Southern African Journal of Anaesthesia and Analgesia 2017; 23(3):57–63
http://dx.doi.org/10.1080/22201181.2017.1332809

South Afr J Anaesth Analg
ISSN 2220-1181 EISSN 2220-1173

RESEARCH

Assessment of delirium in the intensive care unit

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Delirium poses a significant burden on our healthcare, with patients in the intensive care unit (ICU) at an increased risk for developing this disorder. In addition, the ICU environment poses unique challenges in the assessment of delirium. It is paramount that the healthcare provider has an understanding of delirium in ICU, and monitors for it vigilantly. There have been various scoring systems developed to assist in this regard. However, the most commonly used and validated tools for the assessment of delirium are the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC). Biomarkers of delirium are emerging as tools to diagnose delirium, stratify severity, monitor progress, and predict outcomes, potentially changing the way we approach delirium in the future.

Keywords: biomarkers, checklist, critical care, delirium, intensive care units, medical staff, patient care, South Africa

Introduction

Delirium is a prevalent problem in the intensive care unit (ICU),[1–4] with an associated significant morbidity and mortality.[5–8] In the South African context, data are scarce but it appears that the face of delirium differs from our First World counterparts.[9,10] Thus vigilant screening and accurate diagnosis of delirium is paramount for good medical care. This article will take a brief look at delirium itself, and then discuss the methods and issues for the assessment of delirium in ICU.

Understanding delirium

Delirium is defined by the Diagnostic and Statistical Manual 5th edition (DSM-5) as a fluctuating change in attention, awareness and cognition that develops over hours to days.[4] The affected individuals exhibit labile emotions and disordered behaviour including absent cooperation with medical staff, removing catheters or lines, and attempts to escape medical care. Their symptoms often worsen at night due to limited external stimuli, and delirious patients exhibit sleep–wake cycle disturbances. Importantly, the condition cannot be explained by an underlying neurocognitive disorder, and delirium cannot be diagnosed in a comatose state as the diagnosis does require a response from a verbal cue.[1,4,11] The DSM-5 diagnostic criteria are summarised in Table 1.

The incidence of delirium in the intensive care setting varies from 7% to 87%. This marked discrepancy exists as there are differences in studies done with regard to population characteristics, type of ICU used (medical, surgical, both), study methodology, assessment tool used for diagnosis of delirium, staff training, medications used and individual ICU practices.[1–3] There are few data on the prevalence or incidence of delirium in South Africa, but the studies done have shown a wide variation.[9,10,12] In a systemic review of studies done in sub-Saharan Africa, delirium was found most commonly in the 17–65 years age range, which contrasts with the usual predominance in the elderly.[9] There was a high association of delirium with infections, particularly the human immunodeficiency virus (HIV). This was further reinforced by a psychiatry study done in a Johannesburg hospital where most of the medical referrals were due to delirium, with HIV being the most common underlying factor.[10] The differing characteristics have led authors to postulate that the spectrum of delirium will differ in sub-Saharan Africa as compared with developed countries.[9,10]

Pathophysiology and risk factors

The pathophysiology of delirium is poorly understood, but is likely to be multi-factorial as several risk factors are usually present in one patient, and there is considerable overlap in the various mechanisms of action.[13,14] The pathogenesis may differ from case to case with different causes being present.[1] Some theories on delirium pathophysiology are presented in Table 2.

Delirium is a significant problem in ICU due to the increased number of risk factors present in these patients compared with non-ICU patients.[1,14] By identifying these features, one may be alerted to the possibility of a patient developing delirium. It is, however, possible to develop delirium despite no predisposing traits.[22] Predisposing elements may be thought of as those relating to the patient's medical condition, those relating to the surgery if done, and those relating to the ICU stay. This is outlined in Table 3.

Assessing delirium

Morbidity and mortality with delirium is significant with elevated in-hospital mortality, higher incidence of self-extubation and removal of catheters, greater need for re-intubation, worsened functional and cognitive decline, and increased costs.[4–8] However, timely diagnosis and management may curtail the duration and associated morbidity and mortality of delirium.[4,11]

One must note that the diagnosis of delirium in ICU might go unrecognised due to: inadequate bedside assessment; poor knowledge of delirium by medical staff; symptoms attributed to other disorders such as dementia; few direct monitors of the central nervous system; assessment of delirium impaired by lack of verbal contact due to need for ventilation, sedatives or opiates; presence of the hypoactive form of delirium.[4,11,13,14,18,23,7] Brummel

Table 1: Summary of DSM-5 criteria[4]

Diagnostic criteria:
(a) Disturbance in attention (in terms of ability to direct, focus, sustain, or shift attention) and reduced awareness or orientation
(b) Occurs over a short time period (hours to days), fluctuates during the day, and is an alteration from the patient's pre-existing functioning
(c) Disturbance in cognition (memory, orientation, language, visual-spatial ability, or perception)
(d) The above is found to be the direct result of a medical condition, substance intoxication or withdrawal, toxin, or a combination of factors
Specified subtypes:
(1) Acute – delirium present for a few hours to days
(2) Persistent – delirium present for weeks to months
(3) Hyperactive – increased level of psychomotor activity evident by labile mood, agitation, or refusal to cooperate
(4) Hypoactive – decreased level of psychomotor activity evident by sluggishness or lethargy
(5) Mixed level of activity – normal level of psychomotor activity but with disturbances in attention and awareness, which may fluctuate

Table 2: Pathophysiology of delirium[1,2,5,13–21]

Theory		Supporting data
Cerebral inflammation		• May be a response to infection, a risk factor for delirium • Inflammatory mediators are able to cross the blood–brain barrier, increase endothelial permeability, reduce cerebral blood flow by inducing micro-aggregates or vasoconstriction, and interfere with neurotransmitters • Inflammatory state will induce production of interleukins, which are implicated in delirium
Imbalance of neurotransmitters		
	Acetylcholine deficiency	• Acetylcholine is involved in awareness and attention • Anticholinergic drugs may be a risk factor for delirium and cholinesterase inhibitors may reduce the duration of delirium
	Serotonin excess	• Serotonin is associated with learning and memory • Selective serotonin reuptake inhibitors are associated with delirium
	GABA increase	• Inflammation up-regulates $GABA_A$ receptors, promoting neural inhibition • Benzodiazepines promote delirium
	Dopamine excess	• Increased uptake of substrate amino acids (tryptophan, phenylalanine, tyrosine) could lead to increased production of dopamine and noradrenaline • Hypoxia and opioids, which are risk factors for delirium, increase dopamine
Cerebral hypoperfusion		• Neuroimaging has found reduced cerebral blood flow in delirious patients • Microcirculation abnormalities have been documented in delirium
Cerebral hypoxaemia		• Reduced oxidative metabolism with cerebral slowing shown on EEG • Microglial activation due to ischaemic hypoxia leads to a pro-inflammatory response, aggravating the cerebral inflammatory response and delirium
Genetic		• Alterations in apolipoprotein E

Table 3: Risk factors for delirium in ICU[1–3,5,13–16,18,23–26]

Patient-related	Surgery-related	ICU-related
• Age greater than 70 years • Co-morbidities (visual, hearing, depression, dementia, epilepsy, cerebrovascular disease, congestive heart failure, respiratory/renal/liver dysfunction, infections such as HIV) • Alcohol and psychoactive drug abuse • Malnutrition and dehydration • Greater severity of illness as indicated by an illness severity scoring system (such as APACHE) • Sepsis	• Emergency surgery • Surgery type: hip fracture, vascular (AAA, peripheral vascular), cardiac (CABG, valvular), major abdominal, major ENT, urological, thoracic • Longer duration of surgery • Intraoperative blood loss, blood transfusions, haematocrit drop to less than 30% • Fluctuations in partial pressure of oxygen • Intraoperative hypothermia	• Disruption of sleep cycle • Metabolic or electrolyte abnormalities (acidosis, glucose, sodium) • Physical restraints and immobilisation • Catheters (NGT, bladder, rectal, CVC) • Medications (anticholinergics, sedatives, analgesics) • Pain • Hypotension • Hypoxia • Infection • Prolonged ventilation

Key: HIV = human immunodeficiency virus; APACHE = Acute Physiology and Chronic Health Evaluation; AAA = abdominal aortic aneurysm; CABG = coronary artery bypass grafting; ENT = ear, nose and throat; NGT = nasogastric tube; CVC = central venous catheter.

et al. argue that due to this important association of delirium with increased morbidity and mortality, delirium monitoring should be as routine as measuring the patient's blood pressure or heart rate.[28]

Scoring systems

The gold standard assessment of delirium is by a geriatrician, neurologist or psychiatrist.[29] However, in the ICU setting such evaluations need to be done at the bedside by the attending healthcare staff. Several studies have shown that both intensivists and ICU nurses perform poorly when using clinical judgement alone, resulting in many missed cases of delirium.[28,30,31] Thus delirium assessments are usually aided by a scoring system, modified for the ICU environment due to the unique challenges in this setting as elucidated above. Assessments done in ICU need to be non-verbal, easy to use, short, and able to be done without psychiatric training.[2]

In order to assess delirium, the patient must have an adequate level of arousal or responsiveness.[28] Thus level of consciousness must be measured using scales such as Richmond Agitation–Sedation Scale or Riker Sedation–Agitation Scale.[28,32]

The Richmond Agitation and Sedation Scale (RASS) has a 10-point scale with four levels denoting agitation (+1 to +4), one level denoting a calm and alert state (0), and five to assess sedation (–1 to –5).[33] For the assessment of delirium to be possible, the patient must at least be rousable to voice, usually by stating the patient's name, without the need for physical stimulation (RASS of at least –3).[34]

The Sedation–Agitation Scale (SAS) developed by Riker uses seven categories for differing severity of sedation or agitation. The categories used are: dangerous agitation, very agitated, agitated, calm and cooperative, sedated, very sedated, and unable to rouse. Although less commonly used, this scale has been validated for use in ICU.[35,36] For assessment of delirium, the SAS should be 3 or more.[28]

Several scoring systems have been developed for delirium assessment and tested in ICU. These include, but are not limited to, the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), the Intensive Care Delirium Screening Checklist (ICDSC), the Neelon and Champagne (NEECHAM) Confusion Scale, the Nursing Delirium Screening Scale (Nu-DESC), the Cognitive Test for Delirium (CTD), and the Delirium Detection Score (DDS).[28,37–39]

The CAM-ICU and ICDSC are most widely used, as well as being validated for use in intubated (and therefore non-verbal) patients.[28,32] Both scores have high sensitivity, specificity, and inter-rater reliability, and are recommended by the 2013 Society of Critical Care Medicine 'Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit'.[32] Thus there will be only a brief explanation of the other scoring systems already mentioned in Table 4.

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

The CAM-ICU scoring system has been developed from the standard Confusion Assessment Method (CAM) scoring system, which was developed and validated in general medical wards and based on DSM-IIIR criteria.[28,40–42] CAM-ICU utilises four features of delirium for diagnosis, namely: an acute alteration or fluctuation in mental status, inattention, altered level of consciousness, and disorganised thinking (See Figure 1).[40,41,43]

An acute change or fluctuation in mental status is assessed from baseline or any change within the past 24 h. This criterion has a simple yes or no answer. Inattention is assessed by asking the patient to squeeze the investigator's hand when the letter 'A' is read in a 10-letter sequence, allowing for a maximum of two errors. Any discrepancies can be confirmed with a visual test. Altered level of consciousness is assessed by using that patient's current RASS or SAS score. Lastly, disorganised thinking is assessed by the patient's ability to answer four 'yes/no'-type questions as well as obey a command.[28,43] If the first two steps already indicate the absence of delirium, the scoring system does not have to be done to completion, thus shortening the time required.[28]

Delirium is diagnosed when altered mental state and inattention are present, as well as disorganised thinking or altered level of consciousness.[40] CAM-ICU may be conducted by any trained health professional and each assessment takes less than 5 min to complete.[28,34,37,41] CAM-ICU has a sensitivity of 93% and specificity of 89%, as well as high inter-rater reliability demonstrated by data from several studies.[41,44] Reliability and validity has been assessed extensively against the DSM criteria for delirium.[28] The CAM-ICU scoring system has been found to be easy to understand and use.[38]

However, the CAM-ICU tool does not allow for the assessment of the delirium subtype.[43] Also it represents only a point in time. Thus, to avoid missing delirium, clinicians should perform a CAM-ICU assessment several times daily.[28,43,45] Another factor to consider is that patient cooperation is required to use this scoring tool.[28,38]

Intensive Care Delirium Screening Checklist (ICDSC)

The ICDSC is an 8-item checklist based on the DSM IV delirium criteria, evaluated over a period of 8 to 24 h.[43,47] These include: level of consciousness (which may be given a RASS or SAS score), inattention (difficulty following commands, or easily distracted by external stimuli, or difficulty in shifting focus), disorientation (for place, time or person), hallucinations/delusions/psychosis, psychomotor agitation or retardation, inappropriate speech or mood, sleep/wake cycle disturbances, and symptom fluctuation over 24 h. One point is given for each symptom present in the specified time period, with a score greater than 3 signifying delirium (See Figure 2).[28,43,46]

The ICDSC may be conducted by non-specialist staff and each assessment takes approximately 7 to 10 min to complete.[34] Unlike CAM-ICU where the patient's involvement is required, the patient's involvement in the evaluation with the ICDSC is passive.[44] The ICDSC is also easy to incorporate into daily practice, as it utilises data used during daily patient care.[45,47] This scoring system also has the advantage of being able to diagnose subsyndromal delirium, as indicated by a score of 1–3.[43,46,48]

The ICDSC has greater sensitivity than CAM-ICU (99%) but lower specificity (64%).[5] The lower specificity may be due to the fact that the original validation study did not exclude patients in comas or with conditions which may mimic delirium.[43,47] Level of consciousness is considered the point on the checklist most likely to be incorrectly scored by inexperienced observers, and Bergeron *et al.* wrote that this weakens the scale to an extent.[47] The symptom definitions have been found to require further clarification and validation.[28,43,47]

Table 4: Other delirium scoring instruments[28,32,34,37,38,44,50–52]

Scoring system	Abbreviated title	Items utilised	Scoring of delirium	Disadvantages
Neelon and Champagne Confusion Scale	NEECHAM	Information processing: attention, following commands, orientation	Scores range from 0 (minimal responsiveness) to 30 (normal function)	Little validation against DSM criteria for delirium
		Behaviour: appearance, motor, verbal	Delirium diagnosed with score below 20	Not developed for critical care patients
		Physiological parameters: vital signs, oxygen saturation, urinary incontinence		Unable to use in intubated patients
Nursing Delirium Screening Scale	Nu-DESC	Disorientation	Each item rated a score of 0 to 2	Developed for general medical patients, little validation for ICU use
		Inappropriate behaviour	Maximum score of 10	Sedation not accounted for
		Inappropriate communication	Delirium diagnosed with a score of 2 or more	Higher incidence of false-positive results due to diagnosing prodromal symptoms as delirium
		Hallucination		
		Psychomotor retardation		
Cognitive Test for Delirium	CTD	Orientation	Each item scored from 0 to 6	Designed for research assistants
		Attention	Maximum score of 30	Takes 10–15 min to complete
		Memory	Delirium diagnosed with a score below 19	Assesses cognitive symptoms of delirium only
		Comprehension		
		Vigilance		
Delirium Detection Score	DDS	Agitation	Varying points assigned to each item	Low validation against DSM criteria for delirium
		Anxiety	Maximum score of 56	Symptoms monitored during the course of a shift, increasing the time for scoring
		Hallucinations	Delirium diagnosed with a score greater than 7	High false-negative rate
		Orientation		
		Seizures		
		Tremor		
		Paroxysmal sweating		
		Altered sleep–wake rhythm		

CAM-ICU has been demonstrated by Van Eijk *et al.* to have better diagnostic accuracy than ICDSC,[46] whereas another study by Plaschke shows high agreement between the two.[45] Sensitivity of CAM-ICU has been shown to be lower with bedside nurses compared with research nurses, highlighting the importance of training when scoring systems are implemented in clinical practice.[28,43,49] It has been noted that emphasis should be placed on the consistent, regular and reliable use of either CAM-ICU or ICDSC, rather than the differences between them.[43]

Biomarkers

Biomarkers may provide an important step not only in improving our diagnosis of delirium, but also in monitoring progression, assessing severity, predicting long-term outcomes, and better understanding the pathophysiology of delirium.[53,54] The ideal biomarker would be specific for the brain, cheap, easy to measure, resistant to metabolism, unaffected by renal clearance, and have high sensitivity and specificity for diagnosis and outcome.[55] For all biomarkers, the timing of testing may be challenging given the fluctuating course inherent to delirium.[56] Another important consideration is cost. At the time of writing, neither neuron-specific enolase (NSE) nor S100B protein tests are processed by the South Africa National Health Laboratory Service (NHLS). Private costs for both NSE and S100B by Ampath laboratories are ZAR317.50 each (personal correspondence). Costs of running these tests need to be weighed against the cost of interventions avoided as a result of their use. There has been particular interest in looking at inflammatory markers as well as the neuroprotein NSE and S100B protein, and these will be briefly discussed further.

Inflammatory biomarkers

Studies on inflammatory biomarkers have looked at various cytokines and chemokines.[56] A study by Van Boogaard *et al.* divided patients into two groups, namely 'inflamed' (possessing a positive culture in a specimen of any origin, requiring antibiotics, or with more than two criteria of the systemic inflammatory response syndrome) and 'non-inflamed' (absence of the above). Of the inflammatory markers measured, in the inflamed group a raised level of interleukin-8 was associated with delirium. In the non-inflamed group raised interleukin-10 as well as amyloid-β levels were associated with delirium. The latter, amyloid-β, was associated with long-term cognitive failure, highlighting a role in differentiating between the two groups.[53] Ritter *et al.* in a prospective cohort study also managed to demonstrate that biomarkers involved in sepsis independently predicted the presence of delirium.[57]

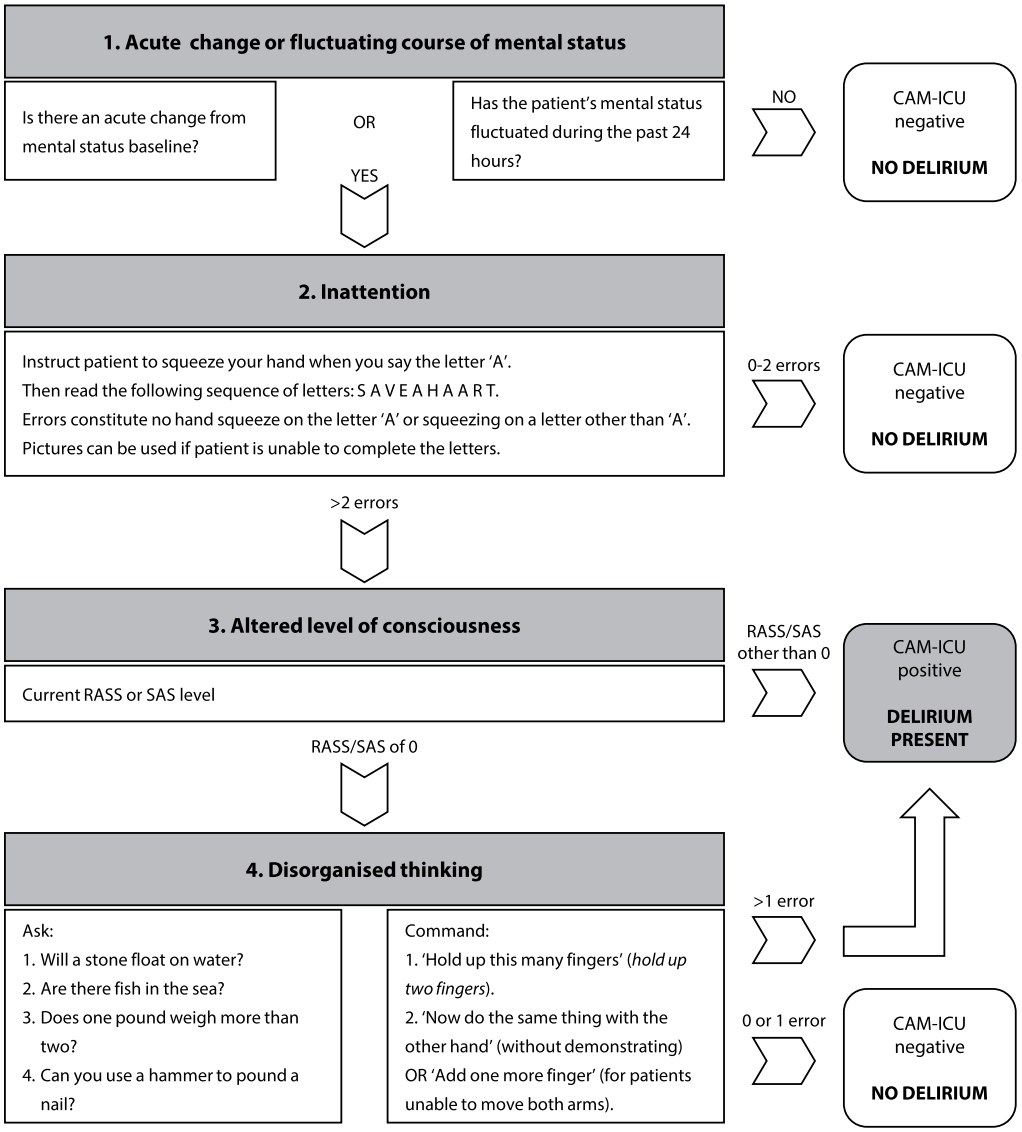

Figure 1: CAM-ICU scoring system.[40]

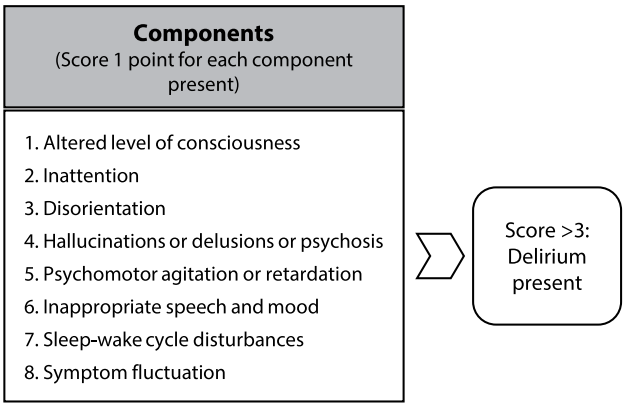

Figure 2: ICDSC scoring system.[47]

However, there have been inconsistencies between studies in terms of which inflammatory markers to use.[53,57,58] One must keep in mind that there may not be a direct effect of cytokines on brain function, but rather that inflammation alters the permeability of the blood–brain barrier and inhibits certain specific drug efflux transporters, exposing the brain to potentially toxic metabolites.[57] Also, inflammatory markers may arise due to complex relationships with neurotransmitters implicated in delirium.[58]

Neuron-specific enolase biomarker

Neuron-specific enolase (NSE) is an intra-cytoplasmic enzyme found predominantly in neurons and neuroendocrine tissue.[56] It catalyses the conversion of 2-phospho-D-glycerate to phosphoenolpyruvate in the glycolytic pathway. Thus levels of NSE will be elevated when cells in the aforementioned tissues rupture. The enzyme, which has molecular weight of 78 kDa, has a half-life of 24 h (in comparison with the shorter half-life of the S100B protein).[56] However, several issues have resulted in conflicting results as to whether NSE may predict poor neurological outcomes, as contamination from non-neural sources of the enzyme, hypothermia, and individual differences caused by genetic polymorphisms may alter findings.[55] Additionally, major injury to the central nervous system such as ischaemic stroke, traumatic brain injury, temporal lobe epilepsy, and neurosurgery may cause the release of NSE independent of delirium.[55,58] Studies specifically pertaining to NSE and delirium have inconsistent results, and it has been suggested that neuronal injury markers such as NSE have more value in

predicting later dementia in a patient who has suffered an episode of delirium.[54]

S100B biomarker

S100 proteins are cytosolic calcium-binding proteins. The subtype of this family of proteins, S100B, is found predominantly in astroglial and Swann cells but does exhibit extra-neural sources.[59] S100B has a half-life of 25 min, but the timing of the peak levels depends on the source of the biomarker.[60] The precise functions of these proteins are unknown, but they are thought to be involved in glial and neuronal proliferation and activation.[55] Astrocytes are activated following brain injury and the subsequent proliferation results in elevations of S100B proteins, which are secreted into the cerebrospinal fluid.[55,61] The majority that are secreted during and immediately after surgery are due to contamination from extra-neural sources.[55] Thus elevations of this protein more than 24 h after surgery are more indicative of a neural cause, and daily serial measurements are recommended.[61] S100B protein elevation has shown promise as a biomarker in a variety of neurological disorders, but has shown an inconclusive correlation with delirium in small studies.[53,62–65]

Conclusion

The awareness and assessment of delirium should be an important feature in ICU care. The use of an ICU scoring system is advocated for this purpose. The CAM-ICU and ICDSC systems are both well validated, but the choice between the two is guided by clinician preference with emphasis on correct and consistent use as part of the daily routine. Regular neural biomarker use is undermined by limited supporting literature and cost constraints. However, as we continue to study ways to diagnose, monitor and essentially understand delirium, so the care of our patients will advance.

Conflict of interest – The authors have no conflict of interest.

References

1. Girard TD, Ely EW. Delirium in the critically ill patient. In: Young GB, Wijdicks EFM, editors. Handbook of Clinical Neurology. 3rd ed. Elsevier; 2008. p. 39–56. doi:10.1016/s0072-9752(07)01703-4
2. Devlin JW, Fong JJ, Fraser GL, et al. Delirium assessment in the critically ill. Intensive Care Med. 2007;33(6):929–40. doi:10.1007/s00134-007-0603-5
3. Vasilevskis EE, Han JH, Hughes CG, et al. Epidemiology and risk factors for delirium across hospital settings. Best Pract Res Clin Anaes. 2012;26(3):277–87. doi:10.1016/j.bpa.2012.07.003.
4. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, fifth edition (dsm-5). Washington, DC: American Psychiatric Publishing; 2013.
5. Shim JJ, Leung JM. An update on delirium in the postoperative setting: Prevention, diagnosis and management. Best Pract Res Clin Anaes. 2012;26(3):327–43. doi:10.1016/j.bpa.2012.08.003.
6. van den Boogaard M, Peters SAE, van der Hoeven JG, et al. The impact of delirium on the prediction of in-hospital mortality in intensive care patients. Crit Care. 2010;14(4):R146. doi:10.1186/cc9214.
7. Salluh JI, Soares M, Teles JM, et al. Delirium epidemiology in critical care (DECCA): an international study. Crit Care. 2010;14(6):R210. doi:10.1186/cc9333.
8. Rudolph JL, Marcantonio ER. Postoperative delirium. Anesth Analg. 2011;112(5):1202–11. doi:10.1213/ane.0b013e3182147f6d.
9. Paddick SM, Kalaria RN, Mukaetova-Ladinska ER. The prevalence and clinical manifestations of delirium in sub-Saharan Africa: A systematic review with inferences. J Neurol Sci. 2015;348:6–17. doi:10.1016/j.jns.2014.10.034.
10. Tema N, Janse van Rensburg A. Psychiatric consultations and the management of associated comorbid medical conditions in a regional referral hospital. S Afr J Psychiat. 2015;21(2):67–72. doi:10.7196/sajp.551.
11. Mistraletti G, Pelosi P, Mantovani ES, et al. Delirium: clinical approach and prevention. Best Pract Res Clin Anaes. 2012;26(3):311–26. doi:10.1016/j.bpa.2012.07.001.
12. Stuart-Clark H, Vorajee N, Zuma S, et al. Twelve-month outcomes of patients admitted to the acute general medical service at Groote Schuur Hospital. S Afr Med J 2012;102(6):549–53. doi:10.7196/samj.5615.
13. Girard TD, Pandharipande PP, Ely EW. Delirium in the intensive care unit. Crit Care. 2008;12(Suppl 3):S3. doi:10.1186/cc6149.
14. van Eijk MMJ, Slooter AJC. Delirium in intensive care unit patients. Semin Cardiothorac Vasc Anesth. 2010;14(2):141–7. doi:10.1177/1089253210371495.
15. Pandharipande P, Jackson J, Ely EW. Delirium: acute cognitive dysfunction in the critically ill. Curr Opin Crit Care. 2005;11:360–8.
16. Calvo-Ayala E, Khan B. Delirium management in critically ill patients. J Symptoms Signs. 2013;2(1):23–32.
17. Gunther ML, Morandi A, Ely EW. Pathophysiology of delirium in the intensive care unit. Crit Care Clin. 2008;24(1):45–65. doi:10.1016/j.ccc.2007.10.002.
18. Field RR, Wall MH. Delirium. Semin Cardiothorac Vasc Anesth. 2013;17(3):170–9. doi:10.1177/1089253213476957.
19. Trabold B, Metterlein T. Postoperative delirium: risk factors, prevention, and treatment. J Cardiothorac Vasc Anesth. 2014;28(5):1352–60. doi:10.1053/j.jvca.2014.03.017.
20. Schiemann A, Hadzidiakos D, Spies C. Managing ICU delirium. Curr Opin Crit Care. 2011;17(2):131–40. doi:10.1097/mcc.0b013e32834400b5.
21. Vijayakumar B, Elango P, Ganessan R. Post-operative delirium in elderly patients. Indian J Anaesth. 2014;58(3):251–6. doi:10.4103/0019-5049.135026.
22. Saporito A, Sturini E. Incidence of postoperative delirium is high even in a population without known risk factors. J Anesth. 2013;28(2):198–201. doi:10.1007/s00540-013-1706-5.
23. Jones SF, Pisani MA. ICU delirium. Curr Opin Crit Care. 2012;18(2):146–51. doi:10.1097/mcc.0b013e32835132b9.
24. Choi JG. Delirium in the intensive care unit. Korean J Anesthesiol. 2013;65(3):195–202. doi:10.4097/kjae.2013.65.3.195.
25. Krzych ŁJ, Wybraniec MT, Krupka-Matuszczyk I, et al. Complex assessment of the incidence and risk factors of delirium in a large cohort of cardiac surgery patients: a single-center 6-year experience. BioMed Res Int. 2013;2013:1–9. doi:10.1155/2013/835850.
26. Zaal IJ, Devlin JW, Peelen LM, et al. A systematic review of risk factors for delirium in the ICU*. Crit Care Med. 2015;43(1):40–7. doi:10.1097/ccm.0000000000000625.
27. Andrejaitiene J, Sirvinskas E. Early post-cardiac surgery delirium risk factors.Perfusion.2011;27(2):105–12. doi:10.1177/0267659111425621.
28. Brummel NE, Vasilevskis EE, Han JH, et al. Implementing delirium screening in the ICU. Crit Care Med 2013;41(9):2196–208. doi:10.1097/ccm.0b013e31829a6f1e.
29. van den Boogaard M, Schoonhoven L, van der Hoeven JG, et al. Incidence and short-term consequences of delirium in critically ill patients: a prospective observational cohort study. Int J Nurs Stud. 2012;49(7):775–83. doi:10.1016/j.ijnurstu.2011.11.016.
30. Mistarz R, Eliott S, Whitfield A, et al. Bedside nurse–patient interactions do not reliably detect delirium: An observational study. Aust Crit Care. 2011;24(2):126–32. doi:10.1016/j.aucc.2011.01.002.
31. Spronk P, Riekerk B, Elias S, et al. The occurrence of delirium is severely underestimated by intensivists and intensive care unit nurses during daily ICU care. Crit Care 2007;11(Suppl 2):P420. doi:10.1186/cc5580.
32. Barr J, Fraser G, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013;41:263–306. doi:10.1097/ccm.0b013e3182783b72.
33. Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients. JAMA. 2003;289(22):2983–91. doi:10.1001/jama.289.22.2983.
34. Grover S, Kate N. Assessment scales for delirium: a review. World J Psychiatry. 2012;2(4):58–70. doi:10.5498/wjp.v2.i4.58.
35. Khan BA, Guzman O, Campbell NL, et al. Comparison and agreement between the richmond agitation-sedation scale and the riker sedation-agitation scale in evaluating patients' eligibility for delirium assessment in the ICU. Chest. 2012;142(1):48–54. https://doi.org/10.1378/chest.11-2100

36. Riker R, Fraser G, Simmons L, et al. Validating the sedation-agitation scale with the bispectral index and visual analog scale in adult ICU patients after cardiac surgery. Intensive Care Med. 2001;27(5):853–8. doi:10.1007/s001340100912.
37. Van Rompaey B, Schuurmans MJ, Shortridge-Baggett LM, et al. A comparison of the CAM-ICU and the NEECHAM Confusion Scale in intensive care delirium assessment: an observational study in non-intubated patients. Crit Care. 2008;12(1):R16. doi:10.1186/cc6790.
38. Luetz A, Heymann A, Radtke FM, et al. Different assessment tools for intensive care unit delirium: which score to use? Crit Care Med. 2010;38(2):409–18. doi:10.1097/ccm.0b013e3181cabb42.
39. Hart RP, Levenson JL, Sessler CN, et al. Validation of a cognitive test for delirium in medical ICU patients. Psychosomatics. 1996;37(6):533–46. doi:10.1016/s0033-3182(96)71517-7.
40. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients. JAMA. 2001;286(21):2703–10. doi:10.1001/jama.286.21.2703.
41. 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(7):1370–9. doi:10.1097/00003246-200107000-00012.
42. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA. 2004;291(14):1753–62. doi:10.1001/jama.291.14.1753.
43. Devlin JW, Brummel NE, Al-Qadheeb NS. Optimising the recognition of delirium in the intensive care unit. Best Pract Res Clin Anaesthesiol. 2012;26(3):385–93. doi:10.1016/j.bpa.2012.08.002.
44. Tomasi CD, Grandi C, Salluh J, et al. Comparison of CAM-ICU and ICDSC for the detection of delirium in critically ill patients focusing on relevant clinical outcomes. J Crit Care. 2012;27(2):212–7. doi:10.1016/j.jcrc.2011.05.015.
45. Plaschke K, von Haken R, Scholz M, et al. Comparison of the confusion assessment method for the intensive care unit (CAM-ICU) with the Intensive Care Delirium Screening Checklist (ICDSC) for delirium in critical care patients gives high agreement rate(s). Intensive Care Med. 2008;34(3):431–6. doi:10.1007/s00134-007-0920-8.
46. van Eijk MM, van Marum RJ, Klijn IA, et al. Comparison of delirium assessment tools in a mixed intensive care unit*. Crit Care Med. 2009;37(6):1881–5. doi:10.1097/ccm.0b013e3181a00118.
47. Bergeron N, Dubois MJ, Dumont M, et al. Intensive care delirium screening checklist: evaluation of a new screening tool. Intensive Care Med. 2001;27(5):859–64. doi:10.1007/s001340100909.
48. Ouimet S, Riker R, Bergeon N, et al. Subsyndromal delirium in the ICU: evidence for a disease spectrum. Intensive Care Med. 2007;33(6):1007–13. doi:10.1007/s00134-007-0618-y.
49. Maarten M, van Eijk MM, van den Boogaard M, et al. Routine use of the confusion assessment method for the intensive care unit: a multicenter study. Am J Respir Crit Care Med. 2011;184(3):340–4. doi:10.1164/rccm.201101-0065oc.
50. Immers HEM, Schuurmans MJ, van de Bijl JJ. Recognition of delirium in ICU patients: a diagnostic study of the NEECHAM confusion scale in ICU patients. BMC Nurs. 2005;4:41. doi:10.1186/1472-6955-4-7.
51. Carvalho J, Almeida A, Gusmao-Flores D. Delirium rating scales in critically ill patients: a systematic literature review. Revista Brasileira de Terapia Intensiva 2013;25(2):148–54. doi:10.5935/0103-507x.20130026.
52. Otter H, Martin J, Bäsell K, et al. Validity and reliability of the DDS for severity of delirium in the ICU. Neurocrit Care. 2005;2(2):150–8. doi:10.1385/ncc:2:2:150.
53. van den Boogaard M, Kox M, Quinn KL, et al. Biomarkers associated with delirium in critically ill patients and their relation with long-term subjective cognitive dysfunction; indications for different pathways governing delirium in inflamed and noninflamed patients. Crit Care 2011;15(6):R297. doi:10.1186/cc10598.
54. Marcantonio ER, Rudolph JL, Culley D, et al. Review article: serum biomarkers for delirium. J Gerontol Series A: Biol Sci Med Sci. 2006;61(12):1281–86. doi:10.1093/gerona/61.12.1281.
55. Cata JP, Abdelmalak B, Farag E. Neurological biomarkers in the perioperative period. Br J Anaesthesia 2011;107(6):844–58. doi:10.1093/bja/aer338.
56. Chu C, Liang C, Lin Y, et al. Biomarkers of delirium: well evidenced or not? J Clin Gerontol Geriatr 2011;2(4):100–4. doi:10.1016/j.jcgg.2011.11.005.
57. Ritter C, Tomasi C, Dal-Pizzol F, et al. Inflammation biomarkers and delirium in critically ill patients. Crit Care. 2014;18(3):R106. doi:10.1186/cc13887.
58. Khan B, Zawahiri M, Campbell N, et al. Biomarkers for delirium-a review. J Am Geriatr Soc. 2011;59(2):S256–61. doi:10.1111/j.1532-5415.2011.03702.x.
59. Kunihara T, Shiiya N, Bin L, et al. Arterio-jugular differences in serum S-100β proteins in patients receiving selective cerebral perfusion. Surg Today. 2005;36(1):6–11. doi:10.1007/s00595-005-3105-5.
60. Snyder-Ramos SA, Gruhlke T, Bauer H, et al. Cerebral and extracerebral release of protein S100B in cardiac surgical patients. Anaesthesia. 2004;59(4):344–9. doi:10.1111/j.1365-2044.2004.03663.x.
61. Bloomfield SM, McKinney J, Smith L, et al. Reliability of S100B in predicting severity of central nervous system injury. Neurocrit Care. 2007;6(2):121–38. doi:10.1007/s12028-007-0008-x.
62. Yardan T, Erenler AK, Baydin A, et al. Usefulness of s100b protein in neurological disorders. J Pak Med Assoc. 2011;61(3):276–81.
63. Herrmann M, Ebert AD, Galazky I, et al. Neurobehavioral outcome prediction after cardiac surgery: role of neurobiochemical markers of damage to neuronal and Glial brain tissue. Stroke. 2000;31:645–50. doi:10.1161/01.str.31.3.645.
64. Gerriets T, Schwarz N, Bachmann G, et al. Evaluation of methods to predict early long-term neurobehavioral outcome after coronary artery bypass grafting. Am J Cardiol. 2010;105(8):1095–101. doi:10.1016/j.amjcard.2009.12.009.
65. Bokesch PM, Izykenova GA, Justice JB, et al. NMDA receptor antibodies predict adverse neurological outcome after cardiac surgery in high-risk patients. Stroke. 2006;37:1432–6. doi:10.1161/01.str.0000221295.14547.c8.

Received: 17-10-2016 Accepted: 17-05-2017