Post intensive care syndrome

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UNIVERSITY OF ZAGREB
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Post Intensive Care Syndrome

Sindrom postintenzivne skrbi

Graduate thesis

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Abbreviations

PICS – Post Intensive Care Syndrome

ICU - Intensive Care Unit

LOS – Length of Stay

IMV – Invasive Mechanical Ventilation

PTSD – Post-traumatic stress disorder

HADS-A – Hospital Anxiety and Depression Scale – Anxiety

HADS-D – Hospital Anxiety and Depression Scale – Depression

STAI - State-Trait Anxiety Inventory

DSM-V – Diagnostic and Statistical Manual of Mental Disorders, 5th edition

ICF – International Classification of Functioning, Disability and Health

ARDS – acute respiratory distress syndrome

6-MWT – 6 Minute Walking Test

ADL – Activities of daily life

IADL – Instrumental Activities of Daily Life

ICU-AW – Intensive Care Unit – Acquired Weakness

CIP – Critical Illness Polyneuropathy

CIM – Critical Illness Myopathy

CINM – Critical Illness Neuromyopathy

MOF – Multi organ failure

APACHE II score - Acute Physiology and Chronic health evaluation score

MRCS score - Medical Research Council sum score

NCS - Nerve conduction studies

Contents

Abstract eng.

The medical advances of the past decades, our growing elderly population, and a global pandemic have shifted our views away from the reduction of mortality and morbidity in the ICU to the long-term consequences of such treatment. With the SARS-CoV-2-pandemic occurring since early 2020 there have been increases in ICU treatment and therefore also a possible increase in disabilities developing related to said treatment. PICS is defined as newly developing or worsening cognitive, physical or mental state during, or following Critical Care treatment and hospital discharge. The physical development of muscle weakness, depression, anxiety and cognitive weakness based on memories, language, or visual and spatial orientation are frequently observed. The pathophysiology has not been elucidated fully yet.
In this work, we will look at the different manifestations of this syndrome and look at the possible management and prevention of PICS.

Sažetak hrv.

Napredak medicinske struke zadnjih desetljeća, sve starija populacija i globalna pandemija su promjenili naš pogled- sa smanjenja morbiditeta i mortaliteta u Jedinicama intenzivnog liječenja (JIL) prema dugoročnim posljedicama liječenja ovih bolesnika. SARS-CoV-2 pandemija s početkom 2020. dovela je do povećanja liječenja u JIL te posljedično do porasta poremećaja vezanih uz navedeno liječenje. Sindrom postintenzivne skrbi je definiran kao novonastali poremećaj ili kao pogoršanje kognitivnog, fizičkog i mentalnog stanja bolesnika tijekom liječenja u JIL ili nakon otpusta iz bolnice. Često postoji razvoj mišićne slabosti, depresije, anksioznosti i kognitivnih poremećaja u obliku poremećaja memorije, vizualne ili prostorne orjentacije. Patofiziološki mehanizmi još uvijek nisu u potpunosti poznati. U ovom radu, prikazat ćemo pregled različitih simptoma, mogućeg liječenja i prevenciju ovog sindroma.

Background

In the past years there has been a shift in thinking about Critical Care. With the advancements in Critical Care medicine and improved survival following Critical Illness(1), the focus moved from reduction in short-term Mortality and Morbidity to thinking about the long-term consequences of Intensive Care management and treatment. Particularly considering the SARS-CoV-2 pandemic requiring many patients to receive Critical Care there needs to be a review about PICS or "Post-Intensive Care Syndrome".

"The term "post intensive care syndrome" (PICS) was agreed on as the recommended term to describe new or worsening impairments in physical, cognitive, or mental health status arising after critical illness and persisting beyond acute care hospitalization. Consequent to this, the psychological health of family members of the survivor may also be affected in an adverse manner, termed as PICS-Family (PICS-F)"(1–3).

Early in the SARS-CoV-2 pandemic (Dec. 2019-May 2020) the rate of ICU admissions was 21% with 69% requiring invasive mechanical ventilation(4). Hopkins et al. showed that across all ages there was a risk of 50% to develop PICS(5) when patients were mechanically ventilated. Additionally, patients with risk factors for developing PICS are showing a history of similar comorbidities to patients who are admitted to the ICU for COVID-19 including Hypertension, diabetes mellitus, chronic obstructive pulmonary disease, asthma, and prolonged period of mechanical ventilation (6,7). Working from these assumptions, we might have to engage more urgently with the assessments of the consequences of Critical Illness management and evaluate the necessity of putting protocols in place to prevent PICS in the future before another crisis within healthcare system develops.

This paper will not include PICS-F or PICS-P due to these Syndromes expanding the scope and direction of this work.

Epidemiology

Determining the epidemiology of PICS is difficult due to a lack of data or heterogeneity, or data that is focused on individual aspects, for example just the cognitive, mental, or physical aspects, of the syndrome itself. Additionally, many places around the world have started to implement protocols for the prevention of Post Intensive Care Syndrome which leads to limited data around the occurrence of PICS. Many studies also suffer from limited sample sizes making an estimation more inconclusive than necessary (5,8–12). However, there have been prospective, multicentered, observational studies of good representative power that allow us to scope or approximate the occurrence of PICS.

Some studies postulate that approximately 60% of patients being treated in an ICU develop PICS. "*Most patients with PICS had problems in a single domain, with cognitive impairment being most common, but disability in ADLs and depression also occurred frequently*."(13) Co-occurrence of PICS impairments is estimated to be in around 17-20% patients. (13,14)

Mental or psychological impairments of PICS is common in survivors of the ICU. They were present according to different studies in around 30-40% of survivors. (9,14,15) Depression is a common sequela following Intensive Care hospitalization. In the "BRAIN-ICU" study by *Jackson et al.*(9) it is suggested that mild depression according to the *Beck Depression Inventory II* is prevalent in 16% of patients after three months and 12% after 12 months, moderate and severe depression appeared to 12% and 9% respectively after 3 months. After 12 months of follow-up, moderate and severe depression are present at 14% and 7%. In this study, they also show the possibly higher incidence in post intensive care depression in patients with a previous history of depression. Post-traumatic stress disorder is another common consequence of Intensive care treatment, its incidence is lower than that of depression but is common with one fifth(1/5) to one quarter (1/4) of patients show signs of PTSD on three month and 12 month follow-up (9).

Physical Impairments

As we have defined before *PICS* is defined by "new or worsening physical, cognitive, or mental health after critical illness",(2,3,10) nearly 2 out of 3 patients newly develop or have a worsening physical condition after Critical illness. It presents most frequently with reduced muscle mass

and function, joint immobility, exercise limitation, fatigue, and decrease quality of life. (2,3,10,13)

Given the impact and the general persistence of these problems, a classification and characterization of these issues would be of utmost importance. This task is not made easier by studies frequently not including premorbid physical status; this can be explained by the urgent or acute nature of Critical Illness where there will not be an opportunity to assess the patient's physical status and measure accurately the level of impairments. The understanding of the way health care would need to be conducted with patients who received critical care, particularly in the transition from hospital-based to primary care, needs clear understanding of the impairments a patient suffers from PICS. Building a solid classification will allow for less fallible evaluation and more patient-centered care and focus on patient-centered outcomes.

Ohtake et al(10). focused their publication "*Physical Impairments associated with Post-intensive Care Syndrome"* on the WHO's International Classification of Functioning, Disability and Health Framework. The ICF-Framework characterizes the breadth of physical problems using the component of body functions and structures, activity, and participation. The concept of the ICF is based round a person's function as "*a dynamic interaction between an individual's health conditions and their unique environmental factors and personal situations*." (10,16)

In their systemic review, *Ohtake et al.*(10) found evidence that the requirement for Intensive Care treatment can cause dysfunction and impairments in the bodily functions and structures, activity, and participation aspects of the ICF-Framework. Body function and structures that were impaired more specifically are pulmonary function and reduced strength of respiratory muscles, limb muscles, and handgrip. The phenomena of reduced or abnormal pulmonary function tests are suggested to appear in nearly 66% of patients being treated for Critical Illness in a study, looking at patients who had met the criteria for *acute respiratory distress syndrome* or *ARDS.*(10,17,18) It is hypothesized that due to the frequent requirement of mechanical ventilation in the setting of critical illness particularly for respiratory failure that the use of mechanical ventilation raises the risk for lung injury induced by the ventilator causing fibrosis linked to biotrauma and barotrauma. (10,11,19) This causality could lead to the restrictive pattern of lung function that is frequently observed. The restrictive pattern is observed in 58% of patients that had met the criteria for ARDS while in Critical Care while 33% had normal pulmonary

function at 6 months. It is suggested by increasing evidence that the reduced demand on the respiratory muscles while the patient is mechanically ventilated, causes *"disuse atrophy and alterations in respiratory muscle structure leading to decreases in muscle strength.*(10,20)*"* An increase in 1-year mortality has been linked to low maximum inspiratory pressure at the time of extubation indicating a possibly worse function of the respiratory muscles to initiate inspiration(10,21,22).

Lower extremity muscle strength was shown to be reduced at 3, 6, and 12 months after Intensive Care treatment, in this case specifically the knee and ankle muscles were weaker(10,23–25). *Poulsen et al.*(24,26) found that muscle mass reduction and muscle strength reduction paralleled each other concomitant to a reduced rate of force development and endurance.(10,24) This reduction in function, capacity and mass of the muscles was persisting up to 12 months.(10,24) Bed rest is an influencing factor in the development of the muscle dysfunction during ICU care but it alone cannot be the singular factor for this reduced function. Due to the length of the weakness persisting and the breadth of it, it is suggested that "*factors associated with critical illness may contribute to the compromise of limb muscle performances"*(10,24,26). In said publication, the reduction in strength for knee extension and flexion against a control group or predicted normal value was 22% for extension strength and 15% on flexion strength indicating a significant reduction at 12 months.(2,10,24,26) Similarly, to lower extremity strength is the change measured in handgrip strength in people who were under intensive care treatment, this reduction was quantified from 20-39% which is approximately to the observed weakness in the lower limb muscles at 9-41%. (10,11,23,24)

It becomes relevant to find how persistent activity limitations are following Critical Illness. Many publications use the 6-Minute Walking test distance to assess this reduction in activity. In nearly all studies measuring 6-MWT distance it was reduced.(10,11,23,27,28) The reductions in capacity were unrelated to age, diagnosis, and mechanically ventilated treatment. *Ohtake et al.'s* systemic review assessed only the outcomes for 6-MWT up to 12 months after Intensive Care requiring illness. It is suggested that these findings of reduced capacity might be more permanent as there is evidence of the reduction in function in publications up to 5 years after Critical Illness(10,29,30). The capacity to exercise ranged from 55%-85% of the predicted value or the control groups value at 3 months of follow-up. There was only limited difference when the

survivors' exercise capacity was tested at 6, and at 12 months, the values reported were 58%-85% at 6 months and 63%-84% at 12 months of the predicted or control group values(10,11,16,25,31). Mechanical Ventilation in the Critical Care setting was found to be not an influence on the 6MWT distance. (10,16,32)

Based on these findings, recommendations to have all critically ill patients assess their limb muscle strength and exercise capacity but one should not assume that a reduction in muscle strength equals a reduction in exercise capacity, they have not been shown to map onto one another(10,12).

The reduction in physical capabilities has an influence on the survivors' life situations making the patients frequently more dependent on others which is taxing on the person providing the care as well as the survivor of critical illness(10,33,34). Patients with increased disabilities in their *activities of daily life* or *ADLs* are at increased risk for institutionalization, they risk higher health care costs, more hospitalizations, and higher mortality rates(10,35,36). 35% of survivors had on 3-month follow-up at least a partial dependence in at least 1 ADL compared to 25% of participants before Critical Illness. At the follow-up after 12 months, 33% of the survivors remaining in the study who had a critical illness were continuously living with partial dependence in at least one ADL.(10,12,35,37) The most common problems for these patients were bathing, dressing, and continence so complex processes in their daily lives.(10,35) Following from these insights, it must be established that a patient's ability to support and improve themselves must take a primary focus in the therapy and management of PICS. Similar to the reduction in ADLs, it was additionally found that "*new or worsening IADL dependency was present in 69% of people who had received intensive care and persisted months to years after ICU discharge."* (10,38,39)

In line with the reduction in ADLs and IADLs is the reduced wage labor participation among Critical Care survivors(10,26,40–42). Following ARDS, only 56% of survivors who were previously employed were re-employed by 12 months following Critical Illness(10,43–45). The patients who had returned to work were in general younger and in better pre-hospital health condition (39 years of age vs 51 years of age) than those who were unable to return to work. Physical therapy, occupational therapy might be beneficial if a disability of bodily function or activity persists which are some of the bigger roadblocks to employment of survivors. Vocational

therapy can bring benefits to patients who are living with the prolonged inability to return to work.(10,39,43,44)

In their work, *Bakhru et al.*(12) attempted to show the "*feasibility of measuring physical function in their ICU Recovery Clinic., determine if physical function was associated with 6-month re-hospitalization and 1-year mortality and compare ICU survivors' physical function to other comorbid populations".*(12) They demonstrated that the "*SPPB is well-validated in other patient cohorts and is a strong predictor of future disability, hospital readmission and mortality in older adults."*(12) SPPB stand for Short Physical Performance Battery, it is a test which can be performed within 10 minutes and its "*validity is based on the fact that it is easy for a clinician to understand how the inability to rise from a chair or the inability to walk at a reasonable gait speed might affect a patient.* "(12) However, the SPPB has shown in patients following Critical illness to have significantly lower scores than other older, comorbid populations, as well as the readmission rates at 6 months and the mortality at one being significantly higher at nearly 44% combined. The SPPB as a tool for Critical Care follow-up still needs to be validated through more research and larger studies and to establish its connection to the recovery process and for the prognosis of readmission and long term mortality(12).

One of the more frequent problems for patients that are receiving Critical Care is the development of *Intensive Care Unit – Acquired Weakness* or ICU-AW. ICU-AW is a generalized muscle weakness that develops while being treated for a Critical illness and „ *for which no other cause can be identified beside the acute illness or its treatment*"(42). It could impact peripheral and respiratory muscles. ICU-AW has been linked to high morbidity and high mortality of acute Critical Illness. It is stipulated that *ICU-acquired weakness* might contribute strongly to PICS.(2,3,12,42)

The incident of ICU-AW is hard to pinpoint due to its dependency on the studied population and the timing of the evaluation. The incidence of patients awakening with weakness following mechanical ventilation over 5-7 days was 26-65%, while 25% remained weakened for 7 days following awakening and extubation(42,46–48). *"In patients suffering from acute respiratory distress syndrome (ARDS), an ICUAW incidence of 60 % has been reported at the time of awakening, and at hospital discharge this incidence was still 36 %."*(11,42,49) With there being potentially 36% of patients being treated for Critical Illness who were still weak at the time of

discharge we have a met the criteria for it being a part of PICS which would be the development of "*new or worsening impairments in physical, cognitive, or mental health status arising after critical illness and persisting beyond acute care hospitalization."*(1–3,42)

Nowadays there is additionally a subclassification for the term ICU-AW in particular about the way the ICU-AW is evoked or used, the diseases classified under it are *Critical Illness Myopathy(CIM), Critical Illness polyneuropathy(CIP),* and a combination of both *Critical Illness Neuromyopathy(CINM).* (37,42,50–53)

The pathophysiological pathways leading to the development of ICU-AW are poorly elucidated and assumably complex and multifactorial and it involves structural and functional changes in the nervous and muscular system.

For Critical Illness Polyneuropathy, from now on only *CIP*, the pathological finding is axonal degeneration. The understanding of how this axonal degeneration develops is incomplete. However, there were some links established between the development of axonal degeneration and microvascular changes in the endoneurium triggered by sepsis causing vascular permeability and allows for toxic factors to enter the neuronal ends.(42,54–56)
As for Critical Illness Myopathy, one of the first signs developing is muscle atrophy sometimes early during Critical Illness. This is caused by increased catabolism and reduced anabolism of muscle proteins. Processes and factors that might influence this occurrence are inflammation, immobilization, the endocrine stress responses, nutritional deficit, dysbalanced microcirculation, and denervation. Some major cytokines are involved in this development including Tumor necrosis factor alpha, Interleukin-1, and Interleukin-6.(42,57–59)
There have been signs that muscle membrane inexcitability caused by Na+-channel dysfunction might be linked to the development of muscle weakness. Similarly, Calcium metabolism and homeostasis within the cell, causing effects on the excitation-relaxation coupling, was connected to reduced contractility in animal sepsis models(42,60,61). "*The muscles of septic patients show signs of bioenergetic failure, comprising oxidative stress, mitochondrial dysfunction, and ATP depletion".*(42,62)

The clinical signs for ICU-AW are symmetrical and flaccid limb muscle weakness and is usually more prominent in the proximal rather than distal muscles. Facial and ocular muscles are frequently spared(42,46,63). Patients react to painful stimuli with grimacing when they develop

ICU-AW but they will not withdraw their limbs. Tendon reflexes usually should be reduced in these patients(42,57). If CI-Polyneuropathy coexists there might be additionally sensory dysfunction like a decreased or absent sensitivity to pain, temperature, or vibration. The establishment of sensory symptomatology is rather difficult in patients on intensive care treatment. Frequently once the ICU-AW presents it will have affected the respiratory muscles which can lead to prolonged mechanical ventilation due to prolonged weaning causing problems clinically for the patients(42,57,64).

Additionally, there is occasionally the development of *small fiber neuropathy*, in which small nerve fibers degenerate or get lost and may be causing neuropathic pain, stocking and glove sensory loss, numbness, cool extremities, and burning pain. This form frequently occurs concomitantly to CIP/CIM with a particularly high incidence in sepsis or *Multi organ failure* (65–68).

There might be a component of *autonomic dysfunction* developing in patients with critical illness involving the peripheral and central nervous system and frequently affecting sympathetic and parasympathetic pathways. Abnormal R-R changes on ECG, the cold face test, denervation of the sweat gland on biopsy, and skin wrinkle test are changes possibly present as part of *autonomic dysfunction.* It is reported together with CIP/CIM, suggesting with some symptoms that there might be a common pathological or pathophysiological pathway. The heart rate variability could not be conclusively linked to ICU-AW due to the presence of many confounders and cannot be established as an indicator for ICU-AW or *autonomic dysfunction*(42,69,70).

What predisposes patients to develop ICU-AW are often factors that are part of the Critical illness like the severity of an illness, shown and reflected by the *Acute Physiology and Chronic health evaluation score.* Sepsis, systemic inflammatory response syndrome, and MOF have been shown in different studies to produces high incidence of neuromuscular complications and be independent risk factors for the development of ICU-AW. Prospective studies have presented more independent risk factors for the development of ICU-AW like the use of vasopressors, aminoglycosides, some inflammatory mediators, and the presence of septic encephalopathy(42,71–73). Glucose control in the blood serum has shown to reduce the electrophysiological and clinical signs of ICU-AW. This means that hyperglycemia is a fixed

risk factor for ICU-AW for its diagnostic and clinical signs(42,71,74,75). Another factor that could be identified was age but this might show the premorbid physical state of the patient. A limited amount of studies have researched the risk factors for respiratory weakness. They showed the relation between infection or sepsis and respiratory muscle weakness, disease severity, and peripheral muscle weakness.(15,37,42) "*The phrenic nerve and diaphragm also show similar electrophysiologic abnormalities as the peripheral nerves and muscles, so these data suggest that respiratory weakness is indeed part of ICUAW* ."(42,64,75,76) Mechanical ventilation length could be associated with weakness, and the atrophy of the diaphragm. *"This time-dependent and early development of diaphragmatic atrophy and dysfunction is also labeled "ventilator-induced diaphragmatic dysfunction"(VIDD)."* (37,42,64,77)

The long-term implications of the recovery from ICU-AW means patients take typically weeks to months from ICU-AW. Majority of people recover within months as the data shows. At discharge 36% of patients had weakness, which declined to 22% at 3 months, 7-15% at 6 months, 4-14% at 1 year, and 9% at 2 years, respectively. Generalized weakness and fatigue were long-term complications persisting in survivors. Patients who had shown muscle weakness in the follow-up period also showed persisting physical limitations, as well as reduced quality of life.(11,42,78–80)

In order to diagnose ICU-AW it has been established that the clinical diagnosis could be made by bedside evaluation of the muscle strength on the basis of the Medical Research Council sum score. The MRCS score evaluates 12 muscle groups and gives each of them a point score from 0 to 5. 0 means no contraction of the muscle, and 5 being normal muscle function. The score can total up to 60 for fully normal functioning. ICU-AW can be diagnosed when the score lies below 48. The MRCS score cannot differentiate between CIM and CIP. It also depends on the patients' overall cooperation(42,63,81–83). The difference between scores 4 (movement against gravity and some resistance, subnormal strength) and 5(normal strength) in MRCS score can be subjective (42,63).

Other diagnostic methods include handheld dynamometry and handgrip strength both of them are performable in the ICU(42,84).

To evaluate respiratory muscle strength one can use the maximal inspiratory pressure starting

with the functional residual capacity. This however still depends on the cooperation of the patient. If a patient is not cooperative one can use a one-way valve to start with(42,85).

Electrophysiological testing could be an option in some settings like nerve conduction studies and electromyography. These methods are extensive, expensive, and time-consuming. Nerve conduction studies show reduced compound muscle action potentials. When CIP is involved, there might be reduced sensory nerve action potentials, there might be normal to slightly slower nerve conduction velocity. Unfortunately, the correlation of electrophysiological abnormalities and muscle weakness has not been established in large patient cohort or populations; we also do not understand the role of electrophysiological changes in the absence of weakness. (42,85,86) Biomarkers could be used to screen or target for ICU-AW. Creatine kinase might be elevated in ICU-AW victims but is not a good marker. "*Plasma levels of neurofilaments, which are biomarkers of axonal injury, are also elevated in patients with ICUAW. Peak neurofilament levels showed good discriminative power for weakness but this peak only occurred after patients were clinically evaluable*"(42,87). This means that it cannot be used for early diagnosis. So far, no biomarkers have been found, there is research being done in to promising candidates. (42,46,87)

The Prevention and Management of ICU-AW is quite complex due to its long-term implications. It was shown that direct, aggressive treatment of sepsis is a necessity for preventing the development of ICU-AW. Anti-inflammatory therapies in sepsis have not shown the desired effects in various studies. Only a few limited, randomized studies have been done into other preventive strategies mostly aimed at the reduction of other risk factors.
As mentioned earlier, Insulin therapy concentrating on the normalization of glycemia as compared to tolerating hyperglycemia up to the renal threshold caused a reduction in occurrence of the electrophysiological signs of CIP and CIM and the requirement for the necessity for prolonged mechanical ventilation in ICU patients.(42,88) A different study showed that strict normoglycemia had an increased mortality as compared to patients whose insulin therapy was targeting a slightly higher blood glucose level(42). The strategy for the best glucose control is still wildly debated.(42,89)
Another strategy that has shown to be somewhat successful is the reduction of the duration of immobilization this can be achieved by reducing the amount of sedation. The aim of sedating

patients on a minimal level for the patient's comfort and safety have shown beneficial outcomes(42,90,91).

The reduction of time of immobilization in combination with early physical therapy were shown to be safe and feasible in the ICU and increase the positive outcomes. Quadriceps strength had improved until discharge when receiving passive and active training involving an ergometer(42,92). The training consisted of "*20 minutes of bed cycling 5days per week, from the 5th day following ICU admission.*(42,93)" Patient outcomes had improved with early mobilization and occupational therapy within 72 hours of starting MV additionally to sedation interruptions. This was done under an individualized training program ranging from passive rang-of-motion exercises in unresponsive patients, to active range-of motion exercises, bed mobility sitting, transfer training and walking. When adjusted for risk factors these trials showed that early mobilization of the critically ill and adjustment of the insulin dosage were clearly beneficial (42,75). The downside of early mobilization is its wide variability from center to center and many factors including resources, time management and staffing, reducing the effective implementation of this method(42,94).

The nutritional requirements for critically ill patients and its influence on the incidence and outcomes of ICU-AW are not well researched yet. Enteric trophic feeding by nasogastric feeding tube has shown to not have any negative effects on physical function and strength up to 1 year following ARDS when compared to full enteral feeding.(42,72,95)

Neurocognitive Impairments

Due to the high stress and physical and psychological experiences on the Intensive Care ward, many of these can cause cognitive impairments in the critically ill. We have got to remember the definition for PICS, *"New or worsening impairments in cognitive function persist months to years after hospital discharge and are associated with poor daily functioning and reduced quality of life."*(37,96–98) Impaired memory function, executive function, language, attention, and visual-spatial abilities are components of cognitive impairments that could develop following critical illness. (37)

Some risk factors have been established like inadequate blood glucose control, hyperglycemia as well as hypoglycemia and fluctuations in serum glucose, delirium, and in-hospital acute stress

symptoms. These are some risk factors could lead to persistent cognitive impairments following intensive care treatment and illness. (37,99–101)

The evidence supports the theory that patients with delirium when on critical care have an increased risk of long-term outcomes of cognitive dysfunction. (37,102,103)

A large prospective cohort study involving around 1040 participants and over 13000 participant-days in which the patients could be assessed analyzed the phenotypes of delirium present in these patients and the outcomes on cognitive impairments. They found that in 31% of participant-days on which assessment for delirium was possible that delirium was present. Out of these nearly 4200 participant-days, one delirium phenotype presented 32% of the time, while two and three delirium phenotypes presented during 29% of the time, and four phenotypes were fund in up to 9%. The most common forms of delirium presenting were hypoxic, septic, or sedative-associated delirium with more than half of patients developing signs of delirium at least once during the stay. Metabolic and unclassified delirium were found in 22% to 25% of patients(104). „*Early in hospital stay, sedative-associated, hypoxic, and septic delirium were common and were often one of multiple delirium phenotypes present on the same day. Metabolic delirium occurred less often, and unclassified delirium was the least common phenotype.*"(104) The rates for patients with metabolic and septic delirium remained stable while the percentage for hypoxic delirium and sedative-associated delirium declined in a time-dependent fashion. After adjusting for risk factors of delirium it was found that long stretches of hypoxic delirusm predicted worse overall cognition scores at three and 12 months following discharge. Sedative-associated and unclassified delirium prognose similarly worse cognitive results at 3 and 12 months. The length of septic delirium did not predict worse outcome at 3 months but only at 12 months. While the length of a metabolic delirium was not associated with worse cognitive outcomes at neither 3 nor 12 month. The delirium phenotypes connected to worse global cognition scores were linked to worse outcomes of MMSE score (Mini-Mental state examination) as well as in various, multiple other cognitive domains tested. (35,103,104)

Analysis of sedative-associated delirium in order to show the influence of different sedative and hypnotic drugs was not able to associate a drug-specific delirium with worse outcomes or identify a pharmacological driver behind the delirium. It has to accepted that *„most sedative-associated delirium days involved exposure to multiple sedating drugs"*.(37,104)

Another relevant factor is Dementia, as a disorder of the memory and cognitive function, it has been linked to ICU treatment. Dementia has been found in up to 15% of ICU survivors over 3 years of follow-up when compared to the 12.2% in the general population. It has to mentioned that pre-existing or pre-morbid cognitive deficiencies in the critical care population is common. A comparative study relayed that nearly 37% of patients over 65 years of age with critical illness have some cognitive deficiencies. It is assumed that pre-existing cognitive weaknesses have a significant effect on the cognitive functionality in PICS. (37,104,105)

Our understanding of the pathophysiological development of the cognitive impairments is not understood yet. More research would be required in these areas. (37,104,106)

Mental Health Impairments

New or worsening psychological states are frequently observed in survivors of the ICU. The psychopathological changes are seen in up to one third of patients requiring intensive care treatment. The major mental health conditions presenting in these patients are anxiety, depression, and post-traumatic stress disorder (PTSD). (9,107,108) 55% of patients met the caseness threshold for at least one of the three conditions at 3 or 12 months, it was 35% meeting the threshold for 2 or more psychopathological issues. PTSD is the rarest alone presenting issue out of the three major psychological conditions. (107)

In *Nikayin et al.*'s meta-analysis and systematic review of *Anxiety Symptoms in Survivors of Critical Illness* they analyzed around 2880 unique patients in 8 RCT, 15 cohort, and 4 cross-sectional studies. Most assessments were done between 1 and 12 months after critical illness. Only 41% of these studies had more than one follow-up check-up within the year. Nearly all of these studies were performed in European nations. (107,109,110)

To diagnose Anxiety and to establish its prevalence we have to understand the tools used to diagnose Anxiety. Many studies use the *Hospital Anxiety and Depression Scale – Anxiety* from here on referred to as the HADS-A and the *State-Trait Anxiety Inventory* referred to as STAI further on. The HADS is an in-hospital screening tool for mood disorder like Anxiety and Depression. The Scale itself consists of two divided subscales the *HADS-A* with 7 items reflecting a state of generalized anxiety and the *HADS-D* with 7 items primed for anhedonia. Overall, the scale consists of 14 items divided into two subscales and every item is scored from 0

(absence) to 3 (extreme presence), overall, a score of 42 is possible describing very severe depression or anxiety(107,110–112). In most of the studies looked at by *Nikayin et al.* HADS-A was used meaning that only the assessment for the anxiety subscale was performed meaning that 21 becomes the highest score possible. (37,107,110–112) A score from 0-7 on the subscale points to a mental state in the normal range, 8 to 10 points are suggestive of a possible mood disorder while 11 and higher are indications for a probable or likely presence of a mood disorder. (111,112)

On evaluation of the studies the prevalence of Anxiety symptoms on follow-up at 2-3 months, 6 months, and 12-14 months with ≥8 points used as the cutoff was 32%, 40% and 34%. If ≥11 points were the cutoff the prevalence of symptoms related Anxiety dropped to 17%,20%, and 17% at the 2-3 months, 6 months, and 12-14 months follow-up. (109,110) *Hatch et al.* found in their cohort study about mental disorders following critical illness that the caseness prevalence of anxiety was around 45% with a cutoff of ≥8 at 3 months, for moderate anxiety symptoms a 36% prevalence was established at 3 months. There was little change from 3 to 12 months in this study and this is similar to *Nikayin et al.'s* review. After performing change analysis including patients who had met the caseness threshold once but not twice on follow-up, *Hatch et al.* found that there is a significant difference in most cases for anxiety with 76% of patients having a changed score of more than 3 points.(9,107,110)

As for Depression, *Davydow et al.* (113) did a systematic review which they analyzed 14 unique patient cohorts after filtering their search. However, the data for this review is fairly heterogenous when it comes to the follow-up after ICU discharge in 6 out of these 14 studies had significant losses with follow-up. A handful of studies excluded people with previous psychiatric diagnoses, some only where there were previously known psychotic disorders or suicide attempts. Three studies included descriptions of the patient's previous psychiatric history and one of these reported recent histories of patient's two weeks prior before the ICU or whether the patient was prescribed antidepressants in the 6 months leading up to the ICU admission. (107,113,114) More than 1200 patients were atleast once evaluated for depressive symptoms, 13 studies used questionnaires and one used a *Structured Clinical Interview for Depression (SCID)* and a questionnaire. Most studies used the *HADS* to evaluate for Depression, 4 used the *Center for Epidemiologic Studies Depression Scale* (CES-D), one used *Geriatric Depression Rating*

Scale-Short Form (GDS-SF), and one the *Beck Depression Inventory-II*(BDI-II). (107,113,115)

Due to this variety of diagnostic methods, there were some challenges to overcome with some having multiple follow-up evaluations, and some studies having treatment groups and control groups. The decisions taken to get to a clean prevalence were for studies with multiple follow-ups to use the median value for each study, and for the ones with treatment groups and control groups to use the prevalence from the whole sample due to the fact that the control groups in these studies do not have to be more representative than the treatment groups. (107,110,113,116)

As there was the HADS used in several studies it happens that two studies chose the more strict threshold for "clinically significant" symptoms of depression of ≥11 points instead of the more common ≥8 points for "probable or likely" mood disorder. The median prevalence for depression in these studies with more than 1200 subjects is 28%, and for clinician-diagnosed depressive disorder 2 months post-discharge was 33% in the one study with 134 patients. Five studies looked at the change of prevalence of symptoms of depression over time and found in three of those studies a significant decrease in depressive symptoms.(113,115,117,118)

When it comes to risk factors increasing the prevalence of Depression, *Rattray et al.* found that female sex significantly increased the rate of post-ICU depression (118), while age was not found to be a risk factor. One study included in *Davydow et al.*(113) compared premorbid psychological pathologies or functioning as a risk factor for post-ICU depression. Reported pre-ICU depressed mood was found to be a predictive factor for depressive symptoms post-ICU discharge at 2- and 6-months time, while antidepressant use did not predict such symptoms(113,118). It is reported that 52% of patients with a history of depression present with high probability for Depression at 3 months post-discharge(9). Poor physical functioning before ICU treatment was an additional factor increasing the risk of post-ICU depression.(113,118)

When it comes to in-hospital risks it was found that Hospital Length of Stay, age, and illness severity measured by the APACHE-II scoring system were not associated with a significant increase in risk for depression. Sepsis was found to be the predictive risk factor for the development of depressive symptoms. The mechanism though is not understood yet. Additionally, recent studies have shown that long term depressive symptoms in post-ICU patients are caused by more somatic manifestations like fatigue or physical disability, rather than

the presentation through cognitive symptoms. Adverse perception of the Intensive Care experience has been associated with worse mental outcomes in-hospital and the year following discharge (9,114,118). It has been suggested that *"mood in the ICU (composed of symptoms such as anger, nervousness, low temperament, and confusion) and early intrusive memories of intensive care were the strongest acute psychological risk factors for PTSD and depression.* (113,116,119,120)"

"*Sleep disruption and deprivation, due to underlying psychological stressors, mechanical ventilation, noise, light, patient care interactions, and medications, are exceedingly common in the ICU and have been associated with delirium, cognitive impairment, and worsened psychological recovery from critical illness*(116,121–123)". There is reporting that lower socioeconomic status is correlated with the development of depression, anxiety, and worse mental quality of life outcomes, this association could not be established for PTSD. Additionally, there were links established between lower educational levels and the development of psychiatric outcomes after Critical Illness. (116,119,124)

Karnatovskaia et al. put forth in their research that memories of the ICU stay are some of the more consistent predictors of psychological dysfunction following the Critical Care management(116). Delusional memories have been associated with majority of patients receiving critical care treatment with disorientation, hallucinations, and nightmares being frequently reported. Particularly, memories of being distressed, of helplessness due to the lack of personal control during the ICU stay were strong predictors for negative psychological outcomes like depression, PTSD, and anxiety at follow-up.(116,125,126) Variations in the depth of sedation increase the incidence of Delirium, even though Delirium is not associated with an increased risk of PTSD, anxiety, and depression, memories of delusion were associated with more negative mental health outcomes. *Nouwen et al.* could not establish a relation between Delirium and emotional outcomes in their systematic review(116,127). In an anecdotal report by an ICU patient,

"*having some memories of what really went on, no matter how terrible it was, seems to be protective against PTSD, as it allows the patient to question the reality of the delusions...one benefits from knowing that some of the remembered events really did happen; that one wasn't entirely mad the entire time*".(116,128)

"*Pain, fear, anxiety, lack of sleep, tense feelings, inability to speak or effectively communicate, lack of control, nightmares, and loneliness were some of the most stressful recollections associated with spells of terror, feelings of nervousness when alone, and poor sleeping patterns*(116,129). *Use of sedatives and decreased arousal level have been linked with the development of delusional memories*" (116,129,130) which in turn increased the risk for negative psychological outcomes.

Not being able to remember the moment of admission is associated with worse quality of life outcomes(116,131). Patients who cannot recall their Intensive Care experience had a higher likelihood to develop more negative cognitive events at one year follow-up and stronger cognitive impairments on leaving the hospital but not at 1-year and 2-year follow-up. Patients who cannot recall their ICU stay had significantly worse than other patients on general intellectual function, executive function, processing speed, and verbal memory.(116,131,132) Therefore, poorly recalling critical illness affects the functioning on cognitive and psychological tests. Additionally, having absent or reduced real or factual memories of critical illness may have the patient remembering delusional or paranoid content with little knowledge or information to debunk the fictitious memories.(116,131,132) This could impact future psychological health, development, and functioning, in particular episodic flashbulb memories of their ICU stay, a symptom of post-traumatic stress disorder. (116,131,132)

Intuition tells us that physical rehabilitation should be beneficial after critical illness. Unfortunately, the usefulness and impact of physical rehabilitation is poorly understood.(116) Different programs exist; a follow-up program led by nurses did not show any evidence of being effective or cost-effective for the patient on 1-year-check-up on the patient's quality of life. (116,133) Similarly, a home-based multicenter trial could not demonstrate effects on physical function or health-related quality of health.(116) On the other hand, there was an investigation done that showed that an 8-week training intervention done after hospital discharge might be feasible and accelerated the natural healing, unfortunately it showed to only be beneficial to the patient`s fitness in the short term run(116,134).

Psychological and cognitive interventions have been difficult to evaluate from studies, one multicenter study, showed a decrease in women's symptoms of depression and PTSD with consults by the way of ICU follow-up(116,135). It has been shown in individual trials or

interventions that in-home cognitive, physical, and functional rehabilitation could improve executive function(116,136). The existence of follow-up clinics has not shown a full grasp of the protocols with their design, implementation and outcome of post-ICU clinics(116,137,138). Training based in the practice of mindfulness or coping therapy might be implicated in a reduction of psychological symptoms and distress(116,139,140). The most concrete and promising intervention in reducing subsequent psychological distress has been the introduction of patient's individual ICU diaries. Due to the relation of memories of delusion and fragmentary memories with psychological pathologies, it is believed that these diaries in which the patient with additions from staff or family of the patient can detail and record the stay. After discharge the patients received their diaries with explanations of the contents. On the three month follow-up, these patients had a significantly lower rate of PTSD(116,141–143). Proposed by the authors is the idea that the diaries might control the delusion patients experience during their stay because of their lacking ability to experience and process their environmental information.(116,141,143)

There have been various reported diary interventions that had an impact on the levels of anxiety and depression experienced by the patient, they demonstrated the ability for critically ill patients to close the holes in their memory, give an order to their experience, and strengthen the relationship with other people while being subsumed by the ICU environment(116,144,145). "Recognizing that accurate memories of ICU care may reduce the future psychological morbidity; it is important that ICU interventions that may favorably impact these memories are vigorously sought.(116)"

When it comes to interventions dealing with cognitive and psychological disturbances within the ICU we have seen the adoption of *early mobilization* in to recent guidelines for agitation, pain, and delirium management.(97,116,146) Various data sets from animal and studies on non-ICU populations have shown the "neuroprotective effects of exercise including increased synaptic transmission and neurotransmitter release, promotion of neurogenesis, improved cognitive function, and reduction of symptoms of depression and anxiety(116,147,148)". Physical rehabilitation being provided early on is an infrequently used intervention even though it is safe and feasible. Patients receiving early full-body rehabilitation had a better functional outcomes at discharge, as well as reduced delirium duration, and less days on the ventilator(93,116). This has been confirmed by more studies and included a reduction in the time of stay on the ICU and

hospital in general(116,147,149,150).
There unfortunately was not a demonstratable effect of early physical therapy and cognitive therapy on the cognition and psychology of the patient at 3 months, this is very likely due to this study being small in sample size(116,150).

The control and use of sedation is a contentious topic due to the association of sleep, delirium and the long-term psychiatric effects(119,151). Modern practice guidelines suggest that sedatives are used to maintain a low level of sedation rather than keeping the patient in a deeply sedated state(146). This is due to the fact that keeping the alertness levels in patients higher leads to better communication with the staff and an improved ability to meet the patient's needs leading to a "better ICU experience"(151). Unfortunately, we do not know what this means in practice and where the balance of beneficial and adverse effects lie. "*Kress et al* (152) *found that daily sedative interruption reduced the symptoms of PTSD. A recent randomized trial demonstrated that protocol of no sedation did not increase the risk of long-term psychological morbidity compared with the standard treatment*(116,153)." Similarly, interventions like the use of noise-cancelling headphones or music therapy as non-pharmacological treatments present with a picture of reduced anxiety and sedation, additionally showing that nonpharmacologic interventions leading to fewer cases of anxiety still hold water(154,155).

The importance of sleep during the stay in the ICU is not well understood, different interventions have been attempted to promote sleep in the ICU ranging from earplugs, relaxation techniques, daytime wakefulness, eye masks, controlled use of drugs and interventions that harm sleep but it was not possible to establish the efficacy of these interventions(116,122,156) There has been reduced delirium duration when there was a protocol with lowered use of delirium-inducing drugs when combined with nonpharmacological sleep enhancement interventions(116,157).

Lastly to talk about the psychological interventions, even though the mountain of evidence for psychological and cognitive dysfunction in patients staying in the ICU is overwhelming, limited resources have been invested in the understanding of these developments. Psychological support or help intuitively seem in order to help patients experiencing the extremes of an ICU hospitalization. There has been a study showing that already just perceived social support while on the ICU reduced the symptoms of PTSD(158). Psychological support provided by clinical psychologists is not widely established in the setting of the intensive care unit even though there

is a demonstrably significant reduction in PTSD showing that it may be worth it to intervene early(159,160). The support meant to be provided by psychologists might be counseling, education, and coping strategies. Other suggestions have been that early mobilization of body and mind increases the chance of better accessing the patient's needs(116,159).

"*it appears that not merely sedation interruption but perhaps even directed early activation of consciousness may have the most positive effect. Activation of consciousness includes facilitation of patients' ability to perceive the world around them and adequately react to the surrounding stimuli as well as the ability to follow commands. Once consciousness is active, we need to approach it from the same perspective as we do physical therapy of the body and engage the patients in tasks that help stimulate their thinking. The earlier we will activate and engage the consciousness and provide patients with psychological support, the fewer delusional memories and psycho-cognitive derangements patients may develop; this, in turn, will also enhance patients' ability to participate in physical rehabilitation*"(116)

PTSD or Posttraumatic Stress Disorder has increasingly gained relevance as one of the more important psychological disorders related to and following the experience and survival with Critical illness. In the DSM-V (*Diagnostic and Statistical Manual of Mental Disorders, 5th edition*), PTSD requires in order to be diagnosed that an individual survives a serious injury or death like an ICU hospitalization. Following these kinds of experiences, an individual has got to develop the subsequent symptoms which are required to last longer than a month and cause relevant distress or impact the patient's daily function: "persistently reexperiencing the event and attempting to avoid trauma-related stimuli; new negative alterations in mood/cognition; and new/increased arousal/reactivity."(108,116,161,162)

Various studies have attempted to establish the prevalence and incidence of PTSD following intensive care intervention. *Parker et al.* (108) performed a meta-analysis of 40 publications with at least one PTSD assessment performed on 4260 patients. Most publications had used the IES or IES-R to establish the point prevalence of PTSD or PTSD symptoms, while two studies used semi-structured psychiatric interviews and 6 had used the Posttraumatic Symptom Scale (PTSS). (108).

Overall, *Parker et al.* were able to establish a point prevalence of 4-62% over the range of publications they were evaluating. The IES or the *Impact of Event Scale* as the most prominent

scale for the assessment of PTSD symptoms is a measurement tool that uses a questionnaire to establish the prevalence of intrusive and avoidant symptoms with higher scores indicating a bigger disruption to a person. It evaluates the patient on a point scale from 0-75 with higher score indication higher levels of intrusive and avoidant thoughts and cognitions. It is suggested that the scale be judged in the ranges of 0-8 being subclinical, 9-25 mild range, 26-43 moderate, and higher than 44 being severe range of symptoms (163,164). When analyzing the publications using IES evaluation at 1-6 months, the pooled mean score was 20 meaning the mean patient had mild symptoms of posttraumatic stress disorder. When one looks at the prevalence of clinically important PTSD, the researchers looked at a IES threshold greater than or equal to 35 and greater than or equal to 20. With these parameters set and using a confidence interval of 95% the prevalence for PTSD symptoms was 25% on ≥35 and 44% on ≥20 points on a 1-6 month post-ICU check-up. When one looks at the studies with 7-12 month follow-up the mean IES score was lower at 17% and the prevalences of symptoms for PTSD were at 17%(≥35) and 34% (≥20), respectively(9,108,118,161). After sensitivity analysis, a process which in theory removes/looks at the heterogeneity of data, the studies with 1 to 6 month follow-up had a pooled mean IES score of 21 and the ones with 7-12 months follow-up had a pooled mean of 19, while the prevalences for the same studies were 24 and 46% for 1-6 months, and 22% and 43% for 7-12 months, respectively. This provides us with an estimation that nearly half of the post-ICU survivors present with mild to moderate symptomatology while severe PTSD symptoms are experienced by nearly a quarter of survivors(9,108,118,161).

Further one has to establish the risk factors for such a high prevalence of PTSD, it was found that only pre-ICU psychopathologies were associated with an increased risk for the development of PTSD symptoms, while a participants' sex or age were not related to with the symptoms of PTSD(9,108,161). As sedation is one of the main components in Critical Care it has to be evaluated whether they have an influence on the risk for developing symptoms of PTSD. *Parker et al.*(108) established in their meta-analysis that patients receiving benzodiazepines, or a higher total dose of benzodiazepines had greater symptoms of PTSD(108,165,166) while the duration of benzodiazepine receipts was not associated with an increased risk in one study(108,153). Protocols for "daily interruption of sedation", light versus deep sedation, analgesia-based protocols and protocols with no sedation did not show an association with higher prevalence in PTSD(9,108,166,167). Additionally, the duration of delirium was not related to the

symptomatology of PTSD. Corticosteroid usage in the ICU was evaluated and showed no association with PTSD (9,116,167,168).

Severity of illness and length of stay on the Intensive care unit have not been found to associated with the development of PTSD symptoms, as well as that the ICU admission diagnosis neither were mechanical ventilation or mechanical ventilation duration associated with the symptoms of PTSD (108,116,167).

Early post-ICU memories of frightening ICU experiences like paranoid delusional thoughts, hallucinations, or nightmares could be linked to increased risk for PTSD. The patients' post-ICU psychopathology was found to be associated with an increased risk. Post-ICU psychopathology means the psychological disorders that might be comorbid with the PTSD symptoms or appearing independently of the symptoms of PTSD like depression, anxiety, and substance abuse(9,108,116,167).

When one looks at the how interventions within the ICU influence the risk of developing the symptomatology of PTSD, one can see that there was a significant reduction of symptoms with the introduction of ICU diaries and self-help rehabilitation manuals, these results were found by 3 studies with a combined sample size of 631 people(108,143,169,170). Other post-ICU interventions like *nurse-led ICU follow-up clinics* did not show any significant benefits for PTSD symptoms, to be more precise one study showed no benefits and another showed benefits for women but not for men(9,108,133).

Overall, PTSD symptoms are associated with a decreased health-related quality of life outcome while it was not related to worse physical functional outcomes (9,37,108,116).

The issue one runs into is that there is no established standardized assessment to measure PTSD symptoms in Intensive care unit patients. Only two instruments that were used have been validated against the "gold standard" – the clinician diagnostic semi-structured interviews, these are the PTSS-14 (77% sensitivity and 97% specificity) and the IES-R (95% of area under the receiving operating characteristic curve [AUROC]).(108,116,171,172) Through the use of validated and common surveys we might be able to advance the field by standardized follow-ups, scoring on surveys, and thresholds for diagnosis. There needs to be still more research done in these directions but we are advancing with an increase in research into PICS and its mental health issues. (9,108,116)

We established that Sedation and “early memories of frightening ICU experiences” were associated with PTSD. One cannot create a link though between benzodiazepine sedation and PTSD symptoms there might be a connection between high in-ICU anxiety and a patient receiving higher doses of benzodiazepines(108,116,120,167).

Beneficial factors for the reduction of the prevalence of PTSD were the interruption of sedation with concomitant spontaneous breathing trials. The interruption of sedation, light sedation, and analgesia-based sedation protocols showed lower levels of PTSD symptoms. Increased use of opiates on the other hand was associated with higher risk for PTSD, while the duration of exposure to opiates showed reduced prevalence of symptoms. This might suggest that pain control may be protective against PTSD when increased or excessive opiates are used they might contribute to the sedation and subsequently increase the symptoms for PTSD.(37,108,173,174)

ICU diaries have become an established practice in many European ICUs and have shown in various clinical trials to reduce the incidence of PTSD, as well as “early intra-ICU psychological intervention”. (9,108,116,122,124,127)

Management and Treatment

When one talks about management and treatment of PICS one has to think first about the possibility of prevention. Many factors increasing the risk for PICS are also factors in the general ICU outcome so that the *ABCDE bundle* could be adopted for the prevention of PICS as well. The *ABCDE bundle* is an evidence-based guideline for intensivists to lead the necessary changes to further and improve the outcomes of the patient on the Critical Care unit. The package is broken down into(175):

“A, airway management, assess, prevent, and manage 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; and E, early mobility and exercise. ” (37,175,176)

The aim of this bundle is to minimize risk factors for the acute and long-term ICU-survivor outcome. One can add *FGH* to this as well, meaning *F* for family involvement, *G* for good hand off communication, and *H* stands for handout or educational material on the topic.(37,175)

The focus here now will be laid on physical rehabilitation or the "*E*" in the *ABCDE bundle*. Early mobility or mobilization has as its goal the improvement of quality of life by strengthening, reestablishing or retaining the daily function and activity of the critical illness survivors (37,177). Intensive Care-acquired weakness, as well as Delirium, have been associated to impaired life quality(11,37,178). Various different critical care guidelines have started to include early physical mobilization or rehabilitation for example the "*Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock*"(37,135,179). The rationale behind early rehabilitation is the betterment of mobility and muscle strength in patients. Studies have started to show that the effects of early physical rehabilitation are limited to decrease the burden of ICU-AW but that it had little effect on the mental health outcomes or the days without delirium(37,180).

An issue present is that "early" has not been clearly defined as of now. In general, it defines the rehabilitation taking place concomitant with regular ICU care while staying on the Critical Care ward. In different studies, the term "early" can change widely from the starting point of the intervention; in some cases, up to a week(37,181). Exercises included frequently in the physical rehabilitation process for critically ill patients are ranging from sitting to walking, passive to active range-of-motion exercises and cycling on an ergometer(37,181). More research needs to be done in this direction to understand the dose-response of early mobility and physical rehabilitation(37,94,182,183). It can not be established whether more intense rehabilitation had better outcomes that less intense exercise(37,184).

In order to maintain the human body one has got to feed it this becomes particularly important during critical illness. The nutritional requirements for the prevention of PICS have become more of a focus point and in particular in the development of ICU-AW. The servicable amount of energy and proteins have to delivered, in order to maintain the muscle synthesis due to it being a major influence(37,185). The second reason for the importance of nutritional therapy is that when the body requires energy that it does not receive from nutrition, it will use muscle catabolism to supply itself (37,186). This is unfortunately linked to a reduction in lean body mass

and then linked to higher mortality (37,186). In more recent times, understanding has shifted to nutrition focusing muscle volume and strength. It has been indicated that „t*he securement of minimum energy delivery with supplemental parenteral nutrition from the acute phase was associated with decreased PICS*“(37,187). On the other hand, one can *overfeed* the patient which can cause autophagy impairment and increase the severity of ICU-AW(37). It becomes even more important to appropriately feed the patient and elude *overfeeding*. Adequate feeding and protein delivery within themselves will not control the incidence of PICS, it occurs to be necessary to provide proper rehabilitation and training in order for nutritional therapy to have the necessary effects for the patient(37,142,188).

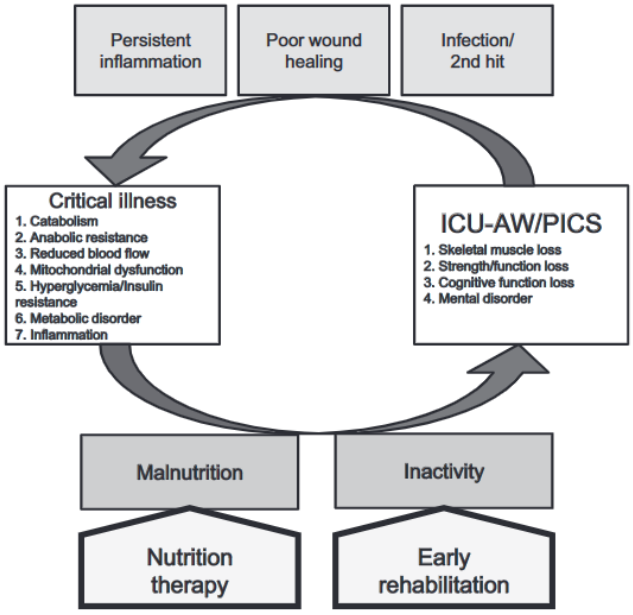

Illustration 1 - Association between Critical Illness and ICU-AW by Inoue et al.(37)

Proper glycemic control has been shown to be linked to reduced incidence of ICU-AW. Normalized blood glucose levels instead of tolerating hyperglycemia up to the renal threshold showed reduced incidence of CIP and CIM as well as reduced requirement for mechanical ventilation. The appropriate glucose levels in blood have not been established yet due studies showing that strict glycemic control had the potential to increase the mortality when compared to patients with higher glucose levels in blood (42,89). What adequate glycemic control looks like is still being widely discussed and debated.

Another factor to evaluate in the prevention of PICS is the environment in which the critically ill patient is healing. The ICU is a noisy, bright and disruptive place between the respirators, perfusors, and the monitoring systems. The reduction of these stressors might improve the outcomes of the patients. Better sleep quality has been recorded in patients with noise reducing interventions like ear plugs or noise-cancelling headphones occasionally in combination with eye masks(37,189,190). The risk of delirium could be reduced by the introduction of ear plugs or other noise reducing interventions, one meta-analysis estimates the relative risk for delirium with ear plugs to be 0.59(37,191). The direct link between environmental ICU factors and cognitive impairments has not been established yet; due to the indirect link with the reduction of delirium after the use of ear plugs there might be a possible connection of long-term cognitive outcomes and reduced sleep quality(37,191).

There is little understanding on how and if the environment influences the mental health of the critically ill. It has been reported that music or noise cancelling headphones reduced anxiety but there is too little data and research done in to this phenomena(37,192).

Nurses are the most involved part of patient care; they spend majority of their time on the patient directly(37,193). This makes them one of the key players in the persistent execution of interventions to prevent PICS for example by implementing the *ABCDEFGH bundle*(37). Nurses can assess and address the patient's needs when compared to their prehospitalization state of function with supportive, functional rehabilitation(37). The usage of non-pharmacological interventions can support the patient's improvement of daily function(194,195). The education and involvement of the family like providing them with information or the writing of an ICU diary can improve the relationship between the medical team, the family and the patient and lead to better family participation(196,197). Nurses can also help in the process of mobilizing the critically ill patient leading to possible improvement of the patient's function(37,198). Care for patients with PICS is a long continuous process; care needs to be provided even after discharge in order to good functional reconciliation. This means that physicians and nurses need to provide good communication with the post-ICU care team like primary care physicians, home nurses, and physiotherapists(3,37).

Intensive care unit diaries were mentioned in the previous paragraph. It is filled in and written by the physicians, nurses, the patient's family members and if possible, the critically ill patient

while the patient is being treated on the critical care unit; the diary can also be made in a different medium like audio recordings or videos(37). It usually contains the description and details of the daily ICU experience of the individual patient. It has been shown that ICU diaries could relieve symptoms of depression, PTSD, and anxiety and therefore could reduce the prevalence of PICS (196,199). These diaries can additionally alleviate the impact of critical care treatment on the family members of the ICU survivor(37). ICU diaries have been become frequent interventions in Critical Care patients.

The responsibility to determine whether such a diary is useful is frequently determined by the nursing team and in particular the bedside nurse for each patient. If the decision to start an ICU diary is taken the idea und execution need to be brought to the patients and their families. Only after they gave their consent can one start the intervention. Frequent contents of these diaries are the notes on the daily happenings, the state of the patient, where they stand in their rehabilitation, and so forth. The diaries can be expanded as mentioned earlier to either include other mediums like pictures taken or be made in a different medium. The physician in control, the physiotherapists, and technicians can also write and expand the diary. When the patient is discharged from the ICU they will be usually given the diary(37).

What happens with patients after their ICU discharge would be the next question. There have been discussions on ICU follow-up clinics which are primarily focused on the patients survive the ICU. Frequently these clinics have been the place for diagnosis and treatment of PICS(37). In Europe one has seen a spread of follow-up clinics over the last decades. There is however no unified or standardized organization of these clinics neither for patient evaluation nor treatment possibilities (37). A recent *Cochrane Review* showed there has been limited evidence for better outcomes between patients who partook in follow-up clinics and those participants that were getting the standard of care (137). Unlike a review performed by *Jensen et al.*(200) who also showed that follow-up clinics had little effect on the quality of life of a patient, their depressive symptoms, anxiety, or their physical and cognitive states, their consultations seem to have improved PTSD symptomatology after ICU discharge(37). Until now, it can not be established if ICU follow-up clinics are effective in treating and addressing PICS. There needs to be more research done in this field due to the existing clinics varying widely in their practices, and their methods.

Discussion

Throughout this text, we established that "new or worsening physical, cognitive, or mental impairments following critical illness and persisting even after hospitalization" is the definition for PICS(2,3,37). We established the different symptoms and domains of this syndrome or symptom complex including possible approaches at prevention and management of ICU survivors suffering from PICS. Nearly up to 60% of ICU survivors develop symptoms related to PICS(13,14). 30-40 % of patients suffer from newly developing mental health disturbances with depression being the most common sequelae following ICU treatment(9,13,37). The physical impairments present most commonly with reduced muscle mass and function, joint immobility, exercise limitation, fatigue, and decreased quality of life (13,16). It is theorized that the need for mechanical ventilation in Critical Illness raises the risk for lung injury by the ventilator causing fibrosis connected to biotrauma and barotrauma(10,11,19) additionally to "*disuse atrophy and alterations in respiratory muscle structure leading to decreases in muscle strength*(10,20)" The reduction in muscle strength and capacity can be seen on 6MWT and by measuring the strength of different muscle groups(10,11,23,27,28). There is evidence of more permanent disability as there are studies showing deficits to after Critical Illness (10,29). Patients presented with reduced ADLs and IADLs following critical illness reduced IADL function was present in nearly 69% of survivors (10,29). One of the most common forms of physical impairment in ICU survivors is the development of ICU-acquired weakness developing frequently during the ICU stay and the persisting until after discharge (11,42,49). Sepsis, Systemic inflammatory response syndrome, and MOF have been shown in different studies to produces high incidence of neuromuscular complications and be independent risk factors for the development of ICU-AW. Prospective studies have presented more independent risk factors for the development of ICU-AW like the use of vasopressors, aminoglycosides, some inflammatory mediators, and the presence of septic encephalopathy (42,71–73,201) . Glucose control in the blood serum has shown to reduce the electrophysiological and clinical signs of ICU-AW. This means that hyperglycemia is a fixed risk factor for ICU-AW for its diagnostic and clinical signs(42,71,74,75).

Impaired memory function, executive function, language, attention, and visual-spatial abilities are components of cognitive impairments that are seen to develop following critical illness The

development of cognitive impairments is linked to inadequate glycemic control, delirium, and acute stress symptoms (37,99–101). Another relevant factor is Dementia, as a disorder of the memory and cognitive function, it has been linked to ICU treatment. It has to mentioned that pre-existing or pre-morbid cognitive deficiencies in the critical care population is common. It is assumed that pre-existing cognitive weaknesses have a significant effect on the cognitive functionality in PICS (37,104,105).

Mental health impairments are frequent following ICU treatment of Illness. The major mental health conditions presenting in these patients are anxiety, depression, and post-traumatic stress disorder (PTSD) (9,107,108). 55% of patients met the caseness threshold for at least one of the three conditions at 3 or 12 months, it was 35% meeting the threshold for 2 or more psychopathological issues (107). Most studies used the HADS-A and HADS-D to diagnose the mental health impairments in PICS(37,107,110–112) particularly Anxiety and Depression. For PTSD, the diagnostic tool used was the *Impact of Event Scale* one of the most prominent tools for PTSD. It evaluates intrusive and avoidant symptoms, the higher the score on the questionnaire the higher likelihood for PTSD (163,164).

For the prevention of PICS and the improvement of Intensive Care outcomes, the ABCDEFGH bundle has been well established (175). Early rehabilitation and light sedation have been found to be beneficial in most cases due to their reduction in deliriant experiences and memories, and due to them giving the patient back “control”. Nutrition has been found to be an important factor in the treatment and management of PICS; “*the securement of minimum energy delivery with supplemental parenteral nutrition from the acute phase was associated with decreased PICS*“(37,187)

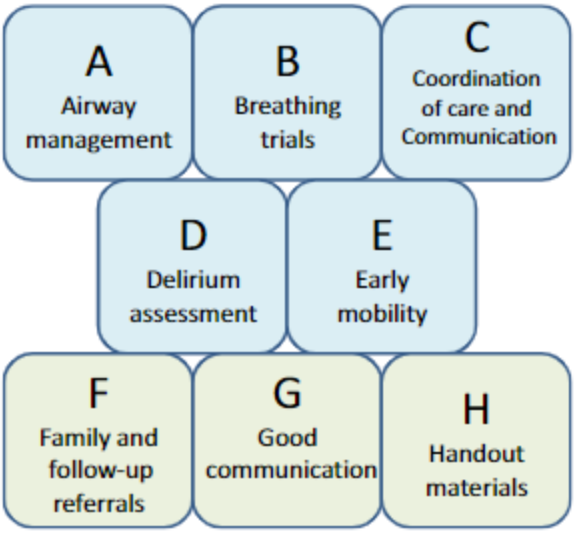

Illustration 2 - ABCDEFGH bundle for ICU treatment(37)

Due to the complexity of this topic, it being very multifaceted and frequently very clinical it has been hard to draw clear lines and establish safe and accepted conclusions and guidelines for diagnosis and treatment of post-intensive care syndrome. The heterogeneity of data and the lack of protocols and inconsistent follow-ups do not allow unfortunately for defining appropriate post-ICU care. What can however be said is that prevention is likely more important than the management of PICS. More research needs to be done into the various aspects of PICS and how the mental, cognitive, and physical field interact with one another.

The choice to leave out PICS-F and PICS-P was made due to lack of time for the research and due to it blowing up the frame of this work. PICS-F was excluded due to it being the syndrome affecting the family or surrounding of an ICU patient and it not being directly linked to PICS developing in the ICU survivor. The exclusion of PICS-P happened due to the pediatric population having different complexes in regards to physiology, their social impact, and their general development.

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Biography

Faris Bergner was born on the 17th of March 1997 in Freiburg im Breisgau, Germany. After going to kindergarten and first grade of primary school in Freiburg, the family moved to Oberkirch in Switzerland in early 2004. For middle and high school, he visited the "Kantonsschule Sursee" with a focus on Latin, Biology and Chemistry, and History. A personal focus at that time were martial arts, particularly Judo and Jiu-Jitsu, Basketball, and philosophy. Following graduation, he did different internships and took different types of work like nursing, gardening, teaching language and physiotherapy. In 2015, he applied to medical school in Zagreb. During medical school he worked as well as a teacher for the German language and did various internships in different hospitals in Germany and Switzerland like Anesthesiology, Gynecology, ENT, Surgery and Geriatrics. Following Graduation from medical school, he plans on specializing in either Emergency Medicine through the Anesthesia & Reanimatology pathway or Intensive Care.