Long-Term Cognitive Impairment, Delirium, and the ABCDEs

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VA TN Valley Health Care System GRECC
Disclosures: ICU Physician Vanderbilt
- Abbott, Hospira, Orion
- NIH and VA U.S. Federal Funding
- Author of PAD Guidelines of SCCM 2013
- Chair of SCCM Delirium section for PAD
- Co-Chair of SCCM ICU Liberation project to aid worldwide implementation
Dr. Swenson explained, "I'll tell you the truth. What I have discovered...is not what I expected. It is something greater, much more ambitious than anything we had hoped for...in science: Never be so focused on what you are looking for that you overlook the thing you actually find."

Ann Patchett - 2011, *State of Wonder*
“I came awake on the fifth day. My first memory is that of floating up from the ocean bottom, my eyes still waterlogged and with what felt like scuba gear stuffed in my mouth and throat. I couldn’t speak. As I broke to the surface, I understood that I was still in the ICU at Our Lady, but I heard nothing of what anybody said.

Abraham Verghese - 2009, *Cutting for Stone*
Delirium
Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit

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www.icudelirium.org

"ICU stays lead to Alzheimer's-like problems in one-third of patients"
CBS News

WATCH THE REPORT

ABCDEs of Prevention and Safety

ABCDE is a standard bundle of ICU measures that includes spontaneous Awakening and Breathing coordination, attention to the Choice of sedation, Delirium monitoring, and Early mobility and exercise. All individual components of this bundle are evidence based and can help standardize communication, improve interdisciplinary patient care, reduce mortality, and improve long-term cognitive and functional outcomes.

what is Delirium?

Delirium is basically inattention and confusion that represents the brain temporarily failing. A person who is delirious is unable to think clearly and can't make sense of what is going on around him.
Take Home Message

Delirium = Dangerous

Patient = Vulnerable

Andros Island by N Rakov, NEJM 2011;365:457
6 out of 10 ICU patients are ≥ 65
Annually

1.4 Million
Seniors Survive the ICU

Wunsch JAMA 2010; 303: 849-856
Society of Critical Care Medicine, Critical Care Statistics in the United States, 2012
50-70% Cognitively Impaired
60-80% Functionally Impaired
ICU Survivorship

...like it was in a huge, empty gray space, sort of like a monstrous underground parking garage with no cars, only me, floating or seeming to float, on something...

-SB
Delirium in Mechanically Ventilated Patients
Validity and Reliability of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)
CARING FOR THE
CRITICALLY ILL PATIENT

Ely EW, JAMA 2003;289:2983-91

Monitoring Sedation Status Over Time in ICU Patients
Reliability and Validity of the Richmond Agitation-Sedation Scale (RASS)
Delirium as a Predictor of Mortality in Mechanically Ventilated Patients in the Intensive Care Unit
Delirium Duration & Mortality

<table>
<thead>
<tr>
<th>Days of Delirium</th>
<th>Relative Hazard of Death (HR)</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 vs 1</td>
<td>1.7</td>
<td>1.27-2.29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0 vs 2</td>
<td>2.69</td>
<td>1.58-4.57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0 vs 3</td>
<td>3.73</td>
<td>1.92-7.23</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Shehabi Y, et al. CCM 2010; 38:2311–2318
Cognitive Impairment: Sepsis

Iwashyna T, JAMA 2010;304:1787-1794
Delirium and Long-Term Cognitive Outcomes

Cognitive Function at 1 year (predicted mean T-score)

Days of ICU Delirium

p=.005

Girard T et al CCM 2010; 38:1513–1520
Delirium and Brain Atrophy

(A) 46 year old, no delirium  (B) 42 year old, 12 days of delirium

Gunther M et al. CCM 2012;40:2022-32
The VISIONS MRI Studies

![Graphs showing hippocampal and superior frontal lobes volumes over days of delirium in hospital.](image)

Gunther M et al. CCM 2012;40:2022-32
Persistent cognitive impairment, hippocampal atrophy and EEG changes in sepsis survivors

Alexander Semmler,1,6 Catherine Nichols Widmann,1 Thorsten Okulla,1 Horst Urbach,2 Markus Kaiser,3,7 Guido Widman,4 Florian Mormann,4,8 Julia Weide,1 Klaus Fliessbach,4 Andreas Hoeft,3 Frank Jessen,5 Christian Putensen,3 Michael T Heneka1

- Bonn Germany, 2 center 6-24 month follow-up of 25 septic and 19 non-septic ICU survivors
- Sepsis survivors showed cognitive deficits in verbal learning and memory
- Significant reductions of hippocampal volume vs. controls
- More low frequency EEG activity indicating brain dysfunction
Bringing to light Risk factors and Incidence of Neuropsychological dysfunction in ICU survivors
INDEPENDENT VARIABLES

- Delirium Duration
- Drug Exposure

DEPENDENT VARIABLES

- Long Term Cognitive Impairment (LTCI) Battery
- Health-Related Quality of Life (HRQL) Battery

Patient enrollment → Time → 12-month follow-up
Long-Term Cognitive Impairment after Critical Illness


ABSTRACT

BACKGROUND
Survivors of critical illness often have a prolonged and disabbling form of cognitive impairment that remains inadequately characterized.
### Global Cognitive Scores

<table>
<thead>
<tr>
<th>RBANS SCORES</th>
<th>3 months</th>
<th></th>
<th>12 months</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td></td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>Extremely low (&lt; 69)</td>
<td>90 (24%)</td>
<td></td>
<td>68 (21%)</td>
<td></td>
</tr>
<tr>
<td>Borderline (70-79)</td>
<td>106 (28%)</td>
<td></td>
<td>85 (26%)</td>
<td></td>
</tr>
<tr>
<td>Low average (80-89)</td>
<td>105 (28%)</td>
<td></td>
<td>103 (32%)</td>
<td></td>
</tr>
<tr>
<td>Average (90-109)</td>
<td>70 (19%)</td>
<td></td>
<td>67 (21%)</td>
<td></td>
</tr>
<tr>
<td>High Average (110-119)</td>
<td>2 (1%)</td>
<td></td>
<td>2 (1%)</td>
<td></td>
</tr>
<tr>
<td>Superior (120-129)</td>
<td>0 (0%)</td>
<td></td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Very superior (&gt;130)</td>
<td>0 (0%)</td>
<td></td>
<td>0 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

Scores of <70 seen in patients with Alzheimer’s disease; mild MCI have scores around 84. Dementias in 80s
The Picture of Dementia Following ICU Care

A

<table>
<thead>
<tr>
<th></th>
<th>&lt;65 Years</th>
<th>&gt;=65 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 Months</td>
<td>12 Months</td>
</tr>
<tr>
<td></td>
<td>3 Months</td>
<td>12 Months</td>
</tr>
</tbody>
</table>

- **Normal**
- **MCI**
- **TBI**
- **AD**

- N=244
- N=227
- N=130
- N=98

RBANS Global Cognitive Score

- 40
- 60
- 80
- 100
- 120
Global Cognitive Scores by Age

<table>
<thead>
<tr>
<th>Age Range</th>
<th>N</th>
<th>3 Months</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=49 Years</td>
<td>97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-64 Years</td>
<td>89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=65 Years</td>
<td>147</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data points correspond to different cognitive levels:
- Normal
- MCI (Mild Cognitive Impairment)
- TBI (Traumatic Brain Injury)
- AD (Alzheimer's Disease)
Delirium and Executive Function

![Graph showing the relationship between the duration of delirium and adjusted Trails B T-Score over 12 months. The graph indicates a downward trend with increasing duration.](image-url)
“Dementia is perhaps the cruelest manifestation of ageing, inexorably melting away all that which makes us individual and human.”

See Editorial page 177
ABCDEs:

Building blocks of managing Pain, Agitation & Delirium
Birth of the ABCDEs


SBT  
SAT  
Remove (A+B)  
Remove Sedation  
Sedation choice  
Sedation choice  
Early Mobility

...quick tour of the RCT literature...
Delirium Prevention and Safety: Starting with the ABCDEs

It is essential to consider delirium management in the broader picture of ICU patient care as a major piece of the current guidelines for Pain, Agitation, and Delirium (PAD) of the Society of Critical Care Medicine (SCCM). Advancements in research and technology are resulting in higher acuity and increased complexity of care, which is resulting in drastic increases in workload and demands on staff. More than ever, there is a great need to develop simpler ways of implementing safer and better care into practice for our sickest patients.

The ABCDE bundle is one way to align and coordinate care, which includes specific focus on delirium as a component of the overall care patients receive including sedation and pain medications, breathing machines, and mobilization. This bundle has multiple, evidenced based components, interdependent, and designed to:

- Improve collaboration and coordination among clinical team members
- Standardize care processes
- Decrease delirium
- Break the cycle of oversedation and prolonged ventilation

What are the components of the ABCDE bundle?
Awake and Breathing Coordination

- Duration of mechanical ventilation
- Duration of coma
- Mortality

Choose light sedation & avoid benzos

- Duration of mechanical ventilation
- Mortality
- Delirium

Delirium monitoring & management

- Delirium detection
- Delirium predictor of mortality and morbidity

Early Mobility & Environment

- Duration of delirium
- Disability
- ICU Length of Stay
- Rehospitalization/Mortality

Morandi et al, Curr Opin Crit Care 2011;17:43-9
Vasilevskis et al, Crit Care Med 2010;38:S683-91
Vasilevskis et al, Chest 2010;138:1224-1233
Zaal et al, ICM 2013;39:481-88
Colombo et al, Minerva Anest 1012;78:1026-33
Liberating from Ventilator

SBT reduced weaning time by = 2 days

Control (n =151)
Protocol (n =149)

$p<.001$

Liberating from Sedation

SAT reduced ventilator time by = 2 days

Control (n=60)  
Protocol (n=68)  

Adjusted $p < .001$

SATs (Daily Interruption) Used in Minority Around World

- Canada – 40% get SATs (273 physicians in 2005)
- U.S. – 40% get SATs (2004-05)
- France – 10% get SATs (44 ICUs in 2005)
- Germany – 34% get SATs (214 ICUs in 2006)
- Brazil – 32% get SATs (1,015 MDs in 2008)
- UK – 28% get SATs, 82% use midazolam (2009)
- Belgium – 18% get SATs (587 nurses / 99 hospitals in 2012)

Mehta S, CCM 2006;34:374-80.
Devlin J, CCM 2006;34:556-57.
Payen JF, Anesthes 2007;106:687-95

Ramaswamy S, Intens Care Med (ESICM 2009)
Salluh J, Brazil, J Crit Care 2009
Sneyers B, Brussels, Abst #324 2012
Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial

ABC Trial: One-Year Survival

NNT=7

ABC approach (n=167)

Control (n=168)

\( p = .01 \)

Sedation Interruption in SLEAP

Mehta S, JAMA 2012;308:1985-92
## Benzodiazepine Use in Trials *

<table>
<thead>
<tr>
<th>Study</th>
<th>Control</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kress NEJM 2000</td>
<td>90 mg/day</td>
<td>53 mg/day</td>
</tr>
<tr>
<td>Girard ABC Lancet 2007</td>
<td>84 mg/day</td>
<td>54 mg/day</td>
</tr>
<tr>
<td>Mehta SLEAP JAMA 2012</td>
<td>82 mg/day</td>
<td>102 mg/day</td>
</tr>
<tr>
<td>OSCILLATE NEJM 2013</td>
<td>141 mg/day</td>
<td>199 mg/day</td>
</tr>
</tbody>
</table>

* All values converted and expressed as mean midazolam dose per patient, median for ABC study were 8 mg and 5 mg, respectively
SPICE Study – first 48 hours
mean 50 mg/d benzos

Panel B

Log rank P=0.04

Number at risk
Deeply sedated 215 172 160 158 158 157 154
Not deeply sedated 36 34 31 31 30 30 30

Shehabi AJRCCM 2012;186:724-31
Awake and Breathing Coordination
- ↓ Duration of mechanical ventilation
- ↓ Duration of coma
- ↓ Mortality

Choose light sedation & avoid benzos
- ↓ Duration of mechanical ventilation
- ↓ Mortality
- ↓ Delirium

Delirium monitoring & management
- ↑ Delirium detection
- ↑ Delirium predictor of mortality and morbidity

Early Mobility & Environment
- ↓ Duration of delirium
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Morandi et al Curr Opin Crit Care 2011;17:43-9
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Vasilevskis et al Chest 2010;138:1224-1233
Zaal et al, ICM 2013;39:481-88
Colombo et al, Minerva Anest 1012;78:1026-33
A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial

Thomas Strøm, Torben Martinussen, Palle Toft

Summary

Background  Standard treatment of critically ill patients undergoing mechanical ventilation is continuous sedation. Daily interruption of sedation has a beneficial effect, and in the general intensive care unit of Odense University Hospital, Denmark, standard practice is a protocol of no sedation. We aimed to establish whether duration of mechanical ventilation could be reduced with a protocol of no sedation versus daily interruption of sedation.

Methods  Of 438 patients screened for eligibility, we enrolled 160 critically ill adult patients who were undergoing
ICU stay reduced by 9.7 days

Benzodiazepines and Delirium Risk

Delirium Risk

Lorazepam Dose (mg)

OR 1.2
P=0.003

Buffalos to Beer to Brain Cells
Cliff the mailman and philosopher

Cliff: “Well you see, Norm, it's like this . . A herd of buffalo can only move as fast as the slowest buffalo. And when the herd is hunted, it is the slowest and weakest ones at the back that are killed first. This natural selection is good for the herd as a whole, because the general speed and health of the whole group keeps improving by the regular killing of the weakest members.”

sitcom CHEERS
“In much the same way, Norm, the human brain can only operate as fast as the slowest brain cells. Now, as we know, excessive intake of alcohol kills brain cells. But naturally, it attacks the slowest and weakest brain cells first. In this way, regular consumption of beer eliminates the weaker cells, making the brain a faster and more efficient machine. And that, Norm, is why you always feel smarter after a few beers.”

sitcom **CHEERS**
CARING FOR THE CRITICALLY ILL PATIENT

Effect of Sedation With Dexmedetomidine vs Lorazepam on Acute Brain Dysfunction in Mechanically Ventilated Patients
The MENDS Randomized Controlled Trial

Pratik P. Pandharipande, MD, MSCI
Brenda T. Pun, RN, MSN, ACNP
Daniel L. Herr, MD
Mervyn Maze, MB, ChB
Timothy D. Girard, MD, MSCI
Russell R. Miller, MD, MPH
Ayumi K. Shintani, MPH, PhD
Jennifer L. Thompson, MPH
James C. Jackson, PsyD
Stephen A. Deppen, MA, MS
Renee A. Stiles, PhD
Robert S. Dittus, MD, MPH
Gordon R. Bernard, MD
E. Wesley Ely, MD, MPH

Context Lorazepam is currently recommended for sustained sedation of mechanically ventilated intensive care unit (ICU) patients, but this and other benzodiazepine drugs may contribute to acute brain dysfunction, ie, delirium and coma, associated with prolonged hospital stays, costs, and increased mortality. Dexmedetomidine induces sedation via different central nervous system receptors than the benzodiazepine drugs and may lower the risk of acute brain dysfunction.

Objective To determine whether dexmedetomidine reduces the duration of delirium and coma in mechanically ventilated ICU patients while providing adequate sedation as compared with lorazepam.

Design, Setting, Patients, and Intervention Double-blind, randomized controlled trial of 106 adult mechanically ventilated medical and surgical ICU patients at 2 tertiary care centers between August 2004 and April 2006. Patients were sedated with dexmedetomidine or lorazepam for as many as 120 hours. Study drugs were titrated to achieve the desired level of sedation, measured using the Richmond Agitation-Sedation Scale (RASS). Patients were monitored twice daily for delirium using the Confusion Assessment Method for the ICU (CAM-ICU).

Main Outcome Measures Days alive without delirium or coma and percentage of days spent within 1 RASS point of the sedation goal.
Daily Risk of Delirium in MENDS

Dexmedetomidine  Lorazepam

$p=0.02$

Pandharipande PP. JAMA 2007;298:2644-53
Pandharipande PP. Crit Care 2010;14:R38
Daily Risk of Delirium in SEDCOM

Riker, et al. JAMA 2009;301:489-499

*p<0.001*
Awake and Breathing Coordination

- Duration of mechanical ventilation
- Duration of coma
- Mortality

Choose light sedation & avoid benzos

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Zaal et al, ICM 2013;39:481-88
Colombo et al, Minerva Anest 1012;78:1026-33
Cardinal Symptoms of Delirium and Coma

2013 PAD Guidelines:

“We recommend routine monitoring for delirium in adult ICU patients”

Grade 1B Recommendation
If delirium is not screened for using a validated delirium screening tool it is missed $\sim 75\%$ of time.

Don’t forget about Dr. DRE

**Diseases**
*Sepsis, COPD, CHF*

**Drug Removal**
*SATs and stopping benzodiazepines/narcotics*

**Environment**
*Immobilization, sleep and day/night, hearing aids, glasses, noise*
Critical Illness
Critical Illness

Delirium

Acquired Weakness

Devlin et al., Intensive Care Med 2007; 35:2721-4
Bergeron et al., Intensive Care Med 2001; 27:859-64
Needham DM JAMA 2008; 300: 1685-90
DeJonghe, et al., JAMA 2002; 288: 2859-67
Baseball (like life) is 90% mental...
Baseball (like life) is 90% mental…
the other half is physical

Yogi Berra
Awake and Breathing Coordination

- ↓ Duration of mechanical ventilation
- ↓ Duration of coma
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Early physical rehabilitation

Proportion of patients with functional independence at hospital discharge (%)

Usual Care (n=49)
Early PT+OT (n=55)

p = 0.048

Schweickert, Lancet 2009; 373: 1874-82
# Mobilization = Less Delirium

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention (n=49)</th>
<th>Control (n=55)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU/Hosp Delirium Days</td>
<td>2 days</td>
<td>4 days</td>
<td>0.03</td>
</tr>
<tr>
<td>Time in ICU with Delirium</td>
<td>33%</td>
<td>57%</td>
<td>0.02</td>
</tr>
<tr>
<td>Time in Hosp. with Delirium</td>
<td>28%</td>
<td>41%</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Schweickert et al, Lancet 2009;373:1874-82
Mobilizing the Brain with Sudoku & Scrabble
"I survived and that is the main thing. And I am so grateful to God that I survived and am now off all oxygen and consider myself all well except that I can’t remember to take my medications...

-SB
Dr. Swenson explained, "I'll tell you the truth. What I have discovered...is not what I expected. It is something greater, much more ambitious than anything we had hoped for...in science: Never be so focused on what you are looking for that you overlook the thing you actually find."

Ann Patchett - 2011, *State of Wonder*
“I came awake on the fifth day. My first memory is that of floating up from the ocean bottom, my eyes still waterlogged and with what felt like scuba gear stuffed in my mouth and throat. I couldn’t speak. As I broke to the surface, I understood that I was still in the ICU at Our Lady, but I heard nothing of what anybody said.

Abraham Verghese - 2009, *Cutting for Stone*
ICU Delirium and Cognitive Impairment Study Group: selected local members

- Pratik Pandharipande
- Jim Jackson
- Jin Han
- Ed Vasilevskis
- Chris Hughes
- Alessandro Morandi
- Paula Watson
- Lorraine Ware
- Gordon Bernard
- Bob Dittus
- Ted Speroff
- Wes Ely
- Leanne Boehm
- Joyce Okahashi
- Cayce Strength
- Brenda Pun
- Lauren Hardy
- Amy Lipsey
- Ryan Black
- Jessica McCurley
- Michael Santoro
- Carrie Jones
- Morgan Crawford
- Mayur Patel
- Tim Girard
- John Gore
- Baxter Rogers
- Stephan Heckers
- Cathy Fuchs
- Heidi Smith
- Ty Berutti
- Brad Strohler
- Elizabeth Card
- Jennifer Thompson
- Ayumi Shintani
- Stephanie Hamilton
Key Epidemiological Points:

1) Patients suffer from long-lasting and disabling aspects of critical illness that demand our attention as a medical community.

2) Acquired or accelerated cognitive impairment is a major public health problem following ICU care for both the old and young.

3) This cognitive impairment appears most pronounced in domains of executive dysfunction and memory.

4) Frontal lobe and hippocampal atrophy are being consistently found in recent studies.

5) This injury is likely distinct from or complementary to Alzheimer’s pathology, though we are in our infancy in learning about this entity (e.g., large pathology study under review).

6) Delirium and drug exposure appear to be the most modifiable aspects of care, with need for more trials to delineate next steps.
Key Management Points:

1) Establish an overarching protocolized approach to daily ICU patient management using 2013 PAD Guidelines

2) Assess & treat pain first (may be sufficient)

3) If patient remains agitated after adequately treating pain, use prn/bolus sedation initially, if frequent boluses (>3/hr) use continuous sedation

4) Avoid traditional benzodiazepines in most patients

5) Turn off sedation daily and restart only if needed at lowest dose to maintain chosen target level of consciousness

6) Deep sedation (RASS -4/-5) appears harmful; target awake/alert

7) Screen for delirium (CAM-ICU or ICDSC); If delirious, first seek reversible causes and attempt non-pharmacologic management

8) Use the ABCDEs to improve outcomes for your patients
2013 PAD Guidelines: Benzodiazepines

1. General Choice: non-benzodiazepine sedation strategies preferred (propofol or dex), with statistically shorter ICU LOS (~0.5 day, p=0.04)
2. Benzodiazepines risk factor for delirium
3. Ventilated patients at risk for delirium prefer dexmedetomidine to benzodiazepine
4. Delirious ICU patients (excluding DTs and benzo w/drawal) - give dexmedetomidine (alpha-2) and not benzo (GABA)

Barr J et al, CCM 2013;41:263-306