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WHAT'S NEW IN INTENSIVE CARE

Does this critically ill patient with delirium require any drug treatment?

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Their swaying bodies reflected the agitation of their minds, and they suffered the worst agony of all, ever just within the reach of safety or just on the point of destruction. Thucydides (460 BC–400 BC).

Delirium is a severe and frequent condition that occurs in 20–40% of patients admitted to the intensive care unit (ICU), with higher rates of 60–80% described in mechanically ventilated patients. The accumulated evidence in the past decades demonstrates that delirium is clearly associated with hospital mortality, lengths of stay, duration of mechanical ventilation and costs [1, 2]. Moreover, the presence of delirium and its duration and severity are risk factors for long-term cognitive impairment in patients surviving critical illness [1]. Although agitated (hyperactive) delirium attracts the intensivist's attention and frequently requires interventions to prevent self-harm and control the symptoms, the hypoactive and mixed forms are extremely common and frequently associated with poor outcomes. However, to correctly diagnose patients with delirium regardless of its presentation form, it is mandatory to use valid and reproducible screening tools such as the Confusion Assessment Method for the ICU (CAM-ICU) and Intensive Care Delirium Screening Checklist (ICDSC).

Despite the increasing knowledge on epidemiology, risk factors and potential preventive and therapeutic interventions [3], the rates of delirium and its associated mortality remain elevated. In a recent worldwide survey, we found that knowledge translation in terms of the application of the best current available evidence to prevent delirium is largely incomplete [4]. Recent quality improvement studies also showed that adherence to current recommendations on delirium and sedation management is low [5, 6].

In this scenario, a daily challenge for clinicians caring for the critically ill ensues when, after screening patients for delirium and making the diagnostic, they are faced with the question: "What should I do now? Does this patient with delirium require drug treatment?" Let us state that implementation of non-pharmacologic strategies to prevent and treat ICU delirium are of paramount importance (Fig. 1) and should be targeted as main goals of ICU quality improvement projects. We are far from achieving this goal; we only have to consider that the majority of ICUs worldwide still have restrictive ICU visitation policies for family members despite knowledge that an extended visitation policy is associated with reductions in the occurrence of delirium [7].

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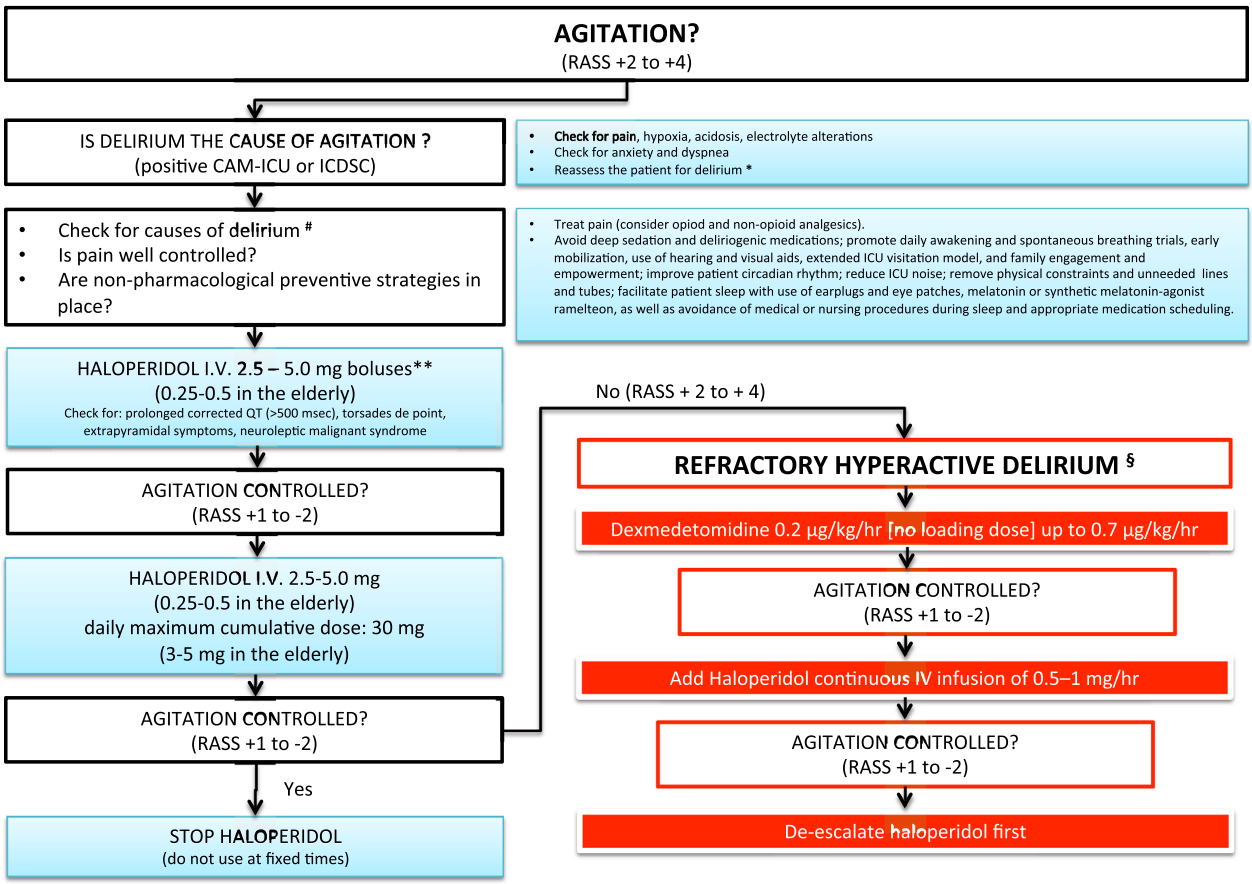

Fig. 1 Flowchart for treating patients with agitated (hyperactive) delirium in the ICU (see Supplementary file for more details). *RASS* Richmond Agitation Sedation Scale; *CAM-ICU* Confusion Assessment Method for the Intensive Care Unit; *ICDSC* Intensive Care Delirium Screening Checklist. *Sensitivity of CAM-ICU and ICDSC varies between 75 and 80%; hence, false-negative cases (delirium undetected) are possible. **Atypical antipsychotics (i.e., intramuscular olanzapine) can be considered if haloperidol is contraindicated. #Several mnemonics such as DELIRIOUS (D Drugs; E Environmental factors; L Labs; I Infection; R Respiratory status; I Immobility; O Organ failure; U Unrecognized dementia; S Shock) are available for the differential diagnosis in patients developing delirium (http://www.icudelirium.org/terminology.html)

In real life, two-thirds of clinicians report the use of haloperidol to treat delirium and 53% the use of quetiapine [4]. However, pharmacologic treatments of ICU delirium have little or no impact on clinically relevant outcomes such as mortality and duration of mechanical ventilation [8]. Even when considering the whole population of hospitalized patients, most studies do not show benefit of antipsychotics in decreasing the duration or severity of delirium [9]. Recently, a well-designed multicenter RCT demonstrated that in critically ill patients currently receiving best-practice nonpharmacologic interventions to prevent delirium, the addition of haloperidol as a preventive treatment did not improve survival at 28 days [10]. Delirium- and coma-free days, duration of mechanical ventilation, and ICU and hospital length of stay were also unaffected. In this study, the number of reported adverse effects was very low and did not differ between groups; however, in the literature several side effects of antipsychotics are reported that are worth knowing, including extrapyramidal side effects such as akathisia and oropharyngeal dysfunction, dystonic reactions such as laryngospasm and trismus, dysphoria, cognitive dysfunction and neuroleptic malignant syndromes. To date, we caution against the prophylactic use of antipsychotic drugs [11, 12].

Concerning pharmacologic prevention, novel data from a small RCT showed that dexmedetomidine may reduce the incidence of delirium when used as a continuous intravenous nocturnal infusion [13]. Although the evidence from this RCT is promising, larger studies with representative ICU patient populations at high risk of developing delirium are needed before dexmedetomidine prophylaxis is adopted in clinical practice. Internationally validated scoring systems such as the PREDELIRIC

and E-PREDELIRIC [14] may help to identify high-risk patients who may mostly benefit from nonpharmacologic and pharmacologic preventive therapies. By integrating easily available clinical data that represent risk factors for developing delirium, these models reliably predict the development of delirium early during the ICU stay.

Treatment of significant agitation [as diagnosed by a +2 to+4 Richmond Agitation Sedation Score (RASS)] associated with delirium remains an indication for drug use in the ICU. Agitation may be due to different causes, often interacting with each other (e.g., pain and delirium). Moreover, agitation involves increased intensity not only in behavioral dimensions but also in psychologic dimensions so that patients may suffer from severe, distressing psychotic symptoms such as hallucinations and delusions [15]. We therefore recognize that delirium is only one of the several possible causes of agitation in the ICU patient. Thus, agitation is only one aspect of delirium that would merit attention from some of the caring physicians. On the other hand, effective treatment of agitation helps in reducing the occurrence of risk events such as unplanned removal of life-supporting devices, which in turn prompt institution of new or additional physical restraints and sedation, thus creating a vicious circle. Agitated delirium is also a distressing experience for the patient and family; hence, the use of drugs may be warranted. Available evidence suggests that dexmedetomidine alone or as rescue agent may be useful for the treatment of agitated delirium [16]. In Fig. 1, we propose a pragmatic approach to the ICU patient with agitated delirium in which timely diagnosis of delirium and prompt initiation of drug treatment may serve to buy time while evaluating potentially treatable causes of delirium.

In conclusion, drug treatment for patients developing delirium in the ICU is indicated only to treat significant agitation. Distressing psychotic symptoms such as hallucinations and delusions may warrant a pharmacologic treatment but their diagnosis in the ICU setting is exceedingly difficult [17]. In such cases, intravenous haloperidol remains the drug of first choice; however, haloperidol as well as other anti-psychotic drugs does not alter delirium severity and duration and should be used to control symptoms for the shortest possible time. Relevant side effects warrant accurate diagnosis of delirium and patient selection. Initial evidence suggests that dexmedetomidine may have a role in preventing delirium and can be usefully added to haloperidol to treat clinically significant agitated delirium.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-018-5310-x) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest
All authors declare that they have no conflict of interest.

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