Diagnosis, prevention and management of delirium in the intensive cardiac care unit

Alejandro Cortés-Beringola, MD;[1,2] Lourdes Vicent, MD, PhD;[1] Roberto Martín-Asenjo, MD;[1,3] Elena Puerto, MD; [1,3] Laura Domínguez, MD; [1,3] Ramón Maruri, MD;[1,3] Guillermo Moreno, RN[1,3,4] María T, MD, PhD;[4,5] Fernado Arribas MD, PhD;[1,3,4], Héctor Bueno, MD, PhD[1,3,4,6].

1 Intensive Cardiac Care Unit. Cardiology Department. Hospital Universitario 12 de Octubre and Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), Madrid, Spain

2 Cardiology Department. Hospital Universitario Infanta Leonor, Madrid, Spain

3 CIBER de enfermedades CardioVasculares (CIBERCV), Madrid, Spain

4 Facultad de Medicina, Universidad Complutense de Madrid, Madrid, Spain.

5 Department of Geriatric Medicine. Hospital General Universitario Gregorio Marañón, Madrid, Spain

6 Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain;

Corresponding author:

Héctor Bueno, M.D., PhD., FESC, FAHA

Intensive Cardiac Care Unit. Department of Cardiology

Hospital Universitario 12 de Octubre

Madrid, Spain

hbueno@cnic.es

Abstract

Delirium is a frequent complication in patients admitted to intensive cardiac care units (ICCU) with potentially severe consequences including increased risks of mortality, cognitive impairment at discharge and dependence, and longer times on mechanical ventilation and hospital stay. Delirium has been widely documented and studied in general intensive care units and in patients after cardiac surgery, but it has barely been studied in acute non-surgical cardiac patients. Moreover, delirium (especially in its hypoactive form) is commonly misdiagnosed. We propose a protocol for delirium prevention and management in ICCUs.

A daily comprehensive assessment to improve detection should be done using validated scales (i.e. Confusion Assessment Method). Preventive measures are of particular relevance and constitute the basis of treatment as well, acting on reversible risk factors, including environmental interventions, such as quiet time, sleep promotion, family support, communication, and adequate treatment of pain and dyspnea. Pharmacological treatment should only be used in patients with confirmed delirium. Dexmedetomidine is the drug of choice in patients with severe agitation, and those undergoing weaning from invasive mechanical ventilation.

As the complexity of the ICCUs increases, clinical scenarios posing challenges for the management of delirium become more frequent. An effort should be done to improve the identification of patients at risk of presenting delirium during admission in order to establish preventive interventions to avoid this complication. Patient-centered protocols will increase the awareness of the healthcare professionals for better prevention and earlier diagnosis and will positively impact on prognosis.

Keywords: *delirium; agitation; intensive cardiac care; prevention*.

DEFINITION AND EPIDEMIOLOGY

Delirium is a clinical syndrome defined as an acute neurocognitive disorder occurring as a consequence of another underlying disease or organic process that disrupts internal homeostasis. It is characterized by a disturbance in attention and awareness that the patient has about the environment [1, 2]. Delirium is a reversible state that occurs abruptly and presents a fluctuating course [1]. Patients may also show language disturbances, psychotic features and consciousness fluctuations [2].

Delirium is important for several reasons. It is a common adverse event in patients admitted to intensive care units (ICU)[1], being the most frequent hospital complication in elderly patients. Its presence is associated with poor short and long-term outcomes,[2] including long-term mortality, and produces a neurocognitive and cognitive impairment during hospital admission that may also persist after hospital discharge [2], leading to a loss of autonomy and institutionalization. Moreover, delirium may have an iatrogenic origin, and in most cases it is a preventable complication. Therefore, the incidence of delirium in ICUs and its correct management must be interpreted as an opportunity to improve patient care quality.

The rate of delirium varies widely, according to the patient´s profile, the interventions received, and the type of unit where is admitted. The incidence of delirium may range between 5.7% in patients with acute myocardial infarction admitted to intensive cardiac care units (ICCU)[3] up to 40% as described in patients undergoing cardiac surgery,[4] suggesting that this complication depends on several factors, including the severity of the acute illness, the patient characteristics, and the diagnostic method used[5, 6]. The real incidence may actually be higher, as this complication is not routinely assessed in many units, and misdiagnosis is very common, particularly in its hypoactive form[6].

PARTICULARITIES IN INTENSIVE CARDIAC CARE UNITS

Coronary care units were designed in the 1960s mainly to monitor and treat early life-threatening arrhythmias presenting in the acute phase of myocardial infarction. Since then, the profile of patients with severe cardiovascular diseases admitted to these units has acquired greater complexity and diversity [7], and now the term ICCUs is more suitable to refer to these units. With these changes, the incidence of delirium has substantially increased [8] and is comparable to the other medical ICUs. However, despite the increase of the incidence of delirium in ICCUs, the most recent publications focused mainly on general ICUs and post-cardiac surgery units. Delirium has been barely studied in acute non-surgical cardiac patients, such as ICCUs, but extrapolation from other types of ICUs is difficult due to the particularities in the profile of patients and their management (**Table 1**), which must be taken into account.

Patients admitted to ICCUs are often old or very old and present frequently with heart failure, acute coronary syndrome or resuscitated cardiac arrest [3]. The admission of very old patients after structural cardiac procedures, such as trans-aortic valvular replacement (TAVR), is increasingly common. Many of these patients have mild to moderate cognitive impairment and are under polypharmacy, which, along with advanced age, are risk factors for delirium[8]. Furthermore, ICCUs have a greater turnover of patients, and shorter length of ICU stay compared to other types of ICUs, which can benefit by shortening the time of exposure but also can lead to greater difficulty in implementing delirium preventing strategies, such as noise control and sleep promotion.

The management of patients after delirium initiation in ICCUs may also have special considerations. Several patients may be in severe clinical situations without profound sedation. For example, patients dependent on temporary pacing or under

percutaneous mechanical circulatory support may be alert and conscious. Any sudden or uncontrolled movement can lead to serious complications including cardiorespiratory arrest and death caused by the displacement of the device. In these situations, hyperactive delirium, particularly agitation and aggressiveness, requires rapid control to prevent damage. In these scenarios, prevention of delirium becomes especially important.

PATHOPHYSIOLOGY AND CLINICAL IMPLICATIONS

Delirium has a multifactorial origin, including neurotransmitters changes, endothelial dysfunction and inflammation [9]. Neural disturbances can be triggered by external factors, but individual host susceptibility is key. The interrelation of three factors predisposes to the occurrence of delirium during admission (**Table 2**) in the majority of cases:

1) Intrinsic host susceptibility: prior cognitive impairment, polypharmacy/therapy, delirium on previous hospital admissions, advanced age, and cardiovascular risk factors are some of the non-modifiable risk factors that predict increased risk of delirium.
2) A precipitating factor, such as the acute disease leading to hospital admission.
3) Aggravating and perpetuating factors, such as immobilization, sleep deprivation, pain, and medications.

Delirium is a marker of poor outcomes in patients admitted to the ICU, especially in those without prior cognitive impairment,[10] as has been associated with increased morbidity and mortality [8], longer time of invasive mechanical ventilation, more prolonged duration of ICU stay, worsening of cognitive capacity, loss of

functional abilities after hospital discharge [10-12], and higher healthcare costs. Although delirium is strongly associated with the clinical characteristics and comorbidities, delirium remains an important risk factor of poor prognosis after adjusting for confounders [12]. Since delirium is a preventable and reversible state, an effort should be made to implement multidisciplinary and patient-centered interventions to reduce its incidence and negative impact.

DIAGNOSIS

Despite its high frequency, delirium is often misdiagnosed because a systematic cognitive status examination of patients admitted to ICCUs is not routinely performed [6]. This situation is aggravated by several factors, including drug sedation, which may be required for various techniques and mechanical ventilation, or hemodynamic instability, reducing the ability of patients to cooperate, needed for the assessment of cognitive status [3].

The diagnosis of delirium relies exclusively on clinical judgment (**Figure 1**). There are two main types of delirium: hypoactive and hyperactive [13]. Hypoactive delirium is more difficult to diagnose, as clinical manifestations are subtler in comparison to hyperactive delirium presentation. Patients presenting hypoactive delirium show apathy, lethargy, and decreased motor responsiveness [13]. Hyperactive delirium is characterized by agitation, restlessness and increased state of arousal [13]. Some patients may show mixed manifestations. Screening tools are useful to support the diagnosis of delirium, although it is necessary to apply them routinely and carry out training of healthcare professionals for this purpose [3, 14]. The implementation of a delirium detection protocol in daily nursing rounds is a feasible alternative that has

proven to be effective [14]. The Confusion Assessment Method (CAM) is a reliable tool that has been tested and validated in patients admitted to the ICU (CAM-ICU, **Figure 2**) [15, 16] and outside the ICU with the Brief Confusion Assessment Method (bCAM, **Figure 3**). This modified version has better sensitivity in non-ICU patients, but may also be more suitable for many patients admitted to ICCUs, as a majority of them are non-ventilated patients.

CAM-ICU and bCAM require minimal training, can be performed algorithmically, taking just a few minutes, and allowing early stoppage if delirium is ruled out in the first steps. In sedated patients (i.e. those mechanically ventilated) it is necessary to evaluate first the level of sedation. The Richmond Agitation-Sedation Scale (RASS scale) is commonly used for this purpose (**Supplementary Table 1**) [17]. If the patient has a RASS score <-3 points, the assessment of delirium is not feasible at that moment. The RASS scale is also a useful method to monitor delirium in non-sedated patients, as punctuations >+1 or <-1 are highly suggestive of delirium [18].

Making a correct diagnosis is the first step, but also a diagnostic approach focused on etiology is important [19]. Delirium may be a subsequent manifestation of another medical condition (i.e. acute organic disease), substance abuse, drugs withdrawal, induced by medications, or multifactorial. Delirium caused by drug withdrawal (especially alcohol withdrawal) is a medical emergency and should be early detected, as it has special prognostic and therapeutic implications [20]. Prevention strategies are of vital importance, being the only case of delirium in which prophylactic treatment with sedative medication is strongly recommended in patients at risk.

As previously mentioned, delirium has a rapid onset, is reversible and evolves with a fluctuating course [6]. Patients with a history of cognitive decline or dementia might experience a worsening of their cognitive status during admission,[2] so it will be

important to know the baseline (before hospitalization) cognitive and functional situation of the patient to differentiate from acute delirium. **Table 3** shows a list of usual possible differential diagnoses in patients with a suspect of delirium.

PREVENTION OF DELIRIUM

Delirium should be considered as a potentially preventable in-hospital complication, so prevention strategies are critical points, where more efforts should be made. Several interventions have shown a reduction in the incidence and duration of delirium[21]. So far, pharmacological therapies have demonstrated mixed results, with questionable efficacy. Avoiding routine administration of antipsychotic drugs is highly recommended [6].

Non-pharmacological interventions are essential for preventing delirium and should focus on avoiding modifiable risk factors. Delirium may be associated with other organic causes, and efforts should be made in order to diagnose and correct potential triggers. The organic causes include electrolyte and fluid imbalance, urinary or fecal retention, clinical worsening of the underlying pathology and adverse effects of other drugs such as opioids, anticholinergic or antihistaminic drugs. Physical restraints worsen the state of delirium in the majority of patients, and specific treatment of unpleasant sensations, such as pain or dyspnea, should be performed. Thus, although many patients have non-modifiable risk factors, such as advanced age, comorbidities, or an acute disease causing the admission, there are several factors on which preventive action can be taken, and these must be identified as soon as possible in order to implement preventive measures [2, 6]. These include:

- Adequate control of pain and other symptoms (dyspnea, fever, constipation)

    - Monitor pain in the daily routine assessment
    - Elaborate a pain management plan individualized for each patient
- Prevent sensory impairment
    - Ensure the use of glasses or hearing aids
    - Promote the access to radio, newspapers, tablets (maintain contact with the outside)
    - Promote the use of clocks and calendars in rooms
    - Address sensory assessment
- Provide orientation and reassurance
    - Promote natural light during the day
    - Repeat instructions
    - Use reminders: notes, blackboards
    - Avoid room changes
- Noise reduction strategies and sleep promotion
    - Mark rest times (quiet time during the night)
    - Reduce environmental stimuli (dim lights during the night, use only indirect lights for patient orientation)
    - Develop effective protocols to uniform periods of minimum assessment times and reduce patient interactions
    - Consider music relaxation
- Minimize the use of sedative drugs:
    - Avoid the use of benzodiazepines in patients older than 65 years or at risk for delirium. If necessary, the use of other hypnotics or anxiolytics is preferable

    - In patients on chronic use of high doses of benzodiazepines, abrupt withdrawal should be avoided and the dose should be lowered gradually
- Reduce invasive procedures if possible
    - Avoid as far as possible the use of central catheters or bladder catheterization (periodic reevaluation of indication should be done)
- Minimize the risk of injury
    - Avoid using mechanical restraints
    - Minimize the risk of falls
- Early mobilization and self-care
    - Sit on bed or armchair, initiate respiratory physiotherapy and passive or active rehabilitation as soon as possible
    - Encourage early self-care: promote independence in activities of daily living during hospitalization
- Ensure adequate hydration and nutritional status
    - Early detection of lack of appetite and/or inadequate oral intake
    - Ensure the use of dentures
- Involve family, caregivers and friends in patient´s care and visiting
    - Promote the presence and communication with the family (open ICCU)
    - Involve the family in reorientation and cognitive stimulation exercises
    - Give the family the option of staying over

Humanitarian preventive measures. The humanization of critical care is an ideological movement promoting a humanitarian environment, where the patient does not feel threatened but cared and loved. Several interventions are developing, such as musicology, mindfulness and positive thinking. The idea of an open visit policy in the

ICU is becoming an innovative intervention showing promising results [22, 23]. The extended visits of families reduced the duration of mechanical ventilation, ICU stay and delirium incidence (from 20% to 10%) [23].

- Maximize positive and personal communication (names and identification of nurses, treating physicians and rest of the healthcare team)
- Manage with respect and love
- Avoid psychological and physical hostility
- Allow stays of relatives overnight if needed

Pharmacological prophylaxis with antipsychotic drugs should not be routinely indicated for preventing delirium. As mentioned before, the exception is the patient at risk of withdrawal syndrome from an additive substance (i.e. alcohol). It is important to identify early these patients and start preventive treatment with benzodiazepines and vitamin B supplements [6, 20].

Proper management of pain, and supporting measures to improve sleep, facilitating an adequate rest during nights are important because these are two modifiable risk factors for delirium [3]. Anti-inflammatory drugs and benzodiazepines should be avoided, especially in older patients. In mechanically ventilated patients, sedative drugs should always be prescribed at the minimal necessary dose, while routine awakening and breathing trials are recommended.

TREATMENT OF DELIRIUM

Once the diagnosis of delirium is established, the following therapeutic interventions should be initiated as soon as possible in order to reduce the duration of the episode, and prevent recurrences:

- Treatment of the acute organic disease, if present.
- Modification of risk factors: Preventive measures (*see above*).
- Pharmacological treatment (**Supplementary Table 2**)
    - It should be indicated judiciously, using the lowest effective dose for the shortest period
    - When choosing the most appropriate drug, the patient's level of agitation, the onset of action, and the need of monitoring should be assessed (**Figures 4 and 5**)
- The most commonly used drugs in the treatment of delirium are the following (**Supplementary Table 3**)
    - α-adrenergic receptor agonists: dexmedetomidine and clonidine.
    - Classic antipsychotics: haloperidol, tiapride
    - Atypical antipsychotics: risperidone, quetiapine, olanzapine

Within the available drugs, dexmedetomidine, an α-2 adrenoceptor agonist with a selective sedative action, provides a conscious sedation state associated with reductions in the incidence of delirium, agitation, and duration of mechanical ventilation in ICUs [24, 25]. Some studies have shown the safety and efficacy of this drug in patients with acute cardiac diseases, even in the oldest patients[26]. Although more recent trials have not confirmed its benefits in outcomes in patients from general or surgical ICUs [27, 28], our clinical experience as well as others' [29] is positive. The starting dose is 0.7 µg/kg/h, which can be titrated to a maximum of 1.4 µg/Kg/h depending on the level of agitation of the patient. A loading dose should be avoided in cardiac patients. This drug

is safe, does not cause respiratory depression, and the most common adverse effects are hypotension and bradycardia, so it should be used with caution in patients with bradycardia, hypotension or cardiogenic shock, always with electrocardiogram (ECG) monitoring [24]. The conscious sedation achieved with dexmedetomidine is particularly useful in the process of weaning from mechanical ventilation [24, 25], so this sedative agent is the first choice in intubated patients undergoing respiratory progression. Dexmedetomidine can be used in combination with other sedatives (such as opioids, propofol) or in patients with difficult sedation. In patients receiving dexmedetomidine for a prolonged period (longer than 3-5 days), it is important to administer clonidine orally, while tapering dexmedetomidine, in order to prevent a withdrawal syndrome after its discontinuation.

In contrast to the clinical scenario observed in conventional ICUs, it is relatively common to find critically ill patients conscious or mildly sedated on spontaneous ventilation in ICCUs. Many patients are dependent on mechanical hemodynamic support (i.e. Impella®, intraaortic aortic balloon counterpulsation, extracorporeal mechanical oxygenation), or may need temporary transvenous pacing. In these cases, as well as in cases of severe agitation or vital risk, it is appropriate to ensure that the patient is immobilized, avoiding uncontrolled movements that could cause the displacement of such devices and significant complications due to loss of support or stimulation, vascular damage or major bleeding. In these cases of vital risk, the prolonged onset of action of antipsychotics and even of dexmedetomidine (5 - 10 minutes) can result too slow to control the agitation, and achieving an urgent superficial sedation with propofol or midazolam at the lowest effective dose may be crucial. These sedative drugs are not specific for the management of delirium but will increase safety for the patient until the effect of antipsychotic drugs takes place.

Antipsychotic drugs may induce a prolongation of the QT interval that should be monitored as it may favor the development of malignant ventricular arrhythmias. An ECG should be periodically performed, especially in patients who receive a combination of drugs associated with QT prolongation (such as antibiotics), or present ionic disturbances, which are common in these patients (hypokalemia, hypomagnesemia). If anti-delirium drugs are administered intravenously, telemonitoring is advised. Extrapyramidal symptoms may occur, especially when typical antipsychotics are used [30] (**Supplementary Table 3**).

The administration of intravenous medication should be overlapped with oral maintenance drugs whenever possible. Once the initial episode of agitation is controlled, maintenance treatment should be administered for 3 to 5 days. The oral route is preferable when the patient is collaborative and oral intake and adequate level of consciousness are ensured.

The treatment of patients presenting with hypoactive delirium is more complex as it often goes unnoticed due to the subtler manifestations, and the pharmacological treatment is less effective in these patients[31], so non-pharmacological interventions are even more important in them.

COMMON CLINICAL SCENARIOS IN THE ICCU

As the complexity of the ICCUs increases, clinical scenarios posing challenges for the management of delirium become more frequent. The general measures mentioned above are useful in most situations described below. The role of open-door ICCUs is not yet well established, although integrating family participation can be very

useful to reduce delirium incidence in patients without hemodynamic instability and not requiring deep sedation [23].

- Acute heart failure. Acute heart failure is one of the most common diagnoses of admission in the ICCU. Due to the clinical profile of these patients (advanced age, frequent comorbidities, frailty, polypharmacy), delirium is very frequent. In addition, cognitive disturbances are usual in patients with heart failure [32], and there are extrinsic factors that may precipitate or aggravate a confusional state, such as hypoxia, medical treatments and invasive interventions or procedures (i.e. mechanical ventilation, renal replacement therapy, coronary angiography, or central venous catheterization [33]). Heart failure is *per se* a clinical condition predisposing to delirium, with an increased risk of delirium seen in all contexts, including cardiac surgery, cardiac procedures and interventions,[33, 34] which is directly correlated to the severity of the acute decompensation [33].

- Syncope and bradycardia. Temporary pacing together with heart failure and ICU admission were associated with a higher incidence of delirium after the procedure, close to 20% in this population.[34] Therefore, avoidance of temporary pacing whenever possible may be recommended in high-risk patients.

- Acute coronary syndrome and percutaneous coronary intervention. The incidence of delirium after acute myocardial infarction is much lower than in patients with surgical revascularization or other cardiac conditions (approximately 6%). Therefore, the general preventive measures described earlier seem to be sufficient in these particular patients

- Cardiac arrest. Delirium is extremely common in cardiac arrest survivors, as nearly all resuscitated patients present some degree of confusion during hospitalization

[35]. Interestingly, although delirium per se is not associated with worse outcomes in cardiac arrest survivors, the duration of delirium is associated with an increased risk of mortality, hospital stay and longer time of mechanical ventilation. Older age and longer times from cardiopulmonary resuscitation to return of spontaneous circulation are associated with an increased number of days with delirium [35]. The incidence of delirium is also high in patients undergoing therapeutic hypothermia. Acute brain dysfunction after cardiac arrest should be viewed as a collateral effect of cerebral hypoxia. Common sedation protocols in the ICU include midazolam, propofol, fentanyl, remifentanil and morphine at high doses. In patients undergoing therapeutic hypothermia, the administration of neuromuscular blocking agents is also warranted to avoid shivering. Dexmedetomidine may have neuroprotective effects and may be considered in this clinical scenario, alone or in combination with other sedative drugs.

- Non-invasive mechanical ventilation is commonly used in ICCUs. Some patients present poor tolerance due to agitation, anxiety, dyspnea and discomfort during this procedure [36]. Delirium is one factor contributing to the failure of non-invasive ventilation. Patients presenting agitation and intense dyspnea before ventilation may benefit from mild sedation [36]. Dexmedetomidine does not cause respiratory depression and may be a safe alternative in this context.

- Mechanical circulatory support is increasingly used in patients with cardiogenic shock. Patients requiring this invasive approach present numerous risk factors for delirium, including the severity of the disease (mainly acute myocardial infarction with hemodynamic instability or advanced heart failure) and mechanical support itself. However, delirium in patients under circulatory support with percutaneous devices has not been well-characterized in large-scale studies, but it seems reasonable to apply the general measures described for previous sections[37] with special

emphasis on the control of mobilization, which should always be done under the supervision and collaboration of the patient, in those who are not under invasive mechanical ventilation. Patients needing mechanical hemodynamic support should maintain bed rest in order to avoid device displacement, which may cause critical complications or loss of circulatory support. Prophylactic administration of sedatives is not recommended, but ensuring night rest and treating pain effectively are crucial aspects.

- Procedures and interventions. A large number of patients are admitted to ICCUs for clinical observation and ECG monitoring after TAVR. These patients are very often at high risk of delirium due to their advanced age, risk factors and medical history. In fact, several show mild cognitive impairment and heart failure before the procedure, and some develop acute kidney injury after the procedure[38]. Approximately one in 5 patients has delirium after TAVR, with a peak incidence recorded 2 days after the procedure [38]. Transapical TAVR significantly increases the risk of delirium, compared with the transfemoral approach[38]. Local anesthesia and mild sedation, avoiding general anesthesia and orotracheal intubation for TAVR, may be effective procedural strategies for delirium prevention [39, 40]. Shortening as much as possible the duration of ICCU stay and early mobilization may be of additional help.

DELIRIUM RED FLAGS IN THE ICCU

The following features are associated with a high risk of developing delirium, and should be screened in all patients admitted to an ICCU:

- Old age

- Previous cognitive impairment/delirium in previous hospitalizations

- Instrumentation: central venous catheters, circulatory support devices, invasive mechanical ventilation, pacing with temporary transvenous pacemaker

- Cardiac arrest as the cause for hospitalization

- History of heart failure

- Polypharmacy, history of drug or alcohol abuse

Future real-life studies are needed to address the efficacy of pharmacological therapies aimed at reducing the incidence of delirium. Developing new drugs (with a potential impact on reducing mortality, disability and improving the cognitive status of patients at discharge) is also a priority.

Disclosures.

Dr. Cortés-Beringola has nothing to disclose.

Dr. Puerto has nothing to disclose.

Dr. Bueno receives research funding from the Instituto de Salud Carlos III, Spain (PIE16/00021 & PI17/01799), Sociedad Española de Cardiología, Astra-Zeneca, Bayer, BMS and Novartis; has received consulting fees from Astra-Zeneca, Bayer, BMS-Pfizer, Novartis; and speaking fees or support for attending scientific meetings from Amgen, Astra-Zeneca, Bayer, BMS-Pfizer, Novartis, and MEDSCAPE-the heart.org.

References

1. Arumugam S, El-Menyar A, Al-Hassani A, et al. Delirium in the Intensive Care Unit. J Emerg Trauma Shock 2017;**10**:37-46.
2. Marcantonio ER. Delirium in hospitalized older adults. N Engl J Med 2017;**377**:1456-1466.
3. Ibrahim K, McCarthy CP, McCarthy KJ, et al. Delirium in the Cardiac Intensive Care Unit. J Am Heart Assoc 2018;**7**. pii: e008568
4. Chang YL, Tsai YF, Lin PJ, et al. Prevalence and risk factors for postoperative delirium in a cardiovascular intensive care unit. Am J Crit Care 2008;**17**:567-75.
5. Girard TD, Pandharipande PP, Ely EW. Delirium in the intensive care unit. Crit Care 2008;**12 Suppl 3**(Suppl 3):S3-S3.
6. Hayhurst CJ, Pandharipande PP, Hughes CG. Intensive care unit delirium: a review of diagnosis, prevention, and treatment. Anesthesiology 2016;**125**:1229-41.
7. Holland EM, Moss TJ. Acute noncardiovascular illness in the cardiac Intensive Care Unit. J Am Coll Cardiol 2017;**69**:1999-2007.
8. Grotti S, Falsini G. Delirium in cardiac patients. Eur Heart J 2017;**38**:2244.
9. Wang X-T, Lyu L, Tang B, et al. Delirium in Intensive Care Unit patients: ten important points of understanding. Chin Med J (Engl) 2017;**130**:2498-2502.
10. McCusker J, Cole M, Abrahamowicz M, et al. Delirium predicts 12-month mortality. Arch Intern Med 2002;**162**:457-463.
11. Leslie DL, Zhang Y, Holford TR, et al. Premature death associated with delirium at 1-year follow-up. Arch Intern Med 2005;**165**:1657-62.
12. Schubert M, Schürch R, Boettger S, et al. A hospital-wide evaluation of delirium prevalence and outcomes in acute care patients - a cohort study. BMC Health Serv Res 2018;**18**:550.

13. Stagno D, Gibson C, Breitbart W. The delirium subtypes: a review of prevalence, phenomenology, pathophysiology, and treatment response. Palliat Support Care 2004;**2**:171-9.

14. Pun BT, Gordon SM, Peterson JF, et al. Large-scale implementation of sedation and delirium monitoring in the intensive care unit: a report from two medical centers. Crit Care Med 2005;**33**:1199-205.

15. Ely EW, Margolin R, Francis J, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med 2001;**29**:1370-9.

16. Gusmao-Flores D, Salluh JI, Chalhub RA, et al. The confusion assessment method for the intensive care unit (CAM-ICU) and intensive care delirium screening checklist (ICDSC) for the diagnosis of delirium: a systematic review and meta-analysis of clinical studies. Crit Care 2012;**16**:R115.

17. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation–Sedation Scale. Am J Resp Crit Care Med 2002;**166**:1338-44.

18. Han JH, Vasilevskis EE, Schnelle JF, et al. The Diagnostic Performance of the Richmond Agitation Sedation Scale for Detecting Delirium in Older Emergency Department Patients. Acad Emerg Med 2015;**22**:878-82.

19. Kaplan NM, Palmer BF, Roche V. Etiology and management of delirium. Am J Med Sci 2003;**325**:20-30.

20. Salottolo K, McGuire E, Mains CW, et al. Occurrence, predictors, and prognosis of alcohol withdrawal syndrome and delirium tremens following traumatic injury. Crit Care Med 2017;**45**:867-74.

21. Hsieh SJ, Ely EW, Gong MN. Can intensive care unit delirium be prevented and reduced? Lessons learned and future directions. Ann Am Thorac Soc 2013;**10**:648-56.

22. da Silva Ramos FJ, Fumis RR, Azevedo LC, et al. Perceptions of an open visitation policy by intensive care unit workers. Ann Intensive Care 2013;**3**:34.

23. Rosa RG, Tonietto TF, da Silva DB, et al. Effectiveness and safety of an extended ICU visitation model for delirium prevention: a before and after study. Crit Care Med 2017;**45**:1660-67.

24. Ng KT, Shubash CJ, Chong JS. The effect of dexmedetomidine on delirium and agitation in patients in intensive care: systematic review and meta-analysis with trial sequential analysis. Anaesthesia 2019;**74**:380-392.

25. Jakob SM, Ruokonen E, Grounds RM, et al. Dexmedetomidine vs. midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. JAMA 2012;**307**:1151-60.

26. Pereira JV, Sanjanwala RM, Mohammed MK, et al. Dexmedetomidine versus propofol sedation in reducing delirium among older adults in the ICU: A systematic review and meta-analysis. Eur J Anaesthesiol 2020;**37**:121-31.

27. Shehabi Y, Howe BD, Bellomo R, et al. Early Sedation with dexmedetomidine in critically ill patients. N Engl J Med 2019;**380**:2506-2517.

28. Kawazoe Y, Miyamoto K, Morimoto T, et al. Effect of dexmedetomidine on mortality and ventilator-free days in patients requiring mechanical ventilation with sepsis: a randomized clinical trial. JAMA 2017;**317**:1321-1328.

29. Gaitan RM, Vicent L, Rodriguez-Queralto O, et al. Dexmedetomidine in medical cardiac intensive care units. Data from a multicenter prospective registry. Int J Cardiol; **In press**.

30. Markowitz JD, Narasimhan M. Delirium and antipsychotics: a systematic review of epidemiology and somatic treatment options. Psychiatry (Edgmont) 2008;**5**:29-36.

31. Carvalho J, Alvim R, Martins J, et al. Pharmacological treatment of hypoactive delirium in critically ill patients: a systematic review. Crit Care 2013;**17**:P36-P36.

32. Leto L, Feola M. Cognitive impairment in heart failure patients. J Geriatr Cardiol 2014;**11**:316-28.

33. Correale M, Altamura M, Carnevale R, et al Delirium in heart failure. Heart Fail Rev 2019:[Online ahead of print].

34. Higashi H, Inaba S, Saito M, et al. Heart failure as a strong independent predictor of delirium after pacemaker operations. IJC Metabolic & Endocrine 2015;**8**:42-45.

35. Pollock JS, Hollenbeck RD, Wang L, et al. Delirium in survivors of cardiac arrest treated with mild therapeutic hypothermia. Am J Crit Care 2016;**25**:e81-e89.

36. Longrois D, Conti G, Mantz J, et al. Sedation in non-invasive ventilation: do we know what to do (and why)? Multidiscp Respir Med 2014;**9**(1):56-56.

37. Acevedo-Nuevo M, González-Gil MT, Romera-Ortega MÁ, et al. The early diagnosis and management of mixed delirium in a patient placed on ECMO and with difficult sedation: A case report. Intensive Crit Care Nurs 2018;**44**:110-114.

38. Tilley E, Psaltis PJ, Loetscher T, et al. Meta-analysis of Prevalence and Risk Factors for Delirium After Transcatheter Aortic Valve Implantation. Am J Cardiol 2018;**122**:1917-1923.

39. van der Wulp K, van Wely M, van Heijningen L, et al. Delirium After Transcatheter Aortic Valve Implantation Under General Anesthesia: Incidence, Predictors, and Relation to Long-Term Survival. J Am Geriatr Soc 2019;**67**:2325-2330.

40. Goudzwaard JA, de Ronde-Tillmans MJ, de Jager TAJ, et al. Incidence, determinants and consequences of delirium in older patients after transcatheter aortic valve implantation. Age Ageing 2020. [Epub ahead of print]

Figure legends.

Figure 1. Principles of delirium diagnosis.

Figure 2. Confusion Assessment Method ICU for delirium diagnosis [15, 16] in intubated patients.

Figure 3. Brief Confusion Assessment Method (bCAM) for delirium diagnosis [15, 16] in non-intubated patients.

Figure 4. Treatment of hyperactive delirium.

Figure 5. Delirium evaluation and therapy during hospitalization.

Table 1. Differences in patients profile and delirium predisposing factors according to the type of ICU.

Cardiac ICU	**Conventional ICU**
Older patients	Medical and surgical patients
High prevalence of cardiovascular risk factors	Common noncardiac comorbidities
Electrical and hemodynamic instability	Respiratory failure
Cardiogenic shock	Septic, distributive, hypovolemic shock
Non-invasive mechanical ventilation as preferred choice	Orotracheal intubation and invasive mechanical ventilation
Shorter duration of orotracheal intubation and invasive mechanical ventilation	Prolonged duration of invasive mechanical ventilation, tracheostomy is not uncommon
Mild and superficial sedation	Profound sedation, general anesthesia
Shorter ICU stay	Longer ICU stay
Bed rest is required in patients with percutaneous mechanical circulatory devices	Prone positioning to improve oxygenation

ICU: Intensive Care Unit

Table 2. Delirium predisposing factors.

	1. Patient's factors	**2. Acute illness**	**3. Environmental factors**
Non-modifiable	- Dementia/cognitive decline - Functional decline - Frailty - Comorbidity - Advanced age - Withdrawal from alcohol, tobacco, sedatives - Nutritional deficit - Previous delirium	- Illness severity (shock, hemodynamic instability, invasive procedures, surgery) - Infections, sepsis, systemic inflammatory response syndrome - Cardiac arrest - Respiratory failure - Renal failure - Cardiovascular disease - Mechanical circulatory support, mechanical ventilation, inotropes	- ICU admission
Modifiable	- Sensorineural deficit	- Uncontrolled pain - Metabolic disturbances - Dehydration, nutrition deficit - Hypertermia/hypothermia - Constipation, prolonged fasting	- Artificial light exposure - Sleep deprivation - Physical restraints - Invasive monitoring, central venous and urine catheters - Benzodiazepines, sedatives

Table 3. Delirium common differential diagnoses.

	Delirium	**Dementia**	**Psychotic state**	**Depression/mood disorders**
Onset	Acute (hours)	Insidious, progressive	Subacute	Subacute
Duration	Short (days/weeks)	Stable, prolonged	Variable	Variable
Daily variability	Fluctuating course	Stable	Stable	Stable
Level of arousal/consciousness	Altered	Normal	Normal	Normal
Attention	Severe deficit	Usually intact	Difficulty concentrating	Variable
Orientation	Abnormal	Abnormal	Normal	Normal
Memory	Impaired	Impaired	Normal	Normal
Hallucinations	Common (visual)	Rare	Common (auditory)	Common