Chronic Critical Illness

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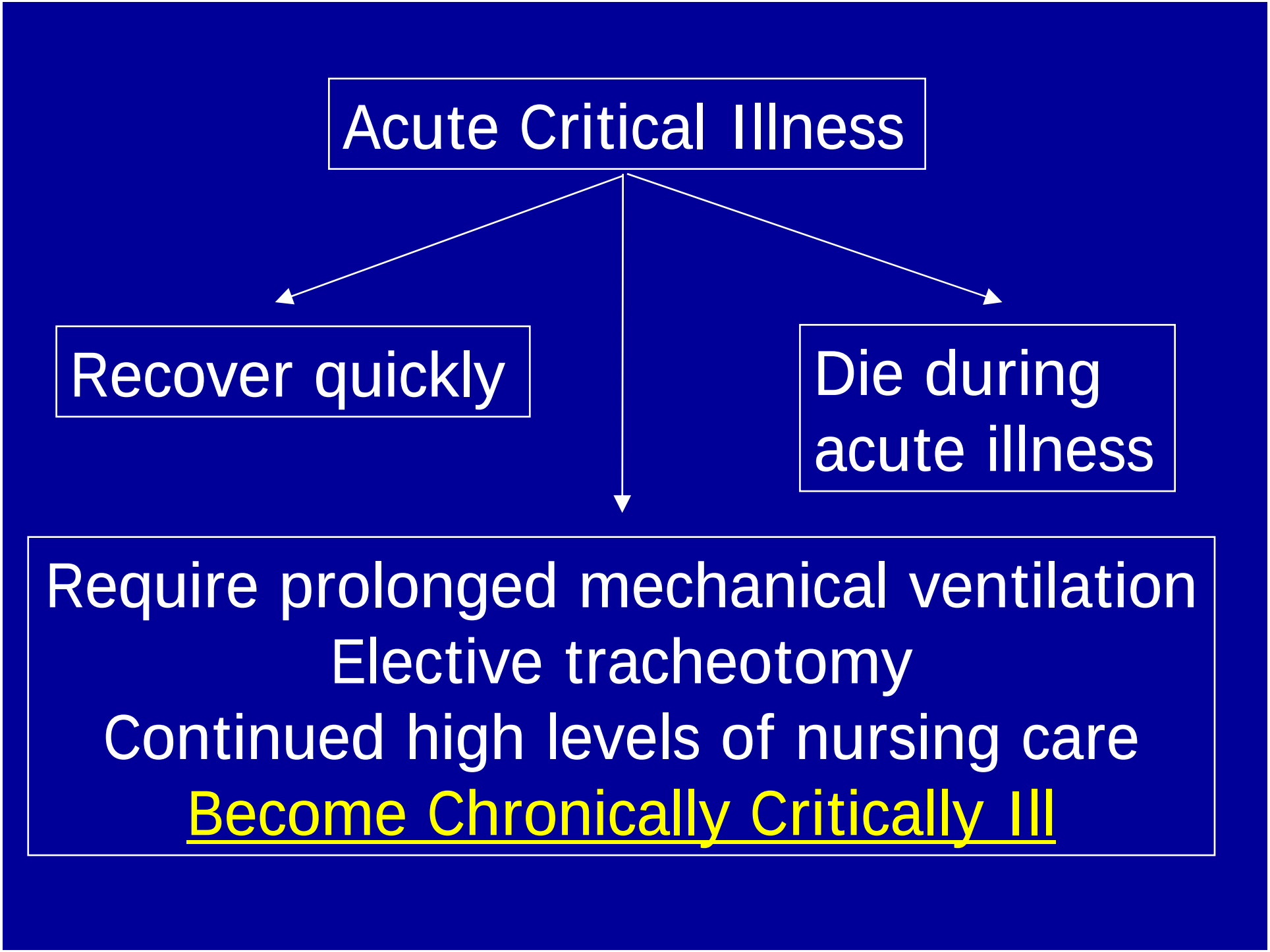

Acute Critical Illness
Recover quickly
Die during acute illness
Require prolonged mechanical ventilation
Elective tracheotomy
Continued high levels of nursing care
Become Chronically Critically Ill

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 thanusing DRGs 541 and 542

  - Cox, Carson, Lindquist, et al, *Crit Care*, 2007;R9 (doi:10.1186/cc5667)

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 hsopitals
  - 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

Age Groups	Number (%)
Age 0 to 21	5,280 (6%)
Age 22 to 49	17,600 (20%)
Age 50 to 64	19,360 (22%)
Age 65 to 74	22,000 (25%)
Age 75 to 84	19,360 (22%)
Age 85 or older	4,400 (5%)

http:/www.ahcpr.gov/data/hcup/hcupnis.htm

Estimated costs

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

National Inpatient Sample: Discharges for DRG 483, 1997

Survival from Chronic Critical Illness

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

1. JK Stoller et al., *Chest*, 2003;124:1892-99; 2. Cox, et al, *Crit Care*, 2007;R9 (doi:10.1186/cc5667)

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 NAMDRC 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

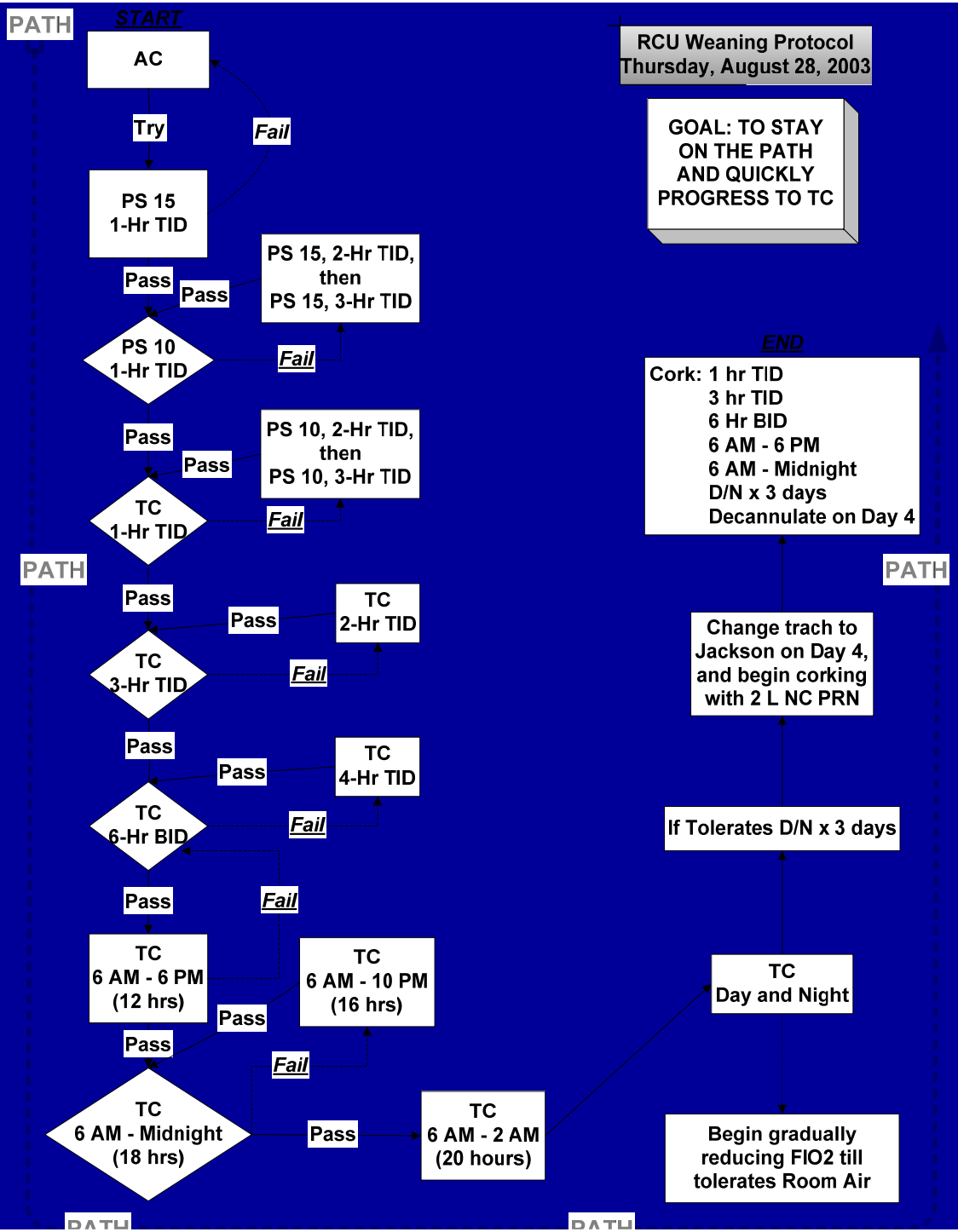
Emphasizing the "4 R's" :

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

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

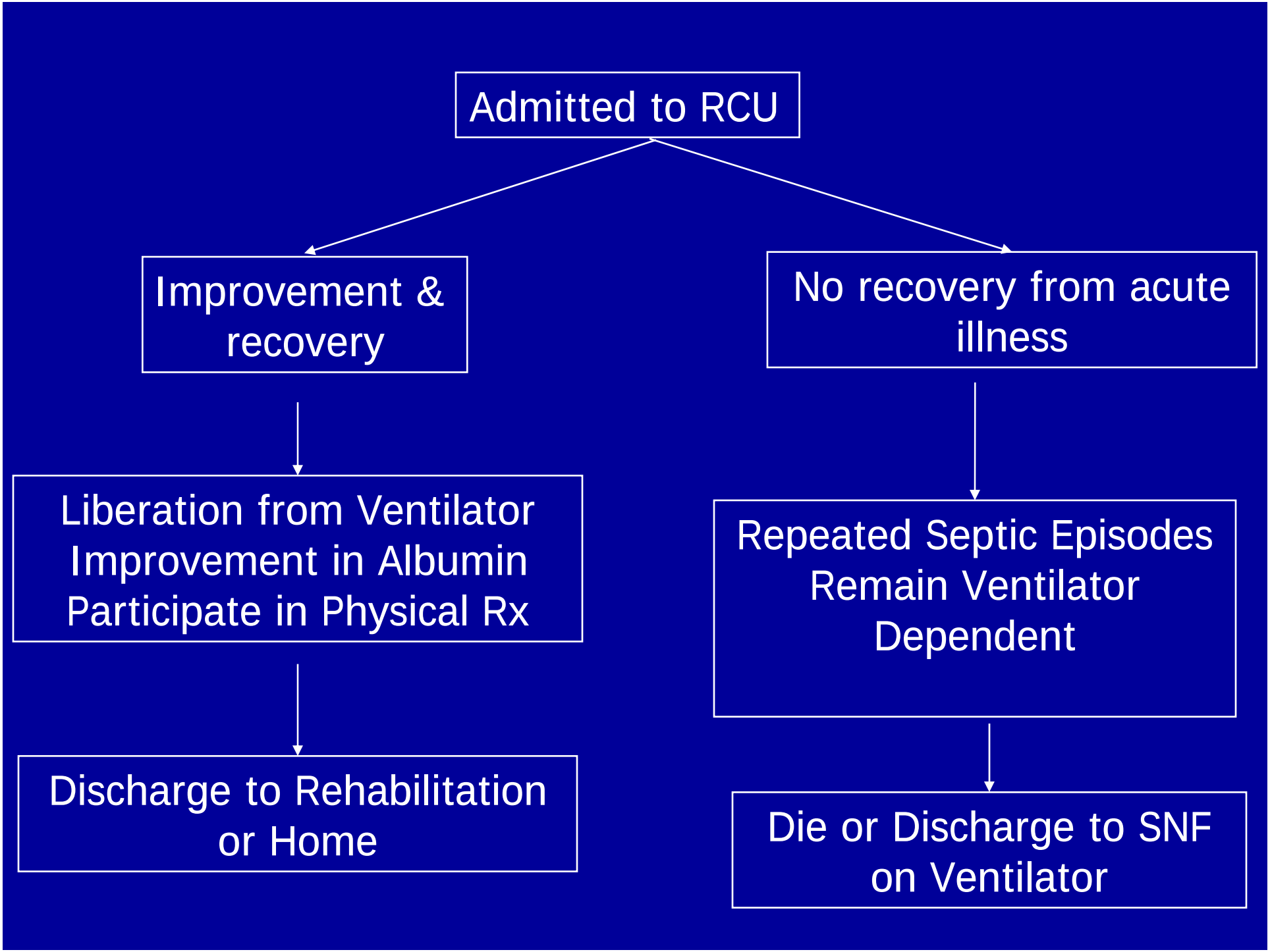
Barriers to discharge from RCU

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

Other weaning protocols

- D. Scheinhorn, et al, *Chest*, 2001;119:236
  - 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
No recovery from acute illness
Liberation from Ventilator
Improvement in Albumin
Participate in Physical Rx
Repeated Septic Episodes
Remain Ventilator Dependent
Discharge to Rehabilitation or Home
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-dihidroxy-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

Adapted from: Mechanick JI. *Curr Opin Clin Nutr Metab Care* 2005; 8:33-39.

Nutritional Pharmacology In CCI Patients: Some supplements to consider

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

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

Hormone,	Acute	Chronic
Somatotrophic Axis		
Pulsatile GH	Increased	Decreased
GH Binding Protein	Decreased	Increased
IGF-I	Decreased	Very Decreased
Thyrotrophic Axis		
Pulsatile TSH	Increased/No change	Decreased
T4	Increased/No change	Decreased
T3	Decreased	Very Decreased
rT3	Increased	Increased/No change

G Van den Berghe, *Frontiers in Neuroendocrinology* 2002; 23:370-91.

Hormone	Acute	Chronic
Gonadotrophic Axis		
Pulsatile LH	Increased/No change	Decreased
Testosterone	Decreased	Very Decreased
Pituitary-adrenocortical Axis		
ACTH	Increased	Decreased
Cortisol	Very Increased	Inc/No Change/Dec
Lactotropic Axis		
Pulsatile Prolactin	Increased	Decreased

Van den Berghe G. *Frontiers in Neuroendocrinology* 2002; 23:370-91.

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 dirunal variation and more frequent peaks, peripheral tissue resistance to GH
  - Chronic critical illness: lower circulating GH levels with loss of dirunal 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*

Nierman DM, Mechanick JI. *Crit Care Med*. 1999;27:2418-21

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 Exhaustion Syndrome”
  - Marik & Zaloga. *Chest* 2002; 122:1784-96
  - 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 *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. *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

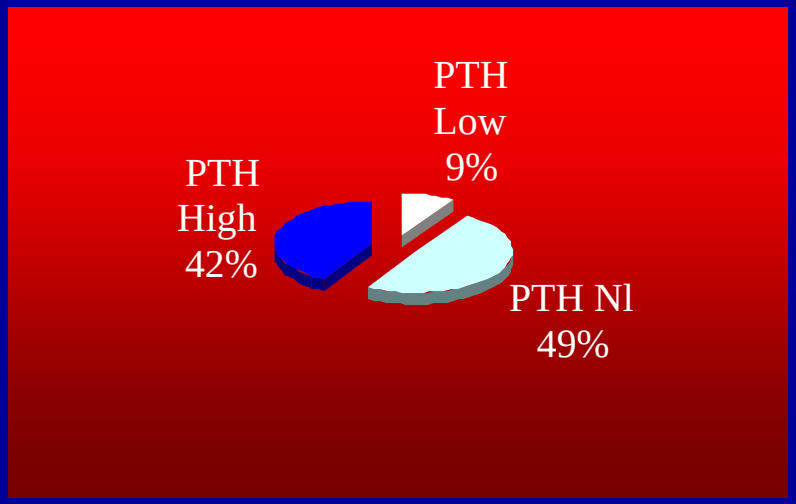
Bone hyperresorption: Laboratory evaluation

- 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-tracheotomy till RCU transfer = 7 days
- *92% of population found to have Abnormal Bone Resorption*



Distribution of PTH levels among Subjects with high urine NTx

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 D_3) 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

	Calcitriol	Calcitriol + Pamidronate
Urine NTX Pre Rx	187 ± 146	329 ± 238
Urine NTX Post Rx	178 ± 123	100 ± 85
p value	NS	*< 0.01*
PTH Pre Rx	93 ± 145	36 ± 29
PTH Post Rx	40 ± 28	53 ± 51
p value	*0.02*	NS

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
  - Mechanick, *Curr Opin Clin Nutr Metab Care*, 2005;8:33-9

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?

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For further, in-depth reading