary inotropic agent (Dobutamine Compared to Milrinone [DOREMI] study) (Mathew et al. 2021). The authors found no difference in terms of mortality, adverse events,

haemodynamic parameters or need for vasopressors. Overall, these studies confirm the haemodynamic efficacy of milrinone in terms of CO increase and vasodilation, but also demonstrate neutral effects on major clinical outcomes, as compared with catecholamines.

Interestingly, an experimental study assessing haemodynamic effect of milrinone and catecholamines in conditions independent from pre- and afterload, showed that milrinone may have no direct inotropic effect contrary to dobutamine. Accordingly, the authors hypothesised that the increase in cardiac output observed with PDE-3 inhibitors may be related to their pre- and afterload modulation properties, rather than a direct increase in cardiac contractility (DeWitt et al. 2016). This might also explain the greater effect on PCWP observed as compared with dobutamine.

Levosimendan

Levosimendan is a relatively new inodilator agent acting as a calcium-sensitiser and PDE-3 inhibitor. It has been extensively studied and indeed is the most frequently investigated inotropic agent ever, with more than 100 RCTs including almost 10000 patients (Belletti et al. 2015). Several early RCTs and meta-analyses of RCTs suggested that levosimendan administration could improve survival in a wide variety of clinical settings (Pollesello et al. 2016).

From mid 2000s, several high-quality, large mRCTs investigated the effect of levosimendan on major outcomes in the settings of acute heart failure, cardiac surgery and sepsis (Landoni et al. 2017; Zangrillo et al. 2016; Mehta et al. 2017; Mehta et al. 2016; Orme et al. 2014; Gordon et al. 2016; Cholley et al. 2017; Caruba et al. 2016; Mebazaa et al. 2007; Packer et al. 2013). Contrary to meta-analyses and early results, all these studies failed to show a convincing beneficial effect of levosimendan on mortality or other major clinical outcomes. These studies confirmed that levosimendan administration leads to reduction in need for other concomitant inotropes and higher rate of hypotension (results that are consistent with its

inodilator effect) and arrhythmias. One post-hoc analysis of a cardiac surgery RCT suggested a potential beneficial effect for the limited group of patients with very low left ventricular ejection fraction undergoing coronary artery bypass graft surgery, when levosimendan is administered prophylactically (van Diepen et al. 2020). Another post-hoc analysis in the setting of acute heart failure suggested greater benefit for patients on chronic beta-blocker therapy, as compared with dobutamine (Mebazaa et al. 2009). These findings should be confirmed in adequately powered trials.

Interestingly, while traditionally considered a calcium-sensitiser, some experi-

mental studies challenged this view and suggested that the haemodynamic effects of levosimendan are almost exclusively related to its effect as inhibitor of the PDE-3 (Ørstavik et al. 2014), and potentially to its effect on vascular K⁺-ATP channels (Maack et al. 2019), while the calcium-sensitising properties exert a very limited effect (Ørstavik et al. 2014).

Angiotensin II

Angiotensin II is a vasopressor that has been suggested as a catecholamine-sparing agent for patients with vasodilatory shock and increasingly studied in recent years .

In the largest and most recent mRCT performed, 344 patients with vasodila-

tory shock requiring > 0.2 µg/kg/min of norepinephrine and with a normal cardiac index were randomised to receive angiotensin II or placebo on top of open-label norepinephrine (Khanna et al. 2017). The study showed that angiotensin II does increase MAP and reduces need for concomitant norepinephrine. The study was underpowered to detect major outcome differences. However, no hints for benefit or harms were reported. A post-hoc analysis investigating patients receiving RRT at randomisation suggested that angiotensin II may improve survival and renal recovery in this subgroup of patients (Tumlin et al. 2018). However, these findings require further confirmation

Drug	Setting	Effect on survival	Additional findings
Norepinephrine	Shock of any aetiology	No improvement (De Backer et al. 2010; Myburgh et al. 2008)	Lower incidence of arrhythmias as compared with dopamine (De Backer et al. 2010) Lower lactate levels as compared with epinephrine (Myburgh et al. 2008)
	Sepsis/vasodilatory shock	No improvement as compared with vasopressin/terlipressin/epinephrine (Annane et al. 2007; Russell et al. 2008; Gordon et al. 2016; Liu et al. 2018) Possible overall higher survival as compared with dopamine as suggested by meta-analyses (Vasu et al. 2012; De Backer et al. 2012)	Lower rate of arrhythmias as compared with dopamine as suggested by meta-analyses (Vasu et al. 2012; De Backer et al. 2012)
	Cardiogenic shock	Possible higher survival as compared with dopamine (De Backer et al. 2010) No improvement and trend towards increased survival as compared with epinephrine (study not powered to detect mortality difference) (Levy et al. 2018)	Lower lactate levels as compared with epinephrine (Levy et al. 2018) Lower CI (with similar stroke volume but lower heart rate) as compared with epinephrine (Levy et al. 2018)
Epinephrine	Shock of any aetiology	No improvement (Myburgh et al. 2008)	Higher lactate level as compared with norepinephrine (± dobutamine)
	Septic shock	No improvement (Annane et al. 2007)	Higher lactate level as compared with norepinephrine (± dobutamine)
	Cardiogenic shock	No improvement Trend towards increased mortality (study not powered to detect mortality difference) (Levy et al. 2018)	Possible trend towards higher rate of refractory shock (Levy et al. 2018) Higher lactate levels as compared with norepinephrine (Levy et al. 2018) Higher CI (with similar stroke volume but higher heart rate) as compared with norepinephrine (Levy et al. 2018)
Dopamine	Shock of any aetiology	No overall improvement (De Backer et al. 2010)	Higher rate of arrhythmias as compared with norepinephrine (De Backer et al. 2010)
	Septic shock	Possible overall lower survival as compared with norepinephrine as suggested by meta-analyses (Vasu et al. 2012; De Backer et al. 2012)	Higher rate of arrhythmias as compared with norepinephrine as suggested by meta-analyses (Vasu et al. 2012; De Backer et al. 2012)
	Cardiogenic shock	Possible lower survival as compared with norepinephrine (De Backer et al. 2010)	

Vasopressin	Sepsis	No improvement (Russell et al. 2008; Gordon et al. 2016)	Possible reduction in need for RRT (Gordon et al. 2016) Possible reduction in norepinephrine requirements (Russell et al. 2008; Gordon et al. 2016)
Terlipressin	Sepsis	No improvement (Liu et al. 2018)	Increase in serious adverse events (Liu et al. 2018)
Levosimendan	Acutely decompensated heart failure	No improvement (Mebazaa et al. 2007; Packer et al. 2013)	Reduction in BNP and improvement in symptoms (Mebazaa et al. 2007; Packer et al. 2013)
	Cardiac surgery	No improvement (Landoni et al. 2017; Mehta et al. 2017; Cholley et al. 2017)	Reduction in need for catecholamines and incidence of perioperative LCOS (Pollesello et al. 2016; Mehta et al. 2016) Possible improvement in survival in patients with very low LVEF ($\leq 25\%$) undergoing CABG (van Diepen et al. 2020)
	Sepsis	No improvement (Gordon et al. 2016)	Improvement in cardiovascular SOFA score (Gordon et al. 2016) Increased risk of arrhythmias and hypotension (Gordon et al. 2016)
Milrinone	Acutely decompensated heart failure	No improvement (Cuffe et al. 2002) Possible increase in mortality in patients with ischaemic heart failure (Felker et al. 2003)	Increased risk of arrhythmias and hypotension (Cuffe et al. 2002)
	Cardiac surgery	No improvement (study not powered to detect mortality difference) (Feneck et al. 2001)	Lower CI (with similar stroke volume but lower heart rate), lower PCWP, lower MAP, and lower incidence of AF as compared with dobutamine (Feneck et al. 2001)
	Cardiogenic shock	No improvement (Mathew et al. 2021)	
Angiotensin II	Vasodilatory shock	No overall improvement (study not powered to detect mortality difference) (Khanna et al. 2017) Possible improvement in survival in patients receiving RRT (Tumlin et al. 2018)	Improvement in MAP and reduction in norepinephrine requirements (Khanna et al. 2017) Possible increase in thrombotic adverse events (Bauer et al. 2018)

Table 2. Summary of current findings from multicentre RCTs on the effect of inotropes/vasopressors on survival in acutely ill patients. Modified from Belletti et al. 2022.

AF: atrial fibrillation; BNP: b-type natriuretic peptide; CABG: coronary artery bypass graft; CI: cardiac index; LCOS: low cardiac output syndrome; LVEF: left ventricular ejection fraction; MAP: mean arterial pressure; PCWP: pulmonary capillary wedge pressure; RRT: renal replacement therapy; SOFA: sequential organ failure assessment.

in adequately powered studies. Of note, some authors suggested that angiotensin II use may be associated with an increased rate of delirium, LCOS, thrombotic events, and fungal infections (Thiele et al. 2011a; Thiele et al. 2011b; Bauer et al. 2018).

Future Directions

Mechanical circulatory support (MCS) is increasingly used in recent years, in particular in the setting of acute heart failure/cardiogenic shock (Combes et al. 2020; Rihal et al. 2015; Atkinson et al. 2016). Interestingly, MCS is increasingly used also in unconventional settings including sepsis (Br  chet et al. 2020) and high-risk surgical/interventional procedures (Monaco et al. 2018). MCS has the potential, theoretical advance of providing different degrees of

haemodynamic and respiratory support (up to full cardiorespiratory support with venoarterial extracorporeal membrane oxygenation) without the potential side effects of vasoactives. In addition, the recently developed concept of mechanical unloading as new paradigm to improve outcome in heart failure and cardiogenic shock is gaining increasing popularity (Burkhoff et al. 2015; Uriel et al. 2018; Baldetti et al. 2021).

However, MCS devices are still associated with high costs, need for expertise, and potential complications themselves (Zangrillo et al. 2013) that requires careful weighing of benefit and risks in each single case (Combes et al. 2020; Rihal et al. 2015; Atkinson et al. 2016). Nevertheless, pilot studies in acute heart failure and cardiogenic

shock comparing pharmacological versus mechanical support have been performed and showed controversial results, with some favouring MCS (den Uil et al. 2019; Lackermair et al. 2021), while others showed no additional benefit with immediate as compared with rescue initiation of MCS (Ostadal et al. 2023). In general, mechanical circulatory support should be considered early in case of dependency on high-dose inotropes/vasopressor {especially with vasoactive-inotropic score [VIS] (Belletti et al. 2021) >20 }. In the future, with increasing clinical experience and technological advances, MCS use is likely to expand, and further trials comparing mechanical versus pharmacological support are ongoing (Banning et al. 2021; Udesen et al. 2019).

In recent years, the concept of metabolic

Catecholamines (norepinephrine) remain first-line agents in almost every setting
Supraphysiological haemodynamic targets are harmful, restrictive targets (e.g. permissive hypotension) may be acceptable in several cases
Norepinephrine shortage is detrimental
Dopamine (high dose) is detrimental
Vasopressin and angiotensin II reduce concomitant norepinephrine doses, increase MAP but do not improve outcomes
PDE-3 inhibitors and levosimendan reduce need for concomitant inotropes but do not improve outcomes as compared with catecholamines
Interaction with preload/afterload/fluids/mechanical ventilation is important and under-investigated
Chose a simple inotropic-vasoconstrictor combination for your department and be ready to change it quickly if the patient is a non-responder or develops side effects
Consider early mechanical circulatory support (especially with VIS>20)

Table 3. Summary of current major evidence and concepts on inotropes/vasopressor use in critically ill patients. Modified from Belletti et al. 2022. MAP: mean arterial pressure; PDE-3: phosphodiesterase-3; VIS: vasoactive-inotropic score

resuscitation for patients with cardiovascular failure became increasingly popular. Metabolic resuscitation includes a combination of steroids and vitamins (vitamin C and vitamin B1) and a large number of RCTs have been performed to test these molecules alone or in various combination (Moskowitz et al. 2018; Fujii et al. 2022). After promising initial results, current evidence collectively suggest that metabolic resuscitation does not provide additional survival benefit (Fujii et al. 2022). Nevertheless, the latest Surviving Sepsis Guidelines (Evans et al. 2021) suggest the use of steroids in septic shock patients since they reduce vasopressor therapy duration and length of ICU stay without increasing adverse events (Fujii et al. 2022).

While haemodynamic management historically focused on so-called micro-

circulation and major haemodynamic parameters (such as MAP and CI), the role of microcirculatory dysfunction in organ dysfunction and failure in critical illness is being increasingly recognised and investigated (Østergaard et al. 2015; Ince et al. 2018). Future research should focus on the different effect of vasoactive medications on microcirculation and tissue perfusion independently of traditional haemodynamic parameters. However, a systematic review found there is no convincing evidence that any vasoactive agent can lead to improved microvascular flow, although available studies are characterised by high heterogeneity in terms of microcirculation assessment and high risk of bias (Potter et al. 2019).

Finally, a concept of broad-spectrum vasopressors has been recently introduced

(Chawla et al. 2019). Some experts suggest a combination use of different vasopressors with different mechanism of action (e.g. norepinephrine, vasopressin and angiotensin II) to reduce the dose of each drug, limit side effects, and individualise vasopressor therapy, in similar way to broad-spectrum antibiotic therapy. Whether this concept will translate into improved outcomes remains to be determined. **Table 3** provides a final take-home message on inotropes and vasopressors use in critical care.

Conclusions

Inotropes and vasopressors may have relevant side effects that need to be known and acknowledged, and incorrect prescription of inotropes administration can increase morbidity and mortality. The choice of molecule or combination of molecules does not seem to influence mortality as long as comparable haemodynamic parameters are obtained. Clinicians should choose the drug or combination of drugs they are most familiar with.

Future studies should focus on identification of optimal haemodynamic targets, investigate interaction between vasoactives, fluids, pre-load and afterload, optimal timing of vasoactive initiations, and the role of MCS.

Conflict of Interest

None. ■

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Zbigniew Putowski

Center for Intensive Care and
Perioperative Medicine
Jagiellonian University Medi-
cal College
Kraków, Poland
putowski.zbigniew@gmail.com
@ZPutowski



Jakub Fronczek

Center for Intensive Care and
Perioperative Medicine
Jagiellonian University Medi-
cal College
Kraków, Poland
jakub.fronczek@uj.edu.pl
@JFronczekMD



Christian Jung

Medical Faculty
Department of Cardiology,
Pulmonology and Vascular
Medicine
Heinrich-Heine University
Düsseldorf
Düsseldorf, Germany
christian.jung@med.uni-
duesseldorf.de
@cjungMD



Wojciech Szczeklik

Center for Intensive Care and
Perioperative Medicine
Jagiellonian University Medi-
cal College
Kraków, Poland
wojciech.szczeklik@uj.edu.pl
@wszczeklik

A Very Old Patient in the ICU: Much More Than an Acute Organ Dysfunction

Treating an elderly patient in intensive therapy requires the integration of many components. The purpose of this paper is to promote a comprehensive assessment of the critically ill patient aged 80 or more years.

chronic diseases, depletion of biological reserves, cognitive impairment, and malnutrition are inseparably associated with ageing. In older adults, critical illness often occurs in the context of a baseline depletion of physiologic reserves, not only posing a medical challenge, but also raising ethical questions about patients' willingness to receive aggressive treatment which may prove futile in the end (Boumendil et al. 2011). Long-term outcomes after intensive care are strongly determined by pre-ICU functional trajectories (Ferrante et al. 2015). Hence, a complex assessment of a patient's health may enhance clinicians' ability to distinguish those who are most likely to benefit from hospitalisation in the ICU and to guide post-ICU treatment strategies. The purpose of this paper is to promote a comprehensive assessment of the critically ill patient aged 80 or more years.

Acute Organ Dysfunction

The incidence of acute organ dysfunction increases with age (Flaatten et al. 2017a). Older patients are more likely to suffer from sepsis than the younger counterparts (Angus et al. 2001). This is usually closely related with acute respiratory failure which constitutes the primary cause for an urgent ICU admission in the older population (Flaatten et al. 2017b). The functional ageing of organs should be considered when treating acute critical illness (Brunker et al. 2023). Examples of such organ changes and the resulting clinical implications are shown in **Table 1** (Brunker et al. 2023). The most popular tool used

for the assessment of organ dysfunction is the Sequential Organ Failure Assessment (SOFA) score (Vincent et al. 1996). First introduced as a tool to describe the severity of organ dysfunction, it was later found to be well correlated with mortality (Lopes Ferreira et al. 2001). Despite a number of caveats (Lambden et al. 2019), SOFA score continues to be a globally utilised universal method for multi-organ failure assessment. With the introduction of the VIP (very old intensive care patients) network, a number of large observational studies have been conducted in this population (Van Heerden et al. 2021). For example, in the VIP-1 study (5021 patients), one-point increase in submission SOFA score was independently associated with 30-day mortality: a hazard ratio (HR) of 1.13 (1.12-1.14) (Flaatten et al. 2017b). In a subsequent VIP-2 study (3920 patients), one-point increase in SOFA produced a similar HR of 1.15 (1.14-1.17) (Guidet et al. 2020). Moreover, in a cluster analysis of the VIP-2 and COVIP studies, the authors derived seven different phenotypes based on SOFA, SOFA sub-scores, age, and geriatric features (Mousai et al. 2022). The phenotype based on the highest SOFA score produced a 30-day mortality of 57% compared to 17% in patients with lower SOFA score. Interestingly, the phenotype based solely on the oldest age was associated with an excellent prognosis (30-day mortality of 2%).

Frailty

Frailty is defined as a state of decreased

Introduction

Ageing of the population combined with a shortage of intensive care unit (ICU) beds results in a demand for intensive care continuously outstripping supply of resources even in highly developed healthcare systems (Guidet et al. 2017). At the same time, the invasiveness and high cost of ICU procedures necessitate careful decision-making in regard to patients who may or may not benefit from admission to the ICU. Such issues are especially relevant in the case of critically ill patients over 80 (Guidet et al. 2018). Accumulation of

System	Ageing changes	Clinical implications
Cardiovascular	<ul style="list-style-type: none"> ↑ vascular stiffness; ↑ sympathetic tone; ↑ ventricle stiffness; ↓ ventricle contractility; ↑ fibrosis of cardiac pacemaker; ↑ valvular calcification; ↑ atherosclerosis 	<ul style="list-style-type: none"> • Consider fluid therapy as the primary tool for resuscitation (↑ preload dependency) • Consider higher blood pressure targets • Acknowledge impaired compensatory mechanisms (e.g. tachycardia) • Higher frequency of type 2 myocardial infarction: detect demand ischaemia • Prevent hypotension during initiation of extracorporeal circuit • Assess fluid tolerance. Avoid hypervolaemia
Respiratory	<ul style="list-style-type: none"> ↑ Alveolar-arterial gradient; ↓ vital capacity; ↓ lung elasticity ↓ secretion clearing of the airways 	<ul style="list-style-type: none"> • Frequently drain respiratory secretions • Early weaning, prevent ventilator dependence
Renal	<ul style="list-style-type: none"> ↓ renal mass; ↓ renal blood flow; ↓ renin-angiotensin system activity 	<ul style="list-style-type: none"> • Frequently screen for ↓ sodium and ↑ potassium concentrations • Frequently assess volume status • Adjust drug dosing to renal function
Liver	<ul style="list-style-type: none"> ↓ liver blood flow ↓ albumin synthesis 	<ul style="list-style-type: none"> • Consider liver function while titrating drug doses • Consider increased protein intake
Central Nervous System	<ul style="list-style-type: none"> ↑ blood-brain barrier permeability; ↓ grey and white matter; ↑ cerebral microbleeds 	<ul style="list-style-type: none"> • ↑ neurological manifestations (delirium) of non-neurologic diseases – implement preventive measures (e.g. ABCDEF bundle) • GCS assessment may be hindered by preexisting cognitive impairment • Promote sleep hygiene
Immune System	<ul style="list-style-type: none"> ↑ proinflammatory stimulation ↓ overall immune system performance 	<ul style="list-style-type: none"> • Frequently assess respiratory and urinary tract for infections • Frequently screen for sepsis

Table 1. Examples of ageing changes and their clinical implications

physiologic reserve that heightens vulnerability to acute stressors (Chen et al. 2014). Older patients, who are most susceptible to frailty, often exhibit various degrees of decreased mobility, weakness, sarcopenia, malnutrition, and impaired cognition (Muscedere et al. 2017). Importantly, a stay in the ICU may be associated with an exacerbation in the above pathologies due to neuropathy, increased catabolism and inflammation (Shepherd et al. 2017;

Van Gassel et al. 2020; Paul et al. 2020). Undergoing critical illness may then be associated with ICU-acquired weakness which aggravates the already existing functional impairment (Vanhorebeek et al. 2020). Frailty increases mortality and prolongs ICU and hospital stay with increased use of organ support (Muscedere et al. 2017). The evaluation of frailty on admission to the ICU requires the use of a validated scoring system. One of the

simplest and most-utilised tools in critical care research is the Clinical Frailty Scale (CFS) (Rockwood et al. 2005). The CFS, being a 9-point scale, stratifies patients based on their functionality. For example, a CFS grade of 1 describes a very fit patient who exercises regularly and is not dependent on any personal assistance. On the other hand, a grade of 8 corresponds to a person who is very severely frail, who is completely dependent and is approaching the end of life. Commonly, CFS ≥5 is regarded as clinical frailty (Church et al. 2020). Using this threshold, it has been observed that frailty is present in 46% of acutely admitted elderly ICU patients (Flaatten et al. 2017b). One-point increase in CFS is associated with a 30-day mortality HR of 1.11 (1.08-1.15) (Guidet et al. 2020). Importantly, frailty should not be diagnosed as "present" or "absent" - different grades of CFS have different prognostic implications, thus no single threshold discriminating patients who are "frail" from those "fit" can be deemed optimal. In sum, frailty contributes up to 9% of new prognostic information about 30-day mortality after adjusting for basic patient characteristics (Fronczek et al. 2021).

Multimorbidity

Multimorbidity is a state in which two or more chronic diseases overlap (Salive 2013). Older age is the single most important risk factor accounting for multimorbidity. Hypertension, diabetes, chronic obstructive pulmonary disease, and cardiac failure are most common diseases in older, multimorbid patients (Salive 2013). An average patient over 80 years old struggles with roughly three chronic diseases (Barnett et al. 2012). Since multimorbidity is not a homogeneous entity, different disease-constellations determine different outcomes (Zador et al. 2019). Importantly, accounting for comorbidities improves prognostication in critical care (Nielsen et al. 2019). One of the validated tools to assess the grade of multimorbidity is the Charlson Comorbidity Index (CCI) (Charlson et al. 1987). In the ICU population, CCI has been shown as a valuable addition to predicting both in-hospital, 30-day or 1-year mortality,

even after accounting for acute physiology scores (Zampieri and Colombari 2014; Stavem et al. 2017). In a study by Zampieri et al. (2014), an increase in 1 point in CCI corresponded with mortality odds ratio of 1.16 (1.07-1.27). Multimorbidity is often associated with polypharmacy, which is a risk in itself. For example, imposition of sepsis on an elderly patient receiving beta-blockers, angiotensin-converting enzyme inhibitors and paracetamol may not only hinder a rapid diagnosis, but also may impair certain compensatory mechanisms (e.g. tachycardia during vasodilation or renal vasoconstriction during relative hypovolaemia). Interestingly, in the VIP-2 study, accounting for polypharmacy (by using the Co-morbidity and Polypharmacy score) made it easier to single out those with a poorer prognosis but did not add any prognostic value to a model containing age, SOFA score, ICU admission diagnosis and frailty.

Cognition

Preexisting cognitive impairment (CI) may be present in over 40% of elderly patients admitted to the ICU (Pisani et al. 2003). CI assessment is difficult in the setting of acute critical illness. Critically ill patients are often exposed to various sedative and analgesic agents that may (at least temporarily) aggravate the already existing CI. Knowledge of the presence and severity of CI can be obtained either from medical history, from relatives or measured by the clinician [e.g. by using IQCODE score (Jorm 2004)]. Usually, IQCODE > 3.5 indicates cognitive decline. Interestingly, this score can be estimated by interviewing close family members, as done in the VIP-2 study (Guidet et al. 2020). In their study, cognitive decline was present in 30% of elderly patients. Greater cognitive decline was associated with 30-day mortality. However, calculation of frailty alone added just as much prognostic value as frailty and cognition measured together, which indicates close relationship between these two entities. Indeed, frail patients are more often found to

have a preexisting CI (Sanchez et al. 2020). Nevertheless, CI is a strong vulnerability factor for delirium (Krzych et al. 2020), which is a known and independent risk factor for mortality and long-term cognitive impairment (Pandharipande et al. 2014). Prevention of delirium improves patient outcomes (Kotfis et al. 2022). One strategy for avoiding delirium is to implement the ABCDEF bundle which underlines the importance of pain management, rapid extubation, non-use of benzodiazepines, routine delirium screening (e.g., CAM-ICU), early mobilisation and family support (Marra et al. 2017). In the elderly, implementation of such measures may be more challenging due to the preexisting CI (impaired communication), frailty (delayed mobilisation) or higher baseline pain due to immobility (Brunker et al. 2023). Importantly, choosing dexmedetomidine over propofol as a sedative drug has shown promise in reducing delirium incidence in the older population (Pereira et al. 2020).

often reluctant to accept life-sustaining treatments, especially invasive mechanical ventilation and renal replacement therapy. This highlighted quality of life as a factor valued the most by these individuals (Philippart et al. 2013). Meanwhile, in the ICE-CUB study, only 13% of elderly ICU patients were asked about their opinion regarding the ICU treatment prior to ICU admission (Le Guen et al. 2016). Understanding the patient's wishes means that even if organ support can be discontinued, comfort measures cannot be withdrawn, and suffering should be avoided at all times (Vincent and Creteur 2022).

Conclusion

In summary, treating an elderly patient over the age of 80 in intensive therapy requires the integration of many components (Figure 1) (Guidet et al. 2018; Jung et al. 2023). At present, there is no single tool for describing the critically ill elderly patient. There is a lack of dedicated guide-

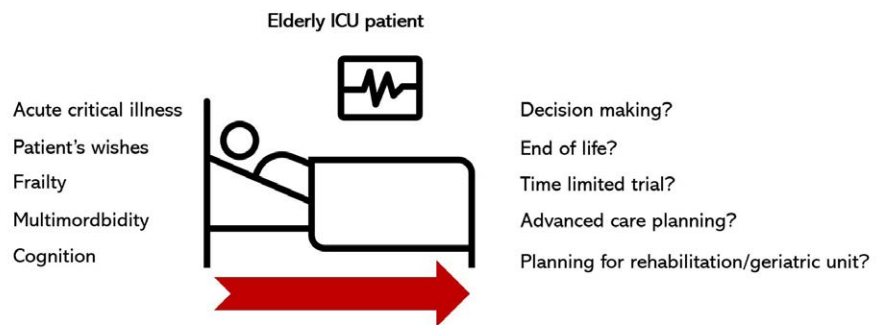


Figure 1. Older patients in the intensive care setting

Patient Wishes

Patient-centred care requires a deep understanding of patients' autonomy and wishes. Hospitalisation in the ICU can be one of the most traumatic experiences in a patient's life, and surviving a critical illness can be just the beginning of long-term psychological and functional sequelae (Burki 2019). In a study by Heyland et al. among the survivors, after 6 months only one-third was independent for all activities listed in Katz's scale (Burki 2019). Importantly, in the ETHICA study, elderly individuals were

lines and sufficient evidence regarding the therapeutic management of such patients.

A comprehensive analysis of the patient's wishes, acute illness, multimorbidity, cognitive status and frailty can help clinicians take optimal action. In doing so, it is worth remembering that age alone should never determine our clinical decisions.

Conflict of Interest

None. ■

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



Pablo Galindo-Vallejo

Division of Nephrology
Medical Center ISSEMYM
Ecatepec
Estado de México, México
galindoziip@yahoo.com
@galindoziip



Marian Elizabeth Phinder-Puente

Intensive Care Unit
General Hospital San Juan
del Río
Querétaro, México
draphinder@hotmail.com
@Mermaid_MD



Josué Luis Medina-Estrada

Intensive Care Unit
General Hospital IMSS
"Vicente Guerrero"
Acapulco, Guerrero, México
j_l_medina23@hotmail.com
@JosueMedinaMC



Fernando Jaziel López-Pérez

Emergency Department
General Hospital IMSS N° 1
Santiago, Coahuila, México
jaziel_lp@hotmail.com



Ernesto Deloya-Tomas

Intensive Care Unit
Hospital General San Juan
del Río
Querétaro, México
deloyajmr@hotmail.com
@E_DeloyaMD



Orlando Rubén Pérez-Nieto

Intensive Care Unit
Hospital General San Juan
del Río
Querétaro, México
orlando_rpn@hotmail.com
@orlandorpn

Kidney Replacement Therapy in the Intensive Care Unit

Kidney Replacement Therapy is a commonly used therapeutic strategy in the intensive care unit for patients who develop Acute Kidney Injury or who already have a diagnosis of chronic kidney disease. ICU staff should know when to use it and which type is most suitable for the circumstances.

Epidemiology and Outcomes of AKI

Acute kidney injury (AKI) is a common complication in critically ill patients. Up to 20-70% of patients will develop some stage of AKI in the intensive care unit (ICU) (Nisula et al. 2013; Libório et al. 2014; Kellum et al. 2015; Bouchard et al. 2015; Hoste et al. 2015). The requirement of kidney replacement therapy (KRT) in the ICU has been reported between 5-15% and will depend largely on the aetiology of the illness (Hoste et al. 2015). AKI has been associated with adverse clinical outcomes and mortality (Liangos et al. 2006). Mortality among critically ill patients and AKI is around 15-30% (Liaño and Pascual 1996; Uchino et al. 2005), rising up to 50-70% in patients that require KRT (Gaudry et al. 2016; Barbar et al. 2018; STARRT-AKI Investigators 2020; Cheng et al. 2020). The association between AKI and mortality in critically ill patients is likely due to multiple factors and not a direct causation; the severity of critical illness is one of the main factors involved in this association (Uchino et al. 2005; Parker et al. 1998).

Kidney Replacement Therapy in AKI

Types of KRT available can go from intermittent haemodialysis, continuous kidney replacement therapies (CKRT) (including peritoneal dialysis) and hybrid therapies that share characteristics of both intermittent and continuous methods (**Figure 1**). The type, modality, dose and timing of KRT have been widely explored as potential improvement variables in patients with AKI.

Indications of KRT

The indications for initiating KRT in the ICU are not perfectly defined. It is reasonable to consider therapy when a life-threatening circumstance arises, such as refractory hyperkalaemia and metabolic acidosis, despite medical treatment (e.g., diuretic therapy, IV sodium bicarbonate, etc.), blood urea nitrogen (BUN) > 140 mg/dL with persistent oliguria, pulmonary oedema, and other complications of fluid overload (Gaudry et al. 2021). It is reasonable to initiate therapy in a critically ill patient with progressive AKI accompanied by oliguria or anuria and a positive fluid balance that is expected to continue to increase in the coming days. On the other hand, if the patient shows improvement in urinary flow, delaying the initiation of renal replacement therapy could be considered.

Type of Therapy

A systematic review and meta-analysis failed to show any difference between intermittent therapies and continuous therapies in mortality or kidney recovery and only showed a potential benefit in mean arterial pressure and use of pressors when using continuous therapies (Rabindranath et al. 2007). At least two other meta-analyses comparing hybrid and intermittent therapies vs continuous therapies also failed to show improvement in mortality or kidney recovery (Zhang et al. 2015; Nash et al. 2017). A recent systematic review and network meta-analysis

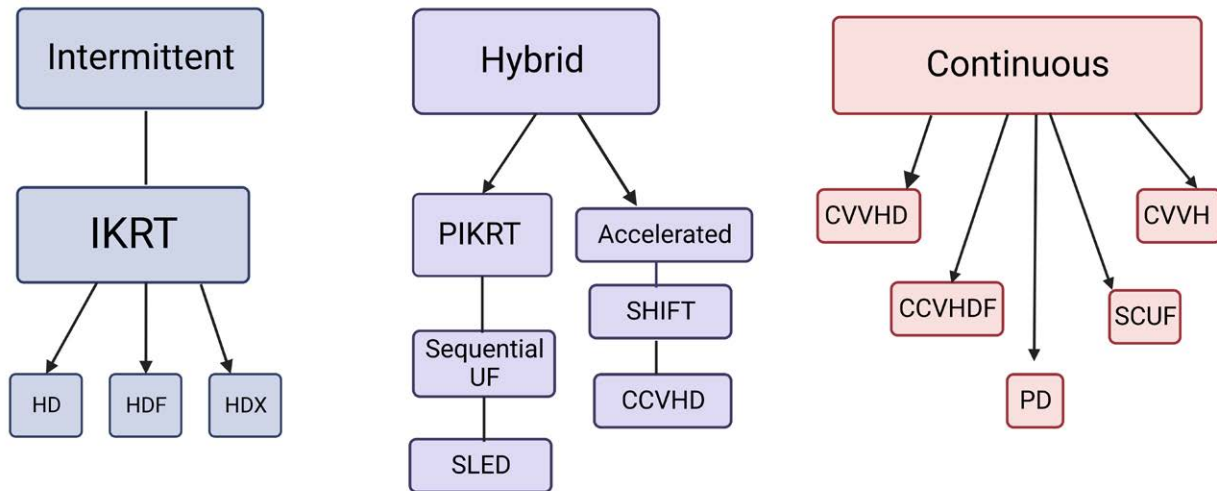


Figure 1. Types of kidney replacement therapy available

IKRT: Intermittent kidney replacement therapy; HD: Haemodialysis; HDF: Haemodiafiltration; HDX: extended haemodialysis; PIKRT: Prolonged intermittent kidney replacement therapy; SLED: sustained low efficiency dialysis; AVVH: Accelerated veno-venous haemofiltration; CVVHD: Continuous veno-venous haemodialysis; CCVHDF: Continuous veno-venous haemodiafiltration; CVVH: Continuous veno-venous haemofiltration; SCUF: sustained continuous ultrafiltration; PD: peritoneal dialysis.

that included all modalities, including peritoneal dialysis (PD), showed slightly better outcomes with PD but with very low certainty of evidence (Ye et al. 2021). A secondary analysis of the AKIK trial and IDEAL-ICU trials showed better survival with intermittent therapies in patients with SOFA score between 3-10 and no difference in mortality among patients with SOFA scores above 10 (Gaudry et al. 2022).

Modality

When using blood-based therapies, solutes can be cleared by convection, diffusion or adsorption. Convective therapies have the ability to remove medium size molecules more efficiently than diffusive therapies (Brunet et al. 1999). The potential benefit of removing medium size molecules in critically ill patients with AKI, especially in inflammatory states, has been explored. A systematic review and meta-analysis failed to show any difference in mortality when using haemofiltration (convection) vs haemodialysis (diffusion) (Friedrich et al. 2012).

Dose

Dosing of KRT in AKI can be challenging, especially when using different types of

KRT, mainly because traditional metrics of dosing can be different for every type of KRT (Table 1). Considering the nature of critically ill patients, higher doses have been proposed as an improvement clinical variable. In CKRT, giving more than 20-25 ml/kg/hr has failed to show any clinically relevant advantage in multiple studies and systematic reviews (Jun et al. 2010; Bellomo et al. 2009; Palevsky et al. 2009). In a clinical trial, intermittent haemodialysis (IHD) showed better outcomes when given daily (weekly KTV 5.8) versus alternate day (weekly KTV 3) but concluded that the results reflected the expected hazard associated with inadequate dosing of therapy rather than a benefit to an augmented dose of therapy (Schiffel et al. 2002). In hybrid therapies, a study failed to show any difference in survival or kidney

improvement when comparing standard extended dialysis (daily treatment and target BUN < 56-70 mg/dl) vs intensified extended dialysis (two sessions per day and target BUN < 42 mg/dl) (Faulhaber-Walter et al. 2009). In PD, no difference in mortality was found when comparing intensified high-volume PD (weekly KTV 5.6) vs standard high-volume PD (weekly KTV 3.5) (Ponce et al. 2012); a later study showed that even minimal standard dosage (weekly KTV 2.2) was not inferior to standard high-volume PD (weekly KTV 3.5) (Parapiboon and Jamratpan 2017).

Timing

Early initiation of KRT (before traditional KRT indications) has been widely studied with overwhelming results proving no difference in survival or kidney recovery

KRT	CKRT	IHD	Hybrid	PD
Metric	Effluent volume in ml/kg/h	Weekly KTV	Weekly KTV	Weekly KTV
Recommended dose	20-25 ml/kg/h	Weekly KTV of at least 2.1	Weekly KTV of at least 2.1	Weekly KTV of 2.2- 3.5

Table 1. Traditional metrics of KRT dosing in AKI

when compared to a late strategy, however systematically showing that nearly 50% of patients that were included in the late strategy never needed KRT (Gaudry et al. 2016; Barbar et al. 2018; STARRT-AKI Investigators 2020). AKIKI 2 trial showed no difference in survival between a late strategy (72 oliguric or BUN 112 mg/dl) and a very late strategy (BUN 140 mg/dl, overload, acidosis, hyperkalaemia) (Gaudry et al. 2021).

Rationale for Prescribing and Delivering KRT

To this day, we have learned that KRT will not give additional benefit to survival or kidney recovery no matter what type, modality, dose or timing is prescribed. Therefore indications, dosing and timing of KRT have to be focused only on solute and volume control (traditional indications). The type and modality of KRT will depend on technology and human resources available.

Technical and kinetic aspects of KRT
Solute and volume control can be achieved mainly by understanding and managing small molecule kinetics. The concepts of efficiency, intensity, frequency and efficacy are fundamental to understanding the different virtues and capacities of all the types of KRT (Pisitkun et al. 2004):

- **Efficiency:** is represented with clearance (K) (volume completely cleaned of a particular solute in a particular time) normally represented in ml/min. (K) will depend on variables related to the molecule itself (size, electric charge, molecular configuration), the host (volume of distribution, protein binding, half-life) and the clearance apparatus (blood and dialysate flow, type of membrane and mechanism of transport).
- **Intensity:** The total volume represented by the product of efficiency times the total time of therapy (K x

total therapy time).

- **Frequency:** The total volume represented by the product of efficiency, intensity and the number of therapies given in a week (K x total therapy time x number of therapies in a week).
- **Efficacy:** represents the effective clinical outcome. Considering all the evidence to this day, the best efficacy metric in AKI and critically ill patients is volume and solute control.

Types of KRT need to be prescribed according to their capabilities to achieve efficacy. For example, to achieve solute and volume control, low-efficiency therapies such as CKRT and PD need high intensity to achieve the goal, while low-intensity therapies such as IHD need a high efficiency to achieve the same goal. Hybrid therapies will target both characteristics according to the particular clinical need (Table 2).

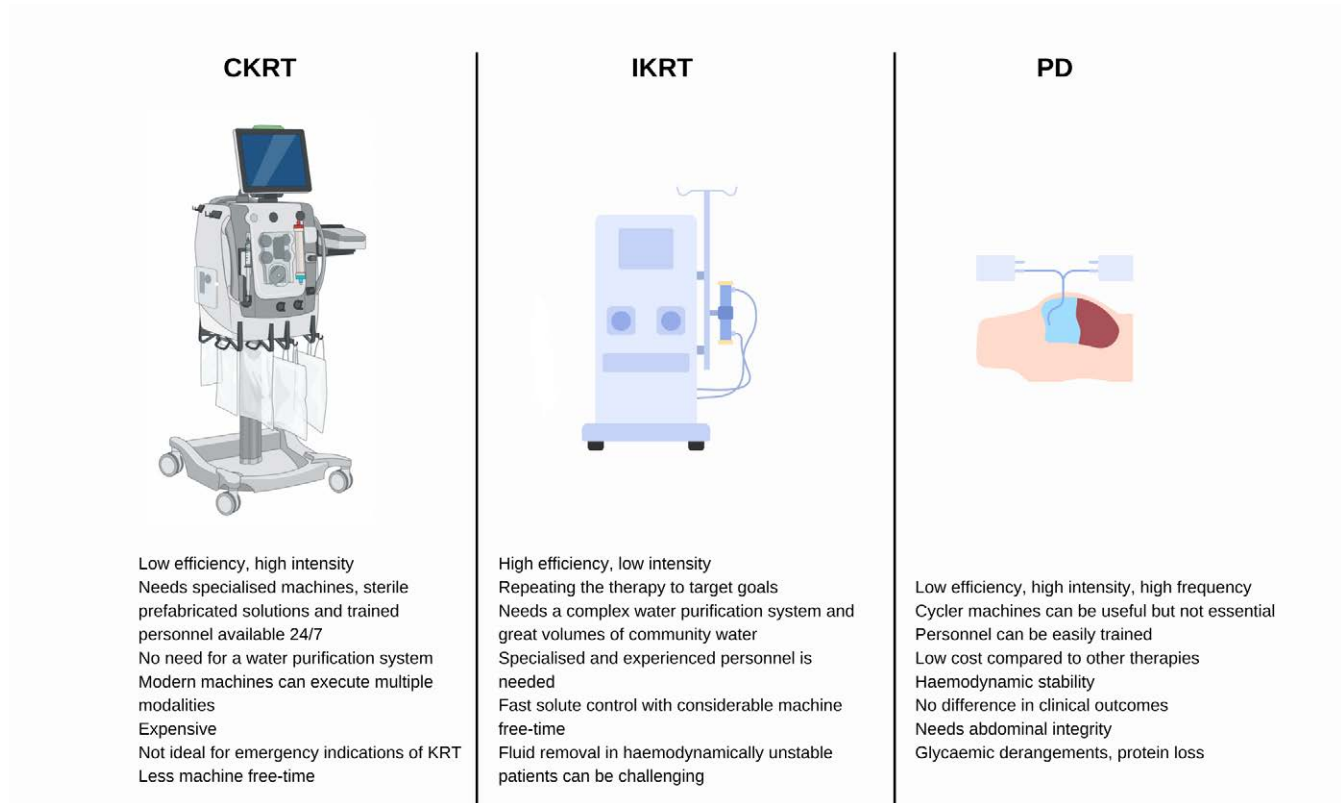


Figure 2. Particular aspects of Kidney Replacement Therapy

Therapy	Efficiency (ml/min)	Intensity (ml)	Frequency (ml)
IHD 4 h 4 x week	200	48,000	192,000
PIKRT 10 h x 4 week	80	48,000	192,000
CKRT 24 h x 7 week	33	48,000	336,000
PD 24 h x 7 week	12	18,000	126,000

Table 2. Efficiency, intensity and frequency of different therapies

IHD: Intermittent Haemodialysis; PIKRT: Prolonged intermittent Kidney Replacement therapy; CKRT: Continuous Kidney Replacement Therapy; PD: Peritoneal dialysis

Kidney Replacement Therapy - Particular Aspects

Intermittent kidney replacement therapies

Mainly extrapolated from chronic haemodialysis, IKRT has been used in AKI since the beginning of dialysis. Modalities can include conventional haemodialysis, on line haemodiafiltration and extended haemodialysis.

- Kinetic characteristics: IKRT are high-efficiency and low-intensity therapies.
- Priorities when prescribing: optimising efficiency (blood flow, dialysate flow, vascular access, membranes) and repeating the therapy to target goals.
- Technical aspects: needs a complex water purification system and great volumes of community water; very specialised and experienced personnel are needed to deliver therapy.
- Pros: fast solute control with considerable machine free time.
- Cons: fluid removal in haemodynamically unstable patients can be challenging. Being a high-efficiency therapy, fast removal of solutes will considerably reduce the removal rate of solutes from other compartments (first-order kinetics), and most patients will require multiple sessions to maintain solute control.

Continuous kidney replacement therapy

From pump-less arteriovenous haemofiltration circuits to complex, highly technical machines, CKRT has been present in critically ill patients with AKI for quite some time now (Samoni et al. 2021).

Modern machines opened the possibility for multiple modalities and options for prescription, including continuous veno-venous haemofiltration, haemodialysis, haemodiafiltration and sustained continuous ultrafiltration (SCUF).

- Kinetic characteristics: CKRT are low-efficiency and high-intensity therapies.
- Priorities when prescribing: being a therapy with very low efficiency, circuit patency is the main priority in these therapies (anticoagulation, filtration fraction, vascular access, monitoring, trained personnel).
- Technical aspects: CKRT needs specialised machines, sterile prefabricated solutions and trained personnel available 24/7.
- Pros: can achieve a very low ultrafiltration rate, osmolarity changes are subtle, no need for a water purification system, modern machines can execute multiple modalities.
- Cons: expensive therapy in comparison with other options, not ideal for emergency indications of KRT (acidosis, hyperkalaemia), considerably less free machine time.

Hybrid therapies

These therapies are born from the adaptation of available tools to achieve particular clinical needs. Hybrid therapies can go from IKRT machines trying to emulate CKRT and vice versa. Therefore, hybrid therapies can be grouped into prolonged intermittent therapies (PIKRT) and accelerated continuous therapies. Most common PIKRT protocols are sustained low efficiency

dialysis (SLED), extended daily dialysis (EDD) and intermittent haemodialysis with sequential sustained ultrafiltration. Accelerated protocols include accelerated veno-venous haemofiltration and SHIFT CVVHD (Zhang et al. 2015; Gashti et al. 2008; Duran and Concepcion 2020).

- Kinetic characteristics: efficiency and intensity are variable and according to clinical needs.
- Priorities when prescribing: optimising efficiency and watching for circuit patency.
- Technical aspects: HD or CKRT machines, off-label circuit adaptations, therapies less than 24 hours, trained personnel.
- Pros: best of both worlds with the tools available, without clinical implications, free machine time.
- Cons: centre protocol dependent, centre-to-centre variability, dosing medications can be challenging.

Peritoneal dialysis

PD has been used for AKI since 1946, but the introduction of extracorporeal therapies led to a drop in its use. Nonetheless, in low-income countries, acute PD never stopped being an option (Ponce et al. 2017). It was not until recent years with COVID-19, that developed countries turned to PD as a viable option. To this day, there is enough evidence of safety, viability and at least no inferiority when compared to other therapies (Ye et al. 2021; Gabriel et al. 2008; Ponce et al. 2013; George et al. 2011; Liu et al. 2017).

- Kinetic characteristics: very low-efficiency high intensity and high frequency.
- Priorities when prescribing: catheter patency, high volume and high-intensity therapy.
- Technical aspects: Requires experience in cath installation for surgical or percutaneous techniques, prefabricated sterile PD solutions, cycler machines can be useful but not essential, personnel can be easily trained, and therapy does not need continuous monitoring.
- Pros: low cost compared to other thera-

pies, haemodynamic stability, no difference in clinical outcomes with more complex and expensive therapies.

- Cons: needs abdominal integrity, can cause glycaemic derangements, protein loss, and rise in intra-abdominal pressure.

Conclusion

AKI in the ICU is very common, with

very high mortality, especially when KRT is needed. Multiple efforts to improve outcomes in these patients by using KRT types, modalities, dosing and timing have failed. To this day, there is no evidence to support a particular type of KRT in patients with AKI. Therefore all efforts should be focused on solute and volume control with the technology, experience and personnel available. Each KRT type has particu-

lar kinetic and technical considerations that make them unique and should be prescribed, managed and monitored with a profound understanding of technical and clinical aspects.

Conflict of Interest

None. ■

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Marianna Puccini

Department of Cardiology
Angiology and Intensive Care
Medicine
Campus Benjamin Franklin
Deutsches Herzzentrum der
Charité
Berlin, Germany
marianna.puccini@dhzc-charite.de



Ursula Rauch-Kröhnert

Department of Cardiology
Angiology and Intensive Care
Medicine
Campus Benjamin Franklin
Deutsches Herzzentrum der
Charité
Berlin, Germany
ursula.rauch@dhzc-charite.de

Introduction

Euglycaemic diabetic ketoacidosis (EDKA) is an uncommon but potentially life-threatening emergency condition that is characterised by euglycaemia and elevated ketones in the presence of metabolic acidosis (Long et al. 2021; Lipscombe et al. 2018). Classically, diabetic ketoacidosis (DKA) is characterised by hyperglycaemia, an anion gap metabolic acidosis, and ketosis. DKA occurs typically in patients with type 1 diabetes and less frequently in patients with type 2 diabetes (Kitabachi et al. 2009). Munro et al. (1973) first recognised that diabetic ketoacidosis can be masked by euglycaemia. EDKA is defined by relative euglycaemia (serum glucose less than 13.9 mmol/l), bicarbonate less than 15 mmol/l, an anion gap greater than 12 mmol/l, and ketosis, leading to a pH in venous blood of less than 7.3 (Bonora et al. 2020; Rawla et al. 2017). Historically, 3 to 7% of the patients admitted to the hospital with diabetic ketoacidosis exhibited euglycaemia (Liu et al. 2020; Long et al. 2021).

More recently, EDKA has been associated with the use of sodium-glucose cotransporter-2 (SGLT2) inhibitors (Diaz-Ramos et al. 2019; Liu et al. 2020; Rauch and Landmesser 2021), and the incidence of EDKA has risen because of increased

Detecting Euglycaemic Diabetic Ketoacidosis Associated With SGLT2 Inhibitors

SGLT2 inhibitor associated EDKA is becoming more prevalent due to the increasing use of SGLT2 inhibitors in cardiovascular medicine and type 2 diabetes. Physician awareness and knowledge about the disease and diagnostic tools need to improve for better management. Point of care blood testing for ketones can allow for rapid and accurate diagnosis.

use of these medications in patients with type 2 diabetes (Blau et al. 2021; Rawla et al. 2017). Patients with insulin-dependent diabetes are more prone to develop EDKA when treated with SGLT2 inhibitors (Blau et al. 2021; Rawla et al. 2017). Although the prevalence of SGLT2 inhibitor associated EDKA is on the rise, it is still relatively uncommon (approximately 2 per 1000 patients). SGLT2 inhibitor associated diabetic ketoacidosis may still be associated with significantly increased glucose levels, or more commonly, normal to slightly elevated glucose levels (Arzneimittelkommission der deutschen Ärzteschaft 2018). EDKA is often undiagnosed due to relatively low serum glucose levels, contributing to delayed therapy and worse clinical outcomes (Long et al. 2021; Blau et al. 2021).

Due to the overall increase in incidence of EDKA with more frequent SGLT2 inhibitor use, the United States Food and Drug Administration (FDA) and the European Medicine Agency (EMA) recently announced warnings, reminding prescribers and medical staff to be alert for SGLT2 inhibitor associated EDKA. Guidelines to reduce the occurrence of SGLT2 inhibitor associated EDKA have been added, especially to lessen the risk of developing ketoacidosis after surgery.

Pathophysiology of SGLT2 Inhibitor Associated EDKA

Absolute or relative insulin deficiency asso-

ciated with insulin resistance contributes to the pathophysiology of EDKA (Kitabachi et al. 2009; Long et al. 2021; Modi et al. 2017). Elevated glucagon generation and release of free fatty acids triggers ketogenesis with production of ketone bodies, leading to acidosis (Figure 1). The synthesis of glucose is at least temporarily reduced due to fasting conditions, as is common under different triggers of stress, or, alternatively, the urinary glucose excretion is increased, e.g. as result of SGLT2 inhibitor intake (Bonora et al. 2020; Long et al. 2021; Rosenstock et al. 2015; Taylor et al. 2015). Table 1 summarises the different conditions that can be associated with EDKA.

SGLT2 inhibitors were initially designed as antidiabetic drugs, which inhibit the sodium-glucose cotransporter 2 protein located in the proximal renal tubules (Rauch and Landmesser 2021). The inhibition of SGLT2 in the kidney abolishes the reabsorption of glucose from urine, contributing to increased insulin-independent excretion of glucose and sodium via the urine. In addition to reducing glucose levels SGLT2 inhibitors also decrease HbA1c values, blood pressure and weight. Importantly, several large randomised clinical studies have shown that SGLT2 inhibitors have cardioprotective and nephroprotective effects (The Nuffield Department of Population Health Renal Studies Group and the SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium 2022; Vaduganathan et al. 2022). SGLT2 inhibi-

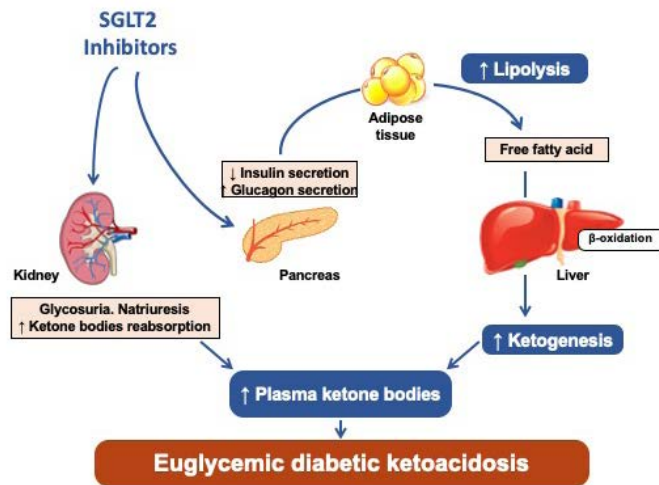


Figure 1. Effect of SGLT2 inhibitors on glucose and lipid metabolism

tors are indicated for the treatment of diabetes, heart failure and chronic kidney disease. The approved SGLT2 inhibitors in Germany include dapagliflozin, empagliflozin, ertugliflozin and sotagliflozin. Ipragliflozin, remogliflozin, sergliflozin and tofogliflozin are other SGLT2 inhibitors not approved in Germany. Due to the low benefit assessment, canagliflozin ceased to be sold in Germany in 2014. In Switzerland, canagliflozin, dapagliflozin and empagliflozin have been approved for use.

Due to the SGLT2 inhibitor associated increase in urinary glucose excretion and accompanied reduction in insulin secretion, serum glucose levels can be much lower in SGLT2 associated DKA than in other cases of DKA. In addition, SGLT2 inhibitors cause an increased reabsorption of ketone bodies in the kidney and, therefore, increase ketone levels in the circulating blood. The heightened level of ketones triggers ketoacidosis, measurable as anion gap (Bonner et al. 2015; Ferranini et al. 2014; Pfütznner et al. 2017).

In several studies, it was noted that 12% to 20% of patients with type 2 diabetes that were treated with SGLT2 inhibitors had an asymptomatic elevation of ketone bodies in blood (Modi et al. 2017; Rawla et al. 2017). Moreover, the majority of SGLT2 inhibitor associated diabetic ketoacidosis was found to be EDKA with a glucose level below 13.9 mmol/l. Regarding the increased risk of EDKA a hazard ratio (HR)

of 3.58 was reported for canagliflozin, a HR of 2.52 for empagliflozin and of 1.86 for dapagliflozin (Douros et al. 2020). Of note, the likelihood to suffer from EDKA is greater in patients on SGLT2 inhibitors who have decreased glycogen stores or a lower body mass index (Handelsman et al. 2016).

- SGLT2 inhibitor use
- Fasting state, perioperative setting
- Surgery, e.g. bariatric operations
- Ketogenic diet
- Anorexia
- Intoxication, alcohol, cocaine
- Insulin pump
- Gastroparesis
- Glycogen storage disease
- Infections, sepsis
- Gastroenteritis, pancreatitis
- Renal disease
- Liver disease
- Pregnancy

Table 1. Conditions for increased risk of EDKA

Diagnostic Tools for the Assessment of SGLT2 Inhibitor Associated EDKA

The clinical signs and symptoms of patients with EDKA are comparable to those with diabetic ketoacidosis with elevated blood glucose levels (Long et al. 2021; Modi et al. 2017). Unfortunately, most of these symptoms are vague and non-specific (e.g., nausea, exhaustion, abdominal pain, confusion, kissing mouth breathing (Long

et al. 2021; Modi et al. 2017). Several clinical courses have been described with SGLT2 inhibitor associated EDKA, leading to life-threatening conditions. Thus, a high index of suspicion for EDKA should be maintained in this patient group, and checking ketones with a point of care device can establish the diagnosis and be lifesaving. Roughly half of the patients with EDKA have a delay in diagnosis (Dizon et al. 2017). Moreover, these patients often come late to the emergency room because home measurements of blood glucose are not significantly increased (Modi et al. 2017). A fruity odour of the breath is a characteristic feature of ketoacidosis together with dehydration visible as dry skin with reduced skin turgor, a dry tongue and mucous membranes. Usually, the patients exhibit tachycardia accompanied with hypotension, the shock index is often positive and admission to intensive care treatment immediately required. To prevent the delay of diagnosis, EDKA should not only be considered in any diabetic patient on SGLT2 inhibitor therapy but also in those with risk factors for EDKA, such as alcohol intoxication, chronic liver disease, fasting conditions, or typical clinical presentation of symptoms as mentioned above (Dhatariya 2016). Early ketone measurement can quickly establish or rule out the diagnosis.

Electrolytes, glucose, creatinine and eGFR as well as liver enzymes, venous blood gas, and serum ketones comprise the laboratory evaluations, which should be performed in case of suspected EDKA. Due to above mentioned euglycaemia in EDKA, elevated glucose levels in blood are not a good indicator of SGLT2 inhibitor associated DKA. A pH of less than 7.30, bicarbonate less than 14 mmol/l and elevated anion gap more than 12 mmol/l as well as ketone bodies are typical for diabetic ketoacidosis. Blood ketones (specifically β -hydroxybutyrate) are the predominant ketone bodies in DKA and have a higher sensitivity and specificity for DKA than urine ketones. In contrast to blood ketones, urine ketone levels in patients treated with SGLT2 therapy might be falsely low due to reabsorption of ketone bodies from the

Category	Blood ketones	Urine ketones
Parameter (measured)	β -hydroxybutyrate as ketone body predominantly produced in DKA measures current concentration, progress controls useful for therapy monitoring	Acetoacetate as by-product measures average urine concentration
Reliability of results	Higher sensitivity and specificity for DKA	Lower sensitivity and specificity for DKA
Time	Rapid, immediate measurement	Possibly delayed at sample collection due to dehydration
Measurement method	POCT meter	Urine test (strip)

Table 2. Comparison of the advantages and disadvantages of ketone measurement methods
DKA = diabetic ketoacidosis. Adapted according to Dhatariya et al. 2016

urine in the tubules of the kidney, leading to a false negative result (Handelsman et al. 2016; Long et al. 2021).

Guidelines recommend using β -hydroxybutyrate in blood as the diagnostic test in the assessment of EDKA (Handelsman et al. 2016). Assessing β -hydroxybutyrate is preferable rather than relying on acetoacetate, because of the much higher concentration of the β -hydroxybutyrate than acetoacetate in blood (ratio of 7-10:1) (Dhatariya 2016; Handelsman et al. 2016; Long et al. 2021; Kilpatrick et al. 2022). Serum β -beta-hydroxybutyrate levels > 3 mmol/L in paediatric patients and > 3.8 mmol/L in adults are reliable for diagnosing DKA (Arora et al. 2011; Kilpatrick et al. 2022; Sheikh-Ali et al. 2008). If serum beta-

hydroxybutyrate is not available, serum acetoacetate and/or urine ketones can be utilised, although these measurements are less specific and sensitive for EDKA.

Blood ketone measurements offer other advantages as well. Blood is easily obtained, where urine may not be due to the dehydration associated with DKA (Kilpatrick et al. 2022; Dhatariya 2016). By using a point-of-care method directly at the site of the patients, measurements can be carried out immediately and results are obtainable within seconds. Thus, the assessment of blood ketone levels by a point-of-care system is today the fastest and most practical method to guarantee a fast and reliable diagnosis (Table 2). Although some disparity regarding the use of blood ketones to assess the success of treatment exists, the contemporary identification and management of patients with suspected diabetic ketoacidosis makes even more use of the measurement of blood ketones than some guidelines currently recommend (Kilpatrick et al. 2022).

Conclusion

SGLT2 inhibitor associated EDKA is becoming more prevalent due to the increasing use of SGLT2 inhibitors in cardiovascular medicine and type 2 diabetes. EDKA is often misdiagnosed or diagnosed late due to relatively low serum glucose, contributing to delayed therapy and worse clinical outcomes. The physician's awareness and knowledge about the disease and diagnostic tools need to improve for better management of patients with EDKA. Point of care blood testing for ketones can allow for a rapid and accurate diagnosis.

Key Points

- Diabetic ketoacidosis is a serious metabolic derailment of diabetes caused by insulin deficiency and is usually characterised by hyperglycaemia as well as ketosis and acidosis.
- Euglycaemic diabetic ketoacidosis (EDKA) has become a major topic of discussion due to its increased incidence associated with the widespread use of SGLT2 inhibitors.
- SGLT2 inhibitors increase renal glucose excretion, reduce blood glucose level and increase the formation and accumulation of ketone bodies, which is further augmented by an increased absorption of ketone bodies in the kidney.
- SGLT2 inhibitor associated EDKA is often undiagnosed or diagnosed late due to relatively low serum glucose levels.
- The diagnosis of EDKA should be suspected in patients on SGLT2 inhibitors and ketones should be measured promptly to avoid progression to life-threatening disease.
- Guidelines recommend measuring the pH together with ketones in blood but not urine as the most specific and sensitive method.
- Serum ketones can easily be quantified by point-of-care systems, which is a fast and practicable method to ensure the diagnosis of EDKA.

Disclaimer

Point-of-View articles are the sole opinion of the author(s) and they are part of the ICU Management & Practice Corporate Engagement or Educational Community Programme.

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Maria-Jimena Muciño-Bermejo

Intensive Care Unit
The American British Cowdray
Medical Center
Mexico City, Mexico

International Renal Research
Institute of Vicenza (IRRIV)
Vicenza, Italy

Medical Division
Médicins Sans – Operational
Centre Barcelona-Athens
Barcelona, Spain
scrivere.a.jimena@gmail.com



Claudio Ronco

International Renal Research
Institute of Vicenza (IRRIV)
Vicenza, Italy

Department of Nephrology
Dialysis and Transplantation
San Bortolo Hospital
Vicenza, Italy

Department of Medicine
University of Padova
Padova, Italy
cronco@goldnet.it

Introduction

As with any other species, human activity modifies the environment at multiple levels and may or may not alter the ecological balance. As from the industrial revolution, the impact of human activities on the environmental balance increased exponentially; even when more efficient use of natural resources become available, its cost diminishes, increasing its demand as per the [Jevons Paradox](#), leading to increased use of natural resources and continuous waste production, leading to climate change.

The healthcare industry is one of the highest carbon-intensive service sectors representing 4.4–4.8% of worldwide greenhouse gas (GHG) emissions and similar fractions of toxic air pollutants (Eckelman et al. 2020; Lenzen et al. 2020).

Life cycle assessment (LCA) is a [cradle-to-grave assessment](#) that impacts every stage of a product's life cycle, from natural resources extraction, process and manufacturing, transportation, use, and disposal. LCA has been introduced as the definitive method for comparing the ecological footprints of products, processes, and systems (McGain et al. 2020).

In order to improve the sustainability of critical care, LCAs with specific

Sustainability and Extracorporeal Organ Support

Extracorporeal organ support (ECOS) involves an extensive use of healthcare resources and clinical problem-solving challenges. The feasibility of applying known ecological analysis and sustainability strategies in healthcare need to be started in this setting.

outcomes are compared, such as the carbon footprint of reusable versus single-use devices, allowing to avoid, reduce, reuse, recycle, and reprocess strategies to prospect. [Sustainability](#) in healthcare must take into account not only clinical outcomes but also economic, social and environmental costs (McGain et al. 2020).

A significant part of the healthcare-related environmental emissions is indirect or implicit in the manufacturing of products and energy that supports hospitals, so an integrated approach to intensive care sustainability must take into account not only solid waste recycling but also carbon emission reduction and efficient utilisation of natural resources towards a circular economy (McGain et al. 2020).

Carbon Footprint in Critical Care Facilities

Healthcare is carbon intensive. Data from the National Health Service in the United Kingdom indicates that two-thirds of GHG emissions arise from purchasing consumables and one-third directly from hospital energy use and transport. Among healthcare facilities, intensive care units (ICU) considerably consume items and generate waste.

A critically ill patient with septic shock has a daily carbon footprint that equates to 3.5 times that of a healthy individual in the U.S. (McGain et al. 2018; Baid and Damm 2021).

McGain et al. (2018), in a prospective, observational LCA that included the use of energy (for heating, ventilation, air conditioning, lighting, machines), consumables and waste involved in the ICU treatment

of septic shock patients, described that the average energy use per patient could reach 272 kWh/day, while the average use of single-use materials per patient per day could reach 8.7 kg. Daily GHG emissions expressed in carbon dioxide equivalent (CO₂-e) could reach 228 kg CO₂-e, with natural gas being the most important source of GHG emissions. This data showed that carbon footprint was mainly due to the use of energy for heating, ventilation and air conditioning, with consumables being less important.

The ECOS Definition and Healthcare Needs Implications

In critically ill patients with severe forms of single or multiple organ dysfunction, pharmacological and/or surgical treatment may not be enough. In these complex cases, a single form of extracorporeal organ support (ECOS) or even multiple organ support therapy (MOST) may be needed and is increasingly seen as a feasible approach (Ronco et al. 2019).

Considering the complex crosstalk mechanism between native organs, it is not surprising that patients with one organ failure may develop multiple organ dysfunction syndrome (MODS) later in the clinical course, thus needing multiple organ extracorporeal support, either by combined or integrated ECOS devices (Ronco et al. 2019; Huber et al. 2020).

MODS is one of the most common causes of death in ICU patients. Based on extensive and long-term use of renal replacement therapy (RRT), ECOS became available for other organ failures. In the beginning, these techniques, including RRT,

extracorporeal membrane oxygenation (ECMO), extracorporeal CO₂ removal (ECCO2R) and extracorporeal liver support, were used as stand-alone single-organ support systems (Ronco et al. 2019; Huber et al. 2020).

The concept of MOST and giving simultaneous and combined support for different failing organs was described more than 15 years ago by Ronco and Bellomo. This concept implicates the advent of multidisciplinary and multiprofessional strategies in the treatment and improvement of MODS patients in the ICU (Ronco et al. 2019; Huber et al. 2020).

Even when there are no specific LCA studies for patients with MODS under MOST, several studies have investigated the ecological burden and plausible strategies to improve the ecological (and human) burden cost/benefit ratio (Huber et al. 2020). First of all, material flow should be taken into account, as it is common to all of the ECOS systems in the ICU. A material flow analysis (MFA) in an academic ICU showed a material mass inflow of 247,000 kg per year, of which 50,000 kg was incinerated as hazardous hospital waste. The environmental impact per patient resulted in 17 kg of mass, 12 kg CO₂ eq,

300L of water usage and 4 square metres of agricultural land occupation per day, with five identified hotspots: non-sterile gloves, isolation gowns, bed liners, surgical masks and syringes (Hunfeld et al. 2023; Barraclough and McAlister 2022).

As many patients needing ECOS will need surgical procedures or may use anaesthetic gases as a part of the sedation strategy during ventilatory support, the ecological burden of anaesthetic gases should be taken into account (Soreze et al. 2020; Fabien et al. 2022; Bellgardt et al. 2021; Bomberg et al. 2016; Romagnoli et al. 2017; Herzog-Niesery et al. 2019).

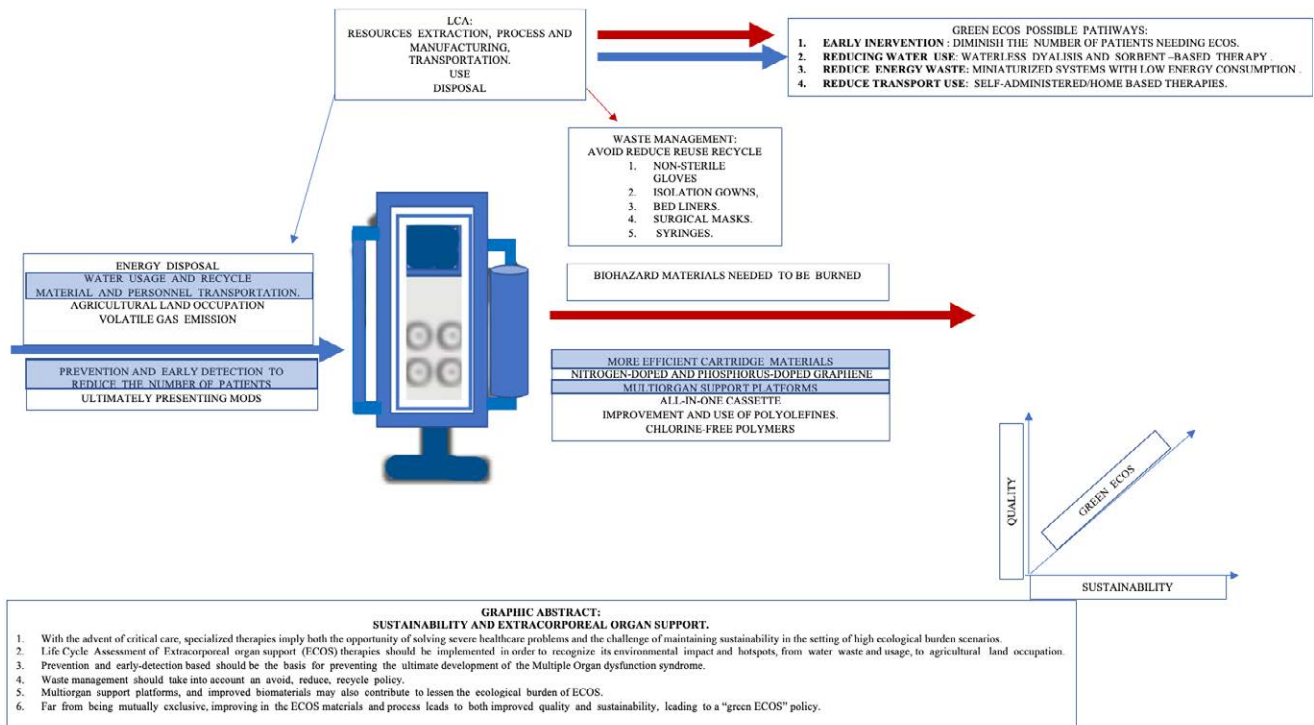
Even when climate change was initially postulated by Fourier in the 1820s, it was in the 1970s that real concerns emerged, with the majority of increases occurring after 1980. Since the 1960s, the effects of other increasing GHGs (most of all CH₄, N₂O, O₃, and halogenated compounds) contribute as much to global warming as increasing CO₂ itself, with halogenated compounds (including volatile anaesthetic agents) accounting for approximately 11%. Nitrous oxide is responsible for the majority of ongoing ozone depletion and approximately 6% of anthropogenic global warming (McGain et al. 2020; Barraclough

and McAlister 2022).

All heteronuclear gases, as well as some limited homonuclear molecules, vibrate/rotate/stretch in the presence of infrared radiation (infrared active). Absorption and subsequent emission of infrared light reduces the heat radiation from Earth to space (also called heat retention), described by the term global warming potential (GWP). Carbon dioxide has, by definition, a GWP of 1, while N₂O has a GWP of 265 (McGain et al. 2020; Barraclough and McAlister 2022).

Solar radiation enters the atmosphere, and [infrared radiation](#) exits as heat. If more radiation is entering Earth than leaving, it is called radiative forcing. Halogenated anaesthetic ethers, isoflurane, enflurane, and desflurane have similar radiative forcings; while sevoflurane has about 25% less radiative forcing. Halothane, not having the great infrared absorption of an ether group, has about half of sevoflurane's radiative force (McGain et al. 2020; Barraclough and McAlister 2022).

Expressing these CO₂e emissions as equivalent distance driven, one MAC-hour (2.2% sevoflurane, 1.2% isoflurane, 6.6% desflurane, at 1L min⁻¹ fresh gas flow), sevoflurane is equivalent to 6.5



km, isoflurane to 13 km, and desflurane 300 km (McGain et al. 2020). The most important, safe, and effective measures to reduce carbon related to anaesthesia are to avoid desflurane and N₂O, practice low-flow anaesthesia, and minimise the use of inhalation agents by using regional and/or total intravenous anaesthesia (TIVA).

Even when there are no large studies on specific ECMO, albumin dialysis or haemadsorption carbon footprint, haemodialysis may be considered a starting comparison point in this model as various initiatives, including the green dialysis initiative, are aimed to address environmental sustainability regarding RRT, and some strategies and algorithms may serve as a template for developing those aimed at other forms of ECOS (Gauly et al. 2022; Barraclough and Agar 2020).

Considered emissions taken into account in the already described studies on RRT carbon footprint have included electricity, natural gas, water, and supply use; patient and staff travel distance, as well as biohazard and landfill waste emission (Sehgal et al. 2022; Barraclough and McAlister 2022).

A study of LCA of GHG emissions in carbon dioxide equivalents (CO₂-eq) associated with 209,481 haemodialysis treatments in the year 2020 reported that annual emissions per facility averaged 769,374 kg CO₂-eq, being the largest contributors to total emissions - patient and staff transportation (28.3%), electricity (27.4%), and natural gas (15.2%) (Gauly et al. 2022; Sehgal et al. 2022).

Each treatment equated to 58.9 kg CO₂-eq, with a three-fold variation across facilities, being the contributors with the largest variation in transportation, natural gas, and water. The annual emissions per haemodialysis facility equates to those in 93 homes; emissions per treatment are equivalent to driving an average automobile for 238 km. Over 500L of water, 7 kW of energy and approximately one kilogram of medical waste are consumed during haemodialysis (Gauly et al. 2022; Sehgal et al. 2022; Wieliczko et al. 2020).

Also, it should be taken into account that the production of 1L of ultrapure water for dialysis requires 1.5–1.7 raw

water (which means 60–70% water), but it is still portable and can be used for cleaning, washing or gardening, saving at least 100,000,000m³ annually (Wieliczko et al. 2020).

Regarding diminishing material waste by improving the efficacy and quality of the platform used in a new HD system, the conventional blood line system (and in the case of on-line haemodiafiltration, additionally a substitution line) is replaced by an all-in-one cassette system unifying all the components of the extracorporeal circuit, diminishing the total disposable weight and simplifying the operation of the HD system (Wieliczko et al. 2020).

Through cassette design improvement and the use of polyolefins, unused disposable is reduced by 100g in comparison to bloodlines used for other HD systems. For a centre performing 10,000 treatments annually, this leads to hazardous waste reduction by approximately 1500–2000 kg. Another alternative to reduce waste by design is performing on-line priming and rinsing in the set-up phase, as well as on-line infusions and reinfusion at the end of the session both in HD and on-line HDF instead of applying saline from an extra bag (Wieliczko et al. 2020).

Waste composition is also relevant to ensure the safe management of healthcare waste, as it is separated into infectious and non-infectious for incineration or landfill and recycling, respectively. For components that will be incinerated (including the extracorporeal system in HD), it is desirable that polyvinyl chloride (PVC) could be replaced by chlorine-free polymers in order to minimise the formation of dioxins and furans, which are generated at insufficiently high temperatures (Wieliczko et al. 2020; Barraclough and Agar 2020).

Another way of improving the sustainability of ECOS is improving the haemofilter, as per the functionality and footprint of the device: improving the quality of ECOS implies not only a water-saving strategy but may also diminish the waste of biohazardous materials:

Adding a biocompatible polymer coating agent to the haemofilters may lower the incidence of thrombosis of the haemofilter,

diminishing the number of haemofilters ultimately being used (Tagaya et al. 2019).

Extracorporeal blood purification can be achieved by diffusion (as in standard haemodialysis), convection (as in haemofiltration), diffusion and convection (as in haemodiafiltration) or by solute adsorption, based on mass separation by a solid agent (sorber). Haemoperfusion may also be used in combination with haemodialysis, haemofiltration and even haemodiafiltration, allowing for toxic solute removal from the blood with lesser use of water. Clinical uses of sorbents in sepsis, acute kidney injury, and liver diseases have so far provided data on their feasibility and safety (Ronco and Bellomo 2022).

Sorbent cartridge design should consider multiple aspects, including the cost of the polymers, high resistance to fouling, maximal biocompatibility, and the absence of undesirable side effects. The porosity, polymers, and internal pathways within the cartridge should maximise the mass transfer along the sorber bed, along with the prospected flow rate (Ricci et al. 2022).

Within the critical care scenarios, sorbents have proved to improve clinical outcomes, including diminishing hospital length of stay in multiple clinical scenarios, including ECMO, sepsis, liver failure, rhabdomyolysis and intoxication (Ricci et al. 2022).

The use of a polymeric sorber based on phenylglyoxaldehyde, that covalently binds urea under physiological conditions has been described as a sorber-based strategy for urea removal as a step towards the wearable artificial kidney (Jong et al. 2020).

Also, molecular dynamic simulation of urea removal on carbon nanosheets has been reported using nitrogen-doped and phosphorus-doped graphene. The results further offer attractive suggestions for novel adsorbents for artificial kidney devices and the development of novel and enhanced urea adsorbents (Karimi and Rahsepar 2022).

In addition, haemoperfusion with a neutral microporous resin column in patients with extrapulmonary sepsis-induced acute lung injury has reported removal of plasma and bronchoalveolar

lavage TNF- α and IL-1, improvement of PaO₂/FiO₂, as well as radiological improvement (Huang et al. 2013).

By reducing both water use and hospital length of stay, haemoperfusion techniques may ultimately reduce the total carbon footprint of a single MODS-related stay in ICU patients. Even when carbon footprint-oriented comparison clinical trials are yet to be developed, sorbent technology may represent a huge contribution to an environmentally friendly ECOS.

Conclusion and Perspectives

Time is pressing, and critical care medicine must participate in the race to zero-emission healthcare systems. ECOS represents both

clinical and ecological challenges, as it implies the challenge of solving severe healthcare problems while maintaining sustainability in high ecological burden scenarios (Bein et al. 2021). In order to improve the sustainability of ECOS, LCA of specific analysis should be done, while the feasibility of strategies already described in the setting of other hospital facilities and clinical scenarios, including RRT, should be considered for other ECOS scenarios (Baid and Damm 2021).

So far diffusion and convection-based extracorporeal therapies that require energy and water consumption have been used. New miniaturised systems with battery-operated pumps, low energy consumption

and waterless dialysis technologies based on sorbents are probably interesting pathways to undertake in order to reduce the ecological impact of ECOS on the ICU, and also to possibly provide the basis for self-administered or even home-based therapies. Clinical trials focused on both improving the efficacy and sustainability of ECOS are yet to come, as critical care poses an utmost responsibility for contributing to the health system sustainability challenge.

Conflict of Interest

None. ■

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Ravindra L Mehta

Professor Emeritus of
Medicine
Director UCSD CREST and
Masters of Advanced Studies
in Clinical Research Program
Department of Medicine
University of California San
Diego
USA
rmehta@ucsd.edu

Background

Multiorgan failure (MOF) and acute kidney injury (AKI) are frequently encountered in critically ill patients and often require acute dialysis for support to facilitate recovery. There is considerable variation in the application of dialysis that is associated with mortality rates >50% and high resource utilisation (Aglae et al. 2019; Ethgen et al. 2015; Silver et al. 2017; Dasta and Kane-Gill 2019; Gaudry et al. 2020; Harding et al. 2020; Ethgen et al. 2022). Decisions for acute dialytic intervention require consideration of who would benefit from dialysis and when would it be best to intervene (Macedo and Mehta 2017). Current guidelines for the timing of dialysis are often disparate and rely largely on the presence of specific indications to identify who needs dialysis with the urgency of intervention depending on the presence of life-threatening complications (NICE guidelines 2019; Bouchard and Mehta 2022). This approach makes it difficult to identify and track high risk patients before they meet an indication and to define the optimal time point for intervention based solely on the presence or absence of the indication. The underlying severity of kidney dysfunction (Stage of AKI, oliguria) is viewed as the major driver for dialytic intervention and was the primary inclusion criteria for all the trials (Gaudry et al. 2016; Zarbock et al. 2016; Barbar et al. 2018; Investigators Canadian Critical Care Trials Group et al. 2020). However, not all AKI stage 3 patients require dialysis and it is often started in the absence of AKI for fluid management or adjunctive organ support and AKI (Ostermann et al. 2016).

Recent trials have shown application of dialysis in the ICU is highly variable and based on current criteria results in over

Predictive Analytics for Kidney Support in the ICU

The timing and application of dialysis in the ICU is highly variable contributing to poor outcomes. A clinical decision support system (CDSS) incorporating a dynamic predictive algorithm for organ support could improve outcomes.

40% of patients not needing dialysis while those who receive it late have a 25% higher mortality (Bouchard and Mehta 2022). In the largest of these trials (STAART AKI) clinician equipoise was utilised to determine enrolment of patients who met a Stage 2 AKI, almost one third of patients were enrolled where the physician was uncertain of the benefit of dialysis (Investigators Canadian Critical Care Trials et al. 2020) An analysis of the patients screened and not enrolled in the STAART trial, showed that clinicians excluded over 89% of provisionally eligible patients due to their personal equipoise, however 8.7% of patients who were mandated immediate RRT were not dialysed and 11% who were considered to not require dialysis received it (Wald et al. 2021). In the latest AKIKI 2 trial comparing the effect of deferring dialysis for severe AKI until there was evidence of severe complications there was higher risk of mortality at 60 days despite similar rates of complications (Investigators

Canadian Critical Care Trials et al. 2020). In a post hoc analysis risk stratification profiles of patients dialysed within 48 hrs. of randomisation to a delayed strategy, showed that patients in the fourth and fifth quintiles of risk would have benefitted from an early intervention demonstrating considerable heterogeneity of treatment effect of early vs delayed dialysis (Grolleau et al. 2022). These clinical trials have led to considerable controversy on whether a “wait and see approach” is preferable to an early intervention (Zarbock and Mehta 2019; Bouchard and Mehta 2020; Meraz-Munoz et al. 2021; Pan et al. 2021; Gaudry et al. 2022). However, there is no clarity on which patients would benefit from waiting, the parameters that should define the waiting period and its duration and how patients should be managed during the waiting period (Bagshaw et al. 2021). The recent COVID-19 pandemic created an unprecedented strain on healthcare resource utilisation, as there was a marked

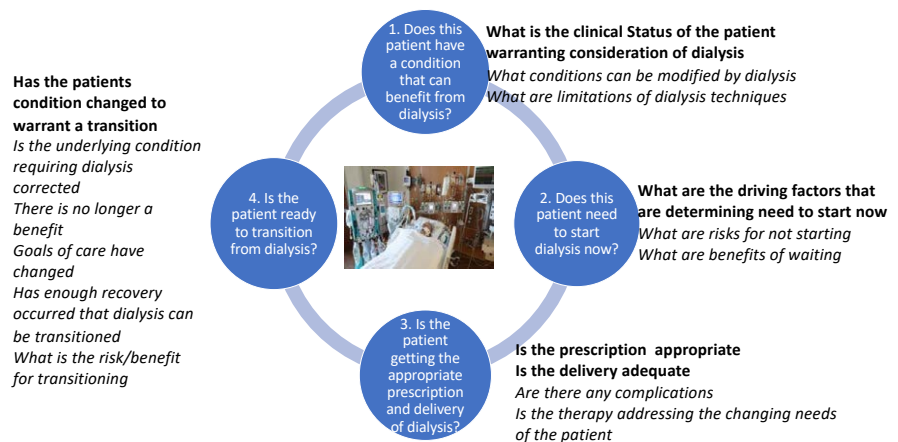


Figure 1. The four decision points for kidney support

increase in patients requiring acute dialysis that overwhelmed available resources in many centres (Chan et al. 2021; Gupta et al. 2021). These experiences highlight the need for standardised comprehensive systems-based approaches for enabling providers and healthcare systems to identify patients who would most benefit from high acuity care while de-escalating care for others (Stevens et al. 2021; Rhee et al. 2022).

The Role of Predictive Analytics

Current lack of accepted standards for timing of dialysis initiation, heterogeneity of patients and variations in care delivery contribute to under and over utilisation of the therapy resulting in high mortality, increased length of stay, rehospitalisation and long-term need for dialysis at a cost of over 10 billion dollars per year in the U.S. Consequently, there is a great need for tools to identify high risk patients who would need dialysis, determine the optimal time for intervention with the best likelihood for benefit while minimising risk and to adjust the operational characteristics to personalise management. While current scoring systems (e.g., APACHE 3, SOFA) provide an objective measure of patient condition and organ dysfunction, they do not support decision making in effective resource deployment of extracorporeal organ support (ECOS) (Aziz et al. 2020). The availability of real time data in electronic health records has led to the development of several machine learning models predicting the development of AKI and subsequently the requirement of dialysis. These models incorporate several variables; however, lack transparency of how the components in the model interact limits interpretability for clinical care and transferability across centres (Koyner et al. 2018; Tomasev et al. 2019; Churpek et al. 2020; Goldstein and Bedoya 2020; Vaid et al. 2021). Biomarker-based approaches have similarly been assessed to predict the provision of dialysis, but no single biomarker has emerged as being predictive (Klein et al. 2018; Fiorentino et al. 2020). The lack of utility for these techniques represents prior approaches that create risk predic-

tions based on assessment of single points in time and do not incorporate changes in patient course and do not utilise available clinical and lab data for dynamic risk assessment and intervention (Wilson et al. 2021; Demirjian et al. 2022).

It is instructive to consider the usefulness of prediction is to assist clinicians in making decisions for diagnostic or therapeutic interventions. When dialysis is considered in critically ill patients, there are four decision points (Figure 1). Assessing the clinical status of the patient and evaluating the potential benefit and risks of intervention are an essential first step where knowledge of the operational characteristics of the therapy (modality, dose, duration) need to be matched with the clinical condition. Once dialysis is determined to be appropriate, defining the optimal time for intervention is paramount to avoid unnecessary treatments and delays that deprive the patient of achievable benefit and may contribute to futility. Deciding the modality, dose, and management strategies to adjust therapy delivery to meet the changing needs of the patients and determine transitions in therapy to match goals of care are additional decision points that are required. There is wide discrepancy in these decision points that lead to variations in care delivery and could be amenable to improvement with predictive analytics. In most cases clinicians make decisions for dialysis support based on an assessment of the accessible clinical and lab data, evaluation of the patient’s condition and the anticipated course.

However, patients span the spectrum of presentation ranging from a relatively stable course to a rapid progression with multi-organ failure. To improve decision making and timely interventions with dialysis it is crucial for physicians to evaluate and integrate disparate pieces of information that are often not concurrently available. Clinical decision support systems (CDSS) can reduce the burden by continuously collecting relevant data within electronic health records (EHR), integrating the information and presenting it to clinicians for timely action (James et al. 2022).

Development of a CDSS for Kidney Support in the ICU

Recent studies have provided evidence for the potential benefit of real-time high-resolution assessments every few minutes, to provide an earlier indication of developing sepsis and organ failure (Adams et al. 2022; Henry et al. 2022). Nevertheless, prediction by itself is not enough as it should provide actionable information leading to specific interventions that influence the course favourably. As shown in Figure 2 predictive analytics applied for informing application of organ support should encompass dynamic assessments in a continuum of care. Identifying high risk patients at ICU admission should lead to active surveillance for thresholds for intervention, guide the choice of dialysis modality and its delivery to address the clinical need and provide measures to monitor the course with appropriate changes in therapy to promote recovery.

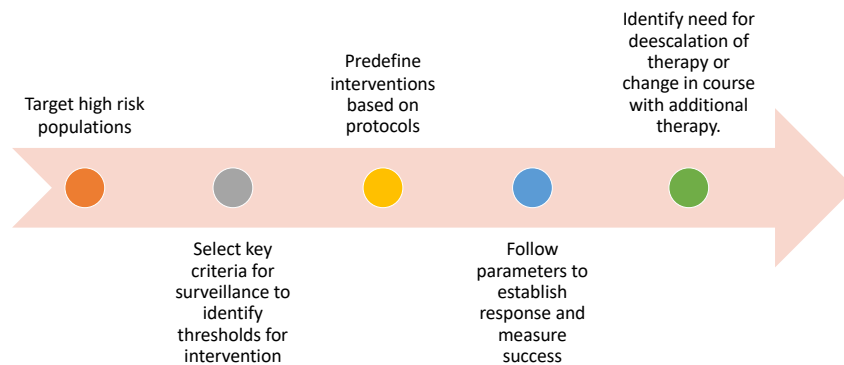


Figure 2. Attributes of predictive analytics for personalised management of critically ill patients requiring extracorporeal organ support (ECOS)

To address these challenges, we have developed a clinical decision support (CDSS) platform for real-time and hospital-wide prediction of acute dialysis requirement. The system relies on a novel method of organ monitoring that assesses the organ's functional capacity and, using only 20 commonly available patient data-points, predicts when capacity is exceeded to the point that dialytic intervention is required. The system dynamically quantifies the need for organ support using a patent pending Demand/Capacity/Mismatch algorithm (DCM) to assess the mismatch (M) of the demand (D) placed on any organ and the available organ capacity (C) (Ostermann et al. 2016). The DCM utilises patient demographics, clinical characteristics and laboratory data routinely recorded as standard of care in ICU's worldwide to dynamically quantify individual parameters

contributing to the demand and residual capacity of each organ and the additional capacity provided by the dialysis system to determine the response to treatment. Using data from over 20,000 patients throughout the United States, Canada and Europe to develop the algorithms with external validation in an independent set of electronic medical record data from 80,000 patients, this algorithm demonstrated an AUC of 0.945 predicting the need for dialysis within 96 hours at any time in the ICU. Our system has a cloud-based platform constructed in the Amazon Web Services (AWS) environment that links to electronic health records through Fast Healthcare Interoperability Resources (FHIR) and HL-7 endpoints to securely obtain real time data from multiple patient records; parse it accurately through the algorithm whenever new data is available

or at defined intervals, to provide clinicians with actionable information in a customisable dashboard that can be configured to alert clinicians at set thresholds (Figure 3). The platform has built in features that support its use across different EHRs and settings and data results can be configured for visualisation in multiple formats.

Conclusions

We have developed and validated a proprietary patent pending, real-time, scalable clinical decision support system (CDSS) to accurately predict risk of organ failure and outcomes in critically ill patients and empower clinicians to achieve timely decisions and implement appropriate organ support at the right time. Our approach to combine real-time predictive risk assessment with prescriptive analytics provides timely, standardised, and optimised clinical decision support through the continuum of a patient's course of disease. We anticipate its deployment and validation in prospective clinical trials and its utilisation to improve care of critically ill patients.

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Conflict of Interest

Dr Mehta has consulting agreements with Baxter, AM Pharma, Biomerieux, Mallinckrodt, GE Healthcare; Sanofi; Abiomed; NovaBiomed; Novartis; Renasym; Fresenius; and Guard. He has also received grant support from Fresenius; Fresenius-Kabi. ■

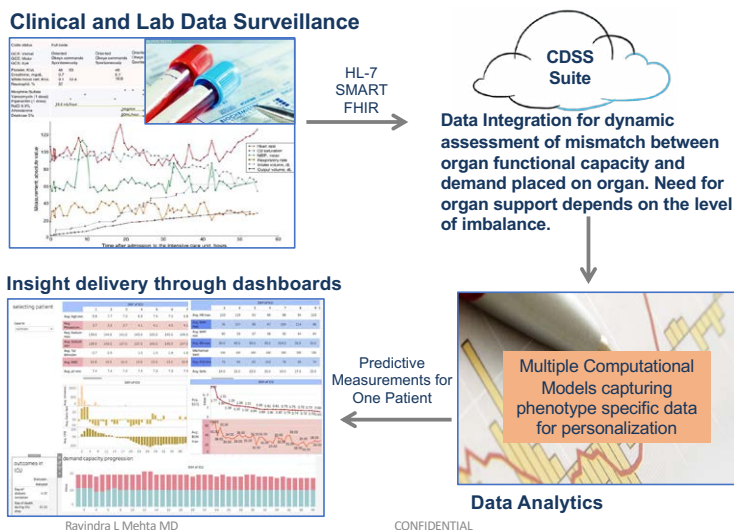


Figure 3. Overview of the clinical decision support system platform for extracorporeal organ support (ECOS) in ICU patients

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



Miguel Angel Martínez-Camacho

Critical Care Physiotherapy Service
Hospital General Hospital de Mexico "Dr Eduardo Liceaga"
Mexico City
Universidad Autónoma de Querétaro
Querétaro, México
lftmiguelangelmtz@gmail.com
@miguemtzcama



Robert Alexander Jones-Baro

Critical Care Physiotherapy Service
Hospital General Hospital de Mexico "Dr Eduardo Liceaga"
Mexico City
rjonesbaro@hotmail.com
@robjonesbaro



Alberto Gómez-González

Critical Care Physiotherapy Service
Hospital General de México "Dr. Eduardo Liceaga"
Mexico City
rehabilitacion.ag@gmail.com
@fisiopocus



Guillermo Espinosa-Ramirez

Intensive Care Unit
Hospital General de Mexico "Dr. Eduardo Liceaga"
Mexico City
argot50@hotmail.com
@MemoKahn



Angel Augusto Pérez-Calatayud

Intensive Care and Extracorporeal Support Unit
Hospital General Hospital de Mexico "Dr Eduardo Liceaga"
Mexico City
gmemiinv@gmail.com
@buddhafactor



Gustavo Rojas-Velasco

Cardiovascular Intensive Care Unit
Center of Excellence Gold ELSO
Instituto Nacional de Cardiología Ignacio Chávez
Mexico City
gustavorojas08@gmail.com

Early Mobilisation in Patients Undergoing Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation is a resource that is accessible in hospitals and intensive care units all over the world. In serious situations, ECMO therapy is intended to provide haemodynamic and/or ventilatory support. Because of this, many people refer to the ECMO patient as "the most critical patient." As a result, there is a very high likelihood that a critical disease will result in physical disabilities. A well-timed commencement to overcome such problems is crucial, as is a rehabilitation team that is well-trained and experienced.

Introduction

The critically ill patient is at high risk of developing functional alterations derived from the severity of the disease. The usage of drugs needed in critical illness, prolonged immobility and other factors directly impact muscle health (Martínez-Camacho et al. 2020). The muscle is an organ that can be severely affected in the intensive care unit (ICU) in various ways, such as fatty infiltrates, necrosis, ion channel alterations, mitochondria involvement and denervation. Together they manifest as generalised muscle weakness, usually symmetrical and that has no other explanation apart from critical pathology. This is known as ICU-acquired weakness (ICUAW) (Calixto-Mejía et al. 2020).

Currently, with the advancement in technology, life support measures have increased the therapeutic arsenal for critically ill patients and extracorporeal assistance is a reality in most units around the world. Among these devices, extracorporeal membrane oxygenation (ECMO) stands out, which, depending on the configuration, can provide pulmonary support (VV-ECMO) or haemodynamic support (VA-ECMO) (Combes et al. 2020; Shah et al. 2021). One of the most used indications for VV-ECMO is severe acute respiratory distress syndrome (ARDS) that does not respond to conventional management (protective mechanical ventilation, prone

position, and neuromuscular blockade). An adequate selection of ECMO candidate patients is crucial to obtain favourable results.

ECMO and Physiotherapy

Before connecting the patient to ECMO, a management plan must be established, and the purpose of extracorporeal therapy must be determined. Nevertheless, ECMO can work as a bridge-to-resolution, bridge-to-transplantation or gain some time while the problem that conditioned the patient to require assistance can be resolved. Given the characteristics of the patients, it is possible to keep them hospitalised for a prolonged period in the ICU (Hayes et al. 2021). This puts these patients at a higher risk of developing relevant functional sequelae, post-intensive care syndrome, difficulty in weaning from mechanical ventilation, etc. Early mobilisation (EM) is a widely used strategy for the prevention of ICU-acquired weakness (ICUAW) in critically ill patients, and patients undergoing ECMO therapy are no exception.

Studies currently support the safety of the implementation of EM in this group of patients, with low adverse effects and many functional benefits (Hogdson et al. 2014; Cameron et al. 2015; Hayes et al. 2021). To carry out an EM programme, it is necessary to implement a highly trained rehabilitation team due to the special

characteristics of this group of patients.

Identifying several situations in patient care before carrying out the exercise in patients on ECMO is crucial. For instance, the ECMO configuration, the type of support provided and the type of cannulation (Table 1). In addition, it is necessary to inspect the extraction and drainage cannula visually (Wieruszewski et al. 2023; Combes et al. 2020) (Figure 1). This can alert us to a malfunction of the membrane. The normal colouration in the extraction cannula is

the lower limbs, since they can be bent and thus increase resistance, in addition to reducing the extraction flow; this is prevented by avoiding hip flexion >90° (Raurell-Torredà et al. 2021). It is recommended to fix the cannulas during the mobilisation of the patient to avoid any adverse event.

Within the general monitoring of the patient on ECMO, a DO₂/VO₂ ratio of at least 3:1 must be guaranteed to consider clinical stability (Lorusso et al. 2021).

VV	Inferior vena cava	Superior vena cava	<ul style="list-style-type: none"> ARDS
VPa	Right atrium	pulmonary artery	<ul style="list-style-type: none"> Right heart failure
VA	Right atrium	Common iliac artery	<ul style="list-style-type: none"> Cardiogenic shock Extracorporeal resuscitation
VAV	Inferior vena cava	Common iliac artery Superior vena cava	<ul style="list-style-type: none"> Respiratory failure during VA ECMO Cardiogenic shock during VV ECMO

Table 1. ECMO configurations and indications

dark red and in the return cannula bright red. This is due to the blood characteristics (deoxygenated and oxygen-rich blood respectively). Also, the inspection of the cannula entry site to identify bleeding, displacement, or infection is crucial for the prevention of adverse effects (Mossadegh et al. 2016). Special care must be taken when moving the cannulas, especially in

For this reason, it is essential to maintain SpO₂ >90% and SvO₂ >60%, which may have a direct correlation. On the other hand, a haemoglobin level >10 g/d is recommended; however, in some cases values >8g/dL, fibrinogen >150 mg/dL and platelets >80,000/mcL may be considered. If available, rotational thromboelastography can help in haematological monitor-

ing. Haemodynamic stability must be continuously monitored at the patient's bedside, verifying perfusion windows, blood pressure, echocardiography and, if required, advanced invasive monitoring. The measurement of cardiac output is important for the termination of the flow and the revolutions per minute (rpm) in ECMO VV, recommending that it be close to 80% or 60 ml/Kg/Hr (Tonna et al. 2021; Ki et al. 2019; Shekar et al. 2020). It should be taken into account that exercise, especially active exercise, can increase oxygen consumption and the need for increased cardiac output, so it may be necessary to modify some parameters such as rpm, flow, FiO₂ or sweep gas, as well as the monitoring of ECMO pressures, which in the face of their alteration, rehabilitation should be temporarily suspended until resolution (Table 2) (Mossadegh et al. 2016).

Considerations to Mobilise VV ECMO Patients

Currently, the main indication for VV ECMO is severe ARDS, which entails some specific challenges for mobilisation in this population (Abrams et al. 2014; Pruijsten et al. 2014; Haji et al. 2021) These patients

Parameter	Relationship with EM during ECMO
Extraction pressure (P1) (mmHg)	It is the negative pressure generated by the centrifuge (cone) with which the patient's blood is extracted. At this point, it has not yet passed through the membrane (low O ₂ level). A sudden change with or without movement of the cannula (wobble or whipping) requires further evaluation (volume requirement, bent cannula, cannula attached to the vein wall or pneumothorax). Hip flexion > 90° can generate a change in this pressure and compromise ECMO extraction, which is why it becomes one of the most important pressures to monitor during the mobilisation of these patients. Like the rest of the pressures (P2, P3, ΔP), the parameters may vary due to equipment and console, as well as the diameter of the cannulas. The medical staff should then be consulted about the trends and values of each patient to determine an alteration.
Pre-membrane pressure (P2) (mmHg)	It is the pressure taken between the centrifuge and the membrane; at this point the pressure becomes positive. The blood in this area is still low in oxygen. Its alteration may indicate a problem in the membrane such as the presence of a thrombus. For this reason, it is important to explore it with a flashlight in addition to evaluating ΔP.
Post-membrane pressure (P3) (mmHg)	It is the pressure taken after the blood passes through the membrane, because of this the pressure drops with respect to P2. At this point the visualisation of the cannula that is directed back to the patient (return) becomes important. Occlusion of the return cannula or increase in preload can increase its values.
Δ Pressure pre-post membrane (mmHg) (ΔP)	The pressure difference between P2 and P3 must be monitored on a recurring basis. A sudden increase would make us suspect an event that compromises the function of the membrane (e.g. thrombi). If membrane dysfunction is suspected due to a significant increase in Δ pressure pre-post membrane, a pre and post membrane gasometrical evaluation is recommended to confirm its integrity and function.

Sweep (l/min)	It is part of the mixture of gases that go to the ECMO membrane, which is in the blender. From the point of view of physiotherapy, it is the main parameter that allows us to regulate the CO ₂ of the patient. It can directly influence the respiratory drive in awake patients (increased CO ₂ levels in the blood increase the respiratory drive). Care must be taken with the repercussion of CO ₂ at the level of cerebral perfusion. CO ₂ levels depend on the sweep and the ventilation of the native lung, the corroboration of PaCO ₂ is important. Capnography is not recommended in VV ECMO since all values and monitoring are done through arterial gases.
FiO ₂ of ECMO (0.21 to 1)	Quantity of oxygen that is provided to ECMO, usually kept at 100% during most part of de therapy. Prior to consider ECMO decannulation, it needs to be as low as 21%. We shall remember that SpO ₂ and PaO ₂ on the VV ECMO patient rely on both ECMO and native lung subjected to mechanical airway assistance.
Flow (l/min)	It is the amount of blood mobilised in one minute by the machine. The flow may be increased during exercise to improve tolerance. The flow (dependent variable) is the consequence of the revolutions per minute (independent variable).
Revolutions per minute (rpm)	It is the number of times that the centrifuge cone rotates per minute. Flow in adjustments are made through the rpm. In other words, to increase the flow, the rpm must be increased or vice versa.

Table 2. Principal parameters and their relationship with early mobilisation during ECMO

usually have significant lung parenchyma damage or inflammation that requires specific measures such as ultraprotective mechanical ventilation, neuromuscular blockade, and deep sedation. One of the most complex situations in the rehabilitation of a patient with ARDS in ECMO is to determine when they are ready for functional progression.

One of the main limitations is the need for deep sedation and neuromuscular blockade. There are some cases where it is necessary to combine ECMO with prone ventilation to reach oxygenation goals (Combes et al. 2020; Tonna et al. 2021). Oxygenation depends mainly on the membrane and the native lung; the latter being severely affected. As in most critically ill patients, sedation withdrawal is recommended as soon as possible to minimise deleterious effects. Early tracheostomy (as in the first seven days after intubation) can help in the rehabilitation process for better airway management, and a higher level of mobility, in addition to reducing swallowing and phonation complications derived from prolonged intubation (Nukiwa et al. 2022; DiChiacchio et al. 2020; Shaw et al. 2015).

Thus far, there is no evidence to mobilise patients in prone position; clinical stability will be the main priority in decision-making (Hogdson et al. 2014; Gómez et al. 2022). The approach can begin with passive interventions such as passive

mobilisation, positioning, stretching, and neuromuscular electrostimulation (NMES) to maintain range of motion, joint health, and muscle preservation; however, priority should always be given to the extent of those possible from active muscle contraction and resisted exercise in and out of bed. Verticalisation can be useful starting with sitting in bed and continuing at the edge of it, depending on haemodynamic stability. Later, when the patient can overcome gravity with the lower extremities and the ability to support the trunk, standing or walking can be considered. If the patient is not cooperative, an alternative can be using hoists, cranes or verticalisation tables. All

interventions should be aimed at improving functionality and activities of daily living (Haji et al. 2021). It is extremely important to establish therapeutic objectives based on functional scales applied in ECMO such as the ICU-Mobility Scale (IMS) or its adaptation for patients with ECMO (IMS-ECMO) (Abrams et al. 2021) (Figure 2).

One of the main concerns with physical exercise in patients with ARDS, especially on ECMO, is the possibility of generating patient self-inflicted lung injury (PSILI). So far, there is no evidence of the impact of exercise on lung injury in this population (Langer et al. 2016). As a precautionary measure, some parameters such as P0.1,

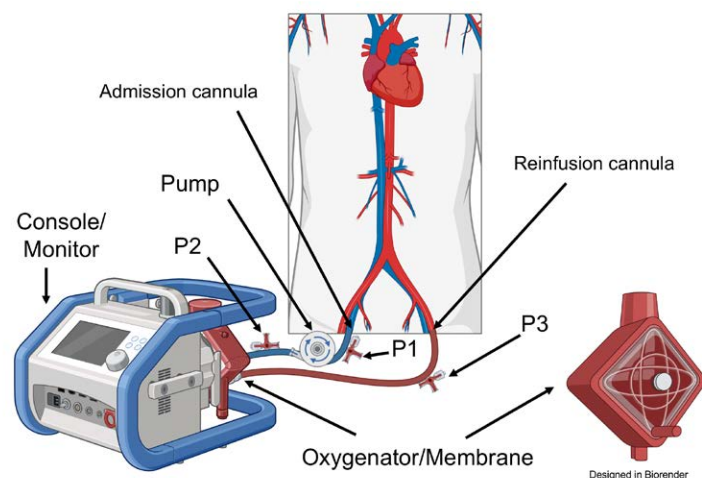


Figure 1. Anatomy of ECMO devices

muscle pressure (P_{mus}), muscle pressure index (MPI) or dynamic transpulmonary driving pressure (ΔP_L) can be evaluated to monitor mechanical ventilation in spontaneous modes, which is recommended in patients who are already awake and who

previously mentioned, it may be necessary to modify some of the ECMO parameters to improve exercise resistance; increasing pressure support or FiO₂ on the ventilator can contribute to this objective.

The ECMO rehabilitation programme

take considerable time. The importance of rehabilitation in critically ill patients has been demonstrated, as well as the patient undergoing ECMO therapy. Therefore, a well-trained team is needed to mobilise a severely ill patient such as those assisted

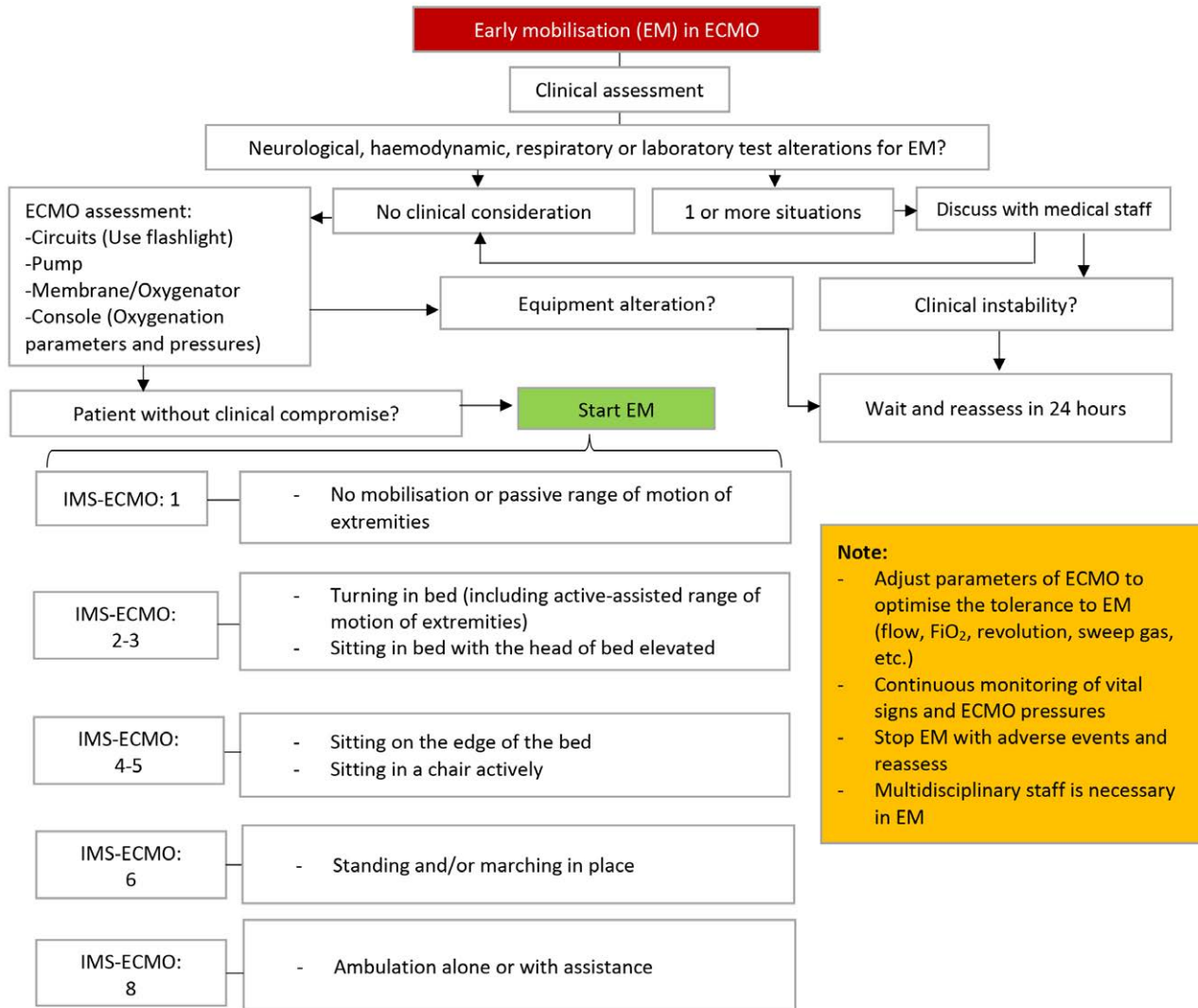


Figure 2. Algorithm early mobilisation in ECMO

are in an active rehabilitation programme (Pavez et al. 2022). On the other hand, continuous monitoring of tidal volume and respiratory rate could be sufficient during the rehabilitation session, in addition to respiratory and haemodynamic stability. As

can be very extensive in these patients because ARDS tends to evolve slowly compared to other respiratory pathologies. In addition, in some cases the patient must be kept mechanically ventilated until a lung transplant is available, which can

through extracorporeal machines in order to increase the chances of recovery and improve its long-term prognosis.

Conflict of Interest

None. ■

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Flavio Eduardo Nacul

Critical Care Medicine
Federal University of Rio de Janeiro
Hospital Pr6-Cardiaco
Rio de Janeiro, Brazil
fnacul@uol.com.br



Iman Alshamsi

Seha Kidney Care
Abu Dhabi
United Arab Emirates
dr.iman.alshamsi@gmail.com



Valentina Della Torre

Adult Intensive Care Unit
Imperial College Healthcare
NHS Trust
St. Mary's Hospital
London, United Kingdom
valentdt@gmail.com

Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is an immune complication of heparin therapy. This review discusses the pathophysiology, incidence, clinical manifestations, diagnostic approach, and management of patients with HIT.

Clinical Manifestations

HIT should be suspected in a patient who develops thrombocytopenia that is usually associated with thrombosis 5 to 10 days after heparin administration. In these patients, the platelet counts are decreased more than 50% from baseline, but severe thrombocytopenia ($< 20,000 \times 10^9/L$) is infrequent. Despite the thrombocytopenia, bleeding is not classically associated with HIT. Moreover, as many as 70% of patients with HIT develop thrombosis of any vascular bed. Thrombosis may affect the venous and arterial circulation, and conditions, such as deep vein thrombosis, pulmonary embolism, cerebral dural sinus thrombosis, adrenal haemorrhagic infarction, arterial thrombosis of the upper limb, lower limb, mesenteric, renal and spinal arteries, acute thrombotic stroke, and myocardial infarction, can occur. Venous thrombosis occurs more often than arterial thrombosis, with lower limb deep venous thrombosis and pulmonary embolism being the most common. Uncommon presentations of HIT are necrotic skin lesions, either at the injection site or distant sites, and acute systemic anaphylactoid reactions.

Diagnosis

The basic clinical feature of HIT is a platelet count decrease beginning 5-10 days after heparin exposure with or without thrombosis. In patients with suspected HIT, the American Society of Hematology (ASH) guideline panel recommends using the 4Ts score to estimate the probability of HIT (**Table 1**). The 4Ts score estimates the pretest probability of HIT compared with other causes of thrombocytopenia while considering 1) platelet count, 2)

timing of the onset of the decrease in the patient's platelet count, 3) thrombosis or other sequelae, and 4) the presence of other causes of thrombocytopenia. A score from 0 to 2 is given for each category. The maximum score is 8. A score of 6-8 is indicative of a high probability of HIT. A score of 4-5 is indicative of an intermediate presence of HIT, and a score of 0-3 is a low possibility of the presence of HIT. If HIT is suspected because the patient has an intermediate or elevated possibility of HIT based on the 4Ts score (4 to 8 points), the laboratory will assist the physician in making an accurate diagnosis. This can be accomplished by several assays that usually fall into two classes: immunological and functional. For immunological tests, immunoassays (ELISA) are used to detect antibodies against the heparin/PF4 complex and show an excellent negative predictive value but a low positive predictive value. The detection of antiheparin-PF4 antibodies by ELISA does not confirm HIT, but a negative ELISA result makes HIT highly unlikely. If positive, a confirmatory functional assay, which may include the serotonin release assay (SRA) or heparin-induced platelet activation (HIPA), should be ordered, as they have high specificity; however, they require a highly specialised laboratory and are not widely available. In patients with acute HIT without clinically apparent thrombosis, the ASH guideline panel suggests bilateral lower extremity compression ultrasonography to screen for asymptomatic proximal deep venous thrombosis (DVT). If an upper extremity central venous catheter is present, the ASH guideline panel suggests ultrasonography of the limb with the catheter to screen for subclinical DVT.

Pathophysiology

HIT is an immune complication of heparin therapy caused by IgG antibodies to complexes of platelet factor 4 (PF4) and heparin. These antibodies bind to the Fc receptor of the platelet surface, leading to platelet activation. Activation of platelets results in platelet aggregation and consumption, which results in thrombocytopenia and thrombosis (**Figure 1**).

Incidence

Approximately 0.2% of patients exposed to heparin develop HIT. The incidence is higher with unfractionated heparin (UFH) compared with low molecular weight heparin (LMWH), and HIT is also more common among surgical patients than medical patients (Jevtic 2012). HIT is very uncommon in patients who receive prophylactic doses and rare in pregnant women. Patients undergoing cardiac surgery and vascular surgery and patients on haemodialysis have high rates of HIT compared to the general medical hospital population.

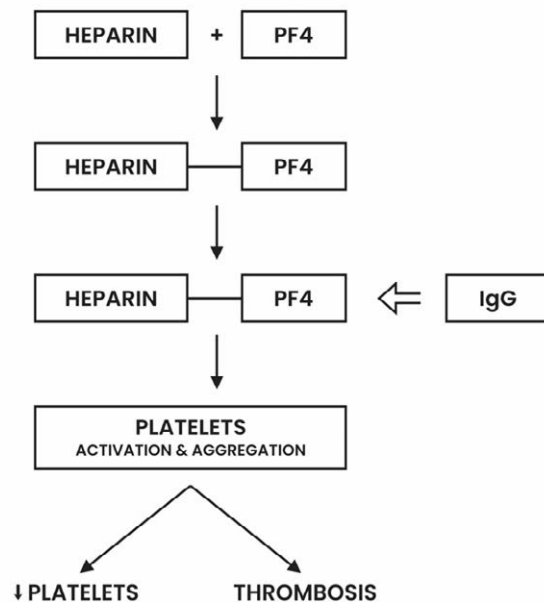


Figure 1. Pathophysiology of HIT. Heparin binds to platelet factor 4 (PF4) leading to the production of an IgG antibody against the heparin-PF4 complex, activating platelets and producing platelets aggregation, thrombocytopenia and thrombosis

Differential diagnosis includes infections, drug-induced thrombocytopenia disseminated intravascular coagulation, liver disease, immune thrombocytopenia, thrombotic thrombocytopenic purpura, and haemolytic-uremic syndrome.

Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a distinct syndrome that consists of an uncommon complication of adenoviral vector COVID-19 vaccines. In VITT, there is a propensity for (1) cerebral and splanchnic vein thrombosis, (2) laboratory features showing consumptive coagulopathy with thrombocytopenia, low fibrinogen, and elevated D-dimer, and (3) anti-PF4 seropositivity. (Arepally 2021). VITT appears to be similar to heparin-induced thrombocytopenia (HIT), with both disorders associated with thrombocytopenia, thrombosis, and the presence of autoantibodies to PF4. Based

on the initial reports, female sex and age younger than 60 years were identified as possible risk factors for VITT (Siegler 2021). The mechanism underlying the development of the prothrombotic state and its association with the vaccine are still only partially known because multiple converging prothrombotic pathways may be involved in the pathogenesis (Cines 2021). Treatment consists of therapeutic anticoagulation with non-heparin anticoagulants and prevention of the formation of autoantibody-PF4 complexes, the latter being achieved by the administration of high-dose intravenous immunoglobulin (IVIG). Steroids, plasma exchange and monoclonal antibodies may be used.

Management

Cessation of all heparin-containing products and the initiation of alternative non-heparin

anticoagulation are the cornerstones of HIT management (Joseph 2019). It is crucial to avoid all heparin-containing products, including catheter locks, heparin flushes, heparin-coated catheters or dialysers, and any heparin-containing medications. LMWH should also be avoided in suspected or confirmed HIT cases, as it cross reacts with HIT antibodies (Davenport 2009). The use of an alternative anticoagulation is mandatory even in those patients with no clinical evidence of thrombosis, as the risk of thrombosis in patients with HIT is high (Warkentin 1996).

The ASH published updated HIT management guidelines in 2018. The initial decision to start non-heparin anticoagulants is guided by the 4Ts score and the risk of bleeding. When confirmatory HIT test results are available, the management plan should be revisited. Regarding the therapeutic agent choice, the ASH suggests the use of argatroban, bivalirudin, danaparoid, fondaparinux, or a direct oral anticoagulant (DOAC) (Cuker 2018). Factors guiding the decision of therapeutic agent choice are mainly related to the drug, the patient, and the centre experience. A meta-analysis found similar rates of platelet recovery, thromboembolic events, haemorrhage, and mortality among the aforementioned anticoagulants (Nilius 2021).

Alternative non-heparin anticoagulation

Argatroban is a synthetic thrombin inhibitor that exerts its anticoagulation effect by reversibly binding thrombin both in the soluble form and within a thrombus. Therefore, in addition to preventing further thrombosis, it also carries an added benefit of targeting older clots. No renal adjustment is required as the drug is hepatically excreted. Moreover, no drug-induced antibodies have been reported with argatroban. No antidote is available; however, aPTT normalises within 2-4 hours of stopping the infusion in patients with no liver impairment. In the absence of liver impairment, the recommended initial infusion dose is 2 mcg/kg/min with dose adjustments according to the aPTT that is checked 2 hours after initiation of the infusion. The target aPTT is 1.5 to 3

4Ts	2 points	1 point	0 point
Thrombocytopenia	Fall > 50% or platelet nadir $\geq 20 \times 10^9/L$	Fall 30-50% or platelet nadir $10-20 \times 10^9/L$	Fall < 30% or platelets nadir $< 10 \times 10^9/L$
Onset of platelet count fall (time)	Onset between 5-10 days after starting heparin	Onset > 10 days or timing is unclear	Onset < 4 days
Thrombosis	New thrombosis & skin thrombosis	Progressive or recurrent thrombosis	No thrombosis
Other causes of thrombocytopenia	None apparent	Another possible cause	Definite another cause

Table 1: The 4T scoring system. Based on their score, patients are categorised in 3 different groups: low risk (0-3 points), intermediate (4-5 points), and high risk (6-8 points)

times the baseline. The maximum recommended infusion rate is 10 mcg/kg/min. In patients with liver impairment, a lower initial dose is recommended. Activated clotting time (ACT) can also be used to

an IV bolus followed by an infusion. The Danaparoid-specific anti-Xa target level is 0.5-0.8 U/mL (Cuker 2018; Linkins 2012) (Table 2).

Fondaparinux is a synthetic penta-

anticoagulation can be performed in the outpatient setting. Additionally, monitoring of the patient's blood tests are not indicated with fondaparinux, which is different compared to argatroban and bivalirudin. A cost effectiveness analysis showed that fondaparinux is a viable alternative to argatroban and should be considered in the treatment of HIT (Tuleja 2022). The recommended dose of fondaparinux is 5 mg (body weight < 50 kg), 7.5 mg (body weight 50-100 kg) or 10 mg (body weight > 100 kg) by subcutaneous injection once daily.

DOACs prevent new and recurrent thrombosis in most cases with minimal bleeding complications (Barlow 2019) (Table 3). Compared to other non-heparin anticoagulants, the advantages of DOAC include oral administration, fixed dosing, and the availability of antidotes (idarucizumab and andexanet alfa).

Traditional treatment is a non-heparin anticoagulant with a transition to vitamin K antagonists (VKA) such as warfarin, upon platelet recovery (platelets > 150 x 10⁹/L). More recently, the ASH guidelines have suggested the use of DOACs over vitamin K antagonists (VKA) (Cuker 2018). Compared to VKA, DOACs carry a decreased risk of bleeding, have fewer drug-drug interactions, require minimal dietary restrictions, allow for the achievement of anticoagulation rapidly, and are not associated with the need for routine laboratory testing. The initiation of warfarin in patients with acute HIT is contraindicated, as warfarin inhibits protein C, leading to a net procoagulant state that can lead to further thrombosis, skin necrosis, and limb gangrene. In patients who are on warfarin prior to HIT diagnosis, reversal of warfarin

Suggested bolus dose	<60 kg → 1,500 U 60-75 kg → 2,250 U 75-90 kg → 3,000 U >90 kg → 3,750 U
Suggested infusion dose	
Accelerated infusion	400 U/h for 4 h Followed by 300 U/h for 4 h
Maintenance infusion	200 U/h IV In patients with normal renal function 150 U/h IV in patients with renal impairment Adjusted subsequently according to danaparoid-specific anti-Xa levels (target, 0.5-0.8 U/mL)

Table 2: Recommended danaparoid dosing [Cuker 2018; Linkins 2012].

monitor the argatroban anticoagulation effect (the target ACT is 400-600 s).

Bivalirudin is a hirudin analogue and a bivalent direct thrombin inhibitor that acts by binding both the thrombin catalytic site and fibrin binding site. It also leads to the breakdown of von Willebrand factor, thus inhibiting platelet aggregation. It has a short half-life of approximately 25 min. It is primarily enzymatically metabolised and is excreted renally. The initial recommended dose is 0.15-0.2 mg/kg/hr with a target aPTT of 1.5-2.5 times the baseline value (Linkins 2012). Dose reductions are recommended in patients with renal or hepatic impairment (Marcucci 2021). Bivalirudin use is not associated with antibody formation (Warkentin 2004).

Danaparoid is a low molecular weight heparinoid that consists of a mixture of sulphated glycosaminoglycans isolated from porcine mucosa. It indirectly inhibits both factor Xa and factor II via its inhibition of AT. It also enhances the detachment of PF4 from the platelet surface and disrupts immune complex formation in HIT (Greiner 2017). The cross-reactivity of danaparoid with PF4 antibodies is low. Its half-life is 24 hours, which may be convenient for dosing but challenging in cases of bleeding. Routine coagulation testing is not needed; however, in cases of renal impairment, anti-factor Xa testing should be performed in addition to dose reduction (Acostamadiedo 2000). The 2012 American College of Chest Physicians and the 2018 ASH guidelines suggest

saccharide that inactivates factor Xa by selectively and strongly binding AT. Two hours after subcutaneous administration, its bioavailability reaches 100%. It is renally excreted, and its half-life ranges between 17 and 21 hours in healthy volunteers. It can be used for thromboembolic prophylaxis and treatment. It has been studied in obese patients, pregnant patients, cancer-related thrombosis patients, and thrombophilic patients (Nagler 2012). While the drug does not generally react with HIT antibodies in vivo or in vitro, there are rare cases in the literature of HIT antibodies isolated from patients who received fondaparinux. A systematic review that aimed to study the efficacy of using fondaparinux in HIT treatment showed that the risk of thrombosis was similar to that of the approved medications for HIT treatment. As fondaparinux is renally excreted, it should be used with caution in patients with renal impairment (Linkins 2018). Fondaparinux can be self-administered subcutaneously, which decreases hospitalisation length. Transitioning to oral

Agent	Dose	Indication
Rivaroxaban	15 mg BID x 21 days 20 mg daily	HITT
	15 mg BID until platelets recovery 20 mg daily	Acute HIT
Apixaban	10mg BID x 7days	HITT
	5 mg BID	Acute HIT
Dabigatran	150 mg BID preceded by 5 days of parenteral anticoagulation	HITT
	150 mg BID	Acute HIT

Table 3: Recommended DOACs dosing in patients with HITT and acute HIT without thrombosis. HITT = HIT with thrombosis (Barlow 2019)

with vitamin K and the concurrent use of alternative anticoagulation are advised.

Platelet transfusion

Even with profoundly low platelet counts, the risk of bleeding in untreated HIT patients is not high. Previous reports have described thrombosis and delayed platelet recovery in patients with HIT who received platelet transfusions. The ACCP and ASH guidelines recommend against platelet

transfusion in patients with an average risk of bleeding. Platelet transfusion may be considered in patients who are actively bleeding, in patients who are at high risk of bleeding, or in preparation for an invasive procedure (Cuker 2018; Linkins 2012).

IVC filter

Based on several studies, the ASH guidelines recommend against using inferior vena cava filters in patients with HIT.

Stepwise Approach

The ASH strongly recommends avoiding the use of alternative non-heparin anticoagulation in patients with suspected HIT and a low 4Ts score. In patients with intermediate- or high-risk 4Ts scores, cessation of heparin and the use of an alternative anticoagulant are recommended initially. In the case of a negative immunoassay, discontinuation of the alternative anticoagulant is recommended, and heparin may be used if still indicated. In patients with high 4Ts scores, additional testing may be indicated. In patients with intermediate or high 4Ts scores and a positive immunoassay, heparin should be avoided, and non-heparin anticoagulation should be continued. When available, a confirmatory activation test is required when the patient has a positive immunoassay test (Figure 2) (Cuker 2018). The duration of anticoagulant use is 4 weeks in patients with isolated HIT and 3 months for HIT with thrombosis.

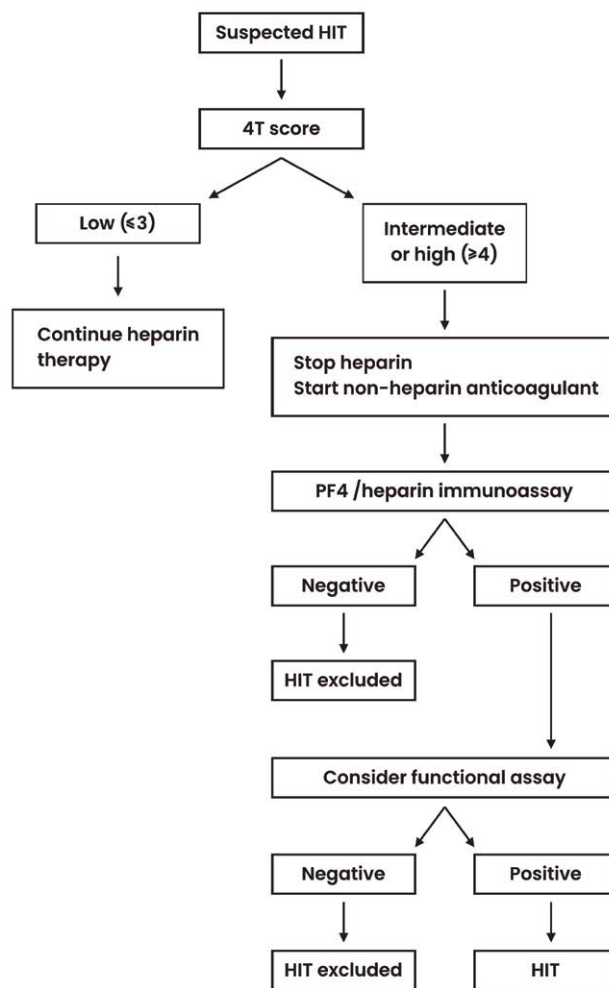


Figure 2. Algorithm approach for HIT guidelines

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Conflict of Interest

None. ■

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COVER STORY: Greener ICU

Climate change is an important issue that needs to be addressed. The process of transitioning to a greener intensive care unit can be challenging. In this issue, our contributors discuss strategies on how critical care can reduce its environmental impact and aspects related to research, education and clinical practice and attaining environmentally-sustainable anaesthesia and critical care.



COVER STORY: Artificial Intelligence in the ICU

The intensive care unit handles some of the most complex clinical situations. In this issue, our contributors discuss the benefits of AI and technology and how advanced tools and systems can enable critical care clinicians to manage the complex demands of care, have access to insightful data, streamline workflows, reduce their cognitive workload and give more time to patients.

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jlvincent@intensive.org

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REGIONAL AMBASSADORS

Dr Adrian Wong, UK avkwong@mac.com
 Dr Audrey de Jong, France a-de_jong@chu-montpellier.fr

GUEST AUTHORS

Iman Alshamsi, Alessandro Belletti, Etrusca Brogi, Ernesto Deloya-Tomas, Silvia De Rosa, Guillermo Espinosa-Ramírez, Francesco Forfori, Jakub Fronczek, Pablo Galindo-Vallejo, Alberto Gómez-González, Robert Alexander Jones-Baro, Christian Jung, Giovanni Landoni, Fernando Jaziel López-Pérez, Miguel Ángel Martínez-Camacho, Josué Luis Medina-Estrada, Ravindra L. Mehta, Maria-Jimena Mucio-Bermejo, Flavio Eduardo Nacul, Angel Augusto Pérez-Calatayud, Orlando Rubén Pérez-Nieto, Marian Elizabeth Phinder-Puente, Marianna Puccini, Zbigniew Putowski, Ursula Rauch-Kröhnert, Gustavo Rojas-Velasco, Claudio Ronca, Wojciech Szczeklik, Valentina Della Torre, Jean-Louis Vincent, Alberto Zangrillo

EXECUTIVE DIRECTOR

Christian Marolt c@icu-management.org

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Katya Mitreva k.m@icu-management.org
 Hilde Geuens h.g@icu-management.org

MANAGING EDITOR

Samna Ghani editorial@icu-management.org

VP MARCOM

Anastazia Anastasiou marcom@icu-management.org

COMMUNICATIONS TEAM

Tania Farooq gdpr@mindbyte.eu
 Mahjabeen Ahmed office@mindbyte.eu

GRAPHIC DESIGNER

Evi Hadjichrysostomou art2@mindbyte.eu

AUDIO-VISUAL

Andreas Kariofillis studio@mindbyte.eu

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 Kosta Ourani, 5 Petoussis Court, 5th floor, CY-3085 Limassol Cyprus
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 Website icu-management.org

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