Weaning From Exogenous Sedation in the Era of COVID-19 Infection:
Recommendations for Sedation and Its Discontinuation

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LESSONS LEARNED AT THE INTERFACE OF MEDICINE AND PSYCHIATRY

The Psychiatric Consultation Service at Massachusetts General Hospital sees medical and surgical inpatients with comorbid psychiatric symptoms and conditions. During their twice-weekly rounds, Dr Stern and other members of the Consultation Service discuss diagnosis and management of hospitalized patients with complex medical or surgical problems who also demonstrate psychiatric symptoms or conditions. These discussions have given rise to rounds reports that will prove useful for clinicians practicing at the interface of medicine and psychiatry.

Have you ever wondered what types of sedating medications are available for use in those who require ventilatory support during the management of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)/coronavirus disease 2019 (COVID-19) infection? Have you been uncertain while caring for critically ill individuals about which agents to use and how much you can give, as well as how quickly those medications can be tapered and discontinued? Have you wondered what complications might arise with a rapid taper and how those manifestations can be managed effectively? If you have, then the following case vignette and discussion should prove useful.

CASE VIGNETTE

Mr A, a 35-year-old man with an unremarkable psychiatric and medical history, presented to a local emergency department (ED) with 2 days of fever, chills, and shortness of breath. He had not traveled outside of the city recently nor had he interacted with anyone known to have SARS-CoV-2/COVID-19 infection. His only outpatient medication was low-dose ibuprofen, as needed, for musculoskeletal pain. He was a married, hard-working, chef with 2 school-aged children. He drank alcohol socially and denied use of other substances. His physical examination revealed a temperature of 102°F, respiratory rate of 20 breaths/minute, blood pressure of 136/84 mm Hg, pulse of 102 beats/minute, and oxygen saturation of 87%. His cardiopulmonary examination was remarkable for bilateral inspiratory crackles. A computed tomography (CT) scan (without contrast) of his chest showed bilateral ground-glass opacities in the upper lobes with rounded morphology. He required immediate supplemental oxygenation, which briefly improved his respiratory status. Shortly after his ED evaluation, he decompensated further and developed respiratory distress, leading to endotracheal intubation. Mr A was admitted to the hospital's intensive care unit (ICU) and placed on mechanical ventilation. A nasopharyngeal swab for SARS-CoV-2 RT-PCR was positive.

Dr B, a middle-aged family medicine physician, was recently redeployed from his outpatient clinic to care for patients in the ICU. Although his team leader was a critical care physician, Dr B had not worked in such a setting since his years of residency training, and he was assigned the task of caring for Mr A, among others. Mr A was placed on synchronized intermittent mandatory ventilation with a 60% fraction of inspired oxygen, a pressure support of 10, a positive end-expiratory pressure of 5, and a tidal volume of 550 mL. A dexmedetomidine infusion was initiated at 0.4 mcg/kg/h and titrated to 0.8 mcg/kg/h. Throughout his hospitalization, Mr A was monitored regularly with arterial blood gases and chest X-rays along with sedation holidays to assess his neurologic and unassisted respiratory status.

Once Mr A was able to oxygenate well on his own on minimal ventilatory settings (positive end-expiratory pressure of 5, pressure support of 10, and 40% fraction of inspired oxygen; on pressure support ventilator

Clinical Points

- During the COVID-19 crisis, career intensive care unit (ICU) physicians and redeployed staff have struggled with the necessary, but novel, challenge of managing critically ill patients while maintaining their safety and the capacity for human compassion.

- Sedation of patients on mechanical ventilation is a balance, as oversedation is associated with longer time spent on the ventilator and a longer ICU stay and undersedation is associated with worsening stress, insomnia, delirium, and development of posttraumatic stress disorder.

- Neurologic assessment is recommended daily and during sedation interruption because it allows for the monitoring of baseline neurologic function and better detection of secondary cerebral illness, as patients are at higher risk for neurologic dysfunction when critically ill even if they are admitted to the ICU for nonneurologic etiologies.

- During the reduction of sedative-analgesic medications, patients should be closely monitored for acute withdrawal phenomenon.

settings), weaning parameters were obtained. He achieved a tidal volume > 700 mL, a rapid shallow breathing index of 64, and a negative inspiratory force of −30 cm H_2O. Therefore, he was considered ready for extubation. Subsequently, his dexmedetomidine infusion was rapidly discontinued. Four hours later, Mr A became acutely anxious and restless; he became hypertensive, diaphoretic, and tachycardic.

DISCUSSION

How Often Do Those With SARS-CoV-2/COVID-19 Infection Require Hospitalization and ICU Care?

Several studies[1–3] have indicated that individuals with COVID-19 infections fall into 1 of 4 severity categories: asymptomatic, mild, severe, and critically ill. Those who are asymptomatic or who have mild manifestations (eg, with pneumonia and little to no hypoxemia) comprise most cases—approximately 80%.[1–3] Those with severe disease account for 14% to 15% of cases and have shortness of breath, hypoxemia, and greater pulmonary involvement on chest X-rays. They typically require hospitalization but not ICU care. However, those with critical illness are likely to develop respiratory failure, multiple organ dysfunction, stroke, or septic shock and require ICU care, often with mechanical ventilation.[2,4] This group accounts for roughly 5% of confirmed COVID-19 cases. According to the World Health Organization,[5] individuals with mild illness tend to recover within 2 weeks of symptom onset, while those with more severe manifestations typically require 3 to 6 weeks of care.

Excluding young children, it appears that individuals of all ages can fall into any of the 4 categories of COVID-19 severity, and those who begin in a less severe category can fall to a more severe state. Nevertheless, COVID-19 infects people in an age-dependent manner. In 1 report,[6] the Centers for Disease Control and Prevention (CDC) analyzed 4,226

cases of confirmed COVID-19 infection in its associated surveillance sites in the US territories. The CDC confirmed the age of 2,449 of these individuals who were distributed as follows: 0–19 years (5%), 20–44 years (29%), 45–54 years (18%), 55–64 years (18%), 65–84 years (25%), and over 85 years (6%). Among patients with age data available, 12% required hospitalization in the 6-week period. Adults 65 or older comprised 31% of cases but experienced 45% of hospitalizations, 53% of ICU admissions, and 80% of deaths. The total hospitalization rate—among all patients with and without age data—was between 20.7% and 30.4%, the total ICU rate was 4.9%–11.5%, and the case fatality rate was 1.8%–3.8%.[6] Research conducted over similar time periods in China reported that between 7% and 26% of laboratory-confirmed COVID-19 infections required ICU care.[7] In concordance with these data, researchers[8,9] in Italy reported ICU admission rates between 5% and 12% among those with laboratory-confirmed COVID-19 infection, and 16% among patients already hospitalized with COVID-19 infection. These rates have remained more or less consistent among infected patients over time, though infection rates have evolved across the world. A wide disparity of figures has been proposed for the overall case fatality rate, which has been difficult to calculate due to the large proportion of asymptomatic cases. It has also remained difficult to track changes in rates of hospitalization, ICU use, and mortality due to inherent delays in recording, analysis, interpretation, and reporting of data.

Older adults are not the only group who are at increased risk for severe illness, hospitalization, and death. Those with hypertension, chronic lung disease, diabetes mellitus, cardiovascular disease, cancer, chronic kidney disease, or any combination of these conditions are at increased risk for negative outcomes.[1,2,10–12] In addition, the CDC added immunocompromised individuals (eg, those with HIV/AIDS), severe obesity, and liver disease to the list of risk factors for severe COVID-19–related illness.[13] Among 355 COVID-19–related deaths analyzed in 1 Italian research study,[14] patients had an average of 2.7 preexisting conditions, with only 3 patients devoid of any significant comorbidity. This disparity is especially accentuated when combined with age. In a Washington State chronic care facility, 101 residents showed symptoms from the virus, with an average age of 83 years, and 94% had a chronic medical condition.[15] A stunning 55% of those residents required hospitalization, and 34% died of their infection.[15]

What Is It Like for Staff Caring for Critically Ill Individuals With COVID-19 Infection?

During this pandemic, health care staff have documented their responses to this unprecedented situation. For example, in an essay in the *Annals of Internal Medicine* published in mid-April 2020, a group of physicians in a New York City hospital reported a collective sense of purpose, certainly, but also fear, uncertainty, and stress.[16] "While providing care in an urban academic medical center's medical wards," they wrote, "we have lost the intimate connection with our

patients at their most vulnerable points; felt powerless in the face of the very real fear."[16(p1)] Worst of all, they felt unprotected. The lack of intimate connection came as the result of distancing measures (staff were advised to remain at least 2 m away from infected patients when possible and to use personal protective equipment [PPE] constantly), restrictions on visits by family and friends, time constraints associated with high patient demand, and limited history taking and physical examination.[16,17] The authors wrote, "Instead of taking a comprehensive history, we focus only on the aspects relevant to COVID-19. And instead of conducting full physical examinations, we focus on the portions of the examination that could reveal respiratory problems to come. Wearing masks, face shields, gowns, and gloves all the time is foreign, awkward, and cumbersome. Though critical to our safety, this physical barrier of personal protective equipment impedes the intimate interactions that we and our patients are accustomed to having."[16(p1)]

Career ICU physicians and redeployed staff have struggled with the necessary, but utterly novel, challenge of managing critically ill patients while maintaining their safety and the capacity for human compassion. In many institutions, patients who required mechanical ventilation were isolated while the ventilators remained in the hallway, allowing staff to manage ventilation without increasing exposure or using excess amounts of PPE. Routine practices, such as placing a hand on the patient's chest to feel for breathing, were restricted in many hospitals. In addition, staff and administrators remained concerned that the national supply of PPE was insufficient to protect health care workers, and this led to consternation on the part of those at risk.[16,18]

In addition, a moral dilemma arose while reconciling professional and societal duties with the safety, assurance, and well-being of family and loved ones. "I feel an immense guilt at having burdened [my family] with this horrible disease because of my career choices," a pediatric otolaryngologist wrote.[19(p2)] Another physician, a resident in internal medicine, wrote, "I am intentionally shifting my responsibilities in the face of this new viral menace," to protect herself from severe asthma exacerbations.[20(p1)] Systemic challenges were also faced by most ICU staff, regardless of personal circumstances. These challenges included limited space and supplies, a lack of effective COVID-19–specific medications, and the need to regularly adapt to constant changes in practice and patient demands.[21]

While one cannot predict everyone's critical caregiving experience—particularly in a rapidly evolving pandemic— these challenges appear to form a meaningful pattern. ICU staff in the COVID-19 era are faced with new and foreign standards of patient interactions, moral and personal distress regarding risk of infection and spread among family and loved ones, adjustments to new forms of treatment and caregiving, concern over a lack of personal protection, and uncertainty due to a constantly evolving situation and set of clinical guidelines. While many staff have managed these challenges with poise and resolve, the process of caring for patients infected with COVID-19 has been trivial for no one.

How Can Recently Redeployed Providers Be Effectively Supported When Working in ICUs Rather Than in Their Primary Discipline?

Support for non-ICU physicians who have been redeployed to caring for critically ill individuals infected with COVID-19 generally fall into 2 categories: professional and personal. Both are important to maintain a well-prepared and mentally healthy workforce throughout the pandemic.

Professional support is perhaps the most intuitive need for providers redeployed from non-ICU specialties. Whether one is a surgeon, a radiologist, a psychiatrist, or a practitioner from another specialty, specific learning and assessment materials are required to prepare for critical care in general and COVID-19-related care specifically. Preparatory materials for general critical care can be found in the "COVID-19 Resources for Non-ICU Clinicians" resource collection developed by the Society for Critical Care Medicine.[22] This collection includes brief overviews on topics ranging from mechanical ventilation to medication dosage and drip rate calculation, as well as a self-assessment knowledge check for physicians preparing to care for patients with COVID-19 in the ICU. In addition, repositories of the most relevant and up-to-date literature regarding COVID-19–specific critical care (and other aspects of the pandemic) can be found in the online versions of most major medical journals.[23,24] Among this pertinent literature, clinical guidelines and synopses may be especially helpful, given their concise and evidence-based nature. As just 2 examples, Poston et al[25] recently published a selection of clinical recommendations for management of critically ill patients with COVID-19, alongside detailed guideline ratings and analyses of the evidence base. Phua et al[26] published a thorough review of the same topic, delineating, describing, and concisely illustrating (in flowcharts and diagrams) pertinent challenges and recommendations to COVID-19–related intensive care. Taken together, such professional resources may help ensure that each redeployed provider is well prepared for his/her new role.

At the same time, personal and social support is also necessary to maintain an effective critical care workforce. Organizations such as the American Medical Association (AMA) have recognized the importance of this support and have collated "practical strategies for health system leadership to consider in support of their physicians and care teams during COVID-19."[27(p1)] The AMA collection, in particular, includes recommendations for institutional policy (eg, workload redistribution, paid sick leave) as well as examples of and online links to initiatives taken by specific companies, hospitals, and organizations for the support of health care workers during the pandemic. The collection lists several food companies offering contact-free and reduced-pricing meal deliveries to hospitals and clinicians, mentions child and pet services and emotional and mental health services, and provides links to the COVID-19 resource pages of other prominent academic medical organizations and institutions.

Which Medication Classes Are Typically Used to Sedate Intubated Patients in the ICU?

Management of intubated patients in the ICU typically includes sedation and analgesia. Sedation reduces stress and anxiety while facilitating mechanical ventilation. The most commonly used medications for sedation include propofol, dexmedetomidine, and benzodiazepines.[28]

Propofol is a sedative with increasing popularity when compared to rates of benzodiazepine or dexmedetomidine use.[29] It is typically preferred if a patient requires periodic neurologic assessments, as it has a rapid onset, short-half life, and inactive metabolites. Notable adverse effects of propofol include hypotension as well as prolonged emergence from sedation, particularly if propofol has been dosed to provide deeper sedation, as it can lead to saturation of peripheral tissues.[30] Practitioners should also be aware that propofol has been related to higher rates of self-extubation.[28]

Dexmedetomidine was initially considered for short-term use (< 24 hours) in ICU patients; however, it has been well tolerated and effective for longer periods. Dexmedetomidine is metabolized in the liver; patients with liver failure or cirrhosis require smaller doses and have a longer emergence from sedation.[30] Notable adverse effects of dexmedetomidine include bradycardia, with a higher risk of hemodynamic instability when given in a loading dose.[31]

Benzodiazepines including lorazepam, midazolam, and diazepam have a place in continuous ICU sedation, particularly when managing agitation or anxiety.[30] However, propofol and dexmedetomidine have been recommended over the use of benzodiazepines for sedation, as they have been found to improve time spent on the ventilator, decrease risk of delirium, and cause less hemodynamic instability.[31,32] Additionally, adverse effects of benzodiazepines (including decreased respiratory drive, hypotension, and development of tolerance if used consistently) should be considered.[30] This recommendation has been reflected in the PADIS guidelines (Pain, Agitation/Sedation, Delirium, Immobility, and Sleep) of the Society of Critical Care Medicine since 2013.[28] However, benzodiazepines continue to have a place in ICU sedation when managing agitation, anxiety, or accompanying seizures or withdrawal.[30]

Adjunctive options for sedative therapy include use of clonidine, which has a similar mechanism of action to dexmedetomidine but provides a lower level of sedation. Clonidine should be tapered, as abrupt discontinuation can lead to hypertension.[33]

Analgesia is often undertreated due to adverse effects of pain medications that include respiratory depression, hemodynamic changes, and addiction potential.[33] Analgesia can be measured by standardized scales, such as the Behavioral Pain Scale and the Critical Care Pain Observational Tool.[34] Options for analgesia include morphine, hydromorphone, fentanyl, and remifentanil. Morphine and hydromorphone are typically administered as intermittent intravenous (IV) injections, whereas fentanyl and remifentanil are administered as a continuous infusion, as they have a faster onset and can be titrated.[33]

Adjunctive options for analgesia include continuous infusion of ketamine, which has been shown in retrospective studies to decrease utilization of analgesic and sedation medications in mechanically ventilated patients[35]; however, further prospective studies are needed to confirm its utility. Use of ketamine requires close monitoring for adverse effects, such as hallucinations or other psychological disturbances.[28]

How Deep Should Sedation Be for Intubated Patients and How Often Should Sedation Be Lightened to Complete a Neurologic Examination?

Sedation of patients on mechanical ventilation is a balance, as oversedation is associated with longer time spent on the ventilator and a longer ICU stay and undersedation is associated with worsening stress, insomnia, delirium, and development of posttraumatic stress disorder (PTSD).[28,33] Therefore, scales such as the Sedation Agitation Scale,[36] the Motor Activity Assessment Scale,[37] and the Richmond Agitation-Sedation Scale (RASS)[38] are used to establish a goal level of sedation and to monitor sedation in a standardized way.[34] Light sedation is preferred to deep sedation in ICU patients who are being mechanically ventilated, as it shortens time to extubation and decreases the tracheostomy rate.[28] Older studies sided toward a target RASS score of −2.[39] However, more recent studies have shown that a RASS score between −1 and + 1 led to significantly shorter ICU length of stays and decreased cost.[40] For this reason, target RASS scores have trended toward lighter and lighter sedation levels, with the most recent PADIS 2018 guidelines defining light sedation as a RASS score of −2 to + 1.[28]

Sedation protocols can be classified as protocol-directed sedation management (or a protocol carried out by the ICU nurse) versus non–protocol-directed management. Review of randomized controlled trials showed no significant difference between outcomes of either of these management options.[41] However, the heterogeneity of the studies on this topic, the nurse-to-patient ratio, and the experience of the individual performing the protocol should be considered.[41] Sedation of patients can also be classified by continuous sedation versus intermittent sedation (typically a daily interruption of sedation). Daily interruption of sedation had multiple benefits, as it shortened mechanical ventilation by 2 days and length of ICU stay by 3.5 days and decreased the total amount of benzodiazepines used.[39] Additionally, it reduced the complications that can accompany prolonged intubation, including ventilator-associated pneumonia, barotrauma, venous thromboembolic disease, upper gastrointestinal bleeding, and cholestasis.[42]

Neurologic assessment is recommended daily and during sedation interruption, as it allows for the monitoring of baseline neurologic function and better detection of secondary cerebral illness. Patients are at higher risk for neurologic dysfunction when critically ill, even if they are admitted to the ICU for nonneurologic etiologies.[43]

The decision to use prone positioning during mechanical ventilation can influence the level of sedation. Particularly in patients with severe acute respiratory distress syndrome

(ARDS), keeping the patient in prone position for at least 12 hours a day showed a decrease in mortality and is suspected to decrease risk of ventilator-related lung injury.[44] Patients in the prone position typically require increased sedation and neuromuscular blockade to better tolerate this position.[45] For management of patients with COVID-19, guidelines from the European Society of Intensive Medicine recommend intermittent use of neuromuscular blockers unless the patient requires deeper sedation or prone ventilation, in which case a continuous infusion of neuromuscular blockers would be recommended.[46]

What Do Withdrawal Syndromes From These Medication Classes Look Like and When Do They Appear?

During the reduction of sedative-analgesic medications, patients should be closely monitored for acute withdrawal phenomenon. In this setting, withdrawal is quite common and can be induced by abruptly interrupting or rapidly decreasing doses and blood drug concentrations. In an observation study[47] of 28 mechanically ventilated patients in an ICU for more than 1 week, 32% experienced an acute withdrawal syndrome. This syndrome manifests with variable symptoms depending on the sedative-analgesic class of medication used. Additionally, monitoring for emergence delirium after weaning of sedation is a crucial task, as it may occur in 68%–87% of medical ICU patients. Prominent risk factors include age >65 years, prolonged ventilation (more than 3 days) and immobility, continued nutritional and electrolyte deficiencies in the setting of COVID-19 infection, and organ failure. The hallmarks of this syndrome are impaired attention, disorientation, and problems with cognition, language, visuospatial ability, or perception.[48] It should be differentiated from more common agent-specific withdrawal features by persistence of altered mentation and confusion, as it can also occur in roughly the same time period.

Opiate withdrawal occurs in approximately 16.7% of patients receiving mechanical ventilation for more than 72 hours. Symptoms include anxiety, agitation, tachypnea, tachycardia, fever/chills, hypertension, mydriasis, rhinorrhea, lacrimation, nausea/vomiting, abdominal cramps, diarrhea, tremor, and piloerection. Opioid withdrawal onset varies depending on the agent used and symptom cluster; however, it typically occurs within 7–12 hours of medication dose reduction.[49] Benzodiazepine withdrawal is characterized by similar features, including agitation, anxiety, tremors, autonomic hyperactivity, and fever. More dangerously, these features may also precipitate seizures. Its prevalence has not been characterized due to the heterogeneity of drugs used and concurrent opioid administration. The onset is typically within 4–10 hours, with a more rapid precipitation if midazolam was used.[50]

Withdrawal from propofol has been noted as "propofol infusion syndrome." Its overall epidemiology, pathophysiology, and diagnostic criteria are not well studied or understood. Propofol withdrawal syndrome has been precipitated by reducing anesthesia after administration of high doses (>5 mg/kg/h) or prolonged duration (>48 hours). Its presentation is highly variable and can involve fever and hypotension, accompanied by metabolic acidosis, rhabdomyolysis, hyperkalemia, or elevated lactate and liver enzymes. Propofol infusion syndrome onset occurs within 24 hours of any reduction in its dose or frequency.[51]

Considering the increasingly widespread use of dexmedetomidine, withdrawal after prolonged infusions has been documented. Its incidence is relatively understudied; however, 1 recent prospective observational study[52] reported that 64% of the 42-patient cohort experienced symptoms. Additionally, withdrawal was found to be more likely to occur in those receiving high cumulative daily doses or elevated peak rates (>12.9 µg/kg/d or 0.8 µg/kg/h) for more than 3 days. Withdrawal signs include hypertension, tachycardia, diaphoresis, and anxiety. The time to onset of these symptoms is currently not well studied but estimated to be within 8 hours of discontinuation.[52]

Compared to the other sedative agents, symptoms of ketamine withdrawal are less often associated with hemodynamic effects and cardiorespiratory events and more so with dysphoric emergence phenomenon. Ketamine withdrawal occurs in 10%–20% of patients and involves depersonalization, dreams, hallucinations, and a general state of distress. The time frame in which this occurs is within minutes to hours of removal of sedation.[53]

How Can Withdrawal Syndromes From These Medication Classes Be Managed?

The first and pivotal question for sedation weaning is to assess readiness by considering improvement of the underlying etiology that resulted in continuous sedation, hemodynamic stability, appropriate neurologic status (RASS score of −2 to 0 with minimal sedation), and adequate gas exchange (partial pressure of oxygen: fraction of inspired oxygen ratio >200 with a positive end-expiratory pressure of 5 cm H_2O). For any pharmacologic agent used for continuous sedation, the sequence and rate of discontinuation should be individualized and optimized. Abrupt or rapid discontinuation is more likely to precipitate withdrawal phenomenon, particularly in those who have been receiving sedation for more than 7 days. A gradual reduction (of 10%–25% per day) is prudent.[54]

For opiate withdrawal secondary to infusions in the critically ill, several strategies have been proposed; unfortunately, controlled trials on this are lacking. These regimens include conversion to a longer-acting oral equivalent (eg, methadone) or augmentation with a α-2 agonist such as dexmedetomidine or clonidine. Dosing varies tremendously if oral equivalents are utilized and depend on the amount and frequency used for continuous sedation. One study[31] of 20 patients used an average of 48 mg of methadone to transition from fentanyl infusions. In the case of dexmedetomidine, doses of 0.7 mcg/kg/h with or without loading doses of approximately 1 µg/kg have been implemented.[55] Clonidine has been administered via a transdermal patch (50–100 µg/d

or 4.2–8.5 µg/kg/d) or an oral formulation of 3–6 µg/kg/d divided every 4 to 6 hours.[55,56] Benzodiazepine withdrawal has also been managed with α-2 agonists, as described above. Additionally, IV or oral lorazepam (0.5–1 mg every 6–12 hours) has been used simultaneously as weaning ensues to prevent and alleviate withdrawal symptoms that arise.[57]

There are no established guidelines for treatment of propofol infusion syndrome. The overall success is more likely to depend on early diagnosis and prevention. These approaches involve avoiding infusion rates > 5 mg/kg/h for more than 48 hours, using propofol in combination with other sedatives, and monitoring pH, lactate, and creatine kinase if prolonged administration is required. Otherwise, acute management is centered on treatment of the ensuing metabolic acidosis by increasing minute ventilation or even using extracorporeal membrane oxygenation in some cases.[51]

Dexmedetomidine withdrawal is a documented yet poorly understood syndrome. As such, there are no specific treatments reported specifically for these cases. Symptomatic treatment of autonomic hyperactivity can be managed with cardiovascular agents, along with a brief course of benzodiazepines for acute anxiety or agitation that arises (lorazepam 0.5–1 mg every 6 hours as needed). With ketamine emergence phenomenon, reactions are often quite frightening or distressful but not particularly dangerous. Calming environmental techniques (eg, music, isolated recovery area) may be utilized. Otherwise, single administration of benzodiazepines has been efficacious shortly before weaning or as needed upon emergence.[53] Propofol has also been combined with ketamine (0.75 mg/kg, ranging from 0.2 to 2.05 mg/kg for each agent) with an observed lower occurrence rate of this withdrawal syndrome.[58]

Are There Long-Term Consequences From Prolonged Ventilatory Support?

Numerous studies have addressed the neurologic, neurocognitive, psychiatric, and functional sequelae of prolonged mechanical ventilation (PMV). In 1 study,[59] comparing outcomes of patients discharged from a Canadian ICU, 47.2% of patients who received PMV were rehospitalized within 1 year, while only 37.7% of those who did not receive PMV were rehospitalized over an equivalent timeframe. Rates of 1-year ICU readmission (19.0% vs 11.6%) and total health care costs (Can $32,526 vs Can $13,657) were significantly increased in those who received PMV. In a separate study conducted in the United States, the authors[60] reported a 56% 1-year mortality rate among patients discharged from the hospital after receiving PMV. Of those who survived beyond 1 year, 62% reported that their health status was better after 1 year than it had been prior to hospitalization, 23% reported worse health, and 15% reported no change. Among the survivors, 28% reported no dependencies for their instrumental activities of daily living (IADLs), 57% were dependent on caregiver support for at least 1 IADL, and 7% were dependent on others for every IADL.[60]

Behind these broad functional deficits lies a list of neurologic and pathophysiologic sequelae associated with PMV. According to a consensus statement from the National Association for Medical Direction of Respiratory Care (NAMDRC), these sequelae include "late mortality, ongoing morbidity, neurocognitive defects, impaired mental health. . . . These stresses, physical and emotional, associated with continued weaning efforts, complications, worsened comorbidities . . . add to the continuum of late sequelae."[61(p3,951)] In a review article[62] developed from the 2002 Brussels Roundtable, the authors noted that these issues are often present at discharge and continue beyond the 1-year follow-up. One study,[63] conducted in the ICU of a large US medical school found that, of 96 patients who underwent PMV during their ICU stay, 44.8% tested as "cognitively impaired" at hospital discharge. In addition, 10.4% of patients met criteria for delirium at discharge and 20.5% met criteria for subsyndromal delirium.[63] Another study[64] conducted among patients with ARDS weaned from PMV and discharged from the ICU found that neurocognitive sequelae can persist long after discharge. After 1 year, 30% of patients in the study[64] experienced global cognitive deficits, and 78% experienced impairment in at least 1 cognitive function, including concentration, attention, and memory. Generally speaking, patients may also experience general constitutive symptoms (eg, weakness, fatigue) as part of the long-term sequelae of PMV and appear to be at increased risk for PTSD and depression.[62,65] Beyond the effects of PMV itself, conditions such as ARDS are associated with their own independent consequences of central nervous system dysfunction. Reviews of ARDS and its neurocognitive sequelae can be found in the literature.[66,67]

One question may be to what extent PMV itself—as opposed to chronic conditions or patient characteristics—is responsible for morbidity in patients receiving this intervention. While the literature has yet to provide compelling or consistent answers to this particular inquiry, recent developments in quality assessment and critical care have provided a framework that may enable clinician researchers to do so. In 2013, the CDC organized a working group that defined ventilator-associated events (VAEs) as a quality benchmark for measuring ventilator-related morbidity and mortality. Prior to this definition, ventilator-associated pneumonia served as the only benchmark of quality for ventilated patients and a relatively unreliable one at that. Its replacement, VAE, stands as a "surveillance definition algorithm," used to "identify a broad range of conditions and complications occurring in mechanically ventilated adult patients," and is broken into 4 definition tiers. The first of these are *ventilation-associated conditions* (VACs), defined as at least 2 calendar days of stable or decreasing ventilator setting followed by consistently higher settings for at least 2 additional calendar days.[68] In other words, a "new respiratory deterioration."[68,69] The second is *infection-related ventilation-associated complication* (IVAC), meaning essentially VAC with evidence of infection. The third is *possible pneumonia*, defined as IVAC with possible

evidence of pulmonary infection. Finally, the fourth is *probable pneumonia*, defined as IVAC with probable evidence of pulmonary infection. Details can be found in CDC documents and explanatory articles.[68,70,71]

These definitions are important to the question of PMV-related morbidity and mortality because without them, clinicians and researchers would be unable to standardize their classifications of what precisely qualifies as a condition for which PMV can be said to be responsible for. Since the CDC established these surveillance definitions, studies have suggested that most VACs, for instance, are attributable to pneumonia, pulmonary edema, atelectasias, or acute respiratory distress syndrome and are not unavoidable consequences of caring for critically ill patients.[68,70,71] Furthermore, these studies[68,70–72] have demonstrated a strong association between VACs and length of stay in the ICU, as well as between VACs and mortality. In 1 single-center retrospective cohort study, IVACs were independently and significantly associated with hospital mortality, and VACs were independently and near significantly associated with the same measure.[73] This study,[73] and the others referenced,[68,70–72] accounted for confounding traits such as age, sex, height, weight, and comorbidities, thus suggesting that while the literature provides little evidence as to what proportion of overall morbidity and mortality in patients receiving PMV is caused by the PMV itself, there is reliable evidence that is indeed independently associated with morbidity and mortality through both infectious and noninfectious complications.

In essence, PMV is associated with a wide range of physiologic, neurocognitive, and functional deficits that can be seen at hospital discharge, and many of these deficits may persist. Given this reality, and that of increasing use of PMV worldwide, ongoing research is being devoted to understanding these sequelae, their treatment, and their prevention.[61]

How Do Critically Ill Patients With SARS-CoV-2/COVID-19 Infection Do After Receiving Intensive Care?

Retrospective observational studies[74] of ICU patients in Lombardy, Italy reported 88% of patients in the ICU required mechanical ventilation. Of the 1,581 patients recorded on March 25, 2020, 920 patients were still in the ICU, 256 patients had been discharged from the ICU, and 405 patients had died in the ICU, with a notable difference in mortality between patients > 64 years old (35%) and patients < 64 years old (15%).[74] Early case series[75] of COVID-19 outcomes in patients in New York City showed 14.2% of patients required ICU-level care and 12.2% of patients required mechanical ventilation. By April 4, 2020, 3.3% of patients requiring mechanical ventilation had been discharged from the hospital, 72.2% were still in the hospital, and 24.5% had died.[75] Median hospitalization was found to be 10 days, 12 days, and 13 days, respectively.[76–78]

How Was Mr A Managed After His Extubation?

Given his underlying illness, critical condition, and prolonged sedation, Mr A likely suffered an acute withdrawal syndrome secondary to dexmedetomidine. He was managed symptomatically with lorazepam 1 mg every 6 hours as needed for anxiety and restlessness, and his vital signs were monitored regularly. The nursing team and staff members were instructed to maintain a quiet and structured environment, with carefully scheduled times for laboratory draws, interviews, and assessments. He improved significantly within the next 36 hours, and his acute withdrawal-related symptoms were alleviated. His respiratory status continued to remain stable and improve. He underwent regular physical therapy and other rehabilitation services to regain his previous functional status.

CONCLUSION

Here, we presented a case vignette highlighting a SARS-CoV-2/COVID-19–positive patient to discuss basic principles of sedation, weaning from sedation, and management of agent-specific acute withdrawal syndromes that may arise. Further studies will be required to determine optimal parameters and treatment regimens for these patients; however, in terms of the sedation weaning and withdrawal management, we anticipate that this information will still be relevant. Given the ongoing and ever-developing pandemic and influx of patients in ICUs, practitioners being enlisted temporarily as intensivists need to be guided by practical information. Finally, note that over the course of the COVID-19 pandemic, a number of organizations have provided online guidelines for managing COVID in the ICU, including the American Thoracic Society,[79] the National Institute for Health Care Excellence,[80] the Intensive Care Society,[81] and the Society of Critical Care Medicine.[22] Many of these societies also provide resources targeted toward non-ICU clinicians.

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