DOI: https://doi.org/10.5114/ait.2020.95164

# COVID-19: What do we need to know about ICU delirium during the SARS-CoV-2 pandemic?

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**Abstract**

In March 2020, the World Health Organisation announced the COVID-19 pandemic caused by the SARS-CoV-2 virus. As well as respiratory failure, the SARS-CoV-2 may cause central nervous system (CNS) involvement, including delirium occurring in critically ill patients (ICU delirium). Due attention must be paid to this subject in the face of the COVID-19 pandemic. Delirium, the detection of which takes less than two minutes, is frequently underestimated during daily routine ICU care, but it may be a prodromal symptom of infection or hypoxia associated with severe respiratory failure. During the COVID-19 pandemic, systematic delirium monitoring using validated tests (CAM-ICU or ICDSC) may be sacrificed. This is likely to be due to the fact that the main emphasis is placed on organisational issues, i.e. the lack of ventilators, setting priorities for limited mechanical ventilation options, and a shortage of personal protective equipment. Early identification of patients with delirium is critical in patients with COVID-19 because the occurrence of delirium may be an early symptom of worsening respiratory failure or of infectious spread to the CNS mediated by potential neuroinvasive mechanisms of the coronavirus. The purpose of this review is to identify problems related to the development of delirium during the COVID-19 epidemic, which are presented in three areas: i) factors contributing to delirium in COVID-19, ii) potential pathophysiological factors of delirium in COVID-19, and iii) long-term consequences of delirium in COVID-19. This article discusses how healthcare workers can reduce the burden of delirium by identifying potential risk factors and difficulties during challenges associated with SARS-CoV-2 infection.

**Key words:** COVID-19, pandemic, SARS-CoV-2, coronavirus, delirium, sedation, pain, PICS, PTSD.

Anaesthesiol Intensive Ther 2020; 52, 2: 132–138

**Received:** 04.05.2020, **accepted:** 08.05.2020

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In March 2020, the World Health Organisation (WHO) announced the Coronavirus Disease 2019 (COVID-19) pandemic caused by the SARS-CoV-2 virus [1]. The priority in the course of SARS-CoV-2 infection is the treatment of severe respiratory failure associated with interstitial pneumonia and severe acute respiratory infection (SARI); therefore, the demand for intensive care unit (ICU) services has been unprecedentedly high [2]. Apart from respiratory failure, it is critical to pay attention to psychiatric and neurological disorders during SARS-CoV-2 infection. In a study by Mao et al. involving a group 214 patients with COVID-19, neurological symptoms occurred in 45% of seriously ill patients, including some symptoms indicating disturbance of consciousness [3].

Delirium occurring in critically ill patients (ICU Delirium) is an acute central nervous system (CNS) disorder [4]. It is worth devoting due attention to the subject of severe delirium in the face of the COVID-19 pandemic for a variety of reasons [5]. Delirium can be divided into the following aetio-

logical subtypes: septic, hypoxaemic, metabolic, sedation-related, or unclassified [6]. In the context of COVID-19, it must be remembered that delirium may be a prodromal symptom of infection or hypoxia associated with severe respiratory failure.

It has been shown that delirium monitoring, although it can be performed quickly by experienced raters, is underestimated during daily routine ICU care [7]. According to studies performed by Ely *et al*., delirium monitoring using the Confusion Assessment Method for ICU (CAM-ICU) takes only two minutes [8–10]. During the COVID-19 pandemic, systematic delirium monitoring using the recommended validated tests, like CAM-ICU or the Intensive Care Delirium Screening Checklist (ICDSC), may be sacrificed [5, 10]. This is probably due to the fact that during the COVID-19 pandemic, the main emphasis is placed on organisational issues, i.e. the lack of ventilators, setting priorities for limited mechanical ventilation options, and the shortage of personal protective equipment [11]. Additionally, patients experience a greater degree of isolation because care is clustered and movement in and out of the patients' rooms is minimised. Moreover, hyperactive delirium and agitation can be a source of intra-hospital cross-infection due to aerosol spread during coughing in agitated patients. On the other hand, patients with hypoactive delirium are likely to be missed and may not receive appropriate attention.

The occurrence of delirium is an independent predictor of higher mortality, higher costs of care, and longer ICU treatment and hospitalisation [9, 12]. Earlier epidemiological studies have shown that up to 75% of patients undergoing mechanical ventilation in intensive care units suffer from delirium at some point during their admission [13]. There is no indication that in the case of COVID-19 this percentage is any lower.

Early identification of delirium is critical in patients with COVID-19 because its occurrence may be an early symptom of worsening respiratory failure, additional organ failure, or infectious spread to the CNS, mediated by potential neuroinvasive mechanisms of SARS-CoV-2 [14, 15]. Delirium monitoring is recommended with one of the two tools validated for the ICU: the CAM-ICU or ICDSC [10, 16–19]. Severity of delirium can be clinically assessed using CAM-ICU-7 (Confusion Assessment Method for ICU-7) [20] or DRS-R-98 (Delirium Rating Scale – Revised-98) [21]. The purpose of this review was to identify problems related to the development of delirium during the COVID-19 epidemic, which are presented in three thematic areas (Table 1):

I. Factors contributing to delirium in COVID-19.

II. Potential pathophysiological factors of delirium in COVID-19.

III. Long-term consequences of delirium in COVID-19.

## FACTORS CONTRIBUTING TO DELIRIUM IN COVID-19

### Social and epidemiological factors

An important factor contributing to delirium in the ICU during the SARS-CoV-2 outbreak is social isolation created by "social distancing" and quarantine strategies. This can be particularly difficult for older people, who are less apt to resort to virtual or electronic methods of interpersonal communication. The situation in which the patient is isolated and personal contact with relatives and familiar faces is impossible is an additional risk factor for delirium [22, 23]. Feelings of loneliness and isolation can lead to a worsening of well-being, depressive symptoms, anxiety, and anger [24], especially in the elderly [25]. Furthermore, this can lead to apathy, undermining the will to mobilise and further increasing the risk of delirium.

**TABLE 1.** Problems related to the development of delirium during the COVID-19 epidemic

| | |
|---|---|
| **Factors contributing to delirium in COVID-19** | • Social and epidemiologic factors: isolation, quarantine, increased healthcare professional workload<br>• Iatrogenic factors: using deep sedation to facilitate MV, prolonged MV, prolonged immobility (prone position during MV), insufficient pain assessment and treatment, delayed extubation due to fear of aerosol spread<br>• Psychological factors: fear of dying, loneliness, fear of global epidemic, anxiety, uncertainty of the future, disorientation, lack of religious or spiritual support, hallucinations, delusions (e.g. misinterpreting gowned and masked healthcare workers) |
| **Potential pathophysiological factors of delirium in COVID-19** | • SARS-CoV-2 neurotropic potential<br>• Generalised inflammatory response during CoV infection<br>• Occurrence of multiple organ failure<br>• New onset neurocognitive dysfunction |
| **Long-term consequences of delirium in COVID-19** | • PICS (i.e. cognitive impairment, depression, muscle weakness)<br>• PICS-F<br>• PTSD<br>• Delayed return to work/social/family life |

COVID-19 – coronavirus disease 2019, MV – mechanical ventilation, SARS-CoV-2 – severe acute respiratory syndrome-coronavirus-2, PICS – post-intensive care syndrome, PICS-F – post-intensive care syndrome in family, PTSD – post-traumatic stress disorder

A review of research regarding the impact of social isolation on the mental condition of patients highlights a decrease in mood, and anxiety, as well as fear and hostility [24]. The negative psychological effects of isolation result from uncertainty and a sense of loss of control [11, 26], as well as boredom and anger [27]. 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 [24]. 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 [5, 10].

### Iatrogenic factors

This group of factors includes elements related to treatment requirements [28], such as the use of deep sedation (especially with the possibility of some hospitals needing to use more benzodiazepines when other drugs are in shortages) or muscle relaxants to enable mechanical ventilation or extracorporeal membrane oxygenation (ECMO) therapy, for fear of accidental extubation and the need for a prone position. Prolonged mechanical ventilation and immobilisation also greatly contribute to increasing the risk of delirium in the ICU [9] because there is no possibility of full-scale physiotherapy during active infection. The course of delirium can be particularly severe in this group of patients. The use of centrally acting drugs, including benzodiazepines and propofol or opioids, may induce the occurrence of sedation-related delirium [29, 30]. No data regarding the effect of immunological medications on delirium has been found by the authors, but this effect cannot be excluded. Pain assessment should be regarded as a priority; however, it may prove difficult in intubated, deeply sedated, and paralysed patients, and even with behavioural pain scales – Critical Pain Observation Tool (CPOT) [31] or Behavioural Pain Scale [32] – it may also seem burdensome for strained healthcare professionals. Nevertheless, regular pain assessment must be provided. Moreover, additional pain sources may be associated with neuropathies from viral invasion of the peripheral nerves.

### Psychological factors

Additional factors triggering the occurrence of delirium may be related to fear, anxiety, and disorientation. Patients presenting to the hospital fear the global epidemic. COVID-19 patients suffer from respiratory distress, and the struggle to breath can trigger anxiety. Many are aware from the news coverage 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, uncertainty of the future and disorientation may be factors associated with delirium, especially due to the lack of religious or spiritual support [5]. Having no direct support from the family may lead to the feeling of abandonment and fear of dying alone.

The patients are aware of the high load of patients in a limited time. The problem of fear may occur in patients with respiratory failure before intubation or in those waiting for admission to the ICU. Patients can experience hallucinations and delusions, which can be frightening. These can be exacerbated by the lack of human contact, where all the healthcare workers are wearing personal protective equipment (PPE) that masks their facial expressions, makes it difficult to hear, and makes them appear to the patients as complete strangers.

## POTENTIAL PATHOPHYSIOLOGICAL FACTORS OF DELIRIUM IN COVID-19

It must be underlined that, as of April 2020, data regarding SARS-CoV-2 and delirium are not available; however, data extrapolated from previous CoV infections are present. The occurrence of delirium symptoms in patients treated for COVID-19 may be the result of patient isolation, but also of direct brain damage by the pathogen and the generalised inflammatory response. SARS-CoV-1 and SARS-CoV-2 coronaviruses have a high affinity to angiotensin-converting enzyme 2, using this combination to penetrate the pulmonary parenchyma and brain [33–35]. Infecting animals with coronavirus induced a significant neurological disorder that could be due to the presence of large amounts of the virus, particularly in the hippocampus [34, 35]. This process, in turn, can induce an inflammatory brain response with uncontrolled activation of astrocytes (astrogliosis) and infiltration of neutrophils through an inflamed blood-brain barrier [36]. When these changes occur, brain neurons are damaged, including around the hippocampus, which may result in nerve cell degeneration with clinical dementia and cognitive impairment. It is worth noting that the induced inflammatory process in the central nervous system can be long-lasting and may cause distant changes in its functioning [37]. It can therefore be concluded that coronavirus infection *per se* increases the risk of delirium.

Considering the viral pathobiology, it should be noted that sudden respiratory failure may indicate SARS-CoV-2 neurotropism with a predisposition to the brainstem. Potential brain pathways include haematogenic or lymphogenic dissemination and direct

CoV entry into the CNS via the olfactory nerves [14, 38]. Studies on coronaviruses indicate that direct CNS invasion appears to occur rarely and late in the course of the disease [15, 39]. It appears that the immune response to coronavirus is mediated by the acute activation of the cytolytic T cells [40], and the role of T cells has been indicated in CNS pathology in many diseases [41]. In case of dysregulation, this response may cause autoimmune encephalopathy [42]. Secondary CNS-damaging elements include cerebral hypoxia or metabolic disorders in the course of lung or other organ failure, which may contribute to the development of delirium [43]. Future investigations are warranted to elucidate the exact pathophysiological mechanism of delirium in COVID-19.

## CONSEQUENCES OF DELIRIUM IN COVID-19

Many patients, after leaving the ICU, experience cognitive, mental, and physical impairment [44–46]. Delirium, including that associated with COVID-19, carries the risk of complications that will occur in people of all ages in the form of post-intensive care syndrome (PICS). The components of PICS include cognitive impairment, mental state disorders (depression, anxiety, and post-traumatic stress disorder [PTSD]) and physical impairment (ICU-acquired weakness [ICUAW]) [47–49]. Social isolation of the patient, inability to move, sensory deprivation, and sleep deprivation are important risk factors in the development of delirium in critically ill people [22, 48, 50]. The general prevalence of delirium diagnosis in intensive care units reaches up to 87% and is associated with worse outcomes, cognitive impairment even 12 months after discharge, and higher mortality [46]. The duration of ICU delirium is an independent predictor of long-term cognitive impairment in patients after severe illness and intensive care [26].

Mental and emotional disorders may also occur in family members of critically ill patients treated in the ICU, in the form of PICS syndrome in family members, i.e. post-intensive care syndrome in family (PICS-F) [49]. Symptoms of stress, anxiety, or depression were observed in up to 30% of family members of patients treated in intensive care units [49]. It has been estimated that depression occurs in 28%, and post-traumatic stress disorder occurs in 22% of patients after discharge from the ICU [49]. Both muscle weakness and mobility disorders occur in at least 25% of ICU patients. A multicentre study by Griffiths *et al*. showed that 64% of patients suffered from mobility disorders six months after treatment in the ICU [51]. Also, sleep disorders are a common problem and can occur in up to 61% of patients within six months of discharge from the ICU [52]. In addition, it has been shown that around 30% of patients were unable to work after the end of ICU treatment, and 20% of the family members had to stop their own work to take care of the patient [53]. These problems affect people of all ages, including young people for whom the return to work and functioning in the family and society will be delayed after COVID-19.

## MEANS TO REDUCE THE OCCURRENCE OF DELIRIUM IN COVID-19

The COVID-19 pandemic is a huge burden and challenge for intensive care teams (i.e. doctors, nurses, physiotherapists). There are no published original data from COVID-19 cohorts. These are sure to come in the next six months, but for now we must learn from the wealth of data available about delirium in critical illness. Insights gained from critical care about how the brain becomes dysfunctional are immensely relevant today in the COVID-19 pandemic, even if the virus is adding a degree of uniqueness to the mix. The other deliriogenic elements must be emphasised in the current crisis, to advise caregivers on the immediate and long-term approach to this pandemic. Mitigating delirium and meeting the needs of critically ill COVID-19 patients depend on the same basics of care that proved helpful in over 21,000 patients from the Pun and Barnes-Daly cohorts [45, 54].

At present, not only the highest quality intensive care is needed, focused on providing adequate respiratory support to critically ill patients, but also to identify the source and degree of mental and spiritual suffering of patients and their families. Workload is often significantly increased with the number of new and deteriorating patients, but priority should be given to maximising humane care and providing a sense of dignity for patients [55]. It should be remembered that despite the sheer volume of work and burden, satisfying the psychological and spiritual needs of patients is a medical intervention [5]. Delirium treatment includes a standard approach and non-standard methods, forced by problems associated with the COVID-19 pandemic.

The standard of delirium treatment worldwide is the implementation of care bundles, such as the ABCDEF bundle (A – Assess, prevent, and manage pain, B – Both spontaneous awakening trials [SATs] and spontaneous breathing trials [SBTs], C – Choice of analgesia and sedation, D – Delirium: assess, prevent, and manage, E – Early mobility and exercise, F – Family engagement and empowerment) recommended by the Society of Critical Care Medicine (SCCM) or the eCASH philosophy (early comfort, using analgesia, minimal sedatives, and maximal humane care) [45, 54, 56], delirium monitoring using CAM-ICU or ICDSC, and pain monitoring using behavioural scales (CPOT or BPS) [16, 31, 32, 55].

It is necessary to reduce the risk of delirium in the ICU using standard methods to adequately treat pain, avoid urinary retention and gastrointestinal problems (constipation), identify and treat hospital infections, and maintain adequate oxygenation. Moreover, it is important to avoid benzodiazepines in sedation and sudden withdrawal of medications that are chronically taken by the patient. Barnes-Daly and Hsieh reported data on a total of 23,000 patients; therefore, the basics of ICU care by implementation of awakening and breathing trials, coordination, delirium monitoring, and management, as well as an early mobilisation bundle, should be obeyed to improve patient outcomes, despite the current pandemic [54, 55]. It is also important to acknowledge that COVID-19 brings new things that are alarming, such as the need to isolate, but healthcare professionals cannot lose their balanced approach to proper care. During the crisis the patients deserve our best knowledge and approach, by using overall good safety principles of humane care in critical illness [56].

The potential problems related to delirium in COVID-19 are numerous [5]. However, reports from the regions of the world most affected by COVID-19 suggest that the approach to delirium treatment algorithms can be quite flexible due to the co-occurrence of other medical problems or the progressive shortage of human resources and mental burnout of medical staff. Despite the problems arising during the current pandemic, also associated with the use of PPE, delirium screening should follow established guidelines. As recommended by the SCCM, both CAM-ICU and ICDSC are appropriate for ICU delirium screening. Delirium screening should be performed at least once per nursing shift, as recommended by SCCM [16]. This is frequently done as part of a general assessment by bedside nurses when assessing a patient's level of consciousness and ability to follow commands [16]. This should be done as standard practice, despite the excessive workload associated with COVID-19 [5].

Given the need for policies that prevent family and loved ones from visiting patients in hospital, additional efforts should be made to support patient-family interaction through telephone conversations and video conferences. Non-pharmacological interventions, such as regular orientation despite social separation and lack of contact with family and caregivers, are extremely important [57]. However, it is obvious that during the COVID-19 pandemic, the potential for non-pharmacological interventions included in the ABCDEF bundle (e.g. patient mobility and physiotherapy, family involvement) may be limited and will require creative workarounds [16]. If delirium in patients with COVID-19 occurs, first the possible cause should be identified, and then both non-pharmacological and pharmacological interventions should be employed as usual during delirium prevention and treatment.

Taking appropriate preventive measures against delirium can help the healing process, as well as reduce the risk of complications such as emotional disorders, and increased feelings of anxiety or hostility. Appropriate emotional preparation of patients who are to experience isolation contributes to the reduction of anxiety [58]. Attention should also be paid to frequent mood disorders among patients isolated in wards detailing factors related to the level of satisfaction they feel, such as: comfortable environment, good communication between staff and patient, as well as ongoing patient information about the procedures and stages of treatment [59]. It is thought that organised non-pharmacological intervention can reduce both the incidence and severity of delirium symptoms by targeting known risk factors such as sensory deprivation, immobilisation, and sleep deprivation [22].

It is worth emphasising the important role of patient education on the necessity and methods of isolation in preventing delirium [24]. This problem is particularly important in cases of such tight isolation that is necessary in the treatment of COVID-19.

Moreover, verbal and non-verbal communication when wearing PPE is far from standard practice. The patients are not familiar with the health workers, especially when reinforcing personnel joins the care team. Therefore, a name badge or a button with a picture of the person taking care of the patient should be provided. The personnel should be advised to speak loudly, using simple words and short sentences. A practical approach should be offered to inform the busy "guest" teams how to deal with these vagaries of care in the pandemic (PPE, communication, teamwork). Despite many challenges, the signs of delirium must be anticipated, and the delirium monitoring and treatment protocol should be implemented effectively [60, 61].

The severity of delirium can be measured with the CAM-ICU-7, and teams can perform this instrument in a minute at the bedside with each patient daily. In time, we may learn that the severity of the patients' delirium may be associated with the severity of hypoxaemia, overall dose of sedative exposure, duration of immobility, or even the degree of social isolation. The severity of COVID-19 patients' delirium may indeed be due to all of these features of their hospitalisation [62]. Paying appropriate attention to all these elements, i.e. reducing sedatives, immobility, and social isolation as a group of interventions to mitigate delirium, gives the patient the best chance for restoration of normal brain function [58].

## CONCLUSIONS

Delirium data in the SARS-CoV-2 era are very limited so far. This virus shows not only tropism to type II pneumocytes, but also features of neurotropism, which suggests that the risk of acute and long-term brain dysfunction in patients with COVID-19 is high. Both the infection caused by SARS-CoV-2 and the immune response of the body, as well as long-term mechanical ventilation or impaired respiratory efficiency after COVID-19 infection, are just some of the elements that may contribute to the occurrence of delirium during the ICU stay. This may lead to subsequent post-intensive care syndrome in patients and in their families (PICS and PICS -F) for ICU survivors. In the era of the medical crisis associated with COVID-19, patients require not only medical care at the highest level, but also psychological support, which is hampered by isolation requirements.

## ACKNOWLEDGEMENTS

1. Funding: JEW is currently receiving grant funding from NCATS (#KL2TR002245). BTP is currently receiving grant funding from NHLBI (#R01HL1467801). EWE is currently receiving grant funding from NIA (#R01AG058639) and NIGMS (#R01GM120484) serves as a consultant for Pfizer and Eli Lilly. The funding sources had no role in the preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.
2. Financial support and sponsorship: none.
3. Conflicts of interest: none.

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