ICU Delirium—A Real Epidemic (or are we delirious)?

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Faculty Disclosures

Dr. Hall

• receives honoraria from the ACCP for board review course and SEEK
• receives honoraria from McGraw-Hill and Taylor-Francis publishing
10 Big Mistakes in Intensive Care Medicine (JLV, JBH, AS)

1-We focus too much on syndromes—prominently ARDS, sepsis, acute kidney injury (AKI), and we spend much time redefining them. Even though we considered sepsis as a too vaguely defined entity, treatments were studied in prospective trials. Most were unsuccessful.......... Better identification of patient populations is the key. Instead of general phenotypes (fever and tachycardia), we should uncover the basic cellular alterations characterizing critical illness, and by doing so better characterize the patients' status.
**ICU delirium** is our neurologic syndrome

# of MS

![Bar chart showing the number of MS cases from 1999 to 2013. The number of cases increases significantly from 2008 onwards.](chart.png)
Both the Confusion Assessment Method for the ICU (North America) and the Intensive Care Delirium Screening Check List (Europe) came into wide Application in 2000-2001
LOS, mortality, morbidity assoc with ICU delirium

Ely, JAMA 2004

Delirium as a Predictor of Mortality in Mechanically Ventilated Patients in the Intensive Care Unit
LOS, mortality, morbidity assoc with ICU delirium

Ely, JAMA 2004
Days of Delirium Are Associated with 1-Year Mortality in an Older Intensive Care Unit Population

For each day of delirium, 1-yr mortality increased by 10%”

Cox Model HR

- Age: 1.03
- IADL: 1.30
- Comorbidity: 1.21

Delirium day: 1.10

Pisani MA et al., AJRCCM 180: 1092
Don’t just stand there.......

Statin Use and Risk of Delirium in the Critically Ill

Valerie J. Page¹,², Daniel Davis³,⁴, Xiao B. Zhao¹, Samuel Norton⁵, Annalisa Casarin¹, Thomas Brown⁶, E. Wesley Ely⁷,⁸, and Daniel F. McAuley⁹,¹⁰

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Table 4: Relationship between Statin Continuation and the Odds of Being Delirium-Free Coma-Free in Persons Prescribed Statins before Admission

<table>
<thead>
<tr>
<th></th>
<th>Statin Continuation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td>Days on statin, per day</td>
<td>1.39</td>
</tr>
<tr>
<td>Age, per year</td>
<td>0.97</td>
</tr>
<tr>
<td>Sex, women vs. men</td>
<td>0.64</td>
</tr>
<tr>
<td>mSOFA, per point</td>
<td>0.79</td>
</tr>
<tr>
<td>Sepsis, yes vs. no</td>
<td>3.23</td>
</tr>
<tr>
<td>Propensity score*</td>
<td>2.03</td>
</tr>
<tr>
<td>Ventilated, yes vs. no</td>
<td>0.71</td>
</tr>
<tr>
<td>Emergency vs. elective</td>
<td>28.2</td>
</tr>
</tbody>
</table>

Definition of abbreviations: CI = confidence intervals; mSOFA = modified Sequential Organ Failure Assessment (excluding Glasgow Coma Scale); OR = odds ratio.

*Propensity score accounting for age, sex, primary hypercholesterolemia, ischemic heart disease, diabetes, peripheral and cerebrovascular disease, and admission for aortic aneurysm surgery.
What is the true incidence of delirium in the ICU?

- Case Mix: 32%
- Assessment Tool: 81%
- Sedation Practice:

32% → 81%
All cases of delirium are created equal, but some are more equal than others.
Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)

Sedation and Delirium Assessments: A Two Step Approach

**Step One: Sedation Assessment (RASS)**

If RASS is -4 or -5, then Stop & Reassess patient at later time
If RASS is above -4 (-3 through +4) then Proceed to Step 2

**Step Two: Delirium Assessment (CAM-ICU)**

- **Feature 1:** Acute onset of mental status changes or a fluctuating course
- **Feature 2:** Inattention
- **Feature 3:** Disorganized Thinking
- **Feature 4:** Altered Level of Consciousness

= DELIRIUM

**Richmond Agitation-Sedation Scale (RASS)**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>+4</td>
<td>Combative</td>
</tr>
<tr>
<td>+3</td>
<td>Very agitated</td>
</tr>
<tr>
<td>+2</td>
<td>Agitated</td>
</tr>
<tr>
<td>+1</td>
<td>Restless</td>
</tr>
<tr>
<td>0</td>
<td>Alert and calm</td>
</tr>
<tr>
<td>-1</td>
<td>Drowsy</td>
</tr>
<tr>
<td>-2</td>
<td>Light sedation</td>
</tr>
<tr>
<td>-3</td>
<td>Moderate sedation</td>
</tr>
<tr>
<td>-4</td>
<td>Deep sedation</td>
</tr>
<tr>
<td>-5</td>
<td>Unarousable</td>
</tr>
</tbody>
</table>

Ely, JAMA 2001; 286, 2703-2710.

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A Day in the Life of RASS
## Sedatives and Delirium

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily ICU Dose, Mean (SD), mg</th>
<th>Cumulative ICU Dose, Mean (SD), mg*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Delirium (n = 41)</td>
<td>Delirium (n = 183)</td>
</tr>
<tr>
<td>-----------</td>
<td>------------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>1.12 (2.2)</td>
<td>4.8 (12.8)</td>
</tr>
<tr>
<td>Propofol</td>
<td>36.6 (258.6)</td>
<td>48.4 (172.9)</td>
</tr>
<tr>
<td>Morphine</td>
<td>5.8 (17.0)</td>
<td>17.3 (163.8)</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.53 (1.7)</td>
<td>0.78 (1.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>9.0 (20.0)</td>
<td>49.2 (131.3)</td>
</tr>
<tr>
<td>Propofol</td>
<td>362.1 (1265.4)</td>
<td>591.2 (3942.2)</td>
</tr>
<tr>
<td>Morphine</td>
<td>48.0 (147.0)</td>
<td>168.1 (1321.9)</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>3.1 (10.3)‡</td>
<td>8.7 (22.9)‡</td>
</tr>
</tbody>
</table>

*P Values are for comparison of patients with delirium to those without delirium.

Ely EW, *JAMA* 291: 1753
Remarkably in > 10 yrs of reporting the incidence of delirium/coma, determining its association with outcomes, and even conducting interventional trials, we have not attempted to disentangle (within the limits of necessary patient care) the sedation-delirium problem.
Rapidly Reversible, Sedation-related Delirium versus Persistent Delirium in the Intensive Care Unit

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Department of Medicine, Section of Pulmonary and Critical Care, University of Chicago, Chicago, Illinois

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Patel et al

- 29% of patients scored as delirious had delirium absent when reassessed after sedation hold (up to 2 hrs)
- CAM-ICU 10.5 x more likely to dx delirium if done during sedation administration than after hold
- This rapidly reversible delirium showed reduced LOS, duration of MV, and improved survival as compared to persistent delirium

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<table>
<thead>
<tr>
<th>Drug</th>
<th>Subjects Exposed (%)</th>
<th>Total h, Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol</td>
<td>97 (95.1)</td>
<td>40 (21, 88)</td>
</tr>
<tr>
<td>Midazolam</td>
<td>55 (53.9)</td>
<td>1 (0, 10)</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>101 (99)</td>
<td>56 (32, 97)</td>
</tr>
</tbody>
</table>

Table 2: Cumulative Sedative and Analgesic Medication Exposures
Point 1 and its corollaries

- 1/4 to 1/3 of MV patients who would be scored by CAM-ICU as delirious have a rapidly reversible delirium demonstrable by sedation hold and their delirium does not associate with poor outcome
  - Should be built into monitoring for delirium
  - These patients should be stratified (excluded?) in intervention trials
  - These patients not likely to yield fruitful results in mechanistic studies
Potential reversible causes of delirium that might not result in long-term brain dysfunction

- **Drugs**
- **Hepatic encephalopathy**
- **Electrolyte disturbances**
- **Cerebral edema**
- **Hypothermia**
The typical severely ill ARDS patient with exposures to both reversible and non-reversible insults

- **Short-term coma/delirium near universal**
- **Extensive delirium testing in extreme AHRF not feasible**
- **Longterm neuropsychiatric dysfunction near universal**
- **Imaging studies not clear as to a macroscopic ‘lesion’ (perhaps just volume loss—VISIONS MRI data)**
- **Correlations not tight for hypoxemia, PPV exposures**
Toward a better understanding of the brain in critical illness

Mechanical Ventilation Triggers Hippocampal Apoptosis by Vagal and Dopaminergic Pathways

Adrián González-López¹, Inés López-Alonso¹, Alina Aguirre¹, Laura Amado-Rodríguez², Estefanía Batalla-Solís², Aurora Astudillo³, Cristina Tomás-Zapico¹, Antonio Fueyo¹, Claudia C. dos Santos⁴, Konrad Talbot⁵, and Guillermo M. Albaiceta¹,²,⁶

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A bad brain-ventilator connection

- Murine model of high + low pressure MV with hippocampal apoptosis and Akt survival pathway studied
- Studies also done in vagotomized, haloperidol-treated, and local brain dopamine-blocked animals

- Findings—MV triggers hippocampal apoptosis as a result of type 2 dopaminergic receptor activation in response to vagal signaling—also causes alterations in dysbindin 1, a protein known to regulate cell surface D2R recycling in neurons
- Dysbindin 1 results confirmed in brain slices of humans who had undergone MV
Figure 6. Dysbindin-1 immunohistochemistry of hippocampal formation sections from nonventilated and mechanically ventilated patients. (A) Immunoreactivity in the ventilated patients was greater in neurons throughout the hippocampal formation (left), but was most apparent in CA2/3 (right). Outlined areas in the left panels correspond to high-power fields on the right. (B) The intensity of immunoreaction was semiquantitatively analyzed, confirming that the difference was significant. (C) Correlation between intensity of the signal and duration of mechanical ventilation. *P < 0.05 versus nonventilated patients.
**Figure 7.** Schematic representation of the mechanisms of cell apoptosis induced by dopamine in our model. Under normal conditions, dopamine activates its type 1 receptors (DRD1, left). The increased release of dopamine (right) activates type 2 dopamine receptors (DRD2), resulting in decreased activation of Akt (i.e., decreased Akt pS473/pThr308) and therefore decreased inhibition of glycogen synthase kinase-3β (GSK3β) (i.e., decreased GSK3β pS9). The resulting activation of GSK3β triggers the intrinsic apoptotic pathway. Mitochondria are damaged and caspases are activated. In the final steps of this cascade, poly(ADP-ribose) polymerase-1 (PARP-1) is cleaved and a 89-kD fragment is released from the nucleus into the cytoplasm. Cleaved PARP-1 is unable to maintain its DNA-repairing capabilities, resulting in apoptosis.

DARPP-32 = dopamine- and cAMP-regulated phosphoprotein of 32 kD.
Point 2

• For the pool of patients in whom we know delirium strongly associates with poor longterm outcome
  – We need to better understand mechanisms linking brain injury to ICU diseases and interventions/environment, such as MV
  – In addition to minimizing exposure to the injurious force (eg high lung vols/pressures) we need to consider interruption of adverse neural pathways or enhancement of neuroprotective pathways