Acute Pain
Management

Acute Pain Management

Pain is frequently encountered in intensive care unit (ICU) patients. Several studies have shown that improved pain management is associated with improved patient outcomes. However, pain management continues to be a significant challenge in the ICU setting.

Effective pain relief is one of the most important priorities in the ICU. The goal is to ensure optimised clinical outcomes and patient comfort. However, this has to be achieved by using flexible multimodal analgesia, minimum use of opioids and minimal sedation. Any pain management strategy within the acute care setting should facilitate pain relief, patient comfort, early mobilisation, early recovery, and minimum long-term complications of an ICU stay.

In our latest cover story, **Acute Pain Management,** our contributors highlight the challenges of pain management in critically ill patients and discuss pain assessment strategies, current pain management guidelines and recommendations, and effective pain management protocols in specific patient populations. They talk about the benefits, appropriate usage and adverse effects of different pain management modalities. They also talk about sedation monitoring and sedation minimisation as important goals when managing pain in critically ill patients.

Gérald Chanques talks about the practical assessment of pain in critically ill patients in the intensive care unit based on current evidence and guidelines. Ambika Tejpal, Sérgio Pereira, and Michael Sklar provide an overview of the cardiovascular and respiratory effects of sedative agents commonly used in the ICU and discuss emerging concepts of mechanical ventilation induced injury to the respiratory muscles and sedation monitoring and sedation minimisation for expeditious liberation from mechanical ventilation.

Ambre Cuny, Audrey De Jong and Gérald Chanques highlight pain management specificities in critically ill patients with obesity and discuss the need for a standard, non-weight-based or weight-based dosing using either ideal body weight or adjusted body weight to limit the risk of overdosing in these patients.

Jhordan Molina-Galeote, Gabriel Patiño-Arreola, Itzel Radillo-Santana and co-authors offer a practical approach to analgesia, sedation and neuromuscular blockade of critically ill patients and discuss potential benefits, adverse effects and current professional international recommendations. Sergi Huerta-Calpe, Ricardo Suárez, Mònica Balaguer, and Elisabeth Esteban provide an overview of the main pain management options currently available in paediatric critical care settings.

Beatriz Lobo-Valbuena, Rosario Molina, Leire de la Oliva Calvo, and Federico Gordo discuss the current management of delirium and provide an overview of new publications and possible new studies that could shed light on a more effective delirium management strategy.

Alberto Gómez González, Miguel Martínez Camacho, Robert Jones Baro and co-authors highlight the most common mistakes during early mobilisation in the intensive care unit. Flavio Nacul, Neymar de Oliveira, Joao da Silva-Jr and co-authors provide evidence supporting perioperative haemodynamic optimisation in high-risk surgery patients and discuss strategies to facilitate its implementation and adoption to improve patient outcomes.

Acute pain management should focus on decreasing the incidence of severe pain among critically ill patients while ensuring appropriate use of analgesic drugs, minimum sedation, and decreased incidence of serious adverse events. Effective pain management is an important quality indicator of care provided in the ICU and should be closely monitored and implemented based on clinical care guidelines and recommendations.

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

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Pain Assessment in Critical Illness

This narrative paper reports the practical assessment of pain in critically ill (ICU) patients, based on current evidence and guidelines.

Introduction

Pain is one of the top stressful symptoms experienced by critically ill patients hospitalised in intensive care units (ICU) (Chanques et al. 2015). This is because critical pathologies are often severely painful (i.e. trauma, surgery, acute pancreatitis…), and because intensive care is basically invasive (multiple catheters and tubes, mechanical ventilation, forced immobilisation on bed…). Thus, most critically ill patients will experience pain during their ICU stay, at rest, or during procedures or mobilisation (Chanques et al. 2006; Puntillo et al. 2014). Also, other causes of pain are related to medical complications that may occur during the ICU stay, such as surgical complications, pneumothorax, phlebitis, myocardial infarction, etc. It is consequently paramount that nurses and physicians are able to detect pain using accurate and sensible tools, even in the most critically ill patients who may not be able to communicate their pain. Moreover, because analgesics can be associated with serious side effects, it is of top priority to measure pain intensity with validated tools, in order to titrate the dose of analgesics, and to minimise the risk of their overuse. Pain assessment, protocolised analgesia, and sedation based on analgesia first are all strategies proved to be associated with patients' outcome in ICU (Chanques et al. 2006), leading to the elaboration of practice guidelines for years (Vincent et al. 2016; Devlin et al. 2018; Chanques et al. 2018a). Pain assessment is the key component of pain management in ICU patients as in other patient populations, even if ICU patients are often unable to communicate, sedated, paralysed, or delirious. The aim of this article is to discuss how to assess pain in the different clinical situations met in the ICU setting.

Patients Able to Communicate (Either Intubated or Nonintubated): Self-Assessment

The priority for pain assessment is to have patients themselves evaluating their pain. Yet, many barriers exist, such as mechanical-ventilation precluding verbal assessment, and physical restraints, which are still often used in European ICUs with high patient-to-nurse ratios. These barriers are more barriers built by health caregivers than by patients themselves. Indeed, intubation is not associated with patient failure to self-report pain intensity using common pain scales, if patients are able to follow simple commands (Chanques et al. 2010). Not trying to ask such patients to self-report their pain could be related to a mental barrier based on prejudgment or anticipated difficulty. Common self-report

difficult to use in ICU patients because it may be impossible for them to use the scale's cursor precisely in case of weakness. The 0-10 NRS, when administered visually (and not orally) using a printed scale (A4 paper size with large numbers), is the most feasible scale (91% of patients able to follow simple commands are able to use it, whether they are intubated or not) and has the best negative predictive value (90%) compared to other scales (VDS and VAS) (Chanques et al. 2010). Non-verbal (intubated) patients can choose to show the number directly on the scale, or to communicate it with their 10 fingers, especially in case of severe ICU acquired weakness (**Figure 1**). Clinicians may help the patients by supporting their arm to point out the number directly on the scale.

Figure 1. 0-10 Visually enlarged Numerical Rating Scale. Source: Chanques et al. 2010

scales include the Verbal-Descriptor-Scale (VDS), the Visual-Analogical-Scale (VAS), and the 0-10 Numeric-Rating-Scale (NRS).

The VDS has five intensity descriptors: no pain, mild pain, moderate pain, severe pain, and extreme pain. Its use may be difficult in non-verbal patients (i.e. intubated patients) but clinicians can show their five fingers to figure the five levels of the scale, helping patients indicate their level of pain directly on the clinician's hand. VAS that has a 10-cm length can be a little more

In case a patient cannot use the NRS, other scales can help, especially the VDS. If this is not possible either, a simple yes/no question - "do you have any pain?" can be asked. However, this simple yes/no question is not recommended to be used solely. Indeed, if used at first, a patient will frequently answer no but could eventually rate her or his pain from 1 to 10 on the NRS, being able to localise pain on body, and even asking for pain relief.

This apparent discrepancy, suggested

by a negative answer to the simple yes/no question, can be explained by the specific context of critical illness and intensive care. For example, an ICU patient who has just undergone surgery may consider that it could be normal to have some pain, or that pain is less severe than expected. Also, patients can figure that the question refers to the surgical site rather than other parts of the body. Specific types of pain (headache, back pain…) may be considered usual and chronic, or even benign because they are not directly related to the surgery or to the admission in ICU. However, some localisations that could be considered insignificant are paramount for the clinicians, such as shoulder pain after abdominal surgery that can be related to subphrenic abscesses, or pain on a leg, that can be the very first symptom of phlebitis. Moreover, patients can be reluctant to receive opioids, or not complaining about catheters or drains

considered as fundamental to their recovery. In mind, several examples of the detection of the "syndrome of no pain but 5/10 rating if I am asking for" can save lives (**Table 1**).

Compared to the yes/no question and even to the VDS, the NRS is much more sensible to detect any pain (Chanques et al. 2010). It is like if the verbal questions (yes/no question or VDS) address a highly complex cerebral task leading to a conclusion that may falsely occult the reporting of all sorts of pain. On the opposite, numerical scales are used by patients more like a basic self-scan of their body, with less interpretation, leading to detect all sorts of pain (chronic pain, localisations that would seem insignificant in the global context…). For the clinician, numerical scales allow for recognition of pain as an alarm, what nociception is made for: a life-saving system.

In all, numerical scales should be preferred as first line self-report pain scales, while VDS

or especially the simple yes/no question should probably be reserved as back-up methods, in patients unable to use the numerical scales.

Finally, there is a recent tendency to prefer positive communication and to use positive (non-negative) words. Coming from conversational hypnosis, it could be a real innovation in nursing and medical behaviour. Pain, a negative experience, could rather be replaced by comfort, a more positive word. Rather than asking patients if they have any pain, it could be asked if they are comfortable. However, as said before, seeking after a painful alarm point was a real progress in global management of ICU patients, from a diagnosis perspective. Thus, these two approaches should be complementary. Beginning with the positive and relaxing approach ("are you comfortable today?") could be preferred, followed by the research of any pain alarms.

Example	Action	Impact
I rate 10, and I really have no pain	Re-explain the use of the scale, some patients may rate analgesia rather than pain.	Moderate
I rate 2, and I consider this is no pain (no need of treatment)	Ask where pain is located, even if 2/10, make a diagnosis (can be a phlebitis, or a skin ulcer that will make the diagnosis of rickettsiosis)	Potentially critical
I rate 5, but this is usual when I lay on a bed that's not mine, you know, I worked 20 years as a builder. I take acetaminophen only when it is 6.	Mobilise as soon as possible (bed seating, standing up if possible, move to seat), look for the best position in bed (and always consider a disease related to critical illness: osteitis, osteoporosis)	Possibly important
I rate 5, but it is alright, I don't want you to order opioids, they make me vomit (or being constipated).	Ask where pain is located, make a diagnosis, propose non-pharmacological therapies (music therapy, hot-water bottle, cold…); consider non opioids (multimodal analgesia, nefopam, lidocaïne…)	Possibly important
I rate 8, it is related to the nasogastric tube. I answered NO when you asked me if I had pain, because I got chewed out by your colleague when I said the tube was painful yesterday, I was told not to talk about it because the tube was vital. But if you insist with your pain scale…	Check if the gastric tube is still necessary, remove it as soon as possible (in the present case, bag was empty, and tube was removed immediately, decreasing pain from 8 to 0).	Critical
In all situations of apparent discrepancy between the YES/NO question and the numerical rating…	… ask patients why they answered NO at first!	Important for learning and experience
I rate 7 on the stomach area (the patient has a severe mood disorder, and answered NO to everything: pain, anxiety, thirst, switching on TV, opening curtains…).	Perform an electro-cardiogram (ECG) systematically (in the present case, 40-yo woman admitted for acute on chronic liver failure related to C viral chronic hepatitis refractory to interferon, ECG shows a ST+, leading to transfer the patient to the coronarography unit immediately.)	Potentially critical
I rate 7, but I cannot localise pain.	Check cognitive functioning (delirium), consider using a behavioural pain scale.	Critical, lead to delirium management

Table 1. Examples highlighting the syndrome of "I have no pain (answering the yes/no question "do you have any pain?") but I rate a number ≠ 0 on the numerical scale if it is shown to me".

Warning about the use of self-report pain scales

After having tried to promote a systematic and thorough use of self-report pain scales, in order to sensitise the recognition of pain, it is important to say that no number should lead to a systematic ordering of analgesic drugs, even for a NRS>6 which indicates a severe pain that requires opioids in most patients. Some types of pain are considered sufficiently acceptable for patients, so that it is unnecessary to prescribe analgesics that can expose the patient to undesirable side-effects. It is, however, important to take into consideration all sorts of pain. For example, a patient with back pain history may not complain of it or ask for analgesics. But because we know this kind of pain may severely increase after days of immobilisation, the early recognition of this kind of pain should encourage mobilising the patient immediately if possible.

Patients Unable to Communicate (Either Intubated or Nonintubated): Observational Behavioural Scales

In some patients, clinicians may fail to use a validated self-report pain scale: patients may rate different numbers inconsistently, or rate a number different to zero but would be unable to localise their pain, or even, may absolutely not follow any command or answer any questions, precluding any use of a self-report pain scale. This is the case for some patients with delirium, one of the top risk of self-assessment failure in ICU (Chanques et al. 2010). Moreover, in deeply sedated patients who are unable to follow simple commands, self-reporting is not appropriate as well.

In these situations, the recommended assessment of pain is based on the observation, by clinicians, of the patient's pain behaviour. To standardise the assessment of pain, several behavioural tools have been elaborated for the past twenty years (Gelinas et al. 2019). Two of them are very close, demonstrating similar psychometric properties and performance to recognise pain in adult ICU patients (Chanques et al. 2014; Gelinas et al. 2019): the Behavioral Pain Scale (BPS, originally elaborated and

validated by Jean-François Payen's team in France) and the Critical Care Observation Pain Tool (CPOT, originally elaborated and validated by Céline Gélinas' team in Canada). Both scales (Payen et al. 2001; Gélinas and Johnston 2007) have been translated and validated in many different languages across the world.

BPS contains three behavioural domains (**Figure 2**): facial expression, upper limb movements, and adaptation to the mechanical ventilator. BPS has been adapted to non-intubated patients, switching the ventilator domain by a vocalisation and verbal domain (Chanques et al. 2009). Each of the 3 domains of the scale includes 4 descriptors from 1=no pain, to 4=maximal pain behaviour. In all, BPS (or BPS for non-intubated patients) can range from 3x1=3 to 3x4=12. A pain threshold of ≥ 5 or 6 was established by discriminative validation studies, and included in pain management protocols (Chanques et al. 2006; de Jong et al. 2013). A threshold of 5 can be used in intubated patients receiving an analgesia-sedation protocol, to give priority to analgesics while minimising the use of sedatives (Chanques et al. 2017a).

The main difference between BPS and CPOT is that BPS has three behavioural domains, each rated using four descriptors, while CPOT has four domains, each rated using three descriptors (from 0 to 2). The muscular domain is subdivided in two parts for the CPOT: tonus+movement. CPOT ranges then from 4x0=0 to 4x2=8. BPS and CPOT have been validated in non-communicant ICU patients, intubated and non-intubated, sedated or delirious, and even in patients with brain injuries. However, if the use of BPS and CPOT is possible and validated in brain-injured patients, their psychometric properties are modified somewhat by neurological injuries. Specific pain behaviour has been described in patients with brain injuries, such as tearing, face flushing and yawning. The Nociception Coma Scale (NCS, from Liège Coma Science Group, Belgium) was elaborated and validated in non-intubated brain-injured patients (Schnakers et al. 2010), and recently adapted to intubated patients (Bernard et al. 2019). CPOT has recently also been adapted for brain-injured patients (Gelinas et al. 2021). However, because original BPS and CPOT keep accept-
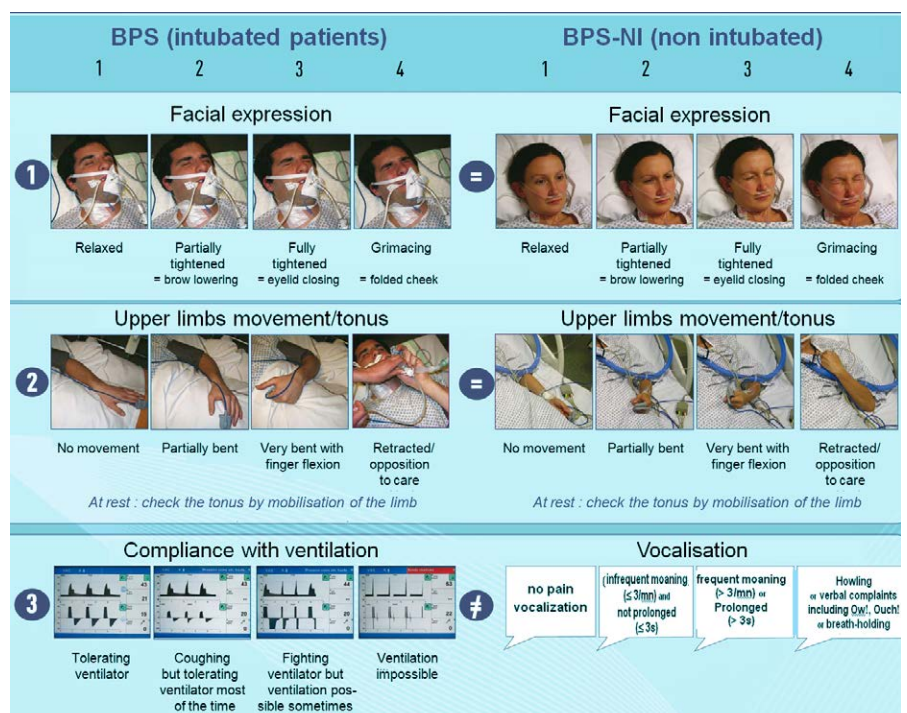

Figure 2. Behavioural Pain Scale (BPS). Source: Payen et al. 2001; Chanques et al. 2009

able psychometric properties in brain-injured patients (Joffe et al. 2016; Bernard et al. 2019), some polyvalent, non-neurological ICUs may prefer using the original version of the scale in all patients, rather than multiply the number of scales in the same ICU.

Warning about the use of behavioural pain scales

Some patients may suffer from the use of behavioural pain scales! Indeed, we often hear clinicians do not believe a patient who communicates a moderate to severe pain intensity (i.e. 4/10 or more), because there is absolutely no pain behaviour observable (BPS=3: CPOT=0). To understand this apparent discrepancy, we should remember that the statistical correlation between self-report pain scales (NRS, VAS, VDS) and behavioural pain scales is very low in patients able to communicate (Chanques et al. 2010). Moreover, implementation of behavioural pain scales may be associated with a decreased use of self-report pain scales, even in patients who are able to communicate (based on our experience, and regular quality control surveys at our institution). One possible reason is that it could be easier and quicker to just give a look at the patients and rate their behavioural score, than to wake them up if they may be sleeping (good reason), or even than to talk to them (bad reason). It is thus paramount to remember that:

- Human beings always underrate others' pain intensity: nurses, physicians and even relatives underrate patients' pain intensity compared to patients' self-assessment of their own pain (Ahlers et al. 2008).
- For this reason, self-assessment of pain by patients themselves is strongly recommended by all medical societies (Devlin et al. 2018).
- Behavioural pain scales should be used only if patients are not able to self-report their pain intensity.
- Behavioural pain scales were basically designed to assess pain in patients unable to communicate.
- Behavioural pain scales were vali-

dated in such populations of patients (patients under sedation, or patients with delirium).

- Social behaviour is modified by vigilance and psychological status.

If any doubt persists regarding the reality of a patient's suffering related to a given self-reported pain intensity, clinicians should:

- Make sure that the patient understood correctly the use of the pain scale (often, patients inverse the numbers, 10 meaning very good analgesia for example).
- Ask the patient to localise their pain in order to assess the consistency of the pain assessment.
- Ask the patient if they would like to receive or not a treatment for this pain.

Patients Unable to Communicate and Without Any Behaviour (Deep Sedation, Paralysis): Electrophysiology

For deeply sedated patients, it is recommended to use a validated behavioural pain scale (e.g. BPS, CPOT), as for moderately sedated patients who are not able to communicate (Devlin et al. 2018). Whether electrophysiology may improve the detection of subclinical pain in order to help managing analgesics and sedatives in deeply sedated patients requires further research. For deeply sedated patients who receive neuromuscular blocking agents (NMBA), the complete paralysis of body muscles preclude any use of behavioural pain scales (which remain usable in case of incomplete paralysis, such as acquired ICU weakness: at least the facial domain of the behavioural pain scales can still be used, facial muscles being generally preserved).

No recommendation can be made today regarding the use or not of an electrophysiological measurement of pain and stress during paralysis (Murray et al. 2016). It is recommended to ensure deep sedation and analgesia before using NMBA, and to interrupt NMBA on a regular basis to check the clinical level of sedation and the absence of pain (Murray et al. 2016;

Chanques et al. 2020).

During paralysis, the observation of a change in continuously monitored vital signs (i.e. heart rate, arterial blood pressure) during a nociceptive care procedure should help determine the need for strengthening analgesia. However, change of vital signs is much less sensible than behavioural pain scales in non-paralysed patients (Gelinas et al. 2019). It is why behavioural pain scales are recommended to be used systematically to assess pain in non-paralysed, non-communicant patients, rather than the only observation of vital signs.

To enhance the electrophysiological measurement of stress response, related to pain or other stressful factors (e.g. anxiety, fear…), new devices have been developed recently. All these devices are based on the measurement of surrogate markers of the adrenergic response: increase of the pupillary diameter (measured by video-pupillometry), decrease of physiological Heart Rate Variability (HRV) related to a decrease of parasympathetic tone (meaning an increase of sympathetic tone), or other parameters, for example the increase of electric skin conductance due to increased sudation.

Literature is contrasted regarding the validity of videopupillometry to detect pain in critically ill patients. A study reported at first that videopupillometry was more sensible for pain detection than the behavioural observation in deeply sedated patients (Li et al. 2009). However, subsequent studies using validated behavioural tools, reported that videopupillometry could not recognise pain during nociceptive care procedures (Bernard et al. 2019). Then, a new strategy was developed, not to measure pain during a care procedure, which is basically highly challenging using a videopupillometer at the same time of doing the procedure, but to measure the pupil dilation, induced by electrical stimulation of the skin. This strategy was able to define subclinical thresholds of pain that are predicting of clinical pain during a real nociceptive care procedure (Vinclair et al. 2019). Following this strategy, it might be possible to avoid any pain response

related to care procedures. This could be very relevant in some patients at high risk of increased stress response (e.g. patients with severe intracranial hypertension). The limit of this strategy is that it can be used only in deeply sedated patients because electrical stimulation is painful in non-sedated patients, and also because pupillary diameter is highly reactive in non-deeply sedated patients.

The analysis of HRV has been increasingly developed in commercialised devices. The Analgesia Nociception Index (ANI) is much more sensible than behavioural pain scales to detect nociception in sedated patients or non-sedated patients (Chanques et al. 2017b; Chanques et al. 2018b). In the absence of studies evaluating the use of HRV devices to help managing analgesics, the routine use of HRV cannot be recom-

mended because of a risk of an overuse of analgesics (especially opioids), due to a high sensibility of the device. In patients who were paralysed, ANI demonstrated a better performance to detect tracheal aspiration than the bispectral index (BIS) monitoring, that was not modified by the recovery from paralysis, contrary to the BIS (**Figure 3**).

Finally, the use of electroencephalogram derived parameters (e.g. BIS), is not recommended in routine in the ICU setting, either in paralysed and non-paralysed patients, because of the high proportion of false positive and false negative measurements of sedation (Murray et al. 2016; Chanques et al. 2020).

Warning about the use of electrophysi-ology
When an electrophysiological monitoring is used in paralysed patients, it should be used only to detect a possible awakening, or a possible increase of stress response (pain, anxiety…). This observation should make consider strengthening sedation and analgesia until the next NMBA window, which is recommended to assess patients' comfort clinically. Pending further studies, these monitoring tools should not be used to decrease sedatives and analgesics. Indeed, it has been reported that a significant proportion of patients can be clinically awake just after the interruption of NMBA, despite an electrophysiological monitoring (BIS) indicating the inverse (Tasaka et al. 2016).

Conclusion
The assessment of pain in ICU patients has been more clearly standardised (**Figure 4**) since the beginning of the century, based on the elaboration of different clinical pain assessment tools adapted to the critically ill patients' condition (unable to communicate or not). These tools have been validated at a large scale in different cultures, and included in studies reporting improved outcomes when pain assessment was standardised and systematic. Thus, their use is now recommended by national and
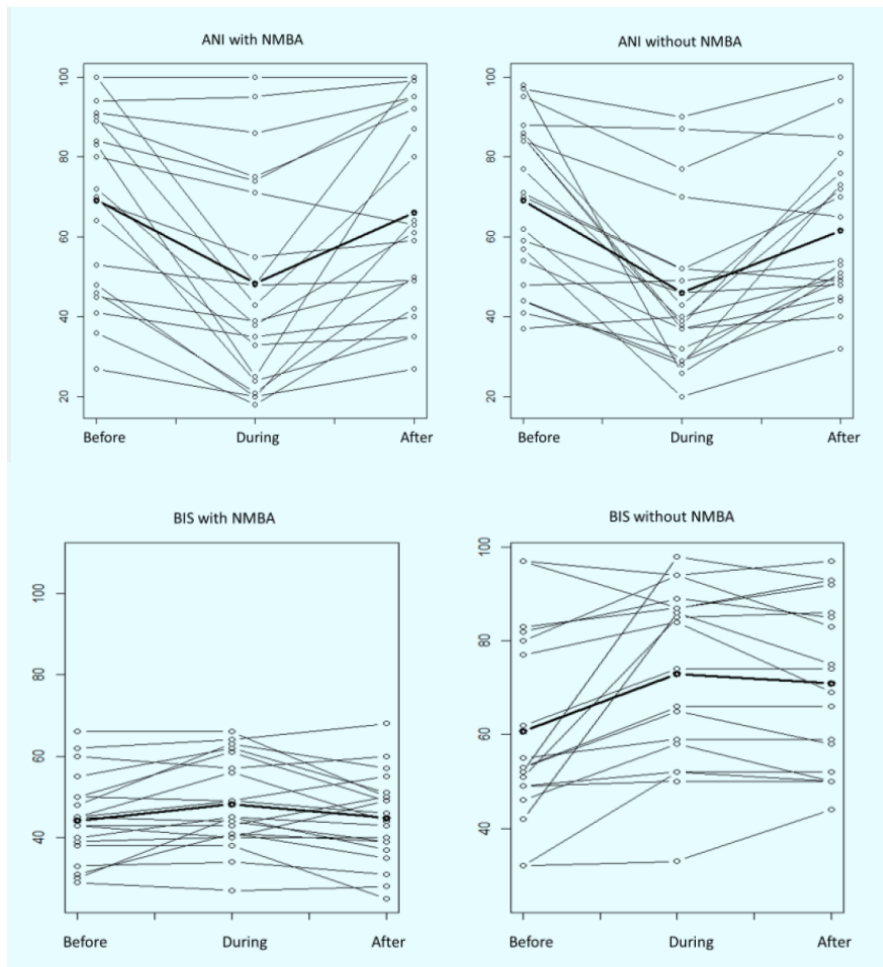
Figure 3. Pain assessment using electrophysiology in paralysed critically ill patients receiving neuromuscu-lar blocking agents, before, during, and after tracheal suctioning.
Analgesia Nociception Index (ANI) is a surrogate marker of the sympathetic/parasympathetic tone balance using Heart Rate Variability analysis. ANI significantly decreased during tracheal suctioning, suggesting that parasympathetic tone decreased, or sympathetic tone increased (stress response related to the nociceptive care procedure) (upper left panel). This decrease was reproduced just after recovery from paralysis (upper right panel). The bispectral analysis of the electro-encephalogram (BIS) increased during tracheal suctioning, suggesting a cortical awakening related to the nociceptive procedure, but in a less discriminative fashion than ANI (lower left panel), including after interruption of paralytic agents, where BIS measurement was modified by electromyogram activity related to the recovery from paralysis, even with a specific electromyogram filter (lower right panel). From Voeltzel J 2020, MD thesis, Montpellier University, France.
ANI: Analgesia Nociception Index; NMBA: Neuromuscular Blocking Agents; BIS: bispectral analysis

Question #1*
**« Hello,
are you comfortable? »**

**Answer:
« No I'm not »**

**Answer:
« Yes I am »**

**No answer
(sedation, delirium)**

**Is the patient
paralyzed?**

**Question #2
« Could you rate any pain from 0
« no pain at all » to 10 « the
maximal pain you could imagine
having »**

No

Yes

**Use a visually enlarged 0-10
scale if the patient has no
experience with numerical
scales, or if the patient does
not understand the question**

• **Use a validated behavioural
pain scale (e.g. BPS, CPOT)**

• **Assure regular interruption of
NMBA to check for clinical
sedation and analgesia**

**Can the patient rate
pain intensity, and if so, is it
consistent with a localisation?**

• **Detect change in vital signs during
nociceptive care procedures,
tearing, or flushing**

• **Consider the use of
electrophysiology in order to
detect suffering more sensitively**

Yes

No

•**Consider treatment**
•**Reassess pain 1h
after treatment**
• **at least /6-8 h in the
absence of pain**

•**Use a Verbal
Descriptor Scale**
• **Check possible
cognitive
dysfunction**

* **Assess pain systematically at rest, on a regular basis
  (at least every 6-8h or more frequently, especially in case of continuous sedation or opioids)**
* **Assess pain systematically at rest before a nociceptive care procedure**
* **Assess pain during and after nociceptive care procedures**

Figure 4. Pain assessment algorithm

international practice guidelines. New technology has been developed also to monitor pain electrophysiologically. These techniques should not be used in place of asking patients what they feel, but in some situations where clinical tools cannot be used, especially during pharmacologically induced paralysis. Further studies are needed to evaluate protocols of use of these new technologies in these situations, with the objective to better manage opioids and sedatives, avoiding their overuse and side effects, while ensuring patient comfort.

Conflict of Interest
None. ◼

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

Practical Implementation of the Pancreatic Stone Protein Sepsis Test

An overview of a discussion on sepsis and the Pancreatic Stone Protein (PSP) biomarker by Dr João Pereira, Hospital De Vila Franca De Xira, Portugal and how it can be used for early diagnosis of sepsis and facilitate decision-making regarding the administration of antibiotics. The discussion was chaired by Prof Pedro Póvoa, coordinator of the Intensive Care Unit (ICU) at Hospital de Sao Francisco Xavier, Lisbon, Portugal.

Introduction

Sepsis is a common problem in the intensive care unit (ICU). Sepsis and septic shock remain challenging health problems and are associated with high morbidity and mortality. In addition, sepsis survivors suffer from long-term problems and complications. One of the biggest challenges in sepsis is the early and accurate identification of positive cases. The symptoms of sepsis can be highly variable, making clinical recognition and assessment of the severity of this condition quite difficult. As a result, false negatives frequently occur, increasing the risk of duplicate therapy and overdiagnosis and unnecessary treatment strategies, such as antibiotics. In addition, false negatives increase the risk of death due to delayed therapy of the underlying disease causing or stimulating sepsis.

There is no gold standard to identify a sepsis infection. Most biomarkers in the management of septic patients are not very well-defined, and only a few have been evaluated in large or repeated studies. Therefore, it is not possible to draw any reliable conclusion about which biomarker could be considered the most promising candidate (Pierrakos et al. 2020).

Pancreatic Stone Protein

There is a complex network of biological mediators underlying sepsis. Since the physiologic criteria of sepsis are quite nonspecific, it is challenging to identify patients who might benefit from antibiotic therapies or more novel therapies. Therefore, biomarkers can help improve diagnosis and therapeutic decision-making for high-risk patients (Marshall and Reinhart 2009).

Some of the clinical benefits of using biomarkers include:

- Diagnostic - improves diagnostic accuracy
- Monitoring - measures response to intervention
- Prognostic - identifies subgroups in need of more aggressive interventions
- Surrogate - predicts a clinical outcome

> ❝❝ PSP is an accurate and promising biomarker for early recognition of nosocomial sepsis ❞❞

Pancreatic Stone Protein (PSP) is a regenerating protein and lithostathine. It is a lectin-binding protein. In patients with an increase in inflammation and the presence of an infection, the blood levels of PSP tend to increase. For example, in trauma patients, levels of PSP can increase in case of sepsis. Similarly, PSP levels at the onset of ventilator-associated pneumonia (VAP) and in patients with septic shock can predict mortality (Boeck et al. 2011).

Findings from a study comparing sepsis biomarkers PSP, soluble CD25 (sCD25) and heparin-binding protein (HBP) show that PSP and sCD25 perform well as sepsis biomarkers in patients with suspected sepsis at the time of admission to the ICU (Llewelyn et al. 2013). Another review shows that using a cut-off value of 44.18 ng/ml, PSP performs better than CRP or PCT across the considered studies (Prazak et al. 2021).

Pancreatic Stone Protein Sepsis Test

The PSP sepsis test is a point-of-care diagnostic tool that measures the concentration of the pancreatic stone protein biomarker in blood. PSP is an accurate and promising biomarker that could potentially allow early recognition of nosocomial sepsis in adults. When compared to other markers, PSP is less influenced by inflammation. Hence, the robustness of PSP serum levels toward inflammatory insults could potentially be an important criterion for a sepsis biomarker (Klein et al. 2020).

Overdiagnosis of sepsis can result in increased use of resources, delayed therapy of the underlying disease that is simulating sepsis, and unnecessary use of antibiotics, further contributing to increased antimicrobial resistance. It is important to remember that there is insufficient evidence to support the widespread use of antibiotics in hospitalised patients. For example, despite an overall low rate of bacterial co-infections in patients with COVID-19, nearly 70% of patients received antibiotics. Co-infection was reported in only 3.5% of patients and secondary infection in 14.3% of patients with COVID-19. The use of antibiotics in critically ill patients remains high even though in many cases, antibiotics are likely to provide minimal benefit and may also be associated with negative consequences such as adverse events, toxicity and resistance (Langford et al. 2020).

Another meta-analysis highlights that antibiotics may be a major factor negatively affecting patients' immune system during viral infections. To date, there is no effective medical treatment for SARS-CoV-2. There

is evidence to show a relationship between COVID-19 death rates and an average dose of antibiotics reported in some European countries. The World Health Organization (WHO) also says that antibiotics do not work against viruses, only bacteria. SARS-CoV-2 is a virus; hence antibiotics should not be used for prevention or treatment. Therefore, it is important to exercise caution when using antibiotics in patients with COVID-19 (Tyszka et al. 2020).

The PSP test is useful in patients when the underlying condition is unknown so that clinicians can improve the certainty of their diagnosis and subsequent treatment decisions. Findings presented during the session revealed that in patients suspected of sepsis infection, 82% of the PSP values were high (> 250 ng/ml). In nearly 50% of the cases, the values were very high (≥ 600 ng/ml). Therefore, the test identified that these patients needed to be treated immediately.

The PSP test can also help decide whether patients need antibiotic therapy. Patients with small increases in C-reactive protein (CRP), fever, and worsening oxygenation are often started on antibiotics. However, using the PSP test in these patients can help determine whether the PSP biomarker is below the 200 ng/ml cut-off. If this is so, clinicians do not have to prescribe unnecessary antibiotics. Therefore, having biomarker results available at the point-of-care and a

total turnaround time of a few minutes can be extremely beneficial.

Personalised treatment of these patients is essential to improve patient outcomes. Specifically, the use of innovative technology in patients at risk of sepsis, such as the abioSCOPE device, could be beneficial to support patient management.

The PSP test may not be necessary when the diagnosis is already clinically obvious. However, when there is an element of doubt, PSP can prove to be beneficial. The most logical path to determine if a particular patient needs a PSP test is to monitor the patient's condition. If the patient is not improving and if their oxygenation is getting worse, blood pressure is decreasing (but is not low enough to be a shock), white blood cell count is going up (but not enough to signal an infection), a PSP test can help determine the underlying cause. If the PSP test results indicate infection, clinicians can escalate antibiotics while additional tests are conducted.

Conclusion

Overall, the rapid PSP test on the abioSCOPE in-vitro diagnostic device allows clinicians to act quickly and ensure patients with sepsis are identified early, and treatment is initiated as soon as possible. This can facilitate overall management and improve patient outcomes. In addition, early diagnosis of sepsis can be a cost-saving strategy

for hospitals. The smart use of biomarkers can allow the identification of the onset of sepsis, allow clinicians to tailor the use of antibiotics and predict disease severity, and help improve hospital care and patient outcomes. The PSP test has shown promising results in real-life situations, meeting important clinical needs and can help pave the way towards more personalised care. ■

Key Points

- Sepsis is a complex condition. If not recognised and managed early, it can evolve into life-threatening septic shock and multiple organ failure.

- Early recognition of sepsis, immediate initiation of treatment and management, and early antibiotic treatment can prevent organ dysfunction.

- Pancreatic Stone Protein (PSP increases with disease severity and increased inflammation in sepsis.

- PSP has proven to be an essential tool to quickly and accurately diagnose sepsis.

- The abioSCOPE in-vitro diagnostic PSP test enables fast results and allows clinicians to make fast decisions in urgent situations.

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Sedation, Analgesia and Respiratory Drive in Mechanically Ventilated Adults

An overview of the cardiovascular and respiratory effects of sedative agents commonly used in the ICU, emerging concepts of mechanical ventilation induced injury to the respiratory muscles and evolving concepts for sedation monitoring and sedation minimisation to achieve the goal of expeditious liberation from mechanical ventilation.

The Use of Sedation in Mechanically Ventilated Adults in the ICU

Mechanical ventilation is the most widely used form of life support employed worldwide (Pham et al. 2017), and consequently sedatives and analgesics are among the most commonly prescribed medications in the intensive care unit (ICU) (Luz et al. 2022). In fact, in the course of an ICU admission, over 90% of patients will be prescribed analgo-sedation (Patel et al. 2013). The use of sedatives in the ICU represents a delicate balance. On one hand these medications are used for pain, anxiolysis and ventilator synchrony, but expose patients to the significant adverse effects including delirium, nosocomial infections, and increased mortality (Devlin et al. 2018; Shehabi et al. 2012). Contemporary epidemiological analysis suggests that, despite a recommendation against using continuous infusions of benzodiazepines for sedation, midazolam is the most commonly used agent for sedation, with fentanyl the most common opioid (Luz et al. 2022). The

prescription of sedatives and analgesics should be with a targeted approach to manage the components of pain, agitation, delirium, immobility and sleep precisely (Devlin et al. 2018). In this review we will discuss the cardiovascular and respiratory effects of sedative agents commonly used in the ICU. We will then describe emerging concepts of mechanical ventilation induced injury to the respiratory muscles, and in particular the diaphragm. Finally, we will explore evolving concepts for sedation monitoring and sedation minimisation to achieve the goal of expeditious liberation from mechanical ventilation.

Cardiovascular Effects of Sedation

Sedatives have important cardiovascular effects. An understanding of the physiologic effects of each agent is important, to tailor the sedation strategy to the patient based on their physiologic state and minimise harms (**Table 1**).

Opioids are μ receptor agonists used for analgesia, but at higher doses can be used for sedation. This class of drug reduces sympathetic tone, and therefore can cause a reduction in both blood pressure and heart rate (Darrouj et al. 2009).

Benzodiazepines are gamma-aminobutyric acid (GABA) agonists and are used for induction and maintenance of sedation.

Although generally considered safe from a cardiac perspective, benzodiazepines can cause a mild reduction in blood pressure and have mild negative inotropic effects (Darrouj et al. 2009; Zakaria et al. 2018). The major limiting factor in their use is the risk of potentiating delirium (Arumugam et al. 2017). The mechanism of action of propofol is similar. While its effect on heart rate is neutral, the effects on blood pressure can be haemodynamically and clinically significant. Like benzodiazepines, propofol has a mild negative inotropic effect. However, unlike benzodiazepines, propofol also decreases systemic vascular resistance and causes venodilation, decreasing left ventricular preload (Zakaria et al. 2018; de Wit et al. 2016). The hypotensive effect can be exacerbated in those with heart disease, therefore, it is generally avoided in those with cardiogenic shock (Zakaria et al. 2018). Etomidate, another GABA agonist, which is used for induction of anaesthesia, has a net neutral effect on haemodynamics, however, it can potentiate adrenal insufficiency and lead to hypotension through this mechanism (Thompson et al. 2014).

Ketamine, an N-methyl-D-aspartate receptor antagonist, causes a dose dependent increase in sympathetic tone. As such, it may increase heart rate, blood pressure,

and cardiac output. In critically ill patients, however, particularly those with cardiac dysfunction, the haemodynamic response to ketamine is less predictable, and the net result may be a drop in cardiac output (Zakaria et al. 2018).

Dexmedetomidine, an alpha-2 receptor agonist, provides light sedation without respiratory suppression, making it an attractive option in mechanically ventilated patients. However, its use is associated with hypotension, bradycardia and asystole. Those with acute decompensated heart failure may be at higher risk of these adverse events (Adie et al. 2021).

Volatile anaesthetics are an attractive option in situations of drug shortages and also have a favourable respiratory profile. Volatile anaesthetics decrease blood pressure in a dose-dependent fashion through peripheral vasodilation. This may cause a reflex tachycardia, though the compensatory response may be blunted and insufficient to maintain cardiac output. Volatiles also have a negative inotropic effect. These anaesthetics may also predispose to both brady- and tachyarrhythmias (Jerath et al. 2020).

The Control of Breathing

Respiratory drive, the efferent output of the respiratory centre, is responsible for carbon dioxide (CO_2) homeostasis. Central and peripheral chemoreceptors respond to deviations from the CO_2 setpoint and provide feedback to the respiratory centre, either increasing or decreasing alveolar ventilation. Hypoxaemia and cortical inputs modulate the intensity of this respiratory drive response (Spinelli et al. 2020). The duration of the inspiratory effort is also influenced by pulmonary mechanoreceptors. When activated by lung inflation, they inhibit chemoreceptors at the respiratory centre and help terminate an inspiration cycle (Spinelli et al. 2020), a reflex known as Hering-Breuer. Ventilatory effort, the clinical counterpart of respiratory drive, depends on the integrity of the inspiratory flow-generation pathway (Vaporidi et al. 2020). A given respiratory drive might result in very different efforts depending on the respiratory muscle strength or the diaphragmatic conformation. For example,

some patients with emphysema and flattening of the diaphragm have respiratory drives out of proportion to their ability to generate inspiratory pressure. Conversely, some conditions are associated with respiratory drives higher than their metabolic demand would require. In situations such as delirium and altered pulmonary mechanoreceptors, excessive ventilatory efforts can lead to hyperventilation and, possibly, patient self-inflicted lung (P-SILI) or respiratory muscle injury (Brochard et al. 2016).

We can illustrate the disruption of the inspiratory flow-generation pathway in an example of two patients. Patient A has an appropriate respiratory drive response and a normal-high CO_2. This patient is recovering from acute illness with low respiratory system compliance and concordance of their brain-ventilation curve (Vaporidi et al. 2020). If they have preserved respiratory muscle strength, this could result in strong inspiratory effort. In this scenario, the issue is not respiratory drive *per se* but rather the adaptation of the brain-ventilation curve to a new condition. Patient B has an inappropriate respiratory drive response and a low CO_2. Patient B is also recovering from acute illness but has a dissociation between what the brain is expecting ventilation to be and what the muscles can provide (Vaporidi et al. 2020). Such a dissociation may stimulate the respiratory drive, which in turn overwhelms lung-protective reflexes (e.g., Hering-Breuer) and results in a $PaCO_2$ lower than that required by acid-base homeostasis. Thus, patient B might generate high tidal volumes and a high respiratory rate that ultimately promotes further lung injury and inflammation.

Sedation and the Control of Breathing

All commonly used sedative and analgesic agents in the ICU will affect the drive to breathe (**Table 1**). A targeted strategy to maintain a safe level of respiratory effort might be an optimal way to balance the risk of respiratory muscle quiescence and excessive respiratory efforts (Sklar et al. 2021; Goligher et al. 2020a; Goligher et al. 2018a; Goligher et al. 2020b). Opioids are currently recommended by clinical practice guidelines as the first agent to

use for an analgesic based approach to facilitate mechanical ventilation (Devlin et al. 2018). Opioids have been associated with less patient-ventilator dyssynchrony and so may be a desirable first agent (Goligher et al. 2020b). Propofol and benzodiazepines both cause respiratory depression, principally by reducing the amplitude of respiratory effort (Goligher et al. 2020b; Vaschetto et al. 2014). Given the shorter half-life and lower deliriogenic potential of propofol it is preferred over benzodiazepine-based sedation strategies. Dexmedetomidine and ketamine are attractive agents for use in mechanically ventilated patients. Unlike other agents, they provide sedation, anxiolysis (ketamine may cause rebound agitation), and analgesia with more limited occurrences of respiratory depression (Goligher et al. 2020b; Belleville et al. 1992; Martinez et al. 1985). Finally, inhalational sedation with volatile anaesthetic agents offers a potential alternative for controlling respiratory effort. At doses that would be typically used in the ICU setting, these agents promote spontaneous breathing with elevated respiratory rates and relatively maintained to reduced tidal volumes (Jerath et al. 2020). This breathing pattern may theoretically potentiate safe spontaneous breathing. Further research is required to more specifically study the impact of sedative agents and the control of breathing and how to monitor and titrate sedation to physiological parameters (Sklar et al. 2021; Goligher et al. 2020b).

Ventilator Induced Diaphragm Dysfunction

Protective mechanical ventilation is a life-saving therapy for patients with and without acute respiratory distress syndrome (ARDS). In addition to gas exchange improvement, mechanical ventilation may help restore blood flow to vital organs, improve oxygenation, and reverse muscle fatigue. Conversely, mechanical ventilation may have adverse effects both to the lungs and diaphragm. While the mechanisms of ventilator-induced lung injury have been extensively studied, only recently the focus has turned towards the effects of mechanical ventilation on the diaphragm

Drug class	Mechanism of Action	Blood pressure	Heart rate	Respiratory rate	Tidal volume	Comments
Propofol	GABA receptor agonist	↓	↓/↔	↓	↓	Hypotensive effects may be exacerbated in those with cardiac dysfunction. Avoid use in cardiogenic shock.
Opioids	μ receptor agonist	↓	↓	↓	↓	Often used in combination with other agents, potentiating their haemodynamic effects.
Benzodiazepines	GABA receptor agonist	Mild ↓	↔	↓/↔/↑	↓	Not recommended by current guidelines for continuous infusion due to risk of delirium. Respiratory effects are dose dependent, with higher doses increasing risk of respiratory depression.
Ketamine	NMDA receptor antagonist	↓/↔/↑	↑/↔	↔	↔	Haemodynamic effects depend on overall volume status, sympathetic tone
Dexmedetomidine - bolus	α2 receptor agonist	↑	↓	↔	↔	Initial bolus can cause hypertension due to stimulation of peripheral vasoconstrictor receptors.
Dexmedetomidine - no bolus	α2 receptor agonist	↓	↓	↔	↔	A third of patients still experience significant bradycardia without a bolus
Etomidate	GABA receptor agonist	↔/↓	↔	↔	↔	Used for induction of anaesthesia, risk of adrenal insufficiency and resultant hypotension.
Volatiles	GABA receptor agonist, AMPA and NMDA receptor antagonist	↓	↑	↓/↑	↓	Decrease in tidal volume may be compensated for by an increase in respiratory rate.

Table 1. Physiological effects of sedation
GABA = gamma-aminobutyric acid, NMDA = N-methyl-D-aspartate, AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

and other respiratory muscles.

Vassilakopoulos and Petrof (2004) defined ventilator-induced diaphragmatic dysfunction (VIDD) as *a loss of diaphragmatic force-generating capacity that is specifically related to the use of mechanical ventilation*. The biological mechanisms of VIDD is not in the scope of this review. Yet, it is important to mention that mechanical ventilation per se does not cause VIDD (Goligher et al. 2018b); in fact, ventilatory settings leading to under-assistance or over-assistance, inappropriate PEEP titration leading to excessive diaphragm shortening, and poor patient-ventilator synchronicity are all related to diaphragm dysfunction (Goligher et al. 2018b). Due to the fact that diaphragm dysfunction may be associated not solely with ventilatory settings

but also with other causes such as sepsis, systemic inflammation, and trauma, experts have recently proposed the term critical illness-associated diaphragm weakness (Dres et al. 2017).

One of the most common ways to assess diaphragm function in critically-ill patients under mechanical ventilation is to measure diaphragm thickness with an ultrasound (Goligher et al. 2015a). Several studies had already associated diaphragm atrophy with mechanical ventilation in selected patients when Goligher et al. (2015b) described the evolution of diaphragmatic thickness over time in more than one-hundred patients admitted to three academic intensive care units. In the first week of ventilation, 44% of patients had decreased diaphragm thickness, 44% had

unchanged, and only 12% had increased. Later, the same authors published a study (Goligher et al. 2018a) where they assessed diaphragm thickness in 191 patients and associated decreased diaphragm thickness with lower probability of liberation from ventilation (adjusted hazard ratio, 0.69; 95% CI 0.54-0.87), prolonged ICU admission (adjusted duration ratio, 1.71; 95% CI 1.29-2.27), and higher risk of complications (adjusted odds ratio, 3.00; 95% CI 1.34-6.72). In a secondary analysis, Sklar et al. (2020) assessed diaphragm thickness in 193 patients and concluded that low baseline diaphragm muscle mass was associated with delayed liberation from mechanical ventilation (adjusted hazard ratio for liberation 0.51; 95% CI, 0.36-0.74), higher risk of acute

respiratory failure (adjusted odds ratio, 1.77; 95% CI 1.20-2.61 per 0.5-mm decrement), prolonged weaning (adjusted odds ratio, 2.30; 95% CI 1.42-3.74), and higher in-hospital mortality (adjusted odds ratio, 1.47; 95% CI 1.00-2.16 per 0.5-mm decrement). Finally, a study with 940 patient-days suggested that changes in diaphragm may (partially) mediate the relationship between respiratory effort and duration of ventilation in ICU survivors (p=0.04), risk of complication of acute respiratory failure (p=0.04), and length of ICU stay in ICU survivors (p=0.02) (Goligher et al. 2018b).

There are yet other tools to assess diaphragm weakness that are not operator-dependent (Supinski et al. 2018). Demoule et al. (2013) used the twitch tracheal pressure (Ptr, stim) in response to bilateral phrenic nerve stimulation to evaluate the diaphragm in eighty-five patients. The authors concluded that diaphragm weakness, defined as Ptr, stim < 11 cmH_2O, was present in 64% of patients admitted to the ICU and was associated with poor prognosis. In another prospective study, diaphragm weakness, also measured with

Ptr, stim on ICU admission and every 48-72h thereafter, was observed in 79% of patients under mechanical ventilation for more than five days (Demoule et al. 2016). Moreover, Supinksy et al. (2016) compared transdiaphragmatic pressure after bilateral twitch simulation with airway pressure during a 30-second inspiratory occlusion in sixty patients and found that both measurements were profoundly reduced in mechanically ventilated patients.

It is adequate to state that diaphragm weakness is a concern that must be addressed in all mechanically ventilated patients. Moreover, it is necessary to gently treat not only the lungs but also the diaphragm. Therefore, a panel of experts recently published a conceptual framework proposing strategies to reduce diaphragm weakness while maintaining lung protective ventilation (Goligher et al. 2020a). **Figure 1** summarises available recommendations of lung and diaphragm protective ventilation together with the latest recommendations, from the ATS/ESICM/SCCM, for mechanically ventilated patients with ARDS (Fan et al. 2017).

Approaches to Treat or Reduce Diaphragm Weakness

Extracorporeal CO$_2$ removal: There is an increased awareness towards preventing diaphragm weakness as it is associated with adverse effects. Conversely, an increased respiratory drive may result in strong inspiratory efforts and ultimately hold deleterious effects in patients on spontaneous breathing. A study evaluated the response to CO_2 removal on eleven spontaneous breathing sheep with healthy and injured lungs (Langer et al. 2014). While CO_2 removal in sheep with healthy lungs successfully reduced minute ventilation (reduction in %, 84±14, P<0.001), some sheep with injured lungs did not, despite a high percentage of CO_2 removal. The authors concluded that the individual response could differ regardless of similar clinical conditions. In line with these findings, Mauri et al. (2016) conducted a proof-of-concept randomised, crossover protocol in eight spontaneously breathing ARDS patients undergoing veno-venous extracorporeal membrane oxygenation (ECMO). The authors assessed the respiratory drive in different sweep settings and
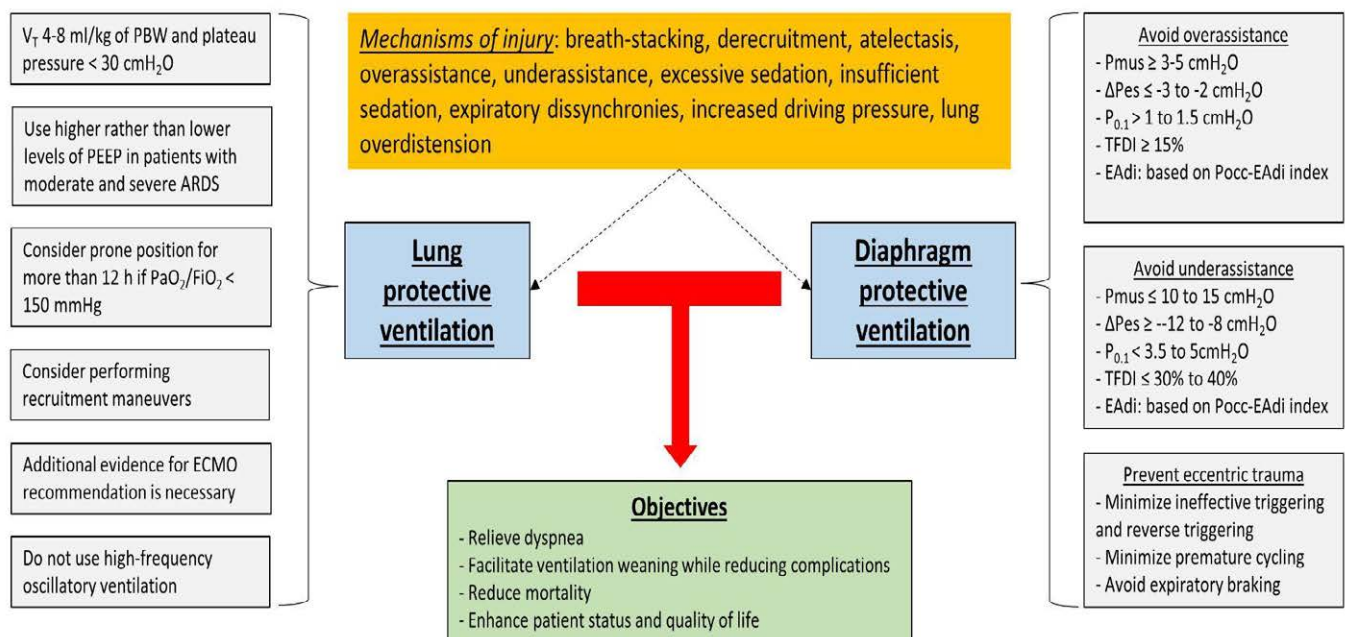

Figure 1. Contemporary recommendations for protective lung ventilation of ARDS patients and for lung-and diaphragm- protective ventilation

found that the amount of extracorporeal carbon dioxide removal directly may influence spontaneous breathing. Respiratory variables such as p0.1, electrical activity of the diaphragm, muscular pressure, pressure time product, and peak transpulmonary pressure were inversely related to carbon dioxide extraction (p<0.001 for all): the higher the extraction rate, the lower those variables. It may be possible to assume that extracorporeal CO_2 removal might be an alternative in patients who are likely to develop P-SILI. However, this strategy may be limited to specialised centres and may be associated with increased costs and workload.

Partial neuromuscular blockade: Instead of modulating the respiratory drive, there are novel alternatives that dissociate respiratory drive output and inspiratory effort. Doorduin et al. (2017) proposed partial neuromuscular blockade in patients under invasive mechanical ventilation. The authors successfully titrated a rocuronium infusion to reduce tidal volume and other respiratory variables to lung-protective thresholds. Despite promising physiology, this strategy still has limitations: (1) it requires careful titration of the infusion, which may ultimately increase the workload of healthcare professionals; and (2) patients need to be under deep sedation. Therefore, while it may reduce the probability of P-SILI, a continuous infusion of low-dose rocuronium is likely associated with worse patient-centred outcomes, including those related to deep sedation, as previously described.

Phrenic nerve block: Recently, Pereira et al. (2022) published a translational study where they bilaterally administered lidocaine perineurally to the phrenic nerve. An animal model of six pigs with ARDS and nine patients with acute lung injury were included. In pigs and humans, bilateral phrenic nerve block was associated with decreased driving pressure, electrical activity of the diaphragm, oesophageal pressure swing, tidal volume, and peak transpulmonary pressure (p<0.05 for all). Furthermore, there was a decrease in pendelluft in four pigs, from nearly 8% to 0% of tidal volume. Although the authors administered lidocaine a single time, it may be possible to insert a perineural catheter and titrate an infusion of local anaesthetic to partially suppress phrenic nerve activity. In this scenario, it would be possible to reduce complications associated with both deep sedation and neuromuscular blocking agents. Yet, the consequences of phrenic nerve block on accessory respiratory muscles have not been assessed and this approach requires training to appropriately identify cervical structures with ultrasound.

Transvenous phrenic nerve stimulation and inspiratory muscle training: If prolonged deep sedation and invasive mechanical ventilation are needed to maintain mechanical ventilation under protective thresholds, transvenous phrenic nerve stimulation and inspiratory muscle training may be alternatives to facilitate ventilation weaning and improve patient outcomes. Reynolds et al. (2017) tested transvenous phrenic nerve pacing therapy in 18 sedated and ventilated pig divided in three groups: (1) pigs with pacing on alternate breaths, (2) pigs similarly sedated and ventilated but without pacing, and (3)

never-paced control animals. There was a significant decline in diaphragm thickness in group 3 but not in group 1 (0.84 [IQR 0.78-0.89] vs. 1.10 [IQR 1.02-1.24]; P=0.001). In the largest trial on transvenous phrenic nerve stimulation, Dres et al. (2022) randomised 102 patients to bilateral phrenic stimulation and standard of care. There were no differences in the incidence of successful weaning (82% in the treatment group vs. 64% in the control group, P=0.59) and mechanical ventilation days (12.7±9.9 in the treatment groups vs. 14.1±10.8 in the control group, P=0.50). In spite of the negative patient-centred outcomes, the difference in maximal inspiratory pressure (95% CI 11.8 [5-19], P=0.001) should warrant further studies on the topic.

Conclusion
Sedation in the ICU is common, but its interaction with the critically ill, mechanically ventilated patient is complex and incompletely understood. The use of sedative agents requires knowledge and appreciation of both cardiovascular and respiratory effects to mitigate the risks of adverse events while employing them safely to achieve their desired actions. Monitoring of sedation is evolving and ongoing research is currently being conducted to better understand the interaction between the patient and the ventilator. Over-sedation can precipitate diaphragm injury and modern ventilatory strategies should be implemented not only to facilitate lung, but also diaphragm protective ventilation.

Conflict of Interest
None. ■

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Pain Management Specificities in Critically Ill Patients With Obesity

In patients with obesity, standard, non-weight-based dosing, or weight-based dosing using either ideal body weight or adjusted body weight, is appropriate to limit the risk of overdosing.

The prevalence of obesity is increasing worldwide (Schetz et al. 2019). This trend is confirmed in the Intensive Care Unit (ICU) where patients with obesity represent 15% to 40% of the population (Schetz et al. 2019; De Jong et al. 2018b; De Jong et al. 2019; De Jong et al. 2018a). Moreover, obesity has several implications for critical illness due to the difficulties of caring for such patients, including positioning, transport, skin care, intravascular access, diagnostic imaging, and ventilator weaning (De Jong et al. 2020; Pepin et al. 2016).

Obesity exerts physical, metabolic, and molecular effects across multiple organ systems and is associated with numerous comorbidities (diabetes, cardiovascular diseases, hypertension, chronic kidney disease, dyslipidaemia, non-alcoholic fatty liver disease, obstructive sleep apnoea and

hypoventilation syndrome, mood disorders and physical disabilities) (Schetz et al. 2019). This underlying pathophysiological setting has both direct and indirect impacts in critically ill patients with obesity (Schetz et al. 2019; Barletta and Erstad 2022; Plečko 2021).

Pain in the ICU

In addition to the treatment of various organ failures in the ICU, one of the challenges is pain management (Kalfon et al. 2020; de Jong et al. 2013). Pain assessment in the critically ill adult remains a daily clinical challenge. Indeed, pain has been shown to be experienced at rest by more than 30% of patients (Chanques et al. 2007) and this percentage exceeds 50% during common care procedures in ICU (Puntillo et al. 2014).

Pain should be monitored routinely in all adult intensive care patients, using validated scales according to the patient's level of consciousness (Devlin et al. 2018; Chanques 2022). Briefly, the 0-10 Numeric Rating Scale (NRS) is commonly used in clinical practice, and an enlarged visual format of the NRS was found to be the most feasible and discriminative self-report scale in comparison to other scales (i.e., visual analogue scale, verbal descriptor scale) and formats (i.e., oral versus visual) for measuring pain intensity in critically ill adult patients (Chanques et al. 2010).

Behaviour Pain Scale (BPS) is used as the gold standard to measure pain in the population of ICU patients unable to communicate according to guidelines,

especially in the sedated and mechanically ventilated patient (Chanques et al. 2020; Chanques et al. 2014; Devlin et al. 2018). The BPS is composed of three criteria: facial expression, upper limbs and compliance with ventilation. Each parameter is scored from 1 to 4 by trained staff and results in a score between 3 and 12 (Payen et al. 2001). In non-intubated ICU patients unable to communicate, pain level can be assessed with the BPS-NI scale (Chanques et al. 2009).

Depending on the numerical value obtained using these pain assessment scales, it is possible to classify pain as moderate or severe on a daily basis and to monitor its evolution during the stay (de Jong et al. 2013).

Pain and Obesity

Obesity is associated with chronic pain by several mechanisms including a mechanical impairment from excessive weight on skeletal muscles and joints and an altered systematic inflammatory status (Janke et al. 2007). However, cause-and-effect relationships between obesity and pain is not clear and cannot be extrapolated to the phenomenon of acute pain. The current literature provides contradictory results, especially in pain sensitivity of patients with obesity (Torensma et al. 2017).

Recent experimental studies support an increase in sensory pain thresholds through several mechanisms. The first hypothesis is mechanical with the evidence of higher thresholds and lower subjective ratings in patients with obesity, especially in areas

with excess subcutaneous fat (Torensma et al. 2017; Price et al. 2013). This could be explained by the stretching of the skin due to excess fat, which leads to a decrease in the density of the nerve fibres, and therefore the pain thresholds.

The second hypothesis relates to an endocrine pattern with an inflammatory environment that could also increase sensory pain thresholds. Excess adipose tissue in patients with obesity is highly metabolically active, and especially visceral adipose tissue which has a deleterious adipocyte secretory profile resulting in insulin resistance and a chronic low-grade inflammatory and procoagulant state (Piché et al. 2018; Neeland et al. 2018).

At the hormonal level, difference in concentrations between patients with and without obesity has been demonstrated for galanin (Yu et al. 2013) and b-endorphin (Price et al. 2013) with higher sensory pain thresholds in patients with obesity.

The last hypothesis still under study is a central dysregulation, including altered regulation of the neurovegetative system (Chanques et al. 2017) associated with neuropsychological changes in patients with obesity (Torensma et al. 2017).

Pharmacokinetics and Pharmacodynamics in Patients With Obesity

Obesity can affect pharmacokinetics (relationship between drug dose and concentrations in the body) as well as pharmacodynamics (the pharmacologic effect resulting from a drug's concentration). Recommendations for medication dosing in critically ill obese patients are not available from adequately powered randomised studies with clinically relevant endpoints.

Medication dosing regimens are often determined by cohorts of normal weight participants, raising questions about their applicability to patients with obesity in whom clearance and volume of distribution (Vd) may be substantially different. Weight-based dosing guidelines often do not specify the use of Actual Body Weight (ABW) versus ideal (based on height and sex) or adjusted (typically between actual and ideal) weight estimates (Barletta and Erstad 2022) and multiple additional factors

impacted by obesity must be considered for appropriate dosing. Further, equations to estimate lean body mass are not reliable in critically ill patients when compared to computed tomography as the gold standard (Moisey et al. 2017).

Multiple additional factors influenced by obesity must be considered for appropriate dosing, such as the presence of diabetes that can lead to glomerular hyperfiltration, or hepatic steatosis that may decrease the clearance of hepatically metabolised medications. In addition, association with one or more organ dysfunctions (e.g., acute kidney injury), may complicate dose selection.

Vd, calculated by dividing the total amount of drug in the body by the plasma concentration, is influenced by medication lipophilicity, molecular size, and protein binding, which alter a drug's ability to move between blood and tissues. Therefore, lipophilic medications may have a larger Vd in patients with obesity, requiring higher loading doses (Barletta and Erstad 2022). Furthermore, these medications have increased elimination half-life explained by multicompartmental pharmacokinetic model with redistribution phenomena before elimination.

Therapeutic Adjustments

Erstad and Barletta (2020) recently proposed a review of the literature based on drug dosing in ICU to develop recommendations for patient with severe obesity (i.e. BMI ≥ 40 kg/m2) in the areas of analgesia, sedation and delirium. Three major therapies were studied for analgesia: opioids, non-opioid analgesics, and ketamine.

In studies suggesting a size descriptor for dosing opioids, recommendations were for ideal body weight, lean body mass, or adjusted body weight as a preferred descriptor, because prospective and retrospective studies performed in the emergency department and post-operative setting have consistently found large variations in opioid requirements and pain control in overweight and patients with obesity that had no relationship to ABW (Xia et al. 2014; Bennett et al. 1982). Similarly, pharmacokinetic studies evaluating various opioids in the perioperative setting have found opioid doses based on ABW are likely to be excessive as evidenced by pharmacokinetic parameters and measured opioid concentrations (Egan et al. 1998; Slepchenko et al. 2003). For dosing opioids, incremental dosing titrated to clinical effect with consistent use of an ideal or adjusted

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Pain assessment in critically ill

Multi-daily clinical assessments using pain scales measured according to the patient's level of consciousness :
- NRS for communicative patients
- BPS for patients unable to communicate

Pathophysiological characteristics of patient with obesity

- Increased Vd and modified clearance half-life
- Lipophilic medications are particularly impacted
- Medication metabolism impacted by multiple additional factors, especially for patients in ICU

Dosing recommendations for medications

- Opioids : use of ideal or adjusted body weight and incremental dosing titrated to clinical effect
- Non-opioid analgesics : use of non-weight based dosing regimens
- Ketamine : use of ideal or adjusted body weight

Figure 1. Summary of pain management specificities in critically ill patients with obesity.
BPS, Behaviour Pain Scale; ICU, Intensive Care Unit; NRS, Numeric Rating Scale; Vd, Volume of distribution.

body weight is suggested for weight-based dosing particularly in patients with more severe forms of obesity, to reduce the risks related to overdosing.

Non-opioid analgesics, such as nonsteroidal anti-inflammatory drugs and acetaminophen commonly administered to critically ill patients, typically use non-weight-based dosing regimens. The few pharmacokinetic and pharmacodynamic studies evaluating the disposition of non-opioid agents show little benefit for dose individualisation based on weight with adverse effect (especially liver disease) when increasing doses beyond those needed to reach the analgesic ceiling effect (Motov et al. 2017; Allard et al. 2019). For dosing non-opioids analgesics, non-weight based dosing regimens are advised.

Regarding ketamine, this molecule has substantial lipophilicity with a large Vd, rapid clearance and active metabolites, all complicate potential dosing recommendations (Clements and Nimmo 1981) and especially in ICU (Hijazi et al. 2003). To loading doses, ABW is appealing as a size descriptor given the lipophilicity of ketamine, since clinical effect in this situation is largely a function of the drug's Vd. With sustained intermittent intravenous injections or continuous infusions of ketamine, accumulation of both parent drug and active metabolite norketamine occurs until steady state conditions occur. Norketamine has one-third the potency of the parent compound, but also has slower elimination that increases the time to reach steady state, thus probably requiring a decrease in dose over time to maintain the same clinical effect. In consequence, the complex estimation of clearance of ketamine (due to a lack of correlation between lean body mass and fat mass in patients with obesity) combined with the complicated determination of an active metabolite suggests the use of ideal or adjusted body weight is preferable for weight-based dosing calculations due to adverse effect concerns associated with overdosing.

Conclusion

In the current state of knowledge and in the face of the complex interrelationships among pain, body weight, comorbid conditions and behavioural/biological contributors, the pain management in patients with obesity in ICU has only recently been described. Further studies are needed to develop analgesia protocols specifically designed for patients with obesity.

In addition, the management of pain in patients with obesity requires, as for any other patients in ICU, multi-daily clinical assessments using pain scales measured according to the patient's level of consciousness to assess pain evolution.

For patients with obesity, there is no high-level clinical evidence available to help design dosing regimens for analgesia in critically ill.

Based on pharmacokinetic studies, the relationship between ABW and pharmacokinetic variables such as Vd and clearance is not linear for most of pain medications. For such medications, standard, non-weight-based dosing, or weight-based dosing using either ideal body weight or adjusted body weight, is appropriate to limit the risk of overdosing. In patients with obesity as in all patients who received a sustained infusion of sedatives and/or opioids, repeated assessment of clinical needs (sedation level, pain intensity) are mandatory to titrate the dose and to avoid analgo-sedation side-effects related to its overuse.

Conflict of Interest

Audrey De Jong reports receiving consulting fees from Medtronic and Drager. Gerald Chanques and Ambre Cuny have no conflict of interest. ■

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Nutrition Monitoring and Patient Data Management Systems

An overview of nutritional targets and their impact on critically ill patients and the need to use a systematic approach to nutritional support for optimal patient outcomes.

Critically ill patients are often hypermetabolic and catabolic and are at a higher risk of underfeeding. Nutritional support for these patients can prevent energy deficits and improve outcomes (Villet et al. 2005). Underfeeding critically ill patients may cause harm to some patients who require a longer stay in the ICU (Wei et al. 2015).

The primary goals of nutrition support are to preserve or restore lead body mass, maintain immune function and avert metabolic complications. Ultimately, the aim of nutritional support is to reduce disease severity, reduce the risk of complications, decrease the length of stay in the ICU and improve patient outcomes (van Schijndel et al. 2009).

Protein loss, in particular, has been observed in all critically ill patients and is associated with increased morbidity and mortality. Muscle mass depletion is also associated with impaired function and poor clinical outcomes. Adequate protein delivery to critically ill patients is essential for optimal nutrition therapy (Hurt et al. 2017). Unfortunately, ICU patients worldwide fail to receive protein within the SCCM-ASPEN recommended range of 1.2–2.0 g/kg/d (McClave et al. 2016).

Caloric deficit in critically ill patients is associated with an increase in ventilator days, complications and increased length of stay (Villet et al. 2005). Protein deficit, in particular, is associated with increased mortality (Allingstrup et al. 2012; Hurt et al. 2017; Nicolo et al. 2016; Weisj et al. 2017). Evidence shows that greater nutritional intake during the first week in the ICU is associated with longer survival and faster physical recovery in patients requiring prolonged mechanical ventilation (Wei et al. 2015).

Findings from an international multi-centre observational study that explored the relationship between nutritional support and clinical benefits showed that the energy and protein intake of critically ill patients was significantly lower than prescribed (Alberda et al. 2009). This could be due to multiple factors, including interruptions for surgery or routine procedures, other critical care procedures or a lack of tracking of nutritional intake.

There is a need to use a systematic approach to nutritional support for critically ill patients as this can improve patient outcomes. A patient's nutritional needs should be individually determined, and a tailored nutritional therapy should be used to clearly identify the type of solution, delivery site and access devices, and administration rate and method (Boullata et al. 2017).

It is important to keep in mind that nutritional monitoring can be complex and may require manual calculations and tracking, which can be time-consuming and susceptible to human error (Berger et al. 2006). However, there are solutions that can help facilitate this process. Computerised patient data management systems can help standardise nutritional care and facilitate patient monitoring. There is evidence that such systems improve data visibility and are associated with a significant improvement in adequate nutrition delivery (Berger et al. 2006).

One such example is the Compat Ella® enteral feeding pump, which makes it easier to monitor nutrition. The device can be connected to a hospital Patient Data Management System (PDMS) to allow real-time tracking of nutrition and improve patient outcomes. PDMS connectivity allows auto-mated data collection and control and helps reduce the workload associated with manual data entry and computation (Berger et al. 2006). This allows healthcare providers to spend more time with the patient and less time calculating nutritional requirements. PDMS connectivity also makes the feeding process visible (Berger et al. 2011; Strack Van Schijndel et al. 2007) and facilitates metabolic monitoring (Berger et al. 2006; Berger et al. 2011).

Key Points

- Critically ill patients are often hyper-metabolic and catabolic and are at a higher risk of underfeeding.

- The primary goals of nutrition support are to preserve or restore lead body mass, maintain immune function and avert metabolic complications.

- Protein loss has been observed in all critically ill patients and is associated with increased morbidity and mortality.

- Caloric deficit in critically ill patients is associated with an increase in ventilator days, complications and increased length of stay.

- Computerised patient data management systems can help standardise nutritional care and are associated with a significant improvement in adequate nutrition delivery

- The Compat Ella® enteral feeding pump makes it easier to monitor prescribed nutrition. It can be connected to a hospital Patient Data Management System (PDMS) to allow real-time tracking of nutrition.

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Analgesia, Sedation and Neuromuscular Blockade in Critically Ill Patients: A Practical Approach for Intensivists

A practical approach to analgesia, sedation and neuromuscular blockade of critically ill patients and a discussion on potential benefits, adverse effects and current professional international recommendations.

Introduction

Patients hospitalised in the Intensive Care Unit (ICU) are naturally prone to experience pain. They may require administration of sedatives and even neuromuscular blockade (NMB) in some cases. At the present moment, there are several clinical practice guidelines in this regard by multiple professional associations. However, there are still some discrepancies on the optimal clinical approach of these patients, namely on drug selection alongside monitoring of their effects. In this paper, we introduce a practical approach to the analgesia, sedation and NMB of critically ill patients, whilst taking into account potential benefits, adverse effects and current professional international recommendations.

Evaluation and Management of Pain in the ICU

More than 50% of critically ill patients experience pain, a situation that is associated with adverse outcomes. These include increasing length of ICU stay and in-hospital stay, increasing days under invasive mechanical ventilation (IMV), and a higher incidence of delirium. Clinicians must implement strategies for the early detection, evaluation and management of pain, in an attempt to maximise patient comfort, since this is considered an essential part of the so-called Humanisation of Intensive Care Units.

The physiological response to pain commonly presents with tachycardia, hypertension, tachypnoea, respiratory alkalosis, among others. This response is related to haemodynamic instability, impairment of the immune system and hyperglycaemia, in addition to the release of catecholamines, cortisol and vasopressin. Persistence of pain predisposes to a wide variety of detrimental psychological effects including agitation, post-traumatic stress disorder, disorientation and depression.

The first step of this approach is to accurately identify pain, which may pose a challenge in patients in which verbal communication is not feasible, for instance, in patients under IMV or sedatives, as well as in patients with paralysis, neurological or neuromuscular disorders, among others. The most widely used scale for pain detection and assessment is the Critical-Care Pain Observation Tool (CPOT) (**Table 1**), which takes into consideration a handful of clinical parameters; of note, this scale can be used in patients who can verbally communicate and also in patients who cannot, such as those under IMV, as it considers facial expression, upper limb movements and compliance with mechanical ventilation.

Once pain is identified, an adequate analgesic treatment must be prompted. The

Figure 1. Left. CPOT 0: Facial expression relaxed, absence of movements, muscle tension relaxed, tolerating ventilator. RASS -2: Light sedation.
Middle. CPOT 4: Facial expression tense, body movements protection, muscle tension rigid, coughing but tolerating ventilator. RASS +2: Agitated.
Right. CPOT 8: Facial expression grimacing, body movements restlessness, muscle very tense or rigid, fighting. RASS +3: Very agitated.

Critical Care Pain Observation Tool (CPOT)		
Facial expression	Relaxed	0
	Tense	1
	Grimacing	2
Body movements	Absence of movements	0
	Protection	1
	Restlessness	2
Muscle tension	Relaxed	0
	Tense, rigid	1
	Very tense or rigid	2
Compliance with the ventilator	Tolerating ventilator or movement	0
	Coughing but tolerating	1
	Fighting	2
Vocalisation	Talking in normal tone or no sound	0
	Sighing, moaning	1
	Crying out, sobbing	2
Goal: <3		

Table1. Critical Care Pain Observation Tool

drugs most frequently used for pain management in the ICU include acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids. Other drugs, such as ketamine, lidocaine, neuromodulators and magnesium sulfate, may also be used. Another strategy to be considered is that of regional analgesia, more widely used in post-surgical patients, which will not be addressed in this review.

Indications for therapeutic or prophylactic administration of pain medications in the ICU include the following:

1. Patients with endotracheal intubation and IMV
2. Polytrauma
3. Burns
4. Post-operative period
5. During procedures such as tracheostomy, placement of pleural tubes, dressing and debridement of wounds, drainage of fluid collections, catheter placements, etc.
6. Chronic pain (e.g., cancer)
7. Neuropathic pain
8. Palliative care

Opioids are considered first-choice drugs for analgesia in critically ill patients due to their high efficacy. These act on the μ, κ and δ receptors of the central nervous system (CNS). The most highly recommended of them are remifentanil, fentanyl, morphine and hydromorphone given their higher analgesic effectiveness. Other less advised opioid medications include buprenorphine, oxycodone, nalbuphine and codeine, which are associated with a higher incidence of adverse effects and a lower analgesic potency.

Opioid accumulation is associated with the following side effects: nausea, vomiting, ileus, haemodynamic instability and respiratory depression. Therefore, their use should be restricted to short periods of time. It is highly encouraged to use the minimum effective dose to achieve the desired effect, since higher doses might cause tolerance and desensitisation of receptors, thereby reducing their effect and, in turn, further requiring higher doses. To minimise adverse effects, a multimodal analgesia with adjuvant drugs may be used, with the aim of blocking the transmission of pain by other mechanisms at the peripheral level and at the level of the spinal cord-hypothalamus-cerebral cortex axis.

Opioid-induced hyperalgesia results from their use for prolonged periods of time along with excessive doses (Lee 2011). It is originated by an impaired action from N-methyl-D-aspartate (NMDA) glutamatergic receptors and an increase in spinal dynorphin levels, resulting in an excessive synthesis and a release of excitatory neuropeptides, thus shifting the balance between antinociceptive and pronociceptive systems. For the above reasons, opioids should be

withdrawn as early as possible - as soon as the cause of the pain is solved.

As a result of its ultra-short action and its elimination by plasmatic esterases, remifentanil is the opioid medication of choice. This drug is associated with lower days under IMV, lower time to extubation and lower length of ICU stay. Its pharmacokinetics are not affected by renal or hepatic impairment; therefore, it is safe in patients with liver or kidney diseases. Its major disadvantages include its high cost and lower availability compared to other opioid medications (Yang 2021). Fentanyl is associated with more days of IMV compared to remifentanil. Morphine is associated with hypotension due to histamine release, pruritus, and a higher incidence of nausea and vomiting. Along with hydromorphone, these drugs are reasonable options for analgesia (Devlin 2018).

Acetaminophen is recommended as an adjuvant analgesic in the opioid therapy of critically ill patients. Dose adjustment should be considered in chronic liver failure, and this drug must be avoided in acute liver failure and in cases of allergy. Nefopam is

a histamine H1 receptor antagonist focused on the inhibition of monoamine uptake in synapses, which would lead to an increase in noradrenaline, dopamine and serotonin. It is advised as an adjuvant treatment to opioids and as a treatment alternative. However, it is seldom available worldwide.

NSAIDs remain an adequate alternative for analgesia. Their effect is comparable to low-potency opioids, thereby reducing opioid consumption, as well as their side effects. There is a wide variety of drugs included in this group such as COX-1, COX-2 and prostaglandin E2 inhibitors. Among critically ill patients, their adverse effects include acute kidney injury and gastrointestinal (GI) bleeding, with even higher risks for patients with pre-existing impaired renal blood flow, older adults, patients with heart disease, and patients with shock or those exposed to other nephrotoxic drugs (Thadhani 1996). Other lower incidence deleterious effects include cardiovascular and cerebrovascular complications, fluid retention, hypertension and thromboembolic events. In particular, ketorolac has been associated with a significant increase in the incidence of anastomotic leaks in

post-operative patients (Wick 2017). However, NSAIDs are not recommended for routine use in critically ill patients.

In subanaesthetic doses, ketamine exerts an analgesic effect comparable to morphine, with a similar need for rescue doses. This drug reduces chronic hyperalgesia mediated by NMDA receptors, as well as that induced by opioid medications (Hirota 2011). Its advantages include the fact that it does not cause respiratory or haemodynamic depression, hence it is useful in patients with shock (Eikermann 2012). Its adverse effects are dose-dependent, and they include hypersalivation, nausea and vomiting, vivid dreams, blurry vision, hallucinations, nightmares and delirium. Due to its dissociative effects, ketamine proves useful in the pain management of severely burned patients or in those with a large number of invasive devices and procedures. It can also be safely used in patients with intracranial hypertension. Ketamine is metabolised via the liver and excreted by the kidneys, nevertheless, no significant adverse effects over hepatic and renal functions have been noted at subanaesthetic doses.

	Mechanism of action	Comments	Dose	Onset; half-life	Contraindications/ cautions	Adverse effects
Acetaminophen	Inhibition of cyclooxygenases (COX-1, COX-2, and COX-3). Acts upon the endocannabinoid and serotonergic systems and influences transient receptor potential channels (TRP) and voltage-gated Kv7 potassium channels. Inhibition of Cav3.2 T-type calcium channels. Acts on L-arginine in the nitric oxide (NO) synthesis pathway.	Reduces opioid consumption. First-line treatment for mild to moderate pain. Weak anti-inflammatory action.	PO/IV: 1 g every 6-8 h Maximum dose: 4 g in 24 h	Onset: IV: 5-10 min PO: 30-60 min $t_{1/2}$: 4-6 h	Caution in patients with significant liver dysfunction. Caution in malnutrition.	Associated with hypotension (IV administration). Liver failure (high doses).
Nefopam	Histamine H1 receptor antagonist focused on the inhibition of monoamine uptake in synapses, which would lead to an increase in noradrenaline, dopamine and serotonin.	Seldom available worldwide	20-30 mg every 6-12 h Maximum dose: 120 mg in 24 h	Onset: PO: 15-20 min IV: 15-20 min $t_{1/2}$: 3-8 h	History of convulsive disorders. IM/IV: Urinary retention linked to urinary or prostate disorders, angle-closure glaucoma. Oral: Concomitant use with MAOIs.	Blurred vision, xerostomia, constipation, urinary retention, tachycardia, palpitations, angina. Nausea, vomiting, diarrhoea, abdominal pain. Dizziness, drowsiness, headache, paraesthesia, tremor, convulsion, light-headedness. Hypotension, syncope.

Tramadol	Acts on the CNS. Binds to μ-opioid receptors and blocks noradrenaline and serotonin reuptake by binding to monoaminergic receptors.	Partial antagonism by naloxone. Considered a mild opioid.	PO/IV: 50-100 mg every 4-6 h Maximum dose: 400 mg in 24 h	Onset: IV: 5-10 min PO: up to 1 h t½: 4-6 h	Accumulation in renal or liver failure. Associated with seizures in patients with epilepsy. Contraindicated with concurrent use of monoamine oxidase inhibitors (MAOIs).	Respiratory depression (less than other opioids). Nausea/vomiting. Ileus.
Gabapentin	Binds to α2δ subunits of voltage-gated calcium channels.	Useful for neuropathic pain. Reduces incidence of hyperalgesia and central sensitisation. Anticonvulsant. Reduces opioid consumption (multimodal analgesia in the ICU).	Start with 100 mg PO every 8 h Maintenance dose: 900-3600 mg/day	Onset: N/A t½: 4.8–8.7 h	Requires renal dosage adjustment. Absorbed in a relatively small portion of the duodenum. Ineffective in patients under jejunal feeding.	Sedation. Confusion. Ataxia. Dizziness.
Pregabalin	Neuromodulator. With potent binding to the α2-δ subunit, reduces calcium influx into presynaptic nerve terminals, with release of excitatory neurotransmitters such as glutamate, norepinephrine, and substance P.	Useful for neuropathic pain. Reduces incidence of hyperalgesia and central sensitisation. Anticonvulsant.	50–300 mg PO every 8-12 h	Onset: N/A t½: 5.5–6.7 h	Requires renal dosage adjustment.	Sedation. Confusion. Ataxia. Dizziness.
Carbamazepine	Blockade of voltage-gated sodium channels. Potent anticholinergic that acts at the level of muscarinic and nicotinic receptors.	Anticonvulsant. Reduces opioid consumption (multimodal analgesia in the ICU).	Start with 50-100 mg PO every 12 h Maintenance dose: 100-200 mg every 4-6 h Maximum dose: 1200 mg/day	Onset: 4-5 h t½: 5-26 h	Caution in AV block. History of myelosuppression and hepatic porphyrias. Caution with concurrent use of monoamine oxidase inhibitors (MAOIs).	Dizziness Ataxia Drowsiness Fatigue Headache Diplopia Urticaria Leukopenia Eosinophilia Thrombocytopenia
Lidocaine	Blockade of voltage-gated sodium channels, leading to a reversible blockade of the propagation of action potentials.	Reduces opioid consumption (when used in infusion). Shortens duration of perioperative ileus. Decreases the incidence of nausea/vomiting.	IV bolus: 1.5-2 mg/kg Infusion: 1.5-3 mg/kg Maximum dose: 5 mg/kg	Onset: immediate (IV) t½: 90-120 min	Caution in congestive heart failure and liver failure.	Dizziness Tinnitus Fasciculations Visual disturbances Arrythmias

Morphine	Stimulates μ, κ and δ receptors distributed in the CNS and peripheral tissues.	Metabolised by glucuronidation. Active metabolites: M6G and M3G. Releases histamine from mast cells, causing vasodilation.	IV bolus: 0.1-0.2 mg/kg Infusion: 0.05-0.1 mg/kg/h	Onset: 5-10 min t½: 3-5 h	Metabolites accumulation in renal failure. Causes histamine release.	Immunosuppression Delirium, sedation, and respiratory depression Tolerance within 48 h Withdrawal symptoms after discontinuation Hyperalgesia and other pain syndromes with long-term use Ileus/constipation/nausea/vomiting Urinary retention Bradycardia
Hydromorphone	Semi-synthetic opioid agonist. Stimulates μ receptors (and δ receptors to a lesser degree) at the supraspinal and spinal levels.	Metabolised mainly into dihydroisomorphine glucuronide and hydromorphone-3-glucuronide (H3G). May require higher doses in patients with history of prior opioid use	IV bolus: 0.2-0.6 mg Infusion: 0.5-5.0 mg/h PO: 2-8 mg/3-4 h	Onset: 10-20 min t½: 2-6 h	Decrease dose in older adults. Requires dose adjustment in patients with morbid obesity, liver/renal failure, COPD, or restrictive lung diseases.	Delirium, euphoria, miosis, drug dependence, tolerance Constipation, nausea, vomiting Pruritus Respiratory depression Urinary retention
Fentanyl	Stimulates μ, κ and δ receptors distributed in the CNS and peripheral tissues.	Synthetic opioid. Fat-soluble. Causes less hypotension than morphine. Hepatic metabolism without active metabolites	IV bolus: 0.3-0.5 mcg/kg Up to 2 mcg/kg Infusion: 1-10 mcg/kg/h	Onset: 1-2 min t½: 1-4 h	Administration should be based on ideal body weight in obese patients. Older adults may require lower doses. Caution in uncontrolled hypothyroidism, lung diseases, decreased respiratory reserve, alcoholism, functional liver/renal damage. Muscle stiffness when rapidly infused.	Sedation, delirium Tolerance within 48 h Withdrawal symptoms after discontinuation Hyperalgesia and other pain syndromes with long-term use Respiratory depression Ileus, constipation, nausea, vomiting Urinary retention Bradycardia
Remifentanil	μ receptor selective agonist, with rapid onset and short duration.	Hydrolysis by plasmatic esterases, without active metabolites. Allows for an early neurologic assessment in neurointensive care. Does not increase histamine.	IV bolus: 1 mcg/kg Infusion: 0.05-2 mcg/kg/h	Onset: 1-3 min t½: 3-10 min	No accumulation in patients with liver/renal failure. Administration should be based on ideal body weight in obese patients. Muscle stiffness may occur.	Immunosuppression Sedation, delirium Respiratory depression Tolerance within 48 h Withdrawal symptoms after discontinuation Hyperalgesia and other pain syndromes with long-term use Ileus, constipation, nausea, vomiting Urinary retention Bradycardia

Sufentanil	High affinity to the μ receptor. Slow dissociation.	Synthetic opioid. 7 to 10 times more potent than fentanyl. Accumulation unlikely.	IV bolus: 0.1-0.3 mcg/kg Infusion: 0.1-1 mcg/kg/h	Onset: 1-3 min t½: 0.5-2 h	Caution with concurrent use of monoamine oxidase inhibitors (MAOIs).	Sedation, delirium Respiratory depression Tolerance or withdrawal symptoms Ileus/constipation Nausea/vomiting Urinary retention Bradycardia
Diclofenac	COX-1 and COX-2 inhibition, which regulate production of prostaglandins and thromboxane from arachidonic acid.	Analgesic, antipyretic, and anti-inflammatory. PO is 100% absorbed.	IV bolus: 75 mg Infusion: 0.04 mg/kg/h	Onset: 15-30 min t½: 2 h	Avoid in patients with risk of acute kidney injury: e.g., hypovolaemia or inotrope-dependent shock. Avoid in patients with risk of GI bleeding: burns, platelet abnormalities, coagulopathy, concomitant use of ACE inhibitors, congestive heart failure, cirrhosis.	Acute kidney injury. GI bleeding. Hypotension.
Ibuprofen	COX-1 and COX-2 inhibition, which regulate production of prostaglandins and thromboxane from arachidonic acid.	Analgesic, antipyretic, and anti-inflammatory.	PO: 400-600 mg every 4 h Maximum dose: 2.4 g/day	Onset: 25 min t½: 1.8-3.5 h	Avoid in patients with risk of acute kidney injury: e.g., hypovolaemia or inotrope-dependent shock. Avoid in patients with risk of GI bleeding: burns, platelet abnormalities, coagulopathy, concomitant use of ACE inhibitors, congestive heart failure, cirrhosis.	Acute kidney injury. GI bleeding.
Ketorolac	COX-1 and COX-2 inhibition, which regulate production of prostaglandins and thromboxane from arachidonic acid.	Analgesic, antipyretic, and anti-inflammatory.	IV: 10-30 mg every 4-6 h, in no less than 15 s Infusion: 5 mg/h	Onset: 10 min t½: 4-6 h	Avoid in patients with risk of acute kidney injury: e.g., hypovolaemia or inotrope-dependent shock. Avoid in patients with risk of GI bleeding: burns, platelet abnormalities, coagulopathy, concomitant use of ACE inhibitors, congestive heart failure, cirrhosis.	Acute kidney injury. GI bleeding. Anastomotic leak.

Table 3. Analgesics

CNS: Central nervous system, MAOIs: Monoamine oxidase inhibitors, COPD: Chronic obstructive pulmonary disease, ACE: Angiotensin converting enzyme, GI: Gastrointestinal bleeding.

Sedation

Although maintenance sedation is a commonly used approach in critically ill patients, it is intrinsically harmful. This intervention is associated with patient weakness, delirium, increasing days on mechanical ventilation and increasing days of hospitalisation and ICU stay (Nedergaard 2022). However, it might be necessary in some specific scenarios. Indications for maintenance sedation include the following (Reade 2014):

1. Moderate to severe acute respiratory distress syndrome (ARDS).
2. Intracranial hypertension (e.g., severe traumatic brain injury with concurrent mass effect).
3. Status epilepticus (when non-responsive to first-line or second-line therapy).
4. Consider in abdominal compartment syndrome, flail chest and patients requiring major surgery, or inability to perform regional anaesthesia.

If opting for sedation, it is highly recommended that the dose of the medications is titrated according to predefined goals based on the patient's condition, as well as continuous monitoring. There are several ways to monitor the sedation state of a critically ill patient; the RASS scale is the most widespread tool for this purpose. If a given patient has an indication for deep sedation (e.g., ARDS or refractory intracranial hypertension) it is recommended that they remain at a level <-3. However, if only minimal sedation is planned (such as in a patient under a weaning protocol), it is reasonable to remain in levels from 0 to -1. It is difficult to find a justification for maintaining a moderate sedation (RASS 2 to 3). There are different technological sedation monitors such as the unilateral or bilateral bispectral index (BIS), entropy monitoring, among others, although none has been shown superior to the RASS scale (**Table 2**), and they could indeed prompt additional expenses.

Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU (PADIS) guidelines endorse propofol and dexmedetomidine as first-choice sedatives. Benzodiazepines are not recommended as maintenance sedatives due to their association with delirium (Devlin 2018). Ketamine might also be considered as a sedative for critically ill patients, even showing benefits in patients with shock including lower rates of hypotension and bradycardia (Umunna 2015).

The haemodynamic changes associated with propofol may include myocardial depression, bradycardia and hypotension. It must be taken into consideration that propofol provides up to 1.1 kcal per millilitre; therefore, it may cause hypertriglyceridaemia, pancreatitis or overfeeding. With regard to dexmedetomidine, this drug frequently causes bradycardia, and it may also contribute to hypotension in patients with shock; nevertheless, its safety profile appears to be better than other sedatives and it has even been associated with greater haemodynamic stability in patients with septic shock. Unfortunately, despite many recommendations discouraging the use of benzodiazepines, midazolam remains the most commonly used sedative in continuous sedation among many hospitals (Luz 2022). It is recommended to consider the use of anti-psychotic agents, volatile anaesthetics or intermittent benzodiazepines in patients with ARDS who do not achieve deep sedation with propofol and dexmedetomidine.

It is important to emphasise that the condition that leads the patient to require sedation must be solved as soon as possible, and a wake-up test must be performed early in the course to prompt a timely ICU discharge, which should be repeated every day until the patient can be safely withdrawn from mechanical ventilation. This procedure is associated with fewer days on IMV, and fewer days of ICU stay.

Richmond Agitation Sedation Scale (RASS)		
Combative	Overtly combative, immediate danger to staff	+4
Very agitated	Pulls on or removes tube (s) or catheter (s) or has aggressive behaviour toward staff	+3
Agitated	Frequent non-purposeful movement or patient-ventilator dyssynchrony	+2
Restless	Anxious or apprehensive but movements not aggressive or vigorous	+1
Alert and calm	Spontaneously pays attention to caregiver	0
Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact to voice	-1
Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice	-2
Moderate sedation	Any movement (but no eye contact) to voice	-3
Deep sedation	No response to voice, but any movement to physical stimulation	-4
Unarousable	No response to voice or physical stimulation	-5

Table 2. Richmond Agitation Sedation Scale

	Mechanism of action	Comments	Dose	Onset; half-life	Contraindications/ cautions	Adverse effects
Propofol	Potentiates activation of GABA-mediated ion channels. Inhibition of NMDA receptors.	Sedative-hypnotic, anxiolytic. Antiemetic.	IV bolus: 1-2 mg/kg Infusion: 20-50 mcg/kg/min ≥60 mcg/kg/min associated with propofol infusion syndrome	Onset: 15-30 s t½: 5-10 min	Hepatic metabolism. Renal excretion. Avoid with triglycerides ≥800 mg/dl.	Respiratory depression Metabolic acidosis Immunosuppression Pancreatitis Hypotension QT prolongation Myocardial depression Green urine
Dexmedeto-midine	α2 receptor agonist. α2 selectivity over α1 receptors (1600:1). Induces sleep by decreasing the firing of noradrenergic neurons of the locus coeruleus in the brainstem, and by activating endogenous pathways that promote non-rapid eye movement (NREM) sleep.	Conscious sedation, sympatholytic, anxiolytic, analgesic. Decreases risk of delirium. Regulates sleep. Reduces opioid consumption (multimodal analgesia).	IV bolus: no Infusion: 0.2-0.7 mcg/kg/h >1.5 mcg/kg/h associated with risk of cardiotoxicity.	Onset: 15-20 min t½: 3-4 h	Caution with concurrent use of esmolol. Consider dose reduction in patients with liver disease.	Hypotension Bradycardia Dry mouth Nausea
Ketamine	NMDA antagonist. Acts upon opioid receptors and monoaminergic receptors. Inhibition of muscarinic receptors. Promotes GABAergic transmission.	Dissociative anaesthesia, sedation, and analgesia. Prevents neuropathic pain. Confers haemodynamic stability (positive chronotropism, increases blood pressure). Bronchodilation. Preserves airway reflexes.	IV bolus: 0.2-4.5 mg/kg IM: 6.5-13 mg/kg Infusion: 2.5-5 mcg/kg/min > 20 mg/kg associated with myocardial depression	Onset: 30-40 s t½: 10-15 min	Porphyria Thyroid diseases	Sialorrhea Laryngospasm Drug dependence Dysuria Urinary incontinence Hallucinations
Etomidate	Modulates and activates GABA_A receptors that contain β2 and β3 subunits.	Anaesthetic, hypnotic. Haemodynamic stability (attenuates responses to ACO and bradykinin). 34% decrease in cerebral blood flow and 45% decrease in cerebral metabolic rate of oxygen (CMRO2) without mean arterial pressure (MAP) being affected. Anticonvulsant.	IV bolus: 0.2-0.6 mg/kg Infusion: no	Onset: 30-60 s t½: 2.5-5.5 h	Hepatic metabolism. Renal excretion. Interaction with metamizole (dipyrone).	Inhibition of adrenocortical axis Myoclonus Nausea/vomiting Injection site pain Nystagmus Hiccups

Midazolam	GABA agonist. Increases the opening frequency of chloride channels.	Hypnotic, sedative, anxiolytic, and amnesic activity. Anticonvulsant (first-line therapy in status epilepticus).	IV bolus: 0.01-0.05 mg/kg Infusion: 0.02-0.1 mg/kg/h	Onset: 2-3 min t½: 3-72 h	Clearance depends on hepatic and renal function.	Hypotension Bradycardia Thrombosis Respiratory depression Delirium Tachyphylaxis Immunosuppression Ataxia Polyneuropathy/Critical illness myopathy
Lorazepam	GABA agonist. Increases the opening frequency of chloride channels. This change results in hyperpolarisation and stabilisation of cell plasma membrane.	Anterograde amnesia. Sedative. Anxiolysis. Anticonvulsant.	PO: 2-3 mg every 8-12 h IM: 0.05 mg/kg IV bolus: 0.02-0.04 mg/kg Infusion: 0.01-0.1 mg/kg/h	Onset: 1-3 min (IV), 15-30 min (IM) t½: 14 h Peak plasma time: 2 h (PO)	Myasthenia gravis, acute angle-closure glaucoma. Caution in obstructive sleep apnoea and severe respiratory failure.	Hypotension Respiratory depression Diarrhoea Delirium Tachyphylaxis
Diazepam	GABA agonist. Increases the opening frequency (but not opening duration) of chloride channels.	Anterograde amnesia, sedation. Highly fat-soluble. Crosses the blood-brain barrier.	IV bolus: 0.1-0.2 mg/kg Infusion: no	Onset: 2-5 min t½: 20-120 h Biphasic half-life with a rapid initial distribution phase and a prolonged terminal elimination phase of 1 to 2 days.	Diazepam and desmethyldiazepam (active metabolite) accumulate with repeated dosing. Accumulation occurs mostly in newborns, older adults and in patients with liver diseases.	Hypotension Respiratory depression Phlebitis Delirium Tachyphylaxis

Table 4. Sedatives
NMDA: N-methyl-D-aspartate, GABA: Gamma-aminobutiryc acid.

Neuromuscular Blockade

Neuromuscular blockade (NMB) can be common among critically ill patients, especially in the course of ARDS treatment. Its indications are limited, and this modality is associated with several adverse effects such as venous thromboembolism, critical illness myopathy, patient awareness during paralysis, autonomic interactions, pressure ulcers, corneal ulcers and residual paralysis (Renew 2020).

Indications of NMB in the ICU include:
1. Rapid sequence intubation (RSI)
2. Moderate to severe ARDS
3. Consider in intracranial hypertension, refractory status asthmaticus, failed sedation, and to temporarily reduce intra-abdominal pressure in patients with intra-abdominal hypertension (IAH), among others (De Laet 2007).

The American Society of Anesthesiologists (ASA) recommends the use of NMB to reduce the number of intubation attempts, thereby decreasing the risk of airway injuries during direct laryngoscopy (Apfelbaum 2013). Rocuronium is the only non-depolarising drug indicated for induction and intubation during RSI.

Regarding the management of moderate to severe ARDS in patients under IMV, meta-analyses have shown a reduction in mortality in the ICU when using an infusion of cisatracurium (Ho 2020), and recently, it has shown greater utility if maintained under continuous infusion for more than 48 hours in patients with respiratory failure under IMV due to COVID-19 (Li 2021). The major advantage of cisatracurium relies on its metabolism by Hofmann elimination, which confers a rapid elimination of its

effects when withdrawn. Moreover, it does not depend on hepatic or renal depuration. A strategy that combines the use of NMB with cisatracurium and low tidal volume could reduce mortality, most likely due to a reduction of asynchrony events and improvement of pulmonary compliance and functional residual capacity, which would translate into an increase in oxygenation (Murray 2016; Battaglini 2021; Chang 2020).

Among neurocritical patients with acute brain injury, the use of NMB has been suggested in order to reduce the number of episodes of intracranial hypertension; however, the level of evidence for this recommendation is low (Renew 2020). Its main effect relies on the reduction of asynchrony events with the ventilator, cough limitation and any other condition that may cause Valsalva manoeuvre (Steingrub 2014). In patients with intra-abdominal hypertension and abdominal compartment syndrome, NMB has also been suggested in order to increase abdominal compliance by relaxation of the abdominal muscles (Malbrain 2005). Nonetheless, conclusive evidence in this regard is lacking.

There are other neuromuscular blocking agents (NMBA) not currently recommended as first-choice drugs; however, their use in specific scenarios may be justified when the latter are not available. In patients with ARDS that require NMB, vecuronium, atracurium or pancuronium may also be used, although with the risk of prolonging neuromuscular relaxation, thereby increasing side effects. In addition, when rocuronium is not available for RSI, succinylcholine can also be considered, which is a depolarising NMB of ultra-short action, although with the risk of hyperkalaemia and even malignant hyperthermia (Zamarrón-López 2019).

Train-of-four nerve stimulation (TOF) is a tool for the monitoring of NMB. A value <0.7 is considered an adequate paralysis (Murphy 2010). In a recent study that compared three strategies for using NMB (a fixed-dose of cisatracurium; titration based solely on TOF and a ventilator synchrony protocol), it was shown that a protocol using ventilator synchrony for cisatracurium titration required significantly less drug compared to TOF-based titration and a fixed dosing regimen (DiBridge 2021).

Several factors affect the duration of NMBA activity: for instance, the concomitant use of diuretics, antiarrhythmics, aminoglycosides, magnesium, lithium, as well as some conditions such as hypokalaemia, hypothermia and acidosis, all increase the potency of non-depolarising NMBA. NMBA potency is inversely related to its speed of onset (that is, the lower the potency of the drug, the faster the onset of neuromuscular blockade after its administration). Patients with myasthenia gravis and glaucoma are especially sensitive to the effects of NMB. On the other hand, patients with burns are resistant to the effects of NMBA due to the proliferation (upregulation) of nicotinic receptors in the sarcolemma (Murray 2016).
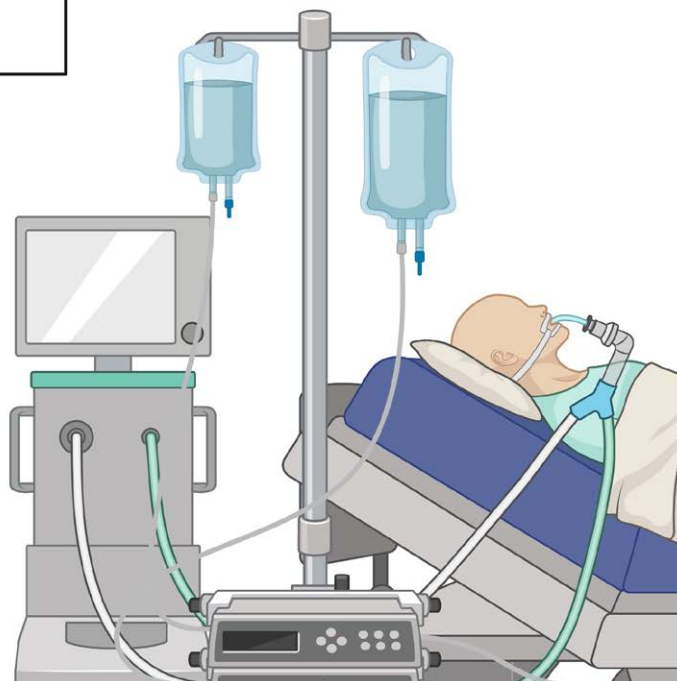

Figure 5. Analgesia, sedation and neuromuscular blockade in critically ill patients

NMBA	Mechanism of action	Comments	Dose	Onset; half-life	Contraindications/cautions	Adverse effects
Atracurium	nNMBs. Intermediate action.	Histamine release. Metabolite: laudanosine (decreases seizure threshold).	IV bolus: 0.4-0.5 mg/kg Infusion: 5-20 mcg/kg/min	Onset: 3-5 min t½: 2-20 min	Does not require dose adjustment in liver/renal failure.	Hypotension Seizures Skin flush Green urine
Cisatracurium	nNMBs. Elimination by plasmatic esterases.	First-line in continuous infusion.	IV bolus: 0.1-0.2 mg/kg Infusion: 1-4 mcg/kg/min	Onset: 2-3 min t½: 22-29 min	Does not require dose adjustment in liver/renal failure.	Histamine release in high doses
Pancuronium	nNMBs. Prolonged action.	Vagal blockade, sympathetic stimulation.	IV bolus: 0.05-0.1 mg/kg Infusion: 0.8-1.7 mcg/kg/min	Onset: 2-3 min t½: 89-161 min	Significant accumulation, prone to residual blockage (3-OH metabolite).	Hypotension Tachycardia Vagal blockade Catecholamine release
Rocuronium	nNMBs. Intermediate action.	Second-line in continuous infusion.	IV bolus: 0.6-1.2 mg/kg Infusion: 8-12 mcg/kg/min	Onset: 1-2 min t½: 1-2 h	Preferable over vecuronium in renal dysfunction.	Unpredictable in recurring doses
Vecuronium	nNMBs. Intermediate action.	Does not cause fasciculations.	IV bolus: 0.1 mg/kg Infusion: 0.8-1.7 mcg/kg/min	Onset: 3-4 min t½: 4 min	Preferable over rocuronium in liver dysfunction.	Vagal blockade with higher doses Arrhythmia Urinary retention

Table 5. Neuromuscular blocking agents
nNMBs: Non-depolarising neuromuscular blockers.

Conclusions

Analgesics, sedatives and neuromuscular blocking agents are commonly used medications in the ICU. An adequate protocol of care involves knowledge of their indications, adverse effects, their correct use and the selection of the most appropriate agent, with the aim of reducing morbimortality in critically ill patients.

Conflict of Interest

None. ■

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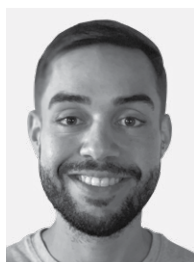
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Pain Management in Paediatric Critical Care

An overview of the main treatment options currently available in paediatric critical care setting.

Critically ill paediatric patients often suffer from pain secondary to trauma, complex medical procedures, invasive testing monitoring devices and illness-induced discomfort. Although the gold standard for assessing patient comfort is self-report, in paediatrics it may be quite difficult due to the wide spectrum of ages, weights, variability in developmental stages as well as the interplay between sedative and analgesic drugs. In addition, it should not be forgotten that clinical signs of iatrogenic withdrawal or delirium may coexist (Harris et al. 2016). That is why standardised assessment tools have been proposed and validated for intubated and preverbal patients in order to limit avoidable variability in assessment.

The aim of this article is to provide a general overview of the current and most used pain treatment options that are available in paediatric intensive care units (PICU), as well as to highlight some observations about their use in paediatrics. The doses are collected in the attached tables.

The Analgesic Therapy
The main goal of analgesic therapy is to provide comfort, reduce the physiological stress response and minimise associated adverse events such as respiratory depression, risk of addiction, haemodynamic instability and end organ injury (Egbuta and Mason 2021). Sedative, analgesic and local anaesthetics are important components of appropriate analgesic regiments, but behavioural techniques should not be forgotten since they can be relevant for addressing the emotional component of pain. Finding the optimal analgesic and sedative therapy require a continuous patient assessment with validated tools as pain scales, attending that many analgesic drugs are synergistic with

sedating agents (Georgiou et al. 2020). The Premature Infant Pain Profile (PIPP) scale in neonates and the COMFORT behaviour scale, Face, Legs, Activity, Cry and Consolability scale (FLACC) and the Multidimensional Assessment of Pain Scale are the most commonly used pain scales in the intensive care settings (Harris et al. 2016).

Non-Pharmacological Measures
The emotional component of pain is particularly strong in children, so the non-pharmacological measures have a vital role in their treatment. They are commonly focused on decreasing patients' anxiety and, consequently, they may reduce the need of analgesic and sedative drugs.

They are usually based on nursing care and environmental measures like relaxing techniques, music therapy, hypnosis, distraction techniques and cognitive therapies addressed to explain the illness or the invasive procedures to the patient. It is important to promote the sleep-wake cycle adapting the lighting to the time of day and avoiding noises or procedures during the sleep. Also, the presence of the parents during the admission and the performance of invasive medical procedures is essential for decreasing anxiety and the discomfort inherent at the intensive care unit admission process. In this same sense, the presence of family pictures or toys in the child's environment can also be useful. In neonates, the use of sucrose via oral and the skin-to-skin contact is significantly effective (Chumpitazi et al. 2022).

Analgesic Medications
Non-Opioid Drugs
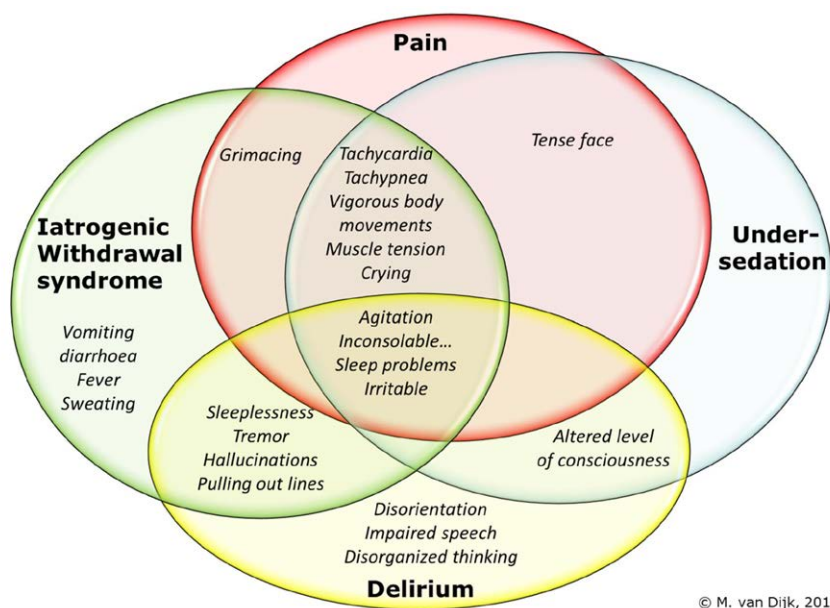These are drugs with limited analgesic effect and no-dose dependent (increasing the

Figure 1. Overlap of behavioural features in pain, sedation, withdrawal syndrome and delirium, based on van Dijk et al. 2011 (Harris et al. 2016)

dose above a certain level does not produce more analgesia). There are two groups: analgesics-antipyretics and non-steroidal anti-inflammatory drugs (NSAIDs).

Analgesics–Antipyretics
These drugs have an analgesic and anti-pyretic effect, but they do not exert an anti-inflammatory action. They are usually used, together with opiates, in moderate or severe pain, if there is a risk of bleeding or in case of minor surgery. Within this group we find drugs such as paracetamol or metamizole. Paracetamol has no toxicity at therapeutic doses but it can develop hepatic and renal toxicity in case of overdose. Metamizole is especially useful for the management of colic pain. It causes few side effects, but it can produce hypotension when administered in fast bolus, especially in hypovolaemic patients. Moreover, it has been related with the appearance of aplastic anaemia and agranulocytosis, which is why it is not marketed in some European countries (Egbuta and Mason 2021).

NSAIDs
These drugs have an analgesic, antipyretic and anti-inflammatory effect, so they are mainly used in presence of mild or moderate pain with an inflammatory component,

as well as in minor surgeries together with opiates. In general, they have more analgesic activity than paracetamol. They should be administered orally or intravenously because rectal absorption is erratic. There have been reported side effects over the gastric mucosa (gastritis, gastric ulcer, digestive bleeding) and platelet aggregation.

Within this group are available drugs such as ibuprofen, dexketoprofen or ketorolac. Ibuprofen is the most used since it is generally well tolerated and it entails less risk of digestive bleeding in comparison with other NSAIDs, although the gastrointestinal complications are the most common. On the other hand, it is not recommended to use dexketoprofen for more than five days or if there is kidney failure (López-Herce et al. 2019).

Acetylsalicylic acid is also included in this group. Despite being a drug classically widely used in paediatrics, it is currently not recommended for patients under 16 years of age with viral infections due to its association with Reye syndrome. As a consequence, its current use is limited as platelet antiaggregant.

Opioid Drugs
Opioids exert their effect by interacting with opioid receptors. They mainly act over

μ receptors (analgesia, miosis, respiratory depression), which are found in presynaptic terminals on central nervous system (brain, spinal cord), peripheral tissue and in other tissues like the adrenal medulla and myenteric plexus. Opioids pose a dose-dependent respiratory depression with increased risk if used with other sedatives. In this sense, naloxone acts as an antidote for the reversal of the effects produced by opiates. Also, they exhibit a risk of dependence and withdrawal, so it is recommended to wean them slowly in those patients who have received high doses of opioid (Barr et al. 2013). In children under six months, the dose should be reduced by 25-50% and the interval between doses should be doubled or tripled the lower the age (López-Herce et al. 2019).

There are many useful opiates in paediatrics such as morphine, fentanyl, methadone or others. Morphine is the oldest of the opiates and it is especially useful for pain management in polytraumatised, burn, post-surgery patients and sickle cell crises. Morphine induces a histaminic release that can explain the appearance of vasodilation, pruritus or hypotension that sometimes appear after its administration. Besides, it has been related with risk of seizures in neonates when used at high doses.

Fentanyl is a synthetic morphine derivative but with better haemodynamic tolerance. It is mainly used during short painful procedures, such as intubation procedure, and for the analgesic maintenance during mechanical ventilation. The duration of its effect is prolonged up to 30 minutes when administered intravenously, but when the administration is continuous and prolonged it can accumulate in peripheral compartments increasing its half-life. Despite being a rare effect, with rapid large doses (> 5 mcg/kg) there is a risk of chest wall rigidity that can result in a respiratory failure especially in neonates and small infants.

Remifentanyl is a synthetic opioid specially recommended in patients with renal or hepatic dysfunction since it is quickly metabolised by plasma esterases. Besides, it can be useful in those patients in whom it is necessary to abruptly interrupt the sedative and analgesic therapy to assess their mental status. However, as other opioids, it can cause respiratory and

haemodynamic failure (it is recommended not to administer in bolus) and it has been suggested that it has a high risk of tolerance and withdrawal when it is used at high doses or for long periods of time.

Other opiates of interest in paediatrics are meperidine, which is especially useful in patients with biliary pathology or pancreatitis (due to its anticholinergic effect over the bile ducts), or tramadol, whose special interest lies in the management of neuropathic pain.

It has been related with mild side effects like nausea, vomiting or constipation.

Methadone is a synthetic μ receptor agonist equipotent to morphine. In the PICU setting it is mainly used to prevent opioid withdrawal for those patients who have received continuous infusions. It has been related with some life-threatening adverse effects, like significant bradycardia or arrhythmias (QT interval prolongation) in those patients with structural heart disease

(Egbuta and Mason 2021).

Patient-Controlled Analgesia
This is a method of analgesic administration through an automatic pump controlled by the patient, looking for better pain control. The main indication for patient-controlled analgesia (PCA) is acute pain (especially of post-surgical origin) or pain related with oncological process. It usually uses the intravenous route and the drugs most used

Analgesic-Antipyretic Drugs	Dose

Paracetamol	O: 10 mg/kg/6h (<3 months)
	     15 mg/kg/6h (>3 months)
	R: 20 mg/kg/6h
	I: 7.5 mg/kg/6-8h (< 1 month or <10 Kg)
	     15 mg/kg/6h (maximum 1 g/dose)

Metamizole	O: 10-20 mg/kg/6-8h
	I: 10 mg/kg/6-8h (< 3 months, off label)
	     16-40 mg/kg/6-8h (maximum 2 g/dose)
	     1-6.6 mg/kg/h

Ibuprofen	O: 5-10 mg/kg/6h (maximum 400 mg/dose) I: 10-15 mg/kg/6h (> 6 years or > 20 kg; maximum 1.2 g/day)
Acetylsalicylic Acid	O: 10-15 mg/kg/6h
Dexketoprofen	O: 0.5 mg/kg/8-12h (maximum 25 mg/dose) I: 1 mg/kg/8-12h (maximum 50 mg/dose)
Ketorolac	O/I/IM: 0.5-1 mg/kg/8h (maximum 40 mg/dose O, 15 mg/dose I, 30 mg/dose IM)
Opioid Drugs	**Dose**
Morphine	O: 0.2-0.5 mg/kg/4-6h (maximum 20 mg/dose) I/SC: 0.05-0.1 mg/kg/2-4h (maximum 5 mg/dose or 15 mg/day) 10-50 mcg/kg/h
Fentanyl	I/SC: 1-2 mcg/kg/2h (maximum 100 mcg/dose) 10-50 mcg/kg/h
Remifentanyl	I: 0.05-2 mcg/kg/min Bolus is not recommended
Methadone	O: 0.1-0.3 mg/kg/6-12h (maximum 10 mg/dose)
Meperidine	I/IM/SC: 0.2-0.25 mg/kg/3-8 h (< 6 months) 1-1.5 mg/kg/3-8h (> 6 months, maximum 100 mg/dose)
Tramadol	/I/IM: 1-2 mg/kg/4-6h (maximum 400 mg/day) 0.2-0.4 mg/kg/h
Other	**Dose**
Ketamine	I: 1-2 mg/kg/dose 5-20 mcg/kg/min IM: 3-7 mg/kg/dose

Table 1. Analgesic medications and their doses
O: oral; I: intravenous; R: rectal; IM: intramuscular; SC: subcutaneous

in paediatrics are morphine and fentanyl, although there are also guidelines described with tramadol and combinations of analgesics with sedatives (López-Herce et al. 2019).

Others

Ketamine

Ketamine is a N-metil-D-Aspartate (NMDA) receptor antagonist, so it prevents the excitatory activity of glutamate. Small doses produce analgesia with amnesia, without impairing the airway protective reflexes. Moderate doses provide analgesia and sedation, while high doses produce general anaesthesia. Ketamine suffers liver metabolism and kidney excretion. Side effects include an increase of respiratory secretions by cholinergic stimulus (it could be attenuated with previous bolus of atropine), hallucinations (they can be attenuated with a benzodiazepine dose), tachycardia, hypertension and, despite having a bronchodilator effect, laryngospasm. Although classically it has been related to increases in intracranial pressure, the results are contradictory and recent studies suggest that it could even decrease it (Chan et al. 2022).

Local and topical anaesthetics

These are drugs that can temporarily prevent the nerve impulse conduction if they are used locally in high concentration. As an example of local anaesthetic, we have lidocaine (which can be used with epinephrine in order to extend its action) or bupivacaine. Also, there are available some topical anaesthetics that achieve local receptor insensitivity for pain in front of painful stimulus.

Only Analgesia?

Usually, in addition to analgesia, sedation should be administered to improve the comfort of the critically ill paediatric patient allowing, for example, adaptation to mechanical ventilation. In this context, it is not always easy to distinguish between pain and discomfort not caused by pain, especially in young children. It is vitally important to remember that sedatives do not provide analgesia. There are multiple sedatives available such as some benzodiazepines, propofol, alpha-2 adrenergic agonists or even ketamine itself.

The alpha-2 adrenergic agonists such as clonidine or dexmedetomidine have been increasingly used for sedation in the PICU over the last decade. They are an attractive choice for sedation since they do not decrease respiratory drive, but the main disadvantage is they can cause haemodynamic instability with bradycardia or hypotension, so they are not usually the first-line choice in young infants or cardiac patients.

Given that all of them are related to potential adverse effects and complications, such as withdrawal or delirium, their dosage should be titrated based on validated sedation scales as the Richmond Agitation Sedation Scale (RASS) or Paediatric Sedation State Scale (PSSS) (Laures et al. 2019).

Conclusion

In conclusion, critical paediatric patients often experience pain during their admission. It may be due to multiple reasons of the same disease process or hospitalisation and supposes a handicap to achieve an adequate adaptation to therapy and to the environment. In children, it is especially important to address the emotional component that usually accompanies pain, so non-pharmacological measures are essential and usually allow reducing the dose of analgesics. There are many analgesic drugs, each with their own characteristics and possible side effects, so their dosage must be titrated according to validated scales.

Conflict of Interest

None. ■

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Delirium: How Can We Protect Our Patients? Detection and Treatment Strategies

In this article, the authors aim to summarise the current management of delirium, emphasising new publications and possible new studies that will shed light on delirium management strategy.

Introduction

According to an updated nomenclature of delirium after an interdisciplinary panel of experts from ten medical societies (Slooter et al. 2020), delirium refers to a clinical state characterised by a combination of features defined by the DSM-5 criteria (**Figure 1**). The panel also recommended using the term sub-syndromal delirium for acute cognitive changes that are compatible with delirium but do not fulfill all DSM-5 delirium criteria. On the other hand, Patel et al. (2014) described a rapidly reversible sedation-related delirium, defined as delirium while receiving sedation that resolved within two hours after stopping sedation during a spontaneous awakening trial.

There is an attempt to categorise the delirium spectrum into subphenotypes, using psychomotor subtypes (known as hypoactive, hyperactive, and mixed) or inflammatory/non-inflammatory delirium. Identifying specific subphenotypes would improve our understanding of the relationship between the clinical symptoms and pathophysiology, suggesting a progression from subphenotypes to endotypes, setting a biological–clinical subtype hybrid (Bowman et al. 2021).

For several years now, and thanks to the efforts of the community of healthcare professionals dedicated to the care of critically ill patients, the attention devoted to delirium has increased considerably, with a steady increase in publications related to its epidemiology, diagnosis, prevention, and treatment. Delirium incidence, once reported in 60–80% of mechanically ventilated patients, is down by about 25% in many ICUs worldwide (Gibb et al. 2020; Stollings et al. 2021).

Delirium development is associated with multiple complications (especially in hypoactive motoric subtype): increased mortality, longer duration of mechanical ventilation, higher reintubation rate, increased hospital stay, higher early instrumental activities of daily living dependence scores, and worse long-term cognition (Salluh et al. 2015; Ely et al. 2017; Girard et al. 2018; Hayhurst et al. 2020; Rengel et al. 2021; Hughes et al. 2021). Since effective treatment of delirium has proven troublesome, prophylactic strategies have become paramount. In this sense, a comprehensive study of the risk factors associated with this clinical entity would facilitate high-risk patients' detection. In recent reviews, factors related to the risk of developing delirium (Zaal et al. 2015) were advanced age, personal history of previous high blood pressure or cognitive impairment, urgent surgery or trauma before admission to the ICU, APACHE II upon admission, and need for mechanical ventilation. A recent study found that the highest risk observed for developing delirium clustered in patients who presented more than two organ failures and patients over 74 years old (Lobo-Valbuena et al. 2021).

Detection and Delirium Severity

Routine monitoring of delirium, using validated scales (such as CAM-ICU or ICDSC), is a good practice statement according to the

latest Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU Guidelines (Devlin et al. 2018), and is a strong recommendation with moderate-quality evidence according to the Pan-American and Iberian Federation of Societies of Critical Medicine and Intensive Therapy (Celis-Rodriguez et al. 2020). According to published data, the CAM-ICU has a sensitivity of around 93%, specificity of 98%, and high interrater reliability ($\kappa = 0.96$; 95% CI, 0.92–0.99) (Ely et al. 2001). Regarding ICDSC, it demonstrated a pooled sensitivity of 74% and specificity of 82% (Gusmao-Flores et al. 2012). Moreover, both assessment tools showed similar moderate-to-good statistical performance, supporting either for early prediction model or recalibrated prediction model (Wassenaar et al. 2019). Both should be used at least once per shift and when the patient's clinical situation (primarily neurological) presents an abrupt change. We must remind that the usefulness of both tools requires training of the health professionals that use them.

Concerning delirium severity, we may use DRS, DRS-R-98, CAM-S, and the CAM-ICU-7 (Trzepacz 1999; Inouye et al. 2014; Khan et al. 2017). A recent study (Krewulak et al. 2020) compared CAM-ICU-7 with ICDSC as measures of the spectrum of delirium severity in critically ill adult patients. The CAM-ICU-7 and ICDSC had a significant positive correlation (0.58, p<0.001), with a moderate agreement between the tools as measures of delirium (kappa = 0.51).

We must highlight that nearly all the clinical trials investigating strategies to prevent and/or treat delirium are based on delirium assessment tools, with the risk that entails (false-positive or negative screening or work overload for healthcare staff). The ability of assessment tools to improve patient outcomes could be associated with the intensity of the training strategy used and the quality improvement initiatives deployed, which points out the need of promoting training for healthcare professionals, family members, and lay population alike (Gélinas et al. 2011; Radtke et al. 2012). A recent study (Fiest et al. 2020) explored the idea of family-administered delirium detection: Family Confusion Assessment Method AUROC was 65.0% (95% CI, 60.0–70.0%), 71.0% (95% CI, 66.0–76.0%) for possible delirium (cutpoint of 4) on the Sour Seven and 67.0% (95% CI, 62.0–72.0%) for delirium (cutpoint of 9) on the Sour Seven. These AUROC were lower than the standard of care (ICDSC or CAM-ICU). Adding the FAM-CAM and Sour Seven to the standard of care improved sensitivity at the expense of specificity.

In recent years, several models have been developed to predict the risk of ICU delirium based on known risk factors for this condition. The prediction of delirium in ICU patients (PRE-DELIRIC) model (van den Boogard et al. 2012) was developed to predict patients' risk of delirium from some clinical features present in the first 24 hours of ICU admission. This tool displayed good discriminative ability and was later recalibrated in an international multicentre trial (van den Boogard et al. 2014). The early PRE-DELIRIC (E-PRE-DELIRIC) (Wassenaar et al. 2015) was subsequently developed to predict patients' risk of delirium at the time of ICU admission but showed a lower discriminative ability than the previous models. An alternative, referred to as the Lanzhou model, also relies on several features present in the first 24 hours of ICU admission. Green et al. (2019) found that the PRE-DELIRIC [AUROC curve 0.79 (95% CI, 0.75– 0.83)], the recalibrated PRE-DELIRIC [AUROC curve 0.79 (95% CI, 0.75– 0.83)], and Lanzhou model [AUROC curve of 0.77 (95% CI, 0.72–0.81)] performed comparably to the original validation studies, and that the e-PRE-DELIRIC [AUROC curve of 0.72 (95% CI, 0.67–0.77)] displayed moderate predictive ability.

Other studies that try to shed some light on the diagnosis of delirium imply the use of magnetic resonance imaging and neurophysiological studies. Pre-operative deep and white matter and thalamic abnormalities on diffusion tension imaging appeared in elderly patients with postoperative delirium (Shiori et al. 2010). On the other hand, EEG slowing, an increase of delta (1–4 Hz) and/or theta power (4–8 Hz), or a decrease of alpha power (8–12 Hz), correlates with the presence of delirium across various types of delirium presentations (odds ratio 10.3, 95% CI 5.3–20.1) (van der Kooi et al. 2015; Kimchi et al. 2019; Boord et al. 2021). Efforts to merge the information provided by the physical examination (through validated scales) and the information provided by some test (in this case, EEG) has led to the publication of the Electroencephalographic Confusion Assessment Method Severity Score (E-CAM-S) (van Sleuwen et al. 2021). This study used CAM short form and CAM-S

Disturbance in attention and awareness	**Attention:** reduced ability to direct, focus, sustain, and shift attention **Awareness:** reduced orientation to the environment
Develops in a short period of time and fluctuates	The disturbance develops over **a short period** of time (usually hours to a few days), represents a **change from baseline** attention and awareness, and tends to fluctuate in severity during the course of the day
Disturbance in cognition	Memory deficit, disorientation, language, visuospatial ability, or perception
Not explained by other neurocognitive disorder	The disturbances are not explained by another pre-existing, established, or evolving neurocognitive disorder, and do not occur in the context of a severely reduced level of arousal, such as coma
Disturbance is a direct consequence from a medical condition	There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiologic consequence of another medical condition, substance intoxication or withdrawal (i.e. because of a drug of abuse medication), or exposure to a toxin, or is because of multiple aetiologies

Figure 1. The DSM-5 criteria

to assess delirium presence and severity, respectively; they afterward calculated the E-CAM-S using four frontal EEG channels. 373 patients were analysed: E-CAM-S reliably quantified delirium severity (it successfully correlated with clinical CAM-S scores with an R = 0.68; p < 0.001) and was independently associated with hospital length-of-stay (correlation with LOS: E-CAM-S, 0.33; CAM-S, 0.41; p = 0.082) and in-hospital mortality (AUROC: E-CAM-S 0.77 [0.72–0.82] CAM-S 0.81 [0.75–0.85]; p = 0.188) across a wide range of acutely hospitalised adults. There is still a long way to go before an accurate diagnosis (through imaging or EEG) of delirium in critically ill patients can be made.

Prevention Strategies

A wide-ranging list of prevention strategies evaluated includes pharmacological, sedation, and non-pharmacological single or multi-component intervention. However, to date, no known effective intervention has shown a significant decrease in the incidence of delirium.

Pharmacological interventions

One of the last published systematic reviews and meta-analyses of pharmacological interventions (Burry et al. 2021) found that dexmedetomidine could reduce the odds of delirium occurrence relative to placebo (OR 0.43, 95% CI 0.21–0.85; moderate certainty). It was the only identified intervention that could probably reduce the length of ICU or hospital stay relative to placebo. It could also do so relative to antipsychotics, but with less certainty. The study concluded with three take-home messages: (1) compared to placebo or benzodiazepines, dexmedetomidine probably prevents delirium; (2) a sedation-minimisation strategy that targets reduced exposure to sedatives might prevent delirium; and (3) antipsychotics may not prevent delirium. Despite the negative results, we are still trying to find a drug that could prevent, at least in part, the development of delirium in the critically ill patient.

A post hoc analysis of the REDUCE trial (prophylactic haloperidol use for delirium in ICU patients at high risk for delirium; (van den Boogaard et al. 2018) assessed the association between treatment haloperidol exposure and mortality in a population of critically ill adults without delirium at the time of ICU admission (Duprey et al. 2021). If delirium occurred, treatment with open-label intravenous haloperidol was administered at clinician discretion. They demonstrated that the use of haloperidol to treat incident delirium (defined as "delirium occurring after (and not before) ICU admission") might be associated with lower 28-day mortality in a dose-dependent, time-dependent manner. Over 28 days of follow-up, each milligram of treatment haloperidol administered daily to a patient with delirium was associated with a 7% decrease in mortality (HR 0.93; 95% CI, 0.91–0.95). Although an association between haloperidol and reduced mortality was observed up to 90 days, it was lower than that observed at 28 days suggesting this effect may wane over time. Indeed, mortality at 90 days among patients with delirium may also be better attributed to the comorbidity burden of patients at baseline rather than the specific delirium care a patient receives during their ICU and post-ICU hospital stay.

Among the latest published protocols and studies, we may find the ProMEDIC study (Prophylactic Melatonin for Delirium in ICU): a multi-centre, randomised, double-blinded, placebo-controlled trial that will determine whether melatonin given prophylactically decreases delirium in critically ill patients (Wibrow et al. 2021).

Non-pharmacological interventions

Non-pharmacologic multi-component strategies have been studied extensively, and most studies suggest these are the most effective methods to prevent delirium, as they use several interventions simultaneously (Deng et al. 2020).

One example of a multi-component strategy is the ABCDEF bundle (**Figure 2**) (Marra et al. 2017). This bundle improved patient outcomes in several non-randomised studies, turning into a large nationwide collaborative. However, to our knowledge, there is currently not a single RCT demonstrating the benefit of the ABCDEF bundle, which is the gold standard for demonstrating therapeutic efficacy. Moreover, a recent meta-analysis (Zhang et al. 2021) has failed to support that bundle interventions effectively reduce ICU delirium prevalence and duration. However, they seem to be effective in lowering the proportion of patient-days with coma, hospital length of stay, and 28-day mortality.

Recently, an expert panel proposed to update the bundle adding an "R" for respiratory drive control. The objectives are (1) reducing sedatives (especially benzodiazepines and opioids), (2) preferring more participative ventilation modes, and (3) optimising management of patient's associated factors of high respiratory demand (metabolic acidosis, fever, pain, anxiety, dyspnoea) (Chanques et al. 2020). Optimisation of ventilator settings should be a priority.

Treatment Strategies

Up to our knowledge, no single pharmacological agent can treat delirium. Haloperidol,

Assess, prevent and manage pain

Both spontaneous awakening trials and spontaneous breathing trials

Choice of analgesia and sedation

Delirium assessment, prevention and management

Early mobility and exercise

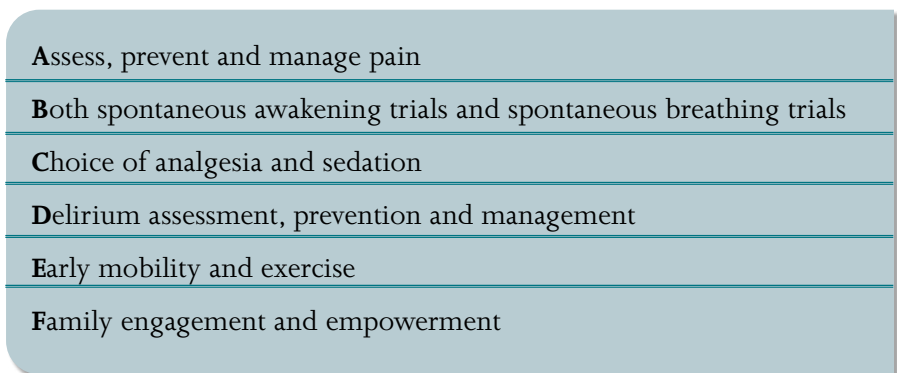**F**amily engagement and empowerment

Figure 2. The ABCDEF bundle

atypical antipsychotics, and other alternative therapies have been thoroughly studied, but we are still far from identifying a silver bullet. PADIS guidelines suggest against routine use of drugs to treat delirium. Nevertheless, the guidelines do point out the need for these drugs to manage agitation or stress-related symptoms. It is essential to realise that it is not treating delirium. We should use the smallest doses and the shortest possible duration.

A retrospective study (Boncyk et al. 2021) tried to describe the prescribing practices for the management of ICU delirium. 45.6% of the patients received pharmacological treatment, including 45.4% receiving antipsychotics. Haloperidol, olanzapine, and quetiapine comprised more than 97% of used antipsychotics, with 48% of the patients receiving two or more and 20.6% continued antipsychotic medications at hospital discharge. Haloperidol and olanzapine were associated with greater odds of continued delirium and increased hazard of in-hospital mortality, while quetiapine showed a decreased risk of in-hospital mortality. Haloperidol, olanzapine, and quetiapine were associated with fewer days alive and free of hospitalisation (P < .001). What conclusions can we draw out? These medications may not portend benefit, may introduce additional harm, and should be used with caution for delirium management. Furthermore, the continuation of these medications through hospitalisation and discharge questions their safety and role in patient recovery.

Within the past decade, it has become evident that antipsychotics do not diminish the risk of ICU delirium, nor do they improve the associated adverse outcomes. Studies, such as the HOPE-ICU study (Page et al. 2013), the HARPOON study (Schrijver et al. 2018), the MIND study (Girard et al. 2010), and the MIND-USA study (Girard et al. 2018) have not found differences when using different antipsychotics. Moreover, a recent systematic review of antipsychotics for treating delirium in hospitalised adults found no difference among haloperidol, atypical antipsychotics, and placebo in terms of delirium duration, hospital length of stay, or mortality (Nikooie et al. 2019).

Regarding the use of other drugs, such as α-2 adrenoreceptor agonists, a randomised, double-blind placebo-controlled trial did not impact ICU or hospital length of stay when using dexmedetomidine (Reade et al. 2016). Conversely, a recent systematic review and meta-analysis (Liu et al. 2021), assessing the role of dexmedetomidine in the treatment of delirium in critically ill patients, showed a reduced duration of delirium to a greater extent than did the placebo (just in one study), a lower-point prevalence of delirium after treatment (OR 0.39; 95% CI, 0.20, 0.76; P=0.006) and a shorter time to resolution of delirium compared with those of other drugs (including haloperidol).

To add fuel to the fire, a recent study (Smit et al. 2021), analysing haloperidol and clonidine in agitated delirious patients, concluded that the use of both drugs in delirious ICU patients could be associated with a reduced probability of delirium resolution. In this case, the likelihood of delirium resolution was lower in delirious patients who received haloperidol (OR 0.47, 95% CI 0.39−0.57), clonidine (OR 0.78, 95% CI 0.63−0.97), or both (OR 0.45, 95% CI 0.36−0.56) compared to untreated delirious patients. Delirious patients who received haloperidol, clonidine, or both generally had longer delirium duration, more delirium and ventilation days, and longer hospital length of stay than untreated delirious patients. These agents did not affect ICU mortality. Other studied drugs, such as statins or ketamine, have ended up with negative results in several randomised controlled trials.

Last Comments

One of the main problems of the studies carried out in this field is the high heterogeneity when publishing results, which hinders a strict and critical evaluation of the published studies. An updated systematic review, focused on the design and analysis of delirium outcomes, identified 65 RCTs conducted among ICU patients with a delirium-related primary outcome. Most of these RCTs were delirium prevention trials, with considerable heterogeneity in the maximum duration of participant follow-up and whether delirium assessments occurred after ICU discharge. Eight unique statistical methods were used to detect differences in delirium incidence across intervention groups. Heterogeneity in statistical methods was similar across the two central populations of patients enrolled in delirium RCTs; surgery and critically ill patients. Therefore, creating uniform standards for statistical analyses and reporting in delirium RCTs could improve the quality of individual trials and the ability to harmonise results across trials (Coulantoni et al. 2021).

An international effort was made to develop a COS (Core Outcome Set) appropriate for clinical trials of interventions designed to prevent and/or treat delirium for critically ill adults (Rose et al. 2021).
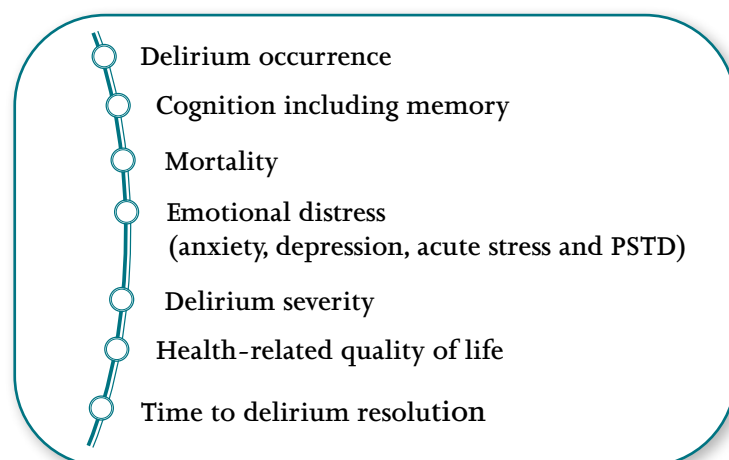

- Delirium occurrence
- Cognition including memory
- Mortality
- Emotional distress (anxiety, depression, acute stress and PSTD)
- Delirium severity
- Health-related quality of life
- Time to delirium resolution

Figure 3. Delirium core outcome set

A COS is an agreed-upon minimum set of outcomes to be measured and reported in "all" studies relating to a specific health condition or intervention. After following the Core Outcome Measures in Effectiveness Trials (COMET) guidelines, seven outcomes were selected for the COS (**Figure 3**).

COS development enhances research relevance and patient-centredness and may facilitate a more rapid understanding of effective treatments and their adoption into clinical practice. Adopting delirium COS as part of future research protocols would also improve the homogeneity of reported outcomes, increasing statistical power, and precision of meta-analyses. It would open doors for evidence-based decisions, improving the clinical care of critically ill adults.

Delirium patients show an increased risk of developing post-ICU syndrome, already known to affect patients' perceived quality of life profoundly (Needham et al. 2012; van der Schaaf et al. 2015). Improving our understanding of risk factors amenable to intervention could improve our clinical management, plus develop post-ICU care programmes. In our case, after a deep statistical analysis of our ICU admitted patients (Lobo-Valbuena et al. 2021), and thanks to the great collaboration of our nursing team, high-risk patients are closely followed-up once discharged. This has led to our first multidisciplinary protocol for managing post-ICU syndrome (coordinating both the hospital team and the primary care health centres attached to the hospital area to which we belong).

After one year of implementation of the protocol, we observed improvement in some mental health components (fear, self-esteem, coping, sleep disorders) and the patient's ability to perform basic activities of daily living (measured by the Barthel index). Positive results on the Zarit scale (measuring caregiver overload) would also stem from the high support perceived by the patients' families and relatives (Lobo-Valbuena et al. 2021). The management of complex patients at risk of PICS requires a multidisciplinary approach, both inside and outside the hospital. For many ICU survivors, discharge from the hospital marks the beginning of an uphill struggle.

Finally, the overall management of delirium in critically ill patients should not lag. We should try to seek new tools in the new and promising technologies. For example, a new study protocol published a few months ago will try to assess the use of virtual reality stimulation as part of the multi-component strategies (Naef et al. 2021). There have already been publications regarding this topic, showing the feasibility, usability, and acceptance of virtual reality stimulation as a new non-pharmacological intervention to comfort patients during their stay in the ICU (Gerber et al. 2017; Gerber et al. 2019). On the other hand, machine learning could predict delirium, especially in the postoperative population (Wang et al. 2020; Fliegenschmidt et al. 2021). In another published study (Davoudi et al. 2019), pervasive monitoring and machine learning were continuously used to assess delirium and agitation. Camera and accelerometers were employed to record facial expressions and movements, and a pre-trained neural network was used for facial recognition and expression detection through single elements.

We cannot rest on our laurels. The impact of delirium on the critically ill patient, both short and long-term, compels us to keep searching and investigating. Only then will we be able, at some point, to reduce the incidence and prevalence of delirium. Only then may we find a new solution or new drug that will help our delirious patients, reducing the physical, emotional, and social impact associated with delirium.

Conflict of Interest
F Gordo has performed consultancy work and formation for Medtronic. The other authors have no competing interests. ■

Abbreviations

APACHE II	Acute Physiology and Chronic Health Disease Classification System II
AUROC	Area under the receiver operating characteristic
CAM-ICU	Confusion Assessment Method for the ICU
CAM-ICU-7	Confusion Assessment Method for the ICU 7 (points) delirium severity scale
CAM-S	Confusion Assessment Method – Severity Scale
COS	Core Outcome Set
DRS	Delirium Rating Scale
DRS-R-98	Delirium Rating Scale-Revised 98 assessments
DSM	Diagnostic and statistical manual of mental disorders
EEG	Electroencephalogram
E-PRE-DELIRIC	Early prediction of delirium in ICU patients
HR	Hazard ratio
ICDSC	Intensive Care Delirium Screening Checklist
ICU	Intensive care unit
OR	Odds ratio
PRE-DELIRIC	Prediction of delirium in ICU patients
RCT	Randomised controlled trial

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Ten Overlooked Mistakes During Early Mobilisation in the Intensive Care Unit

An overview of the most common mistakes in decision making and the practice of early mobilisation in the intensive care unit.

Introduction

Early mobilisation (EM) is a therapeutic strategy implemented to avoid and overcome impairments developed due to critical illness and ICU stay. Several benefits have been described throughout the literature such as overcoming ICU acquired weakness, reduction in days of mechanical ventilation and stay, greater functionality inside the ICU, higher levels of independence, and lower health care costs, among others. The main objective of this article is to highlight the most common mistakes in decision making and the practice of EM.

Here are ten overlooked mistakes during early mobilisation in the ICU:

1. Unnecessary, profound and prolonged sedation

Patients undergoing critical illness that require mechanical ventilation or any other invasive procedure require sedatives and analgesic medication. Such pharmacological agents intend to provide comfort, stability and pain management during their stay in the ICU (Reade et al. 2014). Although indications for profound sedation have been precisely listed, numerous patients will still undergo deep sedation without such indication (Oyler et al. 2018; Moreira et al. 2016). Apart from the patients in need of deep sedation (RASS -4/-5), patients should be awake, alert and cooperative (RASS 0/-1) to ensure all the benefits described in the ABCDEF bundle (Devlin et al. 2018). EM plays an essential role in this bundle but inadequate sedation levels are to this day one of the most common barriers for such practice. Profound seda-

tion in patients that can be included in an early mobilisation programme can have a negative impact on the functional progression, perpetuate immobility effects and prolong the length of stay inside the ICU (Hodgson et al. 2021).

2. Lack of individualisation in deciding the start of EM

Many EM protocols establish a need of initiating the rehabilitation process in the first 24 hours of stay inside the ICU (Hodgson et al. 2021). This will not be accomplished in all scenarios. The decision of initiating an EM programme must be based on the clinical status, not the time inside the ICU. In some cases, rehabilitation programmes can start in the very early stages of critical illness (Hodgson et al. 2014a), in some other cases, especially in acute respiratory distress syndrome (ARDS), instability in critically ill patients can maintain for even weeks. Nevertheless, in neurocritical patients, the early start of the rehabilitation process does impact the functional outcomes of the patient and is a race against time (Hernández et al. 2021). Decision making inside the ICU is an individual process for every patient and rehabilitation cannot be seen as a strict-time protocol.

3. Immobility during extracorporeal support: ECMO and CRRT

Extracorporeal support (ES) is more and more commonly seen in ICUs these days. Extracorporeal membrane oxygenation (ECMO) and continuous renal replacement therapy (CRRT) are some of the most popular among the utilisation of ES therapies.

ECMO configurations are mainly split into two categories: veno-venous (VV) ECMO which provides oxygenation support when conventional treatment fails in severe ARDS and veno-arterial (VA) ECMO that is used in patients who require haemodynamic support due to numerous cardiac centred pathologies (Shekar et al. 2020). Also, CRRT can be seen during ICU stay in patients that have or develop kidney injury. Any of these therapies have to be applied through vascular access catheters or cannulas that can limit mobility in such patients which commonly translates to prolonged immobility due to the fear of catheter removal during mobilisation (Abrams et al. 2022a). Nevertheless, enough documentation on secure practices in such therapies has been available for some years now, especially in well-coordinated and experimented ICU personnel. Hence, it has been described that patients undergoing extracorporeal therapies have a high risk of developing functional deterioration, muscle mass loss and post-intensive care syndrome (PICS) (Hayes et al. 2018). EM must be used as a prevention strategy to avoid these negative outcomes derivative from immobility.

EM is a safe practice in extracorporeal therapies, but special care and knowledge must be taken into consideration before and during mobilisation especially with ECMO cannulas. If femoral access has been established, a hip flexion >90° must be avoided (Raurell et al. 2021), as well as continuous monitorisation in ECMO pressures (mainly the extraction pressure which should be the only negative pressure), precaution with stitches in the cannula attaching it to the patient's leg and ensuring cannulas are maintained in place. ECMO parameters (FiO_2, revolutions or CO_2 sweep) may be modified by the perfusion team to provide a safer exercise tolerance, but no clear evidence has been reported for such matter (Mossadegh 2017). Similar to the previous statement, no evidence has been documented in the consideration of patient self-induced lung injury (P-SILI) as a limitation for mobilisation practices. Hence, monitorisation of tidal volume (TV) and respiratory rate (RR) is recommended during exercise intervals, as well as oxygenation and respiratory drive. It's

important to mention that physiological response to exercise should raise these levels as a normal response. Nonetheless, protective ventilation has to be maintained during these intervals. CRRT tends to have fewer complications during mobilisation due to the smaller catheters needed. The correct functioning of the machine should be checked, the pressures being needed, as well as the haemodynamic response to exercise. Extracorporeal therapies are a big challenge for the whole ICU personnel, including rehabilitation, and a meticulous evaluation of clinical stability in patients during such therapies is key for safe exercise practices (Abrams et al. 2022b).

◀◀ a frequent mistake during EM is underestimating the patient's capacity to accomplish higher mobility and functional levels ▶▶

4. Interventions without functional objectives
Throughout critical illness, patients must receive EM. This intervention has to have functional goals and for this matter, the implementation of tools that evaluate the patient's level of functionality is needed, otherwise poor or no evaluation will result in an inadequate exercise prescription (Parry et al. 2017). Some of the most common and useful tools are the Medical Research Council Sum Score (MRC-SS), handgrip strength through dynamometry (Piva et al. 2019), ICU Mobility Scale (IMS) (Tipping et al. 2016; Hodgson et al. 2014b) and the Chelsea Critical Care Physical Assessment Tool (CPAx) (Corner et al. 2016). The use of such tools will encourage taking patients to their maximum level of functionality and can guide the next steps towards higher functionality levels. Recent studies have correlated the success in the weaning process with greater scores in MRC and handgrip strength. A frequent mistake during EM is underestimating the patient's capacity to accomplish higher mobility and functional levels. This can perpetuate immobility and

waste time with interventions that have no real benefit. For example, why should a physiotherapist decide to move passively (with no effort applied by the patient) the patient's arms if the patient is capable of doing it themselves? Shouldn't the patient be encouraged to actively move and develop strength through exercise? Overload and progression of muscle strength are essential pillars of any exercise applied to the human body. Also, a common approach during EM is centred on strengthening peripheral muscles and excluding some essential components of the human body biomechanics: core musculature, anti-gravitational muscles and proprioception.

5. Delayed rehabilitation in the neurocritical patient
A common neurocritical phrase used among professionals is "brain is time". In acute brain injuries, we run against time in every aspect, including the rehabilitation process. Brain plasticity in the early stages of such pathologies must be taken as an advantage to promote functionality and avoid the permanent establishment of physical and mental impairments. Better outcomes have been found in patients battling critical illness due to a neurological diagnosis when they start their rehabilitation process in the early stages of the pathology's course (Olkowski et al. 2017). A particular group of patients among the neurological pathologies are patients with stroke. Large studies have found the need for initiating rehabilitation after 24 hours of symptoms appearing. In some other cases, patience will reward; in patients with an elevation in intracranial pressure (ICP) such as cerebral haemorrhage or traumatic brain injury, physical interventions should wait until surgical or pharmacological interventions have overpowered the bleed or reason for high ICP (Hernandez et al. 2021; Kumar et al. 2020).

Mobilisation in the neurocritical patient is safe and has no impact on the variation of mean arterial pressure (MAP), ICP or cerebral perfusion pressure (CPP) (Zink et al. 2021). Some interventions may even be an alternative for high ICP management such as early verticalisation of patients, which is known to be safe and can be done even while being mechanically ventilated (Lachance et

al. 2021). Also, early ambulation is related to a reduction in the risk of vasospasm in subarachnoid haemorrhage. Precaution in head positioning, as well as functional positioning and segment alignments, is a fundamental practice for these patients at any stage of their stay in the ICU.

6. Absence of verticalisation or ambulation during mechanical ventilation

Patients in need of mechanical ventilation must not be condemned to bed rest or low mobility levels during this period. Patients capable of maintaining an upright position and with enough strength (gained or never lost) to stand up should be submitted to training intervals that include verticalisation, standing up, marching in place or ambulation (Raurell et al. 2021). In order to achieve such high levels of mobility in these patients the cooperation of a multidisciplinary team must be established into

the routine care (Yang et al. 2021; Miranda et al. 2017). Benefits have been reported in these interventions such as greater lung aeration, easier diaphragmatic pull and neurological stimulation (Hickmann et al. 2021; Hernandez et al. 2021). A simplistic view of the weaning process will avoid professionals to believe that a mechanically ventilated patient can't walk. To think that weaning is merely a muscular issue and does not involve a whole systemic approach (airway integrity, lung parenchyma, cardiac functionality, neurologic status, electrolytic balance, among others) is an obsolete and easy way of conducting therapeutic decisions towards failure. Nonetheless, an immense mistake would be to delay the extubating procedure once the patient is ready for it. Something important to mention is that weakness among respiratory muscles is more common than peripheral musculature weakness; this also explains the reason for

finding patients undergoing severe respiratory muscle weakness being able to walk (Dres et al. 2017).

7. Excluding POCUS

Many pulmonary centred interventions are traditionally guided through auscultation, but this tool has a low sensibility and specificity in the evaluation of such clinical scenarios. Ultrasound evaluation has gained the power to the point it has become the fifth cornerstone of physical exploration (Narula et al. 2018). Physiotherapists and rehabilitation staff have to integrate ultrasound evaluation into their daily basis (Hayward et al. 2018; Hayward et al. 2020; Arnold et al. 2020; Hansell et al. 2021; Vieira et al. 2020). Pulmonary, diagrammatic and muscular ultrasound can guide interventions and decision making in clinical scenarios such as non-invasive mechanical ventilation, utilisation of positive
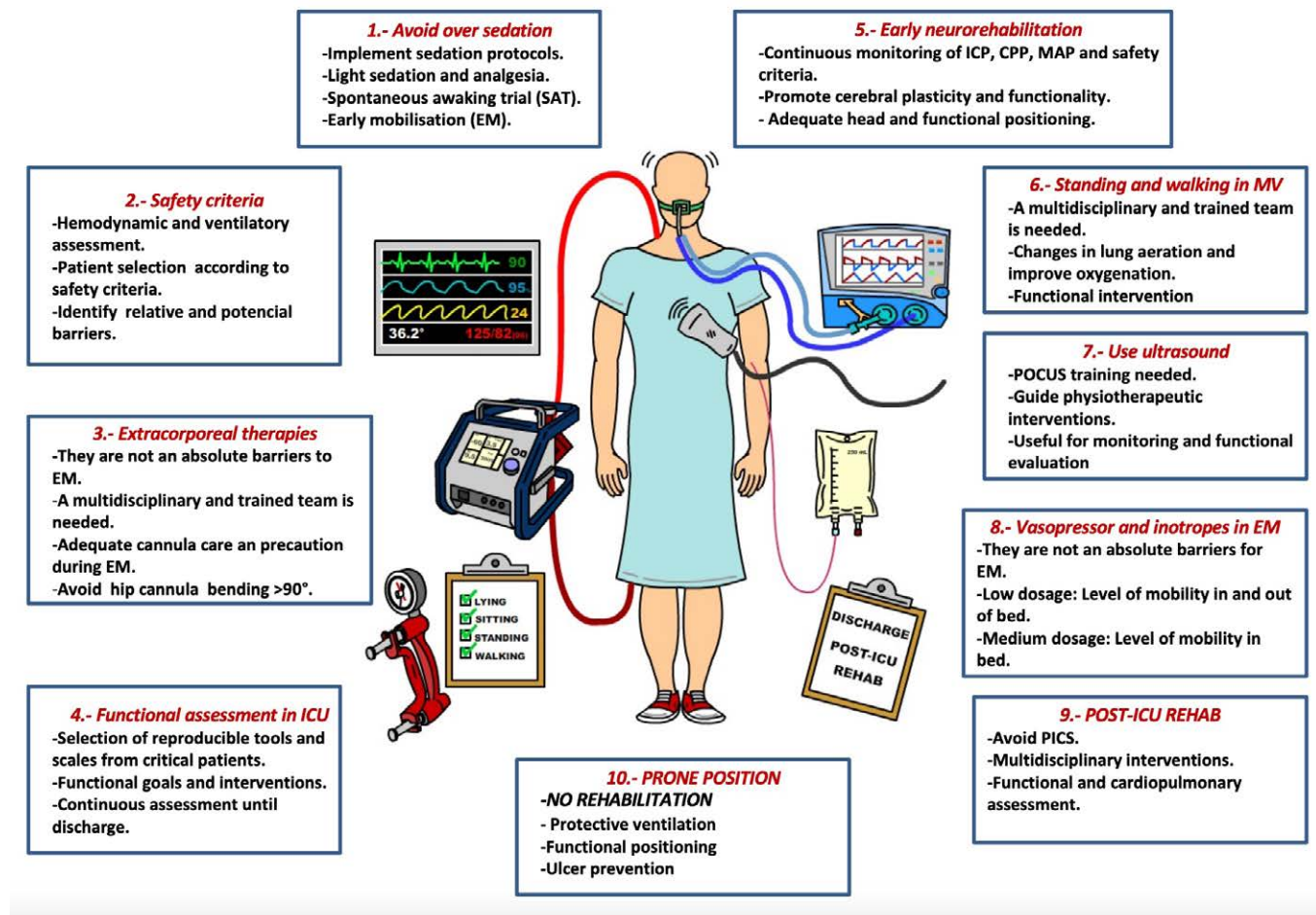
Figure 1. Practical solutions in early mobilisation

expiratory pressure (PEP) device, inspiratory muscle training (IMT), verticalisation, hyperinflation, lung expansion therapies, among others (Bertolone et al. 2021; Leech et al. 2015). Hence, it is a remarkable tool during the weaning process of mechanical ventilation through diaphragmatic, lung and cardiac evaluation. Muscular evaluation can also be accomplished through echography by measuring muscle thickness and the Heckmatt scale. Finally, some interesting findings can be made during such evaluation, findings that can even put the patient at risk. Pneumothorax, pleural effusions, cardiac tamponade, high ICP and other life-threatening situations have been found during the physiotherapeutic evaluation and these could have gone unnoticed if echography was not available (Ntoumenopoulos et al. 2021; Le Neindre et al. 2016).

8. Vasoactive and inotropic medication as a barrier for early mobility

Some of the everyday pharmacological agents used in the treatment of critical illness are vasoactive and inotropic drugs. These drugs are mainly used for shock treatment and the optimisation of haemodynamics and must not be considered a contraindication for the start of an EM programme but should definitely be a precaution in the decision making of such start (Hodgson et al. 2014a). Secure and feasible practices have been reported during the administration of such drugs, although these practices can only be implemented in patients undergoing moderate to low dosages of these agents. Haemodynamic monitoring before and during the implementation of EM in patients receiving vasoactive and/or inotropic agents is fundamental, not only for the identification of haemodynamic stability but also the cardio-circulatory response to exercise (Jacob et al. 2021).

9. Poor post-ICU follow up

When a patient is discharged from the ICU the main objective should be to reincorporate the patient back into his/her social role. This starts with assuring the patient is able to execute basic life activities such as hygiene care, movement and ambulation, talking, eating, etc. The process of reincorporation will eventually evolve in the need of developing more complex motor and mental skills and will finish with the individual's complete independence (Colbenson et al. 2019). During this process functional, mobility, independence and cardiopulmonary evaluations have to be done and will guide future interventions or discharge from the rehabilitation programme (Inoue et al. 2019). Continuing with rehabilitation after ICU discharge will have a direct impact on the patient's quality of life and recovery from impairments established due to critical illness. Patient follow-up after ICU discharge is part of the finishing with what started as a critical illness; failing to give a proper follow-up after discharge will only highlight the lack of interest in the patient's future (Nakanishi et al. 2021; Rousseau et al. 2021).

10. Mobilisation during prone position

The prone position is a widely known strategy in the treatment of ARDS. This strategy is used to optimise mechanical ventilation and improve oxygenation (Guérin et al. 2017; Johnson et al. 2021). Prone positioning translates into severe ARDS, severe oxygenation impairment and is one of the few absolute contraindications of EM (Raurrell et al. 2021; Hodgson et al. 2014a). During this phase, EM or any other physiotherapeutic strategy must be held up, except correct segment alignment, prevention of pressure ulcers and protective ventilation. No evidence has been provided that recommends EM during prone position in severe ARDS.

Conflict of Interest

None. ■

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Perioperative Haemodynamic Optimisation of the High-Risk Surgical Patient

An overview of evidence supporting perioperative haemodynamic optimisation in high-risk surgery patients and strategies to facilitate its implementation and adoption to improve patient outcomes.

A million surgical procedures performed every year worldwide are at risk of complications that can be attributed to the nature of the surgery and/or the physiological status of the patient. Although high-risk surgical patients represent only 10-15% of surgical procedures, they account for more than 80% of deaths and might benefit from perioperative haemodynamic monitoring, which refers to the haemodynamic optimisation of fluids, vasopressors, and inotropes to predefined physiological targets to maintain or restore sufficient oxygen delivery to the tissues. In fact, perioperative haemodynamic optimisation therapy has a significant impact on the outcomes of high-risk patients undergoing major surgery, potentially decreasing the length of ICU and hospital stay, morbidity and mortality (Fellahi et al. 2021).

Historic Background
The oxygen debt was first hypothesised in 1922 (Hill and Lupton 1922; Hill and Lupton 1923). They theorised that the body needs to replace the oxygen used by working muscles during mild to intense exercise. Decades later, Shoemaker et al. (1992) demonstrated the role of oxygen debt in the development of organ failure and death in high-risk surgical patients. In 1985, Schultz et al. (1985) demonstrated the benefit of physiologic monitoring with pulmonary artery catheters in patients with fractures of the hip. In 1988, Shoemaker et al. (1988) demonstrated that targeting specific values for the cardiac index,

oxygen delivery and oxygen consumption using fluids and inotropes to achieve these goals resulted in a reduction in mortality and morbidity. Since then, there have been several randomised controlled trials and meta-analyses supporting the practice of perioperative haemodynamic optimisation (PHO) (Cove et al. 2012).

Physiological Concepts
Oxygen delivery (DO_2) is determined by central and peripheral mechanisms. Among the central factors, DO_2 is determined by the product of cardiac output (CO) and arterial oxygen content (CaO_2). CaO_2 is defined as the amount of oxygen bound to haemoglobin (Hb) plus the oxygen dissolved in plasma. Changes in Hb concentration and arterial oxygen saturation (SaO_2) can be compensated by an increase in CO. However, the converse is not true, as the arterial content depends on CO to reach tissues. A basic example is blood transfusion. It would be logical to expect an elevation in Hb to systematically and predictably elevate DO_2. However, this is not what is observed, since, in addition to generating an inflammatory response, which impairs the microcirculation, the increase in viscosity can lead to a reduction in CO. Thus, the importance of haemodynamic monitoring that provides information about CO and the adequacy of perfusion and oxygenation of the tissues and organ systems. In addition, peripheral mechanisms should also be considered because they can be altered in inflammatory conditions, disfiguring the

control of vascular tonus and providing the formation of microthrombi, which obstruct capillary circulation and lead to an irregular distribution of blood flow.

In the surgical context, the increase in cellular oxygen demand due to the metabolism acceleration is relevant. Major surgical trauma elevates the mean oxygen demand from 110 mL/min/m^2 at rest to 170 mL/min/m^2. In most patients, this increase in demand is accompanied by an increase in CO and tissue oxygen extraction. Nevertheless, patients with little functional reserve may be unable to increase their CO under conditions that accompany the increase in tissue demand, generating hypoxia, cell death, and multiple organ failure. Briefly, on the one hand, increased oxygen demand generated by tissue injury, the endocrine-metabolic response, and other factors such as stress and hyperthermia. On the other hand, comorbidities prevent an adequate increase in oxygen delivery through the increase in CO. The use of inotropic, fluids and vasoactive drugs can increase oxygen supply and may reduce the imbalance between supply and demand of oxygen reducing complications.

Importance of Perioperative Haemodynamic Monitoring

The risk of perioperative complications is related to the patient's condition and comorbidities, the type of surgery performed and its duration, the degree of urgency, the skills and experience of the surgical and anaesthetic teams, and the postoperative management. Insufficient tissue perfusion and cell oxygenation due to hypovolaemia and/or cardiac dysfunction are major causes of perioperative complications and unfavourable outcomes. Low cardiorespiratory reserve seems to be the key factor in the aetiology of complications, which explains its higher incidence in elderly patients with comorbidities and with low functional reserve. Therefore, maintaining adequate DO$_2$ for cells is critical.

Is There Really Evidence of Benefit?

Three important reviews demonstrated that PHO leads to a reduction in perioperative mortality, potentially by reducing the number of postoperative complications. A meta-analysis of 29 PHO studies (Hamilton et al. 2011) found a reduction in morbidity (OR 0.43; 95% CI 0.35-0.55) and mortality (OR 0.48; 95% CI 0.33-0.70) in patients undergoing PHO but noted that the subgroup analysis showed that the mortality benefit was predominant in older studies using pulmonary artery catheter (PAC), fluid-associated inotropic drugs, and those whose haemodynamic goals were aimed at supranormal values. In a systematic review of 32 studies (5056 high-risk surgical patients) of PHO aiming at maintaining tissue perfusion, the authors (Gurgel et al. 2011) found that although PHO reduced the incidence of organ dysfunction in all patients, mortality was only reduced in the cohort of patients with baseline mortality greater than 20% in the control group (OR 0.67; 95% CI 0.55-0.82). A large multicentre, prospective, randomised study of perioperative optimisation versus usual care in high-risk patients undergoing major gastrointestinal surgery showed no difference in postoperative morbidity and mortality, although an updated meta-analysis of these same data showed a reduction in morbidity (RR 0.77, 95% CI 0.71-0.83) with the use of PHO (Pearse et al. 2014).

It is worth highlighting the importance of postoperative complications in major surgeries as predictors of long-term survival. Rhodes et al. (2010) evaluated the long-term survival of patients included in previous PHO RCTs for high-risk surgical patients. They found that 15 years after the original study, long-term survival was related to the PHO group and avoidance of cardiovascular complications. Therefore, the benefits conferred by PHO seem to be linked to several characteristics that consistently appear in these studies:

- use of CO monitors
- use of protocols defined by the clinical team
- early onset of PHO

What is the Real Importance?

Patients surviving major surgery are those with the ability to increase their DO$_2$ and VO$_2$ to supranormal values (Bishop et al. 1993). Monitoring CO and DO$_2$ has now become standard clinical practice to provide adequate tissue oxygenation and forms the basis of PHO. There are currently many CO monitors available for clinical use, with different degrees of invasiveness and measured variables. Below are some of the techniques of haemodynamic monitoring devices most used in clinical practice:

- Pulmonary artery catheter (PAC)
- Blood pressure waveform analysis
- Doppler technique for CO monitoring
- O$_2$ central venous saturation (ScvO$_2$), O$_2$ extraction rate (O$_2$ER) and lactate

Faced with so many alternatives, the choice of the monitoring device must be made based on the following factors (Alhashemi et al. 2011):

- institutional (availability, level of experience, compatibility with existing monitors)
- related to the device (invasiveness, technical limitations, validation and accuracy)
- Patient-specific (arrhythmias, contraindications for insertion, type of surgery and type of treatment protocol)

How to Choose Which Goal to Use and Conduct the Protocol?

For the performance of PHO therapy, specific physiological data of each patient are used to guide interventions that enable the achievement of adequate tissue blood flow goals. Unfortunately, to date, there is no ideal goal for PHO. An ideal goal should:

- reflect organic perfusion
- be readily available in the perioperative period
- generate continuous measures
- be easily reproducible

The ultimate goal of this strategy is to prevent cellular dysoxia through an adequate relationship between DO$_2$ and VO$_2$. As VO$_2$ depends on each patient's own factors, we can actively work to optimise DO$_2$, which is governed by the following equation: $DO_2 = (SaO_2 \times Hb \times 1.34) \times (SV \times HR)$.

The first step is to maximise the systolic volume (SV) through the infusion of intravenous (IV) fluids titrated according to the haemodynamic response. The goal is to achieve a preload that contributes to an "almost maximum" SV or CO in

accordance with Frank-Starling laws. This is technically known as a "proof" or "challenge" of volume. Thus, the clinician can administer fluid, and at the same time, test the patient's recruitable preload reserve (Cecconi et al. 2011). If the target (e.g., DO_2) has not yet been reached and the patient is already in the "plateau" region of the Frank-Starling curve (not responsive to IV fluids), inotropics can be introduced to improve the SV/CO and accordingly DO_2. In terms of mortality reduction, the combination of fluids and inotropics was superior to only fluids (Lobo 2006; Hamilton et al. 2011).

The basic model for a perioperative optimisation protocol can be seen in the organogram in **Figure 1**. Several other indices related to blood flow, tissue perfusion or fluid responsiveness, in addition to DO_2, have been used in recent years, in general: flow time corrected (FTc), that is the flow time duration of blood flow in the aorta in oesophageal Doppler monitoring (Abbas 2008), venous oxygen saturation (SvO_2) (Collaborative Study 2006), oxygen extraction rate (O_2ER) (Donati et al. 2007), lactate concentration (Polonen et al. 2000), and pulse pressure variation (PPV) (Malbouisson et al. 2017). Nonetheless, apparently the use of DO_2 and cardiac index (CI) as endpoints conferred mortality reduction. It is noteworthy that the effects on mortality were more evident when used supranormal values of DO_2 as the resuscitation goal (Poeze et al. 2005; Hamilton et al. 2011; Brienza et al. 2009). However, for the prevention of complications, normal goals seem to be as effective as supernormal goals (Brienza et al. 2009; Rhodes et al. 2010). Evidence also suggests that the use of protocols in PHO is associated with better results.

When to Start PHO?

The replacement of oxygen debt is therefore time sensitive, and once the cell and mitochondrial structure are permanently damaged, attempts to improve oxygen flow are futile (Abid et al. 2000). Oxygen debt can be repaired in the early phases of the systemic inflammatory reaction (SIRS) that accompanies surgery through flow optimisation of oxygen to tissues.

Early optimisation of oxygen flow goals in high-risk surgical patients before the development of organ failure was associated with a significant reduction in mortality (Kern et al. 2002). Patients with an optimisation strategy initiated
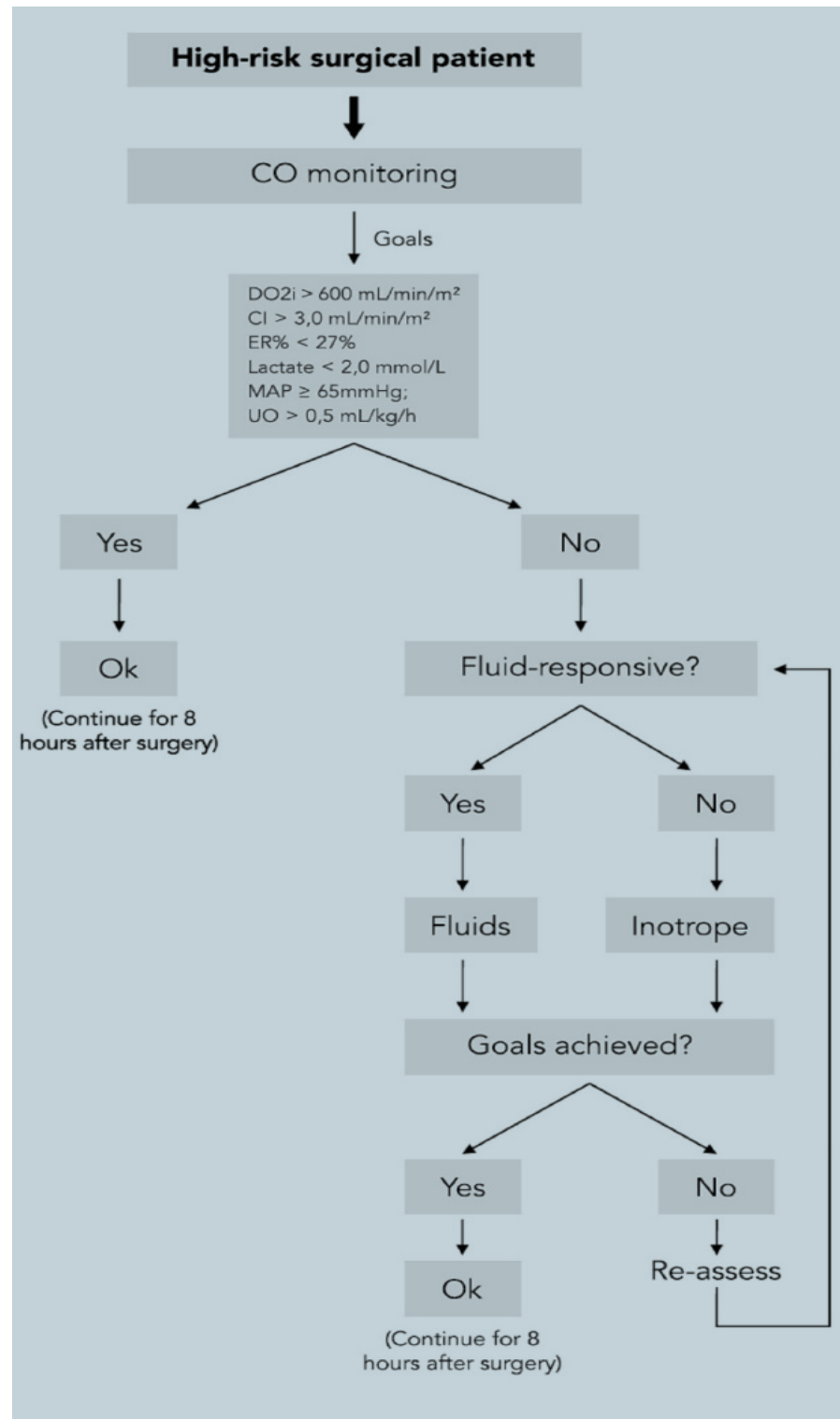
Figure 1. Perioperative haemodynamic optimisation of the high-risk surgical patient. CO=cardiac output; DO2i=oxygen delivery index; CI=cardiac index; ER=extraction rate; MAP=mean arterial pressure; UO=urine output.

after the development of organ failure do not present an improvement in mortality. A systematic review and meta-analysis of 26 RCTs was performed with patients undergoing major surgery, where only studies that started haemodynamic optimisation early (up to 8 h from the start of surgery) were included. Similar results to two previous meta-analyses found that pre-emptively performed GDT was associated with reduced postoperative ARF and gastrointestinal complications (Brienza et al. 2009; Giglio et al. 2009).

PPV > 13%;
SVV > 15%
PLR (↑ > 10% CO)
IVCCi > 18% (MV) or > 50% (non-intubated)

Table 1. Fluid-responsiveness parameters
PRL=Passive leg raising; CO=cardiac ouput;
IVCCi=inferior vena cava collapsibility index;
MV=mechanical ventilation

Economic Impact of PHO

Regardless of the location or the costing modality, the use of haemodynamic handling packages has costs, which may be inherent to the tool itself and/or to the set of interventions performed. However, studies indicate good cost-effectiveness of PHO (Fenwick et al. 2002; Barthaet al. 2012). A meta-analysis (Silva-Jr et al. 2020) from the perspective of a developing country demonstrated a significant total cost reduction in the group of surgical patients who underwent monitoring interventions, with savings of $90,161 USD for every 1000/patients/treated, and a shorter ICU and hospital length of stay compared with the control group.

Conclusion

A significant body of evidence supports perioperative haemodynamic optimisation in high-risk surgery patients. The basic principle of optimisation is based on manipulation of oxygen delivery to improve patient outcome by targeted administration of intravenous fluids, vasopressors, inotropes and blood. CO monitoring is an important component of perioperative haemodynamic optimisation. Preload, afterload, and contractility can be evaluated with a number of haemodynamic monitoring tools that are validated but differ in invasiveness, technology, advantages, and limitations. A profound understanding of the different CO monitoring methods is essential in defining which method will be used (Michard et al. 2019; Lobo and Oliveira 2013; Lobo et al. 2013). Strategies should be developed to facilitate the implementation and adoption of perioperative haemodynamic monitoring in clinical practice to improve patient outcomes.

Conflict of Interest

None. ■

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AGENDA

ICU
MANAGEMENT & PRACTICE

JUNE

1-3
ERAS 2022 – World Congress
Madrid, Spain
https://iii.hm/1eh0

4-6
Euroanaesthesia 2022
Milan, Italy
https://iii.hm/1eh5

4-7
45th Annual Conference on Shock
Toronto, Canada
https://iii.hm/1exk

14-16
40th Vicenza Course on AKI&CRRT
Vicenza, Italy / Hybrid
https://iii.hm/1exl

15
ICU Management & Practice DigiConf
Pain Management in the ICU
Virtual Event
https://iii.hm/1g27

23-25
ESICM LIVES Forum Athens: Major Trauma & Brain Injury
Athens, Greece
https://iii.hm/1exm

27-29
CHEST Congress 2022
Bologna, Italy
https://iii.hm/1exn

28-1 JUL
Intensive Care Society SOA   22 Congress
Belfast, UK
https://iii.hm/1g28

30-3 JUL
5th EuroAsia Conference Delhi
Delhi, India
https://iii.hm/1g29

JULY

12-16
11th Congress of the World Federation of Pediatric
Intensive & Critical Care Societies
Virtual World Congress
https://iii.hm/1g2a

AUGUST

20-22
APICS 2022 - Asia Pacific Intensive Care Symposium
Singapore, Singapore
https://iii.hm/1g2b

SEPTEMBER

3-6
ESPEN 2022 - European Society of Clinical Nutrition
and Metabolism Congress
Vienna, Austria
https://iii.hm/1g2c

4-6
ERS – European Respiratory Society (ERS) International Congress
Barcelona, Spain
https://iii.hm/1g2d

OCTOBER

2-6
ESICM LIVES 2022
Paris, France
https://iii.hm/1g2e

7-11
EAPS 2022
Barcelona, Spain
https://iii.hm/1g2f

15-19
EUSEM Congress 2022
Berlin, Germany
https://iii.hm/1g2g

ICU

MANAGEMENT & PRACTICE