

DELIRIUM IN CRITICAL CARE ANAESTHESIA TUTORIAL OF THE WEEK 232

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QUESTIONS

Please answer the following questions. The answers can be found within the text and at the end of the article.
Which of the following statements are correct?

1. Delirium is a frequent complication of critical illness.
2. The assessment tools available have not been validated for use in patients who are mechanically ventilated.
3. Hypoactive delirium is uncommon.
4. Benzodiazepines should be the first line agents for treatment of agitation and delirium in Intensive Care patients.
5. Prophylactic haloperidol has been shown to prevent the onset of delirium.

INTRODUCTION

Delirium is a common complication of critical illness. It has conventionally been regarded as an unavoidable and benign side effect of long-term sedation on an intensive care unit (ICU). However in recent years this pre-conception has been challenged by the publication of studies demonstrating poorer outcomes in ICU patients with delirium. This article will define delirium, summarise the risk factors for the development of ICU delirium, provide an overview of the current evidence base for its detection and discuss the management of delirium in intensive care patients.

DEFINITION & CLASSIFICATION

The American Psychiatric Association defines delirium as 'a disturbance of consciousness, attention, cognition and perception which develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day'.¹ Delirium can be sub-classified according to aetiology using the DSM IV criteria. This is difficult to apply to the critical care population in whom a multifactorial origin is likely. A more useful clinical classification system was first described in elderly patients by Lipowski in 1983.² Three sub-types of delirium were described.

- Hypoactive delirium – Patients appear subdued, withdrawn and have a poor response to stimulus
- Hyperactive delirium – Patients may display agitation or aggression and may experience delusions or hallucinations
- Mixed delirium – Patients fluctuate between hypo and hyperactive subtypes

Quimet et al first defined sub-syndromal delirium in a patient sub-group who displayed some features of delirium but didn't meet the full diagnostic criteria. This introduced the concept of delirium as a spectrum of disease rather than a single entity.³

RISK FACTORS

Numerous risk factors have been identified for the development of delirium on the ICU.^{4,5,6,7} They are summarised in Table 1.

Table 1: Risk factors for delirium on ICU

Medical history <ul style="list-style-type: none"> • Age over 70 • Hypertension • Congestive cardiac failure • Stroke • Epilepsy • Depression • Dementia • HIV • Renal impairment • Hepatic impairment • Visual or hearing impairment 	Acute presentation <ul style="list-style-type: none"> • Disease severity (APACHE II score) • Metabolic derangement <ul style="list-style-type: none"> ○ Thyroid function ○ Glycaemic control ○ Hyper/hyponatraemia ○ Renal function • Thermoregulation • Sepsis • Hypoxaemia • Anxiety • Uncontrolled pain
Social history <ul style="list-style-type: none"> • Smoker • Alcohol abuse • Malnutrition 	Medications <ul style="list-style-type: none"> • Use of an epidural • Opiates • Benzodiazepines • Propofol • Anti-cholinergics
Environmental <ul style="list-style-type: none"> • Physical restraints • Rectal or urethral catheter • Central venous catheter • Sleep deprivation 	

DIAGNOSIS

Delirium was traditionally diagnosed by a psychiatrist using DSM IV criteria. Whilst psychiatric referral can still be helpful, the development of specific delirium assessment tools for use by the multi-disciplinary team has greatly improved its recognition on intensive care. However delirium is probably still under-diagnosed, particularly in the hypoactive sub-type, where the more subtle features may be overlooked.

The assessment tool most commonly employed in UK clinical practice is the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).⁸ Both CAM-ICU and the Intensive Care Delirium Screening Checklist (ICDSC) have been specifically validated for use on the intensive care unit. Appendices 1 & 2 illustrate how these assessment tools are conducted. Both are easy and quick to perform and have good inter-observer reliability. CAM-ICU, performed once every 24 hours, directly assesses the patient performing tasks to command and can be used during mechanical ventilation. ICDSC, documented every 8 hours, is more subjective as it relies on data collected during routine nursing care without direct assessment of the patient. Patients who are experiencing isolated hallucinations may be assessed as delirium negative by CAM-ICU but delirium positive by ICDSC.

Both CAM-ICU and ICDSC have been shown to have a high sensitivity (97%⁹ & 99%¹⁰ respectively) but CAM-ICU has a much better specificity (99%⁹) than ICDSC (64%¹⁰). Another study, which directly compared the performance of the two scoring systems, suggested a good level of agreement between them.¹¹

INCIDENCE

For many years, the lack of a consistent definition for delirium that could be applied to intensive care patients hampered efforts to determine its incidence in this setting. The development of the two delirium screening tools discussed has

gone some way to address this issue. However reported incidence still varies widely (16.1%-83.3%) depending on the patient demographics, illness severity and screening tool used.^{9,10}

DSM IV

One study in 2001 suggested that the incidence of delirium, when assessed by two independent psycho-geriatricians using DSM-IV criteria, was as high as 81.3% in the 48 study patients.¹² During validation of the ICDSC, a psychiatrist identified delirium in 16.1% of 93 study patients using DSM IV criteria.¹⁰

CAM-ICU

The pilot for the CAM-ICU assessment tool found a high incidence of 83.3% in 111 study patients.⁹ Subsequent studies using CAM-ICU suggest that the incidence varies between 41-74%.^{6,13} This is in comparison to the data from our local mixed surgical and medical ICU in which CAM-ICU screening detected delirium in 31.7% of patients at some point in their admission.¹⁴

Peterson et al noted that the most common delirium subtypes were mixed (54.9%) and hypoactive (43.5%) whilst hyperactive was found to be relatively uncommon (1.6%).¹⁵

ICDSC

Ouimet et al⁷ identified delirium in 31.8% of 764 patients in a mixed specialty intensive care unit using the ICDSC tool. Whatever the true incidence of delirium is, it appears to be much more common than previously thought and the introduction of validated assessment tools has improved the recognition of this important condition.

PATHOPHYSIOLOGY

Currently there is no comprehensive explanation for the mechanism by which delirium occurs in the critically ill. There are however numerous hypotheses and it seems likely that its pathophysiology is multifactorial. An excellent review by Girard et al¹⁶ covers several of the leading suggestions and these are summarised in Figure 1 (adapted from Figueroa-Ramos et al¹⁷):

1. Increased levels of dopamine and reduced levels of acetylcholine are thought to increase neuronal excitability and precipitate delirium. These changes may be caused by changes in the synthesis, release and inactivation of these neurotransmitters. Whether other neurotransmitters (such as GABA, endorphins, glutamate or histamine) are also involved is unknown.
2. Tryptophan is an amino acid which is actively transported across the blood brain barrier via LAT1 proteins. It is a precursor for serotonin and subsequently melatonin production. Low levels of tryptophan, and thus serotonin and melatonin, are hypothesised to cause hyperactive delirium. High levels of tryptophan, serotonin and melatonin may be responsible for hypoactive delirium.¹⁸ It is unclear whether these effects are due to serotonin, melatonin, the neurotoxic metabolites of tryptophan or all of the above.
3. Phenylalanine is another amino acid which is actively transported across the blood brain barrier via the same transport channel as tryptophan. Consequently, high uptake of phenylalanine will compete with tryptophan and reduce levels of serotonin and melatonin. Once across the blood brain barrier, phenylalanine is converted into DOPA and subsequently dopamine, noradrenaline and adrenaline. High levels of phenylalanine have been associated with delirium¹⁹ but it is unclear whether this effect is due to increased levels of noradrenaline and dopamine, reduced serotonin and melatonin or all of the above.
4. The inflammatory response to critical illness causes the release of cytokines into the circulation which results in a pro-thrombotic state. Animal studies suggest that this leads to reduced cerebral blood flow and it is possible that this could trigger delirium.
5. Engel and Romano performed EEG recordings on delirious patients in the 1940s and concluded that the slow EEG appearance they observed was characteristic of a 'derangement in the general functional metabolism of the brain'.²⁰ Other investigators have suggested that this might result in delirium by reducing acetylcholine levels.²¹

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PREVENTION

A recent paper by Morandi et al introduces the concept of an 'ABCDE bundle' which uses an evidence-based approach in the prevention of delirium.²² This is summarised in Figure 2.

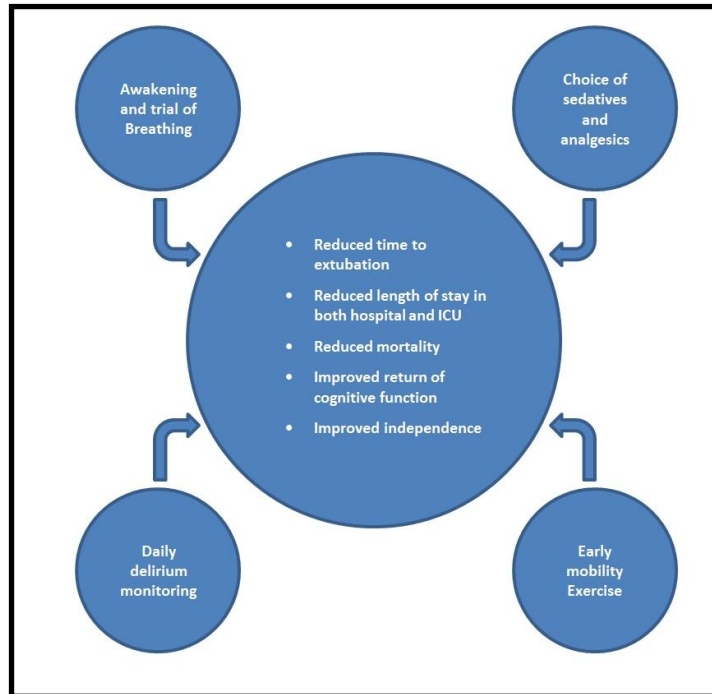


Figure 2: ABCDE bundle²²

Awake and Breathing

The Awakening and Breathing Controlled Trial found that daily sedation breaks paired with trials of spontaneous breathing significantly improved outcome at 1 year.²³ These findings have led to the adoption of this practice in many intensive care units, although in a survey of clinical practice, the majority of practitioners admit that sedation breaks are not performed as frequently as intended.²⁴

Choice of sedation

The mainstay of sedation on ICU has traditionally been propofol, benzodiazepines and opiates, all of which have been implicated in altering sleep patterns.²⁵ Trials involving α_2 receptor agonists (clonidine and shorter-acting dexmedetomidine) have reported a lower incidence of delirium and shorter time to extubation.^{26,27} Remifentanyl is a short-acting pure μ receptor agonist. Its use as a sedative agent in intensive care has been shown to reduce the time to extubation²⁸ but further work is needed to assess its impact on the incidence of delirium. Interestingly, a Danish study randomised 140 mechanically ventilated patients to receive either 'no sedation' or propofol sedation with daily sedation breaks.²⁹ It reported shorter times to extubation and a lower incidence of delirium without an increase in self-extubation in the group randomised to no sedation, but it is unlikely that this practice will become widely adopted.

Daily delirium monitoring

Daily screening for delirium is important as delirium is under-diagnosed without the use of assessment tools.³⁰

Early mobility and exercise

Schweickert et al demonstrated that if physical and occupational therapy was provided at the same time as a sedation break and trial of spontaneous breathing then patients had shorter episodes of delirium and improved function at hospital discharge.³¹

Sleep

It is unclear whether sleep disruption on intensive care is a cause or a consequence of delirium. Studies have shown that the total sleep time is unaffected by sedation but that altered REM patterns are observed, suggesting an impact on the quality of sleep.³² High levels of noise or ambient light, drugs, mechanical ventilation and routine patient care at inappropriate times of the day have all been associated with sleep disruption.³³

TREATMENT: NON-PHARMACOLOGICAL

The first stage in the management of delirium is to recognise its presence by use of an appropriate assessment tool. The next stage is to review the delirium risk factors in Table 1 looking for precipitant causes that may be correctable. Some of the risk factors listed are clearly more amenable to modification than others. The more important modifiable factors include:

General factors

- Correct visual impairment with glasses
- Correct hearing impairment with hearing aids

Medical factors

- Correct metabolic derangement
- Diagnose and treat sources of infection
- Achieve adequate tissue oxygen delivery
- Administer adequate analgesia
- Remove lines and catheters promptly
- Do not use physical restraints routinely but only use acutely to prevent harm

Medications

- Avoid deliriogenic drugs where possible

Environmental factors

- Orientate the patient regularly
- Reduce noise
- Reduce sleep disturbance
- Mobilise where possible

TREATMENT: PHARMACOLOGICAL

There is a lack of randomised control trial evidence for pharmacological treatments for delirium on the intensive care unit. The mainstay of current therapy and that recommended by both the Intensive Care Society and the American College of Critical Care Medicine (level C recommendation) is haloperidol.^{25,34} Surveys of clinical practice in the US³⁵ and the UK⁸ revealed that the majority of clinicians use haloperidol as their first line treatment for delirium. In the UK this remains an off-licence indication for haloperidol administration.

Haloperidol

Haloperidol is a dopamine receptor (D2) antagonist and acts centrally to reduce hallucinations and delusions. It is hepatically metabolised with an elimination half-life of 10-36 hours secondary to active metabolites. Recognised adverse side effects include extra-pyramidal side effects, prolonged QT interval (which can precipitate torsades de point) and neuroleptic malignant syndrome. The optimum dosing schedule has not yet been established by trial evidence but a commonly used schedule is 2.5-5mg intravenously every 6 hours. Doses may need to be reduced in the elderly. It has also been used as a continuous infusion in severe cases but this does not represent routine practice.³⁶

A retrospective study of 989 mechanically ventilated patients identified a significant reduction in hospital mortality in those patients who had received haloperidol during their intensive care stay. However, the study design meant that it was not possible to identify if the indication for commencing the haloperidol was delirium.³⁷

Atypical anti-psychotics

Atypical anti-psychotics (such as olanzapine, quetiapine) are also dopamine receptor (D2) antagonists but have additional antagonistic effects on serotonin receptors (5-HT_{2A}). Enteral administration is required as there are no intravenous preparations available. They are generally metabolised in the liver and have active metabolites. Their half-lives vary according to the preparation with quetiapine having the shortest half-life of 6 hours. The adverse effects that are most likely to be encountered include sedation and anti-cholinergic symptoms.

A randomised but un-blinded trial of enteral olanzapine versus haloperidol in 103 patients demonstrated improvement in daily Delirium Index scores and reduced benzodiazepine administration in both trial groups without a significant difference between them.³⁸

A randomised, double blinded trial of quetiapine against placebo with rescue haloperidol if required found that the quetiapine group had a faster resolution of delirium.³⁹

The recently published MIND study randomly assigned 101 patients to haloperidol, ziprasidone (atypical antipsychotic) or placebo. Doses were adjusted according to the level of delirium as assessed by CAM-ICU. There was no significant difference in the number of days patients survived without delirium or coma in any of the 3 groups in this small pilot study. A further multi-centre placebo trial is planned.⁴⁰

Benzodiazepines

Benzodiazepines have a role in the management of delirium caused by alcohol withdrawal. However, their administration in other patient sub-groups has been identified as an independent risk factor for delirium development. Their use should therefore be avoided where possible in critically ill patients.

An adapted summary of the delirium treatment guidance produced by the UK Clinical Pharmacy Association and the Intensive Care Society is provided in Appendix 3.²⁵

PROGNOSIS

Mortality

A 6-month follow up study by Ely et al determined a statistically significantly higher 6-month mortality in ICU patients with delirium (34% v 15%, adjusted hazard ratio of 3.2).⁴¹ Another study of 102 mechanically ventilated patients determined that ICU mortality was higher for patients with delirium compared to those without (63.6% v 32.5%, hazard ratio of 2.5).⁴² Overall ICU mortality rates were lower in Ouimet et al's study of 537 patients but it was still significantly higher in patients with delirium compared to those without (15.9% v 2.4%).³ Another large international study confirmed the association between delirium and increased mortality in critical care patients.⁶

Morbidity

Patients with delirium are more likely to self extubate and remove invasive medical devices.⁵

Length of stay

A study of 48 patients demonstrated that delirium significantly increased both the hospital and ICU length of stay.¹² A further study of 224 patients found that patients with delirium spent a median of 10 days longer in hospital than those without.⁴¹ These findings are supported by Ouimet et al's study of 538 patients which demonstrated that even sub-syndromal delirium significantly increased length of stay.³

Cost

Milbrandt et al examined the cost of the hospital and ICU stays of 224 medical ICU patients in 2004.⁴³ They reported that patients with delirium had a significantly higher cost of care than those without and that those costs were dependent on the severity of the delirium. The results are displayed in the Figure 3 which has been adapted from the original paper.

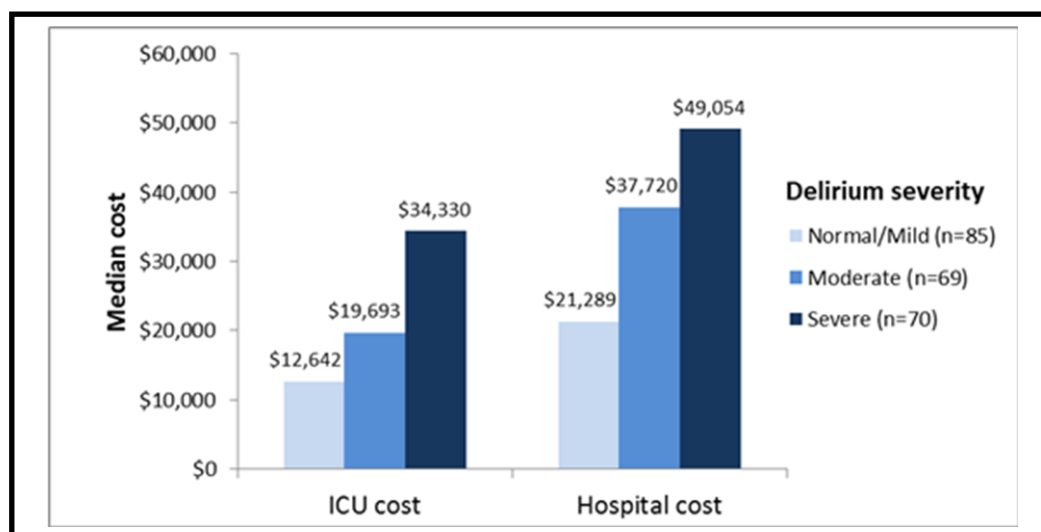


Figure 3: The effect of delirium severity on cost of ICU and hospital

Long-term cognitive impairment

A long term cohort study of 77 ICU patients determined that 79% of survivors had cognitive impairment at 3 months and 71% at 12 months.⁴⁴ A third remained severely impaired a year following ICU discharge. Delirium was identified as an independent predictor of cognitive impairment in this study. Duration of delirium also seems to be important. Patients who experienced delirium for 5 days scored almost 7 points fewer on cognitive testing 1 year following discharge than those who experienced 1 day of delirium.

SUMMARY

Despite the surge of research activity into delirium over the past decade, the condition remains an important problem on intensive care. Standardised assessment tools validated for use in the ICU setting have been developed and have demonstrated a higher incidence of delirium than previously thought. Current treatments have a limited evidence base, particularly with respect to improving patient outcome. Whilst haloperidol currently remains the mainstay of pharmacological management, there is increasing interest in prevention of delirium by modification of its risk factors. Recent evidence suggests that delirium results in longer hospital stays, higher associated treatment costs and increased morbidity and mortality. Further work is needed to determine whether these outcomes can be improved by either prevention or treatment of delirium.

ANSWERS TO QUESTIONS

1. True.

Delirium is a common complication of critical illness although the exact incidence remains unknown. Some studies have reported incidences of over 80% whilst a review carried out in our mixed ICU detected delirium in over 30% of the patients at some stage of their admission.

2. False.

The CAM-ICU assessment method has been validated for use in mechanically ventilated patients.

3. False.

Hypoactive delirium is the second most common form of ICU delirium after mixed hyper- and hypoactive delirium. Pure hyperactive delirium is uncommon.

4. False.

Benzodiazepines should be avoided in this setting if possible. They have a documented role in the treatment of delirium caused by alcohol or benzodiazepine withdrawal but administration to other patient sub-groups is an independent risk factor for delirium development.

5. False.

Haloperidol is the first line agent for the treatment of delirium but there is no evidence to support a role for its prophylactic use.

Appendix 1: Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)

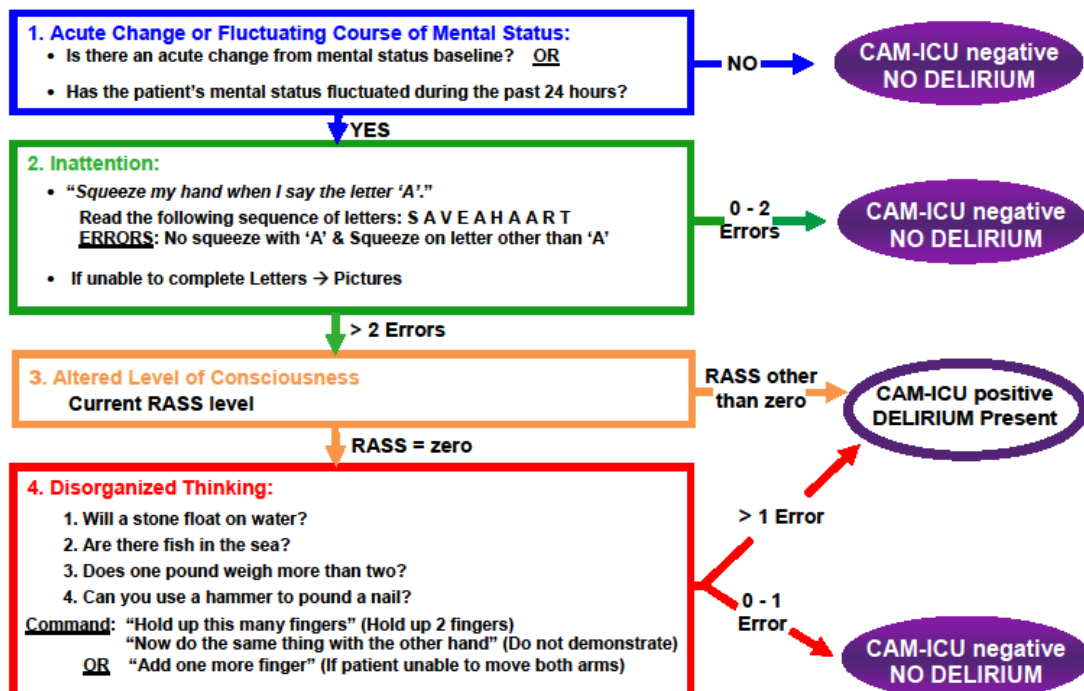
Step 1 Level of Consciousness: RASS

Scale	Label	Description	
+4	COMBATIVE	Combative, violent, immediate danger to staff	VOICE
+3	VERY AGITATED	Pulls to remove tubes or catheters; aggressive	
+2	AGITATED	Frequent non-purposeful movement, fights ventilator	
+1	RESTLESS	Anxious, apprehensive, movements not aggressive	
0	ALERT & CALM	Spontaneously pays attention to caregiver	
-1	DROWSY	Not fully alert, but has sustained awakening to voice (eye opening & contact >10 sec)	
-2	LIGHT SEDATION	Briefly awakens to voice (eyes open & contact <10 sec)	TOUCH
-3	MODERATE SEDATION	Movement or eye opening to voice (no eye contact)	
If RASS is ≥ -3 proceed to CAM-ICU (Is patient CAM-ICU positive or negative?)			
-4	DEEP SEDATION	No response to voice, but movement or eye opening to physical stimulation	TOUCH
-5	UNAROUSEABLE	No response to voice or physical stimulation	
If RASS is -4 or -5 → STOP (patient unconscious). RECHECK later			

Sessler, et al. AJRCCM 2002;166 :1338-1344.²
Ely, et al. JAMA 2003; 289:2983-2991.³

Step 2 Content of Consciousness: CAM-ICU

Confusion Assessment Method for the ICU (CAM-ICU) Flowsheet



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Appendix 2: Intensive Care Delirium Screening Checklist¹⁰

Patient evaluation	Day 1	Day 2	Day 3	Day 4	Day 5
Altered level of consciousness* (A-E)					
If A or B do not complete patient evaluation for the period					
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*	Response	Score
A	No response	None
B	Response to intense and repeated stimulation (loud voice and pain)	None
C	Response to mild or moderate stimulation	1
D	Normal wakefulness	0
E	Exaggerated response to normal stimulation	1

SCORING SYSTEM:

The scale is completed based on information collected from each entire 8-hour shift or from the previous 24 hours. Obvious manifestation of an item = 1 point. No manifestation of an item or no assessment possible = 0 point. The score of each item is entered in the corresponding empty box and is 0 or 1.

1. Altered level of consciousness:

A No response

B The need for vigorous stimulation in order to obtain any response signified a severe alteration in the level of consciousness precluding evaluation.

If there is coma (A) or stupor (B) most of the time period then a dash (-) is entered and there is no further evaluation during that period.

C Drowsiness or requirement of a mild to moderate stimulation for a response implies an altered level of consciousness and scores 1 point.

D Wakefulness or sleeping state that could easily be aroused is considered normal and scores no point.

E Hypervigilance is rated as an abnormal level of consciousness and scores 1 point.

2. Inattention: Difficulty in following a conversation or instructions. Easily distracted by external stimuli. Difficulty in shifting focuses. Any of these scores 1 point.

3. Disorientation: Any obvious mistake in time, place or person scores 1 point.

4. Hallucination, delusion or psychosis: The unequivocal clinical manifestation of hallucination or of behaviour probably due to hallucination (e.g. trying to catch a non-existent object) or delusion. Gross impairment in reality testing. Any of these scores 1 point.

5. Psychomotor agitation or retardation: Hyperactivity requiring the use of additional sedative drugs or restraints in order to control potentially dangerousness (e.g. pulling out IV lines, hitting staff). Hypoactivity or clinically noticeable psychomotor slowing. Any of these scores 1 point.

6. Inappropriate, disorganised or incoherent speech: Inappropriate display of emotion related to events or situation. Any of these scores 1 point.

7. Sleep/wake cycle disturbance: Sleeping less than 4 hours or waking frequently at night (do not consider wakefulness initiated by medical staff or loud environment). Sleeping during most of the day. Any of these scores 1 point.

8. Symptom fluctuation: Fluctuation of the manifestation of any item or symptom over 24 hours (e.g. from one shift to another) scores 1 point.

Appendix 3: UKPCA and ICS delirium treatment guidelines²⁵

ALL PATIENTS	Use a delirium screening tool	DELIRIOUS PATIENTS	General delirium	Withdrawal delirium
	<ul style="list-style-type: none"> Use a delirium screening tool in all patients throughout their critical care stay in addition to other routine monitoring (such as sedation score, pain score, etc). Maintain a high index of suspicion for delirium. Rule out differential diagnoses. Treat contributing factors. 		<p>Mild Symptoms</p> <p><i>1st Line</i> Haloperidol 2-5mg enterally three to four times daily, titrating to symptoms.</p> <p><i>2nd Line</i> Olanzapine 5mg enterally daily in patients unable to tolerate haloperidol (e.g. Parkinson's Disease).</p> <p>Moderate-Severe Symptoms</p> <p><i>1st Line</i> Haloperidol 0.5mg-10mg intravenously (dose depending on clinical parameters). Double the dose if the patient remains unmanageable after 20-30 minutes with no adverse effects, repeating as necessary. Convert to a regular dosing schedule when control is established.</p> <p><i>2nd Line</i> Continuous infusions of Haloperidol 5-10mg/hour may be required in extreme circumstances.</p> <p><i>3rd Line</i> Olanzapine 2.5-10mg intramuscular injection, repeated after 2 hours if necessary in patients unable to tolerate haloperidol (e.g. Parkinson's Disease).</p>	<p>Benzodiazepines Start a benzodiazepine and titrate to the minimum effective dose given by an appropriate route of administration. Taper the dose over days to weeks. Long acting benzodiazepines such as lorazepam can be utilised to facilitate tapering regimes.</p> <p>Opioids Start an opioid and titrate to the minimum effective dose given by an appropriate route of administration. Taper the dose over days to weeks. Long acting opioids such as methadone can be utilised to facilitate tapering regimes. Clonidine has also been used, although side effects may limit usefulness.</p> <p>Antidepressants Restart usual medication as soon as possible. Where this is not possible, consider using the intravenous, buccal or rectal routes if available. Treat symptomatically if no alternative route available.</p> <p>Ethanol Use a benzodiazepine first line titrating to the minimum effective dose. Taper the dose over several days. Clonidine cannot be recommended, as there is no evidence to support its use in alcohol withdrawal delirium.</p> <p>Nicotine Weak evidence exists for the use of nicotine replacement therapy given as a patch where the patient has a history of heavy tobacco use. Enteral clonidine has some evidence base for treating nicotine withdrawal. Clonidine and nicotine replacement may be used together if the withdrawal reaction is particularly intense.</p> <p>Other Illicit Drugs Consensus suggests weaning with benzodiazepines with an adjunctive clonidine infusion where necessary. Where the drug of abuse is known, specific advice may be found in the main text.</p>
	Prevention is better than cure		Adjunct therapies	
	<p>Provide the following in all patients: -</p> <p>Non-pharmacologic interventions</p> <ul style="list-style-type: none"> Psychological support and orientation Unambiguous environment Maintain competence. Remove potential organic drivers <p>Pharmacologic interventions</p> <ul style="list-style-type: none"> Avoid drugs with antimuscarinic activity wherever possible. Avoid drugs that affect sleep patterns wherever possible. Alleviate predisposing factors for delirium. 		<p>Dangerous Motor Activity Midazolam 5-10mg intravenously every 2-3 minutes until the patient is calm (or 5mg intramuscularly every 15 minutes if the intravenous route is not available). Titrate the dose as required.</p> <p>Hypoactive Delirium Consider 10-30mg methylphenidate daily in divided doses in addition to normal therapy if not responding. Titrate to maximum 50mg daily in divided doses if required.</p> <p>Night Sedation 50mg trazadone enterally at night for seven days or 2-5mg haloperidol intravenously at night</p>	

WEB LINKS

www.icudelirium.org
www.icudelirium.co.uk

FURTHER READING

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