

Delirium in Intensive Care Unit Patients: Ten Important Points of Understanding

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Key words: Analgesia; Assessment; Delirium; Intensive Care Unit Management; Sedation

INTRODUCTION

Delirium is a significant independent indicator of poor prognoses for critically ill patients (including in-hospital mortality, prolonged hospitalization, increased medical costs, and long-term cognitive impairment). Intensive care medicine experts have been paying attention to and carried out research on delirium for better prediction, prevention, management, and treatment, and even better prognosis of patients in critical condition. Based on the latest findings of theoretical research and in combination with clinical experience, literature on delirium has been reviewed and ten points of basic understanding of delirium in critically ill patients have been identified.

DELIRIUM IS AT THE CORE OF PAIN, AGITATION, AND DELIRIUM TRIANGLE

Clinically, critical patients often experience severe pain, agitation, and delirium (PAD). Agitation is what the three symptoms share in common, with delirium as the most common cause of agitation.^[1-8] Untreated pain and inadequate analgesia are strong risk factors of delirium in Intensive Care Unit (ICU) patients. Most of the aggressive behaviors are caused by extreme agitation in patients with acute brain dysfunction. Patients with more discomfort due to pain and anxiety might get more medical intervention and evaluation, which increases sleep disturbance or stress response, and may induce delirium. Delirium, in turn, can lead to more acute feelings of pain and agitation.

DELIRIUM IS ESSENTIALLY A DISORDER OF CONSCIOUSNESS

The level of consciousness depends on the level of sanity. People's mental activity, which senses environment, determines the content of consciousness. Delirium is essentially a disorder of consciousness. To be specific, it is a disorder of perception (content of consciousness) of internal and external environments as a result of change in the clarity (level) of consciousness. It is a syndrome characterized by acute brain dysfunction. The level of consciousness in delirium varies and the content of consciousness is disorganized. The main features of delirium include^[1] changes in consciousness with decreased ability to concentrate, maintain or divert attention; fluctuation in many cases; frequent cognitive impairment that cannot be explained in terms of dementia; and physical illness, substance intoxication, and withdrawal or side effects of medication were clearly indicated as the causes of delirium by some case histories, physical examinations, and laboratory data. Delirium is often characterized by impaired attention.

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Received: 09-05-2017 **Edited by:** Yi Cui

How to cite this article: Wang XT, Lyu L, Tang B, Wang C, Liu DW. Delirium in Intensive Care Unit Patients: Ten Important Points of Understanding. Chin Med J 2017;130:2498-502.

Access this article online

Quick Response Code:



Website:
www.cmj.org

DOI:
10.4103/0366-6999.216405

DELIRIUM IS A PATHOLOGICAL STATE IN ADDITION TO AN ABNORMAL MENTAL STATE

The pathophysiological mechanism of delirium includes impaired acetylcholine synthesis, impaired cholinergic synapses, elevated level of dopamine, and decreased levels of norepinephrine, 5-hydroxytryptamine, and γ -aminobutyric acid.^[2-5] "There is a research has confirmed that surgical trauma, infection and other external factors will make vascular endothelial cell activation, destruction of blood-brain barrier, so that inflammatory factors easily through the blood-brain barrier, stimulate astrocytes and microglia cells to activate, Further release of proinflammatory factors, resulting in neurotoxicity and delirium.^[6] And another study confirms that vascular endothelial cell activation increases blood-brain barrier permeability and reduces cerebral blood flow can lead to brain perfusion abnormalities and brain dysfunction leading to delirium.^[7] In addition to the changes in neurotransmitters, Koponen *et al.* have found via imaging that brain structure of delirium patients underwent pathological changes such as ventricular enlargement and brain parenchymal atrophy. Furthermore, Suchyta *et al.*^[8] reported that 64% of critically ill patients underwent head CT examination due to abnormal changes in cognitive function and consciousness, persistent delirium, and other reasons was presented with abnormal imaging performance including brain atrophy, ventricular enlargement, white matter lesions, and cortical or subcortical lesions. Such changes are likely to be the pathological causes of long-term cognitive impairment in critically ill patients who survived, especially those experienced delirium in ICU. In addition, a new study shows that the right hemisphere subcortical white matter and hippocampus injury is a risk factor of delirium symptoms.^[9] Basically, the causes of delirium are disruption of the central nervous system's polysynaptic pathways and changes in the balance between excitatory and inhibitory amino acids.^[10] Therefore, delirium is indeed a "disease" with clearly defined pathophysiological mechanism. ICU delirium should not be regarded as a psychological need to meet, but should be treated as a disease.

REVIEWING DELIRIUM FROM THE PERSPECTIVE OF THE COMPLEX RELATIONSHIP BETWEEN DELIRIUM AND DIFFERENT DRUGS

According to recent meta-analyses and studies, the relationship between delirium and sedative drugs is not clear; the occurrence of delirium during the period of sepsis is associated with the inflammatory mediators of infection and is not clearly related to the use of benzodiazepines.^[6,11] To understand delirium, we must understand the following concepts clearly.

Postanesthesia delirium

It refers to the state of restlessness or excitement that happens during the recovery period after anesthesia. This kind of delirium, which does not last long and is seen in different age groups, especially young people and children, can be treated by means of sedation, analgesia, and other measures. The type of anesthetic during the operation, be in general or regional,

does not seem to affect the risk of delirium.^[12,13] However, the incidence rate of postoperative delirium after light sedation is about 50% lower than that of deep sedation (19% vs. 40%).^[14] The rate of postoperative delirium is high in patients with deep sedation whose electroencephalogram indicated intraoperative burst suppression or those who experienced intraoperative blood pressure fluctuation/arrhythmia.^[15]

Sedation-related delirium

It refers to the discomfort and agitated state patients experience within 2 h after the withdrawal of continuous sedation. With the metabolism of drugs, such symptoms can be gradually relieved; otherwise, sedative treatment has to be restarted.^[1,16-18]

Drug withdrawal-induced delirium

It refers to a series of withdrawal symptoms known as withdrawal syndrome caused by sudden withdrawal of illicit or prescription drugs, sedative drugs and opioids used in conventional treatment in ICU, or alcohol in patients who have developed tolerance to and physical and psychological dependence on the drugs or alcohol over long-term use.^[19] Delirium occurred in ICU patients due to drug or alcohol withdrawal usually falls into the category of hyperactive delirium.^[20,21]

Critical-associated delirium or persistent delirium

It refers to delirium that lasts for more than a week, and that is often closely related to sepsis, acute respiratory distress syndrome, or complex operations such as cardiac surgery, hip fracture repair, or aortic surgery.^[14,15,22-25] If delirium persists, special attention should be paid to the possible risks of deterioration such as latent infection.^[6,11,26] Most critical-associated delirium is reversible, so immediate identification and treatment is very important.^[27-33] Dexmedetomidine (DEX) produced a sedative state in patients similar to normal sleep from which they could be "waken up" through the activation of the locus coeruleus alpha-2 adrenergic receptors and spinal alpha-2 adrenergic receptors. It can accelerate resolution of delirium.^[34] Drug-induced delirium is an adverse drug effect caused by administration of various drugs that affect neural cell metabolism in different ways without distinguishing the internal mechanisms of different states of consciousness of patients with severe systemic inflammatory response and cerebral cortex peripheral circulation reperfusion injury.

ASSESSMENT OF DELIRIUM REQUIRES CONFUSION ASSESSMENT METHOD FOR THE INTENSIVE CARE UNIT COMBINED WITH INTENSIVE CARE DELIRIUM SCREENING CHECKLIST, THE RICHMOND AGITATION-SEDATION SCALE SCORE IS THE BASIS, AND DISTURBANCE IN ATTENTION IS A COMMON PREREQUISITE

Confusion Assessment Method for the ICU (CAM-ICU), a measurement scale of delirium, and Intensive Care Delirium Screening Checklist (ICDSC), are fast, simple, and effective instruments for bedside assessment of delirium. Both CAM-ICU and ICDSC can identify new or persistent delirium, but cannot quantify the severity of delirium. When

the result of CAM-ICU is negative, delirium assessment requires CAM-ICU combined with ICDSC. If patients score one to three points according to ICDSC, they are diagnosed with subclinical delirium.^[2,27,28] If the score is four points or more, the patients are diagnosed with delirium.

Prerequisites for the diagnosis of delirium include changes in the score of Richmond Agitation-Sedation Scale (RASS) and impairment of attention. In other words, RASS score is the basis of delirium assessment.

THE BEST TREATMENT OF DELIRIUM IS PREVENTION, EARLY MOBILIZATION IS THE MOST IMPORTANT MEASURE

Early mobilization has been proved beneficial for critically ill patients according to a lot of research findings in the recent years.^[35-37] In addition to the daily interruption of sedation treatment, early mobilization in combination with professional treatment that begins within 72 h since the start of mechanical ventilation can improve the prognosis of the disease.^[38,39] Early mobilization is the only nondrug intervention recommended for the prevention of delirium in terms of PAD.^[1]

Early mobilization includes daily exercise programs tailored for individual patients, beginning with passive range of motion for unconscious patients, followed by active range of motion, bed activities, sitting up and moving on bed, and eventually walking.^[39-41] Although ICU patients can significantly benefit from the early mobilization, the actual daily practice of diagnosis and treatment varies greatly at different medical centers and under different clinical circumstances, and a lot of obstacles hinder the development of such training.^[37,42]

ATTENTION SHOULD BE PAID TO THE RELATIONSHIP BETWEEN SEVERE SLEEP DEPRIVATION AND DELIRIUM IN CRITICALLY ILL PATIENTS, AS SEDATION DOES NOT MEAN SLEEP

In the process of awakening and sleep, consciousness is transformed into perception, orientation, attention, memory, and emotion.^[43-45] Patients in ICU are prone to sleep deprivation. Sleep deprivation can cause cognitive impairment, depression, or agitation, thereby causing delirium.^[30,46,47] Functional neuroimaging examination showed that, after sleep deprivation, brain activity decreases at the frontoparietal attention network (in the prefrontal cortex and the intraparietal sulcus) and at the prominence network (in the insular and medial frontal cortex).^[45] Hence, nondrug measures that can be taken to improve sleep quality and avoid stimulation to the sleep cycle of patients include lighting and noise control; avoidance of routine nursing activities and advocacy of gentle movements of nursing activities during patients' sleep;^[37] and use of eye shades and earplugs,^[46] all of which improve sleep environment and can effectively prevent delirium.

Although sedative drugs can put patients into sedative state and play the role of hypnosis, almost all the sedative drugs shorten

the period of rapid eye movement, and the vast majority of sedatives and opioids shorten the period of N3.^[44,48] Therefore, sedation does not mean sleep. The key to sleep in a sedative state is to create a favorable sleep environment, put patients into a process that is close to the physiological process of sleep, which then leads to high-quality sleep and prevention of delirium.

DEXMEDETOMIDINE IS USED TO SHORTEN THE DURATION OF DELIRIUM, AND ANTIPSYCHOTIC DRUGS SHOULD BE USED WITH CAUTION

Application of dexmedetomidine can improve the prognosis of delirium patients with mechanical ventilation. It can shorten the duration of delirium in patients with agitated delirium when used in combination with analgesics.^[37,38] Use of antipsychotic drugs in patients with no mental disorders is not recommended. All antipsychotic drugs will lead to prolonged QT interval, and therefore they should be used with caution in patients who already have prolonged QT intervals.^[49,50] The use of haloperidol and atypical antipsychotics should be prohibited in patients with high risks of *Torsades de pointes* ventricular tachycardia.^[51-54] Benzodiazepines play a limited role in the treatment of delirium and are mainly indicated for cases associated with withdrawal of sedative drugs and alcohol and those contraindicated for the use of antipsychotic medications.^[53]

IPAD IS THE MANAGEMENT OF PAIN, AGITATION, AND DELIRIUM, PAIN MANAGEMENT IS THE BASIS OF PAIN, AGITATION, AND DELIRIUM MANAGEMENT, AND DELIRIUM MANAGEMENT IS AT THE CORE OF PAIN, AGITATION, AND DELIRIUM MANAGEMENT

Pain management is the foundation of PAD management. Severe pain itself can aggravate stress response, cause sleep deprivation, disorientation, agitation, and even delirium and posttraumatic brain dysfunction. Research shows that full and effective analgesia can reduce the need and dosage of sedative drugs, and analgesia combined with sedation is more conducive to the hemodynamic stability of patients so as to reduce the occurrence of delirium.

ICU PAD management is one of the basic measures that can definitely improve the prognosis of patients. The primary goals of PAD management for ICU patients include constant attention to patients' safety and comfort and prevention of short- and long-term complications caused by excessive or inadequate treatment. The combination of routine assessment of pain and sedation, pain management, and sedation minimization, and monitoring and prevention of delirium is probably the best solution in ICU to avoid excessive sedation. Such PAD standard practice can also facilitate the communication between ICU health-care providers to develop the most appropriate sedation and analgesia plan for patients. Early identification of delirium contributes to the

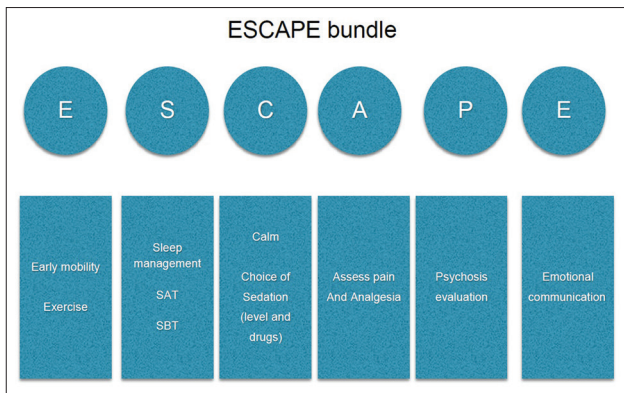


Figure 1: The ESCAPE bundle: Early implementation to manage and prevent delirium.

identification of reversible factors, which prompts medical professionals to give effective treatment of delirium.

THE COMPREHENSIVE MANAGEMENT STRATEGY “ABCDEF” IS THE TREND IN PREVENTION AND TREATMENT OF DELIRIUM

The ABCDEF bundle refers to A for Assess, Prevent, and Manage Pain: prevention of agitation and delirium by adjusting the type and dose of analgesic drugs based on the assessment of patients’ pain levels; B for Both Spontaneous Awakening Trials and Spontaneous Breathing Trials: daily interruption of sedative and analgesic infusions until the patient is awake and can follow instructions, or until the patient feels uncomfortable or agitated, and it is believed that the sedation therapy should be restarted; C for Choice of Analgesia and Sedation: light sedation does not mean inadequate sedation, deep sedation does not mean excessive sedation, sedation assessment means assessment of agitation and sedation, goal-directed sedation and analgesia based on sedation can reduce the severity and duration of delirium, and prevent delirium; D for Delirium: Assess, Prevent, and Manage: daily delirium assessment and constant monitoring of delirium when RASS scores fluctuate is an important measure for the management of delirium; E for Early Mobility and Exercise; and F for Family Engagement and Empowerment: both E and F can promote the recovery of patients and prevent delirium and shorten its duration.

The ABCDEF bundle for delirium management originated from PAD, but is better than PAD. It has been recommended by the US Society of Critical Care Medicine for extensive research and application. Recently, eCASH program was initiated in Europe, which is similar to the ABCDEF bundle, to prevent delirium and related side effects as an important part of the management of critically ill patients.

Combined with the European and American bundles and the actual situation in China, we put forward the "ESCAPE" bundle [Figure 1], more emphasis on early mobility, sleep management and psychosis evaluation (cognitive function assessment) on the importance of delirium management.

In conclusion, for delirium in critically ill patients, we should recognize the importance of delirium, have a correct understanding and evaluation of delirium, comply with the iPad and ABCDEF management strategies, strengthen teamwork spirit of the intensive care team to prevent the occurrence of delirium, treat delirium effectively, improve medical care, and better the prognosis of patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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