

# World Journal of *Critical Care Medicine*

*World J Crit Care Med* 2023 March 9; 12(2): 41-91



## Contents

Bimonthly Volume 12 Number 2 March 9, 2023

## MINIREVIEWS

- 41 Enhancing the awakening to family engagement bundle with music therapy  
*Modrykamien AM*
- 53 Point-of-care ultrasound in diagnosis and management of congestive nephropathy  
*Turk M, Robertson T, Koratala A*

## ORIGINAL ARTICLE

## Observational Study

- 63 Elevated soluble fas blood concentrations in patients dying from spontaneous intracerebral hemorrhage  
*Lorente L, Martín MM, Pérez-Cejas A, Ramos-Gómez L, Solé-Violan J, Cáceres JJ, Jiménez A, González-Rivero AF*

## SYSTEMATIC REVIEWS

- 71 Extracorporeal blood purification strategies in sepsis and septic shock: An insight into recent advancements  
*Mehta Y, Paul R, Ansari AS, Banerjee T, Gunaydin S, Nassiri AA, Pappalardo F, Premužić V, Sathe P, Singh V, Vela ER*

## LETTER TO THE EDITOR

- 89 The artificial intelligence evidence-based medicine pyramid  
*Bellini V, Coccolini F, Forfori F, Bignami E*

**ABOUT COVER**

Peer Reviewer of *World Journal of Critical Care Medicine*, Deng-Gao Peng, MD, Associate Chief Physician, Associate Professor, Department of Emergency Medicine, The Third People's Hospital of Shenzhen, Shenzhen 518112, Guangdong Province, China. 1370211295@qq.com

**AIMS AND SCOPE**

The primary aim of the *World Journal of Critical Care Medicine (WJCCM, World J Crit Care Med)* is to provide scholars and readers from various fields of critical care medicine with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJCCM mainly publishes articles reporting research results and findings obtained in the field of critical care medicine and covering a wide range of topics including acute kidney failure, acute respiratory distress syndrome and mechanical ventilation, application of bronchofiberscopy in critically ill patients, cardiopulmonary cerebral resuscitation, coagulant dysfunction, continuous renal replacement therapy, fluid resuscitation and tissue perfusion, hemodynamic monitoring and circulatory support, ICU management and treatment control, sedation and analgesia, severe infection, etc.

**INDEXING/ABSTRACTING**

The WJCCM is now abstracted and indexed in PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Yi-Xuan Cai; Production Department Director: Xu Guo; Editorial Office Director: Li-Li Wang.

**NAME OF JOURNAL**

*World Journal of Critical Care Medicine*

**ISSN**

ISSN 2220-3141 (online)

**LAUNCH DATE**

February 4, 2012

**FREQUENCY**

Bimonthly

**EDITORS-IN-CHIEF**

Hua-Dong Wang

**EDITORIAL BOARD MEMBERS**

<https://www.wjnet.com/2220-3141/editorialboard.htm>

**PUBLICATION DATE**

March 9, 2023

**COPYRIGHT**

© 2023 Baishideng Publishing Group Inc

**INSTRUCTIONS TO AUTHORS**

<https://www.wjnet.com/bpg/gerinfo/204>

**GUIDELINES FOR ETHICS DOCUMENTS**

<https://www.wjnet.com/bpg/gerinfo/287>

**GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH**

<https://www.wjnet.com/bpg/gerinfo/240>

**PUBLICATION ETHICS**

<https://www.wjnet.com/bpg/gerinfo/288>

**PUBLICATION MISCONDUCT**

<https://www.wjnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjnet.com/bpg/gerinfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>

# Enhancing the awakening to family engagement bundle with music therapy

Ariel M Modrykamien

**Specialty type:** Critical care medicine

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0  
Grade B (Very good): B  
Grade C (Good): C, C, C  
Grade D (Fair): 0  
Grade E (Poor): 0

**P-Reviewer:** Hu B, China; Papamichalis P, Greece; Shelat VG, Singapore

**Received:** October 27, 2022

**Peer-review started:** October 27, 2022

**First decision:** December 19, 2022

**Revised:** December 19, 2022

**Accepted:** February 2, 2023

**Article in press:** February 2, 2023

**Published online:** March 9, 2023



**Ariel M Modrykamien**, Department of Pulmonary and Critical Care, Baylor University Medical Center, Dallas, TE 75246, United States

**Corresponding author:** Ariel M. Modrykamien, MD, Chief of Critical Care Medicine, Department of Pulmonary and Critical Care, Baylor University Medical Center, 3600 Gaston Ave., Dallas, TX 75246, United States. [ariel.modrykamien@bswhealth.org](mailto:ariel.modrykamien@bswhealth.org)

## Abstract

Survivors of prolonged intensive care unit (ICU) admissions may present undesirable long-term outcomes. In particular, physical impairment and cognitive dysfunction have both been described in patients surviving episodes requiring mechanical ventilation and sedation. One of the strategies to prevent the aforementioned outcomes involves the implementation of a bundle composed by: (1) Spontaneous awakening trial; (2) Spontaneous breathing trial; (3) Choosing proper sedation strategies; (4) Delirium detection and management; (5) Early ICU mobility; and (6) Family engagement (ABCDEF bundle). The components of this bundle contribute in shortening length of stay on mechanical ventilation and reducing incidence of delirium. Since the first description of the ABCDEF bundle, other relevant therapeutic factors have been proposed, such as introducing music therapy. This mini-review describes the current evidence supporting the use of the ABCDEF bundle, as well as current knowledge on the implementation of music therapy.

**Key Words:** Bundle; Delirium; Mechanical ventilation; Mobility; Music therapy

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core Tip:** Data support the implementation of the (1) Spontaneous awakening trial; (2) Spontaneous breathing trial; (3) Choosing proper sedation strategies; (4) Delirium detection and management; (5) Early ICU mobility; and (6) Family engagement bundle for mechanically ventilated patients. The role of music therapy is evolving.



**Citation:** Modrykamien AM. Enhancing the awakening to family engagement bundle with music therapy. *World J Crit Care Med* 2023; 12(2): 41-52

**URL:** <https://www.wjgnet.com/2220-3141/full/v12/i2/41.htm>

**DOI:** <https://dx.doi.org/10.5492/wjccm.v12.i2.41>

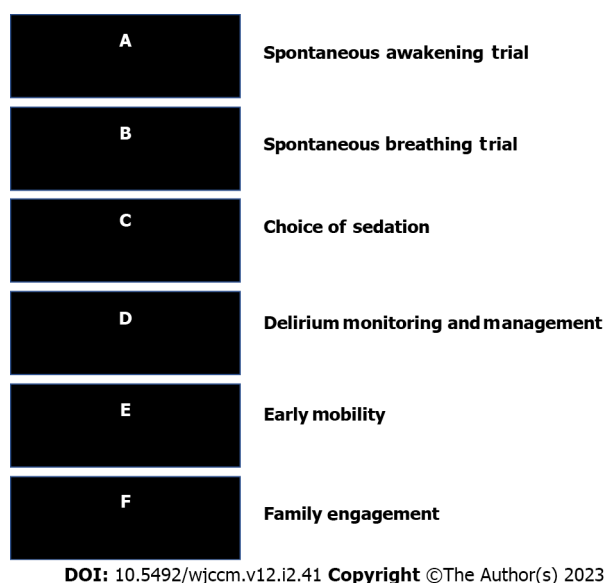
## INTRODUCTION

Innovation of clinical practices and introduction of new technologies have improved survival of critically ill patients[1]. Furthermore, the implementation of specific strategies for mechanical ventilation [2], pharmacotherapy[3], fluid therapy[4] and bundles of care[5] brought about improvement in other relevant outcomes, such as shorter mechanical ventilation or intensive care unit (ICU) lengths of stay (LOS). Despite those aforementioned achievements, a variety of other long-term outcomes directly affected by ICU admissions still remain problematic for patients, families, and the entire society. Over the last two decades, multiple publications have described significant long-term post-ICU impairments. In particular, the presence of muscle waist with its consequent alteration of physical function, and high rates of cognitive dysfunction have been repeatedly reported. A landmark article, which described 1-year outcomes in 109 survivors of acute respiratory distress syndrome (ARDS) revealed that those patients had persistent functional disability[6]. The physical role domain score in the Medical Outcomes Study 36-item Short-Form (SF-36) questionnaire was only 25 points, while the score in normal population was 84. Strikingly, at 12 months from hospital discharge, only 49% of those individuals had returned to work. Among those, only 78% had returned to their original job. Reported reasons for not returning to work included chronic fatigue and weakness, stressing the relevance of general muscular debility as a cause of their inactivity. A follow-up study published by the same group, which addressed functional disability 5 years post-ICU discharge, showed that the mean score of the physical component of the SF-36 remained approximately 1 standard deviation below the mean score of an age and gender-matched control population[7]. Also, the distance walked in 6 min was significantly correlated with the physical-component score of this survey. Interestingly, the mental component domains of the SF-36 questionnaire remained within normal limits over the 5 years of follow up. These long-term quality of life alterations were not only limited to patients with ARDS. A study that followed a large cohort of patients for more than 6 years after admission to surgical ICUs (SICUs) showed significant impact in their response to the EuroQol-6D tool (another quality-of-life questionnaire)[8]. Specifically, 52% of patients reported impairment in mobility, 29% had anxiety and/or depression, and 43% disclosed cognitive impairment. Alterations in physiology during ICU admissions have been linked with the development of neurocognitive impairments[9]. A prospective cohort study that included 126 mechanically ventilated patients admitted in ICU, mostly due to sepsis and/or ARDS, showed that at 12 months post-discharge, 71% presented cognitive impairment[10]. Interestingly, increasing delirium duration was deemed as an independent predictor of poor cognitive performance among this population. Based on the aforementioned data, individual strategies have been studied in order to avoid the previously described outcomes. Specifically, reduction and/or possible avoidance in the use of sedatives, protocolized liberation from mechanical ventilation, selection of drugs with lower deliriogenic effect, detection and management of delirium, early mobilization, and family participation in care have all been investigated. The positive outcomes brought about by these individual strategies concluded with the development of a bundle of care, known as the ABCDEF bundle (Figure 1). Each element of the bundle corresponded to a demonstrated beneficial intervention, such as: (1) Awakening trial (SAT) ; (2) Spontaneous breathing trial (SBT) and mechanical ventilation liberation; (3) Selective choice of drugs, particularly sedatives; (4) Detection, management, and prevention of delirium; (5) Early patient mobilization; and (6) Family and/or caregiver involvement in care. While the ABCDEF bundle has been widely accepted and implemented, other interventions have been found potentially beneficial, and could enhance the bundle. Particularly, the utilization of music therapy may have promising outcomes. The next sections of the manuscript will describe: (1) Evidence supporting individual components of the ABCDEF bundle; (2) Evidence supporting the ABCDEF bundle implementation; and (3) Supporting data for the use of music therapy.

## EVIDENCE SUPPORTING INDIVIDUAL COMPONENTS OF THE ABCDEF BUNDLE

### *Spontaneous awakening trials*

Over the last few decades, the strategies for providing sedation to critically ill mechanically ventilated patients have followed a pendular fashion. In a thoughtful editorial written by Dr. Thomas L. Petty in 1998, he stated: "When we first started our unit in 1964, patients who required mechanical ventilation were awake and alert and often sitting in a chair by being awake and alert, these individuals could interact with their family, friends, and the environment". In another paragraph, referring to practices



**Figure 1 Bundle components.**

held in 1998, he mentioned: “What I see these days are paralyzed, sedated patients, lying without motion, appearing to be dead, except for the monitors that tell me otherwise”[11]. Evidence published by the end of the ‘90s and during the 2000s has caused a movement back towards patient awakening. A prospective observational cohort study that followed 93 mechanically ventilated patients receiving intravenous (IV) continuous sedations *vs* 149 patients receiving sedation boluses or no-sedation showed significant longer duration on mechanical ventilation within the group receiving continuous IV sedation ( $185 \pm 190$  h *vs*  $56 \pm 75.6$  h;  $P < 0.001$ )[12]. Furthermore, the ICU and hospital LOS were also longer within the continuous IV sedation group ( $13.5 \pm 34$  d *vs*  $4.8 \pm 4$ ; and  $21 \pm 25$  d *vs*  $13 \pm 14$ ,  $P < 0.001$ , respectively). A year later, a randomized, control trial studied whether a nurse-implemented protocol-directed sedation strategy *vs.* no protocol resulted in improved outcomes in mechanically ventilated patients[13]. Notably, duration of mechanical ventilation was shorter in the protocol-directed group ( $89$  h  $\pm 134$  h *vs*  $124$  h  $\pm 154$ ,  $P = 0.003$ ). ICU and hospital stays were also shorter within this group ( $5.7 \pm 6$  *vs*  $7.5$  d  $\pm 7$ ,  $P = 0.013$ ; and  $14$  d  $\pm 17$  *vs*  $20$  d  $\pm 24$ ,  $P < 0.001$ , respectively). Based on the aforementioned data, it became apparent that intermittent (rather than continuous) and protocol-directed sedation strategies were beneficial compared with prior usual practices. A landmark randomized control study (RCT), which included 128 mechanically ventilated patients sedated by a continuous IV strategy, allocated patients to an intervention of daily sedation vacation to awakening trials *vs* sedation management at the discretion of clinicians[14]. This study confirmed the previously described findings. In more detail, patients assigned to the intervention group had a ventilator duration of 4.9 d, compared with 7.3 d in the control group ( $P = 0.004$ ). The median LOS in the ICU was 6.4 d *vs* 9.9 d, respectively ( $P = 0.02$ ). Contrary to the sufficient evidence that exists regarding daily awakening trials and using protocol-directed strategies, the depth of initial sedation implemented immediately after intubation has been an area of uncertainty. However, a multicenter, longitudinal cohort study evaluated whether initial sedation depth (assessed by Richmond Agitation-Sedation Scale – RASS) within 24–48 h post-intubation was associated with time-to-extubation and/or survival[15]. Notably, initial depth of sedation resulted an independent predictor of time to ventilator liberation [hazard ratio (HR): 0.90;  $P < 0.01$ ], hospital mortality (HR: 1.1;  $P = 0.01$ ), and 180-d mortality (HR: 1.08;  $P = 0.02$ ). Based on these findings, a strategy of ‘light’ initial sedation upon institution of mechanical ventilation became justified. Finally, a randomized study evaluated 140 critically ill, mechanically ventilated patients to a strategy of no-sedation *vs* a control group, which involved initial sedation with propofol and subsequent midazolam [16]. This group underwent daily awakening trials. Of note, patients receiving no sedation had significantly more ventilator-free d ( $13.8$  d *vs*  $9.6$  d;  $P = 0.0191$ ) than those receiving interrupted sedation. No sedation was also associated with a shorter ICU LOS. As a summary, based on the previously described data, current sedation standard of care involves light or no sedation over deep sedation, daily awakening trials over continued sedation, and protocol-directed strategy over individual clinician decisions. Despite evidence supporting light sedation strategies, certain areas of concern still remained, regarding whether these strategies would affect patient mental health by causing post-traumatic stress disorder (PTSD), anxiety or depression post-hospital discharge. In order to answer that question, a randomized, open-label, control study included 137 patients who had undergone light *vs* deep sedation. Patients self-reported measures correlated with PTSD, anxiety or depression upon hospital discharge and 4 weeks later. Interestingly, at the 4 week follow-up, patients in the deep sedation arm had a tendency toward more PTSD symptoms ( $P = 0.07$ ), more difficulty remembering the

ICU event (37% *vs* 14%;  $P = 0.02$ ) and more disturbing recollection of the ICU (18% *vs* 4%;  $P = 0.05$ )[17]. These findings may be explained by prior evidence, which suggested that memory recall (more commonly seen after light sedation) could have a protective effect against subsequent mental health disorders post-discharge. Conversely, the presence of delusional memories after deep sedation could have an association with development of PTSD.

### Spontaneous breathing trials

Observational studies attempting to identify the best methods for discontinuing mechanical ventilation have been reported for many decades[18]. However, a landmark study published in 1996 provided the framework that would be accepted as current standard of care in ICU. In this study, 149 patients were enrolled to a strategy involving 3 phases: (1) Daily screening of respiratory function; (2) A trial of spontaneous breathing; and (3) Notifying the physician of successful results. 150 other patients were the control group, with physician guided weaning. The results of this study revealed that the median duration of mechanical ventilation was 4.5 d in the intervention group and 6 d in the control group ( $P = 0.003$ )[19]. Furthermore, the weaning time was shortened by 2 d by using the intervention strategy ( $P < 0.001$ ). This study incorporated the notion of protocol-directed weaning. It also confirmed the benefits of SBTs, rather than the gradual reduction of ventilator support. Years later, building on the prior knowledge regarding the benefits of awakening trials, an RCT including 336 mechanically ventilated patients was published. The study allocated half of these patients to an intervention strategy involving the performance of SAT followed by an SBT. The control group involved sedation *per* usual care plus SBT, without coordination[20]. The study showed that patients in the intervention group spent more days breathing without assistance during the 28-day trial period than those in the control arm (14.7 d *vs* 11.6 d;  $P = 0.02$ ). They were also discharged earlier from the ICU (median time in intensive care 9 d *vs* 13 d;  $P = 0.01$ ). Strikingly, at any point during the 12-month follow up, patients included in the intervention arm had less chances to expire compared with subjects in the control one (HR 0.68;  $P = 0.01$ ). The positive outcomes of this study enhanced the rationale of linking SAT with subsequent SBT in clinical practice. In fact, a multicenter quality improvement (QI) collaborative, coordinated by the Center for Disease Control and Prevention Wake Up and Breathe, studied whether the implementation of the SAT/SBT bundle was associated with a reduction of ventilator-associated events (VAEs)[21]. The QI showed that the VAE rate went from around 10 events *per* 100 episodes of mechanical ventilation in 2011 to 5 events *per* 100 episodes in 2013 [adjusted odds ratio (OR): 0.63; 95% confidence interval (CI): 0.42 to 0.97]. Furthermore, the mean duration of mechanical ventilation decreased by 2.4 d (95% CI: 1.7 to 3.1), and the ICU LOS by 3.0 d (95% CI: 1.6 to 4.3) after implementing the SAT/SBT bundle.

### Choice of sedatives

As described above, a strategy of daily awakening trials on sedated mechanically ventilated patients has shown reduction on ventilation duration and ICU stay. In addition, several studies revealed that certain sedatives may be associated with intrinsic complications. A Canadian multicenter randomized open label study allocated patients to be sedated with midazolam *vs* propofol[22]. Patients were subsequently divided for analysis accordingly to length of sedation in: (1) Short time, < 24 h on sedation; (2) Intermediate time, 24 h - 72 h on sedation; and (3) Long time, > 72 h on sedation. Overall, pooled results demonstrated that patients treated with propofol were extubated earlier than those treated with midazolam (6.7 h *vs* 24.7 h, respectively;  $P < 0.05$ ) following discontinuation of sedation. A meta-analysis of 16 studies compared outcomes of midazolam *vs* propofol within groups of post-acute surgery and critically ill patients. The analysis showed that propofol was generally associated with reduced ventilation time of 4.46 h ( $P = 0.004$ , 6 studies). In critically-ill patients, sedation with propofol was associated with reduced extubation time of 32.68 h ( $P = 0.0001$ , 9 studies). For post-surgical patients, propofol was associated with a reduction of ICU LOS of 5.07 h ( $P = 0.006$ , 5 studies), ventilator time of 4.28 h ( $P < 0.0001$ , 3 studies), and extubation time of 1.92 h ( $P = 0.00001$ , 9 studies)[23]. Recently, the introduction of dexmedetomidine in clinical practice brought about new data. A prospective, double-blind, randomized trial conducted in 5 countries compared dexmedetomidine *vs* midazolam in their ability to maintain patients within a predefined level of sedation (RASS range). Secondary outcomes included prevalence of delirium, duration of mechanical ventilation, and ICU LOS. Even though there was no difference between groups in percentage of time within sedation range, there were significant differences in secondary outcomes. In particular, the prevalence of delirium was 54% in the dexmedetomidine-treated patients *vs* 76.6% in the midazolam group ( $P < 0.001$ ). Median time to extubation was about 2 d shorter in the dexmedetomidine group ( $P = 0.01$ ). The ICU LOS was similar in both groups (5.9 d *vs* 7.6 d;  $P = 0.24$ )[24]. Another double-blind RCT, which included 106 mechanically ventilated in medical and surgical ICU at 2 tertiary care centers, compared dexmedetomidine *vs* lorazepam for the outcome of days alive without delirium or coma. The study also aimed at comparing both drugs in terms of the percentage of days spent within 1 RASS point of an established goal. The trial showed that patients sedated with dexmedetomidine had more days alive without delirium or coma (median days, 7.0 *vs* 3.0;  $P = 0.01$ ). Patients assigned to this group also spent more time within 1 RASS point of their sedation goal compared with patients sedated with lorazepam (median percentage of days, 80% *vs* 67%;  $P = 0.04$ )[25]. Finally, two RCTs, which were published simultaneously, compared dexmedetomidine *vs* midazolam and dexmedetomidine *vs* propofol, respectively. In both studies,

outcomes included non-inferiority of dexmedetomidine (compared with control groups) in regards to proportion of time at target sedation level, and its superiority (compared with controls) in regard to mechanical ventilation duration. The secondary outcome included subjects' capability to disclose pain [by utilizing the visual analogue scale (VAS)]. Both studies reveal that dexmedetomidine was not inferior compared with midazolam or propofol in maintaining light to moderate sedation ranges. Nevertheless, median duration of mechanical ventilation was shorter with dexmedetomidine (123 h) *vs* midazolam (164 h;  $P = 0.03$ ). There were no differences on ventilation duration between dexmedetomidine *vs* propofol. Patients' interaction (measured using VAS) was superior with dexmedetomidine compared to both midazolam and propofol ( $P < 0.001$ , for both studies)[26]. In summary, based on the higher deliriogenic effect and prolonged stay on mechanical ventilation, benzodiazepines should not be selected as medications of choice for mechanically ventilated patients. Dexmedetomidine or propofol are currently deemed as preferred medications, the choice between them depending on other anticipated side-effects (*i.e.*, bradycardia, hypotension, *etc.*).

### **Delirium detection, management and prevention**

The presence of delirium in mechanically ventilated patients is common, with some studies describing a prevalence up to 48%[27]. Due to difficulties in assessing this complication in non-communicative patients, a number of tools have been developed to allow its detection. In more detail, the original description of the Confusion Assessment Method for the ICU (CAM-ICU) tool reported sensitivities of 100% and 93% and specificities of 98% and 100% (when performed by two different nurses). The interrater reliability was very high, as well ( $\kappa = 0.96$ ; 95%CI: 0.92 to 0.99)[28]. Another tool, the Intensive Care Delirium Screening Checklist (ICDSC) was also proved to be very accurate. Its ability to predict delirium was assessed by a receiving operating characteristic (ROC) curve, which showed an area under the curve (AUC) of 0.9. Sensitivity and specificity, when using 4 points as a cut-off, were 99% and 64%, respectively[29]. A comparison between the two was performed by a meta-analysis that included 13 studies. Its results showed that the pooled sensitivity of the CAM-ICU was 80.0% (95%CI: 77.1 to 82.6), and the pooled specificity was 95.9% (95%CI: 94.8 to 96.8). The pooled sensitivity of the ICDSC was 74% (95%CI: 65.3 to 81.5), and the pooled specificity was 81.9% (95%CI: 76.7 to 86.4). The AUCs in the CAM-ICU and ICDSC ROCs for their ability in diagnosing delirium were 0.97 and 0.89, respectively[30]. These data revealed that CAM-ICU may have higher accuracy for the detection of delirium in mechanically ventilated patients. Over the years, focus has been placed on describing delirium severity. A recent instrument, the CAM-ICU-7 delirium severity scale has been introduced. In more detail, a 7-point scale (0-7) was derived from responses to the CAM-ICU and Richmond Agitation-Sedation Scale items. The CAM-ICU-7 scores showed correlation with higher odds of in-hospital mortality (OR = 1.47; 95%CI = 1.30 to 1.66) and lower odds of being discharged home (OR = 0.8; 95%CI: 0.72 to 0.9) after adjusting for age, race, gender, severity of illness, and chronic comorbidities. Furthermore, higher CAM-ICU-7 scores were also associated with increased ICU stay ( $P = 0.001$ )[31]. Pharmacologic management of delirium has been studied over many years. Nevertheless, up to this day, no medication has shown clear benefits for its management in mechanically ventilated patients. A randomized, double-blind, placebo-controlled trial allocated 101 mechanically ventilated patients to receive haloperidol or ziprasidone or placebo every 6 h for up to 14 d. During the 21-d study period, patients in the haloperidol group had similar number of days alive without delirium or coma, as did patients in the ziprasidone and placebo groups (14 d *vs* 15 d *vs* 12.5 d, respectively;  $P = 0.66$ ). There were no differences in other outcomes, such as hospital LOS, ventilator-free days, and mortality[32]. A subsequent RTC allocated ventilated and/or patients with shock to receive intravenous boluses of haloperidol, ziprasidone, or placebo. In this trial, dose of drug or placebo were halved or doubled every 12 h intervals, based on the presence or absence of delirium. This study confirmed prior data. In more detail, the median number of days alive without delirium or coma (primary outcome) were 7.9 d, 8.7 d, and 8.5 d for the haloperidol, ziprasidone, and placebo groups, respectively ( $P = 0.26$ )[27]. Another double-blind, placebo-controlled, parallel-group RCT included 74 mechanically ventilated patients with delirium and agitation. Patients were allocated to dexmedetomidine at a rate of 0.5  $\mu\text{g/kg/h}$  (or placebo) and increased up to 1.5  $\mu\text{g/kg/h}$  to reach provider-directed sedation goals. The trial showed an increase in ventilator-free hours within 7 d post-randomization in the dexmedetomidine group (144.8 h) *vs* placebo (127.5 h), ( $P = 0.01$ )[33]. Finally, a recently published multicenter, blinded, placebo-controlled trial randomized 1000 ICU patients with delirium to receive intravenous haloperidol (2.5 mg 3 times daily plus 2.5 mg as needed up to a maximum daily dose of 20 mg) *vs* placebo[34]. The medications were administered for as long as delirium continued. At 90 d, the mean number of days alive and out of the hospital (primary outcome) was 35.8 (95%CI: 33 to 39) in the haloperidol group and 32.9% (95%CI: 30 to 36) in the placebo group ( $P = 0.22$ ). This study re-affirmed the lack of effective pharmacological treatment for delirium management. Of note, some publications reported possible effectiveness of non-pharmacological interventions for the reduction of incidence and duration of delirium. Nevertheless, these multi-component strategies are still under investigation[35]. The recognition of cognitive impairment after development of delirium motivated several researchers at investigating its prevention. An RCT included 142 mechanically ventilated patients within 72 h post-admission. The study allocated patients to receive haloperidol 2.5 mg or 0.9% saline placebo intravenously every 8 h, irrespective of coma or delirium status. As a result, patients in the haloperidol



arm spent about the same number of days alive, without delirium, and without coma as did patients in the placebo one (median 5 d *vs* 6 d;  $P = 0.53$ )[36]. A subsequent study performed at 21 ICUs included 1,789 critically ill patients to receive either haloperidol at 1 mg or 2 mg, or placebo. Haloperidol doses (or placebo) were administered 3 times *per* day intravenously. Whereas the 1-mg haloperidol group was prematurely stopped because of futility, the haloperidol 2 mg and placebo groups showed no difference in 28-d survival ( $P = 0.93$ )[37]. Finally, a two-center, double-blind, placebo-controlled trial randomized 100 delirium-free critically ill adults, already receiving sedatives, to receive nocturnal (9:30 pm to 6:15 am) intravenous dexmedetomidine or placebo. The result of the study revealed that nocturnal dexmedetomidine was associated with a greater proportion of patients remaining delirium-free (80%) *vs* placebo (54%) ( $P = 0.006$ )[38]. In summary, despite high accuracy for delirium detection in ICU patients by using the CAM-ICU and ICDSC tools, the ability to provide pharmacologic management or prevention remains disputable. In addition, underutilization of those tools may result in low delirium detection, as well[39]. Studies using dexmedetomidine showed promising results. However, further investigations are needed to extrapolate these findings in to clinical practice.

### Early mobility

The recognition of physical impairment as one of the most important factors affecting Quality of Life post-ICU admission has triggered a number of investigations to explore the benefits of early mobilization in the ICU setting. In 2007, a pilot study aimed at showing the feasibility and safety of patient mobilization in the ICU[40]. The study reported a total of 1,449 activity events in 103 ventilated patients. The activities involved sitting on the bed, sitting in a chair, and ambulation. Of note, there were less than 1% activity-related adverse effects, as pre-specified by the investigators. Since this experience, other investigators have explored early mobility in ICU, reaching positive results. A prospective cohort study in a university medical ICU included 230 ventilated patients to receive early mobility within 72-hours of intubation *vs* usual care. Patients in the intervention group had at least one physical therapy session compared with those included in the usual care group (80% *vs* 47%,  $P < 0.001$ ). Furthermore, patients in the early mobility group were out of bed earlier (5 d *vs* 11 d,  $P < 0.001$ ). Notably, patients in the intervention group had shorter ICU (5.5 d *vs* 6.9 d;  $P = 0.025$ ) and hospital LOS (11.2 d *vs* 14.5 d;  $P = 0.006$ )[41]. Two years later, a seven-month prospective before-and-after quality improvement project involving the implementation of full-time physical and occupational therapists who followed specific ICU guidelines, showed an increase in the number of rehabilitation events *per* subject (1 pre- *vs* 7 post-implementation,  $P < 0.001$ ), and a higher level of functional mobility (56% *vs* 78%,  $P = 0.03$ ). Furthermore, there was a reduction of ICU and hospital LOS post-implementation (7 d *vs* 4.9 d,  $P = 0.020$ ; and 17.2 d *vs* 14.1 d,  $P = 0.030$ , respectively)[42]. In addition to the aforementioned data, the highest level of evidence was presented by an RCT. This study allocated 104 patients to early exercise and mobilization (physical and occupational therapy) during periods of daily interruption of sedation *vs* daily sedation vacation episodes with therapy as ordered by the primary care team. The primary outcome was defined as the percentage of individuals able to regain functional independence at hospital dismissal. Functional independence entailed the capability to perform 6 activities of daily living, and walk with independence. The primary outcome was seen in twenty-nine (59%) subjects in the intervention arm, whereas it was achieved in nineteen (35%) subjects in the control one ( $P = 0.02$ ). Furthermore, patients in the intervention arm had shorter duration of delirium (median 2.0 d *vs* 4.0 d,  $P = 0.02$ ), and more ventilator-free days (23.5 d *vs* 21.1 d;  $P = 0.05$ ) during the 28-d follow-up period[43]. This study provided the framework for the implementation of early mobility in ICU as standard practice. Further publications with mixed results have been published ever since. A multicenter, international, parallel-group, assessor-blinded RCT in SICUs was published in 2016[44]. Two hundred mechanically ventilated patients were allocated to receive early mobility *vs* usual care. Three outcomes were assessed: The mean SICU optimal mobilization score (SOMS) level; length of stay in SICU; and functional independence, measured by the mini-modified functional independence measure score (mmFIM) at hospital discharge. The study showed a mean SOMS of 2.2 in intervention group *vs* 1.5 in control group ( $P < 0.0001$ ). There was a decrease in the SICU length of stay of 3 d, favoring the intervention group ( $P = 0.0054$ ). Lastly, functional independence measured by mmFIM score was also improved ( $P = 0.0002$ ). Few years later, a systematic reviewed and meta-analysis, which included twenty-three RCTs comprising 2308 critically ill patients, assessed the impact of early mobility[45]. The results showed that early mobilization decreased the incidence of ICU-acquired weakness at hospital discharge [three studies, relative risk (RR): 0.60; 95%CI: 0.40 to 0.90;  $P = 0.013$ ], increased the number of ventilator-free days [six studies, standardized mean difference (SMD): 0.17; 95%CI: 0.02 to 0.31;  $P = 0.023$ ], and increased the discharged-to-home rate (seven studies, RR: 1.16, 95%CI: 1.00 to 1.34;  $P = 0.046$ ). Despite the aforementioned positive studies, a number of articles showing lack of impact with the implementation of an early mobility program were also published. Particularly, a meta-analysis that included fourteen studies with a total of 1753 patients showed that early mobilization had no significant impact on short- or long-term mortality, quality of life, or mechanical ventilation duration ( $P > 0.05$ )[46]. Nevertheless, the program led to greater muscle strength as measured by the Medical Research Council Sum Score, and greater probability of walking without assistance. Both outcomes were measured at hospital discharge. An RCT that included mechanically ventilated patients to receive an intervention of intensive physical therapy *vs* usual care showed that the intensive physical therapy

program did not improve long-term physical performance at 1, 3- or 6-months post-discharge[47]. In this study, physical performance was assessed by a Continuous Scale Physical Functional Performance Test short form. A randomized, parallel-group, assessor-blinded, controlled trial allocated patients who had received a minimum of 48 hours of invasive or non-invasive ventilation to an intervention of 90-min of physical rehabilitation *per day* *vs* a control group, which received 30-min *per day*[48]. At 6 months, there was no difference in the Physical Component Summary of the SF-36 (primary outcome). Another single-center RCT allocated mechanically ventilated patients to an intervention consisting of passive range of motion, physical therapy, and progressive resistance exercises on a daily basis (intervention group) *vs* weekday physical therapy when ordered by the clinical team (control group)[49]. Within three-hundred randomized subjects, the median hospital stay was 10 d [interquartile range (IQR), 6 to 17] in the intervention arm *vs* 10 d (IQR, 7 to 16) in the control one (median difference, 0; 95%CI: -1.5 to 3;  $P = 0.41$ ). No differences were seen in ICU or ventilation LOS. Furthermore, no effects were seen at six months in handgrip ( $P = 0.23$ ), SF-36 physical health score ( $P = 0.05$ ), or SF-36 mental health score ( $P = 0.19$ ). Lastly, a recently published RCT that assigned 750 mechanically ventilated patients to receive early mobilization *vs* usual care showed that the median number of days that patients were alive and out of the hospital (primary outcome) was 143 d (IQR 21 to 161) in the intervention group *vs* 145 d (IQR 51 to 164) in the usual care one ( $P = 0.62$ )[50]. Of note, the difference of mobilization time between groups was only 12.0 min *per day* (95%CI: 10.4 to 13.6). Despite the previously described data, which showed mixed findings, early mobilization remains a broadly accepted treatment by bedside clinicians and patients. Furthermore, the appropriate ‘physical therapy-dose’, which may have explained differences in outcomes, remains unknown.

### Family involvement

In recent years, a growing number of reports supported the benefits of family member or caregiver involvement in the medical care of critically ill patients. A recent before-and-after study showed that a change in the visiting hour policy from 6-hour to 24-hours resulted in a reduction in the incidence of delirium from 12.1% to 6.7% ( $P = 0.03$ )[51]. Furthermore, another study that randomized ICU patients to receiving recorded messages in a family member's voice *vs* same messages in a non-family voice *vs* no messages, resulted in an increase in delirium-free days in the group allocated to receiving familiar voice messages ( $P = 0.044$ )[52]. A recently published retrospective cohort study, which compared the effect of physical presence of family *vs* telephone phone calls *vs* no presence, showed no significant association between those events and the prevalence of delirium. However, physical presence of family and telephone encounters were both associated with a reduction on delirium duration compared with no presence (-1.87 d and -1.41 d, respectively;  $P < 0.001$ )[53]. These studies underscore the importance of family presence and interaction during critical illness. Nevertheless, research regarding this area is still in its infancy.

## EVIDENCE SUPPORTING THE ABCDEF BUNDLE IMPLEMENTATION

In the section above, evidence supporting individual elements of the ABCDEF bundle was described. In this section, the focus is placed on evidence supporting the implementation of the bundle as a whole. Despite its acceptance and broad implementation, evidence supporting the ABCDEF bundle is based on quality improvement projects or observational trials. A prospective cohort quality improvement study, which involved 7 community hospitals within the state of California, assessed hospital survival and delirium- and coma-free days according to the rate of compliance (total *vs* partial) with the ABCDE bundle. Interestingly, among the 6064 patients assessed for survival, for each 10% increment in compliance with the complete bundle, subjects presented 7% higher chances of hospitalization survival (OR, 1.07; 95%CI: 1.04 to 1.11;  $P < 0.001$ ). Similarly, for each 10% increment in compliance with partial components of the bundle, patients presented 15% higher chances of hospitalization survival (OR, 1.15; 95%CI: 1.09 to 1.22;  $P < 0.001$ ). Among the 5581 subjects evaluated for delirium and coma-free days, they experienced more days alive and free of delirium and coma with both total and partial bundle compliance [incident rate ratio (IRR) 1.02; 95%CI: 1.01 to 1.04;  $P = 0.004$ ; and IRR 1.15; 95%CI: 1.09 to 1.22;  $P < 0.001$ , respectively][54]. This study demonstrated the value of implementing bundle elements, even when compliance with the entire bundle was not feasible. A subsequent prospective, multicenter, cohort study from a national quality improvement collaborative, which included 15226 critically ill patients demonstrated the benefit of complete bundle compliance and a ‘dose-effect’ response. In more detail, full bundle compliance resulted in lower likelihood of hospital death within 7 d (adjusted hazard ratio: 0.32; 95%CI: 0.17 to 0.62), delirium (adjusted OR: 0.60; 95%CI: 0.49 to 0.72), coma (adjusted OR: 0.35; 95%CI: 0.22 to 0.56), ICU readmission (adjusted OR: 0.54; 95%CI: 0.37 to 0.79), physical restraint use (adjusted OR: 0.37; 95%CI: 0.30 to 0.46), and dismissal to a facility (adjusted OR: 0.64; 95%CI: 0.51 to 0.80)[55]. Furthermore, a higher proportion of bundle elements utilized in patient care was associated with a lower likelihood of those outcomes. This study demonstrated that full compliance with the bundle was better than partial. Also, within the group of patients who received partial bundle compliance, the higher the number of elements achieved resulted in better outcomes. Finally, a

prospective cohort study assessed the impact of a stepwise implementation of the complete *vs* partial ABCDE bundle on mechanical ventilation duration, ICU and hospital LOS, and costs[56]. At baseline, the ICUs were already compliant with element 'B' of the bundle. In the first phase, elements 'A' and 'D' were implemented in both groups. In the last stage, element 'C' and 'E' were implemented in the group allocated to the fully compliant bundle, whereas no further elements were incorporated in the ICUs allocated to partially compliant. The implementation of the complete (B-AD-EC) *vs* partial (B-AD) bundle was associated with a reduction of ICU LOS (-10.3%;  $P = 0.028$ ), hospital LOS (-7.8%;  $P = 0.006$ ), and mechanical ventilation duration (-22.3%;  $P < 0.001$ ). This study also demonstrated the value of implementing the full ABCDE bundle, rather than partial elements. Further studies assessed the value of the ABCDE bundle in a pre- *vs* post-implementation fashion. An eighteen-month, before-and-after study, which included five ICUs, one step-down unit, and one oncology care unit, showed that patients in the post-implementation period spent three more days breathing without mechanical assistance than those in the pre-implementation group (median, 24 *vs* 21;  $P = 0.04$ ). After adjusting for multiple covariates, patients managed with the bundle had near half odds of presenting delirium (odds ratio, 0.55; 95%CI: 0.3 to 0.9;  $P = 0.03$ )[57]. Another implementation study, which evaluated the effect of the ABCDE bundle in the prevalence and duration of delirium (measured by the ICDSC tool), showed that after instituting the ABCDE bundle, the prevalence of delirium was reduced (from 38% to 23%,  $P = 0.01$ ) and the mean number of days with delirium also decreased (from 3.8 to 1.72 d,  $P < 0.001$ )[58]. Lastly, a recently published meta-analysis that included 20 studies assessed the effect of implementing the ABCDE bundle in ICUs. The results revealed a lower incidence of delirium, shorter time on mechanical ventilation and ICU LOS, increased early mobility, and decreased ICU and hospital mortality after bundle implementation[59]. In addition, the study identified frequent barriers for bundle implementation, which included communication and planning challenges, excessive documentation, and fear of risks to the patient. It is important to note that previously described studies addressed the implementation of an ABCDE bundle, rather than an ABCDEF one. The evidence supporting the importance of family involvement (letter F) in ICU care was recently studied. Therefore, at the time the previously described studies were published, data on the relevance of family support were lacking.

## MUSIC THERAPY IN THE ICU

Over the last few years, evidence has emerged regarding the impact of music listening in the critical care setting. An RCT performed in an academic medical-surgical ICU randomized mechanically ventilated patients to receive personalized music *vs* slow-tempo music *vs* an audiobook. Each session lasted about 1-hour and they were conducted twice a day for 7 consecutive days. The study revealed equivalent delirium-free days in all 3 groups, but provided feasibility of the aforementioned interventions[60]. A systematic review that included eighteen RCTs with a total of 1173 participant showed that music interventions of 20 to 30 min each were efficacious to reduce pain in adult ICU patients, who were able to self-report[61]. Importantly, 'music listening' should be differentiated from the concept of 'music therapy'. While music listening refers to the passive act of listening to pre-recorded music administered by registered nurses or caregivers, music therapy requires specific training and expertise for its delivery. The American Music Therapy Association defines music therapy as "the clinical and evidence-based use of music interventions to accomplish individualized goals within a therapeutic relationship by a credentialed professional who has completed an approved music therapy program." Beyond a Bachelor's degree in music therapy, a minimum of 1200 h of clinical training, in addition to credentialing by the Music Therapy-Certification Board are required to provide this therapy[62]. A recent RCT that included 373 mechanically ventilated patients from 12 ICUs at 5 hospitals in Minnesota allocated subjects to self-initiated patient-directed music (PDM) tailored by a music therapist *vs* patient-initiated noise canceling headphones *vs* usual care. The main endpoints were daily evaluations of anxiety (by a 100-mm VAS), and measures of sedative frequency and intensity. Patients included in the music therapy arm listened to music for a mean of 79.8 min/day. The study showed that the PDM group had an anxiety score that was 19.5 points lower than patients in the usual group ( $P = 0.003$ ). There were no differences compared with the noise canceling group. In terms of sedative intensity and frequency, PDM showed lower points on both aspects of sedation (intensity and frequency) compared with noise canceling ( $P = 0.01$ ) and usual care groups ( $P = 0.04$ )[63]. A subsequent study published by the same group, reported the cost-effectiveness analysis of such music therapy implementation. Direct costs were calculated on US\$ based on 2015 standards. Overall, the total mean cost of the PDM was \$329.14. The mean anxiety scores -VAS were 33 for PDM and 52 for usual care. The cost savings of PDM over usual care included \$2460 in ICU costs, \$170 in physician costs, and \$22 in sedative medication costs, totaling \$2652 (a value eight times the costs of implementing PMD). Notably, the major contributing factor to the cost savings were the estimated 1.4 fewer days of mechanical ventilatory support of patients randomized to PDM[64]. Finally, a recent publication proposed an interesting algorithm for the delivery of music therapy in ICU, incorporating familiar auditory sensory training, in addition to patient-specific music listening. The aforementioned integration resulted in the positive stimulation for medically sedated protocol. Of note, the implementation of this protocol required a previous training in the use of the Music Therapy

Assessment Tool for Awareness in Disorders of Consciousness or its adaptation[65]. In summary, the implementation of music therapy as an enhancement for the ABCDEF bundle is still in its infancy. More studies are needed to assess the effect of such intervention. Nevertheless, current information (although scarce) supports its use in this patient population.

## CONCLUSION

Over the last two decades, strong evidence emerged supporting each element of the ABCDEF bundle. Consequently, observational trials and quality improvement projects reported positive outcomes resulting from full bundle implementation. In the author's opinion, recently described interventions may enhance the ABCDEF bundle. The introduction of music therapy protocols in ICU demonstrated reduction in patients' anxiety and direct costs. This intervention seems to be cost-effective, balancing cost-saving *vs* cost of implementing and could be considered as a possible addition to the ABCDEF bundle.

## FOOTNOTES

**Author contributions:** Modrykamien AM Planned and wrote manuscript.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

**Country/Territory of origin:** United States

**ORCID number:** Ariel M. Modrykamien 0000-0003-2705-7309.

**S-Editor:** Liu GL

**L-Editor:** A

**P-Editor:** Liu GL

## REFERENCES

- 1 **Acute Respiratory Distress Syndrome Network**, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; **342**: 1301-1308 [PMID: 10793162 DOI: 10.1056/NEJM200005043421801]
- 2 **Burns KE**, Lellouche F, Lessard MR, Friedrich JO. Automated weaning and spontaneous breathing trial systems versus non-automated weaning strategies for discontinuation time in invasively ventilated postoperative adults. *Cochrane Database Syst Rev* 2014; **2014**: CD008639 [PMID: 24526330 DOI: 10.1002/14651858.CD008639.pub2]
- 3 **Papazian L**, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, Jaber S, Arnal JM, Perez D, Seghboyan JM, Constantin JM, Courant P, Lefrant JY, Guérin C, Prat G, Morange S, Roch A; ACURASYS Study Investigators. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010; **363**: 1107-1116 [PMID: 20843245 DOI: 10.1056/NEJMoa1005372]
- 4 **National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network**, Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF Jr, Hite RD, Harabin AL. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; **354**: 2564-2575 [PMID: 16714767 DOI: 10.1056/NEJMoa062200]
- 5 **Seymour CW**, Gesten F, Prescott HC, Friedrich ME, Iwashyna TJ, Phillips GS, Lemeshow S, Osborn T, Terry KM, Levy MM. Time to Treatment and Mortality during Mandated Emergency Care for Sepsis. *N Engl J Med* 2017; **376**: 2235-2244 [PMID: 28528569 DOI: 10.1056/NEJMoa1703058]
- 6 **Herridge MS**, Cheung AM, Tansey CM, Matte-Martyn A, Diaz-Granados N, Al-Saidi F, Cooper AB, Guest CB, Mazer CD, Mehta S, Stewart TE, Barr A, Cook D, Slutsky AS; Canadian Critical Care Trials Group. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med* 2003; **348**: 683-693 [PMID: 12594312 DOI: 10.1056/NEJMoa022450]
- 7 **Herridge MS**, Tansey CM, Matté A, Tomlinson G, Diaz-Granados N, Cooper A, Guest CB, Mazer CD, Mehta S, Stewart TE, Kudlow P, Cook D, Slutsky AS, Cheung AM; Canadian Critical Care Trials Group. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 2011; **364**: 1293-1304 [PMID: 21470008 DOI: 10.1056/NEJMoa1011802]



- 8 Timmers TK, Verhofstad MH, Moons KG, van Beeck EF, Leenen LP. Long-term quality of life after surgical intensive care admission. *Arch Surg* 2011; **146**: 412-418 [PMID: [21173281](#) DOI: [10.1001/archsurg.2010.279](#)]
- 9 Hopkins RO, Jackson JC. Long-term neurocognitive function after critical illness. *Chest* 2006; **130**: 869-878 [PMID: [16963688](#) DOI: [10.1378/chest.130.3.869](#)]
- 10 Girard TD, Jackson JC, Pandharipande PP, Pun BT, Thompson JL, Shintani AK, Gordon SM, Canonico AE, Dittus RS, Bernard GR, Ely EW. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. *Crit Care Med* 2010; **38**: 1513-1520 [PMID: [20473145](#) DOI: [10.1097/CCM.0b013e3181e47be1](#)]
- 11 Petty TL. Suspended life or extending death? *Chest* 1998; **114**: 360-361 [PMID: [9726713](#) DOI: [10.1378/chest.114.2.360](#)]
- 12 Kollef MH, Levy NT, Ahrens TS, Schaiff R, Prentice D, Sherman G. The use of continuous i.v. sedation is associated with prolongation of mechanical ventilation. *Chest* 1998; **114**: 541-548 [PMID: [9726743](#) DOI: [10.1378/chest.114.2.541](#)]
- 13 Brook AD, Ahrens TS, Schaiff R, Prentice D, Sherman G, Shannon W, Kollef MH. Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. *Crit Care Med* 1999; **27**: 2609-2615 [PMID: [10628598](#) DOI: [10.1097/00003246-199912000-00001](#)]
- 14 Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med* 2000; **342**: 1471-1477 [PMID: [10816184](#) DOI: [10.1056/NEJM200005183422002](#)]
- 15 Shehabi Y, Bellomo R, Reade MC, Bailey M, Bass F, Howe B, McArthur C, Seppelt IM, Webb S, Weisbrodt L; Sedation Practice in Intensive Care Evaluation (SPICE) Study Investigators; ANZICS Clinical Trials Group. Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. *Am J Respir Crit Care Med* 2012; **186**: 724-731 [PMID: [22859526](#) DOI: [10.1164/rccm.201203-0522OC](#)]
- 16 Strøm T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. *Lancet* 2010; **375**: 475-480 [PMID: [20116842](#) DOI: [10.1016/S0140-6736\(09\)62072-9](#)]
- 17 Treggiari MM, Romand JA, Yanez ND, Deem SA, Goldberg J, Hudson L, Heidegger CP, Weiss NS. Randomized trial of light versus deep sedation on mental health after critical illness. *Crit Care Med* 2009; **37**: 2527-2534 [PMID: [19602975](#) DOI: [10.1097/CCM.0b013e3181a5689f](#)]
- 18 Esteban A, Frutos F, Tobin MJ, Alía I, Solsona JF, Valverdú I, Fernández R, de la Cal MA, Benito S, Tomás R. A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. *N Engl J Med* 1995; **332**: 345-350 [PMID: [7823995](#) DOI: [10.1056/NEJM199502093320601](#)]
- 19 Ely EW, Baker AM, Dunagan DP, Burke HL, Smith AC, Kelly PT, Johnson MM, Browder RW, Bowton DL, Haponik EF. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. *N Engl J Med* 1996; **335**: 1864-1869 [PMID: [8948561](#) DOI: [10.1056/NEJM199612193352502](#)]
- 20 Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, Taichman DB, Dunn JG, Pohlman AS, Kinniry PA, Jackson JC, Canonico AE, Light RW, Shintani AK, Thompson JL, Gordon SM, Hall JB, Dittus RS, Bernard GR, Ely EW. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet* 2008; **371**: 126-134 [PMID: [18191684](#) DOI: [10.1016/S0140-6736\(08\)60105-1](#)]
- 21 Klompas M, Anderson D, Trick W, Babcock H, Kerlin MP, Li L, Sinkowitz-Cochran R, Ely EW, Jernigan J, Magill S, Lyles R, O'Neil C, Kitch BT, Arrington E, Balas MC, Kleinman K, Bruce C, Lankiewicz J, Murphy MV, E Cox C, Lautenbach E, Sexton D, Fraser V, Weinstein RA, Platt R; CDC Prevention Epicenters. The preventability of ventilator-associated events. The CDC Prevention Epicenters Wake Up and Breathe Collaborative. *Am J Respir Crit Care Med* 2015; **191**: 292-301 [PMID: [25369558](#) DOI: [10.1164/rccm.201407-1394OC](#)]
- 22 Hall RI, Sandham D, Cardinal P, Tweeddale M, Moher D, Wang X, Anis AH; Study Investigators. Propofol vs midazolam for ICU sedation : a Canadian multicenter randomized trial. *Chest* 2001; **119**: 1151-1159 [PMID: [11296183](#) DOI: [10.1378/chest.119.4.1151](#)]
- 23 Garcia R, Salluh JIF, Andrade TR, Farah D, da Silva PSL, Bastos DF, Fonseca MCM. A systematic review and meta-analysis of propofol versus midazolam sedation in adult intensive care (ICU) patients. *J Crit Care* 2021; **64**: 91-99 [PMID: [33838522](#) DOI: [10.1016/j.jcrc.2021.04.001](#)]
- 24 Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, Whitten P, Margolis BD, Byrne DW, Ely EW, Rocha MG; SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA* 2009; **301**: 489-499 [PMID: [19188334](#) DOI: [10.1001/jama.2009.56](#)]
- 25 Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, Shintani AK, Thompson JL, Jackson JC, Deppen SA, Stiles RA, Dittus RS, Bernard GR, Ely EW. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA* 2007; **298**: 2644-2653 [PMID: [18073360](#) DOI: [10.1001/jama.298.22.2644](#)]
- 26 Jakob SM, Ruokonen E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ, Bratty JR, Takala J; Dexmedetomidine for Long-Term Sedation Investigators. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. *JAMA* 2012; **307**: 1151-1160 [PMID: [22436955](#) DOI: [10.1001/jama.2012.304](#)]
- 27 Girard TD, Exline MC, Carson SS, Hough CL, Rock P, Gong MN, Douglas IS, Malhotra A, Owens RL, Feinstein DJ, Khan B, Pisani MA, Hyzy RC, Schmidt GA, Schweickert WD, Hite RD, Bowton DL, Masica AL, Thompson JL, Chandrasekhar R, Pun BT, Strength C, Boehm LM, Jackson JC, Pandharipande PP, Brummel NE, Hughes CG, Patel MB, Stollings JL, Bernard GR, Dittus RS, Ely EW; MIND-USA Investigators. Haloperidol and Ziprasidone for Treatment of Delirium in Critical Illness. *N Engl J Med* 2018; **379**: 2506-2516 [PMID: [30346242](#) DOI: [10.1056/NEJMoa1808217](#)]
- 28 Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, Truman B, Speroff T, Gautam S, Margolin R, Hart RP, Dittus R. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001; **286**: 2703-2710 [PMID: [11730446](#) DOI: [10.1001/jama.286.21.2703](#)]
- 29 Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. *Intensive Care Med* 2001; **27**: 859-864 [PMID: [11430542](#) DOI: [10.1007/s001340100909](#)]
- 30 Gusmao-Flores D, Salluh JI, Chalhuh RÁ, Quarantini LC. The confusion assessment method for the intensive care unit

- (CAM-ICU) and intensive care delirium screening checklist (ICDSC) for the diagnosis of delirium: a systematic review and meta-analysis of clinical studies. *Crit Care* 2012; **16**: R115 [PMID: 22759376 DOI: 10.1186/cc11407]
- 31 **Khan BA**, Perkins AJ, Gao S, Hui SL, Campbell NL, Farber MO, Chlan LL, Boustani MA. The Confusion Assessment Method for the ICU-7 Delirium Severity Scale: A Novel Delirium Severity Instrument for Use in the ICU. *Crit Care Med* 2017; **45**: 851-857 [PMID: 28263192 DOI: 10.1097/CCM.0000000000002368]
  - 32 **Girard TD**, Pandharipande PP, Carson SS, Schmidt GA, Wright PE, Canonico AE, Pun BT, Thompson JL, Shintani AK, Meltzer HY, Bernard GR, Dittus RS, Ely EW; MIND Trial Investigators. Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: the MIND randomized, placebo-controlled trial. *Crit Care Med* 2010; **38**: 428-437 [PMID: 20095068 DOI: 10.1097/ccm.0b013e3181c58715]
  - 33 **Reade MC**, Eastwood GM, Bellomo R, Bailey M, Bersten A, Cheung B, Davies A, Delaney A, Ghosh A, van Haren F, Harley N, Knight D, McGuinness S, Mulder J, O'Donoghue S, Simpson N, Young P; DahLIA Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group. Effect of Dexmedetomidine Added to Standard Care on Ventilator-Free Time in Patients With Agitated Delirium: A Randomized Clinical Trial. *JAMA* 2016; **315**: 1460-1468 [PMID: 26975647 DOI: 10.1001/jama.2016.2707]
  - 34 **Andersen-Ranberg NC**, Poulsen LM, Perner A, Wetterslev J, Estrup S, Hästbacka J, Morgan M, Citerio G, Caballero J, Lange T, Kjær MN, Ebdrup BH, Engstrøm J, Olsen MH, Oxenbøll Collet M, Mortensen CB, Weber SO, Andreasen AS, Bestle MH, Uslu B, Scharling Pedersen H, Gramstrup Nielsen L, Toft Boesen HC, Jensen JV, Neblich L, La Cour K, Laigaard J, Haurum C, Olesen MW, Overgaard-Steensen C, Westergaard B, Brand B, Kingo Vesterlund G, Thornberg Kyhnau P, Mikkelsen VS, Hyttel-Sørensen S, de Haas I, Aagaard SR, Nielsen LO, Eriksen AS, Rasmussen BS, Brix H, Hildebrandt T, Schönemann-Lund M, Fjeldsøe-Nielsen H, Kuivalainen AM, Mathiesen O; AID-ICU Trial Group. Haloperidol for the Treatment of Delirium in ICU Patients. *N Engl J Med* 2022; **387**: 2425-2435 [PMID: 36286254 DOI: 10.1056/NEJMoa2211868]
  - 35 **Deng LX**, Cao L, Zhang LN, Peng XB, Zhang L. Non-pharmacological interventions to reduce the incidence and duration of delirium in critically ill patients: A systematic review and network meta-analysis. *J Crit Care* 2020; **60**: 241-248 [PMID: 32919363 DOI: 10.1016/j.jcrc.2020.08.019]
  - 36 **Page VJ**, Ely EW, Gates S, Zhao XB, Alce T, Shintani A, Jackson J, Perkins GD, McAuley DF. Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (Hope-ICU): a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2013; **1**: 515-523 [PMID: 24461612 DOI: 10.1016/S2213-2600(13)70166-8]
  - 37 **van den Boogaard M**, Slooter AJC, Brüggemann RJM, Schoonhoven L, Beishuizen A, Vermeijden JW, Pretorius D, de Koning J, Simons KS, Dennesen PJW, Van der Voort PHJ, Houterman S, van der Hoeven JG, Pickkers P; REDUCE Study Investigators, van der Woude MCE, Besselink A, Hofstra LS, Spronk PE, van den Bergh W, Donker DW, Fuchs M, Karakus A, Koeman M, van Duijnhoven M, Hannink G. Effect of Haloperidol on Survival Among Critically Ill Adults With a High Risk of Delirium: The REDUCE Randomized Clinical Trial. *JAMA* 2018; **319**: 680-690 [PMID: 29466591 DOI: 10.1001/jama.2018.0160]
  - 38 **Skrobik Y**, Duprey MS, Hill NS, Devlin JW. Low-Dose Nocturnal Dexmedetomidine Prevents ICU Delirium. A Randomized, Placebo-controlled Trial. *Am J Respir Crit Care Med* 2018; **197**: 1147-1156 [PMID: 29498534 DOI: 10.1164/rccm.201710-1995OC]
  - 39 **Ritter SRF**, Cardoso AF, Lins MMP, Zoccoli TLV, Freitas MPD, Camargos EF. Underdiagnosis of delirium in the elderly in acute care hospital settings: lessons not learned. *Psychogeriatrics* 2018; **18**: 268-275 [PMID: 30133935 DOI: 10.1111/psyg.12324]
  - 40 **Bailey P**, Thomsen GE, Spuhler VJ, Blair R, Jewkes J, Bezdjian L, Veale K, Rodriguez L, Hopkins RO. Early activity is feasible and safe in respiratory failure patients. *Crit Care Med* 2007; **35**: 139-145 [PMID: 17133183 DOI: 10.1097/01.CCM.0000251130.69568.87]
  - 41 **Morris PE**, Goad A, Thompson C, Taylor K, Harry B, Passmore L, Ross A, Anderson L, Baker S, Sanchez M, Penley L, Howard A, Dixon L, Leach S, Small R, Hite RD, Haponik E. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. *Crit Care Med* 2008; **36**: 2238-2243 [PMID: 18596631 DOI: 10.1097/CCM.0b013e318180b90e]
  - 42 **Needham DM**, Korupolu R, Zanni JM, Pradhan P, Colantuoni E, Palmer JB, Brower RG, Fan E. Early physical medicine and rehabilitation for patients with acute respiratory failure: a quality improvement project. *Arch Phys Med Rehabil* 2010; **91**: 536-542 [PMID: 20382284 DOI: 10.1016/j.apmr.2010.01.002]
  - 43 **Schweickert WD**, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, Spears L, Miller M, Franczyk M, Deprizio D, Schmidt GA, Bowman A, Barr R, McCallister KE, Hall JB, Kress JP. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet* 2009; **373**: 1874-1882 [PMID: 19446324 DOI: 10.1016/S0140-6736(09)60658-9]
  - 44 **Schaller SJ**, Anstey M, Blobner M, Edrich T, Grabitz SD, Gradwohl-Matis I, Heim M, Houle T, Kurth T, Latronico N, Lee J, Meyer MJ, Peponis T, Talmor D, Velmahos GC, Waak K, Walz JM, Zafonte R, Eikermann M; International Early SOMS-guided Mobilization Research Initiative. Early, goal-directed mobilisation in the surgical intensive care unit: a randomised controlled trial. *Lancet* 2016; **388**: 1377-1388 [PMID: 27707496 DOI: 10.1016/S0140-6736(16)31637-3]
  - 45 **Zhang L**, Hu W, Cai Z, Liu J, Wu J, Deng Y, Yu K, Chen X, Zhu L, Ma J, Qin Y. Early mobilization of critically ill patients in the intensive care unit: A systematic review and meta-analysis. *PLoS One* 2019; **14**: e0223185 [PMID: 31581205 DOI: 10.1371/journal.pone.0223185]
  - 46 **Tipping CJ**, Harrold M, Holland A, Romero L, Nisbet T, Hodgson CL. The effects of active mobilisation and rehabilitation in ICU on mortality and function: a systematic review. *Intensive Care Med* 2017; **43**: 171-183 [PMID: 27864615 DOI: 10.1007/s00134-016-4612-0]
  - 47 **Moss M**, Nordon-Craft A, Malone D, Van Pelt D, Frankel SK, Warner ML, Krickels W, McNulty M, Fairclough DL, Schenkman M. A Randomized Trial of an Intensive Physical Therapy Program for Patients with Acute Respiratory Failure. *Am J Respir Crit Care Med* 2016; **193**: 1101-1110 [PMID: 26651376 DOI: 10.1164/rccm.201505-1039OC]
  - 48 **Wright SE**, Thomas K, Watson G, Baker C, Bryant A, Chadwick TJ, Shen J, Wood R, Wilkinson J, Mansfield L, Stafford V, Wade C, Furneal J, Henderson A, Hugill K, Howard P, Roy A, Bonner S, Baudouin S. Intensive versus standard physical rehabilitation therapy in the critically ill (EPICC): a multicentre, parallel-group, randomised controlled trial.

- Thorax 2018; **73**: 213-221 [PMID: [28780504](#) DOI: [10.1136/thoraxjnl-2016-209858](#)]
- 49 **Morris PE**, Berry MJ, Files DC, Thompson JC, Hauser J, Flores L, Dhar S, Chmelo E, Lovato J, Case LD, Bakhru RN, Sarwal A, Parry SM, Campbell P, Mote A, Winkelman C, Hite RD, Nicklas B, Chatterjee A, Young MP. Standardized Rehabilitation and Hospital Length of Stay Among Patients With Acute Respiratory Failure: A Randomized Clinical Trial. *JAMA* 2016; **315**: 2694-2702 [PMID: [27367766](#) DOI: [10.1001/jama.2016.7201](#)]
- 50 **TEAM Study Investigators and the ANZICS Clinical Trials Group**, Hodgson CL, Bailey M, Bellomo R, Brickell K, Broadley T, Buhr H, Gabbe BJ, Gould DW, Harrold M, Higgins AM, Hurford S, Iwashyna TJ, Serpa Neto A, Nichol AD, Presneill JJ, Schaller SJ, Sivasathan J, Tipping CJ, Webb S, Young PJ. Early Active Mobilization during Mechanical Ventilation in the ICU. *N Engl J Med* 2022; **387**: 1747-1758 [PMID: [36286256](#) DOI: [10.1056/NEJMoa2209083](#)]
- 51 **Westphal GA**, Moerschberger MS, Vollmann DD, Inácio AC, Machado MC, Sperotto G, Cavalcanti AB, Koenig Á. Effect of a 24-h extended visiting policy on delirium in critically ill patients. *Intensive Care Med* 2018; **44**: 968-970 [PMID: [29605880](#) DOI: [10.1007/s00134-018-5153-5](#)]
- 52 **Munro CL**, Cairns P, Ji M, Calero K, Anderson WM, Liang Z. Delirium prevention in critically ill adults through an automated reorientation intervention - A pilot randomized controlled trial. *Heart Lung* 2017; **46**: 234-238 [PMID: [28606450](#) DOI: [10.1016/j.hrtlng.2017.05.002](#)]
- 53 **Mohsen S**, Moss SJ, Lucini F, Krewulak KD, Stelfox HT, Niven DJ, Sauro KM, Fiest KM. Impact of Family Presence on Delirium in Critically Ill Patients: A Retrospective Cohort Study. *Crit Care Med* 2022; **50**: 1628-1637 [PMID: [36044306](#) DOI: [10.1097/CCM.0000000000005657](#)]
- 54 **Barnes-Daly MA**, Phillips G, Ely EW. Improving Hospital Survival and Reducing Brain Dysfunction at Seven California Community Hospitals: Implementing PAD Guidelines Via the ABCDEF Bundle in 6,064 Patients. *Crit Care Med* 2017; **45**: 171-178 [PMID: [27861180](#) DOI: [10.1097/CCM.0000000000002149](#)]
- 55 **Pun BT**, Balas MC, Barnes-Daly MA, Thompson JL, Aldrich JM, Barr J, Byrum D, Carson SS, Devlin JW, Engel HJ, Esbrook CL, Hargett KD, Harmon L, Hielsberg C, Jackson JC, Kelly TL, Kumar V, Millner L, Morse A, Perme CS, Posa PJ, Puntillo KA, Schweickert WD, Stollings JL, Tan A, D'Agostino McGowan L, Ely EW. Caring for Critically Ill Patients with the ABCDEF Bundle: Results of the ICU Liberation Collaborative in Over 15,000 Adults. *Crit Care Med* 2019; **47**: 3-14 [PMID: [30339549](#) DOI: [10.1097/CCM.0000000000003482](#)]
- 56 **Hsieh SJ**, Otusanya O, Gershengorn HB, Hope AA, Dayton C, Levi D, Garcia M, Prince D, Mills M, Fein D, Colman S, Gong MN. Staged Implementation of Awakening and Breathing, Coordination, Delirium Monitoring and Management, and Early Mobilization Bundle Improves Patient Outcomes and Reduces Hospital Costs. *Crit Care Med* 2019; **47**: 885-893 [PMID: [30985390](#) DOI: [10.1097/CCM.0000000000003765](#)]
- 57 **Balas MC**, Vasilevskis EE, Olsen KM, Schmid KK, Shostrom V, Cohen MZ, Peitz G, Gannon DE, Sisson J, Sullivan J, Stothert JC, Lazure J, Nuss SL, Jawa RS, Freihaut F, Ely EW, Burke WJ. Effectiveness and safety of the awakening and breathing coordination, delirium monitoring/management, and early exercise/mobility bundle. *Crit Care Med* 2014; **42**: 1024-1036 [PMID: [24394627](#) DOI: [10.1097/CCM.000000000000129](#)]
- 58 **Bounds M**, Kram S, Speroni KG, Brice K, Luschinski MA, Harte S, Daniel MG. Effect of ABCDE Bundle Implementation on Prevalence of Delirium in Intensive Care Unit Patients. *Am J Crit Care* 2016; **25**: 535-544 [PMID: [27802955](#) DOI: [10.4037/ajcc2016209](#)]
- 59 **Moraes FDS**, Marengo LL, Moura MDG, Bergamaschi CC, de Sá Del Fiol F, Lopes LC, Silva MT, Barberato-Filho S. ABCDE and ABCDEF care bundles: A systematic review of the implementation process in intensive care units. *Medicine (Baltimore)* 2022; **101**: e29499 [PMID: [35758388](#) DOI: [10.1097/MD.00000000000029499](#)]
- 60 **Khan SH**, Xu C, Purpura R, Durrani S, Lindroth H, Wang S, Gao S, Heiderscheit A, Chlan L, Boustani M, Khan BA. Decreasing Delirium Through Music: A Randomized Pilot Trial. *Am J Crit Care* 2020; **29**: e31-e38 [PMID: [32114612](#) DOI: [10.4037/ajcc2020175](#)]
- 61 **Richard-Lalonde M**, Gélinas C, Boitor M, Gosselin E, Feeley N, Cossette S, Chlan LL. The Effect of Music on Pain in the Adult Intensive Care Unit: A Systematic Review of Randomized Controlled Trials. *J Pain Symptom Manage* 2020; **59**: 1304-1319.e6 [PMID: [31881291](#) DOI: [10.1016/j.jpainsymman.2019.12.359](#)]
- 62 **Browning SG**, Watters R, Thomson-Smith C. Impact of Therapeutic Music Listening on Intensive Care Unit Patients: A Pilot Study. *Nurs Clin North Am* 2020; **55**: 557-569 [PMID: [33131632](#) DOI: [10.1016/j.cnur.2020.06.016](#)]
- 63 **Azoulay E**, Chaize M, Kentish-Barnes N. Music therapy for reducing anxiety in critically ill patients. *JAMA* 2013; **309**: 2386-2387 [PMID: [23689740](#) DOI: [10.1001/jama.2013.5657](#)]
- 64 **Chlan LL**, Heiderscheit A, Skaar DJ, Neidecker MV. Economic Evaluation of a Patient-Directed Music Intervention for ICU Patients Receiving Mechanical Ventilatory Support. *Crit Care Med* 2018; **46**: 1430-1435 [PMID: [29727366](#) DOI: [10.1097/CCM.0000000000003199](#)]
- 65 **Head J**, Gray V, Masud F, Townsend J. Positive Stimulation for Medically Sedated Patients: A Music Therapy Intervention to Treat Sedation-Related Delirium in Critical Care. *Chest* 2022; **162**: 367-374 [PMID: [35176274](#) DOI: [10.1016/j.chest.2022.02.011](#)]



Published by **Baishideng Publishing Group Inc**  
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

**Help Desk:** <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

