JUMP START

Energize your Research in Parenteral Nutrition

JUMPstart Virtual Meeting

Advanced module: Day 2 Presentation slides

March 28, 2021

Introduction

Dear JUMPstart participants,

We are happy to share with you the presentation slides for the Advanced module. In this document, you will find the content presented in the live meeting on Sunday March 28th. For your convenience, the slide numbers in this booklet correlate with those you will see in the live meeting.

Some slides (indicated by the  icon) will not be shown in the live session but are available for further information within this booklet.

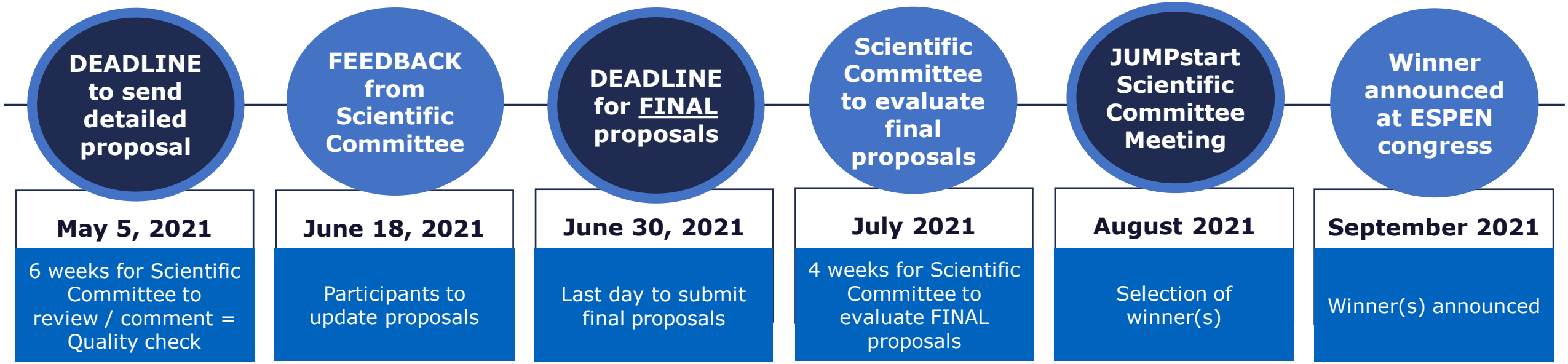
Please feel free to use this document to take notes and refer back to.

Please do not share or reproduce any of the content within this booklet.

If you have any questions please contact: JUMPstart@fresenius-kabi.com.

TIMELINES & PROCESS for review of Research Proposals

Submisson of 'Detailed Research Proposals'



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Meeting agenda: Sunday, Mar 28, Part I

Time (GMT)	Session	Lead
Part I: What really counts: Patient-related outcomes		
14:00	Warming up: Clarifying questions	All
14:10	Moving targets: Muscle mass	Prof. Mette Berger
14:30	Moving targets: Muscle function	Prof. Bob Martindale
14:50	Q&A	Prof. Mette Berger Prof. Bob Martindale
15:00	Functional outcomes and quality of life	Prof. Ho-Seong Han
15:20	Q&A	Prof. Mette Berger Prof. Ho-Seong Han
15:30	**Break**	**All**

Meeting agenda: Sunday, Mar 28, Part II

Time (GMT)	Session	Lead
Part II: Confounding factors in the ICU		
15:50	Impact of gut function and other organ failure	Prof. Bob Martindale
16:10	Insulin and glucose	Prof. Ho-Seong Han
16:30	Discussion	Prof. Bob Martindale Prof. Ho-Seong Han
16:40	Drug interaction	Prof. Mette Berger
16:55	Disease severity scores	Prof. Olav Rooyackers
17:15	How to integrate from a statistician's point of view	Prof. Tim Friede
17:25	Q&A	Prof. Mette Berger Prof. Tim Friede Prof. Olav Rooyackers
17:45	Final wrap-up and next steps	Prof. Mette Berger Dr. Anke Wenn

CT, clinical trial

Contents: Day 2

Part I: What really counts: Patient-related outcomes

- Moving targets: Muscle mass – Professor Mette Berger
- Moving targets: Muscle function – Professor Bob Martindale
- Functional outcomes and quality of life – Professor Ho-Seong Han

Part II: Part II: Confounding factors in the ICU

- Impact of gut function and other organ failure – Professor Bob Martindale
- Insulin and glucose – Professor Ho-Seong Han
- Drug interaction – Professor Mette Berger
- Disease severity scores – Professor Olav Rooyackers

Part I

What really counts: Patient-related outcomes

Moving targets: Muscle mass

Prof. Mette Berger

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Patient related outcomes

Moving targets: muscle mass

Prof. Mette M Berger, M.D., Ph.D

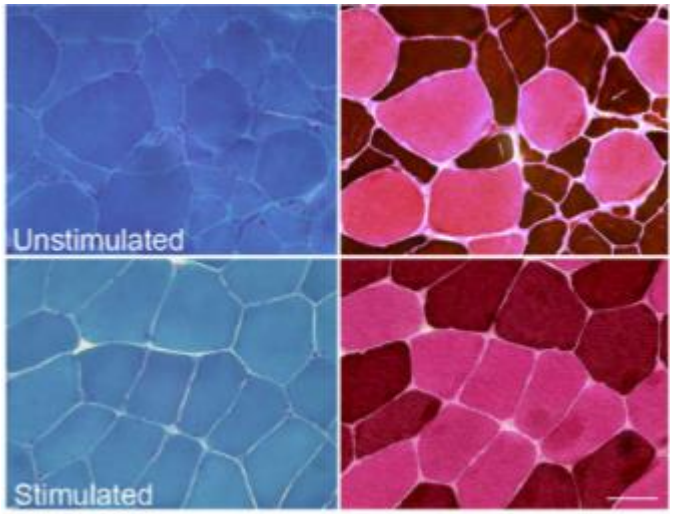
Tools for muscle mass investigation

- Invasive
  - Biopsies
  - DEXA
  - Muscle microdialysis
  - Combinations …. +Double labelled water → EE
  - ENMG
- Non-invasive
  - CT-scan L3
  - Ultrasound: muscle surface
  - Bioimpedance analysis BIA – phase angle

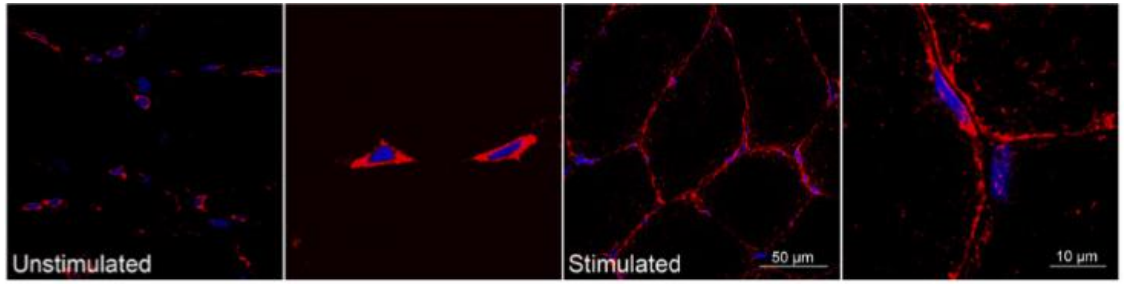
Critical Illness Myopathy (CIM) and GLUT4

Weber-Karstens S et al, Am J Respir Crit Care Med 2013

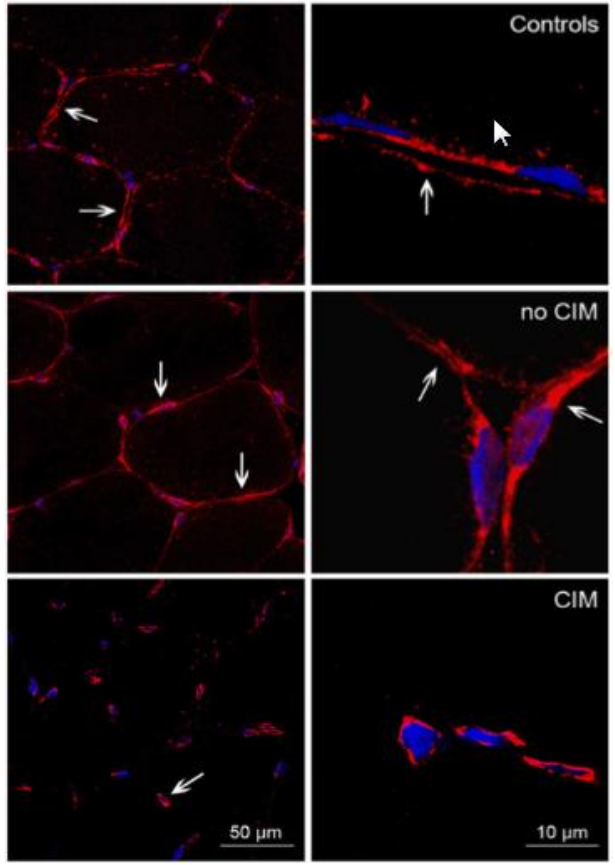
Thirty patients at risk for CIM underwent euglycemic-hyperinsulinemic clamp, muscle microdialysis studies, and muscle biopsy



Unstimulated Vastus lateralis with severe type-2 fiber atrophy and contralateral stimulated Vastus lateralis without type 2 atrophy



Skeletal muscle GLUT4 is detected at the sarcolemma and T tubules after intermittent electrical muscle stimulation

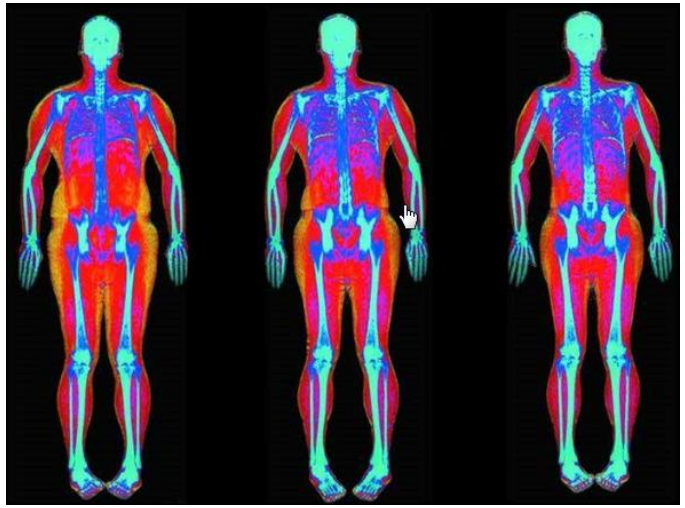


Immunohistochemical localization of GLUT4 in muscles of critically ill Patients (control subjects, GLUT4 (red)

DEXA "dual energy X-ray absorptiometry".

- Bone mineral density (BMD), scores are commonly compared to reference data for the same gender and age by calculating a Z-score.
- Bone mineral content (BMC)
- Fat-free mass (FFM)
- Estimates of percent body fat.

Amount of radiation used during a DEXA scan varies depending on the area of the body being examined, but is very low and <2 days' exposure to natural background radiation (NBR) (chest X-ray → 3 days' NBR)



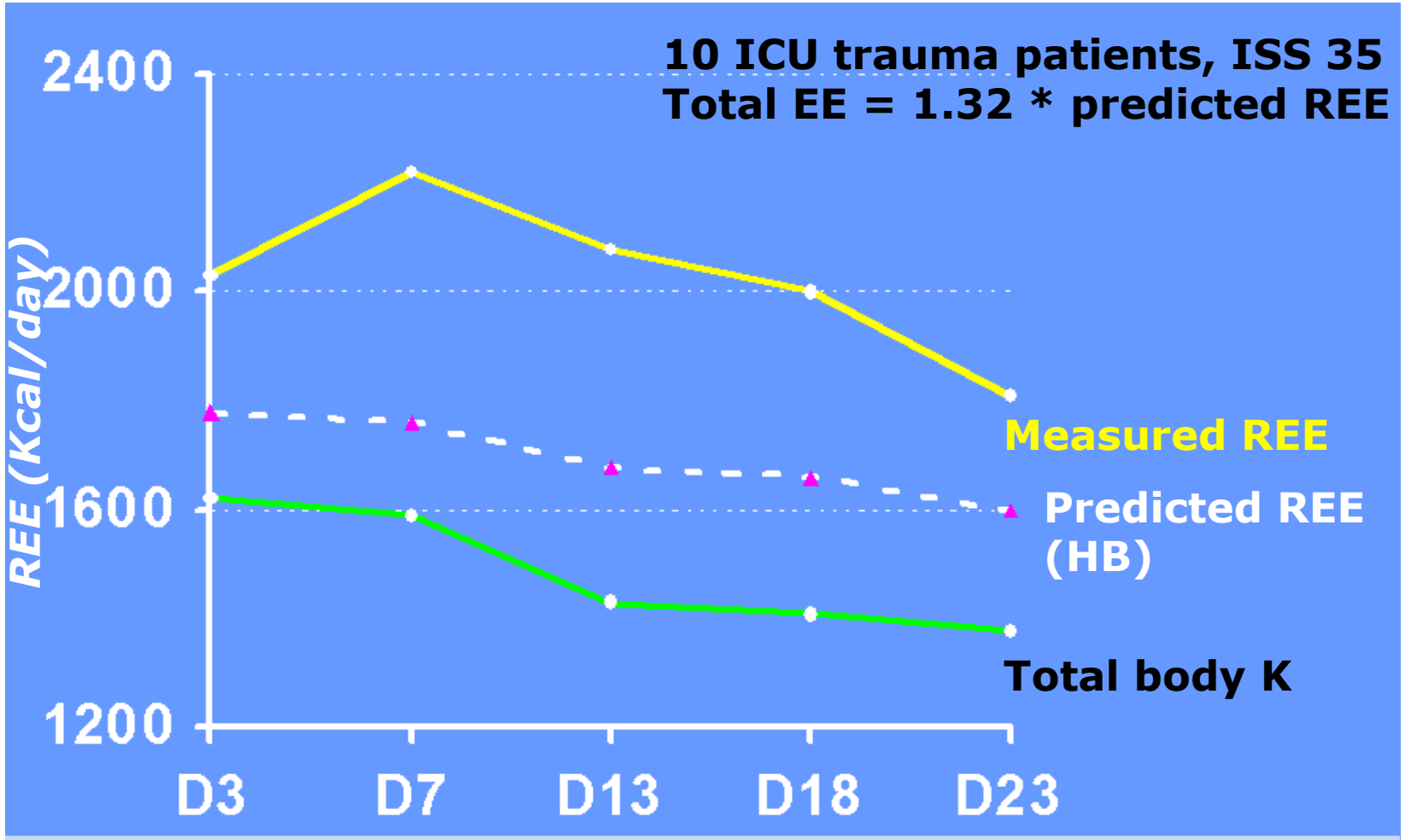
Body composition

Sequential changes in the metabolic response in critically injured patients during the first 25 days after blunt trauma, Monk et al, Ann Surg, 1996: 223: 395

- Total body nitrogen: gamma in vivo neutron activation analysis
- Total body fat: DEXA
- Total body water: tritiated water $^{3}H_2O$
- Extra & intra-cellular water: dilution of sodium bromide
- Total body potassium: gamma spectrum of emitted from naturally occurring K40 – shadow shield counter
- Skeletal muscle: regional analysis of the DEXA data using the Heymsfield method

Sequential changes in Metabolic response to injury

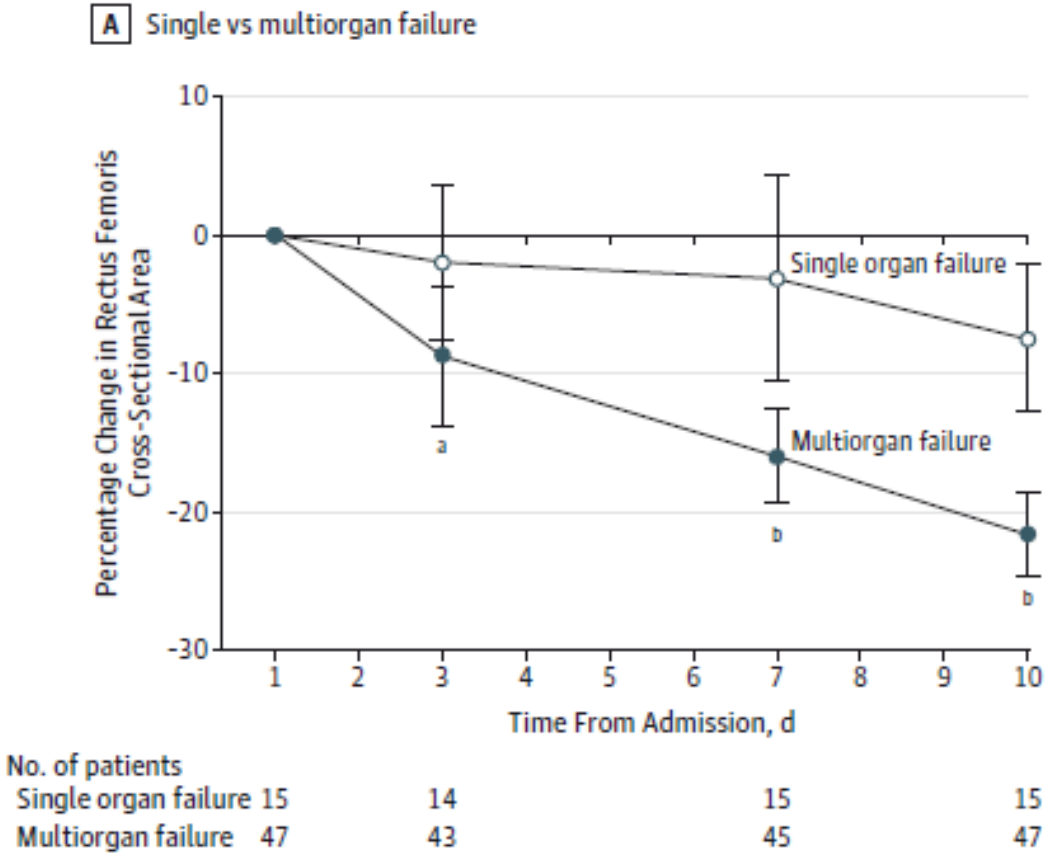
Monk DN, et al Ann Surg 1996; 223: 395

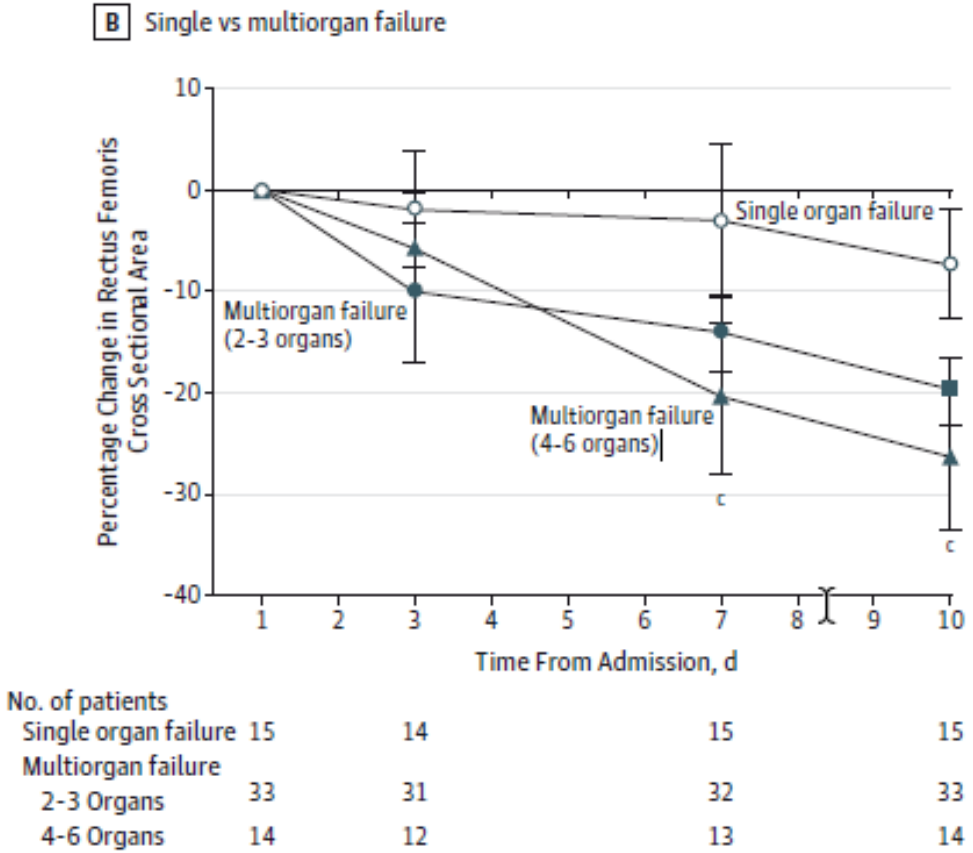


Over the 21-day study period, loss of 16% of total body protein ($p<0.0002$), of which 1.09 kg 67% ← skeletal muscle

Acute Skeletal Muscle Wasting in Critical Illness

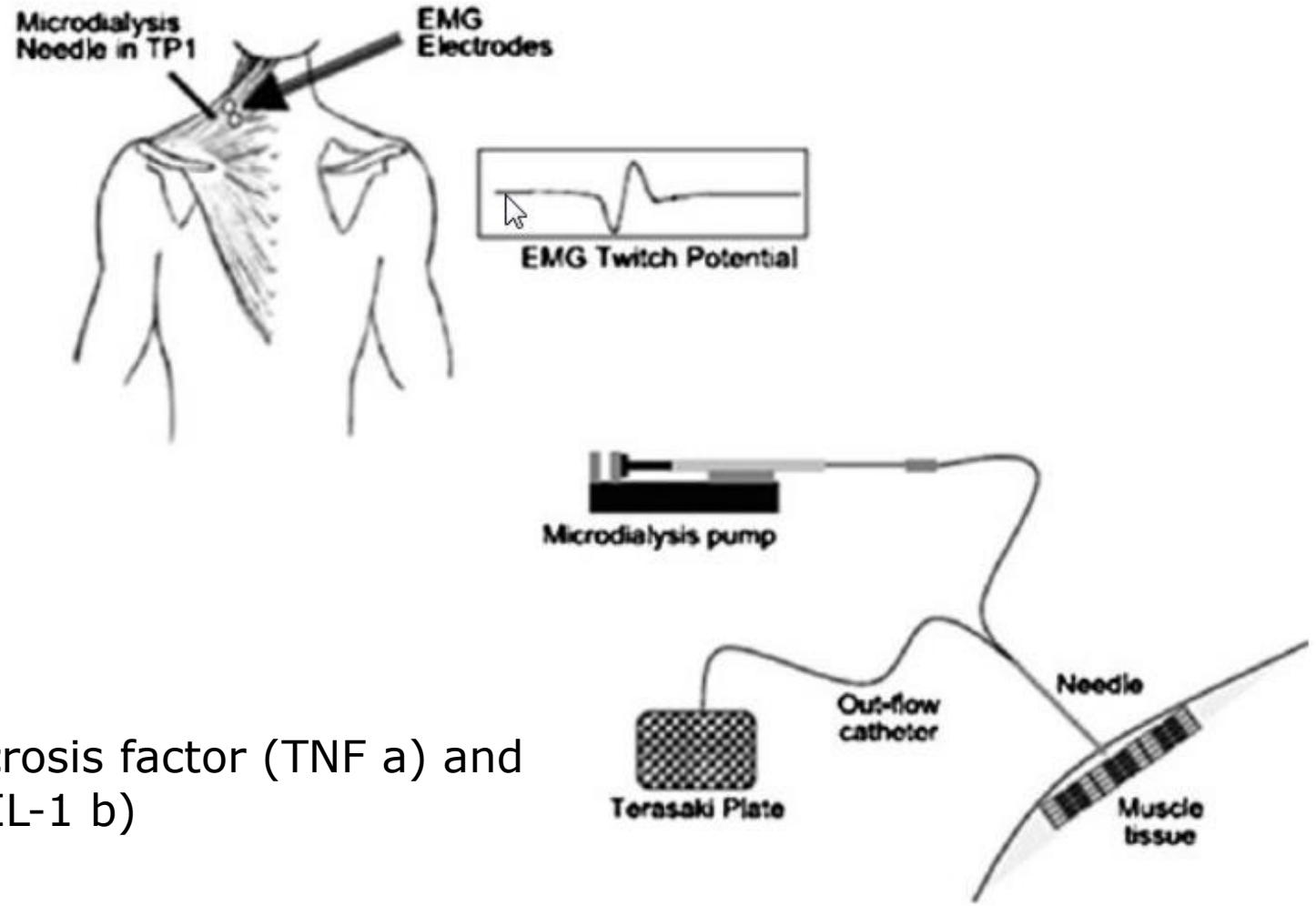
Puthucheary et al, JAMA 2013; 310:1591





Myofascial pain syndromes and their evaluation

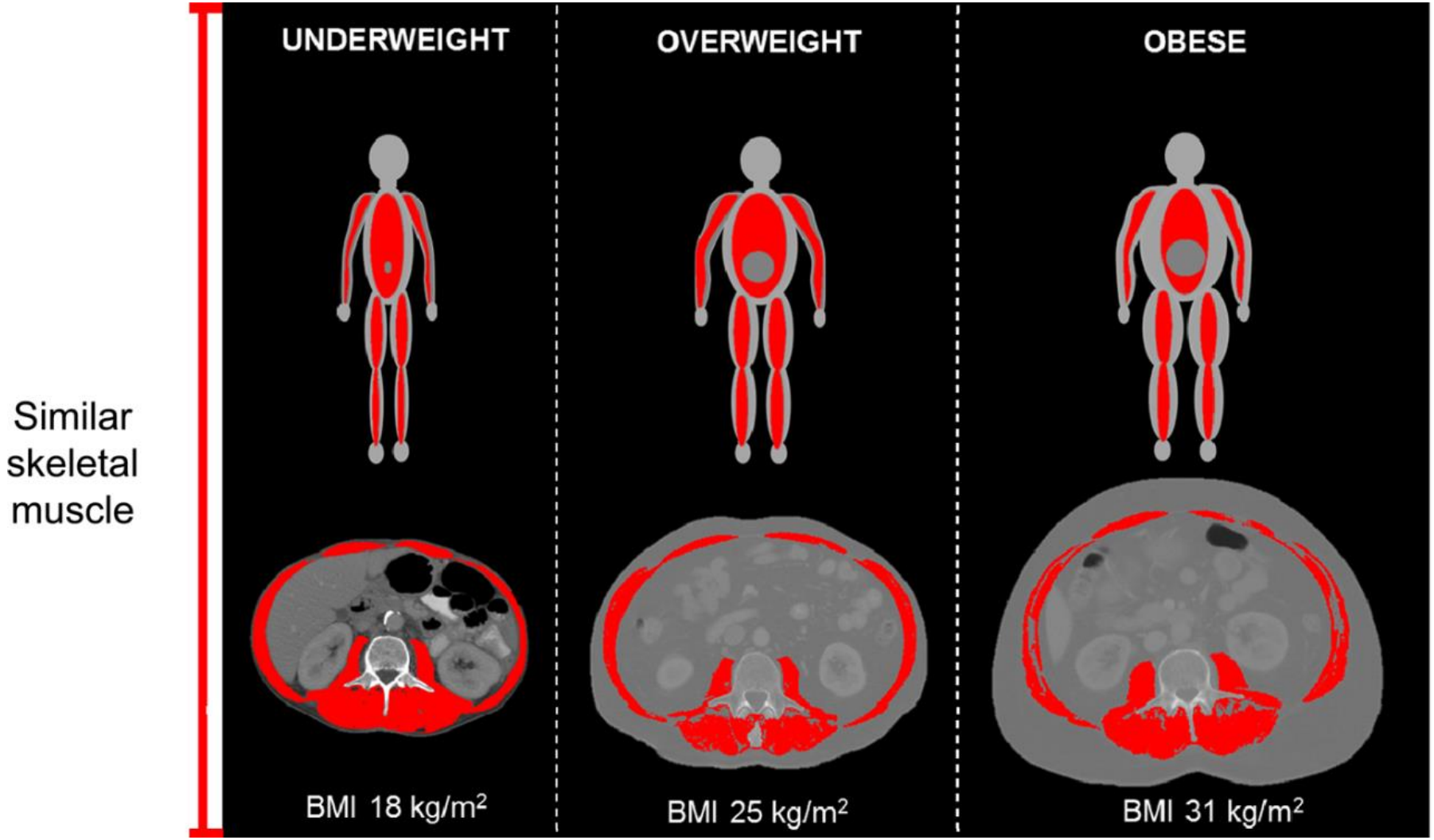
Best practice Clin Rhumatol Bennet RM 2007



→ tumor necrosis factor (TNF a) and interleukin (IL-1 b)

Sarcopenia and cachexia in the era of obesity: clinical and nutritional impact

Prado et al, Proc Nutr Soc, 2016



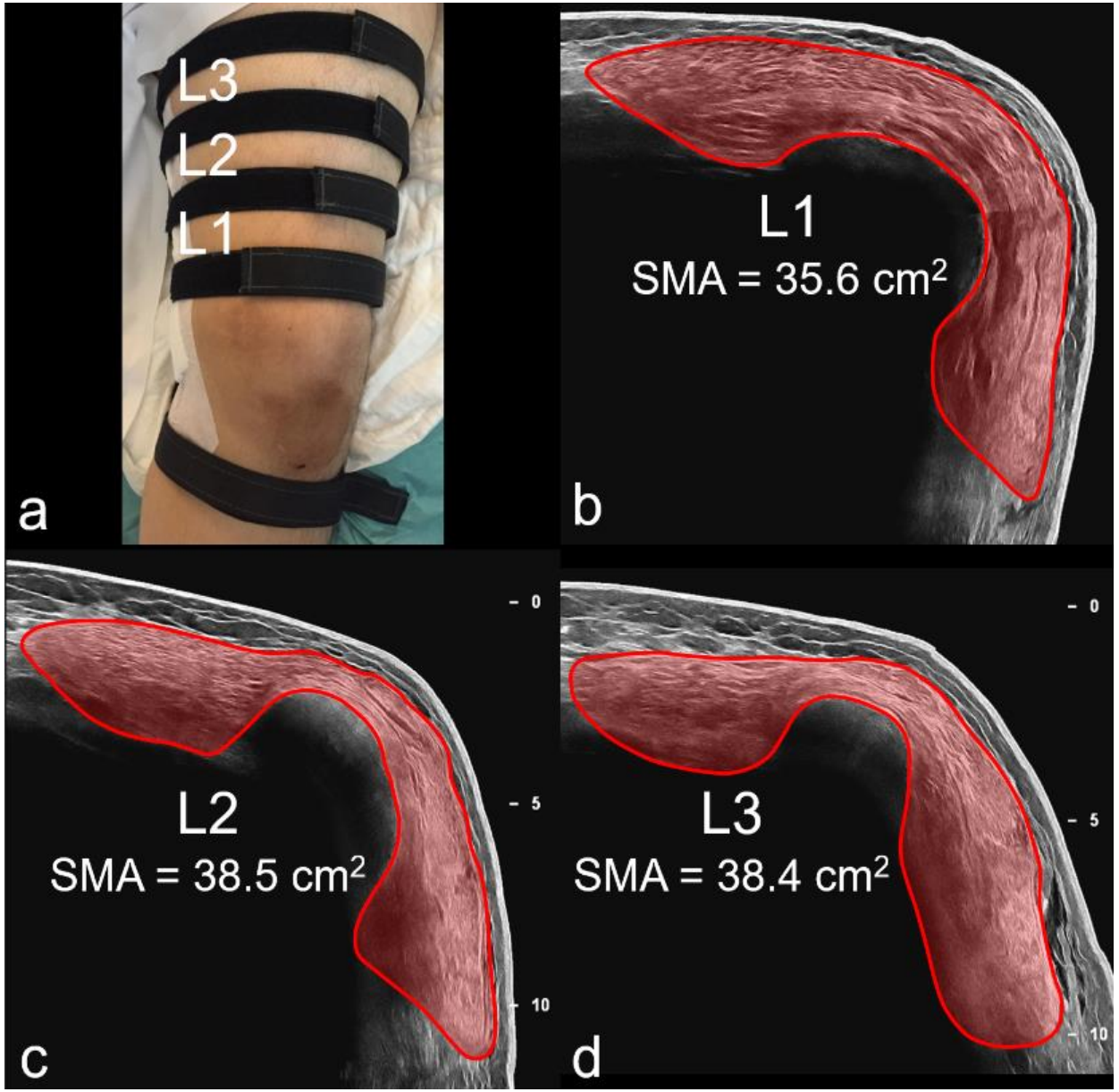
HMB-IC

Berger et al in process

CSA = cross sectional Area of the thigh

SMA = skeletal muscle area

SMI = SMA / height



BIA

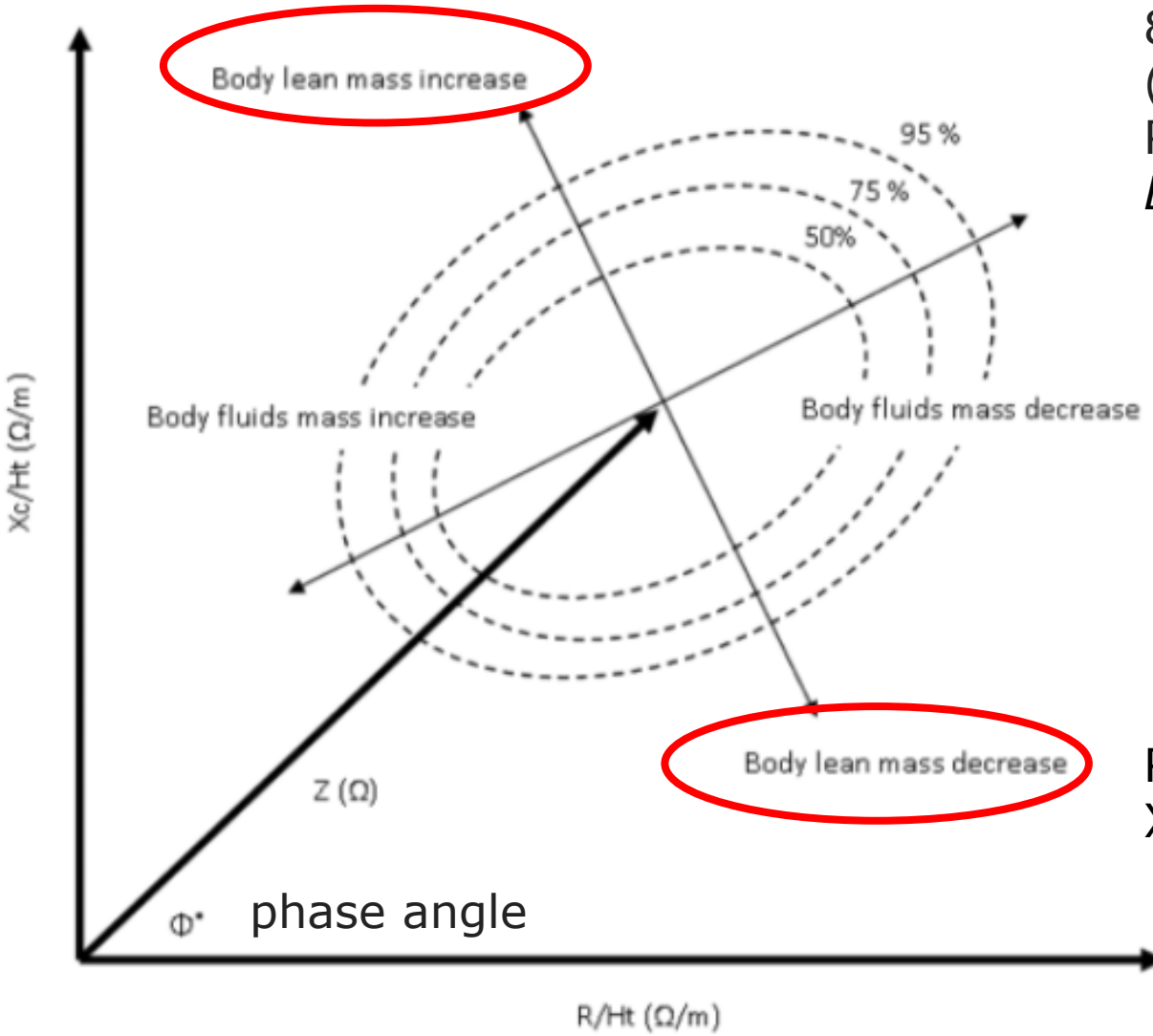
Bioelectrical impedance analysis
InBody S10

Easy to use
Non-invasive
Repeatable
Low cost

Fluid sensitive

Can be done in standing, sitting or lying (dorsal/prone) position

Reactance (Xc), Resistance (R) and Phase angle (Φ)



8,022 normal subjects
(3796 female and 4226 male)
Piccoli *et al. Med. Sci. Sports Exerc.* 1996, *28*, 1517

$$\Phi = \tan^{-1}\left(\frac{X_c}{R}\right)$$

R ← total body water
Xc ← capacitance of the cell membrane

Fat-free mass at admission predicts 28-day mortality in ICU patients: the international prospective observational

Phase Angle Project

Thibault R et al, ICM 2016; *42:1445*

Fat-free mass was assessed by measurement of the 50-kHz phase angle at admission.

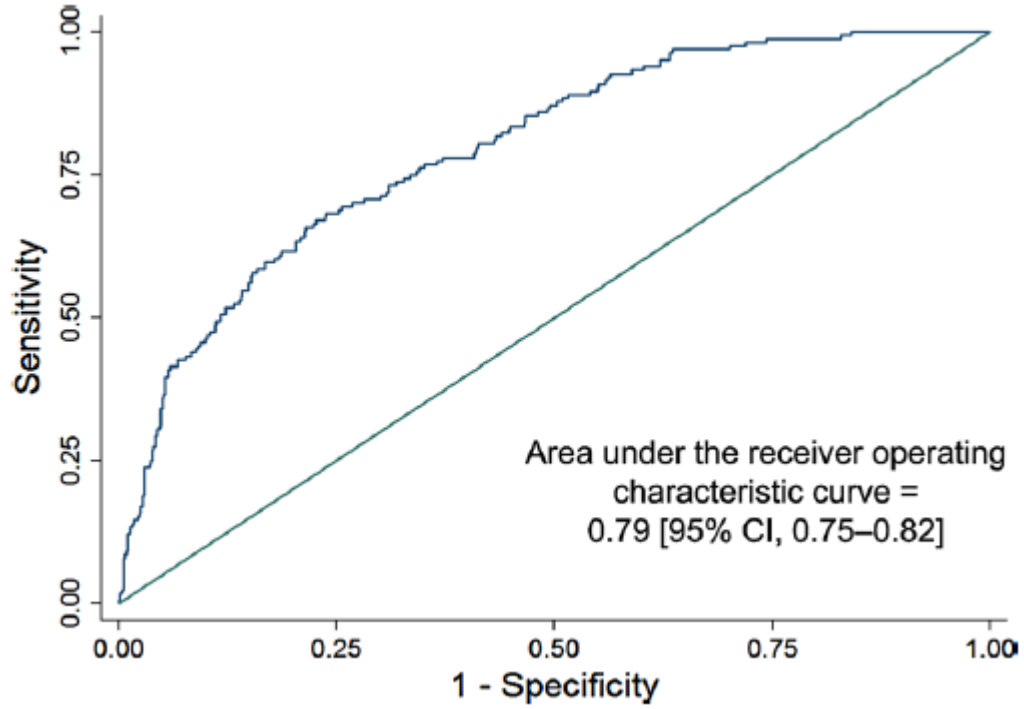
Primary endpoint was 28-day mortality

- 10 ICUs – 9 countries
- 931 patients: age 61 ±16 years, male 60 %,
  APACHE II 19 ±9, BMI 26 ± 6
- day 1 phase angle 4.5 ± 1.9
- PhA lower in patients who eventually died than in survivors (4.1 ±2.0 vs. 4.6 ±1.8, *P* = 0.001).
- Low fat-free mass at ICU admission associated with 28-day mortality

Fat-free mass at admission predicts 28-day mortality in ICU patients: the international prospective observational

Phase Angle Project

Thibault R et al, ICM 2016; *42:1445*



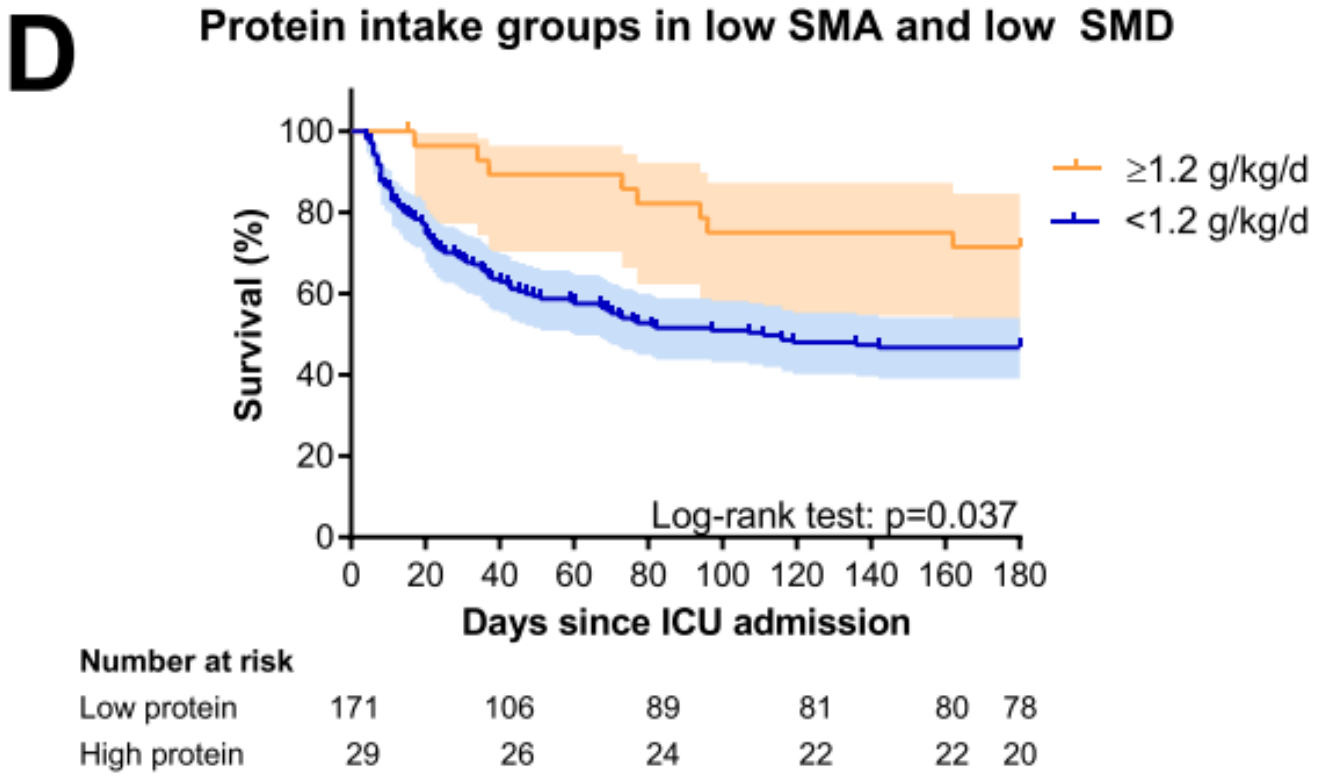
APACHE II and SAPS II values were significantly higher ($P < 0.001$) in patients with a day 1 phase angle of <3.49 versus ≥3.49:

- APACHE II scores: 21.8 ±9.2 vs. 17.7 ±8.7
- SAPS II scores: 48.0 ±19.2 vs. 40.5 ±18.3

Predictive value of the multivariable composite score for 28-day mortality (n = 895):
Phase angle day 1 - APACHE II - age - surgical

Early high protein intake and mortality in critically ill ICU patients with low skeletal muscle area and – density

Looijaard et al Clin Nutr 2020



Early high protein intake is associated with lower mortality in critically ill patients with low skeletal muscle area and -density, but not in patients with normal skeletal muscle area on admission.

MRC Muscle scale

MRC Muscle Scale

The MRC scale for muscle power was first published in 1943 in a document called 'Aids to the Investigation of Peripheral Nerve Injuries (War Memorandum No. 7)'. This became a standard text resource which was reprinted many times, and is referred to widely in a number of documents/papers. In the 1970s the document was republished with the title 'Aids to the Examination of the Peripheral Nervous System (Memorandum No. 45)'.

The muscle scale grades muscle power on a scale of 0 to 5 in relation to the maximum expected for that muscle. In a recent comparison to an analogue scale the MRC scale is more reliable and accurate for clinical assessment in weak muscles (grades 0-3) while an analogue scale is more reliable and accurate for the assessment of stronger muscles (grades 4 and 5).

Tools for muscle mass investigation Conclusion

- Multiple tools are available
- Muscle composition and metabolism can be addressed in depth – non invasive available
- Phase angle reflects cell viability / protein metabolism
- Some require highly experienced investigators – importance of building an interdisciplinary team
- Non-invasive are easier accepted by the patients

Moving targets: Muscle function

Prof. Bob Martindale

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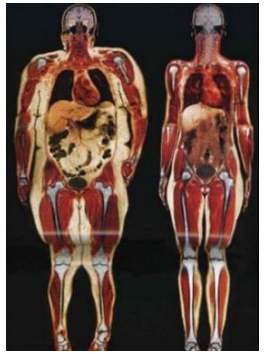

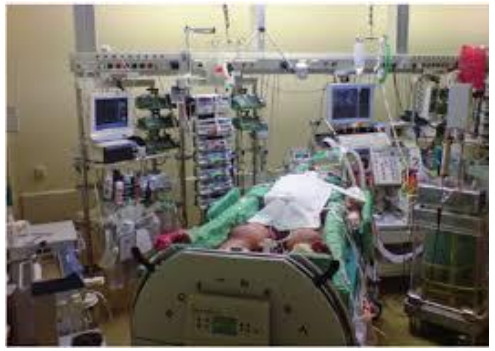

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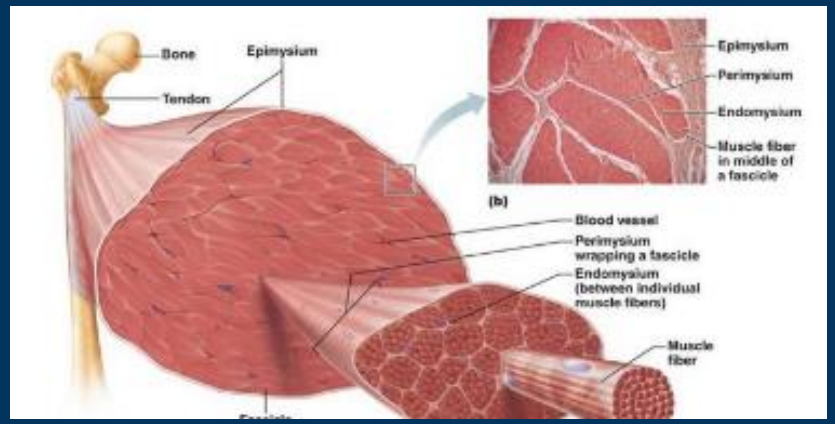
Moving targets: muscle function

Prof. Bob G. Martindale, MD, PhD

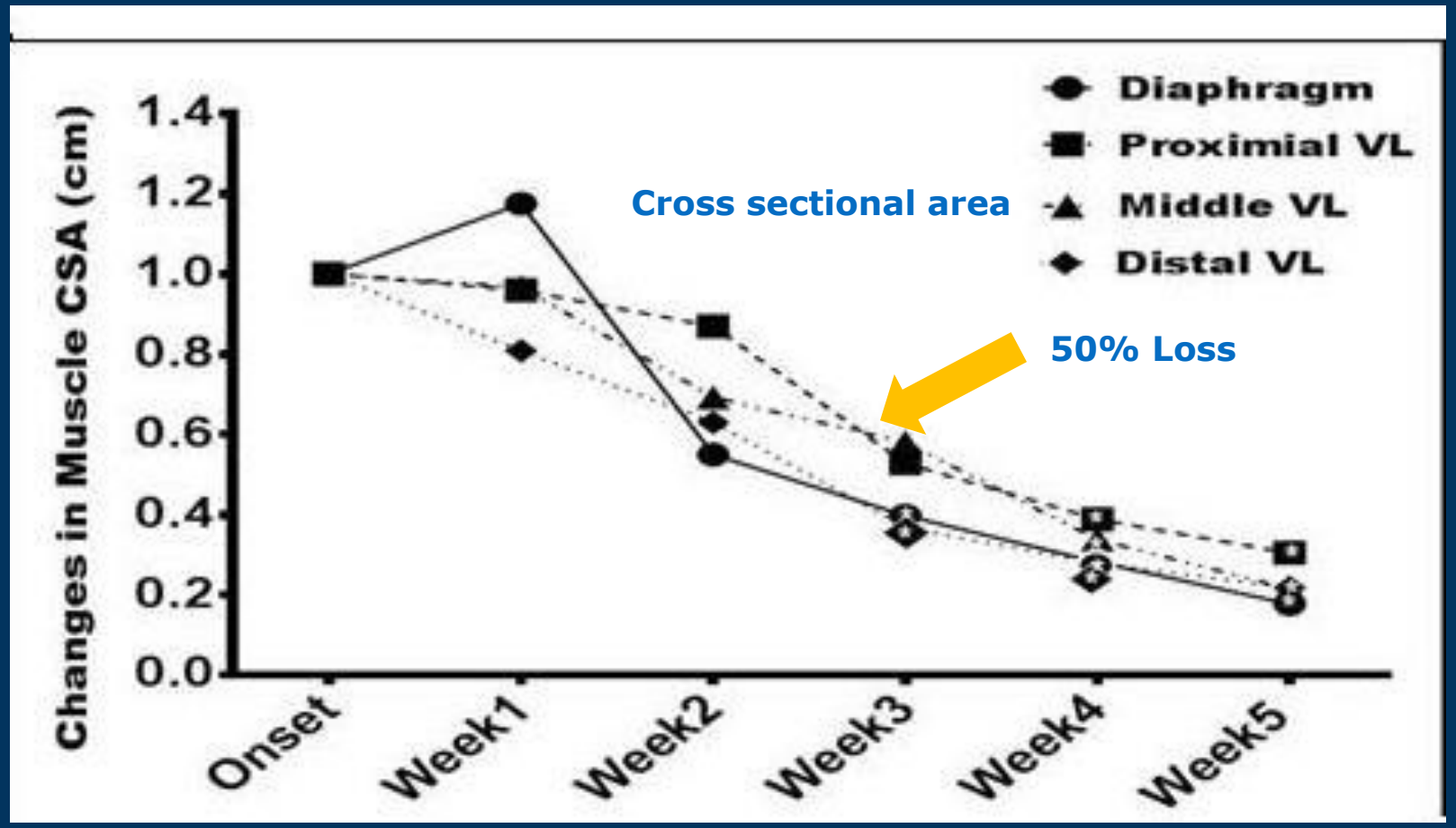
Protein in the Clinical Setting: Basic Principles



- **Skeletal muscle largest available pool nitrogen**
  - **Skeletal muscle largest glucose disposal site**
  - **Considered and endocrine organ**
- **Essentially all protein is functional with no storage form**
  - **Small amount in gut protein available between meals**
  - **Autophagy may utilize "non-functional" intracellular proteins**
- **In the ICU and hospital setting**
  - **Who body protein synthesis rate relatively unchanged acutely and changes with time**
    - **Synthesis increased in immune system and liver but decreased in muscle**
    - **Making peptide bonds require 3 high energy phosphate molecules (1 ATP and 2 GTP)**
  - **Protein degradation of muscle dramatically increased initially and then slows with time**
    - **degradation is uniformly distributed among cellular proteins – contractile, mitochondrial etc**
  - **Protein absorption from GI tract appears adequate, even in sepsis. (Widely variable)**
  - **Most critically ill receive 0.6 to 0.8 g/kg/d (reported in observational studies)**
- **Associations: quality and quantity of skeletal muscle associated with outcomes**
- **Newer studies – timing and mode of protein delivery is key in muscle function**

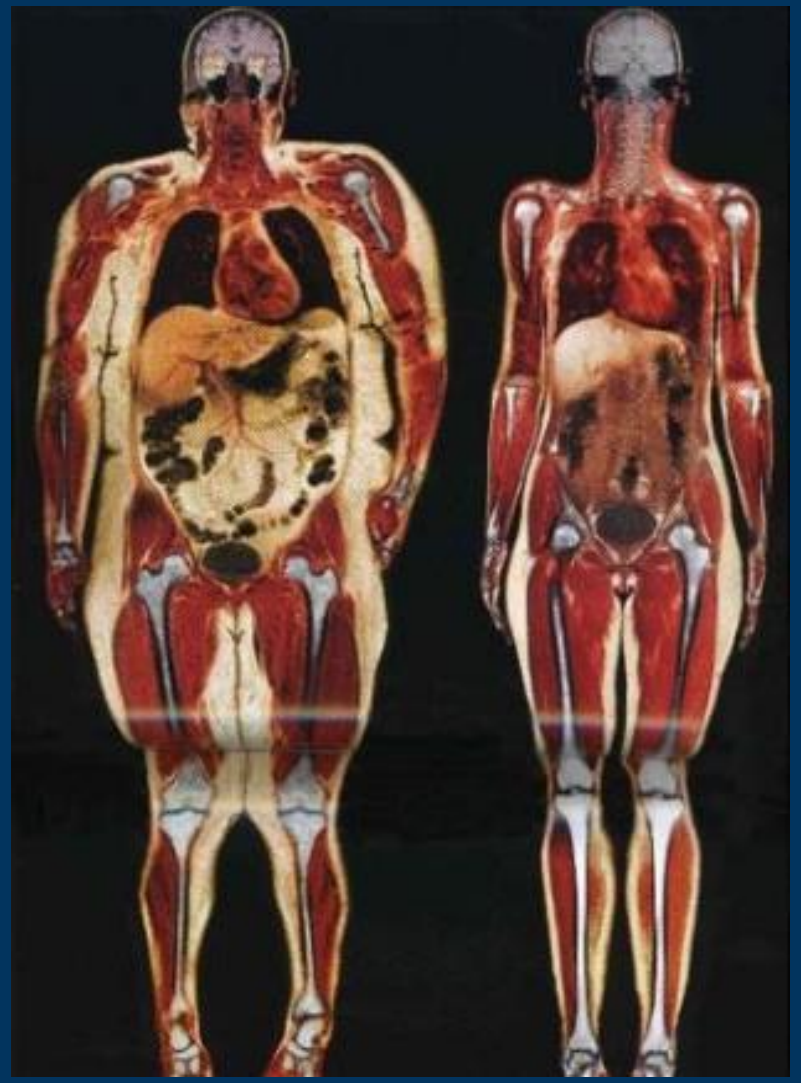
Rehal MS et al Curr Opin Clin Nutr Met Care 2016, Prado CM et al Ann Med 2018, Weijs P et al Critical Care 2014, Coen PM et al Front Physiology 2019 Moisey et al CCM 2013, Rudrappa SS et al Front Physio 2016, Compher C et al CCM 2017, McClave SA et al Curr Opinion CC 2015 , Wollersheim T et al Int Care Medicine 2014, Sandstrom-Rehal MS Curr Opin Nutr Meta Care 2019, Gramin-Cripendorf et al 2018, Liebau F et al Curr Opin Nutrition Metabolic Care 2021

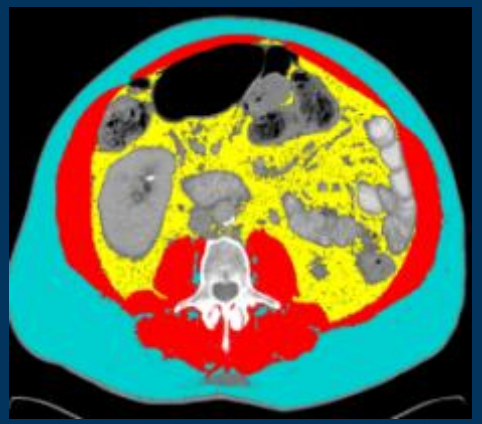
Dr. Moore's PICS study

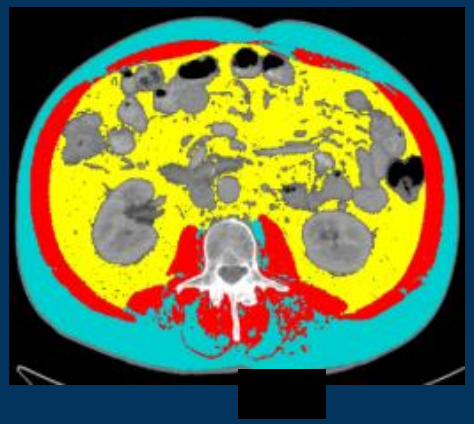


PICs – Persistent Inflammation, Immunosuppression, and Catabolism syndrome

Darden DB, Moore FA et al Critical Care 2021
Cox MC et al Am J Surg 2020







Cross sectional imaging at L_3

Associations with sarcopenia

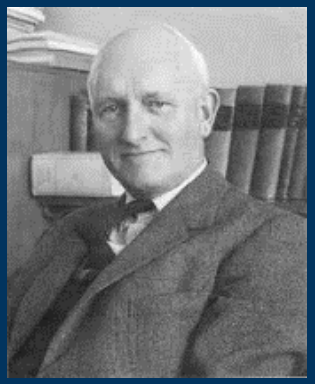
Diseases now proven to have correlated outcome and body composition.

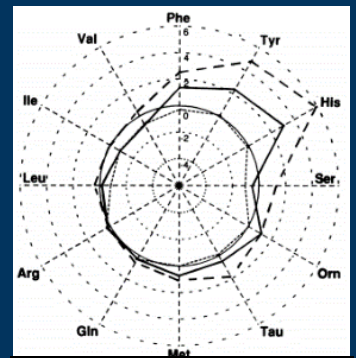
Pancreatic Ca, colorectal Ca, lymphoma, esophageal Ca, elderly trauma ICU, hepatoma, lung Ca, liver transplant, 30 d mortality in sepsis, overall ICU risk of morality, ECMO patients

1) Peng P J GI Surgery 2012
2) Kirk PS et al J Surg Res 2015
3) Okumura S et al Surgery 2015
4) Pedersen M e al Nat Rev Endocrinology 2012
5) Looijaard WG et al Crit Care 2016
5) Moisey LL CC 2013
6) Prado CM et al Ann Med 2018
7) Ji Y et al Jour Crit Care 2018
8) Landi F et al Age Ageing 2013
9) Bear DE et al Crit Care Med 2021

Proteins Role in Critical Illness: Historical Perspective

- Traditionally in the ICU energy requirements were felt to be the critical issue
- When availability of PN was routine the primary focus remained energy (1970's)
  - Protein received little attention
  - Insufficient total energy felt to be reason protein was not effective
- The "protein era"
  - Sir David Cuthberson (1900-1989)
    - » Studying Ca^{++} metabolism bone fx – reported nitrogen lost
  - Frank Cerra
    - » "septic autocannabolism" 1980's





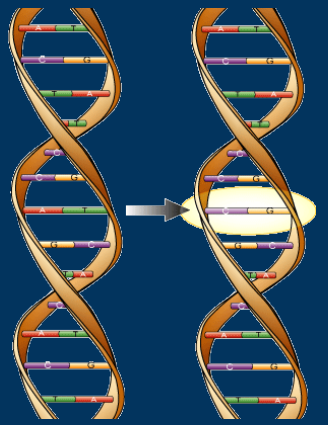
serum AA profile

- Is it time to reconsider macronutrient fuels ?

  Current literature is widely variable !

Heterogeneous Populations Makes Definitive Studies Difficult: Multiple patient factors influencing the protein kinetics

- Age
- Gender
- Genetics
  - Gene SN polymorphisms
- Lifestyle
- Glycemic control
- Body habitus (obesity)
- Diet and nutritional state !
  - Current "western diet"
- Route and timing of feeding
- Type and duration of stress
- Effects of microbiome



Issues Potentiating Muscle Loss / Dysfunction

- **Factors**
  - **Bed Rest / Immobilization**
  - **Systemic inflammation / infections**
  - **Neuromuscular blockade**
  - **Mode of delivery –bolus or continuous feeds**
  - **Uncooperative patients**
    - **Cognitive deficits**
    - **TBI**
  - **Serve hypoxia, acidosis, metabolic abnormalities, impaired microcirculation**
  - **Hemodynamically unstable / pressors**
  - **Hyperglycemia – insulin resistance**
  - **Prone positioning**
  - **ECMO**

Merker M et al JAMA Network Open 2020

Leibau F et al Curr Opin Nutr Met Care 2021

Puthucheary Z et al Crit Care Med 2020

Berger MM et al Clin Nutr 2016

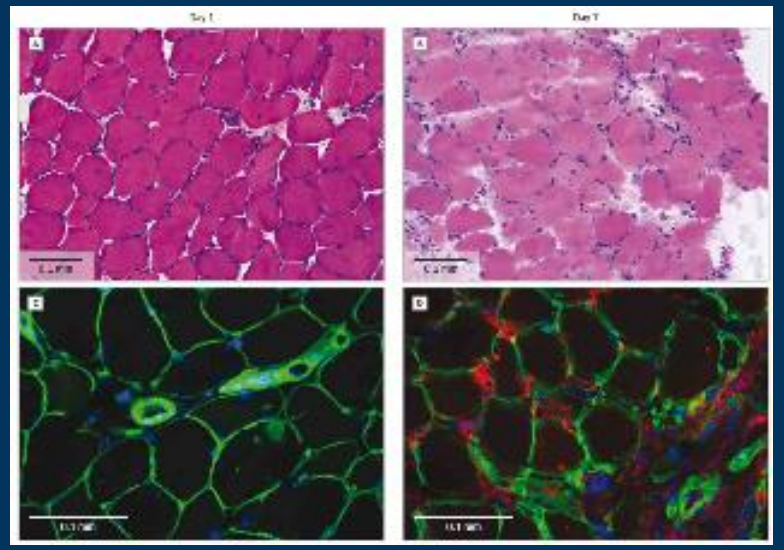
Bell J et al Am J Physio Endo Metab 2005

Sandstrom-Rehal M et al Curr Opin Nutr Met Care 2019

Acute Skeletal Muscle Wasting in Critical Illness

- **Prospective study of 63 critically ill patients**
  - **Expected stay > 7 days, Vent > 48 hours**
  - **– 3 methods to determine muscle loss**
    - **Serial US**
    - **Histology**
    - **Biochemistry – DNA/Protein ration and fractional synthesis breakdown rates. (Leucine uptake etc)**

  - **– Conclusions**
    - **CSA of rectus femoris decrease 10% US**
    - **CSA of muscle fibers decrease 17.5%**
    - **Ratio protein to DNA decrease 29%**
    - **>40% of patients showed myofibril necrosis**
      - » **Significant inflammatory changes in muscle noted**



- **Muscle wasting occurred despite delivery of 0.7gm/kg protein**

Puthucheary ZA et al JAMA 2013

Clinical Guidelines

aspen LEADING THE SCIENCE AND PRACTICE OF CLINICAL NUTRITION
American Society for Parenteral and Enteral Nutrition

Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.)

Journal of Parenteral and Enteral Nutrition
Volume 40 Number 2
February 2016 159–211

DOI: 10.1177/0148607115621863

C4. We suggest that sufficient (high-dose) protein should be provided. Protein requirements are expected to be in the range of 1.2–2.0 g/kg actual body weight per day and may likely be even higher in burn or multitrauma patients (see sections M and P).

[Quality of Evidence: Very Low]

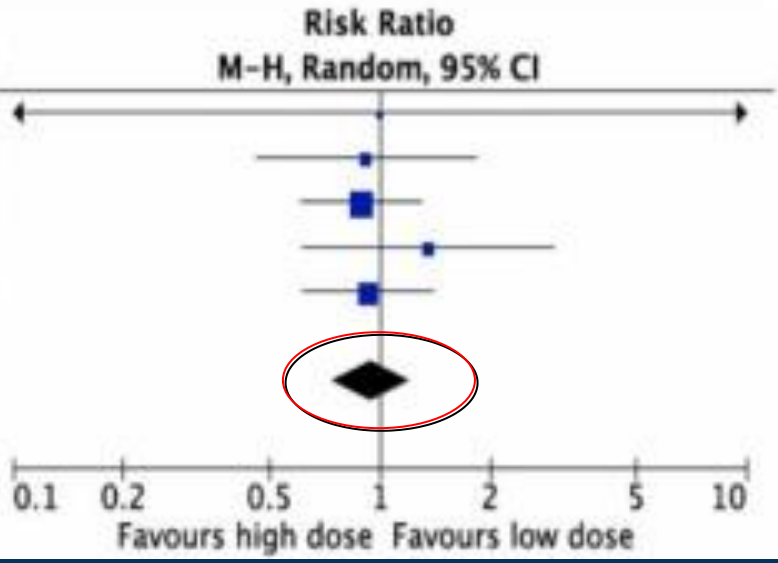
McClave SA, Taylor B, Martindale RG et al JPEN 2016

Systematic reviews of 5 RCT's comparing high vs low protein delivery

Study or Subgroup	High Dose Events	High Dose Total	Low Dose Events	Low Dose Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Clifton 1985	1	10	1	10	0.9%	1.00 [0.07, 13.87]	1985
Rugeles 2013	11	40	12	40	12.5%	0.92 [0.46, 1.83]	2013
Doig 2015	42	236	47	235	42.3%	0.89 [0.61, 1.29]	2015
Ferrie 2016	12	59	9	60	9.6%	1.36 [0.62, 2.98]	2016
Allingstrup 2017	30	100	32	99	34.8%	0.93 [0.61, 1.40]	2017
Total (95% CI)		**445**		**444**	**100.0%**	**0.94 [0.74, 1.21]**	
Total events	96		101				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.93$, df = 4 (P = 0.92); $I^2 = 0\%$

Test for overall effect: Z = 0.46 (P = 0.65)



Note: signal suggests high protein may be better !

Heyland DK, Stapleton R, Compher C. Nutrients 2018

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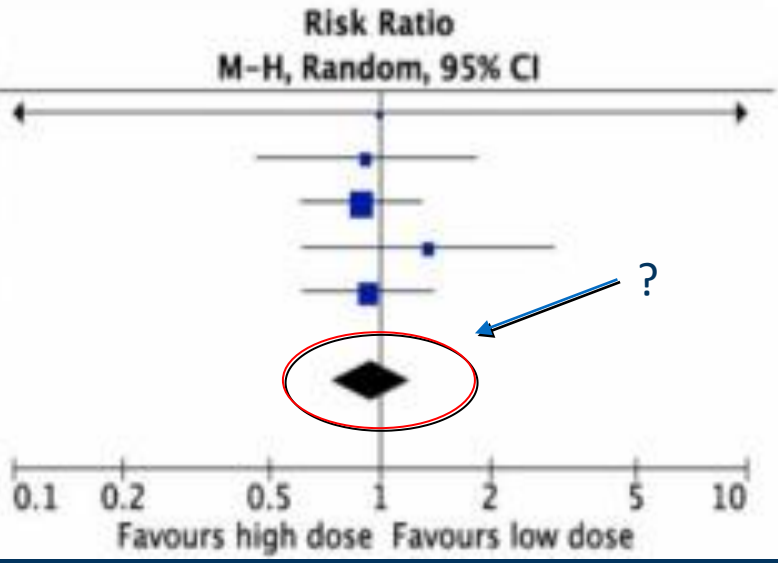
Total (95% CI)		**445**		**444**	**100.0%**	**0.94 [0.74, 1.21]**	
Total events	96		101				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.93$, df = 4 (P = 0.92); $I^2 = 0\%$

Test for overall effect: Z = 0.46 (P = 0.65)



Note: signal suggests high protein may be better !

Heyland DK, Stapleton R, Compher C. Nutrients 2018

The give more protein argument: Mechanistic data support increased infusion of AA's or protein increases net protein uptake in muscle

"Older" studies

Cuthberson - Shils M-- Cahill G--Cerra F--Vars S--Plank L--Cynober L -- Wolfe R

More recent studies

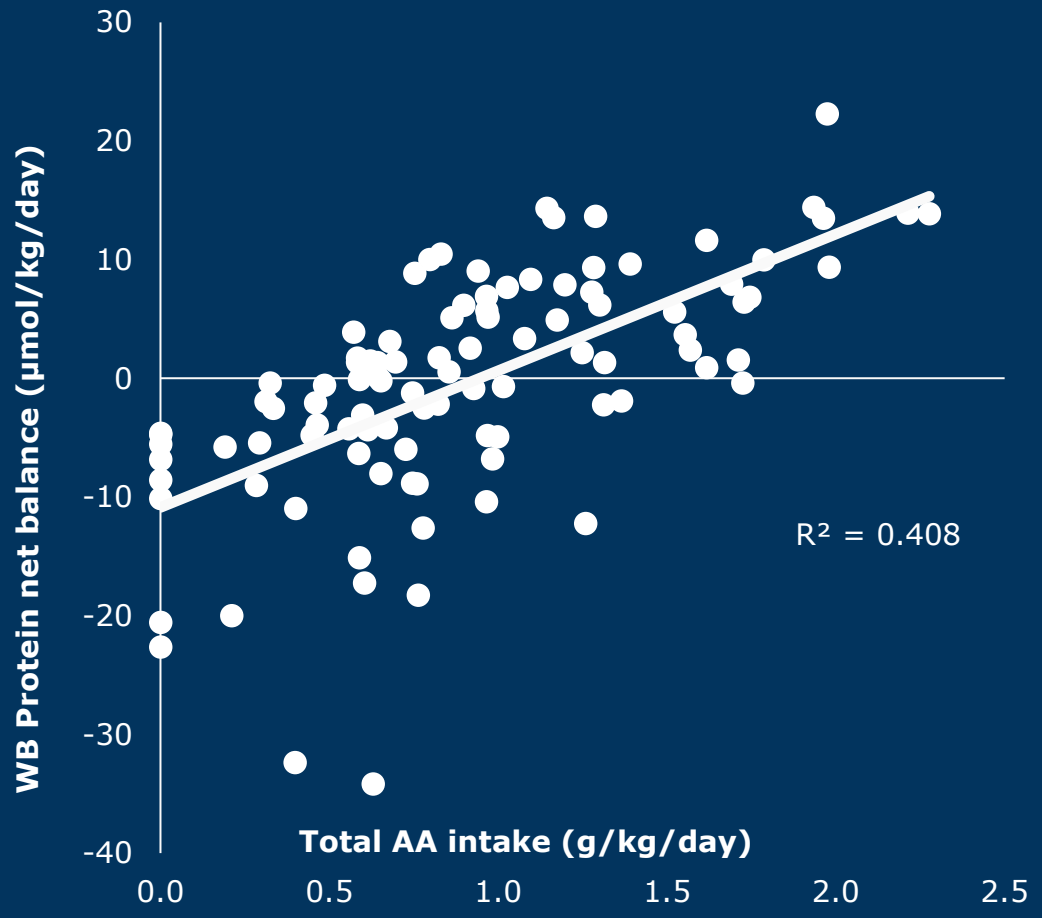
- **Weijs P et al 2014**
  - Protein goal beneficial, energy goal not an issue
- **Rooyackers O et al Clin Nutr 2015**
  - WB protein synthesis – MOF
  - Critically ill are able to utilize additional AA
- **Berg A et al Crit Care 2013**
  - Protein kinetics hypocaloric vs normocaloric feeding
  - Increased protein = improved outcome
- **Liebau F et al Am J Clin Nutr 2015**
  - Enteral protein WB protein turnover
  - Additional protein beneficial
- **Zusman O et al Crit Care 2016**
  - Higher protein improved mortality
- **Ferrie S JPEN 2016**
  - Increase AA infusion
  - Small improvements
- **Sandstrom-Rehal M et al Critical Care 2017**
  - Increase protein infusion increases synthesis in 24h infusion
- **Weijs P et al 2019**
  - N=801 ICU
  - Increase protein increase survival 90d post d/c
- **Danielis M Nutrients 2019**
  - RCT 38 pts improved N balance
- **Nakamura K et al 2020**
  - RCT: High vs Med protein
  - High protein beneficial

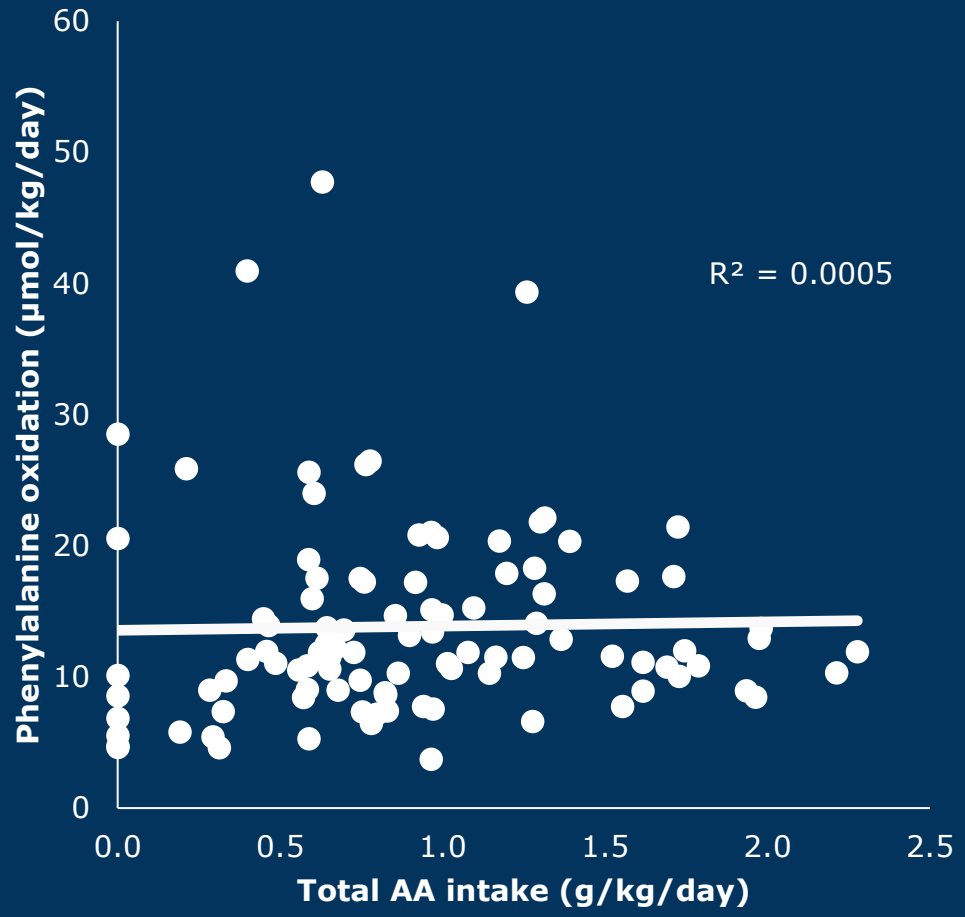
Fraction synthetic rates vs rates of protein breakdown

- **Anabolic response to protein meal**
  - **High protein intake maximizes protein fractional synthetic rates (FSR)**
  - **At high protein intake protein breakdown is suppressed yielding an even greater anabolic response**
    - **Anabolic response = net balance of FSR + decrease breakdown**
  - **Deutz and Wolfe suggest no upper limit to the "anabolic response" to protein and AA intake in the normal metabolic setting**
    - » **Keep in mind this was studied in none ICU patients**

Wolfe R, Deutz N et al 2016
Kim Il, Deutz NP, Wolfe R Clin Nutrtion 2018

What happens to exogenously administered amino acid ?





Rooyakers O et al Clin Nutr 2015, Berg A Crit Care 2013
Liebau F et al 2015 Am J Clin Nutr 2015
Liebau F et al 2016 Curr Opin Clin Nutr Met Care 2016

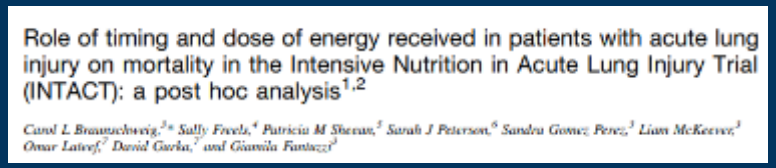
Studies showing increased protein yields worse outcome

- **Casaer MP et al NEJM 2011**
  - **PRCT early vs late PN nutrient delivery**
  - **"protein" inhibits autophagy yields worse outcome**


Early versus Late Parenteral Nutrition in Critically Ill Adults

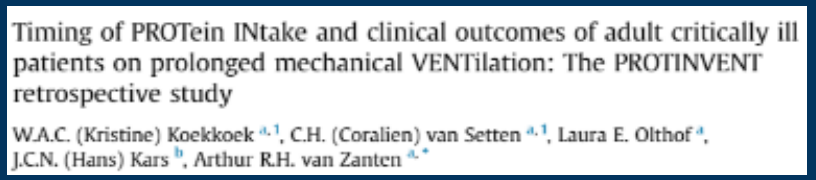
Michael P. Casaer, M.D., Dieter Mesotten, M.D., Ph.D., Greet Hermans, M.D., Ph.D., Pieter J. Wouters, R.N., M.Sc., Miet Schetz, M.D., Ph.D., Geert Meyfroidt, M.D., Ph.D., Sophie Van Cromphaut, M.D., Ph.D., Catherine Ingels, M.D., Philippe Meersseman, M.D., Jan Muller, M.D., Dirk Vlasselaers, M.D., Ph.D., Yves Debaveye, M.D., Ph.D., Lars Desmet, M.D., Jasperina Dubois, M.D., Aime Van Assche, M.D., Simon Vanderheyden, B.Sc., Alexander Wilmer, M.D., Ph.D., and Greet Van den Berghe, M.D., Ph.D.

- **Braunschweig CL et al Am J Clin Nutrition 2017**
  - **PRCT of 78 ALI pts, routine care vs intensive nutrition therapy (30kcal/kg/day)**
  - **Post hoc analysis suggests early protein increased mortality ?**


Role of timing and dose of energy received in patients with acute lung injury on mortality in the Intensive Nutrition in Acute Lung Injury Trial (INTACT): a post hoc analysis[1,2]

Carol L Braunschweig,[3] Sally Freels,[4] Patricia M Sheean,[5] Sarah J Peterson,[6] Sandra Gomez Perez,[3] Liam McKeever,[3] Omar Lateef,[7] David Gurka,[7] and Giamila Fantuzzi[3]*

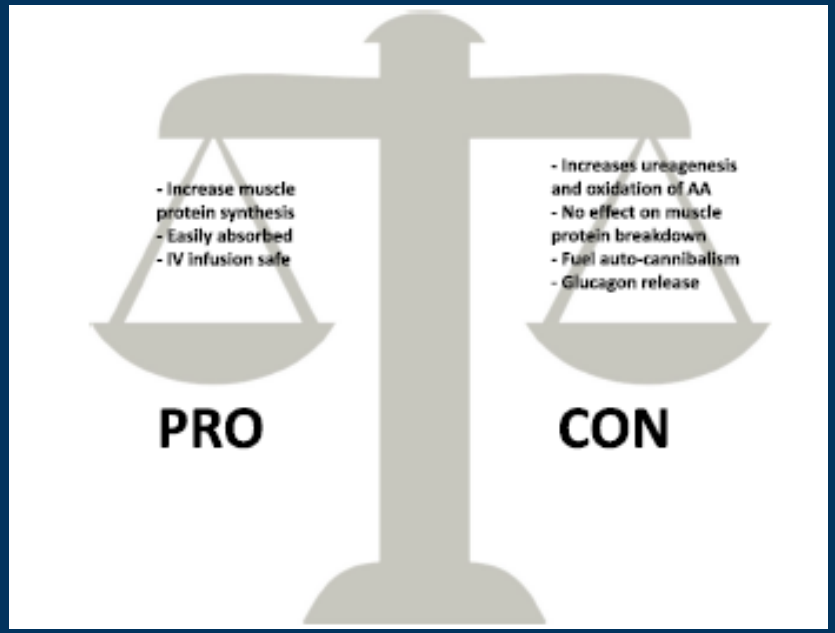
- **Koekkoek WAC et al Clinical Nutrition 2019**
  - **Retrospective study evaluating timing of protein delivery**
  - **Timing is crucial to outcome**
  - **Early (first 48h) delivery of protein harmful, later >3-5 beneficial**


Timing of PROTein INtake and clinical outcomes of adult critically ill patients on prolonged mechanical VENTilation: The PROTINVENT retrospective study

W.A.C. (Kristine) Koekkoek [a,1], C.H. (Coralien) van Setten [a,1], Laura E. Olthof [a], J.C.N. (Hans) Kars [b], Arthur R.H. van Zanten [a,*]

Could additional protein and AA be harmful in ICU population: Theory vs Data ?

- Potential issues with excess protein
  - In patients with refractory hypotension
    - High protein associated with liver injury
  - Azotemia – ammonia toxic to tissues
    - Interferes with cellular protein synthesis
  - Altered WB and hepatic protein synthesis
    - Glucagon release (counter regulatory effects)
      - AA infusions (PN) shown to increase hepatic AA breakdown
    - AA imbalances
  - Altered mental status
    - Many AA are precursors of neurotransmitters or false neurotransmitters
      - » Large nonphysiologic doses--seizures etc
    - Blood brain barrier AA transport changes
- What about autophagy ?
- What about timing of delivery?
- Altered mitochondrial metabolism not conducive to anabolism



Prieser JC CC 2018

Doig G et al 2015

Hoffer LJ et al Am J Clin Nutr 2012

Weijs P et al Crit Care 2014

Thiessen SE et al Am J Resp CC Med 2017

Koekkoek WAC Clin Nutr 2018

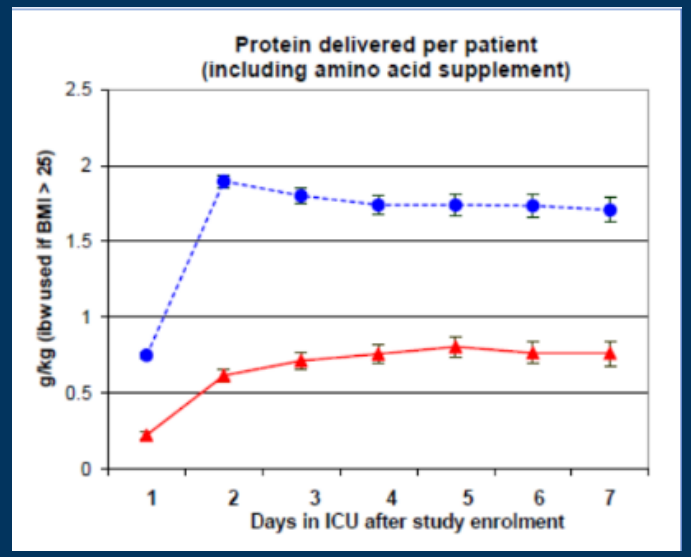
van Niekerk, G Critical Care 2020

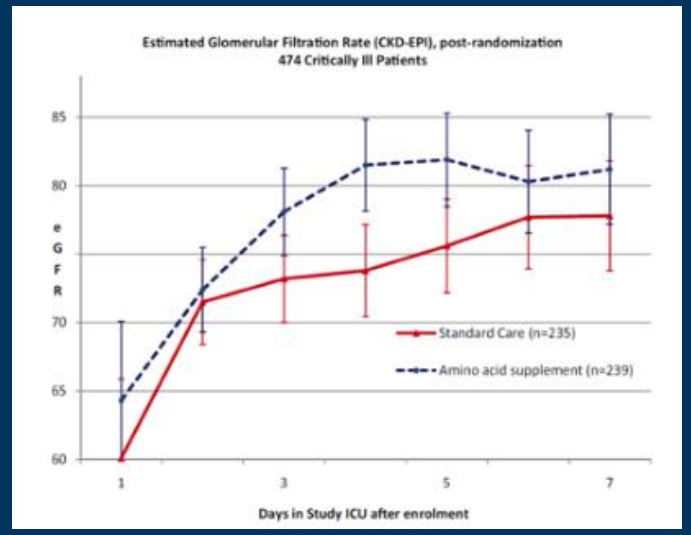
Coen PM et al Front Physiology 2021

No harm *or* benefit for additional protein

Intravenous amino acid therapy for kidney function in critically ill patients: a randomized controlled trial

- **Doig G et al Int Care Med 2015**
  - **Nephroprotect study (N=474)**
  - **RCT 2gm/kg/d vs standard of care**
  - **No major benefit of higher protein**





Trying to Determine What Mechanisms are Involved in the Protein Delivery Story

Is it the satellite cells ?

Is it the inflammatory state ?

Is it the altered mitochondria metabolism ?

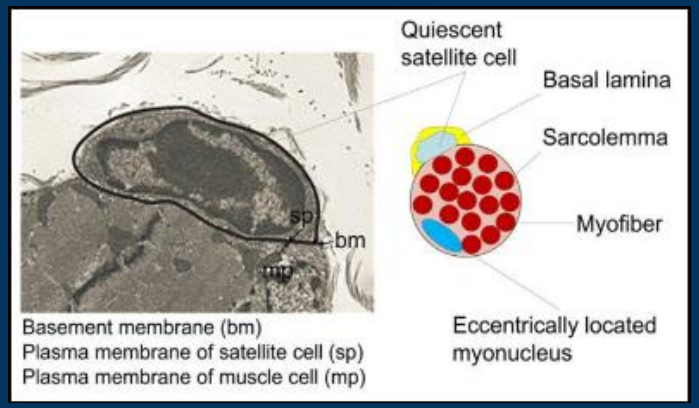
Is it the inhibition of autophagy ?

Are Satellite Cells the Answer ?

Mechanisms of Chronic Muscle Wasting and Dysfunction after an Intensive Care Unit Stay
A Pilot Study

Claudia dos Santos[1,2], Sabah N. A. Hussain[3], Sunita Mathur[4], Martin Picard[5], Margaret Herridge[2,6], Judy Correa[1], Alexandra Bain[7], Yeting Guo[3], Andrew Advani[1,8], Suzanne L. Advani[1,8], George Tomlinson[8], Hans Katzberg[9], Catherine J. Streutker[1,10], Jill I. Cameron[11], Annemie Schols[12], Harry R. Gosker[12], and Jane Batt[1,7]; for the MEND ICU Group, the RECOVER Program Investigators, and the Canadian Critical Care Translational Biology Group

- **Muscle bx at 7 day and 6 months**
- **Conclusion:**
  - **Persistent weakness at 6 month can not explained only by:**
    - **Ongoing UPS-mediated proteolysis**
    - **Muscle autophagy**
    - **Persistent inflammation**
    - **Muscle atrophy**
    - **Changes in mitochondrial structure or content**



  - **Loss of Satellite cells consistently associated with persistent weakness and lack of muscle regrowth**

ORIGINAL ARTICLE

Metabolic phenotype of skeletal muscle in early critical illness

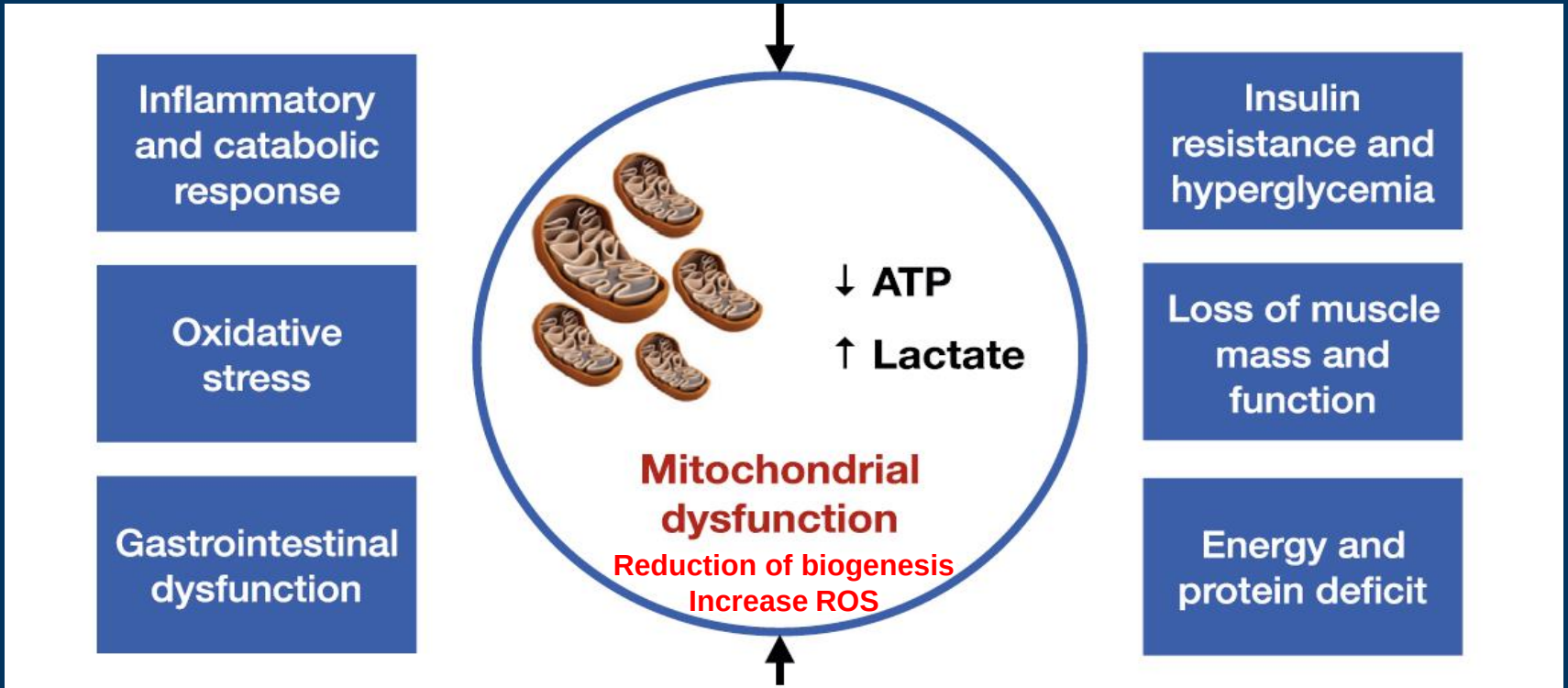
Zudin A Puthucheary,[1,2,3,4] Ronan Astin,[1,2] Mark J W Mcphail,[5,6] Saima Saeed,[7] Yasmin Pasha,[5] Danielle E Bear,[4,8,9,10] Despina Constantin,[11] Cristiana Velloso,[4] Sean Manning,[12,13,14] Lori Calvert,[15] Mervyn Singer,[3,7] Rachel L Batterham,[12,13] Maria Gomez-Romero,[16] Elaine Holmes,[16] Michael C Steiner,[17] Philip J Atherton,[11] Paul Greenhaff,[11] Lindsay M Edwards,[18] Kenneth Smith,[11] Stephen D Harridge,[4] Nicholas Hart,[10,19] Hugh E Montgomery[1,2]

- **Critical Illness**
  - **Decreased muscle mitochondrial biogenesis**
  - **Dysregulated lipid oxidation**

- **Reduced ATP bioavailability**
- **Skeletal muscle wasting associated with impaired lipid oxidation, inflammation**
- **Intramuscular inflammation**
  - **Impairs anabolic recovery**
  - **Alters lipid utilization in mitochondria**

Puthucheary ZA et al Thorax 2018
Wesselink E et al Clin Nutrition 2019

Critical illness → does protein help bioenergetics failure
Searching for the magic bullet to improve mitochondrial function:



Current understanding of mitochondria function

- Significant difference in mitochondrial biogenesis survivors vs non-survivors within 24 hrs of admission
- MOF patients show 2x decrease in mitochondria on muscle biopsies
- Mouse models – restoring bio-energetic ability increases muscle force, cardiac function and survival
- Mitochondrial "uncoupling" or down regulation in severe stress appears protective to cellular survival

Wesselink E et al Clinical Nutrition 2019
Moonen HPFX Curr Opin Crit Care 2020

What about autophagy ?

Desperate Times Call for Desperate Measures: Self-Cannibalism Is Protective During Sepsis*

- **Autophagy is a balance between:**
  - ***Impaired autophagy*** **results in accumulation of damaged organelles, protein aggregates, and altered T-cell response in sepsis**
  - ***Excessive autophagy*** **results in muscle catabolism**

- **Feeding inhibits autophagy but activates the mTOR system leading to greater protein synthesis, inhibiting breakdown**

Autophagy is highly regulated and the simple concept "starvation stimulates autophagy and feeding inhibits autophagy" is naïve

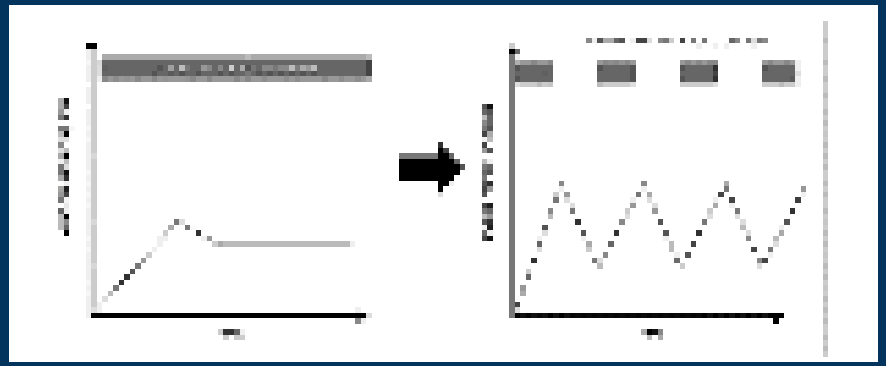
Some growing understanding of variable "autophagy flux in critical illness"

Tardif N, Polia F, Rooyackers O. Sci Reports 2019

Crouser ED, Hotchkiss RS.CCM 2016

"Current" Proposed Strategies in Protein Metabolism and Utilization

- Increase protein/AA delivery
  - Increase quantity and quality of AA or protein
    - Whey vs casein – whey is felt to be insulinotrophic
  - Mode of delivery – bolus or continuous feeding



- Increase delivery of alternate fuels
  - Avoid hyperglycemia
  - Optimize protein sparing influence of glucose
  - Consider MCT , Fish oils

- Decrease protein breakdown
  - Increase inflammation resolution
  - Minimize loss of muscle satellite cells
  - Minimize neuromuscular blockage, sedation holidays, wean from vent ASAP
  - Resistance exercise / early mobilization

Early mobilization

Walking while on ECMO

Waldauf P et al Crit Care Med 2020

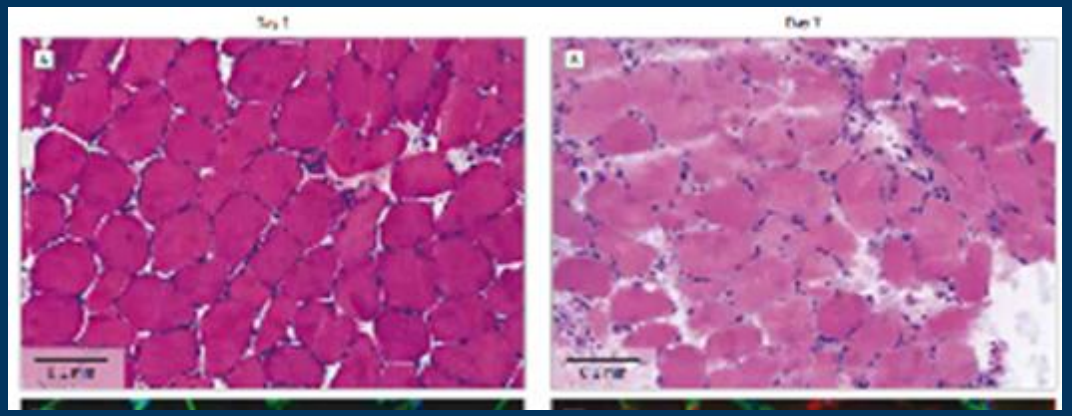
Summary: Protein Delivery in the ICU Setting to Prevent PICS

- **The critically ill can utilize additional protein or AA**
  - **Timing of delivery may depend on phases of critical illness**
    - **Anabolic resistance can be overcome**
  - **Up to 2.5 gm/kg/d appears safe**
  - **AA oxidation is not increased with increase delivery of substrate**
  - **Supplementation beneficial with EN or PN if timed appropriately**
  - **Resistance exercise helps protect LBM**

- **Caution:**
  - **Currently we have little understanding of mitochondrial biogenesis**
  - **Observational trials may not be consistent with RCT's**
  - **High quality studies with major outcome parameters i.e. mortality, LOS, QOL, muscle function and correlation to muscle mass etc are scarce**
  - **Current studies are short interventions, long term studies are needed**
  - **Early vs late delivery of protein may change outcome**

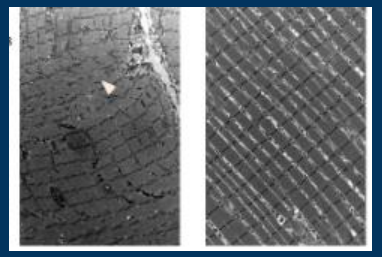
Many unanswered questions

- What is the maximum protein or AA
  - what AA mix, EAA to NEAA ratio, bolus vs continuous protein infusions
- Will protein delivery alter the autophagy response
- Interactions between cellular protein synthesis the 3 different cell proteolytic systems
    - » UPS, Autophagy/lysosomal system, Caspase mediated
- What intensity of exercise is needed to show benefit ?
- What controls muscle satellite cell regeneration ?
- Consider ICU muscle inflammation / mitochondrial biogenesis



What does the future hold for preserving lean body mass ?

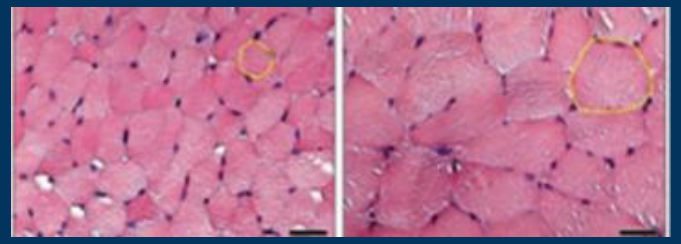
- **Satellite cells**



- **Mitochondrial approaches – changing cellular bioenergetics**

- **mTOR1C and myostatin regulation**

- **The microbiome in the ICU**



- **Exercise with protein intake**

Functional outcomes and quality of life

Prof. Ho-Seong Han

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JUMPstart Training Program

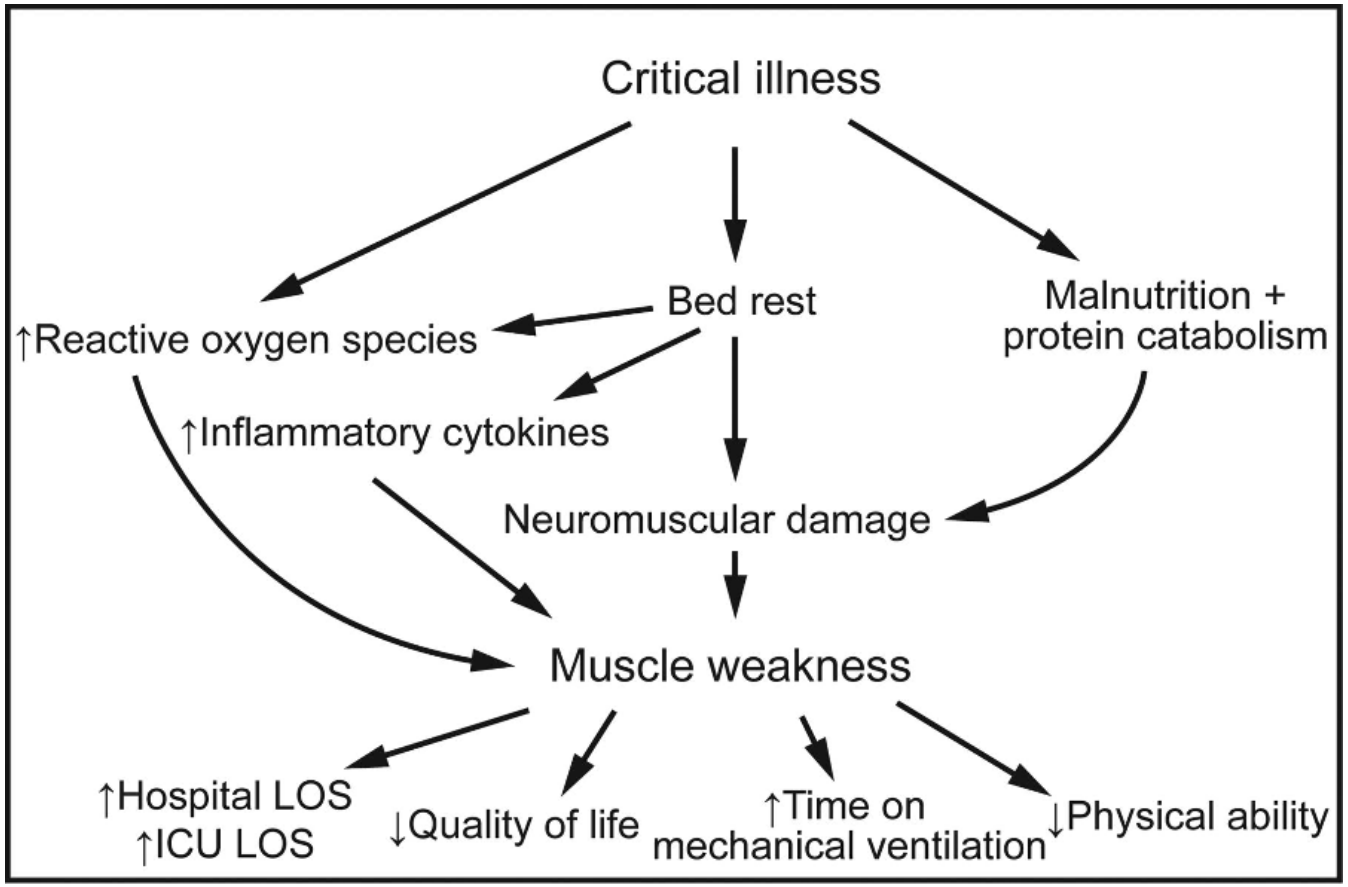
Functional outcomes and quality of life

Prof. Ho-Seong Han, M.D., Ph.D

&

Advanced module, Day 2, Part I: What really counts: Patient related outcomes

Critical Illness Acquired Weakness

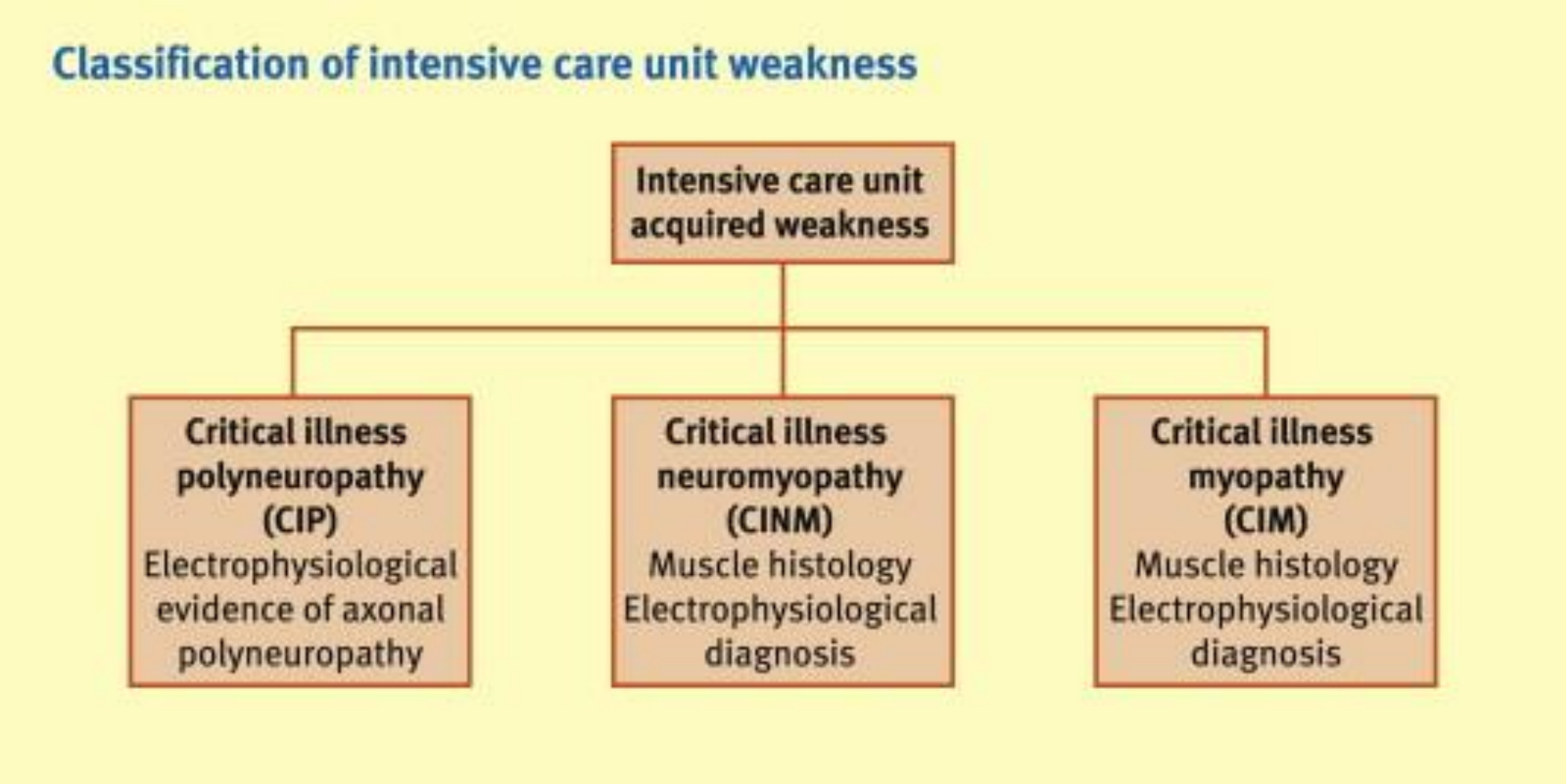


Schmidt UH et al. Respiratory Care. 2016

Contents

- Introduction
- Grading Weakness and Disability
- Rehabilitation

Introduction



John R et al. Anesth & Intensive Care Med. 2015

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

CRITICAL CARE MEDICINE

ICU-Acquired Weakness and Recovery from Critical Illness

John P. Kress, M.D., and Jesse B. Hall, M.D.

Kress JP, Hall JB. N Engl J Med 2014

ICU-acquired weakness and recovery from critical illness

- Many survivors of critical illness have considerable functional impairment
- Recovery is often slow and incomplete in such patients, particularly those who are elderly.
- Although some of the risk factors, such as sepsis, cannot necessarily be prevented,
- Aggressive treatment of such conditions is nevertheless important to minimize subsequent morbidity.
- Early mobilization of patients in the ICU is good strategy to reduce the deconditioning and dysfunction.

Kress JP, Hall JB. N Engl J Med 2014

Pathophysiologic Mechanism

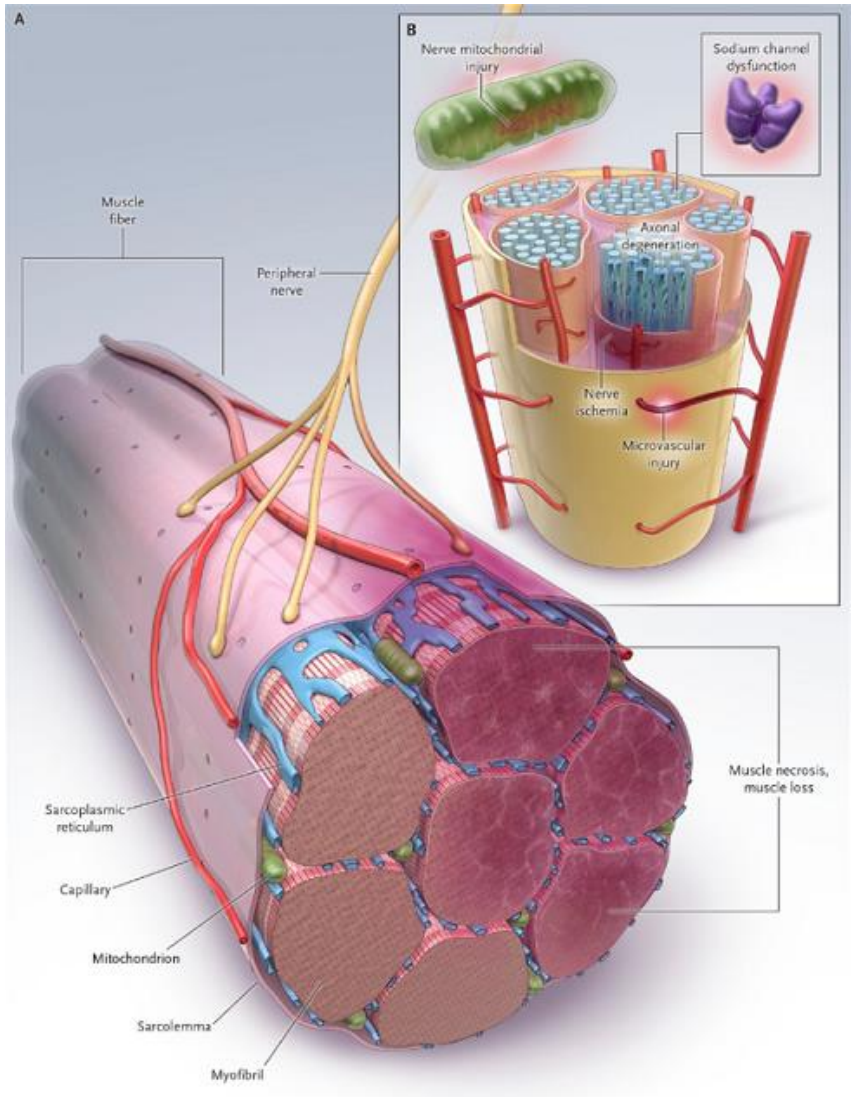


Figure 3. Pathophysiological Mechanisms of ICU-Acquired Weakness.

Panel A shows skeletal-muscle wasting. Possible mechanisms include microvascular ischemia, catabolism, and immobility. Panel B shows polyneuropathy with axonal degeneration. Possible mechanisms include microvascular injury with resulting nerve ischemia, dysfunction of sodium channels, and injury to nerve mitochondria.

Kress JP, Hall JB. N Engl J Med 2014

Consider ICU-acquired weakness

Research

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Acute Skeletal Muscle Wasting in Critical Illness

Zudin A. Puthucheary, MRCP; Jaikitry Rawal, MRCS; Mark McPhail, PhD; Bronwen Connolly, BSc; Gamunu Ratnayake, MRCP; Pearl Chan, MBBS; Nicholas S. Hopkinson, PhD; Rahul Phadke, FRCPath; Tracy Dew, MSc; Paul S. Sidhu, PhD; Cristiana Velloso, PhD; John Seymour, PhD; Chibeza C. Agley, MSc; Anna Selby, PhD; Marie Limb, PhD; Lindsay M. Edwards, PhD; Kenneth Smith, PhD; Anthea Rowlerson, PhD; Michael John Rennie, PhD; John Moxham, PhD; Stephen D. R. Harridge, PhD; Nicholas Hart, PhD; Hugh E. Montgomery, MD

- Acute skeletal muscle is wasted early days in critical illness.
- Survivors of critical illness demonstrate skeletal muscle wasting with associated functional impairment.

Puthucheary ZA et al. JAMA 2013

RF (Rectus Femoris) CSA (Cross Sectional Area) Decline

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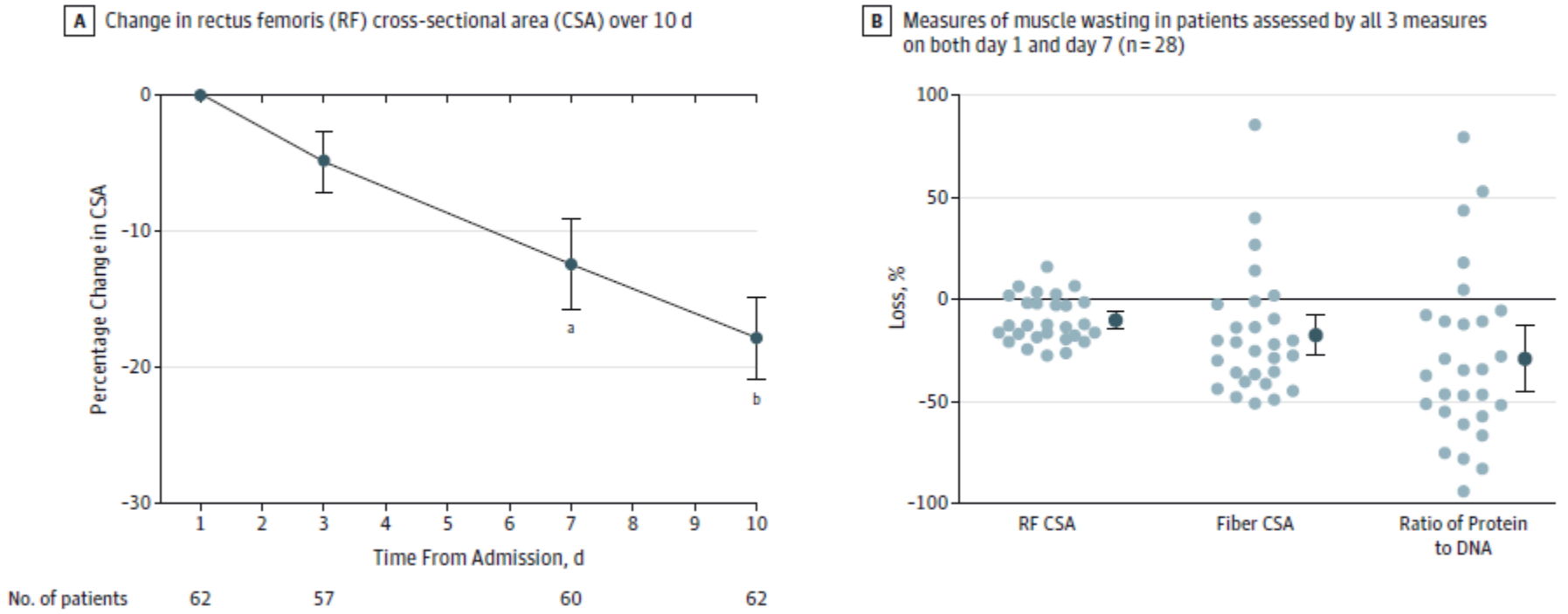
Figure 2. Measurements of Muscle Wasting During Critical Illness



Puthucheary ZA et al. JAMA 2013

Muscle Wasting aggravate with Organ Failure

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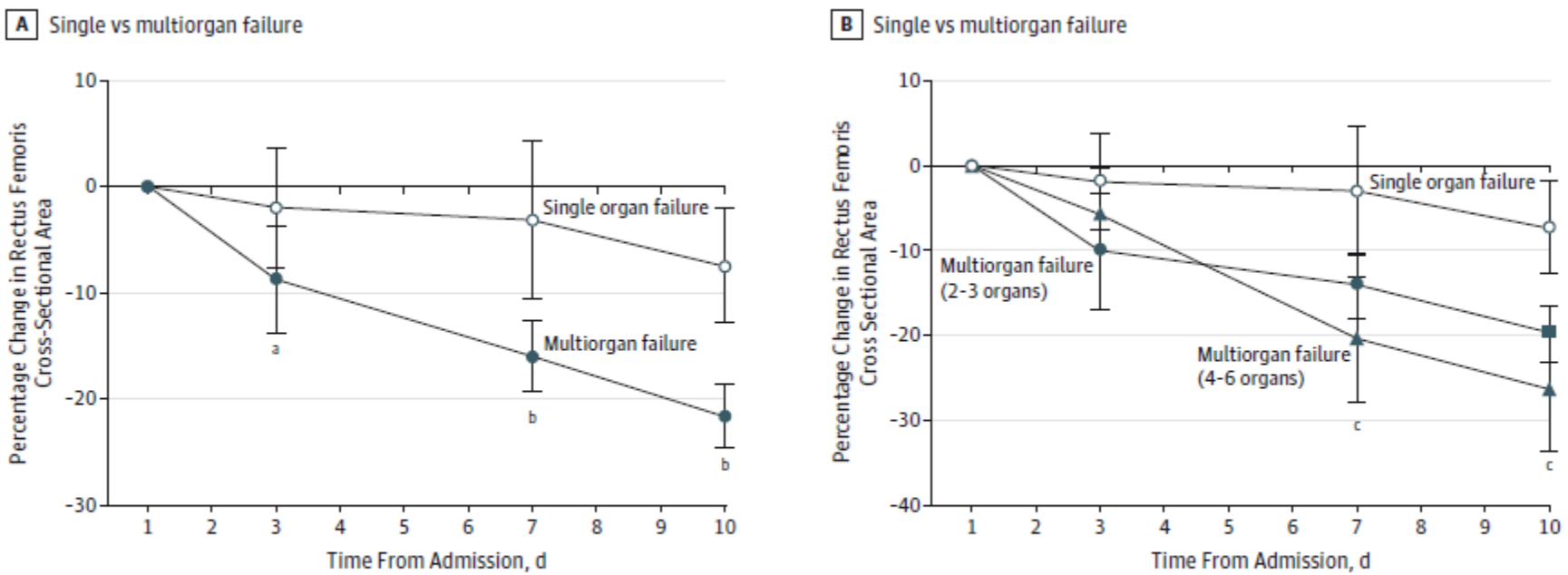
Figure 5. Measurements of Muscle Wasting During Critical Illness by Organ Failure



No. of patients				
Single organ failure	15	14	15	15
Multiorgan failure	47	43	45	47

No. of patients				
Single organ failure	15	14	15	15
Multiorgan failure				
2-3 Organs	33	31	32	33
4-6 Organs	14	12	13	14

Puthucheary ZA et al. JAMA 2013

Skeletal Muscle vs Mortality and Functional Outcomes?

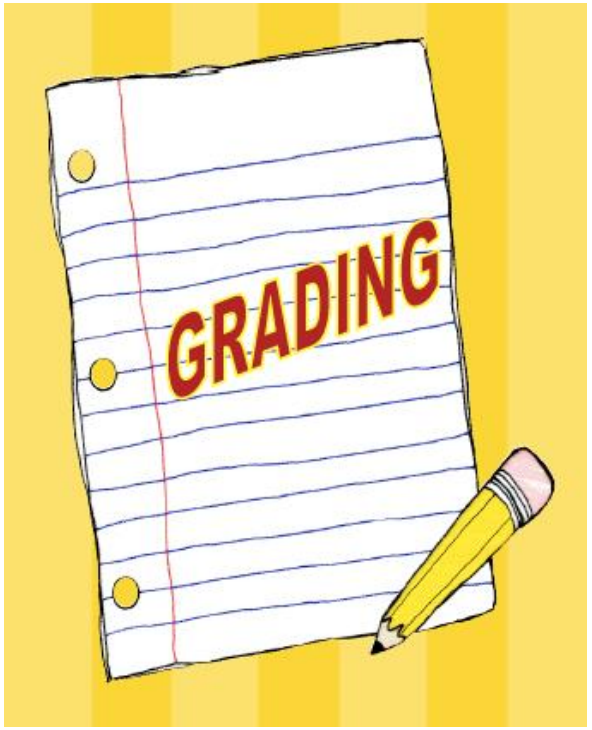
- Low skeletal muscle area is a risk factor for mortality in mechanically ventilated critically ill patients.
- Many critical illness survivors with a low muscle mass on admission, were discharged to a nursing home.

Weijs PJM et al. Crit Care 2014

- Skeletal muscle mass and mortality - but what about functional outcome?
- Muscle mass on admission to ICU can be used as part of a clinical practice algorithm in prognostication.

Puthucheary ZA et al. Crit Care 2014

Grading Weakness & Disability



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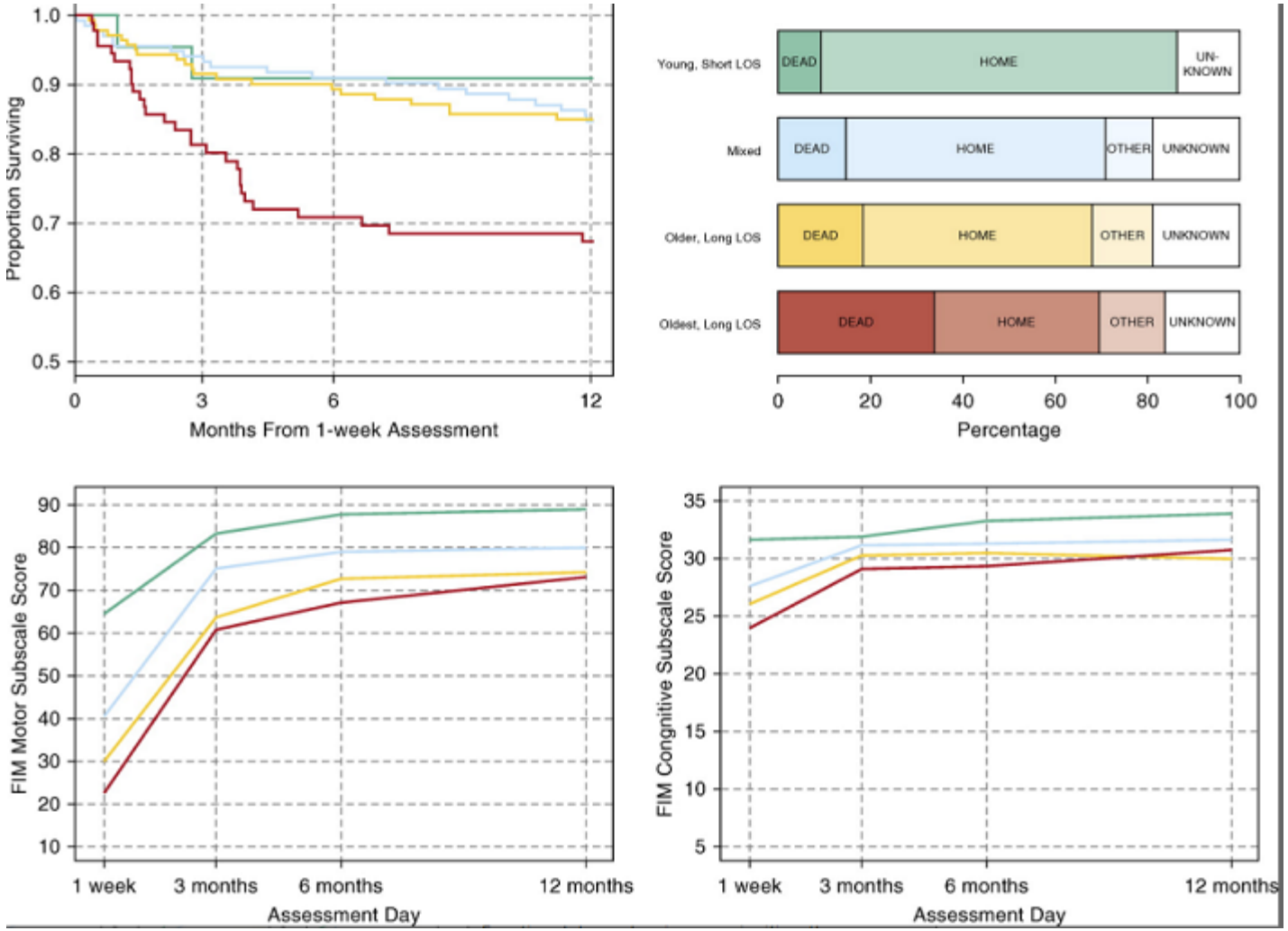
ORIGINAL ARTICLE

The RECOVER Program: Disability Risk Groups and 1-Year Outcome after 7 or More Days of Mechanical Ventilation

Margaret S. Herridge[1,2,3,4,5], Leslie M. Chu[5], Andrea Matte[2], George Tomlinson[1,6,7,8], Linda Chan[5], Claire Thomas[2], Jan O. Friedrich[3,9,10,11], Sangeeta Mehta[3,12], Francois Lamontagne[13,14], Melanie Levasseur[14], Niall D. Ferguson[1,2,3,4,5], Neill K. J. Adhikari[3,15], Jill C. Rudkowski[16,17], Hilary Meggison[18], Yoanna Skrobik[19,20], John Flannery[21,22], Mark Bayley[21,22], Jane Batt[9,11], Claudia dos Santos[3,9,10,11], Susan E. Abbey[1,23], Adrienne Tan[1,23], Vincent Lo[2,24], Sunita Mathur[24,25], Matteo Parotto[1,2,3], Denise Morris[2], Linda Flockhart[2], Eddy Fan[1,2,3,4,5], Christie M. Lee[3,12], M. Elizabeth Wilcox[1,2,3], Najib Ayas[26], Karen Choong[27], Robert Fowler[3,6,7,15], Damon C. Scales[3,15], Tasnim Sinuff[3,15], Brian H. Cuthbertson[3,15], Louise Rose[15], Priscila Robles[5,24,25], Stacey Burns[2], Marcelo Cypel[4,5,28], Lianne Singer[1,4,5], Cecelia Chaparro[1,4,5,28], Chung-Wai Chow[1,4,5], Shaf Keshavjee[1,4,5,28], Laurent Brochard[3,9,10,11], Paul Hebert[29,30], Arthur S. Slutsky[3,9,10,11], John C. Marshall[3,9,10,11], Deborah Cook[27,31], and Jill I. Cameron[32]; for the RECOVER Program Investigators (Phase 1: towards RECOVER) and the Canadian Critical Care Trials Group

- Stratify patients for post-ICU disability and recovery to 1 year after critical illness.
- ICU survivors of greater than or equal to 1 week of MV may be stratified into four disability groups based on age and ICU length of stay.

Herridge MS et al. Am J Respir Crit Care Med. 2016



Kaplan-Meier curve (*top left*), disposition at 1 year (*top right*), FIM motor subscale (*bottom left*), and FIM cognitive subscale (*bottom right*) stratified by disability group. Survival $P < 0.001$: all comparisons
FIM = Functional Independence Measure;

Herridge MS et al. Am J Respir Crit Care Med. 2016

ORIGINAL RESEARCH

Clinical Frailty Scale in an Acute Medicine Unit: a Simple Tool That Predicts Length of Stay

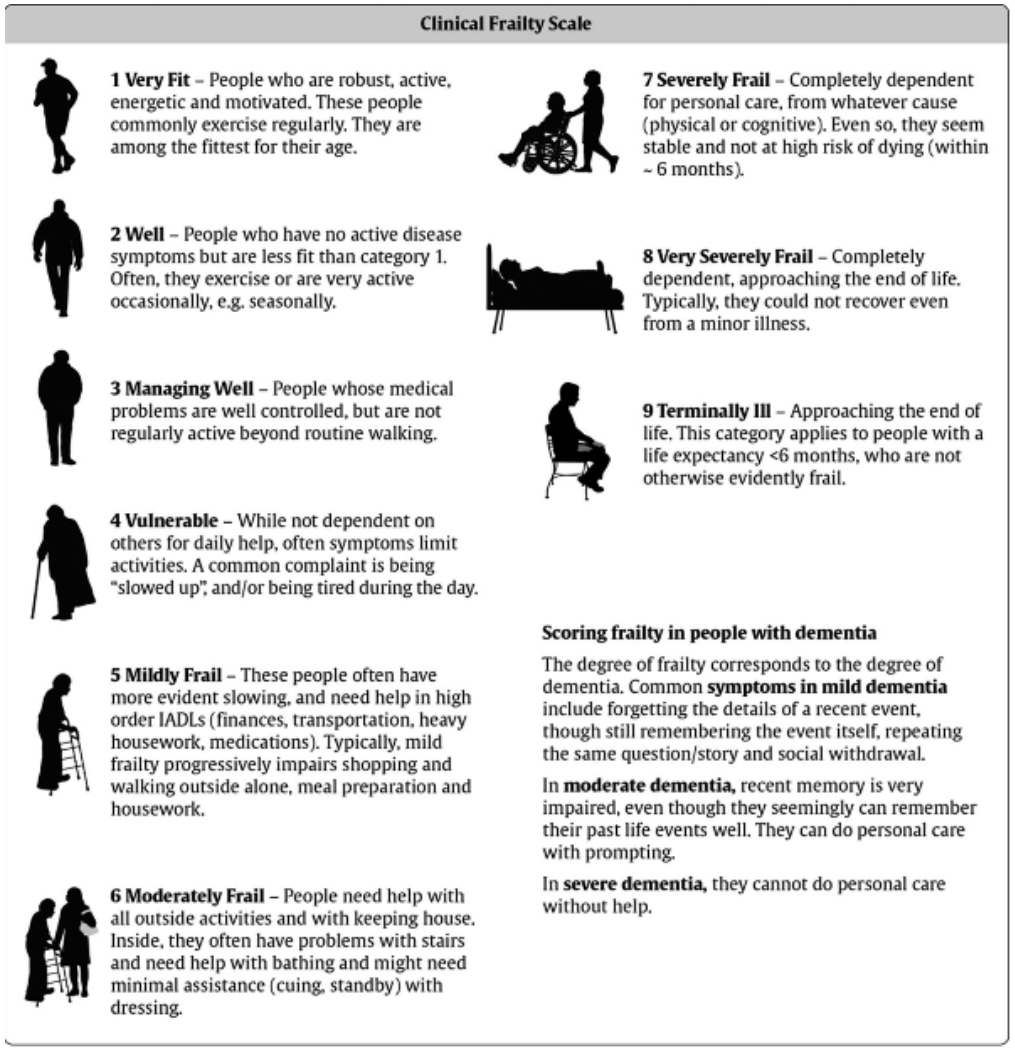
Salina Juma, MD[1], Mary-Margaret Taabazuing, MD, FRCPC[2], Manuel Montero-Odasso, MD, PhD FRCPC, AGSF[1,2,3]

[1]Department of Medicine, Internal Medicine, London Health Sciences Centre, The University of Western Ontario, London, ON; [2]Department of Medicine, Division of Geriatric Medicine, The University of Western Ontario, London, ON; [3]Gait and Brain Lab, Lawson Health Research Institute, Parkwood Hospital, London, ON; [4]Department of Epidemiology & Biostatistics, The University of Western Ontario, London, ON, Canada

- The CFS is an easy to use tool which can detect older adults at high risk of complicated course and longer stay.
- The CFS target interventions to prevent complications and to implement effective discharge planning in high risk older adults.

Juma S et al. Can Geriatr J. 2016

Clinical Frailty Scale



Clinical Frailty Scale

1 Very Fit – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 Well – People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally, e.g. seasonally.

3 Managing Well – People whose medical problems are well controlled, but are not regularly active beyond routine walking.

4 Vulnerable – While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up", and/or being tired during the day.

5 Mildly Frail – These people often have more evident slowing, and need help in high order IADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 Moderately Frail – People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.

7 Severely Frail – Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 Very Severely Frail – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9 Terminally Ill – Approaching the end of life. This category applies to people with a life expectancy <6 months, who are not otherwise evidently frail.

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia,** recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia,** they cannot do personal care without help.

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Clinical Frailty Scale ©

Background

There is no single generally accepted clinical definition of frailty. Previously developed tools to assess frailty that have been shown to be predictive of death or need for entry into an institutional facility have not gained acceptance among practising clinicians. We aimed to develop a tool that would be both predictive and easy to use.

Methods

We developed the 9-point Clinical Frailty Scale© and applied it and other established tools that measure frailty to 2305 elderly patients who participated in the second stage of the Canadian Study of Health and Aging (CSHA). We followed this cohort prospectively; after 5 years, we determined the ability of the Clinical Frailty Scale© to predict death or need for institutional care, and correlated the results with those obtained from other established tools.

Results

The CSHA Clinical Frailty Scale was highly correlated ($r = 0.80$) with the Frailty Index. Each 1-category increment of our scale significantly increased the medium-term risks of death (21.2% within about 70 mo, 95% confidence interval [CI] 12.5%–30.6%) and entry into an institution (23.9%, 95% CI 8.8%–41.2%) in multivariable models that adjusted for age, sex and education. Analyses of receiver operating characteristic curves showed that our Clinical Frailty Scale© performed better than measures of cognition, function or comorbidity in assessing risk for death (areaunder the curve 0.77 for 18-month and 0.70 for 70-month mortality).

Clinical Frailty Scale©

Interpretation

Frailty is a valid and clinically important construct that is recognizable by physicians. Clinical judgments about frailty can yield useful predictive information.

Clinical Frailty Scale. 7 © 2007-2009. Version 1.2.

Various Score System

- MRC score; Medical Research Council
- Functional Independence Measure: FIM
- Chelsea CPAx score
- Etc.

MRC (Medical Research Council) score

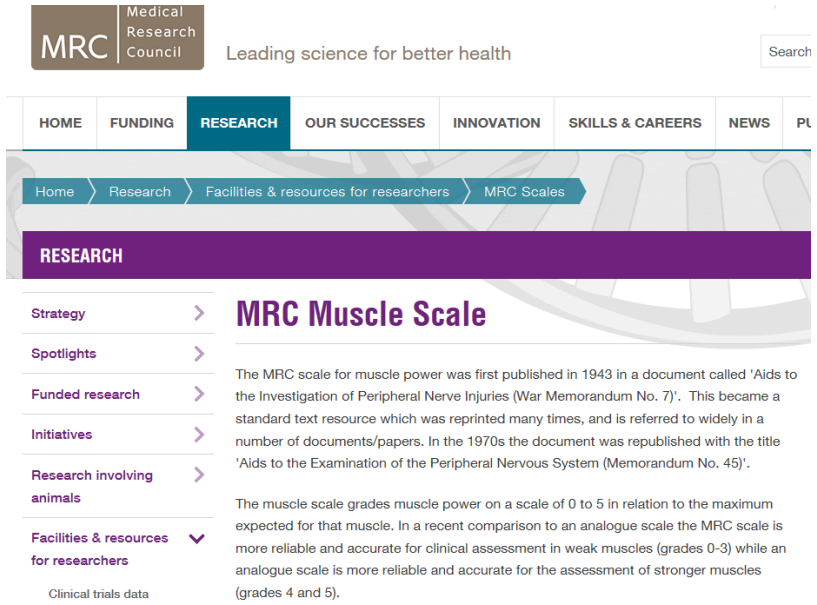

Table 1 – Medical Research Council (MRC) Score

Evaluated movements
■ Shoulder abduction
■ Elbow flexion
■ Wrist extension
■ Hip flexion
■ Knee extension
■ Ankle dorsal flexion
Muscle strength degrees
■ 0 = No movement is observed
■ 1 = Visible contraction, no segment movement
■ 2 = Active movement upon resistance of gravity removed
■ 3 = Active movement, against gravity
■ 4 = Active movement against gravity and examiners' resistance
■ 5 = Normal strength

Consists of six bilaterally evaluated movements, and each movement muscle force was rated between 0 (total palsy) and 5 (normal muscle strength). Total scores ranged between 0 (complete tetraparesis) and 60 (normal muscle strength). Source: Adapted from De Jonghe et al. (2005).[6]

- The MRC scale for muscle power was first published in 1943 in a document called 'Aids to the Investigation of Peripheral Nerve Injuries.

Functional Independence Measure (FIM)

motor subscale (max. 91)	cognition subscale (max. 35)
Eating	Comprehension
Grooming	Expression
Bathing	Social interaction
Dressing, upper/lower body	Problem solving
Toileting	Memory
Bladder/bowel management	
Transfers - bed/chair/wheelchair, toilets, baths/shower	
Walk/wheelchair	
Stairs	

Independent
7 Complete Independence (Timely, Safely)
6 Modified Independence (Device)
Modified Dependence
5 Supervision (Subject = 100%+)
4 Minimal Assist (Subject = 75%+)
3 Moderate Assist (Subject = 50%+)
Complete Dependence
2 Maximal Assist (Subject = 25%+)
1 Total Assist (Subject = less than 25%)

- FIM was also developed to offer a uniform system of measurement for disability based on the International Classification of Impairment, Disabilities and Handicaps (McDowell & Newell, 1996).

ELSEVIER

Physiotherapy 99 (2013) 33–41

Physiotherapy

The Chelsea Critical Care Physical Assessment Tool (CPAx): validation of an innovative new tool to measure physical morbidity in the general adult critical care population; an observational proof-of-concept pilot study

E.J. Corner [a,*], H. Wood [a], C. Englebretsen [a], A. Thomas [b], R.L. Grant [c,d], D. Nikoletou [c,d], N. Soni [a]

[a] *Chelsea and Westminster NHS Foundation Trust, 369 Fulham Road, London SW10 9NH, UK*
[b] *The Royal London Hospital, Barts and The London NHS Trust, London, UK*
[c] *Faculty of Health and Social Care Sciences, Kingston University, Kingston, UK*
[d] *St. George's Hospital Medical School, University of London, London, UK*

- To develop a scoring system to measure physical morbidity in critical care – the Chelsea Critical Care Physical Assessment Tool (CPAx).

Chelsea CPAx to measure physical morbidity

Physiotherapy. 2013 Mar;99(1):33-41. doi: 10.1016/j.physio.2012.01.003. Epub 2012 Mar 30.

The Chelsea critical care physical assessment tool (CPAx): validation of an innovative new tool to measure physical morbidity in the general adult critical care population; an observational proof-of-concept pilot study.

Corner EJ[1], Wood H, Englebretsen C, Thomas A, Grant RL, Nikoletou D, Soni N.

Author information

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Abstract

OBJECTIVE: To develop a scoring system to measure physical morbidity in critical care - the Chelsea Critical Care Physical Assessment Tool (CPAx).

METHOD: The development process was iterative involving content validity indices (CVI), a focus group and an observational study of 33 patients to test construct validity against the Medical Research Council score for muscle strength, peak cough flow, Australian Therapy Outcome Measures score, Glasgow Coma Scale score, Bloomsbury sedation score, Sequential Organ Failure Assessment score, Short Form 36 (SF-36) score, days of mechanical ventilation and inter-rater reliability.

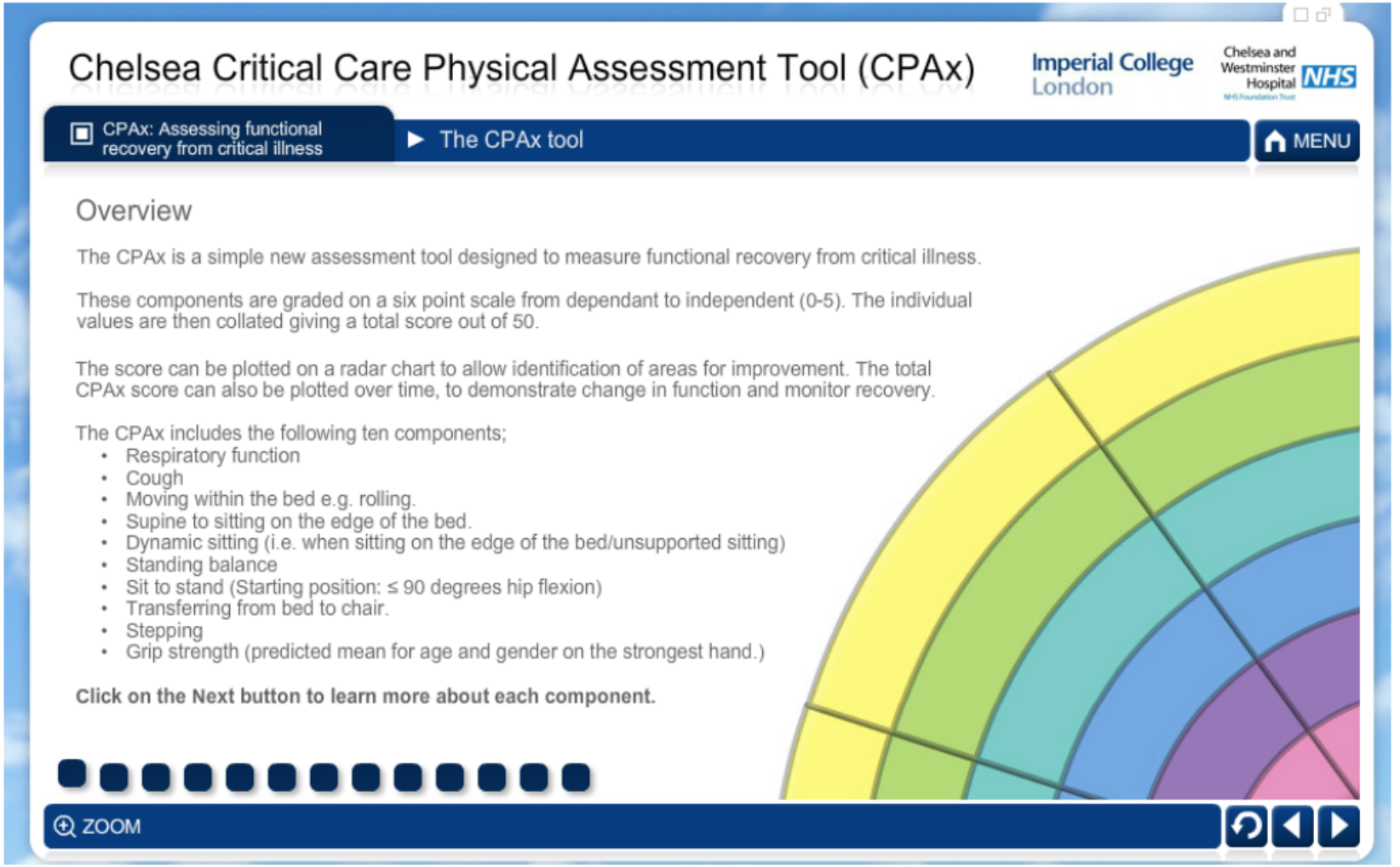
PARTICIPANTS: Trauma and general critical care patients from two London teaching hospitals.

RESULTS: Users of the CPAx felt that it possessed content validity, giving a final CVI of 1.00 ($P<0.05$). Construct validation data showed moderate to strong significant correlations between the CPAx score and all secondary measures, apart from the mental component of the SF-36 which demonstrated weak correlation with the CPAx score ($r=0.024$, $P=0.720$). Reliability testing showed internal consistency of $\alpha=0.798$ and inter-rater reliability of $\kappa=0.988$ (95% confidence interval 0.791 to 1.000) between five raters.

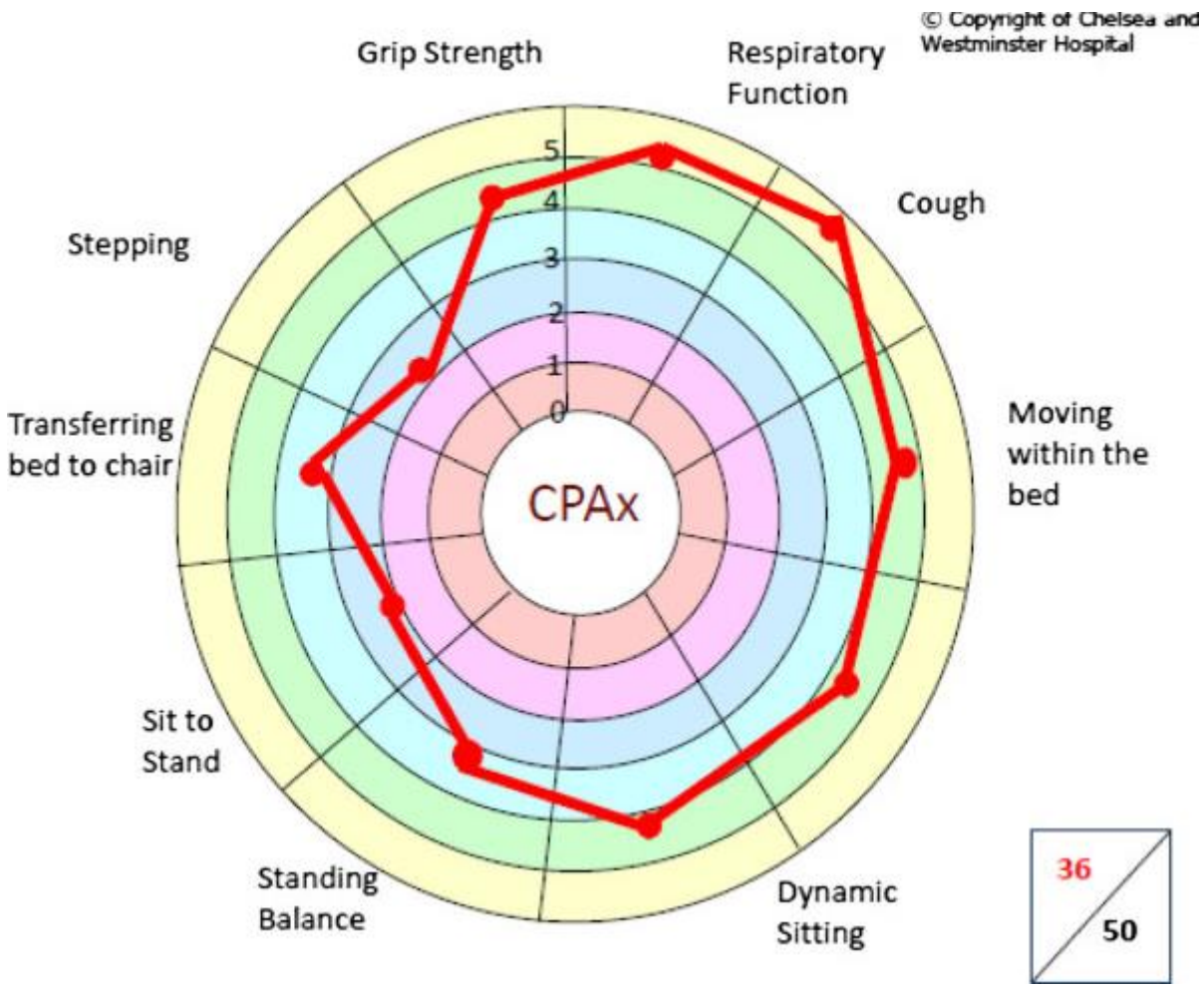
CONCLUSION: This pilot work supports proof of concept of the CPAx as a measure of physical morbidity in the critical care population, and is a cogent argument for further investigation of the scoring system.

PMID: 23219649 DOI: 10.1016/j.physio.2012.01.003

Chelsea CPAx score



Chelsea CPAx score - example



Rehabilitation

Rehabilitation after Critical Illness.

- Rehabilitation after critical illness requires a multidisciplinary effort.
- Nutrition support aims to correct the imbalance between protein synthesis and degradation to maximize strengthening and muscle mass.
- Physical and occupational therapists focus on optimizing strength and mobility through functional activity.
- Aim is to help the patients return to their precritical illness level of function and improve quality of life.
- Early mobility has become the new standard of care for ICU patients

Koester K et al. Nutr Clin Pract. 2018

Proper Nutrition

Exercise Device for Rehabilitation

Koester K et al. Nutr Clin Pract. 2018

Open Access Research

BMJ Open

Early rehabilitation to prevent postintensive care syndrome in patients with critical illness: a systematic review and meta-analysis

Ryota Fuke,[1] Toru Hifumi,[2] Yutaka Kondo,[3] Junji Hatakeyama,[4] Tetsuhiro Takei, Kazuma Yamakawa,[5] Shigeaki Inoue,[6] Osamu Nishida[7]

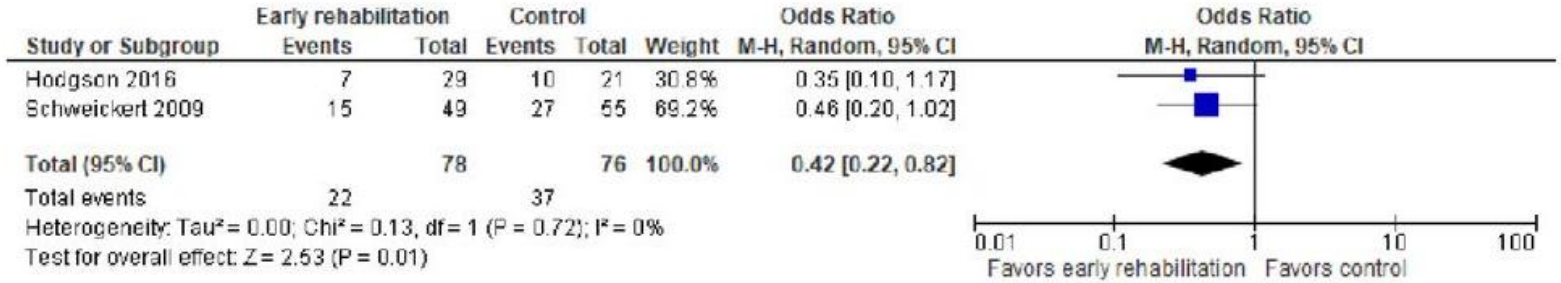
Fuke R et al. BMJ Open. 2018

Short-term Outcome after PICS

Short-term outcome

1. Physical-related outcomes

A Incidence of ICU-AW



B MRC

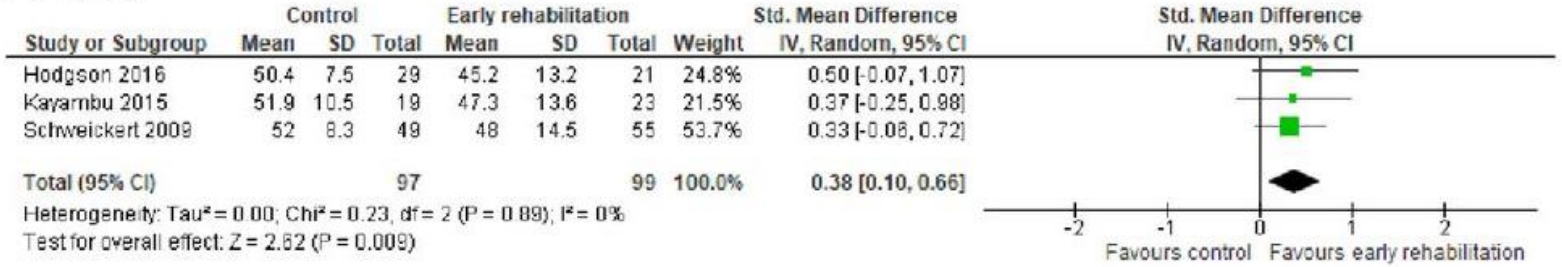


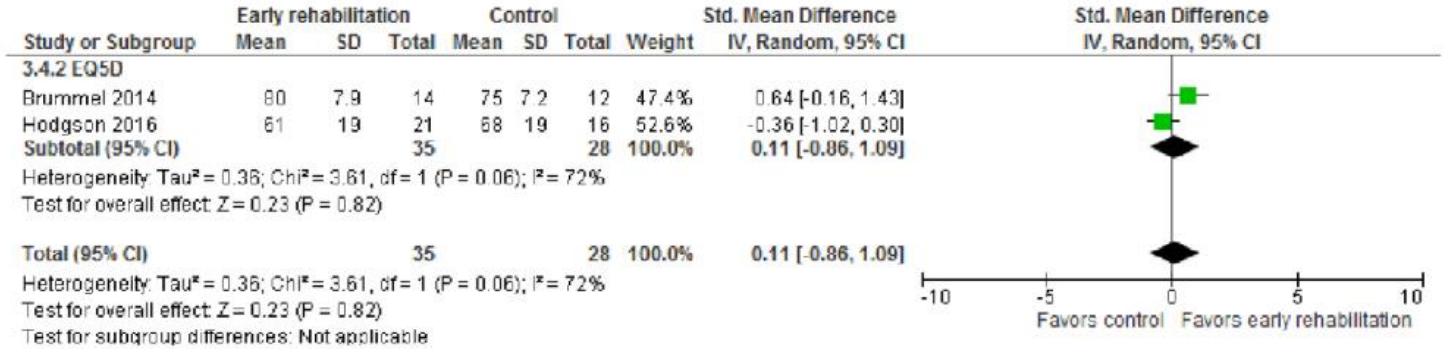
Figure 3 The effect of early rehabilitation on short-term outcomes in postintensive care syndrome (PICS) in intensive care unit (ICU) patients. (1) Physical-related outcomes (A) Incidence of ICU-acquired weakness (AW). (B) Medical Research Council (MRC) sum score.

Fuke R et al. BMJ Open. 2018

Long-term Outcome: Quality of Life

Long-term outcome

1 Health-related QOL scores



2 SF-36PF

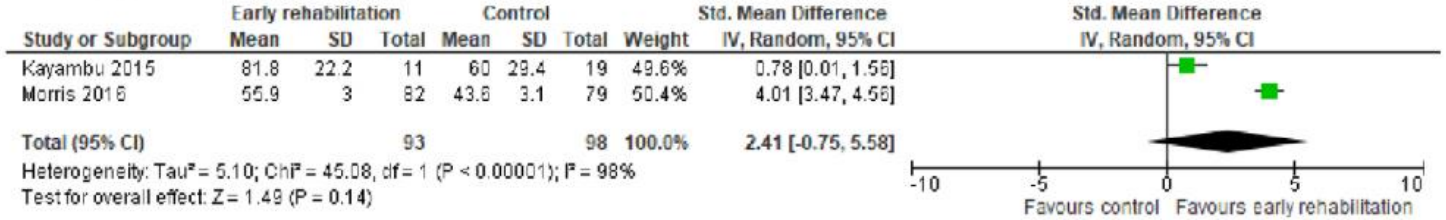


Figure 4 The effect of early rehabilitation on long-term outcomes in postintensive care syndrome (PICS) in intensive care unit (ICU) patients. The effect of early rehabilitation on health-related quality of life (QOL) scores and in ICU patients. (1) Health-related quality of life (QOL) scores calculated from the EuroQol 5 Dimensions (EQ5D). (2) Medical Outcomes Study 36-Item Short Form Health Survey Physical Function scale (SF-36 PF).

Fuke R et al. BMJ Open. 2018

Connolly *et al. Trials* (2018) 19:294
https://doi.org/10.1186/s13063-018-2678-4

Trials

STUDY PROTOCOL Open Access

Physical Rehabilitation Core Outcomes In Critical illness (PRACTICE): protocol for development of a core outcome set

Bronwen Connolly[1,2,3,4*], Linda Denehy[4], Nicholas Hart[1,3], Natalie Pattison[5,8], Paula Williamson[6,9] and Bronagh Blackwood[7,10]

Trial status

The systematic reviews of quantitative and qualitative literature have been completed, and recruitment is currently underway for the qualitative interviews. Delphi consensus participants are currently being identified and recruited.

Conclusion

- The patients survived after critical illness may have considerable functional impairment. The early rehabilitation may prevent this complications and enhance quality of life.

Part II
Confounding factors in the ICU

Impact of gut function and other organ failure

Prof. Bob Martindale

FRESENIUS KABI
caring for life

JUMPstart Training Program

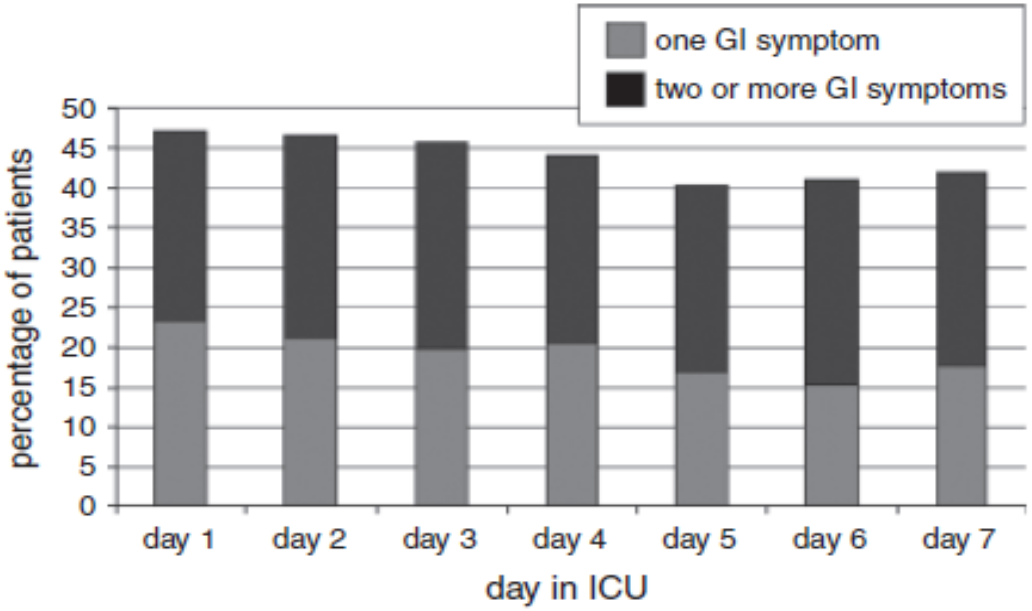
Impact of gut function and other organ failure: Is the gut the motor for multiple organ failure ?

Prof. Bob G. Martindale, MD, PhD

Gastrointestinal symptoms and outcome in ICU patients

- **60 % of patients present at least one GI symptom**
- **20 % have two or more GI symptoms during their stay**

Mechanically ventilated patients



GI failure can be manifested by impaired:

- GI dysmotility
- Absorption abnormality
- Mucosal barrier disruption
- Endocrine dysfunction
- Immune function compromised

GI Symptoms

- Vomiting
- GRV
- Diarrhea
- GI bleeding
- Ileus
- Abnormal BS
- Bowel dilation

Reintam Blaser A, et al. Intensive Care Med. 2013; 39(5):899-909,
Iyer D, et al. Acta Anaesthesiol Scand 2014
Taylor R. Critical Care Clinics 2016;32:191-201

Historical Perspective

MULTIPLE ORGAN FAILURE

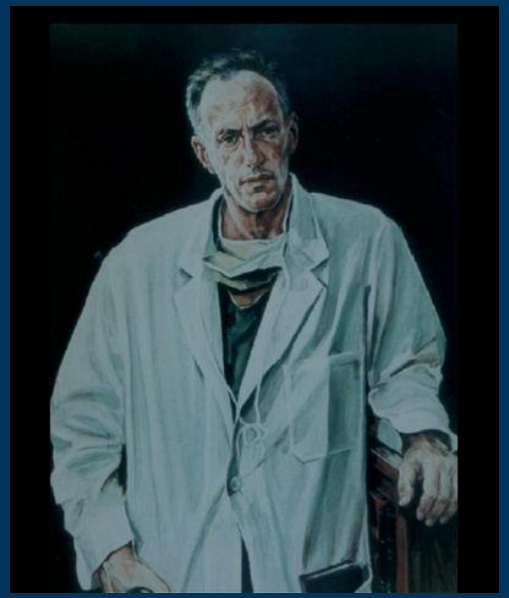
B. Eiseman, M.D., F.A.C.S., R. Beart, M.D., *and* L. Norton, M.D., F.A

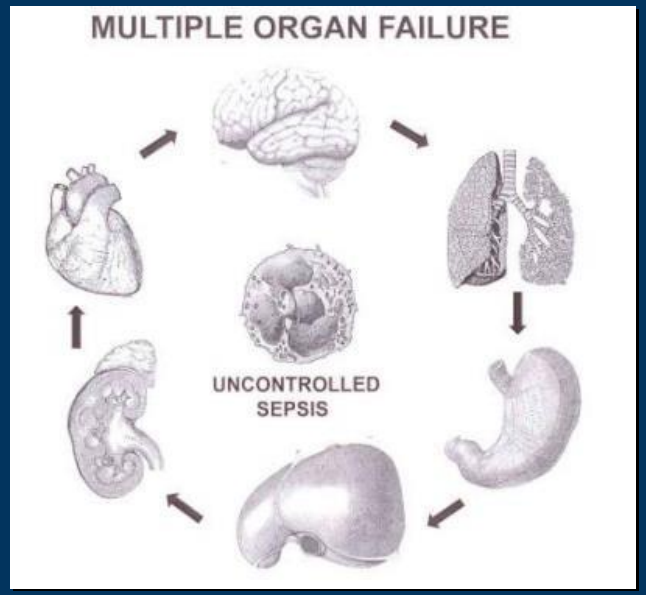
Denver, Colorado

Surg Gyn Obstet 1977

Multiple-Organ-Failure Syndrome

C. James Carrico, MD; Jonathan L. Meakins, MD, DSc, FRCSC, FACS; J. C. Marshall, MD, FRCSC; Donald Fry, MD; Ronald V. Maier, MD

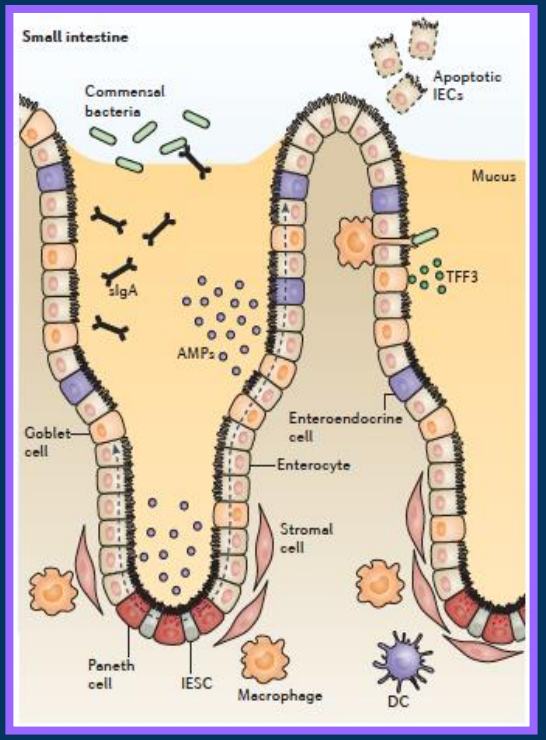




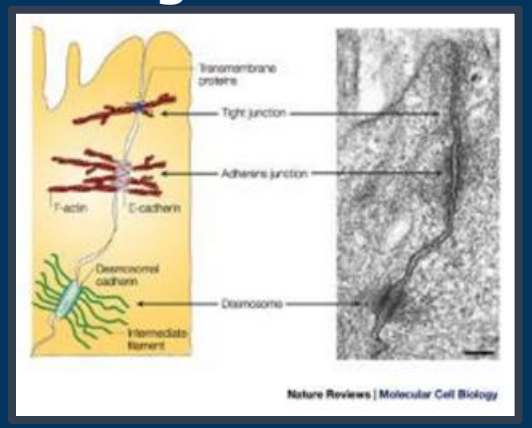
- **MOF described 1969-77 primarily attributed to sepsis [1]**
  - **Assumed intra-abd abscess, need for exploratory laparotomy**
- **Awareness of non-bacteremic clinical sepsis [1]**
  - **Clinical course identical to those with bacteremia**
  - **No clinical focus of infection present**
- **Suggested GI tract was "motor" of MOF syndrome**
  - **Described loss barrier function, pathogenic orgs**
- **Documented bacterial translocation to mesenteric lymph nodes in post-op pts (5-21% all gut origin) [2]**

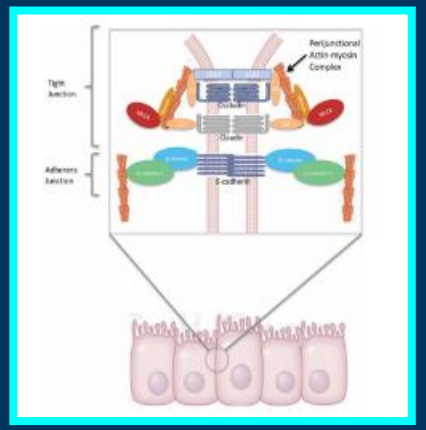
[1] CJ Carrico (Archives Surg 1986;121:196)
[2] EA Deitch (Surgeon 2012;10:350)

Gut in Homeostasis: Barrier Function



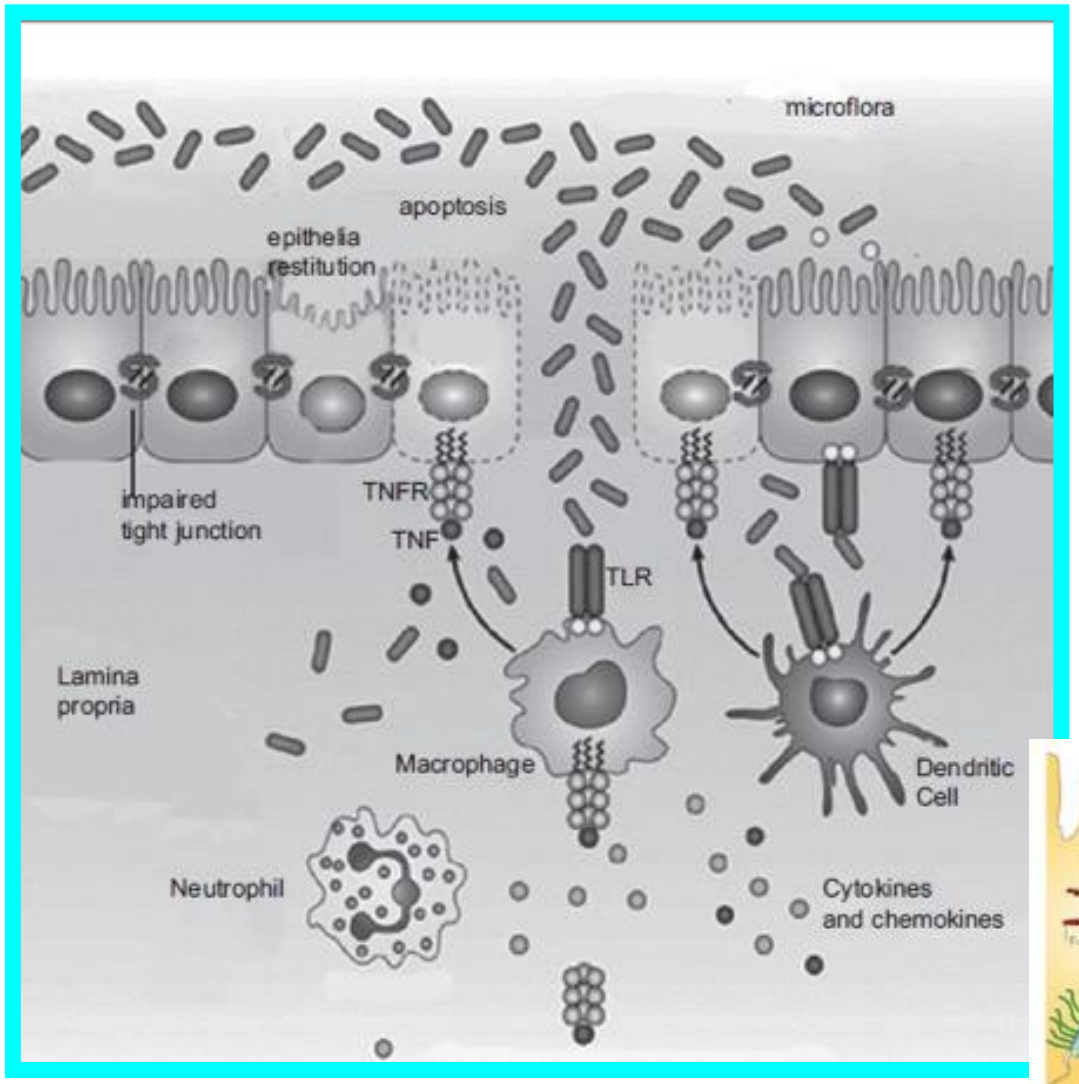
- Epithelial stem cells proliferate to four subtypes:
  - **Enterocyte** - absorption
  - **Goblet** - mucus
  - **Paneth** - defensins
  - **Enteroendocrine** - hormonal regulation
- Cells undergo proliferation and migration, replacement every 3-5 days
- Controlled apoptosis
- Mucus layer
- Barrier function – Adherens Junction cadherins (adhesion)
  - Tight Junction - occludins, claudins, actin-myosin (seal)

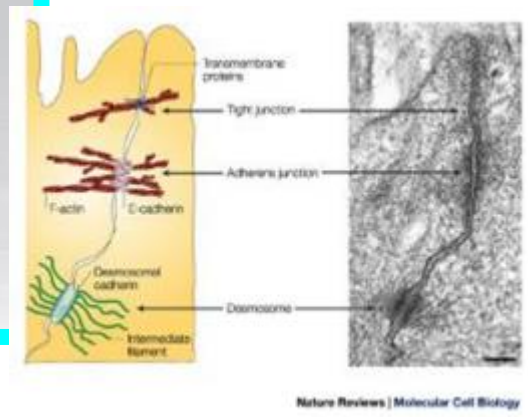




Mittal (Trends Molec Med 2014;20:214)
NJ Klingensmith (Crit Care Clin 2016;32:203)

Impact of Critical Illness on Gut Barrier





Increased permeability

Tight junctions are breached

Increased apoptosis, physical defects

Repair mechanisms compromised

Microbes penetrate thru wall and engage receptors, dendritic cells

Thinning of mucus layer

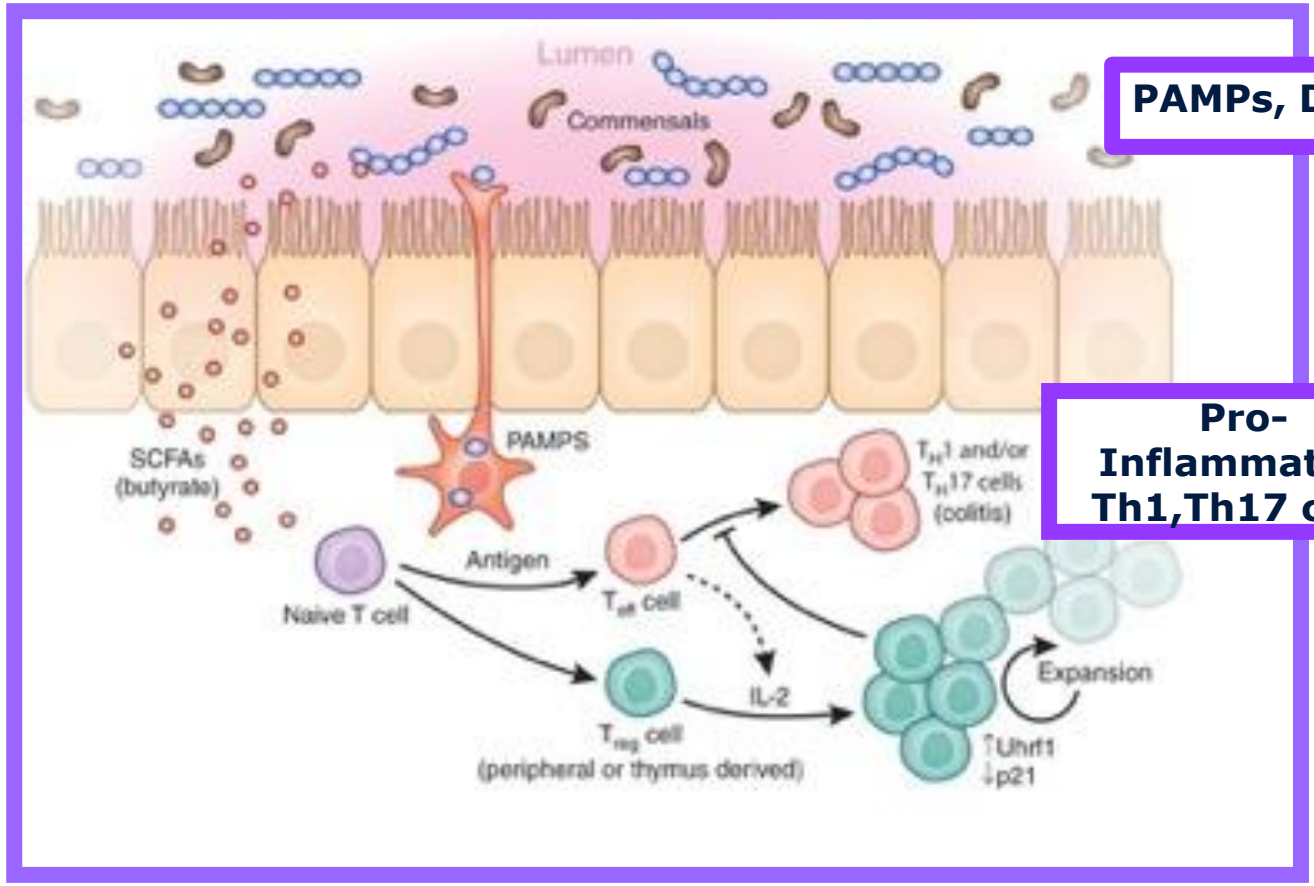
Toxic gut-derived lymph formed

Induction of virulence factors

R Mittal et al Trends Molec Med 2014,
E Sertaridou et al Ann Gastro 2015,
Ma Y et al Translational Reviews 2021

Impact of Critical Illness

Immune Dysregulation = Gut Sepsis → MOF



Cross-talk signals change from MAMPs to PAMPs=pathogens, DAMPs=alarmins

MA Krezalek, JC Alverdy (Shock 2016;45:475)
M Hayakawa (Dig Dis Sci 2011;56:2361)

Sequence of Events at the Organ Level

Septic Insult

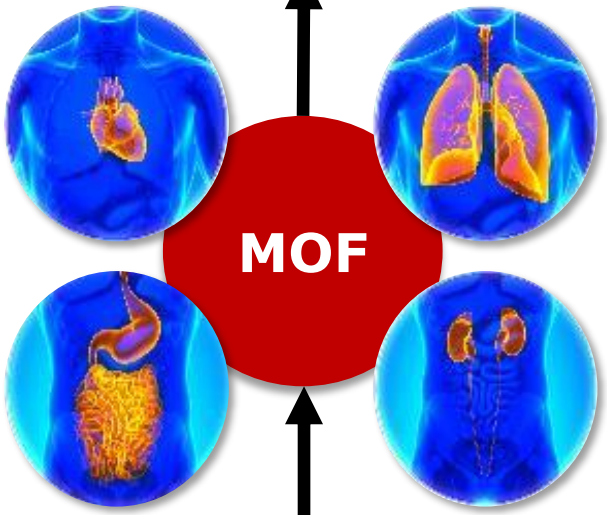
Hypotension and / or hypoxia

Gut hypoxia

Mesenteric ischemia---
Loss of mucosal integrity.
Mitochondrial dysfunction

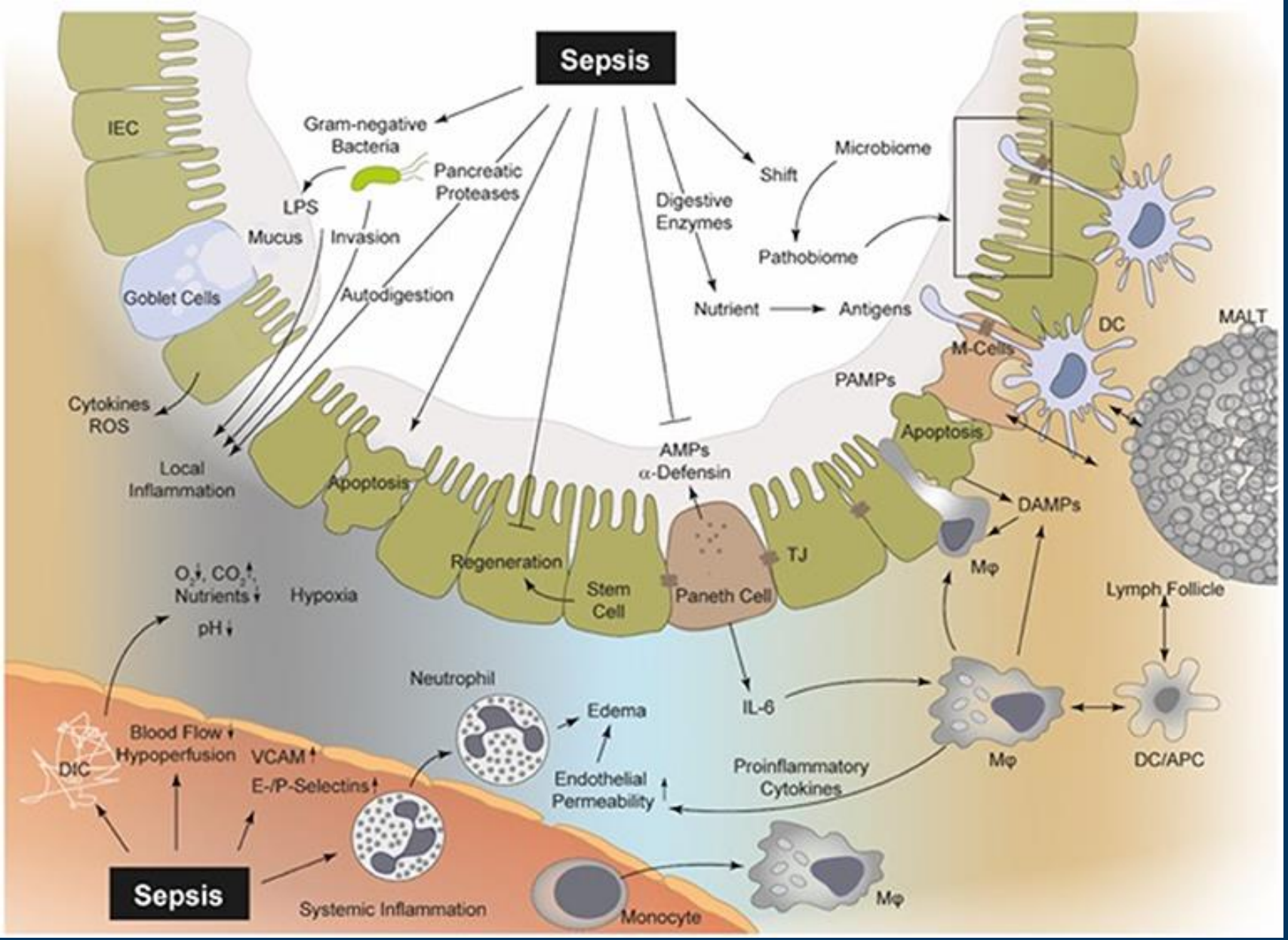
Toxins and Bacterial translocation
Altered Immune response
Decrease bacterial diversity
"Microbiome to virulent pathobiome"

Bacteremia, Endotoxins, TNF IL1, IL6, pancreatic lipase, FFA enter circulation via PV and Lymphatics
Decrease in SCFA (butyrate)



Further hypoxia, increased inflammation

Further hypoxia



Hypoperfusion:

- Gut barrier breakdown
- Converts gut to cytokine generating organ, this is the bodies attempt to vasodilate locally.
- In extreme states the gut looses ability to "self regulate" blood flow

- **Secondary changes:**
  - Edema increases intercapillary distance yielding greater O2 diffusion distance

Haussner F et al Frontiers Immunology 2019

Cross-Talk signaling between gut and other organs:

Activation of several systems by signals

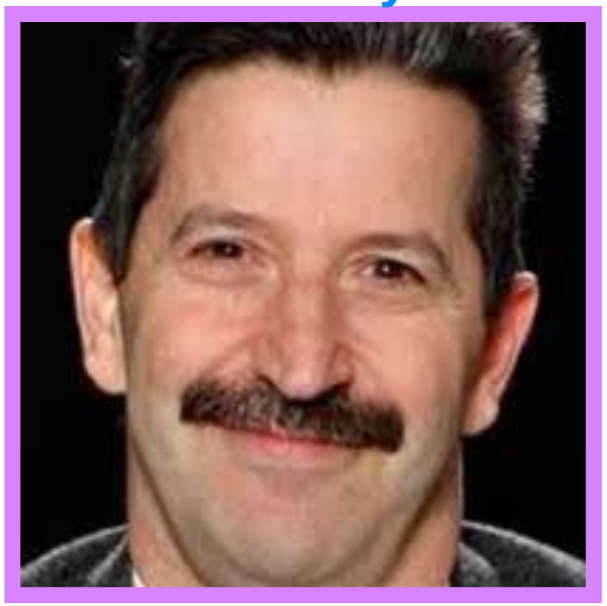
- **Intestinal epithelial integrity, permeability**
- **Immune responses, gut sepsis**
- **Microbiome (MAMPs) vs Pathobiome (PAMPs)**
- **SCFAs (butyrate) – GPRs, HDAC inhibition**
- **Bile salts (FXR)**
- **Mitochondria (mRNA) DAMPs**
- **Macrophage polarization**
- **Gut-Liver axis**

MAMPS=Microbe-associated molecular patterns
PAMPS= Pathogen-associated molecular patterns
DAMPS= Damage-associated molecular patterns
GPR= G-protein receptors
HDAC= Histone-deacetylase
FXR = Farnasoid X receptor

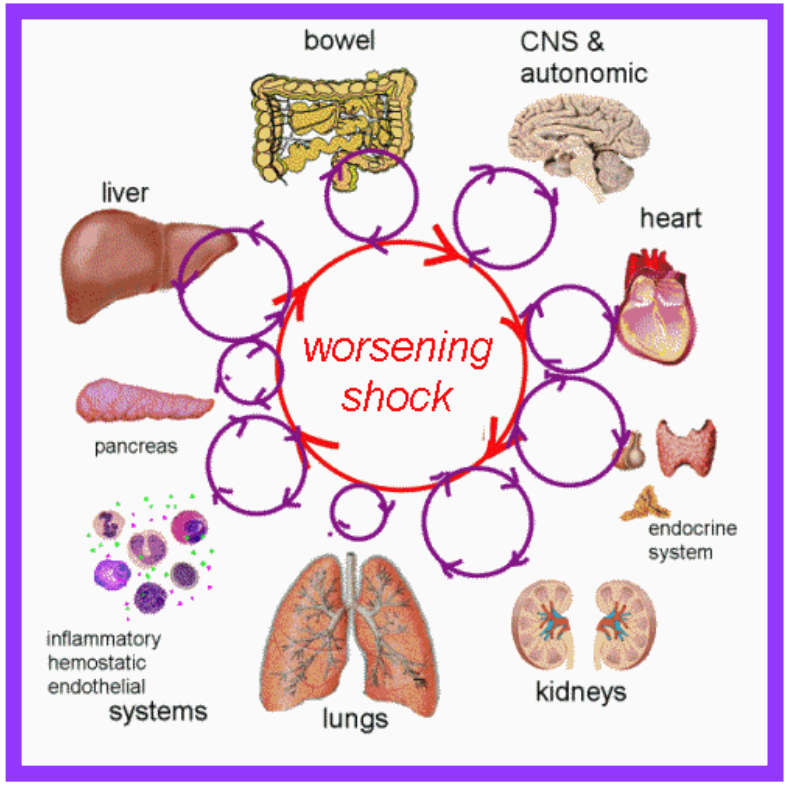
Mitochondrial Dysfunction in Critical illness

Causes of MOF in ICU:

- Shock
- ↓ Gut barrier → Toxic lymph
- Immune Dysregulation (Gut Sepsis)
- Microbiome → Pathobiome
- Mitochondrial dysfunction

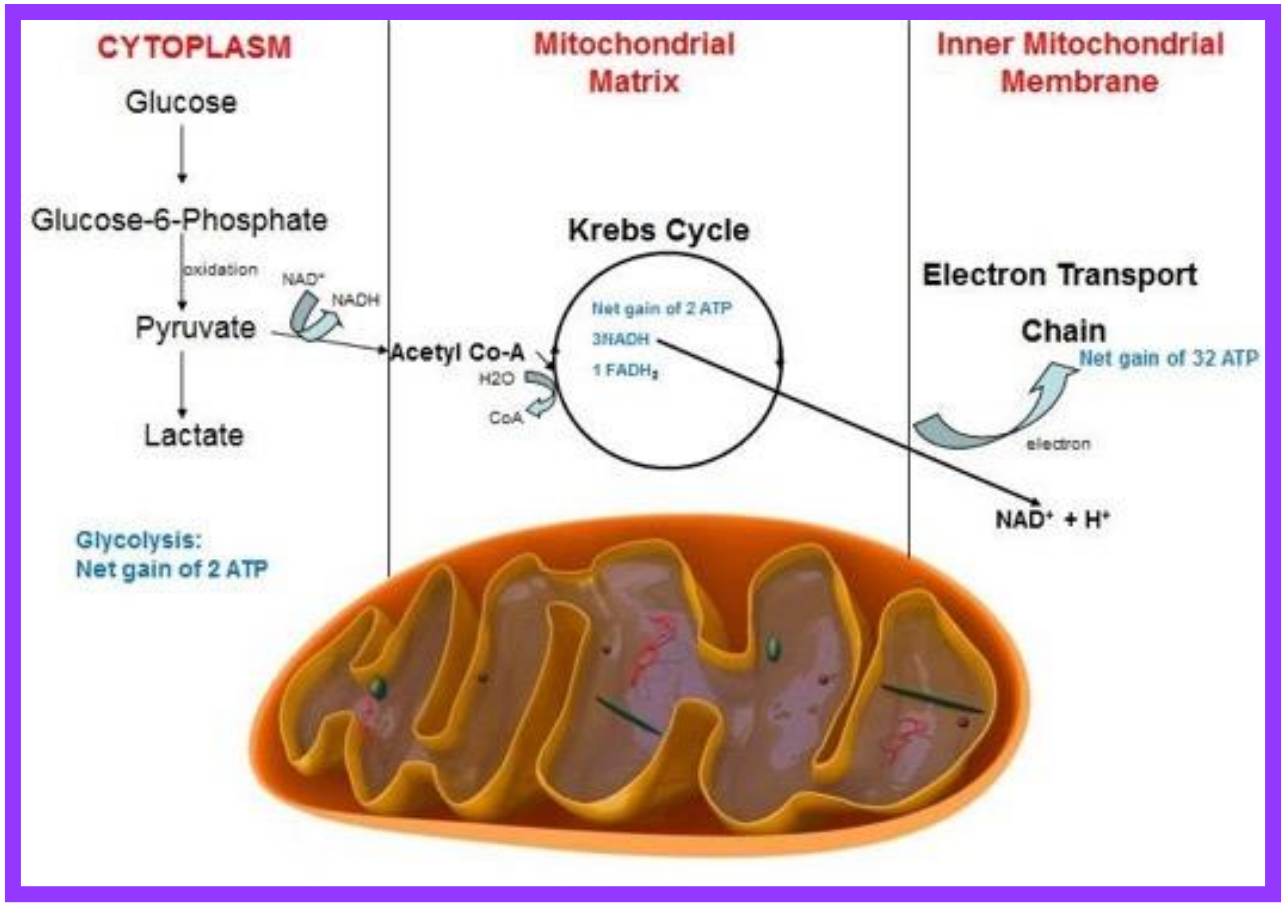


Mervyn Singer
self described "Mitochondriac"



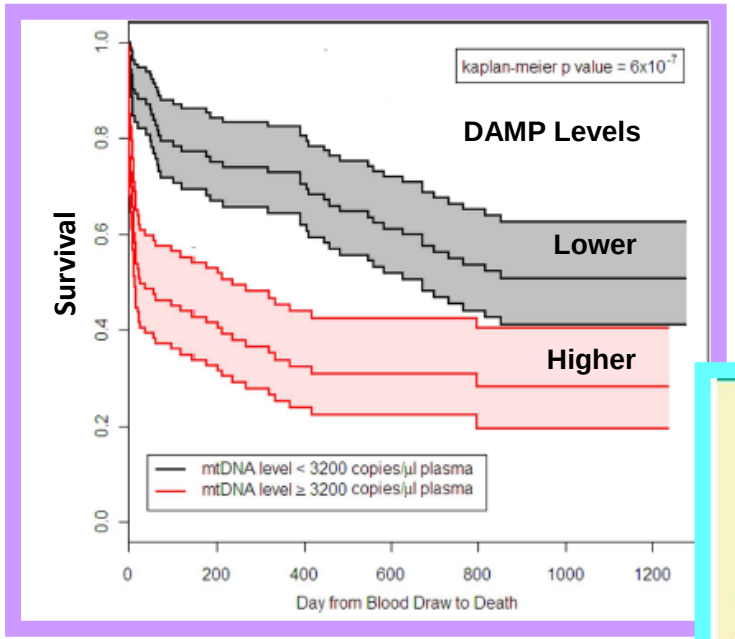
SA McClave, PE Wischmeyer, KR Miller, ARH van Zanten (Current Nutrition Reports 2019)

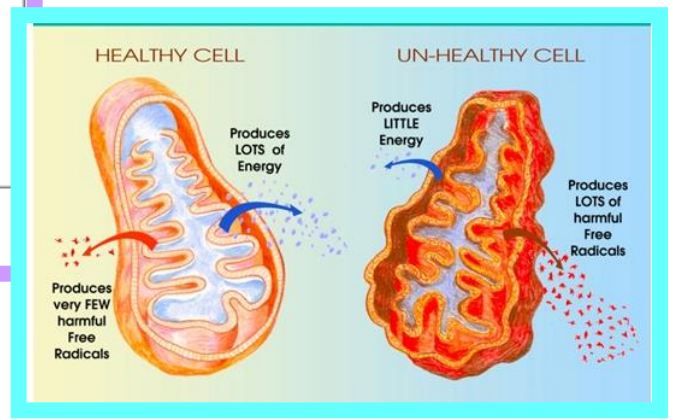
Deterioration of Normal Mitochondrial Function

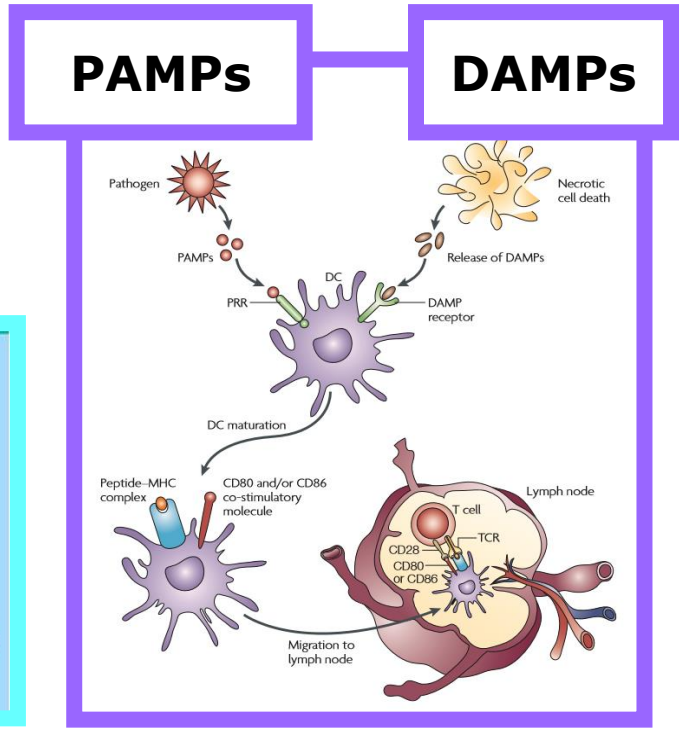


- **ATP generation: Less with Glycolysis than with Krebs Cycle and ETC**
- **Lactic acidosis: Sign of mitochondrial dysfunction**

Signalling from Dysfunctional Mitochondria: Leaking Mitochondrial DNA

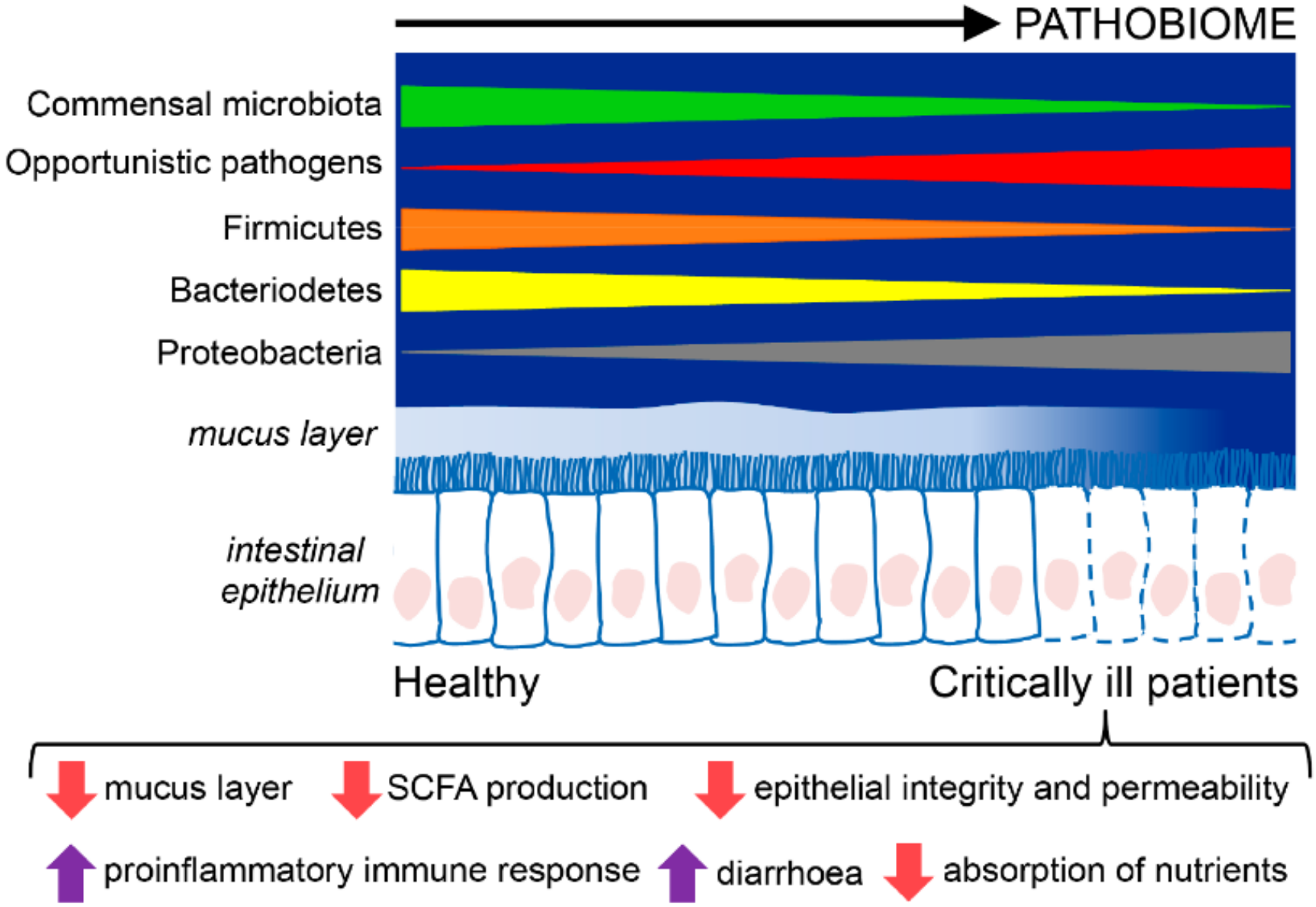






- Leaking mitochondria spill mDNA into circulation (act as DAMPs)
- DAMPs bind to Toll-Like Receptors (TLRs), trigger danger signals
- Process linked to MOF, reduced survival

KM Mogensen (JPEN 2017;41:188)



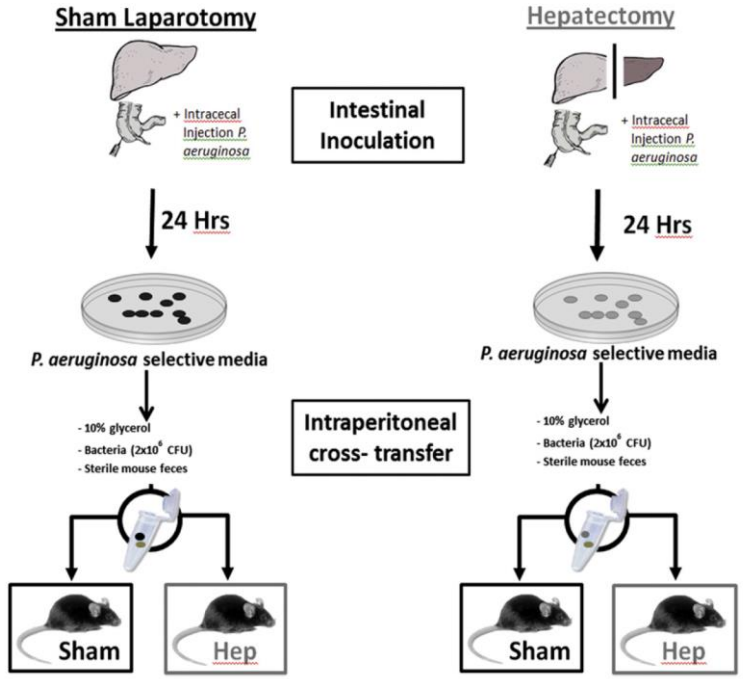
- **Loss of biodiversity**
- **Toxic lymph**
- **Quorum sensing**
- **change to virulence phenotype**
- **adherence**
- **biofilm formation**

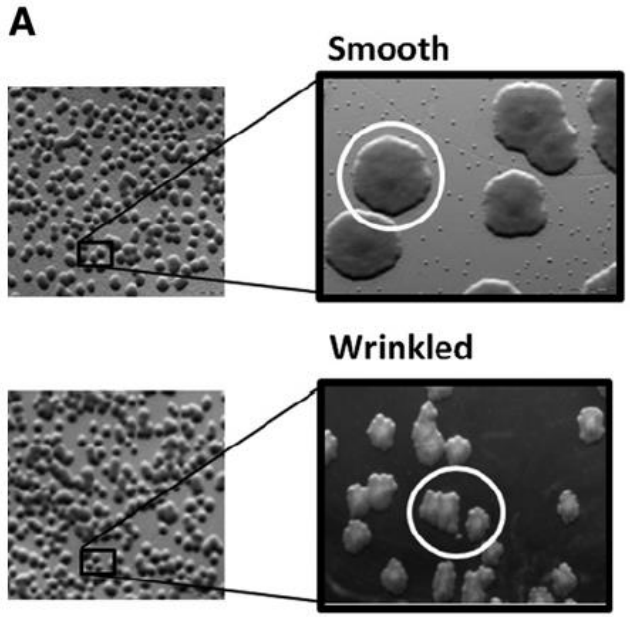
Moron, Nutrients, 2019
Guyton K , Alverdy J et al Nature Rev GI 2018

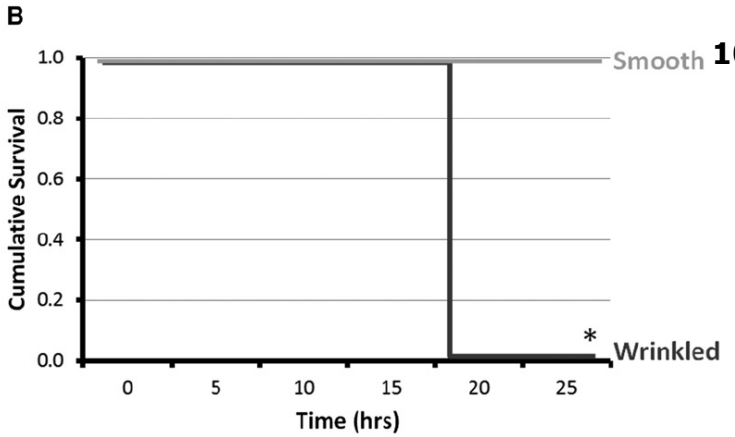
The intestinal environment of surgical injury transforms *Pseudomonas aeruginosa* into a discrete hypervirulent morphotype capable of causing lethal peritonitis

Surgery
Volume 153, Number 1
2013

Within 24 hours, a lethal *P. aeruginosa* morphotype develops







100% SURVIVAL

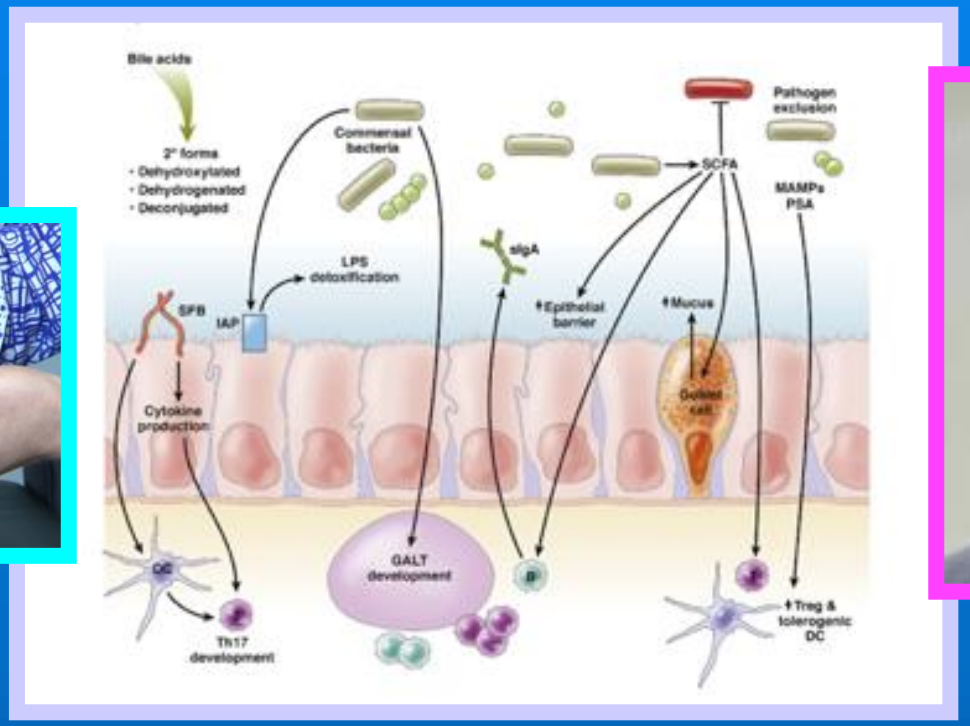
100% FATAL

Microbial phenotype- NOT species, NOT immune background- caused death
so then what actually drives sepsis outcome?
A delicate balance which when disrupted leads to system wide MOF !

Guyton K, Alverdy JC et al Nature Rev GI 2016
Babrowski M, et al Surgery 2013

Effect of SCFAs on the GUT

Butyrate Effect: "Master and Commander"



John Alverdy

Protective Effects: Competitive exclusion of pathogens

- Enhance epithelial barrier fxn
- Promote tolerance (Treg)
- Stimulate protective mucus
- Increase IgA production
- Inhibit NFkB
- Stabilizes hypoxia-inducible factor

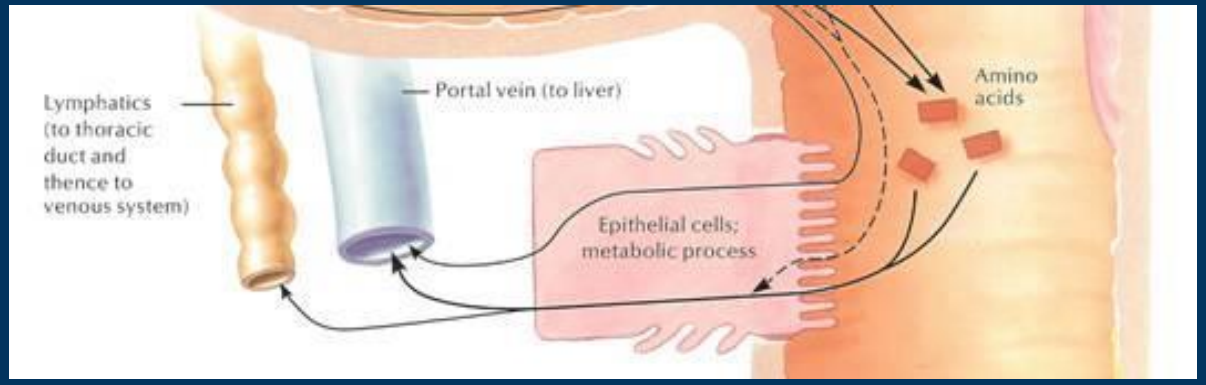
CL Ohland (Cell Molec Gastro Hepat 2015)
M Latorre (World J Gastro 2015)
R Dickson (Lancet Respir 2016)
Alverdy, Gershuni (Nat Rev Gastr Hep 2021)

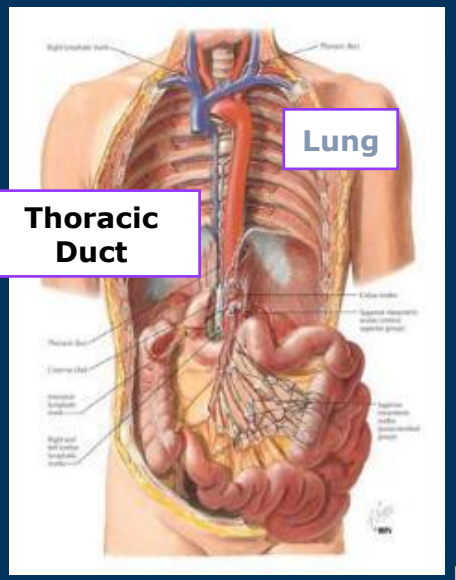
Toxic Gut-Derived Lymph Theory

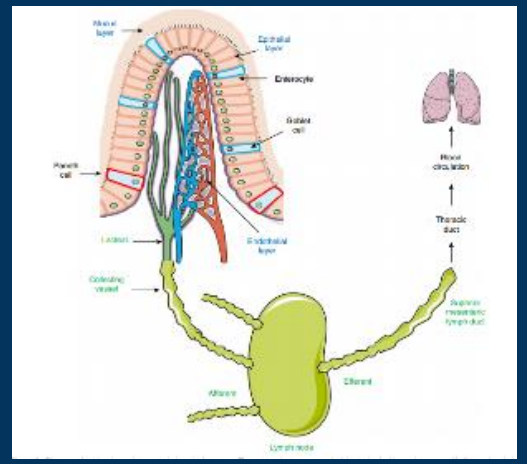
- Early potential factors questioned:
- Live bacteria (cultures neg)
- Bacterial products, endotoxin
- DAMPs / alarmins, mtDNA etc
- Cytokines (proteomics negative)
- Role of chylomicrons
- Newer evidence suggests toxic lymph has:
  - Pancreatic proteases
  - Pancreatic lipoprotein lipase
  - Free fatty acids

Toxic lymph

- induces endothelial toxicity
- ligation pancreatic duct ↓toxicity







Deitch Ann NY Acad Sci 2010,
Mittal et al Trends Molec Med 2014,
Ma Y et al Translational Reviews 2021

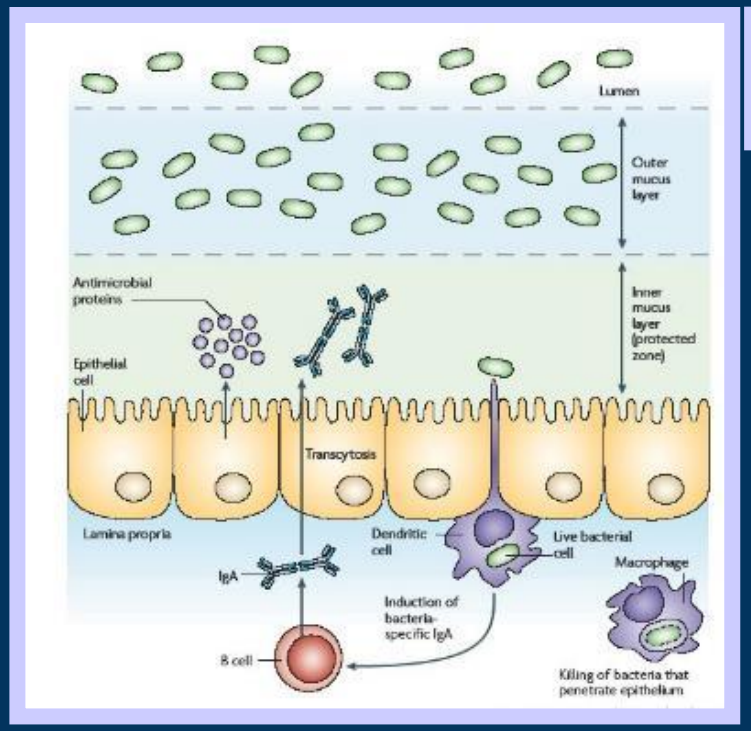
Autodigestion Syndrome

Mucus layer hydrophobic barrier

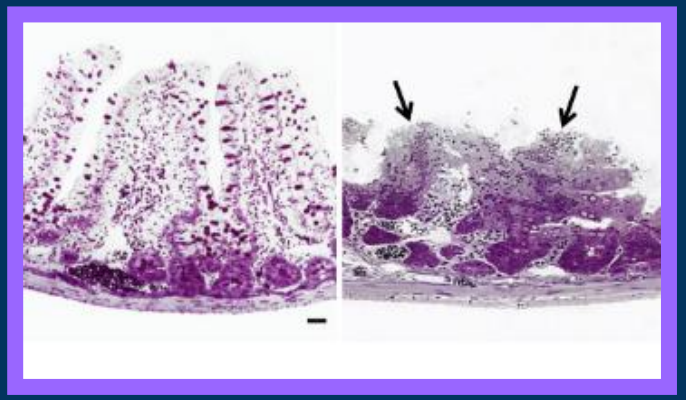
Thinning allows contact pancreatic enzymes

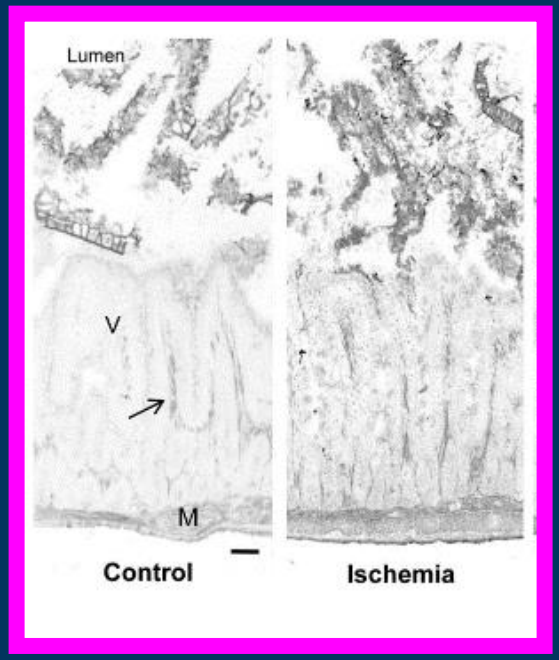
Digestive enzymes enter -disrupt epithelium

Proteases in plasma, PV, peritoneum



Thinning of mucus



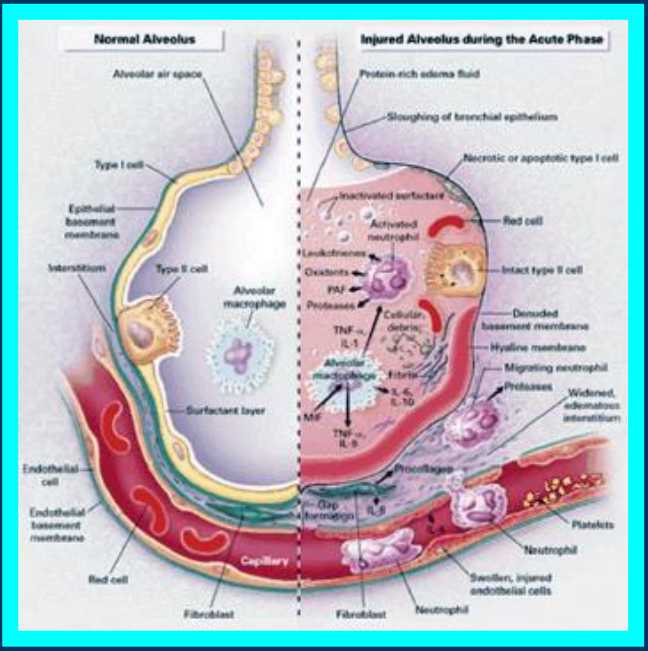


Mittal Trends Mol Med 2014
Schmid-Schonbein Ann Biomed Eng 2014
Meng M et al Curr Opin Crit Care 2017
Zhou Q et al JCI 2018

Why do other Organs Fail?
The Lungs

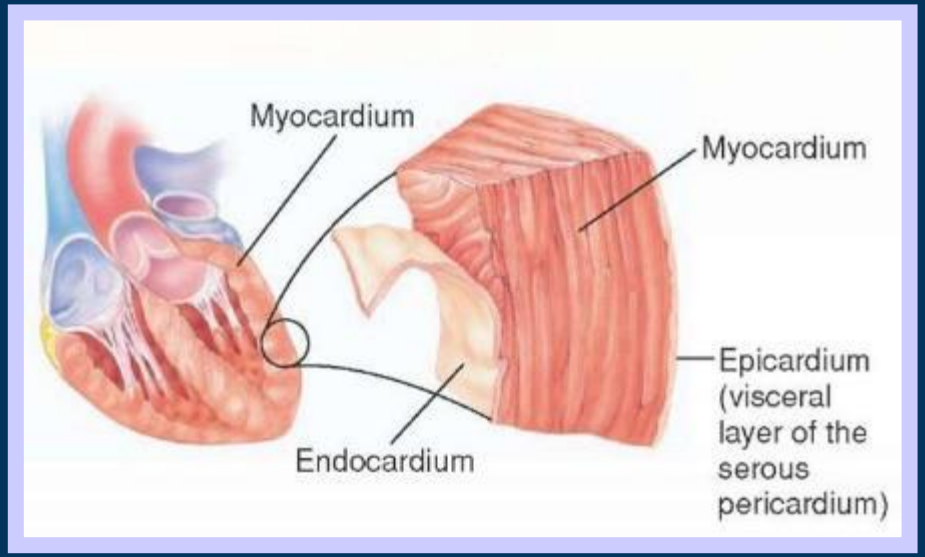
- **Lungs are earliest manifestation of gut-origin MOF**

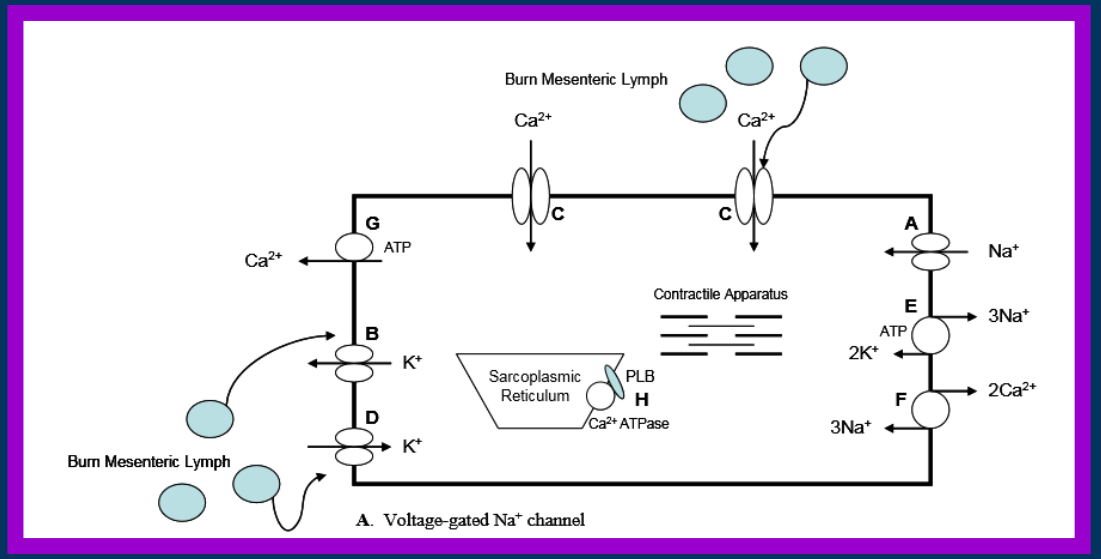
- **Augmentation of non-microbial inflammatory state (SIRS):**
  - **Direct injury to gut not required**
  - **Lymph mediates delivery of toxic mediators (toxic lymph mechanism)**
  - **Toxic mediators interact with TLR4**
  - **Injury to vascular endothelium, priming PMNs**
  - **Pulmonary leuko-sequestration**
  - **Tissue injury at distant sites (ALI/ARDS)**



DC Reino (Shock 2012;38:107)

Why do other Organs Fail?
The Heart

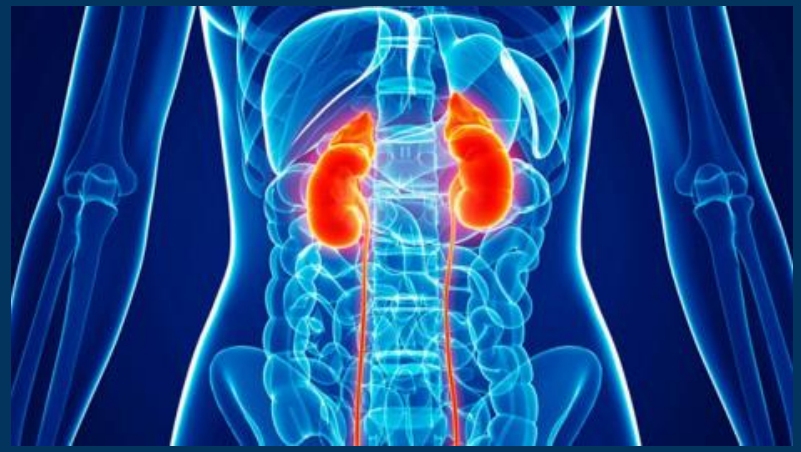




- **Stressed gut liberates pro-inflammatory tissue-injurious factors through lymph**
- **Gut-derived lymph induces contractile abnormalities two ways:**
  - **1) Affect cardiomyocyte ionic channels to ↓contractile function**
  - **2)Cardiac inflammation leads to ↑cardio-depressant molecules (TNF, NO)**

MA Lee (Int J Clin Exp Med 2008;1:171)
Dal-Secco D et al Am J Physiol, Heart Circ 2017

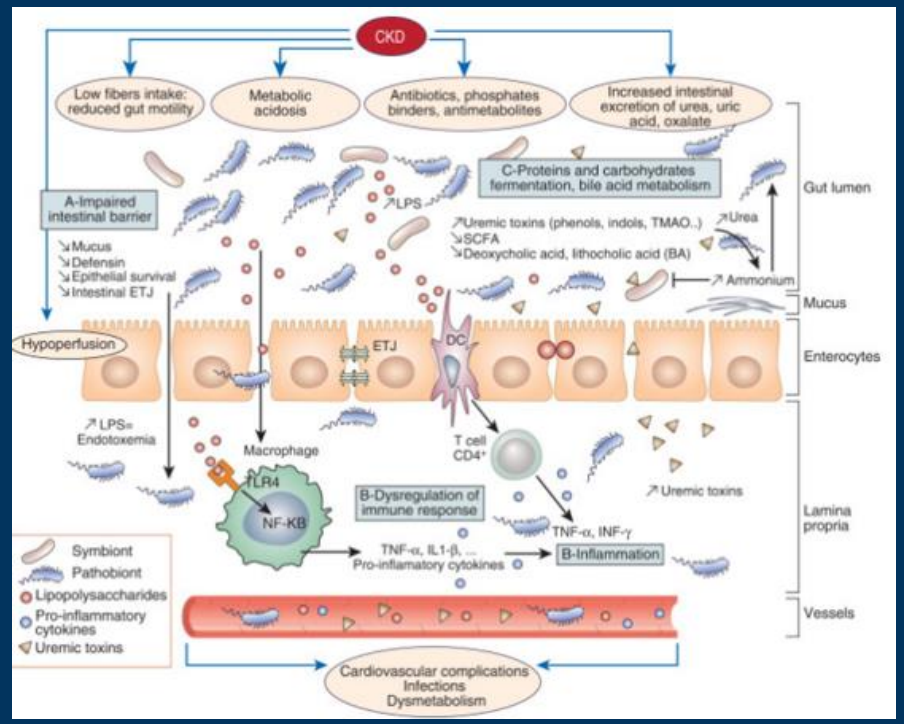
Why do other Organs Fail? The Kidney



The Gut Kidney Axis

- Gut releases
  - Advanced glycation end products
  - Phenols
  - Indoles
  - Thiols

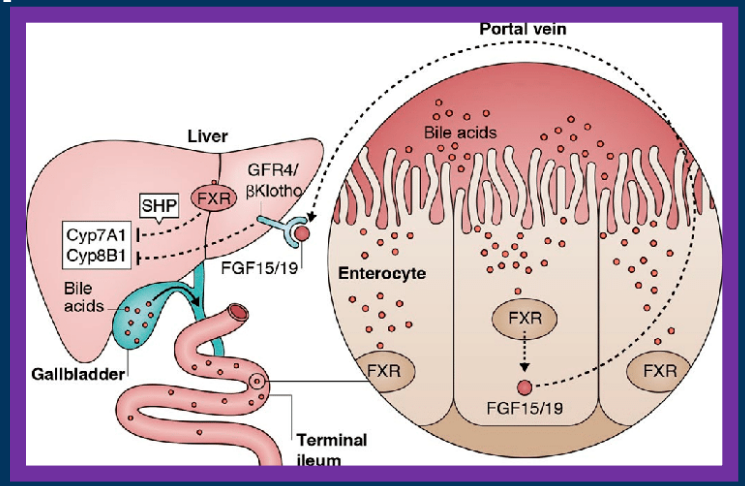
- CKD effects on gut permits translocation of gut derived uremic toxins
  - Progression of CKD, myocardial injury, insulin resistance
  - Sets up systemic inflammatory state

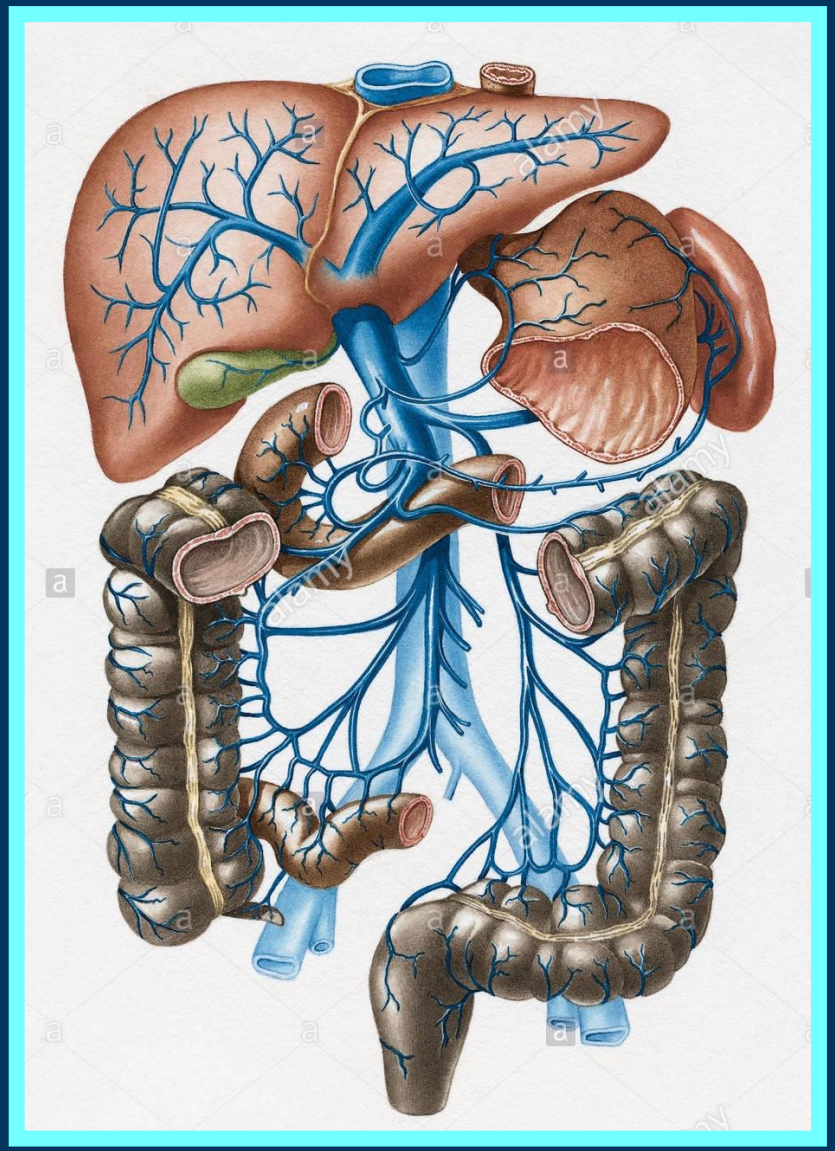


Khoury T et al Hemodialysis International 2017
Ramezani A et al Am J Kidney Dis 2016
Koppe L et al Kidney International 2015

Gut-Liver Axis

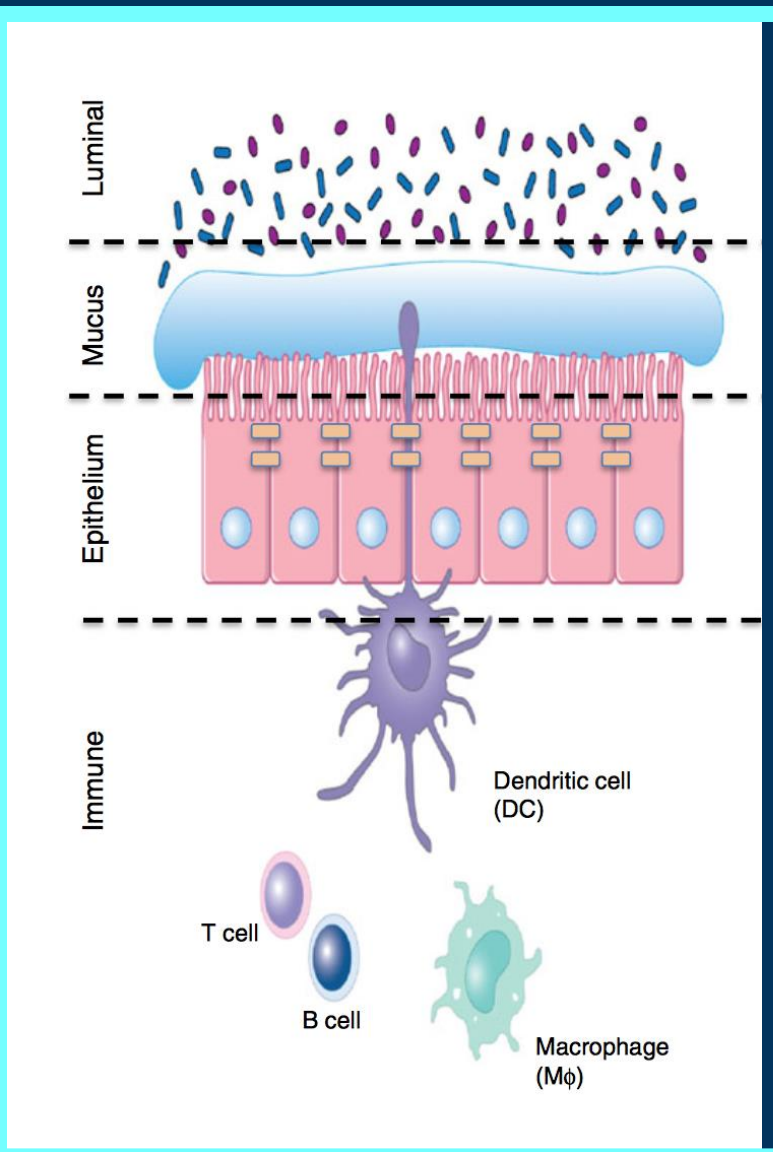
- General effect of Liver
  - Tolerance, ↓ inflammation responses
  - Bacterial clearance
- BAs and Farnesoid X Receptor (FXR)
  - Bactericidal activity
  - ↟ Glucose tolerance, insulin sensitivity
  - ↓ Inflammation, fibrosis, liver injury
  - Supports mucosal barrier function
    - ↓ Permeability to endotoxin
    - Anti-apoptotic





P Pavlidis (Aliment Pharmacol Ther 2015;42:802)

Bile Salts as Signaling Molecules in Health



Anti-Microbial
Membrane toxicity (secretory)

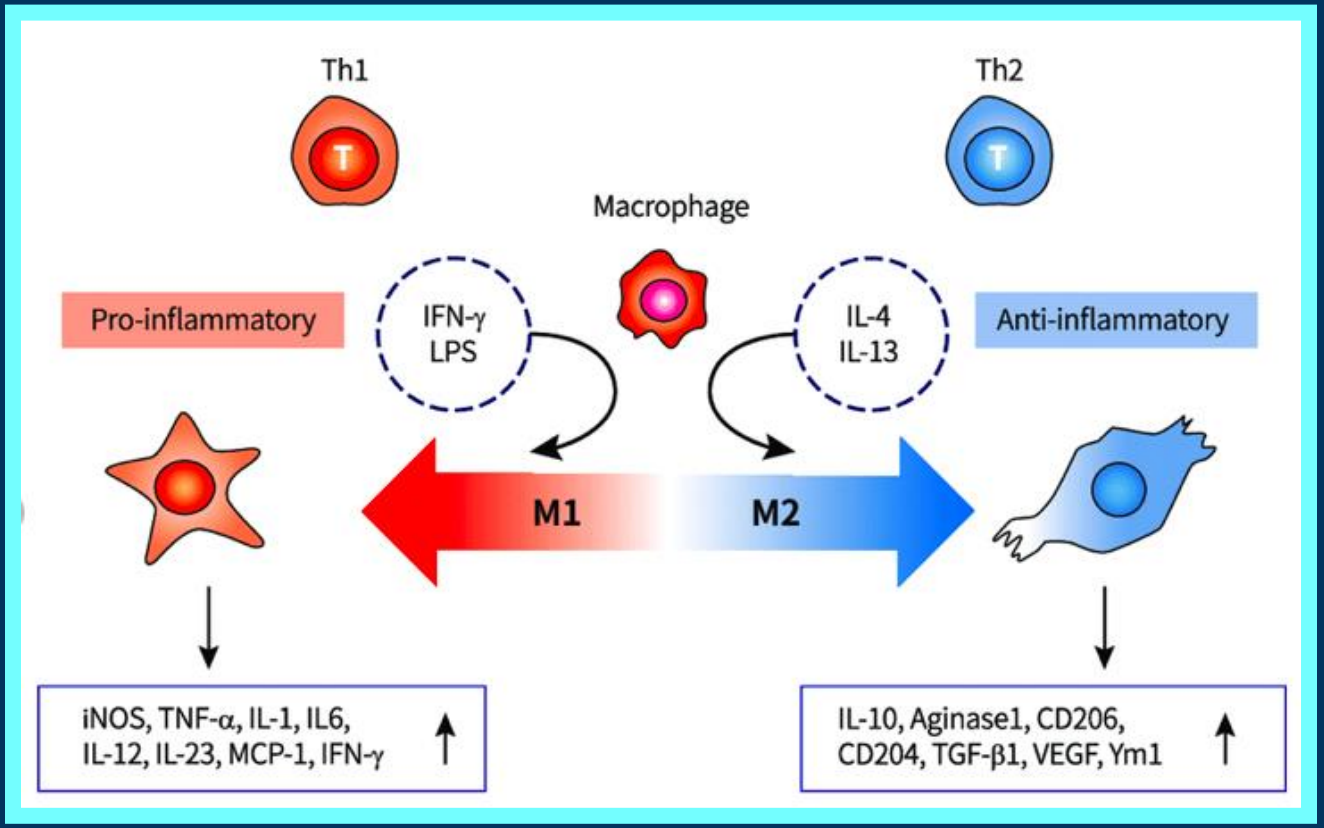
↑ Mucus

↓ Pro-Inflammatory cytokines
↑↑ Epithelial proliferation/repair
↓ ER stress
↑↑ Tight junctions

Immune modulation
Anti-Inflammatory effects on:
Macrophages, DC, Treg, and T cell differentiation

P Pavlidis (Aliment Pharmacol Ther 2015;42:802)

Macrophage Polarization



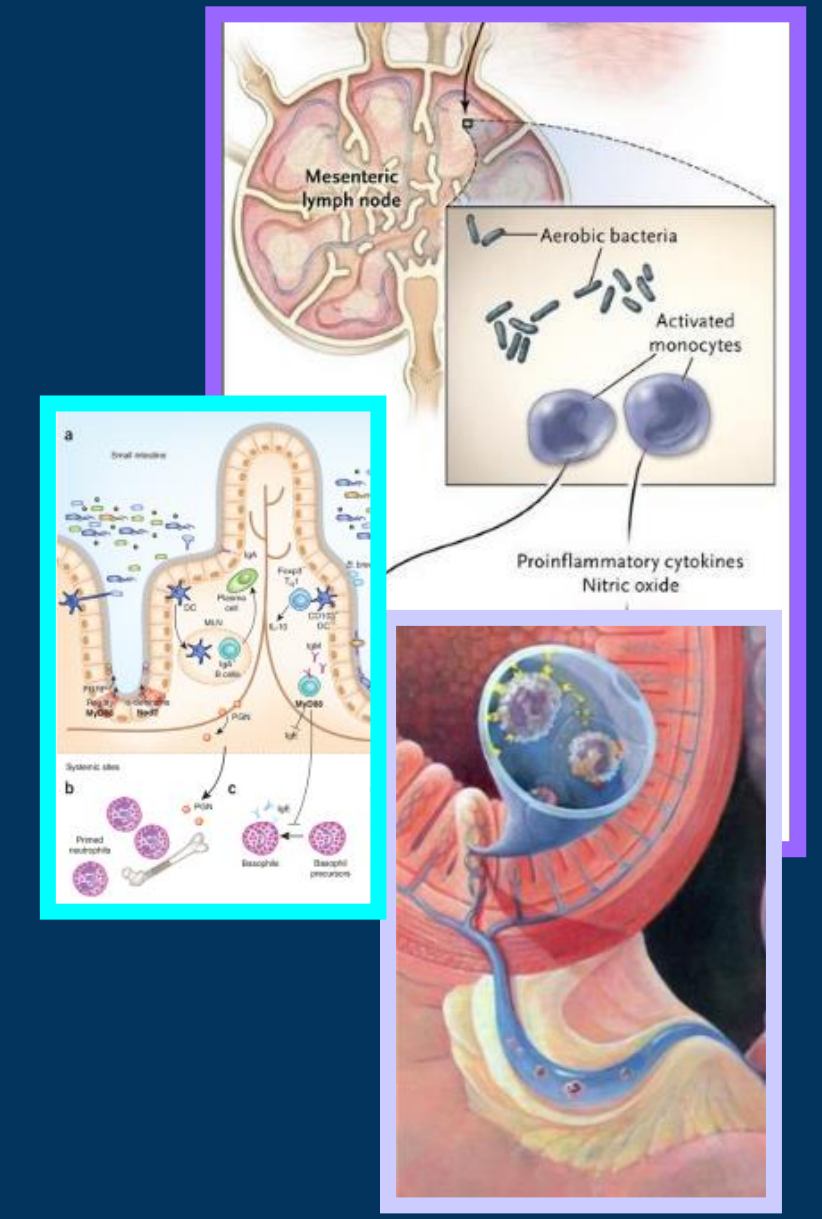
Located everywhere, intestine submucosa, liver (Kupffer), organ systems
Factors driving M1 to M2: Butyrate
Bile Acids
Omega-3 (Fish oil) SPMs (Resolvins)

What Connects Non-microbial Inflammatory States with Distant Organ Failure

- **Common denominators:**
  - **Toxic lymph (pancreatic enzymes, FFAs)**
  - **Activation of TLR4**
  - **Priming of PMNs**

- **Location not clear**
  - **Intestinal submucosa**
  - **Mesenteric LNs**
  - **Distant organ sites**

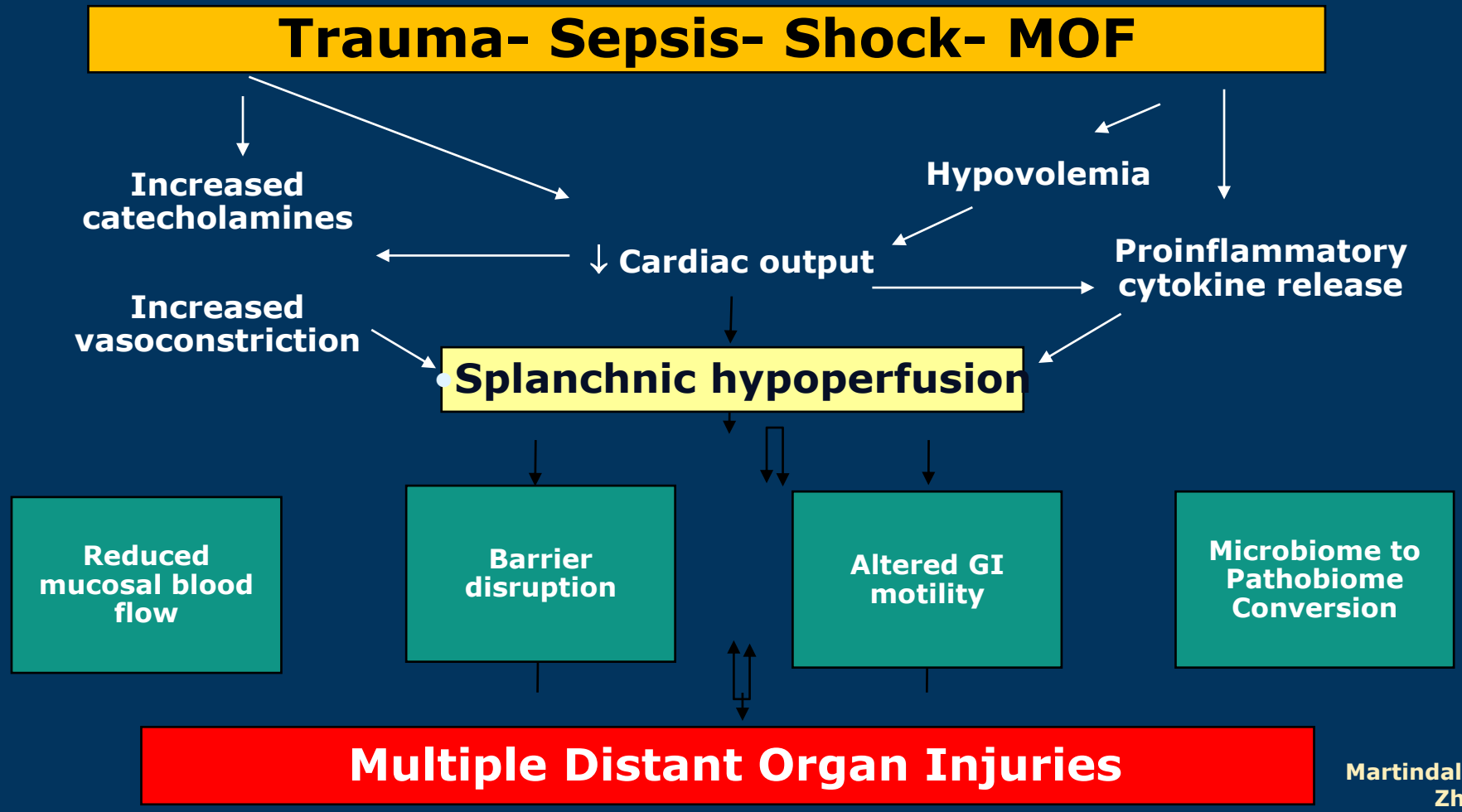
- **Process does reach systemic circulation**
  - **Toxic lymph (FFA) in plasma factor in ARDS**
  - **MAMP peptidoglycan primes PMNs in marrow**



X Qin (Am J Physio Gastro Liver Phys 2012;303:G969)
H Chu (Nat Immunol 2013;14:668)
DC Reino (Shock 2012;38:107)
EL Sarin (J Trauma 2004;57:950)

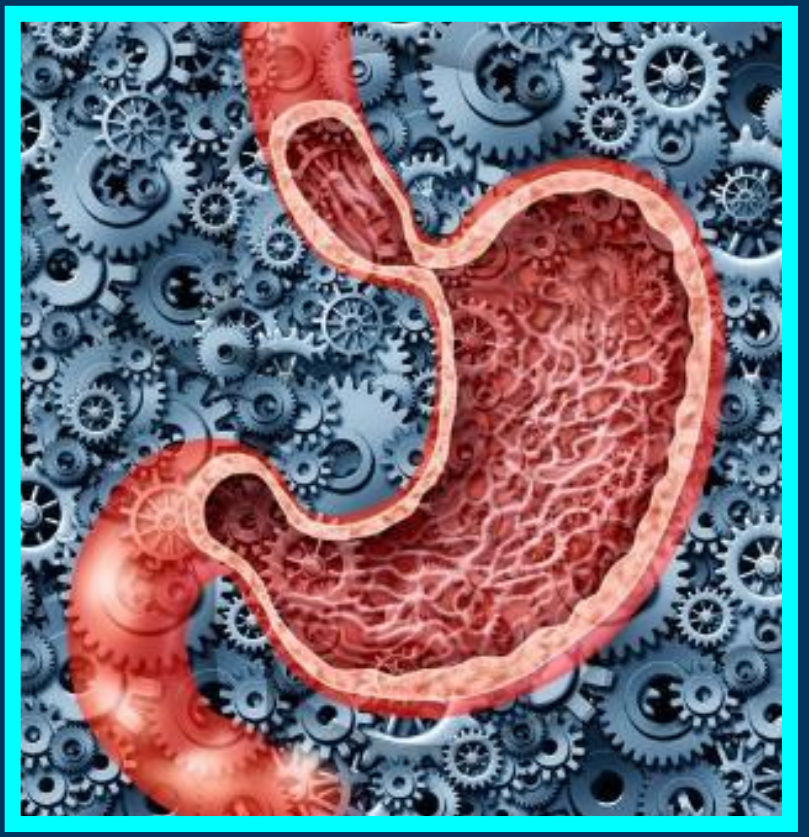
Pathophysiology of Gut Dysfunction Effects on Other Organs:

Immune function—Microbiome—Micro circulation--Mitochondria



Martindale R et al CCM 2014,
Zhou Q et al JCI 2018
Mutlu GM, et al. Chest. 2001

Conclusions



- Gut is still the “Motor of MOF”
- Impact on outcome related to:
  - Largest immune organ
  - Greatest interface with environment
  - Easy access to systemic circulation
- Mechanism of effect continues to be elucidated
  - Mitochondrial dysfunction and lack of biogenesis is the latest hot topic
- Promote early modulation of responses (low levels of EN, SCFAs, FO, probiotics)
- Understanding how gut physiology in health and homeostasis changes in critical illness affords Rx options

Insulin and glucose

Prof. Ho-Seong Han

FRESENIUS KABI
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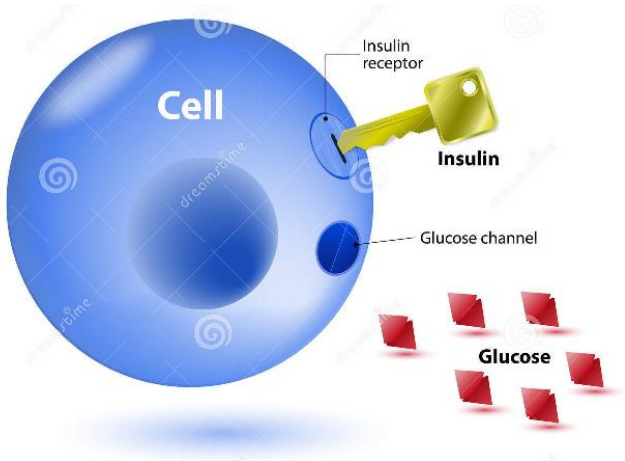
JUMPstart Training Program

Insulin and Glucose

Prof. Ho-Seong Han, M.D., Ph.D



Advanced module, Day 2, Part II: Confounding factors in the ICU

Contents

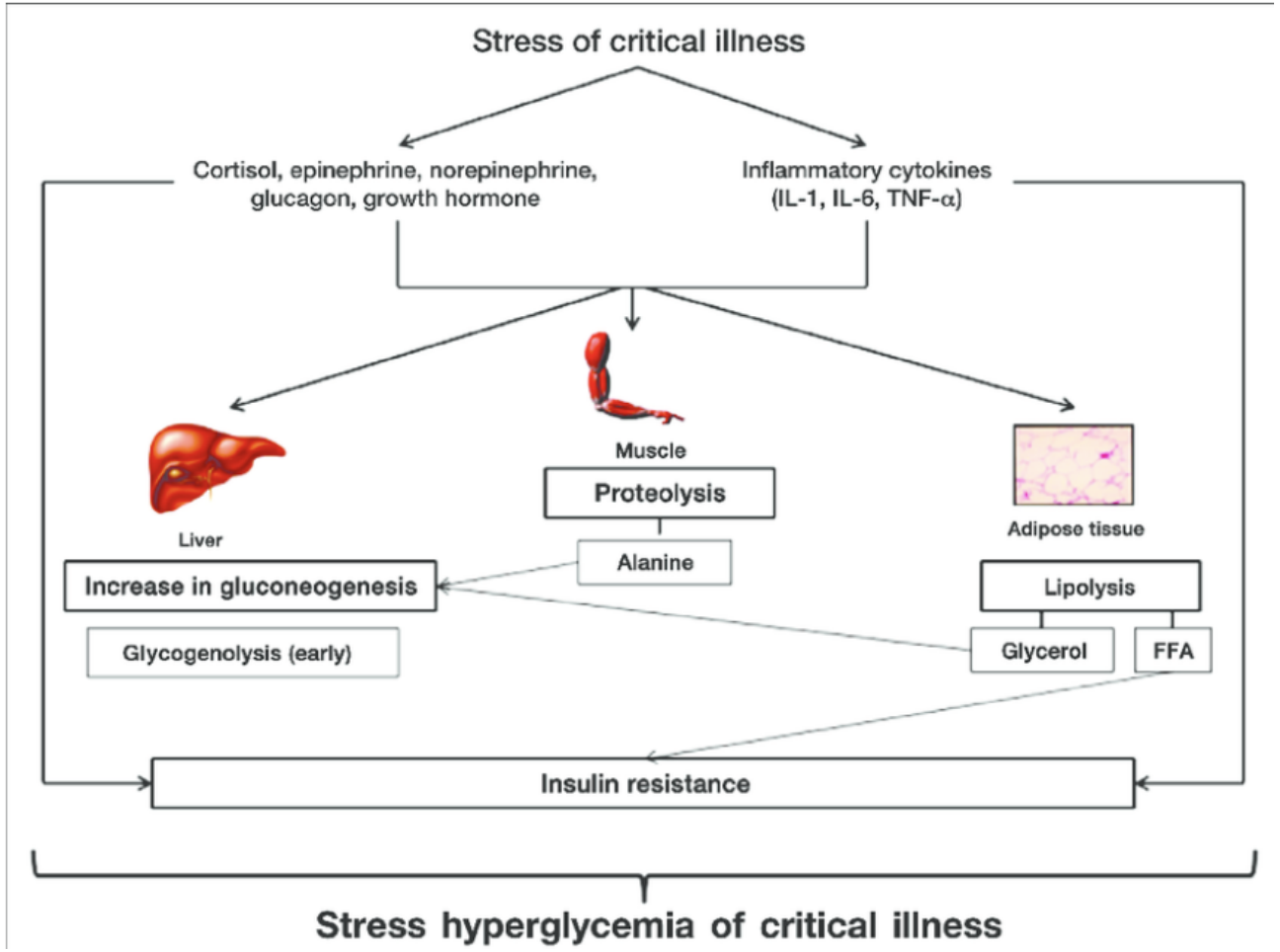
- Introduction
- Intensive Insulin Therapy
- Guideline

Introduction on

Insulin & Glucose

Insulin resistance in critical illness

- In critical illness, insulin resistance and hyperglycemia are common secondary to stress.



Singer P, et al. Clin Nutr 2014.

Glucose Metabolism in critical illness

- The optimal carbohydrate amount to administer is difficult to determine:
- Critical illness alters enteral nutrient absorption.
- Endogenous glucose production is increased and does not decrease even when nutrients and insulin are administered.

Deane AM et al. Crit Care Med 2014.

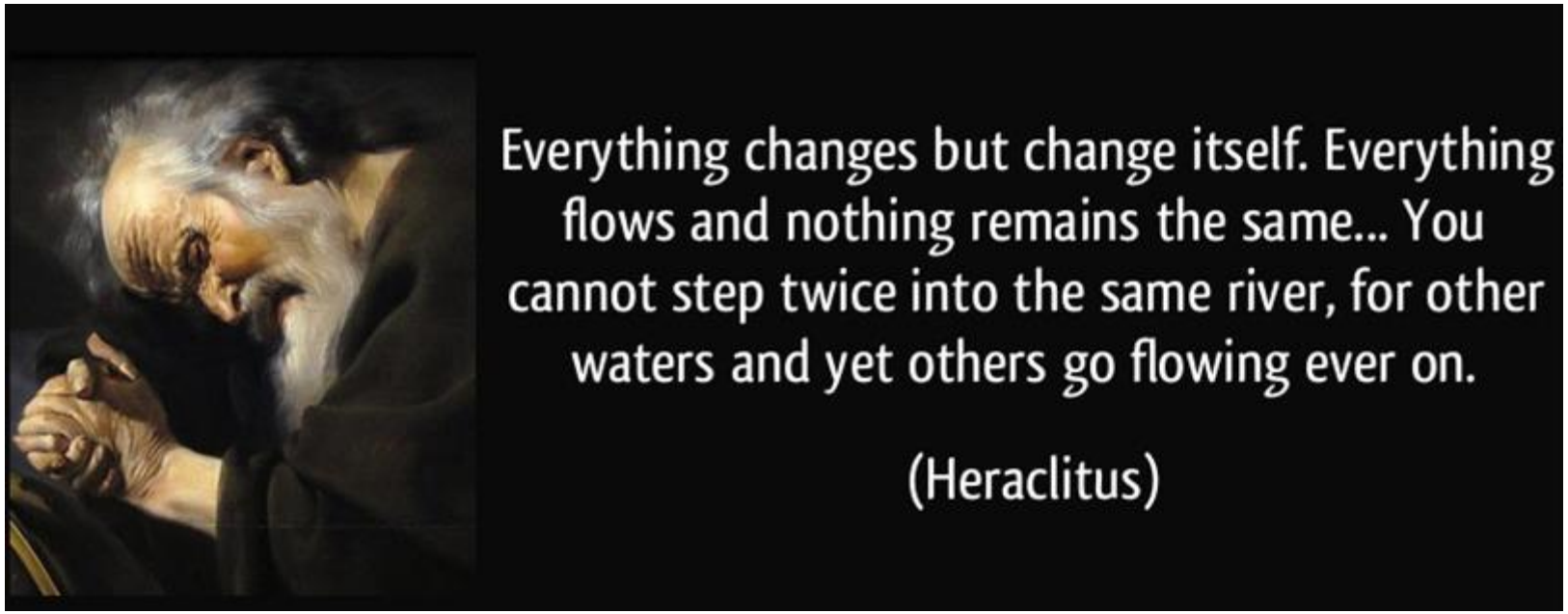
Thorell A, Rooyackers O, et al J Clin Endocrinol Metabol 2014.

Problems of Excessive Glucose

- Excessive glucose is associated with hyperglycemia, enhanced CO2 production, enhanced lipogenesis, increased insulin requirements and no advantage in protein sparing.

Tappy L et al Crit Care Med 1998

Intensive Insulin Therapy



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The New England Journal of Medicine

VOLUME 345 NOVEMBER 8, 2001 NUMBER 19

INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS

GREET VAN DEN BERGHE, M.D., PH.D., PIETER WOUTERS, M.SC., FRANK WEEKERS, M.D., CHARLES VERWAEST, M.D., FRANS BRUYNINCKX, M.D., MIET SCHETZ, M.D., PH.D., DIRK VLASSELAERS, M.D., PATRICK FERDINANDE, M.D., PH.D., PETER LAUWERS, M.D., AND ROGER BOUILLON, M.D., PH.D.

Van den Berghe G, et al. N Engl J Med 2001

TABLE 2. INSULIN THERAPY AND CONTROL OF BLOOD GLUCOSE LEVELS.*

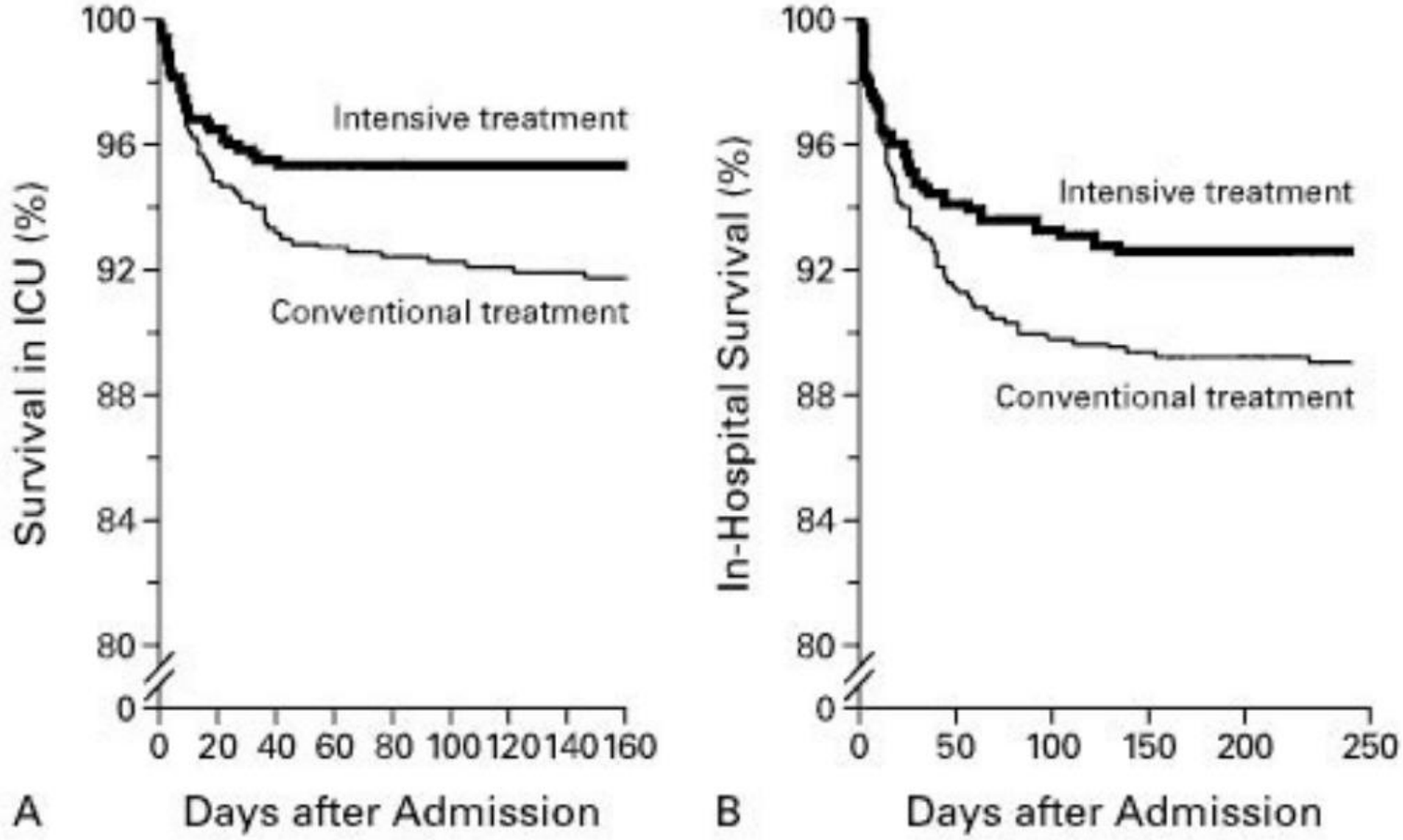
VARIABLE	CONVENTIONAL TREATMENT (N=783)	INTENSIVE TREATMENT (N=765)	P VALUE†
Administration of insulin — no. (%)	307 (39.2)	755 (98.7)	<0.001
Insulin dose — IU/day‡			
Median	33	71	
Interquartile range	17–56	48–100	<0.001
Duration of insulin use — % of ICU stay			
Median	67	100	<0.001
Interquartile range	40–100		
Morning blood glucose — mg/dl§			
All patients	153±33	103±19	<0.001
Patients receiving insulin	173±33	103±18	<0.001

Van den Berghe G, et al. N Engl J Med 2001

TABLE 3. MORTALITY.

VARIABLE	CONVENTIONAL TREATMENT (N=783)	INTENSIVE TREATMENT (N=765)	P VALUE*
Death during intensive care — no./total no. (%)	63/783 (8.0)	35/765 (4.6)	<0.04 (adjusted)
During first 5 days of intensive care	14/783 (1.8)	13/765 (1.7)	0.9
Among patients receiving intensive care for >5 days	49/243 (20.2)	22/208 (10.6)	0.005
In-hospital death — no./total no. (%)			
All patients	85/783 (10.9)	55/765 (7.2)	0.01
Patients receiving intensive care for >5 days	64/243 (26.3)	35/208 (16.8)	0.01

Van den Berghe G, et al. N Engl J Med 2001



Van den Berghe G, et al. N Engl J Med 2001

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TABLE 4. MORBIDITY.*

VARIABLE	CONVENTIONAL TREATMENT (N=783)	INTENSIVE TREATMENT (N=765)	P VALUE†
Duration of intensive care — days			
All patients			
Median	3	3	0.2
Interquartile range	2–9	2–6	
≤5 Days			
Median	2	2	0.2
Interquartile range	2–3	2–3	
>5 days			
Median	15	12	0.003
Interquartile range	9–27	8–20	
Bloodstream infection — no. (%)			
Septicemia during intensive care	61 (7.8)	32 (4.2)	0.003
Treatment with antibiotics for >10 days	134 (17.1)	086 (11.2)	<0.001
Electromyographic evidence of critical-illness polyneuropathy — no./total no. (%)			
At any time	107/206 (51.9)	45/157 (28.7)	<0.001
On more than 2 occasions	39/206 (18.9)	11/157 (7.0)	0.001

Van den Berghe G, et al. N Engl J Med 2001

Subsequent Article after the Reports

- Hemodynamic and metabolic therapy in critically ill patients. [N Engl J Med. 2001]
- Intensive insulin therapy reduced mortality and morbidity in critically ill patients. [ACP J Club. 2002]
- Intensive insulin therapy in critically ill patients. [N Engl J Med. 2002]
- Intensive insulin treatment reduced mortality and morbidity in critically ill patients. [Evid Based Nurs. 2002]
- Benefits of intense glucose control in critically ill patients. [Curr Surg. 2005]
- Utility of intensive blood glucose control: generalizable to all general surgery patients? [Nutr Clin Pract. 2004]
- Intensive insulin therapy in the medical ICU. [N Engl J Med. 2006]
- Understanding the clinical issues involved with glycemic control in the intensive care unit. [Curr Gastroenterol Rep. 2011]

Comments on this Article

- Severely ill patients in intensive care units have a “cytokine storm” with release of tumor necrosis factor α (TNF-α) and macrophage inhibitory factor.
- Insulin has been shown to inhibit TNF-α ; it is also likely that the infusion of glucose and insulin inhibits macrophage inhibitory factor.
- The intensive insulin therapy cause action of insulin on these cytokines.
- Given the practical difficulty involved in maintaining normoglycemia in critically ill patients in community hospitals and the potential dangers associated with attempts to maintain normoglycemia, it is important not to assume that these results are wholly attributable to the normalization of blood glucose levels

Hirsch I B & Coviello A. N Engl J Med, 2002

The NEW ENGLAND JOURNAL of MEDICINE

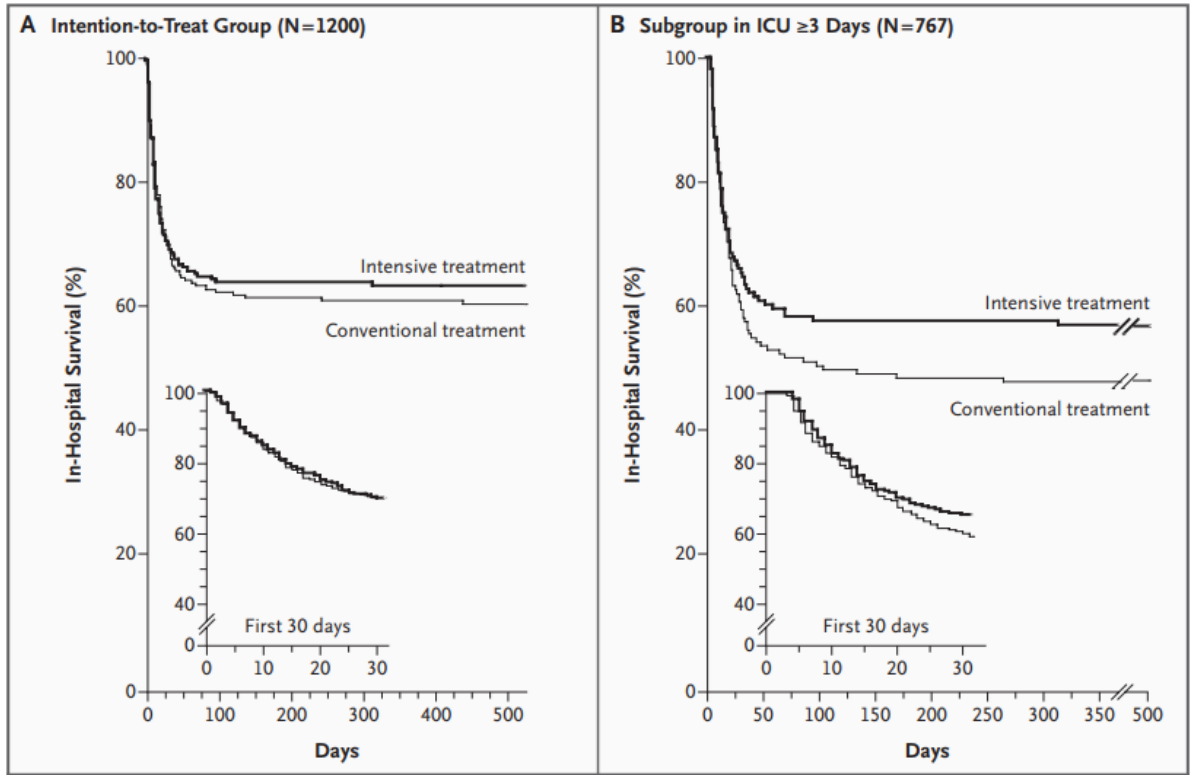
ESTABLISHED IN 1812 FEBRUARY 2, 2006 VOL. 354 NO. 5

Intensive Insulin Therapy in the Medical ICU

Greet Van den Berghe, M.D., Ph.D., Alexander Wilmer, M.D., Ph.D., Greet Hermans, M.D., Wouter Meersseman, M.D., Pieter J. Wouters, M.Sc., Ilse Milants, R.N., Eric Van Wijngaerden, M.D., Ph.D., Herman Bobbaers, M.D., Ph.D., and Roger Bouillon, M.D., Ph.D.

Outcomes of the Study I

- Intensive insulin therapy has no benefit on mortality in medical ICU.
- Significantly greater occurrence of hypoglycemia in the IIT group (18.7% vs. 3.1%, p<0.001)



Van den Berghe G, et al. N Engl J Med 2006

Outcomes of the Study II

- Intensive insulin therapy significantly reduced morbidity in medical ICU.

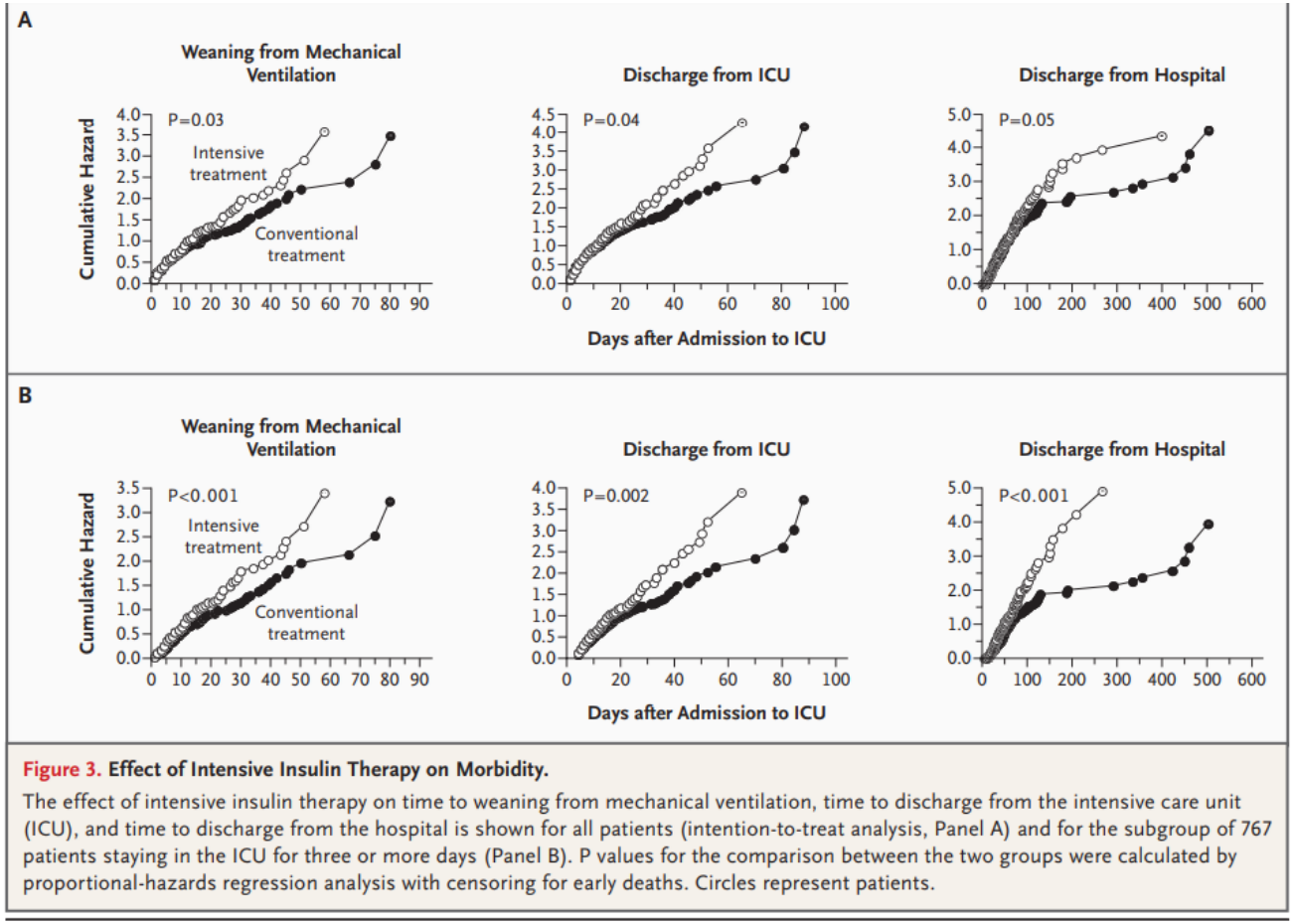


Figure 3. Effect of Intensive Insulin Therapy on Morbidity.

The effect of intensive insulin therapy on time to weaning from mechanical ventilation, time to discharge from the intensive care unit (ICU), and time to discharge from the hospital is shown for all patients (intention-to-treat analysis, Panel A) and for the subgroup of 767 patients staying in the ICU for three or more days (Panel B). P values for the comparison between the two groups were calculated by proportional-hazards regression analysis with censoring for early deaths. Circles represent patients.

Van den Berghe G, et al. N Engl J Med 2006

Journal club critique

Intensive insulin therapy in the medical ICU — not so sweet?

Kyoko Yamada[1], Eric B. Milbrandt[2], and Jason Moore[2]

[1] Clinical Fellow, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA
[2] Assistant Professor, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

Published online: 10th August 2007
This article is online at http://ccforum.com/content/11/4/311

Critical Care 2007, 11: 311 (DOI 10.1186/cc5953)

- IIT may be an important treatment modality in certain critically ill patient populations, such as those who have undergone cardiac surgery.
- Clinicians should consider the potential risks and benefits when implementing IIT in medical ICU patients
- Avoid this treatment modality in those with hepatic or renal failure

Yamada K. et al. Critical Care 2007

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

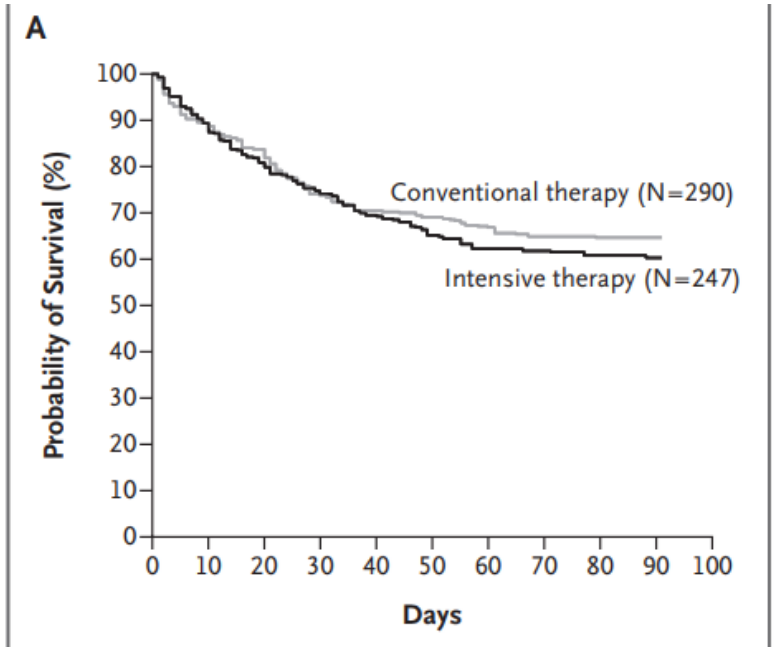
Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis

Frank M. Brunkhorst, M.D., Christoph Engel, M.D., Frank Bloos, M.D., Ph.D., Andreas Meier-Hellmann, M.D., Max Ragaller, M.D., Norbert Weiler, M.D., Onnen Moerer, M.D., Matthias Gruendling, M.D., Michael Oppert, M.D., Stefan Grond, M.D., Derk Olthoff, M.D., Ulrich Jaschinski, M.D., Stefan John, M.D., Rolf Rossaint, M.D., Tobias Welte, M.D., Martin Schaefer, M.D., Peter Kern, M.D., Evelyn Kuhnt, M.Sc., Michael Kiehntopf, M.D., Christiane Hartog, M.D., Charles Natanson, M.D., Markus Loeffler, M.D., Ph.D., and Konrad Reinhart, M.D., for the German Competence Network Sepsis (SepNet)

Brunkhorst FM et al. N Engl J Med, 2008

Outcomes of the Study

- Intensive insulin therapy has no measurable benefit in critically ill patients.
- This therapy increases the risk of hypoglycemic episodes.

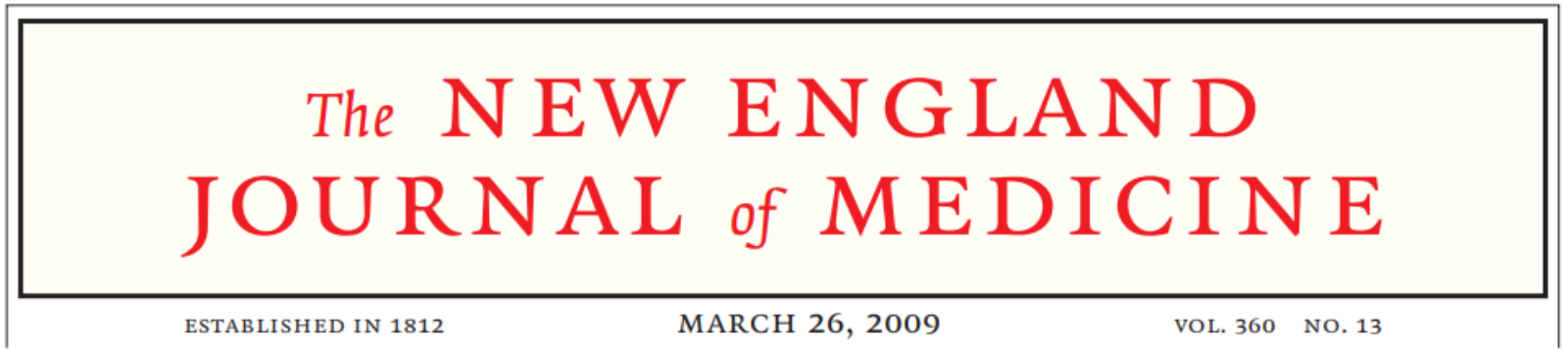


Brunkhorst FM et al. N Engl J Med, 2008

Comments on Van Den Berghe' first Study

beneficial effect was predominantly seen in cardiac surgical patients (accounting for 62% of the study population) who were given intravenous glucose loads (200 to 300 g per 24 hours) on admission to the ICU. It is possible that intensive insulin therapy was beneficial in these patients because it decreased the adverse effect of this high glucose load.

Brunkhorst FM et al. N Engl J Med, 2008

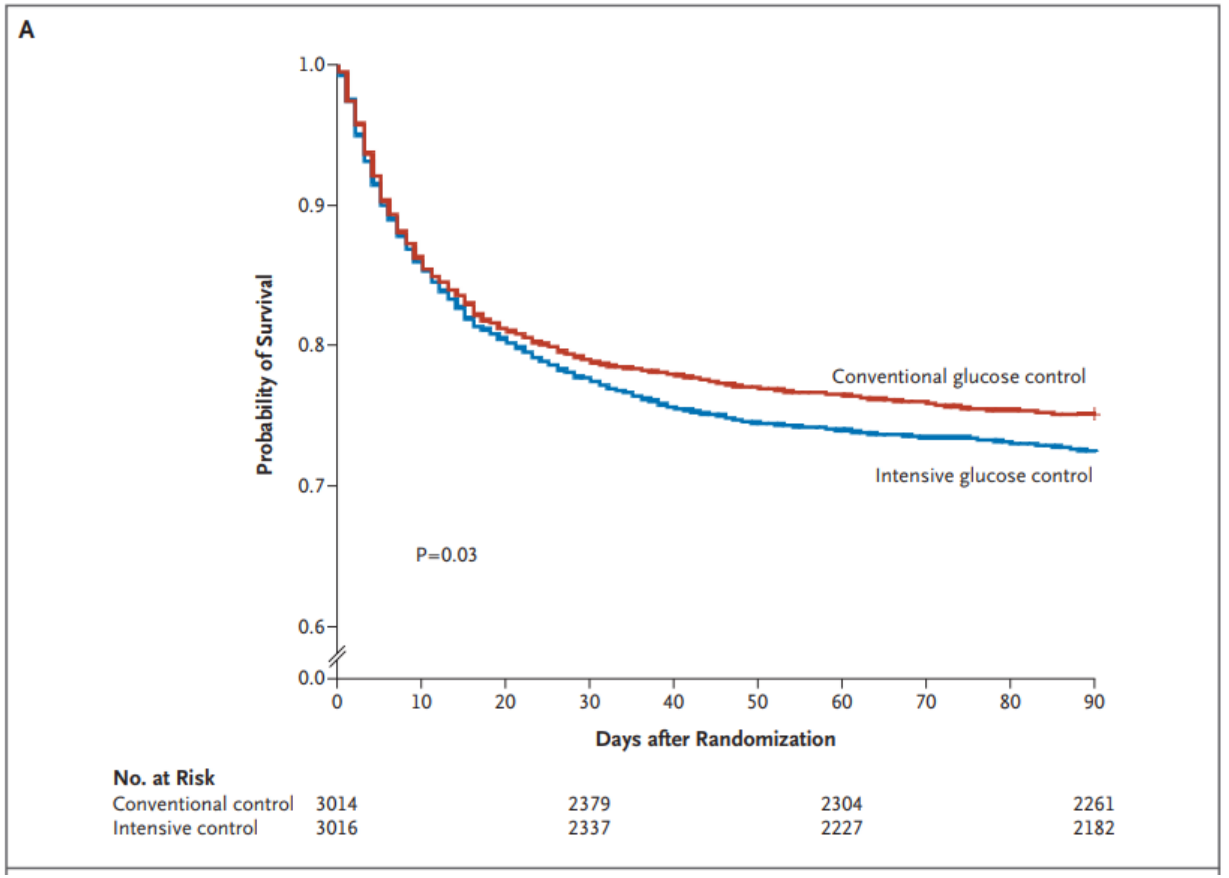


Intensive versus Conventional Glucose Control in Critically Ill Patients

The NICE-SUGAR Study Investigators*

NICE-SUGAR Study Investigators. N Engl J Med 2009

Probability of Survival between two Group



NICE-SUGAR Study Investigators. N Engl J Med 2009

Conclusion of the Study

- Our findings suggest that a goal of normoglycemia for glucose control does not necessarily benefit critically ill patients and may be harmful.
- The harm resulted from the reduced blood glucose level, increased administration of insulin, occurrence of hypoglycemia.
- Blood glucose target of less than 180 mg resulted in lower mortality than a target of 81 to 108 mg.
- We do not recommend use of the lower target in critically ill adults.

NICE-SUGAR Study Investigators. N Engl J Med 2009

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hypoglycemia and Risk of Death in Critically Ill Patients

The NICE-SUGAR Study Investigators*

N Engl J Med 2012;367:1108-18.

NICE-SUGAR Study Investigators. N Engl J Med 2012

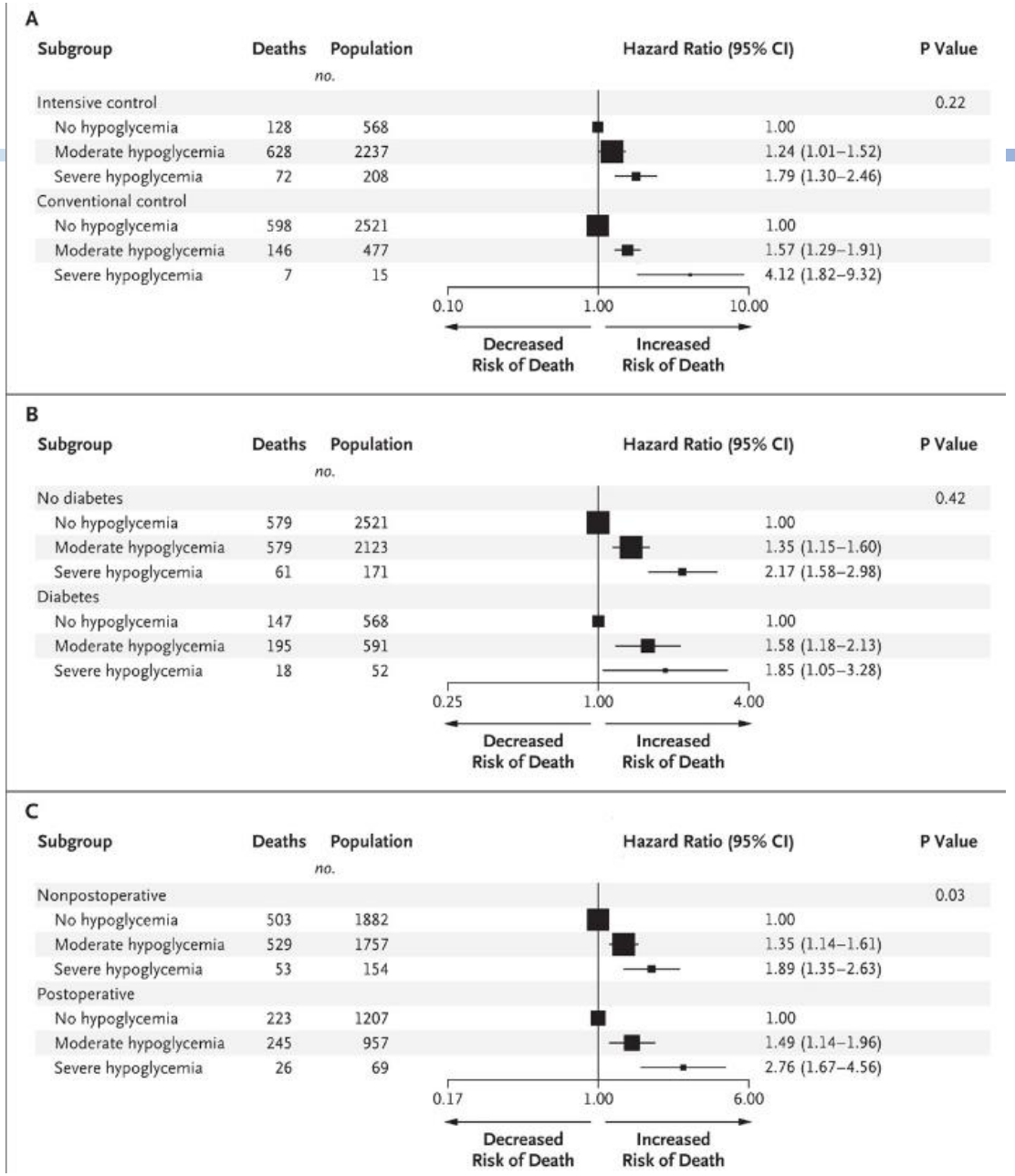
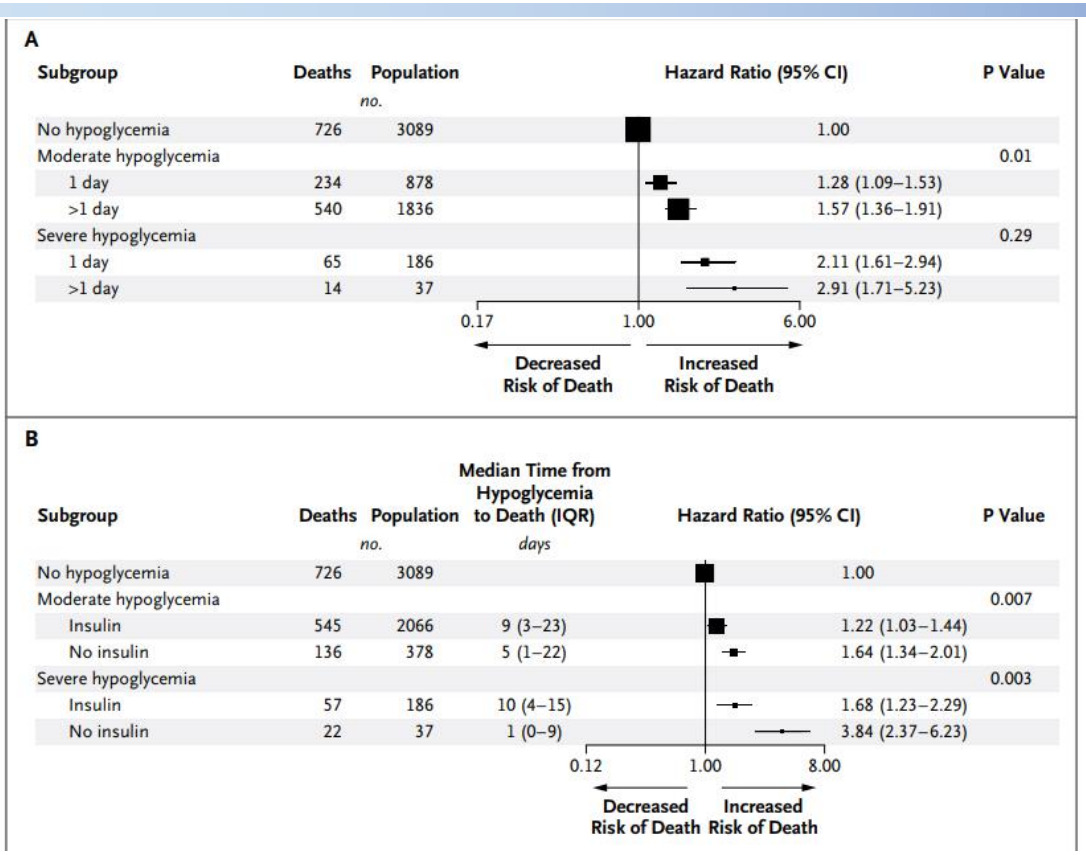


Figure 2. Hazard Ratio for Death According to Treatment Assignment and Status with Respect to Diabetes and Postoperative Status at Baseline.

The relationship between moderate or severe hypoglycemia and death did not differ significantly between patients assigned to intensive glucose control and those assigned to conventional glucose control (Panel A). The relationship was similar among patients with and those without a diagnosis of diabetes (Panel B), but it was stronger among postoperative patients (those admitted to the ICU directly from the operating room or recovery room) than among nonpostoperative patients (Panel C). The size of the squares is proportional to the number of deaths.

NICE-SUGAR Study Investigators. N Engl J Med 2012



NICE-SUGAR Study Investigators. N Engl J Med 2012

Figure 3. Hazard Ratio for Death According to the Occurrence of Hypoglycemia on 1 Day or More Than 1 Day and Receipt or Nonreceipt of Insulin Therapy at the Time of the First Hypoglycemic Episode.

The risk of death was increased among patients who had moderate hypoglycemia on more than 1 day, as compared with just 1 day (Panel A), and among patients who were not receiving insulin when hypoglycemia first occurred, as compared with those who were receiving insulin (Panel B). The interval from the first episode of hypoglycemia to death was shorter among patients who were not being treated with insulin when hypoglycemia first occurred ($P=0.004$ and $P<0.001$ for moderate and severe hypoglycemia, respectively). The size of the squares is proportional to the number of deaths.

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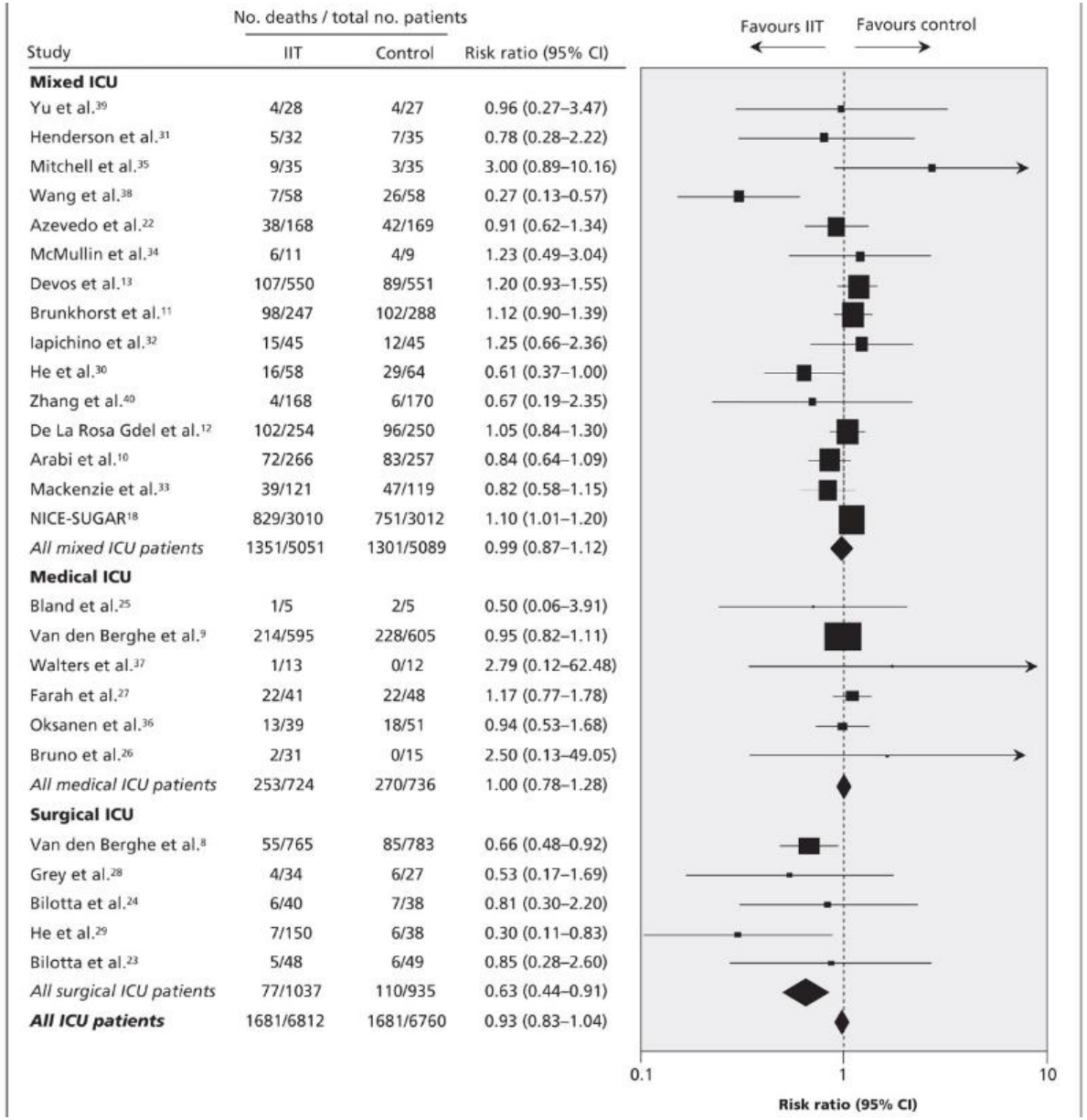
CMAJ RESEARCH

Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data

Donald E.G. Griesdale MD MPH, Russell J. de Souza RD MSc, Rob M. van Dam PhD, Daren K. Heyland MD, Deborah J. Cook MD MSc, Atul Malhotra MD, Rupinder Dhaliwal RD, William R. Henderson MD, Dean R. Chittock MD MS(Epi), Simon Finfer MBBS, Daniel Talmor MD MPH

Published at www.cmaj.ca on Mar. 24, 2008.

Griesdale DE et al. CMAJ , 2008



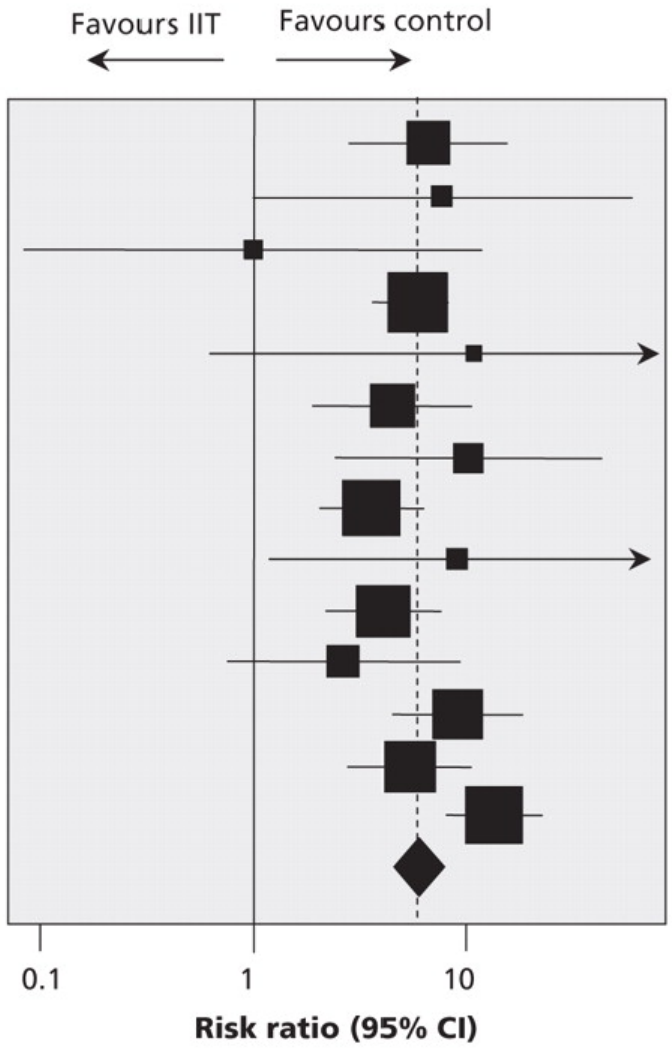
Study	No. deaths / total no. patients: IIT	Control	Risk ratio (95% CI)
Mixed ICU			
Yu et al.[39]	4/28	4/27	0.96 (0.27–3.47)
Henderson et al.[31]	5/32	7/35	0.78 (0.28–2.22)
Mitchell et al.[35]	9/35	3/35	3.00 (0.89–10.16)
Wang et al.[38]	7/58	26/58	0.27 (0.13–0.57)
Azevedo et al.[22]	38/168	42/169	0.91 (0.62–1.34)
McMullin et al.[34]	6/11	4/9	1.23 (0.49–3.04)
Devos et al.[13]	107/550	89/551	1.20 (0.93–1.55)
Brunkhorst et al.[11]	98/247	102/288	1.12 (0.90–1.39)
Iapichino et al.[32]	15/45	12/45	1.25 (0.66–2.36)
He et al.[30]	16/58	29/64	0.61 (0.37–1.00)
Zhang et al.[40]	4/168	6/170	0.67 (0.19–2.35)
De La Rosa Gdel et al.[12]	102/254	96/250	1.05 (0.84–1.30)
Arabi et al.[10]	72/266	83/257	0.84 (0.64–1.09)
Mackenzie et al.[33]	39/121	47/119	0.82 (0.58–1.15)
NICE-SUGAR[18]	829/3010	751/3012	1.10 (1.01–1.20)
All mixed ICU patients	1351/5051	1301/5089	0.99 (0.87–1.12)
Medical ICU			
Bland et al.[25]	1/5	2/5	0.50 (0.06–3.91)
Van den Berghe et al.[9]	214/595	228/605	0.95 (0.82–1.11)
Walters et al.[37]	1/13	0/12	2.79 (0.12–62.48)
Farah et al.[27]	22/41	22/48	1.17 (0.77–1.78)
Oksanen et al.[36]	13/39	18/51	0.94 (0.53–1.68)
Bruno et al.[26]	2/31	0/15	2.50 (0.13–49.05)
All medical ICU patients	253/724	270/736	1.00 (0.78–1.28)
Surgical ICU			
Van den Berghe et al.[8]	55/765	85/783	0.66 (0.48–0.92)
Grey et al.[28]	4/34	6/27	0.53 (0.17–1.69)
Bilotta et al.[24]	6/40	7/38	0.81 (0.30–2.20)
He et al.[29]	7/150	6/38	0.30 (0.11–0.83)
Bilotta et al.[23]	5/48	6/49	0.85 (0.28–2.60)
All surgical ICU patients	77/1037	110/935	0.63 (0.44–0.91)
All ICU patients	1681/6812	1681/6760	0.93 (0.83–1.04)

Mortality on Meta Analysis

Griesdale DE et al. CMAJ , 2008

Risk Ratio of Hypoglycemic Events

Study	No. events / total no. patients: IIT	Control	Risk ratio (95% CI)
Van den Berghe et al.[8]	39/765	6/783	6.65 (2.83–15.62)
Henderson et al.[31]	7/32	1/35	7.66 (1.00–58.86)
Bland et al.[25]	1/5	1/5	1.00 (0.08–11.93)
Van den Berghe et al[9]	111/595	19/605	5.94 (3.70–9.54)
Mitchell et al.[35]	5/35	0/35	11.00 (0.63–191.69)
Azevedo et al.[22]	27/168	6/169	4.53 (1.92–10.68)
De La Rosa Gdel et al.[12]	21/254	2/250	10.33 (2.45–43.61)
Devos et al.[13]	54/550	15/551	3.61 (2.06–6.31)
Oksanen et al.[36]	7/39	1/51	9.15 (1.17–71.35)
Brunkhorst et al.[11]	42/247	12/290	4.11 (2.21–7.63)
Iapichino et al.[32]	8/45	3/45	2.67 (0.76–9.41)
Arabi et al.[10]	76/266	8/257	9.18 (4.52–18.63)
Mackenzie et al.[33]	50/121	9/119	5.46 (2.82–10.60)
NICE-SUGAR[18]	206/3016	15/3014	13.72 (8.15–23.12)
Overall	654/6138	98/6209	5.99 (4.47–8.03)



Griesdale DE et al. CMAJ , 2008

Update of Guideline for

Glucose & Insulin

Clinical Nutrition 36 (2017) 355–363

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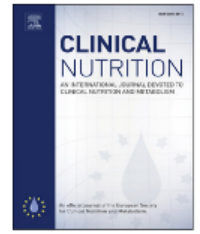

Review

Carbohydrates and insulin resistance in clinical nutrition: Recommendations from the ESPEN expert group

R. Barazzoni [a, *], N.E.P. Deutz [b], G. Biolo [c], S. Bischoff [d], Y. Boirie [e], T. Cederholm [f, g], C. Cuerda [h], N. Delzenne [i], M. Leon Sanz [j], O. Ljungqvist [k], M. Muscaritoli [l], C. Pichard [m], J.C. Preiser [n], P. Sbraccia [o], P. Singer [p], L. Tappy [q], B. Thorens [r], A. Van Gossum [s], R. Vettor [t], P.C. Calder [u]

- Intervene with EN support as soon as possible to limit caloric debt.
- Minimize glycemic variability in patients who must take PN, with a target blood glucose of 90–150 mg/dl
- Avoid hypoglycemia as a result of these approaches

Barrazzoni R et al. Clinical Nutrition , 2017

Clinical Nutrition xxx (2018) 1–32

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

ESPEN Guideline

ESPEN guideline on clinical nutrition in the intensive care unit

Pierre Singer [a, *], Annika Reintam Blaser [b, c], Mette M. Berger [d], Waleed Alhazzani [e], Philip C. Calder [f], Michael P. Casaer [g], Michael Hiesmayr [h], Konstantin Mayer [i], Juan Carlos Montejo [j], Claude Pichard [k], Jean-Charles Preiser [l], Arthur R.H. van Zanten [m], Simon Oczkowski [e], Wojciech Szczeklik [n], Stephan C. Bischoff [o]

Singer P et al. Clinical Nutrition , 2018

Recommendation 23

- The amount of glucose (PN) or carbohydrates (EN) administered to ICU patients should not exceed 5 mg/kg/min.
- Grade of recommendation: GPP – strong consensus (100% agreement)

Recommendation 53

- Blood glucose should be measured initially (after ICU admission or after artificial nutrition initiation) and at least every 4 h, for the first two days in general.
- Grade of recommendation: GPP – strong consensus (93% agreement)

Recommendation 54

- Insulin shall be administered, when glucose levels exceed 10 mmol/L.
- Grade of recommendation: A – strong consensus (93% agreement)

Singer P et al. Clinical Nutrition , 2018

Clinical Guidelines

aspen LEADING THE SCIENCE AND PRACTICE OF CLINICAL NUTRITION
American Society for Parenteral and Enteral Nutrition

Journal of Parenteral and Enteral Nutrition
Volume 40 Number 2
February 2016 159–211

DOI: 10.1177/0148607115621863
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Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.)

Stephen A. McClave, MD[1*]; Beth E. Taylor, RD, DCN[2*]; Robert G. Martindale, MD, PhD[3]; Malissa M. Warren, RD[4]; Debbie R. Johnson, RN, MS[5]; Carol Braunschweig, RD, PhD[6]; Mary S. McCarthy, RN, PhD[7]; Evangelia Davanos, PharmD[8]; Todd W. Rice, MD, MSc[9]; Gail A. Cresci, RD, PhD[10]; Jane M. Gervasio, PharmD[11]; Gordon S. Sacks, PharmD[12]; Pamela R. Roberts, MD[13]; Charlene Compher, RD, PhD[14]; and the Society of Critical Care Medicine[†] and the American Society for Parenteral and Enteral Nutrition[†]

Target Blood Glucose Range by ASPEN Guideline

- **Question: What is the desired target blood glucose range in adult ICU patients?**
- H5. We recommend a target blood glucose range of 140 or 150–180 mg/dL for the general ICU population; ranges for specific patient populations (postcardiovascular surgery, head trauma) may differ and are beyond the scope of this guideline. [Quality of Evidence: Moderate]

- *Rationale: Hyperglycemia is a common response to acute illness and severe sepsis and may lead to poor outcomes. There continues to be controversy regarding the lower point of the range, with SCCM recommending 150–180 mg/dL, while A.S.P.E.N. recommends 140–180 mg/dL.*

McClave SA et al. JPEN , 2016

Glucose control maybe still controversial. This therapy needs precise modulation. And then it will decrease morbidity and mortality

Drug interaction

Prof. Mette Berger

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JUMPstart Training Program

Drug interactions
Sedation, Propofol, Glucose

Prof. Mette M Berger, M.D., Ph.D

Advanced module, Day 2, Part II: Confounding factors in the ICU

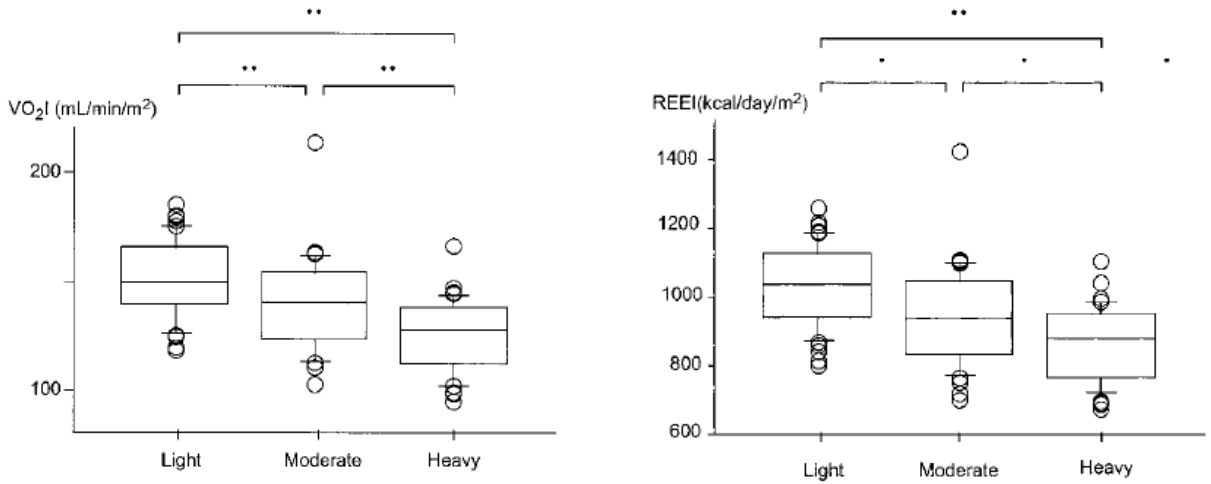
How can drugs interact with nutrition and metabolism?

- Modify metabolic rate
  - Sedatives, neuromuscular blocking agents
  - Propranolol
- Provide non nutritional energy and substrates (GLU, LIP)
  - Compromise substrate proportion and reduce protein proportion of nutrition
  - Excess carbohydrates / fat
- Generate inadvertent hyperalimentation

Quantitative analysis of the relationship between sedation and resting energy expenditure in postoperative patients

Terao Y et al, CCM, 2003

32 postoperative patients undergoing elective surgery, requiring >2 days of mech vent. All patients received analgesia with buprenorphine at a fixed dose of 0.625 μg·kg−1·hr−1 continuously. Midazolam was used for induction and maintenance of intravenous sedation. three states: light sedation (n = 49), moderate sedation (n = 39), and heavy sedation (n = 45). REE measured by indirect calorimetry.



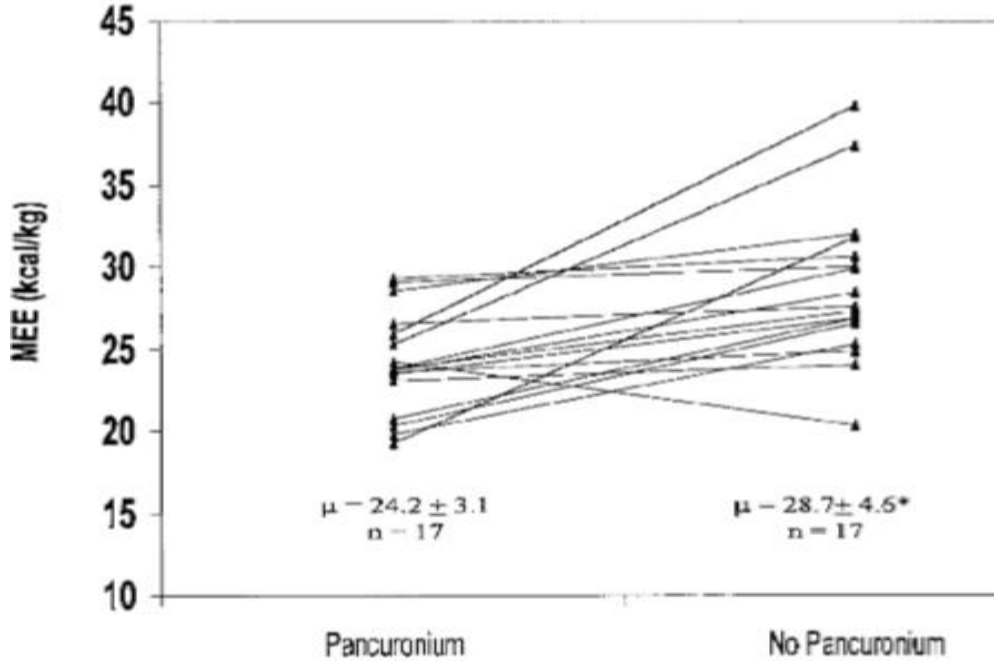
Individual values of oxygen consumption index (VO2I) and REE in light sedation (Ramsay sedation scale 2–3, moderate sedation (RSS 4), or heavy sedation (RSS 5–6).

Effect of neuromuscular blockade on energy expenditure in patients with severe head injury

McCall et al, JPEN, 2003; 27:27

Energy expenditure was measured using IC in 2 groups of ventilated patients-18 with severe head injury during and after administration of pancuronium bromide and morphine, and second, 14 trauma without severe head injury who received morphine **without** neuromuscular blockade.

Mean EE of head-injured patients ↑ significantly once pancuronium was discontinued, from **24.2** ±3.1 to **28.7** ± 4.6 kcal/kg (p = .002). This effect was independent of other variables such as morphine dose, body t°, and nutrition support. Head-injured patients not on neuromuscular blockade had a significantly greater energy expenditure when compared with the trauma group (p = 0.02)

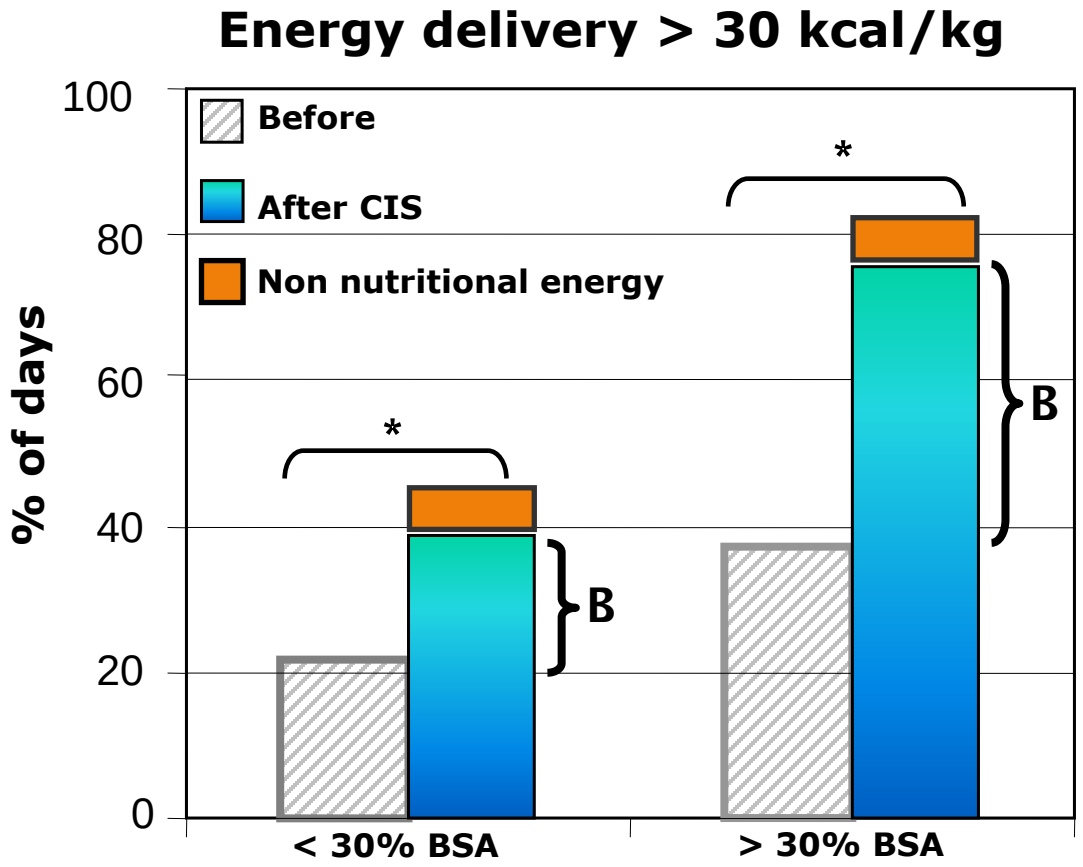


What is non-nutritional energy ?

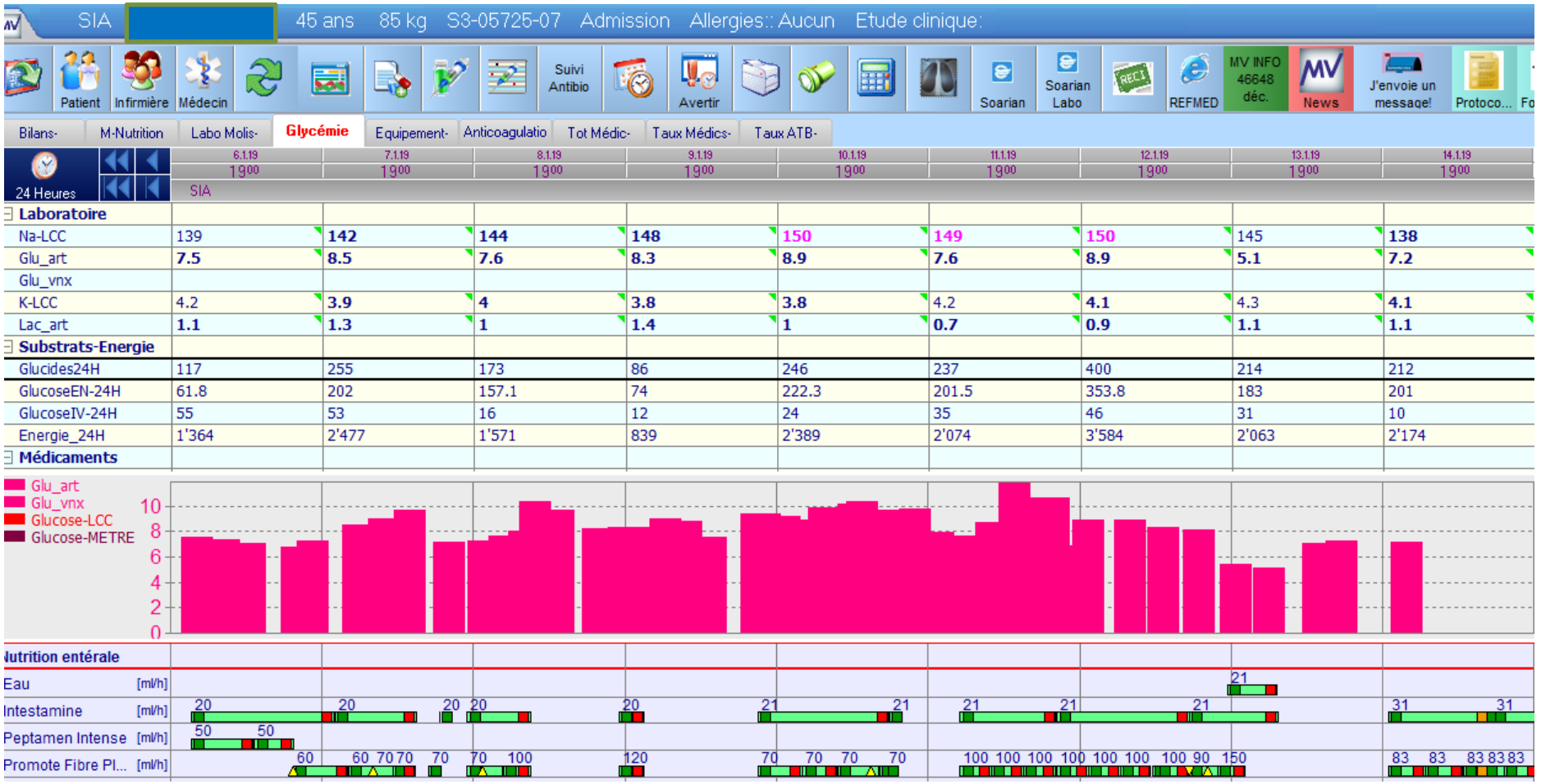
- Substrates delivered
  - Unintentionally
  - Not prescribed as nutrients → lack awareness
- Problem: difficult to detect in absence of PDMS customised for this purpose
- Glucose : used for drug dilution, and treatment of hypernatremia (G5, glucosaline)
  - 1000 ml of Glu5% → 50 g GLU → 200 kcal
  - 1000 ml Glucosaline → 33 g GLU → 132 kcal
- Lipids: mainly fat with Propofol 1% or 2%

Impact of a computerized information system on quality of nutritional support in the ICU

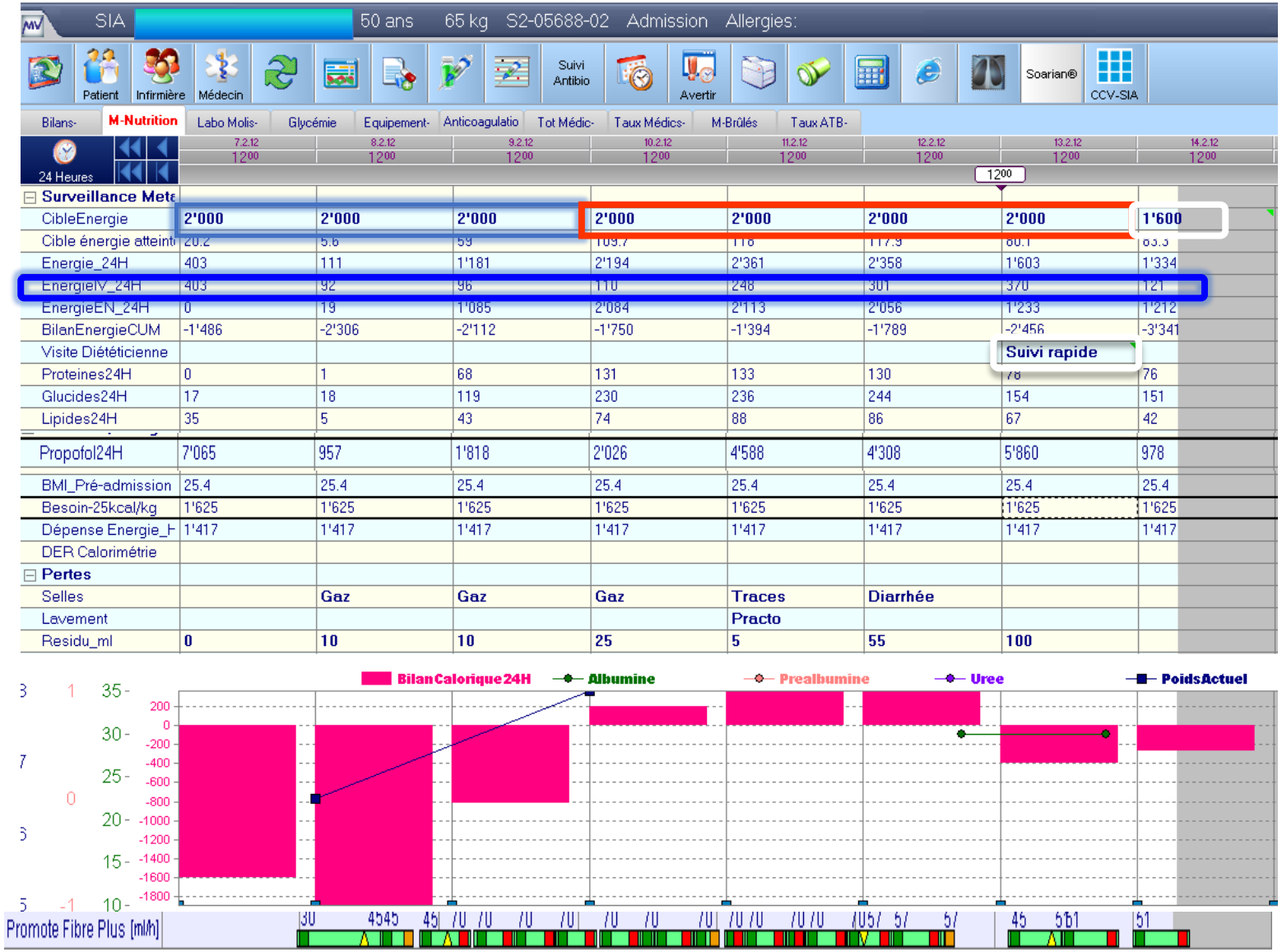
Berger et al, Nutrition 22 (2006) 221

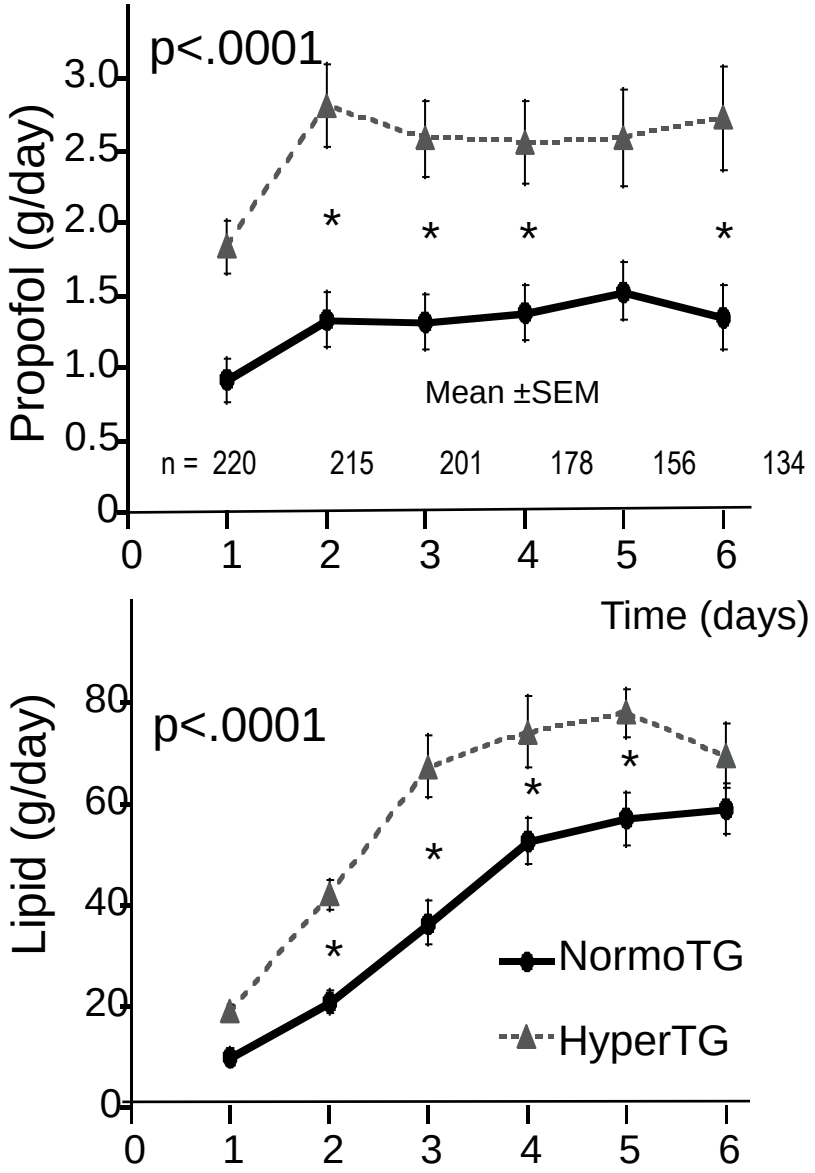


Glucose for hyperNatremia



Patient Brain injury – Propofol → 400 kcal





Hypertriglyceridemia: a potential side effect of propofol sedation in critical illness

Devaud et al.

Intensive Care Med 2012

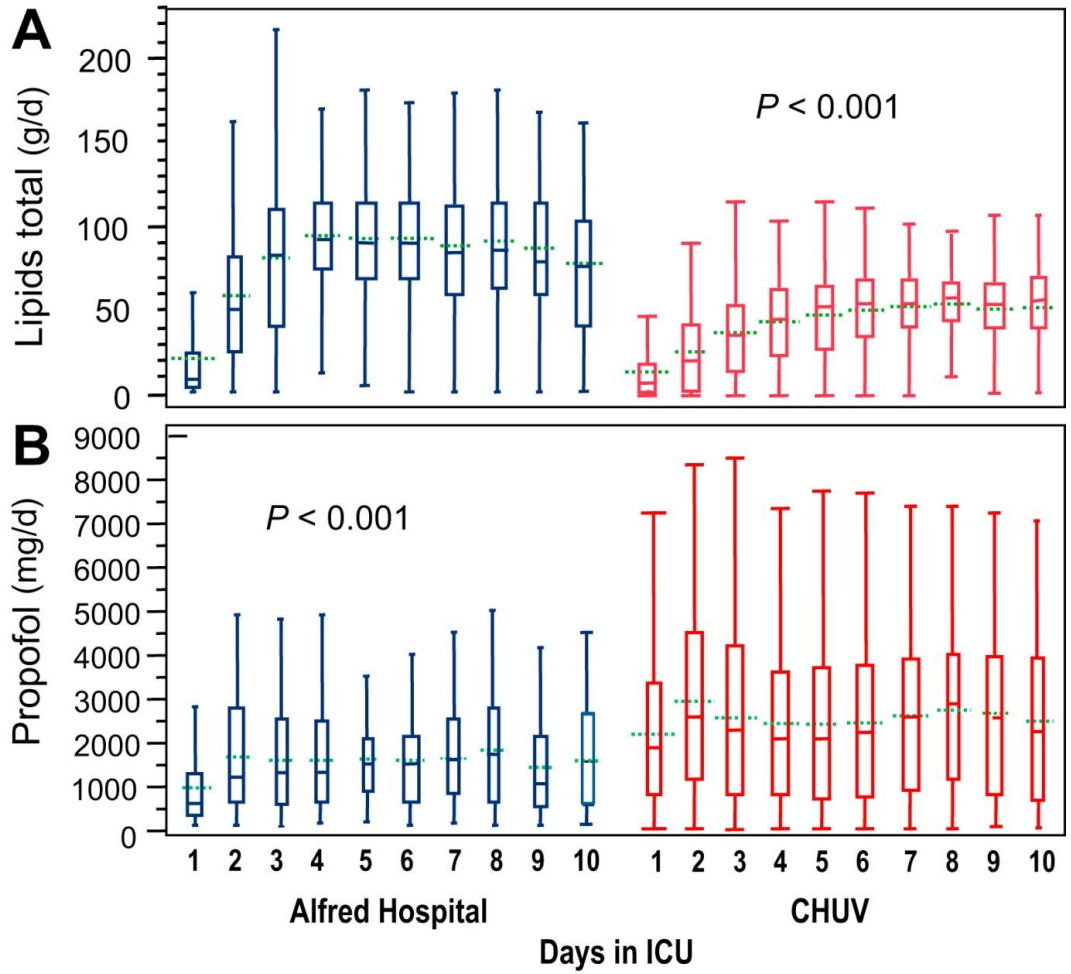
220 / 1300 patients staying > 4 days

99 (45%) had triglycerides > 2 mmol/L

Propofol sedation and fat intake are associated with significantly more hyperTG

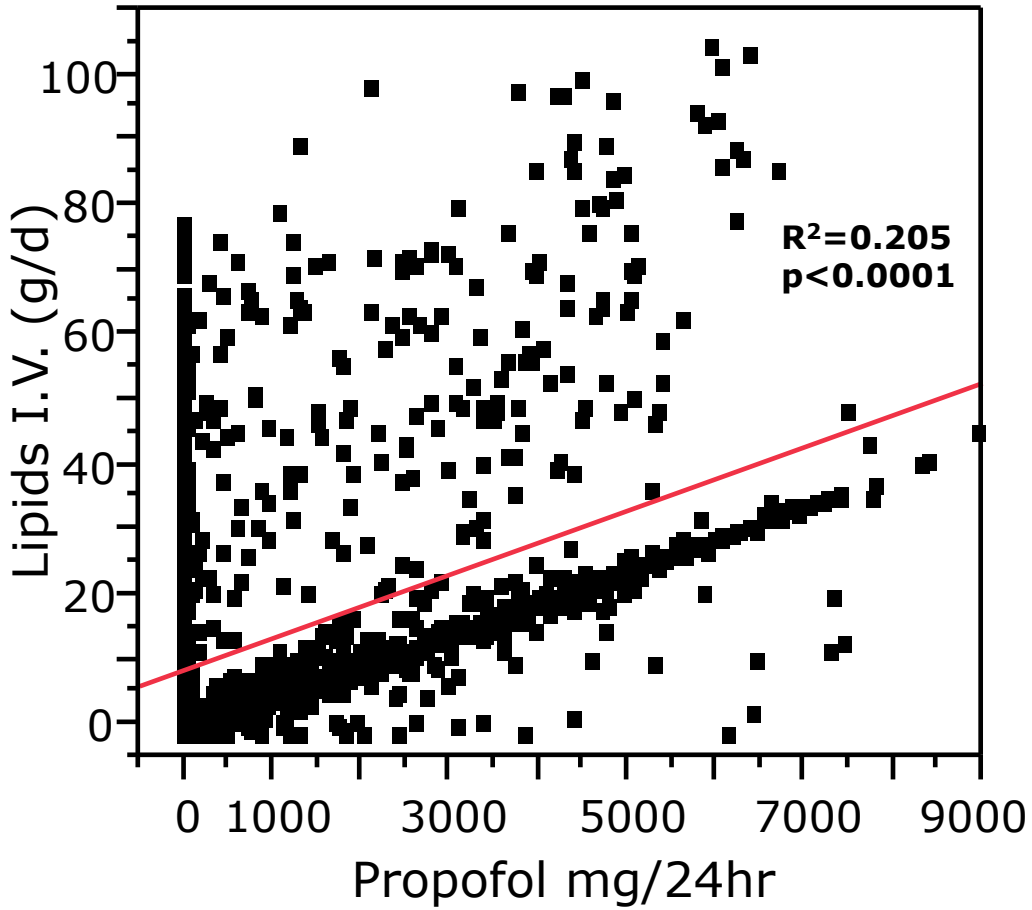
Propofol sedation substantially increases the caloric and lipid intake in critically ill patients

Charrière et al, Nutrition 2017; 42:64



687 patients
Propofol (B) and fat (A) dose by day during the first 10 d in both institutions
3484 Days were with propofol sedation (1623 and 1861 d propofol from CHUV-2% solutions and AH - 1% solution).

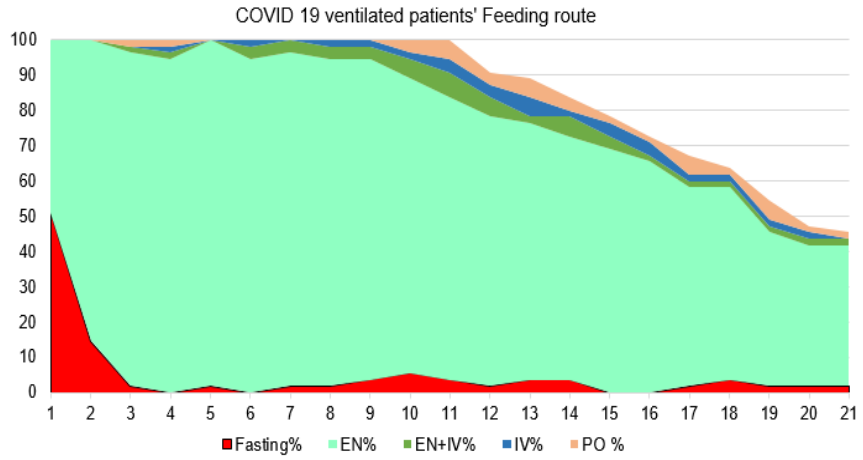
Relation between propofol dose and intravenous fat delivery

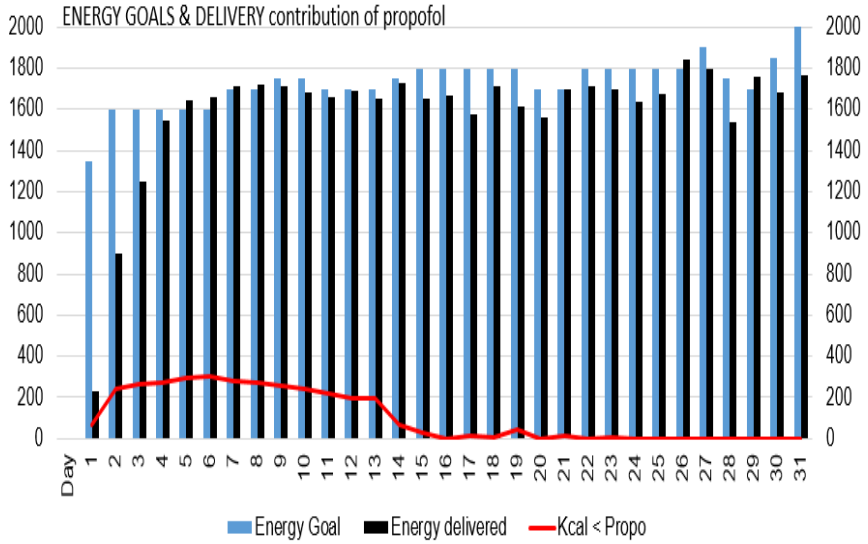


N=687 patients
First 10 day observations

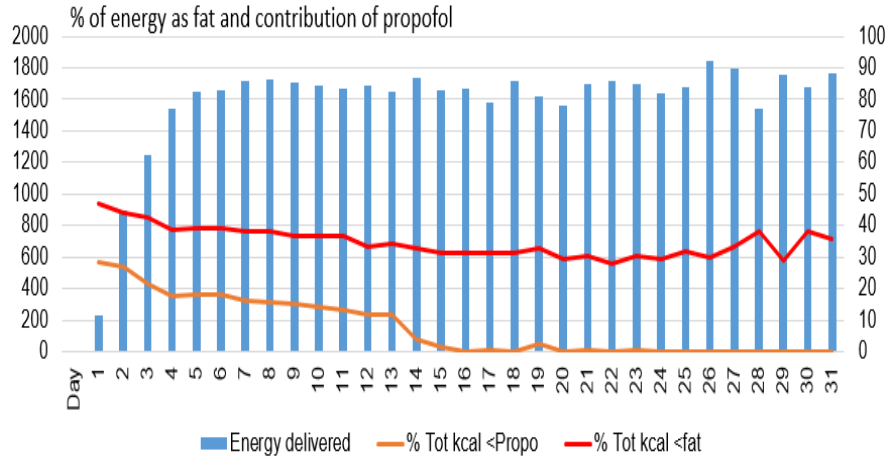
Contribution of propofol sedation to fat intake, Charrière et al, 2017 unpublished

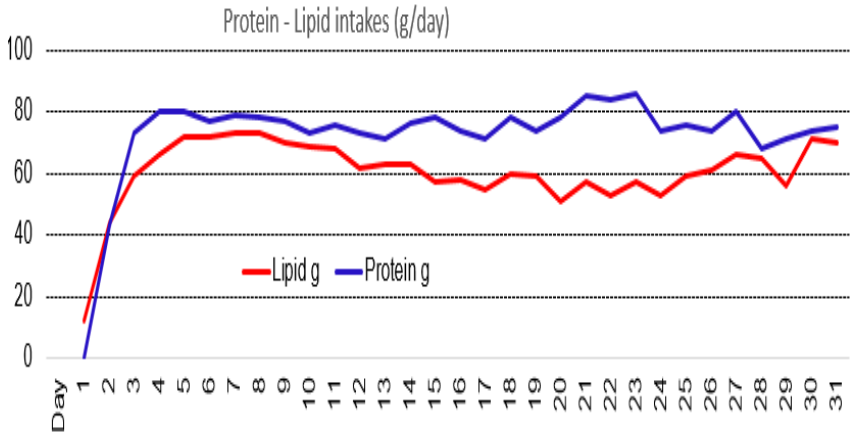
Nutrition support in ICU following COVID-19





50 CO-19 patients on mechanical ventilation
Median age 63 yrs, 84 kg, BMI 27.2, SAPS2 37, NRS 5





Drugs interactions - conclusion

- Drugs such as sedatives and neuromuscular blocking agents modify significantly energy expenditure and hence nutrition needs.
- Equation based targets are particularly exposing patients to inadequate goals
- Nutrient overload may occur inadvertently and non nutritional energy represents 5% and up to 40% of intakes
- Non-nutritional energy may “occupy” the field of proteins

Disease severity scores

Prof. Olav Rooyackers

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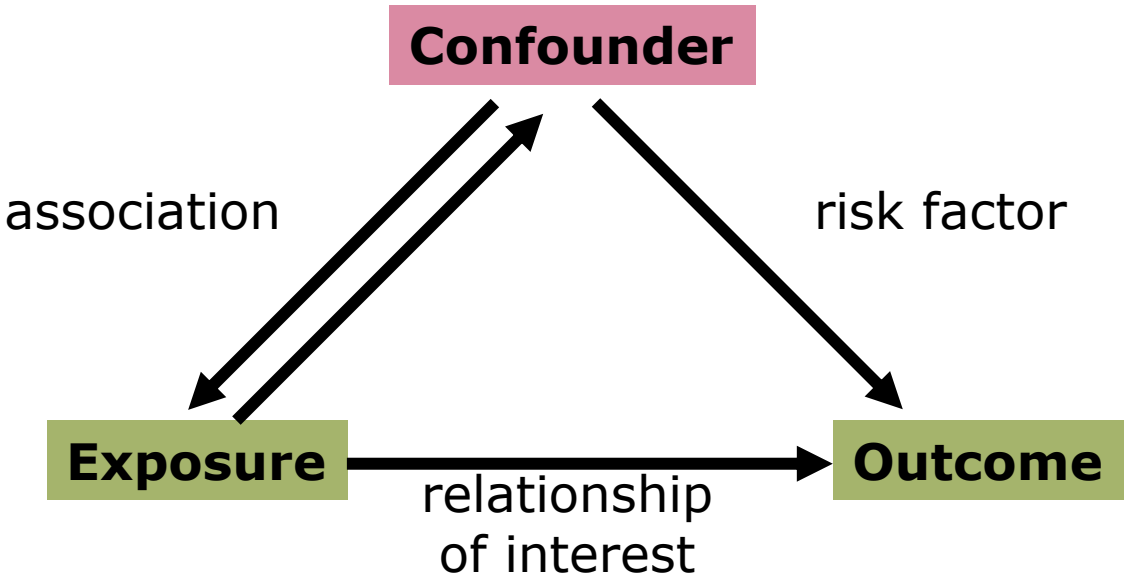
Disease severity scores

Prof. Olav Rooyackers

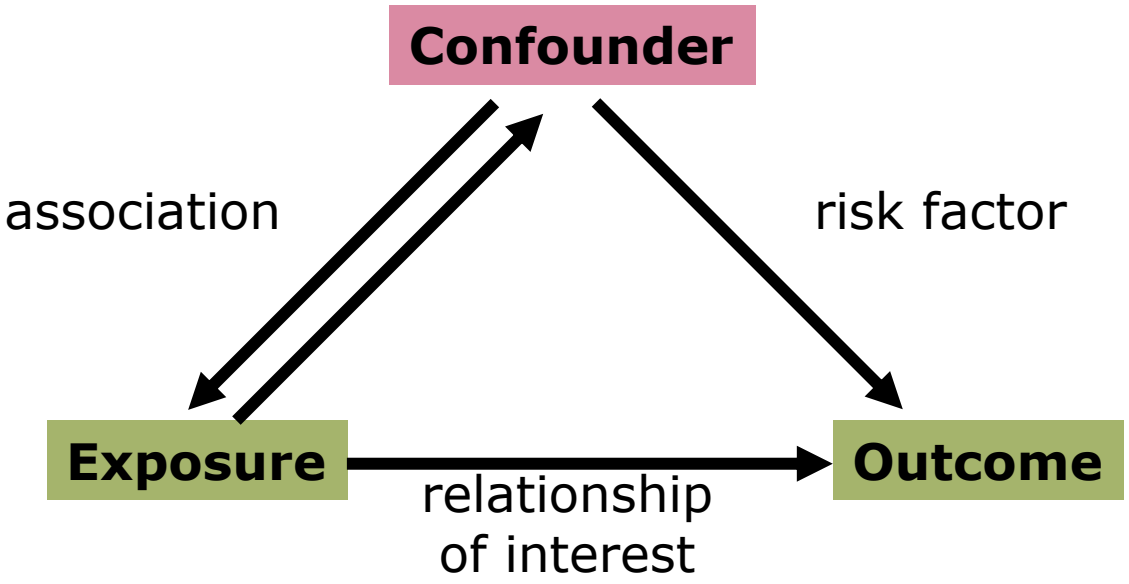
Advanced module, Day 2, Part II: Confounding factors in the ICU

What is a confounder



Jager et al. Kidney Int. 2018

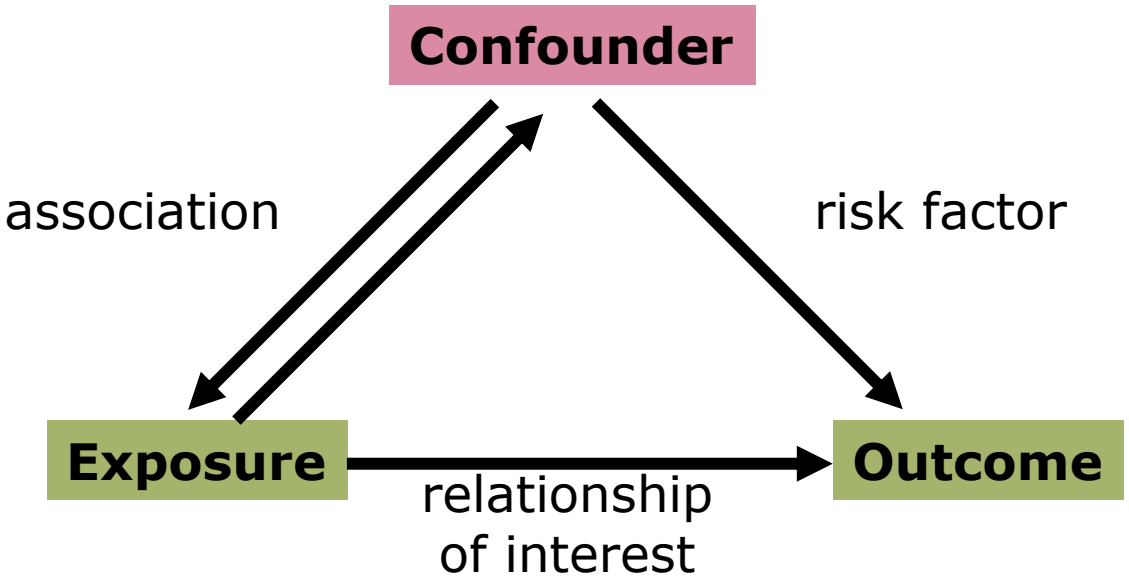
What is a confounder



1. It must have an association with the disease; it should be a risk factor for the disease;
2. it must be associated with the exposure; it must be unequally distributed between the exposed and nonexposed groups
3. it must not be an effect of the exposure, nor be a factor in the causal pathway of the disease.

Jager et al. Kidney Int. 2018

What is a confounder



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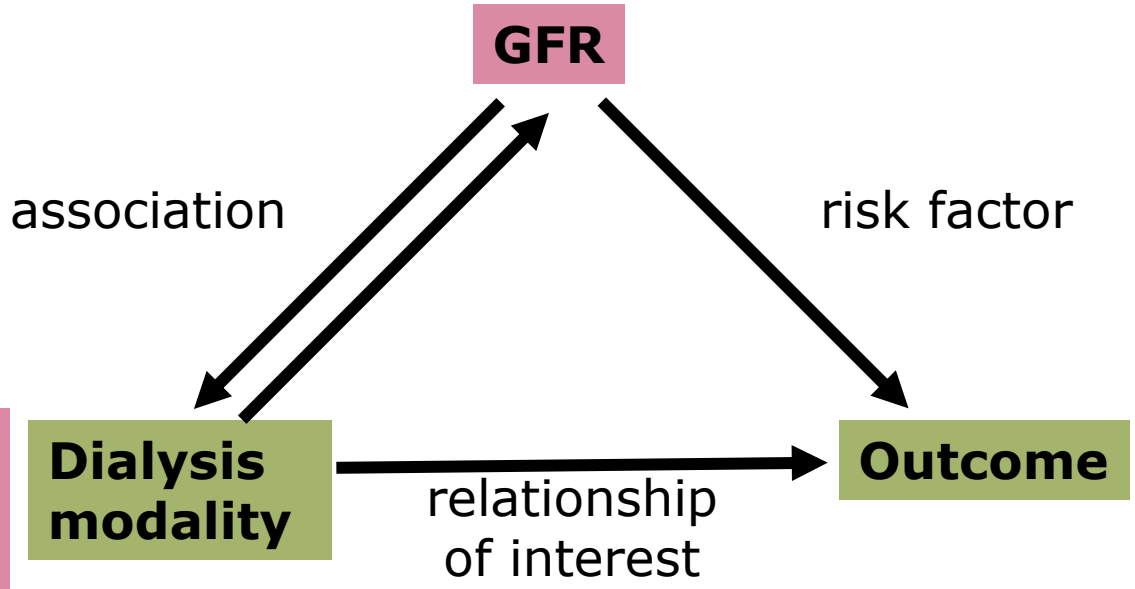
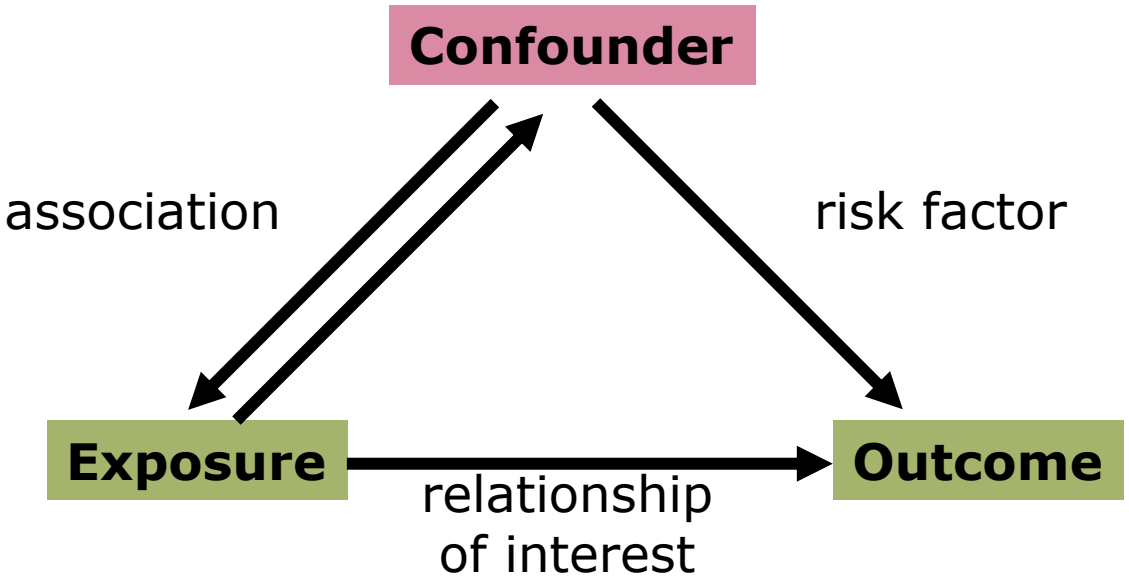
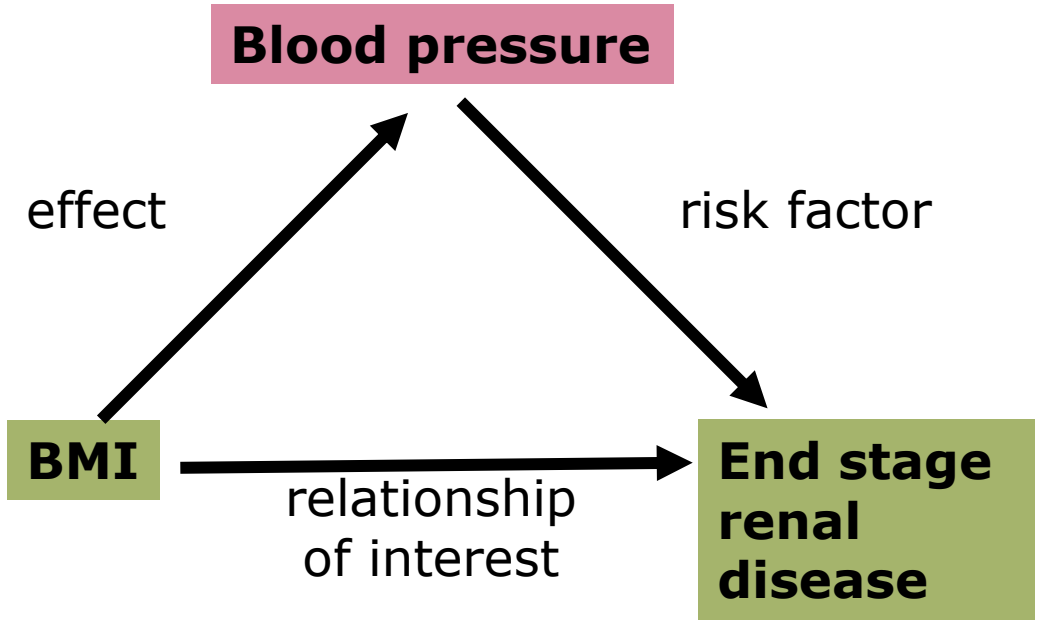


Jager et al. Kidney Int. 2018

What is a confounder



1. It must have an association with the disease; it should be a risk factor for the disease;
2. it must be associated with the exposure; it must be unequally distributed between the exposed and nonexposed groups
3. it must not be an effect of the exposure, nor be a factor in the causal pathway of the disease.



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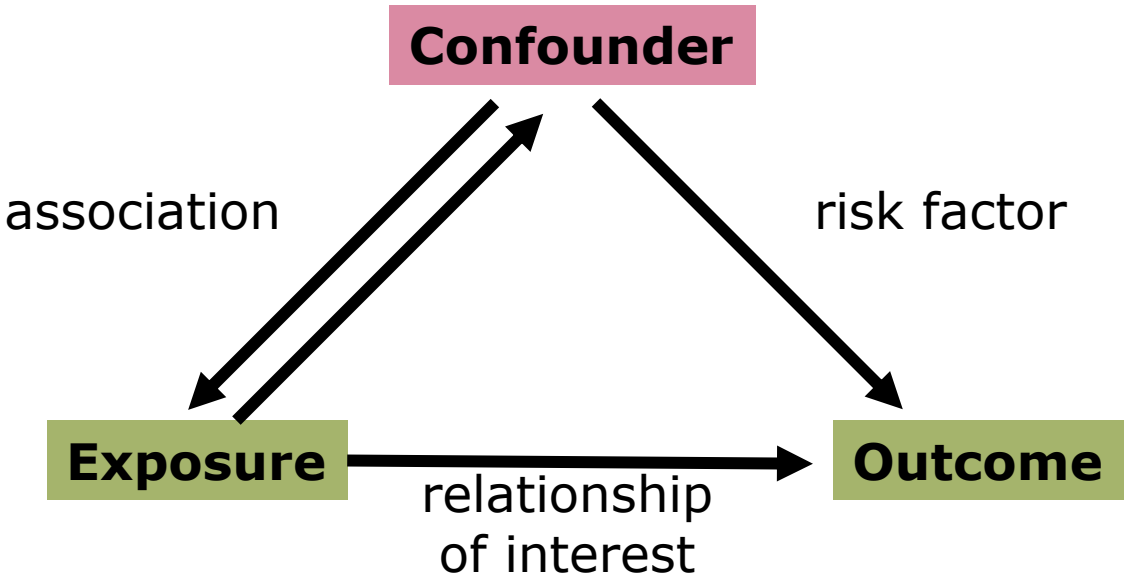
What is a confounder



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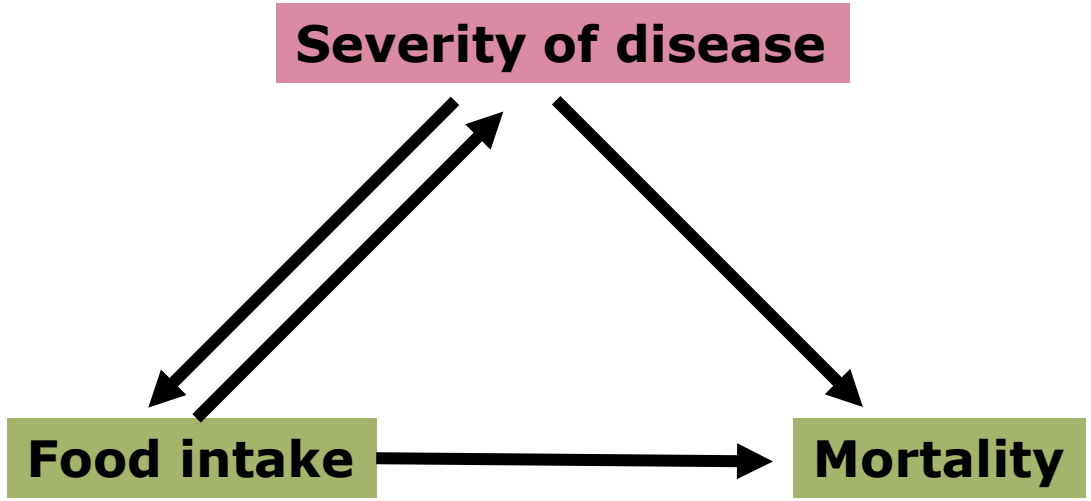

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Dealing with confounders

- **Prevention**
  - Randomization (simple, block, stratified)
  - Restriction
  - Matching

- **Correction**
  - Stratification
  - Multivariate analyses

Jager et al. Kidney Int. 2018

Severity scoring systems in the critically ill

D Christopher Bouch MB ChB FRCA EDIC
Jonathan P Thompson BSc (Hons) MB ChB MD FRCA

- **Anatomical scoring**: ISS (injury severity score)
- **Therapeutic weighed scores**: TISS (therapeutic intervention score)
- **Organ-specific score**: SOFA (sequencial organ failure assessment)
- **Physiological assessment**: APACHE, SAPS
- **Simple scales**: clinical judgement
- **Disease specific**: Child-Pugh, MELD

Bouch et al. Cont Edu Anest Crit Care & Pain, 2008

SAPS

APACHE

ISS

PIM

SOFA

PELOD

NUTRICS

FRAILTY

MELD

CHILD-PUGH

SAPS

APACHE

SOFA

ISS

PIM

PELOD

NUTRICS

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MELD

CHILD-PUGH

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APACHE

ISS

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SOFA

PELOD

Acute Physiology and Chronic Health Evaluation Score

NUTRICS

MELD

FRAILTY

CHILD-PUGH

Development of APACHE

- **APACHE** (Knaus et al. Crit Care Med 1981)
  - → Developed by authors + 5 mixed physicians
  - → Weighed score for 34 physiological parameters and 4 graded chronic health evaluation
  - → First 32 hours
  - → Validated in 582 + 805 patients
  - → Predicting outcome (mortality) on group level

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- **APACHE II** (Knaus et al. Crit Care Med 1985)
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    - Clinical judgement
    - Multivariate comparison
  - → Validated in 5815 patients
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Development of APACHE

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    - Multivariate comparison
  - → Validated in 5815 patients
  - → Predicting outcome (mortality) on group level
- **APACHE III** (Knaus et al. Chest 1991)

The APACHE II Severity of Disease Classification System

Physiologic Variable	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature - rectal (°C)	≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9
Mean Arterial Pressure (mm Hg)	≥160	130-159	110-129		70-109		50-69		≤49
Heart Rate	≥180	140-179	110-139		70-109		55-69	40-54	≤39
Respiratory Rate (nonventilated or ventilated)	≥50	35-49		25-34	12-24	10-11	6-9		≤5
Oxygenation (mmHg) a. $FiO_2 > 0,5$ use A-aDO_2 b. $FiO_2 < 0,5$ use PaO_2	a ≥500	350-499	200-349		<200				
	b				> 70	61-70		55-60	<55
Arterial pH	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
Serum Sodium (mmol/l)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
Serum Potassium (mmol/l)	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
Serum Creatinine (mg/dl, Double point score for acute renal failure)	≥3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6		
Hematocrit (%)	≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20
White Blood Count (in 1000/mm³)	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1
Glasgow-Coma-Scale (GCS)	Score = 15 minus actual GCS								
Serum HCO_3 (venous, mmol/l, use if no ABGs)	≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15
A = Total Acute Physiology Score APS	Sum of the 12 individual variable points								

B = Age Points	
≤44 years	0 points
45-54 years	2 points
55-64 years	3 points
65-74 years	5 points
≥75 years	6 points

C = Chronic Health Points

If the patient has a history of severe organ system insufficiency or is immunocompromised assign points as follows:

a. For nonoperative or emergency postoperative patients – 5 points

b. For elective postoperative patients – 2 points

APACHE II Score = Sum of A (APS points) + B (Age points) + C (Chronic Health points)

(From: Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13(10):818-29)

The APACHE II Score

Chronic Health Points

History of severe organ insufficiency	Points
Non-operative patients	5
Emergency postoperative patients	5
Elective postoperative patients	2

- Organ insufficiency or immunocompromised state must have preceded the current admission
- Immunocompromised if:
  - Receiving therapy reducing host defences (immunosuppression, chemotherapy, radiation therapy, long term steroid use, high dose steroid therapy) or
  - Has a disease interfering with immune function such as malignant lymphoma or leukaemia
- Hepatic insufficiency if:
  - Biopsy proven cirrhosis
  - Portal hypertension
  - Episodes of upper GI bleeding due to portal hypertension
  - Prior episodes of hepatic failure, coma or encephalopathy
- Cardiovascular insufficiency if:
  - New York Heart Association Class IV
- Respiratory insufficiency if:
  - Severe exercise restriction due to chronic restrictive, obstructive or vascular disease,
  - Documented chronic hypoxia, hypercapnia, secondary polycythaemia, severe pulmonary hypertension
  - Respirator dependency
- Renal insufficiency if:
  - On chronic dialysis

SAPS

APACHE

ISS

PIM

SOFA

PELOD

Simplified Acute Physiology Score

NUTRICS

MELD

FRAILTY

CHILD-PUGH

Development of SAPS 3

- **SAPS 3** (Moreno et al. Intensiv Care Med 2005)
  - → Developed by 9 authors and 10 in scientific commitee
  - → 307 ICUs, 35 countries, 6 continents; 19,577 patients
  - → Decision on included parameters primary driven by statistics and secondary by expert opinion

    - **Box I:** What we know about the patient characteristics before ICU admission: age, previous health status, co-morbidities, location before ICU admission, length of stay in the hospital before ICU admission, and use of major therapeutic options before ICU admission.
    - **Box II:** What we know about the circumstances of ICU admission: reason(s) for ICU admission, anatomic site of surgery (if applicable), planned or unplanned ICU admission, surgical status and infection at ICU admission.
    - **Box III:** What we know about the presence and degree of physiologic derangement at ICU admission (within 1 h before or after admission).

Table 1 SAPS 3 admission scoresheet—Part 1

Box I	0	3	5	6	7	8	9	11	13	15	18
Age, years	<40		>=40<60				>=60<70		>=70<75	>=75<80	>=80
Co-Morbidities		Cancer therapy [2]		Chron, HF (NYHA IV), Haematological cancer [3),4)]		Cirrhosis, AIDS [3]		Cancer [5]			
Length of stay before ICU admission, days [1]	<14			>=14<28	>=28						
Intra-hospital location before ICU admission			Emergency room		Other ICU	Other [6]					
Use of major therapeutic options before ICU admission		Vasoactive drugs									

Box II				0	3	4	5	6
ICU admission: Planned or Unplanned					Unplanned			
Reason(s) for ICU admission	please see Part 2 of the scoresheet							
Surgical status at ICU admission				Scheduled surgery			No surgery [7]	Emergency surgery
Anatomical site of surgery	please see Part 2 of the scoresheet							
Acute infection at ICU admission						Nosocomial [8]	Respiratory [9]	

Table 1 continued

Box III	15	13	11	10	8	7	5	3	2	0	2	4	5	7	8
Estimated Glasgow Coma Scale (lowest), points	3–4			5		6			7–12	>=13					
Total bilirubine (highest), mg/dL										<2		>=2<6	>=6		
Total bilirubine (highest), µmol/L										<34.2		>=34.2 <102.6	>=102.6		
Body temperature (highest), Degrees Celsius						<35				>=35					
Creatinine (highest), mg/dL										<1.2	>=1.2<2			>=2<3.5	>=3.5
Creatinine (highest), µmol/L										<106.1	>=106.1< 176.8			>=176.8 <309.4	>=309.4
Heart rate (highest), beats/minute										<120			>=120 <160	>=160	
Leukocytes (highest), G/L										<15	>=15				
Hydrogen ion concentration (lowest), pH								<=7.25		>7.25					
Plateletes (lowest), G/L		<20			>=20<50		>=50<100			>=100					
Systolic blood pressure (lowest), mm Hg			<40		>=40<70			>=70<120		>=120					
Oxygenation [10),11)]			PaO2/ FiO2 <100 and MV			PaO2/ FiO2> =100 and MV	PaO2<60 and no MV			PaO2> =60 and no MV					

Table 1 SAPS 3 admission scoresheet—Part 1

Box I	0	3	5
Age, years	<40		>=40<60
Co-Morbidities		Cancer therapy [2)]	
Length of stay before ICU admission, days [1)]	<14		
Intra-hospital location before ICU admission			Emergency ro
Use of major therapeutic options before ICU admission		Vasoactive drugs	

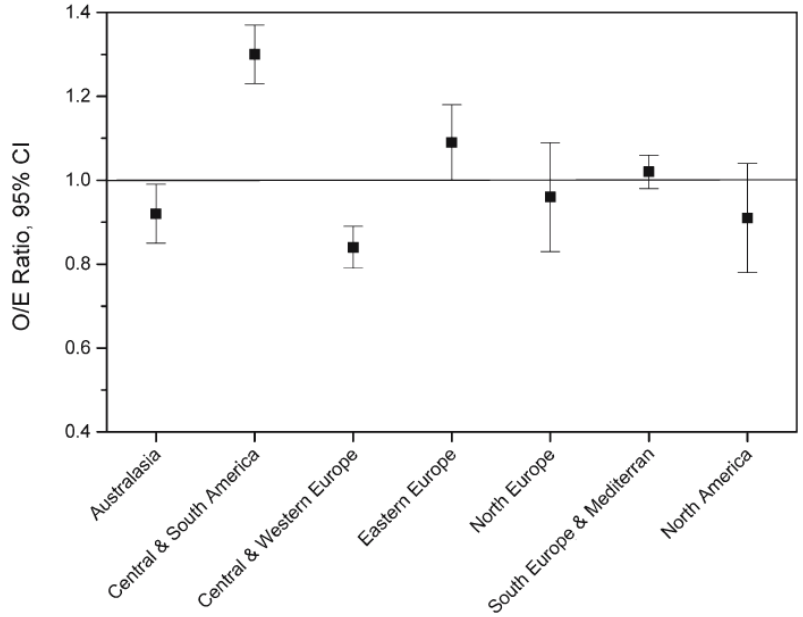
Box II	
ICU admission: Planned or Unplanned	
Reason(s) for ICU admission	please see Part 2 of the scoresheet
Surgical status at ICU admission	
Anatomical site of surgery	please see Part 2 of the scoresheet
Acute infection at ICU admission	

Table 1 continued

Box III	15	13	11	10	8	7
Estimated Glasgow Coma Scale (lowest), points	3–4			5		6
Total bilirubine (highest), mg/dL						
Total bilirubine (highest), µmol/L						
Body temperature (highest), Degrees Celsius						<35
Creatinine (highest), mg/dL						
Creatinine (highest), µmol/L						
Heart rate (highest), beats/minute						
Leukocytes (highest), G/L						
Hydrogen ion concentration (lowest), pH						
Plateletes (lowest), G/L		<20			>=20<50	
Systolic blood pressure (lowest), mm Hg			<40		>=40<70	
Oxygenation [10); 11)]			PaO2/FiO2 <100 and MV			PaO2/FiO2>=100 and MV

Table 2 SAPS 3 admission scoresheet – Part 2

Box II – continued	
ICU admission [12)]	16
Reason(s) for ICU admission	
Cardiovascular: Rhythm disturbances [13)]	–5
Neurologic: Seizures [13)]	–4
Cardiovascular: Hypovolemic hemorrhagic shock, Hypovolemic non hemorrhagic shock. / Digestive: Acute abdomen, Other [3)]	3
Neurologic: Coma, Stupor, Obtuned patient, Vigilance disturbances, Confusion, Agitation, Delirium	4
Cardiovascular: Septic shock. / Cardiovascular: Anaphylactic shock, mixed and undefined shock	5
Hepatic: Liver failure	6
Neurologic: Focal neurologic deficit	7
Digestive: Severe pancreatitis	9
Neurologic: Intracranial mass effect	10
All others	0
Anatomical site of surgery	
Transplantation surgery: Liver, Kidney, Pancreas, Kidney and pancreas, Transplantation other	–11
Trauma – Other, isolated: (includes Thorax, Abdomen, limb); Trauma – Multiple	–8
Cardiac surgery: CABG without valvular repair	–6
Neurosurgery: Cerebrovascular accident	5
All others	0


O/E Ratio, 95% CI
1.4
1.2
1.0
0.8
0.6
0.4
Australasia
Central & South America
Central & Western Europe
Eastern Europe
North Europe
South Europe & Mediterran
North America

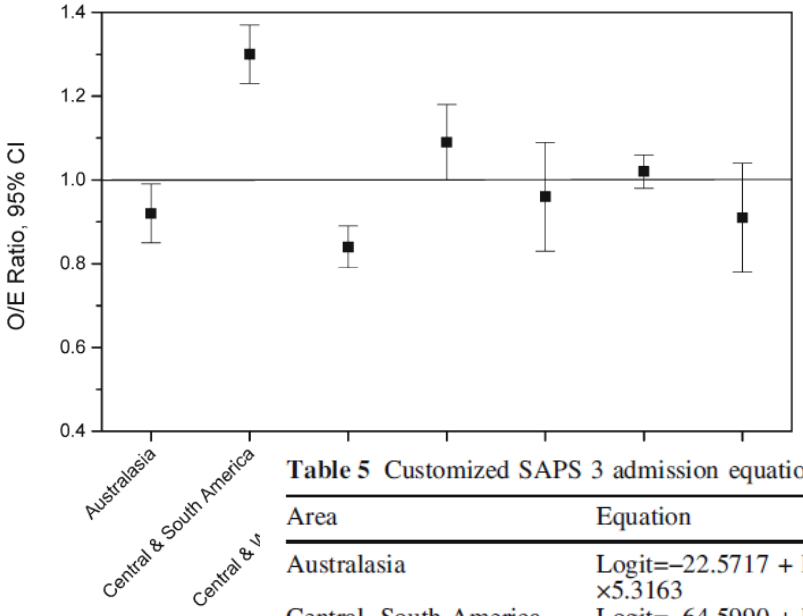


Table 5 Customized SAPS 3 admission equations for the different geographic areas

Area	Equation	GOF $\hat{H}$	*p*	GOF $\hat{C}$	*p*	O/E	CI
Australasia	Logit=–22.5717 + ln (SAPS 3 score + 1) ×5.3163	10.43	0.40	2.20	0.99	1.00	0.93–1.07
Central, South America	Logit=–64.5990 + ln (SAPS 3 score + 71.0599) ×13.2322	8.94	0.54	7.03	0.72	1.00	0.94–1.06
Central, Western Europe	Logit=–36.0877 + ln (SAPS 3 score + 22.2655) ×7.9867	15.13	0.13	12.15	0.27	1.00	0.94–1.06
Eastern Europe	Logit=–60.1771 + ln (SAPS 3 score + 51.4043) ×12.6847	10.13	0.43	7.12	0.71	1.00	0.92–1.08
North Europe	Logit=–26.9065 + ln (SAPS 3 score + 5.5077) ×6.2746	3.45	0.97	2.22	0.99	1.00	0.86–1.14
Southern Europe, Mediterranean countries	Logit=–23.8501 + ln (SAPS 3 score + 5.5708) ×5.5709	5.28	0.87	13.12	0.22	1.00	0.97–1.03
North America	Logit=–18.8839 + ln (SAPS 3 score + 1) ×4.3979	4.22	0.93	4.47	0.92	1.00	0.86–1.14

GOF $\hat{H}$: Hosmer-Lemeshow goodness-of-fit $\hat{H}$ test; *GOF* $\hat{C}$: Hosmer-Lemeshow goodness-of-fit $\hat{C}$ test; *p*: respective p-values; *O/E*: observed-to-expected mortality ratio; *CI*: 95% confidence interval

SAPS

APACHE

ISS

PIM

SOFA

PELOD

NUTRICS

MELD

FRAILTY

CHILD-PUGH

SAPS

APACHE

ISS

PIM

SOFA

PELOD

Sequential Organ Failure Score

NUTRICS

MELD

FRAILTY

CHILD-PUGH

Development of SOFA

- **SOFA** (Vincent et al. Intensiv Care Med 1996)
- Reason:
  - → Organ dysfunction/failure is a process rather than an event.
  - → The time factor is fundamental
  - → The evaluation of organ dysfunction/failure should be based on a limited number of simple but objective variables
- Application:
  - → To improve our Understanding of the natural history of organ dysfunction/failure and the interrelation between the failure of the various organs.
  - → To assess the effects of new therapies on the course of organ dysfunction/failure.
  - → It is important to realize that the SOFA score is designed not to *predict* outcome but to *describe* a sequence of complications in the critically ill.

Development of SOFA

- **SOFA** (Vincent et al. Intensiv Care Med 1996)

- The authors decided:
  → to limit the number of organs studied to 6. As an example, attempting to include dysfunction/failure of the gut was felt to be very important, but also too complex and was therefore abandoned.
  → To use a score from 0 (normal) to 4 (most abnormal) for each organ.
  → To record the worst values on each day.

Development of SOFA

- **SOFA** (Vincent et al. Intensiv Care Med 1996)

Table 3 The SOFA score

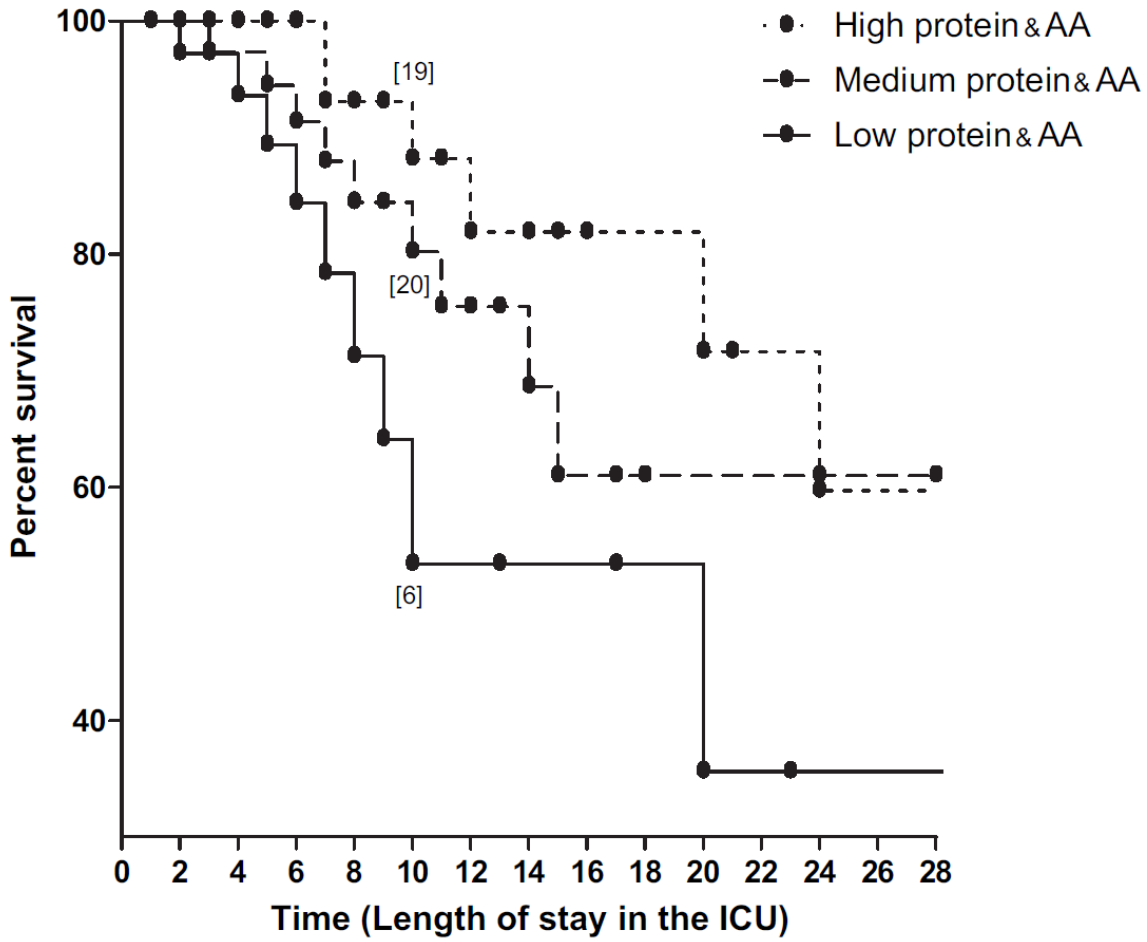
SOFA score	1	2	3	4
Respiration				
PaO_2/FiO_2, mmHg	< 400	< 300	< 200	< 100
			——— with respiratory support ———	
Coagulation				
Platelets $\times 10^3/mm^3$	< 150	< 100	< 50	< 20
Liver				
Bilirubin, mg/dl (μmol/l)	1.2 – 1.9 (20 – 32)	2.0 – 5.9 (33 – 101)	6.0 – 11.9 (102 – 204)	> 12.0 (< 204)
Cardiovascular				
Hypotension	MAP < 70 mmHg	Dopamine ≤ 5 or dobutamine (any dose)[a]	Dopamine > 5 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1
Central nervous system				
Glasgow Coma Score	13 – 14	10 – 12	6 – 9	< 6
Renal				
Creatinine, mg/dl (μmol/l) or urine output	1.2 – 1.9 (110 – 170)	2.0 – 3.4 (171 – 299)	3.5 – 4.9 (300 – 440) or < 500 ml/day	> 5.0 (> 440) or < 200 ml/day

[a] Adrenergic agents administered for at least 1 h (doses given are in μg/kg·min)

Example

Allingstrup et al. Clin Nutr 2012

Example



Allingstrup et al. Clin Nutr 2012

Example

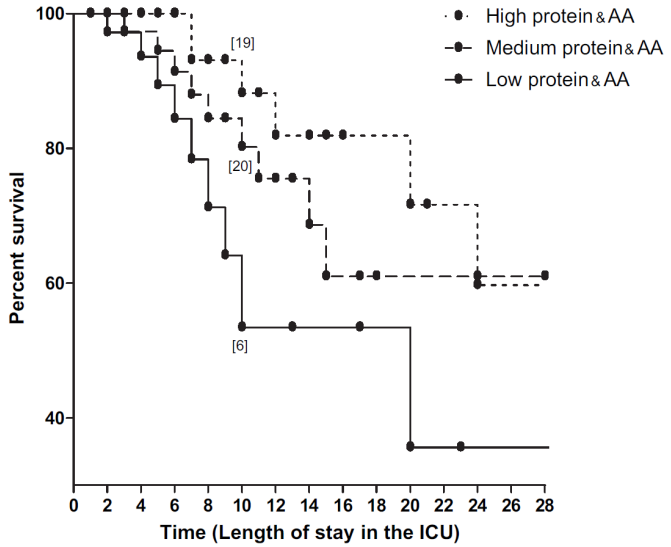


Table 3
Cox regression analysis of ICU mortality ($N = 113$).

Variable	Unadjusted HR	95% CI	*P*	Adjusted for APACHE II HR	95% CI	*P*	Adjusted for SOFA HR	95% CI	*P*	Adjusted for age HR	95% CI	*P*
APACHE II score	1.10	1.03–1.17	0.003	–	–	–	1.08	1.01–1.16	0.023	1.08	1.01–1.15	0.03
Average SOFA score	1.11	1.01–1.21	0.03	1.05	0.94–1.16	NS ($P = 0.39$)	–	–	–	1.09	0.99–1.20	NS ($P = 0.10$)
Age	1.07	1.03–1.11	<0.001	1.06	1.02–1.10	0.002	1.06	1.03–1.10	<0.001	–	–	–
Protein&AA provision, g/d	0.98	0.96–0.99	0.01	0.98	0.97–0.99	0.03	0.98	0.97–0.99	0.014	0.98	0.97–0.99	0.03
Energy provision, kcal/d	0.99	0.99–1.00	NS ($P = 0.20$)	1.00	0.99–1.00	NS ($P = 0.43$)	1.00	0.99–1.00	NS ($P = 0.38$)	1.00	0.99–1.00	NS ($P = 0.38$)

Hazard Ratio (HR) for death in unadjusted, univariate analysis and adjusted for the non-nutritional outcome determinants.

Allingstrup et al. Clin Nutr 2012

Take home

- Confounders are everywhere, some we know, many probably not
- A confounder should have an association with both the exposure and the outcome, but should not be part of the causal pathway
- There are several ways of dealing with confounders, by prevention and/or correction
- Nutritional interventions are often confounded by severity of disease, especially in observational studies BUT this can be corrected for
- HOWEVER, know the purpose and limitations of the severity score you use