Evaluation of a Multidisciplinary Pain, Agitation, and Delirium Guideline in Mechanically Ventilated Critically Ill Adults

Hospital Pharmacy
2019, Vol. 54(2) 119–124
© The Author(s) 2018
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/0018578718769570
journals.sagepub.com/home/hpx

Melissa Heim¹ , Ryan Draheim², Anna Krupp², Paula Breihan², Ann O'Rourke², Jeffrey Wells², and Jeffrey Fish²

Abstract

Background: A multidisciplinary team updated an institution-specific pain, agitation, and delirium (PAD) guideline based on the recommendations from the Society of Critical Care Medicine (SCCM) PAD guidelines. This institution-specific guideline emphasized protocolized sedation with increased as needed boluses, and nonbenzodiazepine infusions, daily sedation interruption, and pairing of spontaneous awakening (SAT) and breathing trials (SBT). **Objective:** The purpose of this study was to evaluate the impact of implementation of a PAD guideline on clinical outcomes and medication utilization in an academic medical center intensive care unit (ICU). It was hypothesized that implementation of an updated guideline would improve clinical outcomes and decrease usage of benzodiazepine infusions. **Methods:** Pre-post retrospective chart review of 2417 (1147 pre, 1270 post) critically ill, mechanically ventilated adults in a medical/surgical ICU over a 2-year period (1 year pre and post guideline implementation). **Results:** After guideline implementation, average ventilation days was reduced (3.98 vs 3.43 days, $P = .0021$), as well as ICU and hospital length of stay (LOS) (4.79 vs 4.34 days, $P = .048$ and 13.96 vs 12.97 days, $P = .045$, respectively). Hospital mortality (19 vs 19%, $P = .96$) and acute physiology and chronic health evaluation (APACHE) IV scores (77.28 vs 78.75, $P = .27$) were similar. After guideline implementation, the percentage of patients receiving midazolam infusions decreased (422/1147 [37%] vs 363/1270 patients [29%], $P = .0001$). The percentage of patients receiving continuous infusion propofol (679/1147 [59%] vs 896/1270 [70%], $P = .0001$) and dexmedetomidine (78/1147 [7%] vs 147/1270 [12%], $P = .0001$) increased. **Conclusions:** Implementing a multidisciplinary PAD guideline utilizing protocolized sedation and daily sedation interruption decreased ventilation days and ICU and hospital LOS while decreasing midazolam drip usage.

Keywords

analgesics, anesthetics, critical care, respiratory

Background

Duration of mechanical ventilation and intensive care unit (ICU) and hospital length of stay (LOS) are reduced when guidelines are used to prevent excessive use of medications for the treatment of pain, agitation, and delirium (PAD) in mechanically ventilated adults.^{1–6} The 2013 Society of Critical Care Medicine (SCCM) guidelines recommend using protocols to manage pain and agitation in mechanically ventilated patients, and routine monitoring for delirium. These protocols should focus on titrating analgesic and sedative doses to defined end points, treating pain first (analgo-sedation), utilizing as needed doses of sedatives or nonbenzodiazepine continuous infusions for sedation if an infusion is needed.⁷ To decrease the duration of continuous infusions, it is recommended to use a daily continuous infusion dose reduction or interruption with retitration (spontaneous

awakening trial [SAT]) coordinated with a spontaneous mechanical ventilation breathing trial (SBT). The purpose of this study was to evaluate the impact of implementing a multidisciplinary PAD guideline, protocol, and order set that incorporated these principles on clinical outcomes and medication utilization in an academic medical center ICU. It was hypothesized that the guideline and protocol would improve clinical outcomes and decrease continuous infusion benzodiazepine usage.

¹William S. Middleton Memorial Veterans Hospital, Madison, WI, USA

²UW Health-University Hospital, Madison, WI, USA

Corresponding Author:

Melissa Heim, William S. Middleton Memorial Veterans Hospital, 2500 Overlook Terrace, Madison, WI 53705, USA.
Email: Melissa.Heim1@va.gov

Methods

The PAD guideline, protocol, and order set were implemented in a 24-bed medical/surgical ICU in September 2012. After receiving exemption from our institutional review board, we conducted this single center retrospective pre-post chart review from September 2011 through August 2012 (pre) and October 2012 through September 2013 (post).

Participants

All critically ill, mechanically ventilated adults in the medical/surgical ICU admitted during the chart review period were included in the study.

Procedures: Guideline, Protocol, and Order Set

The multidisciplinary PAD guideline emphasized assessment and treatment of pain first. Pain was assessed every 1 to 2 hours and treated with intravenous fentanyl (preferred), hydromorphone, or morphine as needed bolus doses (Online Appendix 1). When ordering analgesic medications, providers had to select either a low dose or a standard bolus dosing option. The low dose option was recommended for patients who could be at risk for adverse reactions to higher doses of opioids, such as patients above the age of 65 years and patients with renal dysfunction and/or liver dysfunction. The standard dosing option was recommended for use in most patients who were deemed not at increased risk of adverse reactions to opioids. If a patient received 3 maximum opioid bolus doses in 1 hour and pain persisted, a continuous opioid infusion was started. Pharmacists did not dispense the continuous opioid drip until the maximum opioid bolus doses within 1 hour were administered and documented (unless physician approval to skip the as needed boluses based on patient presentation and clinical judgment).

For agitation, the multidisciplinary PAD guideline encouraged the use of light sedation goals (Richmond Agitation Sedation Scale [RASS] goals of 0 to -1). Prior to the guideline implementation, the RASS scale was not being utilized for sedation monitoring and clear end points for sedation were not included in the medication orders. Previously the Ramsay scoring system was used with the general understanding that the target was ~2. It also emphasized that pain should be adequately treated first (ie, pain goal must be met first with treatment of analgesic agents) prior to assessment of agitation and treatment with sedatives. When agitation is treated, the guideline emphasized treatment with as needed boluses of sedatives first and required the use of 3 maximum sedative boluses within an hour before a continuous sedative infusion could be initiated (unless physician approval to skip the as needed boluses based on patient presentation and clinical judgment). The agent of choice for bolus injections is midazolam. If 3 maximum midazolam boluses were administered in 1 hour, and a sedative continuous infusion was considered

clinically necessary, the guideline prioritized nonbenzodiazepine infusions with propofol as the first-line agent, dexmedetomidine as the second-line agent, and midazolam as the third-line agent (Online Appendix 2). Midazolam infusions were reserved for patients who could not tolerate propofol or dexmedetomidine or who could not achieve goal sedation with dexmedetomidine. In patients who required a continuous sedative infusion who achieved goal RASS, it was recommended that an attempt should be made every shift to decrease the sedative infusion rate. Pharmacists did not discontinue the continuous sedative drip until the maximum sedative bolus doses within 1 hour were administered and documented. The guideline also delegated pharmacists the ability to order laboratory monitoring tests every 2 to 3 days for patients on propofol, such as triglycerides, creatine kinase, and lactate.

Delirium was assessed with the Confusion Assessment Method for the ICU (CAM-ICU) at least every shift. For delirium treatment overall, nonpharmacologic treatment was recommended first-line. For patients with hypoactive delirium, the guideline emphasized reduction of analgesic and sedative medications. It specifically recommended changing patients on midazolam drips to dexmedetomidine drips in order to reduce the duration of delirium. For hyperactive delirium, the guideline recommended use of haloperidol (Online Appendix 3). The guideline provided education about avoiding the use of benzodiazepine sedatives for patients with hyperactive delirium.

The guideline also was supplemented with a nursing practice protocol which provided titration instructions to nurses for the analgesic and sedative continuous infusions (see Online Appendix 4). The protocol required nursing to document the targeted monitoring parameter (eg, RASS score) prior to starting a drip and every 1 to 2 hours until the goal was achieved. An associated PAD order set enabled adherence to the PAD guideline (Online Appendix 5). The order set included orders for as needed bolus analgesics, sedatives, and haloperidol, analgesic and sedative drips if bolus use and frequency requirements were met, and prioritized the choice of analgesic and sedative agents. The order set not only allowed health care providers to order the analgesic and sedative medications but also provided orders for a required daily sedation interruption, and coordination of daily SAT and SBTs. In addition, it included orders to titrate to specific RASS goals. By including all of the needed orders in one organized place, the order set allowed the guideline to be put into practice. All analgesic and sedative medications for intubated patients were required to be ordered through the order set and titrated per the nurse-directed protocol after guideline implementation. The clinical pharmacists in the ICU enforced the use of the order set.

Prior to initiation of a daily SAT, the patient was required to pass a safety screen. The SAT was deemed unsafe to perform if the patient was receiving a sedative infusion for active seizures, alcohol withdrawal, or control of intracranial

pressure, receiving paralytics, RASS greater than 2, documentation of myocardial ischemia in the past 24 hours, undergoing therapeutic hypothermia post cardiac arrest, undergoing withdrawal of life support, or was a difficult intubation. If deemed safe by the safety screen, the nurse turned off the sedative infusion. If the patient did not have a specific need for the analgesic infusion, such as trauma or post-operative, then the analgesic infusion was also turned off. The SAT was terminated if the patient demonstrated a RASS greater than 2 for 5 minutes or longer, pulse oximetry readings less than 88% for 5 minutes or longer, respiratory rate greater than 35 breaths/minute for 5 minutes or longer, new acute cardiac arrhythmias, intracranial pressure greater than 20 mm Hg, or 2 or more of the following symptoms of respiratory distress: heart rate increase of greater than or equal to 20 beats/min, heart rate less than 55 beats/min, use of accessory muscles, abdominal paradox, diaphoresis, or dyspnea. If the SAT was terminated, sedative and/or analgesic infusions were restarted at half the previous rate and retitrated to goal. If the patient passed the SAT, the patient was transitioned to a SBT in coordination with the respiratory therapist. The SBT goal time was 30 min. If the patient failed the SBT or was not deemed to be appropriate for extubation for other reasons, then the nurse reinitiated the PAD protocol, starting with as needed boluses and transitioning to a continuous infusion only if clinically warranted. With implementation of the guideline, a new build was created in the electronic medical record that allowed nursing to document the results of the safety screen, SAT, and SBT.

Prior to guideline, protocol, and order set implementation, there were interdisciplinary education sessions for physicians, nurses, pharmacists, and respiratory therapists. Pharmacists provided education on analgesics, sedatives, and antipsychotics, bolus dosing, and preference of drip options. Nurse specialists provided individual education on RASS and CAM-ICU scoring, titration of medications, and SATs. Respiratory therapists provided individual education to respiratory therapists on SBTs. ICU clinicians were also individually taught the principles of the PAD initiative. When a patient was intubated in the ICU or was admitted to the ICU and was already intubated, the clinical pharmacists in the ICU enforced the use of the order set. Clinical pharmacists were present in the ICU continuously, including overnight, weekends, and holidays. If the order set was not ordered, the pharmacist contacted the ordering provider and the orders were revised to utilize the order set. On daily multidisciplinary rounds, adherence to the guideline, infusion titration to defined end points, selection of analgesic/sedative, SAT, and SBT were discussed.

Outcomes

The primary study outcome was days of mechanical ventilation. Secondary outcomes included 28-day ventilator-free days, duration of ICU and hospital LOS, self-extubation rate,

mortality, and medication and hospital costs. For 28-day ventilator-free days, patients who died were counted as zero ventilator-free days. All values are reported as mean $\pm$ standard deviation unless otherwise specified. Medication utilization was captured through electronic medication administration charting to determine percentage of patients with orders for as needed medications, number of as needed medication administrations, average as needed dose administered, percentage of patients receiving continuous infusions, duration of continuous infusions, and average infusion rate. Intravenous analgesics were converted to fentanyl equivalents (10 mg morphine = 2 mg hydromorphone = 0.1 mg fentanyl), as described by Cammarano et al.⁸ Medication costs were determined from average wholesale price, and hospital costs were determined from estimations from hospital analysts.

Statistical Analysis

To examine differences pre-post implementation of the guideline, Fisher exact test was utilized for categorical variables. The 2-sample *t* test was used for dichotomous outcomes. A *P* value of less than .05 was considered significant.

Results

Participants

All mechanically ventilated patients in the closed 24-bed medical/surgical ICU during the study period were included in the analysis. The age and admission diagnosis remained similar pre and post study (Table 1). A total of 1147 patients (39% surgical patients, 61% medical patients) were included in the preimplementation group and 1270 patients (41% surgical patients, 59% medical patients) in the postimplementation group. acute physiology and chronic health evaluation (APACHE) IV scores were similar pre and post implementation (77.28 ± 32.65 vs 78.75 ± 32.36 , *P* = .27).

Outcomes

Average mechanical ventilation days were reduced after guideline implementation (3.98 ± 4.75 vs 3.43 ± 4.04 days, *P* = .0021), as well as ICU and hospital LOS (4.79 ± 5.31 vs 4.34 ± 4.87 days, *P* = .048 and 13.96 ± 12.09 vs 12.97 ± 12.17 days, *P* = .045, respectively). Self-extubations per ventilator days were unchanged (1.7 vs 1.7%) as well as hospital mortality (19 vs 19%, *P* = .96). The median 28-day ventilator-free days increased post guideline implementation but was not statistically significant (25 vs 26 days, *P* = .3041).

After guideline implementation, the percentage of patients with midazolam infusions decreased (422/1147 [37%] vs 363/1270 patients [29%], *P* = .0001) (Table 2).

The percentage of patients receiving continuous infusion propofol (679/1147 [59%] vs 896/1270 [70%], *P* = .0001)

Table 1. Analgesic and Sedative Medication Utilization.

Characteristic	Pre	Post	P value
Number of patients (n)	1147	1270	
Age ^a (y), mean $\pm$ SD	59 $\pm$ 16	60 $\pm$ 16	.18
APACHE IV score, mean $\pm$ SD	77.28 $\pm$ 32.65	78.75 $\pm$ 32.36	.27
Surgical patients, n (%)	447 (39)	521 (41)	.32
Admission diagnosis, n (%)			
Alcohol/drug overdose	42 (3.7)	48 (3.8)	.92
Chronic obstructive pulmonary disease/asthma	72 (6.3)	73 (5.8)	.61
Gastrointestinal bleeding	44 (3.8)	65 (5.1)	.14
Heart failure/pulmonary edema	22 (1.9)	23 (1.8)	.88
Pneumonia and/or acute respiratory distress syndrome	162 (14.1)	188 (14.8)	.64
Seizure	25 (2.2)	30 (2.4)	.79
Sepsis	84 (7.3)	118 (9.3)	.09
Surgical	323 (28.2)	352 (27.7)	.82
Trauma	128 (11.1)	121 (9.5)	.20
Other	245 (21.4)	252 (19.8)	.36

^aExcludes unidentified trauma patients with unknown age at admission, n = 1140 pre, n = 1261 post.

Table 2. Analgesic and Sedative Medication Utilization.

Medication	Number of patients with order (%)		P value
	Pre	Post	
Midazolam as needed	434 (38)	670 (53)	.0001
Midazolam infusion	422 (37)	363 (29)	.0001
Propofol infusion	679 (59)	896 (70)	.0001
Dexmedetomidine infusion	78 (7)	147 (12)	.0001
Opioid infusion	592 (52)	684 (54)	.27
Haloperidol as needed	62 (5)	88 (7)	.129

and dexmedetomidine (78/1147 [7%] vs 147/1270 [12%], $P = .0001$) increased. Average duration of midazolam infusions (41.5 vs 28.6 hours per patient) and dexmedetomidine infusions (41.5 vs 26.5 hours per patient) were reduced (Table 3). The percentage of patients receiving as needed bolus midazolam increased (434/1147 [38%] vs 670/1270 [53%], $P = .0001$) and the percent who had a continuous infusion opioid increased (592/1147 [52%] vs 684/1270 [54%], $P = .27$) (Table 2). The average continuous infusion opioid rate in fentanyl equivalents increased (39.1 μ g/h vs 61.3 μ g/h). Total as needed analgesic and sedative medication doses increased overall and the number of as needed analgesic and sedative doses per patient increased after guideline implementation (Table 4). Haloperidol use for hyperactive delirium remained similar.

Cost Analysis

Average analgesic and sedative drug cost per month increased (\$13,600 vs \$14,600) as well as total cost per year (\$163,270

vs \$175,000) in the postimplementation group compared with preimplementation group. However, the postintervention group included 123 additional patients. When adjusting for the increased number of patients in the postimplementation group, the average analgesic and sedative drug cost per patient was similar (\$142 vs \$138).

From the decreased ICU LOS, 0.45 ICU days were saved (4.79-4.34). From the decreased hospital LOS, 0.99 hospital days were saved (13.96-12.97). This resulted in 0.54 general care days saved (0.99 hospital days-0.45 ICU days). The estimated variable cost per day at our institution from hospital analysts was \$873 per ICU day and \$428 per general care day. From the decreased ICU and general care lengths of stay, a variable cost savings of \$800,000 per year was estimated (Figure 1).

Discussion

In this single-center retrospective chart review of a multidisciplinary PAD guideline, statistically and clinically significant reductions in days of mechanical ventilation and length of ICU and hospital stays were observed. The reduced days of ventilation and LOS were not attributable to mortality or change in severity of illness as mortality rate and APACHE IV scores were unchanged.

The above clinical outcomes were attributed to consistent interdisciplinary implementation of guideline recommendations. Specifically, the clinical outcomes were attributed to adherence to the recommendation to utilize and maximize as needed bolus analgesic and sedative medications and reserve continuous infusions for when 3 doses of as needed medications were administered within an hour and more analgesia/sedation was clinically necessary. This recommendation was achieved as

Table 3. Continuous Infusion Analgesic and Sedative Medication Duration and Infusion Rate.

Medication	Duration of continuous infusion (average hours/patient)		Average infusion rate	
	Pre	Post	Pre	Post
Midazolam infusion	41.5	28.6	3.8 mg/h	3.7mg/h
Propofol infusion	39.7	33.3	27.3 µg/kg/min	26.8 µg/kg/min
Dexmedetomidine infusion	41.5	26.5	0.6 µg/kg/h	0.5 µg/kg/h
Opioid infusion ^a	54.6	40	39.1 µg/h	61.3 µg/h

^aAll opioid medications converted to intravenous fentanyl equivalents using 10 mg morphine = 2 mg hydromorphone = 0.1 mg fentanyl.

Table 4. As Needed Analgesic and Sedative Medication Utilization.

Medication	Total as needed administrations		Average as needed dose		Average number of as needed doses per patient who received boluses	
	Pre	Post	Pre	Post	Pre	Post
Midazolam	3269	4907	2.1 mg	2.0 mg	7.5	9.8
Opioid ^a	8171	13 493	35.7 µg	42.7 µg	8.1	9.5
Haloperidol	334	377	2.7 mg	2.6 mg	5.4	4.28

^aAll opioid medications converted to intravenous fentanyl equivalents using 10 mg morphine = 2 mg hydromorphone = 0.1 mg fentanyl.

more patients received as needed medications and avoided starting continuous infusions as first-line therapy. Additional recommendations of the guideline were to utilize nonbenzodiazepine infusions. This recommendation was also achieved as continuous infusions of midazolam decreased as well as duration of midazolam infusions. Expectedly, the percentage of patients with dexmedetomidine infusions and propofol infusions increased as percentage of patients with midazolam infusions decreased. Although the percentage of patients with dexmedetomidine continuous infusions increased, the duration of dexmedetomidine infusions decreased. The changes in duration of infusions are attributable to the titration protocols and implementation of SATs and coordinated SBTs.

Prior to implementation of the guideline, there was concern that with fewer continuous infusions and lighter sedation goals, patients being more awake would lead to an increased self-extubation rate. However, no change in self-extubation rate was observed.

Total analgesic and sedative medication costs increased post implementation. However, the objective of the implemented guideline was not to lower drug costs. The purpose was to standardize medication administration based on evidence-based guidelines, which will decrease overall health care costs and improve patient outcomes. By increasing pharmacy department drug costs by approximately \$12,000 per year, more than \$800,000 in overall hospital costs were saved per year and care was provided for 123 additional intubated patients. When the increased number of intubated patients that care was provided for were accounted for, average drug costs per patient were similar.

The cost estimates used in this study are very conservative.⁹ These estimates included variable costs only and did not include other outcomes including decreased risk of infection, backfill time for patients that filled the ICU or hospital beds after patients were transferred or discharged, and the cost of ventilator use. The ICU LOS may be falsely elevated if patients were boarding in the ICU while awaiting transfer to the floor. For the 24 bed ICU, the average census was 20.5 pre versus 21.1 post.

The study included several limitations. The study design is subject to period effect and sample size. In addition, all patients who were mechanically ventilated were included in the analysis, regardless of whether the patient required paralytics at some point. Patient-specific risk factors for PAD were not collected. Use of atypical antipsychotics, such as quetiapine and olanzapine, were not captured in the study. Also, although the PAD order set was required in all patients, analgesic infusions were not always stopped prior to SAT and when a patient failed the SAT, analgesic and sedative infusions were not always restarted at only half of the previous rate. Due to the documentation of the SAT/STB being developed as part of the initiative, we were unable to compare compliance with SAT/STB pre/post. Based on this study, the institution-specific guideline will require a renewed focus on fully implementing existing recommendations, such as to continue to improve treatment of pain first, identify opportunities for patients who would benefit from analgo-sedation, continue to reduce midazolam infusions, and continue to identify patients requiring treatment of delirium. Protocolized analgesic and sedation practices allow for

Categorization of LOS	Calculation (LOS pre – LOS post study)	Resulting LOS days saved
ICU days	4.79 – 4.34	=0.45 ICU days saved
Hospital days	13.96 – 12.97	=0.99 Hospital days saved
General care days	0.99 – 0.45	=0.54 General care days saved
Estimated Costs \$873 per ICU day \$428 per General care day		
Cost calculations from days saved		
0.45 ICU days saved x \$873 x 1270 intubated patients per year		= \$498,919.50
0.54 General care days saved x \$428 x 1270 intubated patients per year		= \$293,522.40
Total cost savings		= \$792,441.90 per year^a

Figure 1. Cost-saving analysis. LOS = length of stay; ICU = intensive care unit.

^aDoes not include savings for backfill for ICU or hospital beds, saved mechanical ventilator time, or nursing ratios.

patient participation in early mobility programs.^{10,11} Therefore, the unit is well-positioned for next steps with early mobility implementation. In addition, this guideline, protocol, and order set will be expanded to other adult ICUs within the institution.

Conclusion

A multidisciplinary PAD guideline emphasizing SCCM PAD principles decreased midazolam drip usage, ventilation days, and ICU and hospital LOS. Drug costs per patient were not increased.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Supplemental Material

Supplemental Material is available at online.

ORCID iD

Melissa Heim <https://orcid.org/0000-0002-5137-549X>

References

- 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(20):1471-1477.
- Girard TD, Kress JP, Fuchs BD, et al. 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(9607):126-134.
- Brook AD, Ahrens TS, Schaiff R, et al. Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. *Crit Care Med*. 1999;27(12):2609-2615.
- Mascia MF, Koch M, Medicis JJ. Pharmacoeconomic impact of rational use guidelines on the provision of analgesia, sedation, and neuromuscular blockade in critical care. *Crit Care Med*. 2000;28(7):2300-2306.
- Marshall J, Finn CA, Theodore AC. Impact of a clinical pharmacist-enforced intensive care unit sedation protocol on duration of mechanical ventilation and hospital stay. *Crit Care Med*. 2008;36(2):427-433.
- Robinson BR, Mueller EW, Henson K, Branson RD, Barsoum S, Tsuei BJ. An analgesia-delirium-sedation protocol for critically ill trauma patients reduces ventilator days and hospital length of stay. *J Trauma*. 2008;65(3):517-526.
- Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med*. 2013;41(1):263-306.
- Cammarano WB, Pittet JF, Weitz S, Schlobohm RM, Marks JD. Acute withdrawal syndrome related to the administration of analgesic and sedative medications in adult intensive care unit patients. *Crit Care Med*. 1998;26:676-684.
- Turunen H, Jakob SM, Ruokonen E, et al. Dexmedetomidine versus standard care sedation with propofol or midazolam in intensive care: an economic evaluation. *Crit Care*. 2015;19:67.
- Morris PE, Goad A, Thompson C, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. *Crit Care Med*. 2008;36(8):2238-2243.
- Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet*. 2009;373(9678):1874-1882.