ICU LIBERATION AND THE ABCDEF BUNDLE: NEW DATA

E. WESLEY ELY, MD, MPH

PROFESSOR OF MEDICINE
VANDERBILT UNIVERSITY SCHOOL OF MEDICINE
Nashville, TN

E. Wesley Ely, MD, MPH, the Grant W. Liddle Chair in Medicine, is a subspecialist in Pulmonary and Critical Care Medicine who conducts patient-oriented, health services research as a Professor of Medicine in the Division of Allergy, Pulmonary, and Critical Care Medicine at Vanderbilt University Medical Center in Nashville, TN. He is also a practicing intensivist with a focus on Geriatric ICU Care, as the Associate Director for Research for the VA Tennessee Valley Geriatric Research and Education Clinical Center.

Dr. Ely’s research has focused on improving the care and outcomes of critically ill patients with ICU-acquired brain disease (manifested acutely as delirium and chronically as long-term cognitive impairment). He has built the Center for Critical Illness, Brain dysfunction and Survivorship (CiBS), amassing several thousand patients into cohort studies and randomized trials that were used to build the methodology for ICU acquired brain disease research. His team developed the primary tool (CAM-ICU, translated into 35 languages) by which delirium and health-related quality of life outcomes are measured in ICU-based trials and clinically at the bedside in ICUs worldwide. Dr. Ely has been continuously federally funded (NIA and/or VA) for 15 years. He has over 350 peer-reviewed publications and over 50 published book chapters and editorials.

Dr. Ely graduated from Tulane University in New Orleans, Louisiana, Summa Cum Laude, with a BS in Biology in 1985. He continued at Tulane to receive his MPH in Public Health, graduating in 1989. He completed his medicine residency program and his postdoctoral fellowship in Pulmonary and Critical Care Medicine in Winston-Salem, North Carolina at Bowman Gray School of Medicine. However, he will be the first to say that his most amazing accomplishments are his three daughters, Taylor, and twins, Blair and Brooke Ely. He adores his wife, Kim Ely is an MD in Anatomic and Clinical Pathology, also at Vanderbilt University Medical Center in Nashville, TN.

OBJECTIVES:
1. To teach the robust evidence that delirium is a risk factor of excess mortality, length of stay, cost of care and dementia following critical illness.

2. To discuss acquired dementia following ICU care as a global public health problem that dismantles our patients’ lives as part of PICS (post-intensive care syndrome).

3. To reinforce new data-driven mechanisms embodied in the ABCDEF Bundle by which to improve patient-centered outcomes (survival, length of stay, successful discharge home) as employed within the ICU Liberation Collaborative in over 15,000 patients.

4. To learn strengths and pitfalls of ABCDEF implementation in order to change culture and care successfully so that ICU teams can better serve patients.
E. Wesley Ely, MD, MPH, the Grant W. Liddle Chair in Medicine, is a subspecialist in Pulmonary and Critical Care Medicine who conducts patient-oriented, health services research as a Professor of Medicine in the Division of Allergy, Pulmonary, and Critical Care Medicine at Vanderbilt University Medical Center in Nashville, TN. He is also a practicing intensivist with a focus on Geriatric ICU Care, as the Associate Director for Research for the VA Tennessee Valley Geriatric Research and Education Clinical Center.

Dr. Ely's research has focused on improving the care and outcomes of critically ill patients with ICU-acquired brain disease (manifested acutely as delirium and chronically as long-term cognitive impairment). He has built the Center for Critical Illness, Brain dysfunction and Survivorship (CIBS), amassing several thousand patients into cohort studies and randomized trials that were used to build the methodology for ICU acquired brain disease research. His team developed the primary tool (CAM-ICU, translated into 35 languages) by which delirium and health-related quality of life outcomes are measured in ICU-based trials and clinically at the bedside in ICUs worldwide. Dr. Ely has been continuously federally funded (NIA and/or VA) for 15 years. He has over 350 peer-reviewed publications and over 50 published book chapters and editorials.

Dr. Ely graduated from Tulane University in New Orleans, Louisiana, Summa Cum Laude, with a BS in Biology in 1985. He continued at Tulane to receive his MPH in Public Health, graduating in 1989. He completed his medicine residency program and his postdoctoral fellowship in Pulmonary and Critical Care Medicine in Winston-Salem, North Carolina at Bowman Gray School of Medicine. However, he will be the first to say that his most amazing accomplishments are his three daughters, Taylor, and twins, Blair and Brooke Ely. He adores his wife, Kim Ely is an MD in Anatomic and Clinical Pathology, also at Vanderbilt University Medical Center in Nashville, TN.
A New Frontier In Critical Care: Saving the Injured Brain

E. Wesley Ely, MD, MPH
CIBS Center, Aging Research, VA GRECC
Professor, Pulmonary & Critical Care Medicine
Vanderbilt Univ Medical Center, Nashville, TN

Disclosures:

• Physician-scientist, Vanderbilt University, Nashville TN, USA
• Honoraria from Pfizer, Orion, Masimo for CME Activities
• PI for MIND-USA and SCCM’s ICU Liberation Collaborative
• NIH and VA U.S. Federal Funding
CRITICAL ILLNESS, BRAIN DYSFUNCTION, and SURVIVORSHIP (CIBS) CENTER
In *Crime and Punishment*, Dostoyevsky used "delirium" 31 times.

"Strange to say, he seemed immediately to have become perfectly calm; not a trace of his recent delirium nor of the panic fear that had haunted him of late. It was the first moment of a strange sudden calm."
1st Report of Haldol for ICU Delirium
40 years ago...1978

No. 395
INTRAVENOUS USE OF HALOPERIDOL FOR ACUTE DELIRIUM IN INTENSIVE CARE SETTINGS

Ned. H. Cassem, M.D. (M), Chief, Psychiatric Consultation-Liaison Service, Massachusetts General Hospital, Boston

SUMMARY:
Patients recovering from cardiac surgery occasionally become so delirious and agitated that immediate tranquillization is necessary. In a series of 15 patients the use of intravenous haloperidol was studied. All patients had indwelling arterial, left atrial, Swan-Ganz, and central venous pressure lines, two pacing wires each in right atrium and left ventricle, Foley catheter, one or more peripheral venous lines, and often the

131st Annual Meeting of the American Psych Assoc, Wash DC
Haloperidol Use for Delirium in the ICU became usual care

Recommendations: Haloperidol is the preferred agent for the treatment of delirium in critically ill patients. (Grade of recommendation = C)

--2002 SCCM Guidelines

Global use of Haloperidol for ICU Delirium

Morandi A. Crit Care Med 2017;45:e1111-22
20 Years of research...1998-2018

Dr. Paul Wischmeyer comments on his own experience with ICU delirium

Fall 2018, Mastering Intensive Care podcast producer Dr. Andrew Davies, Melbourne Australia
Haloperidol Use in the BRAIN-ICU Cohort

500 antipsychotic non-users

292 antipsychotic non-users

52 died in hospital

130 antipsychotic discontinued prior to discharge

370 discharged off antipsychotic

500 - 292 = 208 antipsychotic users

208 antipsychotic users

36 died in hospital

24% discharged

42% treated

Tomichek J. Crit Care 2016;20:378
Should Delirium be Treated by Antipsychotics?

Haloperidol and Ziprasidone for Treatment of Delirium in Critical Illness

Girard TD, et al. NEJM 2018;379:2506-16
MIND, HOPE-ICU, REDUCE

Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: The MIND randomized, placebo-controlled trial

Girard TD et al, CCM 2010;38:428-37 (small N, PO/IM, prophyl/tx)

Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (Hope-ICU): a randomised, double-blind, placebo-controlled trial


MIND Pilot RCT

Girard TD et al, CCM 2010;38:428-37 (small N, PO/IM, prophyl/tx)
Hope-ICU Trial

- Patients without Delirium or Coma (%)
- $p = 0.53$

Haloperidol (n=71) vs Placebo (n=70)

Page VJ et al, Lancet Resp 2013;1:515-23 (max 2.5 mg q8 IV, prophyl/tx)

Boogaard M, et al. JAMA 2018;319:680-90 (n ~715/group, 2mg IV q8, prophylaxis)
Ziprasidone blocks 6 receptors, agonist at 1

Traditional Teaching: “Dopamine blockade in the cerebral cortex improves cognition and reduces delirium.”

### MIND-USA: baseline variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo N=184</th>
<th>Haloperidol N=192</th>
<th>Ziprasidone N=190</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE II</td>
<td>30</td>
<td>28.5</td>
<td>28</td>
</tr>
<tr>
<td>SOFA</td>
<td>11</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Mechanical Ventilation</td>
<td>175 (95%)</td>
<td>185 (96%)</td>
<td>185 (97%)</td>
</tr>
<tr>
<td>Shock on Pressors</td>
<td>65 (35%)</td>
<td>58 (30%)</td>
<td>64 (34%)</td>
</tr>
<tr>
<td>Medical / Surgical ICU</td>
<td>72% / 28%</td>
<td>73% / 27%</td>
<td>71% / 29%</td>
</tr>
<tr>
<td>Admission Diagnoses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARDS or Sepsis</td>
<td>74 (40%)</td>
<td>87 (45%)</td>
<td>68 (36%)</td>
</tr>
<tr>
<td>COPD, CHF, Cirrhosis</td>
<td>35 (19%)</td>
<td>29 (15%)</td>
<td>37 (19%)</td>
</tr>
<tr>
<td>Other Diagnoses</td>
<td>75 (41%)</td>
<td>76 (40%)</td>
<td>85 (45%)</td>
</tr>
</tbody>
</table>

### ABCDE Compliance: all groups *+*

<table>
<thead>
<tr>
<th>Bundle Elements</th>
<th>Study Drug Days</th>
<th>All Patient Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (SAT)</td>
<td>2791 (94%)</td>
<td>4494 (92%)</td>
</tr>
<tr>
<td>B (SBT)</td>
<td>2473 (94%)</td>
<td>3939 (93%)</td>
</tr>
<tr>
<td>C (Coordination nurse/RT)</td>
<td>1363 (88%)</td>
<td>2133 (88%)</td>
</tr>
<tr>
<td>D (Delirium eval/tx)</td>
<td>3846 (99%)</td>
<td>6123 (99%)</td>
</tr>
<tr>
<td>E (Early exercise)</td>
<td>3626 (87%)</td>
<td>6204 (89%)</td>
</tr>
</tbody>
</table>

* MIND-USA was designed before the “F” (Family engagement) piece and other slight modifications were made to construct the modern ABCDEF Bundle  
+ Compliance calculated according to days eligible for each variable (e.g., if you weren’t on a vent, then you weren’t eligible for an SBT)
MIND-USA Results
(primary and secondary outcomes)

MIND-USA: primary outcome
MIND-USA: 90-day survival

Kaplan-Meier Curve, 90-Day All-Cause Death

Death at 90 days

- Ziprasidone: 34%
- Haloperidol: 38%
- Placebo: 34%

Number at risk (cumulative number of deaths)

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>75</th>
<th>90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziprasidone</td>
<td>190</td>
<td>180</td>
<td>170</td>
<td>160</td>
<td>150</td>
<td>140</td>
<td>130</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>175</td>
<td>165</td>
<td>155</td>
<td>145</td>
<td>135</td>
<td>125</td>
<td>115</td>
</tr>
<tr>
<td>Placebo</td>
<td>150</td>
<td>140</td>
<td>130</td>
<td>120</td>
<td>110</td>
<td>100</td>
<td>90</td>
</tr>
</tbody>
</table>

Days after Randomization

MIND-USA: key 2° outcomes

A: Liberation from MV
B: ICU Discharge
C: ICU Readmission
D: Hospital Discharge
MIND-USA: hypoactive delirium

- Adj P = 0.62

MIND-USA: hyperactive delirium

- Adj P = 0.58
MIND-USA: conclusions

• Haloperidol and Ziprasidone do not reduce delirium, time on vent, ICU/hospital LOS, or death

• Arrhythmias, Parkinsonianism (extrapyramidal symptoms), NMS, study drug discontinuation, and other safety concerns were extremely low and similar across all 3 groups

• Antipsychotics remain viable for...
  • Short-term control of agitation (e.g., EtOH or drug withdrawal)
  • Severe anxiety with need to avoid respiratory suppression (e.g., CHF, COPD, asthma)

Girard TD, et al. NEJM 2018;379:2506-16

"A long habit of not thinking a thing wrong, gives it a superficial appearance of being right…"

Common Sense, Thomas Paine, c. 1776
ABCDEF Bundle: science & philosophy
(based on 40 Lancet, JAMA, NEJM papers + ~350 others)

• Analgesia: assess, prevent, manage pain
• Both SATs and SBTs (stop drugs, stop vent)
• Choice of Analgesia and Sedation
• Delirium: assess, prevent, manage
• Early mobility and exercise, Environment
• Family engagement and empowerment

Ely EW, CCM 2017;45:321-30
Delirium Management: using Dr. DRE

Disease remediation
e.g., Sepsis, COPD, CHF

Drug Removal
e.g., SATs, avoiding benzodiazepines

Environment
e.g., mobilization, sleep, day/night, hearing aids, eye glasses, noise redxn

Ely EW CCM 2017;45:321-30
In *Crime and Punishment*, Dostoyevsky writes…

*on family presence and delirium reduction:*
"Until today the patient had been in **delirium** and...no doubt the presence of his family [had] a favourable effect on his recovery and distracted his mind."

Rosa RG, CCM 2017;45:1660-1667
## A-E and A-F Bundle References

<table>
<thead>
<tr>
<th>ABCDE Bundle</th>
<th>ABCDEF Bundle</th>
</tr>
</thead>
</table>

### Survival and Delirium-Coma Freedom

Implementing ABCDEF Bundle in >6,000 patients

- **Mortality Improvement**
  - NOTE: Adjusted for age, APACHE III, and mechanical ventilation
  - 7 California Hospitals, Interprofessional QI Implementation project

- **Delirium and Coma Freedom**

Barnes-Daly MA, CCM 2017;45:171-8
ICU Liberation Collaborative

- Gordon Moore Foundation (Intel Billionaire)
- SCCM (Sepsis, ICU Liberation, Thrive)
- Aug 2015 to April 2017
- 68 Adult American ICUs, 10 Pediatric
- Medical, Surgical, Cardiac, Neuro ICUs
- ABCDEF Bundle implementation
- 15,226 patients
- All regression models adjusted for 18 confounders chosen *a priori*
ABCDEF bundle performance... improves ICU discharge
ABCDEF bundle performance ... improves hospital discharge

Performance...reduces death
Performance improves...
coma, delirium, restraints

Performance increases
reported pain
Performance improves... time on ventilation

Performance reduces... ICU readmission and NH transfers
“Medicine cannot heal in a vacuum. It requires connection. As a patient it is upending to be confronted with the actual fragility of everything you once believed to be a constant, and to have no one around you who is open to discussion of the devastation is patently surreal.”

Rana Awdish, MD

In Shock (2017)
A-F Bundle Rounding Tools

<table>
<thead>
<tr>
<th>ABCDEF</th>
<th>CV</th>
<th>Resp</th>
<th>GL/DUI</th>
<th>Intag</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAIN</td>
<td>HR RHYTHM</td>
<td>OXYGEN sito</td>
<td>UOC/IV</td>
<td>PLI</td>
</tr>
<tr>
<td>PO2</td>
<td>BP</td>
<td>RR</td>
<td>FOLEY Y/N</td>
<td>Maples Y/N</td>
</tr>
<tr>
<td>PUPIL</td>
<td>SP02</td>
<td>RS</td>
<td>DATE INS</td>
<td>Y/N</td>
</tr>
<tr>
<td>AGITATION</td>
<td>TMAX TENDENCY</td>
<td>INHIBITED Y/N</td>
<td>VR X</td>
<td>Y/N</td>
</tr>
<tr>
<td>TARGET BASS</td>
<td>SEDATION</td>
<td>TRASH</td>
<td>E.C.T /VC</td>
<td>VOIDS</td>
</tr>
<tr>
<td>ACTUAL BASS</td>
<td>SAT/SP1</td>
<td>Cardio</td>
<td>Infusion Y/N</td>
<td>OXYGEN</td>
</tr>
<tr>
<td>SEDATION</td>
<td>DATUM</td>
<td>FEEDING TUBE</td>
<td>Infusion Y/N</td>
<td>PLI</td>
</tr>
<tr>
<td>MOBILITY</td>
<td>CARDiac</td>
<td>02 PETCO/PS</td>
<td>Infusion Y/N</td>
<td>PLI</td>
</tr>
<tr>
<td>PT/OT</td>
<td>GTTS</td>
<td>TV</td>
<td>Infusion Y/N</td>
<td>PLI</td>
</tr>
<tr>
<td>Restraints Y/N</td>
<td>CT, CT</td>
<td>CT</td>
<td>Infusion Y/N</td>
<td>PLI</td>
</tr>
<tr>
<td>Order D/T</td>
<td>family</td>
<td>family</td>
<td>Infusion Y/N</td>
<td>PLI</td>
</tr>
<tr>
<td>Pump</td>
<td>family</td>
<td>family</td>
<td>Infusion Y/N</td>
<td>PLI</td>
</tr>
</tbody>
</table>

IV/Intravenous

4/25/2019
Engel and Romano, c. 1959
60 years ago...

Engel – Harvard, Mt. Sinai, Brigham, U of Chicago, Rochester.
Physiologist. Internist. Psychiatrist. Biopsychosocial model - theory of illness and healing
Romano – Rochester, Chair Psychiatry 25 years. Defined original EEG criteria for delirium in 1944 (75 years ago).

"The deficiencies in the education of many physicians ill equip them to recognize any but the most flagrant examples of delirium."

"They seem to have little interest in and, indeed, often completely overlook delirium."

"The physician who is greatly concerned to protect the functional integrity of the heart, liver, and kidneys of his patient has not yet learned to have similar regard for the functional integrity of the brain. This is a serious and, perhaps, tragic omission."

Engel GL and Romano J, J Chron Dis, 9(3):260-277, 1959
“The problem of delirium is far from an academic one. Not only does the presence of delirium often complicate and render more difficult the treatment of a serious illness, but also it carries the serious possibility of permanent irreversible brain damage. With increasing life expectancy and with improved survival through the influence of surgery and antibiotics…Do we know how often…”

Engel and Romano, J Chron Dis, 9:260-277, 1959

---

**Long-Term Cognitive Impairment after Critical Illness**


**ABSTRACT**

**Background**
Survivors of critical illness often have a prolonged and disabling form of cognitive impairment that remains inadequately characterized.
Surgery and Anesthesia Exposure Is Not a Risk Factor for Cognitive Impairment After Major Noncardiac Surgery and Critical Illness

Executive Function and Surgery Exposure
n=1,040

Hughes CG. Ann Surg 2016; 265:1126-1133
Delirium Drives PICS* Dementia

“The practitioner who fails to husband (use economically) his patient’s strength for the long and protracted struggle that may await him, too soon discovers the fatal error he has been enticed into by his own ignorance. That he has indeed dealt his patient a knock-down blow, from which the chances are that he is actually disabled from rising again.”

Delirium SECRETS

Implementing Delirium Screening in the ICU: Secrets to Success

Nathan E. Brummel, MD, MSc[1,2]; Edward E. Vasilevskis, MD, MPH[1,2]; Jin Ho Han, MD, MSc[1]; Leanne Besham, MSN, RN, ACNS-BC[1]; Brenda T. Pan, MSN, RN, ACNP[2]; Elwood Ely, MD, MPH, FCCM[1,2]

Brummel NE. CCM 2019;41:2196-2208

CIBS Center: mission and vision

CIBS Center
At the forefront of discovery and innovation, improving lives of people affected by critical illness.

We advance knowledge, education, and models of care for people affected by critical illness.

Research Turning Mirrors into Windows
CIBS Center: research page

The ‘classic’ care of critically ill patients is similar to a dementia factory. It is up to us to close this factory.

Dr. Raúl Alejandro Gómez, Intensivist Physician, Buenos Aires

Ongoing Research

COPE
A study of the effects of prehabilitation on physical and cognitive recovery in surgery patients.

Learn More

MOSAIC
An ongoing observational study of the association between activity and physical and cognitive function in ICU survivors.

Learn More

CADUCEUS
An ancillary study of inflammation levels in the blood of critically ill patients.

Learn More

CIBS: ICU Recovery Center: Sevin & Co

The ICU Recovery Center at Vanderbilt

We are here to help after leaving the ICU

Stollings JL et al. Ann Pharm 2018;52:713-23