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GAPNA Section

# The COVID-19 conundrum: Where both the virus and treatment contribute to delirium

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## ABSTRACT

Whereas hospitalists and intensivists are treating the life-threatening respiratory conditions that often accompany COVID-19, delirium prevention, identification, and treatment may inadvertently be taking a backseat. However, delirium identification is important as it can serve as a key marker for hospital providers to identify COVID patients at risk for poor outcomes including ICU stay and death.<sup>2</sup> COVID delirium has been difficult to manage because some COVID treatment methods are inherently deliriogenic and some medications traditionally used to manage delirium have been rendered ineffective among this population. Inpatient neurology and psychiatry practitioners are having to postulate new treatment techniques; one such medication algorithm can be found within this piece. It is important that delirium doesn't get lost in the chaos that is management of the COVID patient.

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## Introduction

While there are many unknowns about SARS COVID-19, one item that has been consistently recognized is that this virus can cause confusion and delirium. In fact, the World Health Organization has cited “altered consciousness/confusion” as a presenting symptom of COVID that may precede the onset of fever and cough.<sup>1</sup> Delirium can serve as a key marker for hospital providers to identify COVID patients at risk for poor outcomes including ICU stay and death.<sup>2</sup> For these reasons, identification and management of delirium should be an essential component of care protocols for hospitalized COVID patients.

In this piece, the mechanism by which COVID can cause central nervous system (CNS) injury is briefly discussed as are the external reasons why delirium may be more prevalent with this virus than others. Implications for inpatient management of COVID-induced delirium will be presented in the form of both non-pharmacologic mitigation strategies as well as via a medication algorithm. Special attention will be paid to geriatric considerations.

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*What is delirium?*

To refresh, delirium is an acute confused state that is characterized by compromised cognition, psychomotor disorders, inattention, and a fluctuating course.<sup>3</sup> There are several mechanisms by which delirium is mediated, including oxidative stress, inflammation, neuronal aging, and cellular signaling and messaging dysregulation.<sup>4</sup> The result is thought to be neurotransmitter imbalances of acetylcholine, melatonin, dopamine, glutamine, GABA, serotonin, and histamine.<sup>5</sup>

Delirium can worsen a patient's prognosis and recovery, prolong their length of stay, increase their chance of needing a transitional facility or long-term skilled nursing facility stay post-hospitalization, and raise healthcare costs.<sup>6</sup> The United States' healthcare system is faced with charges of greater than \$150 billion dollars each year due to delirium.<sup>7</sup>

*Risk factors for delirium*

While the exact susceptibilities for developing delirium are not completely clear, it has been noted that the incidence of delirium is

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higher in elderly patients, those who are critically ill, those who suffer chronic cognitive impairments, and those who have experienced orthopedic trauma.<sup>8</sup> One study of 817 COVID positive geriatric patients (mean age of 77.7 years) found that 28% arrived to the emergency department already delirious; it was the sixth most common presenting sign.<sup>2</sup> Specific risk factors associated with COVID delirium include age > 75 years, those who resided in a skilled nursing or assisted living facility prior to hospitalization, prior use of psychoactive medication, vision impairment, hearing impairment, prior stroke, or Parkinson's disease.<sup>2</sup>

The COVID virus itself predisposes one to neuropsychiatric symptoms, even without traditional delirium risk factors, making it a risk factor on its own. By way of illustration, Mao et al (2020) retrospectively analyzed a cohort of COVID patients in Wuhan, China and found that 36.4% experienced neuro-psychiatric symptoms including headache, disturbed consciousness, and paresthesias.<sup>9</sup> Other neurologic symptoms that have been reported include loss of smell and taste, muscle weakness and pain, vertigo, ischemic and hemorrhagic stroke, and seizures.<sup>10</sup> Prevalence of neuro-psychiatric involvement increases as disease severity increases.

### Causes of COVID Delirium

While it is still too early in the setting of a new disease to definitively know all possible causes of COVID delirium, a brief review of the literature reveals some hypotheses as to how the virus is instigating neuropsychological problems. Additionally, this author has postulated some external contributors to COVID delirium from working on the front-lines in a level 1 trauma center.

#### *Intrinsic causes of COVID delirium*

In as little as a few hours after infection, neutrophils and monocytes infiltrate the CNS, and neutrophils seem to be central to the disruption of blood brain barrier permeability.<sup>11</sup> Increased blood brain barrier permeability may permit peripheral cytokines to pass into the CNS thus instigating an indirect neuro-inflammatory reaction.<sup>12</sup> Uncontrolled infiltration of the brain with renin-angiotensin components prompts neuro-inflammatory cascades resulting in extensive neuro-degradation and cognitive dysfunction.<sup>13</sup> Neuro-inflammation triggers demyelination through a process involving activated macrophages. Damaged myelin may be immunogenic leading to further macrophage activation and a sequence of sustained inflammation that might be causing the high rate of neuro-psychiatric anomalies.<sup>14</sup>

#### *Extrinsic contributors to COVID delirium*

The novel nature of this virus has created additional challenges that are likely contributing to the increased incidence of delirium we are seeing in hospitalized patients. External factors contributing to COVID delirium fall into three categories: isolation, medical management, and length of stay/ discharge disposition.

#### *Isolation*

Caring for patients with COVID involves isolation in several ways. Support services such as physical therapy aren't ambulating highly infectious patients in hallways as patients are quarantined to their rooms (except if needing to transport to essential services such as the operating room or for imaging that cannot be performed at the bedside). Direct patient caregivers are spending as little time as possible in COVID patient rooms in an attempt to limit their exposure. Some assessments on COVID positive patients are being conducted via telephone or virtual communication platforms.

In addition to physical isolation in their rooms and from the healthcare team, the COVID patient is also isolated from their family and friends as many hospitals have posed limits on visitors in an attempt to decrease exposure to the virus. Having family and friends present during a hospitalization can help to reorient the patient. Even if hospitals can help to facilitate virtual communication via a video platform or similar between patients and their families such as can be done with a tablet, some patients are too sick to participate or too inexperienced with technology to understand it.

Furthermore, hospital staff are dressed in isolation gowns, face shields, goggles, and N95 masks or respirators. This foreign appearance could be disconcerting to patients, particularly to those who have chronically neuro-atypical brains with co-morbidities such as Alzheimer's disease, vascular dementia, and history of cerebrovascular accidents (CVA) or for those who have processing issues.

#### *Medical management*

Glucocorticoids are commonly being used for the inflammation and respiratory insufficiency/ failure that often accompanies COVID-19. Unfortunately, they are well known to contribute to the altered mental state that is delirium. While these drugs decrease inflammation and reduce immune response which is needed for the treatment of COVID, they are known to cause neuro-psychiatric problems such as delirium, depression, mania, psychosis, mood changes, memory impairments, adverse behaviors, and suicidality.<sup>15</sup> In fact, such neuro-psychiatric symptoms have been reported to take place in 15.7 per 100 person-years at risk for all courses of glucocorticoids, and that incidence rises to 22.2 per 100 person-years at risk for first courses of glucocorticoids.<sup>15</sup> In some cases, these neuro-psychiatric symptoms can persist after the course of steroids has been completed. Glucocorticoids may be a direct contributor to the aggression or hyperactive form of delirium that is being seen among COVID patients.

Moreover, the invasive mechanical ventilation and sedation that is necessitated in some COVID patients due to respiratory failure is highly deliriogenic. Rates of mechanically ventilated patients in the ICU settings have been exceedingly high. Richardson et al (2020) reported that of 1,281 COVID ICU patients in their New York City hospital, 1,151 (89.9%) required ventilation.<sup>16</sup> Similarly, Petrilli et al (2020) stated that of 534 COVID ICU admissions to another New York City facility, they had to ventilate 445 patients (83.3%).<sup>17</sup> Internationally, a study in Italy (Grasselli et al, 2020) found similar rates of mechanical ventilation: 1,150 ventilated of 1,300 COVID ICU patients (88.5%).<sup>18</sup> These studies that have already been published were early reports and this author suspects that the rates of mechanical ventilation for COVID management will diminish as less invasive treatment strategies emerge.

Finally, the use of prone positioning for COVID patients might contribute to the development of delirium. It is known that prone positioning has the potential to improve oxygenation and mortality rates in patients with moderate-to-severe acute respiratory distress syndrome (ARDS) receiving mechanical ventilation.<sup>19</sup> Recent studies have hypothesized that prone positioning may be helpful in non-intubated patients, as well, as it can reduce work of breathing, improve oxygenation, and may decrease the need for mechanical ventilation. There is a dearth of literature looking at the relationship between prone positioning and delirium, but one small study did report a 6% incidence of delirium in this population.<sup>20</sup> While the association is mostly hypothetical at this time, this author found it to be worth noting.

#### *Discharge disposition, length of stay*

A challenge that has been particularly troublesome for the geriatric population is the fact that post-hospitalization skilled nursing

facility (SNF) placement has been so difficult.<sup>21</sup> In November 2020, the Centers for Disease Control and Prevention (CDC) published data about discharge dispositions for COVID patients from their large-scale retrospective study that was data-mined from the Premier Healthcare Database. Discharge records from 865 hospitals revealed 126,137 COVID patients who were hospitalized from March 2020 to August 2020.<sup>22</sup> This study reported that 15% discharged to a skilled nursing facility (SNF), 4% discharged to hospice, and 4% discharged to “ongoing care” (which included but was not limited to long-term acute care facilities (LTAC), a swing bed at the same hospital, a rehabilitation facility, or a critical access hospital).<sup>22</sup> Unfortunately, many SNFs are not accepting COVID positive patients. Other facilities are already overburdened with existing patients who have developed COVID and are struggling to continue providing care to their current population so they have halted admissions. Without a discharge disposition but too deconditioned to go home, patients are forced to remain in the hospital longer than medically necessary which can have a negative effect on mental status. The CDC’s study supported the longer length of stay (LOS) for COVID patients needing SNF upon discharge as those who were able to discharge to home had a mean LOS of four days while those discharging to a SNF had a median LOS of eight days (although age and disease severity were not accounted for in this statistic).<sup>22</sup>

### Delirium mitigation

While medication management is one of the principle aims of this piece, it would be remiss if one did not mention non-pharmacological strategies for delirium mitigation. Nurses should continue routine delirium precautions that include reorientation, maximize daylight during the day, maximize darkness at night, minimize disruptions at night/ bundle cares, reduce sensory impairment, encourage ambulation and activity as safely as possible, and to avoid restraints as able. However, in some situations the use of restraints may be less detrimental to one’s delirium than adding additional medications, as some medications used for agitation can be deliriogenic themselves and then worsen or prolong the delirium’s course. As noted previously, the use of prone positioning may also be a risk factor for delirium so positioning the patient in semi-Fowlers or Fowlers positions could be less deliriogenic.

There are also classes of medications to avoid in an attempt to prevent or not exacerbate COVID delirium further. They include opioids at sedating levels, anticholinergic drugs (including Benadryl) as medically able, systemic steroids (again, a current mainstay of COVID respiratory decompensation treatment), and benzodiazepines as they are likely to worsen delirium course and severity.

### COVID medication management algorithm

The refractory nature of COVID delirium has posed challenges. Other inpatient psychiatry providers such as Dr. Elliot Martin, director of medical psychiatry at Newton-Wellesley Hospital in Massachusetts, have concurred with the challenging nature of COVID delirium management. Dr. Martin was quoted as stating “Never in my experience have we had to resort to such trial and error, and really for the safety of the patients and staff, as many patients (with COVID-19) have been unwittingly violent.”<sup>21</sup> In case reports, many COVID delirium patients have required significantly higher doses of antipsychotics than are typically prescribed with additions of augmenting agents such as anti-epileptics, barbiturates, dexmedetomidine, etc.<sup>21</sup>

#### Algorithm

The following is a step-wise approach that this prescriber has synthesized after reviewing the available, albeit limited, evidence to help

guide treatment of COVID delirium for hospitalized patients. This prescriber would initiate melatonin on all COVID positive patients. First line for agitation would be alpha blockers, followed by anti-psychotics. Adjunctive agents that could be considered include valproic acid and gabapentin.

- i. **Melatonin.** Initiate melatonin 3mg PO (per oral) QHS (at hour of sleep). Due to the role of melatonin in the sleep-wake cycle, melatonin’s use in delirium prevention and treatment has been investigated. Objective data has shown altered serum levels of melatonin and its precursor, tryptophan, in patients with delirium which suggests a correlation between melatonin and delirium.<sup>23</sup> Melatonin might be of additional help with COVID as it has immunosuppressive properties that could help to tamp down the immune reaction/ inflammatory cascades. Time it near patient’s normal bedtime as to not further impair their circadian rhythm as this agent can have a push or pull effect on the circadian rhythm.
- ii. **Alpha 2 agonists.** Enhanced behavioral responsiveness to CNS norepinephrine release may contribute to the pathophysiology of agitation/ aggression. In the ICU setting, consider the use of dexmedetomidine in the setting of hyperactive delirium. Some studies have shown that dexmedetomidine may actually be more effective than antipsychotics (APs) at delirium treatment in non-intubated patients in the ICU setting.<sup>24</sup> In the general medical setting, one could consider clonidine 0.1mg PO BID-TID or a transdermal clonidine patch.
- iii. **Anti-psychotics.** While the literature is mixed as to what anti-psychotics should be prescribed for treatment of delirium, a meta-analysis of 15 studies concluded that second generation APs may treat delirium better than first generation APs like haloperidol.<sup>25</sup> Initiate olanzapine 2.5-5mg PO QHS. This prescriber is more inclined to use low dose olanzapine than quetiapine because quetiapine’s relative dopamine bind is less than that of olanzapine meaning that the dose of quetiapine must be higher to achieve the same effect. And the higher the dose of quetiapine, more anti-histaminic and anticholinergic effects will be seen which may worsen the delirium being that delirium is thought to be at least in part a central cholinergic deficiency. Only in the setting of fronto-temporal dementia, Lewy-Body dementia, or a movement disorder (including if the patient has akinetic mutism or rigidity from COVID) would this prescriber prefer to use quetiapine 50mg PO QHS. If a non-oral route must be used for hyperactive/agitated delirium, this prescriber would select haloperidol; note that when using intravenous haloperidol the equivalent dose is 2-4x less (because first pass metabolism from the liver is being bypassed) than that of intramuscular or oral so avoid high dosages. Ziprasidone, another anti-psychotic that can be administered intramuscularly, should be avoided if possible because it is highly torsadogenic (meaning that it increases one’s risk of torsades de pointes which is a polymorphic ventricular tachycardia that can lead to sudden cardiac death). This prescriber also avoids olanzapine intramuscularly as it is contraindicated when co-administered with benzodiazepines/GABAergic medications (such as zolpidem) due to the potential risk of respiratory depression. This is a clinical pearl that many prescribers forget, so this author has found that it is best to avoid the risk.
- iv. **Valproic acid.** Valproic acid can be considered as an adjunctive agent for hyperactive or mixed-type delirium, particularly for those with prolonged QT, those with severe movement disorder concerns, or those who experience side effects of anti-psychotics such as akathisia. Valproic acid impacts neurotransmitter systems, reduces inflammation and oxidative stress, and influences transcriptional changes implicated in the pathophysiology of delirium.<sup>4</sup> Valproic acid has been found to mitigate agitation and impulsivity. Theoretically, valproic acid might provide additional

protection for COVID patients being that this virus might increase one's risk for seizures and strokes.

- v. **Gabapentin.** While not delirium specific, one could consider initiating gabapentin 100mg PO 2x daily (0900 and 1700) for agitation. This may be particularly efficacious in patients who have delirium from acute pain. Additionally, since gabapentin administration could potentially decrease the amount of opioids that a patient with pain receives, one could even argue that it serves as delirium prevention. Gabapentin appears to alter the activity of GABA, serotonin, and glutamate, all of which are likely to be relevant to behavioral disturbances. It does not decrease the release of acetylcholine, a neurotransmitter whose deficiency is linked with cognitive impairment in Alzheimer's dementia and delirium. When putting together this algorithm, gabapentin was not selected as a first-line agent since it can be GABAergic meaning that there is a chance of disinhibition consistent with that seen in benzodiazepines. Avoid higher dosages of gabapentin because it will then act more like a benzodiazepine.

## Conclusion

The COVID-19 situation continues to unfold, and as such, more information about causes of COVID delirium and risk mitigation strategies will reveal themselves in time. As we treat more COVID delirium patients, this author is hopeful that we find better ways to manage the refractory cases. Particularly since delirium is believed to worsen mortality among COVID patients, it is essential that additional research be conducted on this rapidly evolving facet of hospital medicine.

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