Cognitive Outcomes: The Causes

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• No conflicts of interest to disclose.
Outline

• Definitions
  – Acute vs. chronic brain dysfunction
• Scope of the problem
• Risk factors for cognitive impairment
  – Host and/or environmental
• Possible mechanisms of brain injury
  – Targets for interventions
Cognitive outcomes

Critical Illness → Acute Brain Dysfunction (Delirium) → Long-term Brain Dysfunction (Cognitive Impairment)
Cognitive outcomes

Critical Illness → Acute Brain Dysfunction (Delirium) → Long-term Brain Dysfunction (Cognitive Impairment)

Acute onset of cerebral dysfunction with change or fluctuation in baseline mental status, inattention, and either disorganized thinking or an altered level of consciousness.

Cognitive outcomes

Critical Illness → Acute Brain Dysfunction (Delirium) → Long-term Brain Dysfunction (Cognitive Impairment)

No standard definition; Time to follow-up and measures used in assessing cognitive function have been highly variable.
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Significant cognitive impairment after critical illness

- **73-100%** ICU survivors leave hospital with cognitive dysfunction equating to mild/moderate dementia
- **46-78%** cognitive dysfunction at 1-yr
- **25-47%** cognitive dysfunction at 2-yr

**References**

AlSaidi et al. AJRCCM 2003; 167:A737  
Christie et al. AJRCCM 2006; 169: A781.  
Hopkins et al. AJRCCM 1999; 160: 50-56.  
Mikkelsen et al. Respirology 2009; 14: 76-82.  
Decrement in cognition seen across all domains

- Most commonly affects memory and executive function

All ages experience similar decrements in cognitive performance

- 3 (and 12) months: 40% (35%) and 26% (24%) of patients scored 1.5 SD and 2 SD below the population age-adjusted mean.
Cognitive impairment is new among sepsis survivors

Cognitive screen at discharge does not predict impairment at 6 months.

![Bar chart showing the number of patients with cognitive sequelae vs. those without at 6 months, based on MMSE raw scores at time of discharge.](chart.png)

- **Number of patients with cognitive sequelae at 6 months**
  - **30-27**: 12
  - **26-23**: 9
  - **22-19**: 6
  - **18-15**: 3

- **MMSE raw scores at time of discharge**

Persistent cognitive impairment associated with EEG changes in sepsis

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

J Neurol Neurosurg Psychiatry 2013;84:62–70. doi:10.1136/jnnp-2012-302883

- Low-frequency activity on routine EEG associated with verbal learning and memory deficits
Inability to predict trajectory makes for **costly** rehabilitation strategies

- Improved executive function (measured by Tower Test) in intervention, as compared to control group ($p < 0.01$)

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Risk factors associated with cognitive impairment

• Pathogenesis poorly understood
  – **Vulnerable host** with accelerated neurodegeneration
    (e.g., genetic predisposition [ApoE ε4])
  – **Newly acquired brain injury** from ICU insults
    (e.g., hypoxemia, hypotension, dysglycemia, pharmacologic exposures, inflammation)

Ehlenbach Wj et al. JAMA 2010; 303: 763-70.
Wilcox ME et al. Critical Care Medicine 2013; 41: S81-98
APOE ε4 polymorphism (risk factor for Alzheimer’s) predisposes to delirium

- APOE allele may genetically predispose to longer duration of delirium \((p=0.005)\)

- 53 mechanically ventilated medical ICU patients; mean age 62.5 (SD 15.6)

High sleep fragmentation associated with 1.5X increase risk of AD
Improved sleep consolidation reduces incidence of developing Alzheimer’s disease and improves composite cognition scores

Lim AS et al. JAMA Neurol 2013; 70: 1544-1551.
Sleep disorders are common in ICU

- Extrinsic and intrinsic factors lead to poor sleep (e.g., noise, sedatives, ventilator synchrony)

Elliot R et al. Critical Care 2013; 17: R46.
Factors associated with cognitive impairment

• Pathogenesis poorly understood
  – Vulnerable host with accelerated neurodegeneration
    (e.g., genetic predisposition [ApoE ε4])
  – Newly acquired brain injury from ICU insults
    (e.g., hypoxemia, hypotension, dysglycemia, pharmacologic exposures, inflammation)

Ehlenbach Wj et al. JAMA 2010; 303: 763-70.
Wilcox ME et al. Critical Care Medicine 2013; 41: S81-98
More delirious days, more likely to have cognitive impairment

- 821 patients; medical-surgical ICU; 6% cognitive impairment at baseline

Longer duration delirium, greater brain atrophy and worse cognitive outcome

- Anatomical association with worse overall cognitive performance and executive function.
Risk reduction with sedation stewardship

INTERUPTION OF SEDATIVE INFUSIONS IN CRITICALLY ILL PATIENTS UNDERGOING MECHANICAL VENTILATION

DAILY INTERRUPTION OF SEDATIVE INFUSIONS IN CRITICALLY ILL PATIENTS UNDERGOING MECHANICAL VENTILATION

John P. Kress, M.D., Anne S. Pohlman, R.N., Michael F. O’Connor, M.D., and Jesse B. Hall, M.D.

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


Daily Sedation Interruption in Mechanically Ventilated Critically Ill Patients Cared for With a Sedation Protocol
A Randomized Controlled Trial

Sangeeta Mehta, MD
Genetic polymorphisms are a risk factor for coma

- **CYP450 isoenzymes:**
  - CYP3A4/5: midazolam, fentanyl
  - CYP2D6: haloperidol, codeine, oxycodone, tramadol
  - CYP2C19: propofol

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Possible mechanisms of cognitive impairment

Critical Illness → Acute Brain Dysfunction (Delirium) → Long-term Brain Dysfunction (Cognitive Impairment)

- Acute systemic inflammation
- Cerebral damage (such as BBB disruption, hyperperfusion, cell apoptosis, neuronal loss, general slowing of EEG)
- (Micro)vascular damage in the CNS, vasogenic edema, white matter hyperintensities

Blood-brain barrier integrity and cognitive impairment in sepsis

Independent of age and severity of illness
Biomarkers associated with delirium in critically ill patients and their relation with long-term subjective cognitive dysfunction; indications for different pathways governing delirium in inflamed and noninflamed patients

Mark van den Boogaard¹*, Matthijs Kox¹, Kieran L Quinn², Theo van Achterberg⁴, Johannes G van der Hoeven¹,³, Lisette Schoonhoven⁴ and Peter Pickkers¹,³

• “Inflamed” patients:
  – IL-8, MCP-1, procalcitonin, cortisol, and S100-β were significantly associated with delirium (n = 46)

• “Noninflamed” patients:
  – IL-8, IL-1ra, IL-10, ratio Aβ₁₋₄₂/₄₀, and ratio Aβᵥ₄₂/₄₀ were significantly associated with delirium (n = 54)
Different clinical phenotypes for delirium may exist

- “Reversible” delirium (sedation-related) seems better than persistent delirium
- Not sure if biological correlation exists
Possible mechanisms of cognitive impairment

Critical Illness → Acute Brain Dysfunction (Delirium) → Long-term Brain Dysfunction (Cognitive Impairment)

- Sustained inflammation
- Cerebral damage (increased slow-wave activity on EEG, reduced hippocampus volume, chronic disruption of BBB)
- Increased risk of vascular brain disease (including risk of vascular dementia)
- Presence of tau pathology, increase in amyloid β, and increased risk of Alzheimer’s disease

HMGB1 is a novel mediator of CI induced by septic encephalopathy

- Animal model of polymicrobial sepsis; randomized to anti-HMGB1 monoclonal antibody (IgG2b) or isotype control

Factors associated with cognitive impairment

• Pathogenesis poorly understood
  – **Vulnerable host** with accelerated neurodegeneration (e.g., older age, genetic predisposition [ApoE ε4])
  – **Newly acquired brain injury** from ICU insults (e.g., hypoxemia, hypotension, dysglycemia, inflammation, pharmacologic exposures)

Ehlenbach Wj et al. JAMA 2010; 303: 763-70.
Wilcox ME et al. Critical Care Medicine 2013; 41: S81-98
COGnitive outcomes and WELLness in survivors of critical illness

- Multisite, prospective, observational cohort study of rhythmic cortical electrophysiological activity [EEG], biomarkers, sleep efficiency, genetics and cognitive outcome in survivors of critical illness
- Sample size: 150 patients; 39 enrolled to date
- Registered with ClinicalTrials.gov: NCT0208687
Critical Illness

Sleep/Circadian Disruption

AAPC ε4 allele

Sleep-Dependent Mechanisms

Acute Brain Dysfunction

EEG Abnormalities + Biomarkers

Cognitive Impairment

Psychiatric Co-Morbidities

Sleep-Independent Mechanisms

1 Synaptic reorganization, changes in long-term potentiation, gene expression changes

2 Hypoxic injury, drug effects, septic injury (e.g. gliosis/inflammation from microabscesses), cytokine effects
Not limited to ICU admissions; seen with noncritical illness hospitalizations

**Table 2. Difference in Follow-up Cognitive Scores by Hospitalization Status**

<table>
<thead>
<tr>
<th>Following Noncritical Illness Hospitalization</th>
<th>Difference in Score (95% CI)</th>
<th>P Value</th>
<th>Following Critical Illness Hospitalization</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up CASI</td>
<td>-2.27 (-2.61 to -1.93)</td>
<td>&lt;.001</td>
<td>-2.92 (-5.00 to -0.86)</td>
<td>.006</td>
</tr>
<tr>
<td>Adjusted differenceC</td>
<td>-1.01 (-1.33 to -0.70)</td>
<td>&lt;.001</td>
<td>-2.14 (-4.24 to -0.03)</td>
<td>.047</td>
</tr>
<tr>
<td>Follow-up CASI IRT</td>
<td>-0.28 (-0.32 to -0.24)</td>
<td>&lt;.001</td>
<td>-0.27 (-0.45 to -0.09)</td>
<td>.003</td>
</tr>
<tr>
<td>Adjusted differenceC</td>
<td>-0.12 (-0.16 to -0.08)</td>
<td>&lt;.001</td>
<td>-0.19 (-0.38 to -0.01)</td>
<td>.04</td>
</tr>
</tbody>
</table>

**Table 4. Risk of Incident Dementia by Hospitalization Status**

<table>
<thead>
<tr>
<th>No Hospitalizations During Study (n = 1601)</th>
<th>One or More Noncritical Illness Hospitalizations (n = 1287)</th>
<th>One or More Critical Illness Hospitalizations (n = 41)</th>
<th>P Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases of incident dementia, No.</td>
<td>146</td>
<td>228</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk of incident dementia, HR (95% CI)</td>
<td>1 [Reference]</td>
<td>1.5 (1.3 to 1.9) &lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted risk of incident dementia, HR (95% CI)</td>
<td>1 [Reference]</td>
<td>1.4 (1.1 to 1.7) .001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ehlenbach et al. JAMA 2010; 303: 763-770.
Conclusions

• More patients surviving critical illness but with significant cognitive comorbidity
• Difficult to predict impairment which makes intervention strategies challenging
• Further studies are needed to better elucidate mechanisms of brain injury
• Share common pathways to same disability
  – Best ‘laboratory’ ICU vs. hospital
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Cognitive Decline After Stroke
Relation to Inflammatory Biomarkers and Hippocampal Volume

Efrat Kliper, MSc; Dafna Ben Bashat, PhD; Natan M. Bornstein, MD; Shani Shenhar-Tsarfaty, PhD; Hen Hallevi, MD; Eitan Auriel, MD; Ludmila Shopin, MD; Sivan Bloch, MD; Shlomo Berliner, MD, PhD; Nir Giladi, MD; Uri Goldbourt, PhD; Itzhak Shapira, MD; Amos D. Korczyn, MD, MSc; Einor Ben Assayag, PhD

(Stroke. 2013;44:1433-1435.)

- Elevated ESR associated with hippocampal atrophy
- Smaller hippocampi associated with worse cognitive performance
- Higher ESR and CRP associated with worse memory scores

**Figure.** Longitudinal results of erythrocyte sedimentation rate (ESR) values according to the upper and lower quartiles of hippocampal volume.
Factors associated with cognitive impairment

- Pathogenesis poorly understood
  - Vulnerable host with accelerated neurodegeneration (e.g., older age, genetic predisposition [ApoE ε4])
  - Newly acquired brain injury from ICU insults (e.g., hypoxemia, hypotension, dysglycemia, inflammation, pharmacologic exposures)

Is the ICU to blame?

Ehlenbach Wj et al. JAMA 2010; 303: 763-70.
Wilcox ME et al. Critical Care Medicine 2013; 41: S81-98
Prospective cohort; Health and Retirement Study data

1434 adults ≥ 50 yrs; surviving 1711 hospitalizations for pneumonia, MI or stroke

Independently associated with both subsequent functional decline and cognitive impairment
Can we modify risk (and where)?

**Pre-ICU**

**Risk factors:**
- Age, sex, pre-existing cognitive impairment, multiple comorbidities, baseline functional status, vision/hearing impairment, chronic drug or alcohol use, malnutrition, immunosuppression, genetics (APOE)

**ICU**

**Risk factors:**
- Admission diagnosis, need for resuscitation, lung protective ventilation strategy, sleep disruption, use of steroids and neuromuscular blockade, delirium monitoring and its management, wakefulness (sedation stewardship), glycemic control, metabolic derangement, early mobilization, cytokine mediated inflammation

**Ward**

**Risk factors:**
- Disordered sleep, inadequate intensity of cognitive and physical therapy, delirium monitoring and its management, neurotransmitter abnormalities, mobilization, persistent cytokine mediated inflammation

Wilcox et al. Critical Care Medicine 2013; 41: S81-98.
Right intervention to the right patient

History and clinical exam

Neurophysiology + Neuroimaging phenotype + Biomarker profile

‘Personalized’ intervention
Human and animal models of S1P associated neuroprotection

- Improved disease outcome from cerebral malaria associated with preserved endothelium integrity, reduced host inflammation and T-cell influx into the brain

Delirium associated with LT self-report of cognitive impairment

- N=561 (cohort, 1101)
  - Delirium group divided into: no problems (n=99), mild problems (n=79) and severe problems (n=10)
  - No delirium (n=373): no problems (n=261), mild problems (n=103) and severe problems (n=9)

... but *not* mortality or HRQOL

**Table 2 Risk of death associated with delirium in survivors of critical illness, within one year after ICU admission**

<table>
<thead>
<tr>
<th>Model</th>
<th>Hazard ratio, 95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude</td>
<td>1.91 (1.44 to 2.52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for gender, APACHE IV, type of admission and CumSOFA</td>
<td>1.26 (0.93 to 1.71)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

**Table 4 Risk of problems with cognitive functioning associated with delirium in survivors of critical illness, within one year after ICU admission**

<table>
<thead>
<tr>
<th>Model</th>
<th>OR for mild problems with cognitive functioning, 95% CI</th>
<th>P-value</th>
<th>OR for severe problems with cognitive functioning, 95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude</td>
<td>2.02 (1.39 to 2.94)</td>
<td>&lt;0.001</td>
<td>2.93 (1.16 to 7.42)</td>
<td>0.02</td>
</tr>
<tr>
<td>Adjusted for gender, APACHE IV, type of admission, and CumSOFA</td>
<td>2.41 (1.57 to 3.69)</td>
<td>&lt;0.001</td>
<td>3.10 (1.10 to 8.74)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

The relationship between delirium duration, white matter integrity, and cognitive impairment in intensive care unit survivors as determined by diffusion tensor imaging: The VISIONS prospective cohort magnetic resonance imaging study*

(Crit Care Med 2012; 40:2182–2189)

- Greater white matter disruption associated with worse cognitive performance at 3 months
Cognitive screen at discharge does not predict impairment at 6 months

MMSE raw scores at time of discharge

- Cognitive sequelae
- No cognitive sequelae

Number of patients with cognitive sequelae at 6 months

- 30-27
- 26-23
- 22-19
- 18-15
The Effect of a Quality Improvement Intervention on Perceived Sleep Quality and Cognition in a Medical ICU*

- ICU-sleep promotion intervention
- Significantly improved daily noise ratings, incidence of delirium, and daily delirium/coma free status
- No improvement in overall Richards-Campbell Sleep Questionnaire

Kamdar BB et al. Critical Care Medicine 2013; 41: 800-09.