ABCDEF bundle as a tool for the prevention of Post-Intensive Care Syndrome
a systematic literature review

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Universidade da Beira Interior, Covilhã 25/04 /2023

Dedication

To my uncle Luís and grandfather António.

Acknowledgments

This work, which also represents a mark in this great adventure that has been studying medicine, is only possible through the tireless support of many people, for which I would like to thank them.

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Resumo

Introdução: A SPICI (Síndrome Pós-Internamento em Cuidados Intensivos) refere-se a défices cognitivos, físicos e psicológicos que se podem vir a desenvolver em doentes e/ou na sua família durante o internamento numa unidade de cuidados intensivos, e que persistem após esse período de internamento. Não foram estabelecidos critérios de diagnóstico para esta síndrome e não existe uma ferramenta validada para identificar os doentes críticos em risco de desenvolver SPICI.

O *bundle* ABCDEF é uma estratégia utilizada em cuidados intensivos que segue as recomendações das *guidelines* PADIS *(Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU*) e que, ao incluir a abordagem da dor, ventilação, analgesia e sedação, *delirium*, mobilidade e envolvimento familiar do doente, pode ter um papel na prevenção da SPICI.

O aumento da taxa de sobrevivência dos doentes em cuidados intensivos, devido ao desenvolvimento da medicina ao longo dos anos, tem levado a uma preocupação crescente em descobrir formas de atenuar os fatores desencadeantes da SPICI. Assim, consideramos relevante conhecer a base científica que estuda a relação entre o uso do *bundle* ABCDEF em doentes internados em unidades de cuidados intensivos e o desenvolvimento da SPICI nos que sobrevivem a esse internamento.

Métodos: Este artigo segue a metodologia PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-analyses*). Foi utilizada a estratégia PICO (população; intervenção; comparação; resultados) para a formulação da questão de investigação: "Como é que o uso do *bundle* ABCDEF em doentes internados em unidades de cuidados intensivos pode prevenir o desenvolvimento da SPICI?". Para a pesquisa bibliográfica, foram selecionados artigos de diferentes bases de dados: *PubMed/MEDLINE*, *Cochrane Library* e *Science Direct*.

Resultados: Foram incluídos seis estudos de coorte que cumpriam com os critérios de inclusão estabelecidos. Alguns estudos comparam diferentes níveis de adesão e *performance* total ou parcial do *bundle* ABCDE(F). Outros comparam a utilização do *bundle* com a prática comum de abordagem de doentes críticos em determinadas unidades de cuidados intensivos. Os resultados de interesse para esta revisão estão relacionados com o desenvolvimento de défices nos domínios que envolvem a SPICI. No

geral, a utilização do *bundle* resultou numa diminuição da necessidade de ventilação mecânica, sedação, prevalência de *delirium* e restrição física.

Conclusão: A implementação do *bundle* ABCDE(F) parece resultar numa diminuição do desenvolvimento de fatores desencadeantes da SPICI. Assim, uma vez que se pensa que estes fatores precedem a SPICI, podemos inferir dos nossos resultados que a utilização do *bundle* em cuidados intensivos tem um papel na prevenção da SPICI. No futuro, será importante definir critérios de diagnóstico da SPICI para compreender melhor o efeito direto do *bundle* ABCDEF na prevenção desta síndrome. Para além disso, é necessário realizar mais estudos utilizando o *bundle* na sua versão mais recente, com a inclusão do elemento "F".

Palavras-chave

ABCDEF bundle; Unidade de Cuidados Intensivos; Cuidados Intensivos; Síndrome Pós-internamento em Cuidados Intensivos

Abstract

Background: PICS (Post-Intensive Care Syndrome) refers to cognitive, physical, and psychological deficits that can develop in patients and their families during an intensive care unit (ICU) stay and persist after that. The ABCDEF bundle is a guide for the approach of critically ill patients that, by addressing pain, ventilation, analgesia and sedation, delirium, mobility, and patient's family engagement can have a role in preventing PICS.
The increasing survival rate in intensive care patients, due to the development in medicine through the years, has led to an increasing concern to discover ways to mitigate PICS triggers. Thus, we consider it to be relevant to understand the scientific base that studies the relationship between the use of the ABCDEF bundle in ICUs and the frequency of PICS in its survivors.

Methods: This article follows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) methodology. Using the PICO (participant, intervention, comparison, outcome) strategy for the literature search, articles were selected from different databases: PubMed/MEDLINE, Cochrane Library, and Science Direct.

Results: Six cohort studies meeting the established inclusion criteria were included. Some studies compare different levels of adherence and total/partial performance of the bundle. Others compare the use of the bundle with the usual management of critically ill patients in a given ICU (Intensive Care Unit). The outcomes of interest for this review relate to the development of deficits in the domains involving PICS. Overall, the use of the bundle resulted in a decrease in the need for mechanical ventilation, sedation, the prevalence of delirium, and physical restriction.

Conclusion: The implementation of the ABCDEF bundle seems to result in a decrease in the development of PICS triggers. Thus, since these triggers are thought to precede PICS, we could infer from our findings that the use of the bundle on critical care has a role in the prevention of PICS. It would be important to define criteria for PICS assessment to better understand the direct effect of the ABCDEF bundle on the prevention of this syndrome. Besides, it needs to be conducted more studies using the more recent bundle, including the "F" element.

Keywords

ABCDEF bundle; Intensive Care Unit; Intensive Care; Post-Intensive Care Syndrome

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List of acronyms

AOR	Adjust Odds Ratio
BPS	Behavioral Pain Scale
CAM-ICU	Confusion Assessment Method for the Intensive Care Delirium Screening Checklist
CI	Confidence interval
CPOT	Critical-Care Pain Observation Tool
DFCFD	Delirium-free and coma-free day
HABC-M SR	Healthy Aging Brain Care Monitor Self Report
ICU(s)	Intensive Care Unit(s)
ICU-AW	Intensive care unit-acquired weakness
MRC	Medical Research Council
NRS	Numerical Rating Scale
PICO	Population, Intervention, Comparison and Outcomes
PICS	Post-Intensive Care Syndrome
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analysis
RASS	Richmond Agitation-Sedation Scale
SAS	Sedation-Agitation Scale
SATs	Spontaneous Awakening Trial

SBTs	Spontaneous Breathing Trial
SCCM	Society of Critical Care Medicine
VDF´s	Ventilator free days

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Chapter 1

Introduction

In 2010, the Society of Critical Care Medicine had a conference where it was discussed, among other topics, a nomenclature for post-intensive care unit impairments, having agreed on the term Post-Intensive Care Syndrome to "describe new or worsening impairments in physical, cognitive, or mental health status arising after critical illness and persisting beyond acute care hospitalization."(1) No diagnostic criteria for this syndrome were established. Additionally, there´s no validated tool to identify patients at risk of developing PICS. (1,2)

The improvement of the survival rate in intensive care patients, due to the development in medicine through the years (4) has led to an increasing concern to discover ways to mitigate PICS triggers related to the patient, to the disease, and to the ICU. Lane-Fall *et al.* (5) consider that these triggers include the age of the patient, as for their personal clinical background (having dementia, for example); hypoxemia and infection related to the disease that led to the intensive care unit; immobility, sedation, and invasive procedures inherent to the ICU, as mechanical ventilation. (5)
A tool that has been used to manage intensive care patients on ICU units in order to prevent health-related problems in ICU survivors and, possibly, prevent PICS is the ABCDEF bundle. (6, 7)

Post-Intensive Care Syndrome

Post-Intensive Care Syndrome is a syndrome that involves physical, cognitive, and mental health impairment in patients after ICU discharge. Each domain of this syndrome relates to specific symptoms. (5)

In relation to physical impairment, muscle weakness can be related to Intensive care unit-acquired Weakness. On the other hand, delirium, depression, and dementia are common problems related to cognitive impairments. Finally, mental health diseases among patients that receive critical care include, also, depression, anxiety and post-traumatic stress. (8)

To understand the relevance of getting to know this syndrome and study ways to prevent it, Marra A *et al.* (9) developed a study in 2018 with 406 survivors of critical illness where they concluded that one or more PICS problems (characterized as cognitive impairment, disability, and depression) were present in the majority of survivors (64% and 56% of the patients 3 and 12 months, respectively, after discharge from the ICU).

Unfortunately, it is difficult to diagnose this syndrome since it includes these different health domains and has no diagnostic criteria, as mentioned before. Wang S. *et al* (10) studied the Healthy Aging Brain Care Monitor Self Report (11) (Supplementary material- file 1.1) as a possible clinical tool to assess PICS, having reached to the conclusion that this scale has the potential to screen the symptoms of this syndrome, with psychological and functional subscales that showed to be reliable, even though it was suggested that the cognitive subscale had limited validity. The Post-Intensive Care Syndrome Questionnaire (12) (Supplementary material- file 1.2) is another scale that could be used to measure the syndrome´s presence.

Other options include instruments that measure the different components of PICS, such as the Medical Research Council scale, the Katz index, and the Barthel index for the physical domain; the Repeatable Battery for the Assessment of Neuropsychological Status, and the Montreal Cognitive Assessment test for cognitive domain and Hospital Anxiety and Depression Scale, Beck's anxiety test, Depression Inventory Second Edition scale and Post Traumatic Stress Syndrome-14 scale for the mental domain. (13) Therefore, there is no tool to be used systematically by all ICUs.

It seems logical to study ways to prevent PICS. The SCCM recommends the ICU liberation campaign to reach this goal, by using the ABCDEF bundle as a strategy to implement the PADIS guidelines. (3) Other ways that support the prevention of this syndrome exist: for example, Inoue S *et al* (8) describe how physical rehabilitation, nutrition, environmental management for healing, nursing care for PICS, intensive care unit diaries, and intensive care unit follow-up clinics can also have a role in minimizing sequelae after critical care. In this study, we won't focus on these isolated strategies.

ICU liberation

The ICU liberation bundle (A-F) was developed by the SCCM and arose from the need to create a patient management guideline that included the recommendations made in the Clinical Practice Guidelines for the management of Pain, Agitation, Delirium, Immobility, and Sleep disruption in Adult Patients in the Intensive Care Unit in Critical Care Medicine (PADIS guidelines), updated last in 2018. (1,3)

The necessity to develop an effective program to implement the PADIS guidelines on ICU wards came from the goal to protect patients in intensive care units from the harmful effects of pain, agitation/sedation, delirium, immobility, and sleep disruption and consequently reduce the negative patient outcomes after ICU stay. (7) Thus, it is intended for patients that, when liberated from the ICU, can maintain the quality of life that they knew.

Each element of the ABCDEF bundle includes strategies to implement the guidelines discussed above: (A) Assess, Prevent, and Manage Pain; (B) Both Spontaneous Awakening Trials (SAT) and Spontaneous Breathing Trials (SBT); (C) Choice of analgesia and sedation; (D) Assess, Prevent and Manage Delirium; (E) Early mobility and Exercise and (F) Family engagement and empowerment.

Originally, this bundle didn't have the F element, which was included in 2014. (3) Some of the included studies in this review will refer to the original ABCDE bundle.

Elements of the A-F bundle

A Element: Assess, Prevent, and Manage Pain

This element is necessary, since pain is common in intensive care units, with an incidence of up to 50% of patients. (3)

Assessment can be made by self-report, using the Numerical Rating Scale, or by behavioral and physiological indicators with the Behavioral Pain Scale and Critical-Care Pain Observation Tool (3, 14, 15) (supplementary material-file 2). An indicator for pain interventions is the presence of significant pain (NRS >4, BPS >5, or CPOT >3). (3,16)

For the prevention and management of pain, it is important to understand that most procedures made in the ICU ward are painful, so it must be administered preprocedural analgesia, including non-pharmacologic (such as relaxation/distraction techniques) and pharmacologic interventions (opioids', for example). (3,9) Another strategy is multimodal analgesia, which consists of the use of different, non-opioid, analgesic medications to decrease individual adverse effects. (10)

B Element: Both Spontaneous Awakening Trials and Spontaneous Breathing Trials

B element exists with the goal of decreasing the number of days that a patient receives mechanical ventilation, that consequently contributes to the decrease of ICU-acquired muscle weakness, which has been associated with mechanical ventilation for 6 days or more. (15) This goal can be reached through the Wake Up and Breathe Protocol (supplementary material- file 3), which incorporates safety screens and failure criteria for SATs and SBTs. (17)

SATs consist of stopping narcotics and sedatives every day if the pain is controlled. In case of necessity, these medications can be restarted at half the previous dose and titrated as needed. (9) It is important to evaluate the depth of sedation daily since it has been shown that deep sedation leads to poorer outcomes after ICU care. This assessment can be made with The Richmond Agitation-Sedation Scale and Sedation-Agitation Scale (supplementary material-file 4), that describe deep sedation with the value of -4 and 2, respectively. (9)

The safety screen of SBTs is performed after the safety screen for SATs and can be attempted with T-piece or pressure support ventilation. (3)

C Element: Choice of Analgesia and Sedation

According to the Society of Critical Care Medicine (3), the assessment of sedation should be frequent (every 4 hours), using, as for the B element, the Richmond-Agitation Sedation Scale, or the Sedation-Agitation Scale. The goal for every patient is to reach, if possible, a calm and alert state (light sedation) with analgosedation, ie, pain and discomfort treated before agitation, with opioids as first-line therapy, as discussed in element A. (18)

Opioids also contribute to sedation but, if agitation persists, guidelines recommend the use of dexmedetomidine for light sedation and the use of propofol for deep sedation, since the use of benzodiazepines has been associated with worse outcomes. (3)

D Element: Delirium: Assess, Prevent, and Manage

Delirium, besides having a considerable prevalence in ICU patients, is a cause of prolonged hospitalization and duration of mechanical ventilation, as for the increased risk of mortality and long-term cognitive impairment. (3,9)

Delirium assessment can be made using tools such as the Confusion Assessment Method for the Intensive Care Unit and the Intensive Care Delirium Screening Checklist (supplementary material-file 5). (3,11) Because we don´t have sufficient evidence to support pharmacologic interventions, the PADIS guidelines don´t recommend delirium prophylaxis with medications (9), but support early recognition of delirium with assessment, at least, once a shift. (3)

The prevention of delirium can be made with nonpharmacologic interventions such as the promotion of sleep hygiene, early mobilization, regular orientation to the environment, and providing hearing and visual aids to reduce these impairments, among others. (3,9)

E Element: Early Mobility and Exercise

As said in the precious element, mobility has a role in the prevention of delirium and other functional outcomes.

The Medical Research Council grading for muscle strength (supplementary material- file 6) is used to assess the diagnoses of ICU-acquired weakness (the diagnoses are made with a <48 score). (9,19)

It is necessary to decide a patient's activity goal, according to their clinical status. After this assessment, it's possible to determine the strength of the activity, from passive stretching to active walking. (3)

F Element: Family Engagement and Empowerment

The goal of this element is to engage families in the care of their family members by maintaining patient-centered care with an understanding of the values and beliefs of the patient, giving information about the clinical situation to the patient and their family and involving them in the decision-making process. (3)

Objectives

After this theoretical contextualization, it is important to specify the objective of this work.

With this review, we intend to answer the question: “How can the use of the "ABCDEF" bundle in intensive care units prevent the development of PICS (Post-Intensive Care Syndrome)?”. Thus, our goal is to understand the scientific base that studies the relationship between the use of the ABCDEF bundle in ICUs and the frequency of PICS in its survivors.

Chapter 2

Methods

For the development of this paper, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used as methodology.
The protocol of this review, under the number ID CRD42022359772, is registered in PROSPERO (International prospective register of systematic reviews). The checklist Prisma-P 2015 worked as a guide for its elaboration.

Information sources

The bibliographic search was made through the databases PubMed/MedLine, Cochrane Library, and Science Direct, using the search expression ("Postintensive care syndrome" OR "Patient Care Bundles" [MESH] AND "Intensive Care Units" [MESH] AND "Critical care" [MESH]). Literature published from inception of the database up to 31 August 2022 was included. Further studies were included from the references of the original studies.

Search Strategy

PICO strategy was used for the construction of the research question (How can the use of the [Intervention] "ABCDEF" bundle approach [Comparator] in [Population] intensive care unit patients [Outcome] prevent the development of PICS?); and to guide the bibliographic search. There was no limit made regarding the publication date of the study.

Eligibility Criteria

The articles that were considered eligible met the inclusion criteria predefined with the PICO criteria:
Participants/Population**:** we included studies that referred to critically ill patients admitted to an intensive care unit. Patients in whom no PICS assessment or recognition of possible sequelae was performed after intensive care unit discharge were excluded.

Interventions: studies that referred to the implementation of the ABCDEF bundle in the Intensive Care Unit were included, as for articles that address the prevention of PICS

without the ABCDEF bundle to compare other forms of patient management in intensive care units.

Comparators: critically ill patients whose management in the intensive care unit was made without the use of the ABCDEF bundle were considered eligible.

Expected Outcomes: we were interested in outcomes regarding the symptoms of patients during and/or after intensive care, to evaluate if the management of patients in the intensive care unit was effective for the prevention of PICS.

Data extraction

Using the software program Microsoft Excel, we elaborated a data extraction form, where it included the following information: study reference; study type; the aim of the study; participants, setting, interventions, comparison, symptom-related outcomes, survival outcomes, and other outcomes.

Chapter 3

Results

Selection Process

The initial search was made by one researcher (I. L.), using PubMed, Science Direct and Cochrane Library as databases. It obtained 182, 90, and 51 results, respectively, for a total of 323 articles. Using the Endnote reference manager, 11 articles were automatically removed. Thus, 312 articles were left to be analyzed. After reading the titles and abstracts of those articles it was possible to select 28 articles for full reading. Doubts regarding the inclusion or exclusion of studies were resolved by discussion between the other two researchers (V. B. and R. C.). While reading these articles in their entirety, an additional 13 references were selected for analysis.

In total, 34 articles were excluded as they did not fit the established inclusion criteria, leaving 6 articles for synthesis.

The PRISMA flowchart in figure 1 summarizes the selection process.

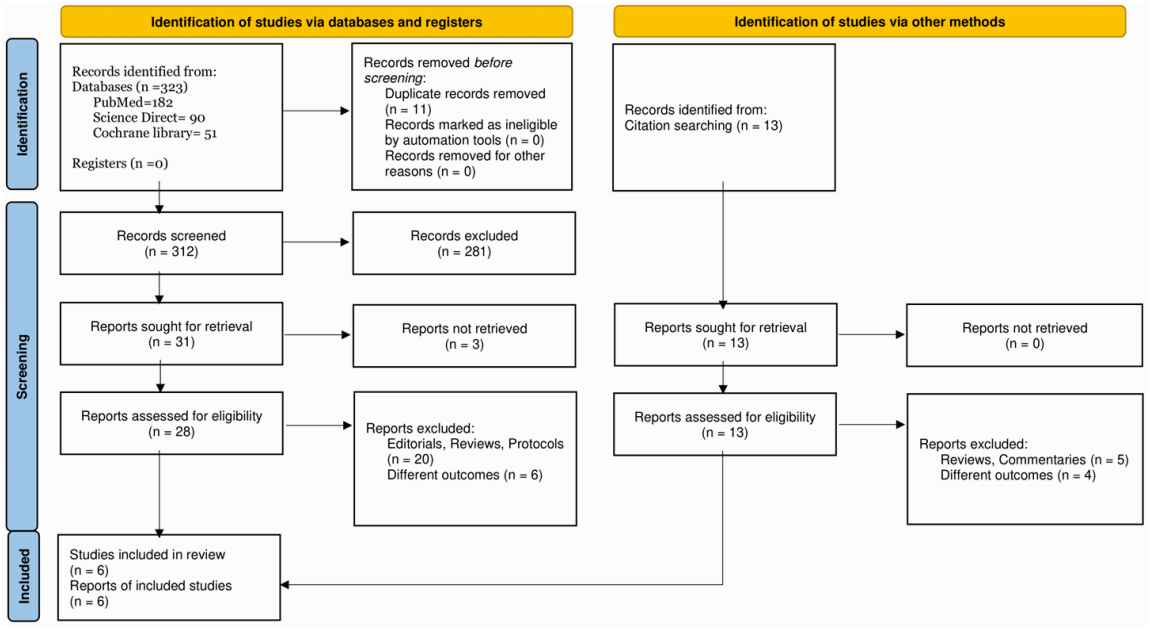

Figure 1 - PRISMA flowchart describing article selection

Study Characteristics

In this review, 6 cohort studies were included for analyses. All of these had as participants ICU patients from various hospitals and the ABCDE(F) bundle as an intervention to study its role in the prevention of symptoms and sequelae associated with PICS. None of the studies had as outcomes the presence of symptoms associated with PICS in patients after ICU discharge. Instead, all of them studied the prevalence of triggers related to the development of this syndrome during the ICU stay. Other outcomes were also studied regarding survival rate, the likelihood of ICU and hospital discharge, the likelihood of ICU readmission, and the likelihood of discharge to a destination other than home.

All these characteristics are described in table 1 and the ones most significant for this review will be explained in more detail below.

Pun B *et al.* (20) studied 15000 patients from 68 intensive care units in order to associate bundle performance with health and system-related outcomes. After bundle implementation, it was recorded data from patients that received complete bundle performance and proportional bundle performance. This study had three different types of outcomes: related to the patient, where was included the risk of death; related to symptoms; and related to the system. For this review, our focus is going to be on the symptom-related outcomes, which included adult patients that were in the ICU ward for at least 48 hours, resulting in 10840 participants eligible for this model. In patients receiving complete ABCDEF bundle, it was seen a lower likelihood of mechanical ventilation (AOR, 0.28; CI, 0.22–0.36; $p<0.0001$), coma (AOR, 0.35; CI, 0.22–0.56; $p<0.0001$), delirium (AOR, 0.60; CI, 0.49–0.72; $p<0.0001$) and physical restraint (AOR, 0.37; CI, 0.30–0.46; $p<0.0001$). Increased bundle dose was also associated with more significant pain episodes ($p < 0.0001$).

Thinking that different levels of bundle compliance could result in different health outcomes for ICU patients, Barnes-Daily M *et al.* (21) studied this relationship in 6064 patients. Total compliance was defined as the proportion of days that a certain patient received all the elements of the bundle during its stay in the ICU ward and partial compliance referred to when only a number of elements of the bundle was used. It was concluded that for a 10% increase in total bundle compliance, patients had a 2% increase in delirium-free and coma-free days (IRR, 1.02; 95% CI, 1.01–1.04; $p = 0.004$), and for

every 10% increase in partial bundle compliance, there was a 15% increase in delirium-free and coma-free days (DFCFDs) (IRR, 1.15; 95% CI, 1.09–1.22; p < 0.001).

Other studies compared the use of the bundle with general critical care. In Balas M. *et al.* (22) study data was collected regarding 146 patients pre-bundle implementation and 150 patients post-bundle implementation. General critical care in the setting of this study consisted of inconsistent and disorganized SATs and SBTs, no delirium assessment, and few mobilization strategies. Thus, the primary outcome assessed for mechanically ventilated patients was ventilator-free days and secondarily, for all patients, it was evaluated the prevalence, duration, and percent of ICU days with delirium and coma. It was verified that the prevalence of delirium decreased by 13,6% with the implementation of the bundle (AOR 0.55; CI 0.33–0.93; p=0.003), as well as the percent of ICU days spent delirious that decreased from 50% to 33.3% (p = 0.003). The percentage of patients who were mobilized during their ICU stay was also favorable, having increased from 48% to 66% (p=0.002). Outcomes regarding coma prevalence were not statistically significant.

Bounds M. *et al.* (23) studied, primarily, the prevalence and duration of delirium in ICU patients pre and post-bundle implementation, although some elements of the bundle were already being used in the 2 hospitals evaluated, prior to this study. Data from 159 patients (80 pre-bundle implementation and 79 post-bundle implementation) was collected concluding that the prevalence of delirium decreased from 38% to 23% (p=0.01) in patients managed with the bundle. Also, the mean number of days of delirium decreased significantly (from 3.8 to 1.72 days; p < 0.001) and delirium-free days increased significantly (from 62% to 77%; p=0.01). Favorable outcomes like these ones were also seen in patients with mechanical ventilation. The mean number of days using analgesia increased from 1,37 to 2,51 days (p=0,03). Regarding other outcomes of interest for this review, it was seen an increase in the percentage of patients being mobilized to a sitting position, from 1% to 10% (p=0.01) and there was no significant change regarding days of mechanical ventilation and VDFs, mobilization out of the bed or mean RASS score.

Kram S. *et al.* (24) aimed to implement evidence-based practice in order to start using the bundle in 1 ICU ward with 6 beds. Data were collected during pre-bundle (47 patients) and post-bundle (36 patients) implementation periods to compare different outcomes regarding the length of stay in the hospital and ICU, the number of days with the ventilator, and the prevalence of delirium. There wasn't a significant decrease in the

number of days with the ventilator for patients on the post-bundle implementation group (2,3 days; p=0.33). Regarding delirium, there wasn't data about the pre-bundle group, so the authors compared the baseline delirium prevalence of 19% over 3 months on the post-bundle group with data in the literature about delirium prevalence in ICU patients (20-80%).

Lee Y *et al.* (6) intended to identify the effects of the ABCDE bundle on the prevention of PICS. For that, it compared outcomes of bundle use in the months following its implementation in an intensive care unit from outcomes of the same bundle but modified through continuous activities to improve quality, mainly in terms of education and protocols. This study included 185 patients from 1 ICU ward with 16 beds, and the results showed an increase of patients that were alert and calm from 58.2% using the early ABCDE bundle to 72.4% using the modified ABCDE bundle (p<.001). Coma prevalence decreased significantly from 45.1% using the early ABCDE bundle to 28.7% using the modified ABCDE bundle (p=.021). Although there was seen improvement regarding days free of the ventilator for the modified bundle, this outcome wasn´t statistically relevant. In terms of mobilization, there was seen an increase in the percentage of patients receiving mobilization interventions with modified bundle (from 11% to 54,3%, p<0,001).

Regarding other outcomes such as survival rates, Pun B *et al.* (20) and Barnes-Daily M *et al.* (21) detected a significantly lower likelihood of death in groups receiving high compliance of full bundle performance. Also, Pun B *et al.* (20) and Kram S *et al.* (24) detected that bundle performance had a role in improving the likelihood of ICU and hospital discharge and lowering the likelihood of ICU readmission or discharge to a destination other than home.

Tabel 1: Characteristics of the included studies

Legend: AOR: adjusted odds ratio; OR: odds ratio; CI: confidence interval; AHR: adjusted hazard ratio; IRR: incidence rate ratio

Reference	Study type	Aim of the study	Participants	Setting	Comparasion	Interventions
Pun B, Balas M, Barnes-Daly M *et al.* 2019	Cohort Study	Associate ABCDEF bundle performance with health outcomes from ICU patients	15226 adults with at least one ICU day	68 ICUs	Complete performance of the ABCDEF bundle from Proportional performance of the ABCDEF bundle	Complete bundle performance: performance of every eligible bundle element Proportional bundle performance: performance of a percentage of eligible bundle elements
Barnes-Daly M, Phillips G, Ely E 2017	Cohort Study	Associate ABCDEF bundle compliance with health outcomes from ICU patients	6064 adults	7 ICUs	Different levels of compliance of total and partial ABCDEF performance	Total bundle compliance: use of all elements of the ABCDEF bundle for which the patient was eligible Partial bundle compliance: use of some elements of the bundle
Lee Y, Kim K, Lim C *et al.* 2020	Cohort Study	Study the effect of early and modified ABCDE bundle on the prevention of PICS	185 adults	1 ICU	Early ABCDE Bundle from modified ABCDE bundle	ABCDE bundle
Bounds M, Kram S, Speroni K *et al.* 2016	Cohort Study	Study the prevalence and duration of delirium in ICU patients before and after implementation of the ABCDE bundle.	159 adults with at least one ICU day	ICUs from 2 hospitals	Implementation of the ABCDE bundle care from the usual care	ABCDE bundle
Kram S, Dibartolo M, Hinderer K *et al.* 2015	Cohort Study	Implement an evidence-based practice for ABCDEF bundle performance	83 adults	ICUs of 2 hospitals	Implementation of the ABCDE bundle care from the usual care	ABCDE bundle
Balas M, Vasilevskis E, Olsen K *et al.* 2014	Cohort Study	Evaluate the effectiveness and safety of implementing the ABCDE bundle	296 adults	5 ICUs, 1 step-down unit, and 1 oncology/ hematology special care unit	Implementation of the ABCDE bundle care from usual care	ABCDE bundle

Reference	Symptom-related outcomes	Survival outcomes	Other outcomes
Pun B, Balas M, Barnes-Daly M *et al.* 2019	Lower likelihood of mechanical ventilation (AOR, 0.28; CI, 0.22–0.36; p<0.0001), delirium (AOR, 0.60; CI, 0.49–0.72; p<0.0001) and physical restraint (AOR, 0.37; CI, 0.30–0.46; p<0.0001) with complete bundle performance Increased bundle dose was associated with more significant pain episodes (p < 0.0001)	Lower likelihood of death (AHR, 0.32; CI,0,17-0,62; p<0.001) with complete bundle performance	Higher likelihood of ICU discharge (AHR, 1.17; CI, 1.05–1.30; p<0.004), hospital discharge (AHR, 1.19; CI, 1.01–1.40; p<0.033), 46% lower likelihood of ICU readmission (AOR, 54%; p<0.001) and a 36% lower likelihood of discharge to a destination other than home (AOR, 64% p<0.001) with full bundle performance
Barnes-Daly M, Phillips G, Ely E. 2017	For every 10% increase in total bundle compliance, patients had a 2% increase in delirium-free and coma-free days (IRR, 1.02; 95% CI, 1.01–1.04; p = 0.004), 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; p < 0.001)	For every 10% increase in total bundle compliance, patients had a 7% higher odds of hospital survival (OR, 1.07; 95% CI, 1.04–1.11; p < 0.001). For every 10% increase in partial bundle compliance, patients had a 15% higher hospital survival (OR, 1.15; 95% CI, 1.09–1.22; p < 0.001)	
Lee Y, Kim K, Lim C *et al.* 2020	Increase of patients that were alert and calm from 58.2% to 72.4% (p<0,001) and decrease in coma prevalence from 45.1% to 28.7% using the modified ABCDE bundle (p=0.021).		Increase in the percentage of patients receiving interventions of early mobilization with a modified bundle (from 11% to 54,3%, p<0,001)
Bounds M, Kram S, Speroni K *et al.* 2016	Decrease in the prevalence of delirium (from 38% to 23%, p = 0,001) and the mean number of days it existed (from 3.8 to 1.72 days, p < .001) with bundle performance. Increase in the number of patients with delirium-free stays (from 62% to 77%; p = 0.01)		Mean number of days with analgesia increased after bundle performance (from 1,37 to 2,51; p=0,003) Number of patients mobilized to a sitting position increased after bundle implementation (from 1% to 10%; p=0,01)
Kram S, Dibartolo M, Hinderer K *et al.* 2015	Delirium prevalence of 19% (no comparison with pre-bundle data) 37% of patients received a passive range of motion exercises.		26% decrease in the length of hospital admission from 6.9 days to 5.09 days (p = 0.06) after bundle implementation
Balas M, Vasilevskis E, Olsen K *et al.* 2014	Decrease by half of the odds of delirium (OR, 0.55; 95% CI, 0.33–0.93; p = 0.03) and decrease in the prevalence of delirium (p=0,03) and on the percent of ICU days spent delirious (from 50% to 33.3%; p = 0.003). Increased odds of mobilizing out of bed at least once during an ICU stay (OR 2.11; 95% CI, 1.29–3.45; p = 0.003) and increase in the number of patients who were mobilized during their ICU stay (p = 0.002). Increase of the days without mechanical assistance (p = 0.04) in the postimplementation period		

Bias risk

Bias risk was assessed using ROBINS-I tool (Risk of Bias in Non-randomized Studies - of Interventions) and the app "Robvis" to create figure 2.

We analyzed bias due to confounding; due to selection of participants; in classification of interventions; due to deviations from intended interventions; due to missing data; in measurement of outcomes and in selection of the reported result.

Overall, three of the studies represented a moderate risk of bias and the other (Kram S. *et al.* (24); Balas M. *et al.* (22); Lee Y *et al.* (6)) classified as having a serious risk of bias. This happens at the expense of the risk of bias due to confounding, which refers to the presence of variables that may affect the variables being studied. Therefore, the studies considered to be at a moderate risk of bias due to confounding considered the existence of confounding factors and did study analysis having them accounted for.

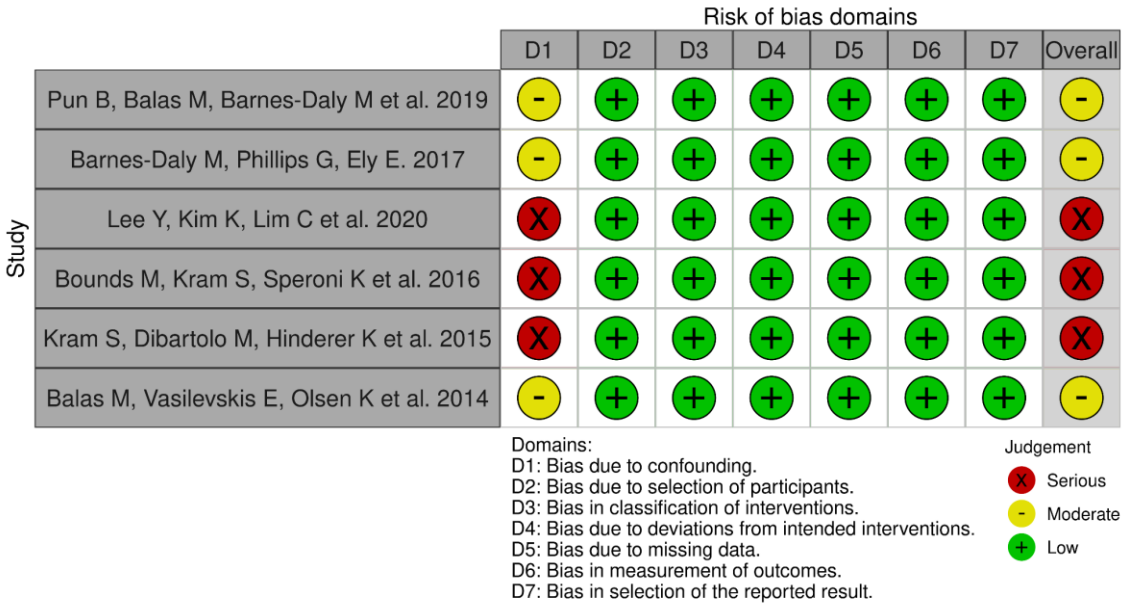

Figure 2- Risk of bias in included studies

Chapter 4

Discussion

In all these 6 cohort studies, the intervention implemented was the use of full or partial ABCDE(F) bundle with different levels of compliance. The comparison groups differed depending on the aim of the study. Thus, Pun B *et al.* (20) compared the full performance of the bundle from its proportional performance, as for Barnes-Daily M *et al.,* (21) even though this last study had, as a comparator factor, different levels of compliance of bundle performance. In general, these studies concluded that full bundle performance and an increase in bundle compliance translated into a decrease in PICS´s triggers, such as mechanical ventilation duration and delirium.

In other 3 studies (Bounds M. *et al.*,(23) Kram S. *et al.* (24) and Balas M *et al.* (22)) it was compared the usual ICU critical care with the use of the ABCDE bundle as management for ICU patients, having reached similar conclusion to those mentioned for the previous study, regarding the decrease on the prevalence of delirium and the increase in mobilization with the use of the bundle.

On the other hand, Lee Y *et al.* (6) aimed to show the effect of the A-E bundle on the prevention of PICS by implementing quality-improving strategies to its performance, having reached to the conclusion that the bundle resulted in a reduction of the level of sedation and immobilization.

Although our review intended to understand if bundle performance has a role in PICS prevention, none of our included studies had the prevalence of PICS in ICU patients as an outcome, maybe for its complex nature and subsequent difficult assessment, since there's no diagnostic criteria defined, as discussed in the introduction. Additionally, none of the studies assessed for symptoms related to PICS after ICU discharge. Thus, our discussion will focus on the effects of the bundle on the prevalence of PICS triggers in ICU patients.

As said in the introduction, mechanical ventilation can contribute to ICU-acquired weakness, so it's logical to think about the relevance of maintaining ICU patients out of the ventilator as much as possible. A lower likelihood of mechanical ventilation was described in Pun B. *et al.*, (20) which was more favorable with full bundle performance. As for comparing bundle performance with usual critical care, Balas M. *et al* (22) concluded that this bundle strategy increases the days without mechanical assistance. Although not a significant conclusion, Kram S. *et al.* (24) described a 29%

decrease in the number of ventilator days per patient, from pre to post-bundle implementation, 3.3 to 2.3 days (P = 0,33). Thus, we could understand the relationship between spontaneous awakening trials and spontaneous breathing trials and their role in decreasing mechanical ventilation days, which correlates with existing evidence. (26)
Continuing to discuss physical impairment, Balas M. *et al.* (22) concluded that bundle performance relates to an increase in the odds of mobilization out of the bed at least once during the ICU stay and it was verified an increase in the number of patients who were mobilized. Although not finding a significant result regarding patients that were mobilized out of bed, Bounds M. *et al.* (23) described an increase in patients mobilized to a sitting position after bundle implementation. According to this, Pun B *et al.* (20) concluded that a full bundle performance, compared with a partial bundle performance, lowers the likelihood of physical restraint. This is a favorable outcome since literature has shown that early mobilization, besides being cost-effective, helps with the decrease of delirium. (3,27)
As for cognitive impairments, delirium was, without a doubt, the outcome for which we could find more data. Pun B. *et al.* (20) concluded that a lower likelihood of delirium was seen in patients receiving full bundle performance. Bundle compliance also influences this, as shown by Barnes-Daly M. *et al.*, (21) since it correlates with an increase in DFCFDs, that is, when the patient was alive and both not delirious (CAM-ICU negative) and not in a coma (RASS, –3 or higher). In Bounds M. *et al.*, (23) the daily mean RASS score indicated slightly less sedation after bundle implementation, but this result was not statistically significant (from -1.01 to -0.72, P = 0,21). Comparing usual critical care with bundle performance, the three included studies that described this relationship, refer to a decrease in the odds of delirium, a decrease in delirium prevalence, and an increase in delirium-free days. In fact, Bounds M. *et al.* (23) studied this relationship for patients receiving mechanical ventilation and for those not receiving mechanical ventilation, having reached similar results.
Psychiatry impairments related to PICS can evolve from deep sedation, which is also a factor for hospital mortality and an increase in ICU length of stay.(3) Lee Y. *et al* (6) described an increase in patients that were alert and calm when strategies were implemented to make the bundle more efficient for that ICU.
In general, we can associate the use of the ABCDE(F) bundle with improvements in different health outcomes, including PICS´s triggers. However, most of the studies that were included in this review don't use the most recent bundle, with the “F” element, which could possibly result in even more favorable outcomes.
Another limitation of this study is the reduced number of studies that met our criteria, plus the fact that none of them assessed for PICS or its symptoms after ICU discharge.

Chapter 5

Conclusion

With the assignment by the SCCM of the term PICS to define morbidities that arise from ICU hospitalization, the question arises as to how we can prevent this syndrome. The ABCDEF bundle emerges as a possible tool for its prevention.

There is a growing awareness of the long-term consequences after critical care, making as a major goal in intensive care, not only the survival of patients, but also an optimization of their recovery. (9) Thus, care bundles emerge as a way to make clinical practices as close as possible to scientific evidence, through holistic protocols for approaching a given procedure, symptom, and/or treatment. (6)

Therefore, we intended to understand if the ABCDEF bundle has a role in the prevention of PICS, to create an evidence-based paper that could possibly be helpful to implement favorable strategies in ICUs.

After analyzing the included studies, we can conclude that the use of this bundle relates to a decrease in PICS´s triggers, such as physical restriction, delirium, sedation, and mechanical assistance, especially with full bundle performance and a greater bundle compliance. Thus, since these triggers are thought to precede PICS, (5) we could infer from our findings that the use of the bundle on critical care has a role in the prevention of PICS. Although not very relevant, we must mention the existence of risk of bias in the included studies, related to co-variants existing, may have played a role in the results achieved, in spite of most of the studies having taken this into account when analyzing the data.

Even though we reached these conclusions, it would be important to define criteria for PICS assessment to better understand the direct effect of the ABCDEF bundle on the prevention of this syndrome. Besides, more studies need to be conducted using the more recent bundle, including the “F” element.

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Supplementary files

Supplementary file 1

Supplementary file 1.1- Healthy Aging Brain Center Monitor Self-Report (11)

Over the past **two weeks**, how often did **your loved one** have problems with: (Use √ to indicate your answer.)	Not at all **(0-1 day)** 0 points	Several Days **(2-6 days)** 1 point	More than half the days **(7-11 days)** 2 points	Almost daily **(12-14 days)** 3 points
Judgment or decision-making				
Repeating the same things over and over such as questions or stories				
Forgetting the correct month or year				
Handling complicated financial affairs such as balancing checkbook, income taxes & paying bills				
Remembering appointments				
Thinking or memory				
Learning how to use a tool, appliance, or gadget				
Planning, preparing, or serving meals				
Taking medications in the right dose at the right time				
Walking or physical ambulation				
Bathing				
Shopping for personal items like groceries				
Housework or household chores				
Leaving her/him alone				
Her/his safety				
Her/his quality of life				
Falling or tripping				
Less interest or pleasure in doing things, hobbies or activities				
Feeling down, depressed, or hopeless				
Being stubborn, agitated, aggressive or resistive to help from others				
Feeling anxious, nervous, tense, fearful or panic				
Believing others are stealing from them or planning to harm them				
Hearing voices, seeing things or talking to people who are not there				
Poor appetite or overeating				
Falling asleep, staying asleep, or sleeping too much				
Acting impulsively, without thinking through the consequences of her/his actions				
Wandering, pacing, or doing things repeatedly				
Over the past **two weeks**, how often did **you** have problems with: (Use √ to indicate your answer.)	Not at all **(0-1 day)** 0 points	Several Days **(2-6 days)** 1 point	More than half the days **(7-11 days)** 2 points	Almost daily **(12-14 days)** 3 points
Your quality of life				
Your financial future				
Your mental health				
Your physical health				
Place Sticker Here	**COGNITIVE SUBSCALE**			
	FUNCTIONAL SUBSCALE			
	BEHAVIORAL AND MOOD SUBSCALE			
	CAREGIVER STRESS SUBSCALE			
	TOTAL SCORE			

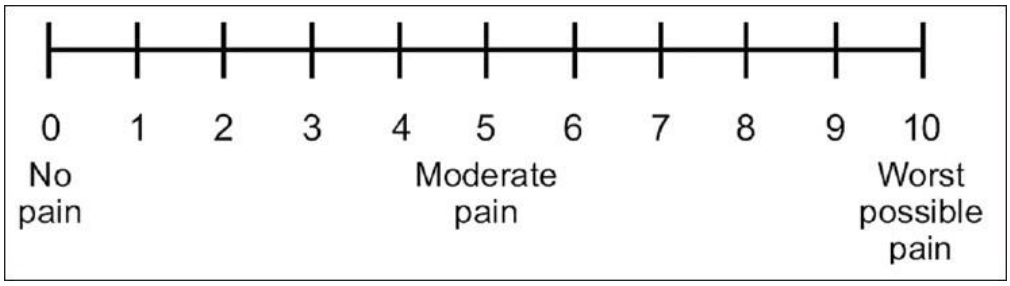
HABC Monitor CG Version – revised 10/19/11 – developed by IDND

Supplementary file 1.2- Post-Intensive Care Syndrome Questionnaire (12)

Items	Never	Sometimes	Most often	Always
1. It's hard to memorise numbers.	0	1	2	3
2. People around me say that I repeat what I said before.	0	1	2	3
3. It is hard for me to find the way.	0	1	2	3
4. I cannot concentrate on reading	0	1	2	3
5. Money management is difficult.	0	1	2	3
6. I am confused with date or time.	0	1	2	3
7. My joints are stiff.	0	1	2	3
8. My hand grip is weak.	0	1	2	3
9. I can hardly climb the stairs.	0	1	2	3
10. My sexual performance has deteriorated.	0	1	2	3
11. I get tired easily.	0	1	2	3
12. I feel sick everywhere in my body.	0	1	2	3
13. My heart is stuffy.	0	1	2	3
14. I have nightmares.	0	1	2	3
15. I am worried.	0	1	2	3
16. I am annoyed or angry.	0	1	2	3
17. I am easily startled	0	1	2	3
18. I have no hope.	0	1	2	3

Supplementary file 2

Supplementary file 2.1- Numerical Rating Scale (3)



Supplementary file 2.2- Behavioral Pain Scale (14)

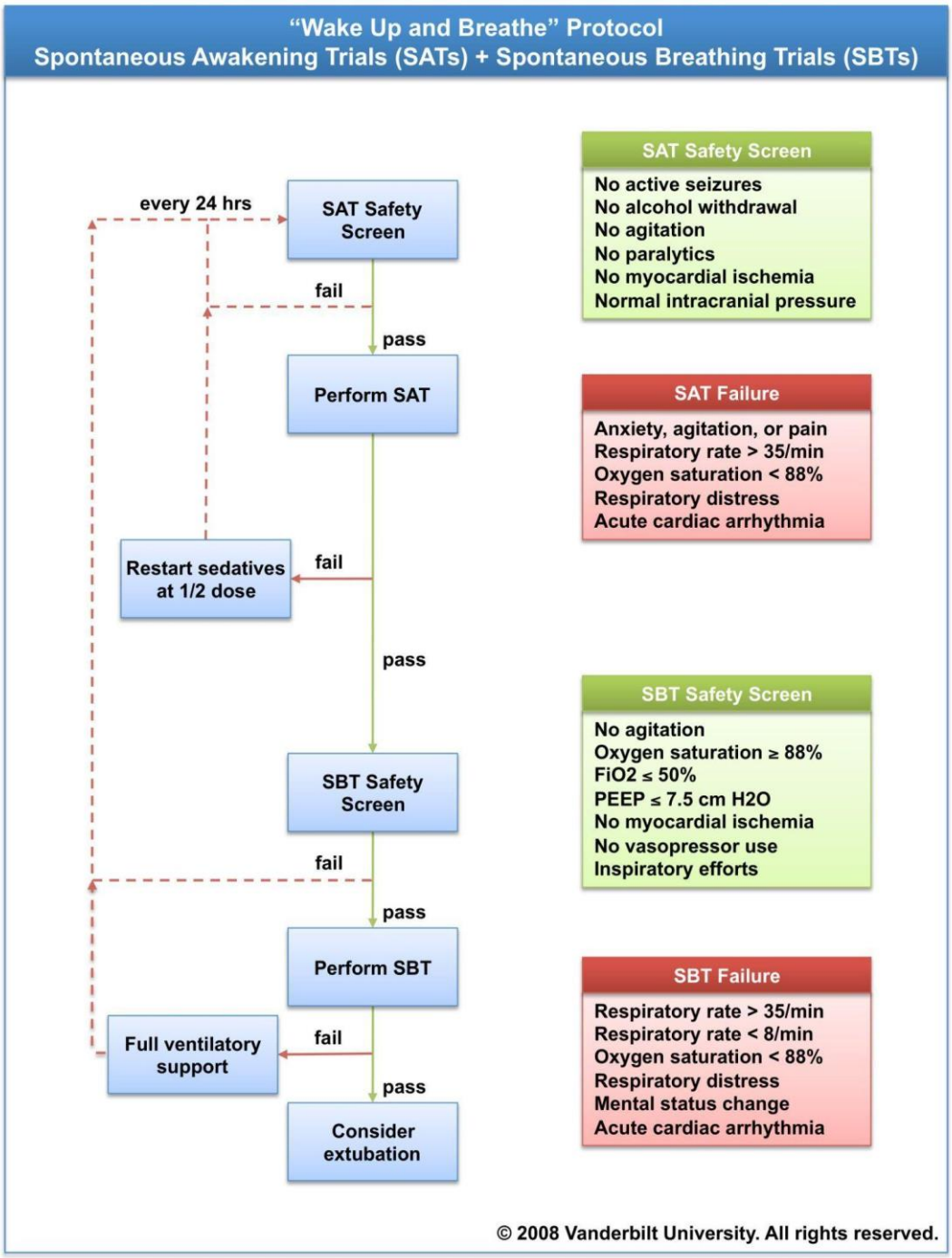
Sub-scale	Description	Score
Facial expression	Relaxed	1
	Partially tightened	2
	Fully tightened	3
	Grimacing	4
Upper limbs	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with ventilation	Tolerating movement	1
	Coughing but tolerating ventilation for most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4

Supplementary file 2.3- Critical Care Pain Observation Tool (15)

Sub-scale	Description	Score
Facial expression	Relaxed, neutral	0
	Tense	1
	Grimacing	2
Body movements	Absence of movements	0
	Protection	1
	Restlessness	2
Muscle tension	Relaxed	0
	Tense, rigid	1
	Very tense or rigid	2
Compliance with ventilation	Tolerating ventilator or movement	0
	Coughing but tolerating	1
	Fighting ventilator	2
Vocalisation (extubated patients)	Talking in normal tone or no sound	0
	Sighing, moaning	1
	Crying out, sobbing	2

Supplementary file 3

Supplementary file 3- Wake Up and Breathe Flowchart (17)



Supplementary file 4

Supplementary file 4.1- Richmond Agitation-Sedation Scale (9)

Term	Score
Combative	+4
Very agitated	+3
Agitated	+2
Restless	+1
Alert and calm	0
Drowsy	−1
Light sedation	−2
Moderate sedation	−3
Deep sedation	−4
Unrousable	−5

Supplementary file 4.2- Sedation-Agitation Scale (9)

Score	Characteristics	Examples of Patients' Behavior
NA	Not applicable	Patient is chemically paralyzed; level of sedation should be assessed during paralytic holiday
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands
2	Very sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
3	Sedated	Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off again, follows simple commands
4	Calm and cooperative	Calm, awakens easily; follows commands
5	Agitated	Anxious or mildly agitated, attempting to sit up, calms down to verbal instructions
6	Very agitated	Does not calm, despite frequent verbal reminding of limits; requires physical restraints, biting endotracheal tube
7	Dangerously	Pulling at endotracheal tube, trying to remove

Supplementary file 5

Supplementary file 5.1- CAM-ICU Worksheet (3)

Feature 1: Acute Onset or Fluctuating Course	Score	Check here if Present
Is the pt different than his/her baseline mental status? OR Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation scale (i.e., RASS), GCS, or previous delirium assessment?	Either question Yes →	☐
Feature 2: Inattention		
Letters Attention Test (See training manual for alternate **Pictures**) Directions: Say to the patient, *"I am going to read you a series of 10 letters. Whenever you hear the letter 'A,' indicate by squeezing my hand."* Read letters from the following letter list in a normal tone 3 seconds apart. **S A V E A H A A R T** **Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A."**	Number of Errors >2 →	☐
Feature 3: Altered Level of Consciousness		
Present if the Actual RASS score is anything other than alert and calm (zero)	RASS anything other than zero →	☐
Feature 4:Disorganized Thinking		
Yes/No Questions (See training manual for alternate set of questions) 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does one pound weigh more than two pounds? 4. Can you use a hammer to pound a nail? **Errors are counted when the patient incorrectly answers a question.** **Command** Say to patient: "Hold up this many fingers" (Hold 2 fingers in front of patient) "Now do the same thing with the other hand" (Do not repeat number of fingers) *If pt is unable to move both arms, for 2nd part of command ask patient to "Add one more finger" **An error is counted if patient is unable to complete the entire command.**	Combined number of errors >1→	☐

Overall CAM-ICU Feature 1 plus 2 and either 3 or 4 present = CAM-ICU positive		
	Criteria Met →	☐ CAM-ICU Positive (Delirium Present)
	Criteria Not Met →	☐ CAM-ICU Negative (No Delirium)

Supplementary file 5.2- Intensive Care Delirium Screening Checklist (11)

1. Altered level of consciousness. Choose one from A to E		
A. Exaggerated response to normal stimulation	SAS = 5, 6, 7 or RASS = +1 to +4	(1 point)
B. Normal wakefulness	SAS = 4 or RASS = 0	(0 points)
C. Response to mild or moderate stimulation (follows commands)	SAS = 3 or RASS = −1 to −3	(1 point)
D. Response only to intense and repeated stimulation (e.g., loud voice and pain)	SAS = 2 or RASS = −4	Stop assessment[a]
E. No response	SAS = 1 or RASS = −5	Stop assessment[a]
2. Inattention (1 point if any present)		
A. Difficulty in following commands or		
B. Easily distracted by external stimuli or		
C. Difficulty in shifting focus		
Does the patient follow you with their eyes?		
3. Disorientation (1 point for any abnormality)		
A. Mistake in either time, place, or person		
Does the patient recognize ICU caregivers who have cared for him/her and not recognize those who have not? What kind of place are you in? (list examples)		
4. Hallucinations or delusions (1 point for either)		
A. Equivocal evidence of hallucinations or a behavior due to hallucinations (hallucination = perception of something that is not there with no stimulus) or		
B. Delusions or gross impairment of reality testing (delusion = false belief that is fixed/unchanging)		
Any hallucinations now or over past 24 hr? Are you afraid of the people or things around you? (fear that is inappropriate to the clinical situation)		
5. Psychomotor agitation or retardation (1 point for either)		
A. Hyperactivity requiring the use of additional sedative drugs or restraints in order to control potential danger (e.g., pulling IV catheters out or hitting staff) or		
B. Hypoactive or clinically noticeable psychomotor slowing or retardation		
Based on documentation and observation over shift by primary caregiver		
6. Inappropriate speech or mood (1 point for either)		
A. Inappropriate, disorganized, or incoherent speech or		
B. Inappropriate mood related to events or situation		
Is the patient apathetic to current clinical situation (i.e., lack of emotion)?		
Any gross abnormalities in speech or mood? Is patient inappropriately demanding?		
7. Sleep/wake cycle disturbance (1 point for any abnormality)		
A. Sleeping < 4 hr at night or		
B. Waking frequently at night (do not include wakefulness initiated by medical staff or loud environment) or		
C. Sleep ≥ 4 hr during day		
Based on primary caregiver assessment		
8. Symptom fluctuation (1 point for any)		
Fluctuation of any of the above items (i.e., 1–7) over 24 hr (e.g., from one shift to another)		
Based on primary caregiver assessment		
Total Intensive Care Delirium Screening Checklist score (add 1–8) _____		

[a]Delirium assessment can not be completed in patients who are stuporous or comatose.
SAS = Riker Sedation-Agitation Scale, RASS = Richmond Agitation-Sedation Scale.
Modified from Devlin JW, Marquis F, Riker RR, et al: Combined didactic and scenario-based education improves the ability of intensive care unit staff to recognize delirium at the bedside. *Crit Care* 2008; 12:R19.

Supplementary file 6

Supplementary file 6- Medical Research Council grading of muscle strength (19)

Muscle group evaluated	Appointed score
Wrist extension	0, no visible/palpable contraction
Elbow flexion	1, visible/palpable contraction without movement of the limb
Shoulder abduction	2, movement of the limb, but not against gravity
Dorsiflexion foot	3, movement against gravity
Knee extension	4, movement against gravity and some resistance
Hip flexion	5, normal