Intensive Care Med (2022) 48:1625–1628
https://doi.org/10.1007/s00134-022-06806-x

LASTING LEGACY IN INTENSIVE CARE MEDICINE

Evolution of sedation management in the intensive care unit (ICU)

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Intensive care unit (ICU) sedation practices have dramatically changed over the last 20 years [1–4]. Historically, patients were often deeply sedated to "let them rest" [4]. Strong evidence indicates these practices are dangerous and associated with poor outcomes [5, 6]. Current practice is to use minimum sedation and wake patients up daily while assuring patient comfort [2] (Supplementary Fig. 1).

ICU sedation management has changed over the years (Fig. 1). The first set of guidelines on sedation management were published in 1995. These guidelines recommended using midazolam or propofol for short-term sedation and lorazepam for long-term sedation [4]. The Clinical Practice Guidelines for the Sustained Use of Sedatives and Analgesics in the Critically Ill Adult (SAG) [3] were published in 2002. Sedation guidelines were recommended based off data by Brook et al. in 1999 showing protocol-driven sedation resulted in decreased time on ventilation [3]. SAG also suggested to set a daily sedation goal or provide daily interruption of sedation. This recommendation was based off data from Kress et al. showing that a spontaneous awakening trial (SAT) resulted in decreased time on ventilation [3]. In terms of medications, SAG recommended propofol if patients needed rapid neurologic assessments and midazolam for short-term sedation. Lorazepam was recommended as sedation for most patients; no mention of titrating lorazepam to light levels of sedation occurred. Statements indicating paradoxical agitation and post-traumatic stress disorder (PTSD) with light sedation were included.

The Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult ICU Patients (PAD) were published in 2013 [1]. PAD recommended sedatives be titrated to a light level of sedation unless contraindicated. This recommendation was based on studies like Girard et al. which showed that daily SAT coordinated with daily spontaneous breathing trial (SBT) resulted in better clinical outcomes [1] and Treggiari et al. which showed that patients receiving deep sedation were more likely to have PTSD [1]. The concept of "analgosedation" was introduced in the early 2000s by Muellejans et al. [1] using remifentanil based sedation, while Strom et al. implemented a "no sedation" strategy using intermittent morphine [1]. The Richmond Agitation Sedation Scale (RASS) and Sedation Agitation Scale (SAS) were determined to be the most accurate level of arousal assessment tools.

PAD suggested non-benzodiazepines may be preferred to improve clinical outcomes. Carson et al. found that patients randomized to propofol had shorter time on ventilation versus patients that received intermittent lorazepam [1]. Maximizing the Efficacy of Sedation and Reducing Neurological Dysfunction (MENDS) showed that patients that received dexmedetomidine had less delirium and coma and were more likely to be within 1 point of target RASS versus lorazepam [1]. The Safety and Efficacy of Dexmedetomidine versus Midazolam (SEDCOM) study showed that patients that received dexmedetomidine spent less time on ventilation and had less delirium [1].

The ICU Liberation Bundle (ABCDEF: "A" Assessment, Prevention, and Manage pain; "B" Both SAT SBT; "C" Choice of Analgesia and Sedation; "D" Delirium Assess, Prevent, and Manage; "E" Early Mobility and Exercise; and "F" Family Engagement and Empowerment) was

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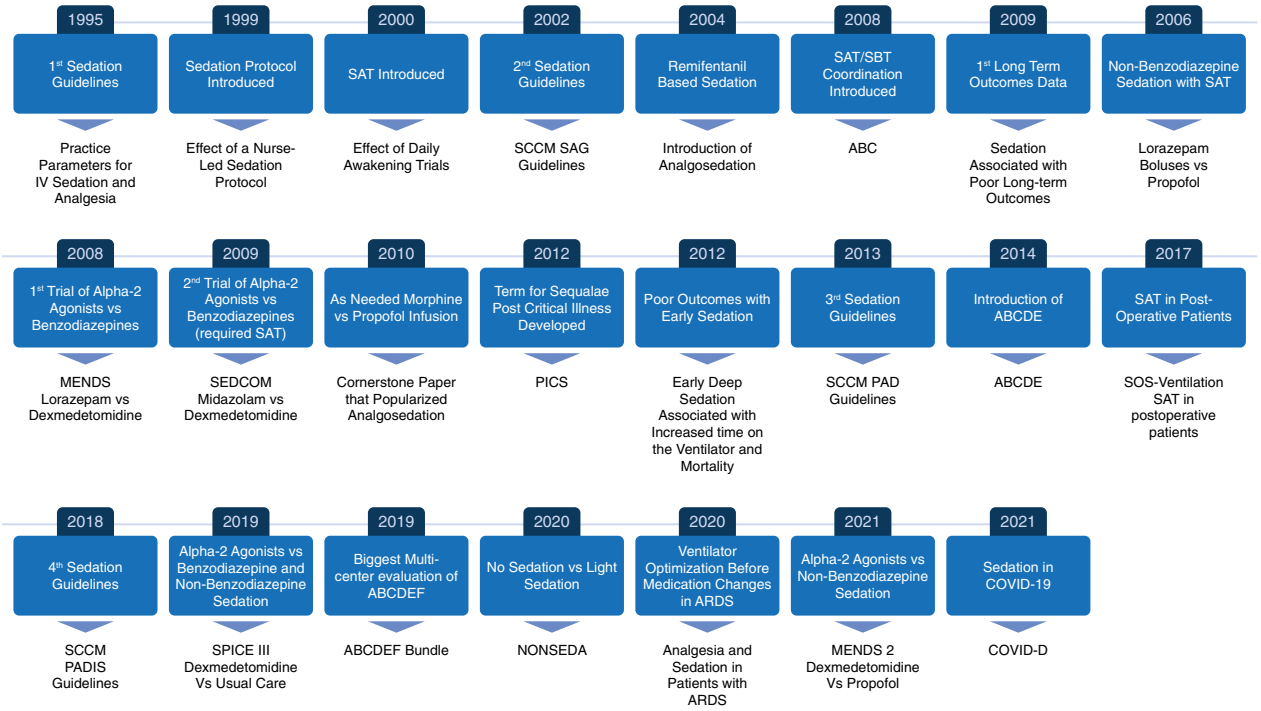

Fig. 1 This is timeline of selected landmark trials involved in the evolution of sedation in the ICU. References for this figure are listed from left to right starting at the top in the Electronic Supplementary Material 2. *IV*, intravenous; *SAT*, spontaneous awakening trial; *SCCM*, Society of Critical Care Medicine; *SAG*, The Clinical Practice Guidelines for the Sustained Use of Sedatives and Analgesics in the Critically Ill Adult; *SBT*, spontaneous breathing trial; *MENDS*, Maximizing the Efficacy of Sedation and Reducing Neurological Dysfunction; *SEDCOM*, Safety and Efficacy of Dexmedetomidine versus Midazolam; *PICS*, Post Intensive Care Syndrome; *PAD*, The Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult ICU Patients; *ABCDE*, Awakening and Breathing Coordination, Delirium monitoring/management, and Early exercise/mobility; *SOS*, Immediate interruption of sedation compared with usual sedation care in critically ill postoperative patients; *PADIS*, The Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU; *ABCDEF*, "A" for Assessment, Prevention, and Manage pain; "B" for Both Spontaneous Awakening Trials and Spontaneous Breathing Trials; "C" for Choice of Analgesia and Sedation; "D" for Delirium Assess, Prevent, and Manage; "E" for Early Mobility and Exercise; and "F" for Family Engagement and Empowerment; *SPICE 3*, Sedation Practice in Intensive Care Evaluation; *NONSEDA*, No Sedation or Light Sedation in Critically Ill, Mechanically Ventilated Patients; *ARDS*, Acute Respiratory Distress Syndrome; *MENDS 2*, Maximizing the Efficacy of Sedation and Reducing Neurological Dysfunction and Mortality in Sepsis

developed to implement PAD [7]. ABCDEF has now been studied in over 25,000 patients showing improvement in clinical outcomes. In 2012, Post Intensive Care Syndrome (PICS) was defined as patients that have physical, cognitive, and/or psychological impairment post critical illness [6] which is often secondary to delirium and increased time in the ICU. In 2012, Shehabi et al. found that early deep sedation resulted in increased time on ventilation and mortality [5]. In postoperative patients without severe acute respiratory distress syndrome (ARDS), Chanques et al. reported that the immediate interruption of sedation compared to moderate sedation was associated better clinical outcomes [8].

The Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU (PADIS) were published in 2018 [2]. PADIS suggested light sedation. PADIS suggested using propofol in cardiac patients and either propofol or dexmedetomidine in medical or non-cardiac surgical patients.

Since publication of PADIS, Sedation Practice in Intensive Care Evaluation (SPICE 3) [9] and Maximizing the Efficacy of Sedation and Reducing Neurological Dysfunction and Mortality in Sepsis (MENDS 2) [10] have been published showing no difference in dexmedetomidine versus usual care (SPICE III) or propofol (MENDS 2) in clinical outcomes. No Sedation or Light Sedation in Critically Ill, Mechanically Ventilated Patients (NONSEDA) randomized patients to no sedation versus light sedation finding no difference in 90 day mortality or ventilator/ICU free days [11].

Greater than 503 million cases of coronavirus disease 2019 (COVID-19) have been reported as of April 2022.

Patients with severe COVID-19 can develop ARDS sometimes require deep sedation placing patients at risk for delirium and coma. The COVID-D study found that 64% and 71% of patients received benzodiazepines and propofol for a median of 7 days respectively [12]. In patients with ARDS, choosing the best ventilator setting should be prioritized over increasing analgosedation [13]. However, it is clear that light sedation is not possible in most with severe ARDS or during neuromuscular blockade. This highlights the importance of daily interprofessional discussion of the ABCDEF Bundle to ensure that an individualized approach is taken toward sedation management and utilization of light sedation occurs again when possible.

High quality evidence is lacking in sedation research secondary to heterogeneity of data and resistance to practice change. Future directions include using a standardized approach allowing for meaningful comparisons between studies [14]. Additionally, use of inhaled anesthetics for sedation of critically ill patients is promising [15].

This paper provided an overview of how ICU sedation practices have evolved over the last 20 years. Contemporary ICU sedation practices include light levels of sedation, SAT, and use of non-benzodiazepines. The current COVID-19 pandemic has placed unprecedented demands on ICU workforce and challenged sedation practices [13]. It is urgent that clinicians reengage bundled based strategies such as the ABCDEF Bundle to promote liberation from the ventilator and promote recovery and survivorship.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1007/s00134-022-06806-x.

Conflict of interests
JLS is the Vice Co-Chair of the Society of Critical Care Medicine's most recent Pain, Agitation, Delirium, Immobility and Sleep Clinical Practice Guideline Committee. MCB is the Co-Chair of the Society of Critical Care Medicine's most recent Pain, Agitation, Delirium, Immobility and Sleep Clinical Practice Guideline Committee. GC is the Analgesia Lead of the Society of Critical Care Medicine's most recent Pain, Agitation, Delirium, Immobility and Sleep Clinical Practice Guideline Committee

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Funding
MCB currently receives research support from the National Heart, Lung, and Blood Institute of the National Institutes of Health under award number R01HL14678-01. She has received past honoraria from the Society of Critical Care Medicine for her work related to the ICU Liberation Collaborative. GC received fees for speaker (Orion Pharma, Aspen Medical) and for expert board (Orion Pharma).

Publisher's Note

Received: 5 April 2022 Accepted: 25 June 2022
Published: 29 July 2022

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