In Response

The challenges related to sedation of mechanically ventilated patients with coronavirus disease 2019 (COVID-19) that we outlined during the early pandemic[1] have since been studied by Kapp et al.[2] In a single-center cohort study, the authors found that the median daily dose of opioids administered in their mechanically ventilated COVID-19 patients (n = 19) was 3 times greater than the cohort of patients with acute respiratory distress syndrome (ARDS) that received high-frequency oscillatory ventilation (n = 275) in the 2013 OSCILLATE trial. Interestingly, patients receiving neuromuscular blocking agents (n = 10) in the study by Kapp et al[2] were administered higher doses of opioids when compared to patients (n = 9) who were not paralyzed. Despite its limitations (small single-center study, comparison with a historic ARDS trial cohort), this retrospective study supports the findings of increased sedation requirements in mechanically ventilated patients with COVID-19 compared to non–COVID-19 critically ill patients. Furthermore, the study highlights several important barriers to improving sedation practices in critically ill patients receiving mechanical ventilation including those with COVID-19:

1. There has been wide variation in reporting of the types and quantities of sedatives administered to patients who were enrolled in major ARDS clinical trials (Table). These inconsistencies in reporting sedation may hamper ARDS research given that there are well-known associations between depth of sedation, sedative side effects and key outcomes, including length of mechanical ventilation and mortality.[4] It seems reasonable to propose that detailed data on sedation administration and sedation depth should be considered when effects of ARDS interventions (eg, ventilator management, antiviral and immunomodulatory therapies) are evaluated in multicenter clinical trials, or when outcomes are reported in smaller cohort studies.
2. Although prioritizing pain control before adding sedatives in mechanically ventilated patients is recommended by Society of Critical Care Medicine guidelines,[5] liberal use of intravenous opioids in conditions that are not associated with significant pain (eg, COVID-19 pneumonia, influenza pneumonia) may promote opioid tolerance, hyperalgesia, chronic pain, and gastrointestinal dysfunction.[6] In patients with increased respiratory drive, such as those with severe COVID-19, increased administration of sedatives and opioids has most likely been related to difficulties in achieving ventilator synchrony. However, Kapp et al[2] report increasing doses of opioids in patients who received neuromuscular blockade and in whom opioids should arguably no longer be needed in high amounts to suppress respiratory drive and facilitate ventilator synchrony. This illustrates the need to examine the indications for opioid administration in daily intensive care unit (ICU) practice and to reduce the dose when the acute indication has ceased.
3. Variations in sedation practices exist between ICUs and these may be further exacerbated by local drug shortages during the pandemic, and the deployment of non-ICU medical personnel less familiar with managing sedation in "COVID surge" ICUs. Although Kapp et al[2] report that midazolam infusion was administered in every patient, midazolam infusions are less routinely used in many centers where propofol or dexmedetomidine are favored. Additionally, preserved hemodynamics in many patients with COVID-19 ARDS[7] may have allowed clinicians to escalate the doses of sympatholytic drugs such as propofol, dexmedetomidine, benzodiazepines, and opioids to reach levels that would not be tolerated in patients with other etiologies of ARDS in whom distributive shock is more common.

As the pandemic continues in the United States and across the world, there is clearly a need for research and practice guidelines for optimal sedation strategies of critically ill patients with COVID-19. Such strategies should be individualized taking into account patient's sedation needs, respiratory parameters, tradeoffs between deep sedation and paralysis to achieve ventilator synchrony, and considering short-term and

Table. Reporting of Sedation Data in Major Clinical Trials of ARDS

Trial	Publication	Sedation Data Reported
ARDSNet	*N Engl J Med* (2000)	Percentages of days on which sedatives were administered
ALVEOLI	*N Engl J Med* (2004)	None
FACCT	*N Engl J Med* (2006)	None
ACURASYS	*N Engl J Med* (2010)	48-h and 7-d cumulative exposure to sufentanil, midazolam, ketamine, and propofol
PROSEVA	*N Engl J Med* (2013)	Mean duration of sedation
OSCILLATE	*N Engl J Med* (2013)	Median duration of sedation Median daily dose of midazolam, fentanyl, and propofol
SAILS	*N Engl J Med* (2014)	None
ROSE	*N Engl J Med* (2019)	Daily sedation scale parameters from baseline through study day 7

Abbreviations: ACURASYS, xxx; ALVEOLI, xxx; ARDS, xxx; ARDSNet, xxx; FACCT, xxx; OSCILLATE, xxx; PROSEVA, xxx; ROSE, xxx; SAILS, xxx.

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long-term effects. Broader awareness that spontaneous modes of mechanical ventilation with lighter sedation targets may be feasible and noninjurious in COVID-19 ARDS is also needed. As an important first step, reporting sedation practices across centers, as now done by Kapp et al,[2] will be essential to better understand variations in practice and allow comparison of patient outcomes between cohort studies.

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