Review

Delirium in ICU: diagnosis and management

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Delirium is a debilitating form of brain dysfunction frequently encountered in the intensive care unit (ICU). Delirium is the most common manifestation of brain dysfunction in critically ill patients. The condition is estimated to affect 30 to 50% of patients being treated in the intensive care unit (ICU), in patients on mechanical ventilation (MV) delirium occurs in up to 80% of patients. [1] In ICU, duration of delirium is predictive of death, length of stay, cost of care, acquired dementia and the cognitive impairment that persists long after hospital discharge.

Delirium is a worsening or change in a person's mental state that happens suddenly, over one to two days. The person may become confused, or be more confused than usual or they may become sleepy and drowsy. Delirium might be the first sign that someone is becoming unwell, symptoms of delirium often fluctuate over the course of the day.

Delirium was one of the challenges faced of health professionals caring for patients with COVID-19 faced, studies showed that nearly one in every three COVID-19 patients had delirium on or during hospital admission with a pooled mortality approximately three times higher than in those without delirium.[2]

Delirium is defined by Diagnostic and Statistical Manual of Mental Disorders and DSM-5 criteria as an impairment in attention and awareness that develops over a relatively short time interval that is associated with additional cognitive deficits such as memory deficit, disorientation, or perceptual disturbances. Delirium, also termed as 'acute confusional state', 'toxic or metabolic encephalopathy', 'acute brain failure'.

Delirium is categorized into three types based on the psychomotor behaviour.[3] They are: hyperactive, hypoactive and mixed delirium. Among older people, including those with dementia, hypoactive and mixed delirium are more common.

Hyperactive delirium:

A person with hyperactive delirium may: seem restless, be agitated (for example, with more walking about or pacing), resist personal care or respond aggressively to it or unusually vigilant. Someone with hyperactive delirium can easily get very distressed due to not understanding where they are or losing track of time. They may have delusions or hallucinations that carers are trying to harm them.

Hypoactive delirium:

A person with hypoactive delirium may be: withdrawn, feeling lethargic and tired, drowsy, unusually sleepy, unable to stay focused when they're awake. It can be easy not to notice that someone has hypoactive delirium, because they may be very quiet. The person may stop eating as much or become less mobile than usual. They may spend more time in bed.

Mixed delirium:

A person with mixed delirium has symptoms of hyperactive delirium at times and symptoms of hypoactive delirium at other times. They will switch between these symptoms over the day or from one day to the next. For example, they could be very agitated at one time and then later become very drowsy.

Causes:

The identifiable leading causes of delirium are as follows: Infectious, alcohol/substance intoxication or withdrawal, Wernicke's disease, metabolic, hypoglycemia, medications, trauma, neurocognitive, seizures, vascular, hypoxia, vitamin

deficiencies, endocrinopathies and toxin or heavy metal ingestion.

Risk Factors for Delirium: [4] There are multiple risk factors for delirium: older age, cognitive impairment, visual impairment, alcohol abuse, respiratory disorder, illness severity, terminal illnesses, comorbidity, infection, major surgery (e.g., complex abdominal, hip fracture, and cardiac surgery). Interestingly, a mnemonic bundle (DELIRIUM) was proposed (Saint Louis University Geriatrics Division and St. Louis Veterans Affairs) for assessing the main causes of delirium:

Illness and Treatment-Related Causes of Delirium

D	Drugs
E	Eyes, ears, and other sensory deficits
L	Low O2 states (e.g., heart attack, stroke, and pulmonary embolism)
I	Infection
R	Retention (of urine or stool)
I	Ictal state
U	Underhydraton/undernutrition
M	Metabolic causes (DM, Post-operative state, sodium abnormalities

Within the ICU setting, numerous risks have been identified: Pre-existing dementia, mechanical ventilation, sepsis, history of hypertension, high severity of illness on admission, pain, stroke, psychiatric disorders, depression, traumatic head injury, myocardial infarction, COPD, steroids, hypertension, psychoactive medications including narcotics, deep levels of sedation , environmental factors such as the absence of visible sunlight, immobility and physical restraints, poor sleep quality, social factors like alcohol abuse and smoking, lack of visitors, anticholinergic drug exposure (e.g., diphenhydramine, promethazine, and cyclobenzaprine)

Pathophysiology: The delirium pathophysiology is not fully elucidated and may not be due to a single pathway given the wide variety of causes. Derangements of different neurotransmitter pathways have been seen in the pathophysiology of delirium, most importantly, dopamine and acetylcholine. Dopamine excess and acetylcholine depletion have been found linked to delirium.

Other neurotransmitters like glutamate, gamma-aminobutyric acid, serotonin, and endorphins also play a role. Inflammatory markers produced during a critical illness like cytokines, chemokines, tumour necrosis factor-alpha initiate a sequence of events leading to microvascular compromise, thrombin formation, and endothelial damage. Inflammation can cause brain dysfunction by decreasing cerebral blood flow due to the formation of microaggregates of fibrin, platelets, neutrophils, red blood cells in the cerebral microvasculature. Reduction of cerebral oxidative metabolism leading to alteration of neurotransmission. Failure of cerebral oxidative metabolism is found to be important in the pathogenesis of multiple organ dysfunction in critical illness. Neurotransmitter level and function are directly influenced by plasma concentration of many amino acids, and decreased availability of neutral amino acids can lead to delirium in patients admitted to ICU.

DSM-5 criteria state that these new changes in mentation must be in the absence of a neurocognitive disorder that could explain the confusion, and do not occur in the setting of a reduced level of arousal (e.g., coma). Thus, although an identifiable cause of the delirium is often not found, a thorough evaluation for reversible causes of delirium is warranted, and multiple causes may be present in combination. In this regard, there is a large array of possible causes of delirium that range from intoxication and withdrawal states to other serious neurological insults like meningitis and stroke.

Diagnosis: There are no imaging or laboratory tests to diagnose delirium.

Delirium is a diagnosis of exclusion that requires careful clinical testing and observation. The prevention, identification, and management of delirium have important consequences for patient outcomes, both during admission and after discharge.

Because delirium represents the most common clinical manifestation of acute brain dysfunction in ICU, affecting up to 83% of ICU patients on mechanical ventilation (MV), new-onset confusion in the adult patient always warrants further evaluation. However, the clinical evaluation must be accurate as it can often be difficult to distinguish this phenomenon from other clinical conditions. Following laboratory and radiographic testing should be done to rule out any metabolic or biochemical disorders like hypoglycemia, electrolytes, ammonia, vitamin deficiencies etc., possible infectious causes like urinary tract infection, meningitis, etc., possible intoxication or withdrawal (urine drug screen), Neuro imaging to rule out any possibility of neurological or vascular insults and do work up for possible endocrinopathies.

Treatment: Prevention & Management:

The Confusion Assessment Method-ICU (CAM-ICU)[5] and the Intensive Care Delirium Screening Checklist (ICDSC) are both extensively validated and used for delirium diagnosis and evaluation of delirium over time.

They allow the assessment of attention, orientation, memory. These tools allow nonpsychiatric ICU personnel to diagnose the complication rapidly and reliably and can be adopted even when the patient is unable to speak due to endotracheal intubation.

The CAM-ICU provides two steps. In the first one, the level of consciousness/arousal is evaluated through a standardized sedation scale such as the Richmond Agitation-Sedation Scale (RASS). This latter is a 10-point scale ranging from +4 to -5, where a RASS value of 0 indicates a calm and alert patient; RASS scores of -4 and -5 are indicative of coma and cannot be further assessed for delirium. All other individuals (moderately sedated, RASS score -3 or more alert) should also be evaluated through the second step assessment for four characteristics of delirium. The categories include acute onset of altered mental status, inattention, disorganized thinking, or altered level of consciousness. Three out of four features are required for a diagnosis of delirium. The tools, validated in 1990, have been updated by Marcantonio et al. in 2014, in the 3-Minute Diagnostic Assessment for Delirium (3D-CAM). It is an algorithm easy to perform and can be used by personnel with minimal additional training.

Through the ICDSC, the level of consciousness is firstly evaluated on a 5-point scale (A to E) that ranges from unresponsive (A) to exaggerated response (E). Patients who are scored in the categories 'A=No response' or 'B=Response to intense and repeated stimulation' are no further assessed. The other patients (C to E levels of consciousness) are checked for information collected during the previous 24 hours, investigating eight items (rated present or absent) with a total score of 0 to 8. A score of 4 or greater is considered diagnostic of delirium. In addition to the tools for ICU detection, a careful clinical assessment must be performed.

Pharmacological and Non-pharmacological Management Strategies: It is generally accepted that there are no identified therapies (medications or interventions) proven to decrease the duration of delirium. As a consequence, treating the underlying physiological insult is of key importance. Also, other interventions should be considered for delirium management: Treatment of the underlying cause, correction of potential electrolyte disturbances, removal of offending pharmacological agents, maintain proper sleep/wake cycles, manage pain, address sensory impairments (hearing, vision), encourage family visits and frequent reorientation, early mobilization.

Interventions for symptomatic ICU treatment can be divided into pharmacological and non-pharmacological strategies.

Medications: There is much debate regarding the utility of antipsychotics and other medications such as physostigmine, rivastigmine, and donepezil in preventing and decreasing the duration of delirium. Historically, antipsychotic medications were the mainstay of delirium treatment in the critically ill. Based on more recent literature, the Society of Critical Care Medicine (SCCM) guidelines suggest against routine use of antipsychotics for delirium in critically ill adults. In the ICU setting, although there is no evidence that treatment with haloperidol will reduce the duration of delirium, it is the most commonly adopted treatment. Moreover, there is some evidence that atypical antipsychotics may be useful. Now it is known that antipsychotics and other psychoactive medications do not reliably improve brain function in critically ill delirious patients. ICU teams should systematically screen for predisposing and precipitating factors. These include: exacerbations of cardiac/respiratory failure or sepsis, metabolic disturbances (hypoglycaemia, sodium disturbances, uremia and hyper ammonia) receipt of psychoactive medications, sensory deprivation through prolonged immobilization, uncorrected vision and hearing deficits, poor sleep hygiene and isolation.

Antipsychotics. This category includes haloperidol and atypical antipsychotics. Haloperidol is a dopamine (D2) receptor antagonist. It is given at the dosage of 2-10 mg (IV every six h); it is useful, especially in the hyperactive form. Atypical antipsychotics used for this purpose are olanzapine (IM 5-10 mg; max: 30 mg/d), risperidone (0.5-8 mg), quetiapine (orally 50 mg; max 400 mg/d), and ziprasidone. A special issue concerns antipsychotics-related toxicity. For instance, cardiotoxicity such as QT interval (QT) prolongation, torsade de pointes, and hypotension is reported at high doses of haloperidol, whereas a dosage of 2 mg can be safely administered. Caution should be taken when antipsychotics are used with other QT-prolonging medications. Other commonly used classes of drugs that are associated with QT prolongation include, but are not limited to, antiarrhythmics, antibiotics, antiemetics, and antidepressants as well as methadone, lithium, octreotide, and tacrolimus, among others. A baseline EKG and further assessment may be warranted. Antipsychotics can also induce extrapyramidal symptoms (EPSs) expressed as parkinsonism featuring

dystonic reactions or akathisia.[6] Rarely, haloperidol can cause neuroleptic malignant syndrome, whereas insomnia and agitation can often be observed. In the case of atypical antipsychotics, EPSs can manifest at high doses. Again, olanzapine and quetiapine may induce excessive sedation, whereas ziprasidone is more associated with QT prolongation.

Dexmedetomidine: This alpha-2-adrenergic agonist with sedative, analgesic, and anxiolytic actions is useful in adults on mechanical ventilation when hyperactive delirium can delay the weaning. Due to the low-quality evidence of investigations assessed, a panel of experts did not recommend its use. Side effects include bradycardia and hypotension or hypertension.[7]

Short-acting benzodiazepines (BDZs) : These agents, such as midazolam and lorazepam, can have a neurogenic effect. They are exclusively useful in patients with alcohol or sedative withdrawal, or for delirium resulting from seizures.

Other drugs: Although rivastigmine, donepezil, physostigmine has been proposed for ICU delirium management, evidence of effectiveness is currently very scarce.

Non-pharmacological interventions:

Behavioural strategies: This category includes several strategies focused on patient reorientation useful in cooperative patients with delirium. Occupational therapy and patient, and family training have been successfully proposed for this aim. Early ICU mobility therapy can accelerate mechanical ventilation weaning, ICU length of stay, and delirium duration.[8] Physiotherapy plays an important role in preventing and managing ICU delirium. Perhaps the most important measure is engaging patients in early mobilization in conjunction with nurses, occupational therapists, and physicians.[9] Careful use of soft restraints only if and after behavioural and pharmacological interventions fail and if reasonably possible. The use of restraints should be used for the shortest possible time and should be focused to deter a specific behaviour that is impeding the delivery of care.

Prevention: In the general medical ward, there is some evidence that targeting modifiable risk factors and multicomponent patient-centred approaches may decrease the incidence and average duration of delirium. These include interventions improving cognitive impairment, good sleep hygiene, mobility, vision, and hearing. Besides, strategies for preventing infection, dehydration, constipation, and hypoxia are mandatory. Currently, no pharmacological agents have enough evidence to recommend their use in preventing delirium. In the ICU setting, mechanically ventilated adult patients at risk of developing delirium may benefit from dexmedetomidine infusions (e.g., 0.1 µg/kg per hour) over BDZs infusions in regards to decreasing the prevalence of delirium. Melatonin is probably useful for ICU delirium, but further studies are needed. There is also evidence that early mobilization of the adult ICU patient population may reduce the duration and incidence of delirium. A mnemonic ABCDEF bundle was proposed for assessing and preventing the complication.

Evidenced-Based Prevention and Treatment Strategies for ICU Delirium

A	Assess, prevent and manage pain
B	Both Spontaneous Awakening Trials (SAT) and Spontaneous Breathing Trials (SBT)
C	Choice of analgesia and sedation
D	Delirium: assess, prevent and manage
E	Early mobility and exercise
F	Family engagement and empowerment

Wassenaar et al proposed the UNDERPIN-ICU (nUrsiNg DEliRium Preventive INterventions in the ICU), which consists of standardized protocols aimed at implementing several modifiable risk factors for delirium. The interventions are mainly focused on cognitive impairment, sleep deprivation, immobility, and visual and hearing impairment. Different tools for ICU delirium prediction, such as the prediction model for delirium (PRE-DELIRIC) and the early prediction model for delirium (E-PRE-DELIRIC), have been proposed. Both models showed to have moderate-to-good performance.

Prognosis and outcomes: Six months' survival is lower in patients' delirium as compare to patients who do not have delirium. Delirium can lead to long term cognitive impairment in patients who survive critical illness. It may take weeks or months to fully recover from both the physical and mental problems related to ICU delirium. For some, these problems can last the rest of their lives. This can lead to needing full-time care.

Possible outcomes could be

Increased mortality due to secondary infections, like aspiration pneumonias, recurrent UTI DUE to need for long term urinary catheter etc.

longer duration of mechanical ventilation because of becoming dependant on respirator even at home after discharge and the need for tracheotomy,

Higher incidence of ICU readmissions due to worsening of general condition from time to time.

Increase cost of care as the patient might require a care taker for maintaining air way patency, to follow feeding precautions to avoid aspiration, to avoid bed sores etc.[10]

Conflict of interest: None

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