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Delirium in the intensive care unit: a narrative review

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Critically ill patients frequently suffer from various acute organ dysfunctions. The most common clinical manifestation of central nervous system dysfunction defined as acute encephalopathy is delirium. Since delirium in intensive care unit (ICU) patients has been associated with worse outcomes, its early diagnosis, prevention, and appropriate treatments are strongly recommended. The PADIS guidelines recommend routine monitoring of delirium with the CAM-ICU or ICDSC, which should be performed at least once during each nursing shift and whenever patients show a change in the level of consciousness. Neuroimaging is useful for studying the pathophysiology of delirium, and it might be helpful in the differential diagnosis, although various and non-specific patterns can be observed in both MRI and functional MRI. Also, the electroencephalogram (EEG) showed different non-specific patterns associated with delirium and its role in the differential diagnosis of neurological complications of the critical patient is still uncertain. This narrative review presents the epidemiology and risk factors of delirium in ICU patients, the different diagnostic tools and procedures useful for its early detection, and the pharmacological and non-pharmacological treatments required for its management.

Key words: delirium, intensive care medicine, hyperactive delirium

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INTRODUCTION

Delirium is the most common manifestation of acute encephalopathy in critically ill patients [1] and consists of a rapid onset and reversible neurobehavioral syndrome caused by transient disruption of normal neuronal activity secondary to systemic disturbance, characterized by alterations in attention, awareness, cognitive functions, and fluctuating course, that cannot be explained by pre-existing neuropsychiatric disorders [2,3].
The American Psychiatric Association (in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition) defines delirium based on the following five criteria: (1) disturbance in attention (i.e., a reduced ability to direct, focus, sustain, and shift attention) and awareness; (2) a disturbance that develops over a short period of time (usually hours to days), represents a change from baseline, and tends to fluctuate during the day; (3) an additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception); (4) a disturbance that is not better explained by another preexisting, evolving, or established neurocognitive disorder and which does not occur in the context of a severely

reduced level of arousal, such as coma; and (5) when there is evidence from medical or familial history, physical examination, or laboratory tests that the disturbance is caused by a medical condition, substance intoxication or withdrawal, or medication side effect [2,4].

Despite the high incidence of delirium in critically ill patients, the pathophysiology of this disorder is still debated [5]. The main pathophysiological models of delirium are based on neuroinflammation. In this model, brain microvascular dysfunction, altered brain perfusion, endothelial damage, blood-brain barrier breakdown, and dysregulation of the physiological balance between neurotransmitters, result in widespread alteration of normal neuronal electro-metabolic activity [1,3,5,6]. Unfortunately, the exact causal relationships between these alterations are unknown.

Delirium can be classified into three psychomotor subtypes: hyperactive (characterized by restlessness, agitation, and aggression), hypoactive (characterized by drowsiness, motor hypoactivity, and lethargy), and mixed (fluctuation between hypoactive and hyperactive subtypes). The Richmond Agitation-Sedation Scale (RASS) is commonly used to identify delirium subtypes. Delirium has been associated with worse outcomes including increased mortality and complications such as prolonged hospital and ICU length of stay, prolonged duration of mechanical ventilation, accidental removal of endotracheal tube and catheters, and consequent re-intubation rate [7,8]. Subsyndromal delirium (SSD) is thought to represent a subthreshold state related to delirium and is associated with poor posthospitalization outcomes similar to those associated with delirium. Subsyndromal delirium lacks a standardized definition, even in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) where it is only mentioned as an "attenuated delirium syndrome" without specific criteria. This article briefly describes the current evidence regarding the clinical management of delirium in critically ill patients, referring to the clinical case of a patient with cognitive impairment and a diagnosis of delirium during ICU admission for septic shock.

EPIDEMIOLOGY AND RISK FACTORS

Delirium is the most common neuropsychiatric syndrome found in the acute care setting [9,10]. The high heterogeneity in the reported incidence of delirium in the ICU (20-80%) is attributable to several factors including age, the need for invasive mechanical ventilation and deep sedation, the cause of admission to the ICU (medical or surgical), the severity of the critical illness, and the application of evidence-based strategies for delirium prevention and management [1,11-14]. Delirium is estimated to affect 60-80% of mechanically ventilated and 20-50% of non-mechanically ventilated critically ill patients admitted to the ICU [15]. Hypoactive delirium is the most incident (11%) and prevalent (17%) subtype in patients admitted to the ICU, accounting for 45% of all delirium cases. Hypoactive delirium is even more prevalent in critically ill patients who are mechanically ventilated (35%) or have predicted mortality of greater than or equal to 50% as indicated by their severity of illness (29%) [12].

The risk of delirium in critically ill patients is dependent on a complex interaction between predisposing and precipitating risk factors (Tab. I) [16,17]. Age, dementia, ASA score, and hypertension but not sex have been found as predisposing factors for delirium in critically ill adults. Precipitating risk factors for delirium in the ICU include trauma or emergency surgery before ICU admission, the Acute Physiology and Chronic Health Evaluation II score (APACHE II), delirium or coma on the previous day, use of psychoactive medication, ICU admission because of neurological disease and blood transfusions [17]. There is growing evidence that the use of dexmedetomidine for light sedation during the ICU stay reduces delirium prevalence [18].

Among the medications used for sedation during ICU care, benzodiazepines have been identified as an independent risk factor for the development of delirium [19], whereas evidence of an association between the use of opioid medications and the development of delirium remains inconsistent [7,17].

Table I. Risk factors for delirium in ICU (from Devlin et al., 2018, mod.) [17].

Level of evidence	
Predisposing risk factors	
Increased age	Strong
Dementia	Strong
Increased ASA score	Strong
History of hypertension	Moderate
Precipitating risk factors	
Benzodiazepine use	Strong
Blood transfusion	Strong
Emergency surgery or trauma	Strong
Increased APACHE score	Strong
Previous coma	Strong
Delirium previous day	Strong
Psychoactive medication	Moderate
Neurologic admission	Moderate
Polytrauma	Moderate

DELIRIUM DIAGNOSIS

The gold standard for the diagnosis of Delirium is based on the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria. Noteworthy, Delirium is frequently underdiagnosed in critically ill patients, especially when symptoms of the hypoactive subtype are predominant [20].

To overcome this deficiency, the Pain, Agitation and Delirium (PAD) guidelines recommended routine monitoring for delirium, using validated and reliable tools both in ventilated and non-ventilated ICU patients (strong recommendation, with moderate quality of evidence). The authors of the PAD guidelines also compared the psychometric properties of five delirium monitoring tools: Cognitive Test for Delirium (CTD), Confusion Assessment Method for ICU (CAM-ICU), Delirium Detection Score (DDS), Intensive Care Delirium Screening Checklist (ICDSC), and Nursing Delirium Screening Scale (Nu-DESC). The results demonstrated that CAM-ICU and ICDSC are the most valid, reliable, and feasible tools (strong recommendation with high-quality evidence), indeed they should be primarily used for detecting delirium in ICU patients [21]. An updated psychometric analysis confirmed this statement, demonstrating the very good psychometric properties for CAM-ICU and ICDSC (with weighted scores of 19.6 and 19.2 respectively), moderate for Nu-DESC (13.6), low for DDS (11.2) and very low for CTD (8.6) [22].

Concerning the sensitivity and specificity values of the CAM-ICU and ICDSC tools, a systematic review (SR) and metanalysis (MA) was published in 2012 by Gusmao-Flores et al. [23], demonstrated the high overall accuracy of the CAM-ICU, with pooled sensitivity and specificity values of 80 and 95.9%, respectively, whereas the ICDSC showed a pooled value for the sensitivity of 74% and a specificity value of 81.9%. According to this analysis, the CAM-ICU should be more accurate than ICDSC for the screening and diagnosis of delirium in intensive care patients, while the ICDSC should be used for the diagnosis of subsyndromal delirium, because of its good inter-rater reliability and its features of not been dichotomous. On the contrary, the results of an SR and MA published in 2012 by Neto et al. [24] showed a higher sensitivity of the ICDSC than the CAM-ICU, which nevertheless proved to be a good tool to exclude delirium due to its higher specificity. The latest SR and MA published in 2021 by Chen et al. [25], finally clarifies, updates, and overcomes the limitations of previous publications: CAM-ICU and ICDSC have comparable pooled sensitivity (84 *vs* 83%), but the higher specificity of the CAM-ICU makes it superior in detecting delirium, especially in those critically ill patients receiving mechanical ventilation.

The 2018 Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption (PADIS) guidelines confirmed the importance of using a validated tool for the early diagnosis of Delirium (good practice statement), to improve the patients' outcomes, such as lower in-hospital mortality, shorter ICU length of stay, and shorter time on mechanical ventilation [26]. Furthermore, the level of arousal may influence delirium assessment (ungraded statement), but there is still a lack of studies in the literature examining the value of delirium screening in unconscious or sedated patients [17].

The delirium assessment should be carried out in two steps [27]. First of all, it's necessary to establish the level of arousal, preferably using the Richmond Agitation-Sedation Scale (RASS). If the level of RASS is between -3 and + 5, it's possible to assess the content of consciousness using the CAM-ICU tool (second step). Lower RASS levels (-4 and -5) are defined as coma or stupor: the patient is unable to respond to stimuli and the CAM-ICU is not applicable (Fig. 1).

The content of consciousness assessed by the CAM-ICU scale, encompass different step (Fig. 1).

Step 1 – **Acute change or fluctuating course of mental status**: patients with delirium should manifest sudden changes in mental status compared to the baseline mental status and/or mental status fluctuations.

Step 2 – **Inattention**: Alertness allows a patient to react to various proposed stimuli and to ignore irrelevant and distracting stimuli. The inattention is tested in the CAM-ICU asking the patients to "squeeze my hand when I say the letter 'A' " reading the sequence of the letter contained in the word "SAVEHAART".

When Step 1 is true (patient has an acute change or fluctuating course of mental status) AND steps 2 is true (more than 2 errors) we can proceed to steps 3 and 4.

Step 3 – Altered level of consciousness: when a patient has an altered level of consciousness (i.e. RASS other than 0) we can diagnose delirium. On the opposite (i.e. RASS = 0) we should test Step 4.

Step 4 – Disorganized thinking: to assess the level of organized thinking, the CAM-ICU uses simple questions with 2-degree commands (yes or no) to allow patients intubated and mechanically ventilated or with muscle impairments to carry out the task. When more than 2 errors are made by patients with RASS = 0, delirium is diagnosed.

Some caveats should be mentioned. Many cases of delirium are unrecognized, especially hypoactive delirium and subsyndromal delirium, therefore it is important to apply the CAM-ICU on regular basis, at least once during each nurse shift, and whenever patients show a change in the level of consciousness. Moreover, since delirium also manifests itself outside the ICU, non-ICU

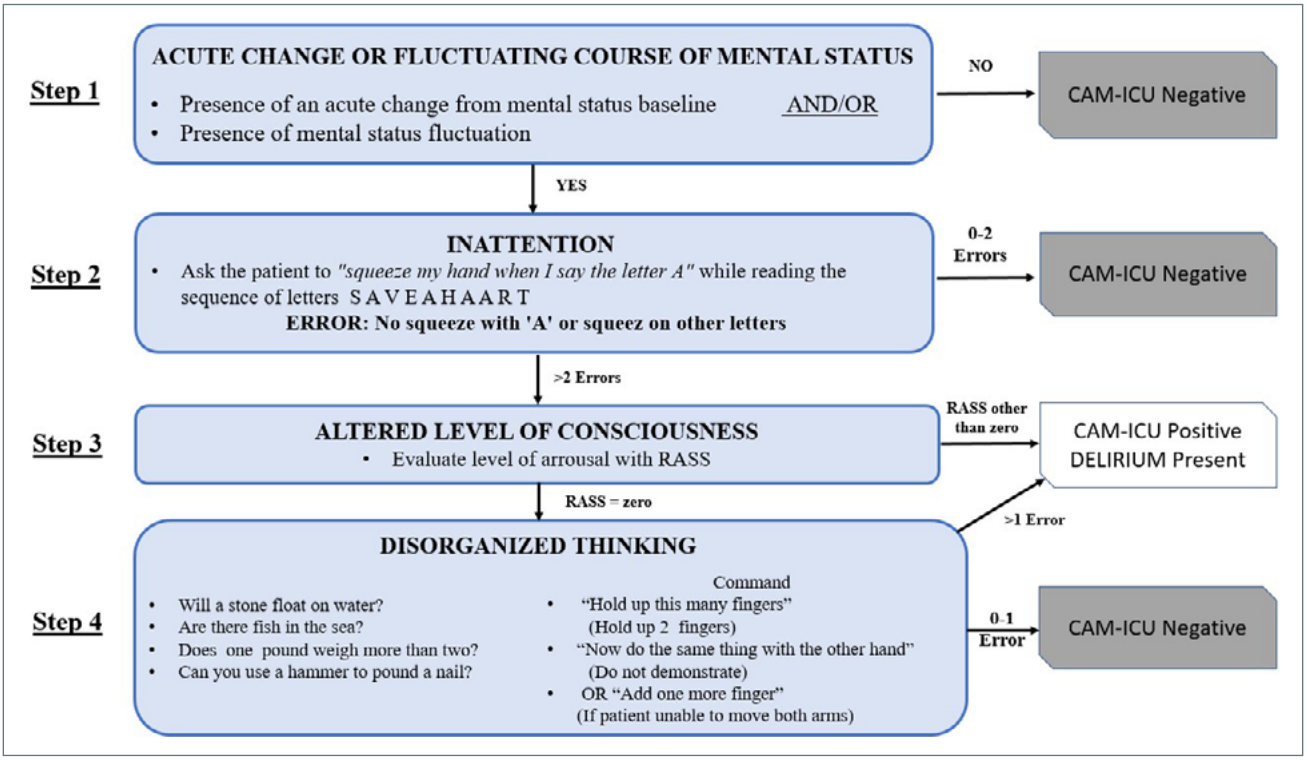

Figure 1. CAM-ICU assessment tool for delirium.

nurses and medical staff should be trained to diagnose delirium using CAM-ICU.

Neuroimaging and electroencephalography (EEG) may help in the differential diagnosis of delirium. Studies on MRI in patients with delirium are very heterogeneous in patient selection and in the MRI technique used. Various combinations of non-specific patterns including ischemic lesions, brain atrophy, vasogenic edema with signs of posterior reversible encephalopathy syndrome, and white matter hyperintensity could be found [28]. Indeed, MRI is greatly used for research purposes, especially functional MRI to better understand the physiopathology of delirium, or to exclude alternative diagnoses (i.e. encephalitis, meningitis, cerebral hemorrhage, and stroke). Although EEG patterns described in delirium are not specific, they occur in most patients. Thus, normal EEG makes the presence of delirium very unlikely. EEG abnormalities include generalized slowing in the background activity, and the presence of theta and delta waves, which are the indicators of diffuse cortical dysfunction, anteriorization, and occipital slowing [29]. In a recent prospective cohort study of non-intubated patients, delirium was assessed with the 3D-CAM tool within 1h of an EEG, using the standard international 10- to 20- electrode placement by qualified technicians, then clinically evaluated by neurophysiologists. The results showed that a generalized theta or delta slowing on EEG is strongly correlated with delirium (odds ratio 10.3, 95% CI 5.3-20.1), with high sensitivity (83.5%), but lower specificity (67.1%) due to the prevalence of confounding states in the control cohort (e.g. sedation, pathologic brain lesions). Furthermore, after adjustment for delirium presence or severity, EEG slowing predicted poor clinical outcomes, such as increased length of stay, worse Glasgow Outcome Scale scores, and increased mortality [1,30].

Although these results have also been confirmed by other studies, integration in daily delirium screening with full EEG monitoring seems to be difficult and time-consuming in ICU wards, as it can only be performed and interpreted by trained personnel. To overcome these limitations, the use of EEG monitoring with automatic processing and with detection protocols using a limited number of electrodes might be more technically feasible. In a recent observational study, an EEG recording with only two electrodes in frontoparietal derivation (F8-Pz) was used in a homogeneous population of non-sedated patients, who underwent cardiothoracic surgery. The largest difference between patients with and without delirium was observed in EEG epochs with eyes closed and as a relative delta power in F8 to Pz derivation (ie, the lowest p-value) [31]. Further studies are needed to develop other feasible and validated EEG techniques.

DELIRIUM MANAGEMENT IN ICU

To date, there are no evidence-based *pharmacological options* that have demonstrated efficacy in the prevention and/or treatment of delirium. The practical guidelines [32] do not suggest the routine usage of haloperidol, atypical antipsychotics, or statins in case of delirium. If antipsychotics are chosen to manage the hyperactive behavior of delirious patients, or stress-related symptoms (anxiety, hallucinations, delusion, fear, etc.), they should be used in the lowest dose and for the shortest period necessary. A recent systematic review and meta-analysis of 77 trials comprising 11,997 critically ill patients found that in mechanically ventilated adults, the use of dexmedetomidine compared to other sedatives resulted in a lower risk of delirium, and a modest reduction in the duration of mechanical ventilation and ICU stay at a cost of increasing the risk of bradycardia and hypotension [33]. Prophylactic use of antiepileptic drugs is not recommended, but EEG monitoring should be used in comatose or deeply sedated patients to detect non-convulsive seizures and guide therapy [34].
Non-pharmacological approaches, such as the ABCDEF bundle has been shown to improve different patient outcomes. Implementation of such a bundle may increase days alive and free of delirium and coma [35], lower the likelihood of death within 7 days, physical restraint use, ICU readmissions, discharge to a facility other than home [36], and ICU and hospital length of stay [37]. The 'ABCDE' bundle is a multi-component process that is designed to prevent and monitor delirium, especially in the ICU setting. The first step of the bundle ('A' assess, prevent, and manage pain) allows for reducing pain occurrence, an important risk factor for delirium. Letter 'B' (both spontaneous awakening and spontaneous breathing trials) aims to break the cycle of over-sedation-prolonged mechanical ventilation. Daily interruption of sedatives allows clinicians to evaluate the patient's readiness to wean from mechanical ventilation and to perform trials of spontaneous breathing (SBT). Protocolized interruptions of sedation and mechanical ventilation should be coordinated. When patients need to be sedated or treated for pain an accurate choice of analgesic and sedation (letter 'C') should be made. In particular, avoiding benzodiazepines and minimizing the dosage of sedatives, aiming to obtain a RASS level of 0 to -1 [38]. Once awakened, patients should be routinely evaluated for the presence of delirium ('D'), using validated screening tools (CAM-ICU, ICDSC), as mentioned earlier. Moreover, early mobilization ('E') of ICU patients has been the only intervention resulting in a decrease in days of delirium [39]. Family ('F': Family Engagement and Empowerment) should be engaged and empowered in the care of the patients since it has positive effects on safety and can decrease anxiety, and confusion [14].

DELIRIUM PROGNOSIS IN ICU SURVIVORS

Delirium impacts short-term and long-term outcomes. A review by Salluh et al. [40] summarizes the effects of delirium through a meta-analysis of 34 studies on short-term outcomes and seven studies on long-term outcomes. The authors found significantly higher mortality during hospital admission, longer durations of mechanical ventilation, and a longer length of stay in the intensive care unit and in the hospital in patients with delirium when compared to patients without delirium. Moreover, delirium has been associated with an increased risk of long-term mortality [41,42] and cognitive dysfunction [43-46].

DELIRIUM IN COVID-19 PATIENTS

Special mention should be made of the emergence of delirium in critically ill patients with COVID-19. In a large international cohort study of more than 2000 patients with severe COVID-19 admitted to the ICU, 80% of patients had coma, while 54.9% developed delirium, with a median duration of 10 and 3 days for coma and delirium respectively [47]. As stated in a recent systematic review, the prevalence of delirium in COVID-19 patients admitted to ICU raged from 65 to 79.5%, and higher rates were reported in those patients with severe respiratory disease [48].
The etiology of delirium in patients with COVID-19 seems to be related to multiple factors. First of all, delirium may be a manifestation of direct central nervous system (CNS) invasion by the SARS-CoV-2 virus through hematogenous or neural retrograde dissemination, although there are conflicting evidences in literature [49]. Secondly, the complications of pneumonia and the ARDS determined by COVID-19 infection (hypoxia, respiratory acidosis, respiratory failure, disseminated intravascular coagulation, systemic organ dysfunction) may be indirect causes of delirium. Also, the systemic inflammatory response caused by COVID-19 dissemination plays a key role in precipitating delirium, increasing the blood-brain barrier permeability and allowing the occurrence of an intracranial cytokine storm and neuronal damage [48]. Furthermore, critically ill ARDS patients with or without COVID-19 required neuromuscular blockade (NMB) and deep sedation for long periods, because of increased ventilator-patient dyssynchrony, agitation, and need for prone positioning. A recent retrospective cohort study demonstrates that excessive

sedation represents an important risk factor for delirium both in COVID-19 and non-COVID-19 ARDS ICU patients and this may increase ICU length of stay (LOS), Hospital-LOS, and duration of mechanical ventilation [50]. Another important risk factor contributing to the occurrence of delirium during the SARS-CoV-2 outbreak has been social isolation due to social distancing strategies and quarantines, which may contribute to disorientation and lack of awareness in COVID-19 patients.

An important factor that contributed to the increased risk of delirium in SARS-CoV-2 patients, could have been the limited application of non-pharmacological intervention, such as the ABCDEF bundle. The implementation of the ABCDEF bundle could have been limited not only by the critical condition of patients but also by the excessive workload of healthcare professionals.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

All authors contributed to the literature review, drafting, and critical revision of the manuscript.

Ethical consideration

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