



# Chronic Critical Illness

A New Neuroendocrine Paradigm?

Patrick Neligan MA MB FCARCSI DICM

## Contents

- Critical illness may really be two distinct disease syndromes
- Acute stress response
- Physiologic reserve
- Prolonged critical illness
- Neuroendocrine exhaustion
- HPA, GH axis, Thyroid axis, Gonadal axis & Prolactin

## What is Critical Care?

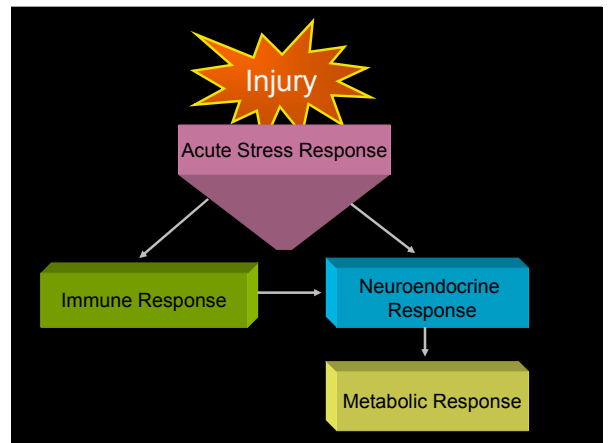
- A location
- “Non specific constellations of physiologic and biologic abnormalities forming syndromes” (Hebert 2002)
- Homeostatic abnormalities resulting in ICU admission are in late stages at time of admission.
- Underlying pathology <-> abnormal physiology

## Death from Critical Illness



## Prolonged Critical Illness

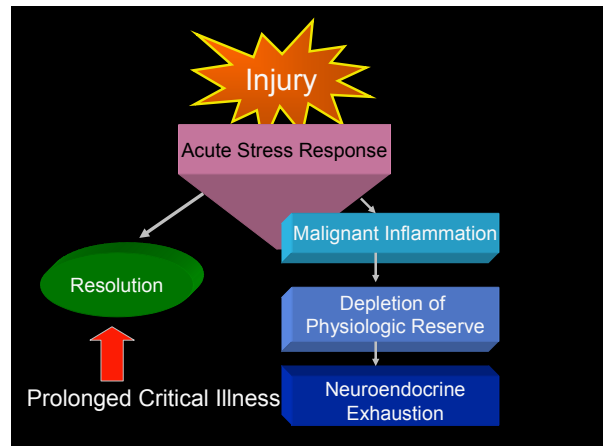
May not affect 28 day mortality,  
but will affect mortality  
“down the road”



## Stress Response

Three arms all inter-related:

- Cytokine Activation
- Neurohormonal Response
- Metabolic Response



## Stress Response – Why?

1. Maintenance of essential organ perfusion
2. Conservation of intravascular volume
3. Increased availability of metabolic substrate: pro-inflammatory tissue.
4. Increase Oxygen availability for inflammatory cells
5. Hypercoagulability: to prevent bleeding
6. Endorphin release: to minimize pain

## Physiologic Reserve

Capacity of the body to deal with the stress response

## What Reserve?

- Increasing  $O_2$  delivery to match metabolic demand in hyperdynamic conditions
- Functional residual capacity of lungs
- Hemoglobin concentration
- Cardiac output
- Capacity to increase HR and SV (CAD)
- Intact vascular tree

## What Reserve?

- Adequate GFR to excrete by products of metabolism
- Adequate lean body mass to maintain, in particular, respiratory function
- Capacity of HPA to increase sympatho-medullary output

## Reserve

- CVS
- Respiratory system
- Metabolic-excretory (liver and kidneys)
- Neuroendocrine system
- Nutritional, neurochemical and electrolyte Stores
- Lean body mass and musculoskeletal system
- Hematopoetic and immune systems

## 2 month mortality and functional status after prolonged MV

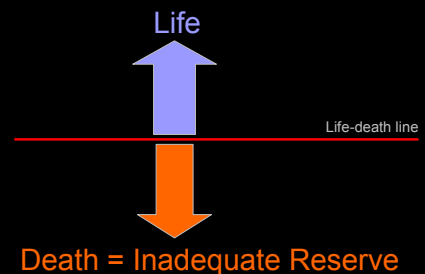
- 1 institution, 4 ICUs
- 817 patients
- Median duration MV = 9 days
- 2 month mortality 43%
- Increased mortality associated with increasing age, premorbid functional status and co-morbidity & Apache II score

*Chest 121 Feb 2002*

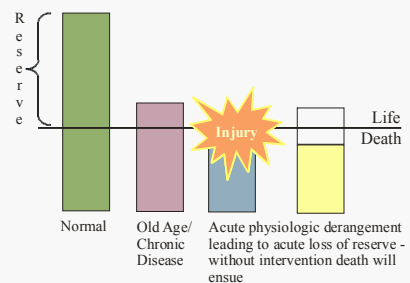
## Reserve Depleted by

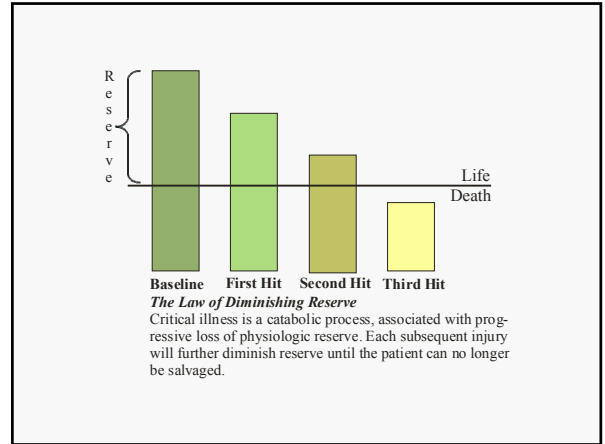
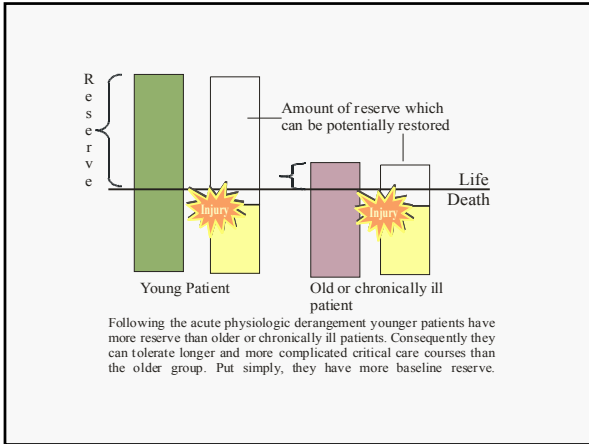
- Advancing age
- Co-morbidity (heart disease, cirrhosis, chronic inflammatory disorders)
- Alcoholism
- Malnutrition
- Prolonged admission to ICU

## Reserve

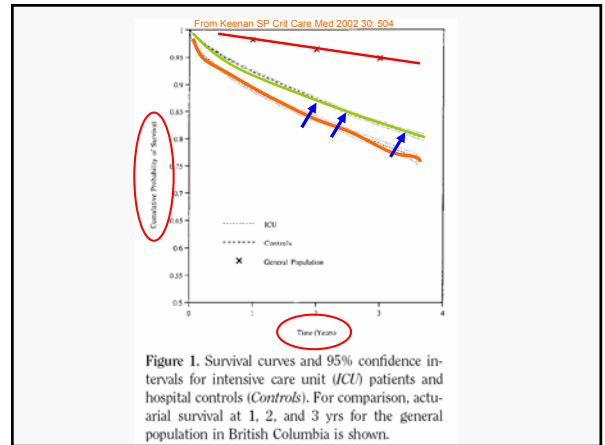


## Reserve





Why is this Important?



Neuroendocrine Function

- Acute Critical Illness**
- Actively secreting anterior pituitary gland & peripheral inactivity of anabolic hormones
  - Similar irrespective of cause
  - Acute loss of reserve – can be restored

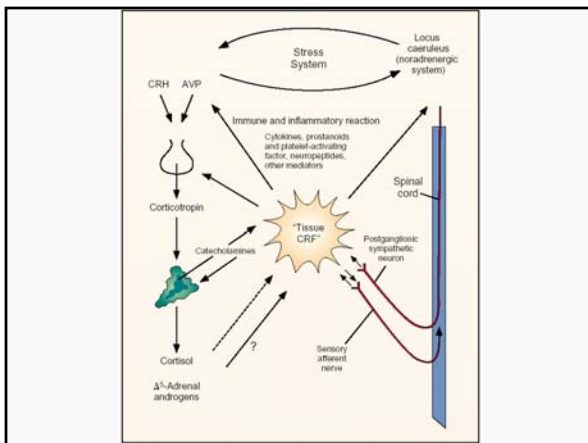
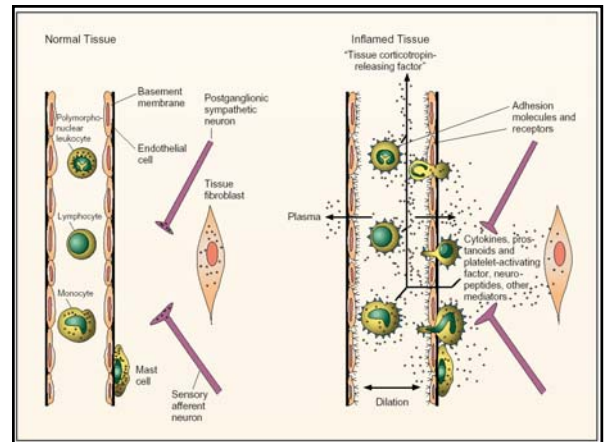
## Prolonged Critical Illness

- Neuroendocrine Exhaustion
- Restoration of peripheral sensitivity  
-loss of central drive
- Permanent loss of reserve (=aging)

## Adrenal Cortex HPA

## Elevated Cortisol

- Tissue injury
- Macrophage activation
- Cytokine release
- Cytokines act directly to stimulate ACTH from the pituitary gland.
- Tissue corticotropin releasing factor



## Adrenocortical Function

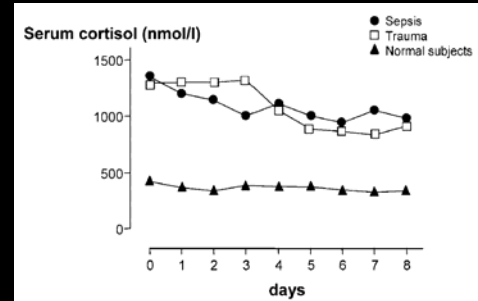
Acute Critical Illness- elevated blood cortisol

- Increased blood sugar
- Anabolism is postponed
- Intravascular fluid retention
- Increased inotropic and vasopressor response to catecholamines and angiotensin II
- Reduced immune response: self muting

## Cortisol

- Maintains vascular tone (facilitates the vasoconstrictor effects of catecholamines)
- Increasing number and sensitivity of  $\alpha$ -1 and  $\beta$ -adrenoreceptors, and reduced down-regulation of these receptors
- Positive inotropic effect
- Vascular permeability. Total body water
- Modulation of inflammation –  $\uparrow$  anti-inflammatory cytokines IL-4 & IL-10 may increase cortisol receptor binding affinity

## Cortisol - ACI

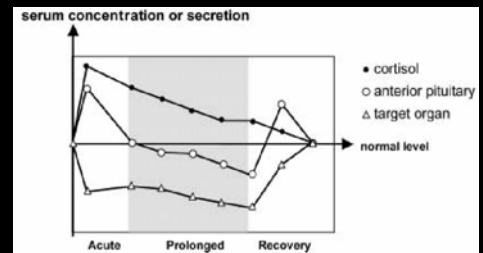


Vermes, I. J Clin Endocrinol Met 1995 p1285

## Prolonged Critical Illness

- Decreased ACTH levels, but [cortisol] remains elevated
- Cortisol release is driven by an alternate pathway
- Decreased androgens such as DHEAS
- Pregnenolone is preferentially converted to cortisol
- Renin levels high, but there is paradoxical diminution of aldosterone

## Cortisol Pattern



Van den Berghe, de Zegher F, Bouillon R. Clinical review 95: Acute and prolonged critical illness as different neuroendocrine paradigms. J Clin Endocrinol Metab 1998; 83(6):1827-1834

## Adrenal Gland PCI

- Preferential production of cortisol over androgens and mineralocorticoids
- ? Hemodynamic benefit
- Prolonged hypercortisolemia may lead to:
  - Increased risk of infection
  - Impaired wound healing
  - Prolonged catabolism
  - Myopathy -> failure to wean

## Serum cortisol (nmol/l)

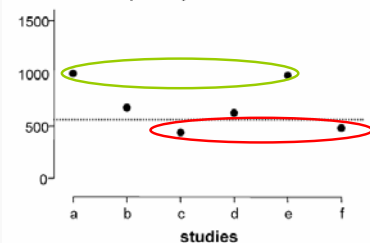


Fig.3a-f Mean serum cortisol levels as published in several studies in ICU patients. a Forty medical ICU patients with septic shock [3]; b fifty-four post-operative patients after ruptured aortic aneurysm [4]; c twenty patients on a multidisciplinary ICU surviving septic shock [8]; d thirty-two patients with septic shock [5]; e seventy intensive care patients [6]; f one hundred and fifty-nine intensive care patients, > 7 days ICU-stay [7]. Dotted line: maximum (unstimulated) serum cortisol level in healthy persons (from [74])

From JJ, Girbes AR, Beentjes JA, Tulleken JE, van der Werf TS, Zijlstra JG. Hormones in the critically ill patient: to intervene or not to intervene? Intensive Care Med 2001; 27(10):1567-1577.

## Relative Adrenal Insufficiency

- Inadequate cortisol production relative to severity of illness
- Catecholamine dependent hyperdynamic state

## Relative Adrenal Insufficiency

Barquist *J Trauma* 1997 42: 27-32

- Measurement of serum cortisol in 1000 surgical ICU patients
- 0.7% of these patients had relative adrenal insufficiency, increasing to 7% in prolonged stay

## Relative Adrenal Insufficiency

- Rivers *Chest* 2001 119:889-896
- Using conventional cortisol of 550nmol/l, and ACTH response of <250nmol/l
- 1/3 of high risk surgical ICU patients were adrenally insufficient.
- Significant resolution of vasopressor therapy within 24h with hydrocortisone

## Relative Adrenal Insufficiency

Diagnosis is difficult because:

- The baseline cortisol is an unreliable indicator
- The quantitative response to ACTH is variable and the “normal” response is unknown
- The dose of ACTH is controversial

## Adrenal Insufficiency

- Bollaert et al *1998 Crit Care Med* 26: 645-650
- 41 patients with septic shock who required catecholamine support for >48 hours
- Randomly assigned to hydrocortisone 100mg iv q8h or placebo [duration 5 days]
- Improved shock reversal and significantly lower 28 day mortality
- Shock reversal similar in responders and non responders

## When should steroids be given?

- Patients with septic shock who are not weaning from catecholamines
- In whom source control has been effected
- In relatively low dosage e.g. 100 mg hydrocortisone
- ACTH stimulation test probably unnecessary

## Somatotropic axis in ACI

Increased production of GH  
Peripheral resistance

## Growth Hormone

- Growth hormone is a polypeptide with anabolic, immunomodulatory and lipolytic properties
- GH secretion is stimulated by GHRH and inhibited by somatostatin.
- Effects (partly) mediated by IGF-1

## Somatotropic Axis

Acute phase

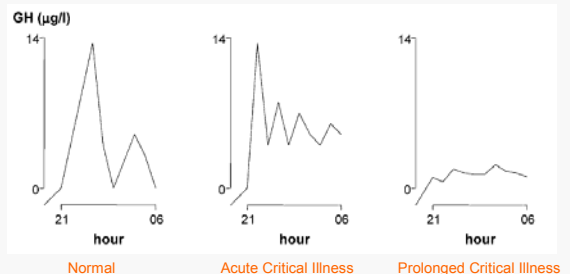
- Increased growth hormone levels
- Loss of pulsatility: interpulse peaks are high
- Decrease in IGF-1 (peripheral resistance)
- Circulating IGF binding proteins are low also

## Peripheral Resistance

- Catabolic effects (releasing glucose) predominate
- Insulin antagonism
  - Direct effects of GH function
- Anabolic properties are, essentially, switched off
  - Indirect effects
- Mediated by cytokines

## GH in ACI

Changes in GH secretion and IGF-1 function appear to tally with the body to postpone anabolism and direct substances needed for survival to vital organs.



## GH axis in PCI

- Reduced pulsatility of GH
- Peak GH lower, trough higher
- So mean GH levels are low-normal
- GH release is erratic
- Decreased IGF-1, IGFBP and acid-labile subunit
- - Wasting Syndrome

## Growth Hormone does not work

Without Pulsatility

## Growth Hormone Rx

- Takala, J 1999 *NEJM* 341: 785-792
- 532 patients in ICU x 5-7 days and who expected stay > 10 days
- Either GH @ 0.07 – 0.13mg/kg or placebo until discharge from ICU or x 21/7
- GH increased mortality by 19% to 24% (with higher dose).
- Relative increase in risk of death 1.9 & 2.4

## Growth Hormone

Should not be given in PCI?

Study criticized:

- High dose of GH administered
- Very high IGF-1 levels
- Apoptotic triggers? – organ failure
- Aggravation of hypoadrenalism and hypothyroidism

## GH Secretagogues

- Hypothalamic dysfunction - ? deficiency in endogenous GH releasing peptide.
- Increased release of GH, IGF etc
- Normal GH function returns
- Secretagogue administration has advantage over high dose GH therapy in that negative feedback mechanisms operate.

## Thyroid Axis

“Sick Euthyroid Syndrome”

## Thyroid Axis

Metabolic activity of T3

- Inotropy, Chronotropy (indirect increase in responsiveness to catecholamines)
- Decreased PVR
- Facilitation of GH action and responsiveness
- Protein anabolism (both excess and deficiency inhibit protein synthesis)

## Thyroid Axis

- Thyroid hormones enhance the rate of intestinal absorption of glucose and galactose
- And facilitate insulin and glucose utilization

## Thyroid Axis in ACI

- Normal TSH
- Decreased circulating T3 (due to reduced peripheral conversion of T4 to T3) and increased turnover.
- The magnitude of drop reflects severity of illness.
- Reduced rT3 degradation
- Altered hypothalamic feedback

## Thyroid Axis in ACI

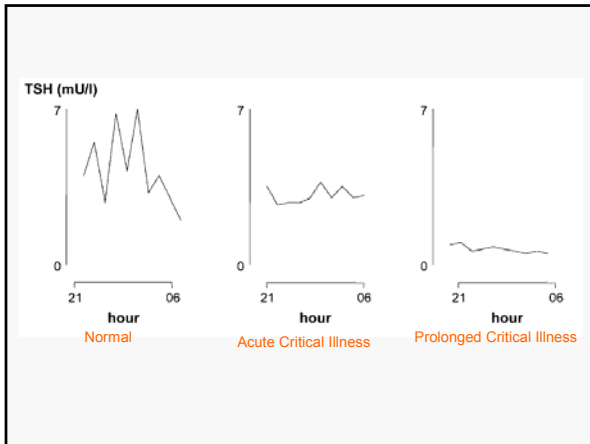
- “Low T3 syndrome”
  - Mechanisms unknown
  - Possibly due to cytokines
  - Possibly increased levels of FFA, decreased binding proteins
- Why?
- Probably to reduce energy expenditure & conserve body protein

## Rising T3 concentration

Indicates recovery from critical illness

## Thyroid in PCI

- There is reduced T3 and TSH
- Mechanisms – increased concentrations of dopamine (endogenous/exogenous), hypercortisolemia ?
- Central hypothyroidism – feeding resistant catabolic state of critical illness
- Thyroid axis can be reactivated by intravenous admin of TRH
- No evidence that T3 or T4 beneficial



## Thyroid Replacement Rx

- Brent 1986 *J Clin Endocrinol metab* 83: 309 – 319
- MICU patients with ↓ concentrations
- Thyroxine replacement therapy increased T3 and T4 levels, but TSH dropped
- Mortality equal in both groups (75% control vs 73% T4)

## Thyroid Secretagogues

- Van Den Berghe et al
- Investigated TRH or TRH with GH secretagogues in PCI
- This led to reactivation of thyroid axis (T3, T4 and TSH)
- When administered in combination with GH secretagogues, pulsatility of GH returned and ↓T3

## Gonadal Axis

## Gonadal Axis

- Testosterone is an essential anabolic hormone (steroid)
- Testosterone deficiency is associated with negative nitrogen balance.
- Virtually all catabolic states are associated with testosterone deficiency
- Testosterone levels are low in spite of normal LH levels

## Gonadal Axis in PCI

- Hypogonadotropic hypogonadism (decreased LH and testosterone)
- This is further diminished by administration of exogenous dopamine.

## Prolactin

## Prolactin

- Appears to be an immuno-regulatory hormone:
  - There are prolactin receptors on T and B lymphocytes (which appear to require prolactin to function)
- Increased PRL in physiologic stress

## PRL in PCI

- Loss of PRL pulsatility
- Immune dysfunction
- Dopamine reduces PRL synthesis and causes T cell dysfunction and impaired neutrophil chemotaxis

## Dopamine

Adverse effects on neuroendocrine function it suppresses:

- Prolactin
- Luteinizing Hormone
- Growth Hormone
- Thyroid Stimulating Hormone
- DHEAS
- Testosterone

## ● KEY POINTS

- Prolonged critical illness is a new paradigm
- Characterized by permanent depletion of physiologic reserve = accelerated aging
- Conventionally intensivists have focused on cardio-respiratory function
- However neuroendocrine and metabolic dysfunction may underlie PCI and may be directly responsible for slow recovery

## Key Points

- Adrenal abnormalities in PCI include persistent hypercortisolism and relative adrenal insufficiency
- Hypothalamic undersecretion leads to GH, T3, PRL and gonadal hormone deficiency
- Direct hormone replacement has not been successful
- Secretagogue therapy is encouraging

