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SCIENCE AND RESEARCH

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The ICU stands at the forefront of modern medicine, tasked with managing life-threatening conditions in the most vulnerable patients. Treatment success and patient survival depend on robust scientific inquiry and rigorous research. From developing life support technologies to refining clinical protocols, evidence-based practice is the engine that drives safer, more effective care in intensive care.

Recent milestones demonstrate this trajectory. Precision ventilation strategies, such as low-tidal-volume ventilation in ARDS, have markedly reduced ventilator-induced lung injury and improved outcomes. This aligns with the broader shift toward precision medicine, guided by biomarkers and individual patient characteristics, that tailors ventilatory and therapeutic approaches to maximise benefit.

Infection management, particularly for sepsis and ARDS, has also evolved. New international definitions and guidelines provide a consistent basis for diagnosis and treatment worldwide. These standards, along with breakthroughs in pharmacological therapy, have reshaped critical care medicine globally.

Life-support technologies, such as extracorporeal membrane oxygenation (ECMO) and continuous renal replacement therapy (CRRT), have expanded the arsenal for supporting failing organ systems in the sickest patients. Meanwhile, the integration of artificial intelligence (AI), big data, and telemedicine has catalysed transformative change ranging from AI-powered early warning systems to tele-ICU platforms that extend expert care to remote settings.

Beyond technological innovation, research into healthcare delivery itself through quality improvement initiatives has also had a significant impact. Evidence-based clinical protocols implemented in ICUs have led to measurable reductions in mortality. Coupled with structured quality improvement and education, these efforts reinforce clinical practice and equip teams to translate research into real-world benefits.

Challenges remain, particularly the difficulty of conducting ethical and timely clinical trials in critically ill patients; yet the commitment to scientific rigour remains unwavering. As the most acute setting in medicine, the ICU demands constant innovation, precision, and safety. By relying on science, critical care medicine continues to elevate standards of care, protect patients, and drive evidence-based progress.

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POINT-OF-VIEW

Using Recovery Rooms (PACUs) Differently: Addressing the Hidden Pandemic

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There is increasing interest in extending PACU-based care in order to better address the growing problem of early postoperative complications and their impact on patient and hospital outcomes. There is promising evidence of benefit in this approach, but still a great deal to be learned, such as the optimal target patient population, the precise value generated, and the structures, processes and specific care needed to generate that value.

The Problem

The landscape of surgical care is undergoing a significant transformation with substantial demographic shifts (ageing populations, chronic disease burden) and increased demand for surgery (Meara et al. 2016; Bagshaw et al. 2017; de Lange et al. 2020; Ludbrook 2022). These older, frailer and more medically complex surgical patients are at risk of developing postoperative complications and their sequelae - prolonging recovery, extended hospital stay, reduced quality of life and mortality (Tevis et al. 2016; Pinto et al. 2016).These complications are costly. Each patient with postoperative complications incurs, on average, an additional US$19,626 in hospital costs, representing nearly 20% of their total surgical expenditure, which threatens the long-term sustainability of hospital systems (Healy et al. 2016).

Postoperative complications remain a leading cause of avoidable harm in surgical care. Their insidious nature and low detection rates on general surgical wards (Khanna et al. 2023) have led to descriptions of a 'hidden pandemic' (Ludbrook 2022).

Amid these pressures, a distinct, underserved patient group has emerged: the medium-risk surgical patient. These individuals are often unsuitable for routine ward care yet do not meet intensive care unit (ICU) admission thresholds. In response, specialised high-acuity postoperative care units have been established to bridge the gap between general wards and ICU.

PACU-Based Solutions

Conventional postoperative pathways involve a stepwise transition from operating theatre to recovery room (post-anaesthesia care unit; PACU), to general ward. If needed, a high acuity setting such as a high dependency unit (HDU) or ICU may be used. This model remains largely tradition-driven, with limited supportive evidence (Wong et al. 2019).ICUs, while essential for critically ill patients, are resource-intensive and costly (Anesi et al. 2019). Routine ICU admission for low-acuity patients has not been shown to improve outcomes (De Robertis 2018; Emerson et al. 2023). Furthermore, limited ICU capacity contributes to broader system pressures, including surgical cancellations and strained triage decisions (Groenland et al. 2019; Harris et al. 2018).

Specialised high-acuity postoperative units have emerged as an intermediate care model. First introduced in the UK in the 1980s, often driven in response to ICU bed shortages and hospital congestion (Ziser et al. 2002; Kiekkas and Tzenalis 2022), extended postoperative care units (EPCUs) provide short-term high-acuity care for surgical patients at moderate risk of deterioration (Aps 2004).Compared to the ward, these units offer enhanced nurse-to-patient ratios, continuous monitoring and timely interventions, such as non-invasive ventilation or vasopressor therapy. These focus on the critical window of the first 24-48 hours after surgery when many of the complications arise, and may improve patient outcomes, reduce ICU demand and optimise resource utilisation (Thompson et al. 2003).

In recent years, this concept has evolved to using anaesthesia care in PACUs differently. Simply extending PACU stays, however, can be associated with increased nursing workload, missed care, delays in allied health input and psychological distress for patients and families (Ziser et al. 2002; Nelson et al. 2020).In contrast, highly structured anaesthesia-led models, such as Advanced Recovery Room Care (ARRC), which extend and enhance PACU care, are growing in response to high quality evidence of improved outcomes, resource utilisation, and cost (Ludbrook et al. 2025a; Ludbrook et al. 2023; Leaman and Ludbrook 2023; Koning et al. 2024) **(Table 1)**.

	ARRC, Adelaide	Arnhem, the Netherland
Casemix	Non-cardiac surgery ASA 3; predicted mortality 0.5 - 5%	Non-cardiac surgery ASA 3; predicted mortality circa<5%
Duration of care	>95% overnight only	45% overnight only
Medical staff	Anaesthesiologist + resident	Anaesthesiologist + resident
Care	Preop triage, rigid criteria Liaison during surgery Care from arrival in recovery Early weaning from support Early mobilisation, oral intake Scheduled rounds all night 'Aggressive' Rx to be ward ready by a.m.	Preop triage Liaison during surgery Early weaning from support Early mobilisation, oral intake
Limits	Continuous monitoring Vasopressors, TTE / monitors HFO (CPAP)	Continuous monitoring Vasopressors, Inotropes PPV < 12 hours
Other units available	ICU Mixed use HDU	ICU Mixed use HDU

Table 1. Examples of anaesthesia-led high acuity postoperative care using recovery rooms differently. Adapted from Ludbrook et al. 2025b.

These models appear distinct from ICUs and aim at a lower risk group – mortality of 2% compared to 8% in ICUs (Schockaert et al. 2025). However, they are inconsistent in name, in the patients managed and, in the processes, and procedures provided (Schockaert et al. 2025; Tran et al. 2025). Further, data on effectiveness and cost are relatively sparse, and several important questions remain:

1. Who are optimal candidates for admission?

2. What specific care processes contribute to effectiveness?

3. What are the clinical and economic benefits?

4. Where next?

1. Who are the optimal candidates for admission?

These Postoperative Care Units (PCUs) provide intermediate-level care for surgical patients at increased risk of complications but not requiring full ICU-level support (Centre for Perioperative Care 2020). They are not substitutes for ICUs and typically lack the resources for invasive organ support, such as mechanical ventilation. The ideal PCU candidates are noncardiac surgery patients at moderate risk of deterioration – those too complex or unstable for general ward care, yet not critically unwell enough to warrant ICU admission.

However, there is no universally accepted framework for categorising surgical patients into low-, medium-, or high-risk groups (Pearse et al. 2011; Sankar et al. 2015). Risk stratification in current practice is variable and often relies on subjective clinical judgement or disparate tools, such as the NSQIP surgical risk calculator, ASA physical status or APACHE-II, all with limitations in accuracy and consistency. In the UK, expert consensus recommends critical care for patients with a predicted 30-day mortality between 1–5%, but there is no standardised method for estimating this risk (Centre for Perioperative Care 2020).A recent systematic review illustrates this heterogeneity, with included studies applying different thresholds of moderate risk ranging from 0.7% to 5% (Tran et al. 2025).

While preoperative scoring systems are useful for estimating risk (usually mortality out to 30 days), they reflect a static assessment. Incorporating clinician judgement and real-time reassessment into triage decisions is therefore essential. Further, it can be argued that it is the risk of identifiable and rapidly treatable early complications which should be considered for triage to early postoperative care. Developing dynamic, evidence-informed models that integrate both objective and evolving clinical datamay improve PCU admission practices and optimise resource utilisation (Saugel et al. 2019).

2. What specific care processes contribute to effectiveness?

The effectiveness of PCUs lies in their ability to deliver timely, targeted interventions beyond the capabilities of general surgical wards. Several factors may contribute to this. Preoperatively, risk identification and planning allow early identification of patients who may benefit from higher acuity care. Postoperatively, continuous monitoring and more frequent observations in the PACU onwards enable early detection of deterioration. The first 24 hours after surgery are often termed the 'golden hours' due to the high incidence of complications (Thompson et al. 2003). Accordingly, PCU admissions are typically short, focused, and often limited to 24 hours.

PCUs also offer an expanded capacity to support vital organ systems through use of fluids, vasopressors and inotropes guided by advanced haemodynamic monitoring. Respiratory support varies, but high-flow nasal oxygen and non-invasive ventilation are common limits of care. Importantly, these interventions are delivered by staff with high acuity care expertise in adequate numbers. Nurse-to-patient ratios, for example, typically range from 1:1 to 1:3, compared to 1:4 to 1:7 on general wards (Ludbrook et al. 2023; Stahlschmidt et al. 2022; Costa-Pinto et al. 2023; Falk 2023; McHugh et al. 2020; Clarke et al. 2000).There is ready access to skilled medical staff.

This is supported by a peri-operative culture of active and proactive intervention to achieve early ward readiness (Ludbrook et al. 2025b). This includes precise adherence to Enhanced Recovery After Surgery (ERAS) principles, such as early mobilisation and oral intake (Peden et al. 2023).

The effectiveness of PCUs likely reflects a complex interplay of patient-specific, clinical and systemic factors. Future research should aim to identify which factors most strongly influence postoperative outcomes and resource efficiency.

3. What are the clinical and economic benefits?

Value generation (outcome and cost) from such models can be considered from a range of perspectives. Hospital value can be generated from fewer expensive complications and lower resource utilisation. Short-term measures such as length of stay and 30-day readmissions may show improvement (Koning et al. 2024), although measuring longer-term outcomes may reveal a more comprehensive picture (Leaman and Ludbrook 2023; Brown et al. 2021).

Mortality is a key measure of generating societal value, but short-term improvements can be hard to measure in a medium-risk patient population. A significant mortality reduction out to 18 months has been shown with ARRC (Ludbrook et al. 2025a) and suggests the demonstrated association between early postoperative morbidity and long-term mortality (Moonesinghe et al. 2014) may be preventable.

The business aspect of these units may require different data from academic studies and will be contextual. From a hospital perspective, cost savings may be made from hospital-funded care, but what is funded (such as rehabilitation or new nursing home care) varies across healthcare systems. Further, analyses need to account for evolving approaches to post-discharge care, which may impact length of stay, such as models of supported home care. Measures such as Days at Home (DAH) will be insufficient in such cases unless granular data on patient locations is measured. The financial benefit of sparing bed days will also depend on financial structures. For example, saved bed days in some systems may be used to further generate profit through opportunities to grow high-margin care.

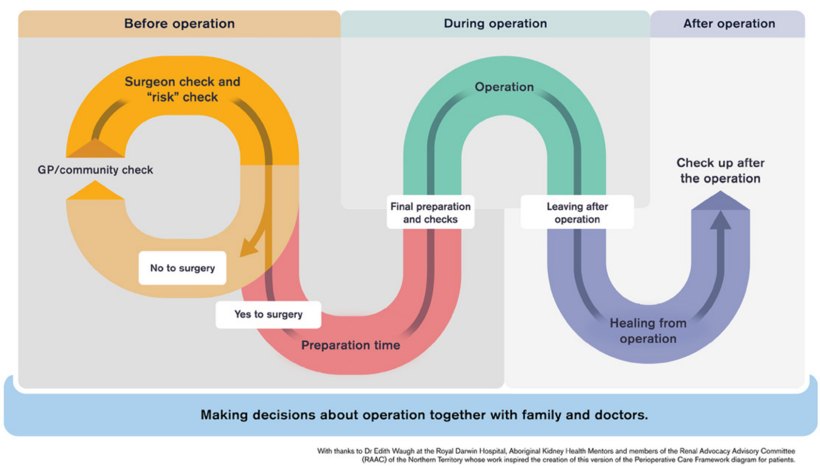

Figure 1. The Australia and New Zealand College of Anaesthetists peri-operative pathway. Available from https://www.anzca.edu.au/patient-information/about-perioperative-medicine/the-perioperative-care-model-1.

4. Where next? (Implementation and trials/data; integration into POM)

To ensure that PCUs evolve into a consistently effective model of care, future efforts must focus on integration, data generation and rigorous evaluation.Integration within a broader perioperative medicine (POM) framework is essential **(Figure 1)**. PCUs should function as part of a multidisciplinary continuum, from preoperative risk assessment and shared decision-making to postoperative monitoring and recovery, delivered collaboratively by surgeons, anaesthetists, intensivists, nurses and allied health professionals. The positive impact of preoperative interventions, such as prehabilitation, on some patients will influence both patient triage and the need for enhanced postoperative care.

Equally important is building a stronger evidence base. It would be disappointing to revisit this field in another decade without greater clarity on the value generated and the specific processes that drive effectiveness. Existing units should be encouraged to collaborate - sharing data, benchmark outcomes and embed continuous quality improvement through global collaborative platforms. Randomised controlled trials remain important, although often limited by inter-centre variability, but pragmatic designs such as registry-based studies, stepped-wedge designs, cluster randomised trials, and causal influence from non-randomised studies, may offer practical insights while aligning with routine clinical workflows (Moonesinghe 2016).

The next decade must focus on embedding PCUs within national perioperative strategies, strengthening data capability and fostering multi-institutional collaboration. Through these coordinated efforts, we can refine the PCU model, improve patient outcomes and deliver on the promise of safer perioperative care on a system-wide scale.

Conflict of Interest

None.

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Biomarkers and Point-of-Care Innovation in the Emergency Department

Biomarkers are essential tools in the emergency department for improving early detection, risk stratification, and patient management. This article reviews challenges in biomarker integration, the diagnostic and prognostic value of pancreatic stone protein (PSP), and the role of point-of-care solutions such as the abioSCOPE® in advancing personalised emergency medicine.

Introduction

Emergency departments (EDs) are under constant pressure to rapidly identify, triage, and treat patients presenting with acute and often life-threatening conditions. Clinicians are expected to make decisions based on limited information and under strict time constraints, which increases the risk of delayed or missed diagnoses. Biomarkers have been proposed as critical tools to support clinical judgment, enabling early disease detection, risk stratification, and treatment monitoring.

However, the clinical integration of biomarkers in the ED remains challenging. Conventional markers such as troponin, D-dimer, BNP/NT-proBNP, and procalcitonin are widely used, but concerns limited availability, and false positives have restricted their impact (Luka et al. 2025). Also, current evidence largely derives from retrospective studies rather than prospective validation, limiting their utility for guiding patient care in real-world settings (Ware et al. 2017). That is why there is a growing interest in identifying novel biomarkers that not only improve diagnostic accuracy but also integrate seamlessly into ED workflows.

Pancreatic stone protein (PSP) has emerged as a promising candidate, with an expanding body of evidence supporting its diagnostic and prognostic value in sepsis and other critical conditions. This article reviews the challenges of biomarker use in the ED, examines PSP as a novel biomarker, particularly in combination with other clinical tools, and discusses the role of the abioSCOPE® as a point-of-care solution for PSP testing.

Biomarkers in Early Detection: Challenges and Opportunities

The use of biomarkers in the ED is well established. However, these biomarkers are not without limitations. Challenges such as cost, availability, and accuracy concerns are consistent with global literature emphasising the need for scalable and reliable diagnostic tools in high-pressure settings (Luka et al. 2025).

Personalised medicine in critical illness represents the next frontier, with biomarkers forming the foundation of precision approaches to sepsis, acute respiratory distress syndrome (ARDS), and acute kidney injury. The ED presents unique challenges, as patients often present with nonspecific symptoms and limited clinical history. In this setting, biomarkers that are both rapid and reliable are needed to complement clinical risk scores and support triage decisions (Schuetz et al. 2015).

Pancreatic Stone Protein: A Novel Biomarker in Sepsis

Diagnostic and Prognostic Value

PSP has gained significant attention as a versatile biomarker with applications across sepsis, infection, and critical care populations. Several studies have demonstrated its ability to predict sepsis earlier than other biomarkers (Pugin et al. 2021; Klein et al. 2020; Niggemann et al. 2021; Klein et al. 2021; Belletti et al. 2025).

In a large multicentre investigation, Pugin et al. (2021) reported that PSP levels increased significantly and earlier than other inflammatory biomarkers in patients with sepsis. PSP values correlated with disease severity and clinical outcomes, allowing for earlier identification of patients at risk of organ dysfunction. The study highlighted that PSP could discriminate between sepsis and non-infectious causes of systemic inflammation, supporting its use for both diagnosis and early risk stratification.

Studies in burn ICU patients found that PSP levels remain stable after burn injury and surgical procedures, unlike CRP and PCT, which rise with inflammatory or surgical stress, suggesting PSP is a more specific sepsis marker (Klein et al. 2020). In another burn cohort, PSP increased 3.3–5.5-fold up to 72 hours before sepsis diagnosis (Niggemann et al. 2021) and was the strongest indicator of sepsis in patients with inhalation injury and ARDS (Klein et al. 2021).

Meta-analyses and systematic reviews highlight PSP's superiority over traditional markers. PSP outperformed C-reactive protein (CRP) in infection diagnosis, and the combination of PSP with CRP further improved accuracy (Prazak et al. 2021). This synergistic approach suggests that PSP may be best deployed not as a standalone biomarker but as part of a multimodal diagnostic strategy.

These findings demonstrate that PSP provides earlier and more accurate detection of sepsis compared with traditional biomarkers, making it particularly valuable in the ED, where timely recognition and intervention are essential for improving patient outcomes. The findings are supported by targeted analyses in specific populations, including patients requiring mechanical circulatory support, where PSP demonstrated relevance in predicting infection risk and guiding clinical management (Belletti et al. 2025).

Integration With Clinical Scores

The role of PSP extends beyond direct biomarker comparison. Integrating PSP with ED clinical scores, such as those used for sepsis triage and risk stratification, has the potential to significantly enhance performance. Personalised, biomarker-guided emergency medicine with PSP in combination with established scoring systems could provide clinicians with actionable insights at the point of care (Arturi et al. 2025).

A study of 285 patients (148 with suspected sepsis, 137 with sepsis) compared PSP, procalcitonin (PCT), and SOFA score. PSP and PCT showed similar diagnostic accuracy for sepsis. Sepsis was more common when both biomarkers were elevated (89%) versus when one or neither was elevated (21–48%). Higher biomarker quartiles correlated with worse SOFA scores and poorer outcomes. Adding PSP to SOFA improved risk prediction, with PSP showing particular strength in predicting kidney replacement therapy. While neither biomarker independently predicted outcomes, PSP demonstrated diagnostic and prognostic value, especially for kidney dysfunction, and could complement existing clinical assessments (Lee et al. 2024).

Economic Benefits

Sepsis places a substantial economic burden on healthcare systems. In high-income countries, the average hospital cost of sepsis exceeds US $32,000 per patient (World Health Organization 2024). A cost-impact model evaluated rapid PSP testing in U.S. ED and ICU settings and showed that, compared with standard care, PSP testing reduced costs by $1,688 per patient in the ED and $3,315 per patient in the ICU, primarily through improved diagnostic sensitivity and specificity. When extrapolated nationally, sepsis-related costs were estimated at $40.8 billion with standard care versus $37.7 billion with PSP-guided care, yielding $3.1 billion in savings (Schneider et al. 2022).

These findings highlight how incorporating PSP testing can alleviate the financial strain of sepsis by reducing unnecessary resource utilisation, supporting both better patient outcomes and more sustainable healthcare delivery in resource-constrained, high-throughput environments such as the ED.

The abioSCOPE®: Bridging the Gap Between Science and Clinical Practice

The abioSCOPE® is a point-of-care platform specifically developed for rapid PSP testing, delivering laboratory-quality results from just one drop of blood in minutes. By enabling PSP measurement directly at the bedside, it provides clinicians in emergency settings with fast, accurate, and actionable information where speed and ease of use are critical. This immediate integration of PSP biomarker data into clinical workflows is particularly valuable in the ED, where delayed results can hinder timely intervention. Evidence suggests that PSP-guided approaches have the potential to reduce healthcare expenditure by promoting earlier intervention and optimising resource allocation.

Conclusion

Biomarkers have long been considered key to advancing emergency medicine, yet challenges in availability, cost, and clinical validation have limited their widespread adoption. PSP represents a significant step forward, with strong evidence supporting its diagnostic, prognostic, and integrative potential. When combined with clinical scores, PSP enhances risk stratification and could play a key role in ED triage.

The translation of this evidence into clinical practice is now made possible by the abioSCOPE®, a point-of-care platform that delivers rapid, reliable PSP measurements from a single drop of blood. With several ongoing studies investigating the role of PSP in ED triage, the integration of PSP into personalised emergency medicine is on the horizon.

Disclaimer

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

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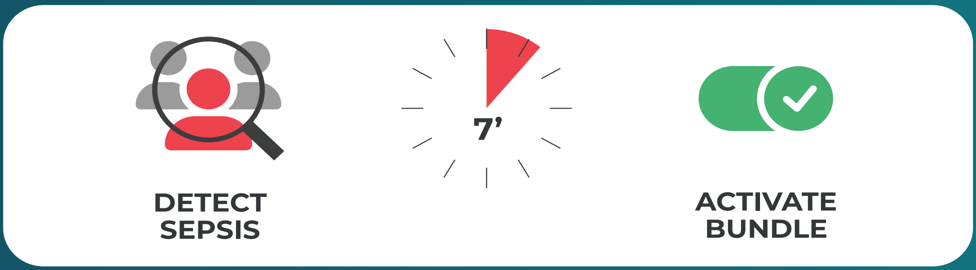

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Rethinking Delirium in Critical Care

Delirium is a common but under-recognised ICU complication with short and long term cognitive, psychological, and functional consequences. It urges for a cultural change in critical care using routine screening, multidisciplinary prevention, and patient and family centred interventions to prioritise mental recovery alongside physical survival.

Mr D, a 70-year-old engineer, was admitted to the ICU with chest sepsis and acute kidney injury (AKI). Twenty-four hours later, he was intubated, sedated and ventilated. He battled through multiple organ failure, vasopressors and mechanical ventilation. When sedation was lightened, he became agitated. The ICU team re-sedated him. When extubated, he recalled fragments of terrifying hallucinations. "I thought I was dying, and no one was helping me," he said. Weeks after discharge, he struggled to manage even simple tasks and was haunted by bad memories from his ICU stay.

Delirium: A Misunderstood Syndrome in the ICU

Delirium in the ICU is an acute, fluctuating disturbance in consciousness and cognition with three motor subtypes: hyperactive, hypoactive, and mixed. It's extremely common, especially in ventilated patients, but frequently under-recognised.

Delirium, often dismissed as a temporary inconvenience or simply ICU confusion, is a complex acute brain dysfunction with long-term consequences. Despite its prevalence, it remains underdiagnosed, undertreated, and misunderstood-even in the most advanced ICUs.

The Paradox of High Prevalence But Low Recognition

Delirium is one of the most common complications of critical illness, affecting an estimated 30–50% of non-ventilated ICU patients and up to 80% of those on ventilators. Delirium is associated with increased morbidity, mortality, and long-term cognitive decline (Girard et al. 2008).

Studies have shown that ICU teams miss up to two-thirds of delirium cases without the use of standardised screening tools. This paradox, where a syndrome so prevalent remains so underdiagnosed, reveals a systemic blind spot in critical care. The rate of missed diagnosis of delirium remains as high as 55-60%, and no effective drug has been available to prevent and treat ICU delirium (Ma et al. 2025). Reporting of delirium is poor in the U.K., indicating that awareness and reporting procedures need to be improved (NICE Guidelines 2023).

Unlike other ICU syndromes like acute respiratory distress syndrome (ARDS) and sepsis, delirium remains under-recognised and lacks clear protocols or urgent management strategies. Part of the problem is that delirium doesn't always look like the well-known version of confusion. Hypoactive delirium, particularly, is frequently mistaken for fatigue or depression. Its fluctuating nature means that it might not be captured during ward rounds or at shift changes, especially when systematic screening is not routine.

Delirium independently increases the risk of death, longer ventilation, extended ICU and hospital stays, and long-term cognitive issues. Despite this, it is often diagnosed late, missing the chance for effective intervention.

How Delirium Disrupts Mind and Care Flow

Delirium deeply affects both patients and ICU care. It distorts the patient's mind with fear, confusion, and hallucinations, often leaving lasting emotional and cognitive scars. It also disrupts care delivery, hinders team communication, and raises the risk of harm.

Delirious patients may bring out the use of physical and or chemical restraints, both of which can further worsen delirium. Communication becomes nearly impossible as patients cannot participate in decisions, express needs, or reliably report symptoms. This leads to reactive management strategies instead of thoughtful, patient-centred approaches.

From a systems perspective, delirium complicates weaning from the ventilator, delays mobilisation, and prolongs ICU stays. ICU team must continuously adapt their plans to the patient's unpredictable behaviour, often at the cost of other tasks or patients. Conclusively, delirium interferes with recovery, impairs decision-making, and fractures the therapeutic alliance.

A Perfect Storm for Delirium

ICU is paradoxically an environment provoking delirium. Alarms, lighting, sleep disruption, immobility, and unfamiliar faces create a sensory landscape that is disorienting at best and terrifying at worst. For patients who are critically ill, sedated, or mechanically ventilated, this environment becomes the setting for cognitive and psychological deterioration.

Sleep deprivation is a key factor. ICU patients are routinely exposed to noise levels far exceeding World Health Organisation (WHO) recommendations (Delaney et al. 2017; Simons et al. 2018), with frequent disruptions for vital signs, medication administration, and procedures. Without normal, uninterrupted rest, the brain loses one of its basic tools for maintaining orientation. Despite evidence that early mobilisation reduces delirium risk, many patients remain bedbound for days. That deepens the disconnection between body and mind.

Patients may lie in rooms where they cannot see a clock or window while being overwhelmed with unfamiliar voices and beeping monitors. Language barriers, hearing loss, or the presence of an endotracheal tube can make communication nearly impossible. The result is an environment where nothing makes sense, but everything feels urgent.

The ICU's critical environment often prioritises physiologic stability over psychological safety, maintaining a culture in which delirium is accepted as inescapable, rather than avoidable.

Environmental factors in the ICU create a perfect storm for delirium. Minimising sedation, normalising day-night cycles, reducing noise, and promoting early mobility are essential prevention strategies (Reade et al. 2014). As emphasised by evidence-based care bundles, e.g., A2I (ABCDEFGHI bundle) and Pain, Agitation, Delirium (PAD) guidelines, routine monitoring and systematic non-pharmacologic interventions protect cognitive health and improve patient-centred outcomes.

The ICU becomes more than a place of treatment; it becomes a neurocognitive stress test. And in its current form, many patients fail. Not for lack of medical care, but because the brain was not protected as importantly as the heart or lungs. If cognitive outcomes mattered as much as ventilator settings, the culture of critical care would look very different.

Emotional, Psychological, and Factual Impact

For ICU patients, delirium is not just confusion. It's terrifying, isolating, and painfully traumatic. Survivors often describe it as a vivid and disturbing agony. Some patients believe they are being held hostage, tortured, or abandoned. Others remember hearing voices, seeing insects crawling on walls, or feeling a profound sense of despair. These are not just delusions; they become memories. Patients frequently report flashbacks, nightmares, and post-traumatic stress disorder (PTSD) after discharge.

When Time Becomes Disordered: The Patient Experience of Delirium

"*I thought I was in hell.*"

In a study, Svenningsen et al. (2016) interviewed ICU survivors and found that patients frequently experienced terrifying hallucinations. One patient recalled: "I saw the devil and believed I had died. I didn't know what was real anymore."

The classic sensation of locked-in delirium is described in a 2021 meta-synthesis of ICU survivor interviews: *"I lay there without moving a muscle, totally stiff, people all around me, but no one answering me! I would be calling out to people, but no one would even look up."*

"I Can Remember Sort of Vivid People… but to Me They Were Plasticine." Darbyshire et al. (2016) in Delusions on the Intensive Care Unit: What Do Patients Think Is Going On? described the devastating experiences of delirious patients in the ICU. *"Each time I went under, the nightmares flooded back. So, when they were telling me to sleep, I couldn't sleep because a blackness just came back over me, so I stayed awake."*

The emotional fallout is profound. Many patients express guilt, shame, or fear when reflecting on their behaviour during delirium. Some question whether they are losing their mind or developing dementia. Importantly, when no one explains what delirium is, these perceptions go unverified, leaving psychological wounds unhealed.

Salluh et al. (2015) found that delirium has long-term consequences, with studies indicating an association between delirium and a higher likelihood of death, functional disability, admission to residential care, cognitive impairment, and dementia after discharge.

Approximately three-quarters of critically ill patients who were interviewed two weeks after surviving their initial illness reported delusions, and those with limited factual recall of their hospitalisations had significantly increased anxiety and symptoms of PTSD (Mart et al. 2020).

Listening to patients' stories reveals a truth often noted in daily ICU practice: delirium is not just a clinical diagnosis. It is an experience that can shape a patient's entire memory of critical illness, colouring their recovery with fear, confusion, and uncertainty.

Failure to See Delirium

We fail to see delirium not because it is unseen, but because we are not always trained to look for it. Despite its frequency and consequences, delirium remains one of the most under-recognised syndromes in the ICU. This failure is not due to lack of concern, but due to a combination of diagnostic challenges, system limitations, and cultural blind spots.

Delirium is fluctuant, often appears subtle, and can present in forms that defy our expectations. Hyperactive delirium is more likely to be noticed due to agitation or aggression. But hypoactive delirium often masquerades as fatigue, depression, or quiet compliance. Many patients appear calm but are, in fact, profoundly disoriented. In busy ICUs, this presentation is easily missed.

Clinicians often rely on intuition rather than structured assessments. Without tools like the Confusion Assessment Method for

ICU (CAM-ICU) or the Intensive Care Delirium Screening Checklist (ICDSC) used routinely, delirium is underdiagnosed. A 2005 study by Ely et al. found that ICU staff missed two out of every three delirium cases when relying on clinical impression alone.

Early detection with CAM-ICU or ICDSC leads to prompt assessment and intervention. Without validated assessment, up to 75% of delirium will be missed. It is noted that delirium assessment tools such as CAM-ICU have not been validated in autistic populations and, as such, may present challenges to delirium assessment (ICS guidelines 2025).

Notably, delirium can and often does coexist with underlying neurological disease, such as dementia, traumatic brain injury (TBI), and stroke, and so is not precluded from developing in these patients (Mart et al. 2020). This leads to inappropriate treatment with antipsychotics when not needed, or additional sedation that deepens the problem.

Delirium is still conceived by many as an unavoidable part of critical illness. Unlike sepsis or stroke, it lacks a sense of urgency. This concept undermines efforts to prevent or treat it, perpetuating the cycle of inattention.

The consequence of missing delirium in patients can cause distress to both patients and families. Once a diagnosis of delirium has been made, it can facilitate discussions and support for patients and families about the experience and any long-term consequences it may have (ICS guidelines 2025).

Systemic Gaps in Monitoring, Staffing, and Training

Delirium is not only under recognised at the bedside, but also systemically unsupported at the institutional level. Few ICUs are structurally equipped to detect, manage, or prevent delirium consistently. This failure reflects gaps in staffing, education, and clinical infrastructure that hinder even the most well-intentioned care.

Monitoring is a fundamental weakness. Most ICUs do not routinely monitor brain function unless a neurologic event is suspected. Delirium screening tools exist, but their use is greatly variable, often dependent on individual practice rather than being part of the standard workflow.

The CAM-ICU is the most widely studied and validated diagnostic instrument. However, the accuracy of this tool may be less than ideal without adequate training of the providers applying it (Cavallazzi et al. 2012).

Staffing constraints additionally exacerbate the problem. ICU nurses and physicians are overcommitted, managing complex patients in time-pressured environments. Without adequate nurse-to-patient ratios, even the basics, like minimising sedatives, can be dropped. Delirium prevention often feels like a "nice-to-have" rather than a core task, particularly when life-saving interventions attract the greatest ICU team's attention.

Training gaps remain, as many clinicians receive little formal education on delirium. It's often seen as inevitable, not preventable, and its cognitive impact is overlooked. Ongoing ICU education rarely prioritises it unless driven by local interest or adverse events.

There is some evidence from multicomponent prevention studies to suggest that an education programme for healthcare professionals who care for people at risk of delirium reduces the incidence of delirium (NICE Guideline 2023).

The outcome is a system where delirium is everyone's responsibility, but no one's mandate. Until we embed delirium prevention and detection into the culture, infrastructure, and standards of ICU care, we will continue to fail patients in ways that are both preventable and profound.

Can We Prevent the Fog?

Despite the huge challenges, progress is already underway in ICUs that have adopted structured, evidence-based approaches. Consistent application of evidence-based nonpharmacological interventions is needed in adult ICUs to address the gap in delirium care (Johnson et al. 2024). In another study, nonpharmacological interventions have been suggested as more effective than the use of drugs (Chen et al. 2022).

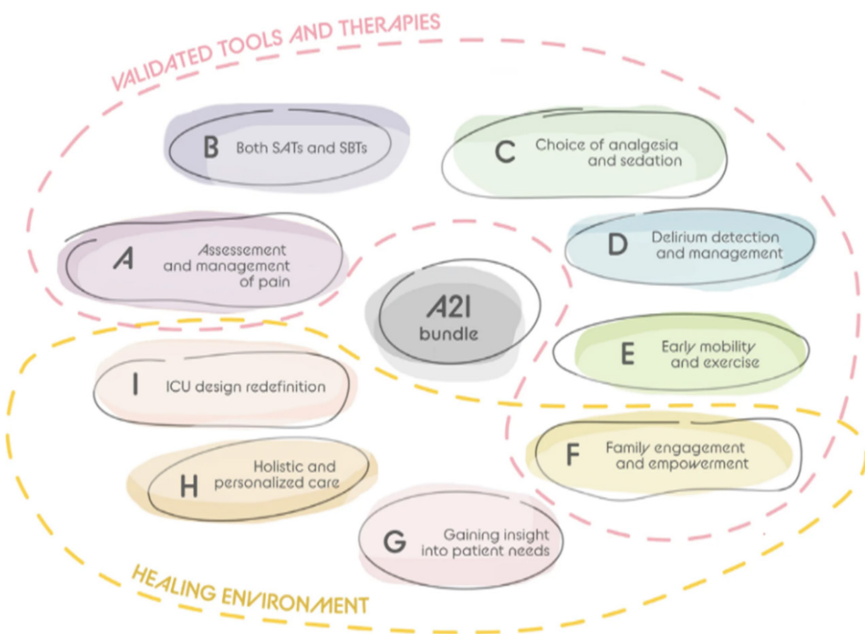


Figure 1. A2I bundle. Source: Kotfis et al. 2022

Variable	Value (mean ± SD. range)
ICU LOS (days)	15 ± 33 (0 - 278)
Hopital LOS (days)	30 ± 99 (1. - 1057)
APACHE Score	28± 14 (3-64)
Gender	Male 59% female 41%
Age (years)	mean: 54.5 ± 17.2 Range: (18 - 89)

Table 1. Patient demographics delirium project in a tertiary hospital. Six ICUs in London, U.K., over three consecutive weeks. A retrospective observational study looking into patients admitted to the ICU who developed delirium

A multicomponent approach to delirium prevention and management may benefit ICU patients and clinicians significantly. The evidence supporting the use of multicomponent nonpharmacological interventions for delirium prevention and management is more substantial than a single component (Burton et al. 2021).

One of the most effective is the ICU Liberation initiative, bonded by the A2I bundle, which has re-evaluated how we think about patient-centred, brain-conscious critical care **(Figure 1).**

Each component targets a known risk factor for delirium-oversedation, immobility, isolation, unmanaged pain, and fragmented care. Together, they form a practical strategy that embeds brain-protective practices into daily ICU practice.

The ICU Liberation Collaborative, a multi-centre QI initiative involving over 15,000 patients, showed significant reductions in delirium duration, ventilator days, ICU length of stay, and mortality. Vitally, implementation success depended not only on protocols, but on team culture, leadership support, and sustained education. A2I bundle performance showed significant and clinically meaningful improvements in outcomes, including survival, mechanical ventilation use, coma, delirium, restraint-free care, ICU readmissions, and post-ICU discharge disposition (Pun et al. 2019).

With commitment, coordination, and consistency, we can create an ICU culture that prioritises the brain as much as the lungs or heart. The A2I bundle is not just a checklist, but a philosophy that acknowledges the centrality of cognition in recovery as well.

Examples from Practice

A retrospective study at a U.K. tertiary hospital ICU examined 218 delirium patients over three separate 24-hour periods, tracking bed occupancy and collecting data on demographics, diagnoses, comorbidities, length of stay, substance misuse, psychiatric history, neurodiversity, and CAM-ICU scores. The findings highlight the complex psychiatric needs of ICU patients and the significant mind-body connection **(Table 1)**. Delirium affects existing mental illness and can cause new psychiatric issues, especially in long-stay patients **(Figures 2 and 3).** More research is needed to better understand and manage delirium.

Interdisciplinary Collaboration in Delirium Care

The future design of delirium-free ICUs should emphasise a multidisciplinary approach, involving physicians, nurses, physiotherapists, clinical pharmacists, psychologists, speech and language therapists, dieticians, occupational therapists, spiritual care providers, and social workers to address the comprehensive needs of each patient. This ensures multidimensional diagnostics and therapeutics for thorough assessment, treatment, and follow-up.

Psychologists play a critical role within the ICU team by providing daily consultations to mitigate distress, manage mood and sleep disorders, and address the psychological impact of sedation and delirium, thereby improving patient and family outcomes. Early interventions are essential to facilitate recovery, communication, and long-term care planning.

Additionally, dieticians are integral in managing the gut-brain axis through evidence-based nutritional strategies, as disruptions to the gut microbiome exacerbated by anaesthetics and sedatives contribute to delirium pathogenesis. Dieticians support both nutritional needs and delirium prevention by modulating neuroinflammatory pathways.

Healthcare providers should undergo structured education and training to enhance their ability to recognise, diagnose, and manage delirium. A recent international survey among delirium experts within European countries reported that low delirium awareness, inadequate knowledge

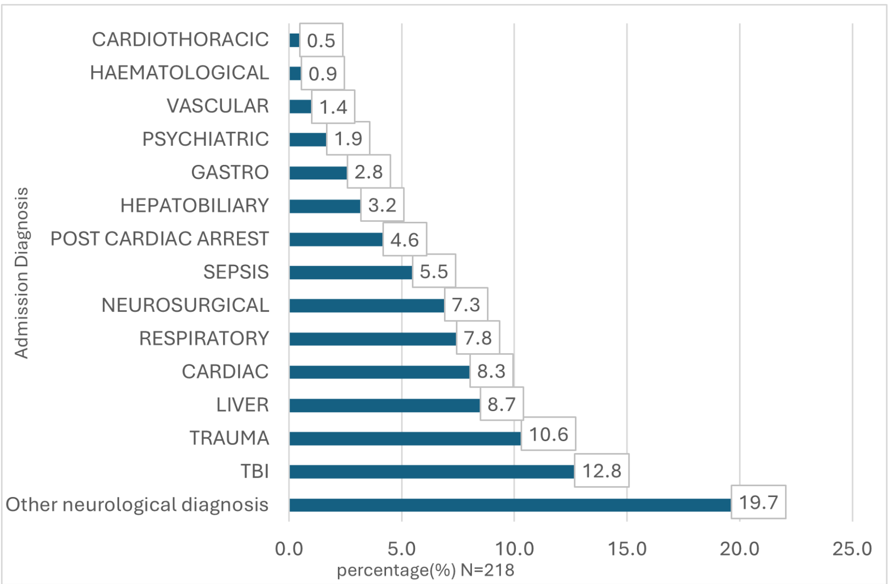


Figure 2. Percentage of admission diagnoses of patients admitted to ICUs in a tertiary hospital in the U.K. over three consecutive weeks. The highest percentage was in patients admitted with neurological disorders and traumatic brain injury (TBI).

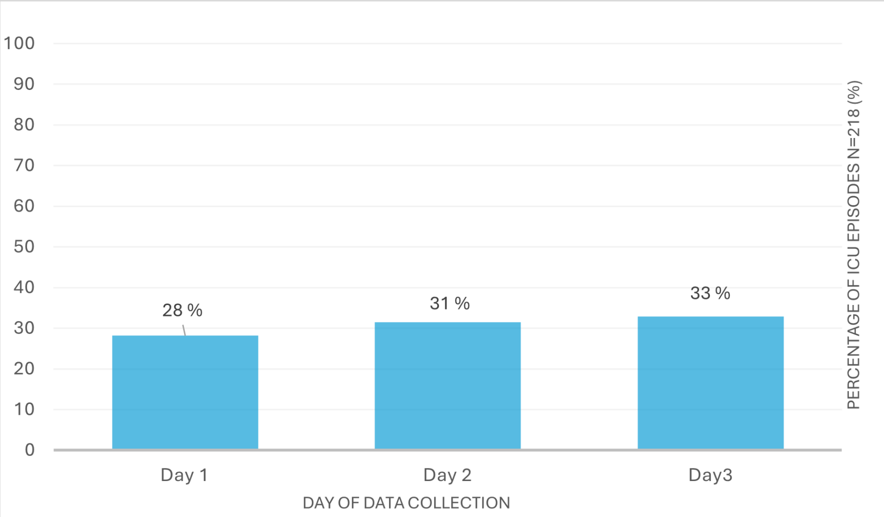


Figure 3. Percentage of the patients who developed delirium in ICU over three consecutive days, with one week in between each day, with at least CAM ICU +ve once in 24 hours.

or incompetence, lack of education, and lack of time for assessment were identified as the four main barriers to improving delirium detection (Morandi et al. 2019).

Empowering the use of guidelines or protocols has been shown to be efficient in improving the care of delirium, with a direct effect on delirium outcomes. Collaboration among healthcare professionals such as, but not limited to, European Delirium Association (EDA), European Geriatric Medicine Society (EuGMS), European Academy of Nursing Science (EANS), Council of Occupational Therapists for European Countries (COTEC), World Confederation for Physical Therapy (WCPT) and the International Association of Physical Therapists working with Older People (IPTOP) is hugely important for the future management of delirium.

Over the past 10 to 15 years, using reminders and implementing guidelines or protocol strategies effectively improved delirium care, with measurable impacts on patient outcomes. Ongoing collaboration between the above-mentioned organisations plays a significant role in advancing the management of delirium. E-learning has been described as a novel approach to facilitate the possibility of providing education for large groups of people (Morandi et al. 2019).

Nurses are the first to notice cognitive changes, yet their visions are sometimes undervalued in clinical decision-making. Pharmacists help reduce delirium-inducing medications and optimise sedation strategies. Physiotherapists promote early mobility, which is one of the most effective approaches for reducing delirium. Facilitating spontaneous breathing trials (SBTs) and reducing sedation show a great benefit. Physicians must coordinate all these efforts and integrate delirium assessment into daily ward rounds.

Family members, too, are key partners. Their presence provides familiarity and emotional support that can be profoundly protective against disorientation. Involving them in reorientation, communication, and even decision-making braces the human connection that delirium so often ruins.

Incorporating family education into delirium care significantly enhances the holistic management of the condition. Educating families improves their understanding of delirium, fosters effective communication, and supports patient-centred care throughout the clinical course.

A video-based ICU delirium education intervention was effective in educating family members of ICU patients on the detection of delirium symptoms, its prevention and management using nonpharmacologic strategies. That may act as a primer for family members to partner with the ICU care team in delirium-related patient issues or empower families to participate in delirium-focused discussions (Krewulak et al. 2020).

Creating a culture where delirium is everyone's responsibility requires strategic team development, shared responsibility, and mutual respect. In this way, delirium becomes not just a clinical aim, but a unifying challenge that anneals ICU teams and restores a more humane vision of critical care.

Post-ICU Cognitive Dysfunction and Delirium's Legacy

This is just the beginning. For most ICU survivors, the story doesn't end at discharge. Delirium, once dismissed as temporary confusion, is the portal to long-term cognitive impairment. Its legacy can be extreme and persistent. In one study of mechanically ventilated ICU patients, Girard et al. (2010) concluded that duration of delirium was independently associated with long-term cognitive impairment in ICU survivors. Furthermore, the number of days of ICU delirium was associated with higher 1-year mortality after adjustment for relevant covariates in an older ICU population (Pisani et al. 2009).

Up to two-thirds of patients who had ICU delirium develop measurable cognitive impairments that affect memory, attention, processing speed, and executive function. These deficits can mimic mild Alzheimer's disease or traumatic brain injury (TBI), even in younger patients. For some, it means losing the ability to return to work, manage finances, or live independently. For others, it's a lasting sense of being mentally not the same.

Delirium is linked to PTSD, anxiety, and depression. Survivors describe having nightmares, fear of hospitals, and feelings of shame about their uncontrolled behaviour. Families carry the emotional burden, often reporting distress after witnessing their loved ones hallucinate.

Delirium's true cost extends far beyond the ICU, shaping the trajectory of recovery for months or years. It turns a short episode of organ failure into a chronic cognitive illness, affecting quality of life in ways we are far from quantifying. Patients who had prolonged delirium showed poorer global cognition after discharge and greater risks of dementia and long-term cognitive impairment, regardless of the severity and duration of their delirium, as per a review based on the 2018 PADIS guidelines.

Recognising delirium as a predictor, not just a symptom, demands a change in how we define ICU success. Survival is no longer the only benchmark. Preserving the integrity of the mind, the memory, and the self is the legacy we must stand for.

The Societal and Caregiver Burden

It does not end when the ICU stay does. Delirium impacts future ripples, affecting families, caregivers, and health systems in ways that are invisible but profoundly disruptive.

For caregivers, the burden can be life-altering. When a loved one emerges from the ICU with cognitive decline, emotional instability, or personality changes, families are mandated to become untrained caregivers overnight. Many feel unprepared for the aftermath: forgetfulness, paranoia, and lack of insight or motivation. These changes can affect relationships, cause financial difficulties, and lead to emotional stress.

Studies have shown that caregivers of ICU survivors experience anxiety, depression, and even PTSD. Their roles change from partner or child to nurse, advocate, and protector, often with limited support. In the meantime, the healthcare system offers few pathways for follow-up, rehabilitation, or education tailored to post-delirium recovery.

Post-ICU cognitive impairment significantly impacts the economy. Patients often need long-term care or rehospitalisation, and both patients and caregivers suffer from lost productivity, affecting healthcare use and quality of life.

Despite this burden, delirium remains under-recognised. Unlike stroke or dementia, post-ICU cognitive dysfunction lacks public awareness, formal screening programmes, and institutional resources. Many patients and families suffer without language to express their experiences or systems to support them.

Evolution of ICU Environments to Reduce Delirium Risk

The modern ICU design aims to create a more comforting, home-like environment through architectural changes. Features like separate corridors for staff and families, and spacious, ergonomic rooms support this shift.

The visual art has shown potential in reducing stress and improving mental health. Art therapy is gaining recognition as a valuable tool for emotional expression and psychological support in ICU settings. Improvements in the ICU sounds, light control, floor planning, and room arrangement can facilitate a healing environment that minimises stressors and aids delirium prevention and management. The following pictures **(Figures 4 and 5)** demonstrate the future of delirium-free ICU design and highlight the importance of a healing environment (Kotfis et al. 2022).

From Awareness to Action

We must move beyond viewing delirium as a secondary concern and instead treat it as a central clinical, ethical, and human challenge.

The culture of many ICUs still prioritises stabilising haemodynamic, oxygenating lungs, and correcting labs. But the patient's mind, identity, and experience remain in the background. Delirium is frequently under-screened and under-addressed. Prevention is randomly applied. Education is minimal. Families are left out. And the result is predictable: patients leave the ICU alive, but cognitively impaired.

A change is a must. We need a culture where protecting the brain is as routine as protecting other organs, where multidisciplinary teams drive shared accountability for mental clarity, not just survival. Institutions must include delirium awareness into training, quality metrics, and resource allocation. A multicomponent delirium education and training programme for

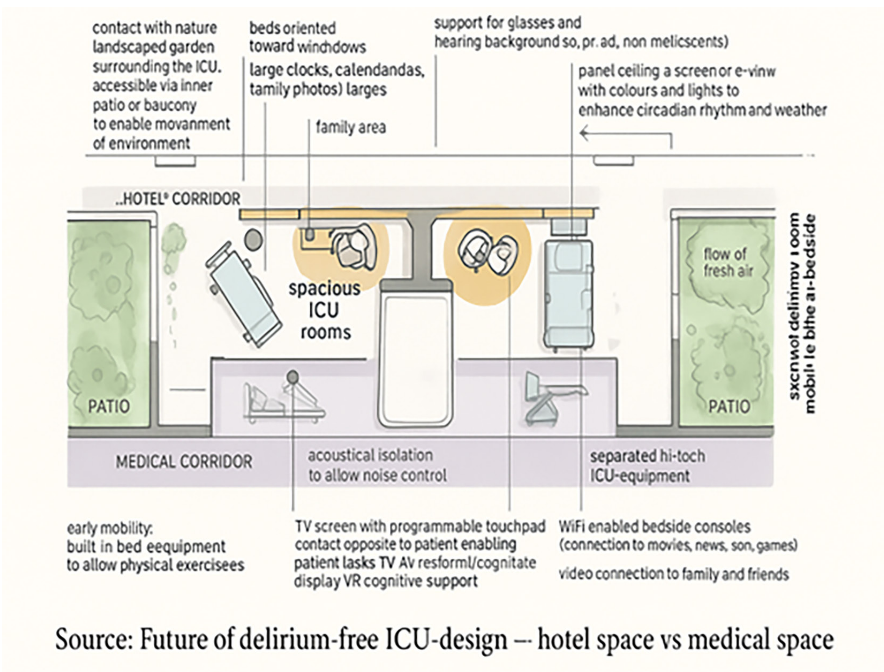
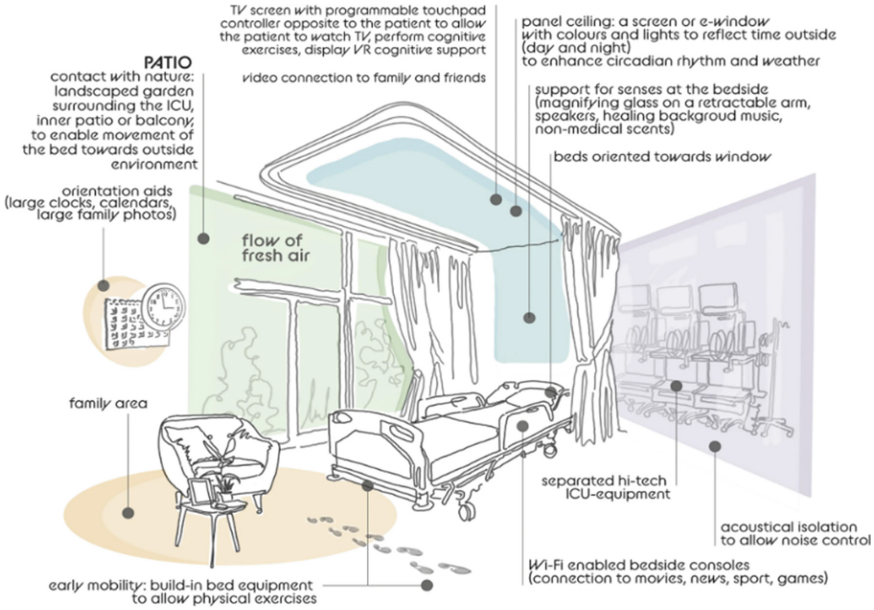


Figure 4. Future delirium-free ICU room design 1. Source: Kotfis et al. 2022



b. Future of delirium-free ICU-design – the importance of healing environment

Figure 5. Future delirium-free ICU room design 2. Source: Kotfis et al. 2022

nurses was rated positively, improved CAM-ICU knowledge, and increased delirium detection. Delirium detection across the health system improved from 9.1% at baseline to 21.2% in ICUs that participated in a delirium education workshop (Sinvani et al. 2021).

Clinicians must use validated tools, act on assessments, and embrace non-pharmacologic strategies even when they require time and creativity. Nurses must be supported to engage in delirium preventive care. Families must be seen as collaborators, not visitors. Without consistent involvement from the healthcare team and patient families, opportunities may have been lost to optimise family-centred care practices in the ICU (Johnson et al. 2024).

Conclusion

Delirium remains hidden because we allow it to be. But behind each case is a voice, a life, and a future at risk. Making delirium visible means more than diagnosing it. It means understanding, preventing, treating it and never again accepting it as inevitable. In the ICU, we are stewards not just of survival, but of identity. This is a cultural issue. The evidence and the tools exist. What's needed now is action. The ICU should be a place not just to preserve life, but to protect what makes that life worth living. Changing the culture around delirium is not optional. It is an ethical mandate.

Acknowledgement

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Conflict of Interest

None

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Redefining Rate Control Strategy With Landiolol in Acute Critical Care: Manage The Rhythm Without Compromising the System

Landiolol, an ultra-short-acting and highly β1-selective intravenous β-blocker, addresses the need for rapid and controllable arrhythmia suppression while maintaining cardiovascular stability. Recently approved in the United States and already in use in Europe, landiolol combines rapid onset and offset with a favourable haemodynamic profile.

Tachyarrhythmias frequently complicate the clinical course of critically ill patients, contributing to haemodynamic deterioration and increased morbidity and mortality, particularly following cardiac surgery or acute myocardial infarction. Therapeutic management necessitates effective rate and rhythm control; however, the use of conventional β-adrenergic blockers and amiodarone is often limited by their potential to exacerbate hypotension, negative inotropy, and other adverse effects. This underscores the need for agents that provide rapid, controllable arrhythmia suppression while preserving cardiovascular stability.

Landiolol, a highly β1-selective and ultra-short-acting intravenous β-blocker, is emerging as a solution to this dilemma. Recently approved in the United States and already integrated into European practice, landiolol combines rapid onset and offset with a favourable haemodynamic profile (Frishman et al. 2025; Rao et al. 2024). New publications across a range of clinical settings suggest landiolol could redefine rate control strategies in the ICU.

Pharmacological Profile: Precision and Safety

The pharmacological profile of landiolol, characterised by rapid onset and offset, makes it an ideal β-blocker for patients with unstable haemodynamics who require immediate and adjustable rate control:

- Half-life of just 4 minutes, allowing real-time titration (Nasoufidou et al. 2025).
- High β1-selectivity (~8 times higher than esmolol), minimising negative inotropy and bronchospasm (Rao et al. 2024).
- Predictable kinetics, with minimal protein binding and no clinically significant metabolites (Frishman et al. 2025).

This "on-off switch" pharmacological profile provides clinicians with the ability to swiftly titrate or discontinue therapy, offering a significant safety advantage in the critical care setting.

Supraventricular Arrhythmias

Placebo-controlled trials formed the basis for FDA approval, confirming that landiolol rapidly and effectively reduces heart rate in supraventricular tachycardias, including atrial fibrillation and flutter (Frishman et al. 2025).

Compared to esmolol, landiolol demonstrates superior cardioselectivity and comparable efficacy, with hypotension the most frequent but usually reversible side effect. This allows safe use even in fragile patients with severe reduced ventricular function (Frishman et al. 2025).

Coronary Artery Disease and STEMI

In acute coronary syndromes, heart rate control can stabilise haemodynamics and reduce myocardial oxygen demand. A 2025 review in Journal of Clinical Medicine summarised promising findings (Nasoufidou et al. 2025):

- In ST-elevation myocardial infarction (STEMI), landiolol reduced progression to higher Killip classes and lowered the incidence of acute heart failure compared with placebo.
- During CT coronary angiography, bolus or infusion regimens enabled target heart rates for high-quality imaging without compromising blood pressure.

Meta-analyses further suggest that early intravenous β-blockade, particularly with landiolol, may improve outcomes even in the percutaneous coronary intervention (PCI) era (Sun et al. 2024). This positions landiolol as a practical and potentially protective option for critically ill coronary patients.

Ventricular Tachycardia and Electrical Storm: A Difficult Setting

Electrical storm (ES) remains one of the most challenging arrhythmia emergencies. Evidence is sparse, but three Japanese studies and a post-marketing survey of 250 patients showed landiolol to be effective in suppressing ES episodes, often in combination with amiodarone (Motazedian et al. 2025).

Landiolol represents a new and useful agent in the critical care armamentarium for managing patients refractory to amiodarone. It is an alternative for unstable patients at risk for hypotension who are not eligible for sedation or stellate ganglioplegia when under anticoagulant therapy.

Although larger randomised trials are needed, existing data suggest that landiolol may serve as an effective adjunctive therapy in cases where conventional treatments are insufficient.

Preventing Postoperative Atrial Fibrillation

Postoperative atrial fibrillation (POAF) is among the most prevalent complications following cardiac surgery and is associated with prolonged intensive care unit (ICU) stays and delayed overall recovery. Here, landiolol demonstrates some of the most robust clinical evidence:

- A systematic review found landiolol reduced POAF from 37.6% to 13.7% in cardiac surgery patients (Fellahi et al. 2025).
- A large retrospective analysis reported significantly lower POAF incidence (18.9% vs 38.7%) and shorter hospital stays with landiolol (Kaminohara et al. 2022).

Considering the adverse effect profile of amiodarone and the frequent hesitation to resume conventional β-blockers postoperatively due to hypotension risk, landiolol's favourable haemodynamic properties and safety profile present it as a viable and well-tolerated option for the prevention of POAF.

Beyond Cardiac Surgery: ERAS and Thoracic Surgery

Enhanced Recovery After Surgery (ERAS) protocols emphasise multimodal optimisation. A 2025 study demonstrated ERAS reduced POAF incidence, and authors noted that safer short-acting agents like landiolol could increase clinician confidence in guideline-adherent β-blocker use (Niessen et al. 2025).

In thoracic surgery, including lung resection, case reports describe landiolol's effectiveness in reducing heart rate and restoring sinus rhythm, without exposing patients to amiodarone's pulmonary toxicity risks (Sauve et al. 2025).

Safety Profile and Practical Considerations

Landiolol is generally well tolerated, with a safety profile favourable compared to other intravenous β-blockers. The most frequently reported adverse event is hypotension, which is usually mild, transient, and reversible upon dose adjustment or discontinuation of the infusion (Frishman et al. 2025). Bradycardia may also occur, consistent with class effects of β1-selective blockers, but is typically manageable and rarely necessitates treatment cessation (Frishman et al. 2025).

Practical dosing considerations:

- Initiate therapy at 1–10 mcg/kg/min, with the starting dose guided by the patient's baseline ventricular function.
- Titrate every 10–15 minutes based on therapeutic response and tolerability.
- In patients with preserved haemodynamics, upward titration can be achieved safely due to landiolol's rapid onset and offset.

Transition to oral β-blockers can be facilitated smoothly due to landiolol's rapid clearance, allowing seamless maintenance of rate or rhythm control after stabilisation (Frishman et al. 2025).

This flexibility in dosing and rapid reversibility makes landiolol particularly well-suited for perioperative arrhythmia management, including POAF, where haemodynamic parameters can shift rapidly.

Conclusion

Landiolol has emerged as a clinically valuable agent across diverse cardiovascular contexts, including supraventricular arrhythmias, STEMI, electrical storm, and POAF. Its ultra-short-acting β_1-selective profile offers reliable rate control with minimal impact on blood pressure and myocardial contractility, making it particularly advantageous in patients with compromised haemodynamics. Landiolol is a useful agent to manage beta-blockade during critical care stay, avoiding discontinuation or optimising early initiation as recommended.

The ability to titrate rapidly and discontinue the drug promptly provides clinicians with a high degree of control, especially in critical care and perioperative settings. Although further large-scale, comparative trials are warranted to refine its positioning among existing therapies, current evidence supports landiolol as a safe, effective, and flexible option for acute heart rate management in complex and unstable cardiovascular conditions.

Disclaimer

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

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Bedside Monitoring of Respiratory Effort in Patients Undergoing Assisted Mechanical Ventilation

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This review explores bedside methods for monitoring respiratory effort in patients undergoing assisted mechanical ventilation. It highlights the risks of lung and diaphragm injury from excessive or insufficient patient effort, reviews invasive and non-invasive pressure-based techniques, and discusses their strengths, limitations, and proposed safety thresholds. The article emphasises integrating these tools into clinical practice to guide lung- and diaphragm-protective ventilation strategies.

Introduction

For many patients who experience acute respiratory failure (ARF), the use of mechanical ventilation is a life-saving intervention. While identifying and treating the underlying cause of ARF, the application of lung-protective ventilation is also key to avoiding the progression of lung injury (Brochard et al. 2017). It is well understood that damage to the lungs can occur during mandatory ventilation. However, what is less widely appreciated is the potential for lung injury during mechanical ventilation in assisted modes of ventilation (Yoshida et al. 2017). Moreover, monitoring respiratory effort is increasingly being viewed as a crucial step to implement lung- and diaphragm-protective ventilation during assisted ventilation (Goligher et al. 2020).

During each patient-triggered inspiratory effort, the volume of gas inflating the lungs is the result of the combined effects of the negative pleural pressure (Ppl) generated by inspiratory muscle activity and the positive airway pressure (Paw) generated according to the pressure support level (Psupp) set by the clinician. The transpulmonary pressure (PL), the effective pressure distending the lungs, represents the difference between Paw and Ppl and is directly correlated with the mechanical stress exerted on the lung parenchyma (Akoumianaki et al. 2014). In controlled ventilation, PL closely reflects Paw, since the ventilator is the sole driver of lung inflation. In contrast, during assisted ventilation, an identical Paw may correspond to widely varying PL values due to the contribution of patient-generated inspiratory effort. This additional hidden pressure, resulting from patient effort, cannot be directly inferred from ventilator waveforms, posing a challenge for accurate assessment.

Therefore, unveiling the pressures generated by the patient's effort of breathing in spontaneous modes of ventilation should be a primary concern for clinicians. In this regard, several practical methods have been proposed to monitor patient respiratory effort (Van Oosten et al. 2024). This review will specifically examine pressure-based methods, both invasive and non-invasive, including oesophageal pressure (Pes), airway occlusion pressure at 100msec (P0.1), end-expiratory occlusion pressure (ΔPocc) and pressure muscle index (PMI).

Mechanisms of Lung and Diaphragmatic Injury During Spontaneous Ventilation

Mechanical ventilation can contribute to lung injury through several mechanisms collectively referred to as ventilator-induced lung injury (VILI) (Slutsky and Ranieri 2013). Although the preservation of spontaneous breathing can enhance the recruitment of dependent lung regions and

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mitigate ventilation-perfusion mismatch, the combination of the patient's effort and ventilation may induce excessive lung stress and strain (Yoshida et al. 2017). This may be particularly relevant in damaged lungs, where the anatomical and functional heterogeneity of the lung parenchyma may result in regionally injurious ventilation due to variations in PL swings throughout the pleural space (Gattinoni and Pesenti 2005).

Elevated PL and high tidal volume (Vt) are well-established contributors to alveolar over-distention, a phenomenon known as volutrauma (ARDS Network 2000). This condition leads to an increase in the overall mechanical stress exerted on the lung parenchyma, with a predominant impact on non-dependent lung regions (Slutsky and Ranieri 2013). Such overdistension may arise from excessive patient-generated inspiratory effort or, conversely, from the combination of over-assisting Psupp levels and minimal respiratory effort (Docci et al. 2023).

A vigorous inspiratory effort amplifies pendelluft, the phenomenon of air movement from one lung region to another without causing a significant change in Vt, thereby increasing the risk of regional cycling opening and closing of alveoli within each breath, a detrimental mechanism predominantly involving dependent lung regions and known as atelectrauma (Yoshida et al. 2013). Furthermore, active expiration and patient-ventilator asynchrony may further exacerbate these effects, contributing to lung injury progression (Chanques et al. 2013).

From the lung perfusion perspective, PL contributes to the pressure gradient across the pulmonary vessels. Elevated PL values may increase the risk of pulmonary oedema by increasing total and extravascular lung water, particularly in the setting of inflammation and increased vascular permeability (Yoshida et al. 2017).

In addition, the appropriate application of assisted ventilation is essential to reduce the risk of diaphragm injury and weakness in critically ill patients. These conditions have been linked to weaning failure, prolonged mechanical ventilation and increased mortality (Dres et al. 2017; Goligher et al. 2015; Goligher et al. 2018). Mechanical ventilation induces myotrauma through various mechanisms, the most extensively described being muscle atrophy resulting from ventilatory assistance (Levine et al. 2008). This pathophysiological process is primarily observed during mandatory ventilation; however, minimal respiratory effort and excessive Psupp (over assistance) are associated with inefficient muscular contraction and development of diaphragm weakness (Goligher et al. 2015). The diaphragm is also sensitive to sustained excessive respiratory workload. Elevated patient effort, insufficient ventilatory assistance, and patient-ventilator asynchrony can lead to excessive muscular activity, secondary diaphragm inflammation, and tissue damage (Jiang et al. 1998).

Invasive Pressure-Based Method: The Oesophageal Pressure (Pes)

Oesophageal manometry is the reference method when assessing respiratory mechanics. The waveform analysis of Pes allows investigators to estimate several surrogate parameters that are considered the gold standard when evaluating respiratory muscle effort and work of breathing **(Figure 1, Panel A)** (Mauri et al. 2016a).

Pes variations reflect changes in Ppl, making the difference between Paw and Pes a reliable estimate of PL. It is important to consider that Pes represents the pressure surrounding the oesophageal balloon, while Ppl varies with a ventral-dorsal gradient across the pleural space due to gravitational forces, parenchymal heterogeneity, *pendelluft,* and the weight of the mediastinum (Yoshida et al. 2018). The safety limits of PL in assisted ventilation remain debated, though a peak inspiratory value below 20 cmH2O has been considered acceptable from studies on both spontaneous breathing in healthy lungs and passive ventilation in injured lungs **(Table 1)** (Mauri et al. 2016a; Baedorf Kassis et al. 2016).

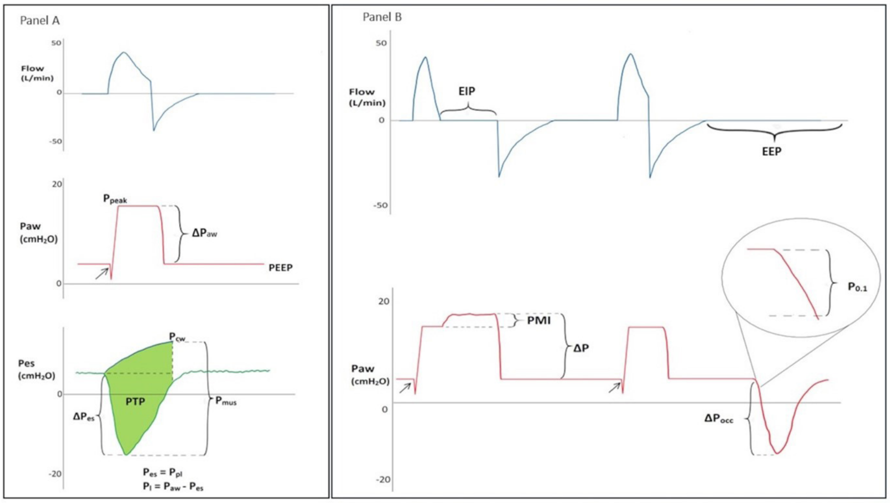

Figure 1. Representation of Invasive (Panel A) and Non-invasive (Panel B) Pressure Parameters to Monitor Respiratory Effort. The black arrows represent the patient's trigger. Paw: airway pressure; Ppeak: peak inspiratory pressure; PEEP: positive end-expiratory airway pressure; Pes: oesophageal pressure; Ppl: pleural pressure; ΔPes: oesophageal driving pressure; PL: transpulmonary pressure; Pcw: pressure to overcome chest wall elastance; Pmus: inspiratory muscle pressure; PTP: pressure-time-product; EIP: end-inspiratory pause; EEP: end-expiratory pause; P0.1: airway occlusion pressure at 100ms; ΔPocc: expiratory-occlusion pressure; ΔP: driving pressure; PMI: pressure muscle index.

Also, Pes directly quantifies respiratory muscle activity in assisted ventilation. Inspiratory muscle contraction generates negative Pes swings (ΔPes), reflecting the magnitude of respiratory effort. The inspiratory muscle pressure (Pmus) is the global pressure exerted by the inspiratory muscles to expand the respiratory system, including the lungs and the chest wall. Pmus is derived from the difference between the pressure required to overcome the chest wall elastance and Pes (Pmus = Pcw – Pes), and its proposed safety thresholds range between 5 and 10 cmH2O (Carteaux et al. 2013). Given that Pcw cannot be accurately measured during active breathing, it needs to be computed during passive ventilation or roughly estimated as 4% of predicted vital capacity (Mauri et al. 2016a). However, in routine clinical practice, it is generally accepted that the correction of Pmus for Pcw can be omitted in most patients, acknowledging that chest wall elastance may be relevant in certain conditions such as obesity, chest wall disorders and increased intra-abdominal pressure (Brochard 2014).

In addition, the use of a double-balloon catheter enables the measurement of gastric pressure (Pga). The difference between Pes and Pga quantifies the transdiaphragmatic pressure (Pdi). This measurement provides valuable insight into diaphragmatic activity and patient-ventilator synchronisation (Akoumianaki et al. 2024).

More complex measurements, such as the pressure-time product (PTP, the area under the Pmus curve over time) and the work of breathing (WOB, the area under the volume-pressure curve), are derived from Pes and Pmus. These parameters are considered the gold standard for assessing respiratory effort due to their strong correlation with inspiratory muscle energy expenditure and oxygen consumption. However, their clinical application remains mainly confined to the research setting (Mancebo et al. 1995).

Although oesophageal manometry provides a comprehensive and detailed evaluation of respiratory effort, its clinical implementation remains limited. Several barriers must be addressed to facilitate its broader adoption in clinical practice, including the need for specialised expertise in catheter placement, validation of balloon positioning and waveform interpretation, as well as challenges related to equipment availability, tolerance in awake patients and costs (Brochard 2014).

Non-Invasive Pressure-Based Methods

Airway occlusion techniques during spontaneous mechanical ventilation **(Figure 1, Panel B)** have been used for over three decades to estimate respiratory effort (Whitelaw et al. 1975; Foti et al. 1997). Numerous studies have described these parameters, emphasising their ease of use, straightforward interpretation, repeatability and non-invasiveness. These characteristics render them practical tools for bedside evaluation of respiratory effort. Moreover, adherence to standardised procedures and the averaging of repeated measurements are essential to achieve stable and reliable values (Kera et al. 2013; Bianchi et al. 2022). It should be emphasised that none of these measures has demonstrated predictive capability to exactly compute measures of respiratory effort or pulmonary mechanics; therefore, there is no definitive consensus on their cutoff values (Telias et al. 2020; Bertoni et al. 2019; De Vries et al. 2023). Table 1 shows the most frequently proposed safety thresholds.

Airway occlusion pressure in the first 100 milliseconds of inspiration (P0.1)

P0.1 is the decrease in pressure generated by the inspiratory muscles in the first 100ms of inspiration against an occluded airway **(Figure 1, Panel B)**. P0.1 represents a physiological manifestation of the cerebral respiratory centres' activity, making it a more precise estimation of the respiratory drive rather than a direct reflection of the effort generated by inspiratory muscles (Jonkman et al. 2020). This is attributable to its independence from respiratory mechanics and voluntary modulation of breathing.

Specifically, since inspiratory effort is initiated at the end-expiratory volume, the pressure drop does not include any

Method	Parameter	Formula	Proposed Safety Cutoff Values
Oesophageal manometry	Peak transpulmonary pressure	P_(peak, L)=P_(peak, aw)-P_(peak, es)	≤ 20 cmH2O
	Oesophageal driving pressure	ΔP_es=ΔP_(es, end-inspiration)-ΔP_(es, end-expiration)	≥ 3 cmH2O, ≤ 8 cmH2O
	Transpulmonary driving pressure	ΔP_L=ΔP_aw-ΔP_es	≤ 15 cmH2O
	Transdiaphragmatic pressure swing	ΔP_di=ΔP_ga-ΔP_es	≥ 5 cmH2O, ≤ 10 cmH2O
	Muscle Pressure	P_mus=P_cw-P_es	≥ 5 cmH2O, ≤ 10 cmH2O
	Pressure time product per minute	PTP_(per breath)=∫_0^(T_i)|P_mus (t)| dt	≥ 50 cmH2O/s/min, ≤ 200 cmH2O/s/min
Occlusion manoeuvre	Driving pressure	ΔP=P_plat-PEEP	≤ 15 cmH2O
	Airway occlusion pressure at 100ms	P_0.1=P_aw (t=0)-P_aw (t=100 ms)	≤ -1.5 cmH2O, ≥ -3.5 cmH2O
	End-expiratory occlusion pressure	ΔP_occ=P_trough-PEEP	≤ -7 cmH2O, ≥ -15 cmH2O
	Pressure muscle index	PMI=P_plat-P_peak	> 0 cmH2O, upper value not proposed

Table 1. Proposed Cutoff Values for Protective Ventilation in Spontaneous Breathing

component derived from the recoil pressure of the respiratory system. The absence of flow during the occlusion manoeuvre removes the impact of airway resistance, the ventilator valves closure guarantees no change in lung volume, and there is no conscious reaction in the first millisecond of an airway occlusion (Jonkman et al. 2020). Furthermore, evidence indicates that P0.1 remains stable in the presence of non-severe muscle weakness and in patients with pulmonary hyperinflation (Holle et al. 1984; Conti et al. 1996).

In critically ill patients, Tellias et al. (2020) reported a moderate to strong correlation between P0.1 and PTP/min, findings corroborated by Rittayamai et al. (2017). Moreover, consistently in multiple studies, P0.1 has shown moderate to high accuracy in detecting both excessive effort (PTP/min ≥ 200 cmH2O s/min) and low effort (PTP/min ≤ 50 cmH2O s/min) (Telias et al. 2020; Rittayamai et al. 2017; Pletsch-Assuncao et al. 2018). It should be noted that although various ICU ventilators can automatically measure P0.1, its value may be underestimated, primarily due to the circuit length (Beloncie et al. 2019).

Multiple factors have been linked to variations in P0.1. Physiological and clinical data have demonstrated a linear association between P0.1 and parameters such as bilateral lung disease, the severity of acute respiratory distress syndrome (ARDS), PEEP and Psupp levels, along with blood oxygen and carbon-dioxide content (Spinelli et al. 2023; Mancebo et al. 2000; Iotti et al. 1996; Alberti et al. 1995; Mauri et al. 2016b). Conversely, P0.1 does not appear to correlate with clinical scores of sedation, pain and delirium, although the influence of type and dose of analgesic and sedative drugs remains relevant (Dzierba et al. 2021).

An abnormally high or low respiratory drive may represent both an indicator of disease severity and a contributor to harmful effects, as previously described. Consequently, P0.1 may hold prognostic value in predicting clinical outcomes. A recent meta-analysis demonstrated a significant association between P0.1 and successful weaning, although substantial overlap in P0.1 values between patients who were successfully weaned and those who were not did not permit the establishment of an accurate cutoff (Sato et al. 2021). Observational data have suggested an association between higher values of P0.1 and reduced likelihood of successful weaning, as well as increased mortality (Le Marec et al. 2024). Interestingly, Bellani et al. (2010) showed that patients who failed a weaning trial had higher P0.1 values and a lower increase in oxygen consumption compared with patients who succeeded, suggesting muscle weakness.

End-expiratory occlusion pressure (ΔPocc)

ΔPocc is the maximum airway pressure drop from PEEP observed during an expiratory hold **(Figure 1, Panel B)**. During an end-expiratory occlusion manoeuvre, the inspiratory effort produces a reduction in Paw that correlates with the swing in Pes (Bertoni et al. 2019). Unlikely P0.1, ΔPocc reflects inspiratory muscle contraction rather than respiratory drive, allowing clinicians to estimate PL (PL ≈ Paw – 0.66 x ΔPocc) and Pmus (Pmus ≈ - 0.75 x ΔPocc) (Bertoni et al. 2019).

In a small cohort of patients, ΔPocc was validated as a reliable indicator of PTP/min, and it showed strong predictive performance for elevated dynamic PL and Pmus (Bertoni et al. 2019). A study involving fifteen COVID-19 patients further supported these findings (Roesthuis et al. 2021). More recently, De Vries et al. (2023) reported wide limits of agreement between

ΔPocc and Pes and Pdi, although higher ΔPocc values robustly predicted elevated PL, outperforming P0.1 in estimating high respiratory effort.

These findings suggest that ΔPocc may serve as a suitable, non-invasive index of inspiratory muscle effort. Consequently, combining measurements of P0.1 and ΔPocc might offer a comprehensive screening tool to identify patients at risk for either elevated or diminished respiratory effort, as well as for a dissociation between respiratory drive and effort, thereby informing the need for more accurate respiratory monitoring.

End-inspiratory occlusion pressure: pressure muscle index (PMI)

PMI is the difference between the plateau pressure (Pplat) and Ppeak measured during an end-inspiratory occlusion manoeuvre in assisted ventilation. Following a circuit occlusion at the end of inspiration, the contracted inspiratory muscles relax and generate an elastic recoil pressure that is reflected in the plateau waveform of Paw, resulting in a Pplat value that exceeds Ppeak **(Figure 1, Panel B)** (Foti et al. 1997). Depending on the degree of the patient's contribution to ventilation, Pplat may be lower than, equal to, or higher than Ppeak.

Under passive mechanical ventilation, an inspiratory hold manoeuvre is used to assess the driving pressure (ΔP), which represents the effective pressure distending the lung parenchyma. ΔP is determined by the interplay between Vt and the mechanical properties of the respiratory system, and increased driving pressure values have been strongly correlated with lung injury and higher mortality rates in patients with ARDS (Amato et al. 2015).

PMI enables the estimation of ΔP even in spontaneous breathing **(Figure 1)**, although its readability requires a stable plateau phase, which can be difficult or even impossible to achieve in many patients. Obtaining a reliable Pplat includes the recently proposed criteria: performing more than one occlusion, short time to reach the plateau (<1sec), sustained plateau duration (>2sec), and limited Paw variation (<0.6 cmH2O) (Bianchi et al. 2022). Nonetheless, even an unstable plateau waveform may be informative, suggesting increased respiratory effort or activation of expiratory muscles (Soundoulounaki et al. 2020). PMI has shown a reliable association with reference measures of respiratory effort. For instance, Bianchi et al. (2022) reported a significant correlation of PMI with PTP, as well as with Pmus. These results are consistent with findings from other studies evaluating PMI in both adult and paediatric populations (Gao et al. 2024; Kyogoku et al. 2021).

From a practical standpoint, evaluating PMI, and by extension ΔP, may serve as an indicator of excessive mechanical stress on the lung parenchyma, following pathophysiological mechanisms similar to those observed in passive ventilation. In addition, PMI values equal to or lower than zero may suggest excessively high ventilator assistance, characterising a "quasi-passive" patient-ventilator interaction (Docci et al. 2023). These observations highlight the potential utility of PMI as a tool for identifying scenarios of over-assistance, reduced respiratory effort, and respiratory muscle weakness, thereby underscoring the need for further research.

Conclusion

Pressure-supported mechanical ventilation carries both benefits and risks, making the implementation of a lung- and diaphragm-protective ventilation strategy essential, albeit challenging. Targeting safe ranges of inspiratory effort is a reasonable strategy when designing bedside algorithms aimed at protective ventilation. For this purpose, Pes-based methods are considered the gold standard, but their invasiveness, costs and discomfort prevent their widespread use in clinical practice. In contrast, P0.1, ΔPocc and PMI are increasingly demonstrating their reliability and usability in inferring patient respiratory effort. Their implementation in routine clinical practice may facilitate a more comprehensive assessment of a patient's condition and disease progression, particularly in distinguishing between extremes of ventilatory assistance and the patient's own breathing effort. However, their application should always be contextualised within the individual clinical scenario, recognising that different aetiologies of ARF and varying clinical phenotypes necessitate tailored management strategies.

Conflict of Interest

None

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Health Information Technology Evaluation: Reimagining Evidence in the Age of Machine Learning and Large Language Models

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In today's rapidly evolving digital era, health information technologies give enormous opportunity and promise to transform patient care. To unlock their full potential, these innovations must be tested with the same scientific rigour as life-saving drugs and devices. This article invites readers to rethink how we evaluate new technologies in healthcare based on a structured framework to ensure it helps to deliver safer, smarter, and more impactful care.

At the beginning of the 20th century, the Heidelberg Electric Belt was a medical hit. These devices used batteries to generate a therapeutic current when wrapped around the body. They were promoted to alleviate a range of conditions, from paralysis to digestive issues and impotence, essentially sold as a general-purpose cure device (Figures 1 and 2). It was distributed worldwide for almost 20 years, with estimated sales reaching hundreds of thousands of copies and was included in many mail-order catalogues.

Around 1910, the American Medical Association and medical press began to more aggressively debunk electric belt claims, which eventually led to a decline in their availability. As medical standards improved, the device was proven ineffective and dropped from legitimate use. It was shown that no real clinical or physiological support for the advertised effects existed.

At that time, no special requirement existed to perform tests of new devices or medications to show benefit to the patient. Manipulated marketing with a chain of endorsements from leading doctors was often used to promote new devices.

Since then, significant progress has been made in regulating pharmaceuticals, consumer products, and medical devices. However, the rapid evolution of health information technology (HIT), including Electronic Medical Records (EMR), Clinical Decision Support Systems (CDSS), and related artificial intelligence (AI) technologies, leaves us in a situation much like the beginning of the 20th century. Vendor-driven case studies and anecdotal reports often shape the narrative of HIT success, yet such accounts can be misleading.

The example above illustrates the dangers of adopting novel technologies without proper scientific validation. It helps us appreciate the importance of evaluation frameworks to protect patients and uphold clinical integrity.

Modern Days: Why Structured Evaluation Matters

Critical care has always been at the forefront of technology adoption - from early waveform monitoring to advanced predictive models for patient deterioration. With this evolution, the importance of evaluation has only grown. Technologies that once offered simple alarms now make complex recommendations. As a result, the field must adapt its evaluation techniques accordingly.

Introduction HIT plays an increasingly critical role in hospital and ICU environments, where clinical decisions are time-sensitive and complex. It is already evident that electronic tools enhance practice and safety, but proper evaluation ensures that these technologies deliver on their promise to enhance care without introducing new risk. In critical care, rigorous evaluation of new HIT aligned with scientific methods is essential for safe and effective use of technologies.

That problem is compounded by the rapid advancement of machine learning (ML) and large language models (LLMs), which have introduced a new class of CDSS. The performance of these models can be dynamic, sensitive to data input variability, and sometimes not easy to interpret. Such complexity and opacity pose new challenges for the evaluation of HIT.

Without controlled studies or a clear implementation context, it is difficult to discern real clinical impact. Anecdotal narratives can mislead as they emphasise success stories while ignoring failures or false positive cases. Vendors use marketing tools designed to build brand reputation and sales. Without scientific evaluation (e.g., peer-reviewed trials), such claims can overestimate benefits and understate risks such as alert fatigue, workflow disruptions or bias in new CDSS. A scientific evaluation framework provides the methodological rigour needed to separate signal from noise. Reliance on unverified testimonials may lead to the adoption of unsafe or ineffective systems.

Traditionally, technical validation was considered a final checkpoint to technology deployment. Today, HIT evaluation must be seen as a rigorous, multidisciplinary scientific discipline. Combining principles from biomedical informatics, human factors engineering, implementation science, and systems design, modern HIT evaluation seeks to generate reproducible evidence that supports both clinical outcomes and operational feasibility.

Initial HIT evaluations focused on the transition from paper to digital systems. These early studies typically measured documentation time, user satisfaction, and basic error rates. While foundational, they lacked the scope to address how HIT influences complex decision-making processes, reproducibility, transparency, and fairness.

The Epic Sepsis Model (ESM) is a modern example of technology that uses promotional materials and hospital press releases to describe its ESM as a powerful tool for early detection of sepsis, claiming improved patient outcomes and reduced mortality rates. An independent evaluation published in JAMA Internal Medicine concluded that the tool had poor sensitivity and clinical utility in the real-world hospital environment. It missed two-thirds of sepsis cases and generated excessive false positives (Wong et al. 2021). Following the critique, promotional materials about the machine learning model for early sepsis detection are now available on the protected Epic User portal, accessible only to authorised users.

Unvalidated technologies and algorithms pose serious risks to patient safety. They can produce excessive false positives, leading to alert fatigue and clinician desensitisation, or miss critical cases, delaying essential interventions. Another challenge is the phenomenon of "pilot purgatory," where promising tools stagnate after small-scale trials due to a lack of generalisable evidence. Many hospital systems are reluctant to scale these tools without a formal evaluation process.

Drawing parallels with pharmaceutical development, HIT should go through phases of evaluation, from concept to post-market monitoring. A staged model ensures each system is vetted across technical, clinical, and operational domains.

Figure 1. Early 1900s advertisement poster "All in search of health should wear Harness' Electropathic Belt." Source: Wikimedia Commons

Figure 2. Another version of an advertisement poster "All in search of health should wear Harness' Electropathic Belt." Source: Wikimedia Commons

What is HIT Evaluation

HIT evaluation differs fundamentally from general IT evaluation because of the clinical context in which it operates. While traditional IT may focus on speed, reliability, and user interface, HIT must be evaluated for its impact on patient safety, clinical workflows, and health outcomes. HIT evaluation is an evidence-generating discipline focused on both the process and outcomes of technology use in healthcare.

Key components include clinical impact (e.g., improved diagnosis or reduced complications), workflow integration (e.g., reduction in cognitive load), safety (e.g., error reduction), usability (e.g., clinician satisfaction), cost-effectiveness, and implementation fidelity. These domains form the backbone of the evaluation matrix and guide the selection of appropriate methods and metrics for each project.

HIT evaluation is built on a wide range of scientific disciplines. While randomised controlled trials (RCTs) are often impractical for HIT interventions, alternative designs, such as interrupted time series, stepped-wedge cluster trials, and pragmatic trials offer robust options. Detailed clinical epidemiology guidance is needed for selecting study designs appropriate that are to the technology and clinical setting. Structured EHR data is foundational but must be supplemented with audit logs, clinician interaction metrics, and outcome indicators such as mortality and length of stay.

Structure of Modern HIT Evaluation

For robust evaluation, no single study can answer all questions. Typically, a five-stage model is needed for systematic evaluation (Herasevich and Pickering 2021):

- Stage 0: Problem Definition and Co-Design – Engage stakeholders to define clinical problems and co-develop technology solutions that meet real-world needs.
- Stage 1: Technical Validation – Evaluate the predictive performance of the tool (ML model) using metrics like AUROC on retrospective datasets.

- Stage 2: Clinical Simulation – Use silent mode testing on real-time data to estimate practical utility before live deployment.
- Stage 3: Real-World Pilot – Conduct a limited-scope deployment to observe initial clinical use and refine the system.
- Stage 4: Implementation and Outcome Evaluation – Measure changes in patient outcomes, clinician behaviour, and system-level metrics.

Evaluating LLMs and Next-Generation CDS

Large Language Models (LLMs, e.g. ChatGPT) introduce unique challenges not seen in traditional CDS tools. Their outputs can vary with slight input changes. Systems are prone to hallucinations and often lack traceable reasoning paths. Evaluation must include dimensions such as output consistency, factual grounding, and prompt sensitivity.

Bias detection, user prompt design, and explainability testing are emerging needs in HIT. It has become evident that standard HIT evaluation metrics are insufficient for LLM testing, and novel approaches such as response quality benchmarking and fairness audits are required.

Finally, regulation has not yet caught up with AI's capabilities. There is a growing need for methodological standards and oversight mechanisms that address dynamic systems.

Conclusion

In modern days, when healthcare is dominated by digital innovations, scientific evaluation is no longer optional. Software tools that influence care must be held to the same evidence standards as drugs and devices. They should be supported by scientific evaluation methodologies in real-world settings.

We call on ICU leaders, clinical informaticians, and developers to embrace evaluation as a core professional obligation. Only through structured, scientific inquiry can we ensure that ML and LLM-based decision support tools truly advance patient care without compromise.

Conflict of Interest

None

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Short-Term Capacity Planning in an Intensive Care Unit: Web-Based Prediction Model and Pilot Study

ICU occupancy varies and cannot be scheduled. To tailor nurse staffing to variable ICU occupancy would potentially decrease both under- and over-staffing. We developed a simple web-based interface for short-term prediction of occupancy and, in a pilot study, compared predicted and observed occupancy.

Introduction

The capacity of intensive care unit (ICU) beds is limited. The main limiting factor for ICU capacity in Norwegian health care is often not funding, rooms or physicians, but the availability of intensive care nurses. A recent Norwegian governmental publication emphasised that the lack of healthcare workers will be the major future issue for Norwegian healthcare (Official Norwegian Report 2023:4). In Norway, the Regional healthcare authorities' directives dictate that intubated ICU patients should have a nurse continuously at the bedside; thus, minimal capacity often equals the number of nurses. Nurses work every third weekend, which results in the number of scheduled nurses at each shift (day, evening, night) during the weekend being lower than during weekdays. In the current Norwegian labourmarket, the availability of intensive care nurses is limited. Therefore, to increase the workload with shifts every other weekend is not an option, as this will result in many nurses leaving the ICU workforce.

ICU patients are acutely ill, and it is not possible to plan a hospital stay or to postpone admittance. This results in a large variability of occupancy, and, ideally, the number of nurses should be tailored to the current need. However, it is not possible to have nurses' work schedules change on a day-to-day basis. Thus, the units are usually staffed in relation to the unit's defined number of staffed beds. For unexpected increases in the number of ICU patients, units have beds not staffed during normal circumstances and call in additional nurses. On the contrary, in periods with low occupancy, the unit may be overstaffed. Nurse overtime is expensive and also a stressor for the nurse workforce, which introduces a risk of increasing an already high personnel turnover. It would be beneficial to predict the expected occupancy during weekends in order to secure adequate staff and, at the same time, not use unneeded personnel resources.

Others have developed models for the prediction of ICU occupancy (Barado et al. 2012; Farcomeni et al. 2021; Ruyssinck et al. 2016). Many of these models are for long-term planning or for special circumstances such as pandemics. Our goal was to contribute to this work by developing a simple model for short-term occupancy planning easily applicable in day-to-day clinical practice and which can be introduced free of cost in ICU departments of different categories and settings. We developed and tested an algorithm for short-term prediction of ICU weekend occupancy based upon expected length of stay (LOS) for patients in the ICU and the expected number of new admissions during the weekend.

Methods

Part One: Development of Instrument

To predict the ICU occupancy during weekends at one day's notice (Thursday), three factors were included.

- For all patients in the unit on Thursdays, a physician predicted for each patient the expected additional ICU LOS (zero, one, two, three or four days or more). This will give an estimate of the expected burden related to patients currently treated in the unit. The prediction of expected LOS was both based on the patients' clinical condition and on organisational issues.
- Expected new admissions were calculated based on the mean number of daily admissions in the last year. New ICU patients' expected LOS was based upon data from last year, which specified the number of patients with a LOS of one day versus two days or more.
- Some patients need more than one nurse due to high complexity. This can also be included in the model.

The project developed a web-based interface where physicians assessed the expected LOS for patients in the unit each Thursday. The model calculates and gives information about expected occupancy. The model was developed and implemented as a web-based interface, which can be customised for each particular unit.

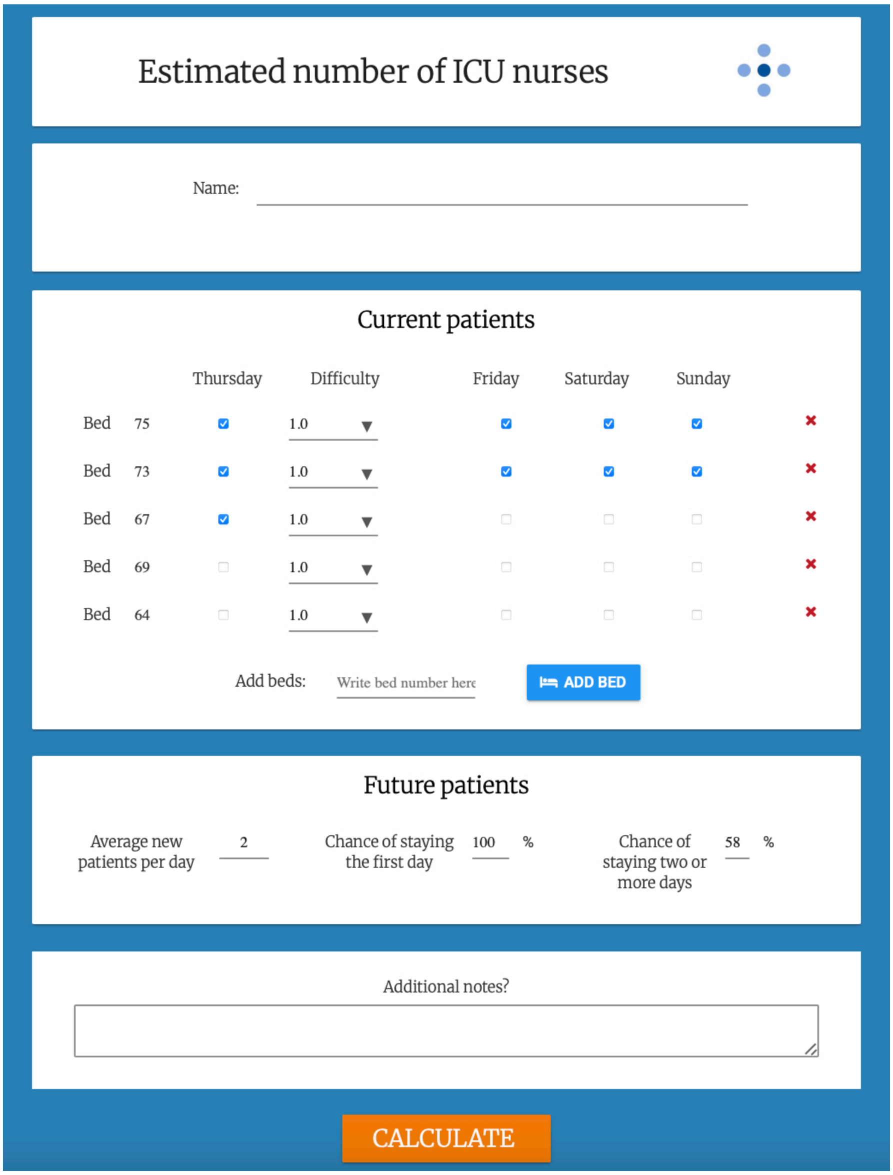

Figure 1. Interface of webpage for users

Part Two: Validation of the Instrument

In a pilot period, the model was tested for its ability to give a prediction of weekend ICU occupancy. The test was performed in a mixed-case 10-bed ICU located in a 900-bed tertiary university hospital. The unit provided care for all categories of ICU patients except children, burn patients and cardio-thoracic postoperative care. The unit is a closed ICU where care of the patients is delivered by ICU physicians. The hospital has several high dependency units (HDU). Therefore, most patients in the ICU are dependent on advanced interventions such as intubation or renal replacement therapy.

In the pilot study, on each Thursday, an ICU consultant assessed the expected LOS for each patient in the ICU. The physician was instructed to consider all elements in this assessment, including expected clinical improvement, expected death and organisational issues related to patient discharge. Examples of the latter are the availability of air ambulance transfer to a local hospital; also, some HDUs in the hospital are closed during weekends. This assessment was the basis for expected occupancy during the weekend for patients who were in the unit on Thursdays. For occupancy of new patients, expectednumbers were based on data from 2022, which showed that two patients would be admitted daily, of whom 58% would have a LOS of two days or more. Combined, these numbers gave a predicted occupancy on the weekend. During the weekends, the actual occupancy was registered daily. Both prediction and registration of actual occupancy were performed related to the number of patients in the unit at 12:00 AM.

Statistics

Descriptive data weregiven for actual and predicted occupancy for all days and specifically for Friday, Saturday and Sunday. The assessment of agreement between predicted and actual occupancy was examined by several approaches. First, agreement at the group level between actual occupancy and predicted occupancy was addressed by the Wilcoxon Signed-Rank test. Second, difference scores for each day (difference = observed minus predicted occupancy) were calculated. A difference score within 1 was classified as good agreement, difference scores ≤ -2 overestimation (fewer patients than predicted) and difference scores ≥2 underestimation (more patients than predicted). Third, the strength of agreement between the assessments was reported using mean absolute error (MAE) and linear regression. This was a pilot study; therefore, no formal sample size calculation was performed. All analyses were done with the Statistical Package for the Social Sciences (SPSS) version 29.0.0.0.

Ethics

The project is a quality improvement project and therefore not within the scope of the regional ethical committee for health research and ethics. The study obtains no clinical data, and the researchers do not know the patient's identity. The project had no influence on the care provided to the patients.

Difference score	-5	-4	-3	-2	-1	0	1	2	3
All days	1	1	5	8	8	8	5	5	1
Friday			1	2	2	5	3		
Saturday	1		1	3	4	2	1	1	1
Sunday		1	3	3	2		1	4	

Table 1. Difference scores (observed minus predicted number of patients)

Results

Part One: Development of Instrument

The web-based instrument was developed in Anvil with integrated Python code (Anvil Works 2024). The computer code can be obtained from the authors. The interface for the user is available at https://cnnsnq5fy7zrz3ip.anvil.app/3XUJCO74GCSGDFJK6MC4IL7H (**Figure 1**). In this interface, the user can add each specific unit's beds. The user can also name each bed, adhering to local specifications. For each unit, the expected number of daily new admitted patients and their expected LOS based upon organisational data are entered. The specified bed names and the numbers for expected new patients are included in future registrations until changed. In the weekly assessment, the physician checks off rooms that are occupied on Thursday and checks off for each day every patient is believed to stay in the unit. The interface also includes an option to enter the expected complexity of patients; for instance, in certain units, some patients only need 0.5 nurse,and some patients need more than one nurse. After this registration is done, the user clicks “Calculate”. The instrument then automatically produces a PDF file which, in addition to the entered data, specifies the calculated expected number of patients on Friday, Saturday and Sunday.

The users completing the instrument were given a short verbal instruction, and the link was added to their browser bookmarks. Generally, users were able to complete the instrument in about 2-3 minutes.

Part Two: Validation of the Instrument

In the pilot study, 14 weekends with a total of 42 predicted days were tested. The occupancies on Thursdays were a median of 8 patients (mean 7.4), ranging from 4 to 11. For the 42 days which were predicted, the mean predicted daily occupancy was 8.7 (SD 1.8) patients compared with the observed occupancy of 8.0 (SD 1.5) patients. The predicted number of patients was significantly different from the observed number of patients (p=0.02). The difference between predicted and observed number of patients for each weekday was not statistically significant (predicted vs observed Friday, Saturday and Sunday; p=0.19, p=0.15 and p=0.15, respectively).

The difference scores (observed minus predicted) ranged from minus 5 to plus 3. Twenty-one days showed good agreement, 15 days overestimation (fewer patients than predicted) and 6 days underestimation (more patients than predicted). The prediction for Fridays was more precise (overestimation 3, good agreement 11, underestimation 0) compared with corresponding numbers on Saturdays (4-7-2) and Sundays (7-3-4). The distribution of difference scores for all days and for each weekday is given in **Table 1**.

The mean absolute error (MAE) difference between predicted and observed number of beds was 1,6 (95% CI: 1.2-1.9). Linear regression between observed and predicted number of beds demonstrated no statistically significant association (P=0.13).

Discussion

This pilot study showed that short-term prediction of weekend occupancy based upon expected stay for patients in the unit on Thursdays and expected number of new admissions during the weekend, in general, overestimated the need for beds during the weekend. Based upon the predictions, the unit would have been understaffed for only a few days.

This study based expected occupancy on the consultant ICU physicians' consideration of expected LOS for each patient within the unit on Thursday. The assessment is based on a combination of factors related to the patient and the organisation. Relevant patient factors are severity of disease, organ failure and functional status. For instance, it is unrealistic that a patient in prone position and high settings for ventilator pressures will be weaned within the next few days. However, increased severity of disease does not automatically imply longer LOS. The patient may, due to severe disease, be expected to die within a short time or may, due to complexity, be planned for transfer to another ICU or hospital. Organisational factors are often related to local hospital capacities; other step-down units may have no free beds or may be closed during the weekends. Which patients are transferred to other units is also different between units; for instance, a unit in a small-volume hospital will often transfer patients to tertiary hospitals. Overall, this suggests a large number of potential predictors with multiple potential for interactions.

Gonzáles-Nóuva et al.(2023) applied artificial intelligence for ICU occupancy estimation. They included data from sensors, medical history and clinical-chemistry results exported from the electronic medical record in the gradient boosting technique for learning. Using a large number of observations, they completed a model that could predict LOS with an MAE of 2.5 days in a unit with a LOS average of 4.3 days. This study estimated LOS, not the number of beds on specified days, and is therefore not directly comparable with our observations. The relatively high MAE suggests that the artificial intelligence model did not perform much better than physicians' assessments. This may be because experienced ICU physicians, consciously or non-consciously, in a heuristic thought process, include the relevant factors when determining expected patient trajectories. Ryussinck et al. (2016), who also used artificial intelligence, found that respiratory organ failure and current LOS are more important for future trajectory than coagulation organ failure. This would be obvious to an experienced clinician.

Perhaps occupancy prediction could be made simpler. Jin et al.(2021) developed a simple formula based on historic 12-month activity data and linear regression. Their department is similar to our unit, an emergency ICU caring for most categories of patients. In their unit, with 12 ICU patients and 20 HDU patients, they calculated the upcoming need for nurses the next day as N = (0.45 x number of nurses needed 24 hours prior) +11. With this simple formula, they had 14% of days with less than minimum staffing and 14 % with more than three extra staff (Jin et al. 2021). These data are comparable to our results of 6 of 42 days (14%) with more than one patient in excess of predicted and 7 of 42 days (17%) with three or more nurses in excess.

From the results cited above, it seems that a complex model using artificial intelligence and our simple model using physicians' assessment, which considered the number of current patients, did not differ much in performance. However, these studies were from different populations, and thus, it is conceivable that a different case mix may have influenced the results.

What are the practical potential implications of the prediction of ICU occupancy? As shown in our study and in other studies, it is not possible to do an accurate estimation of future occupancy. Some uncertainty will exist because of the obvious lack of a schedule for incidents such as cardiac arrests, onset of severe sepsis and traffic accidents. Still, our data suggest that the unit could, for a number of days, expect a lower occupancy than normal and thus have a lower than standard staffing. This can be done by not replacing personnel on sick leave or voluntarily moving personnel to other working days. Another model, as proposed by Jin et al. (2021), is to reduce the standard staffing on weekends and establish an on-call system for nurses, which titrates the needed workforce. Even with financial incentives for nurses to be on-call, this organisation lowered the total cost for the unit.

Our data shows that the expected occupancy was more often overestimated than underestimated. Thus, the risk of being severely understaffed was low. Of the 42 days, 5 days had one more patient than expected which is usually easily managed, 5 days with two more patients than expected which can be managed on a short term-basis using, for instance, staff otherwise occupied with postoperative care, and only one day with three more patients than expected which may require a more urgent need for calling in nurses from their home. On the other hand, the overestimation could lead to being overstaffed unnecessarily on some days. Our data suggest that the department with this model would be staffed in relevant excess for 7 of the 42 days. This may be acceptable in an emergency organisation. Moreover, the nurses would be in excess in relation to the ICU's needs. In many hospitals, including ours, nurses in excess in one unit may contribute to work in other units, such as postoperative care units or paediatric ICUs.

Hospital managers are usually subject to financial budget strain. Thus, there may be an administrative pressure to reduce scheduled ICU staffing. This may be a short-sighted strategy as it may increase workload for nurses, increase the number of unexpected shifts on weekends and due to lack of beds, result in time-consuming administration of patient flow. All these factors are recognised to increase burnout among ICU personnel and staff turnover (Poncet et al. 2007). Recruitment of ICU personnel is time-consuming and costly, as new personnel usually need a training period before they are able to work independently of support from others. Therefore, to minimise staff can paradoxically add costs. To have a model where staff is reduced not by a lower scheduled standard staffing but at a time when low expected occupancy is safe, reduces the burden for employees working on weekends and also reduces costs.

It is important to underline that each model must be developed according to specific ICU department characteristics. Some ICUs admit only emergency patients, which cannot be planned, while some units admit patients from elective surgeries, which can be planned, and, if needed, rescheduled. Some units have a high patient turnover, while other units, such as neurosurgical ICUs, have generally longer LOS. Some hospitals have an HDU acting as a step-down unit, which improves patient outflow from the ICU. Finally, medical interventions and LOS may vary between units. There are also a number of readmissions to the ICU. This number varies based on the medical capacity in the wards.

Our model was a simple one and is therefore to be considered perhaps more as a proof of concept. We did not include the expected complexity of patients; some patients were in need of more or fewer than one nurse. Scoring systems, such as the Nursing Activities Scoring (NAS) system, can quantify the need for nurses but will involve a more time-consuming scoring process (Stuedahl et al. 2015). However, to differentiate between patients is more relevant in units with a mixed HDU and ICU patient population and was therefore less relevant in our unit. To accommodate other units, the web instrument is also designed to register the number of nurses needed for each patient included. Another factor not included is the within-day variability. There will usually be highs and lows for occupancy during each day. To what degree this variability exists depends on the characteristics of the unit. In units with high patient turnover, such as emergency departments, diurnal variability may be high; in more long-term facilities, very low.

We recognise that this study has some limitations. First, it is a pilot study with a limited number of observations. Second, it is a one-centre study, which limits its external validity. The study has also not reported detailed clinical characteristics, making comparisons to other settings difficult. Finally, this instrument is tested during normal working conditions. Special circumstances, such as the COVID-19 pandemic, need more complex forecasting, which includes data from the progression of disease in the general population (Redondo et al. 2023).

In conclusion, we demonstrate that a simple instrument to short-term predict ICU occupancy performed similarly to more complex models. The prediction errors were generally skewed towards overestimation and did not result in a critical lack of nurses. This instrument can aid ICU managers to more precisely tailor weekend nurse staffing to occupancy.

Conflict of Interest

None.

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Nutrition in Critical Care: Evidence-Based Management

Nutritional support is vital in critical care, yet optimal timing, dose, and composition are debated. Guidelines often conflict with recent trials showing that even lower early goals versus aggressive or early escalating dose may be harmful or not relevant. This review synthesises current evidence, highlighting guideline–trial discrepancies and proposing phase-specific strategies for ICU management.

Physiological Basis and Nutritional Risk Stratification in Critical Illness

Response to nutritional therapy in critically ill patients is influenced by profound metabolic heterogeneity, which explains why many nutrition trials have reported conflicting results. During the acute phase of critical illness, a dominant catabolic state develops, characterised by hypermetabolism, anabolic resistance and altered nutrient utilisation. In this context, the organism relies on endogenous substrate mobilisation rather than incorporation of exogenous nutrients. Transitioning from catabolism to anabolism, essential for tissue repair, depends on factors such as inflammation, organ function, hormonal balance, haemodynamic stability, and adequate oxygen delivery(Reignier et al. 2025b).On the other hand, catabolism/autophagy has been hypothesised as a favourable process in which tissue and cellular damage can be controlled, providing nutrients to continue tissue repair and organ function (Van Dyck et al. 2018).

Variability arises from baseline characteristics, including age, comorbidities, pre-existing nutritional status, frailty, and genetic polymorphisms that modulate energy expenditure and immune-inflammatory responses. At the time, there are no clear indicators of metabolic readiness to guide the timing and intensity of nutritional support. Such indicators underline their importance given that inappropriate nutrient dosing at a given time carries risks: overfeeding may worsen hyperglycaemia, hyperlipidaemia, and hepatic damage, whereas underfeeding accelerates muscle wasting, predisposes to infections, dependency and delays recovery.

The Nutrition Risk in Critically ill (NUTRIC) score is the first instrument developed to identify critically ill patients most likely to benefit from early and targeted nutrition therapy. Incorporating age, comorbidities, illness severity (APACHE II, SOFA), and inflammatory status (IL-6 in the original version), it stratifies nutritional risk, linking higher scores to greater mortality, longer ICU stay, and increased vulnerability to muscle wasting. Importantly, the score highlights that not all ICU patients require aggressive feeding; instead, nutrition should be prioritised in those with high NUTRIC scores (≥5), where the impact on outcomes is most significant. Controversy might arise given that this score relies mostly on inflammation/severity markers and lacks "nutrition" variables (Heyland et al. 2011).

The Global Leadership Initiative on Malnutrition (GLIM) criteria provide a complementary framework for diagnosing malnutrition, combining phenotypic (weight loss, low BMI, reduced muscle mass) and aetiologic (reduced intake, inflammation or disease burden) components, thus broadening the ability to identify patients who may derive the greatest benefit from timely and individualised nutrition interventions. Given the dynamic changes during critical illness, baseline status alone may not be an optimal guide for nutritional support. Thus, the physi-

		ASPEN 2016-2021			ESPEN 2023			SRLF/GFRUP 2025		
		When?	Calories	Protein	When?	Calories	Protein	When?	Calories	Protein
Early	EN	⩽48h	12-25Kcal/Kg	⩾1.2g/Kg	⩽48h	Provide <70% of EE; advance to 80–100% when EE is measured by IC.	Escalate to 1.3g/Kg	⩽48h	6-8Kcal/Kg IC probably wouldn't change outcomes	0.2-0.9g/Kg
Early	PN	If high risk or severely malnourished and EN not possible: ASAP	⩽20Kcal/Kg		If high risk or severely malnourished and EN not possible: early and progressive			Within the first week		
Early	SPN	Rather optimise EN			Rather optimise EN			No benefit		
Late	EN		Increase to goal by IC or 25-30Kcal/Kg	1-2-2.0g/Kg if no NB		Increase to goal	1.3g/Kg		20-30Kcal/Kg	1.0-1.3g/Kg
Late	PN	If low risk or well-nourished and EN not possible			Every patient with EN contraindication within 3 to 7 days					
Late	SPN	Every patient not reaching >60% of the goals			Every patient with no full EN tolerance despite optimisation			No clear indication		

Table 1. Comparison of international guidelines for critical care nutrition. Abbreviations: ASPEN, American Society for Parenteral and Enteral Nutrition; ESPEN, European Society for Clinical Nutrition and Metabolism; SRLF, Société de Réanimation de Langue Française; GFRUP, Groupe Francophone de Réanimation et d'Urgences Pédiatriques; EN, enteral nutrition; PN, parenteral nutrition; SPN, supplemental parenteral nutrition; EE, energy expenditure; IC, indirect calorimetry; NB, nitrogen balance.

ological rationale for nutrition in critical care is not the application of uniform prescriptions, but rather the tailoring of therapy to the patient's metabolic trajectory. Tools such as indirect calorimetry, theoretically the most accurate method to estimate energy expenditure, body composition analysis, such as bioelectrical impedance, and dynamic biomarkers may help determine the optimal moment to shift from catabolic to anabolic support (Reignier et al. 2025b).

Guideline Updates in Nutrition for the Critically Ill

International guidelines on nutritional support in critically ill patients, issued by the European Society for Clinical Nutrition and Metabolism (ESPEN) in 2023 and by the American Society for Parenteral and Enteral Nutrition/Society of Critical Care Medicine (ASPEN/SCCM) in 2022, were largely informed by physiological rationale, observational studies, and small heterogeneous trials. Regarding enteral nutrition (EN), both societies recommend early EN within 24-48 hours of ICU admission in patients with a functional gastrointestinal tract and haemodynamic stability (not universally defined at the time). ESPEN advises starting with ≤70% of estimated energy requirements during the first week, then advancing to 20–25 kcal/kg/day, with a progressive protein target of ~1.3 g/kg/day. When indirect calorimetry is used, advancing to 80-100% of the measured energy expenditure after day 3 is recommended by ESPEN(Singer et al. 2023). ASPEN/SCCM recommend 12–25 kcal/kg/day and an aggressive approach of 1.2–2.0 g/kg/day of protein during the first 7 to 10 days. Early parenteral nutrition (PN) is recommended by both societies in the context of high-risk or severe malnutrition with EN contraindications, while PN in low-risk and well-nourished patients could be delayed for one week. Calories and protein doses remain as mentioned by ESPEN; on the other hand, ASPEN suggest ≤20Kcal/Kg and ≥1.3g/Kg during the first week of PN (Compher et al. 2022).

These recommendations, which historically favoured early nutrition with relatively high calorie and protein provision, are now evolving in light of recent large trials with stricter methodologies and patient-centred outcomes, steering critical care nutrition toward a "less is more" approach. Based on these pragmatic randomised studies, the 2025 French Intensive Care Society (SRLF), the Société Francophone de Nutrition Clinique et Métabolisme (SFNCM) and the French-Speaking Group of Pediatric Emergency Physicians and Intensivists (GFRUP) guideline update has challenged this paradigm (Reignier et al. 2025a). Current evidence supports lower early energy (6–8 kcal/kg/day) and protein (0.2–0.9 g/kg/day) targets, associated with fewer infections, shorter ICU length of stay, improved survival, and less harm in patients with acute kidney injury and multiple organ failure. This emerging evidence underscores the urgent need for international guideline updates and invites intensivists to adopt a phase-specific, outcome-oriented approach in the nutritional management of critically ill patients **(Table 1)**.

Trial	Population	Intervention	Comparator	Key Outcomes
NUTRIREA-3 (2023)	3,044 ICU patients with shock, mechanically ventilated (61 French ICUs))	Low feeding: ~6 kcal/kg/day + 0.2–0.4 g/kg/day protein	Guideline-based feeding: 25 kcal/kg/day + 1.0–1.3 g/kg/day protein	90-day mortality: no difference; earlier readiness for ICU discharge (8 vs 9 days); fewer complications (vomiting, diarrhoea, bowel ischaemia, liver dysfunction).
EFFORT Protein (2023)	1,301 nutritionally high-risk ICU patients (85 ICUs, 16 countries)	High protein: ≥2.2 g/kg/day	Usual protein: ≤1.2 g/kg/day	No difference in time to discharge alive at 60 days or 60-day mortality; possible harm in AKI or high SOFA subgroups.
PRECISe (2025)	935 ICU patients, mechanically ventilated	High protein: 2.0 g/kg/day	Standard protein: 1.3 g/kg/day	Bayesian analysis: 0% probability of benefit, ~47% probability of harm (mortality, QoL); no improvement in 60-day mortality.
TARGET (2025)	3,397 ICU patients in Australia & New Zealand (8 ICUs)	High-protein EN formula: 100 g/L	Standard EN formula: 63 g/L	No difference in days alive and out of hospital at 90 days; mortality, ICU/hospital LOS, ventilation duration all neutral.

Table 2. Comparative summary of major nutrition trials in the critically ill: NUTRIREA-3, EFFORT, PRECISe, and TARGET. Abbreviations: ICU, intensive care unit; MV, mechanical ventilation; EN, enteral nutrition; PN, parenteral nutrition; LOS, length of stay; AKI, acute kidney injury; SOFA, Sequential Organ Failure Assessment; QoL, quality of life; HR, hazard ratio; RR, risk ratio; CI, confidence interval.

Less is More: Contemporary Evidence on Nutrition for the Critically Ill

Recent large, randomised trials consistently suggest that in critically ill ICU patients, less may be more when it comes to early energy and protein delivery. These findings challenge long-standing dogma favouring early full-dose feeding and instead support a more restrained, individualised strategy aligned with metabolic tolerance **(Table 2)**.

The NUTRIREA-3 trial (Reignier et al. 2023), the largest RCT to date on acute-phase nutrition, randomised 3,044 ventilated patients in shock across 61 French ICUs to low-calorie, low-protein feeding (~6 kcal/kg/day; 0.2–0.4 g/kg/day protein) versus targets reached within 7 days (25 kcal/kg/day; 1.0–1.3 g/kg/day protein). Ninety-day mortality was similar (41.3% vs. 42.8%; p=0.41), but patients in the low-intake group achieved earlier readiness for ICU discharge (median 8 vs. 9 days; HR 1.12; p=0.015) and experienced fewer gastrointestinal complications, including vomiting, diarrhoea, bowel ischaemia, and liver damage. Low target group showed less incidence of insulin administration and hypophosphatemia, with no differences in hypoglycaemia events. These results support the safety and potential advantages of permissive calorie and protein restriction during the first week of critical illness.

The effect of higher protein dosing in critically ill patients with high nutritional risk (EFFORT Protein Trial) examined protein dosing in 1,301 nutritionally high-risk ICU patients across 85 ICUs in 16 countries (Heyland et al. 2023). High protein intake (≥2.2 g/kg/day) showed no benefit over usual protein (≤1.2 g/kg/day) in time to discharge alive at 60 days (HR 0.91; p=0.27) or 60-day mortality (RR 1.08; p=0.27). Subgroup analyses suggested possible harm in patients with acute kidney injury or elevated SOFA scores, underscoring the need to adapt prescriptions to organ function and metabolic capacity. It's worth underlining that every patient in the EFFORT protein trial was considered at least at nutritional risk, challenging the concept of individualised nutrition therapies according to baseline status.

The Effect of high versus standard protein provision on functional recovery in people with critical illness (PRECISe) trial reanalysed under a Bayesian framework (Schouteden et al. 2025), randomised 935 ventilated patients to high (2.0 g/kg/day) versus standard (1.3 g/kg/day) protein via EN. Bayesian modelling demonstrated a 0% probability of benefit and a 15% probability of clinically relevant harm for health-related quality of life (EQ-5D-5L). For 60-day mortality, the probability of benefit was only 8%, while the probability of clinically important harm exceeded 47%. Although a minor functional signal appeared in the 6-minute walk test, attrition bias (<31% completion) limited interpretation. Collectively, these findings reinforce that aggressive protein delivery may not improve outcomes and could plausibly increase harm.

The TARGET Protein Trial (Summers et al. 2025), a cluster-randomised crossover study in 8 ICUs in Australia and New Zealand, tested high-protein (100 g/L) versus usual-protein (63 g/L) isocaloric enteral formulas in 3,397 critically ill patients. The primary outcome, days alive and out of hospital at 90 days, showed no difference (median 62 vs. 64 days; adjusted median difference −1.97; 95% CI −7.24 to 3.30; p=0.46). Secondary outcomes, including mortality, ventilation duration, length of stay, tracheostomy, and renal replacement therapy, were also unaffected. This trial further reinforces the emerging narrative: augmenting enteral protein beyond standard levels during the acute phase provides no measurable benefit, strengthening the case for a cautious, individualised approach over aggressive supplementation.

The original Effect of Early Nutritional Support on Frailty, Functional Outcomes and Recovery of Malnourished Medical Inpatients Trial (EFFORT) (Schuetz et al. 2019) was carried out in non-critically ill patients with high nutritional risk at eight Swiss hospitals. In this trial, patients were randomised to receive protocol intervention aimed to reach calorie and protein goals versus standard of care (1050 and 1038, respectively). Individualised approach showed less adverse clinical outcomes (OR 0.79, p=0.023) and mortality (OR 0.65, p=0.011), with no difference in side effects. External validity of such a trial is not possible given the target population (non-critically ill patients), but a secondary analysis dividing the total sample according to their CRP (C-Reactive protein) concentrations revealed that the benefit from target goals disappeared in those with CRP>100mg/L. This can help to rethink that people severely ill or in a state of high inflammation (such as critically ill) might not respond to an aggressive nutritional approach(Merker et al. 2020).

Glutamine and Arginine in Critical Illness

The use of glutamine supplementation in critically ill patients has been progressively abandoned following high-quality evidence from large, randomised trials. Studies such asREducing Deaths due to OXidative Stress(REDOXS) (Heyland et al. 2013) and MetaPlus (Van Zanten et al. 2014) demonstrated not only the absence of clinical benefit but also an increased risk of harm, particularly higher mortality in patients with sepsis, multiorgan failure, or renal and hepatic dysfunction. In light of these findings, recent international guidelines consistently recommend against the routine use of glutamine in critically ill populations **(Table 3)**.

Similarly, arginine supplementation has raised concerns in the context of sepsis and shock due to its role as a nitric oxide precursor, with the potential to exacerbate vasoplegia and haemodynamic instability. While some perioperative surgical patients without sepsis might theoretically benefit from arginine's immunomodulatory properties, current evidence does not support its routine use in the ICU setting. Accordingly, the most recent guidelines advise against arginine supplementation in septic or haemodynamically unstable patients, reinforcing the broader shift away from aggressive immunonutrition toward safer, individualised nutritional support.

Beyond the ICU: Linking Nutrition to Long-Term Outcomes

The relevance of nutrition therapy extends beyond the acute ICU stay into the post-ICU period, where many patients develop post-intensive care syndrome (PICS), a

Trial	Population & Design	Intervention	Comparator	Main Outcomes	Key Findings
REDOXS	1,223 critically ill patients with multiorgan failure, many with sepsis; multicentre RCT	High-dose glutamine (0.35 g/kg/day IV + 30 g/day enteral) ± antioxidants	Placebo	28-day mortality, organ failure	Glutamine associated with ↑ mortality (32.4% vs. 27.2%, HR 1.28; p=0.05), especially in renal/hepatic dysfunction; no clinical benefit.
MetaPlus	301 mechanically ventilated ICU patients expected to stay ≥72h; multicentre RCT	Immune-enhancing EN (enriched with glutamine, omega-3 FA, selenium, antioxidants)	Isocaloric, isonitrogenous standard EN	Mortality, infections, ICU/hospital LOS	No difference in infections or LOS; ↑ mortality in medical ICU subgroup (54% vs. 35%; p=0.03).

Table 3. Summary of glutamine supplementation major trials in critical illness: REDOXS and MetaPlus.Abbreviations: ICU, intensive care unit; EN, enteral nutrition; RCT, randomised controlled trial; LOS, length of stay; HR, hazard ratio; NEJM, New England Journal of Medicine; FA, fatty acids.

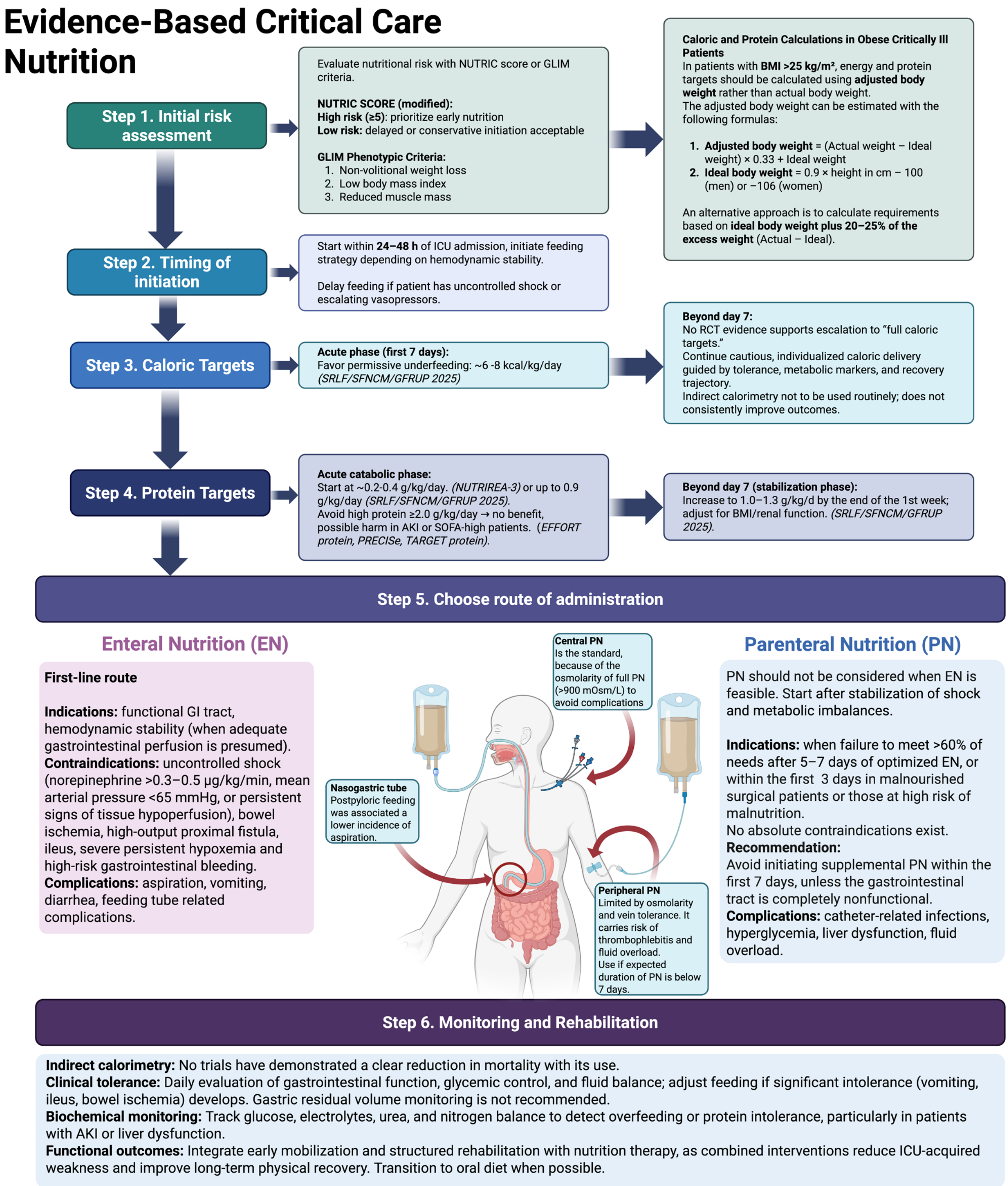

Figure 1. Evidence-based critical care nutrition algorithm. Illustration created with BioRender.com. Abbreviations: BMI, body mass index; EN, enteral nutrition; PN, parenteral nutrition; MAP, mean arterial pressure; NE, norepinephrine; GI, gastrointestinal; ICU, intensive care unit; RCT, randomised controlled trial; SRLF, Société de Réanimation de Langue Française; SFNCM, Société Francophone de Nutrition Clinique et Métabolisme; GFRUP, Groupe Francophone de Réanimation et d'UrgencesPédiatriques; EFFORT Protein, Effect of Early Protein Feeding in Critically Ill Patients; PRECISE, Pragmatic Randomized Evaluation of Individualized Protein in Critical Illness; TARGET PROTEIN, Trial of Protein Dose in Critically Ill Patients; AKI, acute kidney injury; SOFA, Sequential Organ Failure Assessment

constellation of physical, cognitive, and psychological impairments that may persist long after hospital discharge. Malnutrition and prolonged immobilisation are frequent among critically ill patients and strongly associated with poor outcomes, including accelerated muscle atrophy, impaired strength, and delayed weaning from mechanical ventilation. These factors exacerbate ICU-acquired weakness (ICU-AW), with muscle loss reaching up to 20% of total body mass within the first week of critical illness, directly impacting long-term mortality and quality of life (Yang et al. 2018).

To mitigate these risks, nutritional therapy should be conceived as a continuum that extends beyond ICU discharge, integrated with early mobilisation and structured rehabilitation programmes. Such a combined strategy has the potential to limit muscle wasting, preserve physical function, and reduce the burden of PICS. Nevertheless, there is still insufficient evidence to determine the optimal nutritional prescription for the post-ICU phase. Large, high-quality trials specifically addressing nutrition and rehabilitation with PICS as a primary endpoint are urgently needed to guide practice and improve long-term outcomes.

Cost Implications of Restrictive Nutrition in Critical Illness

Restrictive feeding strategies not only align with recent evidence on safety and clinical outcomes but may also reduce healthcare costs by lowering formula consumption. For example, for a 70-kg critically ill patient receiving nutrition over 7 days, standard targets of 20–25 kcal/kg/day equate to ~1,400–1,750 kcal/day, while a restrictive approach of 6–10 kcal/kg/day provides only ~420–700 kcal/day. This represents a daily reduction of ~980–1,330 kcal, or ~6,900–9,300 kcal over one week. Assuming a commercial enteral formula costs 2.5 USD per 1,000 kcal, the restrictive regimen would save approximately 17–23 USD per week per patient. Extrapolated to an ICU admitting 20 such patients per month, this translates into 4,080–5,520 USD in annual savings, underscoring both the clinical and economic implications of lower energy provision during the acute phase of critical illness.

Conclusion

Over the past decade, high-quality randomised trials and updated international guidelines have reshaped our understanding of nutrition in critical illness. Evidence consistently shows that aggressive early provision of calories and protein not only fails to improve outcomes but may also increase complications and mortality in selected subgroups.Strategies emphasising permissive underfeeding during the acute phase, gradual progression of protein delivery, and avoidance of immunonutrition supplements such as glutamine or arginine align better with the metabolic trajectory of critically ill patients **(Figure 1)**.

Looking ahead, nutrition therapy must be individualised, phase-specific, and closely integrated with rehabilitation to support both short- and long-term recovery. While current data support restraint in the acute ICU setting, uncertainties remain, particularly regarding optimal prescriptions for the post-ICU phase and prevention of PICS. Future research should focus on tailoring nutrition to metabolic readiness, functional outcomes, and patient-centred endpoints, positioning nutrition not as a one-size-fits-all intervention but as a dynamic cornerstone of critical care.

Conflict of Interest

None.

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Electrical Impedance Tomography in Critical Children

Electrical impedance tomography (EIT) provides a non-invasive, bedside, radiation-free method for monitoring regional ventilation and pulmonary perfusion in critically ill children

Introduction

Electrical impedance tomography (EIT) is a non-invasive, radiation-free imaging tool that enables real-time monitoring of regional lung aeration at the patient's bedside (Bachmann et al. 2018; Costa et al. 2008; Walsh and Smallwood 2016).

EIT uses electrodes arranged around the patient's thorax to deliver small electrical currents during ventilation. A belt composed of 16–32 electrodes is positioned between the fourth and fifth intercostal spaces, in direct contact with the patient's skin, thereby avoiding the use of interposed bandages.

The resulting electrical impedance changes are converted into a real-time 2D image (corresponding to the real-time representation of the impedance values of each pixel) and a continuous plethysmogram registry (Becher et al. 2022; Franchineau et al. 2024; Nascimento et al. 2022). EIT also enables monitoring of respiratory mechanics simultaneously, as a flow sensor can be placed next to the patient's endotracheal tube or non-invasive ventilation mask. Additionally, EIT enables lung perfusion monitoring, based on changes in electrical impedance due to regional pulmonary blood distribution (Fossali et al. 2022).

As a significant number of children admitted to the Paediatric Intensive Care Unit (PICU) require mechanical ventilation (MV) (Miller and Scott 2022), EIT may play an essential role in understanding how regional air distribution happens during ventilation, allowing for optimising paediatric respiratory strategies (Inany et al. 2020) **(Figure 1).**

Main Concepts

EIT generates a 2D real-time image that follows the same spatial distribution pattern as the CT, with the left side of the thorax represented on the right part of the image, and when in supine position, dorsal regions located in the lower part of the image **(Figure 2).**

The 2D image shows regional lung aeration in different areas, coded by a scale of blue colours (the lighter the blue, the more air is going in and out during ventilation, reaching a white colour, which may indicate overdistension). Grey areas are regions where there are no changes in aeration.

A plethysmogram is a graphical representation of the variation in electrical impedance over time due to regional aeration changes. Each oscillation corresponds to a single breath. The oscillation amplitude, known as Delta Z (ΔZ), is considered a surrogate of tidal volume. End Expiratory Lung Impedance (EELI) corresponds to the baseline of the plethysmogram curve and is regarded as a surrogate of the residual lung volume.

In addition, EIT can assess ventilation segmented into regions of interest (ROIs). Frequently used ROIs include ventral vs. dorsal, as well as right vs. left quadrants: ventral left, ventral right, dorsal left, and dorsal right. Layers include ventral, mid-ventral, mid-dorsal, and dorsal.

Lastly, regional perfusion (Figure 3) can be assessed through the electrical impedance changes caused by pulmonary blood flow, which are detected by EIT. Depending on the EIT device, ventilation and perfusion may be evaluated simultaneously

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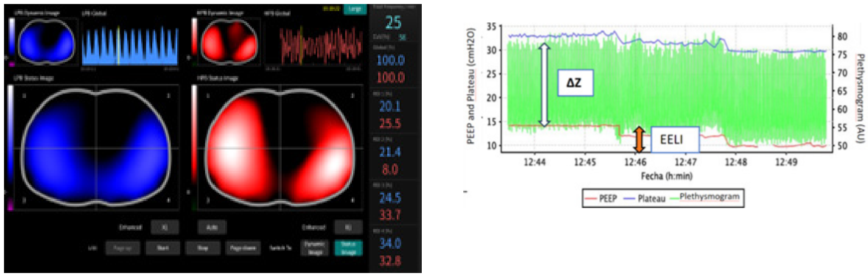


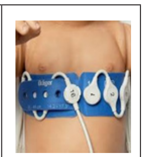
Figure 2. a EIT Ventilation 2D image. bEIT Plethysmogram EIT: Electrical impedance tomography; EELI: End expiratory lung impedance; ΔZ: Delta Z.

and continuously or intermittently; an inspiratory hold must be set to evaluate perfusion after a normal saline IV bolus.

Main Functionalities

Several functionalities have been described:

- Prompt detection of respiratory complications during mechanical ventilation: **(Figure 4)** atelectasis, pneumothorax, accidental extubation or selective intubation.
- Evaluation of the effect of body positioning on regional ventilation: it is advantageous in determining the duration of prone-supine postural changes in ARDS **(Figure 5).**
- PEEP titration during IMV **(Figure 6):** decremental PEEP test evaluates both regional collapse and overdistension. Ideal PEEP consists of the level with the best balance between both standards.
- V/Q mismatch screening: regional ventilation can be compared with regional pulmonary perfusion to evaluate V/Q mismatch. Pulmonary embolism or asthma are some conditions that could benefit from this.

Pulmovista 500		
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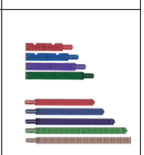
Infivision ET 1000		

Figure 1. Available EIT devices for children

Research on the Use of EIT in Children

EIT-based research has seen an increasing interest in the scientific community in recent years, mainly focused on paediatrics, on understanding ventilation in critical care children.

One of the main addressed topics has been how body positioning (BP) impacts regional aeration in ventilated children. Evidence suggests that adults exhibit a gravity-dependent ventilation phenomenon, with increased ventilation towards the gravity-dependent lung (e.g., Frerichs et al., 1996). In non-ventilated healthy children between 6 months and 9 years, Lupton Smith et al. (2014) found an absence of consistent gravity-dependent phenomena, with high interpatient variability in the predominant lung aeration (dependent vs non-dependent lung). On the other hand, in a cohort of more than 200 ventilated neonates and infants monitored with EIT, Becher et al. (2022) reported that preterm neonates followed the classical adult pattern; however, a challenging finding was observed in non-preterm neonates and infants, with predominant ventilation towards the gravity-dependent lung and regions. More studies are required to better understand the possible gravity dependence phenomenon in children. How ventilation mode influences ventilation represents another challenging point. When comparing controlled vs supported ventilation modes, Inany et al. (2020) and Nascimiento et al. (2022) documented a decrease of the dorsal contribution to global aeration in children under controlled modes of ventilation versus spontaneous supported modes, which may be related to a loss of diaphragm contribution.

EIT has also assessed the effect of chest physiotherapy (CPT) on children under MV. Davies et al. (2019) first proposed EIT as a possible method to monitor CPT. McAlinden et al. (2020) compared, in an EIT-based study of MV patients admitted to the PICU, the use of CPT plus periodic suctioning versus suctioning alone, finding the CPT-suctioning combination to be significantly more effective.

Although it seems that this tool is helping to improve the understanding of physiol-

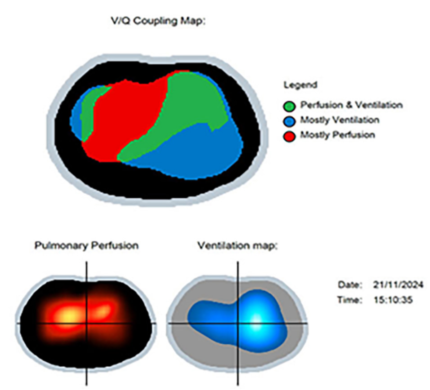


Figure 3. Perfusion and ventilation 2D image with resultant V/Q coupling map.

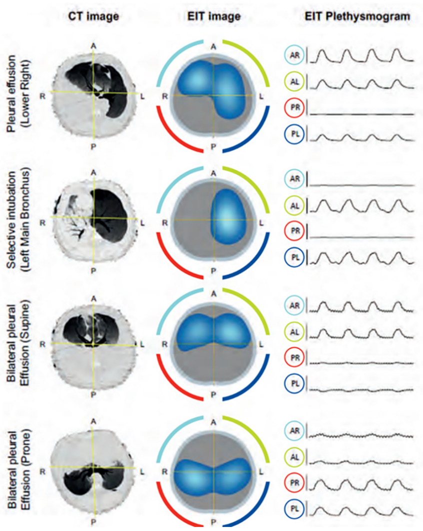


Figure 4. Detection of respiratory complications during mechanical ventilation with EIT.

ogy in mechanically ventilated patients, unfortunately, studies showing improved outcomes after the implementation of this technology are still lacking.

Its use is spreading in the paediatric community, so we expect the proper studies to rapidly increase the level of evidence.

Experience in PICU of a Quaternary Children's Hospital

a) EIT- guided respiratory therapy in children

EIT has been applied to children admitted to SJD Children's Hospital PICU since 2020. In our unit, 45 and 80 patients annually are admitted due to respiratory conditions requiring invasive and non-invasive mechanical ventilation, respectively. The main limitation of EIT implementation that we have encountered, as will probably have happened to other units, is the availability of only one EIT monitor. In addition, a significant investment in fungible is required, as 5-10 different sizes of electrode belts are needed for children between 0 and 18 years old, which may limit its widespread use, especially in public PICUs.

EIT has been found to be especially useful at the bedside, particularly for PEEP titration purposes. Severe ARDS patients or children with severe tracheobronchial Malacia benefit from an EIT-based PEEP election, as improvements in lung aeration and balance between the percentage of lung with hyperinflation and collapse can be assessed in real time at the bedside.

Body positioning has been another key point addressed with EIT. Prone positioning to improve dorsal aeration is a widely implemented tool in respiratory patients in the PICU, but there is no clear evidence on its ideal duration. Our PICU usually implements a 20:4 hours of prone: supine approach. Since the EIT acquisition, prone duration has been titrated based on the aeration of the lungs' dorsal and ventral regions, demonstrating that some patients need to switch to supine after 2 hours of prone positioning and others after 3 days. Thus, an individualised approach of prone-supine can be achieved with EIT monitoring.

Finally, another key point to consider with EIT is assessing atelectasis response to respiratory manoeuvres, such as bronchoscopy, changes in body positioning, or suction of mucus plugs. This approach avoids unnecessary additional suctioning,

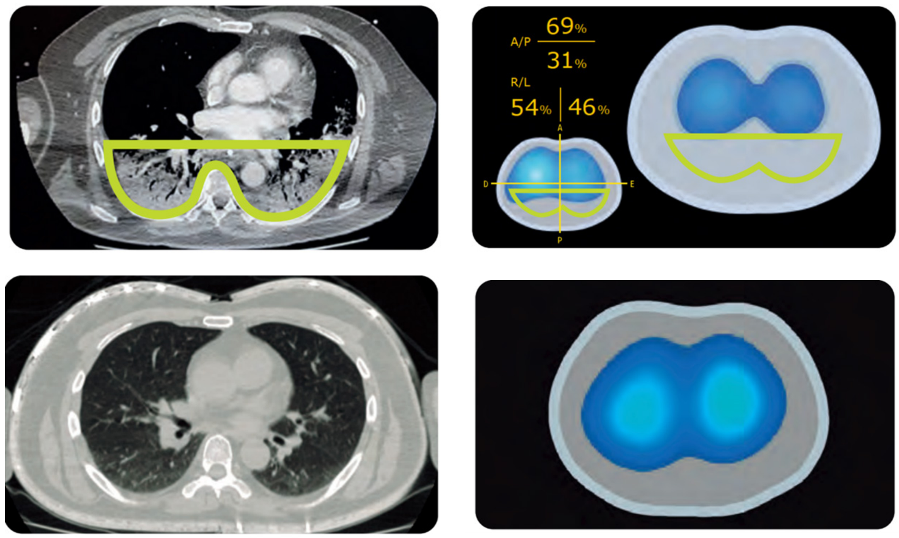


Figure 5. a Dorsal collapse in patient with ARDS. b Reaeration of dorsal regions in a patient supined after 20 hours of prone positioning.

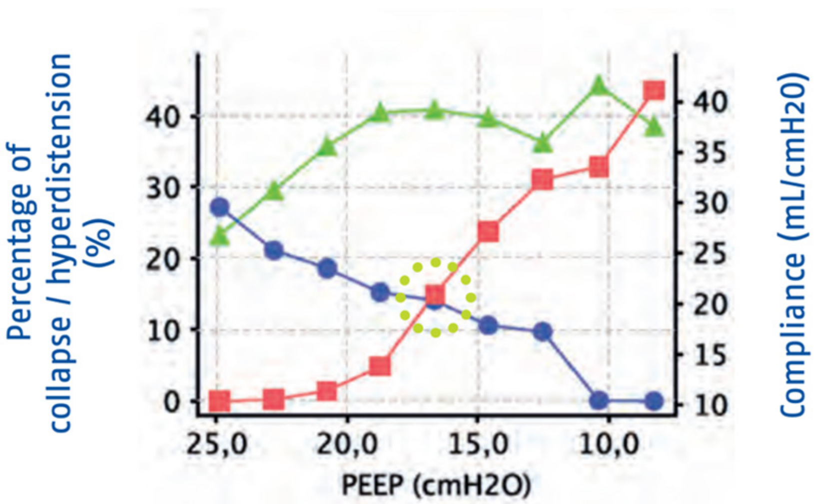


Figure 6. EIT-based decremental PEEP titration. Ideal PEEP of 17 cm H2O matches the cross-point between the percentage of lung collapse (red) and hyperdistension (blue). Compliance is represented in green

PEEP increase or clearance manoeuvres, allowing detection in real-time of the resolution of atelectasis.

b) EIT-based research in children

Assessing a possible gravity-dependent ventilation phenomenon in mechanically ventilated children is probably the main challenging research question we have addressed in recent years. The paediatric population, as reflected above, lacks evidence in this matter. We are currently running a 3-year clinical trial to assess through body positioning changes how gravity affects children's aeration and ventilation while under MV.

Conflict of Interest

None

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Rapid Blood Pressure Lowering in ICH: Evidence-Based Practice or Persisting Dogma

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This review examines blood pressure management in intracerebral haemorrhage, highlighting the need to prevent haematoma expansion without causing cerebral hypoperfusion. Guidelines recommend early intervention with systolic targets of 130–150 mmHg, avoiding levels below 130 mmHg. The absence of standardised regimens underscores the need for individualised, evidence-based strategies.

Introduction

Intracerebral haemorrhage (ICH) results from the rupture of cerebral blood vessels, leading to bleeding within the brain parenchyma. It is a major cause of mortality and long-term disability, particularly in low- and middle-income countries. According to the 2021 Global Burden of Disease Study, there were approximately 2.44 million new cases of ICH worldwide, with an age-standardised prevalence of 40.8 per 100,000 population. ICH was responsible for an estimated 3.31 million deaths and accounted for 79.46 million disability-adjusted life years (DALYs), with an age-standardised DALY rate of 92.4 per 100,000 population (Xu et al. 2024).

Given this substantial burden, identifying effective strategies to reduce mortality and disability is essential. This review explores the current approach and available evidence regarding the importance of early and aggressive blood pressure reduction in the management of ICH.

Cerebral Autoregulation and Impairment Following Intracerebral Haemorrhage: A Haemodynamic Perspective

Cerebral autoregulation refers to the ability of the cerebral vasculature to maintain relatively stable cerebral blood flow (CBF) despite fluctuations in cerebral perfusion pressure (CPP) **(Figure 1)**, typically preserved within a mean arterial pressure (MAP) range of approximately 60 to 150 mmHg in healthy adults (Lassen 1959).

Under physiological conditions, CBF is regulated through dynamic changes in arteriolar diameter, which modulate cerebrovascular resistance (CVR) in accordance with the Hagen–Poiseuille equation, which describes laminar flow of a fluid through a cylindrical tube of constant cross-section:

$$Q = \frac{\pi \cdot r^4 \cdot \Delta P}{8 \cdot \eta \cdot L}$$

In simpler terms, when mean arterial pressure (MAP) decreases, cerebral arterioles vasodilate to increase the radius and preserve flow. Conversely, when MAP rises, arterioles vasoconstrict to reduce the radius and protect the brain from hyperperfusion. However, when MAP falls outside the autoregulatory range, this mechanism fails and CBF becomes passively pressure-dependent, increasing the risk of ischaemia (at low pressures) or cerebral oedema (at high pressures). From a pathophysiological perspective, the Poiseuille equation offers a theoretical framework to understand the alterations in CBF in the setting of impaired autoregulation following ICH. A case-control study comparing patients with acute ICH to healthy controls demonstrated that individuals with ICH had significantly higher cerebrovascular resistance index (CVRi), calculated as the ratio of MAP to mean flow velocity (MFV). This elevation in

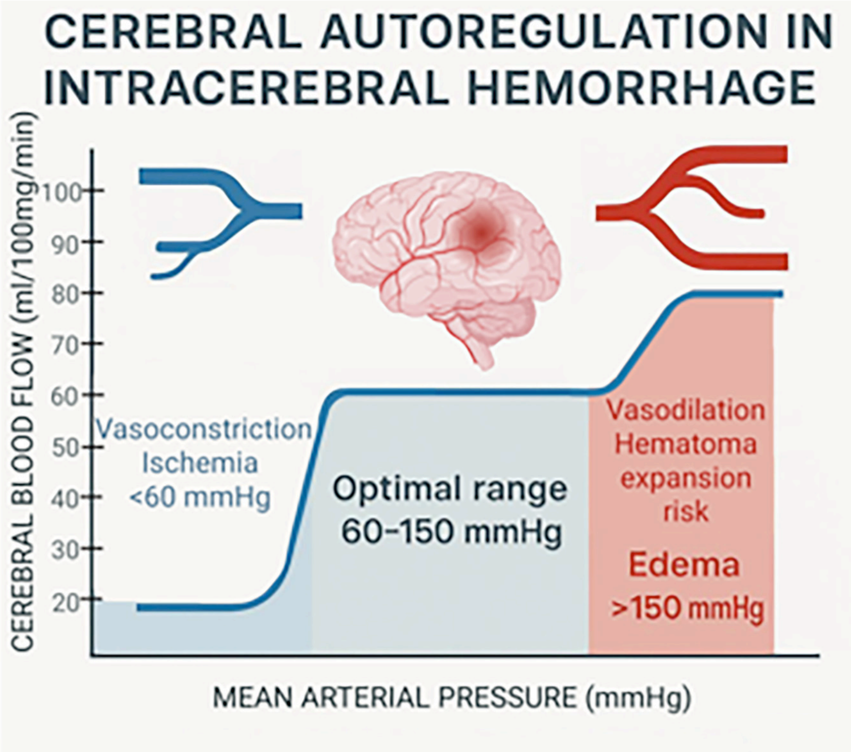

Figure 1. Schematic representation of cerebral autoregulation in intracerebral haemorrhage. Cerebral blood flow is maintained constant within the autoregulatory range of mean arterial pressure (60–150 mmHg) through vasoconstriction and vasodilation. Below this range, hypoperfusion increases the risk of ischaemia, while above it, hyperperfusion predisposes to cerebral oedema.

CVRi reflects increased vascular resistance. Additionally, patients with ICH exhibited higher gain values on transfer function analysis, indicating greater amplitude of flow oscillations in response to pressure changes—a sign of impaired dynamic autoregulation. This contradicts the buffering effect normally exerted by an intact autoregulatory system (Nakagawa et al. 2011). Similarly, a systematic review and meta-analysis including 293 patients with acute ICH assessed physiological disturbances using transcranial Doppler (TCD) ultrasonography. The findings revealed significantly lower mean CBV velocities in both the ipsilateral (49.7 vs. 64.8 cm/s; $p < 0.0001$) and contralateral hemispheres (51.5 vs. 64.8 cm/s; $p = 0.0006$) compared to healthy controls (Minhas et al. 2018) From the perspective of the Poiseuille model, a sustained reduction in arteriolar radius—or failure to adapt this radius in response to pressure changes—could account for the observed hypoperfusion. Therefore, although current guidelines recommend intensive blood pressure lowering in acute ICH, such strategies might worsen cerebral hypoperfusion in regions with impaired autoregulation. Nevertheless, the underlying pathophysiology, including reductions in CBF, does not fully explain observed variations in mortality or neurological outcomes in this patient population, highlighting the need for further targeted research.

Current Guideline Recommendations

According to the current American Heart Association (AHA) guidelines for the management of spontaneous ICH, it is recommended to initiate blood pressure control within the first two hours and to reach the target within the first hour. Early intervention has been associated with a reduced risk of hypertensive oedema. For patients with mild to moderate ICH, maintaining systolic blood pressure between 150 and 220 mm Hg is advised, whereas for severe cases, the target range is 130 to 150 mm Hg. These recommendations are supported by a level of evidence 2b (weak) (Greenberg et al. 2022). However, the 2024 update strengthened the recommendation to level 2a (moderate), reinforcing the importance of early and controlled blood pressure management in patients with ICH (Ruff et al. 2024).

Similarly, the European guidelines align with the American position, recommending systolic blood pressure (SBP) levels between 150 and 220 mmHg, also based on low-quality evidence and a weak recommendation. However, expert opinion suggests maintaining values below 140 mm Hg in the acute phase and avoiding fluctuations in systolic blood pressure. Both the AHA/ASA and European guidelines caution against lowering SBP below 130 mm Hg, as this may be associated with adverse outcomes (Steiner et al. 2025). More recently, a consensus statement from the American Medical Association, the American College of Cardiology, and the AHA proposed a more aggressive approach. These guidelines recommend immediate SBP reduction to 130–140 mmHg in patients presenting with initial values between 150 and 220 mmHg, with maintenance of this target for at least seven days after haemorrhage onset. This strategy has been linked to improved functional outcomes, although blood pressure management should be discontinued if SBP falls below 130 mmHg (Jones et al. 2025). The differences between guideline recommendations are summarised in **Figure 2**, highlighting the therapeutic window that balances the risk of ischemia at lower pressures and oedema at higher pressures.

Evidence on Clinical Outcomes Over the Years

The INTERACT2 trial (Anderson et al. 2013), which enrolled 2839 patients, compared intensive treatment (SBP <140 mmHg, n=1403) with standard treatment (<180 mmHg, n=1436). The primary outcome (modified Rankin Scale [mRs] 3–6 at 90 days) did not significantly differ

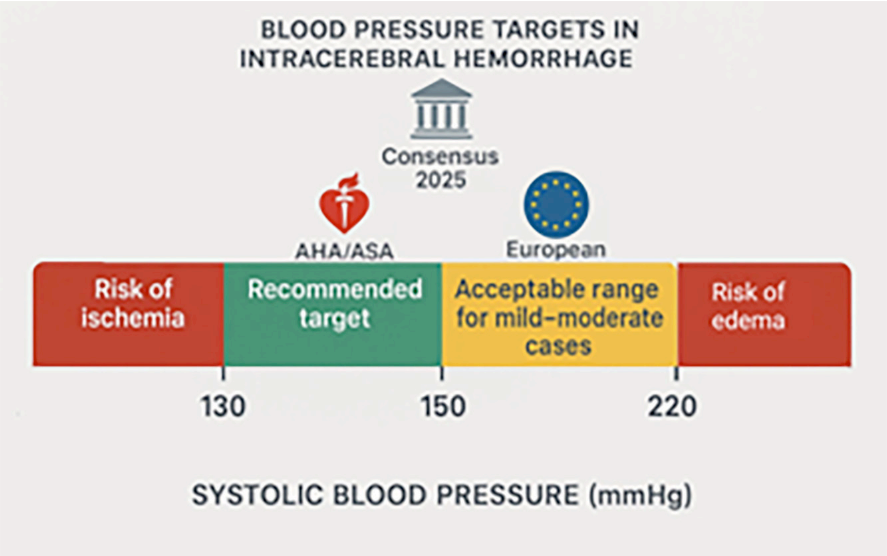

Figure 2. Blood pressure targets in spontaneous intracerebral haemorrhage according to major guidelines. The American Heart Association/American Stroke Association (AHA/ASA) recommends early reduction to 130–150 mmHg, while European guidelines allow systolic pressures between 150–220 mmHg in mild to moderate cases. The 2025 consensus suggests an optimal range of 130–140 mmHg, maintained for at least 7 days. Pressures below 130 mmHg may increase the risk of cerebral ischaemia, whereas values above 220 mmHg are associated with oedema and haematoma expansion.

between groups (52.0% vs. 55.6%; OR 0.87; 95% CI 0.75–1.01; p=0.06), nor did all-cause mortality (11.9% vs. 12.0%; OR 0.99; 95% CI 0.79–1.25; p=0.96). There were no significant differences in early neurological deterioration (14.5% vs. 15.1%; OR 0.95; 95% CI 0.77–1.17; p=0.62) or hematoma expansion (35.1%; p=0.27). However, an ordinal analysis of the mRS suggested improved functional outcomes in the intensive treatment group.

The ATACH-2 trial (Qureshi et al. 2016), which included 1000 patients (mean age 62 years, 60% male), compared intensive SBP lowering (110–139 mmHg, n=500) with standard treatment (140–179 mmHg, n=500) using intravenous nicardipine within 4.5 hours. There was no significant difference in the primary outcome (mRS 4–6 at 90 days: 38.7% vs. 37.7%; p=0.84). Mortality was lower in the intensive group (6.6% vs. 9.0%), but this did not reach statistical significance (p=0.09). Severe hypotension was more frequent in the intensive group (12% vs. 2%), while hematoma expansion occurred in 18.9% compared with controls (p=0.09).

The INTERACT3 trial (Ma et al. 2023), a large multinational stepped-wedge, cluster-randomised trial including 7036 patients from low- and middle-income countries, tested a "care bundle" incorporating intensive SBP control (110–140 mmHg), glucose management, normothermia, and rapid anticoagulation reversal. Compared with usual care (n=3815), the intervention bundle (n=3221) resulted in significant improvement in the primary outcome (ordinal mRS at 6 months; OR 0.86; 95% CI 0.76–0.97; p=0.015). Additionally, early neurological deterioration was significantly reduced (OR 0.56; 95% CI 0.34–0.92; p=0.02), with overall improvement in functional outcomes.

Taken together, the evidence indicates that lowering SBP to around 140 mmHg is safe and may improve functional outcomes, although it does not significantly reduce mortality. The greatest benefit appears to occur when blood pressure management is implemented as part of a multidimensional care bundle, as demonstrated by INTERACT3.

Limitations of Current Evidence (Drug Heterogeneity)

There is significant heterogeneity in the management of hypertensive emergencies in the context of ICH, as reported in major clinical trials. This variability is largely due to the absence of a standardised protocol identifying the most effective or "safest" antihypertensive agent for blood pressure reduction in ICH.

For instance, in the ATTACH-2 trial, nicardipine was used as the primary intravenous antihypertensive, with additional agents including labetalol, diltiazem, or urapidil (Qureshi et al. 2016). In contrast, the INTERACT3 trial employed a broader range of medications, such as urapidil, nicardipine, sodium nitroprusside, labetalol, and nimodipine (Ma et al. 2023).

Even when considering only these two pivotal studies, the variability in antihypertensive regimens highlights the lack of a universal treatment approach for blood pressure management in ICH.

Recommended Strategies for Rapid Blood Pressure Reduction

A medical treatment strategy based on the implementation of intensive systolic blood pressure reduction to <140 mmHg within one hour—using fast-acting intravenous agents such as urapidil—appears to be the most commonly applied approach in clinical studies. This strategy has shown effectiveness in improving neurological outcomes and reducing mortality in patients with ICH.

Conclusions

The concept of cerebral autoregulation-guided therapy is promising, particularly in the context of individualising CPP or MAP targets for each patient. Nevertheless, definitive evidence demonstrating that direct modulation of autoregulation improves clinical outcomes remains lacking. Current data support rapid systolic blood pressure reduction as the most effective strategy, although further studies are needed to validate and refine this approach. Standardisation of antihypertensive agents is also essential to facilitate broader applicability of treatment protocols. Based on evidence from INTERACT2, ATACH2, and INTERACT3, we recommend targeting systolic blood pressure within the range of 130–140 mmHg, which appears to provide the best balance between reducing the risk of hematoma expansion and avoiding cerebral hypoperfusion.

Conflict of Interest

None

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Establishing an Awake and Walking ICU: Fundamental Concepts and a Case Report


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Immobilism Syndrome is an often neglected disorder in the critical care setting. The repercussions of this condition are frequently detrimental and enduring, leading to a significant decline in patients' overall ability to operate. Enabling the movement of patients, even when they are undergoing mechanical ventilation and other artificial organ supports, is not only feasible but also advantageous. This article provides a comprehensive examination of the fundamental components of an Awake and Walking Intensive Care Unit and the burden caused by excessive sedation and immobilism.

Introduction

Immobilism Syndrome is a disorder that is often overlooked by most doctors and other health professionals, despite its potential to cause harmful consequences. Many experts acknowledge that prolonged durations of bed rest have detrimental effects, although the full degree of the injury is frequently disregarded. Immobilism is a sickness that gradually causes damage to many organs and systems. These patients have cardiovascular, pulmonary, gastrointestinal, musculoskeletal, neuroendocrine, urinary, and psychological harm, which can result in long-term effects. A significant number of patients who were confined to bed for an extended period of time describe a permanent decrease in their cognitive and physical abilities following a severe illness that rendered them immobile. Multiple organic dysfunctions can result in detrimental consequences due to a lack of exercise and immobility. Many patients are unable to regain the functionality they lost as a result of a protracted period of bed rest.

Prolonged immobility experienced during hospitalisation can lead to functional impairment lasting for a year, resulting in individuals being unable to resume employment due to persistent debility and exhaustion (Zhang et al. 2019). The documented effects of weightlessness on astronauts produce similar repercussions to those experienced during prolonged periods of lying down, as observed in the field of aerospace medicine (Sprague 2004). While the negative effects of excessive rest have been recognised since the era of Hippocrates (1984), it was not until the latter part of the 20th century, with advancements in military medicine, that the practice of early mobilisation of patients was initiated. The recognition of immobilism syndrome as a significant contributor to lifelong functional impairment, with the possibility for fatality, is of utmost importance and requires urgent attention. Mobilising critically ill patients is an even greater challenge, as they present several barriers intrinsic to their severity. It is necessary to change the local culture and develop well-established protocols so that this task can be performed satisfactorily.

Causes and Consequences Associated With Extended Periods of Immobility

Diverse ailments can lead to prolonged periods of immobility, affecting individuals across various age groups. Patients in advanced stages of dementia often suffer from immobility, as do individuals who have had a stroke. As individuals grow older, they commonly undergo a decline in physical vitality, leading to an inclination towards reduced activity and more sedentary behaviour. Psychiatric patients,

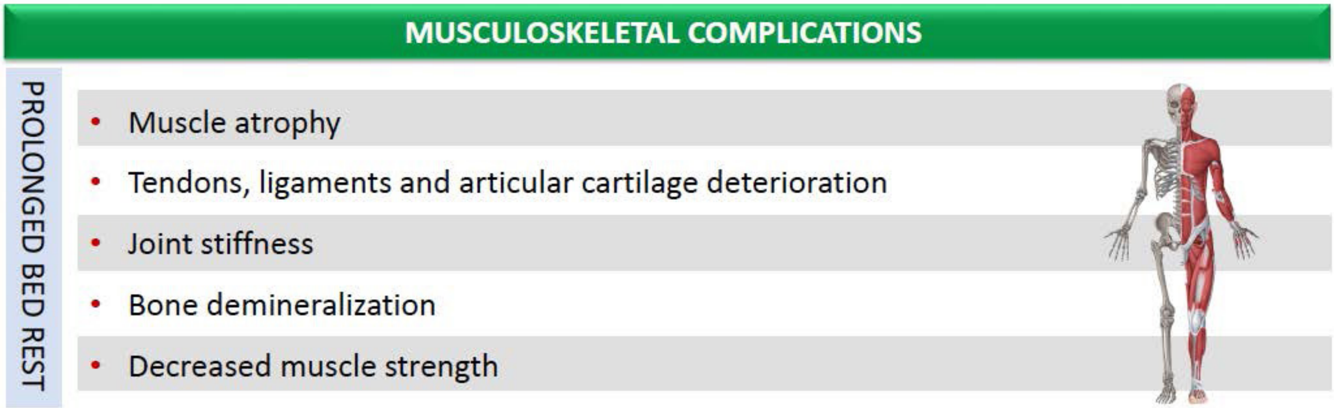

Figure 1. Musculoskeletal complications related to immobility

especially those suffering from depression or requiring high doses of sedative medications, may encounter immobility. Young patients who suffer from several traumatic events and endure diverse orthopaedic injuries may require extended periods of immobilisation. Severely malnourished patients may experience immobility as a result of significant muscle loss or neurological issues resulting from famine. Common joint problems, such as osteoarthritis or arthritis, have the potential to extend the duration of time that a patient is confined to bed. Septic patients and others experiencing other types of haemodynamic shock may also experience an extended period of immobility. These patients often require the use of mechanical breathing and vasoactive medications, which pose considerable challenges to mobilisation. The increasing prevalence of morbid obesity poses a challenge for the multidisciplinary team in terms of mobilisation. Neuroendocrine diseases, such as myxoedema coma, can lead to extended periods of bedridden immobility.

Sarcopenia, a condition characterised by substantial muscle loss, is a consequence of immobility **(Figure 1)**. Immobility results in an elevation of pro-inflammatory cytokines and reactive oxygen species, leading to a decrease in muscle mass and an increase in proteolysis (Sartori et al. 2021). To mitigate this issue, it is advised to engage in resistance training and incorporate dietary protein supplements as remedies for sarcopenia resulting from bed rest. Critical illness is characterised by a state of catabolic stress, in which patients often have a systemic inflammatory response. This reaction is associated with consequences that contribute to malfunction in numerous organs, longer hospital stays, and higher rates of sickness and death (Fan et al. 2014).The condition of a severe illness is characterised by the breakdown of skeletal muscle caused by the inability to maintain a proper equilibrium between protein synthesis and degradation (Bloch et al. 2012; Rennie 2009). The breakdown of muscle proteins increases due to the activation of intracellular signalling pathways (Poulsen2012). The ubiquitin-proteasome system is widely regarded as the primary pathway involved in the breakdown of proteins. Within this system, two specific enzymes, atrogin-1 (Muscle Atrophy F-box) and MuRF-1 (Muscle Ring Finger -1), have been identified as key players in the process of skeletal muscle atrophy. These enzymes are activated in response to both inactivity and inflammation (Teixeira et al. 2021).

Cortisol levels will increase, indicating an association with stress. Consequently, blood glucose levels rise as a result of gluconeogenesis and increased insulin resistance. In response to stress, the body breaks down skeletal muscle, which

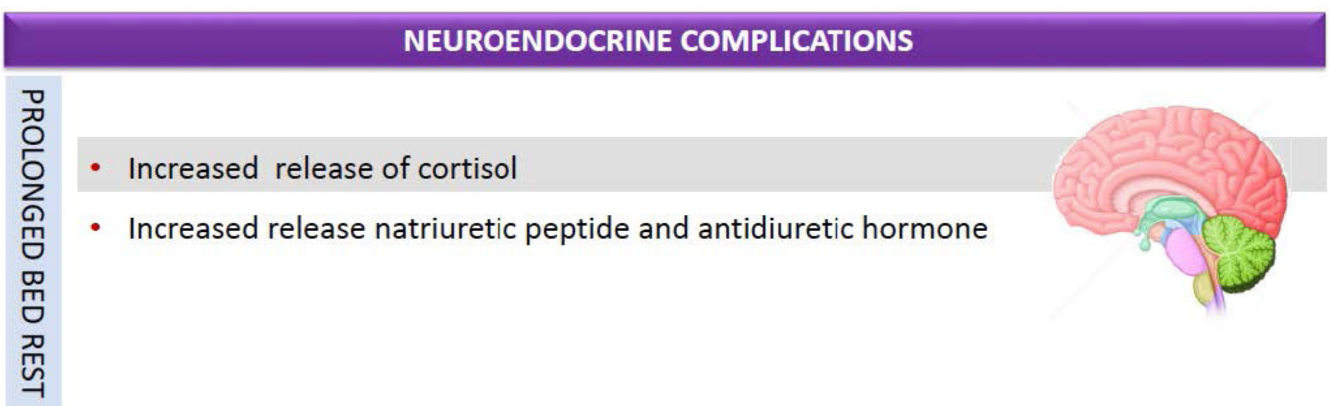

Figure 2. Neuroendocrine complications related to immobility

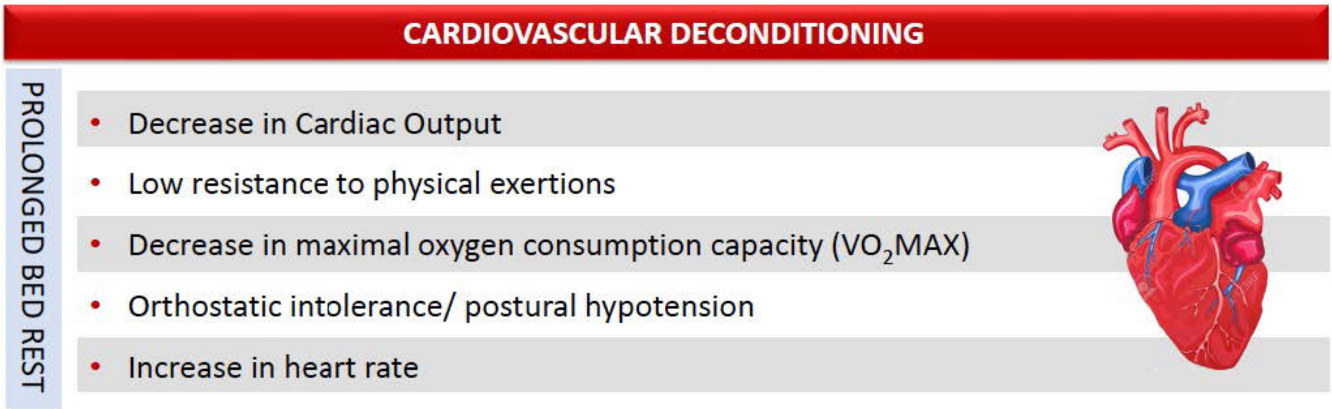

Figure 3. Cardiovascular deconditioning associated with immobility

exacerbates sarcopenia (Knight et al. 2009a) **(Figure 2)**.

The supine position also induces a redistribution of bodily fluids. The blood is redirected from the lower extremities to the torso and head, thereby enhancing the flow of deoxygenated blood back to the heart. This procedure induces significant enlargement of the right heart chambers, leading to elevated levels of atrial natriuretic peptide. Consequently, there is an elevation in diuresis, leading to a decrease in plasma volume. Over time, there will also be a decline in the volume of red blood cells. The renin-angiotensin-aldosterone system will be stimulated in an effort to maintain blood pressure despite the decrease in intravascular volume (Knightet al. 2009b).

Extended durations of immobility result in patients experiencing a deterioration in their capacity to control their torso and becoming fatigued at a faster rate. There is a reduction in aerobic capacity and VO2Max (maximum capacity for oxygen consumption). Every day of complete inactivity leads to a decrease of 0.3% in VO2Max **(Figure 3)**. Plasma volume, red blood cell mass, vasodilator function, muscles, and peripheral oxygen diffusion capacity all decrease. Bed rest for a period of 72 hours results in a 30% decrease in stroke volume and an increase in resting heart rate, ultimately leading to orthostatic intolerance (Convertino et al. 1997).

From a pulmonary perspective, the reduction in tidal volume is caused by the limitation of lung expansion due to the pressure exerted by body weight on the rib cage **(Figure 4)**. Manoeuvres can be performed to expand the lungs and reduce complications, such as atelectasis and pneumonia. Nevertheless, it is important to note that individuals who are able to breathe on their own but lack neurological interaction may pose a barrier, as they will not be able to cooperate with manoeuvres. In such instances, EPAP and breath stacking may be employed; however, there is currently insufficient scientific evidence to support their efficacy (Morais et al. 2021).

Young patients who have highly active lifestyles may undergo significant psychological distress due to immobilisation, typically induced by acute conditions such as lower limb fractures or ligament injuries. In such situations, it is crucial to develop a detailed strategy for sending patients home, as they will often attempt to resume their usual activities despite their injuries. This can result in additional injuries, hence prolonging the healing period. Moreover, it is imperative to provide psychological assistance, since the inability to work can lead to the development of depression and anxiety (Batista Filho et al. 2024). Delirium, post-traumatic stress disorder (PTSD), and chronic pain are among the most prevalent complications associated

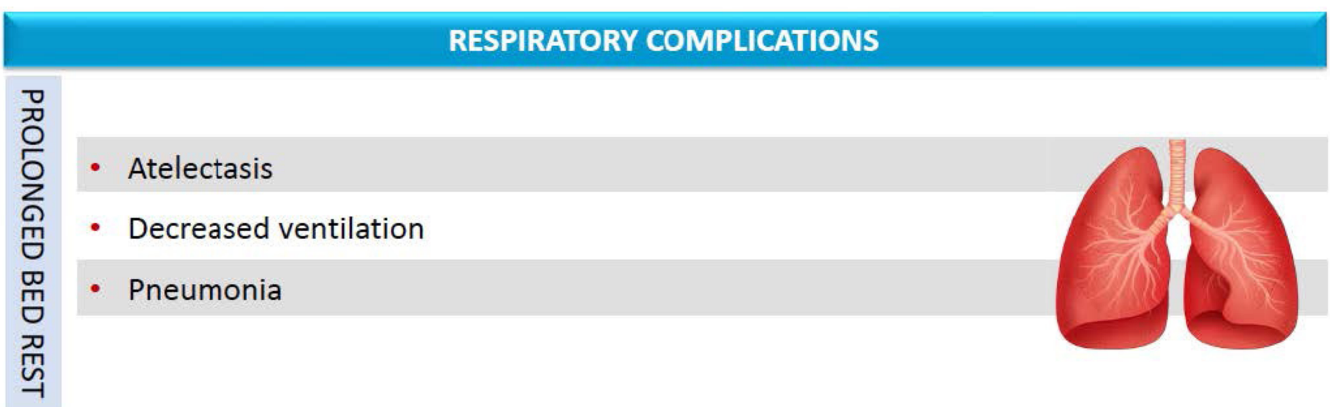

Figure 4. Respiratory complications related to immobility

Figure 5. Gastrointestinal complications related to immobility

with protracted immobility in the intensive care unit (ICU).

From a gastrointestinal standpoint, prolonged bed rest in patients leads to decreased hunger and impaired movement in the gallbladder, stomach, and intestines **(Figure 5)**. Therefore, these people are prone to developing gallstones (Hjaltadottir et al. 2020), experiencing oesophageal reflux, and suffering from constipation (Ghoshal 2007). The evacuation of the intestines is further hindered by the challenge of assuming a seated position and the insufficient consumption of water and absence of dietary fibre.

Immobility also increases the risk of developing deep vein thrombosis and pulmonary thromboembolism, as it worsens Virchow's Triad, which consists of blood flow stagnation, increased blood clotting, and damage to the inner lining of blood vessels (Knight et al. 2009a) **(Figure 6)**.

When it comes to skin problems, it is important to mention pressure ulcers, which occur when the weight of the body puts excessive pressure on bony areas. The areas around the ankles, sacrum, and trochanters are particularly prone to pressure sores (Grey et al. 2006). Another important condition to mention is contact dermatitis, which occurs as a result of contact with sweat, bed linens, or even diapers. Fracture patients may experience an intensified immune response when in contact with plaster, potentially leading to confusion in diagnosis with other illnesses, such as angioedema and lichen planus (Li and Li 2021). Patients with atopic dermatitis have an increased likelihood of also developing contact dermatitis **(Figure 7)**.

Immobile patients are more prone to experiencing kidney stones at a higher rate. Bedridden patients experience increasing bone demineralisation, leading to elevated levels of calcium in the blood and urine, which raises the likelihood of stone formation. Additionally, there is an increased level of urine stasis, which promotes the growth of germs and increases the likelihood of urinary tract infections. Moreover, patients who are immobilised experience heightened challenges in maintaining hygiene in the genitourinary tract, hence creating a more conducive environment for bacterial growth (Okada et al. 2008) **(Figure 8)**.

Obstacles to Early Mobilisation of Critically Ill Patients

Implementing routine early mobilisation of patients in the hospital, especially in the intensive care environment, faces numerous obstacles. There are obstacles pertaining to patients, the infrastructure of the intensive care unit, the culture of

Figure 6. Thromboembolic complications related to immobility

Figure 7. Skin complications related to immobility

the intensive care unit, and associated processes (Dubb et al. 2016).

Regarding the patient, we may remark the presence of haemodynamic instability, the extent of illness severity, respiratory instability, pain, malnutrition, obesity, muscle weakness, sedation, patient refusal, weariness, delirium, agitation, and cognitive impairment.

When discussing Intensive Care Unit (ICU) devices, we can identify haemodynamic monitoring equipment, bladder and venous catheters, and surgical drains as potential impediments. Structural impediments, such as insufficient personnel and resulting time constraints for team members to mobilise the patient, are limitations. This problem particularly affects developing countries (Batista Filho et al. 2022) since these nations are the most affected by the lack of labour. It is not uncommon for physiotherapists in countries with limited resources to work with extreme workload, making adequate rehabilitation work impossible. Furthermore, the absence of mobilisation guidelines and inadequate training for the interdisciplinary team also pose significant obstacles.

Nevertheless, we must emphasise that an abundance of protocols might contribute to increased complexity. In a healthcare system that is becoming more and more concerned about the availability of empty hospital beds, discharging patients prematurely before they have completed their mobilisation can disrupt their recovery process. This issue warrants significant attention when discussing the hospital release process, as patients frequently face challenges related to their socio-economic, cultural, and infrastructure circumstances, which hinder their ability to complete their recovery fully. The injury may lead to long-term repercussions, characterised by a significant impairment of functionality.

Additionally, there are also cultural obstacles that pertain to the practices of healthcare workers employed in hospitals. A significant portion of professionals lack a culture of mobilisation, and there remains a dearth of comprehensive understanding of the adverse effects of immobilism. As a consequence of a lack of comprehension of the detrimental effects on the patient, early mobilisation is not considered a priority. At times, there might be a subset of professionals that support the concept of mobilisation, but they lack the support of the rest of the team.

Regarding processes, one issue that can be highlighted is the absence of coordination among the team, resulting in misplaced expectations. The allocation

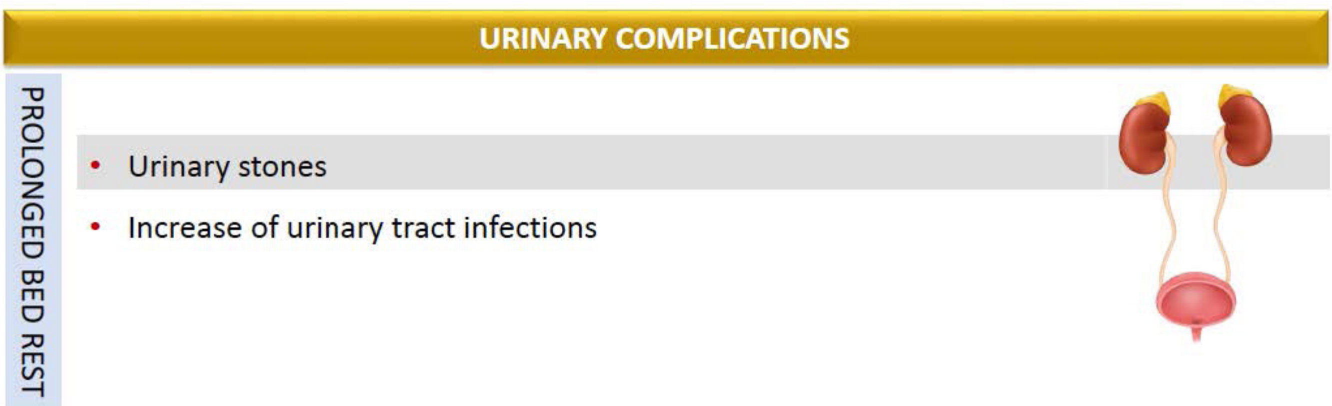

Figure 8. Urinary complications related to immobility

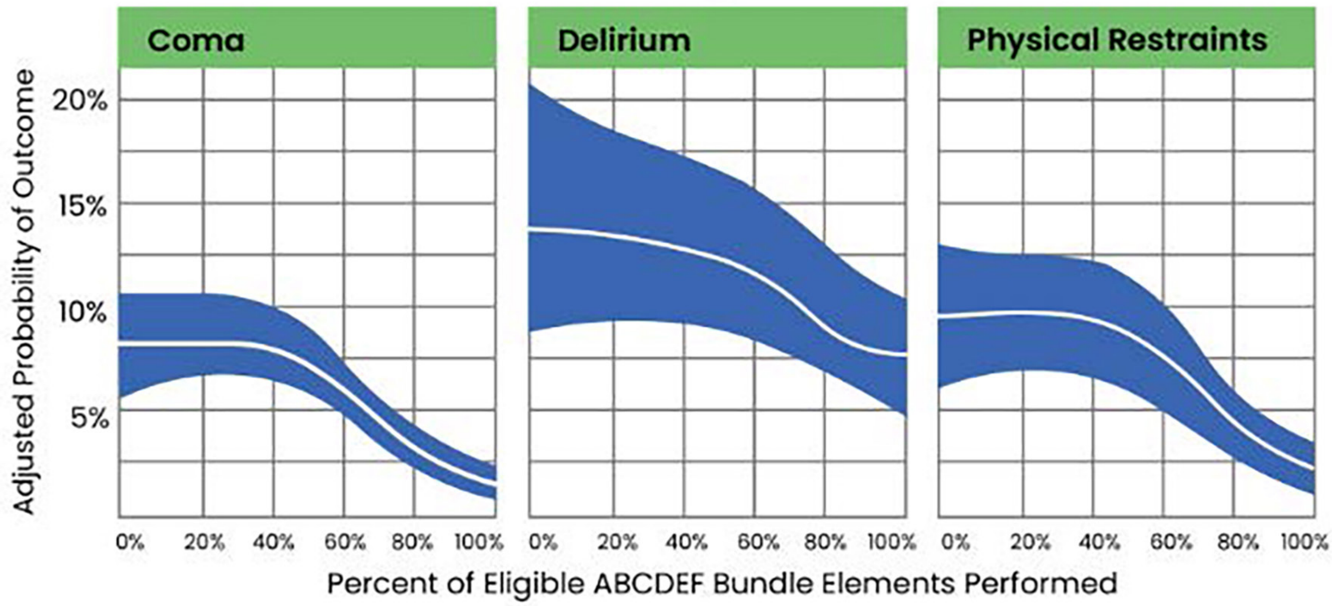

Figure 9. Enhanced compliance with the ABCDEF bundle decreases the occurrence of coma, delirium and the necessity for physical restraints

of responsibilities among team members is frequently ambiguous, mostly because of insufficient interprofessional communication and collaboration. Performing daily mobilisation eligibility assessment among patients is also essential. Moreover, it is crucial to monitor the potential hazards associated with mobilisation for the professionals engaged and accurately determine the optimum team size for each specific scenario.

The ABCDEF Bundle: Powerful Ally to Create the Awake and Walking ICU

The standardised practice of restricting patients to bed rest for extended periods in the ICU is a primary modifiable risk factor for numerous iatrogenic problems that arise in this setting. The ICU emancipation initiative introduced treatment components aimed at enhancing patient outcomes and mitigating the risks associated with sedation and immobility via the ABCDEF Bundle (Ely 2017). The detrimental effects encompass diaphragm atrophy, ICU-acquired weakness, ICU delirium, post-ICU post-traumatic stress disorder (PTSD), and post-ICU cognitive deficits, all of which constitute post-ICU syndrome (PICS) (Needham et al. 2012). PICS is found in around 50% of all ICU survivors (Carel et al. 2023). The ABCDEF bundle comprises the following tools:

A: Assess, Prevent, and Manage Pain

B: Both Spontaneous Awakening Trials (SATs) and Spontaneous Breathing Trials (SBTs)

C: Choice of Analgesia and Sedation

D: Delirium: Assess, Prevent, and Manage

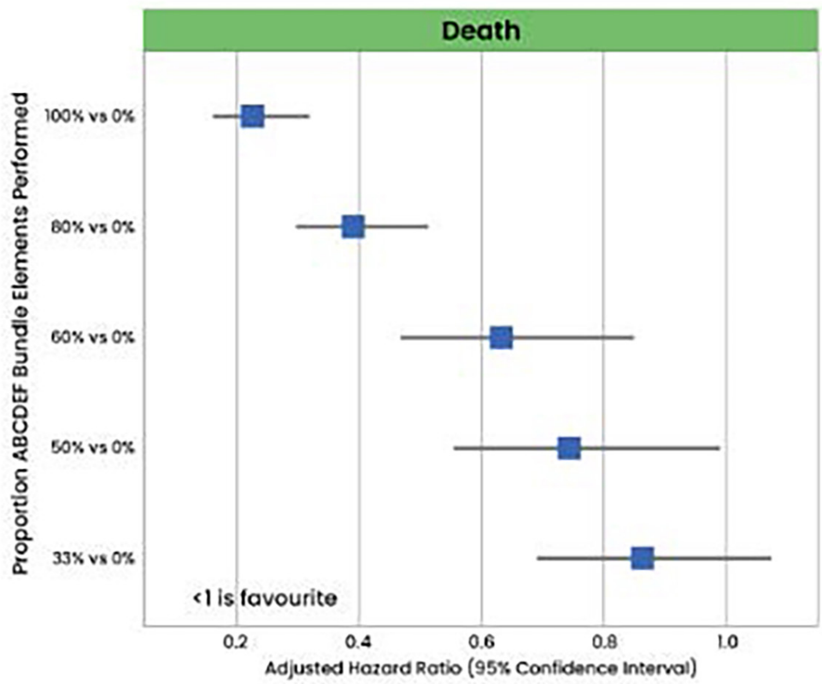

Figure 10. Enhanced compliance with the ABCDEF bundle decreases the occurrence of coma, delirium and the necessity for physical restraints

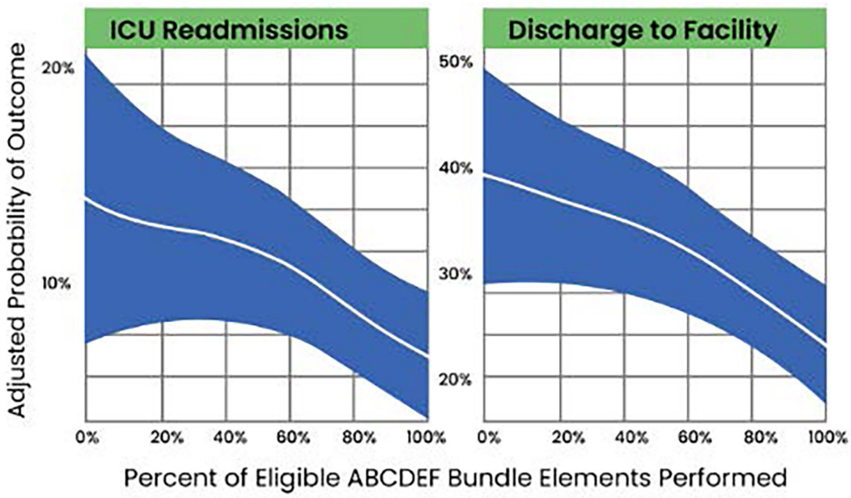

Figure 11. Enhanced compliance with the ABCDEF bundle decreases the occurrence of ICU readmissions and discharge to a facility

E: Early Mobility and Exercise

F: Family Engagement and Empowerment

To effectively execute the ABCDEF Bundle and extend the advantages of early mobility to all eligible patients, it is crucial for ICU staff to possess a comprehensive awareness of the fundamental purpose of this bundle. The objective is to cultivate persons who demonstrate enhanced vigilance, engaged cognitive involvement, and improved physical mobility, while fostering patient autonomy and the ability to express unmet physical, emotional, and spiritual needs (Pun et al. 2019).

Before mobility can be considered, ICU teams must initially address sedation management to ensure that patients are cognitively engaged, autonomous,

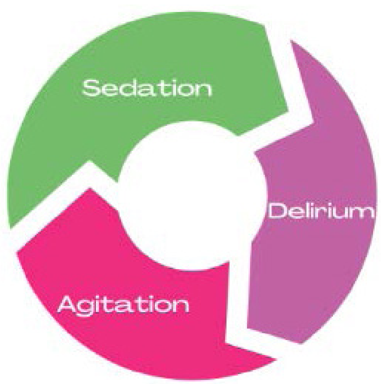

Figure 12. The pernicious cycle of excessive sedation. Sedation induces delirium, which then results in agitation, necessitating the administration of more sedation

communicative, and cognisant. An Awake and Walking ICU is established when an ICU team achieves mastery of the ABCDEF bundle by achieving these objectives for each patient (Dayton 2020).

Notwithstanding the efficacy of the ABCDEF bundle, intensive care units frequently have difficulties in achieving 100% compliance. The 2019 ABCDEF bundle study demonstrated that outcomes from bundle adoption were assessed across 68 sites and over 15,000 patients; merely 8% of patients received the complete bundle. Merely 12% of patients were ambulating with weight-bearing capability. The advancements in administering reduced sedation, incorporating daily awakenings, breathing trials, and facilitating mobility for certain patients significantly improved patient outcomes. Seven-day mortality declined by 68%, incidence of coma and delirium reduced by 25-50%, utilisation of physical restraints diminished by 60%, ICU readmission fell by 46%, and patients exhibited a 36% increased likelihood of being released home from the hospital. Outcomes were observed to be dose-dependent **(Figures 9, 10, and 11).** Outcomes improved with reduced sedation and increased patient mobilisation (Pun et al. 2019).

Despite the established correlation between patient survival and adherence to the care bundle, prevalent ICU practices continue to favour routine sedation and immobility for all intubated patients. The instruments included in the ABCDEF bundle can be manipulated to sustain longstanding cultural practices that confine patients to their beds. Obstacles to maintaining patient alertness and mobility encompass the perception that sedation equates to "sleep," is "humane," and is "indispensable for all intubated patients." The bundle is regarded as a checklist employed as a mechanism for rapid initiation and cessation of sedation during a sedation holiday. Awakening experiments are conducted solely to assess the potential for extubation and are restarted if a breathing trial is unsuccessful. Sedation is reduced sufficiently to allow occasional eye-opening, but seldom enough to facilitate communication and motion. Mobility is utilised as a rehabilitation technique post-extubation to mitigate delirium and ICU-acquired weakness, rather than being employed as a proactive rehabilitative strategy to avert these issues from arising. There exists a pervasive apprehension that permitting patients to autonomously mobilise their bodies during mechanical breathing may result in an increase in falls and inadvertent extubations.

When patients are sedated for the purpose of tolerating mechanical ventilation and avoiding ventilator-induced lung injuries, the brain, bone, and skeletal muscle systems are depleted by sedation plus immobility; thus, accepting an unproven concept that other vital organ systems must be sacrificed to save respiratory function. Sedation medications lengthen the time patients require mechanical ventilation, need added pressor medications with harmful vasoconstricting side effects, cause delirium that leads to cognitive impairment comparable to early onset dementia, deplete skeletal muscle, which would not just allow a patient to maintain the survival skill of walking, but also reduces systemic inflammation and supports immune function. As Herridge (2008) stated in her seminal research on post-intensive care disability, "there appears to be significant potential for harm arising from the traditional ICU culture of patient immobility and an often excessive or unnecessary use of sedation".

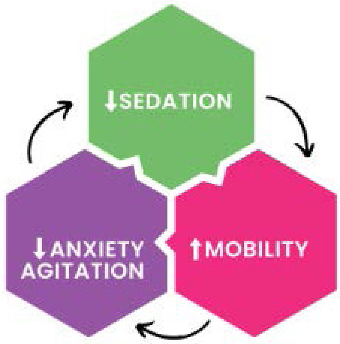

Figure 13. The virtuous cycle of sedation reduction involves decreasing sedation levels, which in turn promotes mobilisation, leading to increased mobility and decreased levels of anxiety and agitation

When patients are sedated to endure mechanical ventilation and prevent ventilator-induced lung injuries, sedation combined with immobility depletes the brain, bone, and skeletal muscle systems; consequently, this supports an unverified notion that other essential organ systems must be compromised to preserve respiratory function. Sedation medications prolong the duration of mechanical ventilation, necessitate additional pressor agents with detrimental vasoconstrictive effects, induce delirium resulting in cognitive impairment akin to early-onset dementia, and diminish skeletal muscle, which is essential not only for maintaining ambulation but also for reducing systemic inflammation and bolstering immune function. According to Herridge (2008) in her pivotal study on post-intensive care impairment, "there seems to be considerable potential for harm resulting from the conventional ICU culture of patient immobility and frequently excessive or unwarranted sedation."

At each shift, the inquiry must be posed: "Recognising that sedation is detrimental to patients, how can I reduce the cumulative dosage administered to facilitate optimal mobility, timely extubation, abbreviated ICU duration, diminished delirium, and a return to their normal lives?" To optimise early mobility, teams must recognise that the presence of an endotracheal tube and mechanical ventilation does not inherently need sedation. The C of the ABCDEF bundle necessitates the inquiry, "Is there a justification for sedation?" Indications for sedation in the ICU encompass exceptions such as refractory status epilepticus, intracranial hypertension, acute respiratory failure, and the prevention of awareness in patients receiving neuromuscular blocking medications (Reade et al. 2014).

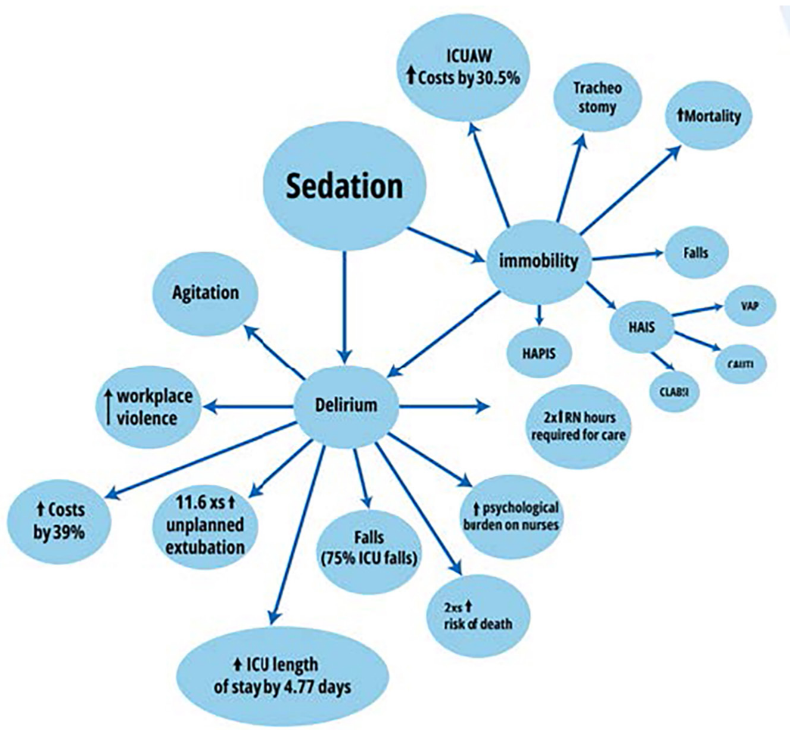

Figure 14. An expanded perspective on the detrimental effects of excessive sedation and its resulting outcomes, namely, delirium and immobility. HAPIS = Hospital Acquired Pressure Injuries, HAIS = Healthcare-associated infections, VAP = Ventilator-associated pneumonia, CAUTI = Catheter-associated urinary tract infections, CLABSI = Central line associated bloodstream infection, ICUAW = Intensive Care Unit Acquired Weakness

When the culture in the ICU transitions from automatic sedation to symptom management (Eikermann et al. 2023), many patients can remain free from sedation while intubated (Strøm et al. 2010). When sedation is indicated, awakening trials should be conducted to evaluate the resolution of the condition, and sedation should be terminated when it is no longer necessary. The discontinuation of sedation shortly after ICU admission has been shown to be both safe and practical (Cuthill et al. 2020). Patients cannot attain optimal mobility when affected by ongoing or residual sedation. The E component of the ABCDEF bundle has the lowest compliance (Barr et al. 2024). The primary obstacles to mobility in the ICU are sedation and agitation. Paradoxically, sedation elevates the likelihood of delirium. Delirium subsequently elevates the likelihood of agitation by a factor of 24 (Almeida et al. 2016). Increased sedation levels may exacerbate the severity of delirium (Ortiz et al. 2022). This is an unavoidable loop that must be terminated **(Figure 12)**.

This is probably due to patients not sleeping peacefully while sedated (Weinhouse et al. 2011). They frequently encounter alternative and vivid worlds encompassing terrible situations such as abduction (Richards et al. 2023), violence, and torture. Mobility is a primary intervention for the prevention and treatment of delirium. Mobility reduces the incidence of delirium by 23% (Duceppe et al. 2019). This likely explains why early mobility enhances patient anxiety and animosity (Klein et al. 2018). Avoiding early sedation post-intubation can mitigate two primary obstacles to mobility **(Figure 13)**.

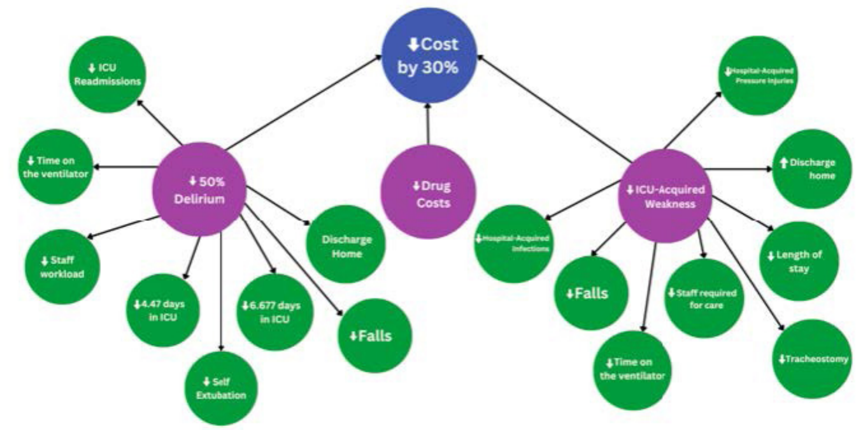

Figure 15. An in-depth analysis of the advantages of an Awake and Walking ICU

Practical Application: Case Report

Joan (pseudonym) is a 38-year-old female with a history of tobacco smoking, who was brought to an external hospital in September 2018 for acute respiratory failure due to influenza, which subsequently progressed to acute respiratory distress syndrome (ARDS). She was intubated and sedated at a small community hospital before being transferred to an Awake and Walking Intensive Care Unit.

Joan states that while sedated during transport, she experienced a vivid alternate reality in which she perceived the physicians surrounding her as minors attempting to inflict harm, such as sawing off her hands at the wrists.

Figure 16. Patient sitting and texting her family out of bed, even under mechanical ventilation

Upon her arrival at the Awake and Walking ICU, the new team promptly conducted a risk-benefit analysis to address sedation and mobility management for Joan. The standard ICU protocol would maintain Joan in a sedated and immobilised state until her ventilator settings were reduced to a minimum, at which point her readiness for extubation would be assessed.

The subsequent outlines the hazards and advantages of continuous sedation and immobility for Joan. Continuous sedation will inhibit respiratory drive and enable total regulation of each breath administered to her. Implementing lung-protective methods utilising reduced tidal volume will mitigate the risk of ventilator-induced lung injury (ARDSnet 2000). Complete regulation of respiratory rate and inhibition of spontaneous breaths may alleviate concerns over self-induced lung injury (Brochard et al. 2017), although the evidence remains inconclusive (Carteaux et al. 2021).

Administering sedation to Joan may provide nurses with a sense of efficacy, as 65.7% believe sedation enhances patient comfort, while 59.2% find it facilitates the care of sedated patients (Guttormson et al. 2019). Joan will be incapable of articulating her discomfort, pain, anxiety, or terror, which may lead clinicians to be less troubled and concerned about her experience during mechanical ventilation.

HAPIS = Hospital Acquired Pressure Injuries, HAIS = Healthcare-associated infections, VAP = Ventilator-associated pneumonia, CAUTI = Catheter-associated urinary tract infections, CLABSI = Central line associated bloodstream infection

Maintaining Joan sedated may jeopardise her present and future cognitive abilities. She possessed numerous risk factors for delirium, including tobacco use (Hshieh et al. 2015), admission to the ICU, mechanical ventilation, and hypoxaemia. She faced the potential for an extended hospitalisation and sleep disturbances in the ICU, which elevate the likelihood of delirium (Ormseth et al. 2023). If Joan experienced delirium, her mortality risk in the hospital would double (Salluh et al. 2015). The probability of mortality would escalate by 10%, and the likelihood of enduring cognitive impairment would increase by 35% for each day of delirium (Ely 2004). At the age of 38, delirium can result in cognitive impairments akin to mild Alzheimer's disease and moderate traumatic brain injury (Pandharipande et al. 2013). This may result in the incapacity to work and financially support herself and her family following the ICU stay (Ahmed et al., 2021). Brain damage resulting from sedation would irrevocably alter her life.

If Joan experienced delirium, she would face an increased risk of prolonged ventilation, averaging an additional 4.47 days in the ICU and 6.67 days in the hospital (Dziegielewski et al. 2021), with ICU expenses rising by 39% (Millbrandt et al. 2004). Her risk of self-extubation would escalate by 11.6 times (Kwon and Choi 2017), the risk of falls by 2.81 times (Kalivas et al. 2023), and the likelihood of ICU readmission by 7% (Lobo-Valbuena et al. 2021).

Sedation constitutes an independent risk factor for delirium, with an odds ratio of 2.268. If the ICU team maintained Joan in a sedated, restricted state in the ICU for more than 7 days, her risk of delirium would escalate with an odds ratio of 30.950 (Pan et al. 2019). The sole method to mitigate Joan's risk of delirium was to manage her pain, facilitate genuine interaction with her family, promote mobility, and ensure adequate sleep (Kotfis et al. 2022). Sedation would impair her capacity to

Figure 17. Devices outside the bathroom, while the patient showers standing up, even under mechanical ventilation

communicate discomfort, interact with her family, mobilise, and achieve restorative sleep. Given her susceptibility to delirium, vigilance is important while administering deliriogenic drugs, including sedatives.

The interdisciplinary team had to evaluate the adverse effects of sedation and immobilisation on Joan's pulmonary function. Sedation and immobility prolong ventilator duration (Strøm et al. 2010), elevate the risk of ventilator-associated events (VAE), potentially doubling mortality risk (Klompa et al. 2019), and may exacerbate existing neutrophilic lung injury (Files et al. 2015). Joan's secretion mobilisation and clearance, as well as lung aeration, would be compromised during sedation (Volpe et al. 2021). Propofol is a mitochondrial poison (Finsterer and Frank 2016) and is probably an independent risk factor for diaphragm malfunction and atrophy (Bruells et al. 2014). Maintaining Joan in a drugged and immobile state would elevate her risks of ventilator-associated events, prolonged ventilatory support, diaphragm dysfunction, tracheostomy, and maybe fatality.

Sedation and immobility would place Joan at a heightened risk for ICU-acquired weakness and diaphragm dysfunction, potentially reducing her two-year survival probability by 43% (Saccheri et al. 2020) and escalating expenses by 30.5% (Hermans and Van den Berghe 2015).

Patients in the ICU typically have a daily loss of 2% of muscle mass (Fazzini et al. 2023). Sedation induces the most rapid and significant muscular atrophy relative to other primary causes of muscle loss (Parry and Puthucheary 2015). Consequently, 40% of muscle strength may be diminished within the initial week of immobilisation (Topp et al. 2002). If Joan continues to receive propofol, she will experience diminished muscle excitability due to the disruption of sodium channels in the muscles (Trapani et al. 2000) and decreased glucose utilisation, as propofol elevates insulin resistance in cardiac and skeletal muscle (Yasuda et al. 2012).

The administration of sedation and the resultant immobility may profoundly affect Joan's psychological safety. During sedation, she would be incapable of expressing her needs, desires, preferences, and inquiries. She would become wholly vulnerable and reliant on the ICU care, thereby exacerbating panic and trauma. If she develops ICU-acquired frailty, she will become physically reliant on others for fundamental life functions. Physical reliance elevates the likelihood of anxiety, depression, and PTSD during ICU admission (Teixeira et al. 2021).

Delirium constitutes a risk factor for post-ICU PTSD (Girard et al. 2007). If Joan is sedated and experiences delirium, she risks becoming ensnared in a vivid, violent, and horrific alternate reality sometimes referred to as "hallucinations" (Richards et al. 2023). Ambiguity and indistinct recollections heighten the risk and intensity of PTSD (Ehlers et al. 2000).

Joan's team had to evaluate the alternatives to sedation and immobility, weighing the associated dangers against the benefits of maintaining her consciousness and movement. The incidence of adverse events during early mobility is 0.6%, encompassing falls, extubation, removal or malfunction of intravascular catheters, removal of other tubes, cardiac arrest, haemodynamic fluctuations, and desaturation (Nydahl et al. 2017), despite patients exhibiting a median PF ratio of 89 (Bailey et al. 2007).

Safeguarding Joan from delirium will preserve her cognitive function both in the ICU and beyond. ICU mobility reduces the risk of delirium by 23% according to one study (Duceppe et al. 2019) and by 95% in another (Bersaneti and Whitaker 2022). If Joan develops delirium, mobility will reduce the length by two days (Schweikert et al. 2009). Mobilising within 48 hours post-intubation, as opposed to delaying for many days (Patel et al. 2023), can enhance cognitive performance by 20% one year following discharge **(Figure 14)**.

Permitting Joan to remain awake and seated will enable her to cough, mobilise, clear her secretions, and enhance lung aeration (Hickmann et al. 2021). Enabling her to assume an upright posture will reduce alveolar strain and enhance ventilation-perfusion mismatch. Engaging in active mobility, including sitting, standing, and walking, will stimulate her diaphragm and mitigate the risk of diaphragm dysfunction and atrophy (Dong et al. 2021). With each day of enhancement in mobility, her chance of ventilator-associated pneumonia diminishes by 40% (Qi et al. 2023). Absence of sedation will reduce her ventilator duration by an average of 4.2 days (Strøm et al. 2010). For each day of movement out of bed, her ventilator time will diminish by 10% (Fazio et al. 2024), possibly due to the preservation of muscular strength and cognitive function necessary for independent respiration, efficient coughing, and airway protection post-extubation.

If Joan awakens immediately, she is likely to retain her cognitive and fine motor skills, enabling her to write with a pen and paper or text on her cell phone, thereby providing her a voice during a vital and vulnerable period in her life. She will be able to communicate her pain management requirements and preferences to her ICU team, as well as connect with her husband and children. She will maintain the physical ability to manage her own oral hygiene, dressing, toileting, etc., so as to preserve her dignity, identity, and autonomy. Access to communication, control, and effective pain treatment can safeguard her against PTSD (Myhren et al. 2009). Joan's lack of sedation will not elevate her risk of PTSD (Strøm et al. 2011), since less sedation has been demonstrated to diminish PTSD risks (Kress et al. 2003). Authentic recollection of her ICU experience may safeguard her against PTSD (Jones et al. 2001).

To avert post-ICU syndrome, Joan must be mobilised within 72 hours following intubation (Matsuoka et al. 2023). Timely mobilisation will facilitate prehabilitation to avert delirium and ICU-acquired weakness, rather than rehabilitating post-complication (Topp et al. 2002). Each 10-minute increment of early movement in the ICU will reduce her hospital stay by 1.2 days (Jenkins et al. 2024). An early mobility programme in the ICU reduced hospital-acquired pressure injuries by 77.2% (Vollman et al. 2024) **(Figure 15)**.

Awake and Walking

Joan entered the hospital exhibiting dyspnoea and hypoxia the day before her admission to the Awake and Walking ICU. With her oxygen levels stabilised and respiratory support in place, there was no longer a contraindication for Joan to engage in her maximum movement (**Figures 16, 17 and Table 1**):

- Sat in a chair during the day
- Walked around the ICU 3 times a day
- Showered while intubated
- Texted/wrote on clipboard
- Helped daughter with homework
- Connected with husband
- Extubated and discharged home
- Resumed running her own business afterward

Joan's hospitalisation and life were significantly influenced by her early awakening and mobility following intubation. She may have easily become chronically crippled, akin to 50% of ICU survivors (Geense et al. 2021). Among ARDS survivors, 73% experience delirium (Hsieh et al. 2015), 60% develop ICU-acquired weakness (Fan et al. 2014), 70-100% exhibit severe cognitive impairments upon hospital discharge (Herridge et al. 2016), 39% are diagnosed with PTSD (Mikkelsen et al. 2012), and merely 49% return to work within the first year post-discharge (Kamdar et al. 2018). Prompt ambulation safeguarded Joan from delirium, ICU-acquired frailty, elevated mortality risk, and post-ICU syndrome. Six years post-discharge, Joan has a fulfilling life with her expanding family, which now includes three additional grandkids.

Conclusion

Mobilising patients in critical condition is a recurring difficulty. The successful execution of this task requires a high level of determination from the multidisciplinary team, as well as a thorough understanding of the adverse effects that can result from extended sedation and immobilisation. While the primary objective of an ICU is to sustain the patient's life, it is equally crucial to prioritise the patient's post-ICU quality of life and level of functionality. Patients sometimes suffer lasting consequences following a severe illness and protracted hospital stay, which might be significantly minimised with more proactive rehabilitation interventions. An Awake and Walking Intensive Care Unit specifically deals with the challenges posed by profound sedation and immobility in patients who require mechanical ventilation. It is important to implement research findings on the treatment of ICU delirium, ICU-acquired

Sedation: Continuous **RASS:** -3 (target) **Mobility:** Passive ROM **Communication:** None	**Sedation:** Continuous **RASS:** -3 **Mobility:** None **Communication:** None	**Sedation:** No sedative infusion **RASS:** 0 **Mobility:** Ambulated 200ft and 400ft **Communication:** Writing on a clipboard, interacting with her husband and children at the bedside, texting friends on her phone.
Day 3- Ventilator Settings: PRVC/A:C PEEP 14-16, FiO_2 0.5 **Actual Case:** She remained sitting in the chair for most of the day. She was a standby assist to sit, stand, and walk. She suctioned her own mouth, brushed her own teeth at the sink, walked to the toilet, and put her own socks on while sitting.		
Sedation: Continuous **RASS:** -3 (target) **Mobility:** Passive ROM **Communication:** None	**Sedation:** Continuous with sedation vacation **RASS:** -3 **Mobility**: Passive range of motion **Communication:** None	**Sedation:** No sedative infusion **RASS:** 0 **Mobility:** Ambulated 200 ft x 3 **Communication**: Writing on a clipboard, interacting with her husband and children at the bedside, texting friends on her phone
Day 4- Ventilator Settings: PRVC/A:C - CPAP with Pressure support of 5, PEEP 5-12, FiO_2 0.4, P/F Ratio 160 **Actual Case:** She remained sitting in the chair for most of the day. She was a standby assist to sit, stand, and walk. She suctioned her own mouth, brushed her own teeth at the sink, walked to the toilet, and put her own socks on while sitting. Joan helped her daughter with her homework.		
Sedation: Continuous includes midazolam **RASS:** -5 (target) **Mobility:** prone position none **Communication:** None	**Sedation:** Continuous with sedation vacation **RASS:** -3 **Mobility:** Active assisted range of motion x1 **Communication:** None	**Sedation:** No sedative Infusion **RASS:** 0 **Mobility:** Ambulated 200 ft x 3 **Communication:** Writing on a clipboard, interacting with her husband and children at the bedside, texting friends on her phone
Days 5-9- Ventilator Settings:PRVC: A/C / CPAP + PS 5, PEEP 5, FiO_2 0.4 **Actual Case:** She remained sitting in the chair for most of the day. She was a standby assist to sit, stand, and walk. She suctioned her own mouth, brushed her own teeth at the sink, walked to the toilet, and put her own socks on while sitting. Joan texted her daughter before her daughter's prom date.		
Sedation: Continuous **RASS: -3** **Mobility:** Passive ROM **Communication:** None	**Sedation:** Continuous with interruption for mobility **RASS:** -1 **Mobility:** Sitting edge of bed x1 **Communication:** Head nods "yes" and "no".	**Sedation:** No sedation **RASS:** 0 **Mobility:** Ambulated 200 ft x 2 and 1500 ft x 1 **Communication:** Writing on a clipboard, interacting with her husband and children at the bedside, texting friends on her phone
Sedation: Continuous **RASS:** -3 **Mobility:** bed level exercise and sitting EOB **Communication:** None	**Sedation:** Continuous with interruption for mobility **RASS:** 0 - (-1) **Mobility:** Stood at the bedside with an assist device **Communication:** Mouthing words and head-nods (Unable to write due to ICUAW)	**Sedation:** No sedation **RASS:** 0 **Mobility:** Ambulated 800 ft x 2 **Communication:** Writing on a clipboard, interacting with her husband and children at the bedside, texting friends on her phone
Sedation: Continuous with interruption for mobility **RASS:** -3 **Mobility:** bed exercise, sitting EOB **Communication:** None	**Vent mode:** Failed CPAP trial **Sedation:** Continuous with interruption for mobility **RASS:** 0- (-1) **Mobility:** Marching at the bedside x1 **Communication:** Mouthing words, head-nods, pointing to words on letterboard	**Sedation:** No sedation **RASS:** 0 **Mobility:** Ambulated 800 ft x 2 **Communication:** Writing on a clipboard, interacting with her husband and children at the bedside, texting friends on her phone

Vent mode: Failed CPAP trial **Sedation:** Continuous with interruption for mobility **RASS:** -3 **Mobility:** bed exercise, sitting EOB **Communication:** None	**Vent mode:** Failed CPAP trial **Sedation:** Continuous with interruption for mobility **RASS:** 0 - (-1) **Mobility:** Marching at the bedside x1 Communication: Writing on clipboard with assistance	**Sedation:** No sedation **RASS:** 0 **Mobility:** Ambulated 1,000 ft x 3 **Communication:** Writing on a clipboard, interacting with her husband and children at the bedside, texting friends on her phone
Vent mode: Failed CPAP trial **Sedation:** Continuous with interruption for mobility **RASS:** -3 **Mobility:** bed exercise, sitting EOB **Communication:** None	**Vent mode:** Failed CPAP trial ***Tracheostomy placed*** **Sedation:** Discontinued **RASS:** -1 **Mobility:** None post-tracheostomy placement **Communication:** Mouthing words, head-nods, point to words	**Extubated** **Sedation**: No sedation **RASS:** 0 **Mobility:** 1,000 ft on NRB 15L **Communication:** Talking
Joan remained in the ICU for three more days as her oxygen needs weaned down from oxymiser to nasal cannula. She was discharged home with a 2L nasal cannula and was able to walk, eat, and care for herself independently. She returned to running her own business 2 months after discharge. She denies cognitive, physical, and psychological impairments (Dayton 2020).		

Table 1. Timeline of the patient's evolution

weakness, post-ICU PTSD, post-ICU dementia, prolonged time on the ventilator, and mortality associated with sedation and immobility practices to improve outcomes in both the short and long term. Full recovery is not impossible. This study serves as a rallying cry and a movement to prevent the occurrence of disability through the excessive use of sedation and immobilisation.The multidisciplinary team should consider adopting an F-to-A bundle. If there are family members who are motivated and early mobility is the most compliant part of the ICU liberation bundle, patients must also have the other criteria satisfied. Patients initiate ambulation when their pain is managed (A), they are conscious, and the ventilator is adjusted to their requirements (B and C), while delirium is evaluated and adjusted (D). It is essential to provide exercise-based therapy to all ICU survivors to achieve full recovery. However, it is important to first allow them the chance to maintain as much physical and cognitive ability as they can. Implement an F to A ICU liberation package strategy to effectively avert the significant physical handicap caused by the ICU, as evidenced by the care Joan received in the Awake and Walking ICU (Bailey et al. 2007).

Conflict of Interest

None.

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Moral Distress and Heroic Life-Sustaining Treatment: The Mitigating Role of the Patient Perspective

This article illustrates two cases of critically ill patients where protracted and burdensome life-saving measures led to discord and moral distress among the ICU team, eventually mitigated by eliciting clear goals and wishes from the patient despite the plan of care and clinical interventions remaining unchanged. The takeaway in these cases is how to understand (and respond to) the multilevel perception of moral distress

Introduction

Balancing perspectives when it comes to the critical care of patients that require protracted and burdensome therapy in the intensive care unit (ICU) is a fine art that comes with skill and experience (Rice et al. 2008). Challenges with prognostication of critically ill patients is one of the leading causes of miscommunication, conflict and stress in the ICU (Yin et al. 2024). Issues with communication can lead to differing perspectives about the "right" thing to do, or what "good" care looks like for the patient. These diverging opinions can give rise to moral distress when clinicians feel unable to take the action they believe is ethically correct (Mason et al. 2014).

When clinical teams make choices about life-sustaining care, the balance of proportional burden versus benefit of therapeutic decisions is, ideally, based on patient preferences. When such preferences are absent (or unable to be elicited due to the patient lacking decision-making capacity, as is often the case in the ICU), intensive and often burdensome care without an immediately obvious resolution can lead to feelings of despondence and burnout among clinicians (Boitet et al. 2023). In what follows, two cases are presented that highlight how to understand (and respond to) the multilevel perception of moral distress, nuanced as it is, in real time and the mitigating role that clarity around patient preferences can play in alleviating this moral distress, even when the actual plan of care is not altered.

Cases

An 86-year-old patient was admitted to the ICU after a ruptured abdominal aortic aneurysm. After several weeks on the ventilator with worsening organ failure and escalating support, the ICU nurses and physicians started questioning the utility of continuing life-sustaining therapy, expressing concern over the patient's suffering and the limited likelihood of a full recovery. The patient's family and loved ones, however, felt that the patient would have wanted to 'keep trying until there is no stone unturned.' The surgeons believed that the complications were being managed and were potentially reversible. The intensivist team held several family meetings with social work and palliative care teams present. Due to the uncertainty of her prognosis and the family's surgeon's perspectives, life-sustaining measures were continued. The ICU team, including the physicians and nursing staff, experienced moral distress due to their perception of the 'pain and suffering being caused.'

However, after several more weeks, the patient's cognitive status improved and the patient was able to awaken enough to interact with the team, despite still requiring dialysis, vasopressors and mechanical ventilation. Once her decision-making capacity was ascertained, her wishes and preferences were elicited in the presence of family. She expressed that this clinical trajectory was aligned with her goals of care and what she wanted, and she was hopeful that she could recover. In the next few weeks, she slowly recovered and was weaned off major life-sustaining intervention.

The ICU team taking care of her felt an immediate relief and "decrease in their moral distress" once they perceived that potentially inappropriate care was not being thrust upon her, and that her wishes and autonomy were being preserved.

Similarly, a 76-year-old, post-liver transplant patient had a months-long, protracted course in the ICU with prolonged mechanical ventilation with a tracheostomy, dialysis, vasopressors, gastrostomy feeding and muscle wasting. He was anxious at baseline and was being managed with anxiolytics as well as antidepressants. He was often awake and interactive, but had repeated bouts of sepsis, and his mental status waxed and waned. The nursing staff began to express extreme moral distress at the invasive care this patient was undergoing without any ostensible improvement. On discussing with the surgeons, who had a long relationship with the patient, they felt that the patient had known the possible complications and had signed up for the long journey. However, despite hearing the surgical team's perspective, the nursing staff were obviously upset at seemingly providing non-beneficial care to their patient and potentially exacerbating his anxiety, which they felt was due to such care.

Discussion

Providing treatment to a patient when the patient's values and goals are unknown, especially in the ICU and at the end of life, is stressful. Providers and families ask themselves: Is this what the patient wants? Am I respecting the patient's values? Typically, we look to families to answer the questions, but even with the most conscientious surrogate, there can be great uncertainty. Moral distress occurs when clinicians feel unable to follow what they perceive to be the ethically "correct" plan of care, or when they feel complicit in providing care that they assess to be morally wrong (Epstein et al. 2019). Moral distress is one of the driving forces leading to the attrition of critical care nurses and ICU staff (Fumis et al. 2017). The literature demonstrates repeatedly that delivering care for patients in the ICU against their stated wishes or when clinicians perceive it to be non-beneficial are primary sources of moral distress among ICU clinicians, and especially nurses. In both of the aforementioned cases, moral distress was described by clinicians when the burdens of ongoing care were felt to be disproportional to the observable benefit. However, when the patient's preferences were elicited, it became clear that continued aggressive intervention was goal-concordant, even if the chance of recovery was small. In both cases, the patients were able to communicate that they wished to keep trying if the alternative was death. Once the alignment between the current plan of care and the patient's preferences was evident, the ICU teams in both instances felt relieved, and the morale improved dramatically.

The cases described above illustrate a common yet often insufficiently addressed phenomenon involving palpable tension and deeply emotional response to the perceptions of inappropriate care, resulting in interpersonal and personal strife. This dynamic arises from the complex relationships between ICU physicians, nurses, families and patients when there is uncertainty of prognosis and patient autonomy. The perception of the 'inappropriateness' of aggressive ICU care in a critically ill patient when the burden of treatment may outweigh the benefit, can cause a great amount of guilt for team members and family members alike. When coupled with an often-hierarchal system where nurses may feel unempowered to make decisions, trainees may feel unsafe or unsupported speaking up or raising concern, families may feel that they lack enough control or information to make informed decisions, and senior physicians may be faced with the dilemma of offering non-beneficial clinical care without the express consent of the patient, significant burnout and interpersonal strife can occur. When the patient's own preferences, values, and wishes are not known, or when they are not in alignment with the family's or the ICU clinician's own preconceived values and opinions in the given context, there can be discord leading to moral distress (Kon et al. 2016). ICU clinicians, and especially nurses, are staunch patient advocates, upholding their autonomy-based obligations to the patient in preserving the patient's respect and dignity (Nsiah et al. 2019). When care decisions are made that make upholding these values challenging, moral distress and general discord can result. As both cases demonstrate, the ICU physicians and nurses believed that the complex, protracted, and burdensome ICU courses of both patients were unlikely to reflect their true preferences, and that a reasonable person would likely choose to pursue limitations of life-sustaining treatment and comfort-focused care (Abbasinia et al. 2020). Clinicians at the point of care are confronted with bed sores, protruding tubes, grimaces with turning and repositioning, recurrent infections and secretions, and invasive artificial

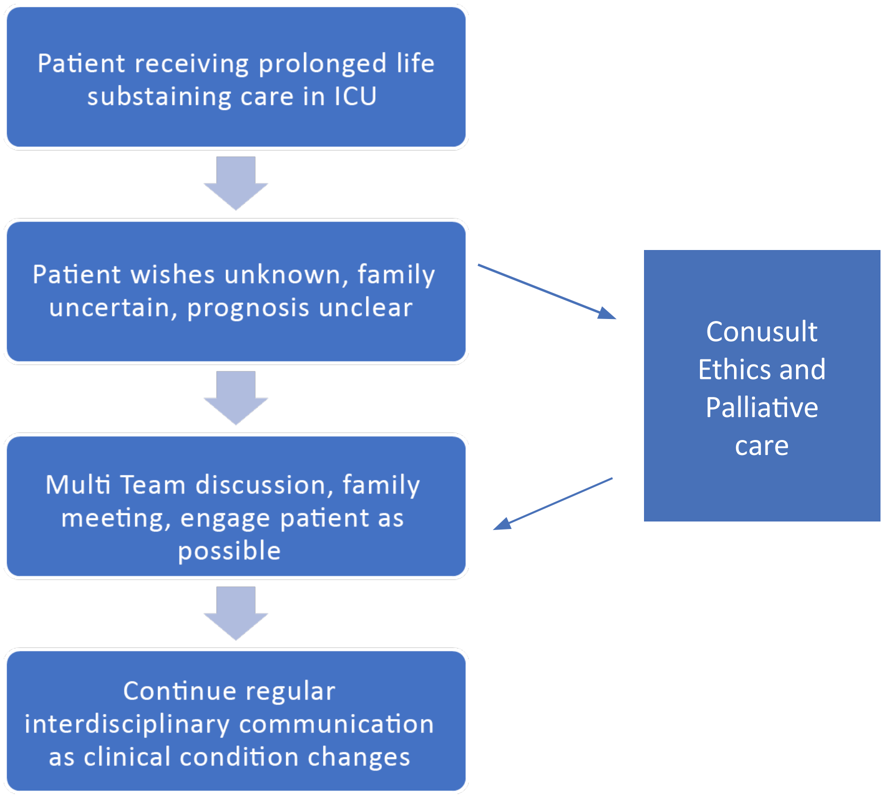

Figure 1. When a patient is receiving prolonged life-sustaining care

nutrition and hydration. In this context, with limited improvement and frequent setbacks, clinicians may assess this to be a burden out of proportion to the benefit of therapy. For them, the slow improvements are not as visible as the daily discomfort they encounter during patient care.

Further, within a close group of caregivers, a groupthink can develop where the tendency is for people to conform to the beliefs of the entire group, often verified by confirmation bias (Saposnik et al. 2016). Previous experiences of moral distress can result in "moral residue" leading clinicians to become quickly distressed again by similar-seeming cases (Epstein and Hamric 2013). If a patient is unable to express their own preferences, the prevailing assessment of the group may be implicitly assumed to represent the goals of the patient, absent evidence to the contrary. Even with robust discussion with surrogate decision-makers, developing a "substituted judgment" of what the patient would choose is challenging, and the values that are used in shared decision-making are quite subjective (Chavira et al. 2022). Very few caregivers, including family, would actually know what the patient would truly want in the given circumstance. Research demonstrates that the accuracy of surrogate decision makers is little better than chance (Shalowitz et al. 2006). Advanced care directives can give broad guidance, but again lack specificity and context. Given the importance of ascertaining patient preferences and the difficulty in uncovering this information in the ICU context, it is no wonder that moral distress is such a commonly occurring experience.

The article explores how people might form judgments or emotional reactions that are not fully grounded in rational or thoughtful reasoning but instead are more instinctual and based in emotion. This could suggest that the responses are more reactive, based on immediate feelings or assumptions, rather than carefully considered viewpoints informed by accurate information. Indeed, moral distress is often mitigated through carefully orchestrated opportunities for communication, where perspective-taking can occur. In most cases, as we highlight here, the clinical care need not change for the experience of moral distress to diminish; this suggests that affective responses to high-stress environments can be tempered with a more complete set of facts and an understanding of the full range of perspectives. **Figure 1** describes a possible algorithm for clinicians to consider when such situations arise.

In the cases described above, the moral distress felt by the ICU teams was quickly alleviated when the patients themselves voiced their preferences. In both cases, the care being delivered was assessed to be burdensome, yet still medically indicated by surrogates and clinicians. As such, the values of the patients were vital in deciding whether the proportionality principle favoured continuing life-sustaining care. In both instances, the actual plan of care and related interventions did not change once the patient's preferences were elicited. What changed was the clinical team's perception of these interventions. Addressing morally distressing cases in a timely manner, as well as reflecting on behavioural patterns, either through ethics or palliative care consultation, interdisciplinary debriefing, or ethics rounds, can minimise the escalation of distress and potential groupthink (Cocker and Joss 2016). These cases highlight the way obtaining views from ICU patients, when possible, can have an immense alleviating effect on the morale and quality of care delivered to the patient and mitigate moral distress and burnout (Batson et al. 1987). While it is, of course, not always possible to involve the patient in decision-making in real-time in the ICU, these cases demonstrate that, in the instances when it becomes possible, it is invaluable.

Conclusion

The cases described above illustrate the way the lack of timely communication and uncertainty regarding the patients' wishes can create moral distress. Leadership and ICU clinicians should strive to improve patient-centred communication, especially in cases where the burdens of life-sustaining intervention are substantial. The first-person perspective of the patient, when obtainable, can mitigate significant distress. In addition, physical and mental rest, and systems that can support these aims, are crucial for people delivering intense and burdensome care in the ICU.

Conflict of Interest

None.

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Future Directions in Critical Care Research: Autophagy and Muscle Hacking

One of the many facets of critical illness is myopathy, which is associated with increased morbidity and mortality. Here, we delve into the metabolic drivers of muscle wasting, its overlap with frailty syndromes, and how insights into the pathways involved may unveil po-tential therapeutic strategies.

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Critical care reflects gruelling illness. Medium to long-term outcomes also reflect a degradation in quality of life, by multiple measures. For example, patients report disruption to sleep, mood, exercise tolerance, levels of independence, loss or reduced employment, increased care burden and experience higher rates of hospital admission and health limitations than non-ICU controls (Hill et al. 2016). Muscle loss is marked and seriously impairs patients' respiratory wean in addition to ongoing rehabilitation, in turn affecting what their optimal functional outcomes could be.

Historically and culturally, the metabolic failure component of critical illness has been omitted from trials and general interest areas, because it is complicated and realistically difficult to find targeted therapies for. Enteral nutrition, the most studied intervention, has witnessed repeated rounds of failure to improve muscle strength despite increased protein supplementation (Bels et al. 2024).

This is a meander through mechanisms for muscle loss in critical illness, the evolutionary purpose of skeletal muscle sacrifice, and what strategies or screening criteria we can consider when prognosticating what survival from critical illness looks like for patients and their families. There is also now a wide range of potential therapies that we can borrow from sister specialties to offset some of these changes.

What is Autophagy?

Autophagy is a key cellular pathway that recycles cell components to maintain rigorous quality control. The pathway transports cytoplasmic waste or unwanted products to a lysosome for degradation. The most researched form of autophagy is macroautophagy, where a double-membraned structure expands and encloses cytosolic components within an autophagosome. This vesicle merges with a lysosome to become an autolysosome (Bels et al. 2024). Within the autolysosome, proteolytic, lipolytic and glycolytic enzymes divide the sequestered content, allowing the cell to recycle the resulting breakdown products.

Autophagy is finely regulated by a complex system of regulatory mediators and signalling pathways (Fazzini et al. 2023). Human cells have tonic autophagy activity, which is upregulated at times of cellular stress such as insufficient energy, deficient nutrient stores, or following accumulation of waste products.

Beyond its role in large-scale waste product removal, autophagy can selectively target misfolded proteins such as those associated with Alzheimer's disease. It is also vital for preventing time and inflammation-associated damage to tempestuous cell structures such as mitochondria, from which free oxygen radical leak is an ever-present threat.

Successful autophagy is necessary to prevent ageing – failure of this mechanism occurs in chronic illness and frailty. It is also requisite for repairing organs after illness – the bridge between life/organ support, and recovery. It may also represent a ‘biohack’ method of protecting or regenerating muscle after critical illness – the holy grail of critical care.

IL-6 Pathway

How is muscle lost in critical illness

There are multiple pathways through which muscle is lost during inflammation/infection/illness. Two notable pathways include the IL-6 cytokine pathway and the kynurenine pathway. IL-6 is a sentinel cytokine that, in small doses, is released in exercise and can contribute to muscle growth and integrity. However, in the thresholds reached in chronic and acute illness, there are multiple central and peripheral routes by which IL-6 is pathological. Drugs that inhibit this molecule are protective against sarcopenia (Hill et al. 2016).

Kyurenine Pathway

The Kyurenine pathway represents the biological pathway by which 95% of tryptophan, the amino acid, is degraded. The pathway has recently been identified as significant for immune function and muscle atrophy. Tryptophan is significant because it contains a moiety called an indole ring, with niche biological activity. An enzyme called IDO-1 helps regulate this breakdown. A notable number of cell types are dependent on tryptophan as a metabolic substrate for such reasons – T cells being an excellent example (Stone and Williams 2023). Their proliferation is heavily affected by tryptophan availability. Thus, there is a direct amino acid sacrifice to favour a T cell immune response. In addition, the common endpoint of the kyurenine pathway is NAD+, which

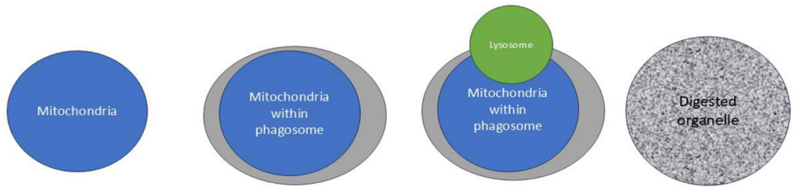

Figure 1. Autophagosome consuming a mitochondrion

feeds directly into the TCA cycle and perturbs mitochondrial activity. Moreover, it modifies DNA expression via the action of sirtuins – this can broadly set cells into a 'feast or famine' state where they grow or repair accordingly.

Why is Skeletal Muscle Sacrificed in Critical Illness?

It is important to remember that muscle is a dynamic living tissue with metabolic roles in addition to biomechanical ones. Locomotion is not a priority in severe illness – be it predator-prey identification, or sedate sickness behaviour; most organisms will slow or still under significant biological stress. It is emerging that beyond the obvious cardiovascular benefits of muscle mass and exercise, immunometabolic roles exist; affected by ageing, frailty and chronic inflammation. Sarcopenia is a direct symptom of frailty and can be considered 'muscle failure' in all its forms, just as heart or renal failure impacts overall physical function.

Muscle is deliberately lost in an acute stress response – and we know this from repeated studies identifying wasting of quadriceps femoris or diaphragmatic loss during mechanical ventilation (Fazzini et al. 2023). It is hard to limit or prevent – countless trials again into supplementation, high protein, rehabilitation, demonstrate a catabolic stress response that is not offset by increasing supply alone. There is a deliberate bodily choice to sacrifice muscle tissue because it feeds and regulates the immune response. IL-6 cytokines and the tryptophan pathway are just two examples of changes induced by inflammation that lead to muscle atrophy for the 'greater good'.

How is This Affected by Frailty?

The proportion of elderly patients admitted to intensive care is increasing, with up to 40% presenting with pre-existing frailty (Moïsi et al. 2024). Frailty itself is an independent risk factor in the intensive care setting (Moïsi et al. 2024), associated with increased all-cause mortality and functional decline.

Frailty is typically scored in the UK with the Rockwood Frailty Score. Any coordinate of frailty correlates well with muscle bulk (e.g. measured in the psoas on imaging) (Ng et al. 2023), grip strength (Spiegowski et al. 2022), and in laparotomies, biomarkers affecting the transport of metabolic intermediates (Ng et al. 2023).

Given this association, an increased proportion of critical care patients will have signs of frailty, diminished muscle mass and a reduced physiological reserve

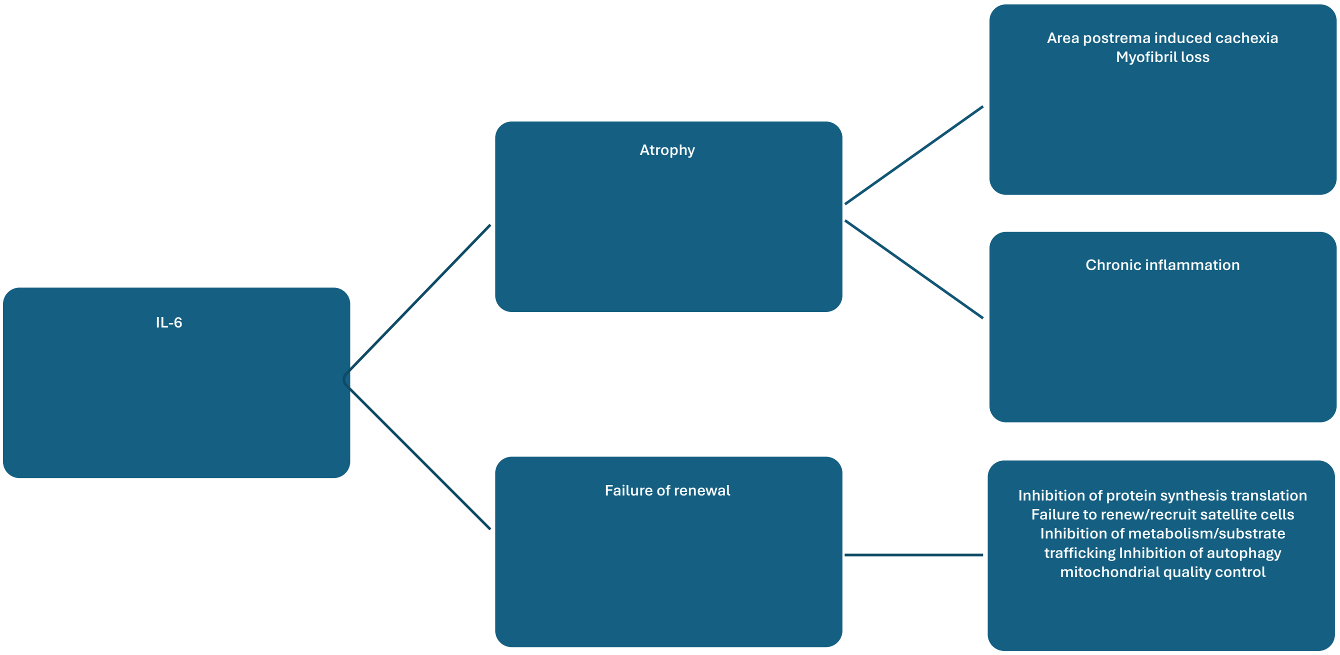

Figure 2. Mechanisms by which IL-6 is enlisted to affect muscle

to adapt to the catabolic state of critical illness. Furthermore, frailty is an independent risk factor for the degree of muscle loss in intensive care, when rectus femoris cross-sectional area measurements were performed seven days following intensive care admission. This suggests that the frail population not only start with a lower baseline muscle function but also suffer from accelerated losses in critical illness.

What are Emerging Therapies?

There are a myriad of emerging therapies, many of which are already in use – for example, flozins – which have a therapeutic effect on metabolic ageing and muscle mass (Conte et al. 2025). IL-6 antagonists, with potential niche use within subtypes of critically ill patients, also reduce muscle loss (Wada et al. 2017).Other experimental treatments may derive from novel discoveries – for example, clock genes regulating circadian cell cogwork are heavily expressed in skeletal muscle (Lau et al. 2004).

Conclusion

It is clear when examining the effects of inflammation and metabolism that muscle sacrifice or signalling has an essential role to play. This is underpinned by studies demonstrating the intractable nature of muscle atrophy in critical illness and brings us to ask, how then, do we offset this parlous condition with the knowledge that we have now? Rivetingly, it may be the expansive network of diabetes research that can own this metabolic mayhem or hacking systems such as autophagy to delay or reduce frailty phenotypes in the first instance.

Conflict of Interest

None.

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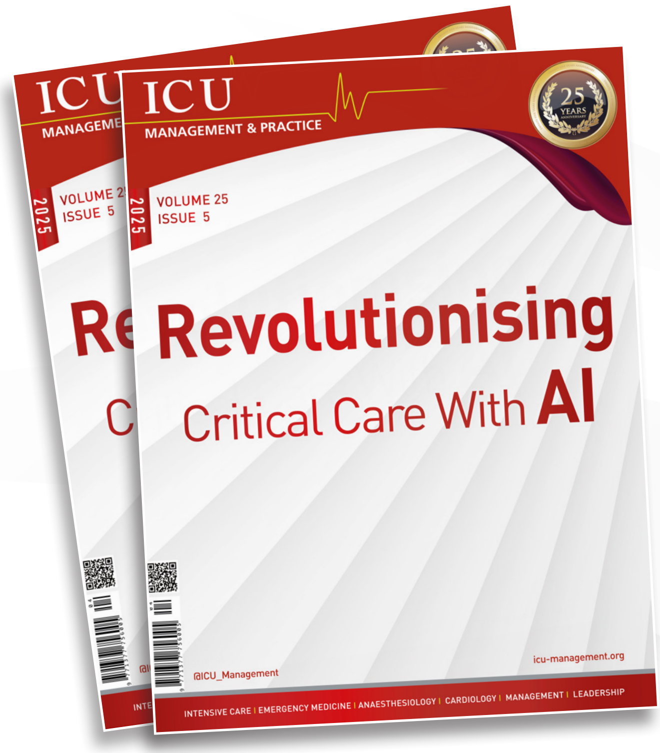
WHAT'S NEXT?



COVER STORY: Revolutionising Critical Care With AI

This issue will explore the transformative potential of Artificial Intelligence (AI) in the ICU. AI is revolutionising care by improving diagnosis, monitoring, and treatment decisions. Our contributors will focus on how AI technologies can enhance patient outcomes, optimise workflows, and reshape the future of ICU management. They will present a forward-thinking approach while keeping a focus on the real-world impact of AI.

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