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Artificial Intelligence in the ICU

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Artificial Intelligence in the ICU

Jean-Louis Vincent

Editor-in-Chief
ICU Management & Practice
Professor
Department of Intensive Care
Erasme Hospital
Université libre de Bruxelles
Brussels, Belgium

JLVincent@icu-management.org

@ICU_Management

Artificial Intelligence (AI) is making significant strides in healthcare, and its application in critical care is no exception. AI technologies can potentially enhance patient care, improve clinical outcomes, and streamline healthcare operations in the ICU.

There are numerous ways in which AI can be effectively utilised in the ICU. AI algorithms can analyse patient data in real-time to detect subtle changes that may indicate deterioration, thus enabling timely interventions. AI can predict patient outcomes, such as the likelihood of infections, sepsis, or readmission, by analysing historical data and current patient information. AI can assist radiologists and clinicians in interpreting medical images and can facilitate the detection of abnormalities, tumours, and other critical findings. AI can optimise drug dosing regimens based on patient-specific factors and help reduce medication errors. AI can help allocate resources efficiently by predicting patient admission rates, ICU bed availability, and staffing needs. AI can help with research by automating data collection and analysis tasks and allowing researchers to focus on the clinical aspect of research findings. AI can enhance EHR systems by automating data entry, extracting valuable insights from unstructured clinical notes, and improving data integrity. AI can aid post-ICU care, monitor patients' progress, and offer personalised recommendations.

While all these uses of AI can benefit ICUs, it is also essential to ensure healthcare systems are prepared to use AI technologies properly. There should be appropriate measures to ensure patient privacy. It is also important to ensure that AI systems are used as decision-support tools rather than replacements for clinical judgment. Also, critical care providers need training and education to utilise AI technologies effectively.

AI has the potential to revolutionise the ICU by improving patient care, reducing costs, and enhancing the efficiency of healthcare delivery. However, careful planning, regulation, and ethical considerations are essential to ensure its effective implementation.

In this issue, our contributors discuss the benefits of AI and technology and how advanced tools and systems can enable critical care clinicians to manage the complex demands of care, have access to insightful data, streamline workflows, reduce workload and give more time to patients.

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

Jean-Louis Vincent

ARTIFICIAL INTELLIGENCE IN THE ICU

POINT-OF-VIEW

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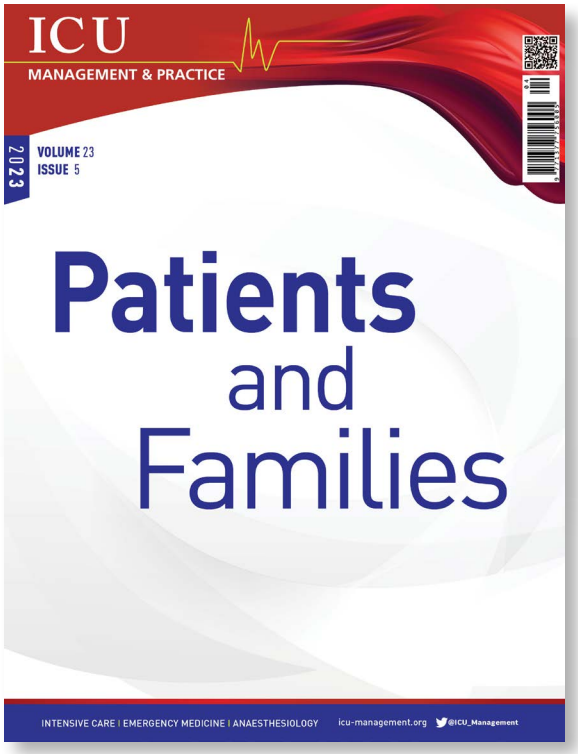
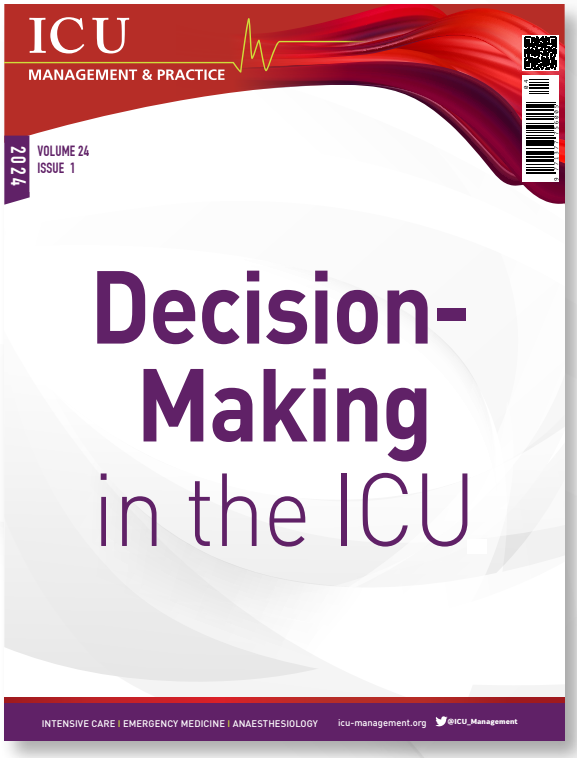


COVER STORY: Patients and Families

There has been an increased focus on ensuring patient and family engagement in critical care. In this issue, our contributors discuss strategies for clinicians to work with patients and families, rationale for patient and family engagement, opportunities to strengthen this engagement, and promoting greater patient and family involvement.



COVER STORY: Decision-Making in the ICU

Critical care practitioners often have to make decisions in high-stress and uncertain situations. In this issue, our contributors explore the decision-making process in the ICU, discuss factors that influence decisions related to critical care treatment and highlight the importance of clear guidelines to help clinicians through the complex decision-making process in critical care.

FOR SUBMISSIONS CONTACT

editorial@icu-management.org

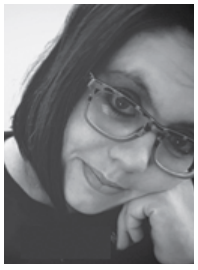
Towards Artificial Intelligence as a Decision Support Tool to Combat AMR in the ICU

Ongoing research and challenges regarding the use of Artificial Intelligence and Machine Learning to leverage data and identify complex interactions to address antimicrobial resistance in the ICU.

Thomas De Corte
Department of Internal Medicine and Pediatrics
Faculty of Medicine and Health Sciences
Ghent University

Department of Intensive Care Medicine
Ghent University Hospital
Ghent, Belgium
thomas.decorte@ugent.be

Jarne Verhaeghe
IDLab
Ghent University - Imec
Ghent, Belgium
jarne.verhaeghe@UGent.be



Femke Ongenae
IDLab
Ghent University - Imec
Ghent, Belgium
femke.ongenae@UGent.be

Sofie Van Hoecke
IDLab
Ghent University - Imec
Ghent, Belgium
sofie.vanhoecke@UGent.be

Jan J De Waele
Department of Internal Medicine and Pediatrics Faculty of Medicine and Health Sciences
Ghent University

Department of Intensive Care Medicine Ghent University Hospital Ghent, Belgium
jan.dewaele@ugent.be

The possibilities of artificial intelligence (AI), and more specifically, machine learning (ML), are being researched across almost all domains of medicine, and the field of intensive care medicine is certainly no exception. Several factors contribute to the intensive care unit (ICU) being one of the focal points of AI/ML research. Intensive care was one of the earliest adaptors of the electronic health record (EHR) (Varun and Marik 2002), making data readily available. A vast amount of diverse data is generated for an individual patient during clinical care, resulting in 6.000–30.000 routinely collected healthcare data points per ICU patient per day. As this data is mostly structured and annotated, it is very suitable for training ML models. Although these datasets still need to be unbolted to be usable for (big) data research in many cases, several ready-to-use publicly available datasets extracted from information in the EHR already exist to date (Sauer et al. 2022; Jin et al. 2023; Rodemund et al. 2023). At the same time, large nationwide data-sharing initiatives are being set up to unlock even more routinely collected healthcare data for clinicians, researchers and data scientists alike. As such, the data-rich ICU environment has and is developing the prerequisites to further enable (big) data research. The expectations for the clinical impact of AI have risen alongside the number of published studies. It is generally expected that AI will harbour benefits for patients as well as clinicians and the whole of society (Topol 2019). This is reflected in the variety of study aims for which AI has been investigated in published studies so far (van de Sande et al. 2021).

From a societal, patient, and research perspective, antimicrobial resistance (AMR) is an interesting research area for AI/ML, as it remains one of the biggest threats to global healthcare. According to the O'Neill report, it is estimated that by 2050, the death toll due to AMR could rise to 10 million lives a year worldwide (O'Neill 2023). AMR is particularly relevant for the ICU patient, as several AMR drivers (e.g., high selective pressure due to frequent antimicrobial use) are present in the ICU, and AMR infections can heavily impact a patient's ICU morbidity and mortality. One way of tackling the increase of AMR is by antimicrobial stewardship, which aims to combat antibiotic resistance by improving antimicrobial prescribing and use (CDC 2022). Antimicrobial stewardship comprises several interventions that can be performed during every step of antimicrobial therapy, and several use cases have been researched to explore how software and/or AI might aid in 'the rights' of antimicrobial prescription: the right drug at the right time and the right dose for the right patient (Grissinger 2010).

Identifying the right ICU patient means identifying the ICU patient that has a higher probability of infection than for inflammation. At present, clinicians use a combination of clinical gestalt and clinical decision rules when making this discrimination by incorporating information from the medical history, clinical examination, technical investigations, and laboratory and microbiological information. Research has shown that differentiating infection from inflammation poses a challenge for ICU physicians, especially when the infection is defined by consensus criteria, for instance, in the case of sepsis or ventilated-associated

pneumonia (Lopansri et al. 2019; Stevens et al. 2014). Parallel to the continuous search for the perfect discriminator of infection and inflammation, researchers have also turned to AI/ML to see if routinely collected healthcare data can be leveraged, with some interesting results. For example, models have been developed that try to discriminate bacterial from non-bacterial sepsis in children using eight routinely available parameters, which outperform currently available biomarkers (Lamping et al. 2018). Another study developed ML models to aid in the diagnosis of bacterial infection in COVID-19 patients, which are currently being tested in clinical practice (Rawson et al. 2021).

Once the right patient is identified, prescribing the correct antimicrobial entails assessing the possible causative pathogens and their potential resistance profile. While

Challenge	Key contributors	Proposed mitigation strategy
Sampling bias	• An insufficient amount of the pathogen might be sampled and cultured to test for resistance, leading to unrepresentative datasets.	• Prospectively constructed datasets using uniform sampling approaches.
Colonisation versus infection	• A cultured organism, especially from a non-sterile culture site, can be either a coloniser or a true pathogen.	• Prospectively constructed dataset with clinical annotation.
Heterogeneity and temporality of resistance mechanisms	• Resistance can be classified as natural resistance (either intrinsic or induced) or acquired resistance. • Resistance can be permanent or temporary. • Cross-resistance and collateral sensitivity can occur.	• Incorporation of domain knowledge in model development to overcome the limitation of data-driven methods regarding infrequently encountered mechanisms.
Ground truth	• Epidemiological cut-off values to classify resistance differ according to the issuing institution and are subject to change. • The two currently most frequently used methods to determine resistance (disk diffusion and broth microdilution) have a certain margin of error, with the possibility of false positive or false negative classification of an organism.	• Standardisation of susceptibility definitions. • Innovative technology to optimise pathogen susceptibility testing.
Informative sampling in routinely collected healthcare data	• The collection of certain types of information is dependent on a patient's past and current characteristics, administered treatments and changes in health state. Information is, therefore, not collected randomly or at fixed time points.	• Prospectively constructed datasets using uniform sampling approaches.
Incomplete datasets	• Several relevant data points from within the ICU (e.g., linkage of health care providers to patients to enable detection of AMR transmission via health care providers) or from outside the ICU (e.g., results from cultures taken in the community) are often not available in current datasets. • Measures taken against or during outbreaks of AMR are often not available in a machine-readable format in the EHR.	• Prospectively constructed digital datasets incorporating all relevant information. • Linkage with information from outside the hospital patient data management system.
Ecology differences	Differences in local microbiological ecology and outbreaks of AMR can lead to: • Data imbalance during model development. • Dataset shift during model implementation.	• Attention to data imbalance during model development. • Prospective evaluation of models. • Monitoring of dataset shift after deployment.

Table 1. Challenges for the development of AI/ML prediction models for AMR

routine colonisation cultures in the absence of infection are performed in many patients during their ICU stay and are often used when prescribing antimicrobials, the value of these cultures to guide antimicrobial therapy during a subsequent infection is subject of debate (Bredin et al. 2022; Barbier et al. 2016). Over the years, several risk factors have been identified that are linked to antimicrobial resistance (De Waele et al. 2018). Based on these risk factors, clinical risk scores to predict the presence of AMR are being developed and tested but have not yet achieved widespread implementation (Burillo et al. 2019; Boyd et al. 2020). For this field as well, AI and routinely collected healthcare data are combined to fill a clinical need (Martínez-Agüero et al. 2019; Pascual-Sánchez et al. 2020). Although promising, the results of these developed models have not yet been tested in clinical practice. Besides predicting infections with AMR organisms, expediting the identification of AMR organisms after obtaining a microbiological sample is another strategy to optimise antimicrobial prescribing. To this end, a variety of ML models combined with various phenotypic and genotypic resistance identification techniques for a range of sample types and organisms are being researched. Some models try to predict resistance based solely on a combination

of limited microbiological (e.g., type of sample and gram stain) and demographic data (e.g., age and gender), while others are directly incorporated into the sample analysis flow of certain techniques such as liquid chromatography with tandem mass spectrometry or Raman spectroscopy (Feretzakis et al. 2020; Roux-Dalvai et al. 2019; Ho et al. 2019).

As demonstrated by these examples, it is clear that the interest in applying AI/ML to the AMR domain is slowly growing. A recent review by Farhat et al. (2016) identified 676 AMR and AI/ML-specific publications, the majority (78.7%) being empirical papers and most of them being published after 2018, which is indicative of the juvenility of this nascent research domain. Despite the recency of this field, some research, such as incorporating AI/ML methods to augment and expedite current AMR diagnostic techniques, is envisioned to swiftly find its way into clinical practice once it has been thoroughly tested. Other research, such as predicting AMR from routinely collected healthcare data, might prove to be a bigger challenge to develop and implement.

We identified seven main challenges for predicting AMR using AI/ML and routinely collected healthcare data. All seven are summarised in **Table 1.** For development, a first challenge is the potential sampling bias in routinely collected healthcare data. During clinical care, information is often not recorded on fixed time points nor randomly but only informatively, i.e., the collection of certain types of information is dependent on a patient's past and current characteristics, administered treatments and changes in health state (Goldstein et al. 2016). In the case of AMR, for example, blood cultures will not routinely be drawn but only when there is a reason to do so. This might hinder the development of AMR prediction models using routinely collected healthcare data as they might not provide a proper AMR baseline status and warrants the development of prospectively designed use case-specific databases to avoid biases. Additionally, antimicrobial resistance is characterised by both intrinsic resistance (i.e., resistance that is universally expressed by a species to a certain antimicrobial, independent of previous antibiotic exposure, and not related to horizontal gene transfer) and induced resistance (i.e., resistance induced by antibiotic exposure or horizontal gene transfer) (Reygaert 2018). To complicate things even further, varying degrees of cross-resistance (when a single molecular mechanism induces resistance to multiple antimicrobial agents) or collateral sensitivity (when a single molecular mechanism induces susceptibility to multiple antimicrobial agents) can occur (Colclough et al. 2019). Adding to this complexity is the fact that AMR pathogens can spread across and within wards due to horizontal transmission, often with the caregivers as an intermediate. Purely data-driven ML models might not be able to identify these specific instances, as these do not occur frequently, and therefore, the necessary data to identify these relationships are often not present in routinely collected healthcare datasets. Alternative methods, such as hybrid AI or incorporating domain knowledge into ML, will have to be researched to incorporate these vital pieces of information into model development.

Considering the implementation of prediction models, antimicrobial resistance ecology might prove to be another challenge. As patient populations and patterns of antimicrobial resistance tend to vary between hospitals and between wards in the same hospital, the external validity of developed ML models will have to be

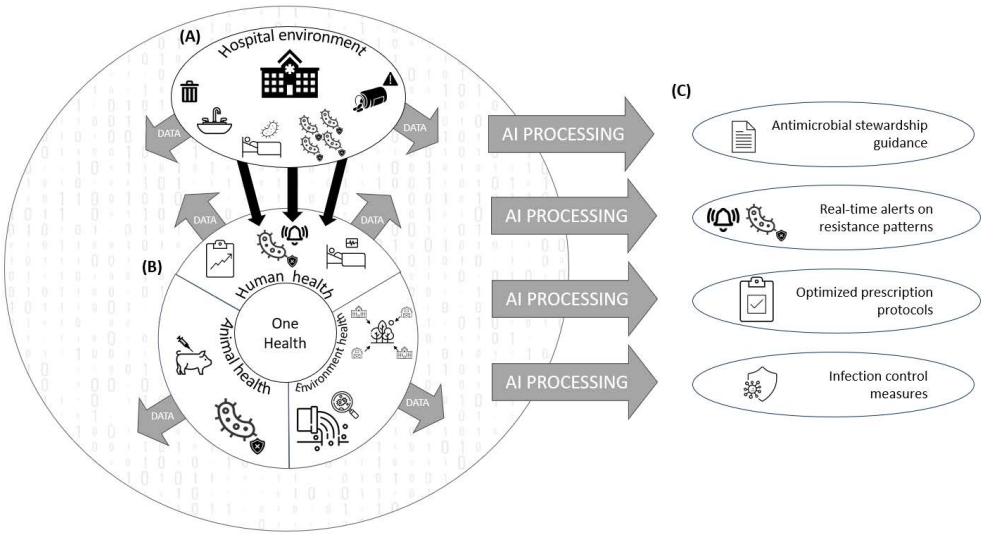


Figure 1. One Health perspective on AMR from an ICU point. Data from (a) the hospital environment (e.g., waste management, outbreak of AMR pathogens and antimicrobial prescriptions) contributes to (b) the human health perspective of the One Health framework, where this information is supplemented with, e.g., antimicrobial prescription patterns in the community and outpatient culture results. Combined with information on animal health (e.g., antimicrobial usage and AMR patterns) and environmental health (e.g., wastewater analysis and impact analysis of healthcare and agriculture on the environment), developed AI/ML models provide integrative support to ICU physicians to combat AMR (c).

carefully evaluated. But even when a model is used in the same ward as where it was developed, validity of the predictions should be carefully monitored, as outbreaks or horizontal transmission can quickly induce a change in local ecology, which in turn can lead to bias and thus malfunctioning of the prediction model due to a discrepancy between the population the model is used on and the population the model was developed on (Finlayson et al. 2021).

Finally, to be able to fully leverage AI/ML in the AMR domain, information will have to be included from outside the boundaries of the ICU. Antimicrobial treatments that were given by general practitioners and culture results from outside the hospital are just two examples of relevant information that can contribute to AMR research. Additionally, as several non-medical factors influence the occurrence of AMR, occupational and environmental information from other sources might also prove to be useful. Integrating all these different information sources will require data from these sources to be findable, accessible, interoperable and reusable (FAIR), as well as a more holistic approach to AMR from clinicians and researchers. Only then will we truly be able to approach antimicrobial resistance from a One Health perspective **(Figure 1).**

In summary, the possibility of AI and ML to leverage vast amount of data to identify complex interactions shows promise to address AMR in the ICU and support antimicrobial stewardship. Possible applications include discriminating inflammation from infection, optimising antimicrobial use, including empirical choices and dose selection, and predicting AMR pathogen involvement in acute infections. However, developing and implementing AMR prediction models in the ICU using a data-driven approach with routinely collected healthcare data poses several challenges due to, inter alia, informative data sampling and the intricacies of antimicrobial resistance. Other strategies, such as the development of goal-specific datasets and the inclusion of domain knowledge in model development, will need to be explored to overcome these issues. Ultimately, to enable a comprehensive AI-based approach to AMR from a "One Health" perspective, integration of diverse data sources beyond the ICU will be crucial.

Conflict of Interest

None.

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Cardiovascular Management in Sepsis: Improving Cardiac and Vascular Functions

Vasopressin and landiolol are critical therapies for ensuring the vascular and cardiac systems are as close to optimal conditions as possible during septic shock. Better cardiovascular management in septic shock can help improve septic shock management.

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection (Singer et al. 2016). Septic shock is defined as a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality. The progression of sepsis is typically measured using the Sequential Organ Failure Assessment (SOFA) Score (Vincent et al. 1996) or a 3-parameter qSOFA version (Koch et al. 2020), with cardiovascular assessment as a key parameter of both scales. In patients with sepsis, the amount of time spent continuously below an MAP threshold of 65 mmHg is a strong predictor of mortality, with each additional 2-hour increment in the longest episode under threshold associated with a progressive increase in mortality rate (Vincent et al. 2018). Accordingly, the Surviving Sepsis Campaign Guidelines (SSCG) recommend intravascular fluid administration (using crystalloids) as the first step to counteract hypotension in septic patients (Evans et al. 2021).

Hypotension Refractory to Initial Fluid Resuscitation

When fluid administration alone is not sufficient to achieve target MAP, vasopressor administration should be initiated to resolve hypotension (Rhodes et al. 2017). Early administration of vasopressor (at less than six hours from initial hypotension) is critical to avoid prolonged hypotension and irreversible damage of vital organs due to low perfusion. The SSCG recommend norepinephrine as the first-line vasopressor for hypotension refractory to initial fluid resuscitation to maintain MAP ≥65 mm Hg (Evans et al. 2021). Septic shock patients are clinically identified by a requirement for vasopressor therapy to maintain a MAP of ≥65 mm Hg and serum lactate level >2 mmol/L (>18 mg/dL) in the absence of hypovolaemia (Singer et al. 2016). Norepinephrine, a catecholamine, activates the α1 and β1 adrenergic receptors and has a minimal effect on heart rate (Evans et al. 2021). Early vasopressor initiation has been reported to increase MAP, shorten the duration of hypotension and thereby improve vital organ perfusion and decrease serum lactate levels, resulting in better patient outcomes and decreased mortality rates (Bai et al. 2014; Colon Hidalgo et al. 2020).

Catecholamine Refractory Septic Shock

However, some patients become catecholamine refractory, suffering from impaired vascular responsiveness to catecholamines due to downregulation or decoupling of α1 adrenergic receptors. Persistent hypotension, despite norepinephrine administration, while the patient has adequate cardiac output and is non-responsive to fluids, is indicative of catecholamine refractory septic shock (Jentzer and Hollenberg 2021). The SSCG state that for adults with septic shock on norepinephrine with inadequate MAP levels, it is suggested to add vasopressin instead of escalating the dose of norepinephrine (Evans et al. 2021). Hence, the use of a second-line vasopressor with an alternative mode of action is recommended to increase vascular tone. It has been proposed that an early combination of moderate doses of multiple vasopressors with complementary mechanisms of action may avoid the toxicity associated with high doses of a single agent (Jentzer and Hollenberg 2021).

Vasopressin is a non-catecholamine endogenous peptide hormone which activates V1 receptors located on the vascular smooth muscles, resulting in increased vascular tone and increased arterial blood pressure. Vasopressin is usually started (at a dose of 0.01-0.03 IU/min) when the dose of norepinephrine is in the range of 0.25–0.5 μg/kg/min (Evans et al. 2021). The combined infusion of vasopressin and norepinephrine can increase MAP in catecholamine refractory (resistant) septic shock, where increasing MAP with norepinephrine alone is not possible (Dünser et al. 2003). Furthermore, by using vasopressin, the norepinephrine dosage can be reduced while maintaining MAP (Evans et al. 2021; Russell 2011). Adverse effects of norepinephrine/catecholamines include myocardial ischaemia and arrhythmia, hence by reducing the requirement for catecholamines, vasopressin decreases the stimulation of arrhythmogenic myocardial β1-receptors and associated myocardial oxygen demand (McIntyre et al. 2018). The positive outcomes from early administration of vasopressin in septic shock patients include a reduced noradrenaline requirement (Russell 2011), a lower risk of atrial fibrillation (McIntyre et al. 2018), less catecholamine-induced anti-inflammatory effects (Stolk et al. 2020), a reduction in the need for renal replacement therapy (Gordon et al. 2010; Russell et al. 2008) and less constriction of pulmonary arteries (Currigan et al. 2014). Moreover, there was a significantly higher probability of survival with vasopressin treatment (Russell et al. 2008) in less severe septic shock patients (norepinephrine doses <15 μg/min) and

when initiated at lower lactate levels (Sacha et al. 2018) or at higher arterial-pH (pH≥7.4) levels in patients with sepsis (Bauer et al. 2022) which collectively supports the early combination of vasopressin with norepinephrine during septic shock.

Compensatory Tachycardia

Tachycardia is very common in ICU patients and is associated with poor outcomes in septic shock (Leibovici et al. 2007; Parker et al. 1987). During sepsis, the sympathetic nervous system plays a key role in maintaining cardiac output and blood pressure, which is achieved through changes in heart rate (HR), contractility and vascular tone (Morelli et al. 2016). The baroreflex is a homeostatic mechanism that maintains MAP by adjusting sympathetic tone to antagonise MAP perturbations (Jentzer and Hollenberg 2021). The integrity of the baroreflex function is critical for the maintenance of haemodynamic homeostasis. Accordingly, in the early phases of sepsis, tachycardia becomes a crucial mechanism for compensating the decrease in stroke volume and indicates the efficacy of baroreflex activity (Morelli et al. 2016). Due to the compensatory origin of such tachycardia, adequate volume resuscitation often results in a concomitant decrease in HR. However, compensatory tachycardia may lead to arrhythmia (Boriani et al. 2019), particularly atrial fibrillation (AF). A clear association between sepsis and arrhythmias has been reported, with new-onset AF reported to be common in patients hospitalised with sepsis, compared to those without sepsis (5.9% vs 0.65%: OR 6.82, 95% CI 6.54–7.11) and has been related to an increased risk of in-hospital stroke (2.7-fold) and mortality (Walkey et al. 2011). After an arrhythmia is confirmed, patients with life-threatening haemodynamic instability (i.e. symptomatic hypotension and/or signs of hypoperfusion of vital organs) require immediate electrical cardioversion (ECV) or defibrillation (Dan et al. 2022). In the case of ECV failure or immediate relapse AF, an optimal next step is acute rate control with landiolol, which has been shown to be superior to standard rate-controlling therapy in septic patients who developed AF, with no significant complications related to hypotension or bradycardia (Dan et al. 2022; Okajima et al. 2015).

Non-Compensatory Tachycardia

Despite achieving haemodynamic stability, in many septic shock patients non-compensatory tachycardia may persist even after adequate fluid resuscitation and vasopressor therapy. In septic shock patients, non-compensatory tachycardia persists when the baroreflex response is impaired due to high levels of endogenous and exogenous catecholamines, leading to a hyper-adrenergic state, which is a sign of excessive sympathetic stimulation (Domizi et al. 2020; Dunser and Hasibeder 2009).

"landiolol ensures the safe reduction of heart rate during non-compensatory sinus tachycardia, reducing with it unnecessary sinus activation and cardiac stress"

Patients who are tachycardic 24 hours after commencing norepinephrine infusion have a three-fold higher risk of death than those without tachycardia, which is likely due to an exhausted compensatory reflex mechanism (Domizi et al. 2020). Persistent tachycardia can detrimentally affect the heart by increasing myocardial oxygen demand, reducing diastolic filling, and inducing direct cardiotoxicity (Domizi et al. 2020). Hence, patients with non-compensatory tachycardia persisting at 24 hours after volume resuscitation and commencement of vasopressors represent a particularly severe subset of septic shock patients with very high mortality risk and with few available treatment options.

Landiolol for the Treatment of Non-Compensatory Sinus Tachycardia

Landiolol is a new ultra-short acting (T1/2=4 min), intravenous, super-selective β1 blocker for the treatment of supraventricular tachyarrhythmias such as AF, atrial flutter and non-compensatory sinus tachycardia (SmPC Rapibloc®). Landiolol is a β1-antagonist and, due to its pure S-enantiomer molecular structure (McKee et al. 2014), has minimal effects on blood pressure and inotropy (Shibata et al. 2012), in contrast to esmolol and metoprolol, which cause hypotension and have negative inotropic effects. Landiolol has excellent efficacy even at low doses (Krumpl et al. 2018), with a low volume distribution and low risk of toxicity (Abialbon 2019). Due to inactive metabolites and breakdown by plasma esterases, landiolol has a favourable safety profile for patients with renal and hepatic comorbidities (Yokoyama 2016), with no dose adjustment required for patients with renal dysfunction. Landiolol is metabolised mainly by pseudocholinesterases and carboxylesterases and not by CYP450, with two inactive metabolites (M1 and M2), which are excreted in the urine. Due to the highest cardioselectivity (β1/β2-selectivity = 255:1), landiolol has a minimal impact on respiratory function (Shibata et al. 2012) and β2-receptor-mediated coronary hyperaemia (Maman et al. 2017).

A randomised controlled study of landiolol versus conventional therapy (control group) investigated the efficacy and safety of landiolol for the treatment of sepsis-related tachyarrhythmias in 151 patients (Kakihana et al. 2020). In the study, non-compensatory tachycardia was defined as a heart rate of 100 bpm or more maintained for at least 10 min without a change in catecholamine dose. Furthermore, patients were only enrolled if the investigator confirmed the aforementioned symptoms and signs within 24h before randomisation. The mean dose of landiolol administered during the study period was 4.15 μg/kg per min with a mean cumulative dose per patient of 1526.20 mg (SD 2110.36) over a total infusion time of 94.5 h. In patients treated with landiolol, MAP was achieved, and a heart rate of 60–94 bpm was reported in most patients, with a significantly larger number of patients in the landiolol group achieving a heart rate of 60–94 bpm at 24 h compared to the conventional treatment

in the control group (55% [41 of 75] vs 33% [25 of 75]; p=0.0031), confirming that landiolol treatment was superior to conventional rate control therapy (Kakihana et al. 2020). Landiolol significantly reduced the incidence of new-onset arrhythmia in patients with sepsis-related tachyarrhythmias (Kakihana et al. 2020) compared with conventional treatment (9% [7 of 75] vs 25% [19 of 75]; p=0.015). Moreover, the efficacy and safety of landiolol were unaffected by patient characteristics, such as septic shock, LVEF≤50%, metabolic or respiratory acidosis or acute renal failure, supporting the use of landiolol in a wide range of patients who develop sepsis-related tachyarrhythmias, for whom the prognosis is otherwise poor (Matsuda et al. 2020). Furthermore, patients with respiratory infection receiving landiolol had lower mortality rates at 28 days (Matsuda et al. 2020) than the control group (hazard ratio 0.259; 95% CI 0.071 to 0.943). In a further study of 61 patients with severe sepsis, landiolol was shown to decrease heart rate in septic patients without causing negative effects on haemodynamics (Okajima et al. 2015).

Conclusion

Vasopressin and landiolol are critical therapies for ensuring that both the vascular and cardiac systems are as close to optimal conditions as possible during septic shock. Vasopressin ensures improvement of the vascular response in patients who are catecholamine refractory, with a significant body of evidence indicating that earlier addition of vasopressin leads to better patient outcomes. While landiolol ensures the safe reduction of heart rate during non-compensatory sinus tachycardia, reducing with it unnecessary sinus activation and cardiac stress, also reducing the risk of new-onset atrial fibrillation and improving patient survival. By improving cardiovascular management in septic shock, a further step can be taken in the overall improvement of septic shock management.

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Neonatal Extracorporeal Membrane Oxygenation

Xenios sponsored a lunch symposium at the 16th European Conference on Paediatric and Neonatal Ventilation (EPNV) in Montreux (CH) in May 2023. Matteo Di Nardo (Italy) introduced the audience to extracorporeal membrane oxygenation (ECMO) in neonates. Florian Kipfmüller (Germany) presented current knowledge and his experience with ECMO in neonates with congenital diaphragmatic hernia (CDH). Heleen van Ommen (Netherlands) shared expert knowledge on coagulation management in neonatal ECMO. This article provides an overview of their talksand discusses the use of ECMO in neonates with CDH and persistent pulmonary hypertension (PPHN) in neonates.

ECMO in Neonates: An Overview

Extracorporeal membrane oxygenation (ECMO) is a form of life support used in neonates and children with life-threatening heart and/or lung problems. The use of neonatal ECMO is indicated in newborns with severe and reversible respiratory and/or cardiac failure with an estimated mortality risk of >80% and who are unresponsive to conventional therapies like surfactant, high-frequency oscillatory ventilation (HFOV), inhaled nitric oxide (iNO), medications for pulmonary hypertension, and medications for acute cardiac failure (Stolar et al. 1991).

The most frequent pathologies treated with ECMO in neonates include Meconium Aspiration Syndrome (MAS), Congenital Diaphragmatic Hernia (CDH), Persistent Pulmonary Hypertension in Neonates (PPHN) and sepsis and septic shock. In recent years, there has been an increase in ECMO runs for cardiac disorders. The most frequent pathologies that are reported for cardiac ECMO include Hypoplastic Left Heart Syndrome (HLHS), cyanotic heart disease with decreased pulmonary flow, cyanotic heart disease with increased pulmonary flow, cardiomyopathy and myocarditis (ECLS Registry Report: International Summary 2022).

ECMO Cannulation

The choice between VA (venoarterial) and VV (venovenous) support for neonatal respiratory ECMO relies on various factors, including the patient's condition, the surgeon's expertise, and the capabilities of the medical centre. When considering cannulation methods, both open cut-down exposure for VA and VV cannulation and percutaneous VV cannulation are valid options, provided they are carried out safely by knowledgeable professionals (Wild et al. 2020). Neck cannulation in neonates is the most common access and used with VA ECMO. There are other types of cannulation, but the use of a double-lumen cannula through the neck is common for VV ECMO.

The ECMO circuit must be downsized to fit the neonatal population. Neonates have immature haemostat systems with an increased risk of bleeding and clotting. They also have fragile red blood cells with immature pfHb learning mechanism. ECMO cannulas in children take up a larger portion of the vessel cross-sectional area than in adults. This becomes especially challenging in infants as their femoral vessels are relatively underdeveloped, making cannulation technically difficult or even impossible. Furthermore, younger children have less developed coagulation systems, including lower antithrombin levels. They are also more susceptible to intracranial haemorrhage due to their delicate germinal matrices. As a result, they are at a higher risk of experiencing complications related to inaccurate anticoagulation and mismanagement of blood products (Butt and MacLaren 2016).

Factors that could potentially influence the outcome in case of oxygenator failure include the severity of the illness, the size of the clot relative to the size of the oxygenator, the availability of a primed circuit and the speed and ease with which a new oxygenator can be primed. For neonates, it is important to improve the design of the oxygenators and ECMO circuits and to allow for adjustment of coagulation parameters to reduce the risk of oxygenator failure (Khoshbin et al. 2005).

There is controversy regarding the ideal pump type for neonatal ECMO, and studies show variation in outcomes with centrifugal pumps and roller pumps. A study comparing conventional roller or centrifugal pumps during neonatal VV ECMO found greater odds of survival with conventional roller pumps (Ündar et al. 2023). This could be due to the different circuit designs. The roller pump is occlusive and overcomes downstream resistance, thus maintaining the same flow rate regardless of changes in pressure. The centrifugal pump, on the other hand, is nonocclusive, and the flow rate depends on rotation speed and downstream resistance. This could lead to haemodynamic variation (Ündar et al. 2023). Roller pumps are associated with fewer episodes of haemolysis and mechanical, cardiac and renal complications. Hence, ECMO with roller pumps may be associated with lower mortality in children and fewer complications.

ECMO in Neonates With PPHN/CDH

Outcome data from the ELSO Registry shows that neonatal respiratory ECMO has a 73% survival to discharge rate (ECLS Registry Report: International Summary 2022). CDH is a major indication, with a high mortality of 41%. In CDH, there is a risk of PPHN and changes in the airway and cardiac function (ESLO Registry Data). The survival rate of paediatric patients with CDH treated with ECMO has changed minimally over the last few

Venoarterial ECMO	Venovenous ECMO
Advantages • Direct cardiac support • Excellent oxygen delivery • Rapid stabilisation • Unloading RV • Cannula size	**Advantages** • Normal Pulmonary flow • Myocardial perfusion with oxygenated blood • Precapillary CO_2 removal • Spares carotid artery • Percutaneous cannulation feasible
Disadvantages • Carotid artery ligation • Nonpulsatile blood flow • Risk of cerebral hyperoxia • Lower myocardial oxygen delivery • Increased LV after load • Risk of postcapillary PH	**Disadvantages** • No direct cardiac support • Bicaval cannulae difficult to install • Lower oxygen delivery • Cannula size?

Table 1. ECMO – VV vs VA.

decades. The recent CDH population has demonstrated a higher risk profile than before because prenatal diagnosis enables timely treatment of severe cases who would die otherwise. Overall, clinical evidence suggests that ECMO can help infants with CDH who may not survive otherwise (Yu et al. 2019).

ECMO serves as an emergency treatment that sustains the functioning of the heart and lungs, facilitating recovery from reversible respiratory issues. Neonates with CDH often experience varying levels of insufficient lung function. The UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation (UK Collaborative ECMO Trial Group 1996) demonstrated the advantages of ECMO in neonates compared to continued intensive conventional management, such as improved survival rates and reduced occurrences of neurodevelopmental disabilities at one year of age. ECMO has consistently improved the survival of neonates with respiratory failure, with many growing up to enjoy a comparable quality of life to continued intensive conventional management. Infants diagnosed with CDH frequently due to pulmonary hypertensive crisis are considered suitable candidates for ECMO (Yu et al. 2020).

Cardiac dysfunction is a key component of the clinical presentation of severe CDH. Biventricular dysfunction can reduce cardiac output and shunting, leading to systemic hypotension, acidosis and hypoxaemia. This can further exacerbate cardiac dysfunction and pulmonary vasoconstriction. Therefore, it is important to consider the contribution of this dysfunction and elevated PVR and pulmonary hypoplasia. Early assessment of cardiac function and pulmonary artery pressure is essential to prevent clinical deterioration (Patel et al. 2020). A study by Patel et al. (2019) showed that ventricular dysfunction in CDH patients was associated with increased mortality. Left ventricular dysfunction was associated with more severe consequences than right ventricular dysfunction. Biventricular dysfunction had a 49% mortality, while those with a normal or only right ventricular dysfunction had a 27% mortality. Therefore, early ventricular function should be routinely evaluated in cases of CDH to improve outcomes (Patel et al. 2019).

> **"for neonates, it is important to improve the design of the oxygenators and ECMO circuits and to allow for adjustment of coagulation parameters to reduce the risk of oxygenator failure"**

VA ECMO vs VV ECMO – Which is Superior in CDH patients?

As with all procedures, it is important to consider the advantages and disadvantages of different ECMO cannulation modalities. VA ECMO provides direct cardiac support, excellent oxygen delivery and rapid stabilisation. At the same time, there is a risk of carotid artery ligation, cerebral hyperoxia, lower myocardial oxygen delivery, increased LV afterload and risk of post-capillary pulmonary hypertension. In contrast, VV ECMO helps maintain a normal pulmonary blood flow, ensures myocardial perfusion with oxygenated blood, precapillary CO_2 removal, spares the carotid artery and makes percutaneous cannulation feasible. The disadvantages of this cannulation include no direct cardiac support, lower oxygen delivery, and the bicaval cannula can be difficult to install.

VA ECMO is used more commonly in neonates with CDH than VV ECMO. In a study conducted in 2009 with 4115 neonates requiring ECMO, there was no difference in mortality between VV vs VA (Guner et al. 2009). Renal complica-

tions and on-ECMO inotrope use were more common with VV, while neurologic complications were more common with VA. Overall, the short-term outcomes of VV and VA were comparable (Guner et al. 2009). The same study was repeated in 2018 and revalidated that the mode of ECMO does not significantly affect mortality or severe neurologic injury in infants with CDH (Guner et al. 2018).

In conclusion, there is no data to support one mode over the other. Poor neurological outcome is associated with VA ECMO; cardiac complications are mainly similar between the two approaches. There may also be issues related to experience and availability of equipment. VV cannulation may also be more time-consuming, and a phenotype-based approach may be the future, but more data is needed before giving any recommendations.

Key Points

- Extracorporeal membrane oxygenation (ECMO) is a form of life support used in neonates and children with life-threatening heart and/or lung problems.
- VA ECMO provides direct cardiac support, excellent oxygen delivery and rapid stabilisation.
- VV ECMO helps maintain normal pulmonary blood flow, ensures myocardial perfusion with oxygenated blood, precapillary CO2 removal, spares the carotid artery and makes percutaneous cannulation feasible.
- The choice between VA and VV ECMO relies on various factors, including the patient's condition, the surgeon's expertise, and the capabilities of the medical centre.
- The ECMO circuit must be downsized to fit the neonatal population as they are at a higher risk of experiencing complications.

Disclaimer

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Why Artificial Intelligence is Not Fixing the Problem of Sepsis in the Hospital

The use of Artificial Intelligence in detecting sepsis, AI prediction/detection models and how these healthcare tools need to complement clinical expertise.

Vitaly Herasevich
Professor of Anesthesiology and Medicine
Department of Anesthesiology and Perioperative Medicine
Mayo Clinic
Rochester, Minnesota, USA
vitaly@mayo.edu

Daniel Diedrich
Associate Professor of Anesthesiology
Department of Anesthesiology and Perioperative Medicine
Mayo Clinic
Rochester, Minnesota, USA
diedrich.daniel@mayo.edu

Brian Pickering
Professor of Anesthesiology
Department of Anesthesiology and Perioperative Medicine
Mayo Clinic
Rochester, Minnesota, USA
pickering.brian@mayo.edu

The potential of Artificial Intelligence (AI) in healthcare has generated significant excitement and discussion. However, it's important to distinguish between the theoretical promise and the current state of evidence-based applications. AI has the capacity to drive a paradigm shift in healthcare, but its real-world impact is still being explored and refined. One of the driving factors behind the AI revolution in healthcare is the increasing availability of clinical data, largely attributed to the adoption of Electronic Medical Records (EMRs). EMRs have transformed the way patient data is stored, accessed, and analysed, providing a rich source of information that can be leveraged for various AI applications.

Adoption of Electronic Medical Records was slow. Mayo Clinic in 2005 was only one of 0.1% of USA hospitals with a fully digitised medical record (HIMSS Stage 7 criteria). That advantage allowed our institution to develop one of the first severe sepsis and septic shock electronic surveillance programme in 2006. This was especially important considering the ongoing challenges associated with sepsis management, particularly in hospitals with limited resources. These results represented a major step forward in leveraging EMR data but were far from exceptional, with sensitivity of 48%, specificity of 86%, and a positive predictive value of 32% (Herasevich et al. 2008). Tuning and optimisation of that algorithm over time resulted in improved performance with a sensitivity of 80% and a specificity of 96% (Harrison et al. 2015). When implemented in practice, the developed sepsis sniffer demonstrated a sensitivity of 79.9%, specificity of 76.9%, positive predictive value (PPV) of 27.9%, and negative predictive value (NPV) of 97.2%, which is similar in performance to other systems (Lipatov et al. 2022), highlighting the feasibility of such surveillance tools in the context of EMRs and sepsis management. Although this study didn't demonstrate changes in bundle compliance or hospital mortality, our experience from early EMR adoption to the development of advanced sepsis surveillance systems underscores the iterative nature of healthcare technology development and implementation.

In the intervening years, the adoption of EMRs has spread across the country and has dramatically increased the availability of clinical data, which may be used for research and development of novel informatics tools and the application of AI.

Last year, we published (ICU Management & Practice, Volume 22 - Issue 2, 2022) a manuscript which highlighted the lessons learned from a decade of studying sepsis surveillance and a possible path forward. In this manuscript, we discuss the use of AI in the detection of sepsis.

The concept of prediction in healthcare, especially in terms of disease onset and outcomes, has been a longstanding interest among physicians and other healthcare practitioners. This interest can be traced back to the time of Hippocrates and his famous aphorism "Primum non nocere" (First, do no harm), and can underscore the importance of predicting disease trajectories in an effort to provide effective treatments and thus minimise harm. Sepsis is a particularly challenging condition when it comes to prediction. Its non-specific early symptoms can often lead to delays in recognition and treatment, which in turn can result in poor patient outcomes. The introduction of the concept of Systemic Inflammatory Response Syndrome (SIRS) was a step toward recognising the broader signs of an inflammatory response in sepsis, but this broad definition has introduced challenges for developers trying to develop specific and accurate prediction algorithms.

Approximately 87% of sepsis cases originate outside of the hospital (Rhee et al. 2017), and this emphasises the critical role of the Emergency Department (ED) in the initial diagnosis and management of this condition. Much effort has been placed on devising an accurate sepsis prediction score for ED providers. Different diagnostic criteria for sepsis, such as the Sequential (Sepsis-Related) Organ Failure Assessment

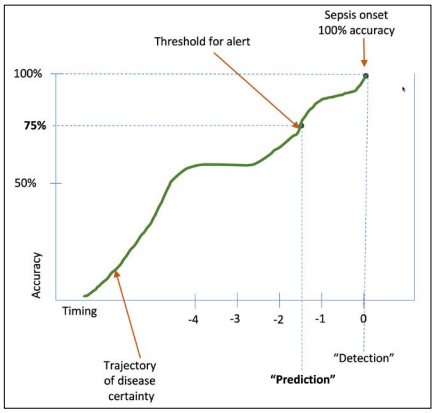

Figure 1. Time "zero" is the onset of disease (sepsis) when that could be predicted/detected with 100% accuracy. Everything earlier is prediction – with different levels of accuracy. The trajectory of disease certainty could have very different shapes.

(qSOFA) score and the Systemic Inflammatory Response Syndrome (SIRS) criteria, have been subject to various studies and evaluations in the ED setting, leading to sometimes conflicting results. One study conducted in two European clinical teaching hospitals in the Netherlands (Mignot-Evers et al.) found that the qSOFA score performed as well as or better than the SIRS criteria for identifying culture-positive sepsis and predicting in-hospital mortality and ICU admission, suggesting that the qSOFA score might be a valuable tool in the ED for stratifying patients' risk and informing clinical decisions. This finding aligns with the growing emphasis on the qSOFA score as a tool for quickly assessing patients at risk of sepsis-related organ dysfunction. A separate study published one year earlier (Gando et al. 2020) found that SIRS criteria had better performance for predicting infection than qSOFA scores in the ED, highlighting the complexity of sepsis diagnosis. It's possible that different patient populations, settings, and factors influence the performance of these criteria. This variability underscores the importance of considering multiple factors, including the specific patient population and the clinical context, when evaluating and applying diagnostic criteria.

These differing results highlight the need for ongoing research and validation of sepsis diagnostic criteria, especially in the ED setting where early and accurate diagnosis is crucial. Additionally, it's important to recognise that clinical assessment and judgment play a significant role alongside these diagnostic tools. The decision-making process should be guided by a combination of clinical experience, available evidence, and the specific needs of each patient. The concept of certainty and accuracy, as well as the practical implications of using AI prediction models, are key considerations when applying these models to real-world healthcare scenarios.

In the context of AI and predictive modelling, the terms "prediction" and "detection" can be seen as points along a continuum of certainty and accuracy. Detection implies a high degree of certainty and accuracy, often approaching 100%. In contrast, prediction involves a range of probabilities or likelihoods of an event occurring, indicating varying levels of certainty **(Figure 1)**. AI experts often quote explainability as the key to usefulness in clinical practice. We would argue that this is less important for acceptability and meaningfulness than the distinction between prediction and detection. In practical terms, for a clinician, the question of when to act boils down to risk versus benefit. AI prediction/detection models in healthcare are tools that should complement clinical expertise. For an AI to be useful, they have to add something to the decision-makers' mental model. They need to reduce cognitive load by parsing data from large volumes of clinical data or to detect patterns and signals in multidimensional data that are difficult for individual clinicians to see in the moment of decision-making. Striking the right balance between accuracy, interpretability, and clinical utility is key. As the field continues to evolve, interdisciplinary collaboration between AI experts and healthcare professionals will be essential to ensure the meaningful integration of these models into the clinical setting.

A critical consideration in the application of AI prediction models in healthcare is the trade-off between accuracy and practical utility. Predicting with 95% accuracy five minutes before the onset of sepsis has very limited practical utility. The same applies to a 12-hour prediction with 25% accuracy. Recent prospective validation of the AL/ML sepsis prediction model from a commercial EMR vendor failed to identify 67% of patients with sepsis and generated an alert for 18% of all hospitalised patients (Wong et al. 2021). Determining what constitutes an acceptable level of accuracy and how early predictions need to be made for meaningful clinical impact is a complex challenge that involves balancing various factors.

1. Acceptable Level of Accuracy: Different settings will have different acceptable levels of accuracy. Sensitivity is important in the home environment through the ED, where the consequences of a missed diagnosis could be devastating. Balancing this against the risks of overtreatment or false positive alert fatigue must be determined with all stakeholders, which will be essential in striking the right balance.

2. Lead Time: Early detection is valuable, but the lead time for predictions must be balanced with accuracy. Predicting an event too far in advance with limited accuracy might not be acceptable. The lead time needed for interventions to meaningfully impact the clinical condition should be used to guide the development of prediction models.

3. Clinical Workflow: The integration of prediction alerts into clinical workflows is vital. If alerts disrupt workflows or lead to alert fatigue, their utility diminishes. Alerts should be timely, actionable, and integrated into the existing care process.

4. Specificity and Sensitivity: It's important to assess both sensitivity (true positive rate) and specificity (true negative rate) of a prediction model. An overly sensitive model might produce numerous false positives, while an overly specific model could miss true positives.

5. Prospective Validation: A model's performance in real-world clinical scenarios might differ from its performance in controlled research settings. Prospective evaluation against gold standard clinical evaluation is essential prior to more widespread implementation.

6. Population Variability: Patient populations can vary, and models should ideally be trained and validated on diverse patient cohorts to ensure generalisability.

7. Continuous Improvement: AI models should undergo continuous improvement based on feedback and real-world performance. Feedback loops that enable refining the model's accuracy and clinical impact are essential. In a related topic, post-market surveillance and reporting should be included with any model deployment. This will ensure that unintended cases of harm resulting from model deployment are picked up early.

Does this mean AI/ML methods are not useful in sepsis prediction? The key to their success lies in developing intelligent and context-aware systems that go beyond simple associative models based on available Electronic Medical Record (EMR) data. While challenges exist, smarter approaches can harness the power of AI to improve sepsis prediction and patient outcomes. Here are some considerations for developing effective AI-driven sepsis prediction systems that we have learned from our experience of building these alerts for over 20 years;

Feature Engineering: Instead of relying solely on raw EMR data, effective sepsis prediction models can benefit from careful feature engineering. This involves partnering with clinicians and selecting relevant patient variables, incorporating time-series data, and considering the mechanisms of sepsis progression. Future generations of AIs (Large language models or generative AI) may have access to such large quantities of data and incorporate powerful new analytics approaches to achieve mechanistic insight without the need for feature engineering, but for now, this is a step we advocate.

Multimodal Data Integration: AI models can be enhanced by integrating multiple data sources beyond EMRs, such as laboratory results, vital signs, imaging data, novel sensors, computer vision, work context, and patient demographics. This broader dataset could be useful in improving the performance of algorithms in real-world clinical situations.

Time-Series Analysis: Sepsis often exhibits dynamic changes over time. Advanced AI methods, like time-series analysis and recurrent neural networks, can capture temporal patterns and trends, allowing for more accurate predictions.

Clinical Context: Incorporating clinical context, such as patient history, co-morbidities, and clinical guidelines, can enhance the predictive power of AI models. This extends to the work setting (home versus ED versus ICU). Context-aware models can calibrate to the operating conditions and offer more meaningful predictions that align with actual clinical scenarios.

Multi-model approach: Combining predictions that take advantage of Boolean logic, multiple AI models or algorithms (ensemble approaches) can improve accuracy and reduce the impact of individual model weaknesses.

Interpretability: Developing models that provide not just predictions but also explanations for those predictions can be useful for stakeholder buy-in, building trust and facilitating shared decision-making.

Continuous Learning: AI models should be designed for continuous learning, adapting to changes in patient populations and healthcare practices over time. A mechanism for automatically capturing clinical insights, health system and patient population outcomes and making these available as training data for the model should be included in the implementation environment. This will facilitate the realisation of a learning health system.

Real-Time Integration: For early sepsis detection, real-time integration with clinical workflows and rapid response systems is essential. This ensures timely interventions and avoids delays in care delivery.

Clinical Validation: Rigorous clinical validation in diverse settings is crucial to demonstrate the effectiveness and reliability of AI-driven sepsis prediction systems.

Human-Machine Collaboration: AI should augment, not replace, clinical expertise. The goal should be to develop models that are implemented in a way that promotes collaboration between AI systems and healthcare professionals.

Taken together with advances in monitoring, data access, computing power and sensor miniaturisation, there is a very high likelihood in the near future that AI-powered clinical digital assistance will be available and used in healthcare settings.

Conflict of Interest

None.

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Artificial Intelligence in Anaesthesia and Critical Care - Temptations and Pitfalls

Frederic Michard
MiCo
Vallamand, Switzerland
frederic.michard@bluewin.ch
@MichardFrederic
michardconsulting.com

Filipe A Gonzalez
Intensive Care Unit
Hospital Garcia de Orta, Almada
University of Lisboa
Portugal
filipeandregonzalez@gmail.com

Patrick Schoettker
Department of Anesthesiology
CHUV
University Hospital Lausanne
Switzerland
patrick.schoettker@chuv.ch

Big data, Artificial Intelligence (AI) and machine learning are buzzwords. In this article, we briefly discuss what they mean for anaesthesiologists and intensivists, focusing on existing clinical applications.

We are today able to collect and store a considerable amount of patient-related data. These "big" data are typically part of Electronic Medical Record (EMR) systems and usually combine demographic, clinical and biological information. They may also contain images (e.g. ultrasound cardiac images) and physiologic waveforms. These data can be analysed with simple descriptive methods to report basic information regarding patient characteristics and outcomes such as hospital mortality, morbidity, and length of stay. This approach, useful for benchmarking and research, does not require artificial intelligence (AI).

A step further in the data analysis process consists of using machine learning (ML) algorithms (a subfield of AI), which have been trained to detect specific patterns of disease states or adverse events. As of today, most ML innovations approved for medical use have been developed in the field of imaging (radiology and pathology). It is indeed relatively easy to train an algorithm with a large database of images so that it becomes capable of detecting abnormalities that could be missed by a medical trainee or a seasoned but distracted clinician. In this respect, many ML algorithms have been designed to analyse chest x-rays and CT scans and to suggest a diagnosis (e.g., tracheal tube not correctly positioned on the chest x-ray of a mechanically ventilated patient or CT scan images suggestive of COVID-19 in a patient with ARDS). Recently, ML algorithms have also been implemented into ultrasound machines to facilitate and automate point-of-care echocardiographic evaluations (Nabi et al. 2019).

AI and Point-of-Care Echocardiography

Several ML algorithms have been trained to recognise heart images and guide users to hold and position their transthoracic probe correctly. Such algorithms are also able to grade image quality and label heart structures. An example is displayed in **Figure 1.** Some ML algorithms can take echocardiographic measurements automatically. For instance, the autoVTI algorithm can recognise a 5-chamber apical view of the heart, automatically position the pulse wave Doppler caliper in the left ventricular outflow tract and record the sub-aortic velocity time integral (VTI) over a short time window **(Figure 1)**. A recent clinical evaluation suggests that the autoVTI algorithm may help trainees to be as efficient as echocardiography experts in estimating VTI, stroke volume (SV ~ VTI x Pi) and cardiac output using ultrasounds (Gonzalez et al. 2022). Several ML algorithms have also been developed for the automatic estimation of left ventricular ejection fraction (LVEF). Comparison studies suggest they may enable novices to measure LVEF as accurately and with better reproducibility than experts taking manual measurements (Varudo et al. 2022). Other ultrasound algorithms have been designed to predict fluid responsiveness in mechanically ventilated patients from the automatic quantification of the inferior vena cava respiratory variation or to detect pulmonary oedema from the automatic quantification of lung B lines.

In summary, the value of ML algorithms to help novices perform point-of-care echocardiographic evaluations has been documented in several clinical studies. However, given the fact that the proportion of intensivists trained to perform echocardiography is increasing sharply, whether AI innovations are necessary to increase the number and quality of ultrasound haemodynamic evaluations remains to be established.

AI and Continuous Blood Pressure Monitoring

In the search for cuffless and continuous blood pressure monitoring techniques, ML algorithms have been proposed to estimate blood pressure and its changes from the

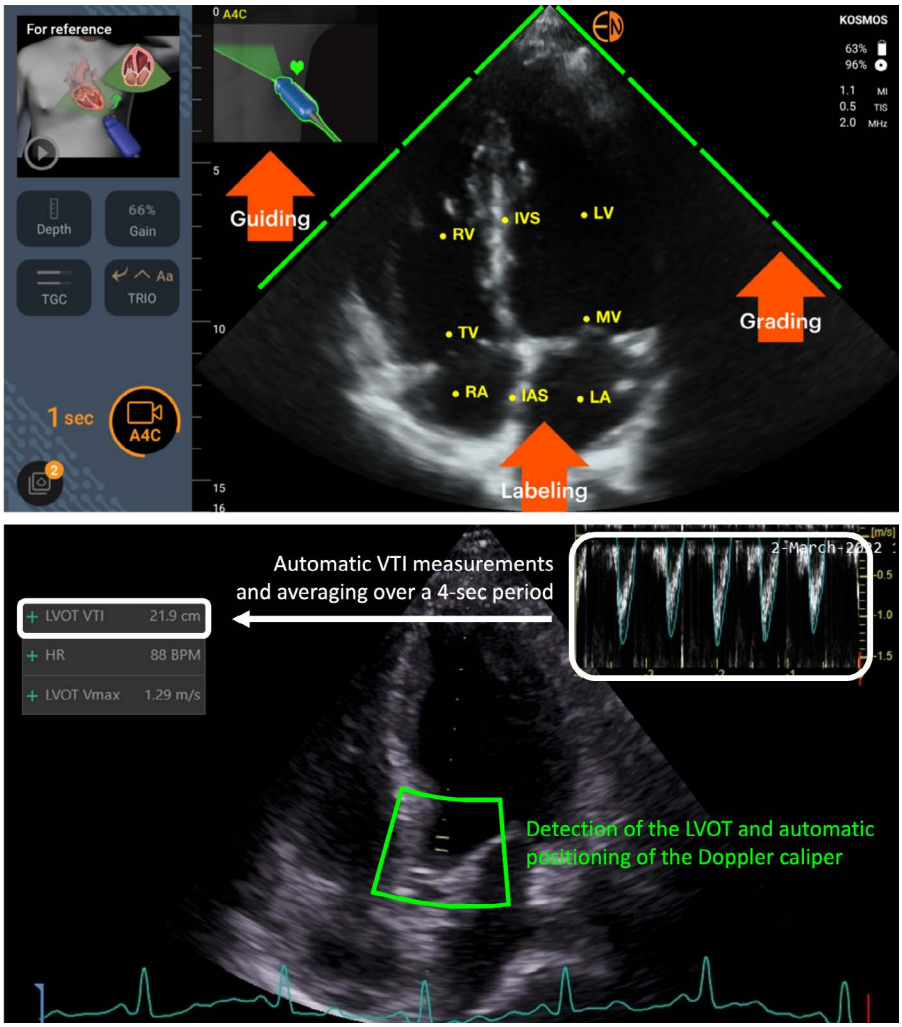

Figure 1. Examples of machine learning algorithms designed for point-of-care echocardiography. **Top** - Auto guiding to obtain an apical 4-chamber view of the heart, auto-grading to ensure optimal image quality, and auto-labelling. From EchoNous (Redmond, WA, USA), with permission. **Bottom** - Automatic detection of the apical 5-chamber view of the heart, automatic positioning of the Doppler caliper in the left ventricular outflow tract (LVOT) and automatic measurements of subaortic velocity-time integral (VTI). From GE Healthcare (Chicago, IL, USA) with permission.

analysis of photoplethysmographic (PPG) waveforms. Historically, PPG waveforms were recorded by medical-grade pulse oximeters, but they are today frequently obtained from smartwatches, adhesive patches, optical bracelets, rings or smartphone cameras (Festo et al. 2023). A few of these devices, mainly designed for the detection or follow-up of patients with chronic hypertension, have been cleared for medical use. Recent independent clinical evaluations suggest they may not always be able to detect the physiologic night-time dipping nor therapeutic changes in blood pressure (Tan et al. 2023). As a matter of fact, these devices require frequent recalibrations and carry the potential to track changes in blood pressure over short time periods rather than measure absolute numbers (Ghamri et al. 2020). Interestingly, this would not be an obstacle to their use during surgery, in ICU patients or even in hospital wards to detect hypotensive and hypertensive episodes and trigger intermittent blood pressure spot-checks with a reference clinical method (e.g., the oscillometric brachial cuff method). In these settings, the reference method would be used not only to confirm changes in blood pressure but also to recalibrate the algorithm.

AI to Forecast Clinical Deterioration

As mentioned above, ML algorithms can detect specific patterns of overt disease states. They can also be trained to detect patterns associated with pre-disease states or patterns observed before the occurrence of specific adverse events.

For instance, multiple ML algorithms have been developed to create scores (e.g., eCART or HAVEN scores) predicting severe adverse events in patients hospitalised in regular hospital wards. Several studies have shown these AI-derived scores are able to predict ICU admission, cardiac arrest, and death with an area under the curve (AUC) around 0.8-0.9 (as a reminder, a random guess would be associated with an AUC of 0.5 and a perfect prediction with an AUC of 1.0). However, their predictive value is frequently only slightly higher when not simply comparable to what is possible to achieve with existing scores such as the modified early warning score (MEWS) or the national early warning score (NEWS) - both scores which are easy to calculate from vital sign spot-checks (Bartkowiak et al. 2019).

Multiple attempts have been made to detect sepsis at an early stage, fasten therapeutic management and improve patient outcomes. As of today, the results of sepsis "sniffer" implementation programmes have been conflicting, with some reporting a decrease in time-to-antibiotic and in-hospital mortality (Shimabukuro et al. 2017), whereas others, including the recent evaluation of the EPIC system (widely used in the US), reported poor discrimination (AUC 0.63) and calibration in predicting the onset of sepsis (Wong et al. 2021). Another potential ML application is known as reinforcement learning. It enables the development of algorithms designed to provide dynamic therapeutic recommendations, which have been shown to be associated with improved organ func-

tion and/or survival (Komorowski 2018). Whether such prescriptive algorithms may be accepted by clinicians (particularly by experts in sepsis management) and may improve clinical outcomes remains unknown.

Machine learning algorithms have also been developed and proposed to predict postoperative morbidity and mortality, with reported AUCs that may exceed 0.9. However, this predictive value does not always overcome what is possible to achieve with simple scores such as the SORT score (Wong et al. 2018). Of note, the subjective prediction made by clinicians has been shown to be associated with an AUC of 0.89! (Wong et al. 2018). Therefore, whether there is a need for complex ML scores to predict postoperative outcomes remains debatable.

Machine learning algorithms have recently been proposed to predict haemodynamic instability and, more specifically, systemic hypotension. The hypotension prediction index (HPI) is a commercially available ML-derived score calculated from the analysis of the arterial pressure waveform. It has been shown to forecast intraoperative hypotension 5-15 minutes ahead with an AUC ranging between 0.75-0.95. However, recent publications have highlighted the fact that HPI is the mere reflection of the mean arterial pressure (MAP) and, as a result, that its predictive value may not be superior to MAP monitoring (Mulder et al. 2023).

In summary, the predictive value of machine learning algorithms is hardly disputable. However, the superiority over existing and simpler methods often remains to be determined, and the complexity/benefit and cost/benefit ratio may therefore be questioned.

The Pitfalls of Predictive Analytics

Predictive analytics is associated with at least four main limitations and/or pitfalls, which are summarised in **Figure 2**.

The first one is to believe that everything is predictable. As highlighted by Chen and Asch in a famous New Engl. J. Med. editorial (Chen and Asch 2017), "no amount of algorithmic finesse or computer power can squeeze out information that is not present". Google X, an Alphabet subsidiary, reported that its initiative to discover a biomarker for depression and anxiety in brainwave data fell short of its goal. Given the fact that they had almost unlimited resources and an army of top-level computer scientists working on this project, it is likely that brainwave data simply did not contain the predictive information they were looking for. In addition, some events are unpredictable by nature. As an example, which algorithm could predict hypotension related to surgical injury (e.g., vena cava injury during liver surgery) or the decision to deepen anaesthesia or sedation with a propofol bolus? During surgery and in ICUs, multiple external factors are susceptible to modify clinical trajectories in one direction or the other. When steady states do not exist, it becomes challenging to predict short-term clinical trajectories (Michard and Teboul 2019).

Secondly, poor data quality is one of the main factors holding up the big data revolution in healthcare (Dhindsa et al. 2018). This limitation is often summarised as "garbage in, garbage out". Indeed, one may use the best predictive algorithm, but if we feed it with wrong data, artefacts and/or damped physiologic waveforms, one may logically end up with wrong predictions.

Thirdly, it is paramount to understand that predicting does not necessarily mean preventing. When the prediction is not followed by one or more appropriate actions susceptible to modify the clinical trajectory, logically, nothing can be prevented. In the largest HPI randomised controlled

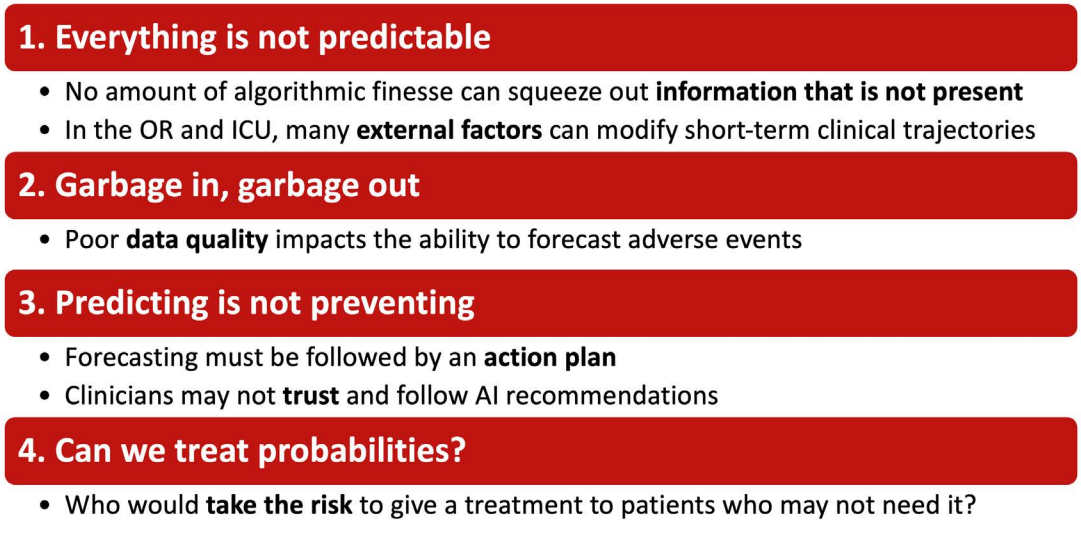

Figure 2. The four main pitfalls of predictive analytics

trial published so far (Maheshwari et al. 2020), anaesthesiologists who were alerted about the risk of hypotension failed to prevent hypotensive events. Interestingly, it appeared that most of them did not feel the need and/or the right to give fluid, vasopressors, or inotropes to patients who were still haemodynamically stable and only had a probability of becoming hypotensive. This finding is an excellent illustration of the reluctance of clinicians to trust and follow AI recommendations (Gaube et al. 2021).

Fourthly, there are risks associated with the treatment of probabilities. Therefore, one may hardly envision being proactive from a therapeutic standpoint. One may be proactive by performing bacteriological samples when predicting sepsis or by upgrading surveillance when predicting clinical deterioration (e.g., by offering continuous monitoring and/or ICU admission). There is no harm in doing so. There might be economic consequences, but no harm to the patient. In contrast, giving antibiotics to a probability of sepsis or administering vasopressors to a probability of hypotension might be risky and is, therefore, questionable (Michard and Futier 2023). Who would accept receiving treatment with known side effects for a predicted disease or adverse event that may never occur? And who would be responsible in case of complications?

Conclusion

Big data, AI, and, more specifically, machine learning algorithms are hot topics for medical journals and scientific events. For start-ups, they are also very useful keywords to raise funds. However, one may acknowledge that, as of today, and from a practical standpoint, the AI elephant gave birth to a mouse in the field of anaesthesiology and intensive care. Prospective clinical trials are indispensable not only to assess the safety of AI innovations but also to demonstrate superiority over existing and simpler methods. In the digital medicine era, whereas many medical students are eager to work on AI projects and to participate in datathons, it might be useful to remind them that "the immediate challenge to improving quality of care is not discovering new knowledge, but rather how to integrate what we already know into practice" (Urbach and Baxter 2005). Therefore, although we should keep our eyes and ears wide open for AI innovations, we should also continue to focus on basic initiatives (more nurses and doctors, better training with simulation, better compliance to existing guidelines, and better use of existing monitoring tools) that are known to improve patient outcomes and satisfaction.

Conflict of Interest

FM is the founder and managing director of MiCo, a consulting and research firm based in Switzerland. FAG and PS have nothing to disclose.

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Aida Felipe Villalobos
Physician
Paediatric Intensive Care Unit
Hospital Sant Joan de Déu
Barcelona, Spain
aida.felipe@sjd.es

Elisabeth Esteban Torné
Physician
Paediatric Intensive Care Unit
Chief of the Paediatric and Neonatal Transport Team
Hospital Sant Joan de Déu
Barcelona, Spain
elisabeth.esteban@sjd.es

Francesc Garcia Cuyàs
Director of Digital Strategy and Data
Deputy Medical Director
Hospital Sant Joan de Déu
Barcelona, Spain
francesc.garcia@sjd.es

Ricard Casadevall Llandrich
Head of the Data Management and Governance Office
Hospital Sant Joan de Déu
Barcelona, Spain
ricard.casadevall@sjd.es

Fsc. Xavier Escayola Elías
Head of Bioengineering Group
Hospital Sant Joan de Déu
Barcelona, Spain
xavier.escayola@sjd.es

Patricia Garcia-Canadilla
Data Scientist
Interdisciplinary Cardiovascular Research Group
Institut de Recerca Sant Joan de Déu
Hospital Sant Joan de Déu
Barcelona, Spain
patricia.garciac@sjd.es

Florencio Llanos Ruiz
Computer Engineer
IT department
Hospital Sant Joan de Déu
Barcelona, Spain
floren.llanos@sjd.es

María Isabel Nova Martínez
Paediatric Nurse
Paediatric Intensive Care Unit
Hospital Sant Joan de Déu
Barcelona, Spain
mariaisabel.nova@sjd.es

Gemma Durban Carrillo
Deputy Chief Paediatric Nurse
Paediatric Intensive Care Unit
Hospital Sant Joan de Déu
Barcelona, Spain
gemma.durban@sjd.es

Iolanda Jordan Garcia
Physician
Paediatric Intensive Care Unit
Deputy Medical Director
Hospital Sant Joan de Déu
Barcelona, Spain
yolanda.jordan@sjd.es

Francisco José Cambra Lasaosa
Physician
Chief of the Paediatric Intensive Care Unit
Hospital Sant Joan de Déu
Barcelona, Spain
franciscojose.cambra@sjd.es

Transforming a PICU in the Digital Age

Digitalisation is ultimately the driving force behind digital transformation. It will take us from a reactive healthcare system to a proactive one that focuses on prediction and prevention.

Introduction

The digital transformation has left a few things untouched in recent years, radically changing healthcare management for citizens, professionals, and public health departments. In the medical field, this digital transformation process is a far-reaching concept that extends to a wide range of situations, which are fundamentally based on the use and processing of digital data.

The concept of digital health is often thought of as being solely related to technological advances (electronic prescriptions, mobile applications, etc.), but in reality, its scope is far broader and entails a paradigm shift. Here, we apply the idea of digital density, which expresses the amount of digitalised data in a system. When the digital density value of a system is equal to 1, this means that all the data is digitalised, implying an impending change in the sector.

Hence, we can say that we are currently undergoing a *digital* revolution, one that follows both the *agricultural* revolution, where land was the underpinning value, and the *industrial* revolution, where the transforming element was energy. Today, value derives from data, and the changes we are experiencing occur at an ever-increasing speed, so we often speak of technological acceleration.

With this backdrop, the Spanish National Health System has been establishing lines of action to foment the digital transformation of the country's healthcare system. Based on recommendations from the World Health Organization's digital health platform and current European programmes, these actions include the development of digital health solutions yielding added value, harnessing of data, and the creation of knowledge through artificial intelligence-based analytics systems. Other lines focus on digital training for professionals, an important aspect of this revolution. All of this must be based on a hybrid cloud architecture in a shared-operability environment where compliance with stringent cybersecurity standards and the legislation in force is assured.

This digital transformation extends, of course, to intensive care units and other hospital units. Here, it begins with the technological improvement of a centre's processes and the growing use of wearables and other devices for the treatment and monitoring of patients, whether remote or *in situ*. These aspects are already present to some degree in most units, but we will see more of this in the near future. Next, the integration of data and processes in clinical record programmes and other digital tools will be paramount and will culminate in the large-scale storage and advanced analysis of data (Big Data), leading to the execution of artificial intelligence (AI) projects. This kind of digitalisation is ultimately the driving force behind the digital transformation and will take us from a reactive healthcare system to a proactive one that focuses on prediction and prevention.

In our field, one of the main objectives of the digital transformation process is the design and development of tools, scores, and algorithms. Some of these allow us to quantify, express, and even predict hospital occupancy and case complexity, helping to

efficiently organise operations and human resources. Others stratify certain patient risks and may even help us anticipate their clinical evolution. In general, these tools allow us to implement healthcare strategies and treatments that can alter the natural course of a disease by employing a more global approach. They are designed to support, and not replace, healthcare professionals in decision-making tasks, thus shortening wait times and minimising risks by offering a higher level of information and more in-depth analyses; in short, they add value.

Next, we will highlight the key points to consider in a digital transformation process based on our experience in Hospital Sant Joan de Déu (Barcelona).

Data Sources

Data has traditionally been generated by medical professionals entering information into patients' clinical records. However, the emergence of devices, wireless tools, sensors, and other technology increases the quantity, quality, and variability of data (the so-called unregulated data). Moving beyond merely clinical data, new systems will be able to receive inputs and analyse data stemming from different sources, such as genomics.

The data obtained in an intensive care unit has characteristics that make it ripe for the development and execution of projects based on data management. Huge volumes of extremely accurate data are generated here at very high speeds, and yet they are varied as regards their type and origin, all of which make them very valuable. When working with data, it is important that we not forget that a series of barriers related to the quality, governance, anonymisation, variability, terminology, and conceptualisation of data must also be addressed. Data can be quite heterogeneous in its behaviour and come from many different platforms. The vocabulary used to describe it can also be quite variable, leading to uncertainty and a lack of consensus regarding specific concepts in data management. For this reason, it has been necessary to ensure internal and external interoperability through the creation of data catalogues and business glossaries based on standards.

In intensive care units, it is imperative that the data available be used as optimally as possible to benefit the patient when it comes to safety, quality of care, and the diagnostic and therapeutic process. Everything mentioned above makes an intensive care unit a natural and, consequently, ideal place for executing a data management project.

Clinical Applications

With data analytics drawing from large datasets as a basis, artificial intelligence solutions can be developed to undertake the actions that a human being would naturally perform but more quickly and efficiently.

These solutions can be divided into four fields of application:

- Solutions to improve the patient-healthcare provider relationship (i.e. patient portals, intelligent assistants, etc.)
- Discovery solutions
- Solutions that support decision-making (i.e. image analysis, risk stratification scores, predictive algorithms of poor clinical evolution, etc.)
- Solutions that support management and operations (i.e. operational panels, smart hospital systems, etc.)

During our intensive care unit's architectural, technological, and digital transformation process, we have created solutions in each of these fields.

Digitally Transforming a Paediatric Intensive Care Unit

Hospital Sant Joan de Déu, located in Barcelona (Catalonia, Spain), is a highly specialised maternal and children's hospital that emphasises a multidisciplinary approach. The hospital has 320 beds and is one of the most important paediatric centres in Europe, especially in neurosurgery, cardiovascular surgery, and comprehensive care for paediatric oncology patients.

In 2018, the hospital's new paediatric intensive care unit was built, which entailed an architectural, technological, and digital revolution.

Prior to that, the unit had a semi-circular distribution with a centralised nature, similar to other intensive care units built in Spain in the 1970s. It had a surface area of 500 m^2, hosting a total of 18 beds. However, the bays were open, with no physical separation between them, and the area had a single surveillance post equipped with a monitoring centre, essentially reducing space for caregivers.

In the new unit, which currently has 28 beds and around 1500 admissions per year, the surface area was quadrupled to 2200 m^2, moving to a decentralised model with closed bays and thus increasing usable space for caregivers. The new model is an essential part of the paediatric therapeutic and recovery process but also serves to increase the visual and auditory privacy of patients.

It is a highly technologically advanced unit, equipped with electronic clinical record systems and semi-protocolised pharmacological prescription systems based on pathology and patient weight. It also has an intelligent drug management and dispensing cabin and continuous infusion pumps with an inserted library of standard concentration solutions. Additionally, the unit is equipped with operating and isolation bays, patient monitoring systems, and state-of-the-art therapeutic devices (continuous extrarenal purification, plasmapheresis, and ECMO systems), all of which send continuous data to external systems.

This process entailed an inevitable paradigm shift that created stress, healthcare fatigue, and resistance to change, but it was ultimately successful and well-received by the team. For the viability of the project, the inclusion of remote systems was essential. First, a system was developed based on establishing a matrix of alarms that are activated when a single parameter changes. Mobile devices were introduced that allow alarms to be transferred to the nurse when they are not physically in front

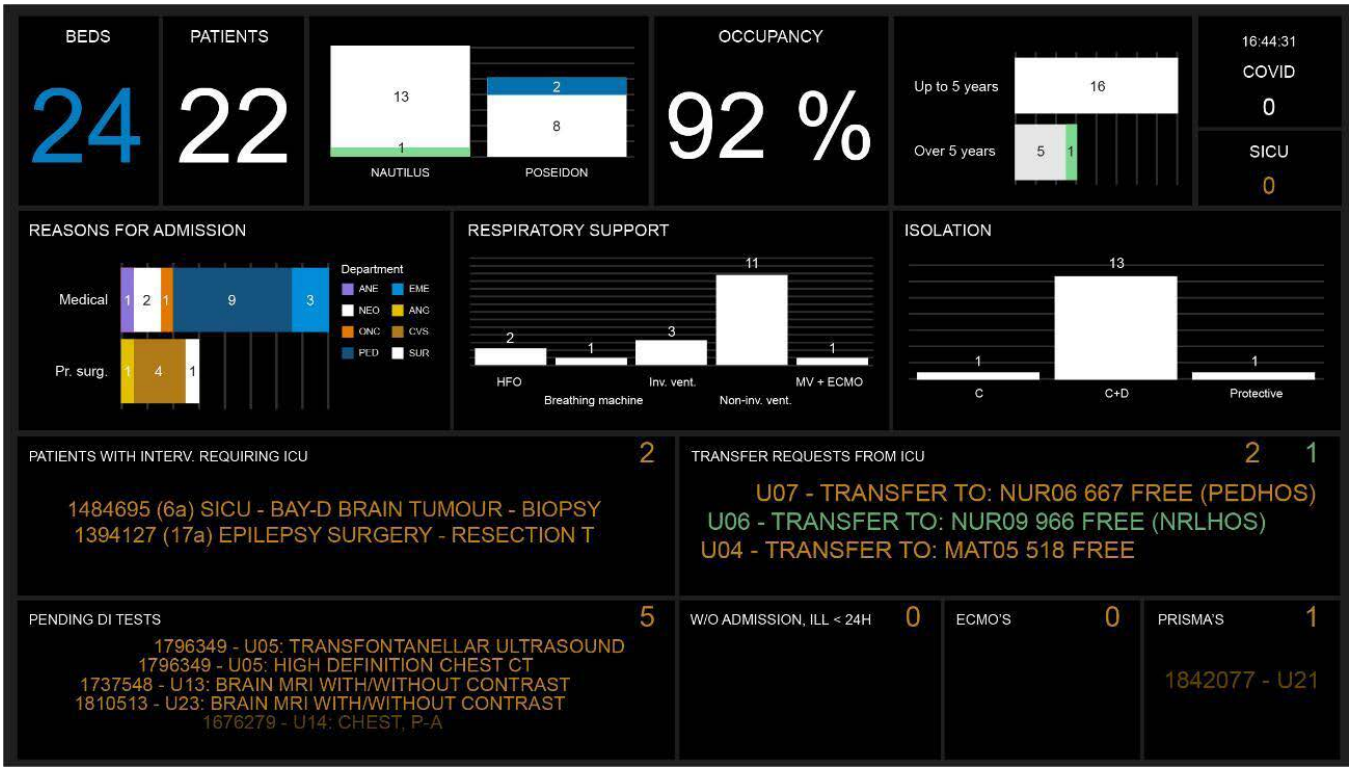


Image of the PICU operational panel, Hospital Sant Joan de Déu

of the device or monitor where the alarm is coming from. The system allows for alarms with different light and sound features depending on the criticality of the alarm. These are escalated in a predetermined manner to other professionals to ensure that all alarms are correctly attended to, increasing patient safety.

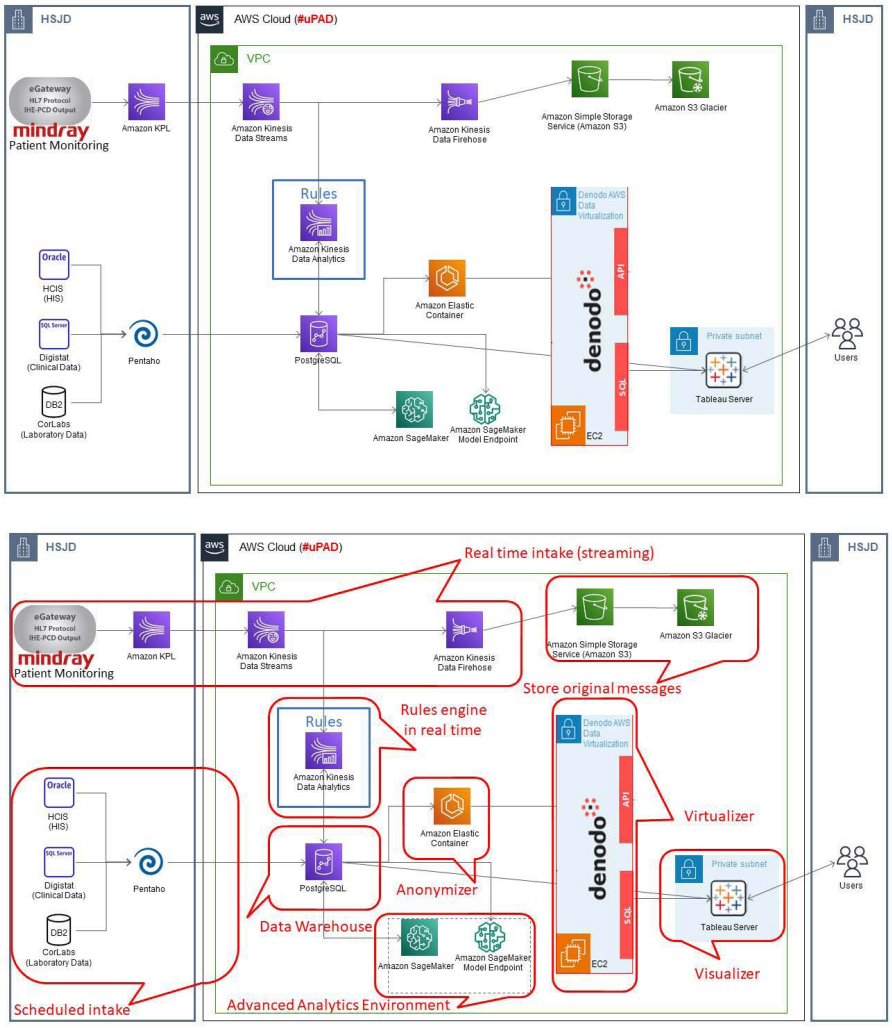
An operational panel was created for managing data generated in the different systems of the unit. It extracts data in real-time through analytics software, which has a dashboard displaying occupancy, a forecast of patient admission/discharge flows, and the complexity of the patients hospitalised in the unit. Therefore, it is also capable of showing human resources requirements (from cleaning staff to nursing and medical care staff) in near real-time and helps streamline patient movements between the PICU and the different areas of the centre.

Traditionally, early warning scores (EWS) using vital signs and risk indicators have been proposed to assess children at risk of clinical deterioration to intervene quickly to reduce the impact of deterioration and risk of death among these patients. However, EWSs are based on measurements performed at a single time point without incorporating trends or prior patient information. Moreover, some of these measurements rely on subjective assessment, leaving them susceptible to different interpretations. All these limitations could explain why the implementation of EWSs in high-resource settings has failed to show a significant decrease in hospital mortality. Using artificial intelligence-based algorithms, we could automatically integrate data from different sources and nature to predict a patient's risk of deterioration.

In the test environment, we now have several algorithms to improve the identification of paediatric patients at high risk for clinical deterioration following cardiac surgery (Garcia-Canadilla et al. 2022), including a bronchiolitis score and a predictive score for anticipating and diagnosing sepsis.

In 2020, our sepsis score (PESERS), which is based on the transformation of the Catalonian sepsis code to a quantitative score, was validated in our children's hospital (Solé-Ribalta et al. 2022). The PESERS score was found to not only improve the screening of sepsis but was also shown to be useful in predicting the evolution thereof. The automation of this score through the instant capture of a patient's variables allows for a continuous calculation of the score, utilising a traffic light alarm system to promptly alert the required healthcare professional. Similarly, the automation of the Bronchiolitis Score of Sant Joan de Déu (BROSJOD) (Balaguer et al. 2017) makes it possible to objectively and continuously categorise the severity of bronchiolitis episodes, allowing therapeutic decisions such as respiratory support escalation or patient transfer to be made.

Today, what we have are scores that tell us what is currently happening to the patient, but in a second, future phase, we intend to apply machine learning tools so our algorithms can learn, increase in complexity, and improve their predictive capacity. This, along with the development of new algorithms, will help us detect the events we want to identify, even before they occur.



Informational platform diagram, Hospital Sant Joan de Déu

The Cortex Project

The digital transformation process undertaken at Hospital Sant Joan de Déu gave rise to something unprecedented - the Cortex project. We have seen that today's healthcare centres simultaneously carry out multiple processes and procedures where a myriad of operational information systems coexist, all generating large volumes of data. Hospital management teams must be able to carry out a posteriori analyses of these data to align their efforts with the needs and characteristics of a new reality in healthcare, one in which active patient participation is just another part of the care process, decision-making cycles are increasingly shorter, and quality standards are increasingly demanding. As highlighted by the COVID pandemic, having reliable, stable, and, above all, real-time information is a critical factor in today's healthcare management.

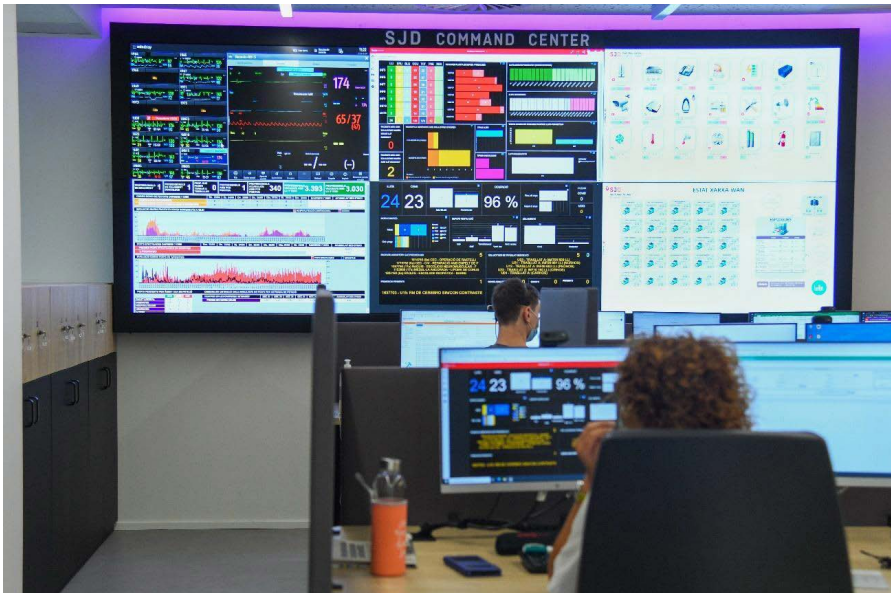
With this in mind, Cortex was launched as the centre's global monitoring station, with a proactive and predictive overview, in which three large areas converge in a proactive and predictive manner: E-care, Command centre, and Contact centre.

In order to carry out this project, one of the actions performed at Hospital Sant Joan de Déu was defining a global data ecosystem, including all the data generated by the systems present in the hospital, located in a cloud system. It is essential to have a Data Control Office in charge of data management, governance, and ethical use in line with current regulatory systems. This is now a reality, and the data ecosystem feeds the Cortex project, providing valuable inputs.

Taking a look at the different areas of Cortex, in the E-care area, we can find the remote monitoring systems and E-care tools, which are defined as those rules or algorithms that allow for stratification by clinical status or the risk of disease evolution for a particular pathology. This helps us execute healthcare or therapeutic strategies in a manner that can alter the natural course of a disease. The main goal is to anticipate and improve decision-making, moving from our current reactive medicine to preventive and proactive medicine.

Next, the Contact Centre area is a more administrative part that manages the information and contact with all of the centre's patients. This is done through a multi-channel service that covers different forms of communication between the centre and its contacts based on Customer Relationship Management (CRM) software. It is a virtual proximity model that uses the personalisation of care to improve the quality of responses, especially since it is sometimes the first point of contact with the centre. Overall, it helps anticipate the needs of the patients and families and provides support during the hospitalisation process.

Lastly, the Command Centre area is intended to manage the operations of the hospital, much like the air traffic control tower of an airport. It represents a comprehensive change in how hospital flows are managed, using process reengineering and a technological platform similar to that found in the centre of operations. For this, we have designed tools that show useful and near-real-time information coming from sensitive areas (the PICU, surgical block, hospital ward, etc.) and algorithms for the control and management of flows, human resources, and materials in the hospital. These tools display their results on what are called operational panels, which allow events to be anticipated so that responses can be organised in advance; it is also useful for decreasing wait times and improving the overall patient experience.



View from the Cortex Command Centre, Hospital Sant Joan de Déu.

Conclusion

In conclusion, the digital transformation that our centre has undergone through the implementation of this project has allowed for better organisational foresight, especially in critical areas, along with more efficient processes, resource management, and hospital flows. This endeavour has and will continue to improve the detection of urgent situations, setting the stage for better predictive algorithms and the harnessing of AI in the service of patients and medical professionals. It is thus incredibly helpful as a decision-making aid at the centre, improving care and support for the patients and their families.

For a project like this to be successful, it is key to have transparent, accurate information that is available in real-time and to have a well-defined data management and governance strategy. As we develop and expand this cutting-edge venture, we hope to showcase what can be accomplished and serve as a blueprint for other centres wishing to implement a similar project.

Conflict of Interest

None.

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Aisling McMahon
Consultant Intensivist and Anaesthetist
Mater Misericoridiae University Hospital
Dublin, Ireland
aislingmcmahon@mater.ie

Using iMg Testing for Clinical Management in the ICU

An overview of ionised serum magnesium as an important biomarker for critically ill patients and how iMg testing is utilised at Mater Intensive Care.

Ionised Serum Magnesium - An Important Biomarker

Magnesium is the fourth most common cation in the body and the second most abundant intracellular cation, exceeded only by potassium. The bulk of it is found in the intracellular space, with the greatest proportion in bone, around one-third in muscle and the rest in soft tissue. Only around 1% of magnesium is found in extracellular fluid where it takes part in several physiologic processes. The magnesium contained in blood exists in different states. Around half is in its ionised form, with the remainder bound to albumin or complexed with anions.

Although in health, there is a good correlation between total and ionised magnesium levels, this is not likely to be the case in critically ill patients. The levels of bound magnesium can fluctuate significantly, often in a very unpredictable way, particularly in the critically ill. This can be because of changes in serum protein levels or in the number of anions in the blood. There are also several drugs administered and clinical states encountered by critically ill patients that can affect magnesium levels, including acid-base disturbances, refeeding syndrome, pancreatitis, diuretics, aminoglycosides, proton pump inhibitors and calcineurin inhibitors, to name a few.

Although dysmagnesaemia is common in critically ill patients, there are relatively few studies looking at the relationship between ionised and total magnesium levels in the ICU. In a study by Johansson et al. (2007)), there was a weak correlation between total and serum magnesium, with 25% of patients having low ionised magnesium in the presence of normal total magnesium and 9% having high ionised magnesium despite normal total magnesium. Escuela et al. (2005) also found that total magnesium levels were a poor reflection of ionised magnesium. In another paper by Yeh et al. (2017), only 18% of low total magnesium levels were considered below the normal range for ionised magnesium. This suggests that up to 80% of patients could be receiving unnecessary magnesium supplementation. Another study in critical care noted that in patients with low total magnesium levels, only 30% of these also had low ionised magnesium (Huijgen et al. 2000). Outside of the critical care population, when looking at acute myocardial infarction patients compared to controls, ionised magnesium has been found to be a more useful monitor in detecting alterations in magnesium levels (Kyriacou 2008). This body of evidence suggests that ionised serum magnesium is an important marker in identifying critically ill patients who may be vulnerable to complications due to magnesium deficiency.

Clinical Complications Due to Hypomagnesaemia and Hypermagnesaemia

Abnormalities in serum magnesium levels are common in critically ill patients. Hypomagnesaemia is more frequent than hypermagnesaemia, occurring in up to 70% of patients admitted to the ICU. Low magnesium levels are mainly secondary gastrointestinal losses (such as nasogastric suctioning, malabsorption, diarrhoea, pancreatitis) and renal losses (renal diseases, osmotic diuresis, acidosis, hypercalcaemia, fluid therapy, drugs). As magnesium is involved in a myriad of physiologic processes, dysmagnesaemia can affect multiple systems and have significant consequences.

Some of the most serious effects of altered magnesium levels are abnormalities in the cardiovascular system. Hypomagmesaemia can result in atrial and ventricular arrhythmias, hypertension, vasospasm and sudden death. Hypermagnesaemia is associated with bradycardias, heart block, hypotension and cardiac arrest. Magnesium deficiency may also increase the risk of post-operative atrial fibrillation in a cardiac surgery population. Abnormal magnesium levels can also have a significant impact on the neuromuscular system. Low levels are associated with seizures, tetany, laryngospasm, paraesthesias, migraine, cramping and hyperreflexia. On the contrary, hypermagnesaemia can lead to muscle weakness and flaccid paralysis with respiratory muscle weakness and coma. Other complications associated with altered magnesium levels include nausea, anorexia, haemostatic abnormalities and metabolic abnormalities, including hypokalaemia, hypocalcaemia and insulin resistance.

The relationship between magnesium levels and mortality varies in the literature, but there is evidence to suggest that both hyper and hypomagnesaemia can affect patient outcomes. In a paper by Chernow et al. (1989), mortality was higher in post-operative intensive care patients with low magnesium levels. Rubeiz et al. (1993) found a similar relationship between magnesium levels and mortality in acutely ill medical patients. In contrast, Guerin et al. (1996) did not find an association between low admission levels of magnesium and death. Mortality was increased in the hypermagnesaemic group, but this only included six patients. In keeping with Guerin, Soliman

et al. (2003) found no association between admission magnesium levels and outcome. However, patients who went on to develop ionised hypomagesaemia during their critical care stay had worse outcomes. In addition to increased mortality, patients with hypomagnesaemia are more likely to experience other electrolyte disorders, require organ support and have a longer ICU stay (Safavi and Honarmand 2007).

Measuring iMg Levels in Intensive Care Patients

Despite disorders of magnesium being relatively common in the ICU, the recent VITA-TRACE survey found that up to 25.4% of respondents did not routinely perform any form of measurement of magnesium levels more than once a week (Vankrunkelsven et al. 2021). This was even though 63.4% gave regular parenteral magnesium supplementation. Ionised magnesium levels are less routinely used in comparison to total magnesium in clinical practice. This is likely because there are no standardised diagnostic reference levels available. There are also relatively few manufacturers offering point-of-care devices that measure ionised magnesium levels in the blood (Dent and Selvaratnam 2022).

Point-of-care devices that offer ionised magnesium levels use methods based on ion-selective electrodes. They allow accurate detection of ionised magnesium from whole blood with a rapid turnaround time and require only a small volume of blood. Monitoring ionised magnesium in critically ill patients is beneficial as it is the physiologically active component (Dent and Selvaratnam 2022; Scarpati et al. 2020). However, despite the many benefits of ion-selective electrodes, magnesium-specific electrodes are vulnerable to interference from other cations. Correction equations may need to be applied based on calcium concentrations. Ionised magnesium levels vary with pH, and the measurements can also be affected by temperature and dilution of the sample (Dent and Selvaratnam 2022; Scarpati et al. 2020). These factors are more commonly found in a critically ill population than the general hospital cohort.

iMg Testing at Mater Intensive Care

The Mater Intensive Care service is a mixed medical and surgical ICU, admitting critically ill patients from all disciplines within the Mater and Rotunda Hospitals and those referred from outside the hospital. There is a prioritised service to the national Cardiothoracic, Heart and Lung transplantation programme, Acute Spinal Injury services, and supra-regional services such as Vascular Surgery and Extra-Corporeal Membrane Oxygenation. The ICU has 18 beds with 1300 admissions annually, a bed occupancy of 107% and an average length of stay of 4.4 days. The HDU has 16 beds and admits approximately 1200 patients annually, has a bed occupancy of >100% and average length of stay of two days.

“ionised serum magnesium is an important marker to identify critically ill patients who may be vulnerable to complications due to magnesium deficiency”

Ionised magnesium levels are measured in all patients admitted to the Mater ICU. As a mixed medical and surgical unit, it cares for a variety of patients at risk of disorders of magnesium and the associated clinical consequences. As mentioned previously, hypomagnesaemia is common in critical care. Many patients will receive ICU therapies that interfere with magnesium homeostasis. These include diuretics, proton pump inhibitors, aminoglycosides and fluid therapy. As a result, monitoring ionised magnesium in all comers is beneficial and allows the detection of hypomagnesaemia and treatment before clinical consequences develop. There are also patient groups with specific indications for magnesium in whom the ability to rapidly measure levels is advantageous.

As a cardiothoracic centre, the Mater ICU routinely cares for patients who have undergone cardiopulmonary bypass. Evidence suggests that magnesium may reduce the risk of postoperative atrial fibrillation in this patient group. In the 2019 guidelines on cardiopulmonary bypass in adult cardiac surgery, its use can be considered prophylaxis for atrial fibrillation (Kunst et al. 2019). Hence, at Mater, the team routinely administers magnesium in these patients to prevent or treat atrial fibrillation and other tachyarrhythmias. The hospital also runs a heart and lung transplant programme. In addition to post-operative arrhythmias, these patients are prescribed calcineurin inhibitors as part of their post-transplant immunosuppression regime. Calcineurin inhibitors increase the risk of hypomagnesaemia, so it is useful to have the facility to routinely monitor ionised magnesium in these two groups.

Sepsis is a common admission category to the Mater ICU, as with many ICUs. There is evidence to suggest that magnesium supplementation in patients with severe sepsis can improve lactate clearance and reduce the length of stay. In a study by Noormandi et al. (2020), supplementation was targeted to the upper limit of normal magnesium levels. More recent observational evidence implies that magnesium use may be associated with reduced mortality in critically ill patients with sepsis. This was irrespective of admission magnesium level (Gu et al. 2023). Khalili et al. (2021) found that magnesium supplementation reduced the incidence of vancomycin plus piperacillin-tazobactam-induced acute kidney injury in critically ill patients. This antibiotic combination would not be uncommonly used in our patients with sepsis. They targeted a serum magnesium level of 3mg/dl (1.24 mmol/L). Detecting asymptomatic hypomagnesaemia and correcting it may also reduce the incidence of acute kidney injury in critically ill patients (Barboas et al. 2016). More evidence and recommendations for target levels are required before adopting this into routine clinical practice but measuring ionised magnesium and supplementing levels to maintain them in the normal range is standard practice in our unit.

Another group of patients that benefit from magnesium supplementation are those admitted with acute severe asthma. Magnesium may have bronchodilator effects. Its use in acute severe asthma may reduce the rate of intubation, and it may also reduce hospital admission in those with minimal response to standard treatment. Recent guidelines recommend considering a single dose if the initial response to bronchodilator treatment has been poor (BTS/SIGN Guideline 2016). The ability to monitor ionised magnesium levels allows administration in this situation while avoiding respiratory fatigue and muscle weakness associated with magnesium toxicity.

The Mater ICU also has an affiliation with the Rotunda Maternity Hospital. Within that remit, it cares for critically ill obstetric patients, some of whom may be at risk of eclampsia. Measuring ionised magnesium in these patients helps prevent hypomagnesaemia, reduces the risk of eclampsia and prevents the complications associated with hypermagnesaemia during treatment. Magnesium can accumulate in patients with renal failure. The ability to perform repeated bedside measurements in these patients can also help prevent the development of hypermagnesaemia.

Magnesium Supplementation Dosing and Monitoring

The initial dose of magnesium administered depends on the clinical situation. If the patient is asymptomatic and found to be hypomagnesaemic after measuring ionised magnesium, the dose would be titrated to the result to aim for a normal level. The standard order for the Mater ICU is a magnesium dose of 10 to 20 mmol (2.5 to 5 grams). In other specific clinical situations, the dose depends on best evidence or guideline recommendations. For example, in acute severe asthma, the British Thoracic Society suggests considering 1.2 to 2 grams of magnesium (BTS/SIGN Guideline 2016). For torsades de pointes, a dose of 1 to 2 grams is generally given. In pre-eclampsia, the magnesium dose given in the MAGPIE trial to prevent eclampsia was 4 grams (Altman et al. 2002).

When magnesium has been administered, ionised magnesium levels are used to monitor the response to treatment. In some situations, this is to ensure adequate supplementation. For example, in patients at risk of or being treated for new-onset arrhythmias, the target would be an ionised magnesium level greater than 1 mmol/L. The ability to monitor ionised magnesium is also used to reduce the likelihood of hypermagnesaemia and its consequences in patients requiring supplementation, for example, during the treatment of asthma or pre-eclampsia. As mentioned earlier, it can be helpful to prevent magnesium toxicity following supplementation in patients with renal failure, in whom magnesium can accumulate.

Conclusion

Magnesium is one of the most abundant cations in the body. It is mainly found in the intracellular space, but it is the free-ionised extracellular magnesium that is physiologically active. Abnormal magnesium levels are common in critically ill patients. There is a poor correlation between total and ionised magnesium levels in critically ill patients, and it is likely that ionised magnesium is more useful and specific in this patient population. Evidence suggests that using ionised magnesium can avoid unnecessary supplementation in critical care patients and that levels are correlated with outcomes. Ionised magnesium can be measured in whole blood at the bedside with a quick turnaround time. Routine measurement can identify at-risk patients and allow tailored treatment for specific indications in the ICU, including atrial fibrillation, in real time while avoiding complications of dysmagnesaemia in a complex patient cohort.

Disclaimer

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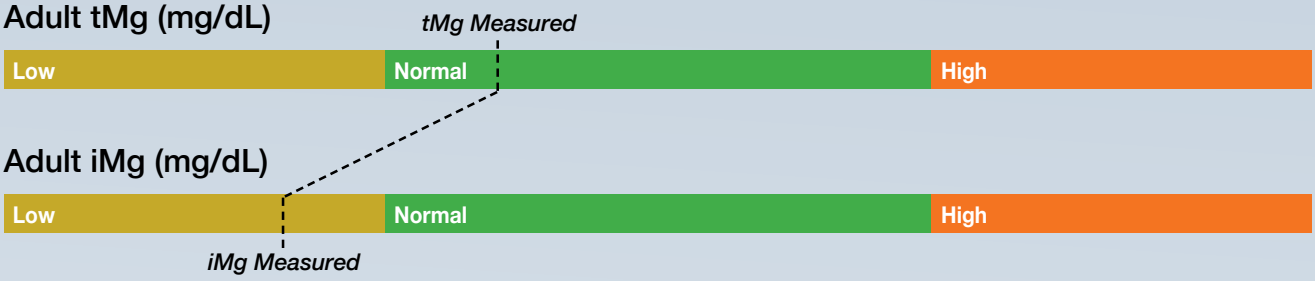
ICU Patient Studies Show Critical Importance of Ionized Magnesium

Patients Undergoing Continuous Renal Replacement Therapy (CRRT)

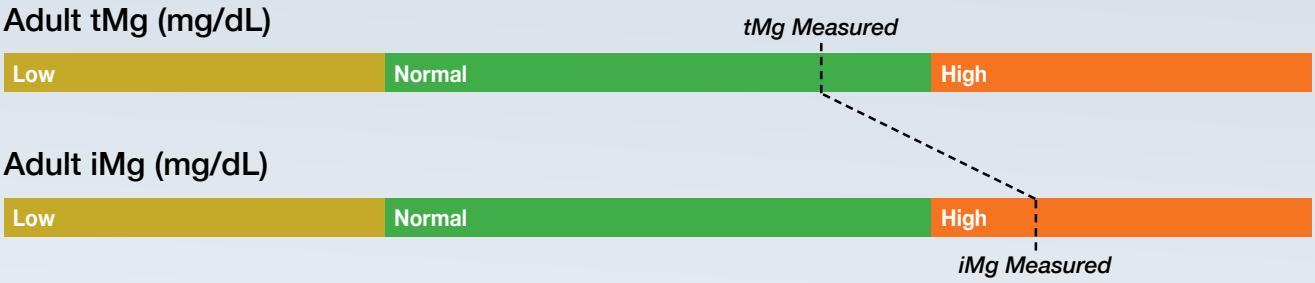
Hutten et. al.[1] found that patients receiving CRRT with citrate anticoagulation had normal tMg levels, but low iMg levels. This is due to magnesium ions being bound by citrate, and the citrate-magnesium complex being measured as tMg. These patients are actually hypomagnesemic but would not be recognized as such if only tMg were measured.



1.Hutten et al., Ionized and not total magnesium as a discriminating biomarker for hypomagnesaemia in continuous venovenous haemofiltration patients. *Nephrol Dial Transplant*, 2021.

Surgical ICU Patients

Yeh et. al.[2] found that 21% of tMg tests which were reported as normal were hypermagnesemic based on iMg. This exposes patients to potential risks associated with undetected hypermagnesemia, including prolonged days on the ventilator, muscle weakness, QT prolongation, and cardiac arrhythmia. In addition, there were many patients with low tMg and normal iMg, which led to unnecessary Mg supplementation and repeat blood draws.



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François Ventura
Intensive Care Unit
Hirslanden Clinique des Grangettes
Chêne-Bougeries, Switzerland

Division of Anesthesiology
Geneva University Hospitals
Genève, Switzerland
francois.ventura@hcuge.ch

Applying the Latest International Sepsis Guidelines by Screening High-Risk Hospitalised Patients With PSP

Hospital and ICU nosocomial sepsis screening for acutely ill and high-risk patients and daily measurement of PSP to diagnose nosocomial sepsis three to five days before the onset of symptoms.

Introduction

Sepsis is a major public health threat and is responsible for 11 million deaths per year (Rudd et al. 2020) among 48.9 million cases. Sepsis and septic shock can be prevented if diagnosed and treated early by appropriate treatment, in particular, antibiotics. Mortality from sepsis increases by about 8% per hour of delayed appropriate administration of antibiotics (Kumar et al. 2006). Two campaigns at the worldwide level have been launched by the *Global-Sepsis-Alliance and the Surviving Sepsis Campaign* (SSC) to improve care and survival rates. Sepsis and, in particular, septic shock are serious illnesses usually requiring intensive care management, resulting in very high hospitalisation costs. Sepsis-related costs in U.S. hospitals surpass U.S. $24 billion annually, making it the most expensive disease to manage (Torio and Moore 2015). The diagnosis of sepsis is currently based on the 2016 Sepsis-3 definition (Singer et al. 2016) as an infection and a dysregulated reaction of the body characterised by organ failure.

Nosocomial Infections and Sepsis

Nosocomial infections, i.e., Hospital Acquired Infections (HAI), occur in 7-8% of hospitalised patients in Europe (Swissnoso) and even 56% of patients hospitalised in intensive care unit ICU (Vincent et al. 2020). The WHO estimated 1.4 million nosocomial infections in 2016 and forecasts 10 million deaths in 2050 (Dadgostar 2019). The main causes of nosocomial infections are bacterial antimicrobial resistance (AMR), lack of adherence to infection control and prevention procedures.

In an epidemiological study published in 2020 (Markwart et al. 2020), the proportion of nosocomial sepsis, i.e., hospital-acquired sepsis (HAS) among all hospital-treated sepsis cases, was 23.6% (95% CI 17–31.8%). In the ICU, 24.4% (95% CI 16.7–34.2%) of cases of sepsis with organ dysfunction were acquired during ICU stay, and 48.7% (95% CI 38.3–59.3%) had a hospital origin. The pooled hospital incidence of HAS with organ dysfunction per 1000 patients was 9.3 (95% CI 7.3–11.9%). Mortality of ICU patients with HAS with organ dysfunction was 52.3% (95% CI 43.4–61.1%). The article concludes, *"there is an urgent need to improve the implementation of global and local infection prevention and management strategies to reduce its high burden among hospitalized patients"*.

In this context, the first recommendation in the latest SSC 2021 guidelines (Evans et al. 2021) propose, *"for hospitals and health systems, we recommend sepsis screening for acutely ill and high-risk patients*

Table 1 : Acutely ill and high-risk patients of nosocomial sepsis
Hospital stay of more than 5 days (with 2 or more co-morbidities)
Critically ill patients (coma patient > 48h, severely burned patients, etc.)
Emergency and abdominal surgery
Trauma patient with open fracture
Invasive mechanical ventilation
Catheters (central venous, arterial, urinary, ...) and pleural drainage
Parenteral nutrition

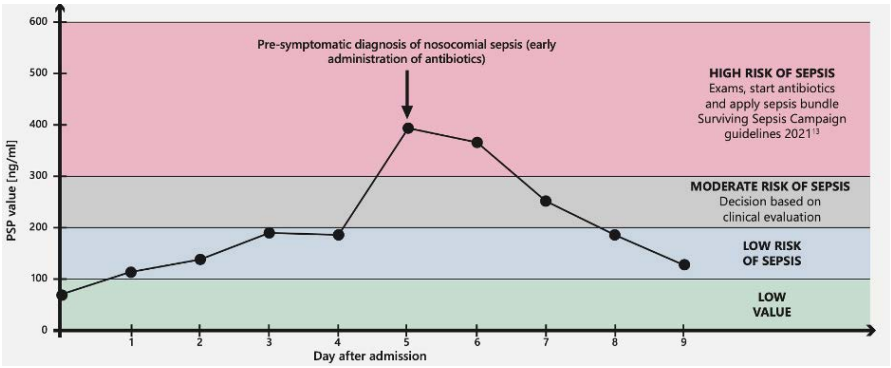

Figure 1: PSP daily measurement for pre-symptomatic diagnosis of nosocomial sepsis

(Strong recommendation, moderate quality of evidence)". But it's not defined how screening should be carried out. Prophylactic administration of broad-spectrum antibiotics is clearly not recommended to avoid exacerbating the major problem of AMR.

Screening of Nosocomial Sepsis for Acutely Ill and High-Risk Patients

The definition of acutely ill and high-risk patients is not specified in the SSC 2021 guidelines, but it is often suggested (**Table 1**) that it is those with an expected hospital stay of more than five days (with two or more co-morbidities), critically ill patients, coma patient >48h, severely burned patients, emergency and abdominal surgery, trauma patient with open fracture, patient with invasive mechanical ventilation, catheters (central venous, arterial, urinary, ...), pleural drainage and parenteral nutrition (Farinas-Alvarez et al. 2000; Appelgren et al. 2001).

Current nosocomial sepsis screening tools are designed to promote early identification, maybe even before symptoms (pre-symptomatic diagnosis of nosocomial sepsis) and consist of manual methods or automated use (with or without artificial intelligence) of the electronic health record (EHR), biomarkers, and/or transcriptomic technology.

Electronic Health Record

According to SSC 2021 guidelines (Evans et al. 2021), *"there is wide variation in diagnostic accuracy of these tools with most having poor predictive values, although the use of some was associated with improvements in care processes. A variety of clinical variables and tools are used for sepsis screening, such as systemic inflammatory response syndrome (SIRS) criteria, vital signs, signs of infection, quick Sequential Organ Failure Score (qSOFA) or Sequential Organ Failure Assessment (SOFA) criteria, National Early Warning Score (NEWS), or Modified Early Warning Score (MEWS). Machine learning may improve the performance of screening tools, and in a meta-analysis of 42,623 patients from seven studies for predicting hospital-acquired sepsis, the pooled area under the receiving operating curve (SAUROC) (0.89; 95% CI, 0.86–0.92); sensitivity (81%; 95% CI, 80–81), and specificity (72%; 95% CI, 72–72) was higher for machine learning than the SAUROC for traditional screening tools such as SIRS (0.70), MEWS (0.50), and SOFA (0.78). Screening tools may target patients in various locations, such as in-patient wards, emergency departments, or ICUs. A pooled analysis of three RCTs did not demonstrate a mortality benefit of active screening (RR, 0.90; 95% CI, 0.51–1.58)".*

Biomarkers

Numerous studies have been carried out on a wide range of biomarkers (Procalcitonin PCT, C-reactive protein CRP, presepsin, leukocytes, Interleukin-6, monocyte distribution width, etc.) to screen for early sepsis when first symptoms appear. Several studies (Klein et al. 2020; Klein et al. 2015; Pugin et al. 2021) have shown that the Pancreatic Stone Protein (PSP) can detect sepsis up to three to five days before the first symptoms appear (pre-symptomatic diagnosis of nosocomial sepsis). In a cohort of 90 severely burned patients (Klein et al. 2020), *"PSP differentiated between sepsis, infection, and sterile inflammation from day 3 onward with an area under the curve of up to 0.89 ($P < 0.001$)".* In an unselected population of cardiac surgery patients (Klein et al. 2015), *"post-operative serum PSP levels were significantly associated with the presence of infection in both the on-pump and off-pump setting."* A prospective multi-centre study published in 2021 in *Critical Care* (Pugin et al. 2021) shows that *"serial PSP measurement demonstrated an increase of this marker the days preceding (up to 3-5 days) the onset of signs necessary to clinical diagnose sepsis".* From then on, numerous centres in dozens of countries proposed to measure PSP daily in acutely ill and high-risk patients to assess the risk of sepsis (**Figure 1**).

As shown by two literature reviews, from 2019 (13 studies) (Eggimann et al. 2019) and from February 2022 (Fidalgo et al. 2022) (23 studies), PSP is confirmed as an innovative tool for early detection of sepsis, infection diagnosis, and to predict severity and mortality. PSP is a 16 kDs C-type lectin protein produced mostly by the pancreas and the intestine and is a damage-associated molecular pattern DAMPs. PSP is measured in seven minutes from a drop of capillary, venous or arterial whole blood at the point-of-care POC (CE certified IVDR 2022, Intended for use: Risk of sepsis, abioSCOPE®, Abionic SA, Epalinges, Switzerland). A 2021 independent U.S. economic study (Schneider et al. 2022) shows that the use of PSP could save the U.S. healthcare system U.S. $7 billion a year.

Transcriptomic

There are a few studies (Bodinier et al. 2023; Lukaszewski et al. 2022) using transcriptomic technology for pre-symptomatic diagnosis of nosocomial infection and sepsis. However, this complex and expensive technology can currently only be used in

clinical research contexts, with unsatisfactory results in everyday practice.

Conclusion

Hospital and ICU nosocomial sepsis screening for acutely ill and high-risk patients is strongly recommended (moderate quality of evidence) by the latest SSC 2021 guidelines (Evans et al. 2021). A specific tool for pre-symptomatic diagnosis of nosocomial sepsis is not currently recommended, but daily measurement of PSP has been shown to diagnose nosocomial sepsis three to five days before the onset of symptoms (Pugin et al. 2021). Compared to the automated study of the patient's electronic health record EHR by complex algorithms (with or without artificial intelligence) and too slow and expensive transcriptomic technology, the cheap PSP assay can be performed at the patient's bedside in seven minutes from 50 ul of whole blood and with major savings potential for healthcare systems (7 billion/year in the U.S.) (Schneider et al. 2022).

Disclaimer

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Ana María Abella Álvarez
Intensivist
Intensive Care Unit
Hospital Universitario del Henares
Coslada-Madrid, Spain
Grupo de Investigación en Patología Crítica
Facultad de Medicina
Universidad Francisco de Vitoria
Pozuelo de Alarcón
Madrid, Spain
a.pucela@gmail.com

Inés Torrejón Pérez
Intensivist
Intensive Care Unit
Hospital Universitario del Henares
Coslada-Madrid, Spain
Professor of Physiology
Facultad de Medicina
Grado de Medicina
Universidad Francisco de Vitoria
Pozuelo de Alarcón
Madrid, Spain
Grupo de Investigación en Patología Crítica
Facultad de Medicina
Universidad Francisco de Vitoria
Pozuelo de Alarcón
Madrid, Spain
inesili@hotmail.com

Sonia Pajares Martínez
Resident
Intensive Care Unit
Hospital Universitario del Henares
Coslada-Madrid, Spain
soni_pm93@hotmail.com

Federico Gordo Vidal
Head of Department Intensive Care Unit
Hospital Universitario del Henares
Coslada-Madrid, Spain
Grupo de Investigación en Patología Crítica
Facultad de Medicina
Universidad Francisco de Vitoria
Pozuelo de Alarcón
Madrid, Spain
Professor of Physiology
Facultad de Medicina
Grado de Medicina
Universidad Francisco de Vitoria
Pozuelo de Alarcón
Madrid, Spain
fgordo5@gmail.com

Individualisation of Mechanical Ventilation in Obstructive Lung Disease: Not All Ventilated Patients Have ARDS

Chronic obstructive pulmonary disease and asthma are pathologies par excellence with an obstructive pattern. It is important to understand the fundamentals of mechanical ventilation management in these patients. Therefore, it is crucial to perform proper measurement of respiratory mechanics in patients with obstructive pathology.

Introduction and Justification

Chronic obstructive pulmonary disease (COPD) and asthma are pathologies par excellence with an obstructive pattern. According to a multicentre Spanish study assessing changes in the epidemiology of mechanical ventilation in Spain from 1998 to 2016, a significant shift in the reason for mechanical ventilation is observed, alongside a decrease in COPD from 12% to 5% as the cause for initiating mechanical ventilation. This decrease may be related to the increased use of non-invasive mechanical ventilation in this condition (Peñuelas et al. 2021). Regarding asthma, an American study estimates that out of the two million annual visits to the emergency department attributed to severe asthma exacerbations, approximately 25% of patients are hospitalised. Among these, between 5% and 10% require admission to the ICU, of which 2.1% require intubation and mechanical ventilation (Louie et al. 2012). As for the mortality of patients with obstructive respiratory pattern, it ranges from 11% to 32% in patients with COPD and from 1% to 7% in patients with asthma.

For all these reasons, it is important to understand the fundamentals of mechanical ventilation management in these patients (Gadre 2018).

Pathophysiology

In a mechanically ventilated patient, expiration occurs because the alveolar pressure (Palv) is greater than the airway pressure (Paw), producing a flow (Q) against an expiratory resistance (Raw) so that expiratory Q = (Palv - Paw)/ Raw. When airflow is obstructed, Raw increases, thus increasing the denominator and resulting in a decrease in expiratory Q.

It is believed that the mechanisms of airflow limitation are related to the collapsibility of the small airways. However, the anatomical location of this limitation is not entirely clear (Junhasavasdikul et al. 2018). In this situation of increased airway resistance and decreased expiratory flow, if we do not give sufficient expiratory time, there will be an increase in volume at the end of expiration beyond the functional residual capacity (FRC), resulting in hyperinflation and consequently in an end-expiratory pressure called intrinsic positive end-expiratory pressure (PEEPi). Therefore, early detection could help in the management of mechanically ventilated patients with flow limitation. This can be suspected using different means, but above all, by observing the ventilator curves.

In patients ventilated in volume-limited mode (**Figure 1**), the inspiratory phase of the pressure curve shows an increase in

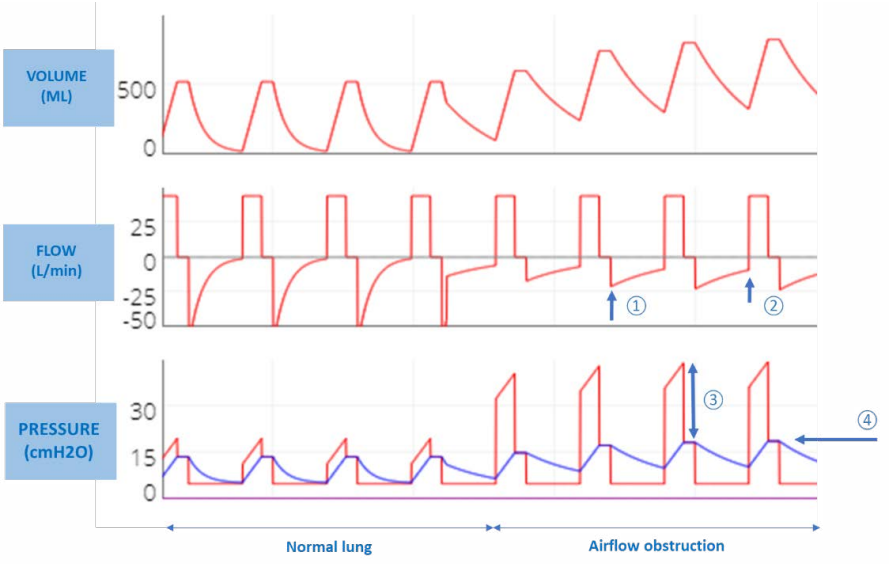

Figure 1. Xlung simulator®: It is observed the difference between a healthy lung and a lung with airflow obstruction with the same volume-limited parameters where ① shows a decrease in the peak expiratory flow, ② shows that the expiratory flow does not reach zero, ③ shows an increase in the resistance pressure and ④ shows that as the obstruction progresses, the plateau pressure increases. Moreover, in the case of the volume/time curve, it can be observed that when the obstruction occurs, the tidal volume (Vt) and the residual volume are added together and increase progressively.

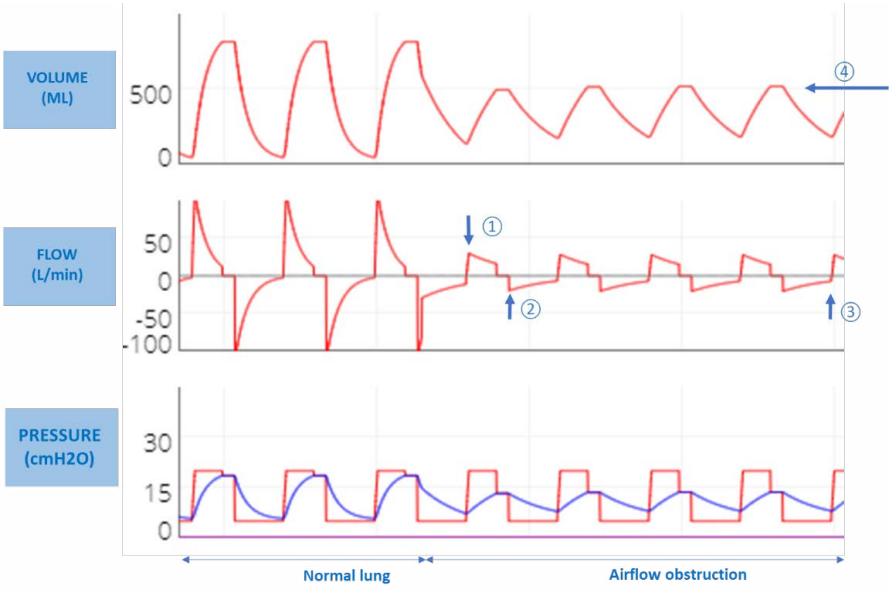

Figure 2. Xlung simulator®: It is observed the difference between a healthy lung and a lung with airflow obstruction with the same pressure-limited mode parameters where ① shows a decrease in the peak inspiratory flow, ② shows a decrease in the peak expiratory flow, ③ shows that the expiratory flow does not reach zero and ④ shows a decrease in tidal volume (Vt). In addition, the pressure/time curve is shown with an inspiratory pause (to observe the actual effect on alveolar pressure despite being in pressure-limited mode).

airway resistance ((peak pressure - plateau pressure)/inspiratory flow). On the other hand, in the expiratory phase, there is a decrease in the peak expiratory flow. In addition, the expiratory curve does not reach zero because the respiratory system does not attain the FRC.

On the other hand, when the patient is ventilated in a pressure-limited mode (**Figure 2**), a reduction in both inspiratory and expiratory flow is observed, as well as a reduction in volume. Also, as with volume modes, the expiratory flow curve does not reach zero.

In both modes, this expiratory flow curve may show a sudden change in slope due to dynamic collapse and flow reduction, even reaching a square root morphology (Correger et al. 2012). In these patients, an increased peak pressure, an increased airway resistance pressure, a non-zero expiratory flow and, as entrapment progresses, an increase in plateau pressure can be observed.

Furthermore, it is essential to consider that entrapment can arise solely from improper ventilator programming, including the use of high respiratory rates that impede complete lung emptying. In a recent study, the presence of PEEPi and dynamic hyperinflation was evaluated in a large population of patients with acute respiratory distress syndrome (ARDS). The study concluded that in patients who are sedated and receiving neuromuscular relaxation without a known obstructive disease, PEEPi is insignificant and, therefore, does not affect respiratory mechanical properties (Coppola et al. 2019). Nonetheless, it is crucial to individualise each case. Accordingly, it is necessary to assess, in cases where shortening the expiratory time is required, the potential for air trapping and secondary effects on respiratory mechanics and haemodynamics, particularly when the patient is not heavily sedated or under neuromuscular relaxation.

Negative effects of hyperinflation

Hyperinflation has adverse effects:

- From a haemodynamic point of view, the increase in intrathoracic pressure due

to air entrapment leads to a reduction in left ventricular end-diastolic volume and systolic volume with consequent arterial hypotension. If the haemodynamic consequences of PEEP are not recognised, it can lead to inadequate fluid restriction or unnecessary vasopressor treatment.

- On the other hand, at the pulmonary level, hypoventilation occurs despite an increase in minute volume. This is due to local overdistension of areas that do not empty on expiration, as well as the collapse of adjacent areas, thereby worsening ventilation. In cases where the pressure generated by hyperinflation is high, there is a risk of barotrauma and arterial hypotension. Therefore, whether due to its haemodynamic effects or its impact at the pulmonary level, arterial hypotension can be differentiated by a simple manoeuvre: disconnecting the patient from the ventilator for about 15 seconds. If the blood pressure rises after this manoeuvre, it is most likely that the cause of the hypotension is pulmonary hyperinflation. By disconnecting, the lungs have been emptied, and the hyperinflation has been reduced. If blood pressure does not rise after the manoeuvre, the possibility of pneumothorax must be considered.
- Another adverse effect of air trapping is the increased work of breathing for the patient when initiating inspiration. This is because the patient must first overcome the pressure created by the trapped air to activate the ventilator. Consequently, greater effort and negative pressure are required to stimulate the trigger **(Figure 3).**

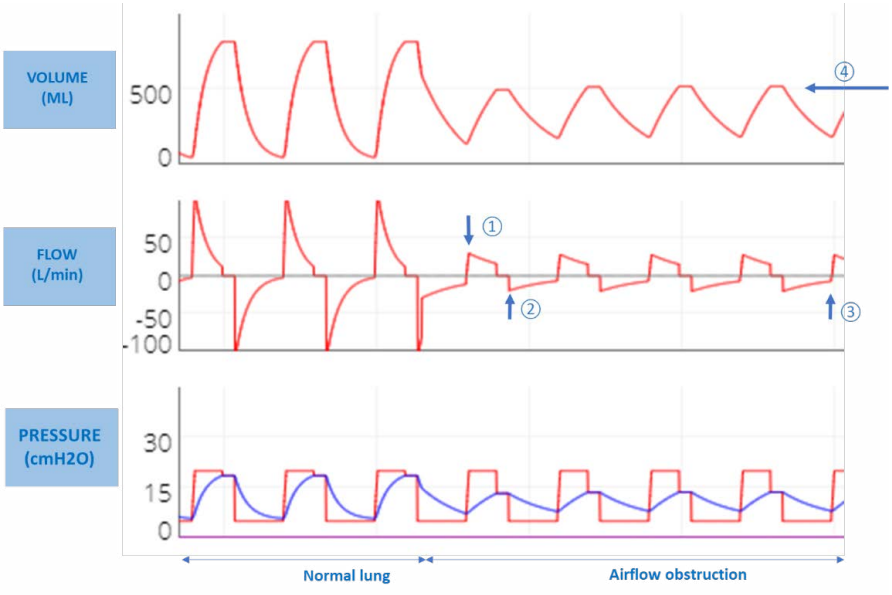

Figure 3. Comparing these two graphs: green represents the normal subject, while red represents the patient with hyperinflation. In the green curve, inspiration begins at point A and continues until reaching the ventilator trigger at point B. In the red curve, inspiration starts from the highest-pressure point C and extends to the ventilator trigger at point D. As a result, it requires a higher negative pressure to activate the ventilator.

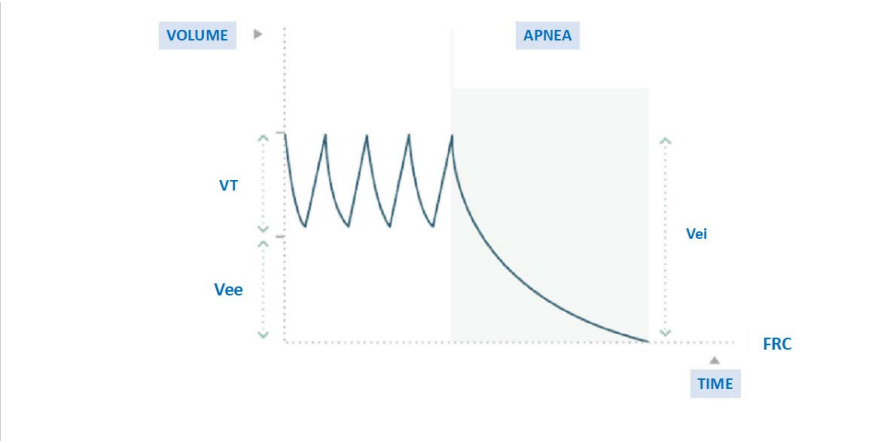

Figure 4. Vei: end-inspiratory lung volume; Vee: trapped volume; FRC: functional residual capacity; Vt: tidal volume

Measuring intrinsic PEEP

Given the effects of hyperinflation, it is important to measure PEEPi.

The most commonly used manoeuvre to measure PEEPi is to perform an expiratory pause of approximately 0.5 to 2 seconds. Thus, at the end of expiration both valves are closed, the pressures are equalised, and the pressure generated by the trapped air is measured. Although this is the most commonly used method for measuring PEEPi, it does not correlate with the risk of complications and is a poor estimator of true Palv.

The measurement that is associated with a higher risk of complications is end-inspiratory lung volume (Vei). This volume is the sum of the Vt and the trapped volume (Vee) **(Figure 4).** It is calculated by measuring the total volume of expired gas in a relaxed patient following a period of apnoea lasting 60 seconds, thereby allowing the lung to attain FRC.

Therefore, a Vei surpassing 20 ml/kg is indicative of complications. The study by Roesthuis et al. (2021) examines bedside methods that offer easier implementation. These methods effectively capture the Vei, leading to the conclusion that airway

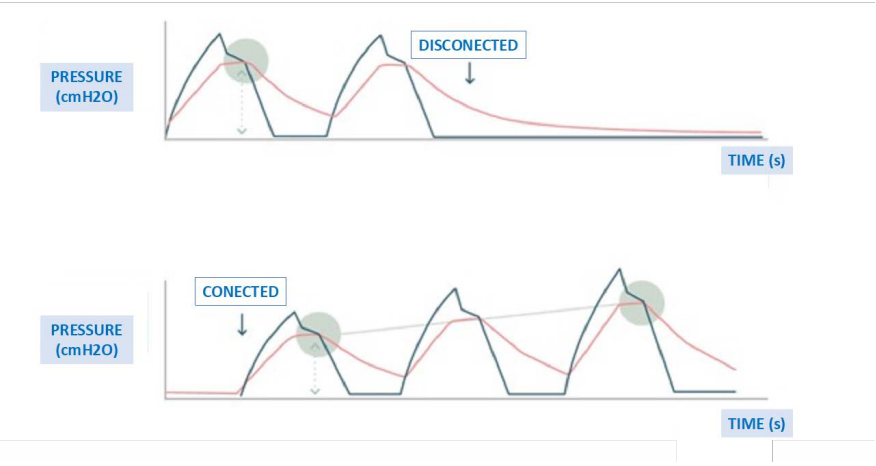

Figure 5: The plateau pressure is measured before disconnection. The patient is disconnected and reconnected after 20 seconds. Immediately after connection, the plateau pressure is measured before any air trapping occurs in subsequent breathing cycles.

pressures do not accurately represent the Vei in COPD patients. Furthermore, the three techniques employed to quantify Vei exhibit low bias but wide limits of agreement.

To enlarge upon the above, another limitation of measuring PEEPi using the expiratory pause manoeuvre is that it measures the air at the end of expiration. This air is in contact with the airway and, consequently, with the ventilator, which is where the pressure is measured. Therefore, it cannot measure the pressure generated by the air trapped behind the closed airways (Mannam 2010). This unmeasured pressure is known as 'hidden PEEP'. In this regard, one way to suspect that all the trapped air present is not measured is when, despite managing to decrease PEEPi through the various manoeuvres discussed below, the plateau pressure does not decrease. Moreover, a manoeuvre that provides a closer approximation to reality is the disconnect and reconnect method, where the difference in plateau pressure is measured before and after. This difference represents the pressure generated by the trapped air **(Figure 5).**

Management

The management of these patients is initially based on medical treatment and even non-invasive mechanical ventilation. However, close monitoring is of paramount importance because if there is no clinical improvement, endotracheal intubation and invasive mechanical ventilation should not be delayed.

The various manoeuvres to adjust ventilator parameters are aimed at increasing expiratory time (Garner et al. 2022). This can be accomplished by decreasing the respiratory rate and Vt, although these adjustments may result in hypoventilation and, subsequently, hypercapnia. Nevertheless, as long as it remains within the limits of what is known as permissive hypercapnia, which does not exceed 90 mmHg and maintains a pH above 7.15, it is considered acceptable and well-tolerated. Furthermore, other adjustments used to prolong expiratory time include increasing the inspiratory:expiratory ratio (I:E) without exceeding 4 seconds of expiratory time, as there is no evidence that more lung clearance is achieved beyond this time. Also, another approach is to increase the inspiratory flow without exceeding 50 cmH_2O of pressure because of this increase in flow. Finally, the last approach is to reduce the inspiratory pause if the patient is in a volume-limited mode.

Apart from this, no differences were found between pressure-limited and volume-limited ventilation modes in these patients. Therefore, the mode chosen is the one with which the specialist is more comfortable, but most importantly, the one that gives the best ventilation to the patient. In this regard, an advantage of the volume mode over the pressure mode is that the curves give more information, and more parameters can be adjusted to prolong the expiratory time.

The expiratory time constant (eTC) is a measure derived from the product of compliance and airway resistance (Demoule et al. 2020). The expiratory time is considered to be at least three times the eTC, so if it is less than twice the eTC, there is a risk of hyperinflation. However, in patients with obstructive pathology, the regional differences in mechanical properties preclude the use of a single eTC for the entire lung (Laghi et Goyal 2012).

Furthermore, another important parameter to consider is the extrinsic PEEP (PEEPe). On the one hand, by appropriately adjusting this parameter, it is possible to achieve a decrease in one of the consequences of air entrapment, namely the workload experienced by the patient. When the pressure trigger is activated, with adequate PEEPe, the patient does not have to make an inspiratory effort from PEEPi to the trigger but from PEEPi to below PEEPe. On the other hand, PEEPe can also serve as a therapeutic measure, as it allows the opening of closed small airways and their emptying at the end of expiration. Moreover, it has been conventionally established that the PEEPe should be set at 80% of the PEEPi. However, considering that the manoeuvres used to measure PEEPi do not consider hidden PEEP, it is difficult to determine a percentage of pressure that cannot be reliably measured. Therefore, in a situation of air entrapment, to find the most appropriate PEEPe in each case to keep the airway open and achieve optimal lung emptying, it is recommended to perform a PEEP trial (Liang and Zhang 2016). This can be done by measuring plateau pressure and/or total PEEP (PEEPt) while increasing PEEPe by 2 cmH_2O per minute. When increasing the PEEPe, if there is no observed increase in plateau pressure or PEEPt, or if the increase is less than 2 cmH_2O, this would indicate lung emptying is taking place. On the

Extrinsic PEEP	14	16	18	20	22	24
Total PEEP	24	23	23	24	23	25
Intrinsic PEEP	9,6	6,7	4,7	4,4	0,6	0,5
Plateau pressure	30	29	30	31	32	34
Compliance	24	29	31	30	39	40
Resistance	31	26	26	23	22	22

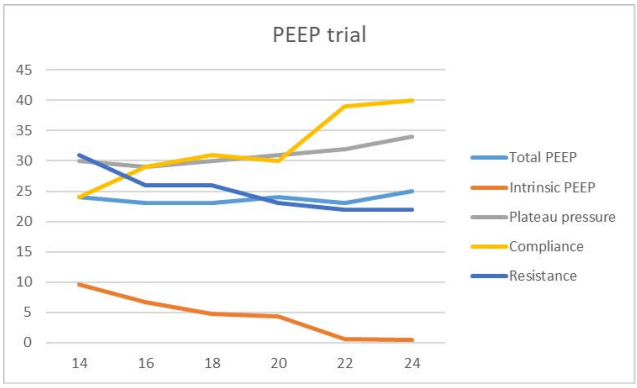

Figure 6. PEEP trial in asthmatic patients. As PEEPe increases from 14 to 24 cmH_2O, there is no significant increase in plateau pressure, total PEEP, or decrease in resistance up to 22 cmH_2O, which is the most appropriate PEEPe.

contrary, once it is observed that the plateau pressure or PEEPt increases proportionally to the increase in PEEPe, it will be considered that there is no further lung emptying (**Figure 6**) (Abella et al. 2023). Therefore, the PEEPe that is prescribed is the one prior to the point at which lung emptying ceases.

Conclusion

The early recognition of air entrapment could aid in the management of mechanically ventilated patients with airflow obstruction. Moreover, this could potentially have an impact on the prognosis. Therefore, it is crucial to perform proper measurements of respiratory mechanics and consider the possibility of hidden PEEP.

To conclude, the objective of adjusting mechanical ventilation in obstructive pathology is to increase expiratory time and perform individualised PEEP trials for each case.

Conflict of Interest

None.

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Davide Chiumello
Department of Anesthesia and Intensive Care
ASST Santi Paolo e Carlo
San Paolo University Hospital
Milan
Department of Health Sciences
University of Milan
Coordinated Research Center on Respiratory Failure
University of Milan
Italy
davide.chiumello@unimi.it

Giulia Catozzi
Department of Anesthesia and Intensive Care
ASST Santi Paolo e Carlo
San Paolo University Hospital
Milan
Department of Health Sciences
University of Milan
Italy
giulia.catozzi@unimi.it

Silvia Coppola
Department of Anesthesia and Intensive Care
ASST Santi Paolo e Carlo
San Paolo University Hospital
Milan
Department of Health Sciences
University of Milan
Italy
silvia_coppola@libero.it

The Mechanical Power as a Guide for Protective Mechanical Ventilation in Patients With and Without ARDS

Mechanical power is an easy bedside tool to guide lung protective ventilation, as it is an index of the energy load applied to the lung during mechanical ventilation and expresses in one formula all the main determinants of ventilator-induced lung injury. Although a threshold value has not already been defined, a mechanical power greater than 17 J/min has been demonstrated to be associated with the risk of death.

Approximately 35% of critically ill patients admitted to an intensive care unit required mechanical ventilation (Bellani et al. 2016). Irrespective of the underlying disease, mechanical ventilation is instituted to ensure adequate gas exchange and reduce the work of breathing and ventilator-induced lung injury (VILI) (Fan et al. 2018).

According to the motion equation, the pressure developed inside the respiratory system is used to generate an inspiratory flow and a change in tidal volume (Gattinoni et al. 2016). For a given flow and tidal volume, the generated airway pressure into the respiratory system can be different according to the elastic and resistive load of the lungs and chest wall. In passive conditions, the possible development of lung injury during mechanical ventilation thus arises from the interaction between the ventilator and the characteristics of the respiratory system.

In daily clinical practice, the tidal volume and the driving pressure are usually considered the main determinants of the VILI, although the respiratory rate and the level of positive end-expiratory pressure (PEEP) could also play a role, albeit to a lesser extent (Fan et al. 2017; Sahetya et al. 2017).

In order to unify all these variables, in 2016 our group proposed mechanical power as an index of the energy load applied during mechanical ventilation, which could be related to the risk of the VILI (Cressoni et al. 2016; Gattinoni et al. 2016). Initially, it was computed including tidal volume, respiratory rate, compliance, resistance and inspiratory flow in the formula. Subsequently, a more simplified formula based only on the inspiratory plateau pressure, applied PEEP, and tidal volume has been proposed (Chiumello et al. 2020; Giosa et al. 2019). However, this more simplified formula can be used only during volume control ventilation with a constant inspiratory flow (Gattinoni et al. 2016). On the contrary, during pressure control ventilation, in which the flow is decelerated, another specific algebraic formula should be applied (Chiumello et al. 2020). Both these surrogate algebraic formulae (i.e. for volume and pressure control ventilation), based on variables commonly provided by the mechanical ventilator (Chiumello et al. 2020), showed an acceptable accuracy compared to the more sophisticated comprehensive formula.

Furthermore, the new generation of mechanical ventilators can both continuously and automatically show mechanical power at the bedside with good accuracy (Chiumello et al. 2022) **(Figure 1).**

A post hoc analysis of a large randomised clinical trial comparing the application of a low versus a high tidal volume (6 ml/kg vs 10 ml/kg of predicted body weight) in healthy patients during general anaesthesia for major surgery, demonstrated that the mechanical power was associated with an increased risk of postoperative pulmonary

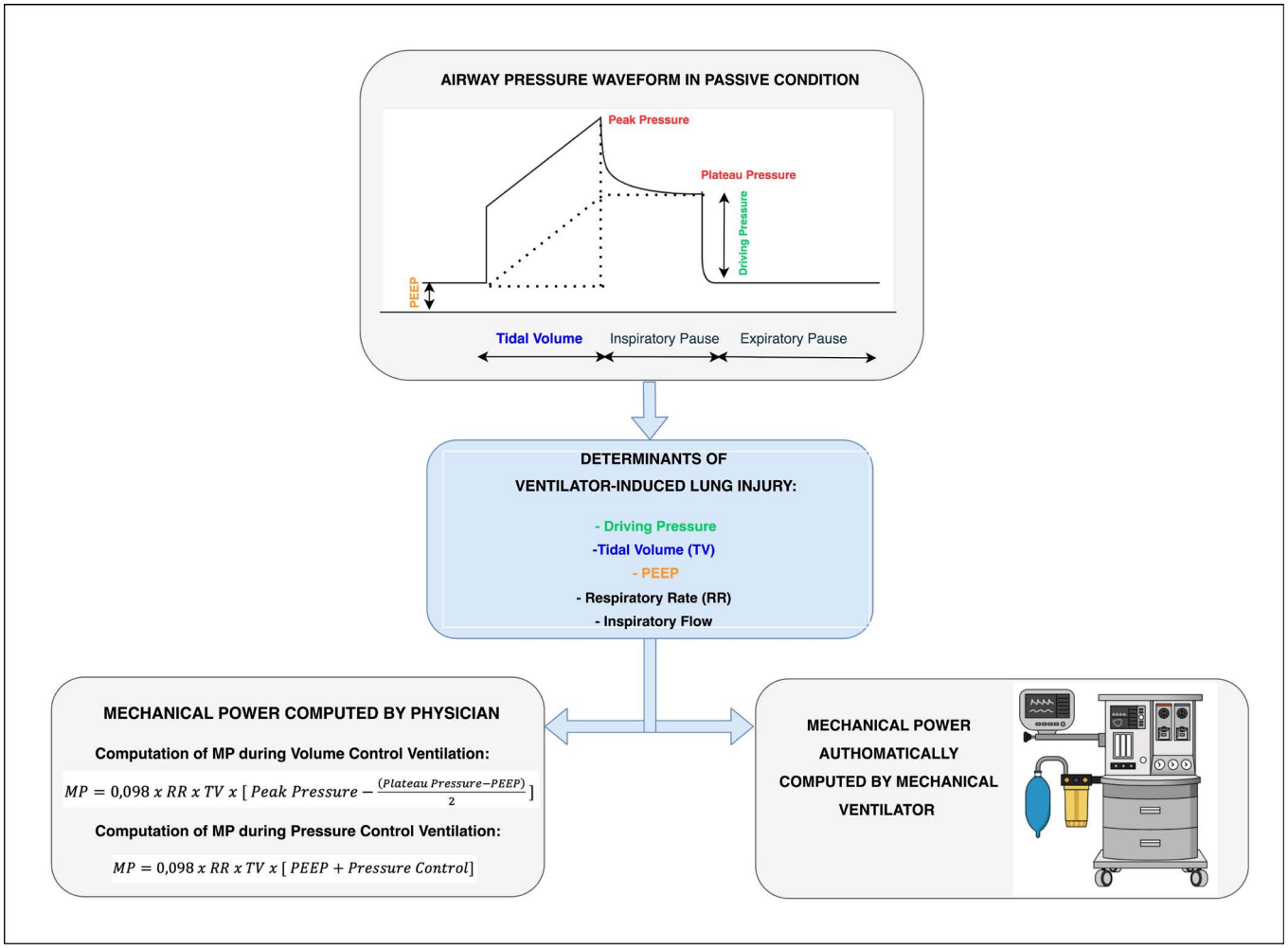

Figure 1. Overview of determinants of ventilator-induced lung injury and the bedside computation of mechanical power during controlled mechanical ventilation.

complications and acute respiratory failure [OR, 1.34 (95% CI, 1.17 to 1.52), P <0.001; OR, 1.40 (95% CI, 1.21 to 1.61), P <0.001] in the first seven postoperative days (Karalapillai et al. 2022). A subsequent retrospective cohort study which analysed data of patients who underwent general anaesthesia between 2008 and 2018, found that the median intraoperative mechanical power was higher in patients with postoperative respiratory failure than in patients without (7.67 vs 6.62 J/min; P <0.001) (Santer et al. 2022). In particular, a higher mechanical power was associated with a greater risk of postoperative reintubation: for each 5 J/min increase in mechanical power, the adjusted risk of reintubation was 31% higher (Santer et al. 2022).

In critically ill mechanically ventilated patients admitted to the emergency department without acute respiratory distress syndrome (ARDS), 8.9% developed ARDS during the intensive care stay (Fuller et al. 2018). Compared to patients without ARDS, those who developed ARDS presented a significantly higher mechanical power at admission (17.5 vs 15.7 J/min, respectively). Interestingly, the incidence of ARDS was significantly higher for mechanical power values greater than 12 J/min.

Analysing critically ill patients admitted to intensive care who were mechanically ventilated for at least 48 hours, the mechanical power after the first 24 hours of ventilation was significantly associated with higher intensive care and 30-day mortality (Serpa Neto et al. 2018). There was a consistent increase in the risk of death for mechanical power values greater than 17 J/min, and these mechanical power values remained associated with higher mortality even in the presence of low tidal volume or driving pressure.

Considering patients with sustained ARDS, mechanical power values greater

than 22 J/min were associated with higher hospital mortality and lower survival at three years (Parhar et al. 2019).

However, a similar mechanical power could result in different degrees of possible lung injury according to the lung and chest wall elastance characteristics. The real distending force of the lung is not the airway pressure but the transpulmonary, computed as the difference between the airway and pleural pressure (i.e. commonly as the oesophageal pressure); consequently, especially in the presence of chest wall impairment, the transpulmonary mechanical power should better reflect the possible lung injury. In addition, ARDS patients are characterised by a huge variability in the lung size (i.e. baby lung), which mainly depends on the severity of respiratory failure. In fact, the possible lung injury could also be related to the amount of aerated tissue and size of the baby lung: a less injured lung could tolerate a higher mechanical power compared to a sicker lung. In other words, a similar mechanical power could be more harmful in severe ARDS compared to moderate ARDS. When the mechanical power was normalised to the aerated lung, it was associated with intensive care mortality (Coppola et al. 2020). In addition, among the different ventilator parameters such as tidal volume, respiratory rate, PEEP, and driving pressure, the mechanical power normalised to compliance had the highest predictive discrimination for the patient outcome (Zhang et al. 2019).

At the present time, according to the available data and based on the pathophysiology of the VILI, the mechanical power, which can be easily computed by physicians at the bedside or displayed in the modern ventilators, should be included in the daily clinical monitoring as an easy tool to guide a lung protective strategy.

Conflict of Interest

None.

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Seven Myths of Mechanical Ventilation in Paediatric and Neonatal Patients

In this article, we will examine clinical concepts that have persisted over time, despite advancements in our understanding of physiology and technological innovations that have demonstrated their inapplicability in the routine clinical care of paediatric patients requiring respiratory support. These enduring beliefs have effectively transformed into myths.

David Pascual Rojas-Flores
Paediatric Intensive Care Unit
Regional General Hospital No. 1 IMSS
Santiago de Querétaro, Mexico
@MedCritPed
pediatriacompleta@gmail.com

Jorge Nestor Soriano-Martínez
Paediatric Cardiac Intensive Care Unit
High Specialty Medical Unit 34 IMSS
Monterrey, Nuevo León, Mexico
@DrBarca26
dr.nestor.soriano@gmail.com

Raúl Toledo-Pérez
Neonatology Department
MAC Hospital San Miguel de Allende and Joya Hospital
San Miguel de Allende, Guanajuato, Mexico.
@rulotoledo
drtoledopr@gmail.com

Gabriela Montesinos-Gómez
Paediatric Cardiac Intensive Care Unit
UMAE 34 Cardiology Unit
Monterrey, Nuevo León, México
dragmontesinos@gmail.com

**All authors are members of the AVENTHO Group for Education and Investigation in Mechanical Ventilation, Paediatric and Neonatal Division*

Background

Invasive mechanical ventilation (IMV) in paediatric and neonatal patients displays heterogeneity concerning ventilator programming and patient monitoring. Despite the presence of guidelines outlining management principles that have demonstrated a reduction in mortality among paediatric and neonatal patients under mechanical ventilation, these guidelines are not universally adopted by clinicians (Bhalla et al. 2021). Furthermore, in developing countries, myths and suboptimal practices surrounding IMV are prevalent due in large part to a scarcity of specialists and insufficient education in patient management (Zenteno et al. 2021). This situation can lead to prolonged hospital stays and readmissions. Additionally, the literature on this topic is sparse compared to studies involving adult patients on IMV, leaving significant gaps in the current body of knowledge. Therefore, we conducted a review focusing on seven of these myths surrounding paediatric and neonatal IMV.

Myth 1: The use of cuffed endotracheal tubes is not recommended for paediatric patients

Historically, uncuffed endotracheal tubes (ETTs) were preferred for young children because the paediatric airway narrows below the vocal cords, creating an anatomical seal around the distal tube. Concerns about tracheal injury associated with cuff usage, such as fistulas or tracheal stenosis, led to the use of uncuffed ETTs for an extended period. The incidence of tracheal injuries from ETTs decreased with the introduction of low-pressure cuffs in the 1970s (Stoller 1999). Prior to 2010, both cuffed and uncuffed ETTs were deemed acceptable for intubating infants and children. Cuffed devices were recommended in specific clinical scenarios, such as low lung compliance, high airway resistance, or glottic air leaks (Kleinman et al. 2010).

Numerous contemporary studies and systematic reviews now support the safety of cuffed ETTs (De Orange et al. 2017; Chen et al. 2018; Shi et al. 2016). Advantages of using cuffed ETTs include improved capnography accuracy, reduced need for tube changes (which can lead to high-risk reintubations or delayed compressions), potential decrease in aspiration risk, and improved administration (and measurement) of pressure and tidal volume during mechanical ventilation—an essential aspect of preventing ventilator-induced lung injury (Chambers et al. 2018; Schweiger et al. 2013; Weiss et al. 2009). Subglottic stenosis is rare when employing cuffed ETTs in children and following meticulous technique (Black et al. 1990). European and North American paediatric cardiopulmonary resuscitation guidelines advocate for the use of cuffed ETTs in paediatrics (Topjian et al. 2020; Van de Voorde et al. 2021). It is vital to monitor cuff pressure and adhere to each manufacturer's recommendations (typically <20 to 25 cm H_2O). Cuff pressures are dynamic during transport at altitude (Orsborn et al. 2016) and with increasing airway oedema.

The smallest internal diameter available for Microcuff© ETTs is 3.0 mm, recommended solely for newborns ≥3 kg. No standardised guideline exists for proper cuff management or methods to determine inflation volume, maximum pressure usage, and frequency of pressure measurements in neonates. Comparative studies between cuffed and uncuffed ETTs in the neonatal population were absent

until 2016 (Thomas et al. 2016). A pilot study published in 2019 with 76 patients compared Microcuff© ETTs with and without cuffs in neonates > 35-week gestation up to 3-month-old infants weighing ≥3 kg and requiring ventilation management in the neonatal and paediatric intensive care unit. The uncuffed ETT group exhibited significantly higher rates of re-intubation at any point during the ventilation period and more frequent episodes of atelectasis or other ventilation-related complications. No differences were observed in post-extubation stridor rates, post-extubation dexamethasone use, nebulised adrenaline post-extubation, or reintubation due to airway obstruction. At 34.7 months of follow-up, none of the patients in either group had developed subglottic stenosis. Caution was exercised in recommending confirmation of these results through larger multicentre studies (Thomas et al. 2019).

Myth 2: Patients weighing less than 10 kg should be ventilated in pressure-controlled assist-control mode, while those weighing more than 10 kg should be ventilated in volume-controlled assist-control mode

The choice of ventilatory mode in paediatric patients has been historically influenced by a paradigm: using pressure-controlled assist-control ventilation (PC-AC) for patients weighing less than 10 kg and neonates, and volume-controlled assist-control ventilation (VC-AC) for those weighing over 10 kg. This was attributed to the following reasons: 1) the belief that VC-AC mode lacked continuous flow and significant leaks from an uncuffed endotracheal tube would interfere with ventilation; 2) the inability to compensate for compressible volume in the airway; and 3) technical limitations of some ventilators to provide the required low tidal volumes (Vt) and flows to prevent volutrauma (Gregory et al. 1971). These largely technical challenges have been addressed with the advent of ventilators and circuits adapted for paediatric and neonatal ventilation. The proximal flow sensor can accurately measure tidal volume and low flows, and these ventilators can deliver tidal volume and low flows while compensating for compressible volume and leaks, providing continuous basal flow.

The advantages of ventilating patients weighing less than 10 kg in VC-AC mode include strict control over tidal volume, potentially avoiding volutrauma, closer monitoring of plateau pressure (Pplateau) and driving pressure (DP), as well as improved alveolar air distribution, resulting in more homogeneous distribution and reduced risk of barotrauma and pneumothorax. The main limitation of VC-AC mode is the lack of consensus on determining the optimal protective tidal volume formula for the paediatric population. An alternative is the use of pressure-regulated volume control mode (PRVC) in premature newborns, which has shown benefits in survival and prevention of volutrauma in bronchopulmonary dysplasia.

A systematic review and meta-analysis in 2017 identified 20 controlled and randomised studies comparing Volume-

Non-invasive support	
High-flow nasal	No
Continuous positive airway pressure	Consider in mixed disease Consider in mild-to-moderate cardiorespiratory failure No recommendation on optimal interface
Non-invasive	Consider in mild-to-moderate disease, but not severe disease Consider in mild-to-moderate cardiorespiratory failure Should not delay intubation
High-frequency oscillatory ventilation	Consider when conventional ventilation fails May be used in cardiac patients
Invasive ventilation	
High-frequency jet/percussive ventilation	No recommendation Do not use high-frequency jet ventilation in obstructive airway disease
Liquid ventilation	Do not use
Triggering	Target patient-ventilator synchrony
Inspiratory time/I:E ratio	Set inspiratory time by respiratory system mechanics and underlying disease (use time constant and observe flow-time scalar). Use higher rates in restrictive disease
Maintaining spontaneous breathing	No recommendation
Plateau pressure	Keep ≤28 or ≤29–32 cmH_2O with increased chest wall elastance, ≤30 cmH_2O in obstructive airway
Delta pressure	Keep ≤10 cmH_2O for healthy lungs, unknown for any disease condition
Tidal volume	Keep ≤10 mL/kg ideal body weight, maybe lower in lung hypoplasia syndromes
PEEP	5 to 8 cmH_2O, higher PEEP is necessary, dictated by underlying disease severity (also in cardiac patients). Use PEEP titration, consider lung recruitment (also in cardiac patients) Add PEEP in obstructive airway disease when there is air-trapping, and to facilitate triggering, Use PEEP to stent upper airways in case of malacia
Extra-corporeal life support	Consider in reversible disease if conventional ventilation and/or HFOV fails

Table 1: Potential clinical implications of the recommendations from the paediatric mechanical ventilation consensus conference (PEMVECC)

Controlled Ventilation (VCV) and Pressure-Limited Ventilation (PLV) in neonates and premature neonates (Klingenberg et al. 2017). VCV compared to PLV resulted in:

1. Shorter duration of mechanical ventilation by 1.35 days.
2. Lower incidence of pneumothorax.
3. Lower incidence of bronchopulmonary dysplasia (BPD) at 36 corrected weeks.
4. Lower incidence of periventricular leukomalacia or grade 3 or 4 intraventricular haemorrhage.
5. A non-significant trend towards lower mortality.

Myth 3: Low PEEP levels of 0 to 4 cm H_2O should be programmed for paediatric and neonatal patients.

Lung volume changes occur only when changes in transpulmonary pressure (PTP) magnitude occur. Contrary to intuition, lung volume change is not solely influenced by the value of alveolar pressure (Palv) but rather by the value of PTP. As the lung fills with air, each lung volume corresponds to a specific PTP value (Medina 2015).

The summary of the aforementioned is depicted in **Table 1.** Regardless of the values of Palv and pleural pressure (Ppl), if PTP is +5 cmH_2O, the lung fills with a volume of air corresponding to functional residual capacity (FRC). If PTP = +30 cmH_2O, the lung volume matches total lung capacity (TLC). And if PTP = +3 cmH_2O, the corresponding volume is residual volume (RV). The penultimate row in the table represents a scenario where the patient has pleural effusion, causing the intrapleural pressure to become positive (+5 cmH_2O). Without applying PEEP of +10 cmH_2O for ventilation, their end-expiratory volume wouldn't reach FRC.

It has been suggested that PEEP ranges of 5-8 cmH_2O are necessary during invasive mechanical ventilation, and higher PEEP levels may be necessary based on the severity of the underlying disease (also in cardiac patients). Adjusting PEEP levels should always be considered, including adding PEEP in obstructive lung disease when air trapping is present. In cases of malacia, PEEP is used to place a stent in the upper airways (Kneyber et al. 2017).

Myth 4: The synchronised intermittent mandatory ventilation (SIMV) mode should be used for weaning off the mechanical ventilator

MV improves survival in patients with respiratory failure, yet this therapy is not without complications, including ventilator-induced lung injury (VILI), ventilator-associated pneumonia, critical illness-associated weakness, right ventricular dysfunction, and increased costs associated with prolonged MV. Consequently, ventilator withdrawal should occur as soon as the patient is capable of maintaining adequate spontaneous breathing.

Ventilator withdrawal encompasses two scenarios: the gradual reduction of respiratory support (weaning) and the removal of the endotracheal tube (extubation). Extubation failure (EF) refers to a set of conditions leading to reintubation and VM reestablishment within the first 72 hours post-extubation. The decision to initiate weaning depends on the fulfilment of specific clinical criteria, including control of the underlying cause necessitating intubation and MV, effective gas exchange, appropriate neuromuscular condition, sufficient consciousness to protect the airway, and stable haemodynamic status.

The most commonly used weaning method in paediatrics involves the synchronised intermittent mandatory ventilation (SIMV) mode. This mode is often programmed with pressure support to achieve a target tidal volume (Vt) based on patient needs. The theoretical advantage is to alleviate additional respiratory effort imposed by the endotracheal tube and mechanical ventilator circuit. However, in adults, it is evident that this method significantly prolongs MV compared to daily spontaneous breathing trials (SBT) and pressure support ventilation (PSV). Therefore, its use is not recommended.

Commonly employed SBT methods include continuous positive airway pressure (CPAP), tube T trials, and PSV. In paediatrics, method choice largely depends on the treating team's experience, as there is no conclusive evidence that one method is superior to another. Implementing a ventilator withdrawal protocol that includes SBT allows for early identification of patients ready for weaning and facilitates a safer withdrawal process.

Myth 5: PSV is ineffective in paediatrics due to children becoming fatigued.

In 2001, evidence-based guidelines were published for weaning and discontinuing ventilatory support. They classified adult studies on weaning from MV into 1) discontinuation assessment trial (ERT) strategies, 2) controlled trials of gradual reduction in mechanical support, and 3) controlled trials of alternative discontinuation strategies.

A study by Esteban et al. (1997) compared 2-hour spontaneous breathing trials with PS of 7 cmH_2O to tube T trials. A higher number of patients in the PS group tolerated the trial and were extubated at the end of the study compared to the tube T group (86% vs. 78%; relative risk of failure, 0.64; 95% CI, 0.43 to 0.94). There was no difference in reintubation rates. A similar second study by Esteban et al. (1999) also showed no differences in reintubation rates between the groups. However, the shorter tube T trial benefited patients by reducing ICU and hospital stays (2 and 5 days shorter, respectively).

Five randomised clinical trials compared alternative methods to reduce ventilatory support in patients where several days of extubation were thought to be needed. The most informative results came from the two largest studies by Esteban et al. (1997) and Brochard et al. (1994). Both showed that when patients were initially evaluated for extubation using a tube T trial, around 76% could be extubated without weaning. The remaining patients were randomly assigned to be weaned using 2-hour spontaneous breathing trials with various modalities: daily multiple tube T/CPAP breathing, PS mode, and SIMV. The Esteban trial also included a

fourth arm, tube T trials once daily. There was no difference in ventilation duration between tube T and PS, and trends were opposite in the two studies: Esteban et al. (1995) favoured tube T weaning, while Brochard et al. (1994) favoured PS. Both studies showed shorter ventilation duration with tube T compared to SIMV. In the PS vs. SIMV comparison, both studies found trends in favour of PS, although the effect in the Brochard study was much larger.

In the paediatric population, there are few studies comparing PS to other weaning methods. Farias et al. (2001) compared spontaneous breathing trials (SBT) using PS of 10 cmH_2O to a tube T trial. The rationale for using PS was to overcome endotracheal tube resistance. The 257 subjects had to tolerate the 2-hour trial (either PS or tube T) to be considered for extubation. The attending physician could interrupt SBT due to objective (e.g., increased RR or SpO_2 <90%) or subjective (e.g., sweating or increased respiratory effort) signs of poor tolerance. There were no differences in extubation failure rates within 48 hours (15.1% vs. 12.8%) or SBT failure (20.8% vs. 22.7%). The study concluded that a 10 cmH_2O PS SBT was as effective as a tube T trial. In 2002, the same authors studied 418 patients intubated for at least 48 hours using a 2-hour SBT with tube T or 10 cmH_2O PS (^60^). Of the 323 patients (77%) who passed the SBT and were extubated, 14% were re-intubated within 48 hours. Respiratory rate, tidal volume, RSBI, and maximum inspiratory negative pressure (PImáx) were poor predictors of extubation outcome. In both studies, patients underwent an SBT only when deemed ready by the attending physician, possibly not at the earliest point when an SBT could have been performed.

In adults, Esteban et al. (1997) found that two-thirds of patients passed an SBT even before weaning started. If the SBT had been performed earlier in the Farias study, there could have been an increased SBT failure rate in the tube T group compared to the PS group. Willis et al. (2005) quantified respiratory work (measured by a surrogate, the product of pressure rate) in 22 patients. They found no difference between CPAP and 5 cmH_2O PS. Both provided reduced respiratory work compared to tube T (with or without heliox) or extubated patients. Patients on tube T had less respiratory work than when extubated. Takeuchi et al. (2000) demonstrated that breathing work through an ETT for infants was only marginally higher than after extubation. They also showed that 4 cmH_2O PS was more than sufficient to compensate for marginal increases in respiratory work through an internal diameter of 3.5 to 4.5 mm ETT and was equivalent to breathing without the ETT. A series of studies involving 634 infants and children (Farias et al. 2001) demonstrated that a safe spontaneous breathing trial lasting up to two hours could be performed using a tube T trial for ERT. While the trend of using PS with PEEP instead of CPAP or tube T breathing to overcome ETT resistance has emerged, evidence shows that the resistance increase is minimal and the additional respiratory work insignificant. If a baby or small child cannot sustain an SBT with CPAP or a tube T for several hours, the likelihood of extubation failure is as probable as with applied PS. Additionally, PS addition likely masks respiratory failure and contributes to a higher extubation failure rate.

Myth 6: In the case of cardiopulmonary resuscitation, mechanical ventilation should not be maintained during resuscitation

Advanced cardiopulmonary resuscitation (CPR) often requires a significant number of healthcare personnel. In situations where an emergency department is overwhelmed, there is a shortage of available healthcare staff, or personnel are less trained in manual ventilation, the use of mechanical ventilation provides advantages. This allows airway-focused personnel to concentrate on other tasks during CPR, such as chest compressions, defibrillation, identifying the causes of cardiac arrest, and more (Weiss et al. 2005).

Positive pressure ventilation can be delivered through an advanced airway using a bag-valve mask (BVM) or a mechanical ventilator. It was found that both ventilation methods were equally effective in terms of arterial gas measurements in a prospective intervention study involving 122 patients with cardiac arrest (Johannigman et al. 1995).

In adults, the "six-dial strategy" has been described for mechanical ventilator programming during CPR. This involves setting six parameters: PEEP of 0 cm H_2O (to favour venous return), using volume-controlled mode with 8 ml/kg of ideal body weight and FiO_2 of 100% (to ensure adequate oxygenation), respiratory rate of 10 breaths per minute (for proper ventilation), inspiratory pressure alarm set at 60 mm H_2O (to deliver the tidal volume during chest compressions), trigger or sensitivity turned off (to prevent triggering during chest recoil), and an I:E ratio of 1:5 (to achieve an appropriate inspiratory time) (Sahu et al. 2020).

For children already on mechanical ventilation, the 2021 European Resuscitation Council Guidelines for Paediatric Life Support emphasise the need to ensure that the ventilator is in a volume-controlled mode, with triggers and limits deactivated. The ventilation frequency, tidal volume, and FiO_2 should be appropriate for cardiopulmonary resuscitation. There is no evidence to support a specific level of PEEP during CPR. Always bear in mind that ventilator dysfunction itself could be a cause of cardiac arrest (Van de Voorde et al. 2021).

More information regarding mechanical ventilation during CPR is anticipated. Recently, a porcine model of paediatric asphyxial cardiac arrest was used to demonstrate that pressure-controlled ventilation at a rate of 20 breaths/minute with FiO_2 of 100% provided adequate oxygenation and appropriate normocapnia.

Myth 7. Maintaining a SpO2 of 100% is safe and appropriate for paediatric and neonatal patients

The critically ill patient presents various nuances in intensive care or emergency settings, where we must recall the oxygenation goals for each specific clinical scenario. Excessive delivery of FiO_2 is linked to an excess of oxygen-free radicals. (Bohnhorst

Clinical Condition	Target
Acute Respiratory Distress Syndrome with PEEP <10 cm H_2O	SpO2 92-97%
Acute Respiratory Distress Syndrome with PEEP >10 cm H_2O	SpO_2 88%-92%
Return of Spontaneous Circulation (ROSC) after Cardiopulmonary Resuscitation (CPR)	SpO_2 94%-98%
Severe Asthma Crisis	SpO_2 ≥92
Severe Traumatic Brain Injury	$SpO_2$94-99%
Potential Organ Donor	SpO_2>95% Less percentage of oxygen as possible)
Carbon Monoxide Poisoning	$SpO_2$100% (If there is no 6-8 wavelength pulse oximeter)
Premature Newborn and Bronchopulmonary Dysplasia	SpO_2 90% - 95%
Acute Chest Syndrome in Sickle Cell Disease	SpO_2>94%
Drowning	$SpO_2$94%-98%

Table 2: Oxygenation goals for different clinical conditions

et al. 2000). We will outline the oxygenation goals for different clinical conditions, aiding in the avoidance of elevated FiO_2 levels, as well as high pressures (positive end-expiratory pressure and peak inspiratory pressure) and utilised tidal volumes (**Table 2**).

Pulse oximeters can serve as a surrogate for arterial blood gas saturation. These devices need to be accurate across a wide range of skin tones and thicknesses and for a broad spectrum of saturations. Generally, pulse oximeters are most accurate at higher saturations, typically above 75% (Bohnhorst et al. 2000; Carter et al. 1998; Fanconi 1988).

Pulse oximetry estimates the percentage of haemoglobin saturation. It is not intended to be a substitute for blood oxygen pressure (PaO_2) measurement, especially at extreme values. The relationship between PaO_2 and oxygen saturation is influenced by multiple factors, including haemoglobin type and the state of the oxyhaemoglobin dissociation curve. The latter is affected by acid-base status, temperature, and 2,3-diphosphoglycerate (DPG) levels. Pulse oximetry is known to be inaccurate during periods of hypoxaemia (saturations, 85%-90%) and generally reads 98% to 100% when PaO2 exceeds 100 mm Hg. Both external and patient-related factors, including movement, ambient light, and low tissue perfusion, can interfere with its accuracy.

Pulse oximeters are not precisely calibrated for low saturations seen in cyanotic congenital heart diseases. However, there is a blue sensor designed for the saturation range found in patients with these clinical conditions. The PaO_2 values need to meet the metabolic demands of a neonate range from 50 to 80 mmHg due to their high proportion of circulating foetal haemoglobin (HbF). In neonates, SpO2 levels between 85% and 95% correlate with PaO_2 levels between 45 and 65 mmHg (Quine et al. 2008). However, these measurements are limited in scenarios of significant hypoaxemia or hyperoxaemia.

For saturations above 96%, PaO_2 levels continue to increase without a significant change in SpO_2, potentially leading to hyperoxaemia. The high affinity of HbF for oxygen shifts the haemoglobin dissociation curve to the left, resulting in relatively high saturations (85%) for PaO_2 levels below the 45 mmHg threshold, leading to complications associated with hypoxaemia. This effect is more pronounced with a higher proportion of circulating HbF, and it's been known for a long time that a neonate born at 28 weeks of gestation can have a circulating HbF percentage ranging from 90% to 97%.

Maintaining high saturations in preterm neonates (96% to 99%) is associated with increased mortality, a higher risk of bronchopulmonary dysplasia (BPD), no reduction in the need for ablation of avascular peripheral retinas in neonates with retinopathy of prematurity (ROP), and longer hospitalisations (STOP-ROP 2000). Using lower saturation ranges in preterm neonates (85% to 89%) is associated with higher mortality in babies less than 36 weeks of gestation, a higher incidence of necrotising enterocolitis, a greater risk of patent ductus arteriosus persistence requiring surgical closure, a decrease in ROP incidence requiring treatment, and a lower risk of requiring supplementary oxygen at 36 weeks corrected gestational age (Askie et al. 2018). Setting the saturation target for preterm neonates between 90% and 95% is a sensible strategy to minimise risks of extreme oxygenation and avoid complications associated with lower saturation ranges (Polin and Bateman 2013) (**Table 2**).

Conflict of Interest

None.

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