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Enhancing the Awakening to Family Engagement Bundle with Music Therapy

ABCDEF bundle and music therapy

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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 the ABCDEF bundle. Awakening and spontaneous breathing trials; choosing proper sedation strategies; assessing, managing and preventing delirium; early ICU mobility; and family involvement; all 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

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Core Tip: Data support the implementation of the ABCDEF bundle for mechanically ventilated patients. The role of music therapy is evolving.

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 wastage 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 minutes 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: (a) awakening trial; (b) spontaneous breathing trial (SBT) and mechanical ventilation liberation; (c) selective choice of drugs, particularly sedatives; (d) detection, management, and prevention of delirium; (e) early patient mobilization; (f) 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; (3) supporting data for the use of music therapy.

EVIDENCE SUPPORTING INDIVIDUAL COMPONENTS OF THE ABCDEF BUNDLE

A. SPONTANEOUS AWAKENING TRIALS (SAT)

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 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+/-190 h vs. 56+/-75.6 h; $p<0.001$)[12]. Furthermore, the ICU and hospital LOS were also longer within the continuous IV sedation group (13.5+/-34 days vs 4.8+/-4; and 21 +/-25 days vs 13+/-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 days \pm 6 vs. 7.5 days \pm 7, $P = 0.013$; and 14 days \pm 17 vs. 20 days \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 days, compared with 7.3 days in the control group ($P = 0.004$). The median LOS in the ICU was 6.4 days vs. 9.9 days, 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-day 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 days (13.8 days vs. 9.6 days; $P = 0.0191$) 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 continues sedation, and protocol-directed strategy over individual clinician decisions. Despite evidence supporting light sedation strategies, certain areas of concern still remain, 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-wk 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.

B. SPONTANEOUS BREATHING TRIALS (SBT)

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; (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 ⁴the median duration of mechanical ventilation was 4.5 days in the intervention group and 6 days in the control group ($P = 0.003$)^[19]. Furthermore, the weaning time was shortened by 2 days by using the intervention strategy ($p < 0.001$). This study incorporated the notion of protocol-directed weaning. It also confirmed the benefits of spontaneous breathing trials, 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 ⁴⁴sedation per usual care plus SBT, without coordination^[20]. The study showed that ¹⁵patients in the intervention group spent more days breathing without assistance during the 28-day trial period than those in the control arm (14.7 days vs. 11.6 days; $P = 0.02$). They were also discharged earlier from the ICU (median time in intensive care 9 days vs. 13 days; $P = 0.01$). 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 CDC Prevention Epicenters 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 ⁷events per 100 episodes of mechanical

ventilation in 2011 to 5 events per 100 episodes in 2013 (adjusted odds ratio [OR], 0.63; 95%CI, 0.42–0.97). Furthermore, the mean duration of mechanical ventilation decreased by 2.4 days (95%CI, 1.7–3.1 d), and the ICU LOS by 3.0 days (95%CI, 1.6–4.3 d) after implementing the SAT/SBT bundle.

C. 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: (a) short time, < 24 h (h) on sedation; (b) intermediate time, 24 h - 72 h on sedation; and (c) 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 ($p < .001$). Median time to extubation was about 2 days shorter in the dexmedetomidine group ($p = 0.01$). The ICU LOS was similar in both groups (5.9 days vs 7.6 days; $p = 0.24$)^[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.)

D. 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 description⁴² of the Confusion Assessment Method for the Intensive Care Unit (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% confidence interval, 0.92-0.99)^[28]. Another tool, the Intensive Care Delirium Screening Checklist (ICDSC) was also⁴⁷ 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 that³ the pooled sensitivity of the CAM-ICU was 80.0% (95% confidence interval (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,¹⁶ 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 of¹⁷ in-hospital mortality (odds ratio = 1.47; 95%CI = 1.30-1.66) and lower odds of being discharged home (odds ratio = 0.8; 95%CI = 0.72-0.9) after adjusting¹⁶ 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 days. During the 21-day 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 days vs. 15 days vs. 12.5 days, 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 days, 8.7 days, and 8.5 days 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 µg/kg/h (or placebo) and increased up to 1.5 µg/kg/h to reach provider-directed sedation goals. The trial showed an increase in ventilator-free hours within 7 days 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 1,000 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 days, 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 days vs 6 days; $P = 0.53$)^[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-day 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 p.m. to 6:15 a.m.) 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.

E. EARLY MOBILITY

The recognition of physical impairment as one of the most important factors affecting Quality of Life (QoL) 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 vs. 11 days, $p < 0.001$). Notably, patients in the intervention group had shorter ICU (5.5 vs. 6.9 day; $P = 0.025$) and hospital LOS (11.2 vs. 14.5 days; $P = 0.006$)^[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 days vs 4.9 days, $P = 0.020$; and 17.2 days vs. 14.1, $P = 0.030$, 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 outcomes 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 days vs. 4.0 days, $P = 0.02$), and more ventilator-free days (23.5 days vs. 21.1 days; $P = 0.05$) during the 28-day 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 days, 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 2,308 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% confidence interval (CI) [0.40, 0.90]; $P = 0.013$), increased the number of ventilator-free days (six studies, standardized mean difference (SMD): 0.17, 95%CI [0.02, 0.31]; $P = 0.023$), and increased the discharged-to-home rate (seven studies, RR: 1.16, 95%CI [1.00, 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 1,753 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 (MRC) 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 (CS-PFP-10). 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-minutes of physical rehabilitation per day vs. a control group, which received 30-minutes per day^[48]. At 6 mo, 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 days (IQR, 6 to 17) in the intervention arm vs. 10 days (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 days (IQR 21-161) in the intervention group vs. 145 days (IQR 51-164) in the usual care one ($P = 0.62$)^[50]. Of note, the difference of mobilization time between groups was only 12.0 minutes 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.

F. 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 days and -1.41 days, 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 6,064 patients assessed for survival, for each 10% increment in compliance with the complete bundle, subjects presented 7% higher chances of hospitalization survival (odds ratio, 1.07; 95%CI, 1.04-1.11; $p < 0.001$). Similarly, for each 10% increment in compliance with partial components of the bundle, patients presented 15% higher chances of hospitalization survival (odds ratio, 1.15; 95%CI, 1.09-1.22; $p < 0.001$). Among the 5,581 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, 1.01-1.04; $p = 0.004$; and IRR 1.15; 95%CI, 1.09-1.22; $p < 0.001$, 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 15,226 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 days (adjusted hazard ratio, 0.32; CI, 0.17-0.62), delirium (AOR, 0.60; CI, 0.49-0.72), coma (Adjusted Odds Ratio, 0.35; CI, 0.22-0.56), ICU readmission (AOR, 0.54; CI, 0.37-0.79), physical restraint use (AOR, 0.37; CI, 0.30-0.46), and dismissal to a facility (AOR, 0.64; CI, 0.51-0.80)^[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, 0.3-0.9; $P = 0.03$)^[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 days, $p < 0.001$)^[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 1,173 participant showed that music interventions of 20 to 30 minutes 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 1,200 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 visual analog scale - VAS), and measures of sedative frequency and intensity. Patients included in the music therapy arm listened to music for a mean of 79.8 minutes/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 \$2,460 in ICU costs, \$170 in physician costs, and \$22 in sedative medication costs, totaling \$2,652 (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 (FAST), in addition to patient-specific music listening (PSM). The aforementioned integration resulted in the positive stimulation for medically sedated (PSMS) 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 (MATADOC) 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.

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