Chronic Critical Illness

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Acute Critical Illness

- Recover quickly
- Die during acute illness

- Require prolonged mechanical ventilation
- Elective tracheotomy
- Continued high levels of nursing care

Become Chronically Critically Ill
Chronic Critical Illness

• A result of modern critical care:
  – Patients who, in the past, would have died from their acute illnesses no survive but require prolonged life support, as long as months or years after the catastrophic illness
  – Mainly elderly individuals with multiple co-morbid conditions who survive a life-threatening episode of sepsis but end up profoundly debilitated and dependent on mechanical ventilation
  – Require extensive and expensive care
Who Is Chronically Critically Ill (CCI)?

• Expression first used by Girard and Raffin, 1985
• In various studies referred to as . . .
  – “Difficult to wean patients”
  – “Patients requiring prolonged mechanical ventilation”
  – “Patients with protracted critical illness”
  – “Patients with prolonged critical illness”
One proposed working Definition of CCI

• Those ICU patients who have an elective tracheotomy performed for failure to wean from mechanical ventilation.
  – Formerly DRG 483, now DRG’s 541 and 542
  – A discrete demarcation point in the episode of illness
  – An elective tracheotomy isn’t done if a patient is expected to wean with the ET tube or to soon die
  – No specific time requirement, includes clinicians' judgment about patient's long-term prognosis
Concerns with this definition

- Using DRGs 541 or 542 to define chronic critical illness may introduce bias because of trends towards earlier placement of elective tracheostomies.

- Using duration of mechanical ventilation >21 days to define “prolonged mechanical ventilation” identifies a group with higher mortality and higher hospital costs than using DRGs 541 and 542.

Chronic Critical Illness in the USA

• > 5 Million patients admitted to ICUs in USA each year
• 1/3 require mechanical ventilation
  – Approximately 20% require ventilation > 7 days, 1-2% > 30 days
    • More than 330,000 patients require > 7 days of mechanical ventilation
    • More than 25,000 patients require > 30 days of mechanical ventilation
Care Environments

- Intensive Care Units
- Post-ICU Respiratory Care Units
- Regular in-hospital nursing units
- Long Term Acute Care (LTAC) Hospitals
  - Freestanding LTAC hospitals
  - Hospital-In-Hospital (specialized LTAC within general hospital)
  - N = 408 (Sept. 2003)
- Currently 22,000 beds nationally, projected need for 81,000 beds
## Age Distribution

**HCUP National Inpatient Sample: Discharges for DRG 483, 1997. Estimated n = 88,000**

<table>
<thead>
<tr>
<th>Age Groups</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 0 to 21</td>
<td>5,280 (6%)</td>
</tr>
<tr>
<td>Age 22 to 49</td>
<td>17,600 (20%)</td>
</tr>
<tr>
<td>Age 50 to 64</td>
<td>19,360 (22%)</td>
</tr>
<tr>
<td>Age 65 to 74</td>
<td>22,000 (25%)</td>
</tr>
<tr>
<td>Age 75 to 84</td>
<td>19,360 (22%)</td>
</tr>
<tr>
<td>Age 85 or older</td>
<td>4,400 (5%)</td>
</tr>
</tbody>
</table>

[http://www.ahcpr.gov/data/hcup/hcupnis.htm](http://www.ahcpr.gov/data/hcup/hcupnis.htm)
# Estimated costs

<table>
<thead>
<tr>
<th>Age Groups</th>
<th>LOS (median/mean)</th>
<th>Charges ($1,000) median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-21</td>
<td>30/53</td>
<td>120 (.6-2,100)</td>
</tr>
<tr>
<td>22-49</td>
<td>30/39</td>
<td>120 (1.2-2,870)</td>
</tr>
<tr>
<td>50-64</td>
<td>32/40</td>
<td>131 (0.07-2,220)</td>
</tr>
<tr>
<td>65-74</td>
<td>32/40</td>
<td>135 (1.9-2,553)</td>
</tr>
<tr>
<td>75-84</td>
<td>32/41</td>
<td>134 (0.3-5,186)</td>
</tr>
<tr>
<td>≥ 85</td>
<td>32/40</td>
<td>120 (0.6-977)</td>
</tr>
</tbody>
</table>

National Inpatient Sample: Discharges for DRG 483, 1997
# Survival from Chronic Critical Illness

<table>
<thead>
<tr>
<th>Study</th>
<th>Hospital Type</th>
<th>Number of Patients</th>
<th>Age</th>
<th>Hospital Survival</th>
<th>One Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spicher 1987</td>
<td>Acute</td>
<td>250</td>
<td>60</td>
<td>39.6%</td>
<td>28.6%</td>
</tr>
<tr>
<td>Gracey 1992</td>
<td>Acute</td>
<td>104</td>
<td>66.3</td>
<td>57.7%</td>
<td>38.7%</td>
</tr>
<tr>
<td>Scheinhorn 1997</td>
<td>RWC</td>
<td>1,123</td>
<td>69</td>
<td>71%</td>
<td>37.9%</td>
</tr>
<tr>
<td>Carson 1998</td>
<td>LTAC</td>
<td>133</td>
<td>71</td>
<td>50%</td>
<td>23%</td>
</tr>
<tr>
<td>Seneff 2000</td>
<td>LTAC</td>
<td>1,702</td>
<td>71</td>
<td>49%</td>
<td>33%</td>
</tr>
</tbody>
</table>

180 days
Chronic critical illness: Long-term survival

- Long-term mortality of 162 patients admitted to in-hospital long-term weaning unit at the Cleveland Clinic (2003-2006)\(^1\)
  - 1-year mortality: 57%
  - 2-year mortality: 68%
  - 3-year mortality: 73%
  - 4-year mortality: 76%
  - 5-year mortality: 81%
- 1-year survival related to age\(^1\):
  - <65 years: 55%
  - 65-74 years: 40%
  - 75-84 years: 29%
- Long-term survivors of chronic critical illness suffer significant functional limitations

Chronic critical illness: Functional status of survivors

• Many who survive CCI live with significant functional impairment

• Activities of Daily Living
  – 3 months: 32% completely dependent in all ADLs
  – 6 months: 33% completely dependent in all ADLs

• Functional Independence Measure - Motor Score
  • Sum of 13 items, 1-7 scale, maximum dependency = 13
  – Hospital admission: 75.2 ± 24.5
  – RCU discharge: 18.0 ± 11.9 (n = 43)
  – 3 months: 46.1 ± 30.5 (n = 22)
  – 6 months: 57.4 ± 34.4 (n = 19)

*Slide courtesy of J. E. Nelson, MD, JD, The Mount Sinai School of Medicine*
Consensus statement

- Management Of Patients Requiring Prolonged Mechanical Ventilation: Report Of A NAMDRRC Consensus Conference
  —Chest 2005;128:393
One model for caring for CCI: Mount Sinai Hospital, New York, NY

- Distinct Respiratory Care Unit (RCU): dedicated long-term weaning unit within the acute-care hospital
- Goals of Care:
  - Recovery of lost strength and function
  - Liberation from mechanical ventilation
  - Palliation of symptom burden
  - Minimization of acquired morbidities that may impact on future level of function and quality of life
- A 14 bed “post-ICU” environment specifically for mechanically ventilated patients from the adult ICUs
- Staffed by specialists in pulmonary and critical care medicine, nurses (3:1 ratio), nurse practitioners, respiratory therapists, social worker
Emphasizing the “4 R’s”:

- Respiratory
- Recovery
- Recuperation
- Rehabilitation
Program of care

• Interdisciplinary Care Map
• Protocolized but flexible weaning protocol
• At RCU admission, nutritional/metabolic screens, early tailored metabolic support
• Specific expertise in nutrition/metabolic support, psychiatry, rehabilitation, neurology and wound healing
• Criteria for when to call for help
Respiratory Care Unit
Weaning Protocol
Mount Sinai Hospital, New York City, USA

Key:
AC = assist control
PS = pressure support
TC = trach-collar

Goal: To stay on the path and quickly progress to TC

Cork: 1 hr TID
3 hr TID
6 Hr BID
6 AM - 6 PM
6 AM - Midnight
D/N x 3 days
Decannulate on Day 4

Change trach to Jackson on Day 4, and begin corking with 2 L NC PRN

If tolerates D/N x 3 days

TC Day and Night

Begin gradually reducing FIO2 till tolerates Room Air
Family support

- At RCU admission, families receive a booklet that describes prognosis and possible outcomes
- Vital component of recovery and hospital discharge
- Family meeting second week of RCU stay
- N.P.s, social worker and psychiatrist work closely with families to understand expectations, plan for discharge
Barriers to discharge from RCU

- Pts. are frequently colonized with resistant organisms
- Pressure ulcers
- Pts often need continued life support:
  - Mechanical ventilation
  - Hemodialysis or parenteral nutrition
- Socioeconomic and family issues
- Unrealistic expectations (family and health care professionals)
- Other:
  - No consent for percutaneous gastrostomy tube, iatrogenic complications
Other weaning protocols

  – Utilizes Intermittent Mandatory Ventilation (IMV) mode with integrated assessments of spontaneous breathing trials
  – Implemented by respiratory therapists
  – Shorter duration of mechanical ventilation compared to historical control subjects
The Biology of Chronic Critical Illness
Admitted to RCU

Improvement & recovery

- Liberation from Ventilator
- Improvement in Albumin
- Participate in Physical Rx

Discharge to Rehabilitation or Home

No recovery from acute illness

- Repeated Septic Episodes
- Remain Ventilator Dependent

Die or Discharge to SNF on Ventilator
Common physiologic disturbances in CCI

- Disruption in anterior pituitary hormones secretion
- Bone hyperresorption
- Male hypogonadism
- Psychiatric disorders
- “Immune exhaustion”
- Severe symptom burden
- Bone marrow suppression

- Specific wasting syndrome leading to adult kwashiorkor-like malnutrition
- Critical illness polyneuropathy
- Pressure ulcers
- Recurrent infections
Fundamental question: Is there a specific syndrome of CCI?

• **Syndrome:** a combination of signs and/or symptoms that forms a distinct clinical picture indicative of a particular disorder
  - *Concise Medical Dictionary, 2000, Oxford University Press*

• **Syndrome of CCI:**
  - Follows an acute critical illness, usually with at least one episode of sepsis
  - Metabolic, endocrine, physiologic and immunologic abnormalities
  - Continued requirement for mechanical ventilation
  - Continued need for high level nursing care
  - Weeks to months
Care of patient with CCI at the Mount Sinai Hospital

- Extensive evaluation of nutritional and metabolic status on admission to the RCU
  - Complete blood count, serum chemistries, pro-thrombin time
  - Capillary glucose measurement q6 hours
  - Hemoglobin A1C
  - Homocysteine level
  - Ammonia
  - Pre-albumin
  - 24-hour urine for urea nitrogen
  - TSH, free T4
  - Intact PTH, 25-hydroxy-vitamin D, 1,25-dihydroxy-vitamin

- Optional
  - Testosterone, total and bioavailable, prostate specific antigen
  - Methylmalonic acid
  - Iron studies
  - Morning serum cortisol, 24-hour urine cortisol
  - Co-syntropin stimulation test (1 mcg or 250 mcg)
  - Anti-thyroid antibodies

**Nutritional Pharmacology In CCI Patients:** Some supplements to consider

<table>
<thead>
<tr>
<th>Agent</th>
<th>Effect</th>
<th>Dose</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitriol</td>
<td>calcium absorption from GI tract</td>
<td>0.25-0.5 mcg qDAYS (IV or enterally)</td>
<td>Must monitor serum Ca, PO4</td>
</tr>
<tr>
<td>Carnitine</td>
<td>Fatty acid oxidation</td>
<td>1 gm enterally t.i.d.</td>
<td>Consider for patients on valproate or with diminished gluconeogenesis</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>Decrease bone resorption</td>
<td>90 mg IV ONCE</td>
<td>May cause fever, Avoid in patients with low Vitamin D</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Treatment of nutritional deficiency</td>
<td>50,000 units enterally once a week</td>
<td>Can take &gt;1 month to replete stores</td>
</tr>
<tr>
<td>Zinc sulfate</td>
<td>May aid wound healing</td>
<td>220 mg enterally b.i.d.</td>
<td>Can induce copper deficiency, anemia</td>
</tr>
</tbody>
</table>

Adapted from: Mechanick JI. *Curr Opin Clin Nutr Metab Care* 2005; 8:33-39
Critical illness and endocrine dysfunction

- Acute and chronic critical illness result in endocrine and metabolic abnormalities
- The following slides summarize some of these abnormalities and when they occur during the course of critical illness
<table>
<thead>
<tr>
<th>Hormone,</th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Somatotrophic Axis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulsatile GH</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>GH Binding Protein</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>IGF-I</td>
<td>Decreased</td>
<td>Very Decreased</td>
</tr>
<tr>
<td><strong>Thyrotrophic Axis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulsatile TSH</td>
<td>Increased/No change</td>
<td>Decreased</td>
</tr>
<tr>
<td>T4</td>
<td>Increased/No change</td>
<td>Decreased</td>
</tr>
<tr>
<td>T3</td>
<td>Decreased</td>
<td>Very Decreased</td>
</tr>
<tr>
<td>rT3</td>
<td>Increased</td>
<td>Increased/No change</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hormone</th>
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<th>Chronic</th>
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<tbody>
<tr>
<td><strong>Gonadotrophic Axis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulsatile LH</td>
<td>Increased/No change</td>
<td>Decreased</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Decreased</td>
<td>Very Decreased</td>
</tr>
<tr>
<td><strong>Pituitary-adrenocortical Axis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Cortisol</td>
<td>Very Increased</td>
<td>Inc/No Change/Dec</td>
</tr>
<tr>
<td><strong>Lactotropic Axis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulsatile Prolactin</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

Wasting syndrome of chronic critical illness

• Possible endocrine abnormalities:
  • Growth hormone-insulin-like-growth factor-1 axis
    – Normal physiology: diurnal peaks of circulating growth hormone (GH) levels, approx. 6 am and 9 pm each day
    – Acute phase of critical illness: higher circulating GH levels with loss of diurnal variation and more frequent peaks, peripheral tissue resistance to GH
    – Chronic critical illness: lower circulating GH levels with loss of diurnal variation, peripheral tissues regain response to GH
  
• G. van den Berghe, *Crit Care Clin*, 2002
Wasting Syndrome: Male Hypotestosteronemia

- 30 consecutive CCI men, median age 73 yrs
- Total testosterone by radioimmunoassay after purification by column chromatography
- Bioavailable testosterone (non-sex hormone binding globulin [SHBG] bound testosterone), by separation of the SHBG bound steroid from the albumin bound and free steroid with ammonium sulfate

Nierman DM, Mechanick JI. Crit Care Med. 1999;27:2418-21
Wasting Syndrome: Male Hypotestosteronemia

- Total testosterone = 104 ± 96 ng/dl
- Bioavailable testosterone (bioT) = 19 ± 20 ng/dl (16 ± 9\% of total testosterone)
- BioT levels averaged 11 ± 11\% of levels found in age-matched normal men
- 29/30 (96\%) men had bioT levels well below the lower limit of normal for their age range.
- However, it is uncertain whether supplementing testosterone leads to improved clinical outcomes

Hypothalamic-Pituitary-Adrenal Axis

- **Acute critical illness**
  - CRH, cytokines and NE stimulate ACTH
  - Hypercortisolism
    - Diverts fuels to vital organs and suppresses anabolism
    - Mutes inflammatory cascade to protect from overstimulation

- **Chronic critical illness**
  - Endothelin possibly maintains hypercortisolism
  - ANP/substance P inhibit ACTH?
  - Prolonged endogenous hypercortisolism may impair wound healing and cause myopathy.
  - This mechanism eventually fails!
Hypothalamic-Pituitary-Adrenal Axis: “adrenal exhaustion”

• 20-fold increase (25-40%) of adrenal insufficiency in critically ill patients > age 50 > 14 days in ICU

• “Adrenal Exhauastion Syndrome”
  – Acquired in the ICU
  – Probably due to a prolonged inflammatory response, with chronic secretion of systemic cytokines and other HPA suppressive substances

• Hypercortisolism + decreased DHEAS + decreased Prolactin = possible susceptibility for infections
“Immune Exhaustion”

- At RCU admission, 8 of 22 patients had low \textit{in vitro} response by peripheral lymphocytes to Candida Antigen (LSA assay)
- 5/8 (63\%) of 8 low responders died; 1/14 (7\%) above normal responders died.
- Initial pro-inflammatory phase in acute sepsis replaced by anti-inflammatory features:
  - Decreased monocyte function
  - Suppression of proinflammatory cytokines (TNF, IL-1, IL-8)
  - Enhanced anti-inflammatory cytokines (TGF-beta, IL-1ra, IL-10)
  - Lymphocyte apoptosis

Kalb T, Goldstein N et al. \textit{AJRCCM} 2000; 161:A90
Bone Hyperresorption

- CCI pts are at risk for accelerated bone loss due to:
  - Vitamin D deficiency
  - Prolonged immobility
- Identification and treatment of bone loss may prevent debilitating fractures after recovery

Nierman DM, Mechanick JI. *Chest*. 1998;114:1122-8
Bone hyperresorption: Laboratory evaluation

- 24-hr urine within 48 hours of RCU admission
- Urine N-telopeptide (NTx) measured, Osteomark® assay
- Serum Intact PTH, 25-vitamin D, 1,25-vitamin D
- Elevated serum intact PTH level diagnostic of physiologically significant vitamin D deficiency

- Elevated Urine NTx = Abnormal Bone Resorption

- If NTx elevated, then:
  - Low PTH = Immobilization
  - High PTH = Vitamin D deficiency
  - Normal PTH = Both
Prevalence of bone hyperresorption in CCI

- 49 CCI patients
- Median age 73 yrs, M/F = 28/21
- 22 Medical, 27 Surgical
- Median ICU LOS = 20 days
- Post-tracheotony till RCU transfer = 7 days
- 92% of population found to have Abnormal Bone Resorption

![Distribution of PTH levels among Subjects with high urine NTx](image)
Treatment of bone hyperresorption

- 157 CCI patients, 19 months, retrospective review
- 131 (83%) pts had ↑ urine NTx
- 55 pts:
  - ↑ NTx levels at RCU admission
  - Treated with either calcitriol alone (n = 44) or calcitriol + pamidronate (n = 11)
  - NTxs remeasured after treatment

- All pts received calcitriol (1,25-dihydroxyvitamin D₃) 0.25 mcg/day enterally (Rocaltrol®) or IV (Calcijex®)
- At endocrinologist’s discretion, pamidronate, 30 mg IVSS qD x 3 consecutive days given (~ $532)
- Indications for pamidronate:
  - Elevated PTH + hypercalciuria
  - Very elevated urine NTx suggesting severe bone hyperresorption

Nierman DM, Mechanick JI. *Chest* 2000; 118:761-6
### Response to Treatment

<table>
<thead>
<tr>
<th></th>
<th>Calcitriol</th>
<th>Calcitriol + Pamidronate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urine NTX Pre Rx</strong></td>
<td>187 ± 146</td>
<td>329 ± 238</td>
</tr>
<tr>
<td><strong>Urine NTX Post Rx</strong></td>
<td>178 ± 123</td>
<td>100 ± 85</td>
</tr>
<tr>
<td><strong>p value</strong></td>
<td>NS</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td><strong>PTH Pre Rx</strong></td>
<td>93 ± 145</td>
<td>36 ± 29</td>
</tr>
<tr>
<td><strong>PTH Post Rx</strong></td>
<td>40 ± 28</td>
<td>53 ± 51</td>
</tr>
<tr>
<td><strong>p value</strong></td>
<td>0.02</td>
<td>NS</td>
</tr>
</tbody>
</table>

NTX Units = BCE/mmol Cr; PTH Units = pg/mL
Pathogenesis of CCI: Hypothetical model

• Unremitting or repeated episodes of physiologic stress result in changes in the homeostatic set-points of various neuro-endocrine axes (hypothalamic-pituitary-adrenal, hypothalamic-pituitary-thyroid, etc.), which eventually result in tissue dysfunction and organ damage, and eventually in the syndrome of CCI
Important Future Questions

• Can we identify patients shortly after ICU admission into those at low and high risk for becoming CCI?
  – Epidemiologically
  – Biologically?
• What should the research agenda be in this area?
• How do cultural and social values contribute to the growing number of CCI patients?
• How does the financing of the health care delivery system contribute?
• Is this primarily an phenomenon in the USA?
Critical Care Clinics,
Volume 18, Number 3
(July 2002)

For further, in-depth reading