

Management of delirium in the intensive care unit

Intensive care psychosis, intensive care unit syndrome, acute confusional state and acute brain dysfunction are all delirium, a manifestation of acute brain failure associated with serious adverse outcomes. Most intensive care delirium is hypoactive and undetected. Screening for and managing delirium could significantly improve outcomes.

Delirium is a manifestation of organ failure characterized by fluctuating mental status, inattention with disorganized thinking and altered level of consciousness (American Psychiatric Association, 2000). Delirium is a medical emergency because it is triggered by an adverse event and is associated with poor patient outcomes. The cost of not recognizing and managing intensive care delirium is high. Each additional day spent in delirium is associated with an average of 10 extra days in hospital and a 10% increased risk of death (Ely et al, 2004). After adjusting for confounding factors such as pre-existing co-morbidity and cognitive impairment, intensive care unit diagnosis and severity of illness, delirious patients are 2–3 times more likely to die (Ely et al, 2004). Most importantly delirium is associated with long-term cognitive impairment equivalent to dementia and with triggering Alzheimer's disease (Jackson et al, 2004; Fong et al, 2009).

Worldwide the incidence ranges from 11% to over 80% depending on the case mix of patients studied and the screening tool used. In the UK among ventilated critically ill patients the incidence is 55–69% (Page et al, 2009). The incidence increases with the severity of sickness.

Motoric types of delirium

Three clinical subtypes have been described based on arousal and psychomotor behaviour:

- Hyperactive (hyperaroused or agitated)
- Hypoactive (hypoalert or lethargic)
- Mixed (alternating periods of agitation and lethargy).

In the intensive care unit hypoactive delirium (43.5%) or mixed (54.1%) are the most common presentations. On intensive care and high dependency units, the pure hyperactive variant accounts for the least number of delirious patients, less than 2% (Peterson et al, 2006). The hypoactive type is more frequent in the elderly and associated with worse outcomes.

Because most intensive care delirium is hypoactive, and patients are often sedated and intubated, delirium is

missed by clinicians even when they are looking for it. One intensive care unit study showed that nurses detected daily delirium in only 34.8% of cases with doctors detecting delirium in only 28% (Spronk et al, 2009).

Monitoring the brain

The first step in managing delirium is recognizing it. Intensive care delirium screening tools are quick, easy and simple; no equipment is needed and there is no risk to the patient. Monitoring the patient's brain involves assessing arousal and awareness, which is done by a sedation score followed by delirium assessment. The majority of UK intensive care units already use sedation scores as an assessment of wakefulness to titrate sedative drugs.

There are two validated delirium-screening tools that are useful in sedated, intubated patients. The confusion assessment method – ICU (CAM-ICU) (Ely et al, 2001) is a shortened non-verbal version of the confusion assessment method taking less than 2 minutes to perform. The confusion assessment method itself is an easy-to-administer instrument that has gained the approval of the British Geriatrics Society. The intensive care delirium screening checklist (Bergeron et al, 2001) is a checklist of symptoms monitored over time. They were both developed and validated as clinical tools to be used at the bedside for the routine screening for delirium. Currently individual units decide which test to use based on local preferences. Resources for intensive care delirium screening can be found at www.icudelirium.co.uk.

The confusion assessment method-ICU

The CAM-ICU (*Figure 1*) can be performed on any patient whether ventilated or on sedation who will open his/her eyes and keep them open to a verbal stimulus. Assess for altered or fluctuating mental status then for inattention by using a 10-letter sequence where the patient is required to correctly squeeze the clinician's hand only when the letter A is stated. Look for disorganized thinking by the patient's ability to answer four simple yes/no questions and a command. Patients are defined as delirious if altered mental status and inattention are present with disorganized thinking and/or reduced level of consciousness. Patients either screen positive or negative and it is a point in time assessment. Because delirium is a fluctuating syndrome it is possible for a patient to

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screen negative at one point and then positive an hour later. Otherwise one assessment per shift is suggested.

The original validation studies against the gold standard *Diagnostic and Statistical Manual of Mental Disorders* diagnostic criteria demonstrated sensitivity of 93% and specificity over 98%, with high inter-rater reliability using this tool (Ely et al, 2001).

The Intensive Care Delirium Screening Checklist

The Intensive Care Delirium Screening Checklist (Figure 2) is a checklist of information gathered over a shift, generally observations that would be collected routinely without the need for an additional test. These include: altered level of consciousness, inattention, disorientation, hallucination or delusion, psychomotor agitation or retardation, inappropriate mood or speech, sleep-wake cycle disturbance or symptom fluctuation. If the nurse observes a feature, e.g. a patient reaching out to grab an unseen object presumably hallucinating, that is ticked off as present during the shift. Inattention is assessed subjectively by observing signs such as being easily distracted or having difficulty following commands. The level of consciousness would not score if the patient were on sedation.

Validation studies using the gold standard criteria demonstrated that this test has a reported sensitivity of 99% and a specificity of 64% (Bergeron et al, 2001).

If a patient is unresponsive such as the deeply sedated or comatose patient, he/she cannot be screened for delirium but is classed as 'unable to assess'. These patients have the worst outcomes (Ely et al, 2004).

Identify and manage the cause

The first and most important treatment strategy is to identify and manage the cause (Table 1). A full medical history is taken with note of any predisposing and precipitating factors including cognitive impairment. Bear in mind that often the commonest cause for an intensive care patient developing incident delirium is a new infection or drugs. Following a complete examination, appropriate investigations should be undertaken looking for infective and metabolic causes. Attention to basic intensive care principles such as restoring oxygenation and blood pressure may in themselves be enough to clear delirium in the sick patient. If the precipitant is not at first obvious, continue to systematically normalize derangements while excluding as many risk factors as possible. There is often more than one precipitating factor in the elderly patient (Pisani et al, 2007; Van Rompaey et al, 2008).

Delirium is triggered by an adverse event which may be quite small in the vulnerable patient, e.g. a benzodiazepine given to aid sleep or a urinary tract infection. Find out the cause and treat it. At the first author's hospital delirium has been treated successfully in different patients with non-invasive ventilation, haemofiltration, stopping steroids, giving fluids, giving antibiotics and

surgical debridement of an infected collection. Treat the cause when possible and the delirium will often clear.

Reduce the risks

It is estimated that around 30% of cases of delirium in the general hospital population are preventable (Inouye et al, 1999). Given the non-exhaustive list of predisposing and precipitating factors, it will not be possible to stop intensive care delirium completely. There remains no doubt, however, that preventing delirium is the most effective strategy for reducing its frequency and complications. Because delirium is a multifactorial syndrome, any successful approach usually has several components targeting modifiable risk factors.

Multi-component strategy

One example of a successful approach was a strategy for elderly medical patients using tested delirium prevention interventions (Inouye et al, 1999). Six factors were tar-

Figure 1. Confusion assessment method-ICU to detect delirium. From Ely et al (2001).

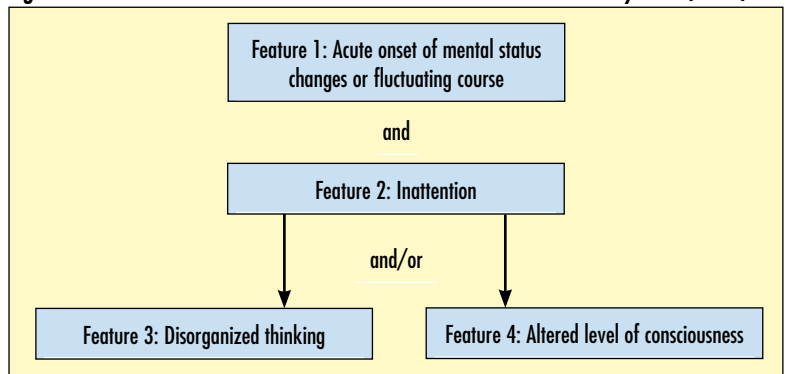


Figure 2. Intensive Care Delirium Screening Checklist. From Bergeron et al (2001).

| Patient evaluation | |
|--|-------|
| Altered level of consciousness* (A–E) If A or B do not complete patient evaluation | |
| Inattention | |
| Disorientation | |
| Hallucination-delusion-psychosis | |
| Psychomotor agitation or retardation | |
| Inappropriate speech or mood | |
| Sleep/wake cycle disturbance | |
| Symptom fluctuation | |
| Total score (0–8) | |
| Level of consciousness* | Score |
| A = No response | 0 |
| B = Response to intense and repeated stimulation (loud voice and pain) | 0 |
| C = Response to mild or moderate stimulation | 1 |
| D = Normal wakefulness | 0 |
| E = Exaggerated response to normal stimulation | 1 |
| Scoring system: Obvious manifestation of an item = 1 point, no manifestation or no assessment possible = 0 point | |

geted for intervention, namely: cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment and dehydration. In the original study delirium developed in 9.9% of patients in the intervention group as opposed to 15% in the usual care group. Total numbers of days in delirium and the number of episodes were both decreased.

Mobilization

Early mobilization is a key part of any intensive care strategy, as immobility is a well-recognized risk factor for delirium. It will require good sedation practices and pain relief. Early active and passive physiotherapy tailored according to the patient’s clinical state decreases duration of delirium and length of stay (Schweickert et al, 2009).

Table 1. Risk factors from intensive care delirium studies: general and cardiac

| | |
|----------------------------|--|
| Pre-morbid | History of dementia |
| | Mini Mental State Evaluation < 27 |
| | Hypertension |
| | Age over 65 years |
| | Depression |
| | Cerebrovascular accident and transient ischaemic attack |
| | Smoking |
| | Alcoholism |
| | Atrial fibrillation |
| Pre-admission | Benzodiazepines pre-admission |
| | Creatinine >180 µmol/litre |
| | Arterial pH <7.35 |
| | Abnormal bilirubin level |
| | Use of epidural (intensive care unit used epidural meperidine) |
| | Lowest intraoperative body temperature (cardiac) |
| In the intensive care unit | Severity of illness |
| | Infection |
| | Hyponatraemia |
| | Sedation-induced coma |
| | Morphine |
| | Benzodiazepines |
| | Corticosteroids |
| | Anticholinergic drugs |
| | H2 blockers |
| | Fentanyl |
| | Lower Glasgow Coma Score (trauma) |
| | Increased blood transfusion (trauma and cardiac) |
| | Lower albumin |
| | Intubation time (cardiac) |

Restraints

Physical and medical restraints are risk factors for developing delirium. Constant electrocardiogram monitoring and indwelling urinary catheters may be unnecessary near to discharge and should be dispensed with as soon as clinically possible.

Sedation and analgesia

Pain relief is essential and has been shown to be important in reducing the incidence of delirium in fracture neck of femur patients (Morrison et al, 2003).

Drugs

All psychoactive drugs have been implicated in the development of delirium. The benzodiazepines are consistently shown to precipitate and maintain delirium in patients (Pandharipande et al, 2006). Different studies have shown use of morphine and fentanyl to be risk factors, but remember pain is also a risk factor. All gamma-aminobutyric acid (GABA) agonist drugs including propofol would be expected to have deliriogenic properties. Clonidine, the α agonist, may be a useful adjunct to sedation in the vulnerable or delirious patient. Dexmedetomidine, a more selective α agonist, is not currently available in the UK.

The manner in which sedation is administered in an intensive care unit is at least as important as which drugs are used. Sedation protocols should incorporate the use of sedation scoring, daily sedation targets and sedation ‘holidays’ (Girard et al, 2008). The actual sedation score used will depend on local practice, it is not the score so much as using it to guide sedation that is important. Use the minimum necessary while maintaining good analgesia.

Sleep

While it is not known whether sleep deprivation in hospitals causes delirium or that delirium results in sleep-wake disturbance it is known that intensive care patients rarely are able to sleep for any period of time (Figuerola-Ramos et al, 2009). Enabling sleep is good practice.

Eyes and ears

Make sure the patient’s ability to communicate is optimized by addressing any visual or hearing impairment.

Pharmacological prevention

Currently there is not enough evidence to support the use of prophylactic antipsychotics in order to prevent delirium (Siddiqui et al, 2007). Studies demonstrating a decrease in delirium have not translated to an improvement in outcomes. This may be related to the study design. In the critical care setting every patient is subject to polypharmacy. Many drugs have anticholinergic properties creating a significant total anticholinergic load. Rationalizing drugs is an important step in reducing intensive care delirium (Naughton et al, 2005).

The need for treatment of alcohol withdrawal with benzodiazepines is rarely disputed. This is grade A evidence

from a meta-analysis and part of national guidelines in the management of these patients (Mayo-Smith et al, 2004).

Pharmacological treatment

The mainstay of delirium drug therapy remains antipsychotics. Haloperidol is the most commonly selected agent. Delirium is caused by a central cholinergic deficiency and relative excess of dopamine. Antipsychotics are thought to work by D2 receptor blockade with associated enhanced acetylcholine release to restore the imbalance of neurotransmitters in the brain.

Haloperidol

Haloperidol is the first-line drug recommended to treat delirium in national and international guidelines alike (Jacobi et al, 2002). The evidence is based on large case series and case reports. In a UK survey of intensive care consultants 74% use haloperidol as a first-line drug (Mac Sweeney et al, 2010). As more delirium is recognized in critically ill patients it is expected that haloperidol will be used in increasing amounts.

Haloperidol is generally considered to be a safe drug to be used in critically ill patients. It has limited respiratory depressant and haemodynamic effects, with variable but usually mild sedation. It is the only antipsychotic that can be given intravenously. Before being given the patient should have an electrocardiogram and his/her potassium and magnesium levels corrected.

The side effects of haloperidol include torsades de pointes (Hassaballa and Balk, 2003). This is a life-threatening multiform ventricular arrhythmia that frequently degenerates into ventricular fibrillation. Haloperidol must not be prescribed in a patient who has a QTc over 500 msec and use with extreme care if the QTc is over 450 msec. It is important to monitor for extrapyramidal side effects which are reversible with short-term use. Neuroleptic malignant syndrome is a rare but serious side effect.

In the UK most intensive care consultants use initial doses of 2.5–5 mg haloperidol intravenously. A number of regimens have been suggested, often involving a doubling of the dose at 30–60-minute intervals until agitation is controlled. Haloperidol can take up to 30 minutes to take effect. Doses of haloperidol are variable and hard to predict. The aim should be to use the minimum dose required for the shortest period of time possible.

Following traumatic brain injury olanzapine may be the drug of choice rather than haloperidol (Warden et al, 2006).

Hypoactive delirium and antipsychotics

When assessing treatment options for hypoactive delirium, before administering pharmacological agents, think about the following points:

- Is the hypoactive delirium hindering progress in weaning from ventilation or mobilizing?
- Is the patient at risk of complications as a result of hypoactive delirium?

- Is the patient fluctuating between hypo- and hyperactive episodes?

Further step-wise treatment protocols may be viewed at www.icudelirium.org.

Atypical antipsychotics

If the evidence for the use of haloperidol is limited there is even less for the use of atypical antipsychotics. That said olanzapine, which can be given intramuscularly, and risperidone are useful second-line drugs (Rea et al, 2007). They are thought to have fewer extrapyramidal side effects than haloperidol.

Research evaluating the association between the use of typical and atypical antipsychotics, adverse events and mortality has produced mixed findings as a result of differences in data source, methodological approach, sample size and geographical variation in treatment practices. Although some have detected a positive association between antipsychotic use and mortality, other studies report that antipsychotics have no effect – or even a protective effect – on mortality (Wang et al, 2005; Raivio et al, 2007).

Other drugs

The association between delirium and a central cholinergic deficit led clinicians to believe that anticholinesterase inhibitors would be useful in the prevention and treatment of delirium. The two that have been tested are donepezil and rivastigmine. However, a Cochrane review in 2008 reported that there is no evidence that acetylcholinesterase inhibitors are effective in the treatment of delirium (Overshott et al, 2008).

Sodium valproate and ondansetron have been reported as having been useful in case reports (Bayindir et al, 2001; Bourgeois et al, 2005).

Benzodiazepines

The use of benzodiazepines has been associated with the development of delirium. A Cochrane review concluded that they are not indicated in the management of hyperactive delirium although in the acute situation they are often considered useful by clinicians (Lonergan et al, 2009). In the intensive care unit small doses of fentanyl, alfentanil or propofol are an alternative in a dangerously agitated patient.

Relatives

The relatives of delirious intensive care patients worry about changes in the patient's mental status (Breitbart et al, 2002). Part of the management of intensive care delirium should include reassuring the relatives regarding delirium, how common it is, that it is usually temporary and that it is being managed.

Post-delirium

Intensive care patients often recollect the delirium experience as extremely distressing (Breitbart et al, 2002). It is very common for them to admit to frightening hallucinations and other perceptual disturbances such as an altered

sense of time either speeding up or slowing down, both in hyperactive and hypoactive delirium. After the patient recovers he/she should be given the opportunity to talk about the experience and informed about the nature of delirium. National Institute for Health and Clinical Excellence (2009) guideline 83 on rehabilitation following critical illness includes consideration of the patient's cognitive function and psychological needs.

Conclusions

Intensive care delirium is more common than most clinicians realize and often goes undetected. The morbidity, mortality and financial costs of intensive care delirium are substantial. All intensive care patients should be screened routinely for delirium so it can be managed. Many risk factors can be targeted and modified using a familiar 'care bundle' approach. The implementation of both routine screening tools and targeted intervention strategies relies on commitment and effective staff education. It is important that intensive care clinicians are informed to enable appropriate delirium management with the expectation of improving patient outcomes. **BJHM**

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American Psychiatric Association (APA) (2000) *Diagnostic and statistical manual of mental disorders*. 4th edn. Text revision. American Psychiatric Association, Washington DC

Bayindir O, Güden M, Akpinar B, Sanisoğlu I, Sağbaş E (2001) Ondansetron hydrochloride for the treatment of delirium after coronary artery surgery. *J Thorac Cardiovasc Surg* **121**(1): 176–7

Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y (2001) Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. *Intensive Care Med* **27**(5): 859–64

Bourgeois JA, Koike AK, Simmons JE, Telles S, Eggleston C (2005) Adjunctive valproic acid for delirium and/or agitation on a consultation-liaison service: a report of six cases. *J Neuropsychiatry Clin Neurosci* **17**(2): 232–8

Breitbart W, Gibson C, Tremblay A (2002) The Delirium Experience: Delirium recall and Delirium-related distress in hospitalized patients with cancer, their spouses/caregivers, and their nurses. *Psychosomatics* **43**(3): 183–94

Ely E, Margolin R, Francis J et al (2001) Evaluation of delirium in critically ill patients: Validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Crit Care Med* **29**(7): 1370–9

Ely EW, Shintani A, Truman B et al (2004) Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA* **291**(14): 1753–62

Figuroa-Ramos ML, Arroyo-Novoa CM, Lee KA, Padilla G, Puntillo KA (2009) Sleep and delirium in ICU patients: a review of mechanisms and manifestations. *Intensive Care Med* **35**(5): 781–95

Fong TG, Jones RN, Shi P et al (2009) Delirium accelerates cognitive decline in Alzheimer disease. *Neurology* **72**(18): 1570–5

Girard T, Kress J, Fuchs B et al (2008) Efficacy and safety of a paired sedation and ventilated patients in intensive care (Awakening and Breathing Controlled trial). *Lancet* **371**(9607): 126–34

Hassaballa H, Balk R (2003) Torsade de Pointes associated with administration of intravenous haloperidol. *Am J Ther* **10**(1): 58–60

Inouye S, Bogardus S, Leo-Summers L, Acampora D, Holford T, Cooney L (1999) A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med* **340**(9): 669–76

Jackson J, Gordon S, Hart R, Hopkins RO, Ely EW (2004) The association between delirium and cognitive decline: a review of the empirical literature. *Neuropsychol Rev* **14**(2): 87–98

Jacobi J, Fraser G, Coursin D et al (2002) Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med* **30**(1): 119–41

Lonergan E, Luxenberg J, Areosa Sastre A, Wyller TB (2009) Benzodiazepines for delirium. *Cochrane Database Syst Rev* **Issue 1**: CD006379

Mac Sweeney R, Barber V, Page V et al (2010) A national survey of the management of delirium in UK intensive care units. *Q J Med* **103**(4): 243–51

Mayo-Smith M, Beecher L, Fischer T et al (2004) Management of alcohol withdrawal delirium. *Arch Intern Med* **164**(18): 1405–12

Morrison RS, Magaziner J, Gilbert M et al (2003) Relationship between pain and opioid analgesics on the development of delirium following hip fracture. *J Gerontol A Biol Sci Med Sci* **58**(1): M76–81

National Institute for Health and Clinical Excellence (2009) *Rehabilitation after critical illness*. National Institute for Health and Clinical Excellence, London (www.nice.org.uk/CG83 accessed 2 June 2010)

Naughton B, Saltzman S, Ramadan F, Chadha N, Priore R, Mylotte J (2005) A multifactorial intervention to reduce prevalence of delirium and shorten hospital length of stay. *J Am Geriatr Soc* **53**(8): 18–23

Overshott R, Karim S, Burns A (2008) Cholinesterase inhibitors for delirium. *Cochrane Database Syst Rev* **Issue 1**: CD005317

Page VJ, Navarange S, Gama S, McAuley DF (2009) Routine delirium monitoring in a UK critical care unit. *Crit Care* **13**: R16

Pandharipande P, Shintani A, Peterson J et al (2006) Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology* **104**(1): 21–6

Peterson J, Pun B, Dittus R, Thomason J, Jackson J, Shintani A, Ely EW (2006) Delirium and its motoric subtypes: a study of 614 critically ill patients. *J Am Geriatr Soc* **54**(3): 479–84

Pisani MA, Murphy TE, Van Ness PH, Araujo KL, Inouye SK (2007) Characteristics associated with delirium in older patients in a Medical Intensive Care Unit. *Arch Intern Med* **167**(15): 1629–34

Raivio M, Laurila JV, Standberg TE, Tilvis RS, Pitkala KH (2007) Neither atypical nor conventional antipsychotics increase mortality or hospital admissions among elderly patients with dementia: a two year prospective study. *Am J Geriatr Psychiatry* **15**(5): 416–24

Rea RS, Battistone S, Fong JJ, Devlin JW (2007) Atypical antipsychotics versus haloperidol for treatment of delirium in acutely ill patients. *Pharmacotherapy* **27**(4): 588–94

Schweickert WD, Pohlman MC, Pohlman AS et al (2009) Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet* **373**(9678): 1874–82

Siddiqui N, Stockdale R, Britton AM, Holmes J (2007) Interventions for preventing delirium in hospitalised patients. *Cochrane Database Syst Rev* **Issue 2**: CD005563

Spronk PE, Riekerk B, Hofhuis J, Rommes JH (2009) Occurrence of delirium is severely underestimated in the ICU during daily care. *Intensive Care Med* **35**(7): 1276–80

Van Rompaey BV, Schuurmans MJ, Shorridge-Baggett, Truijen S, Bossaert L (2008) Risk factors for intensive care delirium: A systematic review. *Intensive Crit Care Nurs* **24** (2): 98–107

Wang P, Schneeweiss S, Avorn J et al (2005) Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *N Engl J Med* **353**(22): 2335–41

Warden DL, Gordon B, McAllister TW et al (2006) Guidelines for the pharmacologic treatment of neurobehavioural sequelae of traumatic brain injury. *J Neurotrauma* **23**(10): 1468–501

KEY POINTS

- Intensive care patients who develop delirium are 2–3 times more likely to die.
- Most delirium goes undiagnosed as it is most commonly the hypoactive variant.
- Intensive care units should routinely monitor for delirium in all patients.
- Prevention should concentrate on patient orientation, communication, mobilization, analgesia, sedation protocols and rationalization of drugs.
- Identify and treat the cause of delirium where possible.
- Haloperidol remains the first-line drug to treat intensive care delirium.