

## Review

# Clinical review: Agitation and delirium in the critically ill – significance and management

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## Abstract

Agitation is a psychomotor disturbance characterized by a marked increase in motor and psychological activity in a patient. It occurs very frequently in the intensive care setting. It may be isolated, or accompanied by other mental disorders, such as severe anxiety and delirium. Frequently, agitation is a sign of brain dysfunction and, as such, may have adverse consequences, for at least two reasons. First, agitation can interfere with the patient's care and second, there is evidence demonstrating that the prognosis of agitated (and delirious) patients is worse than that of non-agitated (non-delirious) patients. These conditions are often under-diagnosed in the intensive care unit (ICU). Consequently, a systematic evaluation of this problem in ICU patients should be conducted. Excellent tools are presently available for this purpose. Treatment, including prevention, must be undertaken without delay, and the ICU physician should follow logical, strict and systematic rules when applying therapy.

## Introduction

Agitation is a psychomotor disturbance characterized by a marked increase in both motor and psychological activities, often accompanied by a loss of control of action and a disorganization of thought. This problem is driven by frequently occurring situations in the intensive care unit (ICU), such as anxiety and delirium. Therefore, it is fairly common in the ICU setting, particularly in older patients, and it may be caused by numerous factors, linked both to the disease itself (metabolic disorders, medications, sepsis-associated encephalopathy, and so on) and to external factors (noise, discomfort, pain, and so on) [1]. Agitation *per se* may be dangerous in the ICU: its occurrence may compromise care, raise metabolic requirements and, finally, increase morbidity and mortality [2]. Length of stay in the ICU as well as in the hospital may also be increased, in turn leading to an increase in costs. In addition, compared to that of similar but non-delirious patients, the post-hospital mortality rate may be higher in patients having presented with agitation and delirium. For all these reasons, these mental disorders should be a source of serious concern and, therefore, vigorously

managed through a systematic approach [3]. It is generally accepted that these symptoms represent a marker of acute cerebral insufficiency.

## Significance of agitation and delirium in the ICU

Besides agitation, several mental disturbances may be observed in the ICU, in particular anxiety and delirium. It is not presently known if these mental states express different types of brain dysfunction, or if they represent some sort of spectrum in the severity of the cerebral insult [1]. Anxiety is a diffuse sensation of fear, which is not related to a real and actual external danger. This sensation is expected to occur in the ICU due to the numerous stressful situations occurring in this setting (pain, noise, and loss of body control, among others) [4]. If a certain degree of anxiety seems to be 'normal' in the ICU environment, some authors have described a 'pathological' anxiety when this sensation appears to be disproportionately high considering its cause, and when it is associated with other severe signs, such as severe dys-autonomia, loss of self-control, and cannot be appropriately treated due to a complete lack of patient cooperation [5].

Delirium is defined as an acute change in mental status, or a fluctuation of mood, associated with impaired attention, disorganized thinking, confusion and an altered level of consciousness [5]. It is often referred to as a state of acute confusion. Most cases of delirium have an acute onset, particularly in the ICU. Typically, this cognitive alteration varies throughout the day, and achieves peak intensity during the night. This symptom is usually reversible within a period of days or weeks, whereas some patients can progress to permanent brain failure. Illusions and hallucinations may also occur. Florid delirium with intense agitation in a combative patient (active delirium) is easy to detect, but delirium can also be present in a calm and quiet patient (hypoactive delirium), the succession of both types being possible [6]. Despite the fact that this disturbance is frequent in the ICU

EEG = electroencephalogram; ICU = intensive care unit.

(occurring in 15% to 40% of patients) [7,8], it seems that critical care physicians' performance in detecting it remains poor; around two-thirds of these patients are not identified [1,9]. Fortunately, simple tools that can be used by non-psychiatrists at the bedside have been developed to detect delirium in the ICU [10,11].

Many difficult but interesting questions regarding agitation and delirium in the ICU remain unanswered. First, it is not known precisely if the prevention [12] or the timely detection and treatment of this condition can favorably influence a patient's outcome [13]. Second, the exact relationships between agitation and delirium, on the one hand, and mortality and cerebral dysfunction, on the other, are poorly understood. In particular, it would be of great interest to understand if the brain is just a passive victim, one of many organs to dysfunction in critical illness, expressing its injury through agitation and delirium, or if it is an active player, participating and contributing to the extracerebral organ dysfunction [14,15]. The indication and type of treatment for agitation and delirium are clearly related to the answers to these questions.

The exact mechanisms causing the mental problems described above in ICU patients have not been fully characterized, except when a metabolic cause is obvious, such as hypoglycemia, or hypoxemia. Nevertheless, these disturbances are believed to have an organic basis [16]. The generalized electroencephalographic abnormalities observed during this condition represent an argument in favor of such a diffuse neurological dysfunction [17].

Several hypotheses are actively discussed today. First, the role of abnormalities at the level of the central neurotransmission process is debated; these abnormalities are characterized by an excess in dopaminergic activity consecutive with a depletion in cholinergic stores [18,19]. Importantly, many drugs prescribed in the ICU have an anticholinergic activity and some of them have been clearly associated with delirium, such as antiarrhythmic medications, antibiotics (penicillin, rifampin), and so on. These drugs should be avoided in delirious patients when possible. Interestingly, an 'inflammatory reflex' has recently been observed, leading to a real cooperation between the central nervous system and the inflammatory pathways [20]. More precisely, an anti-inflammatory action exerted by vagus nerve endings located at the vicinity of macrophages in inflammatory foci, through nicotinic receptors at the surface of these cells, has been demonstrated [21]. These observations could provide some explanation as to the origin of delirium caused by a neuronal dysfunction, as well as a substrate for the causal role of the brain in immunomodulation [15]. Other central neurotransmitters have been thought to play a role in delirium, such as dopamine [22], serotonin [23], or gamma-aminobutyric acid (GABA) [16]. This probably represents the substrate for the delirium occasionally

associated with benzodiazepines or propofol (so-called 'paradoxical reactions'). Note also that benzodiazepines [24] and opioids [25] have been clearly shown to be independent factors for the occurrence of delirium.

The second group of hypotheses to explain the mental dysfunction observed in the ICU relates to the presence of potential organic cerebral lesions not detectable by currently available technology (computed tomography (CT) scan, magnetic resonance imaging, and so on) [26]. There are clinical and epidemiological arguments in favor of these hypotheses. Thus, some patients who suffer a mental dysfunction during their ICU stay never fully recover, whereas a rapid decline in the cognitive function of others has been described after an ICU stay during which delirium occurred [27,28]. It is known that in severe sepsis, for instance, many organs are affected by structural damage, particularly in the microcirculation (microthromboses, endothelial swelling, and so on). There is no *a priori* reason for the brain to be spared by such damage.

Even if the causes of mental disturbance observed in the ICU are poorly known, their consequences have been largely described. Severe psychological sequelae have been documented [29]. A dangerous increase in the metabolic demand due to agitation may compromise already limited myocardial or cerebral functions, and intracranial hypertension may be worsened [3]. Finally, mortality and overall morbidity may be increased by, for example, accidental tracheal extubation, asynchrony with the ventilator, removal of catheters in which vital medications are administered, and so on [3,30], and hospital length of stay is also increased [31].

## Management

### Evaluation of mental disturbance in the ICU

#### *Clinical evaluation*

Before treating agitation, anxiety or delirium in the ICU, these symptoms have to be closely scrutinized, and their diagnosis firmly established. Firstly, the clinician needs to know about the patient's pre-existing mental state in order to establish whether a link exists between the presently observed condition and the disease that resulted in ICU admission. Indeed, it is important to recall that around 30% to 40% of ICU patients present with some degree of cognitive impairment prior to their admission [32]. The second step is to perform an objective assessment of the patient's present mental state. A non-standardized evaluation by a non-psychiatrist is not recommended, especially as several evaluation methods that have been validated in the ICU are presently available; these methods can be used by ICU physicians and nurses at the bedside, without being too time-consuming [33]. The 'reliability' (consistency of the evaluation when repeated over time) and the 'validity' (accuracy when evaluating the patient's mental state) of these measurements, as well their 'reactivity' (ability to detect small changes in the variable being studied) [34], are excellent [33]. Many scores

for evaluating agitation, sedation and confusion in the ICU are presently available [10,11,34-37].

However, all these scores suffer from the same conceptual difficulty: each is constructed in a similar manner, that is, they combine several clinical parameters and psychological measurements into a continuous scale score. This approach, while providing a reproducible and easy to use tool, also carries the risk of lack of specificity regarding specific aspects of mental alterations. Nonetheless, we are convinced that, despite their weaknesses, it is important to measure sedation, agitation and confusion in ICU patients with these tools. This position finds support from recent data showing that not only is caregiver compliance with their use excellent in the ICU [38], but also that their use can improve the management of agitated patients [39]. In addition, for research purposes, an algorithm aimed at detecting delirium has been recently developed [40].

#### Non-clinical investigations

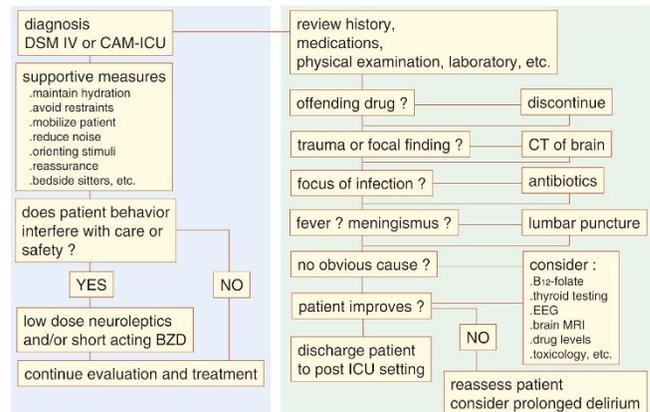
EEGs (electroencephalograms) generally confirm the results of clinical examinations, that is, that mental disorders occurring in ICU patients are associated with a global brain dysfunction. In addition, in some patients, particularly when these disorders are associated with sepsis (sepsis associated encephalopathy) [41], coma [17,42] or brain damage [42], continuously recorded EEGs can detect subclinical seizures or predict the occurrence of ischemic brain lesions. However, no specific EEG recording in mental disorders associated with the ICU has been performed, and several technical concerns remain, particularly for continuous EEG monitoring [43]. In addition, several issues remain unanswered regarding continuous EEG recording in the ICU, namely its exact indication, the required duration of monitoring, and the clinical significance of certain tracing patterns, such as periodic lateralized epileptiform discharges (PLEDs) [44]. Therefore, the consequences of EEG recording on treatment options and patient outcome remain to be investigated in the ICU [45].

Simplified analysis of EEGs, such as bispectral analysis, has been extensively studied in the operating room to assess the depth of anesthesia. However, this technique seems difficult to use in the ICU, even for assessing the degree of patient arousal [46], and it is quite inappropriate for the evaluation of mental disorders such as delirium, either because the patient is agitated, or because of a lack of specificity in a non-agitated delirious patient [47]. Other techniques, among which evoked potentials, are not presently employed in the routine monitoring of ICU patients suffering mental disorders [48,49].

#### Treatment of ICU-associated mental disorders

As stated above, agitation, anxiety and delirium are frequent in the ICU, but they are under-diagnosed, which in turn can have adverse consequences on patient outcome [9].

**Figure 1**



Assessment and management of delirium. BZD, benzodiazepine; CAM-ICU, confusion assessment method for the intensive care unit [32]; CT, computed tomography; DSM, *Diagnostic and Statistical Manual of Mental Disorders* [5]; EEG, electroencephalogram; ICU, intensive care unit; MRI, magnetic resonance imaging.

Therefore, every effort should be undertaken to prevent and treat these problems, even if there is to date no formal proof of an improvement in mortality with treatment [1]. An algorithm may help the clinician to conduct a systematic approach to the management of agitation and delirium in the ICU (Figure 1).

Non-pharmacological treatment must be considered first, common sense and good clinical practice being the rule to avoid light anxiety in ICU patients, for example, reassurance, a comfortable position in the bed, voiding of a full and painful bladder, and so on. Physical restraint can also be considered, keeping in mind the ethical concerns regarding its use [50]. Physically restraining a patient should, therefore, never be considered a trivial measure. It should in our view be the result of a rational, systematic and documented (written) approach, following an accepted algorithm. The patient's family should be given clear, complete and objective explanations regarding treatment choices. Follow-up and monitoring should follow a clear procedure to avoid complications (the lethal strangulation of an ICU patient has even been observed!), and the rationale for pursuing its application in a given patient regularly discussed.

When simple measures are not sufficient to treat agitation, a pharmacological approach must be undertaken. Beforehand, a few simple principles should be remembered. First, before undertaking a symptomatic treatment with drugs, every potential cause of the mental disorder (hypoglycaemia, hyponatremia, and so on) must have been corrected. Second, it should be remembered that several drugs commonly prescribed for agitation (such as benzodiazepines) may, by themselves, cause or increase psychological or cognitive disturbances. Third, the objectives of treatment (for example,

reducing pain, diminishing anxiety, inducing a better sleep rhythmicity, treating delirium, and so on) must be clearly defined in order to choose the appropriate drug. Fourth, the level of sedation and the therapeutic goal when a delirious patient is treated must be strictly adjusted and periodically assessed by objective means (scores and scales) in order to avoid the dangers of both under- and over-sedation.

An abundant literature is available on the treatment of agitation and behavioral disturbances [51], but only a small amount of information is specifically related to the ICU setting [52,53]. Only a few classes of drugs have been sufficiently evaluated in the ICU to be mentioned here, that is, benzodiazepines, propofol and ketamine, as well as classic and atypical neuroleptics. Myorelaxation must remain a rare exception for treatment of behavioral disturbances. Only patients with severe neurotrauma who require a strict control of their movements as a result of intracranial hypertension or vertebral instability, patients with unstable myocardial ischemia before a coronary intervention, or some patients with severe ARDS in whom mechanical ventilation proves very difficult can be considered for a brief course of myorelaxants. A simple approach is to first ensure adequate pain control with opioids, and then treat anxiety with a benzodiazepine, adding a neuroleptic drug if delirium is present. It should be kept in mind that no controlled study is presently available confirming the usefulness of administering neuroleptics in the ICU setting [54]. However, haloperidol remains largely used today in ICU patients, given its various benefits: a rapid onset of action, a lowering of the epileptic threshold (subclinical epileptic seizures are not rare in such patients) and a possible favorable effect on the outcome of patients with delirium, albeit this effect was suggested only in a retrospective analysis [55]. However, many side-effects have been reported with this medication, such as cardiac arrhythmias, extrapyramidal symptoms, anticholinergic action, and so on. To date, there has been no formal study on the new atypical antipsychotic drugs in ICU patients, except for olanzapine [56]. This drug may be useful in case of contraindication or side-effects with haloperidol. Studies should now focus on these drugs in the ICU setting, and one study (MIND) is ongoing, comparing placebo, haloperidol and ziprasidone [57].

## Competing interests

The authors declare that they have no competing interests.

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