Delirium in the intensive care unit: a narrative review of published assessment tools and the relationship between ICU delirium and clinical outcomes

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Delirium is defined as an acute change or fluctuation in mental status, plus inattention, and either disorganised thinking or altered level of consciousness at the time of evaluation. Increasing numbers of studies confirm that delirium is very common in intensive care unit patients. This review summarises current knowledge about ICU delirium and offers some avenues for future research. This is a summary of Dr Waters' dissertation for the DICM.

Keywords: *delirium; ICU; assessment; outcomes*

Introduction

Delirium has received little attention in intensive care because it is often believed to be iatrogenic due to medication, is frequently explained away as 'ICU psychosis' or as an expected outcome of intensive care, or is believed to have no adverse consequences in terms of the patient's ultimate outcome.[1-3] More than 25 terms are used in the literature to refer to delirium, such as ICU psychosis, encephalopathy of critical illness and toxic confusional state, and this has lead to much confusion. All acute disturbances of global cognitive functioning are now recognised as 'delirium', a consensus supported by both the ICD-10[4] and DSM-IV[5] classification systems used in psychiatry.

Delirium is defined as an acute change or fluctuation in mental status, plus inattention, and either disorganised thinking or altered level of consciousness at the time of evaluation.[6] Numerous studies have described the incidence, prevalence and costly impact of delirium with regard to patients in nursing homes and hospital wards, but few prospective investigations have focused on cohorts treated specifically in the ICU.[7-9]

A few studies have now confirmed that delirium is very common and occurs in 60-80% of mechanically ventilated patients.[6,10,11] Only 5% of 912 critical care professionals surveyed in 2001 and 2002 reported monitoring for ICU delirium.[12] However, the Society of Critical Care Medicine (SCCM) has recommended routine monitoring for delirium for all ICU patients.[13] Also, in a report from the international 'Surviving Intensive Care' 2002 Roundtable Conference held in Brussels, the need for future investigations in neuro-cognitive abnormalities among survivors of intensive care received the strongest recommendation from the panel of experts.[14]

Since many aspects of delirium in the ICU may be preventable (e.g. hypoxaemia, electrolyte disturbances, sleep deprivation, overzealous use of sedative agents), routine daily monitoring may be justified if adverse outcomes could be demonstrated within this population, and more importantly, if prevention and treatment of delirium could improve these adverse outcomes. To date only one study has examined the prevention or treatment of delirium in the ICU setting.[15] This paucity of studies has previously been due to the lack of a reliable, validated and practical instrument for assessing delirium in the ICU. The recent validation of several assessment tools opens up a new frontier for the investigation of patient outcomes in delirious patients in the ICU.

Subtypes of delirium

Patients emerging from the effects of sedation may do so peacefully or in a combative manner. On one extreme are the peaceful patients who are often erroneously assumed to be thinking clearly. Delirium in this context is referred to as hypoactive delirium, and is characterised by decreased mental and physical activity and inattention.[16] Physicians and nurses frequently overlook this quiet or hypoactive delirium. Features also include lethargy, confusion and sedation. At the other extreme are agitated or combative patients (hyperactive delirium). Features include hyper-arousal, hallucinations, delusions, disorientation, hyper-alertness and agitation. Patients who have both characteristics are said to have mixed delirium.

Peterson *et al*[17] recently reported on delirium subtypes from a cohort of 613 ICU patients. They found that among patients who experienced delirium, pure hyperactive delirium was rare (<5%), whereas hypoactive and mixed types predominated (~45% each). Lin *et al*[18] recorded in their study of 102

ventilated patients that 22.7% were hyperactive, 63.6% were hypoactive and 13.7% were mixed.

Differential diagnosis of delirium

Some symptoms of delirium are common to other conditions, which may prove especially challenging when these conditions coexist. Cognitive disturbance occurs in both delirium and dementia. Distinguishing features include the sudden change in cognition, and the degree of inattention and lethargy that are seen with delirium. Obtaining reliable information on baseline status is crucial. The cognitive changes in delirium occur abruptly over hours to days, whereas dementia progresses insidiously over months to years. Inattention is usually not a prominent feature of early or moderate dementia. Typically, persons who have dementia will not know the answer but will try to answer to the best of their abilities and will focus their attention on the interviewer. An important feature of attention is eye contact; a person who has dementia will demonstrate good eye contact, whereas a person with delirium will have decreased or limited eye contact and will stare into space. Lethargy is not part of dementia until the advanced stages and should always be evaluated as potential delirium. Agitation is less useful as a distinguishing feature because patients who have dementia, especially in the advanced forms, may become agitated in foreign environments such as the ICU. In dementia, speech is usually ordered but demonstrates aphasia or anomia, whereas in delirium, speech may be incoherent, disorganised or manifest delusions or hallucinations. Taken together, these important distinctions can help clinicians differentiate whether dementia, delirium or a combination of both is present.[19]

Hypoactive delirium may be mistaken for depression, but the timing of the onset of symptoms and cognitive impairment will help clarify the presence of delirium or depression.[20]

Finally, primary psychiatric disorders do not present with an altered level of consciousness. Multiple auditory and command hallucinations are more common in psychiatric disease whereas visual or tactile hallucinations usually occur in delirium.

Delirium assessment instruments

The gold standard diagnostic criteria for delirium are the clinical history and examination guided by the Diagnostic and Statistical Manual of mental disorders, 4th Edition (DSM-IV).[5] Scales and diagnostic instruments developed to facilitate recognition and diagnosis of delirium have routinely excluded ICU patients because of the difficulty in communicating with them.[21,22] Work on the ICU population began with publication of the Cognitive Test for Delirium (CTD) in 1996 and later the Abbreviated Cognitive Test for Delirium in 1997.[23,24] Subsequent published tools include the Intensive Care Delirium Screening Checklist (ICDSC)[25] and the Delirium Detection Score (DDS).[26] In 1990, the Confusion Assessment Method (CAM) was published.[27] While based on the DSM-IIIR[28] criteria, the CAM was specifically designed for use by healthcare professionals without formal psychiatric training, in patients able to communicate verbally. It has been widely used as a delirium assessment instrument owing to its ease of use. Several groups of investigators have recently collaborated to develop and validate a rapid bedside instrument to diagnose delirium specifically in the group of patients who are being mechanically ventilated. This instrument is called the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).[29,30] Critical care nurses can complete delirium assessments with the CAM-ICU in an average of two minutes, compared with a full DSM-IV assessment by an expert in psychiatry, which usually requires at least 30 minutes to complete.

The main limitation of the CTD study[23] is that, for practical purposes, a score below the cutoff (≤18) cannot reliably distinguish delirium from severe dementia. Also, the test was performed by a degree-level psychologist, making it very difficult to transfer to the ICU setting without similar input. As the test takes 10-15 minutes to perform, it is too complex to be performed by bedside nursing staff. Only three patients with delirium scored higher on the CTD than any of the dementia patients. As the clinical diagnosis of delirium and cognitive testing often occurred hours apart, it was possible that these higher scores occurred with those patients whose delirium had started to resolve. Lastly the authors admit that the study did not evaluate the possible effect of education on the CTD scores.

The strength of the ICDSC[25] is that it is user friendly, quick and can be performed by nursing staff as opposed to experts. Also, many items can be evaluated by a nurse in the course of routine evaluation. However, while it was highly sensitive, it had a low specificity and therefore a high false positive rate (36%). Therefore, it is at best a 'screening' as opposed to a 'diagnostic' tool and psychiatric consultation is advised for those with a positive test.

The DDS,[26] while valid and reliable, could also be administered by nurses and doctors who regularly work on the ICU and not by specially trained experts. The DDS also allowed the 'severity' of delirium to be easily assessed. It is the largest of the studies to date and includes 1,073 patients and 3,588 observations. Importantly, the DDS is not highly dependent on the motivation of the patient, unlike other tools such as the CAM-ICU. The main limitation is that the tool was derived from an alcohol withdrawal scale (CIWA-Ar) and assesses the hyperactive form of delirium but does not assess the hypoactive or mixed types.

CAM-ICU: pilot study[29]

The main strengths of the CAM-ICU are that it can be used to monitor delirium both during and after mechanical ventilation. It requires relatively little training, can be performed by ICU staff who are not psychiatrically trained, and is user-friendly as it takes less than five minutes to perform. The CAM-ICU is also highly sensitive and specific, with high inter-rater reliability when compared with the reference standard (DSM-IV). Importantly, in the subgroup analysis of those groups thought to pose the greatest challenge to testing (intubated patients, age >65 years, suspected dementia) the tool still had excellent sensitivity, specificity and inter-rater reliability. However, the CAM-ICU should be tested further in large samples of these same groups.

The main limitation is that, although the CAM-ICU and

DSM-IV were performed within 1.5 hours of each other on average in this study, due to the fluctuating nature of delirium, patients may have scored differently. In fact, there were three discordant readings and likely aetiologies include a dose of sedative or analgesic drug being given between the CAM-ICU rating and the DSM-IV rating, and >3 hours between ratings. Therefore, future studies should employ frequent serial measurement of delirium in ICU. While only a small number of patients were included in the study (n=38), it was in fact powered to detect a sensitivity of 90% and to ensure a lower range of 80% for the confidence interval. Serial Glasgow Coma Scale readings were used to assess whether there had been a change in mental status. Substituting a sedation scale, as the authors recommend, would more accurately reflect changes that occur in critically ill patients attributable to both the fluctuating nature of delirium and the common and often liberal use of sedatives and analgesics.

CAM-ICU: main study[30]

The strengths of this study include the inclusion of a challenging study population of medically diverse, severely ill, mechanically ventilated patients; the large number of patient evaluations and the use of recognised delirium experts for the reference standard ratings.

The main limitation of the study is that, although the CAM-ICU demonstrated 100% sensitivity and specificity for the subgroup of patients with suspected dementia (consistent with the pilot study), the study was in fact not powered for subgroup analyses. The study was also based in a single centre; future studies will need to evaluate the generalisability of performance across multiple sites and other patient populations (e.g. surgical/trauma patients and those with a lower prevalence of delirium). From a purely statistical point of view it is clear that although the CAM-ICU has very good sensitivity and specificity, positive and negative predictive values could change in a setting in which the incidence of delirium were lower. Finally, re-inclusion of patients with a history of psychosis or neurological disease (great 'delirium mimickers,' excluded in the study for validation purposes) could lower the specificity of the CAM-ICU.

CAM-ICU: comparison study[31]

One of the strengths of this study is that 20 (91%) patients had rating interviews 10 minutes apart while two patients had a delay of no more than 120 minutes. In addition, the interviewers underwent extensive training and standardisation before the study with high inter-rater reliability before study onset. Patients with dementia, psychiatric and neurological disease were not excluded, therefore real-life performance of the CAM-ICU and the CAM were evaluated.

The limitations of the study include the small sample size, which is reflected in the wide confidence intervals around the point estimates for reliability and sensitivity. There were four false negatives or discordant results. One was due to temporal separation of tests in a patient with highly fluctuating symptoms, an intrinsic problem in the study of delirium, and two patients were not interviewed immediately due to clinical circumstances and care needs in the ICU. The study was also single-centre thereby limiting its generalisability to other ICUs.

Discussion

In summary, the DSM-IV is the reference standard for assessing delirium in unrestrained, un-intubated patients in the ICU, but must be performed by an expert in psychiatry and requires 30 minutes to perform. The CAM is a more useful reference standard for similar ICU patients, and can be conducted by non-psychiatrists in 10-15 minutes. The CAM-ICU is currently the only delirium tool fully validated for intubated patients. It can be performed by ICU staff and requires 2-5 minutes to perform. Agreement between the CAM and CAM-ICU is moderately high. The CAM-ICU appears to be the most valid test to date and demonstrates a high inter-rater reliability. The standard CAM method appears to detect more subtle cases of delirium in non-intubated cases. The CTD, ICDSC and DDS, are associated with too many problems, to be of any daily practical use in the ICU. To download the CAM-ICU, see www.icudelirium.org.

The association between delirium and outcomes

There are four studies to date, all single-centre prospective cohort studies, looking at the impact of delirium on morbidity and mortality of ICU patients (**Table 1**).[18,32-34]

In the study by Ely,[32] of 224 ventilated patients included in the outcome analysis, 183 (81.7%) developed delirium at some point during the ICU stay. Those who developed delirium had higher six-month mortality rates (34% *vs* 15%, p=0.03) and spent 10 days longer in hospital when compared to those who never developed delirium (p<0.001). After adjusting for covariates (age, severity of illness, co-morbid conditions, use of sedatives and analgesia), delirium was independently associated with higher six-month mortality (Hazard Ratio (HR) 3.2, 95% CI 1.4-3.0, p<0.001). Delirium in the ICU was also independently associated with a longer post-ICU stay (HR 1.6, 95% CI 1.2-2.3, p=0.009), fewer ventilator-free days (19 *vs* 24, p=0.03) and a higher incidence of cognitive impairment at hospital discharge (HR 9.1, 95% CI 2.3-35.3, p=0.002).

Interestingly, of the patients who were alert or easily arousable as measured by the Richmond Agitation and Sedation Scale (RASS) score of 0 or -1, more than half (54.4%) were delirious. Both mean and daily cumulative doses of sedative and narcotic medications were higher in patients in the delirium group, but only in the lorazepam group was this statistically significant. Also, delirium persisted in 11% of patients at the time of hospital discharge.

In the study by Lin *et al*,[18] of the 102 ventilated patients enrolled, 22 (22.4%) were found to be delirious during the first five days of their ICU stay. Delirium developed mostly on the second day of ICU admission. The mean duration of delirium was 3.0 ± 1.6 days. Five (22.7%) of the delirious patients were hyperactive, 14 (63.6%) were hypoactive and three patients (13.7%) displayed the mixed type of delirium.

The overall ICU mortality rate was 39.2%. Four patients died in the first five days. The mortality rate of delirious patients was significantly different from that of patients without delirium (HR 2.57, 95% CI 1.56-8.15, p=0.003). The

Reference	Ely *et al*[32]	Lin *et al*[18]	Thomason *et al*[33]	Ely *et al*[34]
Study aims	To determine if delirium is an independent predictor of 6-month mortality and LOS in ventilated ICU patients	To revalidate CAM-ICU. To investigate independent effect of delirium on mortality of ventilated ICU patients	To determine the relationship between delirium and outcomes among non-ventilated ICU patients	To determine the relationship between delirium in the ICU and outcomes including LOS in hospital
Design	Prospective, Cohort	Prospective, Cohort	Prospective, Cohort	Prospective, Cohort
Ventilated/ Non-ventilated	Ventilated	Ventilated	Non-ventilated	Both
Setting	Adult medical/ coronary ICU	Adult medical ICU	Adult medical ICU	Adult medical ICU
Period	Feb 2000-May 2001	October 2002-March 2003	February 2002-Jan 2003	Unspecified
Delirium tool	CAM-ICU	CAM-ICU	CAM-ICU	DSM-IV
Enrolled	275	109	261	53
Analysed	224	102	260	48
Results	183 (81.7%) developed delirium in ICU. Delirium group had higher 6m mortality + spent 10 days longer in ICU. Delirium is independently associated with higher 6m mortality, longer hospital stay, longer post-ICU stay, fewer ventilator free days, and higher incidence of cognitive impairment at hospital discharge	Delirious patients had a higher ICU mortality. Delirium, shock and illness severity were independent predictors of mortality. Delirium was present in 22% of patients in the first 5 days. CAM-ICU sensitivity: 91%/95% Specificity: 98%	48% of patients experienced delirium. Delirium group had 29% greater risk of remaining in ICU on any given day + 41% greater risk of remaining in hospital. They also had a higher mortality. Time to in-hospital death was not significantly different	Mean onset of delirium was 2.6 days. Mean duration was 3.4±1.9 days. 81% of patients developed delirium, 60.4% while on ICU. Duration of delirium was associated with length of stay on ICU + in the hospital. Delirium was the strongest predictor of LOS in hospital even after adjusting for various covariates
Conclusion	Delirium was an independent predictor of higher 6-month mortality and longer hospital stay after adjusting for relevant covariates.	Delirium is an independent predictor for increased mortality in ventilated ICU patients.	Delirium occurred in nearly half of the non-ventilated ICU patients. Even after adjusting for covariates, delirium was found to be an independent predictor of longer hospital stay.	The majority of patients developed delirium in the ICU + delirium was the strongest independent determinant of LOS in hospital.

Table 1 Summary of delirium outcome studies.

mean duration of delirium in the survival group was not different from the non-survival group (3±1.56 days *vs* 3±1.69 days, p=1.00).

In the study by Thomason *et al*,[33] of 261 non-ventilated patients analysed, 125 (48%) experienced at least one episode of delirium. Patients who experienced delirium had a 29% greater risk of remaining in the ICU on any given day when compared to patients who never developed delirium, even after adjusting for age, gender, race, Charlson co-morbidity score, APACHE II score and coma (HR 1.29, 95% CI 0.98-1.69, p=0.07).

Similarly, patients who experienced delirium had a 41% risk of remaining in hospital after adjusting for the same covariates (HR 1.41, 95% CI 1.05-1.89. p=0.023). Hospital mortality was higher among patients who ever developed delirium versus patients who never developed delirium (19% *vs* 6%, p=0.002). The time to in-hospital death was not significant between the two groups (HR 1.27, 95% CI 0.55-2.98, p=0.58).

In the second Ely study,[34] of the 48 patients studied, 39 (81.3%) developed delirium and 29 (60.4%) developed the complication on the ICU. The duration of delirium was associated with the length of stay (LOS) on the ICU (r=0.65, p=0.0001) and in hospital (r=0.68, p<0.0001).

The mean onset of delirium was at 2.6 days (SD±1.7) and the mean duration was 3.4±1.9 days. Delirium was the strongest predictor of length of stay in hospital (p=0.006) even after adjusting for severity of illness, age, gender, race and days of benzodiazepine and narcotic drug administration.

In summary, delirium in the ICU seems to be associated with higher ICU, hospital and six-month mortality. Delirium is also independently associated with longer post-ICU stay, fewer ventilator-free days and a higher incidence of cognitive impairment at hospital discharge. Up to 81.7% of patients

develop delirium in the ICU, most commonly on the second day of ICU admission, and it lasts on average three days. The vast majority of patients develop the hypoactive subtype.

Future research

While much progress has been made recently regarding delirium assessment tools and the prognostic implications of ICU delirium, the following areas in particular require more research:

- Risk factors pertinent to the ICU population including whether dopamine administration is a risk factor.[35,36]
- Whether prevention or treatment of ICU delirium would change clinical outcomes, particularly with regard to mortality, length of stay, cost of care and long term neuropsychological outcomes.
- RCTs of haloperidol versus the newer antipsychotic drugs with less associated side-effects (e.g. olanzapine). The MINDS study, currently in progress, will compare haloperidol *vs* ziprasidone *vs* placebo.
- Whether any anti-psychotic agent reduces the severity and duration of delirium and importantly long-term outcomes.
- Non-pharmacological management strategies to reduce delirium and improve outcomes.

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