

## *Epidemiology, diagnosis and management of delirium in the intensive care unit: a narrative review of the literature*

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### ABSTRACT

#### **Epidemiology, diagnosis and management of delirium in the intensive care unit: a narrative review of the literature**

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Delirium, a serious and common manifestation of brain dysfunction in critically ill patients gained great attention over the last decade. Important risk factors such as use of benzodiazepines, coma, preexisting cognitive impairment, alcoholism and high severity of illness at ICU admission were identified. Screening tools like the CAM-ICU and the ICDSC were extensively validated in many different ICU patient populations and are recommended for routine monitoring in everyday practice. Sedation with novel sedatives such as dexmedetomidine, implementation of non pharmaceutical, preventive interventions and early mobilization of patients may reduce the incidence of this syndrome. The role of haloperidol and atypical antipsychotics in the prevention and treatment of ICU delirium is still under investigation.

“I was now the dying man. My lungs had failed. A machine did my breathing for me. Unconscious, I had no more idea of death than the dead have. But my head (I assume it was my head) was full of visions, delusions, and hallucinations. These were not dreams or nightmares. Nightmares have an escape hatch...”

Saul Bellow, Ravelstein<sup>1</sup>

### INTRODUCTION

Delirium, a syndrome characterized by clouding of consciousness and global disorganization of cognitive functions<sup>2</sup>, can be present in up

to two thirds of the patients in the Intensive Care Unit (ICU)<sup>3</sup>. In addition, various studies have showed that it is associated with poor patient outcomes such as increased mortality<sup>4</sup>, longer stay in the ICU<sup>5</sup> and long term cognitive impairment in many patients who survive

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their critical illness<sup>6</sup>. The aim of this review is to summarize current knowledge regarding epidemiology, risk factors, diagnosis and management of delirium in the ICU.

### **Confusion about the name...**

Even though, delirium was first used as a medical term in the 1st century AD<sup>7</sup>, until today significant heterogeneity has been noticed in medical literature regarding the name of the syndrome. Terms like "ICU syndrome", "ICU psychosis", acute confusional state, toxic confusional state, acute organic syndrome and encephalopathy etc. have been used<sup>8,9</sup>. A multinational study investigating the terminology of delirium in 13 different languages showed that the term *delirium tremens* was used in all languages to describe delirium due to alcohol withdrawal but only in 7 languages the term *delirium* was used referring to the same syndrome due to another organic cause<sup>10</sup>.

This diversity may impede communication between clinicians of different specialties and confine widespread awareness about this medical entity<sup>11</sup>. The term *delirium* has dominated in the literature, it is included in the international classifications of psychiatric diseases (ICD, DSM) and should be adopted by the clinicians in all fields.

### **How often is the problem?**

Delirium is the commonest psychiatric syndrome found in the non psychiatric patients of

a general hospital<sup>12</sup>. Mechanically ventilated, critically ill patients and hospitalized, end-stage cancer patients seem to be the groups with the greater delirium prevalence<sup>12</sup>.

In different studies involving ICU patients, the incidence of delirium shows great variability and ranges from 11%-40%<sup>13-15</sup> to 70%-87%, in some studies that include only mechanically ventilated patients<sup>3,16,17</sup>. In an multicenter, 1-day observational study that included 104 ICUs in 11 different countries, delirium was diagnosed in 32,3% of the patients<sup>18</sup>.

This significant variation is due to considerable methodological differences between the various studies such as the diagnostic scales that were used, patient populations that were included, frequency of delirium assessments, investigators' training in evaluating delirium and sedation protocols that were followed.<sup>19</sup>

### **Why delirium in the ICU is important?**

Delirium in the ICU is associated with an increased risk of self-extubation and removal of IV catheters<sup>20</sup>, increased mortality<sup>4,21,22</sup>, prolonged stay in the ICU and the hospital<sup>5,23</sup>, more days on mechanical ventilation<sup>5</sup> and higher costs of care<sup>24</sup>. ICU survivors who suffered delirium during their critical illness period are more likely to be discharged in another place than home<sup>25</sup>, have greater functional decline<sup>25</sup> and increased risk of developing long term cognitive impairment<sup>6</sup>.

Numerous studies have shown that delirium is associated with increased mortality rate on ICU and hospital discharge as well as 6 months and 12 months postdischarge<sup>4,21,22</sup>. In addition, the duration of delirium seems to be associated with higher mortality as well, with an estimated 10% increase in risk of death with each additional day of delirium<sup>22</sup>.

A recent meta-analysis, including data on mortality from 5916 patients, confirms this association. In the same meta-analysis, it was also found that delirious patients had an increased length of stay (LOS) in the ICU and the hospital, with a weighted mean difference of 7,32 and 6,53 days respectively compared with non delirious patients and spend 7,22 more days on mechanical ventilation<sup>26</sup>. In the only published study addressing the economic impact of delirium in ICU, Milbrand and colleagues found that delirium is associated with 1,4-fold and 1,3-fold increase in ICU and hospital cost per patient<sup>24</sup>.

One of the most interesting points risen up about ICU delirium in the previous years was its association with short- and long-term, negative, cognitive and functional outcomes for the patients who survive their critical illness. Ballas and colleagues showed that surgical ICU survivors who experienced delirium during their critical illness period were seven times more likely to be discharged to a place other than home (nursing facilities or rehabili-

tation centers)<sup>25</sup>. Girard and colleagues studied the influence of the duration of delirium in the cognitive functions of 77 patients who were hospitalized under mechanical ventilation in a medical ICU. Delirium (in contrast with mechanical ventilation) was found to be an independent predictor of cognitive impairment in 3 and 12 months, after adjusting for age, level of education, severity of illness, preexisting cognitive function, severe sepsis and total exposure to sedatives<sup>6</sup>.

### **What are the clinical features of delirium?**

According to the DSM-IV TR criteria of the American Psychiatric Association<sup>27</sup>, delirium diagnosis is made based on the presence of the following criteria:

- a. Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.*
- b. A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established or evolving dementia.*
- c. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.*
- d. There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiolo-*

*gical consequences of a general medical condition.*

The cardinal feature of delirium was historically referred as "clouding of consciousness"<sup>28</sup>. The patient appears inattentive, confused and unclear about his surroundings. The cognitive functions are globally affected. Memory (especially the short term memory) is impaired, orientation is defective mainly for time and place, thinking is disorganized. Vigilance, visuo-spatial ability, executive function, speech and language are often (more or less) impaired as well<sup>28</sup>. Psychotic symptoms, that mainly concern visual hallucinations and delusions, can be absent in as many as 50% of delirious patients and they are not necessary for making the diagnosis<sup>29</sup>.

Non cognitive neuropsychiatric symptoms are commonly described in delirious patients and they include disorders of psychomotor behavior, disorders of sleep-wake cycle (insomnia, reversal of sleep-wake cycle, nightmares) and emotional disturbances (depression, apathy, irritability, anxiety)<sup>30</sup>.

Based on the psychomotor behavior of the patient, delirium can be classified into 3 different motoric types: *hyperactive delirium* (i.e. an agitated patient pulling to remove IV lines or the endotracheal tube and becoming aggressive towards ICU staff), *hypoactive delirium* (i.e. a drowsy, lethargic and confused patient) and *mixed delirium* (i.e. a patient fluctuating

between hyperactive and hypoactive state)<sup>31</sup>. Despite the fact that most clinicians are more familiar with the hyperactive type of delirium, it has been showed in several studies in ICU and non-ICU patient populations, that hypoactive and mixed types appear in higher incidence<sup>32,33</sup> and hypoactive delirium may be associated with worse prognosis in elderly patients<sup>34</sup>.

### **Diagnosing delirium in the critically ill patients**

The critically ill patients in the ICU have some unique characteristics that make evaluation of clinical features of delirium specifically challenging. Intubated patients or patients with tracheostomy are unable to participate in evaluations requiring verbal responses<sup>19</sup>. Use of sedatives and severity of illness restricts complex, lengthy assessments and ICU staff usually lacks adequate training for the neuropsychological evaluation of these "difficult" patients<sup>19</sup>. However, considering the high incidence, the prognostic significance and the frequent fluctuations of delirium during daytime, it becomes obvious that ICU personnel should be able to screen critically ill patients for delirium without the continuous presence of a psychiatrist.

Up to date, five different scales have been published in the literature, that allow the non psychiatrically trained ICU staff to diagnose

delirium<sup>35</sup>. The Confusion Assessment Method for the ICU (CAM-ICU)<sup>3</sup> and the Intensive Care Delirium Screening Checklist (ICDSC)<sup>36</sup> are the most reliable and valid screening tools for the adult critically ill patients<sup>37</sup>. The Society of Critical Care Medicine (SCCM), recommends routine monitoring of delirium in ICU patients using one of these scales<sup>37</sup>. It has been shown, that delirium in the ICU is severely underestimated by the ICU medical and nursing staff without the use of a validated monitoring instrument<sup>38</sup>.

In a recent systematic review that included nine studies evaluating the CAM-ICU and four evaluating the ICDSC, it has been shown that pooled sensitivity of the CAM-ICU was 80% and pooled specificity was 95,9%<sup>39</sup>. The pooled sensitivity and specificity for ICDSC was 74% and 81,9% respectively<sup>39</sup>. In addition, both tools appear to have excellent interrater reliability<sup>3,36</sup>.

The CAM-ICU has been validated in many different ICU patient populations (medical ICU<sup>3</sup>, surgical ICU<sup>40</sup>, trauma patients<sup>41</sup>, coronary unit<sup>3</sup>, pediatric ICU<sup>42</sup>) and has been translated in more than 10 languages<sup>43</sup>. It is based on DSM-IV criteria for delirium and it allows a relatively easy and fast evaluation of all critically ill patients, mechanically ventilated or not<sup>3</sup>.

The assessment takes place in two steps (Fig. 1). Firstly, the level of consciousness must be

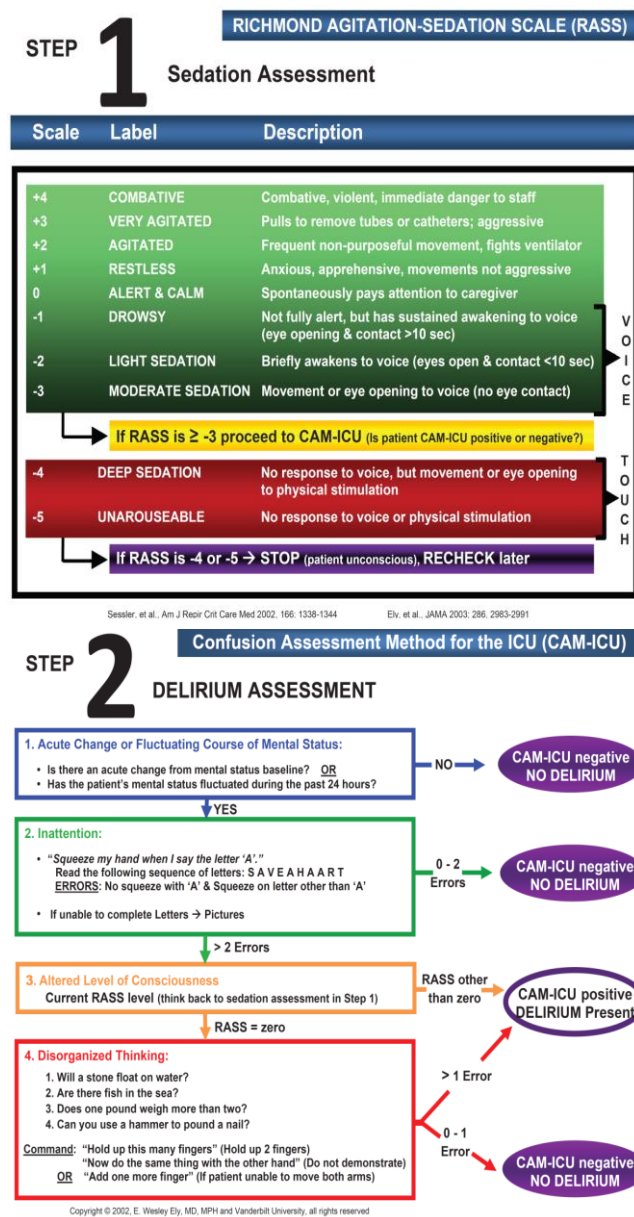
assessed using a validated sedation scale like the Richmond Agitation-Sedation Scale<sup>44</sup>. If the patient appears to have a RASS score  $\geq 3$  (i.e. movement or eye opening in verbal stimuli), then evaluation of delirium using the CAM-ICU can be performed<sup>3,43</sup>. The CAM-ICU includes the assessment of 4 different features: (1) acute change or fluctuating course of mental status (2) inattention (3) altered level of consciousness and (4) disorganized thinking. CAM-ICU is considered positive when features 1 and 2 and either 3 or 4 are present<sup>3,43</sup>.

The ICDSC is an eight-item checklist, which includes the evaluation of (1) level of consciousness (2) inattention (3) disorientation (4) hallucinations/delusions (5) psychomotor agitation or retardation (6) inappropriate speech (7) sleep wake cycle disturbance and (8) fluctuating course of these symptoms<sup>36</sup>. The scale is completed based on the observations collected during each 8-hour shift or from the previous 24h. Each feature takes 1 point if it is present and 0 point if it is absent or no assessments were possible. An ICDSC score  $\geq 4/8$  indicates delirium<sup>36</sup>.

Implementation of daily assessment of cognitive functions of critically ill patients meets several barriers like limited knowledge about delirium and its significance, little familiarity with a validated diagnostic tool, lack of time and difficulty in communication with intuba-

ted patients<sup>45,46</sup>. However, it has been shown that following appropriate training and with a dedicated attitude to improve everyday clinical practice, routine assessment of the ICU patients for the presence of delirium can be feasible in a large scale level<sup>47,48</sup>.

**Figure 1.** Confusion Assessment Method for the ICU<sup>3,16,44</sup>. (With permission from [www.icudelirium.org](http://www.icudelirium.org))



## Who are at risk for developing delirium in the ICU?

Up to date, dozens of risk factors for delirium in the intensive care unit have been studied<sup>13, 14,17,49-54</sup>. Sharon Inouye separated risk factors into predisposing and precipitating ones, a technical classification that is commonly used in the literature<sup>55</sup>. A minor precipitating factor can cause delirium in a patient with great vulnerability (i.e. a urinary infection or a drug in an old patient with dementia), whereas only severe noxious stimuli lead to development of delirium in a patient with low predisposition (i.e. severe sepsis in a young patient with no co-morbidity).

The various delirium risk factors studies show considerable methodological heterogeneity and their results are often controversial. In Table 1 are presented the risk factors that are usually referred in the literature based on studies in ICU and non ICU patient populations. According to the SCCM guidelines the risk factors that are significantly associated with delirium in ICU are preexisting dementia, history of hypertension, alcoholism, high severity of illness at ICU admission, coma and benzodiazepine use<sup>37</sup>.

Even though, dementia is considered to be a significant predisposing factor for delirium, it isn't assessed routinely and is often underdiagnosed in the ICU<sup>56</sup>. In one cross-sectional

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study of 165 patients  $\geq 65$  years old in a medical ICU, prevalence of preexisting impairment of cognitive functions (dementia + "mild impairment of cognitive functions") was found to be 38%, with less than half of these patients diagnosed by attending intensivists<sup>56</sup>. Data from medical records and referring doctors, information taken from the relatives and validated scales developed to assess dementia through responses of patients' proxies (i.e. modified Blessed Dementia Rating Scale<sup>57</sup>, Informant Questionnaire on Cognitive Decline in the Elderly<sup>58</sup>) can help recognize this high risk group of patients.

Benzodiazepines may be a risk factor for developing delirium, according to the recent SCCM guidelines, with a level of evidence B (moderate quality evidence)<sup>37</sup>. Pandharipande and colleagues found that lorazepam is associated with a dose related increase in risk of transitioning to delirium in medical ICU patients<sup>50</sup>. No similar relationship was found between propofol, midazolam or opioids and ICU delirium in this study. In another observational study by the same research group, midazolam was found to be the strongest independent risk factor for developing of delirium in surgical and trauma critically ill patients<sup>52</sup>. In addition, Pisani and colleagues showed that benzodiazepine use is associated with longer duration of the first episode of delirium in the ICU<sup>54</sup>.

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**Table 1.** Common risk factors for delirium

### Predisposing factors

- Dementia
- Increased age
- Alcoholism
- Smoking
- Depression
- Previous stroke
- History of hypertension
- Vision or hearing impairment
- History of use of psychotropic drugs
- History of cardiac, kidney or liver failure
- High severity of illness at admission

### Precipitating factors

#### Factors related with critical illness

- Metabolic and endocrine disorders (hypo/hyperglycemia, hypo / hyperthyroidism e.t.c)
- Electrolytic disorders
- Respiratory failure-kidney failure-liver failure (hepatic encephalopathy)
- Fever-Hypothermia
- Dehydration-Malnutrition
- Anemia
- Infection (systemic or CNS)-sepsis
- CNS impairment (ischemic stroke, cerebral hemorrhage, epilepsy, cerebral metastasis, hypertensive encephalopathy )
- Drug poisoning
- Trauma (especially head trauma)
- Drug or alcohol withdrawal syndrome

#### Environmental or iatrogenic factors

- Drugs (benzodiazepines, opioids) - sedative induced coma
- Absence of daylight
- Inadequate pain management
- Isolation - no visits
- Immobilization - physical restrains
- Sleep deprivation

\* The table includes risk factors for ICU and non ICU patient populations (Ref. 12-14, 17, 49-54)

The data about the relationship between propofol and delirium are inadequate, whereas the role of opioids in the development of delirium in the ICU is controversial<sup>37</sup>. In different studies, opioids have been found to increase,

decrease or have no significant association with the risk of developing delirium in the ICU<sup>50,52-53</sup>. On the other hand, it is also found that inadequate pain management may be a risk factor for delirium as well<sup>59</sup>. Interestingly, a study in medical ICU patients older than 60 years old, showed that large opioid doses (morphine equivalent > 54mg/24h) were associated with persistent delirium, whereas no similar relationship was found with lower doses of opioids<sup>54</sup>. Considering all these, we may assume that opioids used in small doses may reduce the risk for delirium through alleviating patients' pain, as opposed to the use of larger doses and for long periods of time, which may have a deliriogenic effect in the critically ill patients. More research is needed to further elucidate the relationship between administration of opioids and development of delirium in the ICU.

### **Suggestions to improve management of delirium in critically ill patients**

In the field of prevention and treatment of delirium in the ICU, even though significant progress has been noticed in the previous years, there is still a relative paucity of high quality evidence. Here, we try to summarize a few steps for approaching delirium management in the ICU, based mainly on the recommendations of the recently published Society of Critical Care Medicine practice guideli-

nes<sup>37</sup> and the "screening, prevention and restoration model for saving the injured brain" approach, proposed by experts on ICU delirium in Vanderbilt University<sup>60</sup>.

#### 1. Identification of high risk patients for developing delirium in ICU

All patients admitted in the ICU should be routinely screened for major risk factors for developing delirium and high risk patients should be identified. Recently, a model for predicting delirium in critically ill patients was published. The Pre-DELIRIC model can predict delirium for the complete stay in ICU based on calculation of 10 risk factors which are all available in the first 24h of a patient's admission<sup>61</sup>. An automatic version of PRE-DELIRIC model is available at [www.umcn.nl/Research/Departments/intensive%20care/Pages/vandenBoogaard.aspx](http://www.umcn.nl/Research/Departments/intensive%20care/Pages/vandenBoogaard.aspx).

#### 2. Non pharmaceutical strategies to prevent ICU delirium

In a classical study published in *New England Journal of Medicine*, Sharon Inouye and her colleagues implemented, in a non ICU environment, an intervention consisted of six protocols for the non pharmaceutical management of six important risk factors for delirium (cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, dehydration). This intervention showed to significantly decrease the incidence



and the days of delirium compared to the usual hospital care<sup>62</sup>.

Even though similar studies are lacking in the critically ill patients, some non-pharmaceutical interventions can be implemented in the ICU environment. These include: usual reorientation of the patient, limited light, noises and nursing procedures during night, avoidance of sensory deprivation (provide glasses and hearing aids to the patients), avoidance of physical restraints and provision of adequate analgesia<sup>63</sup>. The presence of patients' family and friends should be facilitated as it is found that isolation and lack of visits may be risk factors for ICU delirium. Early mobilization and physiotherapy were also found to reduce delirium incidence in critically ill patients in a randomized, controlled trial (RCT)<sup>64</sup>. Geriatricians or psychiatrists specialized on Consultation-Liaison Psychiatry may help in the development of delirium prevention protocols that can be implemented in the ICU and the other departments of a general hospital.

The authors of the SCCM practice guidelines do not recommend using a pharmacological or a combined pharmacological and non pharmacological protocol to prevent ICU delirium, as there are no sufficient data to support these strategies<sup>37</sup>. A recently published RCT addressed the administration of continuous, intravenous infusion of haloperidol versus placebo for the prevention of delirium in 224 sur-

gical ICU patients. Haloperidol infusion at the first 12 h postoperatively was found to reduce the incidence of delirium in the first 7 postoperative days, prolong the mean time to onset of delirium, increase delirium free days and shorten the length of stay in ICU<sup>65</sup>. No difference in 28 day mortality was found between placebo and the intervention group<sup>65</sup>. Sublingual risperidone was showed to reduce the incidence of delirium in a placebo controlled randomized trial that included ICU patients after cardiac surgery with cardiopulmonary bypass<sup>66</sup>.

In a recent, Dutch study, administration of low dose haloperidol (1mg/8hrs) was found to reduce the incidence, duration of delirium and 28-day mortality in high risk patients of a general ICU<sup>67</sup>. The investigators used a historical control group and a contemporary control group that didn't receive haloperidol to extract their results<sup>67</sup>. Well designed, randomized controlled trials are needed to confirm these promising results in medical ICU patients, who generally present greater complexity and severity of illness.

### 3. Changing sedation practices to reduce brain dysfunction in the ICU

As a result of the progress in research about sedation and delirium as well as the increase of awareness about functional status and cognitive functions of ICU survivors, researchers from Vanderbilt University developed the

"ABCDE" bundle of care for the management of mechanically ventilated critically ill patients<sup>68-70</sup>. This is an evidence based bundle of strategies that include spontaneous **A**wakening trials and spontaneous **B**reathing trials **C**oordination, attention to **C**hoice of sedative agent, routine **D**elirium screening using a validated tool and **E**arly mobilization and **E**xercise of ICU patients. The different components of 'ABCDE" bundle were found to have beneficial impact on important outcomes such as mortality, length of stay in hospital, duration of mechanical ventilation, ICU delirium days and functional status of ICU survivors<sup>68-70</sup>. Regarding the choice of sedative agent, the SCCM guidelines recommend that critically ill patients with delirium, unrelated to alcohol or benzodiazepines withdrawal, should be sedated with IV infusions of dexmedetomidine rather than benzodiazepines in order to reduce the duration of delirium<sup>37</sup>. The SEDCOM study, a multicenter, randomized controlled trial that compared sedation with dexmedetomidine versus midazolam provides the best evidence behind this recommendation<sup>71</sup>. In this study, sedation with dexmedetomidine reduced ICU delirium prevalence by about 25% compared with midazolam. In another study of similar design that compared dexmedetomidine with lorazepam for sedation of ICU patients, no difference in the delirium free days was found between the two groups<sup>72</sup>. In a

subgroup analysis of septic versus non septic patients of this study, septic patients sedated with dexmedetomidine had 1,5 more delirium free days compared to those received lorazepam<sup>73</sup>. Beneficial impact of sedation with dexmedetomidine on delirium was also found in studies including patients after cardiac surgery in comparison with sedation with propofol, midazolam or morphine<sup>74,75</sup>.

#### 4. Prompt etiological management and judicious pharmaceutical treatment of delirium

The "gold standard" of delirium management will always be prompt recognition and correction of the organic cause of the syndrome (i. e. electrolyte disorders, acute respiratory failure, fever, a new administered drug etc). Unfortunately, this is difficult to achieve in the elderly patients of the ICU who are severely ill, under the influence of sedative drugs and with many risk factors for developing delirium during their ICU stay.

Agitated, delirious patients, with no clinical improvement after the management of reversible organic causes, are traditionally treated with antipsychotics. The SCCM practice guidelines report that treatment with atypical antipsychotics may reduce the delirium in ICU, in contrast with the lack of evidence to support that haloperidol administration may shorten the duration of delirium in adult ICU patients<sup>37</sup>. This is a differentiation from the previ-

ous guidelines that suggested haloperidol as the preferred treatment of delirium in the ICU with a level of evidence C<sup>76</sup>.

The recommendation about the use of haloperidol in treatment of ICU delirium was based on low quality evidence from retrospective studies, case series and experts opinions<sup>77-81</sup>. The years following the previous guidelines publication, two prospective studies comparing haloperidol with risperidone and olanzapine for treatment of delirium in critically ill patients were conducted<sup>82,83</sup>. These studies showed a positive impact of antipsychotics on the treatment of delirium, with no difference between haloperidol and atypical antipsychotics regarding safety and effectiveness. Methodological limitations, among them the absence of a placebo controlled group, restricted the quality of these results. In 2010, the first placebo controlled trial that compared haloperidol with placebo and ziprasidone for the treatment of delirium in 101 critically ill patients was published. Even though the study was primarily designed to assess the feasibility of such a trial and not the effectiveness of antipsychotics for delirium treatment, no difference on the days without delirium was found between the three groups<sup>84</sup>. In the same issue of *Critical Care Medicine*, another randomized, placebo controlled trial investigating the role of antipsychotics on the treatment of ICU delirium was published<sup>85</sup>. In this study, the in-

tervention group initially received 50 mg of quetiapine every 12hrs orally or via the nasogastric tube. Intravenous haloperidol was administered to control symptoms of delirium if it was needed. The dose of quetiapine was titrated daily up to a maximum of 200 mg every 12hrs if the patient received at least one dose of haloperidol in the previous 24hrs<sup>85</sup>. The combination of quetiapine with as-needed IV haloperidol resulted in faster resolution of delirium and less agitation compared with placebo. This is the only combination that has been found to be superior than placebo for the treatment of ICU delirium<sup>85</sup> (Table 2).

**Table 2.** Clinical trials investigating efficacy of antipsychotics for the treatment of ICU delirium

Authors	Intervention Drug	Study Design	Number of Patients (Study Population)	Main Results
Skrobik et al. 2004 <sup>82</sup>	Haloperidol vs olanzapine	Prospective open, randomized trial	73 (medical - surgical ICU)	Similar reduction of delirium symptoms between the 2 groups
Han et al. 2004 <sup>83</sup>	Haloperidol vs risperidone	Prospective, double blind, randomized trial	28 ( ICU & Oncological patients)	Similar reduction of delirium symptoms between the 2 groups
Girard et al. 2010 <sup>84</sup>	Haloperidol vs ziprasidone vs placebo	Multicenter, prospective, double blind, randomized, placebo controlled trial	101 (medical - surgical ICU)	Nodifference in delirium days between the 3 groups
Devlin et al. 2010 <sup>85</sup>	Quetiapine vs placebo	Multicenter, prospective, double blind, randomized, placebo controlled trial	36 (medical-surgical ICU)	Quetiapine was associated with faster resolution of delirium & reduced time of delirium and agitation

Even though, its effectiveness is based on low quality evidence, haloperidol is the most common used antipsychotic for the treatment of delirium in the ICU according to international surveys<sup>86-89</sup>. Its appropriate dose, the dose interval and the duration of therapy have not been clarified through well designed studies as well. Considering all these, we may suggest that haloperidol should be used in the smallest possible doses, patients should be evaluated regularly for improvement of their symptoms and therapy should be stopped as soon as possible. Doses larger than 10-20 mg/24hr are not considered to enhance the antipsychotic effect of drug and may only increase the risk of neurological side effects<sup>90</sup>. The most important adverse effects of haloperidol include extrapyramidal symptoms (lower incidence with iv than p.o. administration)<sup>91,92</sup>, QT prolongation and neuroleptic malignant syndrome<sup>77</sup>. SCCM guidelines recommend that patients at high risk for Torsades de Pointes (i.e. baseline QT prolongation, concomitant use of medications known to prolong QT interval, history of Torsades de Pointes) should not receive treatment with haloperidol or atypical antipsychotics<sup>37</sup>.

Benzodiazepines are considered to be the treatment of choice for delirium due to alcohol withdrawal, even though their safety and effectiveness are uncertain<sup>93</sup>. Barbiturates, propofol and  $\alpha_2$ -agonists have also appeared to be effective for the treatment of alcohol withdrawal

syndrome, but the data are limited and more research is needed<sup>93</sup>.

#### 5. Neuropsychological follow up and cognitive rehabilitation of ICU survivors

Cognitive impairment can be present in more than one out of three patients six months after discharging from ICU<sup>94</sup>. Long term cognitive impairment after critical illness (LTCI-CI) mainly includes difficulties in executive function, memory, attention, verbal fluency and visuo-spatial construction and consequently can significantly affect the quality of life of ICU survivors and their families<sup>95</sup>. Experts suggest that ICU survivors with high risk of developing LTCI-CI should be referred for a neuropsychological evaluation and they may benefit by cognitive and physical rehabilitation interventions<sup>60,96</sup>. These high risk groups remain to be identified but elderly patients suffered from ARDS, severe sepsis or delirium in the ICU seem to be in greater danger of developing cognitive deficits postdischarge<sup>6,97-98</sup>. In a recent, pilot study, 20 ICU survivors were randomized to receive either usual care or a multidisciplinary cognitive, physical and functional rehabilitation care over a 3 months period<sup>99</sup>. Participants in the intervention group reported to have better scores on a test of executive functioning and improvement in performance of instrumental activities of daily living (IADL)<sup>99</sup>. Large, prospec-

ctive, randomized trials are needed to confirm benefits of multidisciplinary, rehabilitation interventions on the improvement of LTCl-CI.

### Conclusions

Delirium is very common among patients in the ICU and may increase the risk of death, prolong the length of their stay in hospital and negatively affect their cognitive functions even months or years after ICU discharge. Intensivists should implement into their clinical practice the knowledge that was acquired during the previous decade about delirium in the ICU. Routine delirium monitoring, early identification of high risk patients, use of non pharmacological preventive interventions and change in the traditional sedation practices may help to reduce the incidence of brain dysfunction during ICU stay and hopefully lead to better cognitive and functional outcomes for the patients who survive their critical illness.

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