ICU Delirium and sedation: understanding their role in long-term patient outcomes

Yoanna Skrobik MD FRCP(c)
Conflicts of interest

- Member, SCCM Pain, Agitation and Delirium guidelines writing committee
- Investigator initiated research funding, Hospira
- Academic chair, Université de Montréal
Academic chair

Astellas
Merck
Pfizer
Baxter
Hospira
Otsuka
Novartis
Lilly
plan

- Introduction: sequelae from the ICU
- Delirium in the ICU: how hard can detection be?
- Level of consciousness alterations in the ICU
- Sedation and delirium detection
- Long term cognitive and psychological outcomes
- conclusion
Functional Disability 5 Years after Acute Respiratory Distress Syndrome

Margaret S. Herridge, M.D., M.P.H., Catherine M. Tansey, M.Sc., Andrea Matté, B.Sc., George Tomlinson, Ph.D., Natalia Diaz-Granados, M.Sc., Andrew Cooper, M.D., Cameron B. Guest, M.D., C. David Mazer, M.D., Sangeeta Mehta, M.D., Thomas E. Stewart, M.D., Paul Kudlow, B.Sc., Deborah Cook, M.D., Arthur S. Slutsky, M.D., and Angela M. Cheung, M.D., Ph.D., for the Canadian Critical Care Trials Group
Frozen shoulders (in 2 patients); vocalisation and voice changes (in 1 patient); recurrent reactive airways disease (in 1 patient); and dental implants for ICU-related damage (in 1 patient). There were concerns about cosmesis in 10 patients, with prolonged noninvasive mask ventilation reported that these concerns contributed to social isolation and sexual dysfunction. Causes of disability included bilateral amputations due to necrosis from vaso-occlusive disease (in 1 patient) and new sensorineural loss and tinnitus attributed to ototoxic ICU medications (in 2 patients). Fifty-one percent of patients reported at least one episode of physician-diagnosed depression, anxiety, or both between 2 and 5 years of follow-up; several patients had substantial mental health challenges, including an acute psychotic episode due to post-traumatic stress disorder (in 1 patient) and severe agitated depression and agoraphobia (in 2 patients). Family mental health problems, including anxiety, depression, or post-traumatic stress disorder, as reported by patients or family members, occurred in 27% of cases over the same time period. Other problems, such as social isolation, sexual dysfunction, job loss, and disputes over disability and insurance claims, were also qualitatively discussed during the study interviews.
Delirium in the ICU: what does it lead to? Has to be preceded by: ‘how hard can detection be’?
ICU Delirium diagnostic challenges

- Standardized delirium screening in the ICU setting, and their inherent methodological flaw
- Potential confounders
DSM IV criteria

DSM-IV requires the following essential criteria for a diagnosis of delirium:

- **Disturbance of consciousness** (i.e. reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.
- **Change in cognition** (e.g. memory deficit, disorientation, language disturbance and perceptual disturbance) that is not better accounted for by a preexisting, established, or evolving dementia.
- **Development over a short period of time** (usually hours to days) and disturbance 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.
Delirium scales

ICDSC
(Intensive Care Delirium Screening Checklist)
http://www.icudelirium.co.uk/

CAM-ICU
(Confusion Assessment Method-ICU)
www.icudelirium.org
### DSM-IV criteria

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- **Development over a short period of time** (usually hours to days) and disturbance *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.*
Confounders:

- Other psychiatric diagnoses
Other psychiatric diagnoses

- Delirium (10-80%)
- Depression (35-45%)
- Post-Traumatic stress disorder (35%)
ICU Delirium diagnostic challenges

- Standardized delirium screening in the ICU setting, and their inherent methodological flaw
- Potential confounders
Delirium incidence

From 10% to > 80%

- Intensive Care Med 27:1892-1900
- JAMA 286:2703-2710
- Crit Care Med 29:1370-1379
- JAMA 291:1753-1762
- Crit Care 5:265-270
- Gen Hosp Psychiatry 17:371-379
- Crit Care Med 32:2254-2259
- J Am Geriatr Soc 51:591-598
- Lancet 2010 Nov 27;376(9755):1829-37 (10% of 6572 patients screened)
wakefulness
DSM IV criteria

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Alteration of consciousness and outcome
Alteration of consciousness and outcome

- Coma is bad for you
Figure 3: Kaplan-Meier Analysis Depicting the Impact of Delirium and Coma on Mortality
Figure 3. Kaplan-Meier Analysis of Delirium in the Intensive Care Unit and 6-Month Survival

![Graph A](image1)

No. at Risk
No Delirium 41 34 28 25 22 21 19
Delirium 183 138 116 111 104 98 88

![Graph B](image2)

No. at Risk
No Delirium
Normal 17 15 11 11 10 10 10
Coma-Normal 24 19 17 15 12 11 9
Delirium
Delirium Only 60 51 42 39 34 33 29
Delirium-Coma 123 87 74 72 70 65 59
Early Intensive Care Sedation Predicts long-term Mortality in Ventilated Critically Ill Patients


Figure 4: Kaplan Meier curves for time to extubation and mortality at 180 day

Panel A: Time to extubation was significantly longer amongst patients who were deeply sedated early in ICU compared with those that were not. Median [IQR] 7.7[6.0-8.6] vs 2.4[1.9 - 4.0] days (Log-rank P<0.001).

Panel B: Those who were deeply sedated early (first 48 hours) showed significantly reduced survival (Log-rank P=0.048) compared with patients who were not deeply sedated.
Why people develop coma

Critical Care Medicine

Predisposing factors to coma and delirium: Fentanyl and midazolam exposure, CYP3A5, ABCB1 and ABCG2 genetic polymorphisms, and inflammatory factors.
Why people develop coma

24 Patients with coma

42 Patients with delirium and coma

22 Patients with delirium

12 Patients with no delirium and no coma
Critical Care Medicine

Predisposing factors to coma and delirium: Fentanyl and midazolam exposure, CYP3A5, ABCB1 and ABCG2 genetic polymorphisms, and inflammatory factors.
Iatrogenic coma
Delirium symptoms

Specifically, level of consciousness
DSM IV criteria

- Phenomenologists include:
  - Sedation
  - Neurologic dysfunction
  - Cognitive dysfunction

DSM-IV requires the following essential criteria for a diagnosis of delirium:

- **Disturbance of consciousness** (i.e. reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.
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wakefulness

Does it influence delirium assessment?
Delirium scales

ICDSC
(Intensive Care Delirium Screening Checklist)

http://www.icudelirium.co.uk/

CAM-ICU
(Confusion Assessment Method-ICU)

www.icudelirium.org
Assessment of Delirium Relative to Daily Sedative Interruption

JT Poston MD, MW Sjoding MD, AS Pohlman RN MSN, BK Gehlbach MD, JB Hall MD, JP Kress MD
<table>
<thead>
<tr>
<th>CAM-ICU before DSI</th>
<th>CAM-ICU after DSI</th>
<th></th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DCF</td>
<td>DCF</td>
<td>Delirium</td>
<td>Coma</td>
<td></td>
</tr>
<tr>
<td>DCF</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Delirium</td>
<td>20</td>
<td>20</td>
<td>0</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Coma</td>
<td>2</td>
<td>7</td>
<td>5</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>27</td>
<td>5</td>
<td>55</td>
<td></td>
</tr>
</tbody>
</table>

*Test for symmetry $X^2 = 29$, $p<0.001$*
### Table 2: Delirium and Coma-Free Days (%)

<table>
<thead>
<tr>
<th>CAM-ICU used from Matched-pair data</th>
<th>CAM-ICU Before DSI</th>
<th>CAM-ICU After DSI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ventilator days</strong> <em>(n=177)</em></td>
<td>27%</td>
<td>39%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>ICU days</strong> <em>(n=228)</em></td>
<td>37%</td>
<td>46%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Total days</strong> <em>(n=284)</em></td>
<td>48%</td>
<td>56%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Assessment of Delirium Relative to Daily Sedative Interruption

JT Poston MD, MW Sjoding MD, AS Pohlman RN MSN, BK Gehlbach MD, JB Hall MD, JP Kress MD

- 48% higher delirium identification during sedation administration when compared to assessments made in the same patients after sedation was lightened to the point of wakefulness.
- This difference persisted for analysis of MV days, ICU days, and total hospital days
Wakefulness

- Delirium assessment is sensitive to the timing of evaluation relative to sedative/analgesic infusion and interruption.
- This robust effect can cause significant differences in assessed days of delirium well beyond the time of sedative/analgesic infusion.

Implications

- A standard methodology of assessment accounting for sedative/analgesic infusion and daily interruption should be utilized for future investigation.
- Delirium due solely to sedative/analgesic infusion may portend a different prognosis than delirium that persists in its absence.
# Intensive Care Delirium Screening Checklist (ICDSC)

- **Altered level of consciousness** (A-E)
- **Inattention**
- **Disorientation**
- **Hallucination delusion – psychosis**
- **Psychomotor agitation or retardation**
- **Inappropriate speech or mood**
- **Sleep/wake cycle disturbance**
- **Symptom fluctuation**

<table>
<thead>
<tr>
<th>Patient Evaluation</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered level of consciousness* (A-E)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inattention</td>
<td></td>
<td></td>
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<tr>
<td>Disorientation</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Hallucination delusion – psychosis</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Psychomotor agitation or retardation</td>
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<tr>
<td>Inappropriate speech or mood</td>
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<tr>
<td>Sleep/wake cycle disturbance</td>
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<td></td>
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<tr>
<td>Symptom fluctuation</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Total score (0-8)</td>
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</tr>
</tbody>
</table>

If A or B do not complete patient evaluation for the period

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Bergeron, N. Dubois M.J. Skrobik, Y.
*Intensive Care Medicine*, 2001
**Individual delirium symptoms: Do they matter?**

François Marquis, MD, FRCP(C); Sébastien Ouimet; Richard Riker, MD; Mariève Cossette, MSc; Yoanna Skrobik, MD, FRCP(C)

<table>
<thead>
<tr>
<th>ICDSC Symptom</th>
<th>Hazard Ratio (95% CI), p Value</th>
<th>Adjusted Hazard Ratio (95% CI), p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alteration of consciousness</td>
<td>0.852 (0.424–1.714) 0.6537</td>
<td>0.906 (0.447–1.839) 0.7856</td>
</tr>
<tr>
<td>Disorientation</td>
<td>0.719 (0.392–1.316) 0.2847</td>
<td>0.606 (0.226–1.128) 0.1140</td>
</tr>
<tr>
<td>Inattention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No delirium</td>
<td>2.441 (0.870–6.848) 0.0899</td>
<td>2.011 (0.696–5.812) 0.1970</td>
</tr>
<tr>
<td>Delirium</td>
<td>0.571 (0.254–1.283) 0.1749</td>
<td>0.650 (0.276–1.532) 0.3246</td>
</tr>
<tr>
<td>Sleep-wake cycle disturbance</td>
<td>0.886 (0.372–2.112) 0.7846</td>
<td>0.872 (0.369–2.058) 0.7540</td>
</tr>
<tr>
<td>Psychomotor agitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No delirium</td>
<td>3.116 (1.428–6.799) 0.0043</td>
<td>2.577 (1.162–5.716) 0.0199</td>
</tr>
<tr>
<td>Delirium</td>
<td>0.416 (0.198–0.875) 0.0208</td>
<td>0.470 (0.222–0.998) 0.0494</td>
</tr>
<tr>
<td>Psychomotor slowing</td>
<td>1.741 (0.962–3.153) 0.0671</td>
<td>1.871 (0.992–3.530) 0.0530</td>
</tr>
<tr>
<td>Inappropriate speech or mood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No delirium</td>
<td>2.164 (0.738–6.348) 0.1597</td>
<td>1.664 (0.555–4.987) 0.3635</td>
</tr>
<tr>
<td>Delirium</td>
<td>0.253 (0.100–0.642) 0.0038</td>
<td>0.231 (0.089–0.599) 0.0026</td>
</tr>
<tr>
<td>Hallucinations, delusions</td>
<td>0.330 (0.097–1.126) 0.0766</td>
<td>0.265 (0.075–0.938) 0.0394</td>
</tr>
<tr>
<td>Symptom fluctuation</td>
<td>0.749 (0.318–1.764) 0.5081</td>
<td>0.785 (0.323–1.907) 0.5923</td>
</tr>
</tbody>
</table>
Nicolas Bergeron  
Yoanna Skrobik  
Marc-Jacques Dubois

Is disturbance of consciousness an important feature of ICU delirium?

Accepted: 6 April 2005  
Published online: 21 April 2005  
© Springer-Verlag 2005

Sir: In a recent study Ely et al. [1] monitored consciousness in ventilated ICU patients using two types of bispectral index (BIS) algorithms. The authors compared the BIS levels to the presence or absence of delirium and measures of arousal. Delirium was assessed by the Confusion Assessment Method for the ICU (CAM-ICU) and arousal with the Richmond Agitation-Sedation Scale (RASS). They found a statistical correlation between BIS values and RASS scores but none with the presence of delirium. BIS values could not distinguish delirious from nondelirious patients, even after controlling for level of arousal.

The Intensive Care Delirium Screening Checklist [2] is a clinical tool designed to

appropriate mood or speech, sleep/wake cycle disturbance, and symptom fluctuation. In the checklist’s validation study the level of consciousness was the only item, using Cronbach’s α coefficients that weakened the scale’s accuracy to detect delirium.

The reduced clarity of awareness of the environment and alterations in attention are considered cardinal features of delirium [3]. Electroencephalographic slowing which is correlated with disturbance in consciousness and delirium has been recognized since Romano and Engel’s [4] pioneering work. However, data from the two studies mentioned above [1, 2] suggest that disturbance of consciousness does not discriminate well for delirium status in an intensive care setting.

The CAM-ICU is a useful instrument to help clinicians assess delirium, especially with patients unable to communicate verbally. It is considered positive and suggests a diagnosis of delirium if patients demonstrate an acute onset or a fluctuating course of mental status changes, inattention, and either disorganized thinking or altered level of consciousness [1]. However, in the ICU context altered level of consciousness may not be as valid a discriminator for delirium diagnosis as it is in other populations. Moreover, the Confusion Assessment Method (CAM), from which the CAM-ICU derives, has been criticized as a diagnostic tool [5].

References


N. Bergeron · Y. Skrobik · M.-J. Dubois  
Département de Psychiatrie,  
Centre hospitalier de l’Université de Montréal
Why would you confound the two?
normalcy → delirium → coma
Why this is an issue
Point: Should Benzodiazepines be Avoided in Mechanically Ventilated Patients? Yes

Counterpoint: Should Benzodiazepines Be Avoided in Mechanically Ventilated Patients? No
• Highly lipid soluble
• α-OH midazolam metabolite
• CYP3A4 activity decreased in critical illness
• Substantial CYP3A4 variability

long term outcomes
Consistent predictors of post-ICU PTSD:
- prior psychopathology
- greater ICU benzodiazepine administration
- post-ICU memories of in-ICU frightening and/or psychotic experiences.
- Higher mortality in delirious patients.
- The total ICU population scored lower for quality of life in all domains compared to the reference population.
- Some domains worse for delirious patients.
- Delirium associated with being discharged to a place other than home (61.3% vs 20.5%, p < 0.0001) and have greater functional decline (67.7% vs 43.6%, p = 0.023).

- After adjusting for covariates (SOI, MV), delirium was strongly and independently associated with greater odds of being discharged to a place other than home (odds ratio, 7.20; 95% confidence interval, 1.93 to 26.82).
ICDSC vs. Patient Outcome

Comparison of mortality, ICU LOS and outcome according to DSC score

DSC=0
DSC 1-3
DSC >3

Mortality (%)
LOS Days ICU
Home no help (%)
Home+help (%)
Convalescence (%)
Long Term Care (%)
Other (%)

Subsyndromal delirium in the ICU: evidence for a disease spectrum
Cognitive dysfunction
Cognitive dysfunction

- Two large population based studies showing an association between ICU admission and cognitive decline
- Contrast with a Dutch study where elderly patients with unexpected surgery and ICU admission were similar to age-matched controls
Cognitive dysfunction

**Table 4. Mean EQ Utility Score by Age of the General Dutch Population and for Our Study Group, Both Overall and per Diagnosis at Admission in 575 Patients**

<table>
<thead>
<tr>
<th>Mean EQ Utility Score (No. of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 18-49 y</td>
</tr>
<tr>
<td>Reference population</td>
</tr>
<tr>
<td>Study group</td>
</tr>
<tr>
<td>Overall</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Vascular</td>
</tr>
<tr>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Oncology</td>
</tr>
<tr>
<td>General surgery</td>
</tr>
</tbody>
</table>

Abbreviations: EQ, EuroQol; NA, not applicable (conclusive numbers when \( n \geq 5 \) patients).

Note: The EQ-6D index values are based on the EQ-5D US index tariff (D1). Age at time of answering questionnaire.

**Only 3 patients in this group.**
Delirium as a predictor of cognition at discharge

Delirium as a predictor of long-term cognitive impairment in survivors of critical illness

Timothy D. Girard, MD, MSc; James C. Jackson, PsyD; Pratik P. Pandharipande, MD, MSc; Brenda T. Pun, MSN; Jennifer L. Thompson, MPH; Ayumi K. Shintani, PhD, MPH; Sharon M. Gordon, PsyD; Angelo E. Canonicco, MD; Robert S. Dittus, MD, MPH; Gordon R. Bernard, MD; E. Wesley Ely, MD, MPH

Crit Care Med 2010 Vol. 38, No. 7
The methodology is crucial

- Both psychological well being and cognitive function appear affected after ICU stay
- It would be of interest to identify predictors for both
- Confounder and co-morbidity markers are essential
Thank you