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Delirium assessment in the critically ill

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Abstract *Objective:* To compare available instruments for assessing delirium in critically ill adults that have undergone validity testing and provide clinicians with strategies to incorporate these instruments into clinical practice. *Design:* Medline (1966–September 2006) was searched using the key words: delirium, cognitive dysfunction, assessment, intensive care unit, and critical illness to identify assessment tools that have been used to evaluate delirium in critically ill adults. A special emphasis was placed on delirium assessment tools that have been properly validated. Data on how these tools have been adopted into clinical practice as well as strategies for clinicians to improve delirium assessment in the ICU are highlighted. *Measurements and results:* Six delirium assessment instruments including the Cognitive Test for Delirium (CTD), abbreviated CTD, Confusion Assessment Method–ICU,

Intensive Care Delirium Screening Checklist, NEECHAM scale, and the Delirium Detection Score were identified. While each of these scales have undergone validation in critically ill adults, substantial differences exist among the scales in terms of the quality and extent of the validation effort, the specific components of the delirium syndrome each address, their ability to identify hypoactive delirium, their use in patients with a compromised level of consciousness, and their ease of use. *Conclusions:* Incorporation of delirium assessment into clinical practice in the intensive care unit using a validated tool may improve patient care. Clinicians can adopt a number of different strategies to overcome the many barriers associated with routine delirium assessment in the ICU.

Keywords Assessment · Delirium · Critical illness · Intensive care unit · Nursing · Score

Introduction

While delirium often occurs during admission to the general medical or surgical ward, its prevalence and impact on patients admitted to the intensive care unit (ICU) has only recently been recognized [1–6]. Delirium in the ICU, sometimes incorrectly described as “ICU psychosis” or “ICU syndrome”, is associated with higher mortality, prolonged duration of ICU stay, and greater healthcare costs [1, 2, 5, 7, 8]. The cognitive dysfunction associated with delirium may persist long

after recovery and impact long-term functional ability and quality of life [9–11]. The pathogenesis of ICU delirium is complex, likely multifactorial, and not well elucidated [12, 13].

Although not proven with a strong association or definite causality, many risk factors have been described for the development of delirium (mostly from non-ICU cohorts) and can be categorized as: (a) a preexisting condition of the patient, (b) an acute condition of the patient, and (c) an iatrogenic or environmental factor. The list of major risk factors is as follows [3, 14–17]:

Preexisting condition

- Age > 70 years
- Transfer from a nursing home
- Visual or hearing impairment
- History of depression, dementia, congestive heart failure, stroke, or epilepsy
- Renal disease (creatinine > 2.0 mg/dl)
- Liver disease (bilirubin > 2.0 mg/dl)
- HIV infection
- Alcohol abuse in previous month
- Use of psychoactive drugs
- Malnutrition

Acute condition

- Higher severity of illness score
- Drug overdose/illicit drug use
- Metabolic: hypo-/hyperglycemia, hypo-/hyponatremia, hypo-/hyperthyroidism
- Hypothermia or fever
- Sepsis
- Hypoxemia
- Serum urea nitrogen: creatinine ratio that is 18 or higher

Iatrogenic/environmental

- Medications: anticholinergics, sedatives, analgesics
- Use of physical restraints
- Tube feeding
- Rectal or bladder catheter
- Central venous catheters

The reported incidence of delirium in the ICU ranges widely, from 16% to 89%. This variability relates to a number of methodological differences among available prevalence studies including: the assessment instrument used, the patient population studied (e.g., patient age, underlying severity of illness), the intensity of the delirium assessment efforts, the level of training provided to delirium evaluators, and the amounts and types of sedatives and analgesics administered [18–21]. Given the high prevalence of delirium in the ICU current critical care practice guidelines recommend routine delirium screening [22, 23]. The ability to accurately assess delirium in the ICU is a key component of any systematic strategy that is undertaken in the ICU to prevent and/or treat delirium. It is important to note, however, that while multifactorial intervention programs have been shown to reduce the duration of delirium, length of hospitalization, and mortality when completed in patients outside of the ICU, there is currently a lack of evidence demonstrating that the systematic assessment of delirium in the ICU improves outcome [24].

A number of questions exist surrounding the assessment of delirium in adult critically ill patients, including what assessment tools are available, the validity and reliability of these tools, the specific patient populations

in the ICU where clinicians should target their delirium monitoring efforts, the optimal frequency for delirium assessments, and the best strategies that should be used to educate clinicians about delirium assessment. This contribution reviews methods for assessing delirium in critically ill adults, discusses the validity and reliability of available delirium assessment instruments, highlights differences between these instruments, identifies barriers to delirium screening, and provides recommendations to clinicians on how to implement delirium assessment in the ICU.

Considerations when evaluating ICU delirium assessment tools

Delirium is characterized by an acutely changing or fluctuating mental status, inattention, disorganized thinking, and an altered level of consciousness that may or may not be accompanied by agitation [25]. The diagnostic criteria for delirium according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV are:

- Disturbances of consciousness (e.g., reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention.
- A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia.
- The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.
- There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.

While delirium is classically described as hyperactive (e.g., patient is agitated and combative), current epidemiological evidence suggests that more patients in the ICU with delirium are hypoactive (e.g., psychomotor slowing) or have a mixed picture [26, 27]. It is in these latter two populations where the use of an assessment tool that can identify the hallmark signs of delirium (e.g., inattention, disorganized thinking and a fluctuating course) is paramount. Given the multifactorial and fluctuating nature of delirium, a cursory “one time only” evaluation at the bedside is usually ineffectual and has been shown to be a poor strategy for physicians to identify delirium in acutely ill patients [28]. Use of a validated delirium assessment tool to rapidly screen and identify delirium in critically ill patients, particularly in those patients with risk factors for delirium, may lead to the more expedient application of the appropriate clinical interventions.

While a number of valid and reliable tools are available to identify delirium in non-ICU populations, such the

Confusion Assessment Method [29], the Delirium Rating Scale (DRS) [30], and the Memorial Delirium Assessment Scale (MDAS) [31], a number of unique characteristics in the critically ill restrict the use of these instruments in the ICU, including the inability of intubated patients to participate in the components of the scales that require verbal responses, the reduced and often fluctuating level of consciousness that may prevent patients from being able to respond to complex questions, the hemodynamic and medical instability of many ICU patients that may preclude lengthy assessments and a usual lack of trained psychiatric personnel in the ICU. The characteristics of delirium and the unique features of the critically ill help define the qualities of the delirium assessment instrument that should be used in this population: (a) an instrument that evaluates the primary components of delirium (e.g., consciousness, inattention, disorganized thinking, fluctuating course), (b) has proven validity and reliability in ICU populations, (c) can be completed quickly and easily, and (d) does not require the presence of psychiatric personnel [15].

Descriptions of currently available ICU delirium assessment instruments

While a number of validated instruments are available to diagnose delirium in non-ICU patients, we identified only six different tools to evaluate delirium in the ICU [26, 32–37]. The Cognitive Test for Delirium (CTD) was the first test specifically developed for use in the ICU and is made up of five domains: orientation, attention span, memory, comprehension, and vigilance [35]. Each of the five domains is converted to a score of 6, for a total maximum score of 30. An “abbreviated CTD” was developed by the same group of investigators when the assessment of only two content areas (i.e., visual attention span and recognition memory for pictures) was found to maintain good reliability and discriminate delirium from other disorders affecting cognition (e.g., dementia, schizophrenia) [34].

The Confusion Assessment Method (CAM) considers three of the four key features of delirium, i.e., both an acute onset of mental status changes or a fluctuating course and inattention and either disorganized thinking or an altered level of consciousness (i.e., other than alert). It is widely used to diagnose delirium by nonpsychiatric personnel because its ease of use and extensive validation [29]. A patient is deemed to be delirious (i.e., CAM positive) if both features (a) and (b) (from above) are present and one of either feature (c) or (d) is present [29]. The CAM, however, cannot be used in most ICU patients because a component of the CAM, the Mini Mental State Examination (MMSE), requires that patients be able to verbally communicate. In order to be able to evaluate nonverbal ICU patients (e.g., those intubated and mechanically ventilated) Ely et al. [33] replaced the MMSE component in the CAM with an Atten-

tion Screening Examination (ASE) and called it the CAM-ICU (Appendix 1). If patients cannot participate in picture recognition ASE (e.g., those having visual impairment), a verbal random letter test is administered.

The Intensive Care Delirium Screening Checklist (ICDSC) is an eight-item list based on DSM-IV criteria and other features of delirium and includes assessments of consciousness, attentiveness, orientation, the presence of hallucinations or delusions, psychomotor agitation or retardation, inappropriate speech or mood, sleep/wake cycle disturbances, and overall symptom fluctuation (Appendix 2) [25, 32]. This instrument was constructed using observations from a 3-month pilot study that evaluated the use of a number of previously validated delirium assessment tools (e.g., CAM, DRS, and CTD) in the ICU. The ICDSC was developed to provide ICU providers with an easy to use screening tool at the bedside that circumvents the communication limitations of ICU patients, incorporates data that are gathered during routine patient care, and can be completed quickly by the patients’ nurse or physician. During the evaluation process 1 point is given towards each domain that is present, with a score of 4 or higher out of 8 denoting the presence of delirium.

The NEECHAM scale, an instrument originally designed to detect delirium in acutely ill hospitalized patients, has been adopted for use in the ICU [36, 38] (Appendix 3). This nine-item scale is separated into three different categories: (a) ability to process information (e.g., attention, command, orientation), (b) behavior (e.g., appearance, motor and verbal), and (c) physiological condition (e.g., vital function, oxygen saturation, and episodes of incontinence). The information processing domain is given a greater weighting than either behavior or physiological condition, with a lower score reflecting a greater likelihood for the presence of delirium. Therefore a score of 19 or more points out of 30 indicates moderate to severe delirium. The Delirium Detection Score (DDS), is modified from the Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-Ar) and is comprised of nine domains: agitation, anxiety, hallucination, orientation, seizures, tremor, paroxysmal sweating, and altered sleep-wake rhythm [37] (Appendix 4). It is important to note that while some of its domains (e.g., tremor, sweating) are commonly seen during alcohol withdrawal, they are not usually seen with delirium.

The delirium assessment instruments described above share a number of potential limitations. These include the fact that the data are only dichotomous (yes or no) evaluations for the presence of delirium and therefore do not measure delirium severity, although the value of measuring severity is debatable given the uncertainty as to whether cognitive deficits parallel delirium severity [39]. In addition, they do not account for underlying psychiatric conditions nor provide clinicians with a means to evaluate the impact of therapeutic interventions or predict patient outcome.

Validity and reliability of adult delirium assessment tools

We identified a total of 12 validation studies for the six ICU delirium assessment tools [4, 19, 26, 32–38, 40, 41] (Table 1). The CTD was evaluated in four groups of patients (i.e., delirium, dementia, depression, and schizophrenia) in order to evaluate its ability to discriminate delirium from other similar psychiatric conditions [34]. A CTD cutoff score of 18/19 allowed the clinician to discriminate delirium from the other disorders present with a sensitivity of 100% and specificity of 95%. The CTD score was highly correlated with the MMSE score in patients with delirium and was found to be highly reliable between assessors. In a second study, the abbreviated CTD score was found to be well correlated with the CTD [35].

In the first validation study of CAM-ICU in 38 medical ICU patients, some of whom were not intubated, the results of sequential CAM-ICU assessments completed by two study nurses and two intensivists were compared with each other and to the evaluations of delirium experts who based their diagnosis on DSM-IV criteria [33]. CAM-ICU was found to be highly sensitive, specific, and reliable with delirium occurring in 87% of patients. Neither item reliability testing nor the impact of using the altered level of consciousness evaluation option rather than the disorganized thinking option was evaluated. An analysis of the picture recognition ASE results (which could be completed in only one-half of the patients because of their inability to follow the commands) revealed that a cutoff score of 7/8 correct pictures significantly differentiated the presence and absence of delirium. Specific patient demographic features (e.g., mechanical ventilation, age > 65 years, suspected baseline dementia) did not affect the overall results. A further validation study in 111 mechanically ventilated medical and cardiac ICU patients who did not have a history of psychosis or neurological disorder, but who could have initially been comatose (e.g., drug-induced), and who were able to communicate in English, found CAM-ICU to have a high criterion validity and a high reliability that was preserved across all subgroups of patients [26].

Another validation study was completed in a 37 bed medical ICU at a tertiary care Taiwanese hospital. CAM-ICU, after being translated into Chinese, revealed high sensitivity, specificity and reliability [4]. One report of a large-scale implementation of the CAM-ICU by medical ICU nurses found a high level of agreement between the reference standard (i.e., trained research nurses) and the bedside nurse at both a teaching and community hospital [40]. One later study compared CAM and CAM-ICU evaluations between two pretrained clinician-researchers in alert, nonintubated ICU patients [19]. Rates of delirium were 68% according to CAM and 50% with CAM-ICU and agreement between the two methods was moderately high. Using the CAM as the reference standard, the CAM-ICU was only

moderately sensitive but highly specific. The lower sensitivity of CAM-ICU compared to CAM was attributable primarily to the more detailed cognitive testing that CAM permits in those patient who are able to verbalize and thus allow an MMSE to be completed.

A total of 93 consecutive patients admitted over a 3-month period to a mixed medical-surgical ICU, without delirium at admission, were evaluated with the ICDSC every 8 h by the primary care nurse as well as independently, but consecutively, each morning (on a maximum of 5 days) by a research nurse, an intensivist, and a “gold standard” psychiatrist [32]. Delirium was observed in 16% of the study cohort with an ICDSC score of 4 or higher accounting for 93% of these patients. Fifteen false positives occurred when an ICDSC cutoff score of 3/4 was used to denote delirium, but in 14 of 15 patients other concomitant conditions were able to explain the ICDSC result [i.e., another psychiatric diagnosis ($n=4$), dementia ($n=3$), a structural neurological abnormality ($n=6$), or cirrhosis ($n=1$)]. The receiver operator characteristic curve was 0.9017 and the calculated sensitivity was 99% and specificity was 64%. When item reliability for the checklist was evaluated over the 5 days, α homogeneity coefficients ranged from 0.71 to 0.79. The first item of the ICDSC, level of consciousness, was found to be the factor that weakened homogeneity the greatest with the α homogeneity coefficient improving to 0.78–0.85 when level of consciousness was removed. Interobserver reliability between nurses and between nurses and physicians was high, thus demonstrating that nurses can screen ICU patients as well as physicians.

In a small pilot study of 19 nonintubated, critically ill patients the NEECHAM score was well correlated with DSM-III criteria and item reliability was solid (Cronbach's $\alpha = 0.81$) [36]. In a larger validation study of 105 mechanically ventilated ICU patients the NEECHAM scale when compared to DSM-IV delirium criteria exhibited a high sensitivity and specificity and strong nursing interrater reliability [37]. Internal consistency was high, particularly for the first two subscales (i.e., information processing and behavior). The DDS, when compared to the Sedation-Agitation Scale (SAS) as a means to identify delirium ($SAS \geq 5$), was found to have only moderate sensitivity and specificity but high interobserver reliability [38].

Comparisons between currently available delirium assessment tools

Important differences exist among the delirium assessment tools for use in the ICU, including the specific components of the delirium syndrome addressed, the criterion threshold for diagnosing delirium, accuracy, the ability to identify both forms of delirium (i.e., hypoactive and hyperactive), the ability to be used in a patient with a compromised level of consciousness or compromised visual/auditory acuity,

Table 1 Instruments for identifying delirium in critically ill adults (CTD Cognitive Test for Delirium, CAM-ICU Confusion Assessment Method for the Intensive Care Unit, ICDSC Intensive Care Unit Delirium Screening Checklist, DDS Delirium Detection Score, CCU cardiac care unit, MMSE Mini-Mental State Examination, MICU medical intensive care unit, CI confidence interval, NR not reported, ROC receiver operator characteristic curve, DSM-III-R Diagnostic and Statistical Manual of Mental Disorders—revised third edition)

Instrument	Validation study	Population	Assessments	Validity	Reliability
CTD	Hart et al. [34]	22 MICU patients with delirium per DSM-III-R, mechanical ventilation (NR)	44 assessments, no. of raters not clear	Versus MMSE $r = 0.82$ ($p < 0.001$); ROC analysis: sensitivity 100%, specificity 95%	$r = 0.87$ ($p < 0.001$)
Abbreviated CTD	Hart et al. [35]	19 medical ward and MICU patients with delirium per DSM-III-R, mechanical ventilation (NR)	38 assessments, no. of raters not clear	Versus CTD $r = 0.91$ ($p < 0.001$); ROC analysis: sensitivity 94.7%, specificity 98.8%	$r = 0.79$ ($p < 0.001$)
CAM-ICU	Ely et al. [33]	38 MICU patients, mechanical ventilation (58%)	293 assessments, 4 raters	Accuracy vs. delirium expert assessment using DSM-IV criteria: intensivist 96% (95% CI 80–100), nurse 1 95% (95% CI 86–100), nurse 2 96% (95% CI 86–100)	Intensivist vs. nurse 1 $\kappa = 0.84$ (95% CI 0.63–0.99), intensivist vs. nurse 2 $\kappa = 0.79$ (95% CI 0.64–0.95), nurse 1 vs. nurse 2 $\kappa = 0.95$ (95% CI 0.84–1.00)
	Ely et al. [26]	96 MICU and CCU patients, mechanical ventilation (100%)	471 paired daily assessments by 2 nurses	Accuracy vs. delirium expert assessment using DSM-IV criteria: nurses 1 and 2 combined 98.4% (95% CI 92–100)	Nurse 1 vs. nurse 2 $\kappa = 0.6$ (95% CI 0.92–0.99)
	Lin et al. [4]	111 MICU and CCU patients, mechanical ventilation (100%)	204 paired daily assessments by 2 research assistants	Versus psychiatrist evaluation using DSM-IV criteria: sensitivity: assessor 1.91% (p NR); assessor 2.95% (p NR); specificity: assessor 1.98% (p NR); assessor 2.98% (p NR)	Assessor 1 vs. assessor 2 $\kappa = 0.96$ (p NR)
	McNicol et al. [11]	22 alert elderly MICU patients, mechanical ventilation (0%)	22 assessments by 2 trained clinician-researchers	Versus CAM: sensitivity: 73% (95% CI 60–86), specificity: 100% (95% CI, 56–100)	Interrater reliability between CAM-ICU and CAM: 82%, $\kappa = 0.64$ (95% CI 32–94)
	Pun et al. [40]	377 MICU patients at teaching hospital, mechanical ventilation (57.2%); 131 MICU patients at community hospital, mechanical ventilation (20.1%)	Random paired spot checks ($n = 508$) by the patient nurse and pretrained expert nursing raters	—	Versus “expert nursing raters”: teaching hospital $\kappa = 0.92$ (95% CI 0.90–0.94), community hospital $\kappa = 0.75$ (95% CI 0.68–0.81)
ICDSC	Bergeron et al. [32]	93 mixed medical/surgical ICU patients, mechanical ventilation (% NR)	Daily (independent) grouped assessments for 93 patients by: patient nurse, research nurse, intensivist, and psychiatrist (total no. of assessments NR) 19 subjects; no. raters not clear	Versus psychiatrist evaluation using ICDSC: Sensitivity 99%, specificity 64%	Nurse vs. nurse: $r > 0.94$ (p NR), nurse vs. intensivist: $r > 0.94$ (p NR)
NEECHAM	Csokasy [36]	19 mixed medical/surgical ICU patients, mechanical ventilation (0%)	253 ratings performed daily by both ICU research and bedside nurses	Accuracy vs. DSM-III score $r = 0.68$ (p NR)	Researcher vs. patient nurse 0.81 (p NR)
	Immers et al. [37]	105 patients in mixed medical/surgical ICU unknown med/surg ICU, mechanical ventilation (% NR)	3,588 paired assessments by patient’s physician and nurse at least once every shift	Vs. DSM-IV $\chi^2 = 67.52$ ($p = 0.001$), sensitivity 97.2%, specificity 82.8%	Research nurse vs. patient nurse $\kappa = 0.60$ (p NR)
DDS	Otter et al. [38]	1,073 SICU patients, mechanical ventilation (% NR)	—	Versus SAS (> 5 = delirium) area under the ROC 0.80 (95% CI 0.72–0.90, $p < 0.001$), sensitivity 69%, specificity 75%	Cronbach’s $\alpha = 0.667$ (p NR)

and the ease of use. Clinicians should consider these differences before implementing any of these scales into clinical practice.

Given the fluctuating and often compromised levels of awareness in critically ill patients and the fact that disturbances in consciousness are a diagnostic criteria for delirium, it is important that any delirium assessment tool be able to be used in patients with varying levels of consciousness. The delirium assessment tools studied for use in the ICU differ in terms of how they evaluate consciousness and incorporate it into the delirium score. Interventional scales such as the CAM-ICU require the patient to answer and respond to a series of questions to be able to evaluate both inattention and disorganized thinking. A patient with a compromised level of consciousness can theoretically fail either (or both) of these two assessments and be deemed to have delirium when in fact the patient is simply not able to complete the required exercise for a completely unrelated reason (e.g., recent administration of a sedative agent). Therefore, with the evaluation of consciousness being optional with the CAM-ICU, it is possible that false diagnoses of delirium may occur [18]. In contrast, with the ICDSC, level of consciousness is the first domain to be evaluated during ICDSC screening, and if stimulation is required to elicit a patient response (i.e., Riker SAS ≤ 2), the delirium evaluation is truncated until the patient is more awake. Lastly, it is important to note that while an evaluation of consciousness is included in the ICDSC, consciousness was found during validation to be the least accurate item on the instrument, suggesting that level of consciousness alone is not a good discriminator for delirium [36].

Delirium assessment may be confounded in patients with baseline psychiatric conditions (e.g., dementia), neurological injury, or structural abnormalities. A major reason for the higher specificity that is reported with CAM-ICU (89%) than ICDSC (64%) is that patients with neurological injury and structural neurological abnormalities were excluded from the CAM-ICU but not the ICDSC validation studies [2, 32, 33]. Sleep/wake cycle disturbances, although common in the ICU, are not definitely associated with delirium, and thus their inclusion in the ICDSC but not CAM-ICU may also partially account for the lower ICDSC specificity [16]. The fact that the ICDSC incorporates a mandatory assessment of both consciousness and psychomotor retardation may make it a better tool than CAM-ICU to evaluate hypoactive delirium. The NEECHAM scale would be expected to have a detection capability similar to the ICDSC, although hypoactive or mixed delirium subtypes were not prospectively identified in validation studies. Use of the DDS to detect hypoactive delirium would be expected to be poor as the major focus of the scale was to identify hyperactivity and the scale lacks criteria to identify patients who are hypoactive or cognitively impaired.

The incidence of delirium that has been detected during ICU validation studies has varied widely (range 16–84%)

not only between evaluations of different scales (e.g., CAM-ICU vs. ICDSC) but among different validation studies evaluating the same scale (e.g., CAM-ICU) [26, 33]. In studies using CAM-ICU the incidence of delirium was (83 and 87%) in the first two CAM-ICU validation studies but only 47% during a study at another academic center and 22% during a validation study at a teaching hospital in Taiwan [4, 26, 33, 42]. Methodological differences between these studies could not account for this variability as each study enrolled only medical ICU patients, excluded patients with dementia, psychosis or neurological disease, and used trained research personnel (rather than the bedside nurse) to conduct all assessments. In comparison, the original ICDSC delirium study identified delirium with a prevalence of 16% [32]. Several differences between CAM-ICU and the ICDSC studies may account for these reported differences. In comparison to the CAM-ICU studies, the ICDSC studies included patients with dementia, psychosis, neurological injury, or structural neurological abnormalities, who were admitted to both medical and surgical services, and who had a lower severity of illness; excluded patients admitted with delirium or who had a decreased level of consciousness; required observation over the entire 8-h shift (and not merely at a single time point) and truncated patient evaluations at 5 days (when delirium prevalence is known to increase over the duration of the ICU stay).

Given the dynamic nature of critical illness it is paramount that clinicians complete frequent delirium assessments. To this end, clinicians need a scale that can be completed quickly and incorporated easily into their daily routine. The reported time it takes to complete delirium evaluations vary widely among scales. Evaluations of the CTD found that it takes about 10–15 min to complete. While not evaluated, the abbreviated CTD would be expected to take less time. Although the time to complete the CAM-ICU ranged from 2–3 min in the first of the validation study, a recent survey of nurses who had used CAM-ICU in routine practice for more than 12 months found that the time needed to complete the CAM-ICU evaluation was reported as the most frequent barrier to use [26, 33, 40]. The average time to complete the ICDSC evaluation was not reported in the validation study although the tool was described as easy to administer and “user-friendly” [32, 41]. The NEECHAM scale is reported to take an average of 3.6 ± 1.2 min to complete [36].

Barriers to delirium assessment in the critically ill

Despite SCCM practice guidelines that advocate regular delirium evaluation in the ICU, only 40% of physician responding to a 2001 survey report routinely monitoring for delirium [23]. Interestingly, of the 16% of respondents who reported that they used a specific assessment tool to detect delirium, only 7% used a validated delirium assess-

ment tool (CAM-ICU), with most instead using the MMSE (50%), Glasgow Coma Scale (28%) or a sedation scale (16%).

While not formally identified, a number of potential barriers are suspected to prevent the routine evaluation of delirium at the ICU bedside, and if addressed, may improve the use of available delirium screening tools. These include:

- Delirium assessment never shown to improve patient outcome
- Lack of knowledge regarding the presentation and sequelae of ICU delirium
- Lack of familiarity with available assessment instruments
- Available assessment instruments that are too complex
- Descriptors in available tools that are ambiguous and confusing
- Little reported use of assessment instruments outside of validating centers
- Assessment instruments designed for research personnel rather than bedside clinicians
- Lack of clear guidance regarding the patients who should receive priority screening
- Clinician time constraints
- Lack of clarity regarding the health care professional that should be most responsible for identifying delirium
- Inability to complete evaluation in the highly sedated patient
- Lack of experience in surgical populations

Lack of familiarity with the clinical presentation of ICU delirium, its risk factors, its identification with tested assessment tools, and its association with increased patient morbidity and mortality may help to explain the lack of compliance with recommendations for routine delirium screening. In addition, clinicians may be slow to adopt the use of any new tool into practice, particularly one that is complex, if they do not feel confident in performing the assessment [40]. Clinicians may find that the descriptors that accompany the publication of each delirium assessment tool are ambiguous, not detailed enough, or confusing. Few published descriptions exist for the use of delirium assessment tools outside of those centers where the tool was originally validated [4, 42]. In most cases the delirium assessments have been completed by research personnel rather than bedside clinicians. There is currently a lack of clear guidance to critical care clinicians in terms of the types of patients in whom delirium screening is most important to complete and how frequently this screening should occur. Lastly, clinicians may be slow to implement delirium screening in their ICU given the lack of data showing this practice improves patient outcome.

With the rise in clinician workload and the ever increasing numbers of protocols being implemented

into ICU practice, clinicians may feel that there is little available time to evaluate their patients for delirium on a routine basis [7]. In fact, recent surveys of sedation practices suggest that lack of clinician time is a major barrier to routine sedation assessment—a much easier task in terms of both time and complexity than delirium monitoring [43]. Although the bedside nurse is generally recognized as the ICU professional who is best positioned to conduct routine delirium screening, there remains a lack of consensus regarding which types of professionals should be participating in delirium screening. Lastly, the inability to complete a delirium evaluation in a patient who is heavily sedated or comatose usually requires repeated evaluation attempts that may limit its acceptance as a routine monitoring practice in the ICU.

Strategies to improve delirium assessment practices in the ICU

With the goal of providing delirium screening to all patients admitted to the ICU there are a number of potential strategies that can be used by clinicians to improve current delirium evaluation practices. Firstly, the member of the ICU team who is responsible for routine delirium monitoring should be established. The bedside nurse is best suited for this role because of their ability to detect fluctuations in agitation, the presence of hallucinations, changes in emotional responsiveness, and alterations in sleep [13]. Any delirium assessment program needs a champion(s) in the unit that can serve as the driving force behind all implementation and evaluation efforts. Institutions with more than one ICU are encouraged to implement the same delirium assessment tool and standardized procedures throughout the hospital as using one tool consistently in all units of a hospital may improve clarity and reduce confusion. Written policies and procedures should be developed for delirium assessment that outline how the tool will be used, who will complete the evaluations, and how they will be documented in the patient record. The delirium tool should be easily accessible at the bedside, on pocket cards, on ICU flow sheets, and in the appropriate computer systems.

Education should be considered the core component of any delirium tool implementation exercise as it has been shown to improve delirium assessment reliability [40]. Use of CAM by untrained nurses in one study found a delirium detection rate of only 19% [44]. Dedicated time should be devoted to delirium assessment training that should incorporate: an overview of delirium, the key domains and descriptors of the chosen assessment tool, the potential pitfalls and challenges of delirium screening in certain patient subpopulations, case studies, actual practice at the bedside, and a method of self-assessment. Other strategies that can be incorporated into the educational strategy include poster displays on unit bulletin boards and newsletters [40]. It is important to ensure that all members of the critical care

team (including both housestaff and attending physicians) are educated regarding the delirium assessment tool, and that results of the delirium assessments are presented during both morning report and bedside rounds. It is also important to make sure that members of the critical care team are familiar with the descriptive methodology used in the tool. Sedation assessment is a key component of delirium assessment, regardless of the delirium scale chosen, and thus it is important to ensure that nursing staff are routinely evaluating all patients with a sedation scale (e.g., SAS, Richmond Agitation Sedation Scale) before a delirium assessment is completed.

One of the most essential components to the implementation of any delirium assessment protocol development is the need for some form of continuous quality monitoring that will evaluate compliance with the protocol [45]. In the CAM-ICU implementation study regularly scheduled evaluation of delirium assessment practices at both the practitioner and unit level demonstrated an improvement in delirium assessment practices over time [40]. Although not peer-reviewed, educational websites (e.g., <http://www.icudelirium.org>) may represent another source of information for practitioners seeking to implement delirium assessment tools into practice. Lastly, it should be emphasized that any of the delirium assessment tools be considered primarily a screening tool rather than a definite diagnostic tool. A psychiatric consultation may be still be valuable, particularly in situations where the patient's symptoms are atypical or the medical history is unknown.

This review has highlighted a number of areas of research that should be studied regarding the assessment of delirium in the ICU. There is a dire need for studies showing that the routine assessment of delirium improves patient outcome. In addition head-to-head studies are needed that compare the validity, and reliability of different delirium assessment tools (e.g., CAM-ICU vs. ICDSC). Lastly, there remains a paucity of research devoted to understanding the optimal pedagogical strategies that should be used to educate ICU clinicians about delirium assessment.

Conclusions

Six delirium assessment instruments—CTD, abbreviated CTD, CAM-ICU, ICDSC, NEECHAM scale, and DDS—have been published. While each of these scales has undergone validation testing, substantial differences exist among the scales in terms of the quality and extent of the validation effort, the specific components of the delirium syndrome each address, their ability to identify hypoactive delirium and be used in patients with a compromised level of consciousness, and their ease of use. Incorporation of delirium assessment into

clinical practice in the intensive care unit using a validated tool may improve patient care. Clinicians can adopt a number of different strategies to overcome the many barriers associated the implementation of routine delirium assessment.

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

Features and descriptions (absent/present). Overall CAM-ICU assessment (features 1 and 2 and either feature 3 or 4; (yes/no).

1. Acute onset or fluctuating course

- A: Is there evidence of an acute change in mental status from the baseline?
- B: Or did the (abnormal) behavior fluctuate during the past 24 h, that is, tend to come and go to increase and decrease in severity as evidenced by fluctuations on the Richmond Agitation Sedation Scale or the Glasgow Coma Scale?

2. Inattention

Did the patient have difficulty focusing attention as evidenced by a score of fewer than eight correct answers on either the visual or auditory components of the Attention Screening Examination?

3. Disorganized thinking

Is there evidence of disorganized or incoherent thinking as evidenced by incorrect answers to three or more of the four questions and inability to follow the commands?

Questions

1. Will a stone float on water?
2. Are there fish in the sea?
3. Does 1 pound weigh more than 2 pounds?
4. Can you use a hammer to pound a nail?

Commands

1. Are you having unclear thinking?
2. Hold up this many fingers (examiner holds two fingers in front of the patient).
3. Now do the same thing with the other hand (without holding the two fingers in front of the patient).

(If the patient is already extubated from the ventilator, determine whether the patient's thinking is disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject.)

4. Altered level of consciousness

Is the patient's level of consciousness anything other than alert, such as being vigilant or lethargic or in a stupor, or coma?

Alert: spontaneously fully aware of environment and interacts appropriately.

Vigilant: hyperalert.

Lethargic drowsy but easily aroused, unaware of some elements in the environment or not spontaneously interacting with the interviewer; becomes fully aware and appropriately interactive when prodded minimally.

Stupor: difficult to arouse, unaware of some or all elements in the environment or not spontaneously interacting with the interviewer; becomes incompletely aware when prodded strongly; can be aroused only by vigorous and repeated stimuli and as soon as the stimulus ceases, stuporous subject lapses back into unresponsive state.

Coma: unarousable, unaware of all elements in the environment with no spontaneous interaction or awareness of the interviewer so that the interview is impossible even with maximal prodding.

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 behavior probably due to hallucination (e.g., trying to catch a nonexistent 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 potential danger to oneself or others (e.g., pulling out intravenous lines, hitting staff); hypoactivity or clinically noticeable psychomotor slowing. Any of these scores 1 point.

6. **Inappropriate speech or mood:** inappropriate, disorganized 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 h 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 in the manifestation of any item or symptom over 24 h (e.g., from one shift to another) scores 1 point.

Appendix 2: Intensive Care Delirium Screening Checklist

The scale is completed based on information collected from each entire 8-h shift or from the previous 24 h. 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/B: No response (A) or the need for vigorous stimulation (B) 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.

Appendix 3: NEECHAM scale

Subscale 1 (max. 14 points):

Attention

- Full attentiveness/alertness (responds appropriately) (4 points)
- Short or hyper attention/alertness (3 points)
- Attention/alertness inconsistent or inappropriate (2 points)
- Attention/alertness disturbed (1 point)
- Arousal/responsiveness depressed (0 points)

Command

- Able to follow a complex command (5 points)
- Slowed complex command response (4 points)
- Able to follow a simple command (3 points)
- Unable to follow a direct command (2 points)
- Unable to follow visually guided command (1 point)
- Hypoactive, lethargic (0 points)

Orientation

- Orientated to time, place and person (5 points)
- Orientated to person and place (4 points)
- Orientation inconsistent (3 points)
- Disoriented and memory/recall disturbed (2 points)
- Disoriented, disturbed recognition (1 point)
- Processing of stimuli depressed (0 points)

Subscale 2 (max. 10 points):

Appearance

- Controls posture, maintains appearance, hygiene (2 points)
- Either posture or appearance disturbed (1 point)
- Both posture and appearance abnormal (0 points)

Motor

- Normal motor behavior (4 points)
- Motor behavior slowed or hyperactive (3 points)
- Motor movement disturbed (2 points)
- Inappropriate, disruptive movements (1 point)
- Motor movement depressed (0 points)

Verbal

- Initiates speech appropriately (4 points)
- Limited speech initiation (3 points)
- Inappropriate speech (2 points)
- Speech sound disturbed (1 point)
- Abnormal sounds (0 points)

Subscale 3 (max. 30 points):

Vital function

- Blood pressure, heart rate, temperature, respiration within normal range (2 points)
- Any one of the above in abnormal range (1 point)
- Two or more in abnormal range (0 points)

Oxygen saturation

- Normal range (2 points)
- 90–92 or is receiving oxygen (1 point)
- Below 90 (0 points)

Urinary continence

- Maintains bladder control (2 points)
- Incontinent of urine in last 24 h or has condom catheter (1 point)
- Incontinent now or has indwelling or intermittent catheter or is anuric (0 points)

Appendix 4: Delirium Detection Score (DDS)

Orientation

- Orientated to time, place and personal identity, able to concentrate (0 points)
- Not sure about time and/or place, not able to concentrate (1 point)
- Not orientated to time and/or place (4 points)
- Not orientated to time, place, and personal identity (7 points)

Hallucinations

- None (0 points)
- Mild hallucinations at times (1 point)
- Permanent mild to moderate hallucinations (4 points)
- Permanent severe hallucinations (7 points)

Agitation

- Normal activity (0 points)
- Slightly higher activity (1 point)
- Moderate restlessness (4 points)
- Severe restlessness (7 points)

Anxiety

- No anxiety when resting (0 points)
- Slight anxiety (1 point)
- Moderate anxiety at times (4 points)
- Acute panic attacks (7 points)

Myoclonus/convulsions

- None (0 points)
- Myoclonus (1 point)
- Convulsions (7 points)

Paroxysmal sweating

- No sweating (0 points)
- Almost not detectable, only palms (1 point)
- Beads of perspiration on the forehead (4 points)
- Heavy sweating (7 points)

Altered sleep-waking cycle

- None (0 points)
- Mild, patient complaints about problems to sleep (1 point)

- Patient sleeps only with high medication (4 points)
- Patient does not sleep despite medication at night, tired at daytime (7 points)

Tremor

- None (0 points)
- Not visible, but can be felt (1 points)
- Moderate tremor (arms stretched out) (4 points)
- Severe tremor (without stretching arms) (7 points)

References

- Ely EW, Gautam S, Margolin R, Francis J, May L, Speroff T, Truman B, Dittus R, Bernard GR, Inouye SK (2001) The impact of delirium in the intensive care unit on hospital length of stay. *Intensive Care Med* 27:1892–1900
- Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE Jr, Inouye SK, Bernard GR, Dittus RS (2004) Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA* 291:1753–1762
- Inouye SK (1994) The dilemma of delirium: clinical and research controversies regarding diagnosis and evaluation of delirium in hospitalized elderly medical patients. *Am J Med* 97:278–288
- Lin SM, Liu CY, Wang CH, Lin HC, Huang CD, Huang PY, Fang YF, Shieh MH, Kuo HP (2004) The impact of delirium on the survival of mechanically ventilated patients. *Crit Care Med* 32:2254–2259
- Milbrandt EB, Deppen S, Harrison PL, Shintani AK, Speroff T, Stiles RA, Truman B, Bernard GR, Dittus RS, Ely EW (2004) Costs associated with delirium in mechanically ventilated patients. *Crit Care Med* 32:955–962
- O’Keefe S, Lavan J (1997) The prognostic significance of delirium in older hospital patients. *J Am Geriatr Soc* 45:174–178
- Bowton DL (2004) Delirium—the cost of inattention. *Crit Care Med* 32:1080–1081
- Thomason JW, Shintani A, Peterson JF, Pun BT, Jackson JC, Ely EW (2005) Intensive care unit delirium is an independent predictor of longer hospital stay: a prospective analysis of 261 non-ventilated patients. *Crit Care* 9:R375–R381
- Andrew MK, Freter SH, Rockwood K (2005) Incomplete functional recovery after delirium in elderly people: a prospective cohort study. *BMC Geriatr* 5:5
- Levkoff SE, Evans DA, Liptzin B, Cleary PD, Lipsitz LA, Wetle TT, Reilly CH, Pilgrim DM, Schor J, Rowe J (1992) Delirium. The occurrence and persistence of symptoms among elderly hospitalized patients. *Arch Intern Med* 152:334–340
- McNicoll L, Pisani MA, Zhang Y, Ely EW, Siegel MD, Inouye SK (2003) Delirium in the intensive care unit: occurrence and clinical course in older patients. *J Am Geriatr Soc* 51:591–598
- Burns A, Gallagley A, Byrne J (2004) Delirium. *J Neurol Neurosurg Psychiatry* 75:362–367
- Justic M (2000) Does “ICU psychosis” really exist? *Crit Care Nurse* 20:28–37
- Dubois MJ, Bergeron N, Dumont M, Dial S, Skrobik Y (2001) Delirium in an intensive care unit: a study of risk factors. *Intensive Care Med* 27:1297–1304
- Pandharipande P, Jackson J, Ely EW (2005) Delirium: acute cognitive dysfunction in the critically ill. *Curr Opin Crit Care* 11:360–368
- McGuire BE, Basten CJ, Ryan CJ, Gallagher J (2001) Intensive care unit syndrome: a dangerous misnomer. *Arch Intern Med* 160:906–909
- Pisani MA, McNicoll L, Inouye SK (2003) Cognitive impairment in the intensive care unit. *Clin Chest Med* 24:727–737
- Bergeron N, Skrobik Y, Dubois MJ (2002) Delirium in critically ill patients. *Crit Care* 6:181–182
- McNicoll L, Pisani MA, Ely EW, Gifford D, Inouye SK (2005) Detection of delirium in the intensive care unit: comparison of confusion assessment method for the intensive care unit with confusion assessment method ratings. *J Am Geriatr Soc* 53:495–500
- Bergeron N, Skrobik Y, Dubois MJ (2005) Is disturbance of consciousness an important feature of ICU delirium? *Intensive Care Med* 31:887
- Skrobik Y (2003) An overview of delirium in the critical care setting. *Geriatr Aging* 6:30–35
- Jacobi J, Fraser GL, Coursin DB, Riker RR, Fontaine D, Wittbrodt ET, Chalfin DB, Masica MF, Bjerke HS, Coplin WM, Crippen DW, Fuchs BD, Kelleher RM, Marik PE, Nasraway SA, Murray MJ, Peruzzi WT, Lumb PD (2002) Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med* 30:119–141
- Ely EW, Stephens RK, Jackson JC, Thomason JW, Truman B, Gordon S, Dittus RS, Bernard GR (2004) Current opinions regarding the importance, diagnosis, and management of delirium in the intensive care unit: a survey of 912 healthcare professionals. *Crit Care Med* 32:106–112
- Lundstrom M, Edlund A, Karlsson S, Brannstrom B, Bucht G, Gustafson Y (2005) A multifactorial intervention program reduces the duration of delirium, length of hospitalization, and mortality in delirious patients. *J Am Geriatr Soc* 53:622–628
- Anonymous (2000) Diagnostic and statistical manual of mental disorders—text revision. American Psychiatric Association, Washington
- Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, Truman B, Speroff T, Gautam S, Margolin R, Hart RP, Dittus R (2001) Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 286:2703–2710

27. Peterson JF, Pun BT, Dittus RS, Thomason JW, Jackson JC, Shintani AK, Ely EW (2006) Delirium and its motoric subtypes: a study of 614 critically ill patients. *J Am Geriatr Soc* 54:479–484
28. Armstrong SC, Cozza KL, Watanabe KS (1997) The misdiagnosis of delirium. *Psychosomatics* 38:433–439
29. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI (1990) Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med* 113:941–948
30. Trzepacz PT, Baker RW, Greenhouse J (1988) A symptom rating scale for delirium. *Psychiatry Res* 23:89–97
31. Breitbart W, Rosenfeld B, Roth A, Smith MJ, Cohen K, Passik S (1997) The Memorial Delirium Assessment Scale. *J Pain Symptom Manage* 13:128–137
32. 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* 27:859–864
33. Ely EW, Margolin R, Francis J, May L, Truman B, Dittus R, Speroff T, Gautam S, Bernard GR, Inouye SK (2001) Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Crit Care Med* 29:1370–1379
34. Hart RP, Levenson JL, Sessler CN, Best AM, Schwartz SM, Rutherford LE (1996) Validation of a cognitive test for delirium in medical ICU patients. *Psychosomatics* 37:533–546
35. Hart RP, Best AM, Sessler CN, Levenson JL (1997) Abbreviated cognitive test for delirium. *J Psychosom Res* 43:417–423
36. Csokasy J (1999) Assessment of acute confusion: use of the NEECHAM Confusion Scale. *Appl Nurs Res* 12:51–55
37. Immers HE, Schuurmans MJ, van de Bijl JJ (2005) Recognition of delirium in ICU patients: a diagnostic study of the NEECHAM confusion scale in ICU patients. *BMC Nurs* 4:7
38. Otter H, Martin J, Basell K, von Heymann C, Hein OV, Bollert P, Jansch P, Behnisch I, Wernecke KD, Konertz W, Loening S, Blohmer JU, Spies C (2005) Validity and reliability of the DDS for severity of delirium in the ICU. *Neurocrit Care* 2:150–158
39. Smith MJ, Breitbart WS, Platt MM (1995) A critique of instruments and methods to detect, diagnose, and rate delirium. *J Pain Symptom Manage* 10:35–77
40. Pun BT, Gordon SM, Peterson JF, Shintani AK, Jackson JC, Foss J, Bernard GR, Dittus RS, Ely EW (2005) Large-scale implementation of sedation and delirium monitoring in the intensive care unit: a report from two medical centers. *Crit Care Med* 33:1199–1205
41. Roberts B, Rickard C, Rajbhandari D, Turner G, Clarke J, Hill D, Tauschke C, Chaboyer W, Parsons R (2005) Multi-centre study of delirium in ICU patients using a simple screening tool. *Aust Crit Care* 8:6–15
42. Micek ST, Anand NJ, Laible BR, Shannon WD, Kollef MH (2005) Delirium as detected by the CAM-ICU predicts restraint use among mechanically ventilated medical patients. *Crit Care Med* 33:1260–1265
43. Devlin JW, Tanios MA, Epstein SK (2006) Intensive care unit sedation: waking up clinicians to the gap between research and practice. *Crit Care Med* 34:556–557
44. Inouye SK, Foreman MD, Mion LC, Katz KH, Cooney LM Jr (2001) Nurses' recognition of delirium and its symptoms: comparison of nurse and researcher ratings. *Arch Intern Med* 161:2467–2473
45. Hammond JJ (2001) Protocols and guidelines in critical care: development and implementation. *Curr Opin Crit Care* 7:464–468