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VOLUME 20 - ISSUE 4 - 2020

The Post-ICU Patient

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The Post-ICU Patient

Numerous patients are admitted to the Intensive Care Unit (ICU) every year. Many of these critically ill patients receive multiple interventions to treat and manage acute conditions and prevent further deterioration. However, these treatments can often affect a patient's mind and body. That is why many ICU survivors, as they transition out of the ICU, do not have the same abilities as they did before their critical illness. This worsening impairment of a patient's physical, mental or cognitive domain is referred to as the Post-Intensive Care Syndrome (PICS).

Studies show that these impairments can last for as long as five to 15 years after discharge from the ICU. A large number of ICU survivors are unable to get back to their normal routine – many can't go back to work, and those who do cannot perform the same type of jobs. Some cannot conduct daily activities without help, and others suffer from anxiety, depression, mobility issues, and chronic pain. Thus, it is important to understand that critical illness and its treatment in the ICU is only one part of a patient's journey. Management of critically ill patients requires attention not only at the time of admission and hospitalisation, but from the earliest signs of illness to their recovery.

In this issue, our contributors talk about the **Post-ICU Patient** and highlight the importance of closely monitoring patients after they leave the ICU and helping them overcome the challenges they might face after discharge.

Beatriz Lobo-Valbuena, Rosario Molina and Federico Gordo summarise the current management strategies of Post Intensive Care Syndrome (PICS) and Post-Intensive Care Syndrome - Family (PICS-F) and highlight the importance of continuum assessment and support throughout critical disease. Stephen Schaller and co-authors discuss the challenges ICU survivors and their caregivers face in the long-run and propose a patient-centred transition management and well-coordinated post-ICU care.

Jenna Obeid, Carol Hodgson and Emma Ridley summarise the current nutrition evidence in the recovery phase that follows critical illness, while Karen Choong outlines the prevalence, risk factors and management of the post-intensive care syndrome in paediatrics.

Francesco Forfori and co-authors emphasise that intensivists need to be aware of the long-term sequelae of critical illness and must implement changes that would ensure improvement in the quality of life of ICU survivors and their families.

Frederic Michard and Ashish Khanna propose continuous and mobile monitoring in hospital wards to detect clinical deterioration at an early stage and to prevent serious events and minimise risk of ICU readmission while Miguel Martinez-Camacho and co-authors discuss strategies to reduce the incidence of post-ICU complications.

Haifa Algethamy reviews long-term outcomes post-OHCA, while Amy Freeman-Sanderson and co-authors discuss the role of Allied health professionals and how they can help improve patient outcomes by positively contributing to the rehabilitation pathway.

Our contributors also discuss the COVID-19 pandemic. Eileen Kelly and co-authors talk about the impact of prolonged intubation and tracheostomy in COVID-19 survivors and the importance of evaluating laryngeal dysfunction to promote post-COVID-19 recovery. Bruno Tomazini and Luciano Azevedo talk about the use of corticosteroids for COVID-19. Laura Hawryluck and Rebecca Repa discuss innovations in ICU surge capacity, while Chan Yeow provides a historical review of home mechanical ventilation and the need for intensivists to participate in home ventilation teams.

Critical care patients face significant physical and psychological challenges that go beyond hospitalisation. It is important for critical care providers to consider the long-term impact of the ICU experience and to implement strategies that not only treat the acute condition but also make the process of recovery after ICU easier and faster.

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

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Prolonged Intubation and Tracheostomy in COVID-19 Survivors: Consequences and Recovery of Laryngeal Function

Intubation and tracheostomy as a result of COVID-19 critical illness may result in laryngeal dysfunction, which can lead to serious consequences. This article provides assessment and rehabilitation recommendations for those working with critically ill COVID-19 patients in the ICU.

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Introduction

COVID-19 was declared a worldwide pandemic in March 2020, with the virus SARS-CoV-2 causing severe acute respiratory syndrome (Williamson et al. 2020). Among patients hospitalised with COVID-19, up to one quarter required Intensive Care Unit (ICU) admission (Huang et al. 2020). For those where COVID-19 led to severe respiratory disease secondary to hypoxaemic respiratory insufficiency or failure, invasive ventilation via endotracheal tube (ETT) was required (Meng et al. 2020). Laryngeal injury following ETT intubation has previously been widely cited as a transient or lasting complication impacting on voice and swallowing and functional outcome (Brodsky et al. 2018; Macht et al. 2011; Schefold et al. 2017; Wallace and McGrath 2020).

Recovery from laryngeal injury and related dysfunction must be managed by a highly skilled multidisciplinary team (Brodsky 2020). Further insult to a fragile respiratory system from laryngeal dysfunction can lead to serious consequences, including aspiration pneumonia, delayed tracheostomy weaning and lack of functional communication. An emerging, distinctive characteristic of the COVID-19 cohort is the duration of ventilator reliance, reported as high as 20 days (Stam et al. 2020). Prolonged intubation is paired with delayed insertion of tracheostomies, increasing the risk of laryngeal trauma. Furthermore, it is possible that the oropharyngeal symptoms of COVID-19, such as cough, loss of taste/smell and pain in the pharynx may have an additional impact on laryngeal function (Lovato et al. 2020; El-Anwar et al. 2020).

Laryngeal Injury and Dysfunction During Critical Illness

Intubation Phase

Endotracheal intubation in patients with COVID-19 is a high-risk procedure for staff, requiring full personal protective equipment (PPE) which may impact on the procedure (Cook et al. 2020). Furthermore, airway oedema in those with COVID-19 has been highlighted and anecdotal reports of difficult intubations have also been discussed (McGrath et al. 2020). In these circumstances, laryngeal injury such as mucosal trauma and damage to anatomical structures may be heightened.

The ETT sits in a vulnerable anatomical region for laryngeal function. As the ETT tube is inserted, it passes the arytenoid cartilages, cricoarytenoid joints and vocal folds which are all susceptible to trauma and residual laryngeal complications, manifesting as airway, voice and swallowing impairments (Mota et al. 2012). The recurrent laryngeal nerve innervating the laryngeal musculature is vulnerable to compression by the tube cuff especially if the cuff sits too high, or the cuff pressure exceeds capillary perfusion pressure (Miles et al. 2018). A recent study in over 200 patients intubated for more than 48 hours found that larger tube size was associated with an increased risk of aspiration and laryngeal granulation tissue (Krusciunas et al. 2020).

For those with COVID-19, additional risk factors contributing to laryngeal injury have not yet been investigated. Characteristics that may predispose patients with COVID-19 to neuropathy include age, obesity, diabetes mellitus, hypertension, corticosteroids, extracorporeal membrane oxygenation and laryngopharyngeal reflux (Tadié et al. 2010; Williamson et al. 2020). Ponfick et al. (2015) found pathologic swallowing in 91% and hypoaesthesia of the larynx in 77% of patients with critical illness polyneuropathy. While the

sedative management of COVID-19 patients during the intubation phase often precludes verbal communication, during the sedation hold phase some patients may attempt to vocalise while the ETT remains in situ, posing further risk of laryngeal trauma.

It is well known that prolonged intubation results in laryngeal complications but even transient intubation has been shown to cause mucosal trauma and laryngeal injury (Ng et al. 2019). Prolonged intubation is also known to correlate with post-extubation complications, including laryngeal stenosis, with a reported incidence of 5% in those intubated for 6-10 days (Bonvento et al. 2017). Piazza et.al. (2020) highlights the need for a high-level of suspicion for laryngotracheal stenosis development in COVID-19 patients following long-term intubation and tracheostomy. A description of stenosis in a COVID-19 patient is detailed in the case study below. Laryngeal oedema may negatively impact decision making regarding the safety of extubation, and increase the need for tracheostomy insertion (McGrath et al. 2020). In the COVID-19 RECOVERY trial, critically ill patients assigned to receive dexamethasone corticosteroid resulted in a lower 28-day mortality (Horby et al. 2020). Whilst the use of the dexamethasone may reduce oedema and airway complications, the reported side-effects such as hyperglycaemia, weakness and delirium may further impair communication, laryngeal and swallowing functions.

Prone ventilation has been used as an adjuvant therapy for treatment of acute respiratory distress in those with COVID-19, with some patients being proned repeatedly for up to 16 hours (Zang et al. 2020). Whilst adverse effects such as nerve palsies, pressure ulcers and oropharyngeal swelling are reported, the direct effect of proning on the larynx is not fully understood (Kwee et al. 2015). However, it may be hypothesised that the pressure exerted by the ETT on the laryngeal mucosa may exacerbate laryngeal dysfunction. Furthermore, prolonged bed rest, immobilisation and critical illness are key causes of muscle wasting and loss in ICU patients (Koukorikos et al. 2014; Parry and Puthucheary 2015). Up to 30% muscle mass loss is reported to occur within the first 10 days, however in patients undergoing prone ventilation this may be expedited (Kortebein et al. 2008). A combination of these factors may contribute to sarcopenia-related dysphagia, which has been demonstrated in elderly patients (Zhao et al. 2018). Generalised decline in muscle mass can coincide with weakening of the swallowing musculature and whilst the average age of ICU admissions is lower for COVID-19 patients, the potential impact of muscle wasting should remain a consideration and an age-related red flag.

Tracheostomy Phase

The timing of tracheostomy insertion in the critically ill COVID-19 patient has been a key area of discussion. For patients with COVID-19, tracheostomy insertion was deemed a high risk and an aerosol generating procedure (AGP) (ENT UK 2020). The balance between delaying insertion to reduce risks to staff during the patient's most infective period and the extended duration of intubation has been discussed (McGrath et al. 2020). While prolonged ventilation is often necessitated in the COVID-19 cohort, clinicians should remain cognisant of the long term effects of prolonged intubation on laryngeal function. Following insertion, the presence of a tracheostomy tube and inflated cuff can impact upper airway sensitivity, respiratory/swallowing synchronisation and lead to disuse atrophy of laryngopharyngeal musculature (Garuti et al. 2014). Careful assessment of secretion management, cuff deflation tolerance and cough effectiveness by the multidisciplinary tracheostomy team should aim to determine risks to and optimise recovery of pulmonary function in the COVID-19 patient (Garuti et al. 2014). In-depth assessment by SLTs using Fibreoptic Endoscopic Evaluation of Swallowing (FEES) is the most accurate method for assessing oropharyngeal secretions, detecting and managing aspiration risks and for guiding multidisciplinary management and rehabilitation of laryngeal complications (Hafner et al. 2008; McGrath and Wallace 2014; Scheel et al. 2015).

While respiratory compromise associated with COVID-19 has been the most frequently reported, concomitant central and peripheral nervous system impairments have also been detailed (Paterson et al. 2020). Encephalopathy, encephalitis, ischaemic stroke and Guillain-Barré syndrome have all been observed in patients with Covid-19 (Paterson et al. 2020). The presence of central and peripheral nerve involvement further increases the risk of neurogenic laryngeal dysfunction (McIntyre et al. 2020; Schefold et al. 2017). Glossopharyngeal and vagus nerve neuropathies have been identified in a case study of a severely ill COVID-19 patient (Aoyagi et al. 2020). Cranial nerve impairments may exacerbate laryngeal dysfunction and these issues frequently delay recovery times.

Delirium and COVID-19

The inability to vocalise during critical illness can be a significant contributing factor to delirium, anxiety and psychological distress. A range of studies report this as one of the most frustrating and anxious experiences for mechanically ventilated patients (Ford and Martin-Harris 2016). Hospital policies restricting family visitations due to infection control precautions during the pandemic may further contribute to feelings of isolation and disorientation. When unable to vocalise patients have reported feeling trapped, caged, and a loss of personhood and control (Ford and Martin-Harris 2016).

Delirium occurs as a consequence of direct central nervous system invasion as a secondary effect of multiple organ system failure, sedation or environmental factors such as staff wearing PPE (Kotfis et al. 2020). Early restoration of voice can reduce anxiety levels in patients with tracheostomies (Liney et al. 2019). Early evaluation by the SLT and physiotherapist, to assess readiness for cuff deflation or a one way valve application facilitates greater patient participation in treatment. Input from clinical psychology for those experiencing psychological distress has been highlighted previously in the ICU cohort and remains essential in the COVID-19 population (GPICS 2019). Considerations of late sequelae of mental health issues such as anxiety should also be considered by the MDT in the rehabilitation and follow up clinic phases.

Recovery of Laryngeal Function – ICU Treatment Options

Facilitating Laryngeal Airflow

For tracheostomised patients, cuff deflation followed by placement of a one way valve provides increased Positive End Expiratory Pressure (PEEP), upper airway sensation and restoration of the ability to verbally communicate. Evaluation of one-way valve tolerance and resultant voice quality by SLTs enables the multidisciplinary team to be aware of any potential laryngeal impairments. Intensivists, nurses, psychologists, dietitians and physiotherapists may all utilise the one-way valve during their interactions with the patient, restoring the opportunity for verbal communication between the clinician and the patient. The use of a one way valve by the patient during video calls to family members who have been unable to remain at the bedside has been highlighted as a

Case Summary

Dysphagia is an enduring symptom of COVID-19.

The following still from Videofluoroscopy demonstrates silent aspiration of oral intake below the level of the vocal folds. This 58 year old patient received mechanical ventilation via ETT for 21 days, failed initial extubation and was subsequently intubated for a further 6 days. Prior to admission he was independently living and had a previous medical history of T2DM, HTN and obesity. He was diagnosed with a left vocal cord palsy by ENT surgeons and severe oropharyngeal dysphagia by SLT. The severity of the dysphagia necessitated the insertion of a gastrostomy. At five month follow up, the patient had begun to re-introduce oral intake and removal of gastrostomy was being considered.

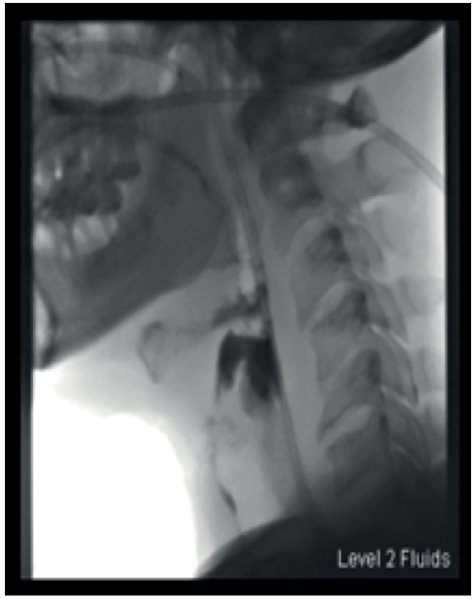

Figure 4. Silent aspiration below vocal cords

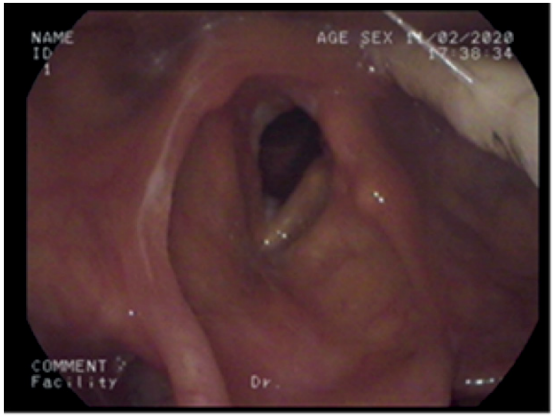

Figure 5. Right vocal fold palsy, mucosal trauma and atrophy

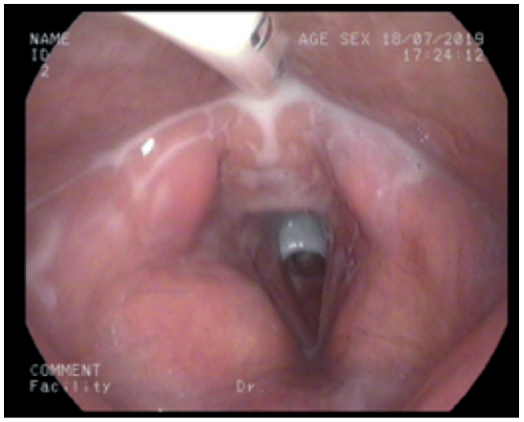

Figure 6. Supraglottic and glottic oedema with silent aspiration of milk via the interarytenoid space

significantly positive experience by patients, families and staff alike during the pandemic.

Use of the one-way valve may also contribute to dysphagia rehabilitation, with improvement to sensory awareness of any aspiration of oral intake (ICS NTSP 2020; Suiter et al. 2003). Any residual vocal cord impairments should be identified early in the management of tracheostomised patient to inform decannulation decisions. Anecdotally, for COVID-19 patients, the authors have observed patient-reported larygopharyngeal hypersensitivity and reduced tolerance of one-way valve application. This may be due to a range of factors; laryngeal oedema, breathlessness and tachypnoea (McGrath et al. 2020). Impaired laryngeal sensation, secretion clearance and cough strength/sensitivity all delay ventilator and tracheostomy weaning and decannulation (Garuti et al. 2014).

For those unable to tolerate one way valve application, Above Cuff Vocalisation (ACV) may be carefully considered. Airflow is introduced via the subglottic port of the tracheostomy tube and has been shown to potentially restore laryngeal sensitivity, increase cough response to pooled laryngeal secretions and increase an airway protective response (McGrath et al. 2018). However, ACV is an AGP that requires balancing the associated risks. Inability for airflow to escape via an upper airway which is fully or partially obstructed may cause subcutaneous emphysema, evident in swelling of the neck and face. Potential contraindications for ACV include patients with occult laryngeal oedema or vocal cord palsy. Direct visualisation of the larynx using nasendoscopy or FEES to assess the safety of ACV would mitigate this risk. Reports of COVID-19 associated upper airway oedema have been identified and therefore close observation and careful evaluation is recommended for both one-way valve and ACV techniques (McGrath et al. 2020).

Dysphagia Rehabilitation in COVID-19 Critical Illness

Dysphagia in the critically ill impedes recovery and is associated with adverse outcomes (Schefold et al. 2017; Macht 2011). Post extubation dysphagia is common, with an incidence reported as between 40-60% in ICU patients, with 38% presenting with silent aspiration due to altered glottic and subglottic sensation (McIntyre et al. 2020). Initial guidance recommending the cessation of FEES for COVID-19 patients was borne out of

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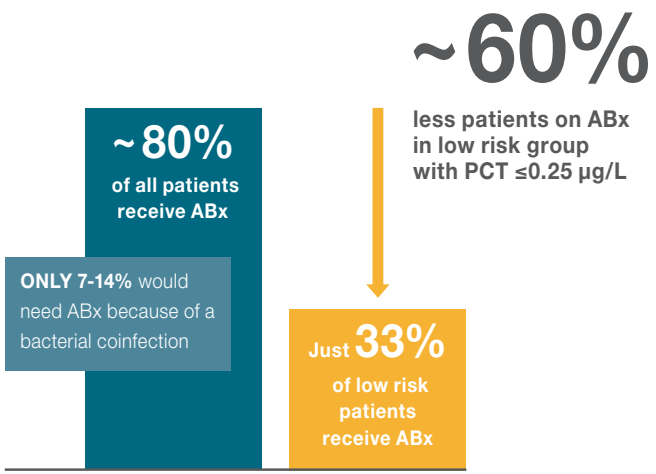

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Reference: 1. Williams EJ et al., preprint doi: https://doi.org/10.1101/2020.06.29.20136572 posted July 2, 2020.

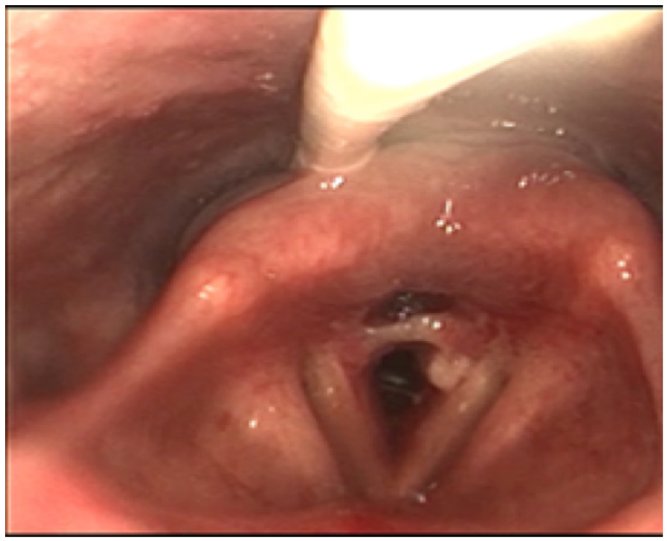

Figure 7. Intubation granuloma on left posterior glottis and narrow posterior web. Bilateral oedema and erythema of vocal folds

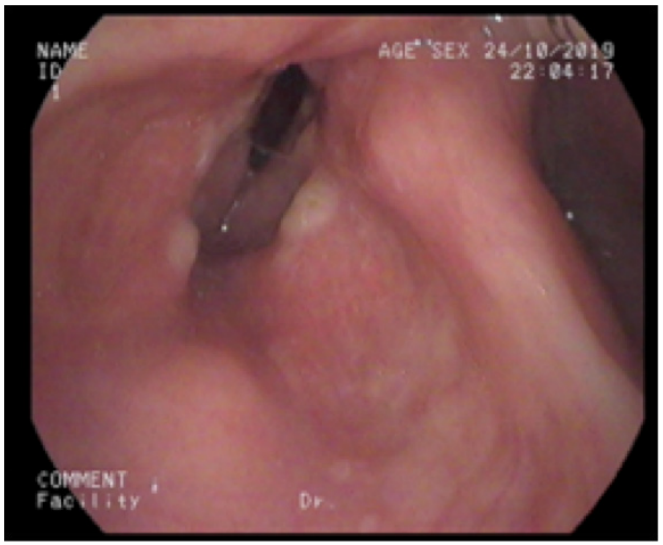

Figure 8. Bilateral ulceration of false vocal folds and anterior region, oedematous vocal folds

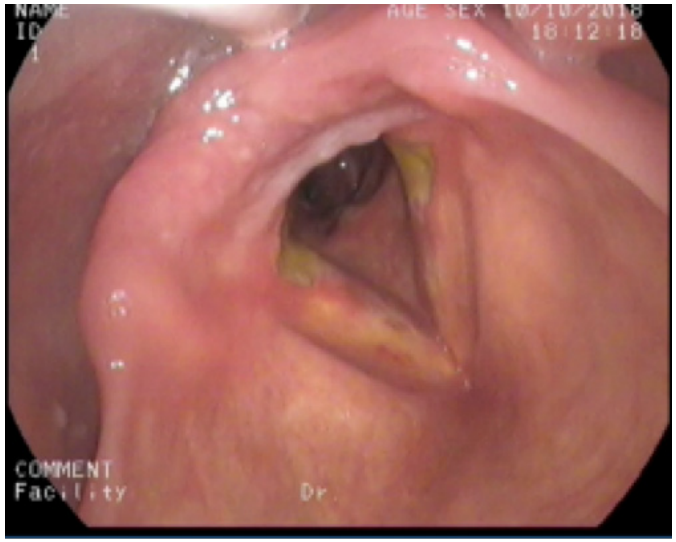

Figure 9. Intubation trauma with ulceration to posterior glottis, bilateral oedema and erythema and mucosal injury

concern regarding the nasopharynx being a known reservoir for high concentrations of the virus (Zou et al. 2020). Our understanding of the infectious period for COVID-19 patients is evolving, and the viral load of patients at the time of a FEES examination is likely to have declined, given that the initial intubation is likely to be up to 20-24 days after the onset of symptoms (McGrath et al. 2020; Bolton 2020). Rapid guidance has been developed during the COVID-19 pandemic to address the initial cessation of FEES, and following thorough review its use has been restored with additional protective measures in place (Royal College of Speech and Language Therapy [RCSLT] 2020; Zaga 2020; Herazo 2020). SLTs have also been exploring alternative adjuvant methods to support clinical decision-making for the assessment of upper airway and swallowing. An international working party of SLTs are currently evaluating the potential contribution of ultrasound to evaluate vocal cord function and airway patency, particularly for use in the ICU.

Lima et al. (2020) suggested that whilst those with COVID-19 remain intubated for longer, the number of rehabilitation sessions focusing on swallowing was fewer and patients appeared to return to oral intake sooner than the comparison cohort. The authors reiterate this finding, except in the presence of neurological complications and severe global weakness. Isolated cranial nerve impairment must also be considered, with a case study by Aoyagi et al. (2020) reporting glossopharyngeal and vagal neuropathy resulting in dysphagia. Tailored rehabilitation for dysphagia usually consists of swallowing exercises to target the physiological impairment identified on instrumental examination. These may include established rehabilitation exercises or newer equipment-based therapies such as Pharyngeal Electrical Stimulation (PES) and Expiratory Muscle Strength Training (EMST). PES is indicated for patients with sensory dysphagia, which is frequently the main component in laryngeal dysfunction in critical illness. Research in this population is in its early stages but indications are that it may be beneficial for return to oral intake (Wallace 2020). The use of compensatory strategies as directed by SLT can also support return to safe oral intake, including altering bolus size and delivery and diet and fluid modification.

Dysphonia Rehabilitation in COVID-19 Critical Illness

For those with persistent dysphonia, a multidisciplinary team approach is advisable. Though for the majority of extubated patients dysphonia is typically transient, up to 10-35% of patients may present with residual symptoms (Mota et al. 2012). In those with persistent dysphonia, surgical intervention for glottal insufficiency may be indicated following joint comprehensive assessment and evaluation by ENT surgeons and SLTs. Alterations to a person's typical vocal quality may have implications for their vocational rehabilitation, and further justifies the need for careful consideration and validation for timely intervention.

Prolonged Rehabilitation Following COVID-19 Critical Illness

Rehabilitation Frameworks

The longer a patient remains in ICU, the greater the risk for long term and residual complications (Stam et al. 2020). Post intensive care syndrome (PICS) describes physical, cognitive and/or mental impairments in patients following critical illness, with these impairments persisting beyond the intensive care unit (Biehl and Sese 2020).

Phase	COVID-19	Potential effects of Laryngeal Dysfunction in ICU
1. Acute	During COVID-19 infection	• Intubation trauma • Damage to laryngeal mucosa with ETT in-situ • Delirium/Psychosis • Muscle mass wastage • Dysphagia • Dysphonia
2.Post-acute	Continuing from the acute phase of COVID-19 and it's treatment	• Tracheostomy weaning • Vocal fold palsy • Dysphonia • Dysphagia • Nutritional support • Physical manifestations (reduced mobility) • Residual delirium
3.Permanent	Unresolved or not solvable, resulting in a new health condition	• Laryngeal/tracheal stenosis (if untreated) • Inducible Laryngeal Obstruction • Breathlessness • Chronic dysphagia • Vocal abnormalities and dysphonia • Altered taste and sensation
4.Late-onset	Appeared as a consequence of COVID-19, but after the end of the acute phase	• Post ICU mental health presentation • Voice dysfunction impacting on vocational rehabilitation
5.Acute, post-acute, late-onset or permanent on a pre-existing health condition	Impact of COVID-19 on people with a disability and/or experiencing disability at the time of infection	• Further injury to pre-morbid decompensated swallow function • Inducible Laryngeal Obstruction • Breathlessness

Table 1. COVID-19 Phases of Rehabilitation Related to Laryngeal Dysfunction
Adapted from REH-COVER and WHO-RP 2020

While data pertaining to the length of recovery for those who survive a COVID-19 related intensive care admission is still being collated, anecdotal experience across ICUs in the United Kingdom indicates a high proportion have significant residual impairments (RCSLT 2020). Multidisciplinary team pathways have previously been established for those recovering from intensive care admission (GPICS 2019; NICE 2014). During COVID-19 a national multi-professional collaborative led by the Intensive Care Society (ICS) developed a gold standard rehabilitation framework for assessing early rehabilitation needs post ICU (ICS 2020). Guidance on potential laryngeal, voice and swallowing sequelae, methods of screening using the PICUPS tool and a

rehabilitation prescription tool are all embedded within the guidance. Now, more than ever, the need for a coordinated rehabilitation approach is essential (Biehl and Sese 2020; McGrath et al. 2020; Stam et al. 2020).

REH-COVER and WHO-RP have delineated proposed phases of COVID-19, which have been adapted below to serve as a guide when evaluating laryngeal dysfunction and it's long term implications. Guidance on in-depth assessment by SLTs is also provided in ICS framework and the RCSLT documents (ICS 2020; RCSLT 2020).

Evaluation of the most appropriate rehabilitation pathway for COVID-19 patients at step-down from ICU to ward and from ward to discharge may be structured using the PICUPS tool (ICS 2020). The tool supports early detection of issues on ICU, triggers referral for specialist assessment and may also serve to include the patient in the ongoing assessment process.

ICU Follow-Up Clinics

Previous research has identified the potential for long term and residual complications of laryngeal injury (Brodsky et al. 2017). While published evidence on the long term effects of post COVID-19 laryngeal dysfunction is pending, the RCSLT have prepared an evaluation tool to guide clinicians running ICU follow up clinics in order to signpost those requiring additional intervention (RCSLT 2020). Persistent laryngeal dysfunction may manifest as dysphagia, dysphonia, altered taste/sensation, breathlessness or chronic cough. Clinicians must also remain cognisant of laryngotracheal stenosis and inducible laryngeal obstruction (ILO) as potential aetiologies for long term airway and laryngeal dysfunction (Halvorsen et al. 2016).

Lessons Learned from Initial COVID-19 Peak

In the early stage of the pandemic, clinicians were advised to minimise the risk of AGPS. For these reasons, cuff deflation and application of a one-way valve (PMV) in-line with mechanical ventilation was delayed as was use of endoscopy for swallow assessment. Given our emerging knowledge regarding the reduction in the patient's viral load over time, once local risk assessments have been carried out, the treating team may wish to explore initiating these interventions at an earlier stage in the COVID-19 patient's recovery.

The effect of PPE on ICU delirium has yet to be reported, however given anecdotal reports from patients the need for early facilitation of communication cannot be overemphasised. Early intervention by SLTs in critical care is needed now more than ever (GPICS 2 2019; NCEPOD 2014; ICS FICM 2020).

Recovery of laryngeal function may be prolonged and requires an integrated MDT approach. Patients being followed up by ICU outreach nurses and SLTs via telehealth have reported ongoing problems with voice, swallowing solid oral diets and taste alteration during the recovery phase. Further research is required to evaluate the nature of these residual impairments, to explore the unknown potential for residual SARS-Cov-2 pathogens in the larynx, and impact of prolonged intubation on laryngeal function in COVID-19 patients.

Conclusion

Early identification and consideration of laryngeal dysfunction in the ICU patient is essential to minimise further respiratory compromise and commence the patient on the most appropriate treatment. Laryngeal dysfunction impacts the wider ICU multidisciplinary team, given its impact on verbal communication, liberation from ventilation, respiratory function and nutrition. The role of the SLT is essential for robust assessment, diagnosis and management of laryngeal dysfunction and any consequent dysphagia or dysphonia and airway concerns. Whilst we await further research, evaluation of laryngeal dysfunction should remain a vital part of clinicians evaluations to promote optimal recovery post COVID-19.

Conflict of Interest

ZP has received honoraria for consultancy from GlaxoSmithKline, Lyric Pharmaceuticals, Faraday Pharmaceuticals and Fresenius-Kabi, and speaker fees from Orion and Nestle. ■

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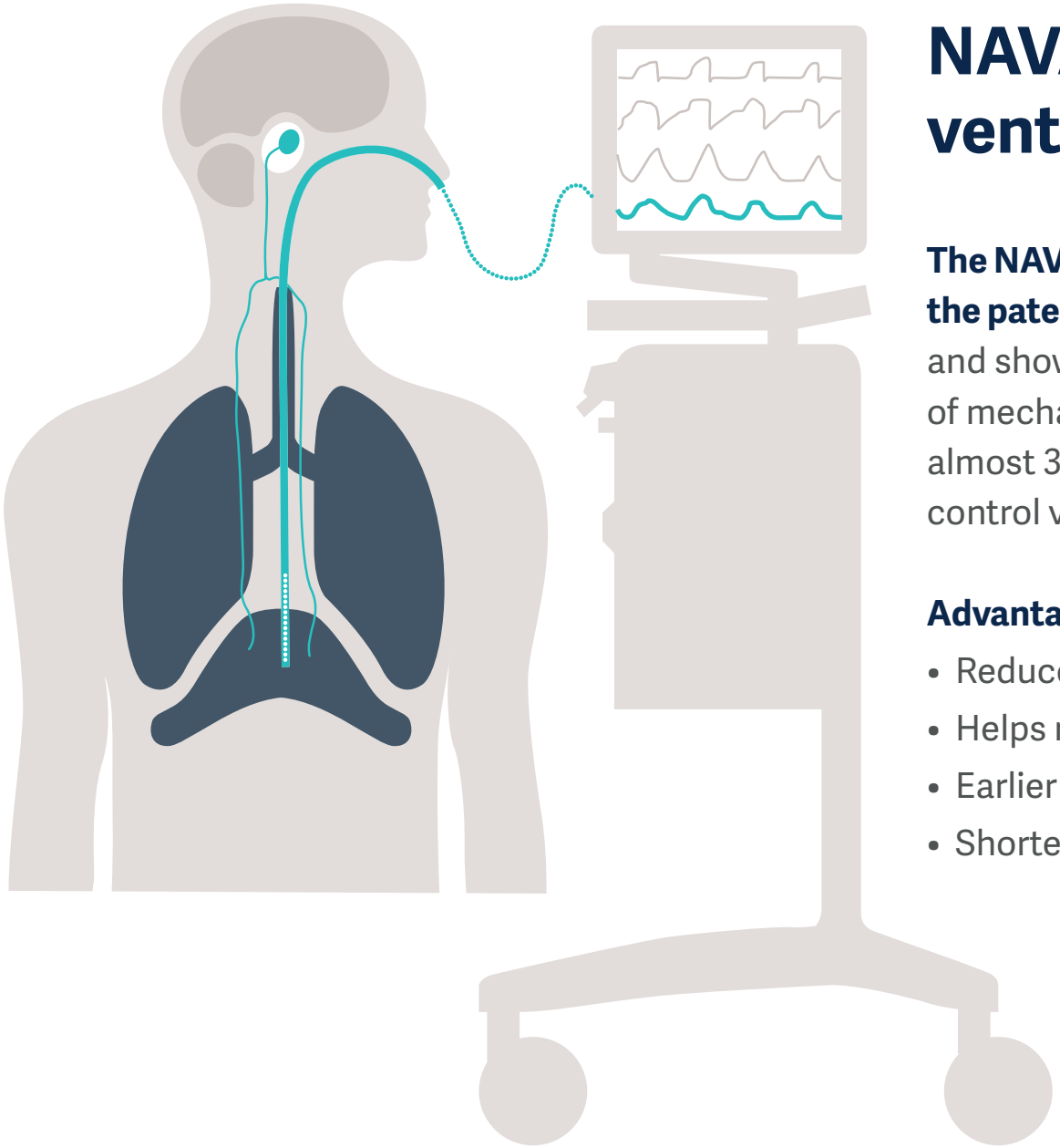

NAVA shortens time of mechanical ventilation by almost 35%

The NAVIATOR study[1] proves the clinical effectiveness of the patented Neurally Adjusted Ventilatory Assist (NAVA) and showed that the use of NAVA could reduce the duration of mechanical ventilation from 12 to 8 days (corresponds to almost 35%) by using the patient's own respiratory drive to control ventilator assistance.

Advantages of NAVA:

- Reduce complications
- Helps monitor and reduce sedation
- Earlier and more successful weaning
- Shorter time of mechanical ventilation

Find out more about the NAVIATOR study and the neurally adjusted ventilation mode NAVA.

[1] Kacmarek et al ICM 2020; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7474954/pdf/134_2020_Article_6181.pdf

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Biomarkers and Their Impact in ICU Patient Outcomes

The laboratory plays a critical role in ensuring optimal outcomes for ICU patients. Several biomarkers are valuable in this context and can help clinicians achieve improved patient outcomes and decreased expenses for healthcare.

Improving both in-ICU and post-ICU clinical outcomes often depends on actions taken much sooner in a patient's pathway during hospitalisation. Regardless of the underlying diagnosis which brings someone to the ICU, there are a few very common complications in this patient population, which are strongly associated with the overall mortality and morbidity expected during the course of hospitalisation. Among these complications, the most prevalent and significant ones are sepsis and acute kidney injury (Sakr et al. 2018; Case et al. 2013).

Challenges of Sepsis

Sepsis occurs when a patient develops an infection, which triggers an exaggerated, un-controlled and sustained inflammatory response. While a simple infection leads to local damage to the organs and tissues where the offending organism is present, in sepsis the damage is caused by the body's own immune response. It is a systemic disease, possibly affecting all organs in the body, including the most vital ones such as the brain, lungs and kidneys. Sepsis is associated with very high morbidity and mortality (Sakr et al. 2018) - a simple skin infection which would never be life threatening per se can quickly lead to a patient`s demise if this infection triggers sepsis, for example, due to respiratory failure caused by an overwhelming inflammation in the lungs.

Once a septic event is already fully established, there is very little physicians can do to help. It is therefore critical to recognise sepsis early on, when simple measures such as the administration of fluids and broad-spectrum antibiotics have been shown to significantly improve a patient`s mortality and morbidity. The challenge is that early clinical signs and symptoms of sepsis, such as fever, respiratory difficulty, and fatigue, are unspecific and overlap with those of much less severe conditions, such as a simple flu. In this context, treating physicians need additional support beyond their clinical assessment in order to recognise early sepsis and start appropriate interventions at a time when they are most effective. This support is provided by the laboratory through critical biomarkers which can help discriminate sepsis from the myriad of other simpler and less severe clinical conditions which can present with a very similar clinical picture.

Biomarker for Early Sepsis Identification

A biomarker for early sepsis identification is procalcitonin (PCT). While PCT is originally a hormone involved in calcium metabolism, multiple studies have shown how levels increase in the presence of bacterial infection, and this increase is proportional to disease severity and most pronounced when patients develop sepsis. This biological behavior of procalcitonin enables it to answer some key clinical questions critical to the proper management of sepsis which ultimately impact a patient's in-ICU and post-ICU outcomes. These key clinical questions are:

- Early recognition of sepsis when therapies are most effective.
- Discrimination between bacterial and viral infections, guiding the decision whether antibiotics are indicated.
- Establishing when a lower respiratory tract infection has been controlled and antibiotics can be discontinued safely.

Acute Kidney Injury (AKI)

Another common complication in ICU patients which can lead to severe long-term consequences and worsened post-ICU outcomes is acute kidney injury (AKI). This disease is characterised by a rapidly progressive loss of renal function, over days or even a few hours. AKI is classified in 3 different stages of worsening severity, based on criteria relying on levels of urine output and blood concentration of creatinine, a waste product typically filtered by the kidney and which accumulates in renal failure. ICU patients who develop AKI typically have worse mortality, longer duration of stay in the ICU often requiring haemodialysis, and quite often will go on to develop chronic renal failure requiring either dialysis for the rest of their lives, or renal transplantation.

The main risk factors for acute kidney injury are critical diseases very common in ICU patients, such as sepsis, major trauma or surgery, acute heart failure and respiratory failure. Risk factors also include clinical interventions common in ICU patients, such as the use of nephrotoxic antibiotics or contrast media for radiology studies. Taken together, these factors lead to AKI prevalence rates as high as 40% in ICU patients, leading to billions of dollars in excess expenses to health care systems.

The actions clinicians can take to lower the risk of acute kidney injury among ICU patients are well known and are based primarily in minimising exposure to nephrotoxic measures. The challenge is that these nephrotoxic measures are also beneficial to treat the underlying critical condition the patient is facing. For example, the best antibiotic combination to treat a septic patient may also be the most toxic to the kidney, or the use of contrast media in radiology exams may be critical to diagnose a pulmonary embolus. In this scenario, intensivists are faced with a challenging choice between doing what is best to save a patient's life and protecting their renal health.

Biomarker to Help Prevent AKI

A novel biomarker for acute kidney injury has been introduced into medical practice and is helping physicians navigate this challenging clinical predicament. Nephrocheck is an index biomarker generated by measuring two cell cycle arrest biomarkers, called tissue inhibitor of metalloproteinase 2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP-7). These proteins are responsible for stopping cellular division and are typically released by renal tubular cells under situations of kidney stress. As such, patients with elevated Nephrocheck values are at higher risk of developing moderate and severe acute kidney injury within 24 hours of testing.

The advent of Nephrocheck enables clinicians to recognise those patients already undergoing renal stress and take decisive action to avoid additional nephrotoxic measures which would take the patient into overt AKI. Using this biomarker, intensivists can make better decisions between when to go full speed ahead and focus on treating the underlying critical condition the patient is facing, versus when to be more conservative to preserve renal function and improve post-ICU outcomes. For example, patients recovering from cardiac surgery often benefit from inhibitors of the angiotensin converting enzyme (ACE inhibitors), but these drugs do increase the risk of AKI. In this scenario, clinicians can rely on Nephrocheck to recognise when it is safe to focus primarily in cardiac recovery and deploy the ACE inhibitors to their patients.

A study with post-cardiac surgery patients at the University of Muenster, Germany, demonstrated how patients screened for higher risk of acute kidney injury using Nephrocheck benefited from a nephroprotective care bundle, consisting of aggressive optimisation of volume status and haemodynamics, avoidance of nephrotoxic drugs and close monitoring for hyperglycaemia (Meersch et al. 2017). Patients randomised to the "care bundle" cohort had a 30% decrease in rates of moderate and severe AKI, when compared with usual care. Patients in the "care bundle" cohort had moderate or severe AKI rates of 29.7%, compared to 44.9% in the control group (Meersch et al. 2017). Most importantly, in this study the majority of patients had Nephrocheck values within normal limits, indicating no need for a change in their routine care. Since the care bundle increases the complexity and cost of care, it is prohibitive to be deployed in all ICU patients. But as demonstrated in this study, use of a biomarker such as Nephrocheck can guide clinicians to identify those patients for whom special attention with their renal function is required. Once they are identified, the deployment of aggressive nephroprotective measures is effective in lowering the rates of moderate and severe AKI, and the in-ICU and post-ICU complications derived from AKI.

> "it is critical to recognise sepsis early on, when simple measures such as the administration of fluids and broad-spectrum antibiotic have been shown to significantly improve a patient's mortality and morbidity"

A similar observation was made in a study with patients undergoing major abdominal surgery. Patients were randomised to receive either usual ICU care, or an optimised nephroprotective care bundle as described above. In the overall study population, there were no differences in AKI rates, but in a sub-group analysis including only patients with elevated Nephrocheck values, the incidence of AKI was reduced from 48% in the usual care group, to 27.1% in the "care bundle" group (Goecze et al. 2018). This study offered additional evidence that a nephroprotective care bundle is beneficial to prevent AKI in ICU patients, but only in those with a higher risk of kidney damage, as identified with the use of Nephrocheck.

These are just two examples of how the laboratory plays a critical role in ensuring optimal outcomes for ICU patients. Several other biomarkers are valuable in this context, for example high-sensitivity troponin and NTproBNP, critical for the management of cardiac diseases. Health administrators can greatly benefit by enabling greater communication and collaboration between pathologists and intensivists, leading to improved patient outcomes and decreased expenses for the institutions they manage. ■

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COVID-19, Corticosteroids and the Road to Enlightenment

The use of corticosteroids for respiratory diseases has been a matter of discussion. Here, we present recent evidence of corticosteroids benefits for COVID-19, including improvements in mortality and ventilator-free days.

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More than six months riding treacherous waves in the COVID-19 storm had passed until a glimpse of a rudimentary old harbour appeared. Corticosteroids. The first drug to decrease mortality in critically ill COVID-19 patients. And it took only a few seconds after we touched land to hear some sailors whispering that they all knew the way to the corticosteroids harbour and that all maps pointed to its direction. Really? Was the path that clear? We are afraid not. All the maps we had pointed out to the other direction. Of course! They were pre-COVID-19 era maps, ancient history for some. But within each old map there were tips pointing to the true north. And fortunately, we found them.

It may seem unnecessary to discuss the use of corticosteroids in critically ill patients with COVID-19 when high-quality evidence (Horby 2020; Sterne 2020) is available. However, we'd like to move backwards to a moment when there was only uncertainty and possibilities.

Shortly after the COVID-19 outbreak, it was clear that we would face a tsunami of viral pneumonia leading to acute respiratory distress syndrome (ARDS). Fortunately, we know how to support ARDS patients: lung protective ventilation (Brower 2000), prone position (Guérin 2013) and neuromuscular blocking agents (Papazian 2010; Moss 2019) are all well known to intensivists. But was that enough? Probably not.

An overwhelming number of possible repurposing therapeutic drugs begin to pop-up. And with all science misinterpretation, the COVID-19 pandemic was a fertile field for clinical trials and a real time lesson on how low-quality evidence can be detrimental. From hydroxychloroquine to convalescent plasma, lopinavir/ritonavir, ivermectin and tocilizumab had their chance, unfortunately without any real success until now. And of course, corticosteroids.

Looking Back

We have been using corticosteroids in critical care for more than 50 years (McConn 1971). However, looking at published data, we have more doubts than certainties. Corticosteroids for traumatic brain injury? Not effective (Roberts 2004). For refractory septic shock? Why not (Venkatesh 2018; Annane 2018). For chronic pulmonary obstructive lung disease? Always. How about ARDS? Pneumonia? Viral diseases?

Before discussing the role of corticosteroids in COVID-19, we will discuss some evidence of the pre-COVID-19 era.

Corticosteroids for ARDS

A series of trials in late 90s and early 00s investigated the role of corticosteroids for ARDS. Different drugs (mostly hydrocortisone and methylprednisolone) administered in different time-points of the disease (early vs late) were investigated. The essence of these trials might be highlighted by the larger ARDSNet trial (Steinberg 2006), which demonstrated increased ventilator free days and shock free days with corticosteroids but no difference in the primary outcome of mortality at 60 days. And along with this study, most of the well-designed randomised trials of that period showed no mortality benefit. Why was that? Were the trials underpowered for mortality? Or was the timing of the intervention? Most of the studies were indeed underpowered for mortality, and most of them evaluated the intervention late in the disease process. The most recent piece in the puzzle of the evidence for corticosteroids in ARDS was the publication, in early 2020, of the DEXA-ARDS (Villar 2020) randomised controlled trial. Despite some limitations such as small sample size and early interruption for low recruitment, this study showed benefit of early dexamethasone (<24h after ARDS onset) use in moderate-severe ARDS. Patients in the intervention group received dexamethasone 20mg daily for 5 days followed by 10mg daily for 5 days or until extubation, whichever occurred first. Patients in the intervention group had higher number of ventilator free days at 28 days (12.3 vs 9.0; p<0.001) and lower all-cause mortality at day 60 (19% vs 31%, p=0047). Up to now, the use of corticosteroids in non-COVID-19 ARDS is still an unresolved issue.

Corticosteroids for Community Acquired Pneumonia (CAP)

Several studies and meta-analyses yielded conflicting results regarding the use of corticosteroids for CAP. A meta-analysis published in 2017 (Stern 2017) showed no mortality benefit of corticosteroids for hospitalised patients with severe CAP (Risk ratio = 0.80, 95% CI 0.54-1.19) when analysing only trials with low risk of bias, while another meta-analysis (Siemieniuk 2015) showed a mortality benefit of corticosteroids in this same population (risk ratio 0.39, 95% CI 0.20-0.77). However, the small number of patients included in this analysis undermine the results.

Corticosteroids for Viral Pneumonia

Prior to the COVID-19 pandemic the hypothesis was that corticosteroids increase mortality in viral pneumonia according to the results of two meta-analyses (Lansbury 2019; Ni 2019). Lansbury reported a mortality odds ratio of 2.23 (95% CI 1.54-3.24) for corticosteroid use while Ni reported a mortality risk ratio of 1.75 (95% CI 1.3-2.36). In both meta-analyses the majority of patients had influenza pneumonia and mild disease. Also, early use of corticosteroids increase plasma viral load in patients with SARS-CoV-1 (Lee 2004) and is associated with delayed viral clearance in patients with Middle East Respiratory Syndrome (MERS) (Arabi 2018).

Corticosteroids for COVID-19

If we, somehow, were able to sail back to early 2020, abstracting the knowledge we now have, the most scientifically honest discussion on the prospects of corticosteroids use in COVID-19 would follow this rationale:

All the available evidence we have show that corticosteroids use in respiratory viral diseases might be harmful. Also, we cannot rule out a possible benefit of corticosteroids in community-acquired pneumonia and there is recent evidence of a potential mortality benefit when used early in moderate and severe ARDS. However, there might be an intersection zone, which is exactly the one missing in the corticosteroids' trials for influenza: critically ill patients with viral pneumonia. Also, what if COVID-19 does not behave like the other viral diseases? Inflammation, coagulopathy and ARDS histopathology, which now are clear for us, were not at that time.

A comparison of histologic lung examination between deceased patients with COVID-19 and severe influenza pneumonia shows diffuse alveolar damage, oedema, and fibrin deposition, hallmarks of ARDS in both diseases (Ackermann 2020). However, differently from influenza, patients with COVID-19 have the distinctive features of endothelial injury, microangiopathy and angiogenesis. Data suggest that corticosteroids administration can downregulate the inflammatory pathways responsible for these findings (Arabi 2020). Thus, COVID-19 shares some of the physiopathology features of other viral diseases, such as influenza, but also has its own features.

Therefore, this unique set of events: a new relatively homogeneous disease, knowledge on the effects of corticosteroids in ARDS, and the scientific perception that maybe in the severely ill patients with COVID-19 corticosteroids might play a role, set the ground for future research. At that time, surely nobody could affirm that corticosteroids would work. Equipoise it's all there was.

Shortly, randomised controlled trials started to recruit patients and sooner or later we would be able to make decisions according to evidence-based medicine. As Neil deGrasse Tyson once said: "The good thing about science is that it's true whether or not you believe in it." Of course, in the meantime we saw all forms of flamed passions defending one therapy or another, without any evidence-based discussion.

In mid-June the results of the corticosteroids-arm of the RECOVERY Trial (Horby 2020) were published. In an unprecedent effort they were able to randomise more than 6000 patients to either dexamethasone 6mg daily or standard of care. Overall, dexamethasone use resulted in lower 28-day mortality than control (rate ratio 0.83, 95% CI 075.0.93). However, a subgroup analysis showed that this mortality benefit was mainly driven by patients requiring oxygen support, with a possible sign of harm with dexamethasone use in patients without oxygen support. Although from a subgroup analysis, this information merged with the previous data on the possible harms of corticosteroids in other viral diseases allowed us to suggest the subgroup of patients that would mostly benefit from this intervention. Even though the evidence is compelling, the RECOVERY trial had its limitations. The lack of important data, such as organ dysfunctions, severity of hypoxaemia, infection rates, among others (De Backer 2020) elicit questions regarding the balance between treatment arms and subgroups.

"with all science misinterpretation, the COVID-19 pandemic was a fertile field for clinical trials and a real time lesson on how low-quality evidence can be detrimental"

Another trial (CoDEX) including only patients with moderate or severe ARDS due to COVID-19 (Tomazini 2020) showed that dexamethasone increased ventilator-free days. A meta-analysis (Sterne 2020) of randomised trials also showed a mortality benefit of corticosteroid use in critically ill patients. All the trials included in the meta-analysis had their limitations. Some were open label, different corticosteroids and doses were used, and all trials but RECOVERY stopped before the target sample size was reached (after the RECOVERY publication). Also, data on safety and long-term outcomes are still scarce.

Now steroids are used for all hospitalised patients with COVID-19 under oxygen support. However, since science is always tricky, there are still gaps to be filled. Which corticosteroid is better? Which dosage? Does time from disease onset matter? We cannot rule out a corticosteroid class effect, but the evidence available today shows that dexamethasone might be the drug of choice. However, as recommended by the WHO guidelines (Lamontagne 2020), if dexamethasone is not available, it is reasonable to assume a class effect and use any corticosteroid available. The matter of dosage is more difficult and it is hard to make any recommendations. As for the time from disease onset, although the RECOVERY trial found no benefit in early use (<7 days) we should keep in mind that time from disease onset and disease severity are extremely collinear. Therefore, the trigger for initiating corticosteroids should be the severity, despite the time the disease started.

In the end, we cannot precise right now the exact pathway in which corticosteroids exert their beneficial effects in COVID-19. What we did was to use all the available evidence at the time together with scientific reasoning to propose an intervention that should face the test of randomised controlled trials. Fortunately, the effect was positive on mortality, but it would have paid off even if it was not. Because although we all want to find drugs and interventions to benefit our patients, ultimately, we're searching for evidence-based answers. Scientia vinces.

Conflict of interest

Bruno Tomazini and Luciano Azevedo report receiving research grants from Ache Laboratorios Farmaceuticos to carry out a trial on corticosteroids for COVID-19. ■

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The Seraph® 100: Evidence and Perspectives

An overview of the clinical application and future perspective of the Seraph® 100 haemoperfusion in critically ill patients with sepsis.

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Background

Over the last few decades, sepsis has been spreading worldwide to such an extent that it has been declared global health priority by the World Health Organization (Reinhart et al. 2017). Sepsis is an old disease (Cutuli et al. 2017) and many efforts have been exerted by the scientific community in order to define this syndrome (Singer et al. 2016) and drive its management by evidence-based recommendations (Rhodes et al. 2017). Early identification and few, timely, interventions have been shown effective to improve sepsis-related clinical outcomes (Seymour et al. 2017). Rapid administration of appropriate antimicrobials and control of source infection are necessary to treat sepsis (Rhodes et al. 2017). However, the heterogeneous characteristics of this syndrome (mostly associated with patients' inflammatory response to infection and comorbidities), the emergence of multi-drug resistant pathogens (Vincent et al. 2020), and the paucity of new discoveries in this setting (Laffey and Kavanagh 2018), have been challenging critical care clinicians. In the light of this view, extracorporeal blood purification by Seraph® 100 Microbind Affinity Blood Filter (Seraph-100, Exthera Medical Corporation, Martinez, CA), offers the possibility to remove bacteria, viruses and fungi from the systemic circulation (Seffer et al. 2020). Moreover, this newly designed membrane provides immune modulation by clearing the blood from inflammatory mediators, thus controlling both pathogen load and host response. Accordingly, Seraph® 100 Microbind Affinity Blood Filter represents a new frontier in the management of sepsis, prefiguring itself as a bridge to setup appropriate antimicrobial therapy as well as provide definitive control of source infection.

In the present paper we will report structural features, laboratory and clinical evidences supporting the application of Seraph® 100 Microbind Affinity Blood Filter in critically ill patients with sepsis. Finally, we will point out future perspectives in this field.

Structural Features

The Seraph® 100 Microbind Affinity Blood Filter is a single use, sterile, disposable column, made by polyethylene beads (diameter of 0.3 mm) which surface has been modified to contain end-point attached heparin (Seffer et al. 2020). The amount of heparin released to the systemic circulation during extracorporeal blood purification is negligible. Heparin mimics negatively charged heparan sulfates of cell surface. This feature fosters electrostatic interactions with many micro-organisms, inflammatory mediators and drugs, thus allowing their removal from the blood (Seffer et al. 2020). The Seraph® 100 Microbind Affinity Blood Filter is an extracorporeal haemoperfusion device, which is intended for use with standard, commercially available bloodlines compatible with the pump system used. When concomitant renal replacement therapy is performed, Seraph® 100 Microbind Affinity Blood Filter should be placed prior to the haemofilter (**Figure 1**). A large bore (12-13 French), double-lumen, venous catheter is required in order to deliver up to 400 mL/min blood flow rate.

Laboratory Evidence

Pathogens

Preclinical investigations showed that the Seraph® 100 Microbind Affinity Blood Filter clears the bloodstream from pathogens, inflammatory mediators and drugs. Specifically, pathogens are restrained into the column through electrostatic interactions with the negatively charged heparin graft of the Seraph® 100 Microbind Affinity Blood Filter. Among bacteria, *Staphylococcus Aureus* was demonstrated to adhere to heparinised beads (Mattsby-Baltzer et al. 2011). This pathogen represents one of the most common causes of infections among critically ill patients and recent epidemiological reports described an increasing incidence of methicillin-resistant strains (Vincent et al. 2020), which implies the risk of prescribing inappropriate empiric antibiotic therapy and worsen patients' related clinical

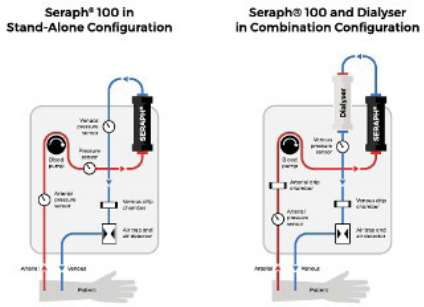

Figure 1. Seraph 100 placed in a stand-alone or in dialyzer-combination configuration

outcome. Accordingly, early removal of Methicillin-resistant Staphylococcus Aureus by Seraph® 100 Microbind Affinity Blood Filter may represent an effective complementary treatment to control the development of infection, especially when empiric antibiotic therapy is not appropriate and the spectrum of sensitivity to antibiotics is unknown.

Moreover, recent laboratory investigations showed that Seraph® 100 Microbind Affinity Blood Filter reduces bloodstream viral load of Zika virus (87%), Cytomegalovirus (79%), and Adenovirus (62%). Furthermore, previous evidences observed that the surface protein "Spike 1" of Sars-CoV-2 virus binds heparin and unpublished researches demonstrated that such pathogen is removed by the Seraph® 100 Microbind Affinity Blood Filter (Seffer et al. 2020).

Inflammatory mediators

Cytokines may be theoretically adsorbed by the Seraph® 100 Microbind Affinity Blood Filter. In an in vitro research, a significant reduction of tumour necrosis factor alpha concentration (which approximates 59%) was observed when blood from donors was exposed to heparin beads (Seffer et al. 2020).

Drugs

Schmidt et al. (2020) investigated the in vitro adsorptive properties of the Seraph® 100 Microbind Affinity Blood Filter on 18 anti-infective drugs (acyclovir, amphothericin B, ceftazidime, cefazolin, clindamycin, daptomycin, fluconazole, fosfomycin, gentamicin, levofloxacin, linezolid, meropenem, moxifloxacin, piperacillin, rifampicin, tazobactam, tobramycin and vancomycin) added to human donor plasma. The authors demonstrated that extracorporeal haemoperfusion with this device reduced the concentration of gentamycin and tobramycin within the first five minutes of treatment. Although plasma level concentrations of the remaining drugs were also reduced within the same time-point, the variation was smaller compared to aminoglycosides. Moreover, no additional drug plasma level changes were observed at 60 minutes from the commencement of haemoperfusion for any of the investigated antimicrobials.

Clinical Evidence

The safety of Seraph® 100 Microbind Affinity Blood Filter was demonstrated in 15 patients undergoing renal replacement therapy. In this study, a reduction of bacteria load (assessed by colony forming units/mL or time to positivity of blood cultures) in the bloodstream was observed within the first 4 hours of treatment. More recently, Olson et al. (2020) reported their preliminary experience with the Seraph® 100 Microbind Affinity Blood Filter in two critically ill patients with Sars-CoV-2 infection requiring mechanical ventilation and vasopressor support. The authors observed haemodynamic parameters improvement, vasopressor load reduction and body temperature modulation associated with this treatment (Olson et al. 2020).

Future Perspectives

The Seraph® 100 Microbind Affinity Blood Filter use has been widely increasing and many studies have started with the aim to collect further evidences on the application of this device in clinical practice. Currently, the research agenda includes four trials on this topic registered in ClinicalTrials.gov (Identifier: NCT04361500, NCT04413955, NCT04547257, NCT04260789). A prospective, multicentre, open-label, randomised, controlled clinical investigation has been recently commenced, with the aim to evaluate the safety and performance of Seraph® 100 Microbind Affinity Blood Filter in the reduction of pathogen load from the blood in septic patients with suspected, life-threatening bloodstream infection (primary endpoint). This trial will collect evidence on 232 adult critically ill patients, evaluating also 90 days all-cause mortality, persistence/recurrence of bacteraemia, sepsis, organ dysfunction-free days, reduction of intensive care unit complications, ventilator-free days, length ICU and hospital stay within 7 days from the enrollment in the trial.

Conclusion

The Seraph® 100 Microbind Affinity Blood Filter is a newly designed device for extracorporeal blood purification, which offers promising clinical perspectives in the management of sepsis. This device may become of paramount importance in the era of multidrug resistant pathogens, giving time to the clinician in order to prescribe effective antimicrobial therapy, identify and resolve the source of infection and modulate inflammatory-mediated organ dysfunction, thus controlling the development of sepsis and improving patients' related outcome. ■

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Innovations in ICU Expansion Solutions: From Tents to Modified Shipping Container Mobile Pods

This article discusses the 2020 innovations in ICU surge capacity, their benefits and challenges and how they may prevent or delay the need to enact triage criteria /decision-making in pandemic and mass casualty situations.

Introduction

Even though governments in many countries have taken unprecedented steps to shut down their economies and impose massive self-isolation, social distancing and masking policies to help their healthcare resources meet the demands for care, COVID-19 has caused intensive care units (ICUs) globally to develop, revise or expand their surge planning as the virus has ravaged communities around the world (Carenzo et al. 2020; Junyang et al. 2020; Litton et al. 2020; Shadman et al. 2020). Such surge plans are key to maintaining essential services and to providing care for large amounts of people affected by the pandemic. Surge plans have traditionally involved expansion into spaces that can readily accommodate critically ill patients (e.g. post anaesthesia care units, emergency departments, operating rooms) and exploring other more "hostile" spaces that can however be adapted (with minimal alterations/construction) to meet the air, oxygen and suction needs required to provide ICU care (Einav et al. 2016; Sprung et al. 2010; Kersten et al. 2020). Redistributing patients within regions to optimise resource availability is also a key strategy in meeting needs (Michaelson et al. 2020). Once these options are exhausted though, currently difficult triage decisions must be faced. Triage generally combines a utilitarian (greatest good for greatest number) approach with a scientific evidence- based assessment of the ability of critical care to help the patient; including such evidence as exists for those affected with the novel pathogen (Christian et al. 2006; Baumrucker et al. 2020; Dougherty et al. 2014). After the SARS outbreak in Toronto, and in the face of a subsequent potential influenza pandemic, triage criteria combining utilitarianism with scientific evidence and military colour coding to allocate ICU resources were created and formed the foundations of triage planning worldwide (Christian et al. 2006). The proposed triage plan was not perfect: it lacked details for particular categories of illnesses; was not stringent enough nor flexible enough to adapt as resources become increasingly consumed. In the face of dire prediction modelling forecasted ICU surge capacity being overrun (Joebges and Biller-Andorno 2020; Lamblin and de Montgolfier 2020; Litton et al. 2020), COVID-19 resulted in the rapid development and adoption of triage criteria globally building on these past experiences (Baumrucker et al. 2020; Leclerc et al. 2020; Maves et al. 2020; Singh and Moodley 2020; Vincent and Creteur 2020).

As in the past, triage criteria in 2020 have also proposed giving weight not only to scientific evidence for likelihood of ICU survival but also to other societal "values", with some arguing for the incorporation of social utilitarianism, fair innings provisions, lotteries, and more resources to disadvantaged members of societies (White and Lo 2020; White and Angus 2020). Such considerations have given rise to internal tensions and contradictions within COVID-19 triage policies, ethical tensions among and within healthcare teams, and ethical dilemmas in their proposed application (Vincent and Creteur 2020). COVID-19 triage planning has however also brought new scientific evidence into criteria development: outcome based evidence from neurocritical care, more sophisticated illness specific prognosticating scales, the concept of physical and cognitive frailty, decreased silos in healthcare as seen by concepts of expansion into different less affected regions of countries and criteria by which the allocation of resources becomes more stringent and harsh as scarcity progresses (Baumrucker et al. 2020; Leclerc et al. 2020; Maves et al. 2020; Singh and Moodley 2020; Vincent and Creteur 2020).

Most intensivists have fortunately never had to face triage decisions such as those that occur in the final stages of critical care resource availability and most dread making tough decisions and apply policies about the allocation of the last ICU bed. What if there was a way to not have to face difficult triage decisions in a pandemic at all? What if there was another way to quickly expand ICU capacity and bring this capacity to places in need? This paper will explore the innovative ICU expansion solutions of 2020 that are at the forefront of what could be a new reality for critical care medicine.

ICU Expansion Solutions: Importance and 2020 Innovations

ICU tents and repurposed spaces

To delay, for as long as and as much as possible, triaging of critical care resources, for the first time, ICUs have, on a massive, global scale, explored expansion options outside their usual bricks and mortar hospital boundaries. In the first COVID wave, societies bore witness to the deployment of hospital tents including ICU beds, hospital naval ships, and the conversion of large hotels, auditoriums and conference centres into field hospitals. The provision of hospital and critical care in tents and naval ships is not new and has been successful in other natural disaster and war trauma situations (Brosh-Nissimov et al. 2015; Nam et al. 2018; Fisher et al. 2018; Wenfang et al. 2009;Wu et al. 2008). Hospital naval ships which also include some ICU beds are limited national military resources, require a port to be able to accept patients and thus are not a viable solution for many countries. Tents are rapid to deploy, adaptable yet require variable set up time once on site. Most hospitals that have used tents, have deployed them as external screening facilities, though some have used them as treatment facilities for patients requiring hospital ward level care. A few hospitals have also used tents to expand their ICU capacity (e.g. New York City). Tents require generators, oxygen and water supply and equipment including personal protective equipment (PPE) and HEPA filters have to be shipped and then installed. Information is lacking on infection control practices and environmental disinfection requirements that arise when providing pandemic care in tents-in particular during aerosol generating procedures. The use of tent-based solutions may also pose additional challenges depending on the climates in which they are being deployed and the resulting impact on the working environment. Most tent hospitals and tent ICUs are not negative pressure environments. The innovation arising from the COVID-19 pandemic is that more companies around the world are now developing negative pressure tents making these more available and accessible as an ICU resource.

The creative conversion of hotels, auditoriums and conference centres into hospitals has not been previously done on such a global scale. The set-ups used have varied with commonalities being the division of space into rows upon rows of beds, with construction to create some sort of privacy barriers between patients. While they can host large numbers of patients, they also inherently lack negative pressure capability, oxygen, gas and suction lines and equipment required for ICU care and pose significant infection control challenges in HEPA filtering, in disinfecting and cleaning the environment around and between patients. Though they provide significant ICU expansion solutions by their very pre-existing structural nature, and are climate controlled, these infection control challenges in disinfecting the walls and spaces of either tents or converted auditoriums and large conference rooms in particular after the aerosol generating procedures may create situations where breaches in IPAC procedures are unavoidable, posing as yet unknown safety risks for healthcare workers.

Once no longer needed, the storage of tents is relatively simple though requires some additional costs to properly store and maintain. Auditoriums and conference centres will engage additional "de-construction" costs. Once again attention must be paid to decontamination of the tents and materials of the makeshift hospital spaces to prevent spread of illness to disassembly teams and workers.

Modified shipping containers: Mobile ICUs

By far, the most innovative development in ICU surge capacity to arise from this pandemic, is the transformation of shipping containers into mobile ICU units. The first of these was designed and created in four weeks by the open-source, not-for-profit CURA group in Italy with an international task force including designers at Carlo Ratti Associati with Italo Rota, engineers at Jacobs, and health technology company Philips for medical equipment supply (curapods.org). The concept of a mobile pod solution is a game changer for ICU care allowing the rapid expansion of surge capacity, and of negative pressure rooms, an increasingly valuable, yet currently limited, commodity in most hospitals, within a slightly smaller footprint. These mobile units can be quickly constructed, maintain the ability to offer speedy deployment and flexibility in both size and configuration of inter-unit connections as seen with tent based solutions. The units are negative pressure units and already pre-set up as ICUs with all the required equipment, PPE and HEPA filters prior to deployment and shipping, significantly decreasing the time from deployment to readiness to use. They are climate controlled and can be deployed in a wide range of global settings without problem by truck, rail, plane or ship. They can be connected to a hospital as an extension or, like tent-based solutions, can function independently with generators, oxygen and water supplies. Unlike most tent based solutions, these units have windows to decrease the incidence and severity of patient delirium - a frequent complication in COVID-19 patients (Kotfis et al. 2020). Each CURA mobile ICU pod can care for two critically ill patients per 20 foot container. The first prototype, sponsored by UniCredit Bank was installed in Turin Italy and the World Economic Forum has extended support to the project (curapods.org/).

In Canada, FERO International (ferointl.com) has taken the concept even further and designed and developed larger units that unite two 40 foot containers which can provide care to two ICU patients (1 patient per 20 feet), with their larger size providing the added features of an anteroom to house supplies, maintain donning and doffing of PPE practices and an added bedside nursing station/workspace for each ICU nurse). The FERO International ICU/OR and hospital units are constructed with hospital grade walls and flooring, include Drager technology that decreases the inter-professional ICU team's frequency of need to enter the COVID patient's rooms while maintaining high standards of observation, monitoring and ability to respond to changing care needs. In an additional innovation, FERO International units can be switched from negative to neutral to positive pressure units while they are deployed providing the added advantage of conversion from operating rooms (positive pressure), to ICU

units (neutral or negative pressure) in mass casualty situations. The units have wireless connectivity to maintain family contact and enable the timely provisions of situational updates from healthcare workers, important considerations when caring for COVID-19 patients whose families are typically not allowed to visit. The design includes remote monitoring capabilities at a centralised nursing stations (ferointl.com/).

Each mobile unit is designed to either function independently or can be joined together (using different techniques depending on the manufacturer) to form a larger ICU and/or hospitals with hallways, remote nursing stations and common areas in configurations that fit the space designated for their deployment. Once they are no longer needed, complex disassembly is not required, the units can just be picked up and transported to storage facilities. Cleaning to meet IPAC specifications is generally more straightforward depending on the materials used for walls and floors, decreasing the risk to healthcare workers and disassembly crews. Long-term storage of such units does however require more planning and a proper facility. Regular maintenance checks while in storage are also required to ensure the units are functional and ready to be deployed at any time. While these logistics should not be overly complicated, they do engage additional costs and expertise as compared to tent-based solutions.

While the modified shipping container mobile ICU units present many attractive advantages, the key question is are they functional? Can patients be provided with high quality inter-professional care in these spaces? Will people and equipment actually fit? Are there biomedical concerns that would prohibit certain kinds of care? Infection control precautions and environmental services concerns that would jeopardise either patient or staff safety? The answers to these questions were recently addressed by FERO International in a rigorous, week-long, multi-pronged evaluation of their modified shipping container mobile negative pressure ICU units with anterooms and bedside nursing stations conducted by University Health Network (UHN), a tertiary academic centre associated with the University of Toronto. The goal was for the multi-pronged teams to identify potential areas of concern and to propose solutions. UHN's Biomedical, IPAC, Environmental Services each conducted their own independent evaluations of the units. UHN's Human Factors team facilitated workflow and functionality testing with two days of inter-professional ICU team simulations. The simulated scenarios ranged from activities of usual daily care and escalated to crisis/resuscitation situations. Each stage of the inter-professional crisis simulations required the rapid entry of multiple team members, resuscitation activities, including/followed by the entry of supplies and equipment such as a portable x-ray machine, portable ultrasound machines, defibrillators and resuscitation medications in order to evaluate changes to workflow patterns, issues in communication in particular in crisis situations and to discuss potential ways to mitigate any perceived or real disruptions to usual components of patient care. Each inter-professional team member provided feedback as an individual and as a member of the simulated patient's care team. The results of these evaluations were overall very positive with suggestions from the teams to further maximise floor space, to ensure greater patient visibility from the beside nursing stations without compromising the sturdiness required for deployment and

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facilitating improved intra-team communication even beyond what exists in many traditional brick and mortar ICUs. Further adaptations of these units will permit the provision of haemodialysis which, since in this pandemic 20% of critically ill patients with COVID-19 develop acute kidney injury (Hansrivijit et al. 2020), is not an insignificant consideration and means dialysis needs can be addressed without moving the patients back into the main hospital setting. From the testing results, the answer to the most fundamental question—can high quality ICU care be provided in these mobile units? – is an unequivocal yes.

Other Considerations: Implications for Healthcare Workers

The ability to increase physical surge capacity is crucial in global pandemics. Yet physical space is not the only need: the space is nothing without healthcare workers, the medications and equipment they need to provide care. COVID-19 has led to a broader understanding of the role of telemedicine in providing ICU support to healthcare teams such as what has been used by MSF Canada for decades to support its field teams around the world (www.telemedhub.org/about-telemedicine; Lilly and Mullen 2020). COVID-19 has also led to the concept of broad re-deployment and role expansion, whereby physicians, nurses and inter-professional healthcare workers are asked to stretch their skills and practice outside their usual area of expertise. Quick online ICU training courses have proliferated (Brickman et al. 2020; Coughlan et al. 2020; Fraher et al. 2020; Nunez-Villaveiran et al. 2020; Price and Campbell 2020) yet the required speed of their development has meant little input by or real appreciation of the educational needs of the wide range of end-users of the material occurred. As such, an interesting future research topic will be to assess how well ICU faculty anticipated the needs of those who were being "trained" to treat critically ill patients independently or under the supervision of an actual intensivist or ICU nurse. Additional challenges for learners in critical care, have subsequently been the stressful global shortages of key medications to provide such care such as narcotics, sedatives and neuromuscular blockers, as global demand has outstripped production requiring further adaptation of clinical education and practice (Haina 2020). Yet even more challenging to anticipate and understand is the interplay between the role expansion/re-deployment and working in new innovative ICU environments such as tents, conference centers or mobile modified shipping container ICUs. Data on healthcare workers and support staff experiences, patient care and outcomes is lacking though it will hopefully soon be forthcoming as healthcare teams publish their experiences in providing care in such settings to enable us to understand the challenges and practical solutions in order to provide safe, consistent, effective patient care in such environments and not compromise patient outcomes.

Conclusions

Fundamentally critical care medicine is about helping more than it hurts, saving those lives that can be saved, easing pain and suffering, and not continuing to treat to achieve a life that the person would not want to live and not prolonging their death when death is the only possible outcome. Central to all these critical care goals is the concept of trying intensively every day to help people in need. Triage is a challenging concept: in usual practice, ICU teams do not stop before they even begin, when there is an ability to help and the person wants to be helped, such as what is seen in triage decision-making. Nor do teams identify people on whom life support is to be withdrawn because they no longer meet allocation criteria yet in other times could survive their critical illness. For a field that is trained to respond, trained to try, standing down in the face of need, is deeply heart wrenching and haunting.

For these reasons, innovative ICU expansion solutions are a vital component of this and of future pandemics and need to be considered in any mass casualty situation in order to help the greatest number of people possible, maintain essential healthcare services for those unaffected by the situation and achieve the best possible outcomes without invoking increasingly harsh triage decisions. Though all expansion solutions have a role to play in these situations, a a fundamental future consideration for such solutions is as follows: when everything is new, when everyone is exhausted, worried and even scared, the more a mobile expandable solution can resemble a "traditional" ICU, the more readily healthcare workers can adapt to the new environment and provide the care needed to give patients with life-threatening illnesses the best chances at survival.

Conflict of Interest

Laura Hawryluck volunteered her time to assist FERO International understand requirements to care for critically ill patients and to develop and participate in the inter-professional simulation scenarios for University Health Network's Human Factor's evaluation of the FERO International mobile ICU. Rebecca Repa led the recruitment of the UHN multi-pronged evaluation teams of the FERO units to assess the provision of care, patient and staff safety in such spaces. ■

Abbreviations

IPAC: Infection Prevention and Control

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Treatment of Catecholamine Refractory Hypotension in Septic Shock:Beyond First-Line Vasopressor

Hypotension during septic shock is a strong indicator of patient outcome and mortality. Arginine vasopressin is a naturally produced human hormone with vasoconstriction effect via V1 receptor activation and a short 5-20 minutes half-life and is recommended by the Surviving Sepsis Campaign guidelines to be added as a second-line vasoactive agent when increasing mean arterial pressure with norepinephrine alone is not possible and/or to reduce norepinephrine dose.

Hypotension during septic shock is one of the most important indicators of 30-day outcome, including mortality (Varpula et al. 2005; Dünser et al. 2009), which is why vasoactive agent management for haemodynamic stability is an integral part of the Surviving Sepsis Campaign (SSC) guidelines (Rhodes et al. 2017).

Norepinephrine is recommended as first-line agent to increase mean arterial pressure (MAP) (Rhodes et al. 2017), but for severe septic shock patients who do not achieve target MAP despite norepinephrine (NE) infusion, arginine vasopressin is recommended as second-line vasopressor to increase MAP and reduce norepinephrine infusion (Rhodes et al. 2017). In this article, we will discuss why hypotension in certain patients become catecholamine refractory, how to identify it, and why is vasopressin recommended for such patients.

Understanding Hypotension in Septic Shock

Hypotension in septic shock can be linked to loss of vascular tone, myocardial dysfunction, or insufficient intravascular volume (Varpula et al. 2005).

Loss of vascular tone in septic shock is a major contributor of hypotension. This is linked to an increased production of nitric oxide (NO), a potent vasodilator as a result of the inflammatory response to infection (Dalimonte et al. 2020), accompanied by a drop in endogenous vasopressor production, such as vasopressin (Russell 2011) and catecholamines (Rittirsch et al. 2008).

Vasoactive agents, which can be classified into catecholamine or non-catecholamines (Dalimonte et al. 2020), activate specific receptors located on vascular myocytes, such as α_1 adrenergic and V1a receptors, which increase cytosolic calcium concentrations in vascular myocytes, leading to vasoconstriction, increasing vascular tone and consequently increasing MAP (Jentzer and Hollenberg 2020). Norepinephrine, a catecholamine, increases vascular tone by activating the α_1 adrenergic receptors and like other catecholamines (i.e. epinephrine, dopamine) also activates the ß-adrenergic receptor, such as $ß_1$ and $ß_2$.

> "impaired vascular responsiveness to catecholamines is due to downregulation or decoupling of α1 adrenergic receptors ...in such cases, vasopressors with an alternative mode of action are needed to achieve vasoconstriction and increase blood pressure

Catecholamine Refractory Septic Shock

In certain patients, catecholamine infusion is unable to stimulate the α1 adrenergic receptors to induce vasoconstriction and increase MAP. This impaired vascular responsiveness to catecholamines is due to downregulation or decoupling of α1 adrenergic receptors (Jentzer and Hollenberg 2020), primarily caused by lactic acidosis (Rittirsch et al. 2008).
This could be identified by persistent hypotension despite norepinephrine infusion of >0.2-0.3µg/kg/min combined with infusion of fluids and adequate or high cardiac output (Jentzer and Hollenberg 2020) indicative of catecholamine refractory septic shock.

In such cases, non-catecholamine vasopressors with an alternative mode of action are needed to achieve vasoconstriction and increase blood pressure.

Arginine Vasopressin as Second-line Vasopressor

Arginine vasopressin, also known as vasopressin, argipressin, and anti-diuretic hormone, is a naturally produced human hormone and a non-catecholamine vasopressor. It achieves vasoconstriction by activating the V1a receptors and as a result can increases blood pressure and MAP (Dünser 2013). Based on that, arginine vasopressin is recommended by the SSC guidelines to be added as a second-line vasoactive agent (0.01-0.03IU/min) when increasing mean arterial pressure with norepinephrine alone is not possible, and/or to reduce

catecholamine infusion (Rhodes et al. 2017). Unlike synthetic vasopressin analogs, which have an 8-hour half-life, arginine vasopressin has a half-life of 5-20 minutes only. This short effective half-life provides a high degree of control, as the vasopressor effect could be quickly halted once infusion is discontinued in case of unwanted side-effects (Tanja et al. 2006).

The early combination of arginine vasopressin has also shown to decrease the need for Renal Replacement Therapy (RRT) by 55% for septic shock patients at risk of renal failure (1.5x serum creatine based on the RIFLE criteria) and reduce the progression to renal failure (Gordon et al. 2010).

In a systematic review of 23 randomised controlled trials (3088 patients), the addition of arginine vasopressin to catecholamine vasopressors compared with catecholamines alone was associated with a lower risk of atrial fibrillation (RR, 0.77) (McIntyre et al. 2018). This can be related to a reduction in adrenergic stimulation provided by the catecholamine sparing effect of arginine vasopressin.

Additionally, arginine vasopressin does not seem to constrict pulmonary arteries, as at low doses (0.01-0.03 IU/min) arginine vasopressin causes endothelial nitric oxide release in pulmonary arteries, when V1a receptors are activated (Currigan et al. 2014; Chan et al. 2015; Holmes et al. 2004).

Arginine vasopressin is marketed by AMOMED under the following brand names: Empressin®, Embesin®, Embesyn®, Empesin®, Empressine® and ReverPleg®. For more information regarding the product, please visit amomed.com. ■

Key Points

- Septic shock patients suffering from hypotension despite >0.2-0.3µg/kg/min of norepinephrine infusion combined with fluid administration and high adequate cardiac function is indicative catecholamine refractory septic shock.
- Arginine vasopressin is a naturally produced human hormone with vasoconstriction effect via V1 receptor activation and a short 5-20 minutes half-life.
- Arginine vasopressin is recommended by the SSC Gudielines as a second-line vasopressor to increasing mean arterial pressure and reduce norepinephrine dose.
- The early combination of arginine vasopressin has shown to decrease the need for Renal Replacement Therapy.
- The addition of arginine vasopressin to catecholamine vasopressors compared with catecholamines alone was associated with a lower risk of atrial fibrillation.

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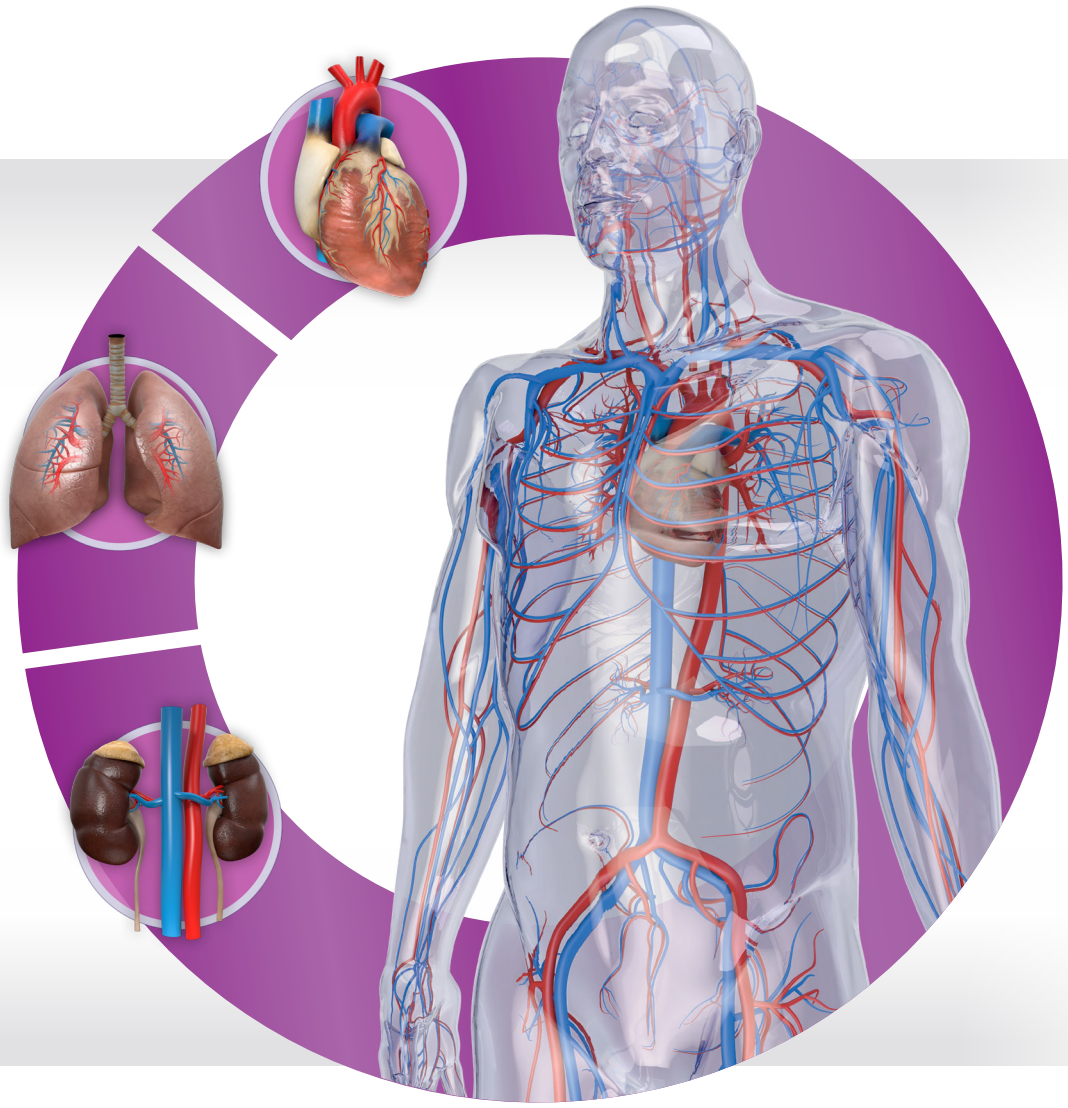

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Why Intensivists Should Participate in Home Ventilation Teams

A historical review of the birth of intensive care medicine and home mechanical ventilation; and an opinion piece on the merits of intensivists participating in home ventilation care teams.

The world is currently reeling from the ravages of COVID-19. It is still too early to know how healthcare will be transformed as a result of this epidemic. For now, it appears that COVID-19 will leave behind large numbers of survivor-victims who will need to cope with various degrees of disability. It is instructive then to look back at another pandemic that occurred seventy years ago.

Polio – Copenhagen, Kenya, London

An earlier epidemic in the 1950s – the polio epidemic – led to the naissance of intensive care medicine, and eventually the birth of home mechanical ventilation in Europe and the Americas.

Home ventilation began as a rebellion; ventilator dependent individuals wanting to leave the ICU, not to die, but to live!

In 1952, Bjorn Ibsen revolutionised the management of polio by introducing tracheostomy ventilation, with medical students performing manual ventilation in shifts. The first beneficiary was Vivi Ebert, a twelve-year old girl on the brink of death. Dr Ibsen went on to establish what is arguably the first intensive care unit in the world, in 1953, at the Kommunehospitalet, the municipal hospital of Copenhagen (Berthelsen 2003).

In 1958, Robin Cavendish, a young businessman in Kenya, contracted polio and became a "responaut." He was transferred back to England for treatment. He survived against the expectations of his doctors and chose to leave hospital against medical advice after one year. In 1962, with his friend Professor Teddy Hall, he developed a wheelchair with a built-in ventilator, bringing mobility to himself and other polio patients.

He lived a full and impactful life, helping to develop and market equipment that improved the lives of the disabled, and raising money together with Dr Geoffrey Spencer and others to build "The Netley Waterside House" for the recreational needs of the disabled.

Sixty years on, we can draw a few lessons from the life of Robin Cavendish. Firstly, that Intensive Care saves lives. He would not have survived and gone on to accomplish all his philanthropic deeds without the initial intensive care. Secondly, intensivists (in this case his friend Dr Geoffrey Spencer) continued to make an impact on his life, and the lives of people needing prolonged mechanical ventilation. Thirdly, and this remains true after sixty years, we make mistakes in prognostication and are often, in the name of realism and pragmatism, too nihilistic.

The Development of the CPAP Machine

Prior to the invention of the CPAP machine in 1981, patients with severe obstructive sleep apnoea received tracheostomies. The first CPAP machine was a modified paint compressor with the motor reversed! (Interview with Bron Lehrhaft- Resmedica Clinical Newsletter: Issue 14, 2011).

Many patients with neuromuscular diseases develop obstructive sleep apnoea and also may have hypoventilation during sleep. Modalities for monitoring such as continuous oximetry and transcutaneous CO_2, allow for diagnosis and treatment of sleep disordered breathing. However, not all physicians practicing long term ventilation regularly employ sleep studies in titrating ventilatory settings.

Who Should be the Home Ventilation Physician?

If we survey the past and contemporary landscape for physicians looking after people on prolonged mechanical ventilation (PMV), we find a variety of specialties, namely – anaesthesia/intensive care (Dr Geoffrey Spencer, Dr Lawrence Duncan); neurology (Dr Augusta Alba); Physical Medicine and Rehabilitation (Dr John Bach); Respiratory Medicine/Intensive Care (Dr Nicholas Hart, Dr Joshua Benditt); Respiratory Medicine/Sleep Medicine (Dr Mark Elliott, Dr Douglas McKim, Dr Anita Simonds, Dr Jesus Gonzalez). The above list is by no means exhaustive.

Dr Mark Elliott has written a review about the necessary attributes of a physician prescribing NIV, namely – an understanding of physiology, diagnostic skills, knowledge of sleep medicine, communication skills, leadership skills, and specific education about both acute and chronic ventilation (Non-invasive ventilation: Essential requirements and clinical skills for successful practice). To this list, I would add, facility with routine and advanced tracheostomy care, including speech and swallow with tracheostomy, and facility in decannulating suitable patients. Additionally, a good grasp of the technical aspects of prolonged mechanical ventilation - the nomenclature, circuits (circle system, active circuits, passive circuits), NIV interfaces (including mouthpiece ventilation), different modes, and how patients with different diseases and at different stages respond to various ventilatory interventions. Importantly, the chronic ventilation physician needs to be flexible and understand how ventilator users may "exploit" ventilation to help them speak louder, swallow better, even

walk farther, and hence that ventilation prescription strictly to blood gases or polysomnographs is sometimes inadequate or incompletely relevant. Finally, a good grasp of the natural history of neurological and respiratory diseases, which is arguably best appreciated longitudinally by home visits, as acute wards and outpatient clinics cannot allow a complete revelation of the real baseline state.

Why Some Intensivists Should Practice Prolonged Mechanical Ventilation

If we examine all these knowledge and skill requirements, we recognise that they are not currently comprehensively taught by any one specialty, implying that chronic ventilation physicians must necessarily learn on the job, via apprenticeship with an experienced colleague if possible.

Home mechanical ventilation is an extension and fulfillment of intensive care. The intensive care unit allows the patient to survive by augmenting or replacing dysfunctional physiology using technology. Home ventilation allows the ventilator dependent patient to live at home with autonomy to express individuality, whilst providing physiological support with mechanical ventilation, delivered intermittently or continuously, invasively or non-invasively.

Should intensivists perform home visits? In the 2012 recommendation by the Canadian Agency for Drugs and Technology in Health, it is suggested that respirologists and/or hospitalists make home visits, over and above care provided by general practitioners. A recent review (Kastrup 2017) noted that one of the drawbacks in the German system is that home ventilation adjustments are made by general practitioners who are not familiar with this technology, resulting in high emergency service personnel involvement, unnecessarily high rate of hospital admissions, and a revolving door phenomenon.

Some UK units (e.g. Northeast Assisted Ventilation Service, Newcastle; Lane Fox Unit, London) have a Clinical Nurse Specialist functioning as the main care coordinator, patient and family educator, and frontline clinical practitioner. This Clinical Nurse Specialist has to be familiar with intensive care technology, mechanical ventilation and sleep. Such a system additionally allows for scheduled and urgent visits by the consultant physician, which in their case include intensivists and pulmonologists. Such a system might arguably provide the most seamless care for patients, unnecessary acute care readmissions, since both the nurse and physician are competent and confident in the care of the complex home ventilator user - able to handle the primary disease, the respiratory insufficiency and other conditions arising.

The same Clinical Nurse Specialist-Intensivist team/couple are also invaluable, when ventilator users develop other problems that need acute hospital attention – orthopaedic injuries after a fall, acute retention of urine due to prostatic hypertrophy, per rectal bleeding due to colorectal malignancy, cerebrovascular accidents. Being a ventilator user does not magically exempt one from all these other problems. Many of these problems may need acute hospital admission, and some may need operative, endoscopic or angiographic treatment. Someone using a cuffless tracheostomy allowing leak speech may need to undergo surgery. Balancing challenges of breathing circuit leakage vs need for communication during the perioperative period would vex the unfamiliar clinician. The familiarity with acute care colleagues as well as the needs of the chronic ventilated patient makes the Clinical Nurse Specialist- Intensivist team ideally suited in coordinating or even delivering such care.

As intensivists, we are at great risk of negativity and burnout, as we only see patients in critical illness, with a significant proportion dying under our watch. When patients stabilise, they leave the unit, and unless we conduct post-ICU rounds or manage post-critical care clinics, we really do not know what happens to them. Home visits by intensivists allow patients to benefit from the breadth and depth of our medical training, while it allows us to see both the possibilities of independent living despite various disabilities, as well as the problems that sometimes originate from our practices or our oversight in the ICU.

"I think (and communicate), therefore I am"

Did you know that people with locked-in syndrome can have a sense of humour?

"I prefer "Thermometer"; her dedication would be beyond reproach if she did not regularly forget the implement she thrusts under my armpit." This is Jean-Dominique Bauby's description of his bedside nurse! A former editor of Elle, he had suffered a massive pontine stroke, and he wrote his memoir by blinking his eyelid whilst scanning letters read by his speech therapist (Jean-Dominique Bauby: "The Diving Bell and The Butterfly")

Do we know how to treat our critically ill patients with gentle and respectful attention?

We are rational creatures with intellect and will, what defines being human is the ability to choose, and to communicate. During critical illness, these are often lost amidst the fog of sedation or delirium. All too quickly, we reach for our trusted haloperidol or quetiapine, or restrain the patient who is restless.

Speech and communication of abstract thoughts are essential aspects of human living. When a patient is orally intubated, speech is impossible. However, not all intensivists are familiar with facilitating oral speech in the tracheostomised and ventilated patient, often settling for vague "lip-reading." Do we not often encounter an ICU patient having a tracheostomy cuff inflated unnecessarily? How many of us know that we can alter PEEP and Ti to improve speech quality, or have actually coached a patient to vocalise? This despite clinical reports demonstrating the safety and efficacy of leak speech or speaking valve use in tracheostomised patients since the early 1990s.

"The tone of voice left no doubt that henceforth I belonged on a vegetable stall and not to the human race. France was at peace; one couldn't shoot the bearers of bad news. Instead I would have to rely on myself if I wanted to prove that my IQ was still higher than a turnip's" (Jean-Dominique Bauby: "The Diving Bell and the Butterfly").

Are most intensivists familiar with both high-tech alternative and augmentative communication aids (AAC) such as eye gaze trackers? Do we know how to converse with locked-in patients using letter charts? Have we read that a fair number of patients with locked-in syndrome score their satisfaction with life at "acceptable" levels (Bruno 2011)? If not, our locked-in patients could be seen erroneously to be "as good as vegetables" to us, and we really have no moral authority to judge their quality of life and prognosis.

Patients And Families: Are We The Hosts or the Guests?

Many of our ICUs have moved towards open visitation hours. We recognise the importance of family members. However, for many of us, it is an uneasy truce. Deep down, we still yearn to be in full command. Therein lies the root of much of the angst and mistrust between patients, families and ourselves.

"In my view, we doctors are not our patients' partners; we are guests in our patients' lives" (Berwick 2009). Home ventilation demands that we truly honour this dimension of our profession. We do indeed learn, through home visits, that we are guests in our patients' journey, privileged to participate and share, to help, and to grieve together.

Helping a Patient Transition From ICU

Helping a ventilator user to go home is a test of clinical acumen and teamwork. It is not something a care coordinator or junior doctor should undertake alone. The ventilator regimen, nutritional plan, medication prescription etc. should be tailored to realities at home and should be manageable by family members or caregivers. Staff in the acute hospital need to teach patient, family members and caregivers on care-tasks. The use of audiovisual material, mannequins, electronic learning material are all necessary and helpful; but empowering patient, family members and caregivers by teaching a clinical reasoning- based approach may be more advisable than adhering to rigid checklists. Such instruction is best done by staff experienced with both poles of the patient's care spectrum – both ICU and home.

Organ Support, Life Extension and Rehabilitation, Dying

Medicine is often portrayed as an epic struggle against our mortality. When the kidneys failed, we invented dialysis. When breathing was insufficient, the ventilator. We learnt to pace the heart, to assist the ventricles. Exoskeletons and eye gaze trackers are now realities. Expert centres worldwide are racing to develop brain-computer interfaces.

Life extension is not the be-all and end-all. Each day alive is an opportunity - to see a sunrise; to smell or touch a rose; to say "I love you" to someone; to snuggle with a dog; to read the classics; watch the latest movie or soccer match; to write a memoir; to discover the next astrophysics theorem.

When, finally, the organs cannot be supported, when suffering cannot be relieved without robbing the patient of his faculties and control, the ventilator user needs to be allowed to "go gently into the night;" the loved ones need to be supported. This is palliative medicine. This is humanity. This final step in the journey is best accompanied by the faithful and familiar intensive care cum home ventilation team.

Acknowledgements

Deepest gratitude to Dr Anita Simonds and the team at the Royal Brompton Hospital; Dr Thomas Similowski and Dr Jesus Gonzalez and the team at L'Hopital Pitie-Salpetriere; Dr Robert Bullock and Sister Alison Armstrong and the team at North-East Assisted Ventilation Unit; Dr John Bach; Dr Miguel Goncalves; Dr Joshua Benditt; Dr Douglas McKim; Dr Nicholas Hart and the team at the Lane Fox Unit; Dr Kampelmacher and the team at Home Ventilation Centre, Utrecht; Dr Santino Marchese; Dr David Orlikowski and Dr Helene Prigent and the team at L'Hopital Raymond-Poincare, Dr Michel Toussaint, Dr Michael Laub and the team at Home Ventilation Centre East, Copenhagen; Dr W. Windisch and the team at Home Ventilation Centre, Cologne; Dr Tiina Andersen; Dr Roger Goldstein and the team at WestPark, Toronto; and all others who have contributed to the establishment and growth of the Tan Tock Seng Hospital Home Ventilation and Respiratory Support Service.

Conflict of Interest

None. ■

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Post-Intensive Care Syndrome

Patients and families need to know they are not alone

In this article, we aim to summarise the current management of Post Intensive Care Syndrome (PICS) and Post-Intensive Care Syndrome – Family (PICS-F), understanding the need for continuum assessment and support throughout critical disease.

Illustrating PICS

People who have been admitted to an Intensive Care Unit report a reduced quality of life for up to twelve years following critical illness compared to the general population (Flaatten and Kvåle 2001). This may not be surprising for most of the readers of this journal. First and foremost, during the first year following critical illness, patients state this lower quality of life, particularly within the physical domain (experiencing impairments in body function, basic and instrumental activities of daily living and participation) (Ohtake et al. 2018). These referred symptoms are part of a broader set, which together make up the post-intensive care syndrome (PICS), named after two expert meetings that took place in 2010 and 2012, including the Society of Critical Care Medicine and international specialists from non-critical care organisations. PICS was then defined as "as new or worsening impairment in physical, cognitive, or mental health status arising and persisting after hospitalisation for critical illness" (Needham et al. 2012; Harvey and Davidson 2016).

PICS is described in 30-50% of patients after ICU admission; differences are due to patient population included in the studies, patient comorbidities, measurement tools, and time frames. At the time of hospital discharge, between 46% and 80% of survivors experience cognitive impairment; 3 and 12 months after discharge, 40% and 34%, respectively. At 12 months, clinically significant symptoms of anxiety, depression, and post-traumatic stress are present in 20% to 30% of survivors. Patients also refer other health problems: sleep disturbances (55%), ongoing pain (52%), airway irritation (45%), gastrointestinal rhythm disturbances (40%), dyspnoea (23%), dysphagia (19%), and nightmares about their time in ICU (14%) (Rai et al. 2019). Moreover, Marra et al. (2018) demonstrated in a multicentre cohort study that one or more post-intensive care syndrome problems were present in the majority of survivors. Still, concurring difficulties were coeval in only one out of four, being able to describe the possible existence of PICS subtypes, yet to be clearly defined.

Conversely, PICS can occur in both surviving and deceased patients' families (named PICS-Family or PICS-F). The long-term consequences on families are psychological, physical, and social. Approximately 10-75% of families suffer from anxiety; around 35% of families have depression and 8-42% symptoms accordant to post-traumatic stress disorder, which can persist for years (Schmidt and Azoulay 2012) **(Figure 1).**

Managing PICS effectively requires a clearer understanding of the associated risk factors. Lee et al. (2019) performed a systematic review of the risk factors for PICS and determined their effect size. Sixty risk factors were identified: those ICU related (uncontrolled pain or inappropriate sedation, presence and duration of delirium, immobility, steroids, prolonged mechanical ventilation, prolonged length of stay…) and those associated intrinsically to the patient (such as personal traits, own previous experiences, pre-existing anxiety, sepsis or ARDS on admission …). Significant risk factors for PICS included older age (OR 2.19), female sex (OR 3.37 for mental health), previous mental health problems (OR 9.45), disease severity (OR 2.54), negative ICU experience (OR 2.59), and delirium (OR 2.85). On the other side, major risk factors for PICS-F are poor communication between staff, lower educational level, and having a loved one who died or was close to death.

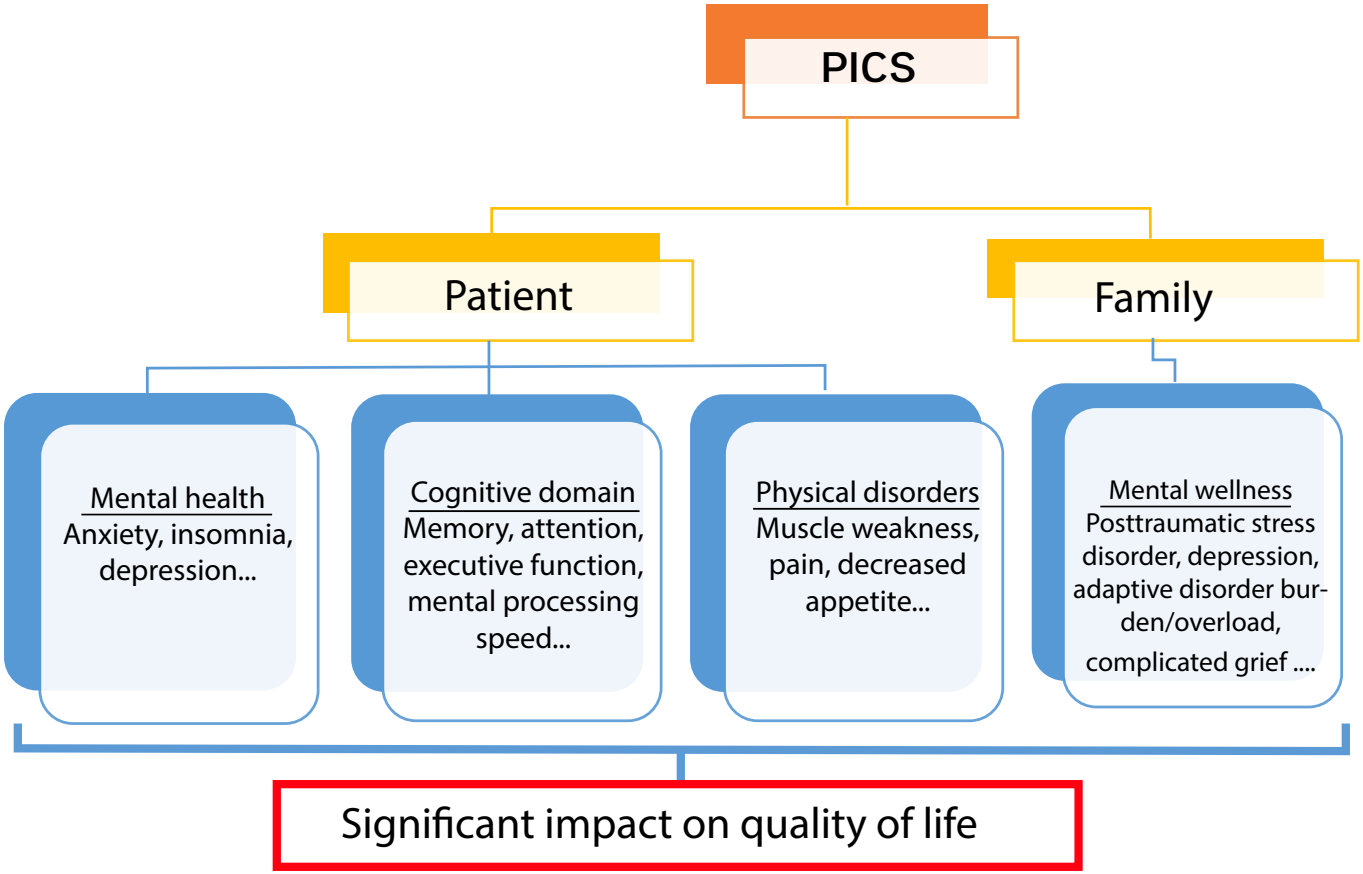

Figure 1. PICS environment

Decreasing PICS Incidence: Is it Possible?

Prevention strategies

To avoid the development of PICS, we must, as health professionals dedicated to the care of the critical patient, focus first on prevention measures:

- Following the updated Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit (ICU PAD guidelines; Devil et al. 2018), adapted into the world-wide known ABCDEF bundle (Marra et al. 2017; Lee et al. 2020) **(Figure 2).**
- Early mobility programmes by integrating physical therapists and occupational therapists into the ICU setting (Fuke et al. 2018).
- Early psychological interventions by integrating psychologists in the critical care team, offering both patients and families, support, counselling, and education on stress management (Peris et al. 2011; Czerwonka et al. 2015).
- Use of ICU diaries: an illness narrative for patients written by nurses and patient's relatives, allowing patients to reconstruct the story of their critical illness, helping them understand the seriousness of the process, and filling in gaps of memory. Its maintenance has inconsistently shown (depending on the methodological differences between trials) decrease in symptoms of PTSD and could be used as a tool to provide support and care to the patient and family (Garrouste-Orgeas et al. 2019; Kredentser et al. 2018; Garrouste-Orgeas et al. 2014; Jones et al. 2010).
- Keeping favourable nutritional status and sleep quality.
- Modifying the ICU environment, using patient care space as a treatment tool (Luetz et al. 2019).

Management strategies

However, once the patient presents symptoms consistent with PICS, we must first make an early diagnosis, and then try to manage the symptoms with the tools we currently have available. One significant barrier in the assessment of PICS is the lack of a single, validated clinical tool to assess impairments in all three domains of PICS rapidly. Wang et al. (2019) managed to validate the Healthy Aging Brain Care Monitor Self Report version (HABC-M SR) psychological and functional subscales as reliable tools to measure the severity of symptoms of PICS. Besides, Jeong and Kang (2019) aimed to develop a PICS questionnaire consisting of 18 items covering all three domains, demonstrating excellent reliability (Cronbach's alpha of 0.93). Future studies in search for a quick clinical tool to rapidly assess PICS are still needed.

Regarding management of PICS, developed different strategies are:

- **Post-ICU rehabilitation programmes,** including patient-directed exercises, in-home therapist sessions and telehealth delivery of therapy, bundled with cognitive rehabilitation (Denehy and Elliott 2012; Jackson et al. 2012).

- **Post-discharge follow-up programmes** (Busico et al. 2019; Van Der Schaaf et al. 2015; Mehlhorn et al. 2014). A possible example can be seen in **Figure 3** and outlined below:

Management of acute illness within the ICU

Following ABCDEF bundle and patient's ICU discharge plan made on advance through the Continuity-of-Care Nursing team (search of patient's needs, assure a satisfactory hand-off with hospital ward team and discuss next steps with the patient and family).

Hospital recovery

- Follow-up programme by the ICU outreach team (span time and objectives agreed in advance).

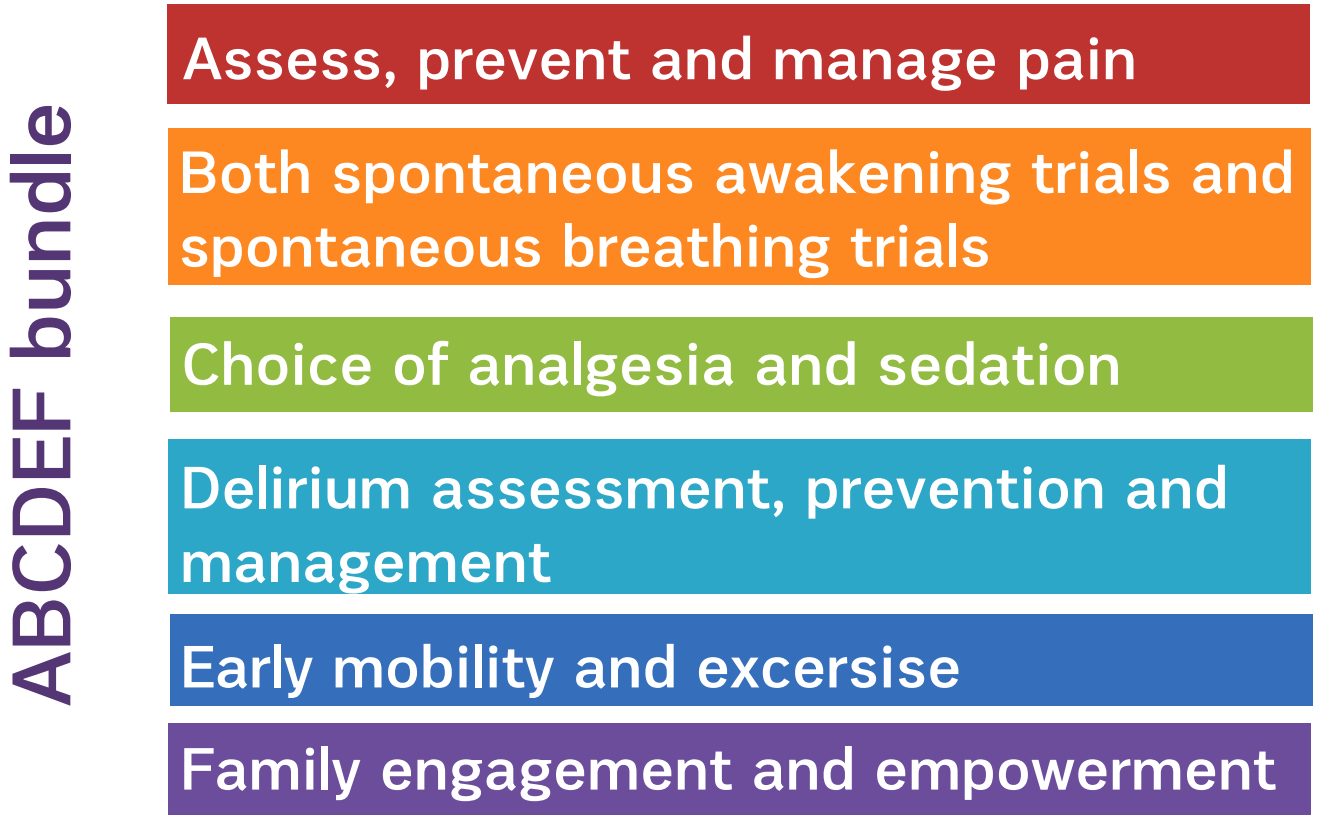

Figure 2. ABCDEF bundle (Source: Marra et al. 2017)

- Nurse-led follow-up in the hospital ward (coordination with healthcare professionals and resource planning). Ward-discharge plan with the corresponding level of health care, guaranteeing the continuity of care.
- Optimal rehabilitation therapy: exercise, physical therapy, occupational therapy, speech-language pathology, or cognitive rehabilitation.
- Need of other subspecialties: Cardiology, Pneumology, Psychiatry, Otolaryngology
- Support programme for families/caregivers, aimed at reducing stress and anxiety, supporting fluid communication about the patient's condition and prognosis. Priority to the patient's values and wishes in the shared decision-making process.
- Social work: assess the need for social support upon discharge (institutionalisation, Day Centre, home help...) and will inform and facilitate the necessary procedures to obtain economic and social support if needed.

Post-discharge recovery

- Targets: return the patient to baseline by promoting continuous care, sharing knowledge, professional experience, and availability of resources among professionals at all levels of care.
- Comprehensive assessment of the patient at the Primary Care Provider or PICS "clinic": screening deficits in following areas: motor and sensory functions, communication problems, swallowing problems, post-traumatic stress symptoms, symptoms of anxiety and depression, cognitive functions, psychosocial and sexual adaptation.
- Assessment to be carried out at intervals defined by each of care programme (at discharge, at one month, at three months, at six months, at 12 months...).
- The programme must also include a plan for unforeseen health changes and what advice should be given to patients and caregivers in these cases.

Although it is widely accepted that follow-up activity at discharge is an effective intervention, research on such programmes has been disappointing. High quality randomised controlled trials with well-intentioned interventions designed and delivered by ICU teams after ICU discharge have not produced the desired results, and clinical evidence published to date is neither homogenous nor standardised (Schofield-Robinson et al. 2018; Walsh et al. 2015; Cuthbertson et al. 2009). There are several reasons why these interventions may have been ineffective. Among them: the complexity of the pathophysiology, the inability to identify and target high-risk groups, the impossibility of individualising therapy, and, in some cases, the lack of input from other expert providers such as physical therapists, neurologists, psychiatrists, geriatricians, and rehabilitation physicians. According to the data provided, it is unlikely that follow-up interventions will be useful in the future if we do not achieve greater collaboration between the different parts of the health system.

- **ICU survivor peer support groups** provide an adequate space for survivors to share experiences, feelings, empathy, advice… with others, collaborating and helping each other through problems. They allow mental reframing, effective role-modelling, information sharing, and practical advice that is not readily available to healthcare professionals. These have also proved favourable in other situations (mental health disorders, substance abuse issues, or cancer survivors) and can lead to empowerment, self-advocacy, and improved overall outcomes (Mikkelsen et al. 2016; Haines et al. 2019).

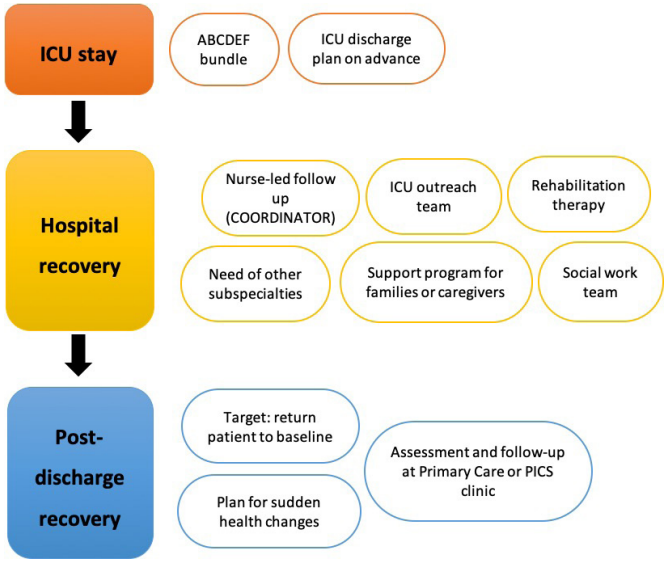

Figure 3. Post-discharge follow-up programme example

What about PICS-F?

Most critical patients cannot express their wishes, ask questions, or assert their rights. In these settings, family members (or primary caregivers) take the lead: they start making decisions, sometimes decisive ones, continually trying to think about what the patient would have wanted at any given time. It is clear that, in this situation of uncertainty and fear, there is a risk of psychological distress. Therefore, symptoms such as anxiety, depression, or acute stress disorder may appear. Withal, it is only the beginning, since once the patient is discharged, he/she requires caregiving until recovery and return to baseline. Who would not burden in this situation? (Davidson et al. 2012; Torres et al. 2017; Petrinec and Martin 2018).

Moreover, caregiver problems may start early during ICU admission. They may require the greatest support at that time, even though issues such as posttraumatic stress disorder may not appear until a few months after discharge.

Possible interventions to decrease the psychological burden and improve family members' experience could be (Schmidt and Azoulay 2012; Haines et al. 2018):

- Communication strategies: literature regarding family involvement in medical decision-making is growing, and extent data suggest that different methods of communication and inclusion in decision-making may play a vital role in outcomes.
- Access to information (brochures, adapted explanatory documents for laypersons…).
- Family participation in care: open visiting hours, regular meetings with nurses, and ICU staff…
- Psychological screening and support: need of psychologists during difficult times, developing coping strategies [problem-focused coping, emotion-focused coping, building resilience (Sottile et al. 2016)].
- Follow-up programmes for families: family debriefing visits, "family clinics," increasing awareness of possible long-term consequences of intensive care among ICU survivors.
- Engaging intensive care survivors and caregivers to co-design recovery programmes.
- Peer support and development of social support networks.

As previously said with PICS, PICS-F is also a complex problem, and will probably require global, proactive, and multimodal interventions.

Conclusion

PICS is a growing public health issue. We must empower healthcare professionals from a range of different disciplines who give care to ICU survivors with information, education, and resources.

In the following months, considering the COVID-19 pandemic, the teams dedicated to this issue will face the conundrum of the increase in PICS/PICS-F cases. Patients who suffered the viral infection in its most severe form will present significant deterioration.

Improving the psychological outcomes of critically-ill patients and their families is challenging, as it depends on previous mental health, social and economic background, and cultural and geographic factors. Future research requires a precise framework to risk-stratify patients and family members, a consensus regarding what are the best tools to measure outcomes, and standardised follow-up approaches. We must emphasise the prevention of cognitive, physical, and psychological sequelae. We must meet the current gap in health services. Patients and their families need to know they are not alone.

Conflict of Interest

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

Abbreviations

PICS – post-intensive care syndrome
PICS-F - post-intensive care syndrome family
ICU – intensive care unit
OR – odds ratio
PAD – Pain, Agitation and Delirium
PTSD – posttraumatic stress disorder

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The Post-ICU Patient

Management of long-term impairments after critical illness

Survivors of critical illness and their caregivers frequently face long-term impairments of cognition, mental health, mobility and beyond, which demand for a patient-centred transition management and well-coordinated, outpatient post-ICU care.

Introduction

In recent years, the post-ICU sequelae of survivors of critical illness have become a focus of attention in research and patient care. This is the result of progress made in critical care throughout the last decades, which led to vast increases in survival rates and, therefore, growth of the cohort of post-ICU patients (Iwashyna et al. 2012; Zimmerman et al. 2013). Early investigations outlined that post-ICU patients are burdened with multifaceted consequences of critical illness summarised under the term post-intensive care syndrome (PICS). Notably, patients often perceive such functional impairments that potentially result from treatment as extremely relevant (Fried et al. 2002; Needham et al. 2012). The aim of this narrative review is to provide an overview over the established and further extended PICS domains and outpatient management of post-ICU patients.

Cognition

Studies in different patient populations and settings have established the association of critical illness and long-term cognitive impairments (**Figure 1**) (Adhikari et al. 2009; Hopkins et al. 2005; Iwashyna et al. 2010; Jackson et al. 2011; Jackson et al. 2003; Marra et al. 2018; Mitchell et al. 2018; Pandharipande et al. 2013; Wolters et al. 2013). Across studies, cognitive impairments were found in 4% to 62% of patients with follow-up periods from 2 to 156 months (Wolters et al. 2013). However, there has been no consensus on categorisation of cognitive impairments and tools of assessment, which partially explains the variations.

Upon ICU discharge, the frequency of cognitive impairments is high, and after an initial improvement (Hopkins et al. 2005), impairments persist for years. They pertain to almost all domains of cognition, including memory, verbal fluency, attention and executive function (Wolters et al. 2013). Additionally, ICU survivors face a 60% increase in relative risk to suffer from dementia three years after discharge (Guerra et al. 2015). Presence and duration of delirium is a risk factor for long-term cognitive impairment (Girard et al. 2010; Goldberg et al. 2020), but the underlying pathophysiology is widely unknown. Few studies have considered pre-ICU cognitive functions. Two population-based, prospective cohort studies found a decline in cognitive functions in ICU survivors when compared to their pre-ICU status (Ehlenbach et al. 2010; Iwashyna et al. 2010), and in a cross-sectional study, 37% of ICU patients showed pre-existing cognitive impairments (Pisani et al. 2003).

Considering the connection between delirium and cognitive impairment (Goldberg et al. 2020), preventing delirium seems rational. Regular screening for delirium (Luetz et al. 2014), implementation of bundles such as the ABCDEF bundle (Barnes-Daly et al. 2017; Marra et al. 2017), the preference for non-benzodiazepine sedatives if sedation is necessary (Pandharipande et al. 2007; Pandharipande et al. 2010), and modifications of the patient environment can reduce delirium (Litton et al. 2016; Luetz et al. 2019). Unlike a no-sedation strategy (Olsen et al. 2020; Strøm et al. 2010), no or light sedation has been shown to prevent delirium (Hager et al. 2013; Pandharipande et al. 2007). This is also the subject of current guidelines (Barr et al. 2013; Taskforce DAS et al. 2015).

As a brief screening for cognitive impairments, Spies et al. (2020) proposed to use the MiniCog (Borson et al. 2003) and Animal Naming test (Sager et al. 2006). If the patient is above threshold, the Trail Making test (Reitan 1958) and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph 2012) provide in-depth assessment. Data on treatment of already manifest cognitive impairment is limited. Two pilot studies showed promising results of cognitive rehabilitation (Jackson et al. 2012; Wilson et al. 2018), while another study using a combined cognitive-physical rehabilitation did not detect an effect on executive functions (Brummel et al. 2012). In the future, larger trials need to investigate the potential of cognitive rehabilitation and have to consider pre-existing cognitive impairments. Studies also need to investigate if delirium prevention improves cognitive outcomes – an association still to be established.

Mental Health

Mental health impairments after critical illness pertain to depression, anxiety, and post-traumatic stress disorder (PTSD) (Marra et al.

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2018). Symptoms of depression are present in about 30% of post-ICU patients, persisting even five years after discharge (Bienvenu et al. 2018; Davydow et al. 2009; Rabiee et al. 2016), but studies did not consistently use the same assessment tools, definitions and time frames (Rabiee et al. 2016). With regards to anxiety, 32% to 40% of patients show symptoms within the first year after discharge (Nikayin et al. 2016). Just like depression, anxiety symptoms remain relatively stable (Bienvenu et al. 2018; Hopkins et al. 2005). For PTSD, prevalence varied from 4% to 62% across studies, with a pooled prevalence of 17% to 44% in the year after ICU discharge (Parker et al. 2015). After eight years, PTSD prevalence was still 24% (Kapfhammer et al. 2004). Notably, a large number of patients show overlapping symptoms (Huang et al. 2016; Marra et al. 2018). For instance, Wolters et al. (2016) found that 63% percent with any mental health symptoms showed symptoms of anxiety, depression and PTSD. Analogous to cognitive impairments, very few studies assessed pre-existing psychiatric symptoms, but results indicate that prevalence is high (Davydow et al. 2009; Rabiee et al. 2016). For instance, 6.2% of mechanically ventilated ICU patients had a psychiatric diagnosis and about 50% received a prescription for psychoactive medication in the five years preceding their ICU stay, significantly more than in the general population. ICU treatment increased the risk for a psychiatric diagnosis and psychoactive medication prescription, with hypnotics and antidepressants being most commonly prescribed (Wunsch et al. 2014).

Risk factors associated with mental health impairments are nightmares and extreme fear in the ICU (Parker et al. 2015; Rattray et al. 2005; Samuelson et al. 2007), lack of recollection of ICU experience (Rattray et al. 2005), and delusional memories from the ICU (Jones et al. 2001; Nikayin et al. 2016). Further, pre-ICU psychiatric morbidity (Wade et al. 2012; Weinert and Meller 2006), stress during ICU treatment (Wade et al. 2012), and psychiatric symptoms at hospital discharge were associated with post-ICU depression, anxiety and PTSD (Davydow et al. 2009; Nikayin et al. 2016; Rabiee et al. 2016; Rattray et al. 2005). Interestingly, neither age, severity of illness, or sex were identified as risk factors. Likewise, delirium, was not associated with PTSD or depression in the ICU context (Girard et al. 2007; Jackson et al. 2014; Wolters et al. 2016), even though post-operative delirium was found to be a risk factor for PTSD (Drews et al. 2015). It has been shown that mental health problems significantly diminished health-related quality of life (Davydow et al. 2009; Parker et al. 2015).

As a screening tool for mental health impairments, the Patient Health Questionnaire-4 was proposed, followed by the more detailed Patient Health Questionnaire-8 for depression, Generalised Anxiety Disorder Scale-7 for anxiety (Kroenke et al. 2010), and Impact of Event Scale-revised for PTSD (Spies et al. 2020; Weiss 2007). For treatment, ICU diaries reduced PTSD symptoms in one large randomised controlled trial and one prospective, non-randomised study (Garrouste-Orgeas et al. 2012; Jones et al. 2010), and anxiety and depression symptoms in another small randomised controlled trial (Knowles and Tarrier 2009), whereas a recent, large randomised controlled trial published in JAMA did not detect an effect of ICU diaries on PTSD, anxiety or depression (Garrouste-Orgeas et al. 2019). Provision of a self-help manual reduced PTSD symptoms but not depression or anxiety symptoms (Jones et al. 2003), and the benefit of post-ICU follow-ups remains inconclusive (Cuthbertson et al. 2009; Schandl et al. 2012). Interestingly, physical rehabilitation has been shown to reduce anxiety and depression (Jones et al. 2015; McWilliams et al. 2009), whereas a recent review concluded that early physical therapy does not reduce anxiety or depression (Fuke et al. 2018). Clearly, there is a demand for randomised controlled trials that rigorously compare different approaches such as self-help manuals and post-ICU follow-ups to provide evidence on strategies to reduce mental health impairments after critical illness.

Mobility and Physical Impairments

Physical impairments manifest early during the ICU stay as intensive care unit-acquired weakness (ICUAW), which is a muscular weakness defined by a Medical Research Council (MRC) score < 48 that occurs during critical illness in absence of any other plausible aetiology (Fan et al. 2014a). It has consistently been shown that muscle weakness during the ICU has a direct impact on the treatment success, like liberation from mechanical ventilation and discharge from the ICU as well as hospital (Hermans et al. 2014). Furthermore, muscle weakness at discharge from the ICU is a predictor for long-term mortality, physical function and health-related quality of life up until five years after discharge (Hermans et al. 2014; Van Aerde et al. 2020). Interestingly, Van Aerde et al. (2020) observed a dose-response relationship between muscle strength at ICU discharge and 5-year mortality. Furthermore, the optimal cut-off for predicting 5-year mortality and morbidity is a MRC score ≤ 55, which is above the diagnostic cut-off of 48 for ICUAW.

For screening of physical impairments, Spies et al. (2020) recommended to use handgrip strength (Roberts et al. 2011) and the Timed Up-and-Go (Podsiadlo and Richardson 1991), followed by the more elaborate Short Physical Performance Battery (Pavasini et al. 2016) and 2-Minute Walk Test (Brooks et al. 2006). Long-term follow up studies have shown that muscle strength measured with the MRC score fully recovers one year after ICU discharge, while muscle endurance measured via 6-minute walk test remains at 75% of predicted values (Fan et al. 2014b; Herridge et al. 2011; Wollersheim et al. 2019). This suggests that the physical impairments extend beyond muscle strength and that muscle endurance or regenerability might be a more relevant parameter during long-term evaluation. The term introduced by Van Aerde et al. (2020) "ICU-acquired neuromuscular complications" might therefore be more appropriate than the commonly used ICUAW, as weakness appears to be only one aspect of the spectrum of physical impairments. Just like cognitive and mental impairments, there is little evidence on pre-existing physical impairments, even though worse functional physical status right

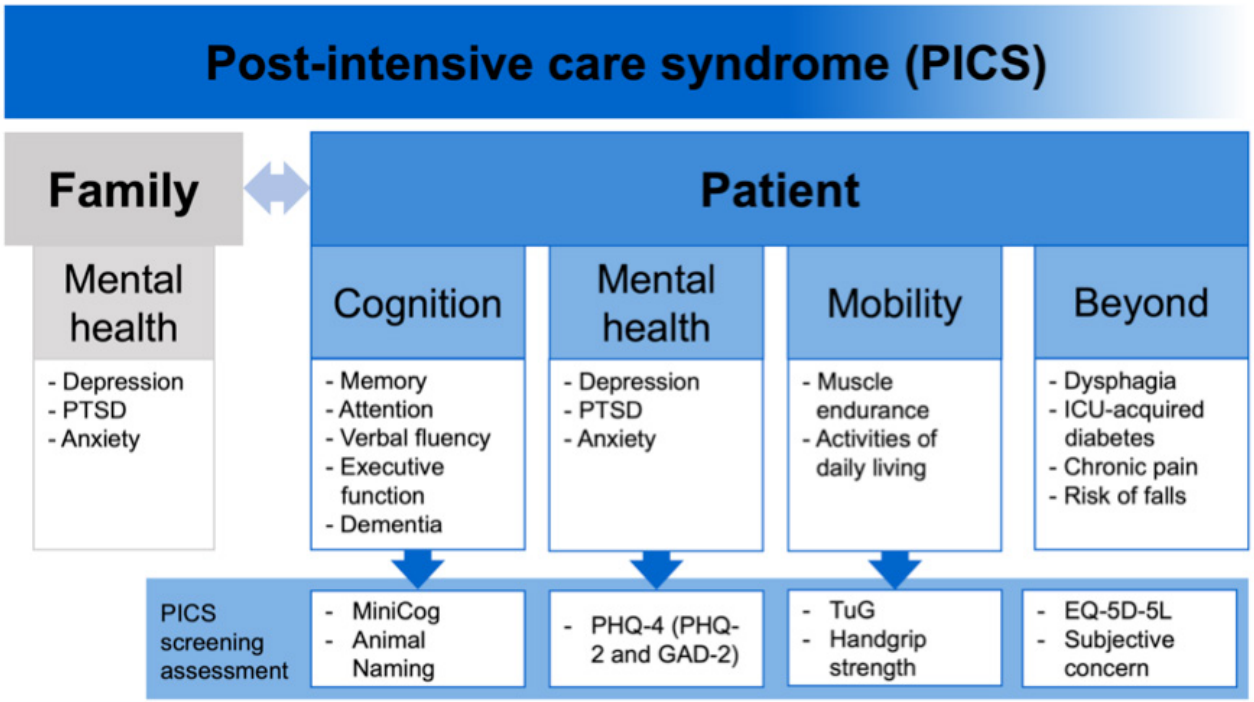

Figure 1. Domains of long-term impairments in post-ICU patients and caregivers (modified and extended from Needham et al. (2012)) and instruments used for ambulatory PICS screening after ICU treatment as proposed by Spies et al. (2020). EQ-5D-5L and items for the patients' subjective concern about functional impairments are used to assess health-related quality of life.

Abbreviations: PICS=Post-intensive care syndrome; PTSD=Post-traumatic stress disorder; ICU=Intensive care unit; PHQ=Patient health questionnaire; GAD=Generalised anxiety disorder scale; TuG=Timed up-and-go; EQ-5D-5L= European quality of life 5 dimensions 5 level.

before hospital admission was associated with increased ICU mortality (Zampieri et al. 2017).

Current recommended management encompasses the early, goal-directed therapy of the critical illness itself in conjunction with early (within 72 hours after ICU admission) protocol-based mobilisation to improve physical function, reduce duration of a possible delirium, counteract muscle atrophy and shorten time on mechanical ventilation and in the ICU (Bein et al. 2015; Ding et al. 2019; Schaller et al. 2016; Schweickert et al. 2009; Wollersheim et al. 2019).

Other Functional Impairments

PICS was initially defined around physical function, cognition and mental health. Yet, additional post-ICU sequelae have been discovered outside the classical PICS domains. Dysphagia, for instance, is commonly observed after endotracheal intubation and has an incidence of up to 62% depending on the study cohort and length of intubation (Skoretz et al. 2010). It is an independent risk factor for 28- and 90-day mortality (Schefold et al. 2017), but Brodsky et al. (2017) were able to show that 100% of ARDS survivors discharged with dysphagia had recovered until five years after discharge.

Critical illness-associated hyperglycaemia is common and affects mortality (Plummer et al. 2014). The hyperglycaemia during acute treatment has been thoroughly investigated, while progression to a permanent dysregulation of the glucose homeostasis was neglected (NICE-SUGAR Study Investigators et al. 2009; Van den Berghe et al. 2006; Van den Berghe et al. 2001). A recent meta-analysis has shown that critical illness-associated hyperglycaemia increases the risk of developing diabetes with an odds ratio of 3.5 (Ali Abdelhamid et al. 2016). Systematic screening for ICU-acquired diabetes after discharge for early diagnosis and prevention of long-term consequences might therefore be warranted (Preiser and de Longueville 2017).

ICU patients regularly receive analgesic therapy as pain frequently occurs in critically ill patients. Interestingly, pain is also among the top three symptoms reported four months after ICU discharge, which has led to systematic investigations showing that chronic, ICU-related pain has a major impact on patients' daily life (Baumbach et al. 2016; Choi et al. 2014).

Another organ system that has received increased attention is the skeletal system, which is affected immensely by immobilisation during and after the ICU stay (Leblanc et al. 1990). ICU survivors experience an increased bone resorption, leading to decreased bone mineral density (Orford et al. 2016). The combination with frequently observed falls in post-ICU patients cumulates to an increased risk for fractures and imposes a major detriment on recovery (Parry et al. 2020).

Family and Caregivers

The family's role for the ICU patient is twofold, whereby family is used as a surrogate for all people the patient wishes to be included in his or her care (Brown et al. 2015). Firstly, the family is a treatment resource in a concept termed "patient-family-engagement" (PFE), which was defined by Braun et al. (2015) as "[...] an active partnership between health professionals and patients and families working at every level of the healthcare system to improve health and the quality, safety, and delivery of healthcare." Secondly, the family bears a huge burden during the ICU treatment, which can manifest in anxiety as well as depression and can lead to subsequent symptoms of PTSD (Azoulay et al. 2005; Pochard et al. 2001). Additionally, in the post-ICU care, family members regularly work as unpaid caregivers, which can cause depres-

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sive symptoms (Cameron et al. 2016). Notably, symptoms in family members are positively correlated to the degree of impairments in the post-ICU patient himself (Choi et al. 2014).

Family support interventions can reduce the ICU length of stay, most likely by facilitating the shared-decision-making process of futile interventions since no impact on mortality could be detected (Lee et al. 2019; White et al. 2018). Even though families were more satisfied with the communication with the ICU team, no benefit for their mental health was detected (Carson et al. 2016; Shelton et al. 2010; White et al. 2018). Nevertheless, the implementation of structured family support is weakly recommended in current guidelines (Davidson et al. 2017). An additional measure to include the family in the ICU treatment is a flexible or extended visitation policy, since evidence indicates towards reduced anxiety and depression in family members as well as reduced anxiety and delirium in patients (Nassar Junior et al. 2018; Rosa et al. 2019; Rosa et al. 2017). On the contrary, extended visiting hours might increase the risk of ICU staff burnout (Nassar Junior et al. 2018).

Post-ICU Care Trajectories and PICS Management

With a growing cohort of ICU survivors (Kaukonen et al. 2014; Pronovost et al. 2004), more patients require transition management from inpatient to outpatient care. Post-ICU rehabilitation should be organised to mitigate functional disabilities, enable social participation and foster return to work. These demands are hardly met, as shown in a study of 103 mechanically ventilated ICU patients followed for one year post discharge and characterisation of their care pathways and quality of life (Unroe et al. 2010). Patients experienced multiple transitions of care locations, and 67% were re-hospitalised at least once. Simultaneously, each patient accrued more than $300,000 of health care costs (Unroe et al. 2010), with re-hospitalisations being an expensive element of post-ICU care (Kress and Herridge 2012). Only 9% were independently functioning and 27% were considered having a good quality of life (Unroe et al. 2010). Several studies showed approximately 50% of previously employed survivors of critical illness were unemployed one year after discharge (Hopkins et al. 2005; Myhren et al. 2010; Norman et al. 2016), leading to a 60% loss of income (Kamdar et al. 2017). The economic consequences for the society have not been thoroughly quantified yet but are likely to be substantial. Devoid of structured post-ICU follow-up, ICU discharge has been described as "ejection" instead of smooth "transition" (Sevin and Jackson 2019).

In light of complex impairments and fragmented patient trajectories, attention should be given to coordinated and evidence-based transitions from inpatient to outpatient care. Description of ideal patient pathways and implementation of intersectoral quality indicators, as defined for mechanically-ventilated patients in Germany (Kastrup et al. 2017), can help streamline the process. In more detail, these quality indicators comprise the handover to the outpatient care physician, individualised needs assessments, and transfer conferences with stakeholders from inpatient and outpatient care (i.e. transfer manager, physician, and respiratory therapist).

After transitioning to an outpatient setting, post-ICU clinics can serve as a hub to guide patients and ensure that their health concerns are addressed (**Figure 2**). These clinics should be staffed with intensivists, regularly assess patients for long-term impairments (Spies et al. 2020), and work in close communication with the patients' general practitioners to exchange information. Drawing on a network of specialists such as psychotherapists and physical therapists, post-ICU clinics can develop care plans tailored to the patients' individual needs to pave the tedious road to recovery. With continuity in post-ICU care, costly hospital re-admissions might be avoidable, PICS symptoms alleviated and return to work more likely. A similar concept was implemented at Vanderbilt ICU Recovery Center, but evaluation of effectiveness is still pending (Sevin et al. 2018). Another post-ICU programme in the UK, which included functional assessments and referrals, did not show an effect on quality of life or mental health outcomes after twelve months (Cuthbertson et al. 2009). Yet, post-ICU care was led by nurses, even though, as noted by Sevin and Jackson (2019), intensivists might be more sensitive to ICU-specific problems such as ICUAW. A Cochrane review on post-ICU follow-up services concluded that there are large variations in the design of interventions and insufficient evidence to draw conclusions at this point (Schofield-Robinson et al. 2018). Taken together, large-scale randomised-controlled trials need to rigorously assess the potential of intensivist-led, outpatient post-ICU clinics to guide patient care after critical illness.

Conclusions

Over the last two decades, functional outcomes of critical illness have gained a centre stage of intensive care research, due to the growing cohort of ICU survivors and, thus, more patients with impairments. Clinical research does not merely focus on survival, but also how the patient manages to recover in the subsequent months and years. Despite a broad consensus that a fragmented care process imposes risks on patients, evidence on effective interventions to counter impairments is scarce, and post-ICU care trajectories are an area of future improvement. In collaboration with patients' general practitioners, post-ICU clinics might function as integrative hubs, which are embedded in a broad referral network of specialists. These institutions can harmonise inpatient-to-outpatient transitions and streamline post-ICU care processes to ensure optimal patient recovery.

Conflict of Interest

All authors declare no conflicts of interest for the submitted work. For grants, personal fees, non-financial support and patents outside the submitted work, International Committee of Medical Journal Editors (ICMJE) disclosure forms are available upon request. ■

Abbreviations

ICU - Intensive care unit
PICS - Post-intensive care syndrome
RBANS - Repeatable Battery for the Assessment of Neuropsychological Status
PTSD - Post-traumatic stress disorder
ICUAW - Intensive care unit-acquired weakness
MRC - Medical Research Council
PFE - Patient-family-engagement

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ICUnutrition

Nutrition in the Post ICU Period: Where is the Evidence?

This article summarises the current nutrition evidence in the phase of recovery that occurs following critical illness.

Introduction

It is plausible that the importance of nutrition may differ across different phases of illness. Reflecting this, the most recently updated clinical nutrition practice guidelines for critical care from the European Society for Clinical Nutrition and Metabolism (ESPEN) recommend tailoring nutrition provision according to illness phase. The phases are defined as: 1) acute phase, early period (days 1-2); 2) acute phase, late period (days 3-7) and; 3) late/chronic phase (after day 7) (Singer et al. 2019). There are limited recommendations for the nutritional management of patients in the chronic phase of critical illness, and beyond Intensive Care Unit (ICU) admission.

The acute phase of critical illness is characterised by an altered metabolic response, including mobilisation of endogenous glucose stores, hyperglycaemia, hypertriglyceridaemia and protein catabolism, leading to changes in metabolic rate, body composition, reduced muscle mass and function (Merriweather 2020; Massanet et al. 2015; Preiser et al. 2015). Nutrition focussed research in this period has failed to show benefit (and one large study indicated harm), possibly due to the length of intervention, lasting approximately 7 days (Target Investigators 2018; Casaer et al. 2011).

In the chronic phase of critical illness, occurring after day 7 in ICU or out on the ward following ICU discharge, critically ill patients may be more physiologically able to process nutrients, possibly making this a key time for nutrition to support recovery (Wischmeyer 2017). During this phase, the body experiences a substantial increase in metabolic requirements and total energy expenditure (Wischmeyer 2017). Therefore, failure to provide adequate nutrition in this phase could negatively affect skeletal muscle mass, physical ability, or functional recovery (Bear et al. 2017). Furthermore, given that the acute phase only represents a small proportion of the patient journey, it seems logical that the next step for nutrition research should be to investigate the effect of a nutrition intervention provided in both the acute and chronic phases following critical illness.

Evidence from outside of critical care show promise for an intervention that covers the whole hospitalisation period. Conducted in eight ICUs in Switzerland, a recent randomised controlled trial (RCT) including 2088 elderly patients, investigated specialised nutritional support versus standard hospital food provision across whole acute hospitalisation (Scheutz et al. 2019). Compared to standard hospital food provision, those who received individualised nutritional support after 30 days, had lower rates of adverse clinical outcomes and better survival rates.

What Do We Know So Far?

It is well documented that adequacy of nutrition in the acute phase of ICU is below clinician estimates. A retrospective analysis of the International Nutrition Survey data from 2007-2013 including 17,154 patients worldwide who received enteral nutrition (EN) and/or parenteral nutrition (PN), showed that only 56% energy targets were achieved and 52% protein (Ridley et al. 2018). This is consistent with other studies and practice has largely remained unchanged in the past decade (Cahill et al. 2010; Bendavid et al. 2017; Rougier et al. 2020).

And for those who exclusively eat orally within the ICU, less energy and protein are received than those who receive artificial or combination nutrition therapies. In a single-centre observational study conducted in Germany, intake was measured in 289

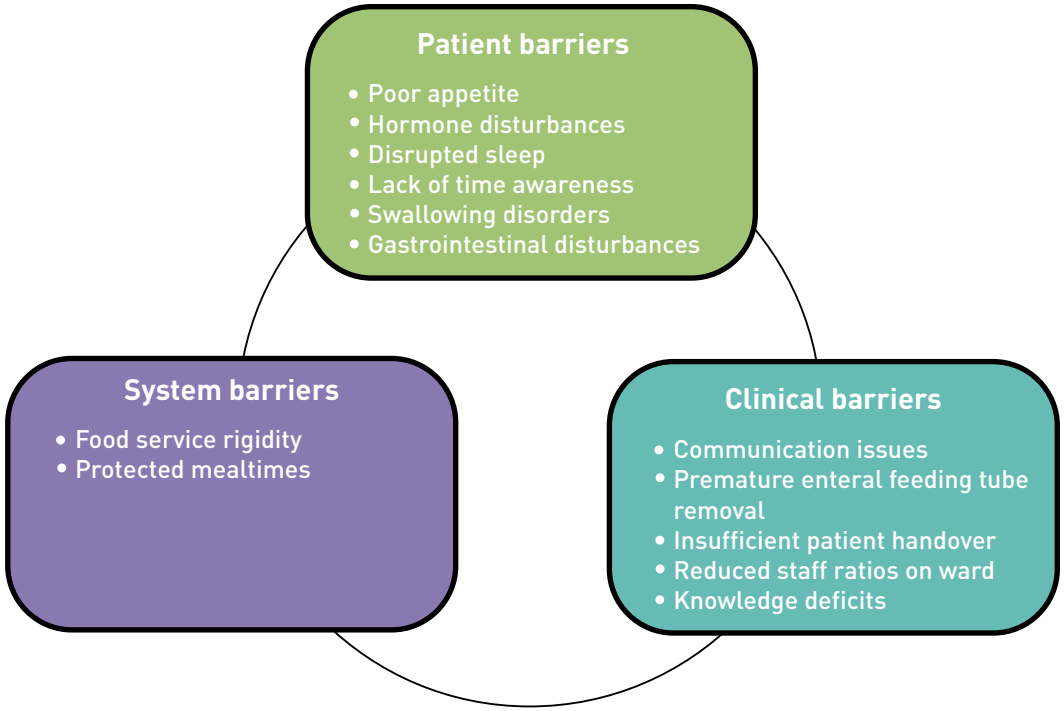

Figure 1. Barriers to nutritional adequacy in the post ICU period

patients within a mixed medical and surgical ICU (Rougier et al. 2020). In the 126 patients who received oral nutrition only, they received poorer energy and protein intake than the overall study average. Furthermore, of the oral-only patients who had an ICU stay of ≥7 days (n=37), 51% never received ≥80% of their energy targets and 94% never received ≥80% of their protein targets (Rougier et al. 2020).

There are also documented issues immediately post extubation. One of the first reports, a single centre observational study from the Unites States, reported in 50 patients that average energy and protein intake failed to exceed 55% of predicted requirements on any day in the 7 days post extubation (Peterson et al. 2010). Multiple barriers to oral intake were reported, including mental status (47%), appetite (38%), nausea/vomiting (26%), and therapeutic (restrictive) diets (22%). In New Zealand, an observational study of 79 patients followed critically ill patients upon commencement of oral intake and identified inadequate oral intake in 62% (n=49). For most patients, this occurred early in ICU admission with 25% continuing to experience poor oral intake beyond ICU day 5 (Jarden et al. 2020). More recently, an observational study of 19 patients quantified energy and protein intakes for up to 14 days following liberation from mechanical ventilation (Moisey et al. 2020). The median [IQR] amount of protein and energy received compared dietitian prescription was 46% [74] and 71% [62], respectively. However, on days oral diet was the sole source of nutrition, median intakes compared with prescription were 27% [26] for protein and 47% [37] for energy.

Similar issues have been documented following ICU discharge. In an Australian single-centre prospective observational study of 37 patients with a traumatic brain injury, energy and protein deficits were larger on the ward than during ICU admission and adequacy was lower in those who received oral nutrition compared to EN (75 (37)% energy and 74 (40)% protein vs 89 (34)% energy and 76 (34)%, respectively) (Chapple et al. 2016). Similarly, a second Australian cohort study examined nutrition intake in 32 patients (predominantly cardiac and trauma diagnosis) from 2 centres on the ward following ICU discharge and found the lowest median [IQR] adequacy was achieved on days where oral nutrition was received with no supplementation (37 [21-6]% energy and 48 [13-63]% protein) and the highest when oral nutrition was combined with EN (104 [66-132]% energy and 99 [60-127]% protein) (Ridley et al. 2018).

Despite the chronic phase of critical illness being of potential importance in recovery, what is known during this period is concerning; nutrition intake is often worse than in the acute phase. This undernutrition could potentially lead to poor recovery in the long-term and warrants further investigation (Bear et al. 2017; Merriweather 2020).

What is Causing Poor Nutritional Adequacy in the Post ICU Period?

More research is required to fully understand why these issues exist, but they can loosely be divided into patient, clinician and system barriers (Ridley et al. 2020) **(Figure 1).**

Patient Barriers

Poor appetite

Poor appetite, early satiety, and taste changes are commonly reported as affecting oral intake following extubation, and this can persist throughout acute hospitalisation (Moisey et al. 2020; Peterson et al. 2010; Merriweather et al. 2018). However, the exact mechanism is unclear and likely multifactorial. One study in 16 ICU patients compared to 36 healthy volunteers found lower plasma concentrations of ghrelin (appetite-stimulating hormone) and higher levels of pancreatic peptide YY (PYY) (which acts to reduce appetite) in ICU patients compared to healthy controls. By the fourth week following critical illness, ghrelin had increased, and a positive relation was found with hunger. Alterations in gut hormones could explain changes in oral intake and appetite in the critically ill and should be further explored.

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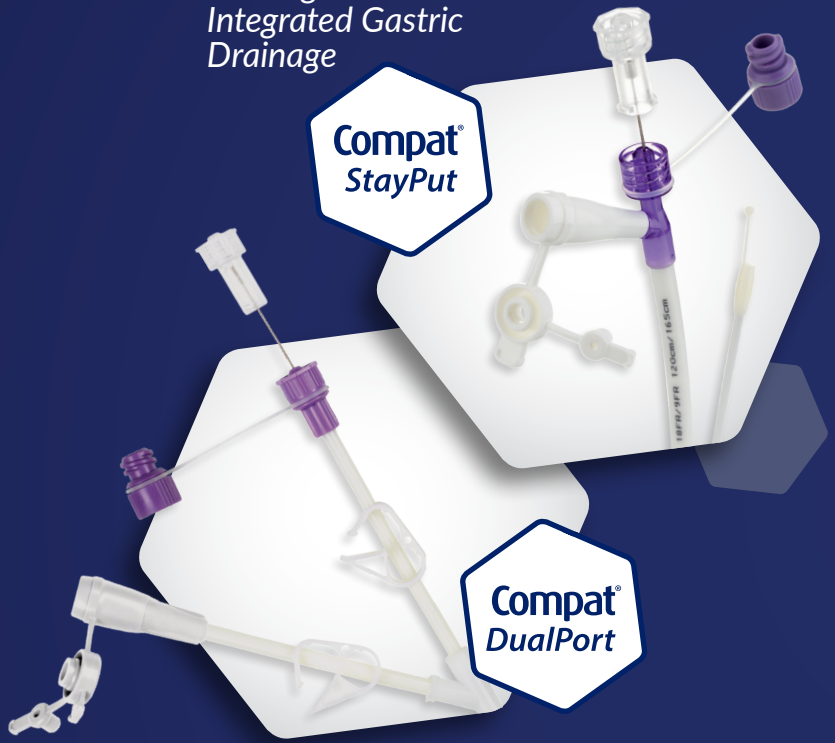

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Poor appetite has been associated with longer length of hospitalisation and inflammation. In a cohort of 193 adult ICU survivors, longer length of acute ward admission following ICU and higher levels of serum C-reactive protein were associated with poorer appetite measured using a visual analogue scale (Merriweather et al. 2018).

Irrespective of any hormone changes, it is plausible that the ICU environment itself could affect appetite. For example, disrupted sleep and a lack of awareness of time and the concept of day versus night is likely to disrupt appetite-stimulating hormones leptin and ghrelin (Morselli et al. 2012)

Swallowing disorders

The length of intubation has been associated with dysphagia. A systematic review included 14 studies and indicated that dysphagia, or swallowing disorders, were present in 3-62% of patients following extubation (and in whom were intubated for 125-347 hours prior) (Skoretz et al. 2010). Furthermore, in Europe, in an observational study conducted in two ICUs, 933 patients were analysed and 12.4% (n=116) had dysphagia at 3 hours post extubation, with 10.3% (n=96/933) having dysphagia at ICU discharge (Schefold et al. 2017). Dysphagia at hospital discharge continued in 60% of these patients (n=58/96). In this same study, patients who experienced dysphagia required more days on enteral feeding, had a longer length of mechanical ventilation and hospital stay, and had higher rates of hospital mortality.

Gastrointestinal (GI) disturbances

GI disturbances such as nausea, vomiting, diarrhoea, and high gastric residual volumes are common during the acute phase of critical illness, which if they persist, may lead to a compromised nutritional state (Peterson et al. 2010; Reintam et al. 2009; Chapman et al. 2011; Chapman et al. 2013). An Australian single-centre study compared gastric emptying in 51 ICU survivors three months following ICU discharge with 25 healthy individuals and found no differences in gastric emptying (Chapple et al. 2019). This study suggests that gastric emptying issues that occur during acute phase of critical illness may resolve in the chronic phase.

Clinician Barriers

Some factors affecting nutrition following ICU discharge exist between clinicians or clinical disciplines.

Communication issues

Premature removal of enteral feeding tubes, prior to establishment of adequate oral intake may be an explanation for the poor oral nutrition adequacy in the recovery phase of illness. A single-centre observational study in Scotland conducted in 17 patients reported that 9 patients were transferred with a nasogastric tube (NGT) in situ; 6 were removed within 48 hours of arrival to the ward based on medical staff advice, prior to any formal assessment of nutritional intake by the dietitian (Merriweather et al. 2013).

The National Institute for Health and Excellence (NICE) guideline in Rehabilitation after critical illness recommends that upon discharge from ICU, there should be a handover including the ongoing nutrition treatment plan (NICE 2009). A qualitative study found that this was not routinely provided by nursing, with limited nutrition documentation provided upon transfer from ICU to the ward, and verbal handover only detailing the route of nutrition or commencement of oral intake (Merriweather et al. 2013).

Resource issues

Once a patient is transferred to the ward following ICU discharge, there is often a reduction in nurse to patient ratio. This leads to competing priorities and multiple work-related pressures for nurses and challenges to prioritising nutrition-related care on the ward (Marshall, et al. 2019). This may negatively impact nutrition intake as critically ill patients in the chronic phase of illness are often deconditioned and require feeding assistance and support.

Although oral nutrition is the most common mode of nutrition following ICU discharge, it has been reported in a single-centre study of 37 patients that 71.5% of dietitians time was spent managing patient's receiving EN and 20.4% of time was oral nutritional management (Chapple et al. 2016). Understanding effective models of nutrition care is important to overcoming some of these issues.

Knowledge deficits

A systematic review including 24 studies synthesised the nutrition education provided to medical students and found that regardless of country, setting or year of medical training, nutrition is insufficiently incorporated into medical education leading to reduced knowledge, skills and confidence in implementing nutrition care to patients (Crowley et al. 2019).

System barriers

Food service times and structure

Qualitative studies have shown that patients feel frustrated with the rigidity of meal service times and the structure of three large meals per day with minimal snack options as it tended to differ from many patients' usual eating patterns (Merriweather et al. 2013). This rigid structure may impact nutrition intake and ability to meet nutrition requirements orally, however implementing strategies to counteract these issues could improve intake.

A team in Australia implemented a room service model for food selection and delivery in a public hospital where meals are prepared and delivered within 45 minutes of patient orders (McCray et al. 2018). Energy and protein intakes were significantly higher in the room service model than the traditional model and plate wastage was reduced. Patient satisfaction and food costs overall improved significantly.

Protected mealtimes

Many health services have implemented strategies to ensure uninterrupted mealtimes with minimal distractions, however these are not always adhered to (Merriweather et al. 2013). Additionally, mealtimes are protected from family member visits, which could be a further concern for the patients who require feeding assistance due to poor dexterity or poor functional capacity on the ward following ICU discharge.

What Can Clinicians Do To Help Patients Nutritionally in the Post ICU Period?

The ESPEN ICU nutrition guidelines recommend considering any patient that had an ICU admission of 48 hours or more as 'at risk' nutritionally (Singer et al. 2019). This recommendation should continue throughout the entire hospitalisation, particularly if

known weight loss or muscle wasting has occurred during the acute phase of illness. During the chronic phase of critical illness, it should be considered that additional nutrition supplementation will be required where oral intake is received.

Another change to service provision lies within the dietetic service. Shortfalls exist in nutrition provision following ICU discharge and we are only just beginning to understand that multiple patient barriers exist following extubation or prolonged critical illness. We also know that in the following ICU discharge, there is an increase in physical therapies and the body shifts to a more anabolic stage of recovery (Massanet et al. 2015). Further, it could be hypothesised that meeting nutrition requirements in this phase will ensure rehabilitation occurs; this requires prospective investigation. Given that oral patients get the least amount of time spent on their care yet have the poorest nutrition adequacy, the most effective models of care need to be explored (Chapple et al. 2016; Ridley et al. 2018).

Lastly, nutrition related research in the area of critical illness needs to encompass the chronic phase. There is a discord between current nutrition research that measures long term functional recovery yet delivers short-term nutrition interventions. Furthermore, it is currently unclear what impact specific nutrition interventions may have on recovery in relation to critical illness (Lambell et al. 2020). We are unaware what happens to patients once they are transferred to the subacute setting and once discharged home. The issues and barriers patients face from critical illness are likely to exist for long periods beyond the acute care setting. Therefore, the next logical step is to extend nutrition interventions into the chronic phase following ICU discharge (that is, the post ICU period) to better understand how nutrition effects recovery after critical illness and whether it improves physical function and/or quality of life (Bear et al. 2017).

Conclusion

Nutrition interventions in the chronic phase of critical illness have been identified as a research priority, with this period currently under-investigated. The studies published to date have identified several issues, including gross nutrition inadequacy (particularly with oral nutrition) and some of the factors that affect this. More research is needed in this area to truly understand the impact of nutrition interventions on long-term recovery from critical illness, with a specific focus on the application of longer-term nutrition interventions. In the meantime, there are patient, clinician and system level strategies that could be adopted to improve nutrition intake in patients who are recovering from critical illness across the spectrum of recovery.

Conflict of Interest

None. ■

Abbreviations

ICU: Intensive Care Unit
EN: Enteral Nutrition
PN: Parenteral Nutrition
PYY: Pancreatic peptide YY
NGT: Nasogastric Tube
ESPEN: European Society for Clinical Nutrition and Metabolism

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Post-Intensive Care Syndrome – The Paediatric Perspective

This article outlines the current understanding, prevalence, risk factors and management of the post-intensive care syndrome in paediatrics.

Introduction

Persistent critical illness acquired morbidities have been well known to affect adults since our attention was drawn to this in the landmark publication by Herridge et al. in 2003. What was first labelled as intensive care unit-acquired weakness, was broadened as we began to understand the physical, neurocognitive and psychological sequelae that can affect not only patients, but their caregivers. The Post-Intensive Care Syndrome (PICS) was coined in a 2012 publication, to capture the three key affected domains of mental health, cognitive function and physical sequalae that adult survivors experience (Needham et al. 2012). This understanding of long-term impact of critical illness on patients has prompted clinicians and researchers to expand our focus beyond acute care and survival, to optimising survivorship and longer-term functional and health-related quality of life (HRQL) outcomes in our patients and families.

PICS has only recently been described in the paediatric population (Herrup et al. 2017; Watson et al. 2018). Challenges leading to a delayed recognition of PICS in children include the paucity of long-term follow-up research in critically ill paediatric survivors, the heterogeneity of outcome measures used to assess the key domains of PICS, challenges with respect to measuring functional disability or recovery trajectories in children, a dependency on surrogate reporting of these outcome measures, and evolving paediatric populations with increasing medical complexity and chronic illness being admitted to our Paediatric Intensive Care Unit (PICUs) today. The application of the PICS framework to the PICU population was unclear until an international, interprofessional Pediatric Critical Care working group conceptualised a Post-Intensive Care Syndrome-Pediatric (PICS-p) framework (Manning et al. 2018). PICS-p recognises the following key nuances in children:

1. The paediatric population is heterogeneous; it encompasses infants to adolescents, spans across children with a wide range of physical, social, cognitive and developmental function, and includes a broad spectrum of acute to complex, chronic disorders.
2. A child's critical illness occurs at a time of significant growth and maturation that can impact their physical, cognitive and emotional development. The PICS-p model recognises that the child's unique baseline health status and the impact of critical illness on the stage of their development influences their trajectory of recovery, and that trajectory is varied (Choong et al. 2018).
3. The PICS-p framework recognises the interdependency between family and child, and therefore integrates family outcomes in the functional recovery of paediatric critical illness survivors. The child-family dyad are inseparable - the child's critical illness can have significant impact on family members' own physical and mental health (PICS-family); the family members' stress and coping in turn, are intricately related to and influence a child's functioning and quality-of-life (Jarvis et al. 2019b).
4. "Social health" is added as a fourth core domain in the PICS-p model, recognising the important role of the social environment around the child, and impact of critical illness on the child and family's social functioning **(Figure 1)**.

Prevalence of PICS-p

Previous studies report a variable prevalence of PICS-p in large part due to challenges in study methods, the identification of and measurement of the domains of PICS-p (Ong et al. 2016). The majority of earlier studies focused on assessing single domains, rather than a multi-system phenomenon (Watson et al. 2018). Recent evidence demonstrates that PICS-p is much more common than previously understood, and suggests that over 80% of paediatric survivors develop newly acquired functional deterioration as a direct result of their critical illness admission (Choong et al. 2018). The current literature reveals that each of the key domains of physical mobility, social and cognitive functioning as well as HRQL are collectively and significantly affected in children (Choong et al. 2018; Watson et al. 2018). Recovery trajectories from PICS-p are variable.

Prospective studies reveal that 67% experience some improvement in functioning 6-months post discharge, however, up to 20% of survivors experience persistent morbidities 1-2 years post PICU discharge (Ong et al. 2016; Pinto et al. 2017). The pattern of recovery from PICS-p is also varied. Evidence from the prospective longitudinal "Weecover" study suggest that physical functioning lags behind the recovery of other domains at six months, and that social well-being appears to lag behind the recovery of psychological well-being in HRQL assessments (Choong et al. 2018). Parents describe negative behavioural changes, and decreases in their child's self-esteem and emotional function (Als et al. 2015); children report anxiety, medical fears, changes in friendships and their sense of self (Rennick et al. 2009). Disruptions in cognitive function after critical illness is particularly important in the developing brain. The reported prevalence of acquired cognitive impairments ranges widely from 3% to 73% amongst PICU survivors, depending on the nature of the study (Watson et al. 2018).

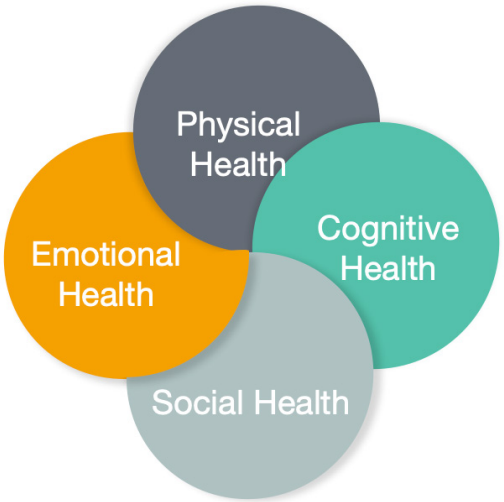

Figure 1. The four key domains of PICS-p model

Cognitive deficits vary in severity, from lower IQ to severe deficits in attention and memory (Als 2013). These deficits may persist for years, and in some cases, worsen over time (Mesotten et al. 2012). Psychological functioning has been challenging to evaluate in the heterogenous paediatric population, however, the evidence reveals that a significant proportion of critically ill children are affected long after PICU discharge - 35-62% experience post-traumatic stress symptoms, 7-12% experience symptoms of depression, 33% recall delusional experiences, and 20% of paediatric survivors are at risk of a general psychiatric disorder (i.e. emotional, hyperactivity, or conduct disorders) (Nelson et al. 2012). These data highlight the importance of growth, development and the social environment when considering how PICS affects children; critical illness significantly impacts a child's functioning, their HRQL, and their ability to re-integrate into their home, school and community long after PICU discharge (Kastner 2019; Khetani et al. 2018).

Risk Factors for PICS-p

The risk factors for the development of PICS-p are multifactorial, and may be categorised into 1) pre-morbid, 2) critical illness and PICU care, and 3) post-discharge related factors.

Pre-morbid factors

Baseline patient characteristics such as functional status, older age at presentation, chronic complex disease, malignancy and immunodeficiency have been identified as risk factors for poor functional and HRQL outcomes in critically ill children (Choong et al. 2018; Killien et al. 2019; Watson et al. 2019). Pre-existing comorbidities influence a child's self-care and dependency on caregiver support. Maternal mental health, family functioning and lower socioeconomic status have also been shown to have important influence on a child's adaptive behaviour and emotional health, predisposing them to poor recovery from PICS-p symptoms (Small et al. 2006; Yagiela et al. 2019).

Critical illness and PICU-care related factors

Admission diagnosis, in particular a neurological insult and septic shock, and severity of illness are risk factors for poor functional outcomes and HRQL (Choong et al. 2018; Killien et al. 2019). Not only are the diagnoses and critical illness severity important, but the way in which we provide critical care is an under-appreciated, important modifiable risk factor for the development of PICS-p. Sedation management regimens, inadequate analgesia, and the number of invasive procedures are associated with adverse physical and psychological sequelae in children (Herrup et al. 2017). Prolonged immobilisation and excessive sedation are inter-related, and have repeatedly been associated with adverse downstream effects of prolonged mechanical ventilator requirement, delirium, iatrogenic withdrawal and ICU-acquired weakness (Choong 2019). We now understand that the development of one or more of these specific PICU-acquired complications predicts a greater decline in long-term physical, social and neurocognitive function (Choong et al. 2018). The development of these PICU-acquired complications also increases parental stress, and predisposes patients to increased PICU mortality and longer lengths of stay (Choong et al. 2018; Kukreti et al. 2014; Traube et al. 2017). Long-stay patients have similar mortality rates, but are at greatest risk of prolonged PICS-p symptoms and poor recovery, compared to those with shorter stays (Matsumoto et al. 2019).

Post-discharge related factors

Family functioning and well-being, the environment, community and peer support around the patient, caregiver strategies and access to resources for rehabilitation, financial support, and knowledge of healthcare provider and preparedness of family caregivers are all important factors demonstrated to influence the trajectory and nature of recovery of PICS-p symptoms following hospital discharge (Fayed et al. 2020; Hartman et al. 2020; Jarvis et al. 2019b).

Management of PICS-p, From Within to Beyond the PICU

Recognising and educating clinicians on the magnitude and impact of PICS-p on our patients and families is the crucial first step in reframing our priorities in critical care to focus not only on survival, but survivorship. Within the PICU, this begins with early recognition, resuscitation, and stabilisation in accordance with recommended best practices and supportive evidence in order to reverse and prevent new or progressive multi-organ dysfunction. Potentially modifiable targets should focus on the key factors shown to adversely affect short and long-term patient outcomes, specifically, excessive or prolonged sedation, immobility, delirium, and disrupted sleep. This requires a paradigm shift and the integration of evidence-based harm-reduction and rehabilitation strategies as soon as possible after a patient is resuscitated and stabilised, rather than deferring these practices to the later stages of care, when PICU-acquired morbidities have already occurred (Choong 2019). Specific objective screening for pain, delirium, pressure ulcer risk, readiness to mobilise and spontaneous breathing trials, are evidence-based, recommended standards that should be implemented in PICUs as it is in adult ICUs (Devlin et al. 2018; Harris et al. 2016). Early recognition therefore applies not only to resuscitation, but also to recognising the risk factors for PICS-p. Consultation of physiotherapy, occupational therapy, speech and language therapy, and physiatry where available, are important in the acute rehabilitation and longitudinal planning of a child's recovery.

Beyond the PICU, the transition of care to the ward can be an extremely anxious and insecure time for patient families, and requires accurate and detailed transfer of information, and smooth

continuation of appropriate clinical care, rehabilitation, and monitoring for PICS-p symptoms. The recognition and management of PICS-p outside of the PICU and following discharge often falls on primary care providers, non-critical care subspecialists, rehabilitation clinicians and indeed patients and families themselves who may not be aware of nor appreciate the impact of PICS-p. Many if not the majority of PICS-p symptoms such as somatic complains (pain, weakness, sleep disturbance), emotional, psychological and behavioural symptoms are only identified well after hospital discharge during outpatient visits. This requires education and training on the screening and management of PICS-p. Unfortunately in paediatrics, there is currently a knowledge gap and there is at present no recommended standard for how to or when to screen for PICS-p. While early screening may be used to risk stratify adults and intervene in patients with PICS (Wang et al. 2019), this has not been well studied in children to date. Educating and providing anticipatory guidance to patient families around PICS-p improves their understanding, symptom identification, enables them to identify coping strategies, organise supports and access resources for rehabilitation, prepare the home, community and school environment where necessary (Esses et al. 2019). These in turn may improve the child's behaviours, reduce stress and anxiety, and optimise physical, emotional and neurocognitive outcomes (Jarvis et al. 2019a; Jarvis et al. 2019b). Not only have some institutions developed excellent family resources (www.afterpicu.com). families have also taken the initiative to create peer-support groups (m.facebook.com/makinglemonade.pfcc)

There is evidence that the current supports for families to address the many needs of their child recovering from a critical illness is limited. Clinicians do not routinely assess for long-term functional outcomes of PICU patients (Treble-Barna et al. 2019). 67% parents reported that their healthcare provider did not discuss child's return to school (Kastner 2019). Supports from community and education are also suboptimal - 20% parents reported that schools did not adequately address school reintegration (Kastner 2019). Diary programmes are emerging in PICUs and to date, the evidence is strongest for prospective use of diaries to prevent and manage psychological symptoms following critical illness (Lasiter et al. 2016). Post-PICU clinics are emerging in paediatrics to address a growing need. The role of post-ICU follow-up clinics for the general PICU population has been evaluated in a small number of studies (Colville et al. 2010; Gledhill et al. 2014). The evidence to date suggests that while those who utilised these clinics found the follow-up and interventions helpful, the uptake is suboptimal (25-33% of eligible families attended). This is in part attributable to the potential burden and perception of yet another follow-up clinic, in a population where many have medically complex needs and require multiple appointments with numerous sub-specialty services. Nevertheless, there is a need for post-PICU clinics to address PICS-p which is currently under-recognised amongst healthcare providers, patients and families. While feasible, important logistical challenges include the infrastructure considerations for post-PICU clinics, which require the support of multi-professional clinicians trained to recognise, manage and counsel the multitude of physical, emotional and neurocognitive sequelae of PICS-p in both the patient and families.

Future Directions

As PICU mortality continues to fall, this outcome is no longer the most appropriate indicator of the quality and effectiveness of our care. We now have a good understanding that survivorship, as defined by functioning and HRQL, are the outcomes deemed most important by patients and families (Fayed et al. 2020). Much of the attention in paediatric critical care has now turned to how we may best identify, quantify, prognosticate and ultimately intervene in the mutldimensional, complex PICS-p that far outlasts critical illness. Research priorities have been identified (Watson et al. 2018), which has been accompanied by significant research progress in this field (Choong 2019; Manning et al. 2020). Moreover, current clinical trials are increasingly including measures of longer term functional and HRQL outcomes in their study design.

Conclusion

Mortality is very low amongst critically ill children. Increased survival is unfortunately accompanied by an increasing proportion of children who leave the PICU with newly acquired morbidities. This phenomenon known as the PICS-p is a constellation of physical, emotional, neurocognitive, and social sequelae that persists well beyond the resolution of acute critical illness. The paediatric framework recognises the important role of the social environment around the child, and the interdependency between family members on both the child and family's functioning and recovery from critical illness. PICS-p is not benign, and has important, long-lasting sequelae in critically ill children and families. The care of the critically ill child is no longer restricted to an acute life-threatening event, but extends well beyond the PICU. We have a responsibility to not only save lives, but to care for the lives that we have saved. This responsibility rests not only on critical care clinicians, but relies on a team of multiple healthcare professionals, family and community. Future research will help us determine how best to identify and manage the needs of these patients in-order to optimise recovery from within, to beyond the PICU.

Conflict of Interest

Karen Choong has received the Academic Health Sciences Alternate Funding Plan Innovation Grant to conduct the Early Rehabilitation in Critically ill Children – the PICU Liber8 Study (Reference no. HAH-18-04) ■

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The Post-ICU Patient

"The success of intensive care has not to be measured only by survival statistics, as though each death is a medical failure. It has to be measured by the quality of lives preserved or restored and by the quality of dying of those in whose interest is to die." This statement of G. R. Dunstan, Prof. of Morals and Social Theology, dating back to 1995, represents a warning to all intensivists. Since then, the importance of the quality of life and the cognitive, psychological and physical impairments that intensive care unit (ICU) survivors may experience has been increasingly stressed by the literature. Therefore, it is essential for all intensivists to be aware not only of the long-term sequelae of critical illnesses and their treatments, but also of the organisational changes and improvements that can be implemented to improve quality of life of the ICU survivors and their families after discharge.

The Post Intensive Care Syndrome (PICS): Definition and Prevalence

There is more to life than measuring death.

At first, there was only survival or death. Critical care is a relatively new branch of medicine that emerged in the 1950s during the large polio epidemic in Northern Europe. For decades, the primary objective of intensive care was to save as many lives as possible, regardless of the severe disabilities that could ensue and then weigh on the residual life of the patients. In the 1970s, though, critical care outcomes after ICU discharge have increasingly reported. Particularly significant is a 1976 article ("Survival, hospitalisation costs, and follow-up results in critically ill patients") published in NEJM (Cullen et al. 1976) about 1-year follow-up outcomes of ICU survivors. The article described a novel approach to treatment in ICU, more focused also on post ICU outcomes. In this study on 226 critically ill survivors, the one-year mortality rate was as high as 73%. Moreover, only 42% of the one-year survivors had the same functional level as before, while 16% had a partial recovery and were in a nursing home. Cullen et al. (1976) also demonstrated, as expected, a profound negative effect of age (≥65 years) on survival and long-term cognitive decline. It is noteworthy that this first comprehensive analysis on outcomes related to post-discharge items revealed many problems that ICU survivors still have to deal with today (Cullen et al. 1976). Since then, our awareness on long-term sequelae increased and in the 2012 the concept of post intensive care syndrome (PICS) was established to indicate the overall chronic disabilities that plague ICU survivors and their caregivers (PICS-Family) (Rawal et al. 2017).

Current evidence shows that this syndrome can affect up to 50% of patients discharged from ICU. Cognitive impairments of different grade of severity and duration occur in up to 30-80% of ICU survivors (Harvey and Davidson 2016; Pandharipande et al. 2013). Psychiatric disorders, such as anxiety, depression, or post-traumatic stress disorder (PTSD) often lasting for years can occur in 8-57% of patients (Harvey and Davidson 2016). A new physical disability can also be developed by 25-80% of patients (Griffiths et al. 2013), and new symptoms such as dyspnoea, pain, sexual dysfunction, or impaired exercise tolerance may be experienced as well.

PICS prevalence is also related to the admission diagnosis; among critically ill septic shock patients, PICS can reach 70% with long-term cognitive impairments observed more frequently than in post-surgical patients (Brück et al. 2018).

The ICU Patient Identikit: Risk Factors and Prevention Strategies

Broadening perspectives in daily practice.

Even though a growing number of reports on PICS occurrence and epidemiology are available, the risk factors and biologic mechanisms involved and the applicable preventive and treatment strategies have yet to be completely clarified.

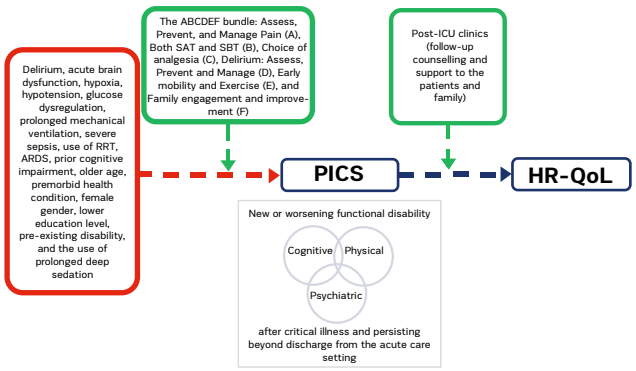

Figure 1. Risk factors (red box) and preventive interventions (green box) of PICS
PICS post intensive care syndrome, HR-QoL health related- quality of life, RRT renal replacement therapy, ARDS acute respiratory syndrome, SAT spontaneous awakening trials, SBT spontaneous breathing trials

As far as physical impairment is concerned, literature highlights the critical role of Intensive Care Unit-Acquired Weakness (ICU-AW). ICU-AW is defined as the acute muscle weakness of the extremities in a symmetric pattern, related to critical illness, which may be classified as critical illness polyneuropathy (CIP), critical illness myopathy (CIM), critical illness neuromyopathy (CINM), and muscle deconditioning (Latronico and Bolton 2011). The incidence of ICU-AW is 40% in critically ill adult patients (Appleton et al. 2015), with CIP being the most common category (Bednarik et al. 2003). The physiopathological mechanism is multifactorial (Latronico): microvascular ischaemia, catabolism, and immobility can lead to skeletal muscle wasting, while microvascular injury with nerve ischaemia, dysfunction of sodium channels, and mitochondria injury could contribute to critical illness-related neuropathy, myopathy, or both. Risk factors for ICU-AW and consequently for long term physical impairment have been identified as female sex, sepsis, catabolic state, multiorgan failure, systemic inflammatory response syndrome (SIRS), long duration of mechanical ventilation (MV), immobility, hyperglycaemia, glucocorticoids, and neuromuscular blocking agents (Latronico and Bolton 2011).

Critically ill patients may experience not only physical stress but also psychological derangements. This type of stress may generate new cognitive impairments or worsen pre-existing conditions lasting months to years, resulting in a reduced quality of life (Wolters et al. 2013). Cognitive impairments include impaired memory, executive function, language, attention, and visual-spatial abilities. Hypoglycaemia, as well as hyperglycaemia, delirium, and other acute stress symptoms, have been identified as risk factors for persistent cognitive impairment (Hopkins et al. 2010; Pandharipande et al. 2013; Davydow et al. 2008). There is a strong evidence that patients with delirium are at greater risk of long-term adverse cognitive outcomes (Katz et al. 2001; Guerra et al. 2015).

Long ICU stays can represent a traumatising event. With regards to mental health, anxiety, depression, and Post Traumatic Stress Disorder (PTSD) are the most frequent psychiatric disorders observed in ICU survivors, respectively in 70%, 30%, and 10% (Davydow et al. 2008; Garrouste et al. 2012). The risk of PTSD after ICU care is higher for women. Other risk factors for acquired mental illness include pre-existing depression, anxiety, a lower education level, and alcohol abuse (Davydow et al. 2008).

In daily clinical practice, preservation of health-related quality of life (HRQoL) must be routinely pursued. With this aim a bundle of intervention has been elaborated:

The **ABCDE** is the bundle for sedation, delirium, and immobility management in ICU patients. ABCDE is composed of:

A: Airway management, assessment, prevention, and management of pain;

B: Breathing trials, including daily interruptions of mechanical ventilation, spontaneous awakening trials and spontaneous breathing trials;

C: Choice of analgesia and sedation, coordination of care, and communication;

D: Delirium assessment, prevention, and management;

E: Early mobility and exercise.

The ABCDE bundle has been recently complemented with **FGH** for PICS prevention. FGH includes:

F: Family involvement, follow-up referrals;

G: Good handoff communication;

H: Handout materials on PICS and PICS-Family (Devlin et al. 2018).

Besides, guidelines focus on other strategies such as environmental management, nursing care, diary and, mostly, nutritional therapy, which has become a cornerstone for PICS prevention, especially for ICU-AW (Inoue et al. 2019). A proper nutritional strategy should target muscle volume and strength while avoiding overfeeding (McClave et al. 2016; Singer et al. 2018) that could induce autophagy and worsen ICU-AW (Casaer et al. 2013). Avoiding muscle catabolism and lean body mass loss through adequate energy delivery and protein intake (Phillips SM, Kim IY) has proven to reduce long-term mortality (Demling et al. 2009). While in healthy individuals muscle protein synthesis is maximised with exercise, in critically ill patients appropriate rehabilitation exercises, and adequate nutrition are both necessary (Morton et al. 2018).

The Post-ICU Patient Identikit. What Monitoring Tools?

The Post-ICU management: a new target for the intensivist.

Despite efforts in identifying risk factors and implementing prevention strategies, PICS remains underdiagnosed mainly due to:

- Lack of specific follow-up programmes
- Discharge documents focused exclusively on organ-specific damage: physical and/or cognitive deficits, possibly acquired or newly detected during hospitalisation, are usually not emphasised
- Lack of universally validated tools for PICS screening and diagnosis

While some categories of patients, e.g., stroke survivors or Chronic Obstructive Pulmonary Disease (COPD) patients, usually fall under a structured programme of rehabilitation because of their chronic diseases, ICU survivors suffering from PICS are not recognised as 'chronically ill' and often do not have follow-up schemes.

Van der Schaaf et al. (2015) underlines that the optimal timing of first visit after ICU discharge are lacking in the literature (between 1 to 12 months after discharge). However, a panel of Dutch experts has suggested that the optimal timing is about 12 weeks after hospital discharge (Van Der Schaaf 2015). This period of time seems long enough to rule out all ICU survivors who face early hospital readmission or death. It also appears to be an adequate time period for any physical, cognitive, and psychological

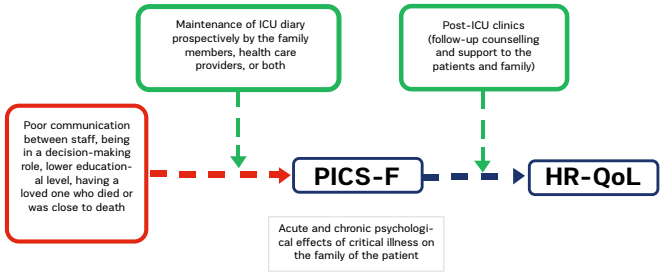

Figure 2. Risk factors (red box) and preventive interventions (green box) of PICS-F PICS post intensive care syndrome, HR-QoL health related- quality of life

sequelae to emerge and be noticed by family members or caregivers and, therefore, be reported at the follow-up consultation as significant impairment for quality of life.

With reference to the duration of the follow up, some studies suggest up to 10 months after discharge for those patients who report sequelae related to ICU admission disease and up to 1 year for family members or caregivers who develop psychological repercussions from their family member's experience (Griffiths et al. 2013).

Currently, organisational models are not univocal and different tools are adopted to measure physical, psychological, or cognitive disabilities. Some literature examples are the Modified Rankin Scale (MRS) and the Medical Research Council (MRC) scale for physical dysfunction, the Hospital Anxiety and Depression Scale (HADS) and the Post Traumatic Stress Disorder (PTSD) Checklist for psychological disorders, the Mini-Mental State Examination (MMSE) for cognitive alterations. EuroQol-5 Dimension (EQ-5D) is a widely used HRQoL measurement tool (Brooks et al. 2003) which consists of two distinct sections. The first one evaluates five subjective dimensions (mobility, self-care, daily activities, pain/discomfort, and anxiety/depression). The second section includes a visual analogue assessment (VAS) of perceived health level. A specific algorithm finally obtains a synthetic score.

Based on global literature data, the follow-up schemes could be structured as follows:

- First step during ICU stay: prevention measures and early rehabilitation interventions according to ABCDEFGH protocol.
- Second step before hospital discharge: recovery path description and enrolment for follow-up clinics
- A three-six-month follow-up visit with a direct physical examination, vital signs recording, and quality of life measurement.
- One-year last follow-up visit for those who had shown PICS symptoms at the first visit.

Moreover, the first follow-up visit represents an early opportunity to identify any physical, psychological, and/or cognitive deficits. Hence, the need to create a post-intensive support network, including physiotherapists, psychologists, psychiatrists, and others, to guarantee continuous assistance to post-critical patients.

PICS is gaining more and more importance as a consequence of COVID-19 pandemic, both because of the elevated number of ICU survivors and because of the significant likelihood that COVID-19 ICU patients will evidence a greater incidence of PICS. In fact, the long sedation that these patients require to allow mechanical ventilation is a risk factor for delirium, which is closely related to cognitive impairment. Additionally, due to infection control bundles, family members are restricted from in-person visiting and even health care staff may reduce the time they spend in contact with patients. This reduction in human interaction causes a decrease in cognitive stimulation, reorientation and reassurance to patients, causing further anxiety, depression and demoralisation. This creates a vicious circle of mental health impairment (Hosey et al. 2020). Considering the crucial role of evaluating COVID-19 long-term effects, technological advances should be leveraged to facilitate remote follow-up and comply with social distancing measures (Warnakulasuriya et al. 2020).

Conclusion

PICS is a widespread but under-recognised syndrome that can involve up to 80% of patients surviving acute respiratory failure who have received mechanical ventilation in ICU. Therefore, especially during this COVID-19 pandemic, it is of utmost importance for intensivists to implement evidence-based interventions (ABCDE) and to establish rehabilitation programmes that begin in ICU and continue after discharge. These actions can optimise survivorship experience and minimise long-lasting physical, cognitive and mental health impairments which cause profoundly disabling functional problems such as persistent fatigue, chronic pain, sleep dysfunction and overall low health- related quality of life.

"If you do not know what you are doing and how well you are doing it, you have no right to be doing it at all," Professor Sir Bruce Keogh, NHS Medical Director ■

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Continuous Monitoring Beyond the ICU

The rise of mobile solutions

Post-ICU patients are at high-risk of clinical deterioration. Continuous and mobile monitoring on hospital wards is useful to detect clinical deterioration at an early stage. It may help to prevent serious adverse events and ICU readmission.

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Most patients discharged from ICUs are old and have co-morbidities. Even when they are young and were healthy before ICU admission, the days or weeks spent in the ICU increase the risk of complications such as nosocomial infections, pulmonary atelectasis, airway obstruction, metabolic disturbances, cardiac arrhythmia, thromboembolic events and delirium. Therefore, post-ICU patients are at high risk of clinical deterioration and ICU readmission (Frost et al. 2009). As intensivists, we see the far too common and often frustrating middle of the night preventable ICU readmission. We also recount sad stories of patients who spent weeks recovering from life-threatening conditions and who unexpectedly died hours or days after ICU discharge.

When patients leave the ICU (or the step-down unit) they usually transition from a care area with a high nurse/patient ratio where they are closely monitored to a general ward where nurses have to deal with a large number of patients and often spot check vital signs only every 4-8 hours. The intermittent nature of vital signs monitoring explains that nurses may miss up to 90% of hypoxaemic events (Sun et al. 2015) and 50% of hypotensive events occurring in the wards (Turan et al. 2019). In this setting, continuous monitoring of vital signs has been shown to be associated with a decrease in calls for rescue interventions and cardiac arrest, in ICU transfer and in hospital mortality (Taenzer et al. 2010; Bellomo et al. 2012; Brown et al. 2014; Subbe et al. 2017). However, until recently, monitoring systems were bulky, expensive and designed for the OR and the ICU. **Solutions are emerging to upgrade and simplify the way we monitor patients on hospital wards** (Vincent et al. 2018, Michard and Sessler 2018; Khanna et al. 2019). **They include contact free sensors and wireless wearables**, as well as triage tools to help operationalise the use of these. At the same time, rigorous validation and interventional outcome studies are needed as we attempt to bring about a culture change and improve patient safety (Saugel et al. 2020).

Contact Free Sensors (or "Stay-in-Bed" Monitoring Solutions)

Contact free sensors are either bed sensors or video cameras (**Figure 1**). Bed sensors are piezo-electric pads to be put under any bed mattress or part of modern high-end hospital beds (Zimlichman et al. 2012). They basically feel heart beats and respiratory movements. They have been used in several clinical studies, including an outcome study showing a reduction in calls for cardiac arrest and in hospital length of stay after implementation (Brown et al. 2014). Video cameras can track subtle changes in colour face to count heart beats and in chest or abdominal movements to detect respiratory rates. Several attempts have also been made to estimate oxygen saturation and blood pressure from video monitoring (Luo et al. 2019), but validation studies done in real hospital conditions are lacking. Contact free solutions are very appealing for patients because they do not need to be connected to any device nor to wear any sensor. However, they do not follow patients when they leave their bed (e.g. to go to the bathroom) or their room (e.g. for physiotherapy). As a matter of fact, we expect most patients to leave their beds as soon and as often as possible to prevent thrombotic complications and bedsores. In surgical patients, early mobilisation is a key element of enhanced recovery (aka ERAS) programs. Therefore, wireless and wearable sensors are highly desirable to make continuous monitoring a reality for a large number of patients who need and wish to move out of their hospital bed as often as possible.

Wireless Wearable Sensors (or Mobile Monitoring Solutions)

Several mobile monitoring systems have been developed and/or validated over the last few years (Michard et al. 2019a; Khanna et al. 2019). They include necklaces, finger sensors and adhesive patches. The first monitoring system specifically developed for the wards comprises a finger sensor to measure oxygen saturation and pulse rate, a wireless brachial cuff for intermittent blood pressure measurements and chest electrodes for the detection of heart beats and the calculation of the pulse wave transit time (PWTT) **(Figure 1)**. The PWTT is the time difference between the peak of the R wave

Figure 1. Examples of solutions for continuous monitoring on hospital wards
Top = "Stay-in-bed" monitoring with video cameras (left), and piezo electric pad under the mattress (right). Bottom = mobile monitoring with multiple sensors (electrodes, brachial cuff and finger pulse oximeter) (left), and a single wireless adhesive patch measuring heart rate, respiratory rate and axillary temperature (right).

on the ECG (ventricular contraction) and the arrival of the plethysmographic pulse in periphery (finger sensor). The PWTT depends on blood flow and vascular tone so that any change in PWTT indicates either a change in cardiac output or a change in vascular tone. From there, and the knowledge of baseline BP, it becomes possible to estimate BP or, more realistically, to predict a change in BP and hence trigger a brachial cuff measurement. This system has been shown to be useful to decrease the number of rapid response team calls (Weller et al. 2018). The combination of a wireless brachial cuff to measure BP, abdominal adhesive patch to capture RR and finger pulse oximeter to monitor SpO_2 and pulse rate has been used with success in a large UK study where continuous ward monitoring was associated with a significant decrease in cardiac arrests and mortality (Subbe et al. 2017). Other "all-in-one" solutions have been developed. They include necklaces, finger devices, and adhesive patches integrating accelerometers, photoplethysmographic, piezo electric and/or bioimpedance sensors. They have the advantage to enable the simultaneous monitoring of several vital signs from a single device **(Figure 1)**.

Who Should Be Monitored?

We now live in a world where smartphones and smartwatches can be used to monitor pulse rate, to detect cardiac arrhythmia, to measure oxygen saturation and to record up to 9 ECG leads (Michard et al. 2019b). Soon they may also be able to detect changes in BP, if not measuring it. Therefore, given what is becoming possible from home, one may argue that all inpatients should benefit from close, if not continuous, monitoring (**Figure 2**). However, old habits die hard and hospital resources are limited so that the transition from intermittent spot-checks of vital signs towards continuous monitoring for all inpatients will likely take time. A first necessary step could be the identification of patients at high risk of clinical deterioration. This subset of inpatients could be identified using simple scores, such as a classic Early Warning Score (EWS) or the new PRODIGY score in patients receiving opioids (Khanna et al. 2020). These scores are easy to calculate but their sensitivity and specificity to predict adverse events remain limited. Once enough clinical and biological data have been collected in the electronic medical record (EMR) hospital system, predictive analytics may help to better identify patients at high risk of deterioration. For instance, the Safety Index, which is a smart fusion of five vital signs has been shown to predict cardiorespiratory deterioration hours before it becomes overt (Hravnak et al. 2011). The eCART, which is a machine learning-derived fusion of age, vital signs and lab data, has been shown to be the best predictor of cardiac arrest, ICU transfer and deaths when compared to the national EWS, the modified EWS and any individual vital sign (Churpek et al. 2016). In other words, **predictive analytics has potential to improve the prediction of clinical deterioration and rationalise the use of continuous monitoring techniques on the wards** (Michard and Teboul 2019).

What Should We Monitor?

All vital signs have potential value to detect clinical deterioration, but their respective value logically depends on the adverse event to be detected. For instance, in patients with cardiac disease or metabolic disorders (e.g. dyskalaemia), at high risk of cardiac arrhythmia, monitoring heart rate and heart rate variability may be the priority. In contrast, in patients hospitalised for the new coronavirus disease 2019 (COVID-19), who are susceptible to develop ARDS, monitoring RR and SpO_2 seems to be a minimum, and enables the calculation of the ROX index (Hill and Ruthazer 2019). Both RR and SpO_2 can be monitored with a pulse oximeter, which may also be useful to quantify the respiratory swings in the pulse oximetry waveform (aka pulsus paradoxus), an easy-to-measure marker of respiratory effort (Michard and Shelley 2020). In non-cardiac surgical patients, a nationwide study (Michard et al. 2015) including >200,000 patients from >500 US hospitals showed that most common postoperative

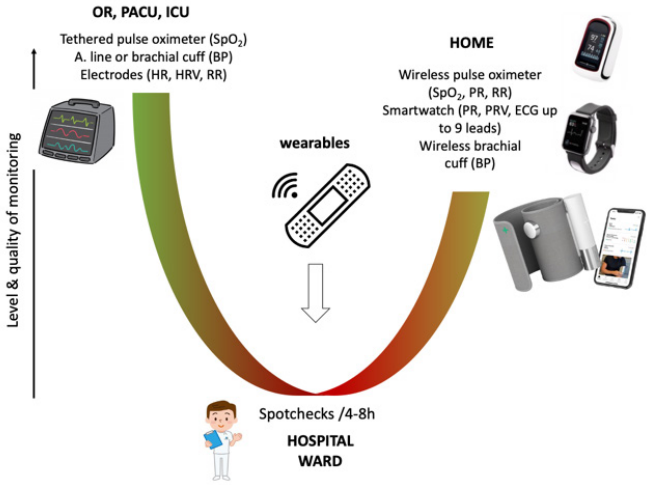

Figure 2. Filling the gap between ICU and home monitoring with wearable sensors
Abbreviations: OR, operating room; PACU, post anaesthesia care unit; ICU, intensive care unit; BP, blood pressure, HR, heart rate; HRV, heart rate variability; RR, respiratory rate; PR, pulse rate; PRV, pulse rate variability.

adverse events are respiratory and infectious complications, emphasising the importance of monitoring respiratory variables (RR and SpO_2) and temperature in this context. Evidence also suggests a strong association of postoperative hypotension and myocardial injury after non-cardiac surgery, and since this insult is devoid of clinical signs and symptoms, continuous monitoring of blood pressure is currently being investigated in pragmatic cluster randomised trials (clinicaltrials.gov/ct2/show/NCT04574908?term=khanna&cntry=US&state=US%3ANC&draw=2&rank=1). During post-operative patient-controlled analgesia (PCA) with opioids, rates of bradypnoea (RR < 10) lasting >3 min can reach 41% (Overdyk et al. 2007). Therefore, monitoring RR becomes the priority.

In the general medical and surgical ward population, studies have repeatedly ranked RR, HR and systolic BP as the top three variables to be monitored. In a study including >250,000 patients and using machine learning methods for predicting clinical deterioration in ward patients (Churpek et al. 2016), RR had the highest "weight" in the predictive algorithm followed by HR, systolic BP, temperature and SpO_2. In line with these observations, the National Institute for Health and Care Excellence in the UK stated that "RR is the best marker of a sick patient and is the first observation that will indicate a problem or deterioration in condition" (www.nice.org.uk/guidance/CG50). Anyway, most sensors are now able to measure several vital signs at the same time and the combination (aggregation or fusion) of several variables logically improves the ability to detect clinical deterioration at an early stage and may enable future algorithms to recognise specific patterns and suggest a diagnosis (Michard et al. 2020).

Conclusion

Most patients discharged from the ICU are at high risk of clinical deterioration and may benefit from close monitoring until they fully recover. There is today a gap between ICU monitoring and home monitoring options that could be closed by upgrading monitoring strategies on hospital wards **(Figure 2)**. Emerging solutions to improve and simplify patient monitoring on hospital wards include contact free sensors and wireless wearables. Both enable the early detection of clinical deterioration and may help to prevent severe adverse events such as cardiac arrest and ICU readmission. Wireless wearables give patients the freedom to leave their bed and increase their physical activity, which is useful to enhance clinical recovery, decrease hospital length of stay and improve patient satisfaction.

Conflict of Interest

FM is the founder and managing director of MiCo, a Swiss consulting and research firm. AKK consults for Edwards Lifesciences, Medtronic, Philips North America and Zoll Medical. AK is on the clinical advisory board for Retia Medical and is a founding member for BrainX LLC, a collaborative platform for research and development of AI products in healthcare. He is also funded with a Clinical and Translational Science Institute (CTSI) NIH/NCTAS KL2 TR001421 award for a trial on continuous postoperative haemodynamic and saturation monitoring. ■

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Post-Intensive Care Syndrome. A Necessary Harm in the Critically Ill?

Critically ill patients can develop a series of complications due to ICU risk factors that may lead to permanent disability. The implementation of strategies to reduce its incidence is essential.

Nowadays, the possibilities of survival of critically ill patients have grown due to technological and medical advances. This leads to a series of consequences owing to the critical pathology itself, medical procedures and the length of stay in the Intensive Care Unit (ICU). Many functional and physical impairments can be established during this critical time and remain even beyond hospital discharge. Furthermore, cognitive performance, psychological status and quality of life (QoL) can be compromised not only for the patient but for their family as well. A build-up effect can be generated if any of the impairments affect one or some of these individuals, starting from a disorder in a micro-state of the individual climbing up to an insult in their social role, establishing a disability that could not only affect the individual's functionality but the whole society as well (Van Zanten et al. 2013; Needham et al. 2012; Elliot et al. 2014).

Different modifiable and non-modifiable factors can influence the functional outcome of the critically ill patient. Modifiable factors and relatively simple interventions can be taken into consideration inside the ICU, focused on preventing functional complications. Some of these are early mobilisation (EM), reduced sedation, non-pharmacological anti-delirium measures and the empowerment of the family in patient care. Age, gender, previous functionality, chronic diseases, sarcopenia and fragility before hospital admission are some non-modifiable situations that can impact directly in the functional prognosis. Hence, the best way of predicting the future of the patient is by thoroughly and comprehensively knowing the individual's past. Complications that culminate into a disability should be considered in conjunct as Post-Intensive Care Syndrome (PICS) (Elliot et al. 2014).

The conceptualisation of PICS involves three specific domains: physical, cognitive and mental health related (psychological) functions. Any affection in these domains obtained in the ICU that endure through hospital discharge in the patient and its family (PICS-F) should be considered part of this syndrome, including paediatric population (PICS-p). Alterations after a patient's death are considered PICS-F. These impairments caused by PICS can perdure years after hospital discharge and an appropriate follow-up is needed in order to minimise the impact and presence of any disability (Harvey and Davidson 2016).

Post-Intensive Care Syndrome

PICS can affect the patient in the three domains mentioned above: physical, cognitive and mental health related (Elliot et al. 2014; Harvey and Davidson 2016).

Physical Impairment

The majority of the physical sequelae derives from ICU-acquired weakness (ICU-AW). ICU-AW is defined as a neuromuscular dysfunction alongside symmetrical and progressive muscular strength loss without any cause other than the admission into the ICU. It is clinically diagnosed with the Medical Research Council Sumscore (MRC-SS) of ≤ 48, or by the measurement of grip strength (< 7 kg in women and < 11 kg in men). The aetiology can be due to critical illness myopathy, critical illness polyneuropathy

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or a unity of both, known as critical illness polyneuromyopathy. Owing to the hypermetabolic state through which the critically ill patient undergoes, muscle mass is susceptible to decline drastically. This is associated with poorer outcomes. Therefore, nutrition and exercise are fundamental keys towards the preservation of muscular health (Turan et al. 2020; Farhan et al. 2016; Hermans and Van den Berghe 2015; Ali et al. 2008).

The incidence of ICU-AW oscillates between 25-100% resulting in longer lengths of stay inside the ICU and hospital, weaning failure due to its relation with diaphragm dysfunction, and increase in mobility problems and mortality. Physical sequelae, including ICU-AW, occur in 25-80% of individuals who undergo invasive mechanical ventilation (IMV) (Harvey and Davidson 2016, Vanhorebeek et al. 2020; Kress and Hall 2014; Desai et al. 2011). ICU-AW is much more complex than muscular atrophy secondary to immobility. It is a muscular disorder that compromises the excitability, quality, and mitochondrial function of the myocyte. This could lead to more severe complications such as muscle infiltrations and necrosis (Kress and Hall 2014; Sandri 2013). Alterations in functionality that come from ICU-AW can perdure years after hospital discharge, affecting directly the QoL and the possibility of reincorporation into their previous activities (Kress and Hall 2014; Formenti et al. 2019; Hopkins et al. 2017).

On the other hand, a deterioration in the resistance to physical exercise in patients undergoing critical illness has been found within 6 to 12 months after ICU discharge, characterised by a decrease in the metres travelled during the 6-minute walk test. Also, the patient can go through a decrease in respiratory function, especially those who have been treated for acute respiratory distress syndrome (ARDS) and in whom the pulmonary parenchyma is damaged permanently. Diaphragm dysfunction also may have a negative impact in resistance to physical exercise. Some patients have been found with a reduction in maximum inspiratory pressure (MIP) up to 15% even 12 months after discharge. Altogether, this generates a decrease in aerobic capacity that can influence the possibility to achieve a successful performance in basic life activities (Hopkins et al. 2017; Herridge et al. 2016).

Additional physical alterations have been reported and involve aesthetic and osteoarticular disturbances. Some of these include stiffness, pain, dental loss, frozen shoulder, skin damage by fluid overload, surgical scars, burns, damage due to endotracheal intubation, IMV, or oxygenation therapy such as post-extubation dysphagia and swallowing and phonation disorders that can have adverse emotional and social impact on the patient (Herridge et al. 2016; Beduneau et al. 2020).

Cognitive Impairment

Cognitive impairment occurs in 30-80% of patients admitted to the ICU. A decrease in correct chore execution, attention span, information processing, problem resolution and accurate perception in location and object position have been observed. Changes in neurological structures have been described among ICU survivors and have been associated with cognitive impairment and delirium. Lateral ventricle enlargement, brain atrophy in frontal lobes and hippocampus, altered white matter, corpus callosum and internal capsule are frequently related (Harvey and Davidson 2016; Desai et al. 2011; Hopkins et al. 2017; Herridge et al. 2016; Briegel et al. 2013; Brummel et al. 2015; Fernández-Gonzalo et al. 2020; LaBuzetta et al. 2019; Ohtake et al. 2018; Inoue et al. 2019; Haines et al. 2015; Davidson et al. 2013).

Delirium

Delirium is a common acute brain dysfunction that affects critically ill patients. Even though delirium was first described 50 years ago, it still remains an underdiagnosed condition in the ICU (Engel and Romano 1959). Evidence has been described in order to prevent, manage or treat delirium in important programmes such as the Society of Critical Care Medicine's (SCCM) 2018 Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility and Sleep Disruption in Adults Patients in the ICU (PADIS) and the ICU Liberation (ABCDEF) Bundle (Barr et al. 2013; Vasilevskis et al. 2018). In both of these,

Table 1. Strategies for PICS prevalence decrease in patients and family members

In patients:
-Risk factors reduction associated to PICS
-Early mobility programmes implementation
-Post-discharge follow-up programmes
-Early psychological assistance
-ICU diaries
-ICU humanisation
-Functional progress checklist
-ICU Liberation ABCDEF-GH Bundle

In family members:
-Family-centred care programmes
-Frequent and understandable communication about patient's condition and progress
-Shared decision making
-Early psychological assistance
-Family presence and participation in care programmes
-Skill development centered in post-discharge management
-ICU diaries and education on how to use them properly
-Functional progress checklist
-Information about PICS and PICS-F
-Knowledge in prevention and treatment of PICS-F

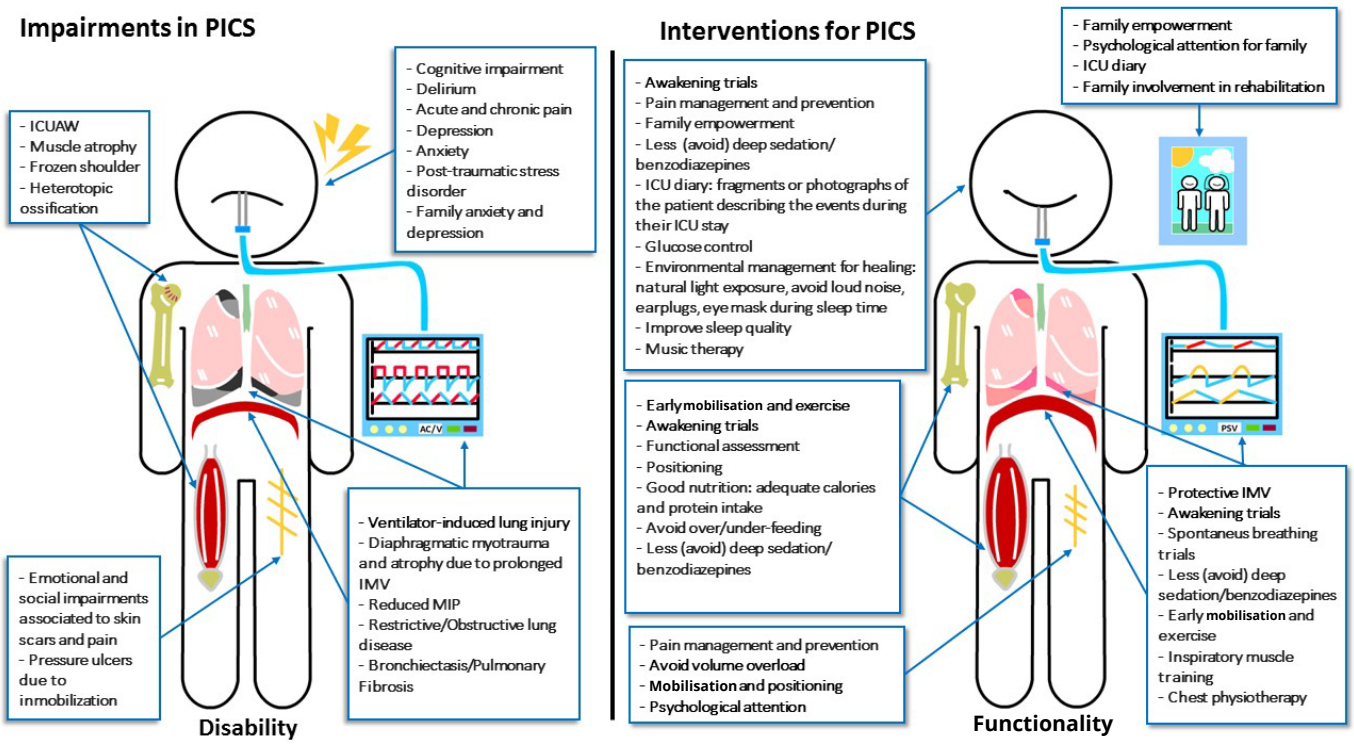

Figure 1. Risk factors for developing PICS (left) and Interventions aimed to prevent or minimise PICS prevalence in the ICU (right).
ICUAW = Intensive care unit acquired weakness; IMV = Mechanical ventilation; MIP = Maximum inspiratory pressure.

EM takes an important role to overpower many of the consequences that critical illness comes with, such as delirium. Delirium prevention and management is stated to need a multidisciplinary approach with routine delirium assessment with validated tools and a standardised EM process that is intimately related with minimising sedation, which means awakening and spontaneous breathing trials need to be in coordination (Trogrlić et al. 2015).

Delirium has been associated with an increase in morbidity, mortality, length of stay in the ICU and long-term cognitive impairment (Vasilevskis et al. 2018). Therefore, the need to assess and identify it is evident. The most common method to diagnose delirium in the ICU is the Confusion Assessment Method for Intensive Care Unit (CAM-ICU) (Salluh et al. 2009), with recent studies supporting its use over other ways of diagnosis. Delirium rates are varied depending on the population that is studied and over the interaction of other 100 risk factors described in the literature. A meta-analysis that included 16,595 patients going through a critical illness showed a delirium rate of 31.8% (LaBuzetta et al. 2019; Salluh et al. 2015; Arias-Fernández et al. 2018; Denehy et al. 2017).

The implementation of the correct measures is important for the prevention of delirium much like the decrease in sedation (specially with the use of benzodiazepines), analgesic optimisation in the presence of pain (supporting non-pharmacological measures), considering physiological sleeping time (avoiding nocturnal procedures), allowing sunlight exposure, avoiding restraints or any movement restriction and establishing effective communication channels between patient-staff and patient-family (Inoue et al. 2019; Pandharipande et al. 2010; Smonig et al. 2019; Devlin et al. 2018).

Mental Health-Related Impairments

Psychological consequences include anxiety, depression and sleeping disorders that can persist for months or years. Approximately 10-50% of patients undergoing clinical illness manifest post-traumatic stress disorder (PTSD), persisting up to eight years. These conditions do not only involve the patient but their family as well, during and after clinical illness or death (Harvey and Davidson 2016, Herridge et al. 2016; LaBuzetta et al. 2019; Inoue et al. 2019; Arias-Fernández et al. 2018, Wintermann et al. 2015; Parker et al. 2015).

Disability

The mobility level and participation in daily life activities (DLA) and daily life instrumented activities (DLIA) can suffer alterations after critical illness and, in some cases, patients may not be able to reach their functionality level prior to the ICU. A year after critical illness, 33% and 5% of the patients still have problems in at least one DLA or DLIA, respectively. Returning to previous occupation can also be compromised. Three months after ICU, only one third of the patients will return to their jobs and half of this population will return a year after discharge. Survivors of ARDS report an important decline in QoL and functionality up to two years after ICU - manifested by physical exercise intolerance, inability to work or depression (Herridge et al. 2016; LaBuzetta et al. 2019; Inoue et al. 2019; Devlin et al. 2018)

PICS is proven to have a high impact on functionality, QoL, survival and even in economic status among patients and family members overcoming critical illness. This highlights two main necessities: 1) Prevention, and 2) Lowering risk factors associated to PICS.

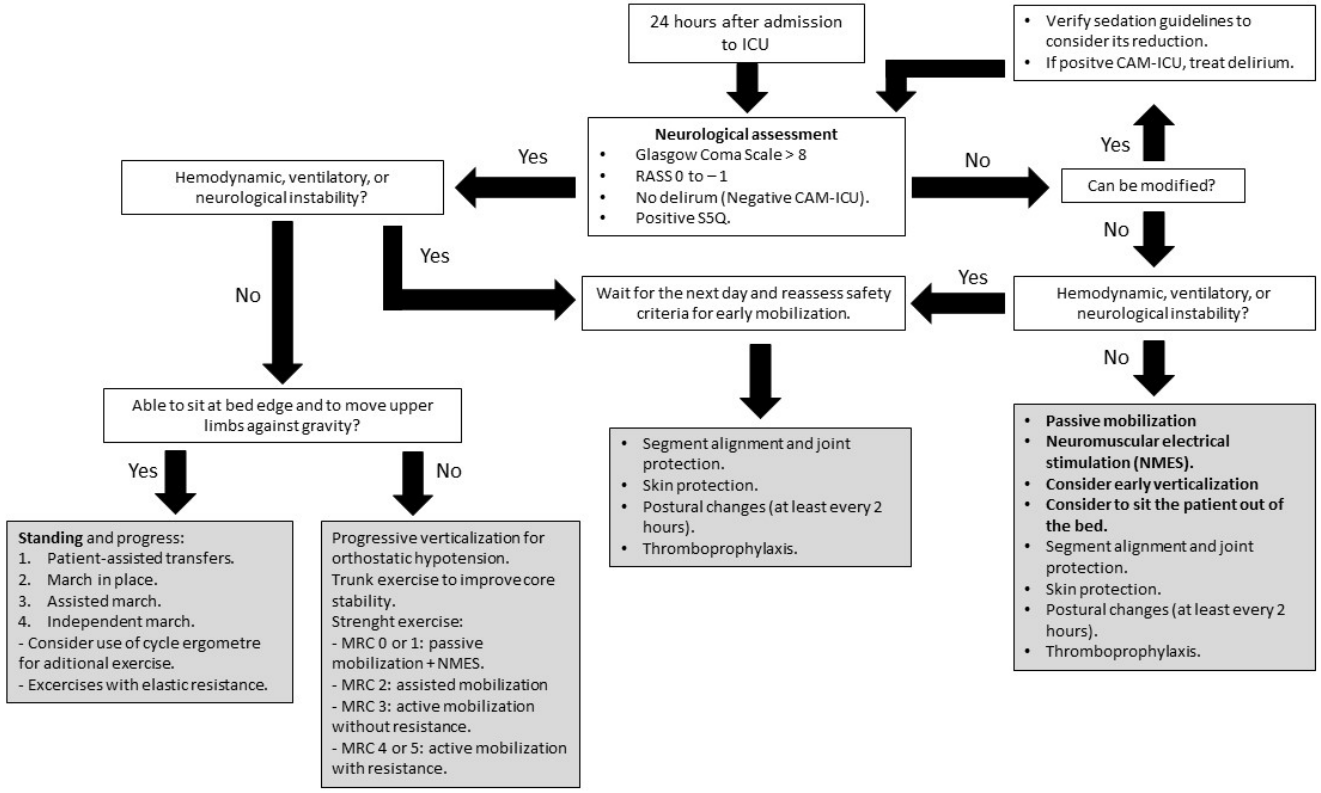

Figure 2. EM algorithm proposal

PICS Prevention Strategies

Identifying symptoms related to PICS can be challenging because of the lack of clinical follow-up between ICU stay, discharge, and home care. Hence, staff in charge of the critically ill patient must be aware of signs associated with PICS.

Prolonged immobility, days undergoing IMV, days inside ICU, sepsis, ARDS, hyperglycaemia, inflammation, hypoxia, electrolyte disorders, malnutrition, dysregulated opioid use, sedatives and neuromuscular blockers are all risk factors associated with PICS in any of its domains. In addition, the effectiveness in PICS management once it is identified tends to be, in the best case scenario, modest. This is why, the most effective way to defeat PICS, is by preventing and minimising its risk factors from day one (Herridge et al. 2016; Inoue et al. 2019; Pandharipande et al. 2010; Devlin et al. 2018; Wischmeyer and San-Millan 2015).

Up until today, the ICU Liberation (ABCDEF + GH) bundle proposed by the SCCM is one of the best strategies in PICS management. This bundle evaluates risks resulting from deep sedation, delirium and immobility (Inoue et al. 2019, Pandharipande et al. 2010, Devlin et al. 2018; Wischmeyer and San-Millan 2015). ABCDEF-GH stands for:

A. Assessment, prevention, management of pain;
B. Both spontaneous awakening and breathing trials;
C. Choice of analgesia and sedation;
D. Delirium assessment, prevention, management;
E. Early mobility and exercise;
F. Family engagement and empowerment; follow-up referrals and functional reconciliation;
G. Good handoff communication; and
H. Handout materials on PICS and PICS-F.

International guidelines provide the interdisciplinary and multidisciplinary teams a set of considerations, recommendations and tools needed for adequate identification and management of PICS (LaBuzetta et al. 2019; Inoue et al. 2019; Pandharipande et al. 2010; Devlin et al. 2018; Devlin et al. 2020). This set is stated in **Table 1** and schematically compared with risk factors in **Figure 1**.

Early Mobilisation – A Cornerstone Against PICS

Certainly, a key intervention in preventing and treating PICS is EM. EM refers to the "E" in the ABCDEF Bundle.

EM and exercise is a strategy used worldwide for the prevention of physical impairments during the ICU stay, among which, ICU-AW, pressure sores and deep vein thrombosis stand out (Wang et al. 2019). Active participation in exercise (referred to as movement generated by the patient) is preferable over passive movement (movement executed by complete assistance, with no voluntary effort by the patient) since it influences reduction in sedation, analgesia optimisation and humanisation of services inside the ICU (LaBuzetta et al. 2019; Inoue et al. 2019; Pandharipande et al. 2010; Devlin et al. 2018; Devlin et al. 2020; Martinez et al. 2020).

EM should start between the second and fifth day of critical illness (Cameron et al. 2015). The implementation of EM protocols based on functional objectives provides a different point of view in the management of the critically ill patient, guiding interventions for the prevention of disability after discharge. Muscular strength assessment through MRC-SS, grip strength or ultrasonography (qualitative and quantitative, like Heckmatt scale or muscular diametre) should be included in such interventions. Nevertheless, in order to achieve an integral approach, functional assessment will expose the true muscular status (Turan et al. 2020; Formenti et al. 2019; Parry et al. 2017; Annetta et al. 2017).

Broad spectrum of functional scales to assess the critically ill have been designed and can guide mobility in a dynamic perspective. It is worth mentioning that the tool selection to identify and

diagnose functional status depends on the needs of each service, time availability, and human and material resources at disposition (Parry et al. 2017).

Among the most recognised stand Chelsea Critical Care Assessment Tool (CPAx-Tool), ICU Mobility Scale (IMS), Perme Score, Physical Function in Intensive care Test (PFIT), Functional Status Score for the ICU (FSS-ICU), and others. Functional assessment will individualise the management and highlight opportunities for physical therapy (PT) personnel to prioritise. PT is crucial in the prevention of many of the impairments so far mentioned. One of the major tasks for experts in human movement and functionality is to prioritise the prevention of functional alterations. This is essential considering the association with higher care costs, non-reincorporation to labour activities and even death (Martinez et al. 2020; Parry et al. 2017; Saladin and Voight 2017; Sahrmann 2017).

Implementing an EM programme will assure the development of patient necessity based management and promote the functional preservation of the individual. The ultimate goal is to achieve a positive impact in QoL, socioeconomic status and family wellbeing (Hodgson et al. 2018;, Escalon et al. 2020).

For this purpose, we vastly recommend the implementation of EM programmes as a daily and common practice. An algorithm for the initiation of an EM programme, developed by our team, is illustrated in **Figure 2**.

Additionally,implementing EM programmes promotes the constant evaluation in sedation, analgesia and delirium. These evaluations can be made through known scales such as Richmond Agitation Sedation Scale (RASS), Confusion Assessment Method for the ICU (CAM-ICU) and Standardized 5 Questions (S5Q). Institutional EM programmes encourage ICU multidisciplinary teams to work towards functional objectives, decreasing the impact of immobility and consider the removal of unnecessary equipment, which is also a risk factor in the development of delirium and a barrier for EM (Hodgson et al. 2018; Zang et al. 2019).

Conclusion

Identifying, preventing and management of long term complications of critical illness is now part of the daily activities for health care providers. Paradigm change in management and objectives inside the ICU, and improvement in the awareness of PICS relies on the whole multidisciplinary team attending critically ill patients. Minimising risk factors associated with PICS requires effective communication, role and capacity recognition, and an understanding of the importance of these during the ICU stay. The correct use of these concepts allows the ICU environment itself to be perceived as an open space and where dialogues are encouraged for the benefit of the centre pieces in this puzzle - the paitents and their families.

Conflict of Interest

None. ■

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Out-of-Hospital Cardiac Arrest

Long-term outcomes and their predictors

Out-of-hospital cardiac arrests (OHCA) are associated with very high rates of mortality and poor cognitive outcome. This paper reviews long-term outcomes post OHCA and the pre-hospitalisation factors that predict them.

Introduction

Cardiac arrest is among the most common health emergencies worldwide, suffered by over a half million patients annually in the United States alone. Among these, roughly six in ten (61%) occur outside a hospital (Kronick et al. 2015). Estimates of mortality from out-of-hospital cardiac arrest (OHCA) vary widely, largely depending on the time point from which mortality is measured e.g., among all patients who suffer an OHCA or only among those who have already survived to hospital discharge. Considering all OHCA patients, the survival rate is low, generally ranging from 2-12% (Brison et al. 1992; Debaty et al. 2017; Hamilton et al. 2016; Hollenberg et al. 2005; Holler et al. 2007; Horsted et al. 2007; Geri et al. 2017; Sasson et al. 2010; Shuvy et al. 2017; Andrew et al. 2017a; Bunch et al. 2004a; Hawkes et al. 2017; Kempton et al. 2019). Alternatively, among patients who already have survived to hospital admission or discharge, long-term survival rates are much higher, with one-year survival of almost 50% reported amongst patients who survive long enough to receive treatment in an intensive care unit (Abazi et al. 2019), up to 90% or better among those surviving to hospital discharge (Andrew et al. 2017b; Shuvy et al. 2017).

Survival is not the only outcome of importance however, as some OHCA patients suffer potentially catastrophic, long-term cognitive and other neurological deficits that markedly impair their quality of life and level of independence, as well as activity-limiting fatigue in roughly half, and psychological symptoms like depression, anxiety and post-traumatic stress in roughly one third of patients (Moulaert et al. 2017). Of these, by far the most studied has been cognitive status which, in itself, is a predictor of long-term survival (Martinell et al. 2017). The purpose of the current paper is to review current knowledge on pre-hospitalisation predictors of long-term survival and long-term cognitive outcomes among adults who have experienced a non-traumatic OHCA.

Predictors of Long-Term Survival and Function

Compiling data from three large patient registries in which all non-traumatic cases of OHCA were counted, and for which data are published on survival both at hospital discharge and one-year post OHCA — from Australia (Andrew et al. 2017b) (n=33,212), Canada (Shuvy et al. 2017) (n=28,611), and the USA (Chan et al. 2016) (n=16,208) - totalling 78,021 patients, mortality rates at hospital discharge and one-year follow-up compute to 91.9% and 92.9%, respectively. This means that, of all the OHCA patients in these three databases who were deceased by one-year post OHCA, 98.9% of the deaths occurred prior to hospital discharge. For this reason alone, it is impossible to consider predictors of long-term survival from OHCA without also considering predictors of survival to hospital discharge. Consistent with this, discharge from hospital has also been identified statistically as an independent predictor of longevity post OHCA (Andrew et al. 2017b).

For both survival to hospital discharge and long-term survival, several potential predictors that precede a patient's hospital admission have been studied, including baseline patient characteristics, factors pertaining to assessment and treatment administered prior to hospitalisation, and the patient's health status at the time of hospital admission.

Baseline Patient Characteristics

The baseline patient characteristic that has most consistently been found to predict both short- and long-term outcomes is patient age, with both in-hospital and long-term survival consistently reduced among those who are older (Andrew et al. 2017b; Brison et al. 1992; Bunch et al. 2004b; Chan et al. 2016; Herlitz et al. 2005; Hiemstra et al. 2018; Martinell et al. 2017; Rey et al. 2020; Wang et al. 2005). In one study, among 131 patients discharged from the hospital, five-year mortality rates were more than five times higher (6 versus 34%) among patients under versus ≥65 years old ($p<0.001$) (Bunch et al. 2004b). All three published combined-factor models predicting long-term survival from OHCA include age as a factor (Herlitz et al. 2005; Martinell et al. 2017; Rey et al. 2020). Older age also appears to predict long-term functional outcomes post OHCA (Andrew et al. 2018; Bunch et al. 2004b; Martinell et al. 2017). In one retrospective registry analysis of 20,103 patients ≥65 years old, each 10-year increase in age was associated with 41% and 66% reductions in the odds of good functional recovery and independent living, respectively (Andrew et al. 2018).

Comorbid illness is another baseline patient characteristic that has been consistently identified as a predictor of OHCA outcomes (Andrew et al. 2017a; Antonelli et al. 2017; Jang et al. 2016; Kang et al. 2017; Nehme et al. 2016; Voruganti et al. 2018; Shuvy et al. 2017). Data show that comorbid illness in general (Andrew et al. 2017a), and specific comorbid illnesses like diabetes (Antonelli et al. 2017; Jang et al. 2016; Nehme et al. 2016; Voruganti et al. 2018), cancer (Kang et al. 2017; Shuvy et al. 2017), and renal failure (Antonelli et al. 2017), adversely affect both survival and

functional outcomes in OHCA patients. In one Australian study of 15,953 patients, worse scores on the Charlson Comorbidity Index were associated with both an increased rate of dying after hospital discharge, and reduced likelihoods of good functional recovery and health-related quality of life at 12-month follow-up (Andrew et al. 2017a).

Other baseline patient characteristics that appear to influence survival and functional outcomes are gender and race. In terms of gender, women appear to have a higher rate of mortality post OHCA than men (Blom et al. 2019; Mahapatra et al. 2005; Safdar et al. 2014), but the data are conflicting, In one study, women were less likely to be resuscitated and to survive to hospitalisation and hospital discharge, but these differences all were explained by more women having non-shockable rhythms when first evaluated (Blom et al. 2019). In another study, women were more likely to survive than men up to age 47, but less likely afterwards (Safdar et al. 2014). And, in a third study, though less likely to survive to hospital discharge, women were more likely to survive to hospital admission, and there was no difference in survival at five-year follow-up (Mahapatra et al. 2005). With respect to race, in a meta-analysis of 15 American studies, relative to Caucasians, African-American patients were less likely to survive both from hospital admission (OR=0.59, 95% CI= 0.48-0.72) and discharge (0.74, 0.61-0.90), but also less likely to receive bystander cardiopulmonary resuscitation (0.66, 0.55-0.78), have a witnessed arrest (0.77, 0.72-0.83) and have an initially-shockable cardiac rhythm (0.66, 0.58-0.76) (Shah et al. 2014).

Pre-Hospital Care

Among factors pertaining to the initial, out-of-hospital assessment of OHCA patients, one factor consistently shown to impact both short and long-term survival is the type of cardiac rhythm identified; more specifically, was the original rhythm identified by the EMT is shockable or non-shockable. Shockable rhythms include ventricular fibrillation and ventricular tachycardia, while non-shockable rhythms are asystole and pulseless electrical activity (PEA) (Soar et al. 2012). Consistently, survival has been found to be better among patients whose initial cardiac rhythm was shockable than non-shockable (Andrew et al. 2014; Dumas and Rea 2012; Goto et al. 2013; Grimaldi et al. 2014; Herlitz et al. 2005; Luo et al. 2017; Martinell et al. 2017; Meaney et al. 2010; Rey et al. 2020; Sasson et al. 2010; Shuvy et al. 2017; Thomas et al. 2013). This link between shockable initial rhythms and enhanced survival extends as far out as five-years post-OHCA. In one study, among 1001 (17%) of 5958 successfully-resuscitated OHCA patients who survived to hospital discharge, five-year survival from the time of hospital discharge was 73% among those whose initial cardiac rhythm was either ventricular fibrillation or tachycardia, versus just 45% in patients with asystole or PEA (p<0.001) (Dumas and Rea 2012). As for patient age, the presence of a shockable cardiac rhythm when first assessed is retained in all three published models predicting long-term outcomes in OHCA patients (Herlitz et al. 2005; Martinell et al. 2017; Rey et al. 2020). This said, survival has not been shown to be enhanced by converting an initially non-shockable rhythm to a shockable one prior to hospital arrival (Thomas et al. 2013), suggesting that supportive management to sustain patient circulation and oxygenation plays a larger role.

> **“some OHCA patients suffer potentially catastrophic, long-term cognitive and other neurological deficits that markedly impair their quality of life and level of independence”**

The initial cardiac rhythm identified, in turn, appears to be influenced by ambulance response time (Bunch et al. 2004a; Herlitz et al. 2005; Hollenberg et al. 2005; Hollenberg et al. 2007; Mathiesen et al. 2018) and time to initiating resuscitative efforts (Eisenberg et al. 1984; Rey et al. 2020). In one study comparing the two largest cities in Sweden, overall survival to hospital discharge was roughly 2½ times as common in Göteborg as in Stockholm (6.1 vs. 3.3%) (Hollenberg et al. 2005). Meanwhile, the average time between the cardiac arrest and ambulance arrival was 4.5 minutes less (8.5 vs. 13.0) and the likelihood of identifying ventricular tachycardia almost twice as high (31 vs. 18%) in Göteborg; otherwise, the two patient populations were similar.

Another factor that appears both to be linked to ambulance response time and to influence outcomes is whether a given patient is gasping when first evaluated by the EMT response team. For this potential outcome predictor, two meta-analyses have recently been published, encompassing 9822 and 10,797 patients, respectively (Zhang et al. 2018; Zhao et al. 2015). In the former analysis, gasping was associated with statistically-significant increases in rates for an initial shockable rhythm (RR=2.25; 95%CI=2.05-2.48), return of spontaneous circulation (ROSC: 1.87; 1.64-2.13), long-term survival (3.46; 1.70-7.07) and favourable neurological outcome (3.79; 1.86-7.73) (Zhang et al. 2018). The latter investigators generated a fixed effects model that identified gasping patients as 3.53 times (95% CI: 3.028-4.104; P<0.01) as likely to survive to discharge (Zhao et al. 2015).

Other factors associated with OHCA outcomes include whether a patient's collapse is witnessed by others (Herlitz et al. 2005; Lahmann et al. 2020; Sasson et al. 2010; Wang et al. 2005), whether it occurs at home or in public (Herlitz et al. 2005; Martinell et al. 2017), whether a bystander initiated cardiopulmonary resuscitation (CPR) (Herlitz et al. 2005; Mathiesen et al. 2018; Sasson et al. 2010), and whether a patient's OHCA occurs at night or daytime (Lin et al. 2019), with night-time OCHA associated with decreased survival up to 30 days post OHCA. Interestingly, despite consistent associations between patient outcomes and either ambulance response time or factors linked to ambulance response time (rhythm type, gasping), in a meta-analysis of 46,417 patients, no link was identified between outcomes and the time required to transport patients to a hospital (Geri et al. 2017).

Epinephrine

Numerous contradictory studies have been published on the potential effectiveness of epinephrine, administered either in the field or emergency room to assist in restoring a functional cardiac rhythm. These include the recent publication several meta-analyses (Atiksawedparit et al. 2014; Aves et al. 2020; Kempton et al. 2019; Lin et al. 2014; Ng and Teoh 2019), also yielding conflicting results. In two slightly older meta-analyses published in 2014 (Atiksawedparit et al. 2014; Lin et al. 2014),

no benefit of epinephrine was detected, either for survival at any time point or for neurological outcomes. In a third, more-recently published meta-analysis, a greater percentage of patients survived to hospital admission; but no survival benefit was observed beyond this (Kempton et al. 2019). In a fourth meta-analysis, relative to receiving placebo or nothing, those who received epinephrine experienced an increased rate of ROSC, and increased survival at both hospital admission and discharge (Ng and Teoh 2019); while in the fifth, survival benefits were noted through three months (Aves et al. 2020), largely due to the inclusion of a recently-published randomised clinical trial (RCT) in which a slight increase in overall survival (3.2 vs. 2.4%) was observed at 30 days among those receiving epinephrine versus placebo (Perkins et al. 2018). In that same RCT, however, severe neurological impairment was more common (in 31 vs. 18%) among those receiving epinephrine. Consistent with this, no neurological benefit of epinephrine was detected in any of the five above-noted meta-analyses (Atiksawedparit et al. 2014; Aves et al. 2020; Kempton et al. 2019; Lin et al. 2014; Ng and Teoh 2019). Other studies assessing long-term outcomes among patients receiving versus not receiving epinephrine have generally identified decreased survival among epinephrine recipients (Grimaldi et al. 2014; Martinell et al. 2017; Reynolds et al. 2019; Wang et al. 2005). Epinephrine use also remains as one of ten predictors of poor long-term outcome post OHCA in a model with an area under the curve (AUC) of 0.842 (0.840-0.845), along with older age, OHCA at home, initial non-shockable rhythm, longer duration of no flow or low flow, bilateral absence of corneal and pupillary reflexes, Glasgow Coma Scale motor response=1, lower pH, and a partial pressure of carbon dioxide in arterial blood value <4.5 kPa at hospital admission (Martinell et al. 2017).

Patient Status at Hospital Presentation

An OHCA patient's clinical status upon hospital arrival also impacts the likelihood they will survive to hospital discharge and beyond. For example, as stated earlier, converting a non-shockable to a shockable rhythm by the time of a patient's arrival at the hospital does not appear to impact survival (Thomas et al. 2013), suggesting that other factors, other than the rhythm itself, are outcome determinants. This conjecture is supported by the association between indicators of oxygenation and tissue perfusion - like arterial pH (Martinell et al. 2017; Reynolds et al. 2019) and blood lactate level (Grimaldi et al. 2014) - and survival. Such factors were included in the predictive model of survival published by Martinelli et al. (2017), as was a longer duration of no flow or low flow, adrenaline administration, bilaterally absent corneal and pupillary reflexes, and a Glasgow Coma Scale (GCS) motor score=1 (Martinell et al. 2017). A higher overall GCS score at hospital admission has also been linked to better long-term neurological outcomes (Corrada et al. 2013; Hifumi et al. 2015).

Conclusions

Long-term survival with good cognitive outcomes remains very uncommon after an OHCA. Young patients who are otherwise in good health, accessed quickly by EMT services, are gasping, and having a shockable cardiac rhythm do best, as do those presenting to the emergency room with less-impaired cognitive function. Those whose OHCA occurs at home, limiting the likelihood of witnesses and bystanders to initiate CPR, do worse. Using all these criteria except gasping as part of the predictive model proposed by Herlitz et al (Abazi et al. 2019), survival likelihood among those for whom all six criteria are favourable is almost 60 times higher (23.8 vs. 0.4%) than among those with all six criteria unfavourable. Unfortunately, only one of the seven above-listed criteria (ambulance response time) is modifiable. Given that up to 50% of OHCA patients are alive when they reach emergency rooms, besides hastening ambulance arrival, further research is necessary to identify ways to modify the course of OHCA once patients arrive in hospital.

Conflict of Interest

The author of this paper has no conflicts of interest to report, and no funding of any kind was received for the preparation or submission of this manuscript. ■

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Rehabilitation of the Critically Ill: The Role of Allied Health Professionals

Rehabilitation and recovery following ICU admission aims to improve patient outcomes, optimising function and recovery. Allied health professionals are key members in the multidisciplinary team, positively contributing to the rehabilitation pathway.

Survivorship after admission to intensive care (ICU) has moved beyond mortality. Reducing associated morbidity, and improving the quality of physical, cognitive, and psychological recovery for patients is the primary focus and goal of the multidisciplinary team (MDT). The COVID-19 pandemic has increased utilisation of ICU beds globally (Grasselli et al. 2020; Richardson et al. 2020), highlighting the need to plan and implement rehabilitation services on a larger scale, during and after ICU discharge (Ceravolo et al. 2020; Hosey and Needham 2020). This narrative review aims to describe the essential role of allied health in the recovery and rehabilitation of adults across the arc of care from ICU admission through to post-hospital settings.

Allied health professionals (AHP) work within the multidisciplinary team, to provide expertise in the assessment and diagnosis of functional, biological and psychosocial impacts of illness and rehabilitation of patients admitted to ICU. Although there are a number of diverse professions within allied health, published evidence has reported the benefits of dietetics, physiotherapy, social work, and speech pathology within provision of ICU care to enhance patient rehabilitation and outcomes (Berney et al. 2012; Freeman-Sanderson et al. 2016; Hodgson et al. 2016; Tipping et al. 2017). Recently with the global pandemic, ICU workforce planning with AHP inclusion is a pivotal component of ICU recovery pathways (Marshall et al. 2020; National Post-Intensive Care Rehabilitation Collaborative 2020; Ridley et al. 2020b). Workforce training and skill development are indicated to provide this specialist level of care (Intensive Care Society 2018). The provision of patient-centred care from AHPs aims to reduce impairment, to increase activities and participation that considers and reflects individuals' needs and goals during and after their admission to ICU.

Admission to the ICU can result in both short and long-term physical, psychological, and cognitive changes to an individual's function - recognised as post-intensive care syndrome (Needham et al. 2012). Increased severity of illness and necessitation of prolonged mechanical ventilation can result in physical impairments including decreased mobility, muscular strength, endurance, and reduced nutrition intake. Yet the ability to predict post-ICU impairments is currently limited (Haines et al. 2020). A combination of physical and cognitive impairments after ICU admission impact on an individual's activities beyond hospital discharge, with one third of ICU survivors unemployed 60 months post-admission (Kamdar et al. 2020; McPeake et al. 2019b).

The World Health's Organization International Classification of Functioning, Disability and Health (ICF) is a framework for measuring an individual's health status across the domains of function, participation and activity, and in various environments and contexts (World Health Organization 2001). Measuring health status needs to consider the impact beyond impairment itself, and consider impact on function and wider social and community participation. Additional to measurement of function and disability, quality of life is an important construct but is unique to each individual and

their own conceptualisation. Within the critical care context, AHPs work to address future disability and to maximise patient participation, which has societal impacts. Our patient-centred approach to care delivery specifically addresses key elements of the WHO's ICF framework.

Dietetics

The role of the dietitian within critical care varies internationally depending on the country of training and practice. In many settings, Dietitians specialising in critical care provide expert recommendations based on many aspects of nutrition care including use of medical nutrition therapy for various clinical conditions and modification of dietary strategies to improve nutrition intake.

As the focus of the MDT moves to survivorship and quality of recovery, we are also learning about nutrition and the challenges during critical illness. Thus, the role of the dietitian is expanding to encompass more of the varied skills dietitians can offer, but which were not utilised previously in critical care. In previous years, the focus of nutrition was during the ICU period alone, and specifically on the provision of nutrition via a gastric tube (enteral nutrition) or intravenously (parenteral nutrition). Literature has shown in the past that dietitians spend the most amount of time with patients who are within ICU receiving enteral nutrition (Chapple et al. 2016). But, as the population within critical care, medical care and our understanding of nutrition has evolved, it is becoming clear that those who eat oral food and/or are non-mechanically ventilated may be at greatest nutrition risk. Multiple studies have now shown that oral nutrition intake both within and outside of ICU in critically ill survivors is well below clinician estimates (Peterson et al. 2010; Ridley et al. 2020a; Ridley et al. 2019; Rougier et al. 2020) and the issues faced by patients in relation to ability to eat are far more complex than originally appreciated and can be loosely divided in patient, clinical and system factors (Ridley et al. 2020a). It is now vitally important that effective models for nutrition care that will assist in patient recovery are explored.

Within ICU, dietitians play an important role in the advocacy and monitoring of nutrition progress within the context of the individual patient's clinical condition, as well as providing expert advice regarding strategies to manage any problems encountered. In the late ICU and post-ICU period, the role for dietitians should be to tailor individualised nutrition plans to patients based on the specific barriers each patient is facing regarding nutrition intake. This should include dedicated individual assessment, nutrition interview and counselling with patients and families to come up with a personalised plan. Other important considerations for the future that will contribute to our understanding about the impact of nutrition and dietitians in recovery include; education of medical and nursing in the understanding and appreciation of nutrition care, as well as the complex issues experienced (Merriweather et al. 2014); advocacy for improvements in hospital food service systems to better meet patients nutrition needs (McCray et al. 2018), and ensuring a dedicated nutrition handover is provided on transfer from one hospital location to another (Merriweather et al. 2014). In the future, understanding the impact of extension of nutrition care beyond hospital discharge, to rehabilitations and/or home, as well as the model of care dietitians could use in these periods is a vital gap for investigation.

> **"published evidence has reported the benefits of dietetics, physiotherapy, social work, and speech pathology within provision of ICU care to enhance patient rehabilitation and outcomes"**

Physiotherapy

Physiotherapists are commonly embedded within the ICU team. Within some countries such as Australia, physiotherapists are primary contact practitioners (Berney et al. 2012). An advantage of the Australian model is that physiotherapists within the ICU can independently and comprehensively screen, assess, and treat physiotherapy amenable problems (Berney et al. 2012), without relying on other clinicians to make a referral to physiotherapy (where there is potential for some problems to be missed). Treating muscular weakness and restoring physical function via exercise rehabilitation, are primary aims of physiotherapy in the ICU setting, and across the spectrum of care.

Moderate to high quality evidence supports the use of physical rehabilitation interventions early in critical illness, although there is limited evidence of effects of interventions delivered post-ICU discharge (Connolly et al. 2016). Key exercise rehabilitation interventions can include functional retraining such as sitting, standing, marching on the spot or walking - all tasks with high-specificity to achieve a level of function to support discharge from hospital. Other newer modalities in the ICU include use of functional neuromuscular electrical stimulation, in-bed cycling (Nickels et al. 2020), and use of technological adjuncts such as Nintendo Wii video gaming. Families are also an integral aspect of supporting the rehabilitation process within and beyond the ICU, and should be invited to be engaged in rehabilitation dependent on both patient and family preferences, and the ability of clinicians to support family members in this process (Haines 2018).

Post-ICU discharge, physiotherapists continue to care for patients across the arc of care. ICU-based physiotherapists often have experience working across this arc of care, which makes them uniquely positioned within the ICU team to provide this 'whole of health service' view, that is distinct from other members of the ICU team who often practice solely in the ICU setting. Such knowledge, experience, and skills may be leveraged to help support patients and their families across the transitions of care, which can be a source of high stress for patients and families.

Goals of ward-based care are to continue to restore the patient's function to a level that is commensurate with returning home or to supported living facilities, and to facilitate hospital discharge and referral onto community-based rehabilitation services. Post-ICU programmes such as ICU follow-up clinics and peer support groups are currently being explored as a

strategy to mitigate post-intensive impairments (McPeake et al. 2019a). Such programmes are often designed replicating the interprofessional ICU team (Haines et al. 2019), and should include physiotherapists as experts in physical rehabilitation.

Social Work

Social workers consider the psychological, social, economic, cultural and environmental factors which impact the health and wellbeing of patients and their supports during an ICU admission. Social work in ICU aim to maximise independence, self-determination and the wellbeing of patients (Australian Association of Social Workers 2016; Simpson et al. 2016). A myriad of services are provided by social workers to patients and their support networks throughout their ICU admission and rehabilitation including psychosocial assessments, facilitation of complex communication between parties, grief and bereavement support, adjustment to illness/reduced function, counselling, risk assessments, crisis intervention, practical assistance and education. Child focused approaches to care are also championed by social workers, where the impact of the ICU admission on the children's wellbeing and long term health is considered (Laurent et al. 2019). Locating social work in ICU allows for the identification of complex psychosocial needs, delivery of trauma informed interventions and initiation of complex discharge planning. Alongside the multidisciplinary team, social work expertly navigate the interface between health and community services (e.g. National Disability Insurance Scheme, Centrelink, housing services) throughout the patient's hospital admission and advocate for sustainable, patient centred care.

Decision making

In the ICU, social workers aim to optimise patient's capacity to make informed decisions, practice self-determination and receive equitable access to health care. Social workers play a key role in facilitating patient led decision making, particularly when decision making capacity is impaired. Expertise in relevant legislation and ability to navigate complex psychosocial situations allows social workers to maintain focus on patient's wishes and preferences, facilitate supported decision making and respond to risk during ICU admission and throughout rehabilitation. Furthermore, social workers in ICU provide support to patient's loved ones who face challenging decisions regarding medical treatment and shift to palliative approaches. Furthermore, social workers in ICU provide support to patient's loved ones who face challenging decisions regarding medical treatment and shift to palliative approaches.

> "a combination of physical and cognitive impairments after ICU admission impact on an individual's activities beyond hospital discharge, with one third of ICU survivors unemployed 60 months post-admission"

Adjustment and loss

An admission to ICU commonly results in physical, psychological and social changes for patients and their supports. For many an ICU admission induces feelings of terror, dread, uncertainty, loss of control and fear of death. Concurrently, patients and families face psychosocial stressors associated with extended hospitalisation and changed function, including financial stress, homelessness, unemployment, child safety concerns, disability issues, immigration and legal matters (King et al. 2019; Moon & McDermott 2020). The location of a social worker in the ICU multidisciplinary team allows for timely specialist psychosocial support and counselling for patients and their support network.

Education and information

The delivery of repeated, clear and accessible health information to patients and their support networks during an ICU admission may improve understanding, reduce distress, aid long term recovery and initiate adjustment to changed physical, psychological and social abilities (King et al. 2019; Lee et al. 2009; Simpson et al. 2016). Social workers regularly assist in coordinating and supporting the delivery of complex health and social care information to vulnerable patients and their supports, through leadership of family meetings, engagement of communication supports, and regular 1:1 meetings (Simpson et al. 2016). Social workers continue this role as patients transition throughout the health service and require support to enter into the complex social care system, in readiness for discharge.

Speech Pathology

Speech Pathologists provide management and rehabilitation for communication and swallowing functions for patients during, and in the post-ICU recovery period (McRae et al. 2019; Royal College of Speech & Language Therapists 2020). Scope of practice extends to the management of both ventilated and non-ventilated patients, however models of care and access to speech pathology services vary across ICUs (Cardinal et al. 2020).

Communication

Communication is multifaceted and can encompass production of voice, speech, and language comprehension and expression. Patients admitted to ICU can experience one, or many changes to their ability to effectively communicate. Physical and environmental factors including underlying medical aetiologies, or iatrogenic sources as artificial ventilation via endotracheal and tracheostomy tubes can result in decreased communication function (Freeman-Sanderson et al. 2019). Speech pathologists provide restoration and rehabilitation of communication function during and after ICU admission, education, training, and advocacy for communication rights across the arc of recovery (McLeod 2018).

Specific to the ICU population, speech pathology aims to increase effectiveness of patient communication via voice restoration (Freeman-Sanderson et al. 2016; McGrath et al. 2019) or through provision of alternative and augmentative communication systems (Hemsley et al. 2012), ultimately

aiming to increase patient involvement in their care choices and decisions (Karlsen et al. 2020). Disordered voice quality, or dysphonia, is commonly reported in patients post-extubation (Brodsky et al. 2018) resulting in altered voice quality and loudness. Recovery of voice can be protracted beyond ICU admission (Miles et al. 2018), with impacts of dysphonia leading to reduced participation in social settings, and reduced quality of life (Golub et al. 2006). There is also increasing evidence of cognitive communication deficits following critical illness and ICU admission (Helms et al. 2020) with persistent deficits equivalent to moderate traumatic brain injury (TBI) and mild Alzheimer's disease (Pandharipande et al. 2013). Social inclusion, participation, and relationships are negatively impacted with cognitive communication disorders (Palmer et al. 2016), highlighting a need for ongoing rehabilitation. The benefits of inclusion and training of communication partners on communication effectiveness in TBI have been established (Togher et al. 2013), and further investigation of the impact and effectiveness of communication rehabilitation post-ICU is needed.

Swallowing

Changes to function including the ability to safely and effectively swallow, eat, and drink are commonly reported during and post ICU (Brodsky et al. 2020a; Macht et al. 2011). Disordered swallowing, termed dysphagia, is a common sequelae of ICU admission and is multifactorial in aetiology (Skoretz et al. 2020; Skoretz et al. 2010). Dysphagia has been described in ICU patients following artificial ventilation (Brodsky et al. 2017; Brodsky et al. 2020b) with severity of critical illness associated with protracted recovery post-ICU (Zielske et al. 2014). Patients can be at increased risk of silent aspiration, and require access to early speech pathology assessment and rehabilitation to maximise safety and reduce further associated morbidity such as aspiration pneumonia and malnutrition (Daly et al. 2016). Informed decision making for management of dysphagia during and post-ICU admission can be facilitated with the use of instrumental assessment (Dziewas et al. 2019) and multidisciplinary team management (Brodsky et al. 2020b). The role of speech pathology in ongoing rehabilitation of swallowing function in the post-ICU patient includes optimisation of oral intake, use of compensatory strategies and rehabilitation of swallow function.

Conclusion

Allied health professionals provide specialised and targeted patient rehabilitation to patients across the arc of care – from ICU to through to post-hospital settings to optimise recovery. Rehabilitation aims to improve and increase function to reduce disability and subsequent impact on an individual's activities and participation. Rehabilitation goals aim to target physiological, physical, cognitive, and psychosocial facets of health and empower ICU survivors to thrive in their day to day life. Whilst the trajectory of post-ICU recovery is yet to be fully understood, inclusion and early access to AHP during ICU admission and along the ICU recovery pathway should be considered.

Conflict of Interest

EJR has received honorarium from Baxter Healthcare (United States and Australia), Nestle and Nutricia (Australia). ■

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For full references, please email editorial@icu-management.org or visit https://iii.hm/15y5

THE POST-ICU PATIENT

KEY FACTS

1. Post-intensive care syndrome (PICS) refers to a condition when a patient experiences new or worsening impairment in the physical, cognitive, or mental domain after ICU admission
2. These impairments could persist beyond the ICU for as long as 5 to 15 years
3. One-third of patients do not go back to work, another third of patients do not go back to their pre-ICU job or pre-ICU salary
4. ICU survivors are at high risk for readmission to the hospital and ICU
5. One quarter of patients require assistance in activities of daily living a year after ICU admission
6. Approximately half of families providing care have to make a major adjustment to their lives

Source: https://breathe.ersjournals.com/content/15/2/98

ICU-ACQUIRED WEAKNESS (ICUAW)

- Muscle weakness that develops during an ICU stay
- Occurs in **33%** of all patients on ventilators
- Occurs in **50%** of all patients admitted with sepsis
- Occurs in up to **50%** of patients who stay in the ICU for at least one week

Source: https://www.sccm.org/MyICUCare/THRIVE/Post-intensive-Care-Syndrome

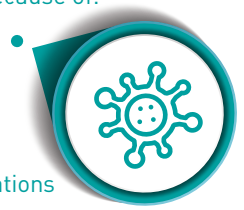
CHALLENGES FOR ICU SURVIVORS

- ANXIETY AND POST-TRAUMATIC DISORDER
- DEPRESSION
- CHRONIC PAIN
- BONE LOSS
- MUSCLE LOSS
- PROBLEMS WITH PHYSICAL FUNCTION
- COGNITIVE IMPAIRMENT
- ANXIETY AND STRESS FOR FAMILY AND CAREGIVERS

Source: https://bjgp.org/content/67/663/477

PICS AND COVID-19

Patients with COVID-19 are at a higher risk of PICS because of:



- Constraints on social support
- Prolonged mechanical ventilation
- Exposure to high amount of sedatives
- Limited physical therapy due to risk of infection transmission
- Limited access to post-ICU care due to services limitations and restrictions
- Limited visitation policies

Source: https://www.ccjm.org/content/early/2020/07/29/ccjm.87a.ccc055

PREVENTION INTERVENTIONS FOR PICS

- → ABCDEFGH bundle
- → Nutrition therapy
- → Environmental management
- → Improved communication
- → Family support
- → Family presence in the ICU
- → Specific consultations
- → Shared decision making

Source: https://onlinelibrary.wiley.com/doi/10.1002/ams2.415

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Using Realistic Simulation to Design a New PICU

Building before building: designing the dream PICU

Hospital Sant Joan de Déu (HSJD) is a paediatric and maternity hospital located in Barcelona. In 2018 the new 24-bed Pediatric Intensive Care Unit (PICU) was inaugurated, featuring modern facilities and the latest technology. We moved from an area with open spaces to a unit structured into individual rooms, in order to facilitate 24-hour access for parents. This represented a major challenge in terms of space and process design. We decided to use clinical-simulation-based analysis strategies to understand the implications of the transition to enclosed patient rooms and to optimise design elements related to safety, efficiency, and patient and family experience. In this article, we will explore how this service line was applied to the creation of our new PICU.

The construction of the new PICU was a challenge in terms of space and process design. The application of simulation to construct this new unit was a collaboration between the PICU, the HSJD Simulation Program, and the Boston Children's Hospital Simulator Program (SIMPeds), Boston MA. Since 2014, HSJD and SIMPeds have maintained a collaboration agreement where SIMPeds provides support and mentorship to accelerate the development of the HSJD Simulation Program among four service lines focused on systems analysis (SIMTest), team performance (SIMTrain), scaling of training (SIMNetwork) and production of novel simulators and training devices (SIMEgineering). The SIMTest line, consists of evaluating spaces, processes and equipment using highly realistic clinical simulation.

Why Did We Use Simtest Simulation to Design the New PICU?

It is readily understandable how useful it is to test a product before putting it on the market. Nevertheless, this practice is common in other industries but rare in healthcare. SIMtest consists of bringing together professionals, simulators, actors, real medical equipment and even patients and families, in a real or pre-built facility, to understand the work in depth and resolve questions about work spaces and processes. The SIMTest methodology has a several conceptual foundations that are important to emphasise

The first is the model of different perspectives of work, as described by Shorrock: -- namely "work as imagined", "work as prescribed", "work as disclosed" and ultimately and most precisely "work as done." In practice, these four perspectives never completely overlap. Through SIMTest, we attempt to bridge the gap between work-as-imagined and and most closely approximate work-as-done. And we do it in a physically and psychologically safe environment, where an error or a design deficiency has no consequence for patients and professionals.

The second is Argyris' double-loop reflection model – referring to the finding that humans have deeply held mental models or "frames" (Eg. assumptions, culture, unwritten rules, personal factors) that drive their decisions and actions. Through SIMtest debriefings we are able to reveal those mental frames and better understand how people tend to prefer to perform work in a certain way. This information is essential to designing ergonomic and intuitive work environments and processes for greatest safety and efficiency.

The third pillar relates to "Safety Model" – namely "Safety 1 and Safety 2." According to Hollnagel, preoccupation with traditional primary focus on error and risks ("Safety 1") often leads to an underappreciation of an equally important safety force – namely inherent human resilience and prevention measures ("Safety 2), understanding things that go well in daily work. Fostering an appreciation for both Safety 1 and 2 is the key to creating the largest impact on quality, efficiency and patient safety. SIMTest offers opportunities to elucidate and illuminate Safety 2 activities within the system.

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How Did We Implement SIMtest?

The planning and execution of a SIMTest activity is a process with several stages, which are specified in **Figure 1**.

Firstly, conducting an accurate needs assessment is critical to the entire process. We carried out working sessions with a multidisciplinary group of professionals, months before the simulations took place. In the case of the new PICU, the main goal was to analyse key aspects of the transition to individual, enclosed treatment cubicles. Three specific sets of concerns were identified: one related to space (room size, internal distribution, visibility), one related to work processes (adaptation of current processes and new ways of working), and one related to the families' experience (comfort, balance between privacy and safety).

We performed two separate operations: one before building the unit (pre-construction simulations) and another after building it but before admitting patients (post-construction simulations).

Each involved the design of highly challenging simulation scenarios for specific concerns, which were prepared with the relevant technical and logistical aspects in mind. It is important to note that the "worst case" scenario generally allows for a greater number of safety risks and successful adaptations to be identified and for participants' mental frames to emerge more clearly. The SIMTests pose a considerable technical challenge, so having an experienced simulation engineering team is critical.

Each simulation session consisted of an initial briefing (to review objectives, clarify operational roles and rules, and create a psychologically safe environment) and several consecutive scenarios, with their corresponding debriefings. These structured debriefing sessions were conducted by experienced facilitators. In the ensuing discussions, the views of participants and observers were collected and a logical "observation-cause-effect-solution" workflow was followed.

After the simulations, the team conducted a post-process information analysis and wrote a final report on the findings relevant to the design of the new PICU. Sometimes, possible solutions emerged during the debriefings and were included in the report. In other cases, the collected findings allowed the PICU and hospital managers to subsequently identify the most successful solution for each challenge.

What Simulations Did We Use to Get the Most Information?

Pre-construction simulations

Objectives: To address aspects related to room size, internal layout, and the family experience. Additionally, the details of particular work processes that could affect architectural decisions were explored.

Logistics/Implementation: A full-scale part of the future PICU was built in an unused area of the hospital, following the official draft architectural plan. The walls were made of drywall and high-fidelity patient simulators and real medical equipment were placed inside (**Images 1 and 2**). The participants were in-house teams of physicians, nurses, and nurse assistants from the PICU, as well as non-PICU staff when required by the scenario. Actors were incorporated to play the role of families, in order to allow teams to decide their location in complex situations and also to incorporate their experiences. Observers from different disciplines (leading physicians and nurses, engineers, architects, safety and patient experience experts, etc.) were placed at specific viewing points that did not interfere with the scenarios. A total of 62 people were involved in the execution of the 6 scenarios: 35 professionals and actors, 17 observers, and 10 members of the SIMTest team.

During the 3-day SIMTest operation, 6 scenarios were run in the full-scale PICU mock-up. The scenarios were situations that stressed the system and were focused on:

- Assessing the suitability of the planned room size in different situations (e.g., the standard 24 m2 cubicle in cannulation of ECMO patients).
- Identifying elements of the rooms that contribute to or hinder efficient and safe care delivery during critical events.
- Identifying concerns and potential solutions related to transitioning from an open layout to enclosed cubicles.
- Determining the optimal location for the preparation of urgent medications.
- Identifying equipment solutions for families to promote parental presence in closed cubicles (striking a balance between comfort and safety).

After-action review/Debriefings: The structure of the debriefing sessions was determined by the test objectives, although elements related to patient safety, the viability of different processes, and the participants' experiences were always considered. In some cases a rapid simulation-debriefing cycle was used, in which modifications were made to the working environment based on observer feedback during the initial debriefing and parts of the simulations were repeated to test the effectiveness of the proposed changes.

Results: The simulations contributed to decisions about important aspects of the new PICU project. The final report compiled 49 sets of relevant observations and possible solutions identified during the debriefings. In a post-processing stage, the data were analysed in depth, risks and causes were assessed, and final solutions were proposed.

The pre-construction SIMTest allowed some hypotheses regarding the practical use of spaces to be validated. It was found that it was possible to cannulate ECMO on a patient in a standard-size room, as an alternative to larger treatment cubicles planned for more complex patients. It was also possible to perform CPR safely in the smaller rooms.

Figure 1. SIMtest process

The analysis of spaces suggested the appropriateness of incorporating specific elements into the structure of the new PICU cubicles. Examples include the decision to make the parent beds collapsible and wall-mounted to increase work space if needed or positioning a nursing station every 2 rooms to improve safety.

Post-construction simulations

Once built and before admitting real patients, the new PICU was "opened" for 3 days with 6 simulated patients.

Objectives: Focus on the adaptation of work processes to the new environment: it was no longer a question of "where" to work, but rather "how" to do it. It aimed to explore processes that involved intense multi-professional interaction and that were highly dependent on the physical environment: preparation of medications, requests for mutual support between nurses in different situations, organisation of people and resources during a critical event, and the transfer of complex patients between treatment cubicles inside the PICU.

Logistics/Implementation: Seven different scenarios were run in real time with the 6 simulated patients. They involved teams of in-house PICU staff and actors (Image 3).

The medication preparation and administration process was tested by performing a rapid-cycle analysis of 3 scenarios: a complete preparation procedure in the central nurse control area, a complete procedure in the nursing station by the cubicle door, and a mixed model combining actions at both locations. Several safety risks were identified, as well as successful spontaneous adaptations of the professionals to this process. The protocol was modified to make it more robust and efficient.

The other objectives were tested in four different scenarios: a non-critical incident in a patient requiring support from another nurse and the reorganisation of care for the remaining patients, an invasive procedure involving several professionals, a patient with cardiorespiratory arrest, and the transfer of a complex patient with multiple devices to a Heliox room.

Results: The observations of these scenarios made it possible to validate protocols. The simulations led to a very important global change: the hospital approved the creation of a new position with no patients assigned on each nursing shift in order to have someone to maintain situational awareness of the unit's status, monitor the need for resources, and support the other nurses when necessary.

After-action review/Debriefings: As in the pre-construction simulations, the structure of the debriefing was defined by the objectives and also a rapid simulation-debriefing cycle was used in some scenarios.

Additional applications: Before the opening of the new PICU, all the professionals had the opportunity to participate in simulation-based workshops to experience the new spaces and familiarise themselves with the work processes. This helped to improve the experience of transitioning to a new PICU. A specific simulation room was included in the architectural project, with the same monitoring equipment as a standard treatment cubicle. In this space professionals hone their skills and improve teamwork, training on a weekly basis to increase the day-to-day integration between simulation and patient care.

What Have We Learned From the Experience?

The US Agency for Healthcare Research and Quality defines five characteristics of high reliability organisations. One of them is "deference to expertise: " – that people closest to the work are often the most knowledgeable about the work and their relationship to it". One of the strengths of SIMTest is that frontline professionals are deeply involved in the process from start to finish, including design of the space where they will work and in the validation of processes in these new areas. Perhaps not surprisingly, their

Image 1. Pre-construction SIMtest in a full-scale PICU mock-up

Image 2. Pre-construction SIMtest in a full-scale PICU mock-up

Image 3. Post-construction SIMtest scenario: transfer of a complex patient with multiple devices to a Heliox room.

response to the SIMTest work has been outstanding with common expressions of satisfaction emphasising the relevancy to improving their everyday workflow (Eg. "It has been extremely useful to address our concerns during the construction of our dream PICU…", "For me, it was crucial to experience the problems we'll have in the new PICU and learn how to solve them before we move there").

All contributions during the debriefings are based on experiences provided by the simulation, in a safe environment. People's opinions are not only based on evocations of one's own work ("work-as-imagined"). The simulation provides a perspective ("work-as-simulated") that helps enormously to bridge the gap with the real work ("work-as-done").

As an added value, we have observed that it is much easier to achieve consensus among different professionals during a SIMTest than in a traditional meeting. This makes it easier to empathise with other people's points of view and find realistic solutions that everyone can agree on.

An important issue is the costs vs. benefits of SIMTest activities. We did not carry out an exhaustive analysis comparing the costs of the simulations and the cost of the consequences of not having made the proposed modifications. However, we calculated that the SIMTest represented around 0.4% of the total cost of the construction project for the new PICU. The cost of modifying already-built structures or changing already-acquired equipment would have been enormously higher. Furthermore, many measures were adopted to prevent risks that the simulation brought to light. In terms of safety, this benefit is incalculable and enormously valuable to both the patients and the organisation.

Conclusion

In conclusion, SIMTest applied to the new PICU helped us to build a new, safer PICU to provide excellent care in a child and family centered model. This was the first application of simulation to facility design and construction for our hospital and represented a starting point for a line of work that has since grown steadily. Since the PICU SIMTest, about 20 other applications of SIMTests have been organised at HSJD, providing unique tools to improve the design and work processes related to new spaces in the Neonatology Unit and Cancer Center to name a few. As another example, recent SIMTest-based work has contributed to the design of processes related to MRI-guided intracranial tumor ablation, as well as the its timely application to optimising safe care within the COVID-19 pandemic.

SIMTest provides us with a controlled and safe parallel reality and allows us to reflect and learn from experience. This learning translates into better workspaces and safer processes.

Conflict of Interest

Catherine Allan obtained a grant through AHRQ (R18: Advances in Patient Safety through Simulation Research). The other authors state no conflict of interest related to this article ■

Abbreviations

HSJD: Hospital Sant Joan de Déu
PICU: Paediatric Intensive Care Unit
ECMO: Extracorporeal memebrane oxigenation
CPR: Cardiopulmonary Resuscitation

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Intensive Care Medicine: Reflections on the Gender Gap

Is the gender gap a concern for intensive care medicine (ICM)? ICM is not gender friendly by design and this could have a major impact on the discipline given the increase in the number of female doctors. What are the main barriers to career progression for women in ICM? Members of the iWIN Foundation present their views.

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Several authors and organisations have reflected on the future of Intensive and Critical Care Medicine following a significant increase, year on year, in the number of women recruited into medical schools around the world. In general, there is a concern for this phenomenon, which is leading to gender segregation with some specialties such as psychiatry becoming female dominated. Meanwhile, there is a reduction in the number of female applicants to specialties that have been traditionally male dominated such as intensive care medicine (ICM) (Lambert et al. 2003; Goldacre et al. 2005; Dacre 2008).

Data from several countries have shown that women are under-represented in the field of ICM. In Canada for example, ICM is a specialty with some of the lowest representation of women (27.7%) (Canadian Medical Association 2018). In Australia, while women are the majority of medical graduates, this has yet to translate into a significantly increased gender-balance in ICM (Modra and Yong 2019). Auspiciously, the number of women practising ICM in the United States of America (USA) has increased from 6% in 1980 to 27% in 2017 (Goldacre et al. 2005; Dacre 2008). The proportion of doctors, including ICM specialists that are women in the United Kingdom (UK) has grown every year since 2009 according to the National Healthcare System (NHS) workforce statistics by NHS Digital. The representation of women in Japanese academic medicine is not evident (Fujii et al. 2018). The trend of having an increasing number of female doctors is similar in most countries.

Despite this, women continue to be underrepresented in roles such as:

- Full professors in academic critical care medicine (Mehta et al. 2018; Mehta et al. 2017; Parsons et al. 2019; Metaxa 2013).
- Authors of scientific literature (Mehta et al. 2018; Metaxa 2013).
- Speakers at international conferences (Mehta et al. 2018).
- Editors in journals (Mehta et al. 2017; Parsons et al. 2019).
- Members of scientific boards (Mehta et al. 2017; Metaxa 2013).
- Entrepreneurs and CEO of start-up (Kanze et al. 2017; Malmstrom et al. 2017).
- Engineers and designers for medical devices (Kanze et al. 2017; Malmstrom et al. 2017).
- Authors of guidelines (Metaxa 2013; Merman et al. 2018).
- Members task force panels (Mehta et al. 2018; Mehta et al. 2017; Parsons et al. 2019; Janssen et al. 2019).

ICM is not "gender friendly" by design. This will have a major impact on the discipline given the increase in the number of female doctors.

Table 1 summarises the areas where women are under-represented and over-represented in ICM. Merman et al. (2018) showed that there is a significant difference in the authorship of clinical practice guidelines by gender, causing an impact on how problems are approached and solved at the bedside (Merman et al. 2018). Similarly, women are under-represented in task forces determining standards of care and this is relevant in ICM assuming that more women will be involved in the implementation of optimal clinical practice at the bed side (Janssen et al. 2019).

Women are less likely to apply for grants or awards. NHS digital has published the number of women applicants receiving new excellence awards in England and Wales between 2013 and 2016 compared to men. Female applicants were 19% in 2013 and 22% in 2016. However, every year the success rate was the same for males and females applicants.

The difference in the amount of money given to fund research and innovation led by women is not known in the field of ICM. The percentage of female principal investigators for the National Institute of Health (NIH) was 24.6% in 2003, with female investigators achieving, on average, smaller grants (Metaxa 2013). The drivers for such differences are also unknown and unmeasured (Parson et al. 2019). However, looking at women in other professions, there is an enormous gender gap recorded in Venture Capital (VC) funding and

	Women underrepresented	Women over represented
Merman et al.	Authors of Guidelines	
Janseen et al.	Members of Task Forces	
Mehta S et al.	Editorial Boards	
Godrace et al.		Segregation: Career choices in non-male dominated fields
Lambert et al.		Work part time and training part time or less than full time (LTFT)
Devlin et al.	Engineers and medical device developers	
NHS digital		Bedside healthcare and users
Kanze D et al. Malmstrom M et al.	Entrepreneurs	
Malmstrom M et al.	Grants/funding/awards appli cants and winners	
Crane J et al.		Junior doctors
	Senior mangers	
Mehta S et al.	Academic Leaders	
Mehta S et al.	Speakers /Faculty	
NHS digital	Company executive boards	
NHS digital	Hospital executive boards	

Table 1: Areas where women are under-represented and over-represented in ICM.

female entrepreneurs, who are receiving only about 2% of all venture funding in the USA (Kanze et al. 2017). The prevailing desire among academics, policy makers and practitioners alike has been that this gap will narrow as more women become venture capitalists. However, the number of female venture capitalists has increased from 3% in 2014 to an estimated 7% in 2017, but the funding gap has only widened (Kanze et al. 2017; Malmstrom et al. 2017). This scenario mimics reality in ICM (Parson et al. 2019). Prof Parson Leigh has tried to identify the drivers of gender inequity in ICM, but qualitative studies are currently lacking.

Researchers at Harvard have tried to look at human factors and qualitative analysis to understand the nature of this gap (Kanze et al. 2017; Malmstrom et al. 2017). They have observed, for example, the interactions between 140 prominent venture capitalists (40% of them female) and 189 entrepreneurs (12% female) that took place at TechCrunch Disrupt New York, an annual start-up funding competition (Kanze et al. 2017). Authors showed that "67% of the questions posed to male entrepreneurs were promotion-oriented, while 66% of those posed to female entrepreneurs were prevention-oriented." Malmstrom et al. (2017) recorded Venture Capitalists' conversations and analysed how differently they talked about female entrepreneurs. VCs had stereotypical images of women instead of having qualities such as those considered important to being an entrepreneur and questioned their credibility. Conversely, when assessing male entrepreneurs, financiers leaned on stereotypical beliefs about men that reinforced their entrepreneurial potential. Male entrepreneurs were commonly described as being innovative, competent, knowledgeable and having established networks (Malmstrom et al. 2017). Shadowing the example of VCs, the overall proportion of women in ICM is steadily increasing. This has no impact on female representation among leading roles in academia and/or management (Guancial et al. 2006). Only 12% of department chairs, 17% of full professors and 11% of medical school deans in the US are female (Mehta et al. 2017). Inequality between the two genders is evident in other fields of academic medicine such as rank attainment, leadership roles and salaries (Mehta et al. 2017; Parson et al. 2019; Sidhu et al. 2009; John et al. 2012). The assumption is that stereotypes like those that have been measured in the financial world, are present in ICM (Kanze et al. 2017; Malmstrom et al. 2017; Burgess et al. 2012).

The NHS Future Forum has acknowledged the under-representation of women in senior leadership positions and the need for appropriate development opportunities (Dacre 2008). Despite women making up over three quarters of all NHS staff, in 2018, 37% of all senior roles were held by women compared with 31% in 2009, and 36% of consultants were women compared with 30% in 2009. This is less than 10% improvement in nearly a decade (Dacre 2008). Perceptions of gender composition in critical care medicine, including perceived drivers i.e. influencing factors of gender inequity, observed implica-

5 Proactive Strategies for Gender Parity
• Critical Care Societies to establish diversity policies.
• Journals to publish the principles and methods of panel composition for professional document development.
• Publically available metrics of women's representation on panels for definition documents, consensus statements and practice guidelines.
• Gender parity policies to be incorporated into relevant bylaws within all areas of academic critical care.
• Training on diversity and unconscious bias for all critical care academics, particularly for those in leadership positions.

tions i.e. associated consequences and related strategies to encourage and retain women in the specialty, have not yet been comprehensively explained (Parson et al. 2019). Harvard researchers used sensors on employers to study how women interact at work and "no perceptible differences were observed in the behavior of men and women, yet women weren't advancing and men were" (Gavet 2017).

ICM is a discipline where technology is increasingly represented and progressively developed. Unfortunately, there is a significant mismatch between the number of engineers developing medical devices (Kanze et al. 2017; Malmstrom et al. 2017; Devlin and Hern 2017) and the bedside users, which are mostly women (nurses and doctors) (Canadian Medical Association 2018). We cannot quantify such gap in healthcare and in particular in ICM; however, in general, women are a minority in tech companies and engineering. The Guardian recently reported the case of an engineer working at Google, who lost his job because he suggested that "male domination of Silicon Valley is down to biological differences between the sexes" (Devlin and Hern 2017). There are currently 20% of Google engineers that are women, a statistic that is matched roughly across big tech companies.

There are countless scientific studies that claim to identify differences between male and female cognitive aptitudes and in the UK, far fewer girls choose to study computer science in secondary schools (20% of the total number of students), at degree level (16%) and beyond. However, while 16% of computer science undergraduates in the UK and in the USA are female, the balance is different in India, Malaysia and Nigeria where 50% are women (Devlin and Hern 2017). Prof Dame Wendy Hall, a director of the Web Science Institute at the University of Southampton suggested that the gender gap and the "male stereotype" is dated back to the advent of the home computer in the early 80s. As a matter of fact, home computers were marketed as gaming systems for men (Devlin and Hern 2017). Jane Margolls is a psychologist at the University of California, Los Angeles, who interviewed computer science students in the 90s at Carnegie Mellon University, which had one of the top programmes in the country at the time. "Many of the women at Carnegie Mellon talked about computers being in their brother's bedroom and there were a lot of father-son internships around the computer that were not happening with the daughters."

The setting and structure of ICM is "gender unfriendly" by design. Authors could assume that women working at the bedside in ICM have an environment designed by male engineers. Furthermore, they have to use guidelines created by male task force members or authors. Interestingly women have no representation in leadership or academic scale to express their difficulties. This is a system that is designed to fail as soon as the number of women in medicine increases.

To change this culture, our critical care community must acknowledge that gender inequity exists and is problematic. Mehta et al. (2017) advocate for diversity and propose 5 proactive strategies to ensure gender parity, which we have listed in **Table 2**.

Barriers to Career Progression for Women in ICM

The question is: how could it be possible to address system barriers for women's progression in the field of ICM? **Table 3** contains some suggestions:

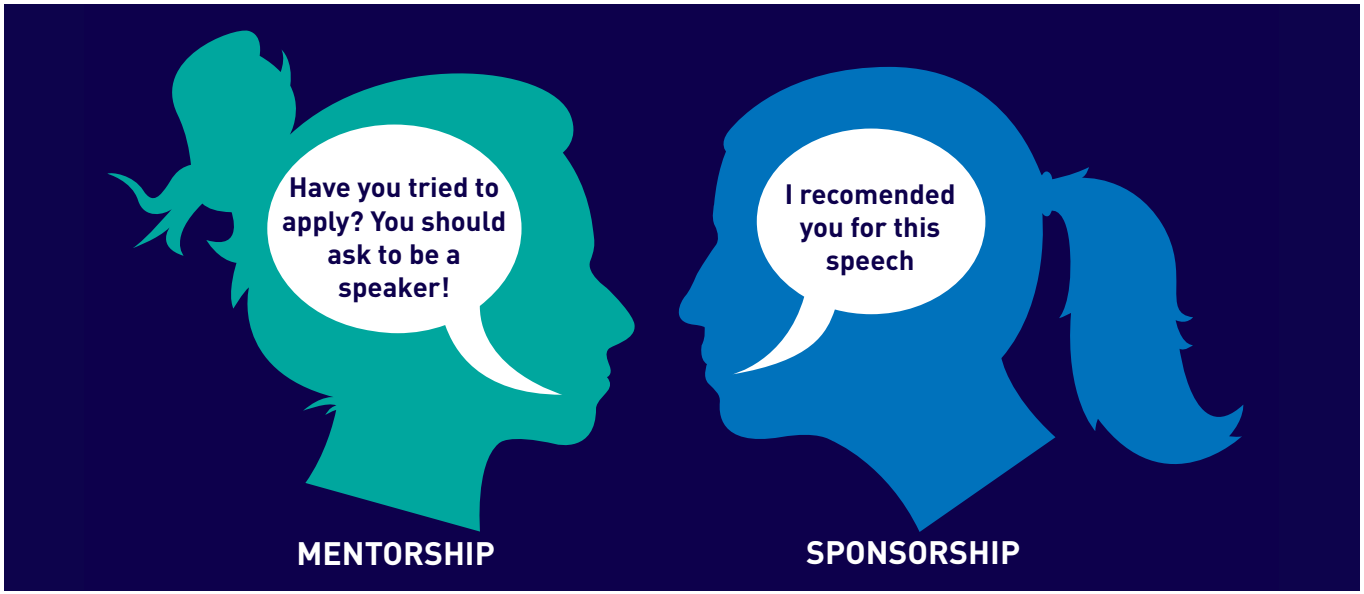
• Change the myth that less than full time work/training equals being lazy or not ambitious. (Encourage flexible working hours)
• Enhance transparency
• Challenge negative behaviours
• Promote sponsorship vs mentoring
• Increase the number of grants, awards and clinical excellence awards applications done by women
• Reduce gender pay gaps within grades and specialties. Changes to mandatory gender pay gap reporting. Reduce gender pension gap

Table 3: Addressing System Barriers for Women's Progression in the Field of Intensive Care Medicine

Frequently, trainees or specialists working outside the full-time scheme are seen as an exception to the 'norm' and sadly affiliate to lack of ambition and enthusiasm. The concept of part time or less than full time (LTFT) employments is crucial and relates very closely to parental responsibilities. It is evident that caring responsibilities continue to have a more substantial impact on women's careers, despite the findings that there is little difference in male and female doctors' personal values and their orientation towards family, children and work. Central to this issue is the need to address the bias that working or training part time or less than full time (LTFT) is a deviation from the 'normal' pathway.

In 2019, The College of ICM of Australia and New Zealand published that it "is committed to providing an inclusive environment that welcomes contributions from the broad diversity of the intensive care community" (cicm.org.au). This is the first formal document suggesting "The College will support accredited ICUs to offer high quality part-time training positions and part-time specialist positions" (cicm.org.au). Nevertheless, public perception of LTFT work is unchanged, identifying individuals in this category as less productive or valued. Younger members of the British Medical Association (BMA) in the UK report that "there are often significant administrative and practical hurdles to gaining LTFT status and concerning reports of bullying and undermining behaviour from managers and colleagues" (Mehta et al. 2017). The Australian and New Zealand documents one of few examples of training institution, college or hospital, which formally addresses this issue. All Royal Colleges and specialist societies should be required to publish the proportion working LTFT in their specialty and at each grade. This would help highlight where it is currently more restricted and encourage action on identifying and removing barriers in those specialities in the future.

Moreover, according to BMA junior doctors' surveys, "traditional career pathway of full-time, uninterrupted training to consultant or



attending is not as appealing to younger generations of doctors and medical students, whether male or female. Widening access to LTFT training and working will help retain more staff, improve wellbeing and reduce burnout in women and men. Employers or trainees who take extended periods of leave, including maternity/parental leave are not guaranteed a return to the rotations that they had previously been allocated. This can have a significant impact on career progression and increase the existing gap." Return to work or training is mostly unsupported. This has a major impact on self-confidence. People returning to work or training in a stressful environment do not feel supported in advancing their career or asking for more responsibility for several months or years. Making senior jobs more accessible and attractive to women include and moving away from the full-time default for senior posts.

Enhance transparency

Recruiting managers and academics is challenging and the interview panel is hardly trained in how to carry out these processes to minimise bias influencing decisions. Job advertisements and role descriptions should be reviewed for gendered language. There is no global regulation and frequently there is no transparency in the way those jobs are offered. There are no specific global requirements for academics to become Professors; as a matter of fact, leading roles in academia could be given without a PhD if "someone" is the right candidate. This is highlighted also in the UK gender gap enquiry by the fact that high level degrees have more value when owned by men compared to women. Transparency must be offered for:

-advertising
-recruiting
-contracting (mangers and academics)

Transparency in advertising and recruiting is likely to increase gender parity by shining a light on areas and processes that need to be improved and making individuals more aware of their rights. The UK government is currently consulting on requiring large employers to be transparent about their work-life policies and flexible work opportunities on job advertisements, which we would support.

Challenge negative behaviours

ICM organisations and societies should produce a set of recommendations on what is needed to effectively challenge behaviour and create a more positive workplace culture. Culture provides the context within which employees judge the appropriateness of their behaviour. Health and safety used to be all about policies, procedures and policing, and the focus on people was not on the agenda. Currently a safe workplace is about changing behaviour and influencing engagement. Safety is more about people, human factor and not policies. ICM specialists need to move away from the command and control mindset, and focus on daily habits, changing attitudes and recalibrating the way people think about safety. Proactive, preventative behaviour needs to be enhanced and in this context challenging negative behaviour should be part of the hospital culture. Women will benefit from this change and might find support in male colleagues. Harvard researchers showed that gender parity efforts are most effective when men believe they have a role to play, that their partnership is valued and that transformation of the workplace is something they can share in (Johnson and Smith 2018).

Promote sponsorship vs mentoring

Providing access to senior level sponsors and advocates could make a significant impact on successfully developing, retaining and progressing women. The General Medical Council in the UK states in its "Duties of a Doctor" guidance that doctors should be willing to take on a mentoring role for more junior doctors and healthcare professionals (gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/good-medical-practice/duties-of-a-doctor). Those specialties which currently have the widest gender pay gaps, are male dominated, and should be prioritised and additional government funding also provided to support an enhanced mentoring and sponsorship programmes.

Increase the number of grants, awards and clinical excellence awards applications done by women.

The process and application to grants and awards should be open and transparent. Women are not empowered when applying to research grants as well as excellence awards. To address the gender imbalance in submissions all possible steps should be taken to train and encourage women to apply. Success rate following application is not different for excellence awards and might increase for research grants in future.

Reduce gender pay gaps within grades and specialties. Changes to mandatory gender pay gap reporting. Reduce gender pension gap.

Laine et al. (2004) reported evidence from the US Census Bureau

The iWIN Foundation for research and networking in ICM
The International Women in Intensive and Critical Care Network (iWIN) is a hub for worldwide research addressing the issues surrounding gender equity. iWIN connects all international groups facing the same challenges. iWIN can interact using different approaches including survey techniques, consensus, workshops, video conferencing, webinars, blogs and ultimately a yearly face to face meeting which will allow team building and networking.

iWIN core values are IDEAL:

Innovation (partnership with industries, tech companies and start-ups for innovation)
Diversity
Equality (equal opportunities for career progression, research, grants, awards and conferences)
Advocacy (which includes education)
Leadership (which includes coaching new generations, role models, experience sharing, mentoring and courses)

iWIN aims at creating a positive culture and allowing women to feel welcome, safe, supported, successful, and respected in these disciplines and girls to see their aspirations of careers in science and medicine as tangible options. Many advocates, including women in academic science and medicine, are tired of initiatives that focus on women as being the problem. iWIN will focus on solutions. iWIN will study common drivers, problems and plan global actions to find ultimate globally applicable solutions.

Gender inequity is due to bias, not differences in behaviour and therefore, iWIN is a global platform for identifying these DRIVERS, define the problems, find solutions and implements global CHANGES.

The inaugural event for iWIN will be held in Catania, Italy on 24-26 June 2021.
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iWIN2021 Faculty includes Karin Amrein, Irene Argao, Marinella Astuto, Anna Batchelor, Irene Bellini, Joana Bergher, Lucia Benvenuti, Lluis Blanch, Karen Burns, Denise Battaglini, Joanna Berger, Gilda Cinnella, Mireia Cuartero Sala, Tomoko Fujii, Pascale Gruber, Margaret Herridge, Krzysztof Kusza, Rhudo Mathiva, Kathryn Maitland, Sheila Myatra, John Marshall, Vittoria Metaxa, Malgorzata Mikaszewska, Maria Concetta Monea, Silvia Mongodi, Marie Cruz Martin DelGado, Tiffany Osborn, Paolo Pelosi, Flavia Petrini, Alison Fox Robichaud, Lara Prisco, Chiara Robba, Orville Victoriano Baez Pravia, Giorgia Rubulotta, Deepak Sharma, Amber Skinner Jozefson, Jerry Sanders, Natalie Urwyler, Maria Theodorakopuolou, Melda Turkoglu, Marcella Vizcaychipi and Janice Zimmerman.

that "female physicians' wages averaged 63% for each dollar earned by their male colleagues."The College of Medicine in the US female academics earned 89% of the average male salary (Connolly and Holdcroft 2007). In April 2018, Department of Health & Social Care (DHSC) commissioned a review, chaired by Professor Dame Jane Dacre, to identify the causes of the gender pay gap in the medical sector. Data are not published, but still a significant pay gap is being recorder in the UK. Additionally, some analysis has been done on the intersection between gender and other protected characteristics such as disability, ethnicity and sexual orientation using the Oaxaca-Blinder decomposition (Elder et al. 2010).

The Gender pension gaps also needs consideration given its impact on gender long term pay inequalities. As women earn less than men on average they accrue less pension, and they are also more likely to take pension holidays to cover family costs such as childcare. Older women may also work less to provide care for others (e.g. care of adults with illnesses and disabilities) meaning they are more likely to give up work or reduce their working hours. Women working LTFT are additionally disadvantaged because pension contributions are frequently calculated on the basis of full-time equivalent earnings rather than actual earnings. ■

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ICU MANAGEMENT & PRACTICE

ICU MANAGEMENT AND PRACTICE IS PUBLISHED BY
MindByte Communications Ltd
9, Vassili Michailidi CY-3026 Limassol, Cyprus
Email — office@icu-management.org
Website — icu-management.org

PRODUCTION, PRINTING AND DISTRIBUTION
Printed in Hungary by ABEL Printing
Total classic and digital distribution: 21,500
ISSN = 1377-7564

icu-management.org @ICU_Management