

PREVENTION OF POST-INTENSIVE CARE SYNDROME (PICS)



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■ TABLE OF CONTENTS

1	INTRODUCTION	7
2	POST-INTENSIVE CARE SYNDROME: DEFINITION, BURDEN, CONSEQUENCES AND RISK FACTORS	9
2.1	PHYSICAL OUTCOMES: ICU-ACQUIRED WEAKNESS	9
2.2	MENTAL HEALTH OUTCOMES	10
2.3	COGNITIVE OUTCOMES	10
2.4	OTHER PATIENT OUTCOMES	11
2.5	CONSEQUENCES ON FAMILY MEMBERS OR INFORMAL CAREGIVERS	11
2.6	RISK FACTORS OF POST INTENSIVE CARE-RELATED OUTCOMES	11
2.6.1	Pre-existing health conditions	12
2.6.2	ICU-associated factors	12
2.6.3	Post-ICU risk factors	12
3	SCIENTIFIC EVIDENCE FOR INTERVENTIONS FOCUSED ON PICS-PREVENTION.....	14
3.1	AIM	14
3.2	METHODS.....	14
3.3	RESULTS	15
3.3.1	Pharmacological interventions	15
3.3.2	Mechanical ventilation strategies	23
3.3.3	Environmental interventions.....	24
3.3.4	ICU diaries as intervention	25
3.3.5	Psychotherapeutic interventions	26
3.3.6	Patient education as intervention	26
3.3.7	Interventions focused towards family and relatives	27



3.3.8	Multi-modal interventions	28
3.3.9	Physiotherapeutic interventions	29
3.3.10	Neuromuscular electrical stimulation (NES)	31
3.3.11	Nutritional interventions	31
3.3.12	Complementary medicine interventions	33
3.4	DISCUSSION	34
4	IMPLEMENTATION OF PICS PREVENTION	34
4.1	AIM	34
4.2	METHOD	34
4.3	IMPLEMENTATION TOOLS	35
4.3.1	Background	35
4.3.2	The PAD guideline	35
4.3.3	The PADIS guideline	36
4.4	THE ABCDE(F) BUNDLES: TRANSLATION OF THE PADIS GUIDELINE INTO PRACTICAL TOOLS	36
4.5	IS THE USE OF THE ABCDE(F) BUNDLE EFFECTIVE?	37
5	BARRIERS AND FACILITATORS TO ADOPT PICS PREVENTION INTERVENTIONS	39
5.1	AIM	39
5.2	LITERATURE SEARCH	39
5.2.1	Databases and date limits	39
5.2.2	Search strategy	40
5.2.3	Inclusion/Exclusion criteria	40
5.2.4	Analysis	40
5.3	FINDINGS	40
5.3.1	Preamble: classification of barriers and facilitators	40



	5.3.2	Barriers and facilitators to the adoption of bundles.....	43
	5.3.3	Barriers to specific interventions	45
5.4		LIMITATIONS	68
6		PREVENTION OF PICS IN BELGIUM	68
6.1		INTENSIVE CARE UNITS IN BELGIUM.....	68
	6.1.1	Definition and status.....	68
	6.1.2	Licensing standards for intensive care function	70
6.2		RISK FACTORS OF PICS IN BELGIUM.....	70
	6.2.1	Characteristics of patients at ICU admission	71
	6.2.2	Risk factors of PICS during ICU stay	74
6.3		INITIATIVES TO PREVENT PICS IN BELGIUM	77
	6.3.1	Introduction	77
	6.3.2	Methods	77
	6.3.3	Results	77
7		DISCUSSION	80
8		CONCLUSION	82



LIST OF FIGURES

Figure 1 – Post-intensive care syndrome (PICS) conceptual diagram (from Needham D. et al. ¹)	8
Figure 2 – Extended definition of Post-Intensive Care Syndrome (From Rousseau AF et al. ⁴).....	8
Figure 3 – Overview of the comparisons between sedative agents and antipsychotics.	16
Figure 4 – Number of intensive care beds per 100 000 population in OECD countries, 2019 (or nearest year) and 2020	69
Figure 5 – Proportion of ICU stays of more than 48 hours by age group and year, 2016-2020	71
Figure 6 – Proportions of psychiatric diseases among ICU stays for more than 48 hours by year, 2016-2020	72
Figure 7 – Midazolam, NMBA, ketamine, dexmedetomidine and propofol consumption in the ICU, 2016-2020	75

LIST OF TABLES

Table 1 – Patients at high risk for PICS according to the International consensus conference of the Society of Critical Care Medicine (May 2019) ⁵⁵	13
Table 2 – Inclusion and exclusion criteria of the integrative review on PICS prevention interventions	15
Table 3 – Summary of the results from prospective studies	20
Table 4 – Number of stays of more than 48 hours in ICU among adult population (>18 years), by year	71
Table 5 – Characteristics and risk factors of PICS at ICU admission in Belgium, by year.....	73
Table 6 – Risk factors of PICS during ICU stay for more than 48 hours in Belgium, by year	76



LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ARDS	Acute respiratory distress syndrome
BZD	Benzodiazepine
CAM-ICU	Confusion Assessment Method - Intensive Care Unit
CFIR	Consolidated Framework For Implementation Research
CIM	Critical Illness Myopathy
CIP	Critical Illness Polyneuropathy
CPOT	Critical care pain observational tool
DEX	Dexmedetomidine
EM	Early Mobilisation
ER	Early Rehabilitation
FG	Focus Group
HAL	Haloperidol
HCP	Healthcare Providers
ICU	Intensive Care Unit
ICU-AW	Intensive Care Unit- Acquired Weakness
IR	Integrative Review
IRR	Incidence Risk Ratio
M	Medical (Focus Group)
MA	Meta-analysis
MD	Medical Doctor
Md	Median
MDFG	Focus group with medical doctors
Mn	Mean



MV	Mechanical Ventilation
N	Nursing (focus group)
NES	Neuromuscular electric stimulation
NIV	Non-invasive ventilation
NMBA	Neuromuscular blocking agent
NS	Nursing staff
OT	Occupational Therapists
PRO	Propofol
QoL	Quality of life
PFG	Patient focus group
PICS	Post- Intensive Care Syndrome
PT	Physiotherapists
PTSD	Post-Traumatic Stress Disorder
PTSS	Post-Traumatic Stress Symptoms
RASS	Richmond Agitation-Sedation Scale
RHM-MZG	Résumé Hospitalier Minimum - Minimale Ziekenhuis Gegevens
RISP	Risperidone
RN	Registered Nurses
RT	Revalidation Therapist
SD	Standard deviation
SR	Systematic review
TDF	Theoretical Domains Framework
VAS	Visual Analogue Scale
ZIPR	Ziprasidone



■ SCIENTIFIC REPORT

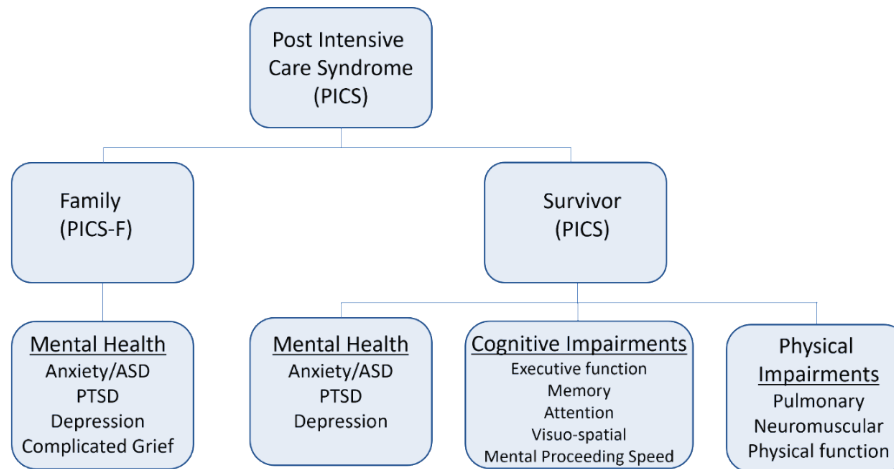
1 INTRODUCTION

Since its outset in the middle of the twentieth century, intensive care medicine has steadily experienced a substantial evolution of therapeutics and techniques, followed by an improvement in outcomes. Along with a worldwide increase in the provision of care, the amount of patients surviving critical illness has consequently gradually grown up.

Although intensive medicine focused initially on mitigating the mortality associated with life-threatening illnesses, the long-term burden of post-intensive care has progressively been recognised after discharge from the intensive care unit (ICU). Survivors of critical illness may indeed present new or worsening physical, mental, and cognitive debilitating impairments, following a stay in the ICU. The concept of “Post-Intensive Care Syndrome” (PICS) was introduced to describe and characterize persisting consequences and disabilities that may develop in the aftermath of critical illness, regardless of the cause of the initial disease. The umbrella term “PICS” was officially established in 2012 during a stakeholder conference and is defined as “new or worsening impairments in physical, cognitive, or mental health status arising after critical illness and persisting beyond acute care hospitalisation” (see Figure 1).¹



Figure 1 – Post-intensive care syndrome (PICS) conceptual diagram (from Needham et al.¹)



ASD: acute stress disorder; PTSD: post-traumatic stress disorder

PICS symptoms may sometimes persist for up to several years.² As such, it has become a public health concern. PICS may also impinge on the quality of life of patients and is associated with health care expenditure and consumption of resources and economic loss (due to long term work disability).³

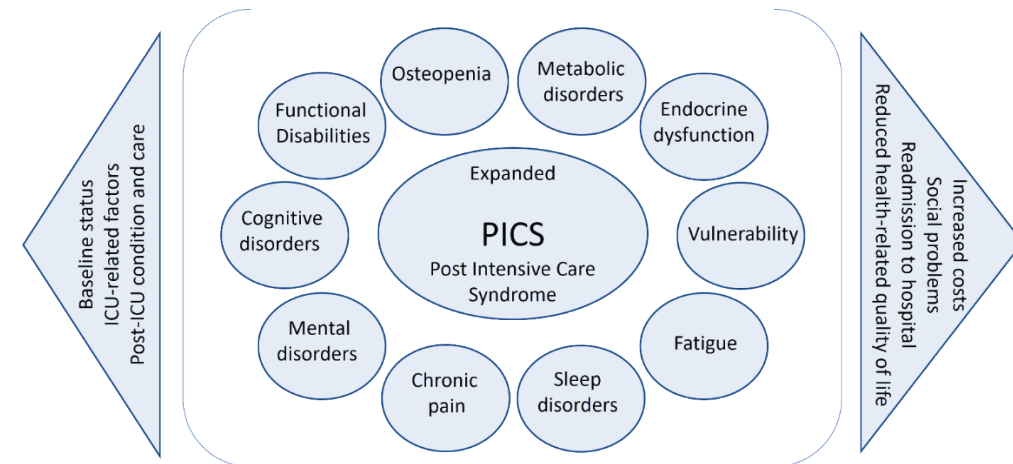
The clinical spectrum of PICS is heterogeneous and includes physical, mental and cognitive health. The most frequent physical impairment is ICU-acquired weakness (ICU-AW) which is characterised by a muscular weakness that may lead to an overall physical disability and unsettled activities of daily living. In addition, respiratory muscles can also be adversely impacted and lead to respiratory disorders. Psychological health can also be affected. Disorders include anxiety, sleep disorders, depression and post-traumatic stress disorders (PTSD). Impairments in cognitive function may manifest as concentration, memory and verbal or executive difficulties, for instance. Furthermore, mental health problems have been

identified in patients concerned by PICS and their caregivers. This component has been described as PICS-Family (PICS-F) (see Figure 1).

In the past few years, new disorders or sequelae have been reported in ICU survivors and experts proposed that these be added to PICS-related conditions. For instance, metabolic disorders (diabetes, cortisol or pituitary hormones derangements), extreme tiredness, or chronic pain have been described (see Figure 2).

It is important to note that many symptoms of PICS go on developing or occurring after ICU discharge and that this project only addressed PICS prevention at the ICU level and not its global management, notably after hospital discharge. As such, the report did not consider an array of post-ICU interventions and services (post-ICU clinics, for instance).

Figure 2 – Extended definition of Post-Intensive Care Syndrome (from Rousseau et al.⁴)



Functional disabilities: swallowing disorders, ICU-acquired weakness



In Belgium, there is a substantial knowledge gap regarding the specific problem of PICS and current practices in ICU can be involved in PICS components. All intensive care clinicians of the major ICU units have confirmed the priority of this problematic. The policy makers have confirmed the need to make recommendations for practices and care trajectories.

This study aims at proposing strategies at ICU level in Belgium to prevent the occurrence of PICS by:

- Presenting interventions that prevent/limit the occurrence of PICS and its related long term outcomes
- Providing a brief overview of the current knowledge on risk factors for the development of PICS
- Identifying which are the (organisational) barriers and facilitators to prevent PICS

The management of post-intensive care syndrome has been addressed by a separate study.⁵

2 POST-INTENSIVE CARE SYNDROME: DEFINITION, BURDEN, CONSEQUENCES AND RISK FACTORS

The clinical spectrum of PICS includes new (or worsening) physical, mental or cognitive disorders, arising after critical illness. These impairments persist beyond the ICU stay and may last for several months to years. The quality of life and the daily functioning of patients may consequently be altered. In addition, family members and relatives could be impacted after a member of their family has stayed in ICU.

2.1 Physical outcomes: ICU-acquired weakness

ICU-acquired weakness refers to neuromuscular damage acquired during the ICU stay and lingering beyond. It is characterized by a symmetrical decrease in the limb muscle function and mass and occurs rapidly after ICU admission. It is most frequently due to critical illness myopathy (CIM), critical illness polyneuropathy (CIP), or the association of both. CIM refers to an acute primary muscle failure not related to a denervation, while CIP manifests as a sensory-motor axonal polyneuropathy giving rise to muscle denervation and subsequent atrophy. CIP has been associated with worse outcomes (persisting disability) than CIM.^{4, 6} It should be noted that the diaphragm and other respiratory muscles can also be involved. Difficulties to wean patients from mechanical ventilation and prolonged ICU/hospital stay may ensue.

The pathophysiology of ICU-AW remains incompletely appraised. Current evidence supports several pathophysiological pathways interplaying.^{4, 7, 8} Inflammation related to the primary illness seems to be the cornerstone pathway involved in the downstream mechanisms participating in the onset of ICU-AW (imbalanced protein turnover, mitochondrial failure, microcirculation disturbances, altered autophagy...). Other factors are potentially involved in the development of ICU-AW and include ICU interventions.^{9, 10} For example, immobilisation during the ICU stay has been associated with muscle mass wasting through the loss of mechanical



loading (called 'muscle silencing'). Although recovery from ICU-AW may mostly occur within 12-24 months², a proportion of patients keep on experiencing physical function impairments in the long run. Such persisting ICU-AW could potentially be associated with long-term structural musdamageages.^{4, 11, 12} Persisting ICU-AW is also associated with higher long-term mortality.^{8, 13}

The prevalence rates of ICU-AW vary widely among studies, depending on several factors such as the type of studied population, the patient's pre-hospital muscle, the timing of assessment and the methods used for diagnosis (functional testing, electrophysiology, imaging, biopsy).⁸ Meta-analyses report the presence of ICU-AW in approximately 40% of patients, at ICU discharge.^{8, 14} It is important to remind that patients developing ICU-AW are commonly those who had long ICU-stay and high severity of illness (sepsis, need for mechanical ventilation, for instance).

Related physical impairments like muscle weakness, loss of muscular mass, fatigue, impaired exercise capacity and functional disability have been described up to several years after discharge from ICU.^{2, 15-17} These disorders may substantially disturb daily-living activities, and impact patients' quality of life.^{7, 18}

2.2 Mental health outcomes

Mental impairment is a component of PICS that is less easy to identify than physical sequelae. Anxiety and depression are potential psychological sequelae after ICU. Studies suggest that there is poor improvement in anxiety and depression over time. Several meta-analyses reported that approximately a third of patients had symptoms of anxiety or depression at one year.^{19, 20}

Patients may experience acute stress disorders during the first month after discharge. Posttraumatic Stress Symptoms (PTSS), belongs to the "PTSD-related symptoms", since it comprises an array of symptoms sharing many similarities with PTSD.^{4, 21} Despite those similarities, PTSS differs from PTSD in terms of symptom duration and intensity. Although PTSS resolves over time, the persistence of severe symptoms for a long time (or the occurrence of symptoms after a quiescent interval) is typical of PTSD.^{22, 23}

Meta-analysis have reported pooled rates of PTSD symptoms in one fifth of critically-ill patients, one year after the ICU stay.²⁴⁻²⁶

PTSD includes several types of symptoms: intrusive memories (flashbacks, re-experiencing memories or nightmares), avoidance of the reminders, mood changes, and emotional problems (arousal symptoms). These intrusive memories are related to the ICU environment like monitoring alarms, or invasive techniques such as the placement of catheters or suctioning through the endotracheal tube. In addition, ICU-patients may misperceive their environment. This may induce fearful feelings and might sometimes be associated with stressful hallucinations contributing to the onset of PTSD. The burden of PTSD is particularly concerning because avoidant behaviour may impede patients to look for assistance to be diagnosed, and appropriately followed.^{4, 21}

The pathophysiology of PTSD is not well described. It is very probably multifactorial and involves alterations of neurotransmitters pathways in the setting of brain inflammation, sedative agents, and metabolic disorders occurring in the ICU.^{27, 28}

2.3 Cognitive outcomes

Persisting cognitive problems are reported in ICU survivors and affects concentration, memory, verbal fluency, attention, or executive functions. People undergoing such disorders have a reduced quality of life, marked by intellectual, social or daily-living difficulties.²⁹⁻³¹ It associates with increased healthcare costs and caregiving needs.³⁰ The occurrence of cognitive disorders vary widely among studies.^{16, 29, 30, 32} Moreover, it may be difficult to discriminate between new cognitive impairment and the exacerbation of pre-existing cognitive decline due to the lack of data on cognitive function at baseline. Such disorders may be difficult to identify and the way to measure them is also important to take into account (subjective assessments versus use of screening cognitive tests).³³

The pathophysiology of long-term cognitive disorders is closely associated to the onset of an acute cognitive dysfunction occurring in the ICU, so-called 'delirium'. Patients who develop delirium are at higher risk for long-term cognitive problems.^{30-32, 34} Delirium is an acute brain dysfunction syndrome,



characterised by modifications or fluctuation in baseline mental status, inattention, or altered level of consciousness.³⁵ Several presentations have been described: (1) hyperactive delirium represents the minority of cases and gathers aggressiveness, hallucination and agitation as main symptoms. (2) On the other hand, hypoactive delirium is characterized by apathy, confusion, lethargy and impaired attention. (3) Fluctuations between both categories define the third subgroup and are called 'mixed delirium'. Hypoactive and mixed delirium are the most frequent.³⁶ Several hypotheses have been proposed to explain the development of delirium and include alterations in the regulation of brain neurotransmitters, or a brain inflammation secondary to the spreading of the pro-inflammatory mediators, in response to critical illness. Accordingly, neuroimaging studies have identified structural modifications within the brain.^{37, 38}

2.4 Other patient outcomes

The quality of life of patients undergoing PICS-related is impacted, and particularly in those with higher severity (mechanical ventilation for severe respiratory failure, severe trauma and sepsis).³⁹⁻⁴¹ PICS-related impairments can also affect patients' ability to return to work and subsequently pose professional, social, and financial burdens.^{42, 43}

Over the past few years, the concept of PICS has progressively been expanded to other newly reported issues after leaving the ICU. For instance, accelerated bone loss with risk of fracture, new-onset diabetes, or hypothalamic-pituitary axis imbalance have been reported, along with chronic pain or extreme fatigue.⁴

2.5 Consequences on family members or informal caregivers

The burden of critical illness may extend to mental health of family members and persist beyond the hospitalisation. This affection is related to "PICS-Family" (PICS-F) and refers to new or worsened mental health impairments. It encompasses anxiety, depression, and even PTSD. As family members generally provide the support required by their relatives, they can be less concerned about their own health status, making PICS-F possibly undiagnosed and unmanaged.⁴⁴⁻⁴⁶

Critical illness may also cause socioeconomic difficulties and increased healthcare expenditures. Reported socioeconomic consequences consist of change of employment status (i.e. work hours reduction, quit job), decreased incomes, lifestyle inferences (i.e. quit activities to take care of the patient, logistics of home life).^{44, 47}

2.6 Risk factors of post intensive care-related outcomes

Different modifiable and non-modifiable factors are associated with PICS and its functional consequences on daily-living activities. Risk factors are generally categorised into three types: those that refer to pre-existing conditions related to the patient's health status, those related to the ICU stay, and those reported at ICU discharge. In addition, the duration of exposition to risk factors, and consequently the duration of the ICU stay, is per se a key-component contributing to the development of PICS.^{9, 16, 32, 48-}

51



2.6.1 Pre-existing health conditions

Older age is associated with long-term physical disorders and post-ICU frailty.^{16, 52}

Patients with previous mental health problems are more likely to develop PTSD or depression after discharge from ICU.^{20, 24, 52}

2.6.2 ICU-associated factors

Regarding physical outcomes, the severity of critical illness is associated with ICU-AW.^{49, 52} The degree of hyperglycaemia in response to critical illness has also been associated with ICU-AW⁸, while the adverse relationship between neuromuscular blocking agents (NMBA) and ICU-AW remains controversial.^{8, 49}

Distress experienced during the ICU stay (fear, nightmares, 'negative' ICU experiences, agitation) is associated with several mental-health-related outcomes.^{19, 20, 25, 52}

The occurrence of delirium (and its duration) is a risk factor for long-term cognitive disorders.⁵²⁻⁵⁴

2.6.3 Post-ICU risk factors

The occurrence of early psychological problems at ICU discharge (PTSD, depression, anxiety) is associated with persisting mental health problems.^{19, 25}

Of note, it should be mentioned that associations may be indirect (relationship between sedative agents, immobility and muscular atrophy, for instance), and that some subgroups of patients may represent a particular underlying pathophysiology, which may favour the effect of several risk factors that would not impact other subgroups (patients with sepsis, for instance).⁸

Identifying risk factors of PICS is limited by the fact that diagnostic tools for PICS disorders varied widely across studies. This factor has been pointed out in the recent international consensus conference on the prediction and identification of long-term issues after critical illness, in 2019^{a, 55}. Characteristics of patients at high risk for long-term consequences, and requiring to be screened for PICS, were highlighted and presented in Table 1. Regarding physical outcomes, it is worth noting that experts focused on post-ICU physical impairments (and not just on ICU-AW).

^a To address the question 'Can we predict PICS', a systematic review to examine risk factors of PICS was conducted, and results were discussed during the conference. A three-round Delphi method was used.

**Table 1 – Patients at high risk for PICS according to the International consensus conference of the Society of Critical Care Medicine (May 2019)⁵⁵**

Functional domain	Before Critical Illness	During Critical Illness	After Critical Illness
Cognition	Pre-existing cognitive dysfunction	Incidence and duration of delirium Sedation (benzodiazepines) Sepsis Shock Hypoxia Acute respiratory distress syndrome Life support (<i>e.g., invasive mechanical ventilation</i>) <i>was identified as a key risk factor for post-ICU problems (weak recommendation, 72% agreement)</i>	
Mental health	Pre-existing mental health problems (anxiety, depression, or post-traumatic-distress disorder)	Memories or frightening experiences in ICU	Early symptoms of anxiety, depression, or post-traumatic-distress disorder
Physical	Pre-existing functional disability Frailty Pre-existing cognitive impairment		

**Key points**

- Post-intensive care syndrome describes a group of persisting symptoms arising in patients who were hospitalised in the ICU for critical illness:
 - ICU acquired weakness (ICU-AW) is a neuromuscular disorder accounting for the most frequent physical outcome of PICS. Persisting ICU-AW may give rise to functional disability impairing daily-living activities and quality of life, and is associated with long-term mortality.
 - Mental health impairments include anxiety, post-traumatic stress disorder (PTSD) and depression. PTSD may be underrated since avoidant attitude may impede patients to look for assistance. Pre-existing mental health problems, psychological distress during the ICU stay, and early psychological symptoms after discharge are associated with long-term mental disorders.
 - Cognitive disorders involve complaints including concentration, memory, verbal fluency, attention, or executive function. Delirium in ICU is its main risk factor. Cognitive dysfunction is frequently underestimated and associated with reduced quality of life and daily-living difficulties.
 - Family members or informal caregivers may also be affected by adverse psychological issues described by the term PICS-Family.
 - PICS brings about a substantial socio-economic burden and impacts the quality of life.

3 SCIENTIFIC EVIDENCE FOR INTERVENTIONS FOCUSED ON PICS-PREVENTION

3.1 Aim

We searched the literature to identify effective interventions to prevent PICS in ICU. However, this review did not intend to redo the work conducted for the PADIS guideline on the prevention of PICS (see section 4.3.3). The most important goal of this integrative review was to identify new (and unused) studies to complete the knowledge base.

3.2 Methods

For this integrative review, in the first stage, we read key publications and textbooks focusing on PICS to get an overview of the dimensions of this syndrome and to identify search terms to use for the literature search. In the second stage, we searched Medline, Cinahl and Embase for systematic reviews on (dimensions of) PICS, published between 2010 and November 2020. The primary papers, used to conduct these systematic reviews, were retrieved. In the third stage, we searched in Medline, Cinahl and Embase for primary papers published between 2018 and November 2020. In the fourth stage, we searched the last version of the PADIS guideline (2018) and a recent PICS handbook (2020)⁵¹, for additional references. One researcher performed the literature search (J.A.). All the retrieved primary papers were screened on title and abstract by two reviewers (G.H. and J.A.) with the web-application Rayyan®. One researcher (J.A.) then checked for a set of predefined inclusion and exclusion criteria and performed the data analysis.

As the intention was to cover all preventive interventions for PICS, this integrative review started from a general and broad PICO:



P: patients in ICU (>48h)

I: any intervention or pharmacological agent to prevent the development of PICS, applied in the ICU

C: any intervention or pharmacological agent, or usual care, applied in ICU

O: any PICS outcome or intermediate outcome (as described in the introduction of this report) in the short or long term

Table 2 – Inclusion and exclusion criteria of the integrative review on PICS prevention interventions

	Inclusion criteria	Exclusion criteria
Patients	ICU	brain trauma, brain surgery or brain damage
Intervention	at ICU level	no control intervention or no patient control group
Comparator	at ICU level (usual care, placebo, or other intervention)	post ICU, perioperative, no intervention
Outcomes	related to PICS or intermediate outcomes	ICD codes, organisational outcomes, length of stay, mortality, biological markers, pain, mechanical ventilation
Design	primary study, RCT and prospective observational studies;	reviews, commentaries, retrospective observational studies, cross-sectional studies, pre/post studies. study size: RCT<20 patients, RCT with pharmacological intervention size <50 patients, observational studies <100 patients
Languages	English, Dutch	French,

^b One study focused on sleep quality during ICU stay as a factor associated with delirium.

This resulted in a set of 903 primary papers for data extraction. Data from these papers were extracted using a predefined extraction template, and grouped, based on the type of intervention and outcome. During the screening and data extraction, 701 studies were still excluded, due to the identification of exclusion criteria in the full text.

The results of the data extraction of the remaining 177 studies can be found in the following literature study. Information regarding the search strategy, studies identified, and the flowchart can be found in the supplement of this report.

3.3 Results

3.3.1 Pharmacological interventions

Sixty-nine articles on pharmacological interventions were included. They mainly focused on delirium^b (53 studies) which is the principal risk factor for long-term cognitive disorders after critical illness (see chapter 2). Other most studied outcomes were mental health and cognitive disorders. It should be reminded here that several clinicians have raised concerns about the fact that decreasing sedation in the critically ill might be harmful to mental and cognitive health. As a result, studies were designed to evaluate whether reducing sedation in patients undergoing mechanical ventilation did affect, or not, mental and cognitive health in the long run. Two studies assessed ICU-AW.

Forty-five studies were randomized controlled trials (RCTs), one study was a post hoc analysis of a RCT and 23 were prospective cohort studies. Twenty-five studies came from Europe (Germany: 3 ; Italy: 2 ; Denmark: 5; UK: 4; France: 2; The Netherlands: 5; Finland: 1; Sweden: 1; Switzerland: 1; Belgium: 1), 21 from the USA, 3 from Canada, 1 from Australia, 2 from



Brazil, 2 from Africa (Tunisia: 1; Egypt: 1) and 10 from Asia (Iran: 1; Japan: 4; India: 2; China: 2; Thailand: 1). Five were international studies.

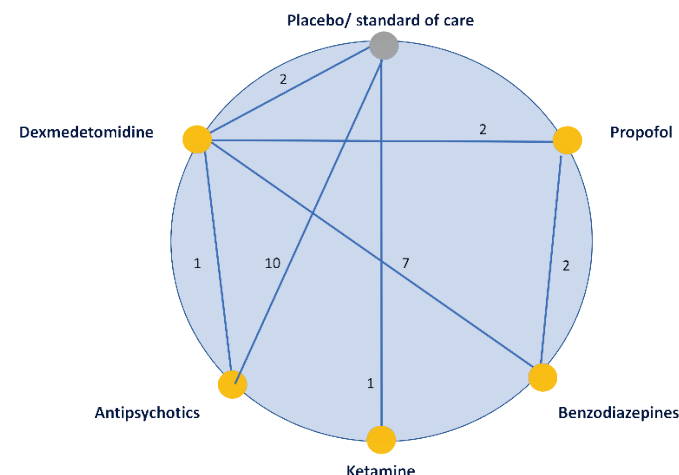
In RCTs, the pharmacological interventions included several classes of medication involved in the sedation and analgesia: benzodiazepines (BZD), propofol (PRO), dexmedetomidine (DEX), ketamine, neuroleptics and opiates. Comparisons were performed with the standard of care (or placebo), or between molecules. The way to administer and manage sedative drugs was also considered in 13 studies. Other molecules included hydrocortisone, hypnotics (suvorexant, melatonin or agonist of melatonin receptors), neuromuscular blocking agents (NMBA) and statins. Prospective observational cohort studies focused on the association of outcomes of PICS (and delirium) with medications given during the ICU stay. Follow-up duration ranges from discharge from ICU to two years after discharge.

Of note, the following analysis will be carried out by making the distinction between RCTs and prospective studies.

3.3.1.1 Sedative drugs studied in RCTs

Several comparative trials have assessed the impact of ICU-sedative drugs on delirium along with other components of PICS. The main comparisons and number of studies including sedative or psychotic drugs are summarized in Figure 3.

Figure 3 – Overview of the comparisons between sedative agents and antipsychotics.



Numbers represent the number of studies assessing the selected comparison
Source: KCE

DRUG COMPARISONS INVOLVING DEXMEDETOMIDINE (DEX)

Dexmedetomidine (α_2 adrenoceptor agonist) has been compared with several sedative agents in 9 studies: 7 of these performed a comparison with benzodiazepine (BZD), including midazolam (MDZ) or lorazepam (LOR). One study was a subgroup analysis of an included RCT.⁵⁶ Two studies compared DEX with standard of care (including MDZ or PRO)^{57, 58}, and two studies with placebo (one of these also included a comparison with an antipsychotic drug that is analysed in the next paragraph 3.3.1.2).^{59, 60} One study performed a head-to-head comparison with PRO.⁶¹ Only four studies assessed delirium as primary outcome.^{56, 59, 60, 62}

All studies included patients on mechanical ventilation (MV) at baseline, except two studies that included people receiving non-invasive ventilation



(NIV) for respiratory failure^{c, 59, 63} Sample sizes ranged from 62 to 1001 participants.

No clear effect of DEX on delirium was shown by RCTs. Characteristics and results of the studies are summarized in the supplement of this report (Table 1).

- The MENDS (*Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction*) double-blinded RCT was conducted on 106 patients in two centres.⁶² Authors compared the effect of DEX with continuous infusion of LOR on the duration of delirium or coma in mechanically ventilated patients. Sedation with DEX resulted in more days without delirium or coma. Nevertheless, when considering only days with delirium, this result did not achieve the statistical significance. A subgroup analysis of the trial distinguished septic and non-septic patients. Septic patients who were given DEX had more delirium/coma-free days but, in the same way, the difference for delirium-free days did not reach the statistical significance.⁵⁶
- The SEDCOM (*Safety and Efficacy of Dexmedetomidine Compared With Midazolam*) multicentric trial, assigned 375 mechanically ventilated patients to receive DEX or MDZ.⁶⁴ In this study, delirium was a secondary outcome. A statistically significant lower prevalence of delirium along with more delirium-free days were reported in the DEX group in comparison with the MDZ group.
- The MIDEX/PRODEX trial is a large international RCT that associated the comparisons of DEX to MDZ, or PRO in mechanically ventilated participants.⁶¹ Delirium was investigated as secondary outcome, and was assessed 48 hours after sedation discontinuation. DEX did not demonstrated any benefit on the prevalence of delirium. Conversely,

delirium was reported less frequently in patients treated with DEX than those receiving PRO.

- The DESIRE (*Dexmedetomidine for Sepsis in Intensive Care Unit Randomized Evaluation*) trial compared DEX with a control group (including BZD and PRO) in septic patients receiving mechanical ventilation, in 8 ICUs.⁵⁸ The number of days free of delirium or coma-free days were assessed as secondary outcome, and no difference between groups was found throughout the seven first days of ICU stay.
- The characteristics of the other studies substantially differed from the previous ones (types of patients, study design or modes of administration of sedation):
 - Two studies assessed the effect of DEX in patients undergoing non-invasive ventilation.^{59,63} One study reported a lower incidence of delirium in comparison with placebo (or haloperidol; see section 3.3.1.2)⁵⁹, while the other did not report any benefit of DEX when compared to MDZ⁶³.
 - A study showed that nocturnal administration of low dose DEX was associated with less occurrence of delirium when compared to placebo, in mechanically ventilated patients^{d,60} The same research team had performed a pilot study on the efficacy of DEX versus standard sedation (MDZ/PRO) for long-term sedation, in mechanically ventilated patients.⁵⁷ Delirium was appraised as secondary outcome and had a higher prevalence in the DEX group than patients with standard care sedation. However, the results of this study are difficult to interpret because more assessments of delirium was performed in the DEX group^e.

^c Respiratory failure was due to several causes: cardiogenic pulmonary oedema, exacerbation of chronic obstructive disease, or post-operative respiratory failure

^d Standard sedation included PRO and MDZ in both groups and was halved during the night.

^e The proportion of positive testing for delirium was comparable in both groups (17.0 % vs. 17.9%, not statistically significant).



DRUGS COMPARISONS INVOLVING OTHER SEDATIVE (OR ANALGESIC) MOLECULES

- **Benzodiazepines** were compared with PRO in 2 studies. The first assigned mechanically ventilated patients to receive intermittent boluses of LOR or continuous infusion of PRO. Although the trial was not designed to analyse **delirium**, its incidence was not different between groups.⁶⁵ Another small study observed that **sleep quality and structure** was better in non-mechanically ventilated patients receiving continuous low-dose PRO rather than those receiving boluses of flunitrazepam.⁶⁶ The impact on delirium was not investigated (see Supplement-Table 2).
- The addition of **low doses of ketamine** to usual analgo-sedation regimen was assessed in one small trial.⁶⁷ Compared to placebo, **incidence and duration of delirium** were lower in patients who received ketamine. Of note, the trial was not initially designed to assess delirium^f (see Supplement-Table 2).
- One study compared the **quality of analgesia** using **remifentanyl-based or a fentanyl-based strategies** in mechanically ventilated patients.⁶⁸ The trial was stopped early⁹ for futility. **Delirium** was appraised as secondary outcome, and did not differ between groups.

WAY TO ADMINISTER SEDATIVE AGENTS

The way to administer sedative drugs was assessed in 13 studies that included exclusively patients who underwent mechanical ventilation. Four studies considered the amount of sedation in critically ill patients, while 6 studies analysed the effects of sedation interruption. Two studies evaluated the impact of the use of standardised procedures, and one study compared oral versus intravenous administrations of sedation. Although primary outcome was not always focused on PICS, all studies reported the impact

of the intervention on delirium, or on the long-term mental or cognitive disorders (safety of sedation reduction).

Overall, reducing sedation was shown to be safe. However, there was no impact of the different sedation strategies on delirium. Characteristics and results of the studies are summarized in Supplement-Table 3.

- **Amount of sedation: no sedation, light sedation versus standard sedation**
 - Two studies^{69, 70} demonstrated that using **light sedation**, or no sedation in mechanically ventilated patients was safe since there was no increase of **mental or cognitive sequelae** at short (4 weeks)⁷⁰ and long term (2 years).⁶⁹
 - A recent large multicentre RCT compared the effects of a management **without sedation versus a light level of sedation** on **mortality** in ICU. In this study, no effect on **delirium** was shown.⁷¹ Another team reported that agitated delirium was more frequent when a no sedation strategy is used.⁷²
- **Daily interruption of sedation**

Six studies assessed the daily interruption of sedative drugs, combined with a spontaneous breathing trial, or not. One study was a secondary analysis of a RCT.⁷³

- Four studies reported on **delirium** and none of these showed any impact on the incidence or the duration of delirium.⁷³⁻⁷⁶
- Regarding the long-term impact, two studies confirmed the safety of this strategy: patients managed with wake-up trials and spontaneous breathing trials resulted in similar cognitive, psychological than those managed with usual care.^{77, 78} One of

^f The goal of the study was to estimate the impact of ketamine on opiates consumption.

⁹ Trials stopped after 50% of inclusion in the remifentanyl arm and 63% in the fentanyl one.



those studies reported fewer symptoms of PTSD at 1 year when daily sedation interruption is used.⁷⁸

- **Standardised protocols of sedation administration**

Two studies assessed the impact of the use of standardised protocols of sedation administration on **delirium**. Khan et al. tested the efficacy of bundles for the pharmacological management of delirium **reducing the exposure to anticholinergic medications and BZD**.⁷⁹ There was no difference in delirium duration nor the severity of delirium, but a greater reduction in delirium severity was observed at hospital discharge. The second study was conducted on a particular group of patients undergoing a weaning from mechanical ventilation, and who were agitated.⁸⁰ Authors showed that the sequential administration protocol of DEX with MDZ was associated with less delirium after extubation.

- **Oral versus intravenous sedation**

One multicentre RCT compared **two sedation strategies** (intravenous MDZ, PRO or enteral hydroxyzine, lorazepam, melatonin) for early achievement and maintenance of a light level of sedation^{h,81}. No difference in the incidence of **delirium** was observed.

3.3.1.2 Anti-psychotic drugs studied in RCTs

Antipsychotic agents were involved in 10 studies. Antipsychotics included haloperidol (HAL), ziprasidone (ZIPR) and risperidone (RISP). Eight of these performed a comparison with placeboⁱ (See Supplement-Table 4). One of these studies performed multiple comparisons with placebo or dexmedetomidine.⁵⁹ Sample sizes were heterogeneous and ranged from 68 to 1789 participants. The majority of patients were mechanically ventilated. **Delirium assessment** was the primary outcome for the majority of studies: six studies focused on the prevention of delirium^{59, 82-86}, while the 3 others

on the treatment of delirium.⁸⁷⁻⁸⁹ One study focused on **quality of life** (mental and physical components) 1 and 6 months after discharge⁹⁰ and another one on **survival at day 28** (but analysed the incidence of delirium as secondary outcome)⁸⁴. One study was a secondary analysis of a RCT⁹⁰, and another one compared the administration of HAL with a historical cohort.⁸⁵

Globally, there was no effect of antipsychotics/neuroleptics on the treatment or prevention of delirium in critically-ill patients.

3.3.1.3 Other drugs studied in RCTs

All studies of this section are described in Supplement-Table 5.

- Studies on **hypnotics** gave inconsistent results: two RCTs identified a positive effect of ramelteon (melatonin receptor agonist), on **delirium** incidence^{91, 92}, while one RCT comparing melatonin to placebo did not.⁹³ Another small RCT assessed the impact of suvorexant (orexin receptor agonist), for delirium prevention.⁹⁴ There was no effect on the incidence and duration of delirium but the time to develop delirium was significantly longer in the group receiving suvorexant.
- **Hydrocortisone** was assessed for PTSS prevention in a small study and did not result in relevant results.⁹⁵ The other RCT (*HYPERPRESS trial*)^j was designed to assess whether hydrocortisone could prevent the occurrence of shock in septic patients in the ICU. Authors observed that **delirium** was less frequent in patients who received hydrocortisone than in those who received placebo.⁹⁶
- **Statins** were sought to counteract the neuroinflammation involved in the genesis of **delirium**. Two RCTs assessing its effectiveness were negative.^{97, 98}

^h Light sedation was defined as RASS ± 1

ⁱ One study compared HAL with other antipsychotic (olanzapine)

^j HYPERPRESS: Hydrocortisone for Prevention of Septic Shock



- In the ACURASYS trial^k, the impact of **cistracrium** (NMBA) on mortality in severe ARDS patients was investigated.⁹⁹ Regarding PICS outcomes, investigators showed that NMBA did not lead to more **ICU-AW**.
- **Rivastigmine** (cholinesterase inhibitor) was tested in ICU patients presenting **delirium** in one trial. It was stopped early because of higher mortality in the rivastigmine arm, and no effect on delirium was shown.¹⁰⁰

3.3.1.4 Results on the medications associated with PICS outcomes from prospective cohort studies

Twenty-four prospective observational cohort studies evaluated the association of the exposure to several medications on (components of) PICS. Main studied outcome was delirium. Other outcomes included mental health (5 studies), cognitive disorders (2 studies), and ICU-AW (1 study). The medications were sedative agents (BZD, PRO), opiates, NMBA, statins, and antibiotics. Sample sizes ranged from 103 to 1 112. A summary of the results is presented in Table 3 and the main results are described in Supplement-Table 6 and 7.

Table 3 – Summary of the results from prospective studies

PICS component	Risk factor	Number of studies with a positive association	Number of studies without an association
Delirium	Benzodiazepines	12	1
	Propofol	1	3
	Opiates	4	1
	Antibiotics	1	
	Statins	1	
Mental health			
Depression	Benzodiazepines	2	1
PTSD	Analgo-sedation* /antipsychotics	1	1
Cognitive disorders	Benzodiazepines	1	1
ICU-AW	Neuromuscular blocking agents	1	

Legend: BZD: benzodiazepines; PRO: propofol; PTSD: post-traumatic stress disorder; * include BZD, PRO, opiates

^k ACURASYS: ARDS et Curarisation Systématique



DELIRIUM

- Overall, a substantial number of studies showed an association between BZD and delirium (see Table 3). A study identified this association only for a continuous infusion of BZD and not in the case of intermittent use, while another one only when deep sedation level were reached^{l,101} Only one study was inconsistent with those previous observations and showed that MDZ was associated with a decreased incidence of delirium. The authors mentioned that it was probably related to the accumulation of MDZ and a slower response when sedative agents are interrupted (subsequent under-detection of delirium).¹⁰²
- Three studies¹⁰²⁻¹⁰⁴ did not report any association between PRO and delirium, while one reported a positive association.¹⁰⁵
- Four studies reported an association between delirium and opiates, or their cumulative dose^{m,105-108} Conversely, one study did not show an association between opiates and delirium.¹⁰²
- The neurotoxicity of cephalosporins was highlighted by one study describing an association between delirium and cephalosporins^{n,109}
- One study investigated the association of delirium with the use of statins. It did not observe a clear difference between prevalence of delirium and delirium-free days, but suggested a possible association between the use of statins and a lower risk of delirium using random effects multivariable logistic regression.¹¹⁰

^l Deep sedation was defined as a RASS scale between -3 and -5

^m One of these studies performed only a univariate analysis

MENTAL HEALTH AND LONG-TERM COGNITIVE IMPAIRMENTS

- Three studies identified an association between mental health issues and BZD/ sedative agents^{111, 112,113}, while two studies did not demonstrated such a relationship in adjusted analysis.^{114, 115}
- Regarding cognitive problems, a single centre study that investigated the contribution of delirium on ICU patients outcome demonstrated that delirium was independently associated with cognitive problems after 6 months, and that the daily cumulative dose of BZD was significantly higher in patients who developed delirium.¹¹⁶ In contrast, a large study (*BRAIN-ICU*) identified that delirium was a predictor of long-term cognitive problems, but without association with the use of sedative or analgesic medications (BZD, PRO, DEX and opiates).³²

ICU-ACQUIRED WEAKNESS

In patients admitted to ICU with sepsis, a small study identified NMBA along with the severity of critical illness as risk factors for polyneuropathy.¹¹⁷

3.3.1.5 Discussion on the pharmacological interventions

DELIRIUM AT ICU

In this section, a consistent finding among studies was the positive association between BZD use and the occurrence of delirium, after adjustment for confounders. Such a relationship between delirium and opiates was also identified in a more limited number of studies.

Moreover, the retrieved evidence show that the pharmacological prevention and treatment of delirium remains substantially limited:

- There is no clear effect of DEX. Pandharipande et al. was one of the first studies that showed a decrease in delirium/coma in patients

ⁿ First-, second-, and third-generation cephalosporins



receiving DEX when compared to patients sedated with LOR. However, when only the delirium-free days were taken into account (without considering the coma-free days), the effect was no more statistically significant. Of note, this trial included a limited sample size. Although the trial from Riker et al. reported a lower proportion of delirium using DEX, other trials such as the PRODEX trial did not report such a benefit. A systematic review from the Cochrane group published in 2015 (7 studies, 1624 patients) including RCTs and quasi-randomized controlled trials conducted on mechanically ventilated patients showed that DEX reduced the duration of mechanical ventilation and ICU length of stay, but there was no evidence for a beneficial impact on the risk of delirium (quality of evidence rated as very low^o).¹¹⁸ Another trial (*SPICE-III*) that was not included in our review, compared early sedation with DEX with usual care^p in 4 000 mechanically-ventilated participants.¹¹⁹ There was no difference on the primary outcome (90-day mortality) and the impact on delirium or coma was rather limited: the number of days without coma or delirium was 1 day higher in the DEX group but the analysis was not adjusted for multiple comparisons. In addition, the distinction between coma and delirium was not considered for this outcome. More recently, the *MENDS 2* trial^q compared DEX to PRO in mechanically ventilated patients with sepsis, and did not identified differences in terms of days without delirium (or coma) and cognitive sequelae at 6 months between groups.¹²⁰

- Finally, a network meta-analysis (MA) on the interventions to prevent delirium in ICU was published after our literature review.¹²¹ Authors mentioned that DEX probably reduces delirium occurrence when compared to placebo^r (moderate certainty) and may reduce it when compared to BZD^s (low certainty). It is worth noting that this SR was

more inclusive than our review, and retrieved more studies on DEX (including post-operative patients, or patients hospitalised in highly acuity units; intervention performed outside the ICU). Studies that were not included in our review mostly included post-operative patients or were published in a language excluded from our search strategy.

- Among the other drugs, our search showed no effect on the prevention or the treatment of delirium with anti-psychotic agents. This result is in line with recent SRs that did not identify any effect of this class of drug on the prevention of delirium in critically- ill patients.^{122, 123} Regarding melatonin or agonists of melatonin receptors, there is no clear evidence for benefits. A recent network MA has included the same studies that we have included, and did not show any benefit^t (low level of evidence due to imprecision and inconsistency).¹²¹
- In this review, the studied sedation strategies (light sedation, no sedation, daily interruption, protocolized strategy) did not display any benefit in the prevention of delirium. In the same vein, Burry et al. concluded their recent network MA, that the evidence was very uncertain that sedative interruption and protocolized sedation may reduce the occurrence of delirium.¹²¹

LONG-TERM MENTAL- HEALTH AND COGNITIVE FUNCTION

A consistent finding was that light/no sedation or daily interruption of sedation in mechanically ventilated patients is safe and do not harm long-term mental health or cognitive function.

Regarding the contribution of medications to mental health and cognitive function, general conclusions are difficult to draw from the available data because of heterogeneous study designs, varying methods of

^o High heterogeneity among studies

^p Usual care mainly comprised propofol, midazolam

^q MENDS 2: Maximizing the Efficacy of Sedation and Reducing Neurological Dysfunction and Mortality in Septic Patients with Acute Respiratory Failure

^r OR: 0.43; 95%CrI: 0.21-0.85

^s OR: 0.21; 95%CrI: 0.08-0.51

^t pooled risk difference: 55 fewer per 1000; 95%CrI: 144 fewer to 178 more



measurement, and differences among patient cohorts. Although a few primary studies have shown a significant association between BZD and mental health problems²⁴, based on the limited available information, analgesics, sedatives or antipsychotics did not appear to contribute to the development of cognitive impairment after ICU discharge.

Key points

- Most of the studies involving pharmacologic agents focused on delirium which is an early risk factor for PICS cognitive component.
- Evidence shows that sedative medications, particularly benzodiazepines, are strongly associated with the onset of delirium.
- There is no consistent evidence on the effectiveness of pharmacological agents for preventing and treating delirium.
- Although sedation strategies (light sedation, no sedation, daily interruption) may be associated with a reduction of mechanical ventilation duration, they do not provide any benefit to the prevention of delirium.
- Regarding long-term mental and cognitive disorders:
 - There is evidence that light/no sedation or daily interruption of sedation in mechanically ventilated patients is safe since it does not increase mental health or cognitive problems in the long run.
 - A relationship between sedative or analgesic drugs on mental or cognitive health seems very unlikely. Sound conclusions are nevertheless difficult to draw from the available data because of heterogeneous populations, clinical management, the timing of assessment, and the probable multifactorial aspect of these outcomes.

3.3.2 Mechanical ventilation strategies

Three studies, conducted in France, focused on the impact of ventilation strategies on sleep quality (assessed by polysomnography) in the ICU (see Supplement-Table 8). Two studies assessed MV modes, and the other one compared two types of ventilators used for NIV. Two studies had a prospective randomized cross-over design, and the other was a randomized trial. Samples sizes were low and ranged from 20 to 26. Patients were aged from 64 to 69 years.

Two studies from the same team compared several ventilatory modes in patients who had acute-on-chronic respiratory diseases (chronic obstructive pulmonary disease), and were almost weaned off from mechanical ventilation.^{124, 125} Both studies showed that total sleep time was altered, with a large proportion of the night spent in wakefulness. Authors showed that enabling the respiratory muscles to rest (through assisted-control or pressure controlled ventilatory modes) improved the quality of sleep. The third study compared two types of ventilators used for non-invasive ventilation in patients with hypercapnic respiratory failure. No difference in sleep architecture was evidenced.¹²⁶

Key points

- Sleep architecture is altered in critically-ill mechanically-ventilated patients.
- In the specific group of patients with chronic respiratory disease in a process of weaning from mechanical ventilation, studies showed that enabling respiratory muscles to rest during the night improved sleep quality compared to being kept under a ventilatory mode allowing spontaneous respiratory activity.



3.3.3 Environmental interventions

Several papers focused on environmental factors (noise and light) to prevent (aspects of) PICS. Indeed, light and noise are environmental factors that can have an impact on sleep quality (in terms of duration, depth and degree of fragmentation) which is a risk factor for delirium.

For this type of interventions, 24 articles were included in this review (23 RCTs and 1 prospective study): five coming from Iran¹²⁷⁻¹³¹, two from India^{132, 133}, four from the USA¹³⁴⁻¹³⁷, one from the UK¹³⁸, five from China¹³⁹⁻¹⁴³, two from Taiwan^{144, 145}, one from Japan¹⁴⁶, one from Thailand¹⁴⁷, one from the Netherlands¹⁴⁸, one from France¹⁴⁹, and one from Belgium.¹⁵⁰

In general, the interventions aimed at auditory sensory perception (ear plugs, headphones with noise reduction, music, nature sounds, environmental changes), visual sensory perception (eye masks, natural daylight, bright light, mirrors, guided imagery) or combinations of both. The outcomes of these studies primordially focused on quality of sleep, stress & anxiety, incidence & duration of delirium, delusions and Health Related Quality of Life (HRQoL). Sample sizes varied from 22 subjects (10/12) to 734 (361/373) (Mean (Mn)=109.8, Median (Md)=60). Regarding the type of ICU, 6 studies were conducted in a surgical ICU, 4 studies in a coronary care unit, 2 in a medical ICU and the others in mixed ICU settings. The mean ages of the participants varied between 53 and 70 years with two outliers (Mn=40 y and Mn=77.4 y). All the results of the studies can be found in the Supplement-Table 9.

3.3.3.1 Results of RCTs

SLEEP QUALITY

In order to improve sleep quality, one should intervene by reducing visual or auditive stimuli coming from the ICU environment. In this optic, one RCT studied how to reduce auditory sensory perception by using **earplugs**¹³⁷, three studied how to reduce visual sensory perception using **eye masks**.^{127,128,129} Five studies **combined** the use of ear plugs and eye masks).^{132, 131, 133, 138, 143} One study assessed the effect of **decreasing the noise level in ICU and dimming the lights** from 11:00 p.m. to 5:00 a.m.

(doors closed, lights dimmed, decreased telephone ring and bedside monitor volume, and grouped or rescheduled disturbing procedures).¹⁴⁴ Earplugs alone^{137, 150}, eye mask alone¹²⁷⁻¹²⁹ or a combination of ear plugs and eye masks significantly help to improve sleep quality. Changing night-time nursing care routines showed also effect.¹⁴⁴

Another type of intervention is to expose patients to **auditory stimuli** like relaxing music (in comparison to ear plugs only)¹⁴¹ or non-commercial music).¹⁴⁵ Both approaches showed an increased quality of sleep.

DELIRIUM

Exposure to ICU noise can be a trigger to develop delirium. Here also, **earplugs** showed to decrease the risk of confusion and delirium by 53% within the first 24 hours).¹⁵⁰ Regular exposure to **music** (personalized or slow tempo) or audiobooks however showed no significant effect.¹³⁶

Other studies exposed a sample of critically ill patients to visual stimuli such as **bright light**¹⁴⁸, for four consecutive days¹⁴⁶ or two hours a day for 3 consecutive days.¹⁴⁷ Results are inconsistent: two RCTs showed no difference in the incidence of delirium¹⁴⁶ or number of delirium-free days, delirium duration or time to the first delirium¹⁴⁸ and one showed a significant preventive effect.¹⁴⁷

STRESS AND ANXIETY

Some authors took a different approach and exposed their patients to auditory stimuli: they used music or other relaxing sounds to prevent stress and anxiety. No effect was found on biomedical markers of stress (cortisol in 24h urine collection).¹³⁴ Several studies showed a decrease in the level of self-perceived anxiety^{130, 135, 139, 140, 142} while one study did not show any significant effect.¹³⁶ Solely noise cancelling was not found to be effective¹³⁵ and only ensuring uninterrupted rest (without music exposure) was less effective.¹⁴²



USE OF PHARMACOLOGICAL SEDATION

One study also found that (patient initiated) exposure to music resulted in a significantly reduced need of pharmacological sedation in frequency and intensity (while this was not the fact in the noise cancelling group).¹³⁵

3.3.3.2 *Result of a prospective observational study*

Smonig et al. (2019)¹⁴⁹ compared the exposure of ICU patients to natural daylight, versus a subgroup with no natural daylight. They found no significant differences in incidence, duration of delirium or duration of coma (measured with the Intensive Care Delirium Screening Checklist, ICDSC).

Key points

- RCTs show that interventions to avoid or limit environmental stressors in ICU patients, by reducing auditory and/or visual sensory perception using ear plugs and eye masks, positively affect their quality of sleep and can lower the risk for delirium.
- Decreasing noise level in ICU and dimming the lights and changing night-time nursing care routine has also impact.
- Exposure of patients to relaxing music and sounds was found to be effective to improve sleep quality.
- Exposure of patients to bright light did not show consistent results.

3.3.4 *ICU diaries as intervention*

A number of papers focused on keeping a diary about the events and evolutions in ICU, both for the patient (to prevent PICS) and for the family (to prevent PICS-F). These diaries can be filled out by ICU-staff or by relatives. On the one hand, the patient could use these diaries after periods of sedation, delirium or coma, or after discharge from ICU. On the other hand, the diaries might be useful for the family to cope with the traumatic period of critical illness of their relative. Eight studies were included in the present integrative review (6 RCTs and 2 prospective observational studies),

one from France¹⁵¹, three from the UK¹⁵²⁻¹⁵⁴, one from Canada¹⁵⁵, one from the USA¹⁵⁶ and two from Sweden.^{157, 158} These studies looked at long term psychological outcomes (anxiety, depression, PTSS), Quality of Life (QoL) and cognitive outcomes (memory) at 2 to 12 months post-discharge from ICU. Sample sizes varied from 30 to 441 (Mn (SD)=194.1 (160.9), Md=140). All the studies were conducted in mixed ICUs. Mean age of the participants varied from 40 years old to 62 years old. All but two studies were RCTs. The study of Akerman et al.¹⁵⁷ and Backman et al.¹⁵⁸ were prospective cohort studies. All the results of the selected studies can be found in the tables in the Supplement-Table 10.

3.3.4.1 *Studies using ICU diaries with endpoints at the patient level*

Results of RCTs

The use of ICU diaries to prevent psychological problems (anxiety, depression and PTSS) showed inconsistent results. One small study showed a significant reduction in anxiety and depression¹⁵², while two studies did not find any relationship^{151, 155}. The combination of ICU diaries with psychoeducation showed however to be effective¹⁵⁵ for anxiety and depression. Regarding PTSS one study did not show any relationship with the use of ICU diaries¹⁵¹ while two other studies had inconsistent results.^{154, 156} For recollection of memories (emotional or delusional), no effect was found.¹⁵¹

Results of prospective observational studies

Two prospective observational studies focused on QoL and found a relationship between the use of ICU diaries and quality of social life at 2 and 6 months¹⁵⁷ and general health, vitality and physical health at 6 months.¹⁵⁸



3.3.4.2 Studies using ICU diaries with endpoints at the family/relatives/carers-level.

Results of RCTs

One included study looked at the effect of ICU diaries (filled out by ICU staff) on anxiety and depression in family and relatives, but could not reveal a significant effect.¹⁵¹ Two studies looked at a relationship with development of PTSS symptoms, from which one found a significant effect at three months after receiving the diary¹⁵³ while the other study could not reveal effectiveness¹⁵¹.

Key points

- The included RCTs did not show consistent results related to the application of ICU diaries to prevent depression, anxiety and PTSS in ICU patients.
- In combination with psychoeducation, one RCT showed a positive effect on anxiety and depression.
- Observational studies showed a positive effect on quality of life in ICU patients at two and six months post-ICU.
- Regarding the effect of ICU diaries on family and relatives, no relationship with anxiety and depression was reported, while results in relation to PTSS were inconsistent.

3.3.5 Psychotherapeutic interventions

Two included papers (RCTs) focused on psychotherapeutic interventions, Holmes et al. (2007) (sample size 90)¹⁵⁹ from Australia and Tecic et al.¹⁶⁰ (sample size 113) from Germany. Both studies looked at long term psychological outcomes (anxiety, depression and PTSS). The studies were both conducted in a trauma ICU. The mean age of the ICU patients was between 30 and 40 years old. The results of the studies can be found in the table in the Supplement-Table 11.

3.3.5.1 Results from RCTs

Two rather small studies regarding the use of psychotherapeutic interventions were included in this review. Nor interpersonal counselling¹⁵⁹, nor short term inpatient psychotherapy¹⁶⁰ showed a preventive effect on anxiety and depression over time (up till 12 months post-ICU). No significant differences between the groups were demonstrated for any outcome and at any time during the study. Dropout in both studies was high and sample sizes were small.

Key point

- RCTs that used psychotherapeutic interventions did not show significant results on anxiety, depression and PTSD.

3.3.6 Patient education as intervention

Three of the included studies (all RCTs) used education as an intervention to prevent PICS outcomes (number of participants: Mn=156.3, Md=158). Bench et al.¹⁶¹ (2015) from UK, Demircelik et al.¹⁶² (2016) from Turkey and Fleischer et al.¹⁶³ (2015) from Germany. Two of the three studies were conducted in a mixed ICU and one study was conducted in a coronary care unit. Mean age of the participants varied between 59 and 69 years old. The results of the studies can be found in the table in the Supplement-Table 12.

3.3.6.1 Results from RCTs

The use of a **user-centred critical care discharge information pack**¹⁶¹, consisting of one booklet for the patient with information regarding the stay and the discharge) and one booklet for the family, given prior to discharge from the ward, seemed to result in less anxiety at 28 days post-discharge. For depression, no significant effect was seen. It must be stated however that dropout in this study was significant. The same positive effect was seen for the use of a **multimedia nursing education** were less anxiety and also less depression at one week post-discharge was reported.¹⁶² The **use of a**



single episode specific information intervention did however not show a relationship with anxiety, delirium incidence or quality of life.

Key points

- RCTs showed a weak but significant relationship between patient education and decrease of anxiety and depression.
- No effect was found regarding delirium incidence or quality of life.

3.3.7 Interventions focused towards family and relatives

This integrative review identified 12 studies (9 RCTs and 3 prospective studies): four from the USA¹⁶⁴⁻¹⁶⁷, two from France^{168, 169}, and one each from Australia¹⁷⁰, Brazil¹⁷¹, Iran¹⁷², Italy¹⁷³, Saudi-Arabia¹⁷⁴ and UK¹⁷⁵. The selected studies used interventions with a focus on family and relatives, in terms of information provision, visiting policy and family support. The outcomes targeted by the studies were on the one hand family oriented, in terms of dimensions of PICS-F (anxiety, depression, PTSS), comprehension and satisfaction, but on the other hand also patient oriented, in terms of incidence of delirium, anxiety, depression and psychological recovery. Seven studies were conducted in mixed ICU-environments, two studies in trauma ICU, one study in a medical ICU, one study in a surgical ICU and one study in a coronary care unit. For all but one study, the mean ages of the participants varied between 36.5 and 68 years old. The study with outliers¹⁷⁵ included participants from 19 to 89 years old. Sample sizes were quite different between studies, ranging from 26 to 1 685 subjects, Mn (SD)=386.1(541.5), Md=131. The results of the studies can be found in the Supplement-Table 13 and 14.

3.3.7.1 Studies with endpoints at the family level.

RESULTS FROM RCTS

The use of an **information leaflet** for the family showed a positive effect on the comprehension of the relatives regarding diagnosis and the therapy applied to their beloved and high levels of comprehension were related to higher levels of satisfaction.¹⁶⁸ The use of a **family navigator nurse**¹⁶⁴ or **application of a multicomponent family-support intervention**¹⁶⁶ (consisting of a regular 'partner-nurse' information moment and a meeting with a clinician-family within 48 hours after discharge) did not show any effect on anxiety, depression and PTSS in the relatives over time (up till 6 months post-discharge).

RESULTS FROM PROSPECTIVE OBSERVATIONAL STUDIES

A **patient-to-nurse ratio of <3**, **information provision by a junior physician** and being helped by their **usual doctor** showed a positive effect on satisfaction in relatives while contradictory information and role ambiguity resulted in a decrease in the level of satisfaction in family members.¹⁶⁹ Application of open visiting hours showed inconsistent results regarding relatives satisfaction. One study showed a positive effect while another did not.

3.3.7.2 Studies with endpoints at the patient level.

RESULTS FROM RCTS

Two out of three studies reported a lower risk for developing delirium when **family members participated in some way in the care of their beloved**.^{172, 175} One study did however not show any result.¹⁷⁰ Three studies looked at the effect of extra or **flexible visiting hours**. One study showed a lower incidence of delirium¹⁷² while a second did not confirm this¹⁷¹, and one study showed lower levels of anxiety over time¹⁷³.



Key points

- RCTs assessing interventions aimed at family showed no effects regarding anxiety, depression or PTSS in patients nor in relatives.
- Family participation in ICU care showed inconsistent results regarding incidence or duration of delirium.
- Open visiting hours had a positive effect on family satisfaction.
- Open visiting hours was correlated with less anxiety in patients, but no effect was seen on depression or incidence of delirium.

3.3.8 Multi-modal interventions

Eight of the included studies (7 RCTs and 1 prospective study) used a combination of interventions (multi-component, multi-modal) to prevent dimensions of PICS. Three studies were from the USA^{79, 176, 177}, one from Chile¹⁷⁸, one from Canada¹⁷⁹, one from China¹⁸⁰, one from Taiwan¹⁸¹ and one from Korea¹⁸². The outcome of 5 out of 7 studies was related to delirium, one focused on cognitive status and quality of life, and one study focused on sleep quality. Five studies were conducted in a mixed ICU environment, one in a trauma ICU, and one in a SICU. The mean ages of the patients varied between 43.3 and 73.7 years. Sample sizes varied from 36 to 351 patients (Mn=122.5; Md=145). The results of the studies can be found in the table in the Supplement-Table 15.

3.3.8.1 Results of RCTs

As the (combinations of) interventions of the included studies are very heterogeneous, the studies are described separately.

- Alvarez et al.¹⁷⁸ (2017) used a **set of preventive measures for delirium in combination with occupational therapy** (2x/day) for 5 days, in an intervention group of non-ventilated patients above 60 years. The multimodal approach consisted of polysensory stimulation (to increase patient's level of alertness), changes in positioning in bed,

cognitive stimulation (a pool of exercised focusing on alertness, memory, praxis, calculus and problem solving), basic activities of daily living (hygiene, personal grooming, eating), stimulation of upper extremity motor function, and family participation (visits by trained family members). Compared to a control group that got usual care, the **incidence of delirium** (measured with the CAM-ICU) was significantly lower (3% versus 20%; $p=0.001$). No difference was found for **severity of delirium**. **Quality of life** (in terms of motor function and cognitive function) and the cognitive status were both better and hand grip strength was higher for both limbs.

- Brummel et al.¹⁷⁶ (2014) conducted a three-tiered study, including a group that received **physiotherapy only** (1x/day), another group that received a **combination of physiotherapy (1x/day) and cognitive therapy** (2x/day) and a group receiving usual care. Regarding the executive **function of the cognitive status** (measured with the Tower test and the DEX test), no significant differences were found between the groups. Also for the global **cognitive functions** (measured with the Mini Mental State Examination, MMSE), no differences were found. Regarding the **Quality of Life** (measured with the Katz scale and the (EQ)5D VAS, no significant differences were seen either.
- Chen et al.¹⁸¹ (2011) applied the Hospital Elder Life Program (HELP), a multimodal intervention consisting of **early mobilisation, nutritional assistance, and therapeutic (cognitive) activities** implemented by a trained nurse, and compared to usual care. They found significantly better results for the intervention group at hospital discharge in terms of **quality of life** (measured with the Barthel index), nutritional status (measured with the Mini Nutritional Assessment), cognitive status (measured with the MMSE), **depression** (measured with the GDS-SF) and **grip strength** (measured with a dynamometer).
- Guo et al.¹⁸⁰ (2016) used a **combination of psychological support, pre-operative ICU visits for patients, pre-operative patient education regarding ICU and surgery interventions, post-operative time/place orientation (calendars, clocks, radio, glasses, hearing aids, cell-phones), and staff training** in general geriatric approaches.



The aim was to prevent delirium in critically ill ICU patients (measured with the CAM-ICU). The incidence of delirium was significantly lower (15% versus 31%, $p=0.006$) and delirium periods lasted less long (28 hours versus 60 hours, $p<0.001$).

- Khan et al.⁷⁹ (2019) used a **pharmacological management bundle** (comprising of reducing cholinergics and benzodiazepines, and prescribing low dose haloperidol) to prevent **delirium** (measured with the RASS and CAM-ICU). They did not find significant differences in delirium free days and a small but significant differences in delirium severity.
- Moon et al.¹⁸² (2015) used a **multimodal non-pharmacological approach**, to prevent **delirium** in ICU patients. The approach consisted of close monitoring of changes in cognitive functioning, sensory abilities, physical functioning, and sociability (signs were decreased concentration, slow response, or confusion, hearing and visual impairment, slow mobility, restlessness, agitation, low appetite, or sleep disturbance, and communication difficulties, mood changes, and inability to cooperate). When parameters changed, people received extra orientation in time, place and person. Personal eyeglasses or hearing aids were offered, indirect light was provided throughout the night, if possible the same nurse in charge was assigned throughout hospitalisation, bed movement within the ICU was minimized, and visitors were permitted to bring patient items typically used in the home. Ambulation as early as possible was encouraged. And finally physiological adjustment was maximized (nutritional status, electrolyte balance) and medication, known to trigger delirium, was limited. Although incidence of delirium was lower (20% versus 33%), no significant differences were found.
- Richardson et al.¹⁷⁷ (2003) combined **relaxation with guided imagery**, twice a day. He did not find any differences between the intervention and the control group, in terms of quality of sleep (measured with the VSH).

3.3.8.2 Result of prospective observational study

- Duceppe et al.¹⁷⁹ (2019) compared people with and without delirium (measured with CAM-ICU) in terms of exposure to **pharmacological and non-pharmacological interventions**. They found lower odds for delirium in people who were administered opioids, who had access to radio and television, and who got more mobilisation. Higher odds for delirium were found in patients receiving physical restraints.

Key points

- RCTs show that multimodal (or multidimensional) interventions in ICU patients in order to prevent PICS resulted in lower levels of depression, higher quality of life, better cognitive status, and more hand grip strength.
- Studies revealed no effect on delirium.
- The composition of the multimodal interventions differed substantially between the included studies. As a consequence, it was impossible to compare the effects in depth or draw general conclusions.

3.3.9 Physiotherapeutic interventions

In this integrative review, 21 studies (16 RCTs, 1 secondary analysis of an RCT and 4 prospective cohort studies) were identified that applied physiotherapeutic interventions to improve PICS related outcomes. One study was from Belgium¹⁸³, one study from Taiwan¹⁸⁴, three studies from Brazil¹⁸⁵⁻¹⁸⁷, two studies from Australia^{188, 189}, one study from Switzerland¹⁹⁰, one study from Turkey¹⁹¹, two studies from France^{192, 193}, two studies from the UK^{194, 195}, six studies from the USA¹⁹⁶⁻²⁰², one study from Japan²⁰³, and one study from Germany²⁰⁴. Sample sizes varied from 20 to 330 (Mn=135.6, Md=108). Five studies were conducted in a MICU, five in a SICU, one in a long-term ICU and the others in mixed ICU environments. For the majority of studies, the mean age ranged between 49 and 72 years old. One study included significantly younger (Mn=46.5 years)¹⁸⁷ and one study significantly older patients¹⁸⁴. Outcomes of the studies were muscle strength, muscle



thickness, mobility, walking distance, quality of life, sleep quality, functional status, anxiety, depression, delirium, nutritional status, and cognitive function. The results of the studies can be found in the table in the Supplement-Table 16.

3.3.9.1 Results of RCTs

Standardised rehabilitation therapy was compared to usual care, to improve muscle strength, functional status, physical function, cognitive function and quality of life. The intervention group had significant better muscle strength¹⁸⁴ and a better functional status at six weeks¹⁸⁴. No significant differences for the other outcomes were seen at ICU discharge but at 6 months, physical function and physical quality of life were better in the intervention group.¹⁹⁷

Standard physical therapy compared with passive cycling was found to result in better muscle strength at 15 days.¹⁸⁷ **Passive mobilisation with blood flow restriction** (limb) resulted in more muscle thickness at ICU discharge.¹⁸⁵ Another study revealed that a **combination of standard rehabilitation and tilting on a table** resulted in better muscle strength than standard rehabilitation alone.¹⁹³ And finally **standard physiotherapy combined with the use of a cyclo-ergometer** was found to result in better muscle strength in critically ill ICU patients compared to standard physiotherapy alone.¹⁸³

Several studies looked at the effect of **early mobilisation**, and found better strength in respiratory muscles¹⁸⁶, better general muscle strength (MRC score)¹⁸⁶, better mobilisation capacity²⁰⁴, better functional mobility²⁰⁴, a longer walking distance²⁰⁰ and a lower delirium incidence and duration^{191, 200}. Two studies^{194, 200} however found no effect at three months regarding physical function, muscle strength, hand grip strength (dynamometer), mobility (1st time out of bed), anxiety and depression, physical and mental quality of life, and cognitive function in critically ill ICU patients. Neither was this for physical function^{189, 190, 198}, quality of life¹⁸⁹, depression¹⁸⁹ and anxiety¹⁸⁹ up till six months.

The **intensity of mobilisation** was found to be predictive for higher muscle strength²⁰² and less delirium²⁰², but no effects were found on physical

function and quality of life up till 12 months^{188, 195}. **Intensive exercise during and after ICU stay** to improve physical function and quality of life did also not result in better outcomes at 12 months.

Patients receiving **early and intensive mobilisation** succeeded significantly earlier to sit on the edge of the bed and to do the first transit from bed to chair, but no difference was seen in the moment of the first time sitting in the chair.¹⁹²

3.3.9.2 Results from prospective observational studies

Pre operative exercise did not show an effect on the incidence of delirium.²⁰³ **A multidisciplinary early mobilisation protocol** was found to be predictive of better general mobility.¹⁹⁶ Patients receiving **early mobilisation and occupational therapy** were found to have lower odds for ICU-AW.¹⁹⁹ One study²⁰¹ investigated the effect of **intensive early mobilisation** in critically ill ICU patients on mobility status. Authors showed that 97% of the subjects receiving the intervention maintained or increased their level of activity had a significant change in the Activity Mobilisation Evaluation Scale (AMES) at 3 months.

Key points

- RCTs show that standardised rehabilitation care was found to result in better functional status and muscle strength compared to usual care.
- A combination of rehabilitation with tilting or cycling was found favourable for the muscle strength and functional status of the patient.
- Results for early mobilisation are inconsistent. However, there is a heterogeneity over the studies in terms of timing: “early mobilisation” was defined in different ways. As a result, a general conclusion cannot be drawn.



- Intensive mobilisation was found to be effective: in the short term, muscle strength, functional status and quality of life were found to be better. On the long term the results of the studies were inconsistent.

3.3.10 Neuromuscular electrical stimulation (NES)

In this integrative review nine studies (8 RCTs and one secondary analysis of an RCT) were included that focused on the use of neuromuscular electrical stimulation (NES) to avoid or diminish PICS-related outcomes. One study was from Egypt²⁰⁵, one study from Austria²⁰⁶, one study from France²⁰⁷, one from Greece²⁰⁸, one study from Australia²⁰⁹, one study from the USA²¹⁰, one study from Japan²¹¹, one from Germany²¹² and one from Italy²¹³. Number of participants varied from 24 to 314 (Mn=80.9; Md=52). One study was conducted in a SICU, three in a MICU and the remaining five in a mixed ICU environment. Mean ages in the selected studies varied from 45 to 77 years old. Outcomes of the studies were muscle strength, status of mobility, exercise capacity, ICU-acquired muscle weakness (ICU-AW), level of anxiety, quality of life, and delirium incidence. Electrical stimulation was often combined with physiotherapy. The results of the studies can be found in the Supplement-Table 17.

3.3.10.1 Results from RCTs

Studies using **NES as intervention** showed less muscle volume loss²¹¹, less muscle weakness²⁰⁵, less ICU-AW in lower limbs²⁰⁸, faster and better muscle strength regain²⁰⁶, better stair climbing at hospital discharge²¹¹ and maximum walking distance at hospital discharge²¹⁰, while no effect was seen for ICU-AW in upper extremities²⁰⁸, handgrip strength^{208, 210} and the ADL score.²¹⁰

NES in combination with in bed cycling²⁰⁷ or with early protocol based physiotherapy and whole body vibration²¹² did not show positive effects on ICU-AW²⁰⁷, delirium incidence²⁰⁷, muscle strength²¹², functional mobility²¹² and quality of life at 6 months²⁰⁷. **In combination with early mobilisation** a significant better physical dimension for quality of life at 6

months was seen²⁰⁹, but no differences were revealed in exercise capacity^{209, 213}, severity of ICU-AW²⁰⁹ and level of anxiety at ICU discharge.²⁰⁹

Sample sizes were small, with only one study exceeding 100 participants.

Key points

- RCTs does not reveal consistent results.
- NES used solely showed less ICU-AW related outcomes, especially in lower limbs.
- In combination with other physiotherapeutic interventions, early mobilisation was found favourable for physical quality of life but no differences in exercise capacity could be revealed.

3.3.11 Nutritional interventions

This integrative review included 12 scientific publications with focus on nutrition (8 RCTs, 3 secondary analysis of RCTs and 1 prospective cohort study): one study from Iran²¹⁴, two from the USA^{112, 215}, one study from Brazil²¹⁶, four studies from Belgium²¹⁷⁻²²⁰, two studies from Australia^{221, 222}, one from China²²³, and one study was a collaboration between 4 countries (USA, France, Belgium and Canada)²²⁴. Number of participants varied from 15 to 4650 (Mn=721; Md=140). Ten studies were conducted in mixed ICU environments and one study was set up in a SICU. Mean ages varied between 44 and 77 years old. The outcomes of the studies were muscle strength and loss, ICU-AW, incidence of delirium, depression, anxiety, cognition and quality of life. The results of the studies can be found in the Supplement-Table 18.



3.3.11.1 Results from RCTs

As the interventions of the included studies are very heterogeneous, the majority of studies is described separately.

- Needham et al.²¹⁵ (2013) compared the use of **trophic feeding (low energy permissive underfeeding) for six days** with initial full energy **enteral feeding** in ventilated patients. The focus of this study was on quality of life, anxiety, depression and cognition after six months and one year. Regarding the quality of life, mental health was found to be better in the trophic feeding group at 12 months, while no significant differences between groups were found for the physical component (SF-36), the utility score (EQ-5D), anxiety and depression (HADS) and cognition (MMSE).
- Wischmeyer et al.²²⁴ (2017) investigated whether **supplemental parenteral nutrition (as an addition to enteral nutrition)** could improve muscle strength at ICU discharge and/or quality of life at ICU discharge and at 6 months post-discharge. Trends (but no significant differences) to improve hospital discharge handgrip strength ($p=0.14$) and 6-minute walk test score ($p=0.2$) were observed in the supplemental parenteral nutrition group versus the enteral nutrition alone group. By six months the change in quality of life was consistently (but not significantly) better in the supplemental parenteral nutrition group.
- Casaer et al.²²⁰ (2011) (RCT) compared **early initiation of parenteral nutrition** (European guidelines) **with late initiation** (American and Canadian guidelines) in adults in the ICU to supplement insufficient enteral nutrition. Late initiation of parenteral nutrition was associated with faster recovery in general and fewer complications, as compared with early initiation, but no difference was seen in functional status at hospital discharge (6-min walking test and ADL). In a later study of the same author²¹⁷ the focus was on muscle loss (measured with CT Scans). They found that parenteral nutrition did not prevent the pronounced wasting of skeletal muscle observed over the first week of critical illness, while the amount of adipose tissue within the muscle compartments increased. Hermans et al.²¹⁹ (2013) did a sub-analysis of the Casaer 2013 study with focus on ICU-AW. They found significant more ICU-AW in the early parenteral nutrition group (43% vs. 34%, $p=0.03$). Multivariate regression analysis revealed that late parenteral nutrition decreased the risk for developing ICU-AW (OR=0.68, $p=0.047$). And finally Doig et al.²²¹ (2013) found a statistically significant but clinically not meaningful effect of early parenteral nutrition on quality of life.
- Liu et al.²²³ (2018) compared **early enteral nutrition** with **delayed enteral nutrition** with focus on ICU-AW at 28 days (diagnosed with the criteria of the American Thoracic Society). Early enteral nutrition was found to give a lower prevalence of ICU-AW (28.6% vs. 53.6%, $p=0.044$).
- Azevedo et al.²¹⁶ (2019) compared the effect of **optimised calorie intake and high protein diet (versus usual nutrition)** on physical quality of life. They found that a negative delta for protein (protein received minus predetermined protein requirement) was associated with lower physical quality of life at 3 and 6 months, while negative caloric balance did not show a relationship.
- Ferrie et al.²²² (2016) compared **high protein (1.2g/kg)** with low protein (0.8g/kg) total parenteral nutrition. Regarding handgrip strength at 7 days, they found better results in the intervention group. They also looked at quality of life (more specific: general fatigue) and found better results in the intervention group.
- Naghibi et al.²¹⁴ (2020) investigated the effect of **additional 2gr omega-3 fatty acids** (compared to a usual care group) on the number of days with delirium. They found a significant better result for the intervention group (Mn(SD)=2.71(2.01) vs. 4.72(2.19), $p=0.032$).
- Hermans et al.²¹⁸ (2007) (secondary analysis of RCT) also focused on glycaemia, more specifically on the comparison of **intensive insulin therapy (glycaemia 80-100 mg%)** and conventional insulin therapy (glycaemia 180-215 mg%) in order to prevent critical illness polyneuropathy (CIP) and myopathy (CIM). They found a lower risk for



CIP/CIM in the group of intensive insulin therapy (39% vs. 50.5%) with OR 0.61 for intensive insulin therapy.

3.3.11.2 Results from prospective observational study

- Dowdy et al.¹¹² (2008) focused their prospective cohort study on the relationship between **glycaemia (hypo-, normo- and hyper)** and prevalence of depression at 3 months post ICU-discharge. Multivariate regression analysis showed significant higher odds if the patient's mean daily minimum glucose in ICU was <100 mg% (OR=2.1; p=0.006) while the use of an insulin infusion protocol did not show a significant relationship with depression.

Key points

No sound conclusion on the impact of nutritional therapy on PICS outcomes can be drawn:

- One study showed early enteral nutrition was found to be related to less ICU-AW.
- Parenteral nutrition does not seem to be involved in the control of muscle loss/ICU-AW.
- Late initiation of parenteral nutrition was associated with faster recovery in general and fewer complications and fewer ICU-AW, as compared with early initiation, but no difference was seen in functional status at hospital discharge.
- Intensive insulin therapy is associated with lower risk for ICU-AW in one RCT. A prospective study showed a higher risk for depression if mean daily minimum glucose in the ICU was < 100 mg/dL.

3.3.12 Complementary medicine interventions

This integrative review identified 5 studies (all RCTs) that apply complementary medicine interventions to prevent dimensions of PICS: one study from Iran²²⁵, one study from Brazil²²⁶, one from Taiwan²²⁷, one from the UK²²⁸ and one from India²²⁹. Number of participants varied from 48 to 195 (Mn=101.6; Md=85). The outcomes of these studies were the level of anxiety, sleep quality, incidence of delirium, days without delirium, delusional memories and health-related quality of life. Three studies were conducted in a mixed ICU environment and two studies were set up in a SICU. Mean ages of the ICU patients varied between 25 and 77 years old. Sample sizes varied from 48 to 120 subjects. The results of the studies can be found in the Supplement-Table 19.

3.3.12.1 Results from RCTs

All included studies were RCTs, but study samples were quite small. **Foot reflexology** in critically ill patients was found to reduce anxiety (compared to a sham procedure).²²⁵ Application of types of **massage** were also found to reduce anxiety.^{226, 229} **Valerian acupuncture** showed to improve sleep quality and duration.²²⁷ And finally, a study was included that used a **structured mirror intervention** (use of a mirror for self-observation and awareness of the environment). This intervention was not related to incidence of delirium, number of ICU days with delirium, delusional memories or health related quality of life but factual memories were better.²²⁸

Key point

- Some complementary medicine interventions were found to result in better sleep quality and less anxiety, while no association was found with delirium incidence or health related quality of life.



3.4 Discussion

As already described in the introduction, this integrative review does not intend to redo the work performed for the development of the PADIS guideline on the prevention of PICS (see section 4.3.3). The most important goal of the review on interventions to prevent PICS was to identify possible new (and unused) studies to complete the knowledge base. This review only partly followed the PRISMA recommendations (i.e., no critical appraisal was performed on the selected studies). Information was then extracted according to the design of the studies (RCTs, prospective observational studies...).

The vast majority of included studies had a small sample size; therefore, we made no distinction between studies based on patient numbers. Moreover, in a number of studies, PICS outcomes were secondary outcomes (where mortality, length of stay, or duration of mandatory ventilation were the primary outcomes). As this might influence the results, conclusions drawn in this integrative review should be interpreted cautiously.

For many interventions to prevent PICS currently in clinical practice, there is little weight of evidence or only weight of evidence based on studies with significant methodological limitations (observational studies with important risk of bias, RCTs with small sample sizes, ...). Although the exclusion criteria for this integrative review attempted to limit these sources of bias (e.g., by excluding retrospective; before-after or very small studies), it must be stated that for a number of interventions level of evidence remains low. The overview of the evidence as described above must be read and interpreted in the light of this finding. However, absence of evidence is not necessarily the same as evidence for absence of an effect. This should invite scientific community to set up a number of studies of high methodological quality in this area in the near future.

If we take into account all of the foregoing, it must be stated that there is insufficient hard evidence to state whether we can prevent PICS. The existing evidence provided in the PADIS guideline (and confirmed by this integrative review) gives some guidance to try to prevent PICS by using the ABCDEF-tool (see section 4.4). More and better quality studies are needed to underpin the existing evidence.

4 IMPLEMENTATION OF PICS PREVENTION

4.1 Aim

In the previous chapter, a wide range of interventions to prevent the (long lasting) consequences of a stay on ICU are described. Some of these are effective while for others, effectiveness is not proven. It is very important that effective approaches are adopted by the work field as soon as possible and are used for every ICU-patient potentially at risk for PICS. The present chapter focuses on tools for the implementation of the present evidence on PICS-prevention. This chapter does however not have the intention to be exhaustive but is an attempt to give an overview of tools to implement interventions to prevent PICS.

4.2 Method

This review uses almost the same methodological approach as the previous chapter, i.e. a pragmatic approach. In a first stage, we searched for key publications and textbooks focusing on PICS were read, to identify search terms to use for the literature search. In the second stage, we searched in Medline and Cinahl for systematic reviews on implementation of prevention of PICS, published between 2010 and November 2018. Relevant primary papers (i.e., responding to the PICO and the selection criteria) were retrieved and analysed. In the third stage, we searched in Medline and Cinahl for primary papers published between 2018 and November 2020. In the fourth stage, we searched in the last version of the PADIS guideline²³⁰ and the website for the ABCDEF-bundle, for additional references (June 2022). All references with focus on (1) guidelines to prevent PICS, (2) the ABCDE(F) bundles and (3) pre-conditions for implementation of evidence regarding PICS-prevention were included.



4.3 Implementation tools

4.3.1 Background

From the early '90s of the past century, more and more research was conducted regarding the long-lasting adverse effects of prolonged mechanical ventilation, sedation and immobilisation. More and more evidence emerged that there was a strong need to rethink procedures and management for patients in ICU. The previous chapter has shown that a wide variety of factors influence the PICS outcomes. Several influential researchers became aware that there was a need to bundle all these findings in one comprehensive document.

The creation of the **Clinical Practice Guidelines for the Sustained Use of Sedatives and Analgesics** in the Critically Ill Adult, published in 2002 by the Society of Critical Care Medicine (USA), was the first initiative to structure all this knowledge. In 2004 the American College of Critical Care Medicine set up a task force to start the update process (in 2006). And, as a result, in 2012 an **Updated Clinical Practice Guideline for the Management of Pain, Agitation and Delirium (PAD) in the Adult Patient in ICU** was published. This guideline differs from the previous guidelines in that, wherever possible, recommendations are based on evidence, rather than on expert opinion or consensus statements.²³¹

This continuous updating of new emerging knowledge has become the best model for subsequent guidelines in individual countries or critical care medicine specialties.²³² In 2013, the Society of Critical Care Medicine (SCCM) created the **ICU Liberation campaign** as a next step following the publication of the PAD-guideline. An important output product of this ICU Liberation Campaign was the creation of a very practical **"Bundle" (ABC-DE-F)** (see under), which represents the implementation strategy used to provide each of the recommendations in the guideline to every patient.²³³ The ICU Liberation Collaborative is a real-world quality improvement initiative initially being implemented across 76 ICUs designed to engage strategically the ABCDEF bundle through team- and evidence-based care.²³⁴

As Pandharipande states "Healthcare providers are thus encouraged to incorporate strategies that lead to early liberation and animation; the ABCDE bundle represents just one method of approaching the organizational changes that need to occur to effect a change of culture that will breed success. [...] The pendulum needs to swing back to having interactive patients with well-controlled pain who can participate in physical and cognitive activities at the earliest possible safe point in their critical illness." (Pandharipande, 2010²³⁵, p.2)

4.3.2 The PAD guideline

In 2006, a task force of experts was recruited to develop the **PAD (Pain, Agitation, and Delirium)** guideline. Four subcommittees comprehensively examined the literature regarding analgesia, sedation, delirium and outcomes in the ICU. Important clinical management questions were formulated and served as the basis for the 32 recommendations and 22 statements that were published in 2013. Recommendations and statements were developed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method. This objective, systematic and transparent process to evaluate the literature and make recommendations (based on quality and strength of evidence) resulted in a robust evidence-based guideline. It must however be stated that for several outcomes in the guideline, limited (or no) evidence was available. As a consequence, for these outcomes, expert opinions were stated.^{236, 237}



4.3.3 The PADIS guideline^u

As more and more new evidence regarding the prevention (or aetiology) of PICS emerged, there was a need for updating and extension of the PAD guideline. This process resulted in the Clinical Practice Guideline for the Prevention and Management of **Pain, Agitation (Sedation), Delirium, Immobility, and Sleep (Disruption) (PADIS)** in adult patients in the ICU (2018), which addresses new management challenges related to pain, agitation, and delirium²³⁸ and by adding two inextricably related clinical care topics—rehabilitation/mobilisation and sleep; by including patients as collaborators and co-authors; and by inviting an international panel of experts from high-income countries as an early step toward incorporating more diverse practices and expertise from the global critical care community.²³⁹ The recommendations in this guideline were again created using the GRADE methodology. The underlying evidence was searched and distilled in a very robust methodological way. Recommendations are intentionally brief and direct and are meant to be used ‘on the spot’.

The guideline contains rationales for 37 recommendations (derived from actionable Patient, Intervention, Comparison, and Outcome [PICO] questions); two ungraded good practice statements (derived from actionable PICO questions where it is unequivocal, the benefits of the intervention outweigh the risks but direct evidence to support the intervention does not exist); and 32 ungraded statements (derived from nonactionable, descriptive questions) across the five guideline sections.²³⁹

Evidence is not strong for every topic of the guideline and as a consequence consensus statements had to be added. Although a strong recommendation is more valuable to clinicians than a conditional recommendation, practice guidelines, including PADIS, generally often contain far more conditional than strong recommendations. Every recommendation is followed by a

rationale section to improve understanding of the underlying evidence and as a result, improve implementation. The PADIS Guideline provides a roadmap for developing integrated, evidence-based, and patient-centred protocols to prevent PICS and provide optimal care for critically ill patients. The PADIS Guideline is expected to be updated every five years, or as new evidence becomes available.²³⁰

"In addition to bridging the gap between the knowledge we gathered and its application, we believe that this will provide tangible support to clinicians, stakeholders, and decision makers in implementing quality in pain, agitation, delirium, early mobility, and sleep and further foster the application of what we understand to be useful in the provision and delivery of excellent care", note the guideline authors.²³⁰ (web page)

4.4 The ABCDE(F) bundles: translation of the PADIS guideline into practical tools

If guideline recommendations and statements are to improve ICU clinical practice, effective knowledge translation and implementation of science efforts are critical.²³⁸ The PADIS guideline represents a wasted effort unless its recommendations can be easily interpreted, understood, and implemented by practising ICU clinicians. As the language used in the PADIS guideline is not typically included in the critical care lexicon, this might hamper the uptake of the guideline.²³⁸ From that viewpoint, an implementation strategy (or tool) is needed.

In a first attempt, Ely and his study group at Vanderbilt University created the ABC bundle. This was in a later stage expanded to an ABCDE protocol. Slight changes were made to the ABC mnemonic, a “D” was added for “delirium”, and an “E” was added for “early mobility.” The new bundle was titled the Awakening and Breathing Coordination, Delirium Monitoring and

^u For the sake of completeness, it should be mentioned here that there have been other lesser-known attempts, to create guidelines on PICS prevention: the Federación Panamericana e Iberica de Sociedades de Medicina Crítica y Terapia Intensiva (FEPIMCTI) guidelines and the Japanese J-PAD guideline,

containing respectively 12 and 5 sections, and 138 and 37 recommendations. The outlines of these guidelines are however similar to PADIS, and all reinforce the management of Pain, Agitation and Delirium to improve patient outcomes.



Management and Early Mobility bundle. The ABCDE Bundle included the same evidence-based recommendations for assessment, treatment, and prevention of pain, agitation, and delirium as the SCCM PAD Bundle. An “F” was later added to the bundle by investigators at Vanderbilt for “family engagement and empowerment” to help keep patients and families at the centre of focused care. The meanings of the mnemonic A, B, and C changed slightly again, and the bundle is currently referred to as the ABCDEF Bundle.^{231, 240}

Thus, the recommendations of the PADIS guideline have been incorporated into a single bundle of best practices, known as the ABCDEF bundle (see Box 1).

Box 1 – Definition of the ABCDEF bundle²⁴¹

- A: Assess, prevent, and manage pain;
- B: Both spontaneous awakening and spontaneous breathing trials [SATs/SBTs];
- C: Choice of analgesic and sedation;
- D: Delirium: assess, prevent, and manage;
- E: Early mobility and exercise; and
- F: Family engagement and empowerment.

The ABCDEF bundle is an organisational approach to screen for and treat a series of variables affecting intensive care patients in an evidence-based manner and is designed to limit iatrogenic harms and improve the care of the critically ill.²⁴² It helps guide well-rounded patient care and optimal resource utilisation resulting in more interactive ICU patients with better controlled pain, who can safely participate in higher-order physical and cognitive activities at the earliest point in their critical illness.²⁴³

To help address early identification of possible causes of delirium, the acronym THINK was created and added as a second tool to the ABCDEF bundle (see Box 2).²³¹

Box 2 – Definition of the THINK as a second tool for the ABCDEF bundle

- T: Toxic situations (heart failure, shock, dehydration, organ failure, and drugs)
- H: Hypoxemia
- I: Infection or sepsis/immobilisation
- N: Nonpharmacologic interventions used (eyeglasses, hearing aids, reorientation, sleep protocols, noise control)
- K: K or other electrolyte problems

4.5 Is the use of the ABCDE(F) bundle effective?

Evidence shows that the SCCM's PAD(IS) guideline can be implemented using the evidence-based ABCDEF bundle with significant and marked associated improvements for both in-hospital survival and days free of delirium and coma even after adjusting for age, severity of illness, and mechanical ventilation. Further, even when delivered incompletely, bundle implementation results demonstrate that perfection is not required to see improvements in patient outcomes.²⁴⁴ In other words, ABCDEF bundle implementation appears to have a significant “dose-response” effect on important ICU patient outcomes; the more of the bundle that is done on more days, the better the physical, psychological and cognitive patient outcomes.²⁴¹ Health care organizations that implement the ABCDEF bundle also have other improved patient outcomes such as decreased ICU and hospital lengths of stay, decreased duration of MV, decreased duration of delirium that are risks of PICS, and decreased health care costs.²⁴⁵

All of the included studies were observational studies.



- Earlier versions of the ABCDEF bundle (versions before the inclusion of pain [current A element] and family engagement and empowerment [current F element])^{241,244} and the study of Kram et al.²⁴⁵ (2015) resulted in substantially improved hospital survival, decrease in hospital stay of 1.8 days and halved odds of developing delirium.
- YoonMi Lee et al.²⁴⁶ (2020) used a slightly modified version of the ABCDE bundle (small changes made to A, D and E-part). They revealed that the percentage of patients showing sedation levels of alertness and calmness increased significantly from 58.2% to 72.4% using the modified ABCDE bundle. Coma prevalence decreased significantly from 45.1% to 28.7%. In the E domain, the percentage of patients receiving early mobility interventions increased significantly from 11% to 54.3%.²⁴⁷
- Pun et al.²⁴⁸ (2019) report a retrospective, multicentre, cohort study from a national quality improvement collaborative, where 68 academic, community, and federal ICUs collected data during a 20-month period, including 15 226 adults with at least one ICU day.²⁴⁸ The complete ABCDEF bundle performance was associated with lower likelihood of seven outcomes: hospital death within 7 days (adjusted hazard ratio (AOR)=0.32; 95% CI: 0.17–0.62), next-day mechanical ventilation (AOR=0.28; 95% CI 0.22–0.36), coma (AOR = 0.35; 95% CI: 0.22–0.56), delirium (AOR=0.60; 95% CI, 0.49–0.72), physical restraint use (AOR=0.37; 95% CI: 0.30–0.46), ICU readmission (AOR=0.54; 95% CI: 0.37–0.79), and discharge to a facility other than home (AOR=0.64; 95% CI: 0.51–0.80). There was a consistent dose-response relationship between higher proportional bundle performance and improvements in each of the above-mentioned clinical outcomes (all $p < 0.002$). Significant pain was more frequently reported as bundle performance proportionally increased ($p < 0.001$).
- Hsieh et al.²⁴⁹ (2019) conducted a multicentre RCT with 1 855 mechanically ventilated patients admitted to the ICU. For the purpose of this study, they split up the ABCDE in B, AD and EC. In the full bundle, 95% of patient days were spent in bed before EC (period 1). After EC was implemented (period 2), 65% of patients stood, 54% walked at least once during their ICU stay, and ICU-acquired pressure ulcers and physical restraint use decreased (period 1 vs. 2: 39% vs. 23% of patients; 30% vs. 26% patient days, respectively; $p < 0.001$ for both). After adjustment for patient-level covariates, implementation of the full (B-AD-EC) versus partial (B-AD) bundle was associated with reduced mechanical ventilation duration (–22.3%; 95% CI: –22.5% to –22.0%), ICU length of stay (–10.3%; 95% CI: –15.6% to –4.7%), and hospital length of stay (–7.8%; 95% CI: –8.7% to –6.9%). Total ICU and hospital cost were also reduced by 24.2% (95% CI: –41.4% to –2.0%) and 30.2% (95% CI: –46.1% to –9.5%), respectively.²⁴⁹
- Barnes-Daly et al.²⁴⁴ (2017) showed that with each 10% incremental increase in **total** ABCDEF bundle compliance, the odds of hospital survival increased to 7% (OR=1.07; 95% CI: 1.04–1.11) and with each 10% increase in **partial** bundle compliance, the odds of hospital survival increased to 15% (OR=1.15; 95% CI: 1.09–1.22) and for patients not receiving palliative care, the odds of hospital survival even increased to 23% (OR=1.23; 95% CI: 1.14–1.32). Moreover, for every 10% increase in total bundle compliance, patients had a 2% increase of delirium- and coma-free days (DFCFDs) (IRR=1.02; 95% CI: 1.01–1.04), and for every 10% increase in partial bundle compliance, there was a 15% increase in DFCFDs (IRR=1.15; 95% CI: 1.09–1.22).
- And finally, Miller et al.²⁵⁰ (2015) conducted a survey in ICU health care professionals and revealed that in adjusted models, those who implemented exercise with sedation interruption and delirium screening were 3.5 (95% CI: 1.4–8.6) times more likely to achieve higher levels of exercise in ventilated patients than those who implemented exercise without both sedation interruption and delirium screening.

**Key points**

- Observational studies show that the use of the ABCDE(F) bundle in ICU patients was effective and resulted in better PICS related outcomes.
- The PAD(IS) guidelines are well-structured evidence-based guidelines to prevent PICS.
- The ABCDE(F) bundles are created to support and facilitate the implementation of the PAD(IS) guidelines.
- The application of the bundles has shown to be effective to improve patient outcomes related to PICS.

5 BARRIERS AND FACILITATORS TO ADOPT PICS PREVENTION INTERVENTIONS

5.1 Aim

To formulate realistic recommendations, we searched for the already known **organisational barriers** and **facilitators** to prevent PICS in ICUs, including qualitative data that make them more tangible. This chapter aimed to identify national and international barriers to enlarge the reflexion.

5.2 Literature search

To approach the barriers and facilitators to prevent PICS, we performed an integrative literature review on barriers and facilitators to ensure the prevention of PICS.

Because ICUs were much solicited during the last months of the SARS-CoV-2 pandemic, with the two KCE studies on ICU^{251, 252} and because we knew that much information is already available in the scientific literature, we opted for a literature review rather than interviews.

5.2.1 Databases and date limits

To identify relevant published evidence we conducted systematic searches of literature in the Cochrane Database of systematic reviews, Medline, Embase, Cinahl and PsycInfo.

A search strategy was developed to search Medline through Ovid interface. This strategy has been adapted to each database. All databases were searched between 22nd December 2021 and 11th January 2022, with no publication date, document types or language restrictions. For Embase, conference papers and duplicates from Medline were excluded. The search results were then imported into Endnote with automatic duplicates removal enabled. The remaining references have then been imported into the Rayyan tool (<https://rayyan.ai>) for the Title-Abstract screening phase.



5.2.2 Search strategy

The Medline strategy used a combination of appropriate MeSH terms and free text words. For other databases, MeSH terms have been replaced by the appropriate controlled thesaurus terms when available. The detail of each strategy with search date and number of references found is provided in the Supplement.

P: patients in ICU (>48h)

I: early mobilisation, delirium prevention, sedation interventions, diary, PADIS, Bundle, cognitive intervention

C: not applicable

O: barriers and facilitators

5.2.3 Inclusion/Exclusion criteria

Publication from 2015 on adult population in ICU were retained. Two researchers (LK and DC) selected articles firstly based on title and abstract. After full text reading, 62 articles have been selected. Reviews, qualitative research, cross-sectional or 1 time survey, cases studies, prospective studies, retrospective studies, mix-methods studies and observational studies were included.

5.2.4 Analysis

A content analysis of the selected articles was done. The aim was not to perform an exhaustive and systematic review, neither to conduct a meta-analysis. No quality check was therefore performed on our corpus of analysis.

To note, data saturation was reached, i.e., no new information raised from additional readings.

To integrate the Belgian perspective, the grey literature was investigated for any documentation related to initiatives of PICS prevention (see chapter Initiatives to prevent PICS in Belgium 6.3). The results were presented to a

stakeholder/expert group to highlight their congruence with the Belgian situation.

5.3 Findings

Literature on barriers consists mainly of literature review, cross-sectional or prospective survey, quantitative or qualitative analysis. These are the best level of evidence available on such research questions. Description of the studies that we have included are available in the Supplement-Table 21. We retrieved quantitative information as well as qualitative information from the literature. We will thus present figures when available or illustrate the findings with reproduction of some quotes published in the different studies. We selected the most illustrative ones where there were several available, allowing to understand what concretely the barriers are.

Because saturation was rapidly reached, we concluded that all the barriers were probably caught. Nevertheless, the literature review was not exhaustive in the meaning that we probably do not identify all the papers on the subject.

5.3.1 Preamble: classification of barriers and facilitators

There are plenty of ways to describe and organise barriers to PICS prevention interventions in the ICU or in general. As a consequence, the concepts and models used are not uniform in the scientific literature. In order to illustrate this diversity and the difficulty to synthesise our findings issued from the scientific literature review, we will briefly present the frameworks that we have identified through our analysis. This list is non-exhaustive.

For example, Cooper et al.²⁵³ conceptualised barriers in three 'simple' categories allowing to identify where/ to whom act in order to overcome these:

1. Patient condition barriers
2. Nurse and health care team barriers
3. Environment-of-care barriers



Dubb et al.²⁵⁴ used another but slightly more complex classification:

- Patient-related barriers, including patient symptoms and conditions (e.g. hemodynamic instability)
- Structural barriers, including human and technical resources (e.g. staffing, equipment, or protocols)
- ICU culture-related barriers, including habits, attitudes, and context within ICUs and institutions (e.g. staff morale)
- Process-related barriers, including how services are delivered and clinician are functioning (e.g. unclear roles and responsibilities)

Parry et al.²⁵⁵ classified their findings regarding barriers and enablers for early mobilisation (EM) in 6 themes emerged from the clinicians focus groups they carried out:

1. Clinician expectations and knowledge
2. Evidence for and application of rehabilitation
3. Patient factors
4. Safety considerations
5. Environmental influences
6. Culture and teamwork

Popoola et al.²⁵⁶ used a classification in themes and subthemes to describe the data of their integrative review on mobilisation in ICU:

- Organizational barriers: staffing levels, time and workload, resources, and care coordination
- Individual barriers: personal and team safety, knowledge and training, beliefs about the consequences of early mobilisation, stress, and other barriers
- Patient-related barriers: medical instability/physical status, patient safety, neurological deficits and sedation, and non concordance of patients

Finally, Barber et al.²⁵⁷ present the barriers they have identified through focus groups data collection according to the type of Health Care Provider (HCP), physicians, physiotherapists and nurses.

Next to these 'self-concepted classifications', other authors referred to theoretical models aiming to explain change behaviour and are allowing to identify barriers regarding the subjacent concepts.

Goddard et al.²⁵⁸ and Tadyanemhandu et al.²⁵⁹ used the **Theoretical Domains Framework (TDF)** that synthesizes constructs from 33 behaviour change theories into 14 "construct domains," or clusters of related constructs that may explain practice change or the absence of change. It has been applied *"as a framework for developing questionnaires and interview topic guides across a range of clinical contexts to systematically explore the barriers and facilitators to clinician behaviour change. Each of the 4 domains represents a range of related constructs that may influence clinician behaviour"* (Goddard, 2018²⁵⁸, p 2). These domains are:

- Social/professional role and identity (i.e., professional identity/role or boundaries);
- Beliefs about consequences (i.e., patient related factors relating to stability or instability of the condition);
- Environment context and resources (i.e., material resources availability and management);
- Behavioral regulation (i.e., action planning and goal setting in the unit).

Because it makes links between theories of behaviour change and it has a comprehensive coverage of possible influences on behaviour, using this framework has the advantage that results could be used in the designing and evaluation of interventions targeted at the implementation of practices as evidence-based practice.²⁵⁹

Talking about implementation of a practice, Costa et al.²⁶⁰ used the **Consolidated Framework for Implementation Research (CFIR)** because it provides a structured approach to examining barriers to implementation. It includes five domains:



1. Characteristics of the intervention, i.e. the actual intervention being implemented;
2. Inner setting, i.e. the social, economic, political, and social environment through which the implementation process proceeds and that will influence implementation;
3. Outer setting, i.e. the economic, social, or political context of the organization;
4. Characteristics of individuals, i.e. the people who play an important role in implementation;
5. Process, i.e. refers to the active changes that occur to encourage or discourage the implementation of the intervention.

Lago et al.²⁶¹ referred to the **Capability, Opportunity and Motivation model (COM-B system)**. The COM-B system can be used to identify the barriers and facilitators of behaviour change and has been applied to the behaviour of health professionals. It suggests that for any behaviour to occur, there must be a change in one or more of the following:

- Capacity, i.e. the individual's psychological and physical capacity to conduct an activity concerned;
- Opportunity, i.e. other factors that make behavior feasible or immediate. It was distinguished between physical opportunity (provided by the environment) and social opportunity (provided by the social setting that dictates the way people think about things);
- Motivation, i.e. the reflexive (brain processes that direct the person's decision and behavior, involving evaluation and plans) and automatic processes (that imply the emotions and impulses that emerge from associative learning and/ or innate dispositions of an activity).

In order to get specific guidance on potential barriers and facilitators to adopt clinical practice, Lin et al.²⁶² opted for the **knowledge-to-action (KTA) framework** because it provides an overall model to promote the use of evidence in practice and identifies the need to understand the context and local barriers and facilitators. Its principles are that, before clinical practice

guidelines can affect patient outcomes, it must first affect clinician knowledge, then attitudes, and finally behaviour.

Box 3 – Thematic framework used to identify barriers and facilitators to prevent PICS

Because we do not aim to discuss critically the theoretical frameworks used, and because we aim to identify as many barriers and facilitators as possible, we will present the barriers and facilitators we identified in our own thematic way:

1. Patient-related barriers
2. Structural / institutional barriers
3. Barriers related to ICU contextual culture
4. Clinician-related barriers
5. Protocol-related barriers
6. Organization-related barriers
7. Environment-related barriers

The results of the literature review will be presented according to the intervention aiming at preventing PICS i.e. early mobilisation, pharmacological therapy, delirium prevention and assessment, ICU-diaries, and multidimensional approach (bundle). For each intervention the up cited categories of barriers/facilitators and potential strategies to overcome barriers will be presented (see Box 3). More particularly, regarding the prevention of delirium occurring during the ICU stay, the multicomponent bundle proposed by Bannon et al.²⁶³ will be used. The latter include measures for the delirium management: (1) education and family participation, (2) sedation minimisation and pain, agitation, and delirium protocol, (3) early mobilisation, and (4) environmental interventions for sleep, orientation, communication, and cognitive stimulation. We will describe their findings separately for each component in the appropriate section.



Our purpose is to identify barriers and, when they are quantified, to present the available figures.

Key point

There is a diversity in the description and classification of barriers and facilitators in general and in particular related to PICS prevention interventions in the ICU. Concepts and models used are not uniform in the scientific literature: some are 'self-made', others are referring to theoretical models, e.g. the Theoretical Domains Framework (TDF), the Consolidated Framework for Implementation Research (CFIR), the Capability, Opportunity and Motivation model (COM-B system), or the knowledge-to-action (KTA) framework. Because of this diversity and heterogeneity, we used our own thematic classification to describe barriers and facilitators for each intervention.

5.3.2 Barriers and facilitators to the adoption of bundles

Bundles translate guidelines into process. Of these, the ABCDE(F) bundle is mainly used (see Chapter 4). The aim of bundles is to deliver quality ICU care and thus reduce exposure to risks factors of PICS, limit the duration of mechanical ventilation and leave as soon as possible the ICU, being able to move around. There is overlap between PICS prevention activities and the use of the bundle.

While this is a recommended practice in critical care, evidence suggests that utilization of the ABCDE bundle is low, and implementation varies.²⁶⁴ All the interventions to prevent PICS could be organized as a bundle.

Costa et al.²⁶⁰ performed a review to identify and catalogue the barriers to the use of ABCDE bundle. They identified four categories of barriers: (1) patient-related (i.e., patient instability and safety concerns); (2) clinician-related (i.e., lack of knowledge, staff safety concerns); (3) protocol-related (i.e., unclear protocol criteria, cumbersome protocols to use) and (4) ICU contextual barriers (i.e., interprofessional team care coordination). With these, they propose that ICU physicians use the identified barriers as a diagnosis checklist of their unit to assess their own unit's barriers to the

ABCDE bundle implementation. Then, they suggest to design and implement appropriate interventions to overcome the barriers, taking into account the context, the interprofessional team and the implantation capacity of the unit.

In the Balas et al.'s study²⁶⁵, some barriers to the implementation of the ABCDE bundle could be overcome by training staff and providing screening tools. Indeed, after eight months of implementation, 50% of the respondents believed that the ABCDE bundle improves patient outcomes and 90% found adequate their knowledge about the ABCDE bundle, compared to 29% and 32% at four months respectively.

Nevertheless, some barriers remained even after implementation and that it became standard of care. These barriers included:

- Inconsistent medical practice;
- Reluctance to follow both new and existing protocols with a lack of acceptance of the bundle;
- Care coordination and communication barriers: because the different specialties all rounded at different times "it makes it very difficult for interdisciplinary rounds to occur." And when rounding did occur, ABCDE bundle related interventions and outcomes were felt to be rarely, if ever, discussed. Communicating at night was reported as particularly challenging;
- Workload and documentation related concerns;
- Protocol related concerns (e.g. fear of treatment related adverse events, timing of SATs and SBT);
- Persistent knowledge deficits related to delirium, sedation, and immobility, and the reported need for more education regarding the CAM-ICU and the bundle in general;
- Availability of appropriate staff.



"Now we are doing the CAM-ICU for all of our patients, but there is no change in what we do with the patient. No one knows what to do with delirium". (RN)²⁶⁵

A key lesson learned through this study was how important it is to assess an institution's "absorptive capacity for change".

Participants suggested to "[provide] continuing educational efforts, simplifying the process (i.e. making the policy shorter and easier to read, merging documentation into existing EMR assessments), adding to daily rounding sheet, creating early mobilisation teams, and creating a "unit champion" award." (Balas, 2013²⁶⁵, p.13) The bundle should be reviewed with everyone every 6-12 months because of staff turnover.

Boehm et al.²⁶⁴ identified that adherence to the ABCDE bundle was influenced by perceived ease of completion, including workload burden of the bundle. The perceived difficulty carrying out the bundle reduce the adherence with early mobility part of the total bundle. This difficulty is associated with organizational domains, i.e., policy and protocol factors, unit milieu, and access to supplies and equipment. In order to overcome these barriers, authors recommend to develop "standardized protocols (e.g., checklists, daily goal sheets), structured rounding processes (egg, interprofessional rounds), and interprofessional training (e.g., simulation training, core competencies)" (Boehm, 2017²⁶⁴, p 45).

With the COVID-19 pandemic, ICUs work was challenged. Liu et al.²⁶⁶ investigated the delivery of the ABCDEF bundle and ICU diary to patients without or with COVID-19 and the impact of COVID-19 on ABCDEF bundle, carrying a world-wide 1-day point prevalence study. They showed that COVID-19 impaired the implementation of the bundle, excepted for the F element that was more frequently performed for patients with COVID-19 infections. Indeed, with this new infection, huge expansion and progresses were made in the field of remote and tele-practice.

Delvin et al.²⁶⁷ showed that the situation of COVID-19 as a novel disease, resource limitations, and risks to medical personnel health have created new barriers to implement the bundle. Indeed, they raised a domino effect resulting from "changes to critical care hierarchy, priorities, and ICU team

composition; 2) significant personal protective equipment shortages cause; 3) reduced/ restricted physical bedside presence favouring; 4) increased depth of sedation and use of neuromuscular blockade; 5) which exacerbate drug shortages; and 6) which require prolonged use of limited ventilator resources." (Delvin, 2020²⁶⁷, p.1)

These barriers to bundle use were however influenced by the degree to which the bundle was implemented prior to the pandemic and the number of COVID-19 ICU admissions at any time relative to institutional ICU capacity and staffing. They identified interprofessional team (IPT) as a key success factor for implementing the bundle and a step that was not easily maintained during the pandemic. Nevertheless, implementing virtual collaboration could be a way to consolidate it.

Key points

- Utilisation of the entire bundle varies across units.
- Barriers to the use of the entire bundle are globally the same as barriers to components of the bundle and could be classified as (1) patient-related (i.e., patient instability and safety concerns); (2) clinician-related (i.e., lack of knowledge, staff safety concerns); (3) protocol-related (i.e., unclear protocol criteria, cumbersome protocols to use); and (4) ICU contextual barriers.
- While some barriers, e.g. perception of the value of the ABCDE bundle and adequacy of knowledge about the ABCDE bundle, are overcome after an implementation strategy, some barriers remain.
- Success depends on "absorptive capacity for change". This has to be assessed when considering implementation of the bundle.
- Strategies for continuing educational efforts, simplifying the process, adding to daily rounding sheet (i.e. electronic health record), creating early mobilisation teams, and creating a "unit champion" award could be useful.



- Adherence to the ABCDE bundle is influenced by perceived ease of completion. In order to overcome barriers, the development of standardised, ICU round processes, and interprofessional training are recommended.
- The COVID-19 pandemic created new barriers and impaired the delivery of the ABCDEF bundle.
- The barriers to the implementation of the ABDCEF bundle related to the COVID-19 pandemic depended on the degree of implementation of the bundle, the number of admission compared to the capacity of the ICU and the staff. In this situation, it was challenging to maintain an interprofessional team.

5.3.3 Barriers to specific interventions

Bundles are general approaches to manage patients in ICUs. They cover specific interventions, i.e., early mobilisation, sedation practices, prevention of delirium and diaries that were studied in the literature. We will go through these interventions and the identified barriers, facilitators or strategies to overcome barriers.

5.3.3.1 Early rehabilitation/mobilisation

Early rehabilitation/mobilisation is classically used during the ICU stay in the setting of PICS prevention. Nevertheless, in addition to the way authors classified the barriers and used different concepts, it is difficult to strictly compare the barriers to early mobilisation (EM) because this last term encompasses a large variability of definitions if any mentioned by the authors. We present the different definitions used in the literature that we have selected in the Supplement-Table 20. Moreover, we stress the fact that the barriers and facilitators are sometimes studied in context where EM is not already implemented.

BARRIERS TO EARLY MOBILISATION (EM)

Our purpose is to identify barriers and, when they are quantified, to present the available figures.

Dubb et al.²⁵⁴ performed a review in 2016 and identified 28 unique barriers to EM in 40 studies. These vary across units and within disciplines. In the study of Sibilla et al.²⁶⁸ in Switzerland, 29% of the respondents (physicians, nurses and physiotherapists) identified no barriers to mobilisation. Wand et al.²⁶⁹ found that ICU nurses who perceived fewer barriers had statistical significantly higher knowledge scores and more positive attitudes regarding EM than those with more barriers.

1. Patient-related barriers to EM

Patient related-barriers represent 50% of the identified barriers to EM in the review of Dubb et al.²⁵⁴

- Restrictive parameters and contraindications
 - There are contraindications to EM that cannot be overcome such as orthopedic or surgical issues, active hemorrhage or coagulation issues and cognitive impairment.²⁵⁴
 - Those that are perceived as barriers are:
 - Medical instability^{260, 270-272} for 76%²⁷³ to 89%²⁷⁴ of the health care partitioners (HCP) (91% of the nurses and 71% of the physicians in Lin et al.²⁶²). However, medical instability is not always a contraindication to EM according to guidelines.²⁷⁵
 - “At times the nursing staff does not want to mobilise the patient because the patient has an arterial pressure catheter in place. Although there are no actual contraindications if the patient is hemodynamically stable (PFG)”.²⁷⁵



- (Excessive) sedation²⁷⁴ for 62% of the HCP^{255, 270, 273, 276-278} for 43%²⁶² to 71%²⁷⁹ of the physicians, 24%²⁸⁰ to 28%²⁸¹ of the physiotherapists (PT), 74%²⁶² to 89%²⁸² of the nurses or 13% of the staff²⁶⁸.
- Drowsiness²⁷¹ or consciousness level (RASS score^v from day 1 to 2 was very low at “-3”)²⁷².
- Endotracheal intubation²⁷⁴ for 72% of HCP²⁷³ or for 21% of the PT²⁸¹.
- Inadequate analgesia.²⁷⁴

- Patient's attitude

The collaboration of the patient is sometimes required for EM, that is why several patient attitudes are mentioned as barriers to EM. These are labelled as patient disengagement²⁶¹, resistance²⁸³, discomfort²⁷⁶ or refusal^{253, 268}, inadequate support from patients (26% of ICU nurses²⁶⁹) or lack of cooperation.^{255, 260}

“The patient mental attitude is another factor. If the patient is sad, upset, suffering in pain, that will affect the conduct of early mobilisation for the staff. [Physician]”²⁶¹

“The patients refused to be mobilised. They will say to the nurses: ‘I’m tired, I have no energy to walk. I don’t want to sit on the chair.’”²⁸³

- Family reluctance^{255, 258, 270}

In ICU, relatives are important stakeholders who also have to be involved and may influence the decision to engage patient in EM. If they are reluctant, it is a barrier for HCP.

“Sometimes family members will be very concerned about what we are going to do, things like sitting out of bed is a classic one, for us we think it's important, but the families will be a bit like ‘but they're so sick’—NS”²⁵⁵

“I think for the most part we're probably undershooting the goals, so we're actually doing less in order to not ... freak out the family.” (RT)²⁵⁸

2. Structural/institutional barriers to EM

Structural barriers represent 18% of the identified barriers to EM in the review of Dubb et al.²⁵⁴

- Human resources: Physicians, nurses, and physical therapists are the primary personnel involved in patient mobilisation and physical therapy.²⁸⁴ As EM requires time, perceived barriers are often related to the human resources available, in terms of number, type, skills and experience. More precisely barriers are:
 - Limited staff^{260, 270, 272, 273, 275, 285, 286} for 41% of the ICU nurses²⁶⁹, limited nurses or PT^{253, 255, 257, 276} for 62% of HCP²⁷⁴, for 5.3% to 66% of the PT^{262, 281, 287} and for 44% of the respondents in a national US survey²⁸⁰.

^v <https://www.mdcalc.com/calc/1872/richmond-agitation-sedation-scale-rass>



"We have 30 something patients to mobilise, and only 3 physios then logistically it's not ever going to work. (M)"²⁵⁷

"...one physiotherapist, running around the room and dealing with chest regular standard stuff and is not available to do more time-consuming mobilisations. (PFG)"²⁷⁵

- Lack of experienced or trained staff.²⁶¹
- Availability of physiotherapist.^{253, 277, 283}
- The current workload²⁶⁰ for 77% of ICU nurses²⁶⁹ restrains the EM or the perceived impact that EM would impact the workload.^{260, 278, 288}

"You already have a busy day, you already have your tasks and order that have to be completed within a certain time frame."²⁸⁸

In addition, the workload is unpredictable and complexifies the EM.²⁷⁵

"The level of activity and the unpredictability in the context. It makes it very complex. (MDFG 1)"²⁷⁵

- EM is time consuming^{255, 260, 270, 272, 275, 284, 286} and more particularly for:
 - Nurses²⁸⁹ (71%²⁶² to 73%¹ of the physicians, 53%²⁷⁹ to 61%²⁶² of the nurses).
 - Physical therapists (67% of the physicians and 50% of the PT²⁷⁹).
 - Respiratory therapists (54% of the physicians²⁷⁹).
 - Related need to work overtime²⁷⁷ (47% of the nurses and 16% of the PT²⁷⁹), with an estimated time for EM between 16 and 45 minutes in general for mobilising the patient for the whole team²⁷⁹.

"Sometimes it takes me an hour to organise. I go a thousand times around ICU2 and ICU1. I am trying to find the [right] time, but I know the orderly cannot be sure of the time [their availability], so it is hard. (MDFG 1)"²⁷⁵

"Time constraint is a problem because you are taking care of another patient and the other patient is going for some procedures. So, it will take some time to facilitate the procedure and then it will take another time to mobilise the patient."²⁸³

The lack of time could lead to de-motivation of the PT to initiate the EM.²⁵⁹

"Motivation to do the job is the main problem. Even if you are attending to a patient who is now stable and recovering well, the type of patients you can do quite a number of sessions with, but you are just de-motivated and do not have time to do that, so you just tell yourself that you will attend to the patient when she/he is discharged to the ward... (PT)"²⁵⁹

- Technical resources:

EM requires specific material and this could be a barrier when it is lacking or damaged:

- Lack of equipment among 66% of HCP²⁷³ or need for specialized equipment^{253, 255, 270, 275, 276, 278} (only in nurses and physiotherapists²⁵⁷), for 32%²⁶² or 50%²⁶⁹ or 58%²⁸² of the nurses and for 24%²⁷⁹ to 29%²⁶² of the physicians.

"We don't have enough [equipment]. it becomes difficult for the nurses and the physiotherapists or anyone who wants to mobilise. We don't have enough so that is it. (MDFG 1)"²⁷⁵



"Is the patient actually appropriate, do I have the right resources, do I even have the right bed available? I recently had a patient who was ready to start sit to stand practice, but the bed was way too high. It took two days to get them transferred onto a different bed. (P)"²⁵⁷

"It is not possible for me to mobilise all the patients in the unit if they are eligible for mobilisation when you are only one (physiotherapist) ... the chairs we have in the unit are the standard chair with arm and back rests and these might be difficult to use with ICU patients because they are too low, and the arm rests are not adjustable (PT)"²⁵⁹

- Damaged or missing seating.²⁶³
- Financial support, depending of the country mainly Germany and UK (>50%).²⁷⁶

3. Barriers to EM related to ICU contextual culture²⁷⁰

ICU cultural barriers represent 18% of the identified barriers to EM in the review of Dubb et al.²⁵⁴.

Culture regarding EM, importance of it and the way to communicate and collaborate are sources of barriers:

- Specific ICU culture regarding EM:
 - Habits of mobilisation depend from one ICU unit to another regarding the use of endotracheal tubes (ETT), sedation or the removal of unnecessary lines or location choice of the lines.²⁵⁷

"I think it's the culture of the unit as I have worked in other units where we would get patients sitting in chairs with ETts. (M)"²⁵⁷

"The position of certain lines is frustrating, for example when the vascaths have been inserted femorally and you are ready to start them sitting, it's just basic planning. (P)"²⁵⁷

- Moreover, professionals, especially those who were risk-averse, were not prepared to adhere to the protocol to provide EM.²⁶¹

"Whereas the nursing staff is probably more worried about making sure that an adverse event doesn't happen under their watch. So, it's more of a safety short term goal, physiotherapists have got more physical rehabilitation long term goals. So, I understand that we're coming from different perspectives. (Physiotherapist)"²⁶¹

- EM is of low priority^{257, 260, 270, 274} in 12%²⁷⁹ to 29%²⁶² of the physicians and in 41% of the nurses²⁶² and 37% of a sample of US PT²⁸⁰ / competing priorities^{253, 255, 276}.

"I don't know how many times the physio comes past and it's like 'no he's on his way to CT' or no we're going to do a lumbar puncture now, and I think that's a common theme throughout ICU that we are trying to achieve for care within 24 hours a day (MD)"²⁵⁵

"In my unit [neurosurgical ICU], I think the priority now is their chest, I think the respiratory system is more important than anything else ... not that I am going to completely ignore mobilisation, I do mobilise but that is not my priority, my priority is the chest ... (PT)"²⁵⁹

"I think the tone of this prioritisation suggests that we are all bubbling away under their thinking that we should be mobilising these patients more. But we have prioritised it lower than perhaps other things. (N)"²⁵⁷



- Lack of buy-in^{255, 276, 288}: Staff needs to believe that early rehabilitation is beneficial. And by some clinicians the conviction or evidence is insufficient regarding the potential benefits.²⁷⁵

*"If you're a rehab team who wants to do this and you don't have buy-in by your nurses and physicians and respiratory, it's not gonna happen."*²⁸⁸

*"There are some staff in ICU that are all for it and are very keen for their patients to get physiotherapy and then there are some staff that might be a little bit more reluctant (PT)"*²⁵⁵

*"... the Salt Lake City study was not an RCT. It was an observational prospective study. We do have some RCTs as well, but you don't know whether it's because they had to change their sedation policy so that they could ambulate. Maybe that was the variable and not the ambulation. (PFG)"*²⁷⁵

- Communication among providers is not good.²⁷⁴
- Interprofessional team care barriers: lack of coordination, communication, and collaboration.²⁶⁰
- Lack of leadership/management^{260, 261, 270}
- Staff turnover²⁶⁰
- Uncooperative, resistive or disengaged team members²⁷⁸

4. Clinician-related barriers to EM

The clinicians have direct impact on the EM of ICU patients. In consequence many types of barriers were identified regarding their role, habits, perception, etc. of EM:

- Habits: Variation in individual nursing practice.²⁸⁹

- Believes about consequences for the patient: If they are not convinced by the potential benefits for the patients or if they fear for their safety, HCP will face barriers to engage in EM.

- Patient safety concerns^{253, 260, 270, 273, 276-278, 286, 288}, in 29%²⁶² to 42%²⁷⁹ of the physicians and in 60% of the nurses²⁶², such as risk of dislodgement or accidental removal of devices or catheters for 58% of HCP or the risk to cause patient physiological instability^{274, 278}.

*"There are, of course, subsets of patients that remain too critically ill just from hemodynamic instability, rising vasopressure requirements that they're just not candidates. The potential for harm is high ...but the important thing is that we recognize that as soon as a patient is able to do so, that we implement physical therapy."*²⁸⁸

*"They were nervous about losing lines and losing tubes, patients self-extubating and causing more harm to the patient than good but once they kind of got over that fear, they were able to work."*²⁸⁸

*"I feel there needs to be more education about it as it is still seen by some individuals as very 'extreme', unsafe and unnecessary in some units/areas and by some individuals."*²⁹⁰

*"EM is challenging because sometimes I am scared patient's haemodynamic parameters will worsen."*²⁸³

- The perception that rest equals healing.²⁶⁰



- Lack of perceived importance²⁶⁰ (25% in PT²⁸⁰). In Koo et al.²⁹¹, 68.8% of the respondents believed that early mobilisation is crucial or very important; in PT more likely than physicians (odds ratio [OR] 2.8, 95% CI: 1.3–5.6, p=0.006).
- Nurse-safety concerns could also be barriers to EM^{260, 276}, e.g. in general for 63% of HCP²⁷⁴ for 42% of ICU nurses²⁶⁹, or regarding injuries as musculoskeletal self-injury²⁷⁷, 71% of the nurses and 41% of the PT²⁷⁹ or staff safety in 18% of the physicians²⁷⁹.
- Believes about the consequence of EM on the workload:
 - EM requires increased effort.²⁵⁷

“We need to recognise that there is a degree of additional work that is associated with sitting patients out. (M)”²⁵⁷
 - Perception that it is time consuming.²⁷⁸
 - Perception that it would cause a risk to excessive stress at work²⁷⁷ for 65% of the nurses and 41% of the PT²⁷⁹.
- Training and skills:
 - Lack of skills of HCP to appropriately perform EM has also been identified as a potential barrier.
 - The training could be perceived as inadequate in general^{273, 274, 278}, the training specific for nurses (among 47% of nurses²⁶⁹), for HCP^{270, 273}, and for PT (29%)²⁸⁰ e.g. in equipment utilisation²⁵⁷.

“I think for me it’s very overwhelming going into ICU in the first place ... I knew that I wasn’t allowed to move the patient if this line was in, but I had no idea what it looked like, so training was really important for that. (P)”²⁵⁷
 - Inexperience²⁶¹ with EM is also perceived as a barrier.

“I think it is very important because it is a scary thing for a physio that has not got experience and it is a scary thing for the nursing staff.” (Physiotherapist)²⁶¹

- PT expertise.²⁷⁶

“... because you will see that it comes with the therapist’s years of experience, someone who recently graduated will not feel comfortable to mobilise a patient, especially during the acute phase, but for someone with more years of experience, they are not reluctant to mobilise the patient even when on a mechanical ventilator. (PT)”²⁵⁹

- Lack of self-efficacy and confidence in protocol implementation.²⁶⁰
- It is important that EM is carried out by a motivated team and if a patient faces a disengaged team, EM is more difficult to implement.²⁶¹
- Memory, attention and decision processes are required in performing EM, the lack of remembering and ability to choose the best care pathways was identified as a barrier to EM.²⁷⁵

“Like you could have a patient who like gets up in the chair most of the days, but he has a certain nurse for the whole weekend. and the patient doesn’t get up in the chair the whole weekend because they [the nurses] just didn’t think of it. (MDFG 2)”²⁷⁵

5. Protocol-related barriers to EM

The existence and quality of a protocol were cited in many studies as an important help for EM. As a consequence, if there is no protocol or if it is not known or adequate, it is considered as a barrier to engage in EM. There is than a barrier to use a protocol but also to develop or implement such tool.



- Availability:

- Unavailability of protocol^{260, 270} for 89% of the nurses²⁸² or written guidelines for 76% of HCP^{253, 273} and for 50% of the ICU nurses²⁶⁹.
- Lack of awareness and knowledge about the protocol.²⁶⁰

- Development and implementation:

- Protocol development cost (money and time).²⁶⁰
- Lack of conceptual agreement with guidelines.²⁶⁰
- Reluctance to follow protocol (due to previous adverse outcomes).²⁶⁰
- Lack of clarity as to who is responsible, steps needed to take, and expected standards for protocol implementation.^{259, 260}

“...even if you want to mobilise the patient, they will (nurses) ask you if that is what the doctor (general practitioner/physician) has recommended for that patient. If the answer is “yes”, they (nurses) are most likely to be cooperative but if that is not the doctor’s (general practitioner/physician) order then they are not keen to assist you on mobilisation... (PT)”²⁵⁹

- Content of the protocol

- Unclear protocol criteria.²⁶⁰
- Lack of confidence in evidence supporting protocol and the guideline developer²⁶⁰ or strength of evidence to support EM in ICU²⁵⁵.
- Lack of confidence in the reliability of screening tools.²⁶⁰

- Learning curve (possibility for the clinician to test guideline and observe other clinicians using the guideline easily).²⁶⁰

- Lack of consultation of the protocol for PT criteria (35%).²⁸⁰

6. Organisation-related barriers to EM

The organisation in the ICU itself is a barrier to use EM:

- Physicians’ orders required is a barrier for 58% of HCP.²⁷³
- Lack of care coordination.²⁷⁶
- Scheduling conflicts (i.e., patient off, at dialysis, and procedure).^{260, 289}

“Because if it’s not [a] scheduled [procedure] it can go 1 of 2 ways. You either leave [the patient] in bed until it happens, or you just get [the patient] up and hope and pray [transport] doesn’t come right away. (nurse)”²⁸⁹

- Inadequate time for EM in 58% of the nurses²⁸² and inadequate shifts in 74% of nurses²⁸².
- Lack of communication during bedside rounds²⁷³.
- Difficulty in identifying and contacting the appropriate people (only in physiotherapist and nurses²⁵⁷).
- Lack of accountability (only in physicians²⁵⁷) implying that mobility orders were not carried through

“I know I have asked to have a patient ambulating and I know others have as well and it doesn’t actually happen. You can write it on the chart and say let’s do it, but it doesn’t actually happen. (M)”²⁵⁷

- Delayed recognition of suitable patients to mobilise.²⁷³
- Lack of EM implementation and recording according to the checklist (90.4% of nurses).²⁸²
- When not yet implemented in ICU but under consideration, EM organisational barriers raised are the need for further planning (34%), competing priorities (32%).²⁷⁶



7. Environment-related barriers to EM

EM requires space without obstacles in order to be able to safely move. Barriers are therefore linked to the:

- Physical environment in general²⁶⁰, and in particular not enough physical space (for 18% of HCP)²⁷³.
- Presence of invasive lines in situ, for 45% of the nurses and 2% of the physicians.²⁶²

*"Definitely the lines, attachments part of the environment, and depending on how many machines the patient's attached can make it seem more or less achievable. [Physiotherapist]"*²⁶¹

*"Sometimes the lines ... you can't move around with them, they are so short that you have to disconnect completely, or things end up falling ... It's never a plan that everything is on one side of the bed so that you can easily manoeuvre...(PT)"*²⁵⁹

- Presence of equipment blocking corridors.²⁶³

FACILITATORS TO EARLY MOBILISATION

Here we describe what have been identified as facilitators or necessities for the practice of early mobilisation in ICU. Several of these are the opposite of the barriers identified above.

1. Patient-related facilitators to EM

Patient features and attitudes are enabling EM:

- Patient hemodynamic stability.²⁷⁸
- Reduced sedation.²⁷⁸
- Patient cooperation/alertness.²⁷⁸

- Family members attitude²⁵⁸ and implication²⁵⁷ have been identified as being rewarding and encouraging. In consequence, they increase patient mobilisation levels and tend to make EM initiation and coordination easier.²⁹²

*"It's very encouraging to the family to see that sort of a normal activity starting to be re-established. Everything else can be quite overwhelming and terrifying to them, so to see their loved one starting to sit, starting to stand, walk that's very encouraging. (PT)"*²⁵⁷

2. Structural / institutional facilitators to EM

- Human resources: Staffing levels: having an adequate^{278, 293} or higher^{257, 261} rehabilitation provider, including physiotherapists^{259, 288} is important to implement an early rehabilitation program.

*"Having two therapists covering the unit ... they help each other ... (PT)"*²⁵⁹

- Equipment:
 - Availability of appropriate equipment.^{261, 288}

*"You know you need appropriate equipment to be able to do these things you know you need wheelchairs, you need a portable vent, you know you need various different pieces of exercise equipment that you can use."*²⁸⁸

*"Another good thing in our unit is the availability of the hydraulic beds [electric beds] so you can prop up patients in bed. Those who can't actively come up to sitting independently ... you can at least prop them up in bed, and by doing that, you are having a positive effect on most systems of the body in that patient ...(PT)"*²⁵⁹



- Provision of more equipment²⁷⁵ (except in physician' perceptions²⁵⁷).

"Even having a permanent monitor down in the window bay there. You could walk along with a little "pleth" then plug them into a big monitor when you get there. . . . It's just little things like that I think would make life a bit easier. (N)"²⁵⁷

"Having the proper equipment to help assist them along with the patient treatment [is essential]. (Rehabilitation provider)"²⁸⁸

- Support and funding for EM program coming from the administration.²⁸⁸

3. ICU contextual culture-related facilitators to EM

Factors that are enabling EM mentioned in the literature are:

- A pro-EM ICU culture^{275, 293} or "Buy in" culture²⁸⁸.

"If you get buy-in from all of the different disciplines, it's definitely easy.(nurse)"²⁸⁸

The buy in culture includes clinician-related attitudes, beliefs and intention (see further).

"Speaker 1: And then it [presence of a dedicated team] also takes care of increasing the awareness of the team towards going in favour of early mobilisation because if you see a dedicated team. you act on it, it is part of our culture, and you are more prone to think about it for your next patient."²⁷⁵

- A shift in ICU culture during and following implementation.²⁸⁸

"I just think it seems so common sense now, it's like why weren't we doing this before? (coordinator)"²⁸⁸

- Staff satisfaction with early rehabilitation²⁸⁸ which includes the psychological benefits to staff of seeing patients out of bed and moving around²⁵⁵.

"To see those small improvements in a patient creates a lot of job satisfaction ... a rewarding feeling. (nurse)"²⁸⁸

- Liaising with medical teams (only in physiotherapists).²⁵⁷
- Leadership²⁸⁶ favouring EM.

"Patients are critically ill, so I think you kind of need always a leader who can guide you through potential situations ... because I can't see how we can run the program without a leader who kind of oversees everything. (coordinator)"²⁸⁸

- Having a mobility champion (only physicians^{257, 261, 293}) among other individual discipline champions²⁸⁸. According to the Cameron et al.'s review, such a champion oversees day-to-day program implementation and has access to upper management; aligning program goals with those of the organization; being considerate of staff workload; and having quantifiable benefits for stakeholders, staff, and patients.²⁸⁴

"I think having a champion, someone who's really pushing it through, pushing it forward especially on the physician side of things makes a big difference."²⁸⁸

"Speaker 1: I said that we need to clone [mentions the name of another nurse].

Others: (waves of laughter)

Speaker 1:.. but seriously, she's a champion, and she's motivated and. yeah, it's a facilitator. (MDFG 3)"²⁷⁵



- Senior level support²⁵⁷, mentoring, i.e. when a senior or more experienced professional acted as a guide to junior or non-experienced staff, including cotreatment of patients²⁶¹, working with experienced colleagues²⁹³ or motivated nurse²⁹².

"I think it is good for more junior staff to see that patients can actually do a lot more on the unit than previously that they thought they could." (Physiotherapist)"²⁶¹

- Opinion leader.²⁸⁸
- An expert who is motivated and skilled to assist staff in EM is perceived as a greater facilitator than a champion who is not involved.²⁷⁵
- Working together, being flexible, and cooperate.²⁷⁸
- Engagement of the whole team²⁷⁸, peer support²⁷⁵ or appreciation and encouragement is motivating for 42% of the PTs²⁸⁷.

4. Clinician-related facilitators to EM

Clinician-related factors that are enabling EM mentioned in the literature are:

- The attitude / attitudinal beliefs of the clinician:
 - Beliefs about consequences^{255, 293} and (expected) positive outcomes:
 - For the patient: the improvement in patients outcomes in relation to early ICU intervention was one of the biggest motivation factors among PTs in the study of Alqahtani et al.²⁸⁷. Moreover, positive outcome expectation was identified as a facilitator to engage EM in ICU staff^{275, 283, 288}, and this, regardless of the discipline background of the HCP (medical, nursing, physiotherapy)²⁵⁵.

"If I knew that every day I got my patient up like twice a day, if I saw that. you know I saw that it cut a week off their stay

in ICU, I would be. pushing that harder to get them up. (MDFG 1)"²⁷⁵

"If the patient can go home early because of EM. Why not? If we see the patient is getting better and better every day, then we feel that EM really helped, then we will carry on with EM."²⁸³

Expected benefits identified are for example^{255, 278}:

- Regaining the physiological and physical function, including strength and independence.
- The improvement of state, e.g. improving respiratory system.
- The prevention of the deterioration of function (functional decline and impairment or muscle weakness and wasting).
- The psychological benefits for patients who feel they have some control and autonomy over their care.
- Reducing icu and hospital length of stay.
- For the institution: financial savings by reducing ICU and hospital length of stay²⁸⁸

"Paying for extra staff, extra equipment, extra space to do these things actually decreases the length of stay so it increases the feasibility of it, the program working and being sustainable over a long period of time. (coordinator)"²⁸⁸

- Beliefs about ones' own capabilities^{258, 293} because early mobilisation is reported as a difficult therapy to deliver²⁵⁸.

"I would describe it as very important but also very challenging, to get the people up at such a ... critical time as their care." (PT)²⁵⁸



- Intention to do EM, i.e. intrinsic motivation and conscious effort of the HCP.²⁷⁵

“Nothing stops me from getting them up if they are able to get up. I will get them up if they can get up. no matter what. (MDFG 3)”²⁷⁵

- Perceived self efficacy: Goodson et al.²⁹⁴ observed that their barrier scores were lower with each additional year of work experience during the first 10 years. When the staff is experienced and confident, higher levels of mobilisation are achieved.²⁶¹

“Certainly, the staff have to be comfortable. They’ve got to ideally be experienced at least, have perhaps mobilised somebody before on the ventilator or even simulated it. I think that’s another important thing to help with implementation. (Physician)”²⁶¹

“[We need] confidence and experience, so you know how far you can push patients”—NS”²⁵⁵

- Training
 - (More²⁵⁷) practical training²⁸³, including continuing education.

“We know the benefits of EM but all of us need training about the EM protocol.” [FGD1-R3]”²⁸³

5. Protocol-related facilitators to EM

Protocol-related factors that are enabling EM mentioned in the literature are:

- The existence of a unit protocol.^{259, 275, 283, 293}

“... I use a mobilisation guideline called MOVE. I check the myocardial stability of the patient, looking at the ECG tracing that there are no signs of arrhythmias, infarctions or cardiac

arrest in the past 24 hours, check blood pressure and heart rate, then check on the orientation of the patient, patient not confused or agitated or sedated, is cooperative and able to follow commands, like you ask them to do something, and they cooperate. Vasopressor use: ... Are they on the lowest possible doses, and [they should] not have been increased in the past 24 hours; and lastly, the effort of the patient: Are they able to actively participate in the mobilisation or will it be more of a passive transfer by checking on the upper limb and lower limb muscle strength? They should be at least a grade 3...(PT)”²⁵⁹

“Well, if it’s protocolised. they should just be done, right. looking for contraindications, not for indications. And I think that’s the key. (PFG)”²⁷⁵

- Protocols regarding patient sedation^{259, 288} or sedation breaks²⁶¹.

“We have protocols, we have an awake cycle, within the sedation days, just to assess the GCS in the morning, unless the patient is completely restless, so they keep them sedated...(PT)”²⁵⁹

- Protocols regarding delirium assessment.²⁸⁸

“Not only did we start decreasing the use of sedation, we started assessing for delirium. (nurse)”²⁸⁸

6. Organisation-related facilitators to EM

Organizational factors that are enabling EM mentioned in the literature are:

- The acceptance to implement EM as standard care is a key for effective implementation²⁵⁹ (except for PT²⁵⁷).

“It should be the assumption that everyone should be just automatically sitting out of bed awake and ambulating, and



*then you have to default out of that. So, unless you opt out, then you would be expected to be awake and alert, SOOB and standing up. . . . If you make it the default that you do that, and then you have to have a reason for not doing it. (M)*²⁵⁷

*"... there has definitely been an improvement and when people walk in and see that we have put a ventilated patient in a chair, no one is having a heart attack. (PT)"*²⁵⁹

- Having a multidisciplinary team that can complement each other.²⁸⁸

*"You have to have a strong multidisciplinary team, just don't assume that it's gonna be a physical therapist doing all the work. (nurse)"*²⁸⁸

*"You need the doctors, you need the nurses, you need physical therapy, you need occupational therapy and you need speech, which is SLP, and rehab techs ... for a good team."*²⁸⁸

- Having good teamwork^{275, 283} allows to be efficace.

*"EM is an interdisciplinary approach and should be done with cooperation and teamwork. So, we [nurses] have to collaborate with the doctors, physiotherapist, respiratory therapist. [FGD1R]"*²⁸³

- Having a dedicated mobility team^{257, 275} or dedicated rehabilitation personnel^{261, 288}.

"If we would have a dedicated team [for early mobilisation], like not using the [regular] orderlies, that will take care of all the probabilities and the uncertainties the regular team takes care of. It lessens the problem of the communication

*because it is a dedicated team that communicates with you. (MDFG 1)"*²⁷⁵

*"...I have worked so long in the unit with the nurses so, I have a very good relationship.... they know how we operate, and they know that if I want to mobilise the patient, I will help them with other nursing duties if they help me... You really grow a relationship with the other staff in the unit, so you can negotiate with them if you want to mobilise a difficult patient and they are not too keen... so you really create a nice relationship, and that is always an advantage... (PT)"*²⁵⁹

...such as a specific physiotherapist assigned to ICU instead of a rotating model.^{258, 259}

*"We should have an additional physiotherapist around to assist with the process because the demand for our nursing staff for a variety of other things is already pretty high. So, I think having additional dedicated staff for the process of mobilisation would also be important. (Physician)"*²⁶¹

*"Having a PT that was dedicated to our unit makes a huge difference.... If you just had champion of the physician but you didn't have the therapist who was involved, it wouldn't happen. (Rehabilitation provider)"*²⁸⁸

- Working with experienced staff: Lago et al.²⁶¹ stated that higher levels of mobilisation were achieved in ICUs in which confident and experienced staff were part of the team.
- Working with a team action planning²⁵⁷ and in coordination²⁷⁵.

"I think it's functional, and so therefore perfect, how about I get in there and I can help you with that transfer but also at the same time they're doing something it's very important



for their nursing care but very good for the patient's psychological state. So, I think combining our exercise therapy with something functional is often the best way. (P)"²⁵⁷

"In terms of organising the planning, I would personally put that higher partly because it's just such low hanging fruit. It's so easy, organisational things we can change almost easily. (PFG)"^{275, 295}

- Interdisciplinary team communication: Need for cooperation and communication between different team members^{275, 288}.
- Follow-up failures (only physicians).²⁵⁷
- Involving patient family (only physiotherapists).²⁵⁷

7. Environment-related facilitators to EM

Environment facilitators are mirroring the environment-related barriers; spatial organization of the ICU allow unobstructed movement²⁵⁹ and an adapted ICU room environment (space, line, attachment) to avoid accidents.²⁶¹

STRATEGIES TO OVERCOME BARRIERS TO EARLY MOBILISATION^{254, 296}:

Next to facilitators that were identified in the various studies, some authors have search for strategies to overcome barriers to EM. Dubb et al. identified 70 strategies to overcome barriers in their review.²⁵⁴

1. Patient-related barriers to EM^{254, 296}

Clinical barriers could be overcome using a stepwise approach, and depending on the type of barrier strategies should target:

- Pain assessment and management before mobilisation;
- Regular assessment of the clinical status of the patient;

- Reduce sedation²⁵⁴, and use new sedative agents and techniques such as daily sedative interruption to allow early rehabilitation²⁸¹;
- In terms of medication: avoid medications with long half-life, avoid use of antipsychotics and reduce the use of benzodiazepines;
- Team meetings to discuss the severity of the patient status and related appropriateness of EM;
- Screening of patient by the PT: for pain, for delirium and nutrition;
- Regarding the respiratory aspects, parameters of the ventilator settings could be adjusted for mobilisation;
- Use of EM protocols including safety criteria, or sleep protocols to improve sleep quality;
- Patient denial, lack of motivation or anxiety could be avoided or limited by patient education and encouragement or discussing the treatment plan with the patient²⁵⁴ and the involvement of family in goal setting²⁵⁵.

2. Structural / institutional barriers to EM

- Lack of human resources could be obviously compensated by foreseeing additional staff (including PT and OT) and or design an independent mobility team and lack of (appropriate) equipment by purchasing it. A financial modelling of economic benefits could be used to increase funds for staffing;
- Training for appropriate use of equipment would increase its use.

3. Barriers to EM related to ICU contextual culture

- In order to make an ICU culture changing, a structured multidisciplinary effort, with clear communication and recognition of the importance of early mobilisation and rehabilitation is required.²⁹⁷ Ongoing education and training of the staff is an orientation to improve it.



- Making early mobilisation the standard of care should reinforce the 'EM oriented ICU culture' and could be promoted by foreseeing an automatic EM order.²⁸⁴
- Finally ,the creation of a mobility team could reinforce importance of early mobilisation in the ICU culture. And timely feedback about successes should create a positive virtuous cycle.

4. Clinician-related barriers to EM²⁹⁶

- By interdisciplinary teamwork, EM mobilisation could be more acceptable and skills could be improved.
- The unclear job expectations and responsibilities should be overcome by implementing interprofessional meetings and rounds, and sharing clinical responsibilities.
- A team-centred approach increases engagement and was therefore identified as helpful as well as training and education about the importance of and procedures to carry out regarding an EM programme.²⁸⁸

"Having all these team members around be supportive of us working with the patients early on is definitely helpful (rehab)"²⁸⁸

"After going to all the teaching, they were all very motivated to do things right(..). When people know why we are doing it that helps a lot. (coordinator)"²⁸⁸

- And the use of strong high quality evidence to start and sustain early mobilisation is a way to improve such programme in ICU.²⁸⁸

"Having the data support what you're implementing beforehand and after ... helps keep the staff motivated to continue the project. (nurse)"²⁸⁸

"You can't debate the evidence that demonstrates that there's a benefit to early rehabilitation. It's like debating the sky is blue. (rehab)"²⁸⁸

5. Protocol-related barriers

- By developing protocols and review safety criteria, barriers could be alleviated.
- *"Studies suggest that the development of patient population specific inclusion and exclusion criteria increases adherence to the protocol"*(Barber²⁵⁷, 2015 p.181)

6. Organisation-related barriers to EM

- In order to shorten the time to first mobilisation, one could reduce the time to a physician order for mobilisation by using methods such as automatic provision of an order or removal of default orders for bed rest (see also above, ICU culture).

"Making daily mobility the standard of care, with exceptions only for patients with true contraindications, would raise levels of mobility: It should be the assumption that everyone should be just automatically sitting out of bed awake and ambulating, and then you have to default out of that. So, unless you opt out, then you would be expected to be awake and alert, SOOB and standing up. . . . If you make it the default that you do that, and then you have to have a reason for not doing it. (M)"²⁵⁷

- Planning and coordinating patient discharge should avoid to discharge patient before the start of the mobilisation.



7. Environment-related barriers to EM

Portable devices, secure lines and drains could facilitate EM. In addition, environmental changes to encourage patients to do EM, such as natural light and exercises on the veranda or outdoors.²⁶¹

Key points

- Early mobilisation (EM) has no unique definition.
- Patient related-barriers to EM are explained by medical limitations, medical instability or contraindications that impair the intervention.
- Sedation, consciousness level of the patient, endotracheal intubation or inadequate analgesia are perceived as clinical barriers.
- The attitude of the patient and the family regarding EM also comes into play.
- The structural barriers identified are related to the availability of human resources (nurses, physiotherapists and /or physicians in terms of time, skills and experience and (specialised) equipment). Financial support for EM may also be lacking.
- ICU culture and ICU culture regarding EM would facilitate or not EM.
- The perceived benefits of EM in terms of evidence also play a role.
- The lacking of communication, coordination and collaboration among providers may negatively impact the implementation of the EM.
- Leadership, staff stability and team commitment were also identified as facilitating or impairing EM.
- Clinicians' habits or beliefs about consequences for the patient when performing EM, concerns about own safety or the safety of other members of the team will influence clinicians' attitude to EM.
- Training and skills of the clinicians were identified as barrier or facilitator, as well as the level of experience with EM and the

perceived self-efficacy. Motivation of the clinician and the team to engage in EM is a key factor.

- Reported barriers are that such a protocol requires time and money to be developed. In addition, its implementation requires adherence and clarity about responsibilities, steps and standards. The content of the protocol has to be supported by evidence.
- In terms of organisation, the bedside rounds are delayed by the necessity of a physician's order for the recognition of suitable patients.
- Environment is important to improve EM because it could be a barrier when patients are not able to move safely because of the lack of space, the presence of lines or equipment blocking corridors.
- In general facilitators are related to barriers: reduction of sedation, clinical stability of the patient, patient and family's attitude, sufficient resources and appropriate equipment, positive culture of the EM in the ICU, good communication, good leadership and existence of a EM protocol, all in a ICU spatially organised to allow unobstructed movement.
- Other identified facilitators are: having a dedicated mobility team with a mobility "champion", a positive attitude of the HCPs, the intention to do EM and the perceived self-efficacy of HCPs. Training, including practical training or working with experienced staff reinforces these factors. Implementing EM as standard of care is essential.
- The existence of a quality protocol or written guidelines was cited in many studies as an important help for EM: it should be available and HCP have to be aware of its existence and use it.
- Useful strategies to overcome barriers include an approach involving assessment (pain, clinical status, delirium, etc.), targeted light sedation or modification of sedative agents, patient consultation and the use of EM protocols. Patient education and family involvement in EM goals improved EM initiation. The provision of adequate human



and material resources and training of the staff could alleviate some barriers as well as initiative to modify ICU EM culture. Delay in mobilisation can be overcome by using automatic prescription or by removing default prescriptions for bed rest. To motivate patients, environmental changes such as natural light and exercises outside of ICU have been described.

5.3.3.2 Pharmacological intervention: sedation

Sedation and analgesia are classically provided and widely implemented in critically ill patients to increase compliance with invasive and uncomfortable procedures and to prevent or alleviate pain, discomfort, anxiety and stress. In consequence, sedation protocols, daily sedation interruptions and analgesia-based strategies may increase patient agitation, discomfort and adverse events.²⁹⁸

Sedation is as such a barrier in PICS prevention (see before) but in this section we will focus on the intervention itself. Compared to EM, we found less literature on sedation barriers and enablers. Here again we classified the type of barriers/facilitators in patient, structural, cultural, clinician, protocol or environment-related barriers.

BARRIERS TO SEDATION PROTOCOLS AND SEDATION INTERRUPTIONS

Barriers to daily sedation interruption that were identified did not differ between sedative agent preferences in Tanios et al.²⁹⁹

1. Patient-related barriers to sedation protocols and sedation interruptions

- Restrictive parameters and contraindications:
 - Brain injuries: In patient with cerebral lesion or brain injuries, it is difficult to identify the source of agitation (i.e. pain, delirium and discomfort). Moreover, the patient's altering consciousness level is perceived as unpredictable. This impairs the decisions on the appropriate sedation–analgesia management.²⁹⁸

“Medical trainee1: Those that are chronic drug users, they are quite hard to manage, because they'll take you to use second-line medication ... it is hard to wean them, to get a balance, to get them to the point that you can extubate them safely

Consultant: And the underlying condition is going to make them delirious or they are demented, or both, so you've got to make sure you've got not too heavy a hammer but you may need a degree of chemical restraint in order to keep things okay until their brain failure achieves its best recovery.

Medical trainee: I think what we haven't cracked is, what we do with people who A doesn't work, B doesn't work or C doesn't work. And maybe next door (other patient) it does...I don't know.

Nurse: I think it is still very early for that. I think we are finding our feet with it.”²⁹⁸

- Moreover, “the lack of appropriate assessment tools, in particular for pain, to identify the source of agitation contributed to this clinicians' uncertainty” (Kydonaki 2019²⁹⁸, p.5).
- Mental condition: Sedation could be commonly increased to manage agitation overnight to ensure patient safety.²⁹⁸

“Advanced nurse practitioner: There's a difference at night as well, like you're stopping sedation during the day, quite a lot of times they ask you to increase it again at night because of agitation, and sometimes to keep them safe.”²⁹⁸

- Mechanical ventilation is perceived as requiring sedation, with 30.5% of respondents indicating an intention to sedate all patients receiving mechanical ventilation. Nevertheless for 48% of respondents it is not.³⁰⁰ When patients with an underlying mental condition are intubated, they are reported to be kept sedated until they are ready for extubation.²⁹⁸



- Consequence for the patient: Regarding the use of daily sedation interruption, 26% of HCP fear potentially respiratory compromise. In addition, 20% of HCP indicated concerns about patient-initiated device removal (extubation, catheter removal, ...).²⁹⁹
- Family: For around 44% of nurses, patients' families requested sedation or influenced their sedation practices.³⁰⁰

2. Structural / institutional barriers to sedation protocols and sedation interruptions

Although staffing levels are reported by 53% as not influencing sedation practices during mechanical ventilation for the majority of the nurses, 45% of respondents indicated that they had sedated an intubated patient in order to complete other essential nursing functions.³⁰⁰

3. ICU contextual culture-related barriers to sedation protocols and sedation interruptions

- A lack of trust between nurses and medical staff, especially regarding sedation management, could be a barrier. Indeed, nurses reported being blamed and challenged in the case of an adverse event (e.g., unplanned extubation).²⁹⁸

"Nurse: No-one believes you when you say they (the patient) tried to punch me.

*Physiotherapist: I would agree...if somebody dislodges a tracheostomy, you do feel a bit guilty."*²⁹⁸

- In UK, staff (incl. nurses, doctors etc.) stated that, historically, deep sedation was required for the management of an intubated and ventilated patient in the ICU. This created a culture of deep sedation often resulting in a reluctance to mobilise these patients because of fear of dislodging their endotracheal (ET) tubes.

"I think if they've got the mask or they have got a [tracheostomy], you slightly do push them further than you would if they had an ET tube." [ICU nurse, F]²⁶³

4. Clinician-related barriers to sedation protocols and sedation interruptions

- Demographics, experience and certification of the HCP: Sedation practices, intention to sedate and attitudes regarding sedation are associated with age, experience and certification in the study of Guttormson.³⁰⁰
 - Sedation practice is related to the age of the clinician ($p < 0.001$), experience of the nurse and having a CCRN (certified acute or critical-care nurse) certification (2.68 vs. 3.08; $p < 0.001$).
 - Attitudes is related with the age and the experience of the HCP ($p = 0.02$): with increase of these variables, propensity to administer sedatives is lower and the evaluation of sedative medications' effectiveness in minimizing distress is less positive.
 - Intention to sedate all patients receiving mechanical ventilation also varied by age, with nurses, aged more than 50, more frequently not intending to do so, compared to nurses aged 31 to 40. The same association is stated according to the increasing experience of the nurses. Moreover, CCRN-certified nurses were more likely to disagree or strongly disagree that they intended to sedate all patients receiving mechanical ventilation ($p < 0.001$).³⁰⁰
 - The use of daily sedation interruption is impaired by the lack of nursing acceptance for it according to 22% of surveyed HCP.²⁹⁹
- Influence of other nurses' knowledge or attitudes on sedation practice is reported by around a third of the responding nurses.³⁰⁰
- Training: The lack of continuous development and education is reported as a barrier to optimal sedation–analgesia practice by interviewed clinicians. Reported educational gaps are the need to focus on the management



of suboptimal sedation, the use of assessment tools, sedation approaches for specific clinical conditions, (such as psychiatric patients) and a broader understanding of pharmacokinetics and pharmacodynamics.²⁹⁸

*“Consultant: So, there is a huge problem for education. People sometimes have to take their own time to be able to educate; and nurses don’t get that time.
Nurse1: ... the only education that we have to do, is to try and sort it ourselves.”²⁹⁸*

5. Protocol-related barriers to sedation protocols and sedation interruptions

The three most common perceived barriers in a survey among HCP (who had a sedation protocol in place) preventing its use were a lack of a physician order for the protocol (38% HCP), a nursing preference not to use the protocol (15% of HCP), and situations where the ICU caregiver would like more control of sedation than a protocol can afford (11% of HCP).²⁹⁹

More globally, documentation of care plans with prescribed sedation dosages and levels, and plans for failure are reported as means to encourage nurses to act autonomously and support their decisions. When it is not standardised, it is hindering information flow and communication among clinicians.²⁹⁸

6. Organisational-related barriers to sedation protocols and sedation interruptions

- HCP regret the absence of an individualised, holistic and target-driven approach to sedation practice. They indicated that such an approach could provide an explicit plan of sedation management with set of daily goals and feedback on patient progress and would promote communication among clinicians. Indeed, currently this lack is allowing debates and inconsistencies between the nurses and the medical staff”.²⁹⁸

*“Consultant: The other bit that kind of gets me and I am probably pretty guilty of this; is failure to plan for failure. Because, I will say ‘great wean them off’ but I don’t actually say what happens if you don’t wean them. You guys probably feel a bit unsupported.
Nurse: The thing is when I have asked to re-adjust the dosage, nobody has ever denied it to me and said, ‘oh no he can’t go up’”.²⁹⁸*

- When the workload is increasing with new admissions or interventions, nurses tended to increase sedation or delay sedation interruptions to ensure patient safety.²⁹⁸ In the study of Bannon et al.²⁶³, staff reported using higher doses of sedation to maintain patient safety especially when covering for staff breaks, transfers, or patient care.

“...just before Christmas there were a couple of days we just couldn’t do sedation holds on patients, because there wasn’t physically staff here. (Nurse)”²⁹⁸

- Moreover, it is easier to perform patient care activities, administration of medication and administrative tasks when a patient is sedated. That is why weaning patient off-sedation is often delayed.²⁶³
- Synchronising sedation breaks in all patients at the start of the day shift is difficult and challenges the management of patient’s agitation as a result of this.²⁹⁸

*“Nurse: After the wash, after breaks when you have got a good couple of hours with your patient and you can just slowly reduce it or stop it; rather than worrying that you are going to go for your morning break and leave a nurse struggling with your patient and their patient.
Consultant: I think if at the end of the day, it has not been tried, it’s unacceptable. But I think you are right, we need to change our culture; if you can justify why, you should just do it when it is suitable.”²⁹⁸*



7. Environment-related barriers to sedation protocols and sedation interruptions

The lack of space and the artificial ICU environment, with e.g. lack of windows to allow daylight, is engendering agitation in patients. And in small ICUs, patients are situated too close to each other (e.g. curtains between two beds), their psychological wellbeing can be affected by an agitated patient who is at the next bed space. In that case, there is no sense of calmness that would allow the patient to relax. On the other hand, large ICUs had reduced visibility of patients and reduced proximity to observe the agitated patients.²⁹⁸

*“Nurse: You’ve just got to shout really loudly to get help and we do have individual cubicles which are quite isolated, so we try not have agitated patients within there.
Consultant: And also, just the architectural design, our visibility, there are concrete pillars in front of them, so these are issues which alter the ability to communicate.”²⁹⁸*

FACILITATORS FOR SEDATION PROTOCOLS AND SEDATION INTERRUPTIONS

As mentioned as a barrier, an individualised, holistic and target-driven approach to sedation practice would provide an explicit plan of sedation management with set daily goals and feedback on patient progress and would promote communication among clinicians.²⁹⁸

Bannon et al.²⁶³ also identified some facilitators for sedation minimisation, particularly in less experienced staff:

- Protocols, guidelines, targeted sedation.
- The use of non-verbal pain scores such as Critical Care Pain Observation Tool (CPOT) allows to better control pain and reduce the need for higher sedation.
- Identification of suitable patients for a sedation interruptions during an evening ward round on the previous day.
- Targetting a specific score (for example, 0 alert and orientated), when using the Richmond Agitation Sedation Score (RASS) for monitoring sedation scores in order to reduce the amount of sedation administered overall.
- Communication training and availability of tools would be useful to help meeting patients' pain and care needs.

Key points

- Sedation is a barrier to EM but also a risk factor of PICS as such.
- The identified barriers to daily sedation interruption did not differ between sedative agent preferences.
- There are restrictive parameters or contraindications to sedation breaks.
- HCPs fear the consequences for the patients (removal of catheters, extubation, anxiety...) and reported they could be influenced by families attitudes regarding sedation.
- Sedation may sometimes be not interrupted because it allows to have time for other essential nursing functions (for instance in period of increased workload).
- There is a culture of deep sedation in some ICUs that causes reluctance to change procedures. Nurses are afraid to be blamed in case of adverse events resulting from sedation breaks.
- Sedation practices are also associated with age and experience of the staff: increase of these variables, propensity to administer sedatives is lower. Knowledge on sedation is also influencing the practice of interruptions. Training is thus important.
- Like for EM, the absence of a protocol or physician order and the preference of the nurses not to use the protocol are barriers to sedation breaks. And further, the absence of an individualised,



holistic and target-driven approach to sedation practice are barriers to sedation practices and prevention of PICS.

- Synchronizing sedation breaks in all patients is difficult.
- The ICU artificial environment is not helpful to keep patients unagitated. It may result in sedative increase.
- Targeted sedation, use of a non-verbal pain score, systematic identification of eligible patients for sedation breaks, use of scales for monitoring sedation facilitate the sedation breaks.

5.3.3.3 Prevention of delirium

Nurses and physicians in intensive care units have an important role in prevention, early diagnosis, and taking care of patients with delirium. Family could also help in prevention of delirium.

To note that the management of delirium is sometimes managed as a multicomponent bundle in itself. The one for delirium management in critically ill patients is comprising (1) education and family participation, (2) sedation minimisation and pain, agitation, and delirium protocol, (3) early mobilisation, and (4) environmental interventions for sleep, orientation, communication, and cognitive stimulation.²⁶³

BARRIERS FOR DELIRIUM PREVENTION AND ASSESSMENT

Regarding the 'multicomponent delirium bundle', difficulty to communicate with the patient because of intubation and upper limb weakness was identified as a barrier to implement many components of the bundle. Indeed, patients feel physically unable to participate or rapidly became frustrated when the staff is not able to understand them.²⁶³

"No way to communicate because [he] couldn't even move a finger and even if [he] could, there wasn't a fingerboard" [patient FG]."²⁶³

1. Barriers for prevention of delirium

Non-pharmacologic activities that HCP can perform to prevent delirium are: to turn room lights on during the day and off at bedtime, open the window blinds in the room during the day, give patient earplugs, give patient eyeshades, talk with the patients and ask them specific questions as a way to stimulate cognitive activity, remind patients where they are or play music in the room. They can also ask family to bring in eyeglasses and hearing aids.³⁰¹

Nevertheless, Smithburger et al.³⁰¹ found that nurses reported as a reason not to perform prevention activities, that their patients were too ill to participate in delirium-prevention activities, whereas physicians most commonly invoked that they were too busy to engage in delirium-prevention activities with patients.

Family involvement in delirium prevention

Family could assist with delirium-prevention activities (for what 93% of surveyed physicians and all nurses agreed) in Smithburger et al.³⁰¹ study. In Bannon et al.²⁶³, family presence was perceived as creating a sense of familiarity and safety for patients. Relatives could be used to assist with communication, orientation, personalising music selection, and personal care if appropriate training and support was available.

"I've seen people who I thought were tipping into delirium actually end it in a much shorter period because of the presence of familiarity and safety around them. [Clinical Psychologist]"²⁶³

Nevertheless, in the Smithburger et al.³⁰¹ survey, it appeared that only half of surveyed physicians and nurses reported they discuss delirium or delirium prevention with family members. Barriers they mentioned impairing them to talk with families are that they believe families do not understand about delirium and prevention ($p < 0.01$) and that family members could accidentally harm the patient ($p = 0.04$). Moreover, they think that stress and anxiety would affect family involvement in preventive care. These barriers are more commonly cited in nurses than in physicians.



They reported that patient family is not educated about delirium or prevention. They attribute it to the lack of time of nurses to explain delirium or delirium prevention or that they don't even think about doing it.

2. Barriers for assessment of delirium

In the study of Biyabanakiet al.³⁰², it appeared that despite the presence of delirium evaluation guidelines, nurses seem not to be familiar enough with the delirium screening tools and do not use these tools in their clinical care.

A reason is that nurses are not required to screen patients for delirium. Another one is that it is difficult for a patient to communicate when (s)he is intubated and in consequence for the nurse to interpret the assessment. Sedation impairs also the screening.

In the Nydahl et al.³⁰³ survey among ICUs in German-speaking countries, lack of time and missing knowledge about delirium and its assessment were the most cited barriers among nurses and physicians to explain why they do not screen for delirium.

3. Interventions for delirium prevention and assessment

In the barriers of the implementation of the delirium bundle, Bannon et al.²⁶³ identified that anxious relatives often created a barrier to the delivery of interventions in two ways; they asked excessive questions that increased staff workload and created a chaotic environment for patients.

When patient family could contribute, HCP think that relatives do not because³⁰¹:

- They do not understand about delirium and prevention, or their level of understanding is below what is needed to prevent delirium.
- They believe the family could accidentally harm my patient, fearing of the setting, including machines, catheters, and ICU sounds.
- Of the stress and anxiety associated with preventative care.
- They are apprehending about getting in the way of health care providers.

- The family does not want to participate.
- No family member visit the patient.

In the family survey, respondents named indeed these barriers³⁰¹:

- They fear of hurting loved one.
- They feel uncomfortable with all of the machines in the room.
- They are afraid to pull out an intravenous catheter or tube.
- They have concerned that the health care staff may get angry or annoyed.
- They think they will get in the way of the health care staff.
- They feel like they do not know how to help.

FACILITATORS FOR DELIRIUM PREVENTION AND ASSESSMENT

The main facilitators we found are related to the family involvement during ICU patient stay.

Family involvement could be facilitated by appropriate training and support²⁶³, e.g. one-on-one education with a health care provider that should also reduce fears³⁰¹ and anxiety²⁶³. Although timing in the patient's illness trajectory would be crucial to enable retention of information.²⁶³

Visiting policy also helps in involving family: the family presence could be encouraged by facilitating more flexible visiting hours³⁰¹ that also have the benefit to spread out the visits over day avoiding too many people at the same time and tiring patient²⁶³. In addition, it is useful to allow family to assist with care, orientation, mobilising, choosing music, and bringing in communication materials.²⁶³

The provision of additional supportive staff, and more in-service education about sedation and its effects were also identified as facilitating delirium prevention and assesment.²⁶³



STRATEGIES TO OVERCOME BARRIERS FOR DELIRIUM PREVENTION AND ASSESSMENT

A one-on-one discussion would create an opportunity for health care providers to specifically address family fears, particularly about getting in the way of a provider while performing delirium-prevention activities.³⁰¹

Key points

- Delirium is a risk factor of PICS and is a target of the ABCDE bundle. Nevertheless the management of delirium is sometimes approached as a multicomponent bundle in itself.
- Barriers to prevent and manage delirium are linked to the difficulties to communicate with the patient and weakness of the patient.
- Workload is an additional factor impairing delirium prevention.
- With regard to the role of families in the prevention of delirium, HCP reported as a barrier that family members may not understand about delirium and prevention. In addition, they miss time to educate them. They also fear that family members could accidentally harm the patient or that stress and anxiety would affect family involvement.
- These are also the reasons why families report to do not participate in the management of the delirium itself, with also the fear to disturb the HCP.
- Lack of time and missing knowledge about delirium and its assessment impair delirium screening by HCP.
- To facilitate family involvement, one-to-one training and support are useful as well as visiting policies with flexible visiting hours. It would be useful to allow family to assist with care, orientation, mobilizing, choosing music, and bringing in communication materials.
- Additional supportive staff is also helpful.

5.3.3.4 ICU-diaries

Diaries are used to improve the quality of life of patients during an intensive care unit stay and their loved ones (see section 3.3.4) We only identified one study about barriers and facilitators to the use of diaries.³⁰⁴ In this study they propose diaries to any patient at high risk for the development of PICS who is mechanically ventilated for more than 48 hours or if the patient is delirious or deemed to be at high risk for delirium by the clinical nurse.

BARRIERS IN USING DIARIES

Concerns of ICU providers in using diaries were related to:

- Professional liability (because of the difficulty to receive formal consent from patient and family)
- Risk that diary could contain medical information that can be read by visitors
- The publication of pictures on social media
- The possibility that the diary could contain complains written by the family
- The destination of unwanted diaries or diaries of patients who passed away

Operational barriers were:

- The practice change
- The awareness of a diary for a patient
- Time to write the first entry (detailing how the patient arrived in ICU)
- Hesitance to initiate the diary when extubation is foreseen in the next 48h.



FACILITATORS IN USING DIARIES

- The designation of diary champions to encourage team and family to write in the diary.
- Targeting 1 entry per shift, at the end of the shift or after the intervention for the physical, occupational or speech therapists. For the relatives they are encouraged to write when the patient is in a procedure.
- Make the existence of the diary visible using signs on the door or mentioning it in the assignment board.

STRATEGIES TO OVERCOME BARRIERS

- To ensure liability, a participation agreement, rather than formal consent, on the first page of the diary has to be completed. *"If acceptance is not obtained by the power of attorney (POA) at the initiation of the diary, it is obtained retrospectively when clinically appropriate. The acceptance form details the right to continue or stop the diary at any point, and that the patient and/or family is responsible for maintaining the diary and its safekeeping once it has been handed over to them."* (Rogan 2020³⁰⁴, p.3)
- Description to conserve confidentiality is described on the first page of the diary, within the entry instructions limiting the entry of sensitive medical information and not part of the health record.
- Designation of standard ICU diary location in the unit.
- Inclusion of standards photos of the ICU room from the patient perspective and photos of the noisy equipment. Additional photos of the patients could be included with specific consent of the patient or family.
- Entry are daily reviewed by a team member to take complains in consideration. In addition, patient and relatives are invited to notify orally directly any concern to the team.
- Unwanted diaries are stored in a secure location during 1 year. If it is still unwanted after this delay, it will be destroyed.

- If the patient dies, the diary is offered to the relatives.
- A standard operating procedure was developed to answer all questions of the staff and the family.

Key points

- Diaries are used to improve the quality of life of patients during the ICU stay and their loved ones.
- Barriers to use diaries are related to concerns about privacy of the patients, professional liability and destination of unwanted diaries or diaries of died patients.
- Strategies to overcome these are suggested as the use of a participation agreement instead of formal consent that could be confirmed retrospectively, instructions in the diary itself about how to conserve confidentiality.
- Operational barriers are related to practical aspects such as the necessity to change practices and when and how to write first entries.
- A diary champions is facilitating as well as targeting minimal entries per day and clarifying who and when should do it.
- Making the existence of the diary visible using signs on the door or mentioning it in the assignment board improve its completion.
- Standards ICU diary location in the unit should help to find and use it.
- Standard photos and review of the entries by a team member should make the diary useful for the team in case of complaints.
- Process to transmit, conserve or destroy diaries have to be foreseen.



5.4 Limitations

The literature on barriers and facilitators consists of literature review, cross-sectional prospective survey and quantitative or qualitative analysis. This is the best level of evidence available on these research questions. Qualitative data collection allows for more spontaneous responses than quantitative survey. Indeed, in the latter, questions are often closed with suggestions for the choice of one or more items. This is more oriented and may lead participants to choose barriers that they have not previously realised or should not spontaneously consider.

The diversity of the frameworks and tools to collect data make a strict comparison or an integrated analysis difficult. That is why we come up with a list of barriers for which we do not assess the level of the evidence in more depth.

6 PREVENTION OF PICS IN BELGIUM

The aim of this section is to describe what an ICU is in Belgium, to describe and quantify the risk factors for PICS in Belgium and highlighted what is known about PICS prevention in Belgian ICUs.

6.1 Intensive care units in Belgium

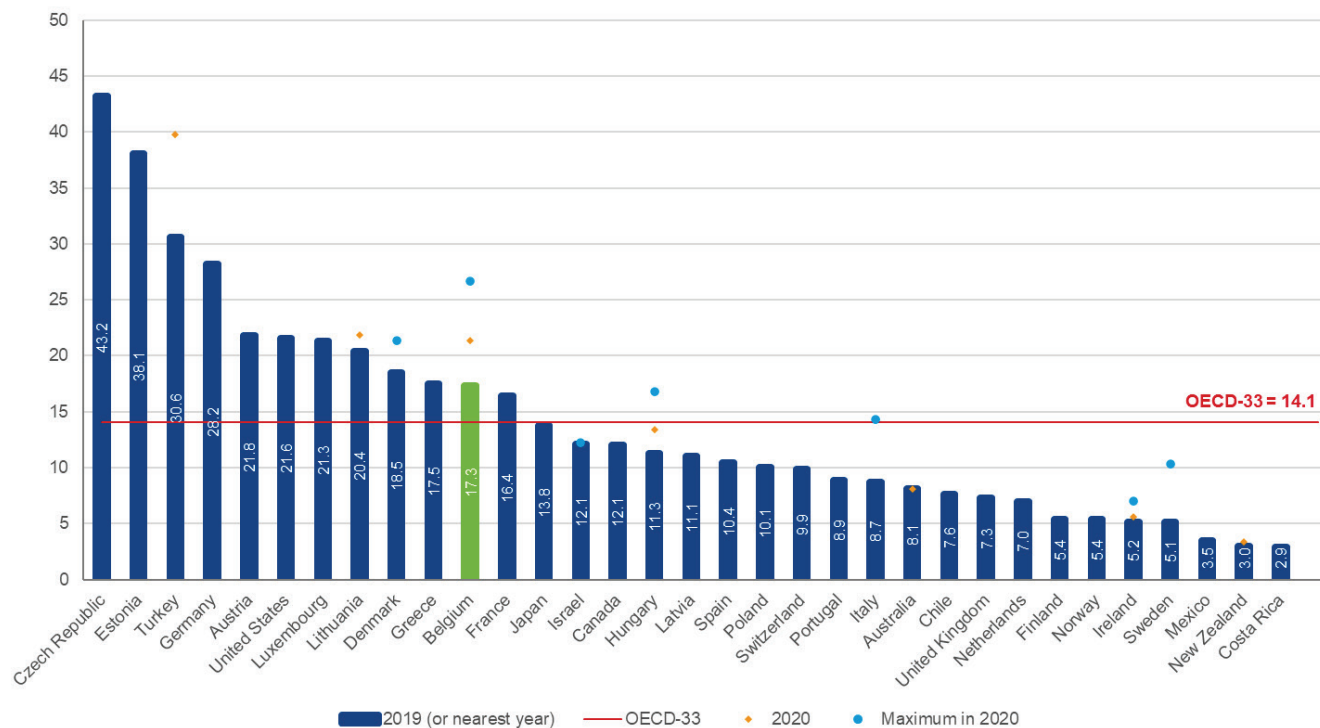
6.1.1 Definition and status

In this study, an intensive care unit (ICU) is defined as follows “special services staffed, designed and equipped to provide intensive care to critically ill patients requiring an enhanced capacity for monitoring, and multiple modalities of physiologic organ support to sustain life during a period of life-threatening organ system insufficiency”.^{305, 306} This is a broad definition that also includes medium care units, burns care units, high-dependency units, etc.

In 2021, there were 100 acute hospitals (123 hospital sites) with ICUs in Belgium; in 2019, there were 17.3 intensive care beds per 100 000 population in Belgium (Figure 4). This number is higher than the OECD-33 average, which was 14.1 intensive care beds per 100 000 population. Belgium's number of intensive care beds was even higher in 2020 (due to the COVID-19 pandemic), with a maximum of 26.7 intensive care beds per 100 000 population.



Figure 4 – Number of intensive care beds per 100 000 population in OECD countries, 2019 (or nearest year) and 2020



Source: KCE report 353



6.1.2 *Licensing standards for intensive care function*

6.1.2.1 *Definition*

The intensive care function is intended for patients who are seriously threatened in one or more of their vital functions. These patients require expert care to support or adjust these functions, using an adapted medical, nursing and paramedical organisation, continuous monitoring and appropriate diagnostic and therapeutic interventions.³⁰⁷

6.1.2.2 *Licensing standards regarding architecture and equipment*

The intensive care function should have a minimum capacity of six beds. These beds are positioned so that each patient can be visually monitored at all times and hospital hygiene and intimacy of the patient are maintained. In addition, the intensive care function should have a separate entrance, at least one isolation room per six beds, separate office for both medical and nursing team, meeting or relaxation area for the staff, private room for the medical staff who ensures permanence, waiting room to facilitate visitors and family members. The aforementioned accommodations, except the waiting room, may be shared with another service, function or unit, provided it is architecturally adjacent to the intensive care function.³⁰⁷

Concerning logistic rooms, the intensive care function must have a separate room for equipment, storing consumables, clean linen, soiled linen and equipment, a service or distribution kitchen and separate sanitary facilities for the staff.

There are no formal regulations regarding working surfaces and the surface area per bed. However, the Royal Decree states that these surfaces must be appropriate for medical and nursing activities. The function may be divided into separate units, but each unit should comply with the minimum capacity and all other standards. Each unit must organise its medical permanency if these units are spread over different buildings.

6.1.2.3 *Functional licensing standards*

Each bed should be equipped with the necessary equipment to monitor and treat critical care patients in the cardiac, respiratory, metabolic, cerebral and circulatory areas, including during possible transport. This equipment must allow oxygen to be administered at each bed, infusions with strictly controlled flow rates, aspirations, (mechanical) ventilation and cerebral or cardiopulmonary resuscitation. Each bed must be height-adjustable and articulated to ensure the correct positioning of the patient.³⁰⁷

The intensive care function must, within the hospital of which it is a part, be able to call upon an operating room for urgent surgical procedures, clinical biology laboratory and a medical imaging department. In addition, the function should have a supply of erythrocyte concentrate O Rhesus negative and plasma substitutes (unless the hospital has its blood bank which can supply these products at any time).³⁰⁷



6.2 Risk factors of PICS in Belgium

According to the risk factors for PICS presented in Chapter 2.6, we investigated which of them could be retrieved in Belgian health databases.

RHM-MZG data were analysed to estimate the number of stays in ICU from 2016 to 2020 and to describe the risk factors of PICS of the patients hospitalised in ICU for the same period. The information with regards to the methods used for the analysis is available in Supplement chapter 3.

From 2016 to 2020 **there were 276 908 stays of more than 48 hours in ICU, i.e., about 55 000 stays per year** (for about 230 168 patients^w). The annual number of stays in ICU has been relatively stable since 2016, despite a slight decrease in 2020 (-11.7% compared to 2016). This decrease is explained by the COVID-19 crisis (less surgery, less elderly come to ICU, patients stayed longer in the ICU, etc.) (Table 4).

Table 4 – Number of stays of more than 48 hours in ICU among adult population (>18 years), by year

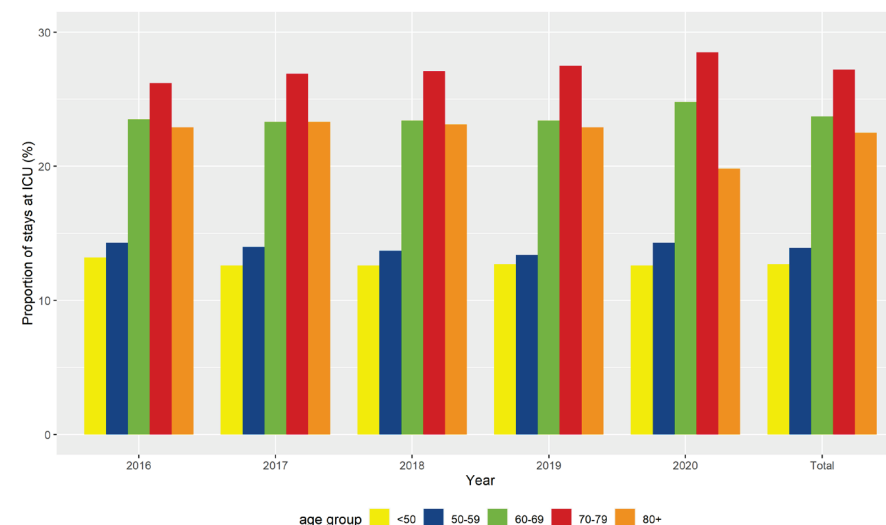
Year	Number of stays	%
2016	57 269	20.7
2017	56 639	20.5
2018	56 126	20.3
2019	56 309	20.3
2020	50 565	18.3
Total	276 908	100

^w We calculated the number of patients based on the patient ID and for 10 386 stays patient ID was unknown

6.2.1 Characteristics of patients at ICU admission

Among the stays, 60.0% of the patients were male and the mean age was 67.09 years (Standard Deviation (SD): 15.33 years). A large proportion of the patients were aged between 70 and 79 years (27.2%) (Figure 5).

Figure 5 – Proportion of ICU stays of more than 48 hours by age group and year, 2016-2020



Data source: RHM-MZG

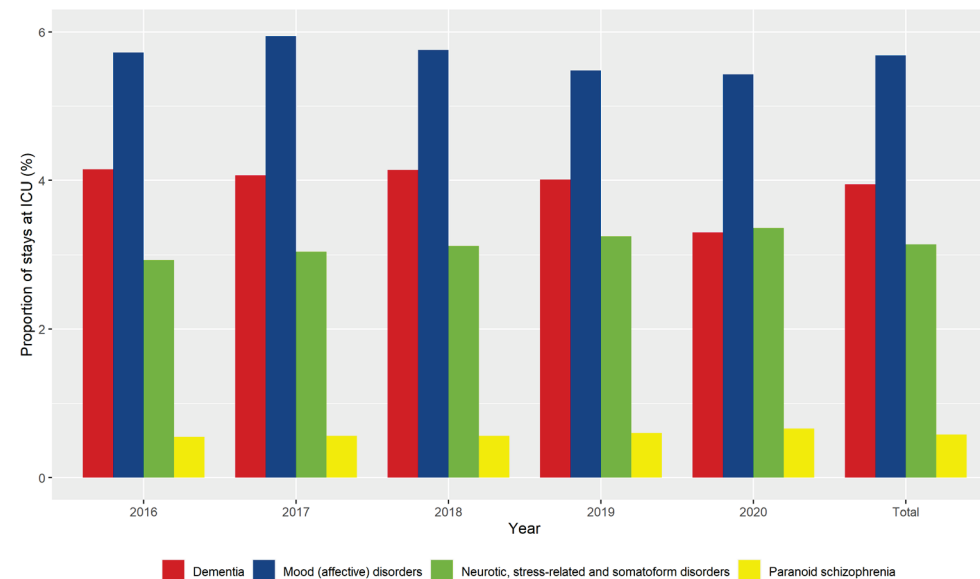


Approximately one-third of the patients had a low socioeconomic status (34.9% had the BIM status^x) (Table 5).

Among the ICU stays, 11.9 % had at least one psychiatric illness at risk of PICS at the entrance. There were 0.58% of stays with paranoid schizophrenia, 4.0% with dementia, 5.7% with mood (affective) disorders and 3.1% with neurotic, stress-related and somatoform disorders). The results are not so different between the years 2016 to 2019 with the exception of 2020, for which there were less stays with dementia history but higher stays with paranoid schizophrenia (Table 5).

In total, 19.0% of the ICU stays resulted in death. The mortality rate was higher in 2020 (21.8%) compared to the years 2016 to 2019 (range 18.0-18.7%).

Figure 6 – Proportions of psychiatric diseases among ICU stays for more than 48 hours by year, 2016-2020



Data source: RHM-MZG

^x Compared to about 20% of BIM status in the Belgian population.


Table 5 – Characteristics and risk factors of PICS at ICU admission in Belgium, by year

		2016		2017		2018		2019		2020		2016-2020	
		N	%	N	%	N	%	N	%	N	%	N	%
Age-groups (years)	18-49	7 542	13.2	7 112	12.6	7 072	12.6	7 145	12.7	6 390	12.6	35 261	12.7
	50-59	8 197	14.3	7 907	14.0	7 713	13.7	7 566	13.4	7 235	14.3	38 618	13.9
	60-69	13 416	23.5	13 183	23.3	13 168	23.4	13 194	23.4	12 533	24.8	65 494	23.7
	70-79	14 982	26.2	15 240	26.9	15 228	27.1	15 495	27.5	14 415	28.5	75 360	27.2
	80+	13 132	22.9	13 197	23.3	12 945	23.1	12 909	22.9	9 992	19.8	62 175	22.5
Mean age +/- SD		66.98	15.6	67.29	15.4	67.26	15.3	67.27	15.4	66.62	67.0	67.0	15.3
Gender	Female	23 188	40.5	22 801	40.3	22 763	40.6	22 615	40.2	19 273	38.1	110 640	40.0
Low socio-economic status*		19 338	35.0	19 285	35.2	18 941	35.0	18 990	35.3	16 433	33.7	92 987	34.9
At least one pre-existing mental health problem (cited below)		6 860	12.0	6 877	12.1	6 827	12.2	6 653	11.8	5 771	11.4	32 988	11.9
	Paranoid schizophrenia	316	0.55	318	0.56	312	0.56	338	0.6	335	0.7	1 619	0.58
	Dementia	2 375	4.2	2 305	4.1	2 322	4.1	2 260	4.0	1 671	3.3	10 933	4.0
	Mood disorders (affective)	3 283	5.7	3 366	5.9	3 232	5.8	3 088	5.5	2 746	5.4	15 715	5.7
	Neurotic, stress-related and somatoform disorders	1 678	2.9	1 724	3.0	1 753	3.1	1 828	3.3	1 700	3.4	8 683	3.1

* Using BIM status as proxy, BIM status was known for 266 522 stays because it is only known for reimbursed stays, SD= Standard Deviation



6.2.2 Risk factors of PICS during ICU stay

The average length of stay was 8.31 days (Standard Deviation (SD) 10.77 days), the median length of stay was 4.76 days (P25-P75: 2.98-8.82 days) and 14.1% of the stays were longer than 14 days.

About a quarter (23.6%) of the patients were mechanically ventilated at least once during their hospitalisation at ICU and from those who were ventilated, 60.5% (39 506/65 257) were ventilated for more than 96 consecutive hours.

Delirium was present among 3.6% of the ICU stays. There is an increase in the proportion of delirium over the years. The proportion of a drug or chemical-induced diabetes is low. The majority of stays (78.0%) had a principal diagnosis with a 3 or 4 level of severity (i.e., major or extreme diagnosis, see also Box 4). In 2020, principal diagnoses were more severe (higher proportion of major or extreme diagnoses) than in the other years (Table 4).

Box 4 – The All Patient Refined Diagnosis-Related Group (APR-DRG)

All Patients Refined Diagnosis Related Groups (APR DRG) is a classification system that classifies patients according to their reason of admission, severity of illness (SOI) and risk of mortality (ROM).

Patients are allocated to an APR-DRG-SOI group on the basis of principal diagnosis, secondary diagnoses and procedures, age and sex of the patient and, for some APR-DRGs (e.g., burns) type of discharge.

Severity of illness is defined as the extent of physiologic decompensation or organ system loss of function and introduces four categories for SOI: 1=minor, 2=moderate, 3=major, 4=extreme. The severity of illness is not comparable between pathologies which means that a cardiac disease with a SOI level 1 is not comparable to a respiratory disease with a SOI level 1.

About medicines at risk of PICS, on average 5.55 Defined Daily Doses (DDD^y, see also Box 5) of neuromuscular blocking agents (NMBA) and 8.70 DDDs^z of midazolam per ICU stay were given. Over years, consumption of NMBA increased whereas consumption of midazolam decreased (excluding 2020). In 2020, there is a very clear increase in the consumption of these two drugs (Figure 7). In 2020, the average midazolam (15.76 DDDs per stay) and NMBA (9.45 DDDs per stay) consumption per stay were higher than the average length of stay in ICU (9.16 days). In other words, the consumption of these drugs was on average higher than the recommended daily dose. The increase in consumption of midazolam could partly be explained by the fact that it was used instead of propofol (see below) when the latter was out of stock during the COVID-19 pandemic (Table 6).

Box 5 – The Defined Daily Dose

The **defined daily dose** (DDD) is the assumed average maintenance dose per day for a drug used for its main indication in adults. DDDs are standardised doses provided as part of the Anatomical Therapeutic Chemical drug classification system maintained by the WHO Collaborating Centre for Drug Statistics Methodology (www.whocc.no/atcddd). The DDD is an internationally accepted unit for measuring medicine use and for making comparisons between countries.

The DDD does not necessarily reflect the recommended or Prescribed Daily Dose in the specific country. Only one DDD is assigned per ATC code and route of administration (e.g., oral intake). The DDD is sometimes a 'dose' that is rarely if ever prescribed because it might be an average of two or more commonly used doses and is based on an adult body weight of 70kg. However, DDDs provide a fixed unit of measurement independent of price, currencies, package size, strength (i.e. amount of drug per unit) and molecule, as one day of treatment receives approximately equal weight whatever the drug. This enables the

^y No equivalence available between DDD and mg

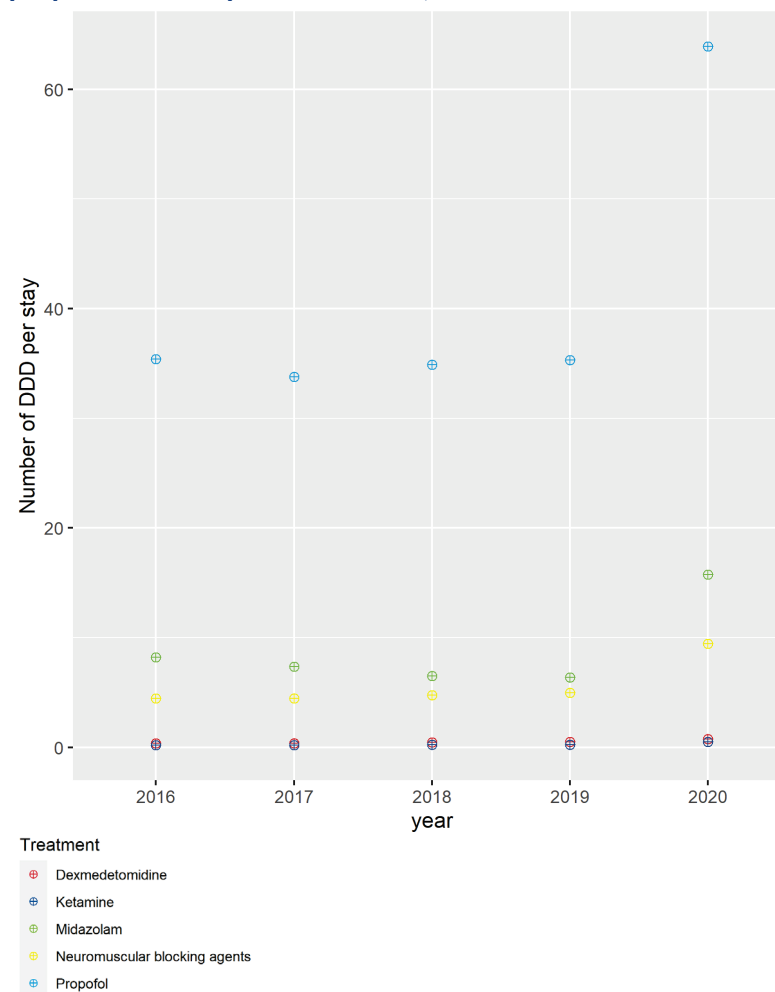
^z One DDD equals 15mg/day (IV), see also www.whocc.no/atcddd



researcher to assess trends in drug use and to perform comparisons between population groups.

With regards to the other sedatives, less at risk of PICS than the previous one, on average the patients received 40.10 DDDs of propofol, 0.50 DDD of dexmedetomidine and 0.28 DDD of ketamine per ICU stay. There was a huge increase in propofol consumption in 2020 (Figure 7).

Figure 7 – Midazolam, NMBA, ketamine, dexmedetomidine and propofol consumption in the ICU, 2016-2020



Data source: RHM-MZG



Table 6 – Risk factors of PICS during ICU stay for more than 48 hours in Belgium, by year

Table 3 – Risk factors of PLOS during ICU stay for more than 14 hours in Belgium, 2016-2020													
		2016		2017		2018		2019		2020		2016-2020	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Length of stay (in days)		8.11	10.61	8.10	10.69	8.17	10.45	8.10	10.57	9.16	11.54	8.31	10.77
		N	%	N	%	N	%	N	%	N	%	N	%
	Less than 14 days	49 626	86.7	49 154	86.8	48 367	86.2	48 880	86.8	41 830	82.7	237 857	85.9
	More than 14 days	7 643	13.3	7 485	13.2	7 759	13.8	7 429	13.2	8 735	17.3	39 051	14.1
Delirium		1 630	2.8	1 910	3.4	2 111	3.8	2 203	3.9	2 185	4.3	10 039	3.6
Mechanical ventilation		12 825	22.4	12 900	22.8	12 861	22.9	12 477	22.2	14 194	28.1	65 257	23.6 [§]
Mechanical ventilation, greater than 96 consecutive hours		7 606	13.3	7 481	13.2	7 539	13.4	7 275	12.9	9 605	19.0	39 506	14.3
Drug or chemical induced diabetes		89	0.15	114	0.20	93	0.17	111	0.20	108	0.21	512	0.18
Level of severity (soi) of the principal diagnosis	0-2	14 576	25.5	13 629	24.1	12 518	22.3	11 010	19.6	9 124	18.0	60 857	22.0
	3-4	42 693	74.5	43 010	75.9	43 608	77.7	45 299	80.4	41 441	82.0	216 051	78.0
		DDD	DDD/stay	DDD	DDD/stay	DDD	DDD/stay	DDD	DDD/stay	DDD	DDD/stay	DDD	DDD/stay
Neuromuscular blocking agents*		255 896	4.47	253 516	4.58	267 220	4.76	281 374	5.00	477 889	9.45	1 535 896	5.55
Midazolam**		470 615	8.22	417 388	7.37	366 049	6.52	358 789	6.37	796 880	15.76	2 409 721	8.70
Propofol***		2 025 060	35.4	1 912 268	33.8	1 959 428	34.9	1 988 158	35.3	3 231 844	63.9	11 116 760	40.1
Dexmedetomidine****		22 009	0.38	22 931	0.40	26 065	0.46	28 347	0.50	39 462	0.78	138 815	0.50
Ketamine*****		11 930	0.21	12 728	0.22	13 368	0.24	13 508	0.24	26 235	0.52	77 768	0.28

*ATC codes: M03AB, AC, AX, **ATC code: N05CD08, ***ATC code: N01AX10, ****ATC code: N05CM18, *****ATC code: N01AX03, SD= Standard Deviation, ^{\$}Using billing data, we arrive at a proportion of about 40% of ventilated patients. The billing data includes all ventilations, i.e., also those of less than 24 hours. This partly explains the differences in results observed.

**Key points**

- From 2016 to 2020, there were about 230 168 patients hospitalised in ICU during more than 48h.
- The majority of hospitalised patients were male, elderly and more than 34% had a low socioeconomic status.
- Regarding the risk factors of PICS during ICU stay, 14% of the hospitalisation lasted more than 14 days, most of the patients had a major or extreme principal diagnosis (3 or 4 APR-DRG-SOI levels), around 3% of the patients developed a delirium during the hospitalisation and 14% of the patients were ventilated for more than 96 hours. The consumption of NMBA and/or midazolam was common.
- In 2020, patients were even more at risk of PICS. Indeed, patients stayed longer, had a more severe diagnosis, experienced more delirium, and received more midazolam or NMBA.

6.3 Initiatives to prevent PICS in Belgium

6.3.1 Introduction

This chapter aims to identify and describe initiatives for PICS prevention developed in Belgian ICUs. More specifically, it focuses only on interventions applied in the Belgian healthcare system, that aimed to prevent PICS, or to identify and overcome barriers to the implementation of preventive measures. Therefore, we retrieved information from peer-reviewed publications and grey- literature on initiatives specifically carried out in Belgium.

6.3.2 Methods

In a first step, we looked for the scientific articles published, over the past 15 years, by authors from ICUs in Belgian university hospitals. To this end, the search was performed in PubMed. It was followed by a snowballing approach from the references of the articles identified in the previous step. It was completed by a search in Embase using 'Post Intensive Care Syndrome' as keyword.

Thereafter, complementary information was sought by exploring grey-literature. We consulted master and doctoral thesis repositories from Belgian universities using the following key-words in three languages: "post intensieve zorg", "post intensieve zorg syndroom", "post soins intensifs", "syndrome post soins intensifs", "post intensive care syndrome", "ICU OR intensive care AND follow-up". The website DART-Europe e-thesis portal was also consulted^{aa}. As a second step, a search was conducted in Google scholar using the same string.

Finally, a meeting with experts was organized at the final of the research process to request references that have potentially been omitted, and that could be informative in this regard.

6.3.3 Results

First of all, it has to be mentioned that many publications from Belgian authors, on several aspects of PICS were identified and encompassed different components and methods. Studies include basic science research on the pathophysiology of muscle and nerve impairments^{218, 308-312}, management of delirium¹⁵⁰, or post-ICU follow-up.³¹³⁻³¹⁵ Nevertheless, according to the inclusion criteria, only those intending to prevent PICS within the ICU stay were retrieved.

^{aa} <https://www.dart-europe.org/basic-search.php>



6.3.3.1 Description of Belgian initiatives

We identified 7 peer-reviewed articles^{183, 316-321}, and one master thesis.^{322, 323} Among peer-reviewed articles, four focused on early mobilisation and physiotherapy^{183, 316-318}, while three others assessed the barriers to the adherence to guidelines on analgo-sedation in the ICU³¹⁹⁻³²¹. Study designs included one RCT¹⁸³, one qualitative study³²¹, one prospective observational study³¹⁷, three surveys^{319, 320, 322} and one narrative review³¹⁶. One master thesis investigated measures to prevent mental and cognitive disorders through a survey.^{322, 323} Results are presented in Supplement-Table 22.

PHARMACOLOGICAL INTERVENTIONS FOR ANALGESIA AND SEDATION

Three articles from the same team provided a description of the **use of analgo-sedation strategies** (protocols, tools for evaluation, daily sedation interruption practices), through a national survey^{319, 320} or through semi-structured interviews in selected hospitals³²¹. The barriers to the adherence of analgo-sedation guidelines, or daily sedation interruption were analysed. The survey was conducted in 94% of Belgian hospitals (including 898 participants). Limited compliance with recommendations for analgesia and sedation was identified: analgo-sedation protocols were available for only one-third of respondents. Besides, validated scales to monitor pain in patients unable to self-report were available in 11% of participants, while protocols for sedation were available in 75%. One third of respondents reported never using daily sedation interruption. Overall, barriers were workload considerations, lack of awareness, information and familiarity with such practices, and the perception that sedation interruption could have a negative impact on patients' comfort.

PHYSICAL OUTCOMES RELATED TO INITIATIVES TO PREVENT PICS IN BELGIUM

Through a RCT performed in 90 stabilised critically-ill patients, the effectiveness of a **cycle ergometer** (as part of physiotherapy interventions) on muscle impairment was assessed by Burtin et al. in a university hospital mixed ICU.¹⁸³ Authors investigated whether a daily passive or active exercise session using a bed-cycle ergometer was safe and could prevent or attenuate the loss of functional capacity and muscular force (measured in the quadriceps). The procedure was proved to be feasible and safe, and lead to a better functional status at hospital discharge (6 minutes walking distance and muscle force were improved in those who received the cycle ergometer sessions). In addition, subjective feeling of functional well-being (SF36 questionnaire) was higher in patients included in the intervention group.

Three other articles described the feasibility to implement a **protocol of early mobilisation** in critically-ill patients, including those requiring supportive therapy.³¹⁶⁻³¹⁸

- One of those described the implementation of a standardised multidisciplinary protocol for early mobilisation in a university hospital mixed ICU. This protocol was developed by the collaboration of two intensivists, five physiotherapists, and two ICU head nurses. It was based on the early mobilisation protocol published by Morris et al. (Start-To-Move Protocol).¹⁹⁶ This protocol is based on a multidisciplinary step-up approach in which the ICU team defines daily the intensity of mobilisation of patients.
- The implementation of this protocol was assessed after several years of use by the same team. Among the different levels of intensity of physiotherapy, an excellent agreement in assignment between providers was demonstrated. Moreover, the excellent association between prescribed and delivered treatments was a good argument supporting its feasibility. Safety events were rare, and patients were substantially satisfied with the delivered physiotherapy sessions.³¹⁸



- Another study assessed whether a teamwork approach could allow to provide very early mobilisation to the majority of ICU-patients, including those requiring multiple supportive therapies. The research was conducted in a university hospital mixed ICU. The team encompassed senior physiotherapists (physiotherapist-to-patient ratio: 1:14), combined with physiotherapists students (students-to-senior physiotherapist ratio: 2:1). The nurse- to- patient ratio was 1:1.6. Early mobilisation was feasible in 81% of patients, including those with mechanical ventilation, renal replacement therapy, or vasopressors. Identified barriers were restricted staffing capacities, diagnostic or surgical procedures, patients' refusal, and severe hemodynamic instability. Patients perception of early mobilisation was positive and safety events were occasional.³¹⁷

MENTAL AND COGNITIVE OUTCOMES RELATED TO INITIATIVES TO PREVENT PICS IN BELGIUM

With the goal to detect barriers for the application of preventive measures for anxiety and delirium, a survey was conducted in a university hospital ICU in 32 participants (physicians, nurses, physiotherapists, psychologists).³²² The use of measures for the prevention of mental or cognitive disorders was assessed through a questionnaire. Different categories of barriers were identified: safety concerns, workload, awareness and knowledge on PICS, along with patients' characteristics (level of severity, for instance). Results were reported in a master thesis.

Key-points

Initiatives specifically conducted in Belgian ICUs to prevent PICS were mainly focused on the implementation of early mobilisation/physiotherapy protocols, and the identification of practices and barriers for appropriate management of sedation and analgesia:

- The implementation of multidisciplinary protocols of early mobilisation in ICU have been shown to be feasible and safe.
- Adherence to protocols for analgesia and sedation and daily-sedation interruption may still be improved.
- Overall, barriers to the implementation of protocols for PICS prevention include staff workload, lack of awareness on PICS, lack of familiarity with preventive measures (bundles), lack of communication within the team, and fear to induce a negative impact on patients' comfort.



7 DISCUSSION

In Belgium, about 55 000 ICU stays longer than 48 hours occur every year among adults. Among them, risk factors of PICS at admission are frequently present in patients. Indeed, at ICU admission, most of the patients were elderly and most had a major or extreme principal diagnosis. During the ICU stay, a long duration of stay (>14 days) or of mechanical ventilation (>96 h) as well as the consumption of midazolam or neuromuscular blocking agents were common. Nevertheless, we have no diagnosis and follow-up data to identify to what extent the patients at risk of PICS, finally developed the syndrome.

PICS cannot be totally prevented but we identified several effective interventions in the scientific literature to prevent PICS: environmental ones, by reducing auditory and/or visual sensory perception, affect the quality of sleep and can lower the risk for delirium. Exposition to relaxing music improves also sleep. ICU diaries in combination with psychoeducation show a positive effect on anxiety and depression. Open visiting hours have a positive effect on family satisfaction and are correlated with less anxiety in patients. Intensive mobilisation is effective on muscle strength in the short term.

Regarding sedative agents, a strong relationship has been shown between benzodiazepines and the occurrence of delirium. Although no evidence on the effectiveness of pharmacological agents for delirium prevention or treatment has been demonstrated, decreasing the level of sedation or interrupting sedation has been shown to be safe.

Next to the interventions themselves, the PADIS guideline has been published and implemented through the ABCDEF bundle to prevent the side effects of ICU stay.

The use of the bundle to structure interventions is associated with significant improvements in ICU patient survival and days free of delirium (even after adjusting for age, the severity of illness and mechanical ventilation). It has also been shown that, even when provided incompletely and despite the lack of hard evidence of effectivity for every element of the bundle, these measures appear to have a significant effect on patient outcomes. This is a

dose-response effect: the longer and the more complete they are implemented, the better the long-term outcome of patients. Other identified improvements are reduced ICU/hospital length of stay, reduced duration of mechanical ventilation, reduced duration of delirium and reduced healthcare costs.

Nevertheless, highlighting the relationship between the ABCDEF bundle/guidelines and specific interventions is not easy because one intervention can have an influence on multiple outcomes, and thus components of the bundle. In addition, psychological outcomes can be influenced by interventions that are not necessarily present in the guidelines/bundles.

The ABCDEF bundle also brings other more indirect benefits, such as standardisation of care processes and reduced variation in practice within ICUs, and improved communication within care teams. However, the implementation of the ABCDEF bundle often requires ICUs to fundamentally transform their care practices. Therefore, other contextual, environmental or cultural factors that may influence the adoption of the guideline must also be taken into account.

The literature on the barriers to the implementation of preventive measures of the PICS allows us to highlight that the majority of them are related to the patient's condition (sedation or coma, active bleeding or coagulation problems, orthopaedic reasons, haemodynamic instability, insufficient analgesia, etc.) and that the cooperation from the patient or the refusal from the family to collaborate impairs prevention activities such as mobilisation. There are also structural barriers such as lack of staff or insufficiently trained staff, lack of time, lack of specialised equipment and/or lack of financial support. The culture of the ICU (sedation, intubation, mobilisation policy, ...), as well as the team motivation, are also key factors to prevent PICS. The importance of leadership and staff stability are also important factors influencing the ICU's willingness to engage in PICS prevention. If communication or coordination between caregivers is lacking, activities will be less practised. Finally, the organisation of the physical environment of the ICU is also important.



Among the facilitators to the implementation of preventive measures of the PICS, many studies mention the existence of a written (local) protocol or guidance as an important element. These should be known by the ICU health care teams and be easily available. But developing a protocol takes time and money, and its implementation requires buy-in from the team and a clear distribution of responsibilities, steps and standards. Therefore, a bundle such as the ABCDEF (based on a guideline), translated into clear protocols, seems to be essential for a PICS prevention policy.

Initiatives specifically conducted in Belgian ICUs to prevent PICS were mainly focused on the implementation of early mobilisation/physiotherapy protocols. They have been shown to be feasible and safe. Another set of publications focused on identifying practices and barriers to appropriate management of sedation and analgesia and showed that adherence to these protocols can be further improved. Overall, the barriers to the implementation of PICS prevention protocols in Belgium include staff workload, lack of awareness of PICS, lack of familiarity with preventive measures (bundles), lack of communication within the team and fear to induce a negative impact on patients' comfort.

This research included **several limitations**.

The integrative literature reviews included studies up till 2020. The main reason for this is that the current research project started in 2019 and was interrupted because of urgent research works regarding the COVID-19 pandemic. We did not conduct an update when the project was restarted. This might imply that we missed some recent studies. No critical appraisal of the included studies in the integrative review on interventions to prevent PICS was performed and therefore the robustness of the results cannot be accurately assessed. However, the results of the review match with the (strength of) recommendations of the PADIS guideline.

It is difficult to reach firm conclusions about the most effective interventions for several reasons. Firstly, because a RCT was not identified for each intervention and study samples were often small. The level of evidence is therefore limited, and the conclusion should be taken with caution. Secondly, the interventions and control groups are heterogeneous which makes the comparison of effectiveness between interventions complicated. Also, the

outcomes and the tools to measure these outcomes (or clinical scales/scores) vary, making head-to-head comparisons difficult to draw. Finally, the definition of standard care also varies across studies (for instance: standard sedative drugs, the definition of the timing of early mobilisation...).

While it should have been useful, we did not interview key-informants to investigate more precisely on the practices related to PICS prevention in Belgian ICUs. ICU units have been highly solicited during the COVID-19 pandemic by the consequent workload and they have been already solicited by the KCE in recent months in the context of two other studies. Therefore, we were not able to document Belgian initiatives to prevent PICS and to include information on the current practice regarding the implementation of the ABCDEF bundle, PAD(IS) guidelines and diaries. Barriers and facilitators have been in consequence to be searched through the literature. And whether we intend to identify barriers per interventions aiming at preventing PICS (the search strategy was built using the intervention as a starting point) it appeared that organisational barriers and facilitators are mainly related to implementation of the protocol, because interventions are included in such process.

Nevertheless, this report gives a good overview of the state of the art regarding prevention of PICS. It also describes extensively the barriers and facilitators to implement this knowledge.



8 CONCLUSION

In conclusion, there is insufficient hard evidence to state whether we can prevent PICS and links between the use of the ABCDEF bundle and separated interventions preventing PICS are not always straightforward. Nevertheless, it appears reasonable to recommend its use. Recommendations to policy makers are part of the synthesis of this report. Seeing that absence of evidence does not mean evidence of non-efficacy, the weakness of evidence of some interventions should be considered as an incentive to conduct new studies. These studies should help to specify which types of interventions are useful in which category of patients, particularly. The moment of each intervention in the timeline of the critical illness should also be considered. Ideally, heterogeneity is important to minimize with standardized procedures. Of importance, relatively long-term outcomes should be assessed. Attention should be paid to the potential barriers to implementation before to proceed.



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