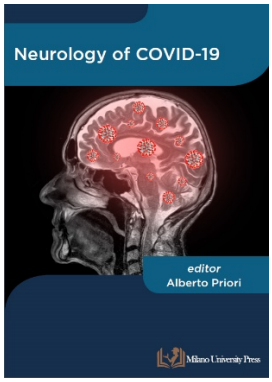

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Chapter 10. **Delirium**

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Chapter 10. Delirium

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Background and epidemiology

Delirium, defined as a disturbance of consciousness or cognitive function with acute onset and fluctuating course, is widely known to be one of the commonest complications of hospitalization in older patients also outside the context of the COVID-19 pandemic[1].

Recently, there has been an increasing recognition of neuropsychiatric manifestations of SARS-CoV-2 infection. Early studies indicate that 20-30% of COVID-19 patients will present with or develop delirium or mental status changes during their hospitalization, with rates of 60-70% in cases of severe illness at all ages[2-4].

The results of a study by Mendes et al. revealed that, although COVID-19 is not associated with a higher prevalence of delirium than other acute illnesses, its development is strongly associated with a higher mortality[5]. Recently, a British study has found that delirium is common and yet under-recognized in hospitalized patients with COVID-19. Out of 31 patients with delirium, only 19 cases had been recognized by the clinical team. Moreover, at 4-week follow-up, delirium was significantly associated with worse functional outcomes independent of pre-morbid frailty[6]. Another study raised the question of whether atypical symptoms of COVID-19 could impact the quality of care, reducing early recognition of symptoms and hospitalization. Among these patients, the clinical presentation of COVID-19 was mostly atypical, and the most frequent symptom of onset was delirium, especially in the hypoactive form[7].

Acute encephalopathy appears to be even more common in critically ill patients. In a recent international cohort study on 2,088 patients with a SARS-CoV-2 infection admitted to an intensive care unit (ICU), Pun et al. described that delirium occurred in 55%[8].

In another recent case series of 58 severe COVID patients, Helms et al. reported that 84% developed neuropsychiatric symptoms[3]. In a cohort analysis of 140 ICU patients described by the same group, the prevalence of delirium was 79.5% in patients admitted to an ICU for acute respiratory distress syndrome (ARDS) due to COVID-19, with a worse prognosis than patients without delirium[9].

Pathogenesis

A major question remains as to whether delirium in COVID-19 represents a primary CNS manifestation, heralding the invasion of the brain by the virus, or whether it simply constitutes a symptom of a secondary encephalopathy caused by inflammation or other systemic effects of SARS-CoV-2[10].

The severity of the systemic illness in some COVID-19 patients, and the associated metabolic derangements and inflammatory cascades, is presumably sufficient to cause the toxic-metabolic encephalopathy often seen in hospitalized patients. However, the presentation of patients with severe confusional states in the absence of respiratory symptoms or other organ failure has raised questions about alternative mechanisms of CNS injury[11].

Several investigators have proposed multiple potential mechanisms by which SARS-CoV-2 may induce changes in mental status, including infection spreading to the CNS by retrograde transport or hematogenous route, a dysregulation of the cytokine activation leading to CNS inflammation, an induction of cell-mediated CNS inflammation, postinfectious autoimmune reactions via molecular mimicry, and hypoxemic/thrombotic neuronal injury[12].

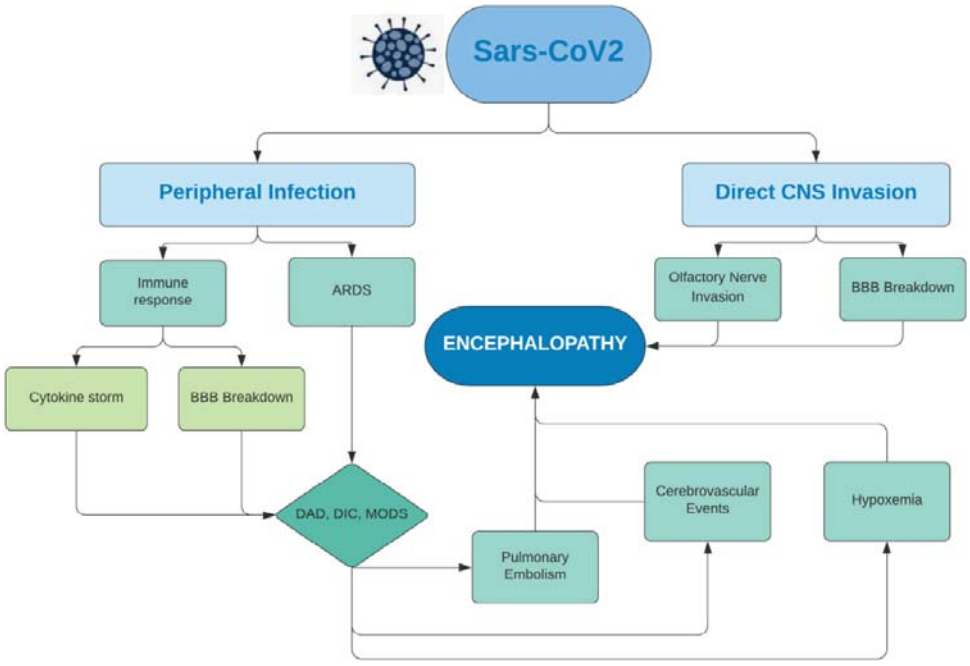
a. *Primary neuro-invasive hypothesis*: neurotropism of coronaviridae has been demonstrated during SARS and MERS epidemics. During the 2002-2003 SARS epidemic, older subjects presented not only with respiratory symptoms and typical febrile response, but also with decreased general well-being, poor feeding, and delirium. Given the fact that SARS-CoV and SARS-CoV-2 are similar in terms of pathogenicity, it is quite likely that SARS-CoV-2 has a similar ability to cause delirium[13]. There are two distinct proposed mechanisms for SARS-CoV-2 invading the CNS to cause a primary encephalopathy: entry route for the virus into the brain may be directly through intra-nasal access via olfactory nerves, or indirectly by crossing the blood-brain barrier (BBB) via hematogenous or lymphatic spread[14]. The first hypothesis would be consistent with the observation of high rates of anosmia and ageusia, which are thought to be caused by the involvement of the olfactory bulb. Given the anatomical positioning, one could imagine the virus travelling along the olfactory bulb toward the uncinate fasciculus and reaching the anterior cingulate and basal forebrain directly via that pathway. Such neuro-invasive potential of SARS-CoV-2 has been postulated to contribute to the respiratory failure observed in infected patients[10]. On the other hand, SARS coronaviruses enter human host cells mainly via the cellular receptor for the angiotensin-converting enzyme 2 (ACE2), predominantly expressed in the entire respiratory tract, but also in the upper esophagus, by the enterocytes and in the brain. In particular, ACE2 receptors have been detected in both neurons and glial cells, which makes them vulnerable to SARS-CoV-2 invasion, but they are also expressed by endothelial cells, and endothelitis has also been implicated in

the pathology of the virus as a result of both direct and indirect mechanisms: general inflammatory response to virus infection impairs BBB integrity leading to massive infiltration of renin-angiotensin components to the brain[15].

b. *Secondary-systemic mechanism hypothesis:* secondary neurological effects include increased CNS inflammatory mediators, cerebral hypoxia, cerebrovascular involvement, multiple organ failure, pyrexia, neurotransmitter imbalance, dehydration, and metabolic dysregulation. Immunologic responses to SARS-CoV-2 are mediated by an acute cytolytic T-cell activation which might also cause an autoimmune encephalopathy[10].

c. *Hybrid model:* a final possibility is a hybrid model, in which the virus may cause either a primary or secondary encephalopathy, or both. This combination would suggest a similarity to human immunodeficiency virus (HIV). Indeed, HIV is known to invade the circumventricular region via two mechanisms: direct and indirect invasion. The circumventricular fenestrated endothelial areas represent the major thoroughfares for diapedesis of HIV-infected macrophages into the brain, and the regions adjacent to these areas determine the neuropsychiatric symptoms. Invasion of the area postrema makes the patient vulnerable to depression and delirium due to selective vulnerability of midbrain neurotransmitter cell bodies, involvement of the pineal gland disrupts the sleep-wake cycle, and the organum vasculosum directly abuts the pregenual anterior cingulate. If SARS-CoV-2 enters the brain directly via disrupted circumventricular fenestrated endothelium or along an olfactory nerve track, we might expect a similar pathophysiological pathway to that seen in HIV encephalopathy[10]

Figure 10.1: Hypotheses of encephalopathy pathogenesis in COVID-19



ARDS: acute respiratory distress syndrome; BBB: blood-brain barrier; DAD: diffuse alveolar damage; DIC: disseminated intravascular coagulation; MODS: multi-organ dysfunction syndrome.

Clinical features and implications

Delirium is usually characterized by a disturbance of consciousness and an alteration of the cognitive state which typically develops over a short period of time (over hours to days) and tends to fluctuate during the course of the day. The features of delirium are unstable, usually becoming most severe in the evening and at night.

Generally, a change in the level of awareness and in the ability to focus, sustain, or shift attention are often described as the earliest manifestations of delirium. Otherwise, in the hypoactive forms, patients could appear drowsy, lethargic, or even semicomatose.

Delirium by COVID-19 may present in its hyperactive form, with agitation requiring sedation, or can otherwise manifest with somnolence and a decreased level of consciousness[4,9]. It could be implied by a variety of clinical manifestations, including psychomotor agitation, sleep-wake reversals, irritability, anxiety, emotional lability, and hypersensitivity to lights and sounds. In a study by Mendes et al. on 235 patients, those who presented with delirium showed hypoactive features in 41.6% of cases and hyperactive or mixed traits in 35.4% and 23.0% of cases, respectively[5].

The clinical aspects of delirium in COVID-19 may be heterogeneous, crossing over the features of encephalitis and meningitis. Some studies show the concomitant presence of pyramidal signs and/or meningeal irritation signs, such as enhanced deep tendon reflexes, ankle clonus, bilateral extensor plantar response, and neck stiffness with positive Brudzinski sign[3,16]. Interestingly, a multifocal myoclonus was found to be more frequent than would typically be observed in delirium[10].

Unfortunately, features of delirium in COVID-19 patients do not significantly differ from other conditions and, especially in the hypoactive form, may be mistaken as secondary to respiratory or sepsis symptoms. For example, in our experience, many patients were diagnosed with delirium several days after the onset of neuropsychiatric symptoms as they had been interpreted as being related to pneumonia or respiratory failure. This was more frequent in patients already affected by neurological diseases such as dementia or Parkinson's disease. Moreover, patients who experience delirium often have cognitive and perceptual problems, including memory loss, disorientation, and difficulty with language and speech, so it is vital to understand the patient's level of functioning prior to the onset of delirium from reliable informants since a mild cognitive impairment could frequently underly delirium. However, collecting complete anamnestic data about previous cognitive disturbances is made difficult by restrictions put in place during hospitalization of COVID-19 patients, thus delaying the diagnosis and treatment of delirium.

Seizures are described along with encephalopathy in patients with COVID-19, just as they can occur in toxic-metabolic encephalopathy in other settings. In a retrospective case series by Somani et al., the authors reported 2 COVID-19 women patients with *de novo* status epilepticus; in one of them, status epilepticus was the initial presentation in an otherwise asymptomatic individual[17]. In a case report by Lyons et al., a young man who had tested positive for SARS-CoV-2 presented with a generalized tonic-clonic seizure three days after complaining of myalgia, lethargy and fever; in the wake of the seizure, he was confused and aggressive, and required sedation[18].

Although in most cases encephalopathy develops in patients who become critically ill, it might also be the primary symptom of COVID-19[19-21]. In a study of 817 older COVID-19 patients (median age 78 years) evaluated in the emergency department, 37% of patients with encephalopathy did not have typical COVID-19 symptoms such as fever or dyspnea[19]. Additionally, after a review of the neurological symptoms of COVID-19 patients, Leonardi et al. found that in a cohort of 2,660 hospitalized patients, 6 (0.22%) presented with acute encephalopathy as the first and only symptom[21].

Ticinesi et al. conducted a retrospective study on 852 patients to assess the incidence of delirium in a large number of patients hospitalized for COVID-19 in Northern Italy. The aim of the study was to verify its clinical correlations and determine its impact on in-hospital mortality. In their study, 11% of the sample developed delirium during the hospital stay. These patients were usually older, were less likely to have common respiratory symptoms (such as cough), more frequently presented atypical symptoms (such as syncope, postural instability and thoracic pain), and had lower oxygen saturation values on room air. Patients who developed delirium also had a higher prevalence of dementia and epilepsy, and had lower functional autonomy in daily activities[22].

Potential factors contributing to delirium during the COVID-19 pandemic

Studies conducted so far in the pandemic consistently show that there are some risk factors associated to delirium in COVID-19 patients.

– *Old age:* COVID-19 is more common in older people, and this is probably due to the synergistic effects of aging, frailty, and comorbidities. In particular, aging of the immune system is characterized by a chronic systemic inflammatory state or 'inflammaging', marked by elevated inflammatory markers, such as IL-6 and C-reactive protein. Frailty is characterized by multisystem dysregulation that leads to reduced physiologic reserve and increased risk of adverse health outcomes. The combined effects of these

factors, added to a high rate of comorbidities, not only increase the risk of severe illness but also lead to an increased risk of delirium as a non-typical presentation of COVID-19[10]. Mendes et al., in a study on 235 Caucasian patients, found that older patients with COVID-19 on admission to acute medical wards had a global prevalence of delirium of 20.4% with the main risk factor being previous cognitive impairment[5].

– *Comorbidities:* comorbidities can facilitate the onset of an acute confusional state[23]. In a case study on ICU patients presented by Van Rompaey et al.[24], the relative prevalence of specific comorbidities was 16.9% for hypertension, 53.7% for other cardiovascular diseases, 1.9% for cerebrovascular diseases, 8.2% for diabetes. In another study involving 509 hospitalized COVID-19 patients, Liotta et al. found that nearly 32% developed encephalopathy. These patients were more likely to have risk factors (including a history of any neurological disorder) than those without encephalopathy[25].
– *Hospitalization and isolation:* long hospital stay along with hospitalization complications such as sleep deprivation, constipation, dehydration, urinary retention, and superinfections increase the risk of delirium in COVID-19. Additionally, hospitals have instituted an extremely limited visitors' policy and have limited interaction with hospital staff, which may increase the sense of isolation and induce patients' disorientation and reduced awareness. While created to minimize contagion, policies that increase isolation and immobility for hospitalized patients, combined with acute illness, produce a high-risk environment for delirium[26,27]. This can be particularly difficult for older people, who are less likely to resort to virtual or electronic methods of interpersonal communication[24,28]. Furthermore, this can lead to apathy, undermining the will to mobilize, further increasing the risk of delirium[13]. In addition, the use of personal protective equipment by staff members can depersonalize them and possibly has a frightening effect on older people, especially those with pre-existing cognitive impairment or dementia. Isolation in the ICU and the need for mechanical ventilation may also further increase the risk of delirium. Earlier epidemiological studies have shown that up to 75% of patients undergoing mechanical ventilation in ICUs suffer from delirium at some point during their hospitalization[14]. It has also been shown that medical personnel devote less time to isolated patients, and less frequently draw attention to the difficulties arising from the need to take precautionary measures, such as wearing personal protective equipment, which may ultimately hinder physical examination[26]. Therefore, respiratory isolation of COVID-19 patients may decrease the frequency and quality of delirium screening, increasing the risk for delirium to persist undetected in vulnerable patients[13,29].

– *Psychological factors*: additional factors triggering the occurrence of delirium may be related to fear, anxiety, and disorientation. Patients presenting to the hospital are often aware of the high volume of patients passing through in a limited period of time and fear a risk of contagion. They are conscious of how severe the disorder can be and know that when admitted to the hospital they will not be able to see their loved ones. Moreover, COVID-19 patients suffer from respiratory distress, and difficulties in breathing can trigger anxiety. Finally, uncertainty about the future and a sense of disorientation may be factors associated with delirium, especially due to the lack of religious or spiritual support[15].
– *Iatrogenic factors*: this group of factors includes elements related to treatment requirements, such as the use of deep sedation or muscle relaxants to enable mechanical ventilation and the prone position[30]. Indeed, the use of centrally acting drugs, including benzodiazepines and propofol or opioids, may induce the occurrence of sedation-related delirium[31]. Finally, the use of medications with an anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients[13]. Prolonged mechanical ventilation and immobilization also greatly contribute to increasing the risk of delirium in the ICU[32] because there is no possibility of full-scale physiotherapy during active infection[13].

Diagnostic work-up

The main aspects of the diagnostic evaluation of delirium include recognition of the disorder and uncovering the potential underlying medical illnesses. As previously mentioned, clinicians often fail to recognize delirium[6]. An early identification of delirium is critical in COVID-19 patients because it could be an early symptom of a worsening respiratory failure or a sign of the spreading of the infection to the CNS.

Neurological examination should always be the first step in the diagnostic work-up to identify focal clinal signs and assess the severity of the clinical picture. Clinicians must pay attention to any changes in the level of consciousness, which could be the first observable clue, and to the ability of the patient to focus, sustain, or shift attention during a conversation. Conversation with the patient may also elicit memory loss, disorientation, or tangential or incoherent speech. Determining whether cognitive impairment or perceptual problems are due to a prior or progressing dementia can be challenging and requires knowledge of the patient's baseline level of functioning. We thus suggest the application of screening tools (i.e., the 4 As Test), that are simple to administer and that require no formal training, to improve the diagnosis of delirium.

Due to the heterogeneity of predisposing factors and plausible causes of delirium in COVID-19, the diagnostic work-up for these patients should include

a complete assessment of prescribed medication and relative collateral effects, metabolic function, hypoxemia, systemic factors (sepsis, liver and renal function, cardiac dysfunction), coagulopathy and hydration status, aiming to investigate all the potential reversible causes of delirium (Table 10.1). Indeed, successful treatment of delirium depends on the early identification of the reversible contributing factors. Medications such as benzodiazepines, propofol, opioids or corticosteroids, commonly prescribed to COVID-19 patients, are the most common reversible cause of neuropsychiatric symptoms, especially in the elderly. Metabolic or systemic abnormalities, such as dehydration, may also be associated to COVID-19-related respiratory failure.

Table 10.1: Potential reversible causes of delirium

Drug and toxins	**Metabolic derangements**
Prescribed medications (sedatives, antipsychotics)	Electrolyte or endocrine disturbances
Withdrawal states	Hyper/hypoglycemia
Alcohol	Hypoxemia
Adverse drug reactions	Wernicke encephalopathy, folate or B12 deficiency
Infections and sepsis	Brain disorders (See Alternative Diagnosis)
Systemic conditions	**Physical disorders**
Cardiac failure	Burns
Acute or chronic liver failure	Hyperthermia
Renal failure	Hypothermia
Coagulopathy	Dehydration
Pulmonary disease with respiratory failure	

Once the potential reversible causes for delirium have been excluded, further investigations such as magnetic resonance imaging (MRI), electroencephalography and lumbar puncture should be considered inorder to rule out a primary CNS involvement. Indeed, COVID-19-related neuropsychiatric symptoms may theoretically be associated with both acute encephalitis caused by direct SARS-CoV-2 CNS invasion or autoimmune encephalopathy[15].

Although autoptic studies confirmed a pronounced CNS involvement with lymphocytic panencephalitis, diffuse petechial hemorrhages, and brainstem neuronal cell damage in COVID-19 patients[33], in most *in vivo* studies, neuroimaging and analysis of cerebrospinal fluid (CSF) were not performed[4,9].

Despite the fact that most patients with encephalopathy typically have no evidence of brain inflammation on neuroimaging studies, a brain CT or MRI should be performed. A spectrum of aspecific neuroimaging abnormalities, such as focal or diffuse subarachnoid abnormalities and contrast enhancement, bilateral fronto-temporal hypoperfusion, but also white matter abnormalities and microbleeds, have been found in patients with COVID-19-related neuropsychiatric symptoms[3,9,34]. Cerebral microhemorrhages, often associated with concomitant leukoaraiosis, seem to be more common in patients with severe respiratory involvement[35]. Cytotoxic alterations in the splenium of the corpus

callosum have also been described in adult patients with COVID-19-related encephalopathy as well as in multi-system inflammatory syndrome in children with COVID-19[36]. Although most of the described radiological abnormalities are likely to be chronic or unrelated alterations, neuroimages may sometimes indicate a specific alternative diagnosis for the patient's mental state, such as stroke, encephalitis, or posterior reversible encephalopathy (PRES)[9,37-39], thus influencing patient management. For example, in a case series of 64 patients with COVID-19-related encephalopathy, ischemic alterations were identified in 17 patients (27%), 10 of whom with focal or lateralizing signs on examination, which suggested possible cerebrovascular accident[38].

CSF testing is suggested at least in cases of suspected viral or autoimmune encephalitis. Although robust data are lacking, CSF analysis was unremarkable in most patients with neuropsychiatric symptoms and the RNA viral load was found only in a few patients[9,37,39]. Only a small proportion of patients showed elevated intrathecal IgG and mildly elevated protein levels[9].

Patients who have undergone electroencephalography have typically demonstrated non-specific findings which, thus far, appear to be largely consistent with the diffuse slowing of background activity expected in encephalopathy[9,40,41]. However, electroencephalography should be considered in patients with unexplained and persistent altered consciousness to rule out Non-Convulsive Status Epilepticus (NCSE) or with clinical suspicion of epileptic seizures.

Table 10.2: Delirium mimics: possible alternative neurological diagnosis in COVID-19 patients

Focal syndromes (encephalitis, stroke, PRES)	Patients with delirium/acute encephalopathy typically have no evidence of brain inflammation on neuroimaging studies. Sometimes MRI findings indicate a specific, alternative diagnosis. CSF testing is suggested at least in cases of suspected viral or autoimmune encephalitis.
Non-convulsive status epilepticus	Electroencephalography should be considered in patients with unexplained and persistent altered consciousness to rule out non-convulsive seizures or with clinical suspicion of epileptic seizures.
Primary psychiatric illnesses	*Depression:* similar to delirium could be associated with sleep disturbance and difficulty with concentration. However, depression is associated with dysphoria, and there is less fluctuation than in delirium. *Mania*: can be confused with hyperactive delirium with agitation, delusions, and psychotic behavior. However, mania is usually associated with a positive history for psychiatric disease.

In conclusion, delirium in the COVID-19 patient is mostly a diagnosis of exclusion of the potential medical reversible causes and the alternative diagnosis (Table 10.2). When in doubt, the most useful rule is to assume delirium and attempt to rule out common medical etiologies. Delirium may be mimicked by acute or subacute brain lesions (such as stroke, encephalitis, or PRES, which

must be ruled out even in the absence of focal deficits on examination) or by a NCSE (facial twitching, unexplained eye movements, automatisms and acute aphasia or neglect without a structural lesion could imply an underlying epileptic condition). Early identification of the key features such as acute onset, fluctuating course, altered consciousness, and cognitive decline should help to distinguish delirium from other neuropsychiatric conditions, such as depression, psychotic illness, and dementia, remembering that even patients with a known psychiatric illness are susceptible to delirium when acutely ill.

Treatment strategies

Non-pharmacological approaches

Every patient admitted to the hospital with COVID-19 should be considered at potential risk of developing delirium, thus prevention strategies should be optimized[42]. Unfortunately, during the COVID-19 pandemic, systematic delirium monitoring using the recommended validated tests may not be put in place[15], probably due to the fact that the main emphasis is placed on organizational issues, such as the lack of ventilators, setting priorities, and the shortage of personal protective equipment[43]. For this reason, it could be useful to implement easy screening tools for delirium, in order to provide prompt treatment. Baller et al. performed a narrative review setting out preliminary guidance for delirium management in COVID-19 patients. Similar to general delirium management, behavioral modifications are first line, but pharmacological options might be necessary for the treatment of psycho-motor agitation and perceptual disturbances[12]. Non-pharmacological interventions, such as regular orientation despite social separation, are actually going to prove vitally important, given the new limitations and challenges related to clinical staff and visitor restrictions in the hospital during the COVID-19 pandemic[15]. It is essential that patients have supervised access to fully charged mobile phones or a tablet to communicate with their families and caregivers, in addition to standard environmental and stimulus control, early ambulation, and care clustering[42].

Moreover, in ICU patients, the concomitant factors which increase the risk of delirium must be managed using standard approaches towards adequate pain management, avoiding urinary retention and constipation, ensuring early identification and treatment of hospital-acquired sepsis, and maintaining adequate oxygenation[15].

Pharmacological treatment strategies

When behavioral strategies alone are not enough to guarantee control of the symptoms, in particular in cases of hyperactive delirium with important behavioral issues, pharmacological management should be considered[44] (Table 10.3).

In COVID-19 patients, the treatment of delirium poses additional challenges considering that sedative agents might further compromise respiratory function, increasing the risk of secondary infections. Furthermore, there could be a considerable risk of drug interactions, particularly regarding QTc prolongation, as these patients are already considered to be at increased risk of torsades de pointes because of the direct effect of the disease on the heart[12].

Nevertheless, antipsychotics are to be considered first-line treatment for the management of delirium in COVID-19 patients. While the National Institute for Health and Care Excellence (NICE) recommend haloperidol[45], the COVID-19 Delirium Workgroup at Massachusetts General Hospital[12] support the prescription of second-generation agents, like olanzapine and quetiapine, due to concerns about extrapyramidal syndrome (EPS). Baller et al. also encourage the use of melatonin due to its action as a sleep regulator, its immunomodulatory role and its good safety profile[46], and of alpha-2 agonists due to their analgesic properties and safety.

In particular, dexmedetomidine, currently restricted to ICU settings, seems to improve delirium, and shorten the time to recovery[47]. Its administration via IV infusion allows for quick titration, and it could be particularly beneficial in ARDS patients because it does not interfere with respiratory function. Drugs with anti-histaminergic and anti-cholinergic profiles can effectively induce short-term sedation, but there may be significant long-term risks, such as daytime sedation, respiratory distress, and further worsening of cognitive performance[44]. The use of benzodiazepines, such as lorazepam, is recommended for patients who are severely agitated, in combination with antipsychotic agents[45]. However, these must be managed with extreme caution given the risk of respiratory suppression in cases with pneumonia or ARDS. Other treatment, such as antidepressants (i.e., trazodone) and antiepileptic drugs (valproic acid) can be considered in patients who may not tolerate antipsychotic agents[12].

Outcome and long-term complications

Delirium itself appears to be a risk factor for poor outcome. Evidence consistently shows that delirium is associated with adverse outcomes in hospitalized patients with COVID-19. Delirium has been associated with post-discharge functional and cognitive decline[48], but its long-term implications in COVID-19 are still unknown.

Liotta et al., in a study of 509 consecutive hospitalized COVID-19 patients with neurological manifestations, found that patients with encephalopathy had longer hospital stay, worse functional impairment at hospital discharge, and a higher mortality rate compared with those without encephalopathy. In particular, even adjusting for the severity of the COVID-19 illness, age, and length of hospital stay, the occurrence of encephalopathy remained independently associated with a higher risk of death at 30 days[25].

Table 10.3: Medications for the treatment of delirium in COVID-19 patients

Medication	Mechanism	Prevalent Use	Sedation	QTc prolongation	Advantages	Disadvantages	Daily doses
Melatonin	Circadian rhythm regulation anti-inflammatory	Add on therapy	-	-	Good safety profile	PO formulation only; caution in immunosuppressed	1-3 mg
Antipsychotics							
Aripiprazole	D2 partial agonist	⬇ agitation in dementia and acute psychosis	-	Low risk	Low risk of EPS	Long half-life	10-30 mg
Chlorpromazine	H1, α1, muscarinic, 5HT2A D2 antagonism	⬇ agitation in acute psychosis	High risk	Moderate risk	PO, IV, IM Lower risk of EPS	Hypotension Anticholinergic side effects	25-300 mg (max 75 mg/die in elderly)
Haloperidol	D2 antagonism	⬇ agitation in acute psychosis	Low risk	Moderate risk	PO, IV, IM	High risk of EPS with PO formulation	1-10 mg (0.5-5 mg in elderly)
Olanzapine	D2, H1, α1, muscarinic antagonism	⬇ agitation in acute psychosis	Moderate risk	Low risk	Fast acting	Anticholinergic side effects	2.5-5 mg
Promazine	H1, muscarinic, 5HT2A, D2 antagonism	⬇ agitation in acute psychosis	High risk	Moderate risk	PO, IV, IM lower risk of EPS	Hypotension Anticholinergic side effects	100-200 mg x 4 (25-50 mg in elderly)
Quetiapine	H1, α1, α2, 5HT2A, D1, D2 antagonism 5HT1A partial agonism	⬇ agitation in dementia and acute psychosis ICU patients	Moderate risk	Low risk	Wide dose range Minimal EPS	PO only	25-20 mg
Risperidone	5HT2A , D2 antagonism	⬇ agitation in dementia and acute psychosis	Low risk	Low risk		High risk of EPS	0.5-2 mg
Benzodiazepines							
Lorazepam	GABA agonism	Add on in severe agitation	Moderate risk	-	PO, IV, IM Rapid onset	Respiratory suppression Can worsen delirium	1-4 mg (0.5-2 mg in elderly)
Other drugs							
Dexmetomidine	α2 agonist	ICU patients	High risk	Moderate risk	IV, rapid titration Analgesic properties	Expensive Restricted to ICU patients Hypotension, bradycardia	0.2-1.4 mcg/Kg/h
Trazodone	α1, 5HT2A antagonism	Ipnotic in geriatric patients	High risk	Low risk	Low risk of EPS	PO only	50-150 mg
Valproic acid	Sodium channel blocker	⬇ agitation	Low risk	Low risk	PO, IV Useful in comorbid seizure	Contraindicated in patients with pancreatic or hepatic failure	250-1200 mg (weight-based loading possible)

EPS = extrapyramidal symptoms; ICU = intensive care unit; IM = intramuscular; IV = intravenous; PO = per os;

These results were confirmed by Garcez et al. in a cohort of 707 patients aged ≥50 years admitted consecutively to a COVID-19 hospital in Sao Paulo, Brazil. They found that the overall occurrence of delirium was independently associated with in-hospital death, length of hospital stay, admission to an ICU, and mechanical ventilation[48].

As with other critically ill patients, neurological dysfunction may persist after acute illness symptoms have resolved. The development of a 'post-intensive care syndrome' (PICS), a new and/or the worsening of previous symptoms which lead to an impairment in any physical, cognitive, or mental domain after critical illness or intensive care[49] has frequently been reported. In particular, a PICS with cognitive impairment is described in 30-80% of ICU patients, and includes memory loss and a dysexecutive syndrome with difficulty in concentration, comprehension, and critical thinking[50.] The major risk factors for the development of PICS appear to be ARDS, sepsis, delirium, prolonged mechanical ventilation, and multi-organ failure[51]. Surviving patients with COVID-19 treated in the ICU should be considered at higher risk for developing PICS given the restraints on social support, prolonged mechanical ventilation with exposure to greater use of sedatives, and limited mobilization[52].

To date, the long-term neurological prognosis of patients with COVID-19-related encephalopathy still needs to be clarified. Prospective cognitive and neurological-focused evaluations through specialized clinics dedicated to further diagnostic assessment are needed and could play a significant role in recovery from this pandemic[25].

Take-home message

- Delirium is common and is still under-recognized in hospitalized patients with COVID-19.
- 20-30% of COVID-19 patients will present with or develop delirium or changes in mental status during hospitalization.
- Although the pathogenesis remains unknown, delirium is thought to be related to a COVID-19 primary CNS manifestation or a secondary encephalopathy, caused by inflammation or other systemic effects of SARS-CoV-2.
- When behavioral strategies alone are not enough to guarantee control of symptoms, pharmacological management should be considered.
- Delirium itself appears to be a risk factor for poor outcome.

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