Update on Critical Care, 2008: ICU-Acquired Neurologic Dysfunction

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Do patients benefit from “sleeping” through the ICU?

- Fewer days on ventilation
- Fewer ICU days
- Less neuroimaging
- More discharges to home (59% vs 40%, p=0.06)
- Trend to lower mortality (36% vs 47%, p=0.25)


Delirium needs to be sought

Delirium in the ICU (CAM-ICU)

Acute onset of mental status changes OR a fluctuating course

Inattention

Altered level of consciousness OR Disorganized thinking

Confusion Assessment Method for the ICU (CAM-ICU)

• Compared to neuropsych exam
  ✓ High sensitivity (93-100%)
  ✓ High specificity (98-100%)
  ✓ High inter-rater reliability (κ=0.96)
• Requires <2 minutes
• Reliability confirmed in other languages
Prevalence of Delirium

**Medical ICUs (40%-80%)**

- Aldemir, '01
- Bergeron, '01
- Dubois, '01
- Skrobik, '04
- Ouimet, '07
- Pandharipande, '07
- Plaschke, '07

**Mixed ICUs (10%-40%)**

- Ely, '01
- McNicoll, '01
- Micek, '05
- McNicoll, '05
- Lin, '04
- Ely, '04
- Ely, '03
- Plaschke, '07
- Ouimet, '07
- Skrobik, '04
- Dubois, '01
- Bergeron, '01
- Aldemir, '01

\[
\text{HR, 3.2; 95% CI, 1.4-7.7; p=0.008}
\]

*After adjusting for covariates, each additional day spent in delirium was associated with a 10% increased risk of death.*


What about delirium and outcome?

Patients with delirium:

- Spent a median of 10 days longer in the hospital
- Had a risk of remaining in hospital twice that of those without delirium
- Had a 60% greater risk of remaining in the hospital after ICU discharge

39% increase in ICU costs
31% increase in hospital costs

Delirium versus Cognitive Impairment

- **Delirium**
  - Rapid onset
  - Fluctuation
  - Clouded consciousness
  - Inattention, disorganized thought
  - Not chronic

- **Cognitive impairment**
  - Variable to insidious onset
  - Not fluctuating
  - No clouding of consciousness
  - Many domains impaired
    - Memory
    - Attention/concentration
    - Language
    - Executive functioning
  - Persistent/chronic (?)

Cognitive Dysfunction in ICU Survivors

Rey Osterrieth Complex Figure

Near normal rendition by unimpaired 69 y/o pulmonary embolus survivor

Jackson et al. Crit Care Med 2003; 1226-34.

Cognitive Dysfunction in ICU Survivors

Rey Osterrieth Complex Figure

Moderate to severely impaired 89 y/o Pneumonia survivor

Jackson et al. Crit Care Med 2003; 1226-34.
Cognitive Dysfunction in ICU Survivors

Rey Osterrieth Complex Figure

Severely impaired 72 y/o ARDS survivor

Jackson et al. Crit Care Med 2003; 1226-34.

34 yo women

54 yo men

53% with significant atrophy

Cognitive Dysfunction after ARDS

- 42% of survivors received rehab
- 12% identified with cognitive impairment
- IQ reached “normal” levels by 2 years
- All memory indices remained below “normal” at 2 years
- Moderate to severe symptoms of depression and anxiety at 2 years in 23%


Delirium vs Long Term Cognitive Impairment

Potentially Treatable Causes of Delirium

- **D** – Drugs, drugs, drugs
- **E** – Eyes and ears (don’t work)
- **L** – Low oxygen (COPD, CHF, MI, PE, ARDS)
- **I** – Infection
- **R** – Retention (urine/stool), Restraints
- **I** – Ictal
- **U** – Underhydration, undernutrition
- **M** – Metabolic
- **S** – Subdural, Sleep deprivation

Follow-up of Kress

32 patients - randomized to usual care vs daily sedation holidays

<table>
<thead>
<tr>
<th>Metric</th>
<th>Usual</th>
<th>Holiday</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recall awakening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTSD Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTSD Dx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic anxiety</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychosocial Adjustment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Further evidence that excess sedation is BAD

- Paired awakening and breathing trials vs targeted sedation and breathing trials
- More vent-free days
- Fewer ICU days

NNT = 7


Maybe the type of sedation matters

- Risk of transitioning from non delirious to delirious
- 20% increase in odds of delirium for every mg of lorazepam

Delirium/Coma-Free Days

Delirium-Free Days

Coma-Free Days

Dexmedetomidine

Lorazepam

$p=0.01$

$p=0.09$

$p<0.001$

Not remembering may be worse than bad memories

Jones et al, Crit Care Med 2001; 573-80.
Key Points: ICU Delirium

- 60-80% of ventilated patients develop delirium
- 20% to 50% of lower severity ICU patients develop delirium
- TRANSLATION: right now ~ 30,000 to 40,000 ICU patients are delirious in U.S. alone
- Hypoactive or mixed forms most common
- Diagnosis requires ACTIVE testing
- Some risks are modifiable = some delirium is preventable
- Delirium is associated with lots of bad outcomes

Key Points: Cognitive Impairment after ICU

- ~2 out of 3 ICU survivors leave the ICU with long-term cognitive impairment that equates to mild/moderate dementia (sometimes severe)
- Deficits tend to be diffuse and occur in domains including memory, attention/concentration, language, executive functioning
- Impaired functional outcomes, quality of life, and depression are common in ICU survivors
- Function improves over 1-2 years and then plateaus
Weakness and Critical Illness

• Is this a problem?
  ✓ 46% of patients with risk factors in the ICU have acute neuromuscular dysfunction\textsuperscript{1}
  ✓ 25% of patients on the ventilator >5 days have objective severe weakness\textsuperscript{2,3}
  ✓ ARDS patients on average suffer 18% lean body mass weight loss after recovery\textsuperscript{4}
  ✓ Reduced 6-min walk distance for at least 5 years\textsuperscript{4}


Herridge MS, N Engl J Med. 2003; Courtesy, M Herridge
Regardless of having a diagnosis of ICU-acquired weakness:

- The longer the duration of illness (coma), the weaker patients were likely to be...

**What is ICUAP?**

- An acquired form of neuromuscular dysfunction that occurs in the setting of another acute primary illness associated with organ failure and the need for life support.

- The weakness is diffuse with relative sparing of distal muscle groups and is partially reversible over months to years
MRC Scale:

- 0- No activation detected
- 1- Barely detectable flicker
- 2- Active movement w/o gravity
- 3- Active movement w/ gravity
- 4- Active movement w/ gravity + resist
- 5- Active movement against full resistance
What causes neuromuscular dysfunction

Also:
- Contractures
- Focal pressure neuropathies (foot drop, etc)
- Heterotopic calcification

Disuse atrophy
- Myonecrosis
- Myosin loss
- Conduction delay

Direct muscle toxicity
- Neuromuscular junction toxicity

Neuron toxicity

Immobilization

Drugs: steroids, paralytics

Inflammation

Sepsis

www.nku.edu/~dempseyd/bio208pg8.htm

ICUAP: who is at risk?

- Prospective assessment of 95 patients requiring ≥ 7 days of mechanical ventilation
- 25.3% incidence of global paresis 24 weak patients
  - Multivariate analysis
    - Female Gender (OR 4.66, 1.2-18.3)
    - # of days ≥ 2 organ failures (OR 1.28, 1.11-1.49)
    - Duration of MV (OR 1.1, 1.00-1.22)
    - Corticosteroids (OR 14.90, 3.2-69.8)
  - Other factors
    - Sepsis
    - Neuromuscular blockade
    - Immobilization

Myosin Loss Myopathy

Baseline

4 wk immobilization

Torque (%-change)

0 20 40 60 80 100 120

Uninvolved leg

Immobilized 2 wks 4 wks


Acute illness

ICU admission

Survival

Successful transition off life support

Recovery

ICU discharge

Successful transition

ICUAP

Gajic, Crit Care Med. 2008 Mar;36(3):676-82
ICUAP and duration of ventilation

French Multicenter Study, 2002, n=95

US Multicenter Study, 2008, n=136

Increased time on the vent was time spent in “weaning” (6 days vs 3 days, p=0.01)

# CIP and Re-intubation

- Sixty-four sepsis patients (≥7 MV)
  - 53.1% developed CIP (NCS on enrollment)

## Re-intubation

<table>
<thead>
<tr>
<th></th>
<th>CIP</th>
<th>No CIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxemia</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Incr. WOB</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Secretions</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Decr. MS</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Atalectasis</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>


174 subjects >5 days MV enrolled

- 16 subjects persistent delirium
- 22 subjects persistent coma

136 subjects examined
### Table

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ICUAP</th>
<th>No ICUAP</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (%)</td>
<td>35 (25.7)</td>
<td>101 (74.3)</td>
<td></td>
</tr>
<tr>
<td>Ventilator use, d</td>
<td>12</td>
<td>6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>(6–19)</td>
<td>(5–9)</td>
<td></td>
</tr>
<tr>
<td>ICU-free to Day 30, d</td>
<td>6</td>
<td>20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>(0–15)</td>
<td>(15–22)</td>
<td></td>
</tr>
<tr>
<td>Hospital-free to Day 60, d</td>
<td>31</td>
<td>43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>(0–38)</td>
<td>(32–47)</td>
<td></td>
</tr>
<tr>
<td>ICU readmission, %</td>
<td>22.9</td>
<td>7.0</td>
<td>0.01</td>
</tr>
<tr>
<td>Recurrent respiratory failure, %</td>
<td>21.2</td>
<td>10.1</td>
<td>0.09</td>
</tr>
<tr>
<td>Discharged to a location other than home, %</td>
<td>83.3</td>
<td>52.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Hospital mortality, %</td>
<td>31.4</td>
<td>6.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Observed Mortality

<table>
<thead>
<tr>
<th>Quartiles of MRC</th>
<th>Observed Mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29.4</td>
</tr>
<tr>
<td>2</td>
<td>9.1</td>
</tr>
<tr>
<td>3</td>
<td>4.2</td>
</tr>
<tr>
<td>4</td>
<td>6.1</td>
</tr>
</tbody>
</table>

**MRC Range**

- 1.0-3.7
- 3.7-4.5
- 4.6-4.7
- 4.7-5.0

**Count**

- 34
- 44
- 24
- 34
ICU Acquired Weakness: Key Points

- Weakness is prevalent and always pathologic
  - Leads to:
    - Prolonged mechanical ventilation
    - Re-intubation
    - Increased mortality
- Many risk factors exist
  - Use of steroids and neuromuscular blocking agents
  - Duration of ventilation
  - Duration of organ failure
- Immobilization may be a key “second injury”

Gajic, Crit Care Med. 2008 Mar;36(3):676-82
Early Mobility Programs

- Activity is anti-inflammatory
  ✓ “Attempts to perform directed PT for patients with ARF”

10 pts w/MV

Early mobility in respiratory failure

- Early mobilization is feasible and safe
  - Respiratory ICU- “vent liberation ICU”
    - 103 consecutive respiratory failure patients
      - Average hosp LOS until RICU admit 10 days
      - All required ventilation > 4 days
    - Attempt to implement PT regardless of the use of a ventilator
    - Goal: ambulate patients > 100 ft

Bailey, CCM 2007

Early mobility in respiratory failure

- Early mobilization is feasible and safe
  - Respiratory ICU- “vent liberation ICU”
    - 103 consecutive respiratory failure patients
      - Goal: ambulate patients > 100 ft
    - Established simple “safety screen”
      - Neurologic criteria: response to verbal stimulus
      - Cardiovascular criteria: no vasopressors or orthostasis sx
      - Respiratory criteria: FiO2 ≤ 0.6 and PEEP ≤ 10

Bailey, CCM 2007
Early mobility in respiratory failure

<table>
<thead>
<tr>
<th>On last ICU day</th>
<th>&lt; 65 yo n=49</th>
<th>&gt;65 yo n=36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambulate &gt;100 ft</td>
<td>73.5%</td>
<td>63.8%</td>
</tr>
</tbody>
</table>

Safety:
14 adverse events (0.96% of events)
- Falls to knees (5)
- SBP<90 (4)
- Desaturation (3)
- NG dislodgement (1)
- SBP>200 (1)

ET tube activity breakdown:
- ~20% sitting position
- ~40% standing transfer to chair
- ~40% Ambulation

Early mobility in the ICU

- Early mobilization is effective and does not add total cost
  - Pseudo-RCT of various respiratory failure patients
  - 165 patients in each group
    - Protocolized PT
    - Usual nursing led PT

Morris, et al, CCM 2008
Early mobility in the ICU

<table>
<thead>
<tr>
<th>ICU admit</th>
<th>Level 1</th>
<th>Level 2</th>
<th>Level 3</th>
<th>Level 4</th>
<th>ICU D/C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unconscious</td>
<td>Passive ROM</td>
<td>Conscious</td>
<td>Passive ROM</td>
<td>Conscious</td>
<td>Passive ROM</td>
</tr>
<tr>
<td>Passive ROM</td>
<td>Turning</td>
<td>• Active resist PT</td>
<td>• Bed Sit</td>
<td>• Dangle legs</td>
<td>• Turning</td>
</tr>
<tr>
<td>Turning</td>
<td>• Bed Sit</td>
<td>• Dangle legs</td>
<td>• Active transfer to chair</td>
<td>• Ambulation</td>
<td></td>
</tr>
<tr>
<td>➔ Arm moves against gravity? Level 3</td>
<td>➔ Leg moves against gravity? Level 4</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Early mobility in the ICU: Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Protocol PT</th>
<th>Usual Care</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days to 1st out of bed</td>
<td>8.5</td>
<td>13.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ventilator days</td>
<td>7.9</td>
<td>9.0</td>
<td>0.29</td>
</tr>
<tr>
<td>ICU days</td>
<td>7.6</td>
<td>8.1</td>
<td>0.08</td>
</tr>
<tr>
<td>Hospital days</td>
<td>14.9</td>
<td>17.2</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Average per patient cost $44,302 for Usual Care and $41,142 for Protocol group, p=0.26

Includes: Costs of additional therapists...

Morris, et al, CCM 2008
Summary: Mobilization in Respiratory Failure Patients

- Patients with respiratory failure can be safely ambulated
- Protocolized therapy can speed respiratory failure patients progress through step-wise therapy
- Protocolized therapy is associated with shorter hospital LOS without increased cost
- Increased ICU PT staffing may not increase overall costs of care
### Summary: ICU-acquired weakness

- Acquired weakness occurs commonly
- Acquired weakness can lead to a cycle of prolonged ventilation, re-intubation and increased mortality
- Immobilization may be the most important reversible risk factor
- Protocolized physical therapy including ambulation should be strongly considered in all patients, even those on mechanical ventilation