Alterazioni metaboliche nel paziente settico: diagnosi e terapia nutrizionale

Lezione MBPE 5° anno CdL Medicina 25.05.2020

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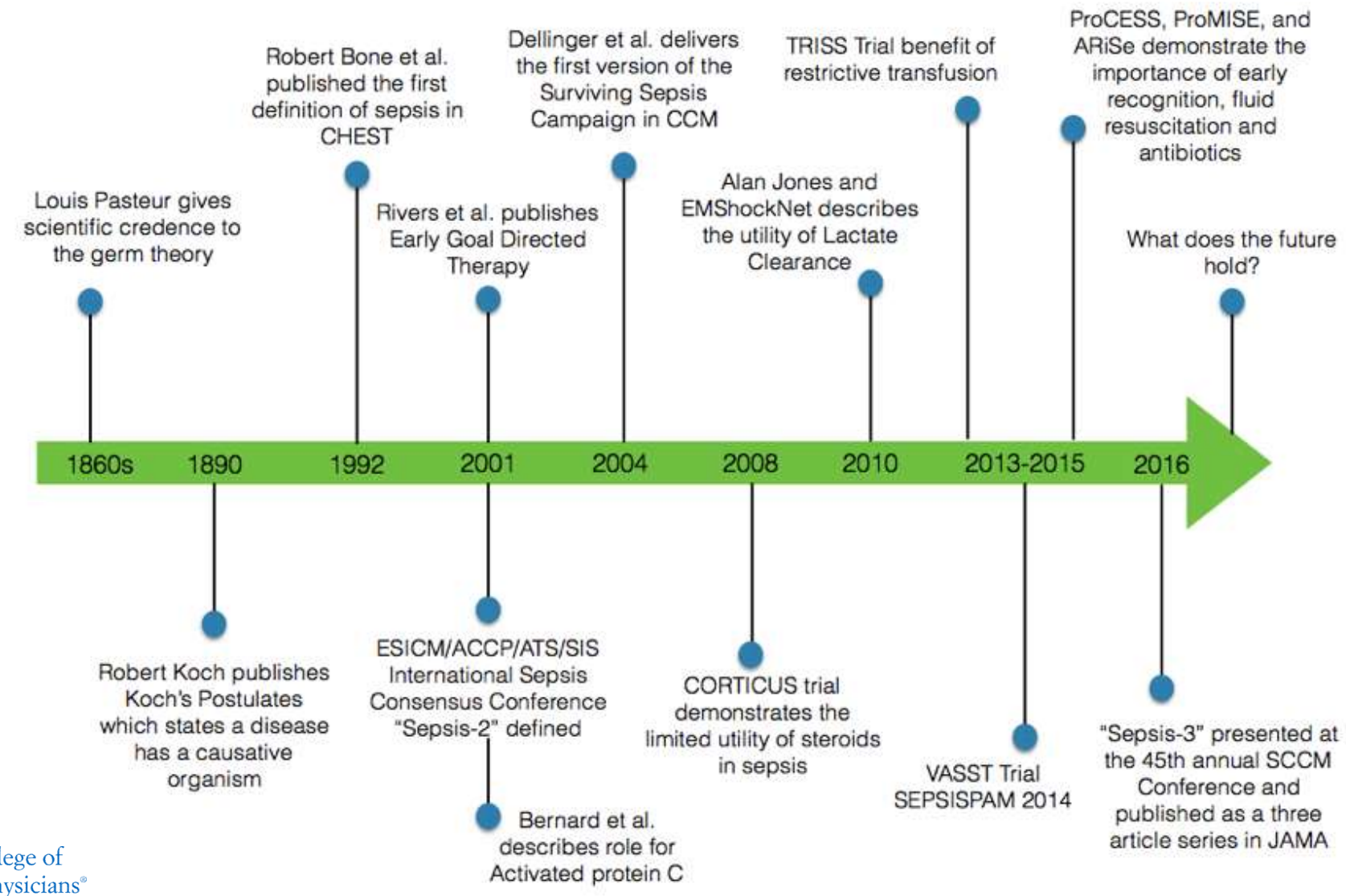
UNIVERSITÀ
DEGLI STUDI DI TRIESTE

History of Sepsis definition



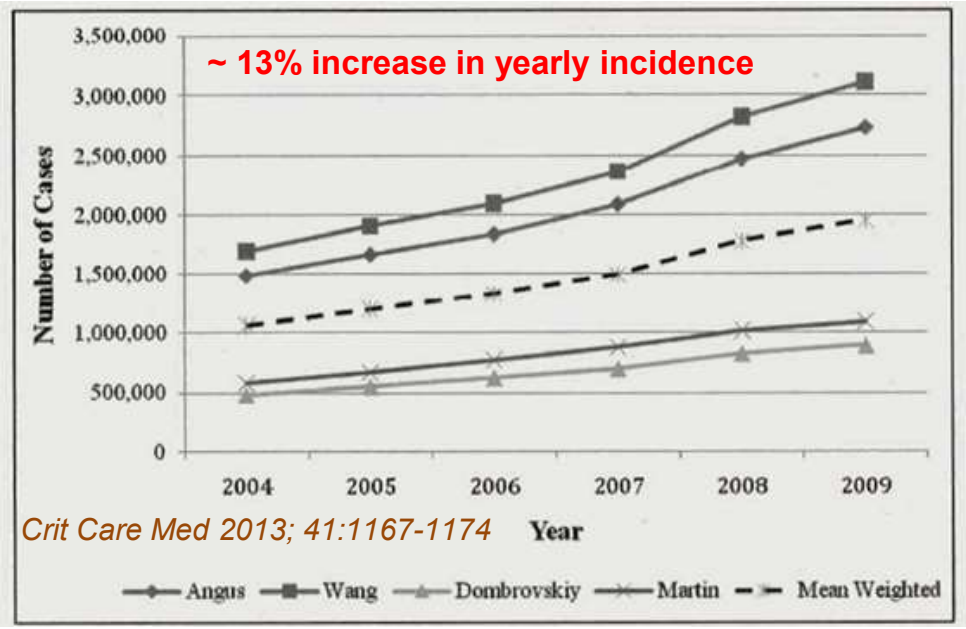
Evolving epidemiology of sepsis

Trajectories

Lancet Infect Dis 2012;12:919-24

	USA	Europe	p value*
ICU patients with sepsis	18766	6609	
Origin			<0·0001
Emergency department	12218 (65·1%)	2159 (32·7%)	
Ward	4763 (25·4%)	3405 (51·5%)	

Yearly incidence (~ 0.5-0.8 %)

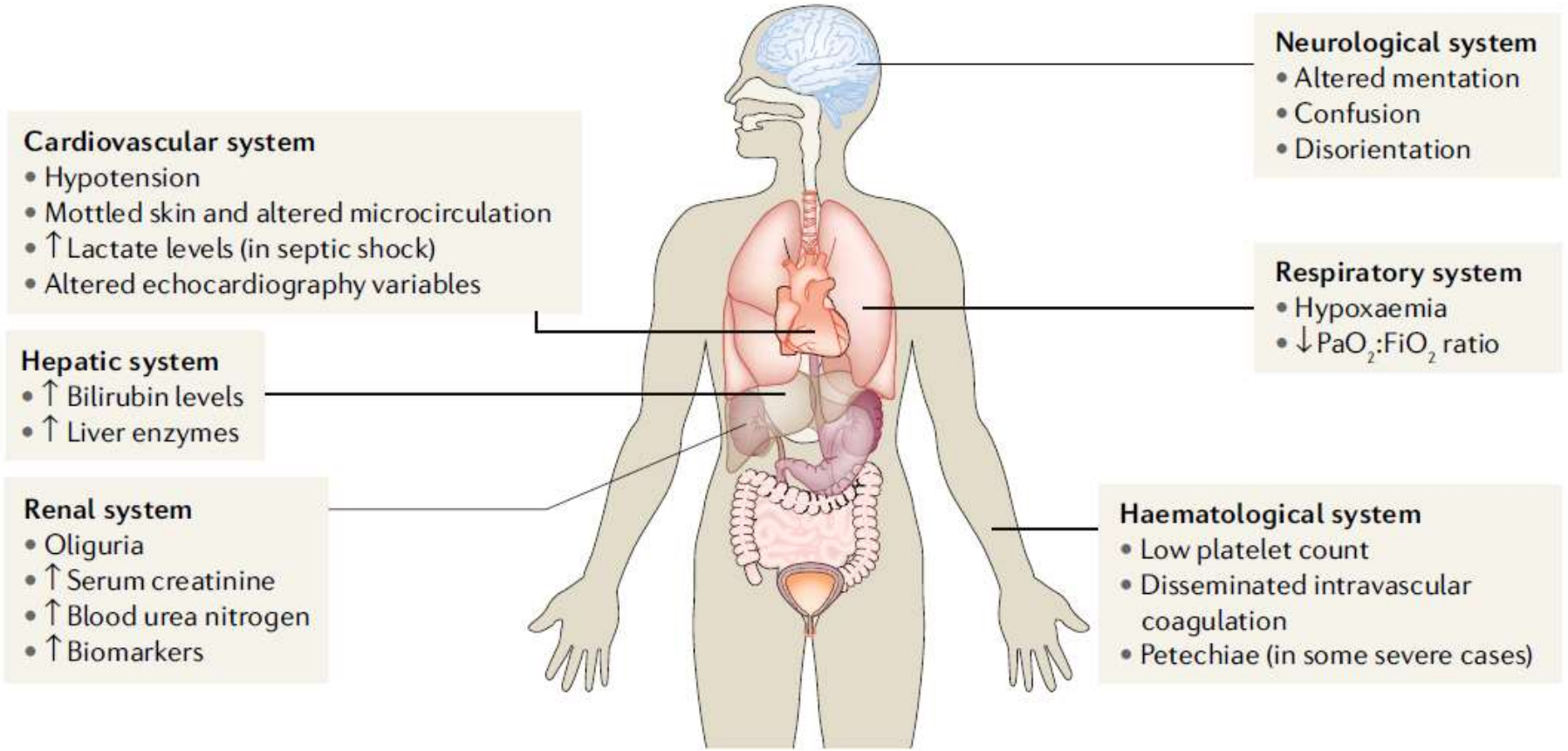


Crit Care Med 2013; 41:1167-1174

Risk factors for developing sepsis

- **Age**
- **Chronic illness**
- **Impaired immunity**
- **Trauma, surgical injury, burns**
- **Catheterization or intubation**
- **Chronic infections**
- **Protein calorie malnutrition**

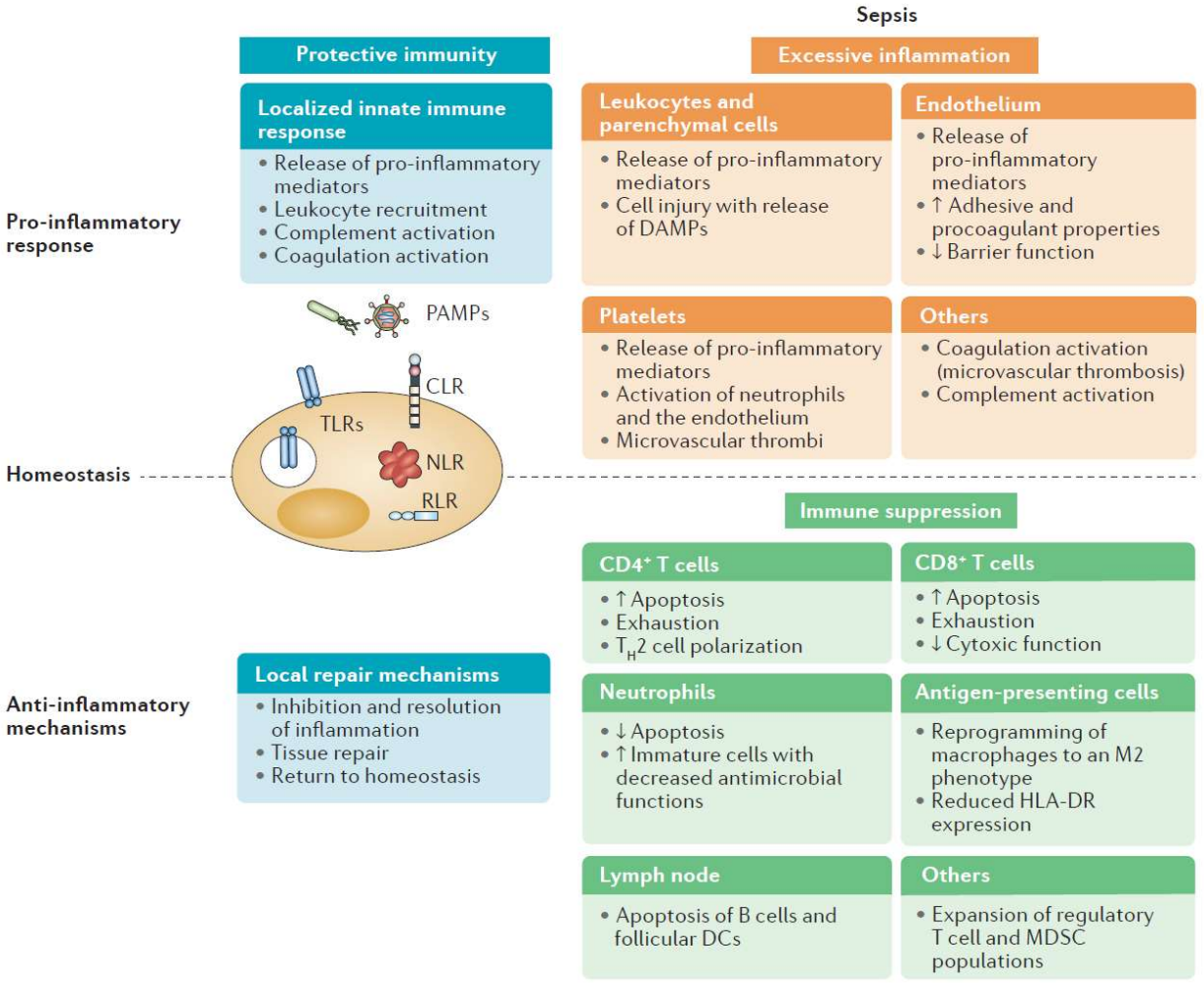
The third international consensus definitions for sepsis and septic shock (Sepsis-3) JAMA 2016: life-threatening organ dysfunction caused by a dysregulated host response to infection



Although dysfunction can occur in any organ in patients with sepsis, dysfunction in some organs, such as the gastrointestinal tract, is difficult to quantify. Six organ systems for which dysfunction has severe consequences or in which dysfunction is readily detectable are usually monitored in clinical practice.

Nat Rev Nephrol. 2018 Jul;14(7):417-427. doi: 10.1038/s41581-018-0005-7.

SEPSIS = DYSREGULATED HOST RESPONSE TO INFECTION



LIFE THREATENING ORGAN DYSFUNCTIONS

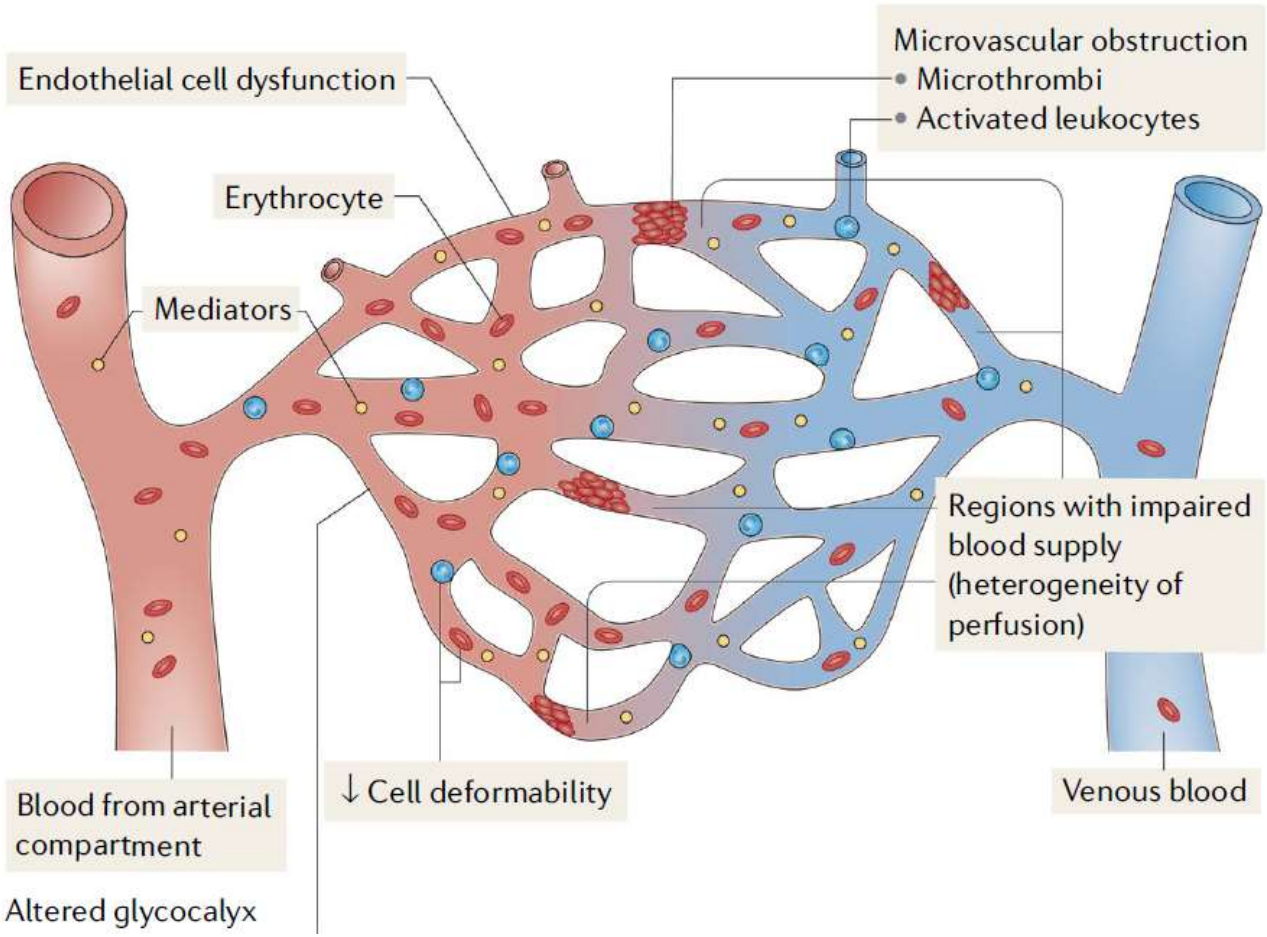
(cardiovascular, respiratory, renal, neurological, haematological, hepatic and gastrointestinal systems)

SEPTIC SHOCK

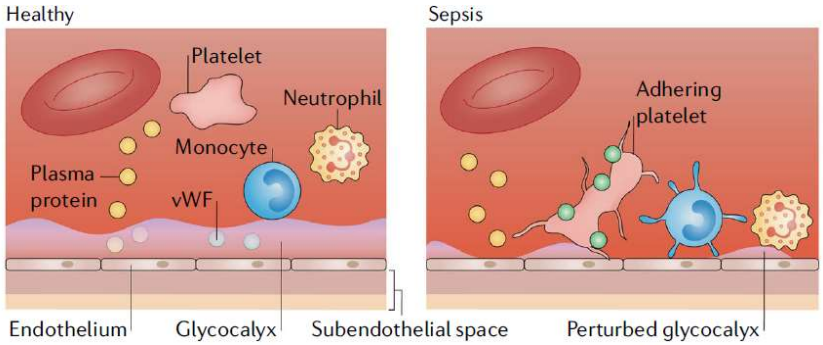
NATURE REVIEWS | IMMUNOLOGY 2017 doi:10.1038/nri.2017.36

Nat Rev Nephrol. 2018 Jul;14(7):417-427. doi: 10.1038/s41581-018-0005-7.

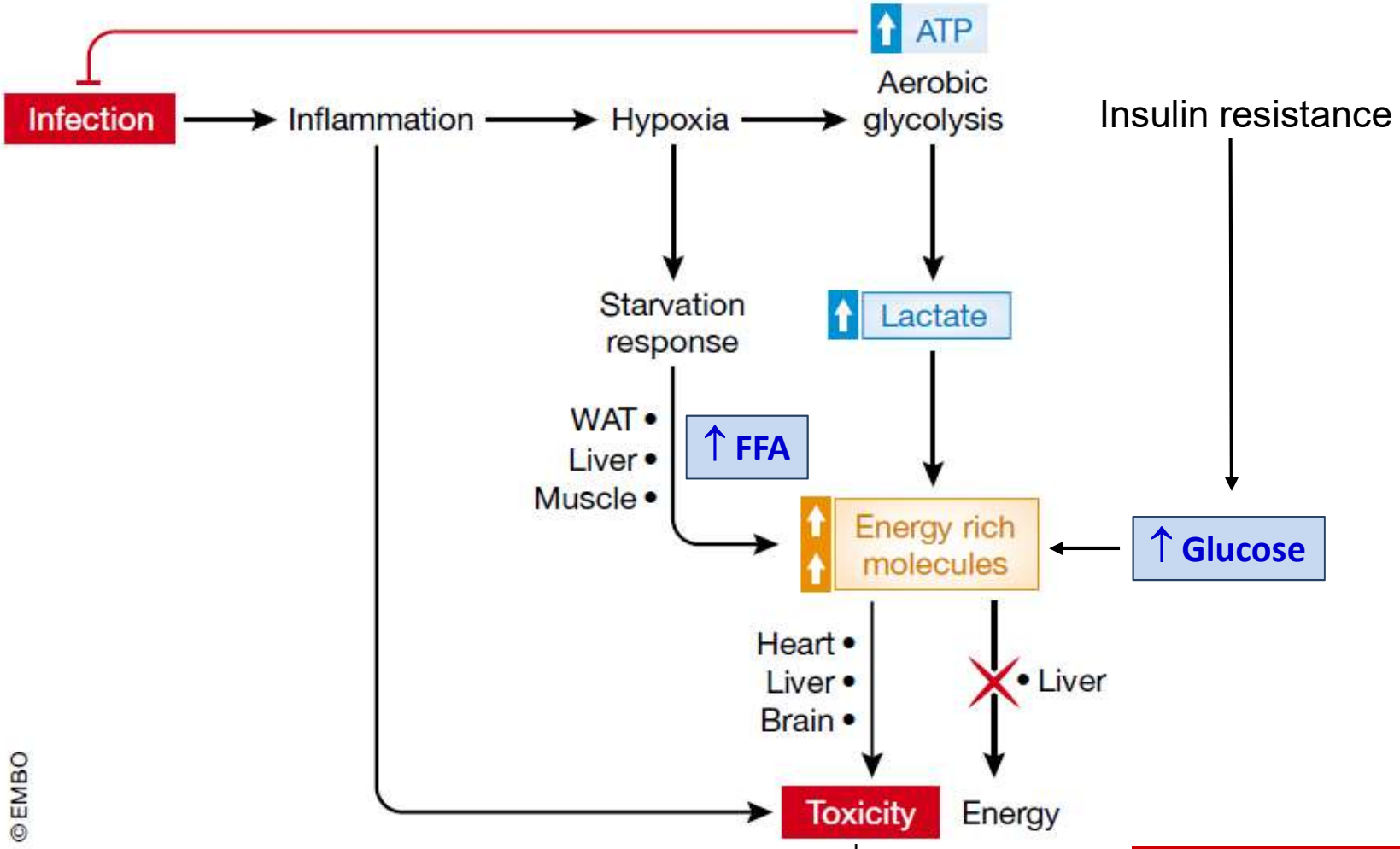
Microvascular and cellular alterations in sepsis



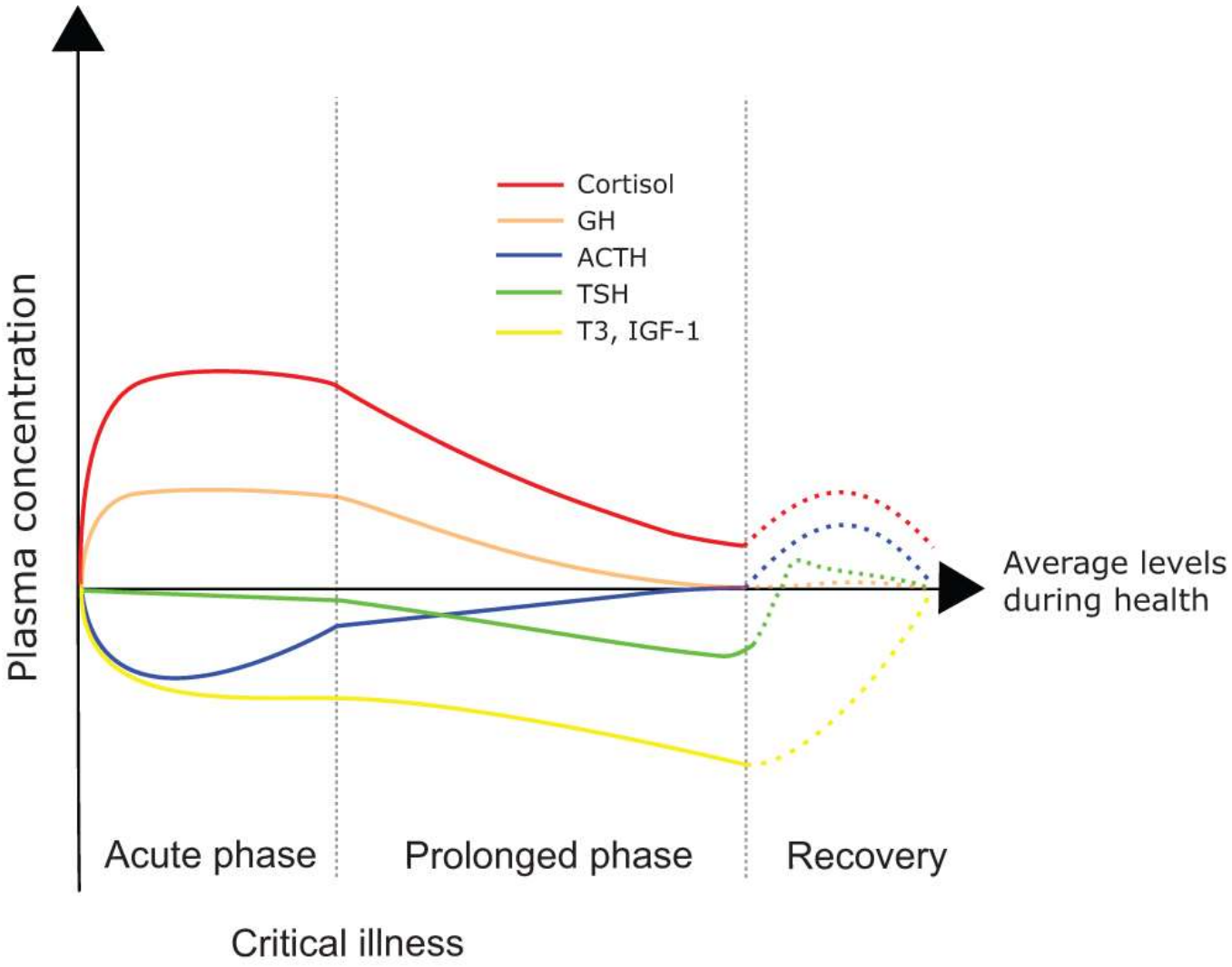
Altered glycocalyx



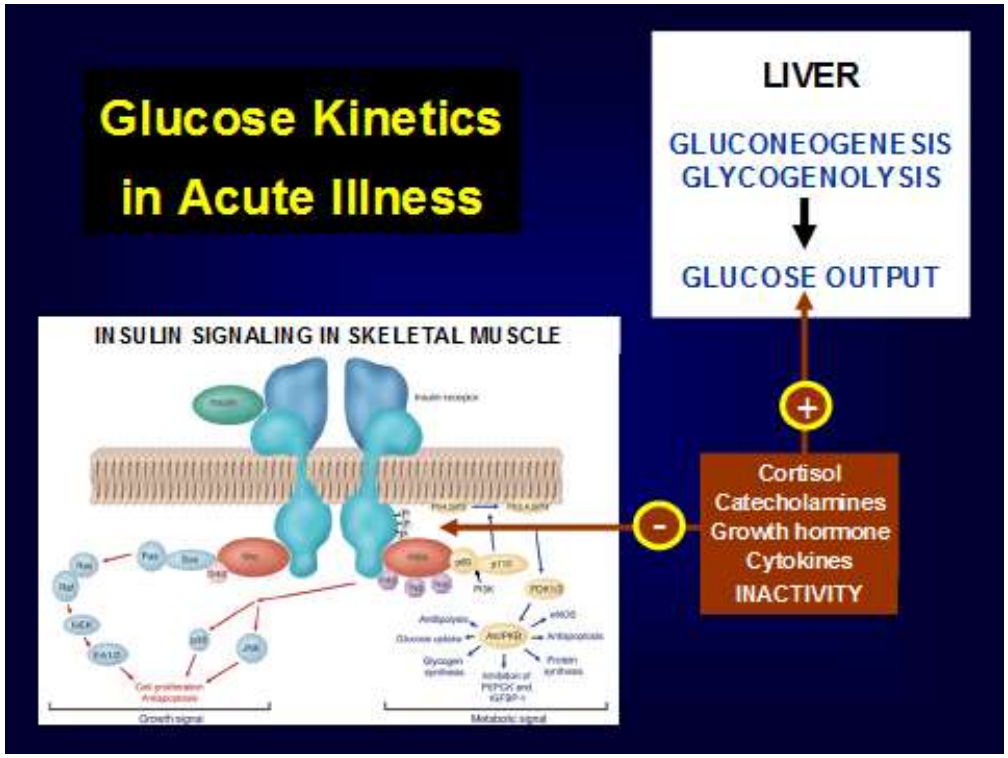
The toxic consequences of metabolic reprogramming in sepsis

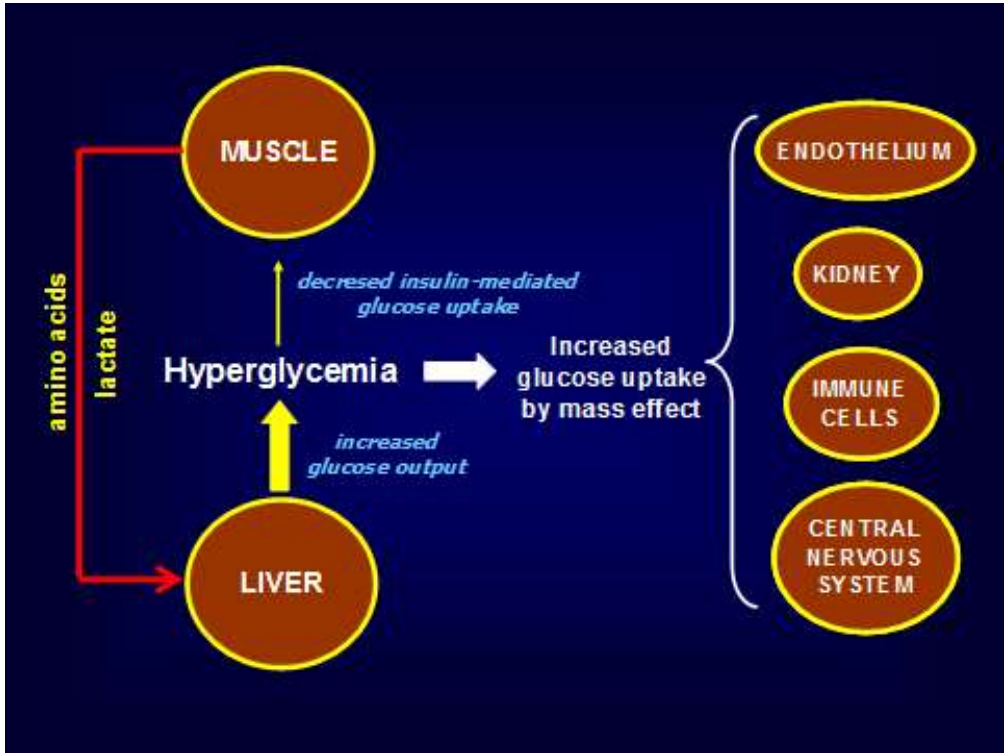


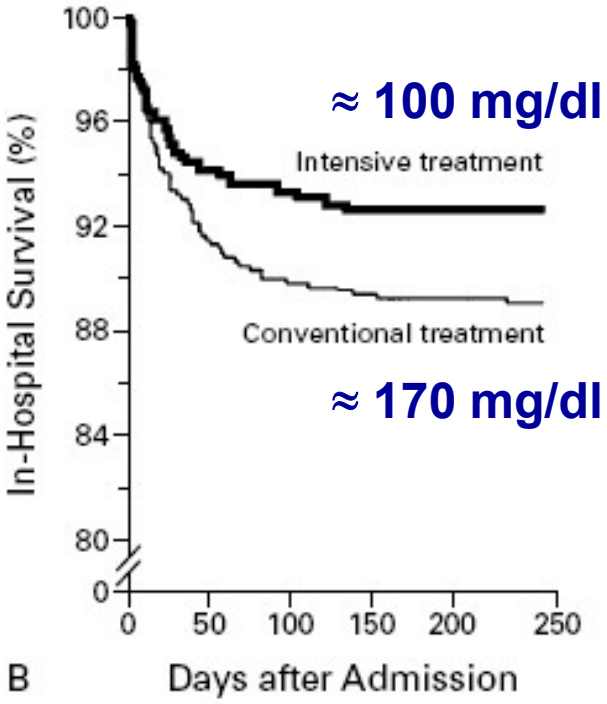
EMBO Molecular Medicine 2018



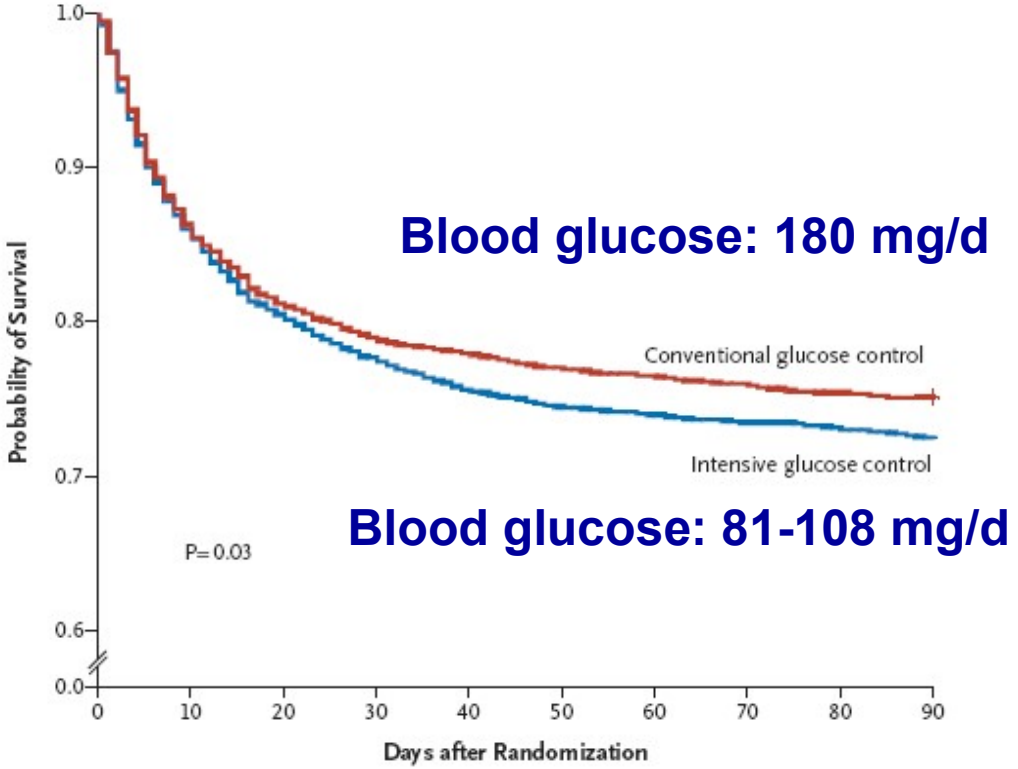
Biphasic neuroendocrine response to critical illness. Trends in plasma concentrations of the most important pituitary and peripheral hormones during critical illness are rendered over time and compared to the physiological ranges in healthy individuals (black line). A rise in growth hormone levels is seen in the first hours after the onset of critical illness (orange line). This rise in GH coincides with a decrease in IGF-I (yellow line). During the chronic phase of critical illness, IGF-I further decreases and GH plasma concentration start to normalize. Thyroid hormone T3 levels rapidly decreases after the onset of critical illness with a further decline during the prolonged phase of critical illness (yellow line). It is currently unclear when the plasma levels of both IGF-1 and T3 fully normalize (dotted yellow line). Although TSH levels (green line) are not significantly altered during the first hours and days of critical illness, plasma concentration decreases when chronic critical illness sets in. When recovery is commenced, TSH transiently rise to supra-normal concentration before returning to physiological levels. Cortisol levels (red line) rise after a severe insult. High cortisol levels plateau in the first week of critical illness. When critical illness is prolonged, cortisol levels start to decrease. ACTH levels are rapidly reduced in acute critical illness but start to normalize after several days of critical illness. During the recovery phase, a rise in plasma concentrations of both ACTH and cortisol is seen (dotted blue line and dotted red line); however, when this rise is dampened and the circulating levels of ACTH and cortisol start to normalize is not clear. ***DOI: https://doi.org/10.1530/EC-19-0318***


Glucose Kinetics
in Acute Illness
LIVER
GLUCONEOGENESIS
GLYCOGENOLYSIS
GLUCOSE OUTPUT
INSULIN SIGNALING IN SKELETAL MUSCLE
+
-
Cortisol
Catecholamines
Growth hormone
Cytokines
INACTIVITY


MUSCLE
amino acids
lactate
decresed insulin-mediated
glucose uptake
Hyperglycemia
Increased
glucose uptake
by mass effect
increased
glucose output
LIVER
ENDOTHELIUM
KIDNEY
IMMUNE
CELLS
CENTRAL
NERVOUS
SYSTEM



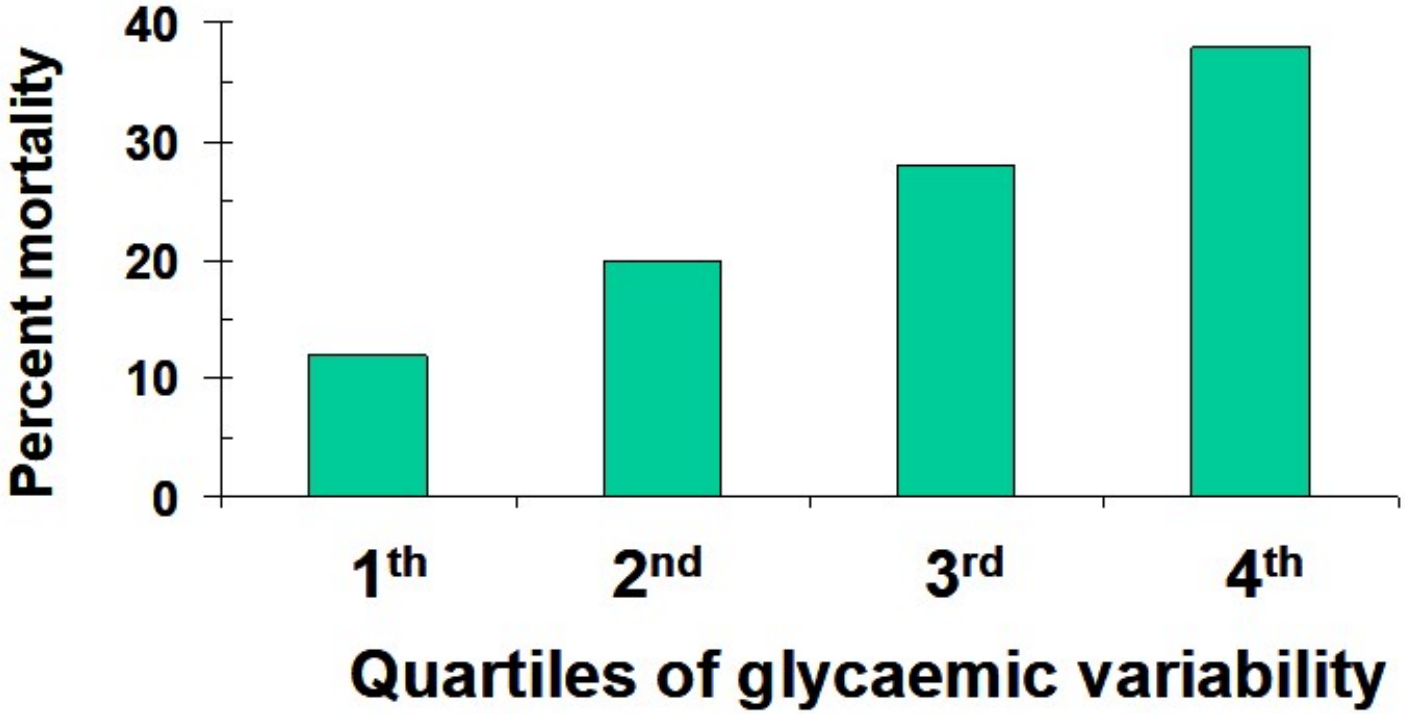
SURGICAL ICU
Van del Berghe
NEJM 2001



MIXED ICU
NICE sugar study
NEJM 2009

Glycemic variability: a strong independent predictor of mortality in critically ill patients

Krinsley, Crit Care Med. 2008



The relationship between glycemic variability and mortality was strongest in the euglycemic range (70-110)

Recommendation 53 and 54

- **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.**

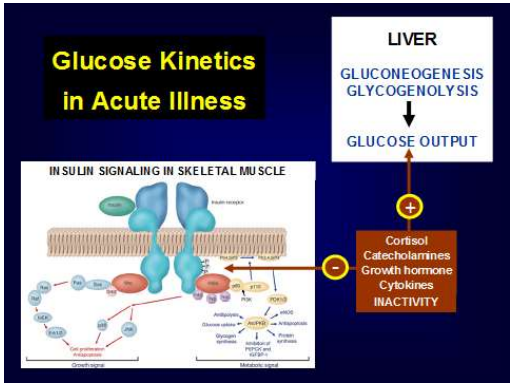
Grade of recommendation: GPP - strong consensus (93% agreement)

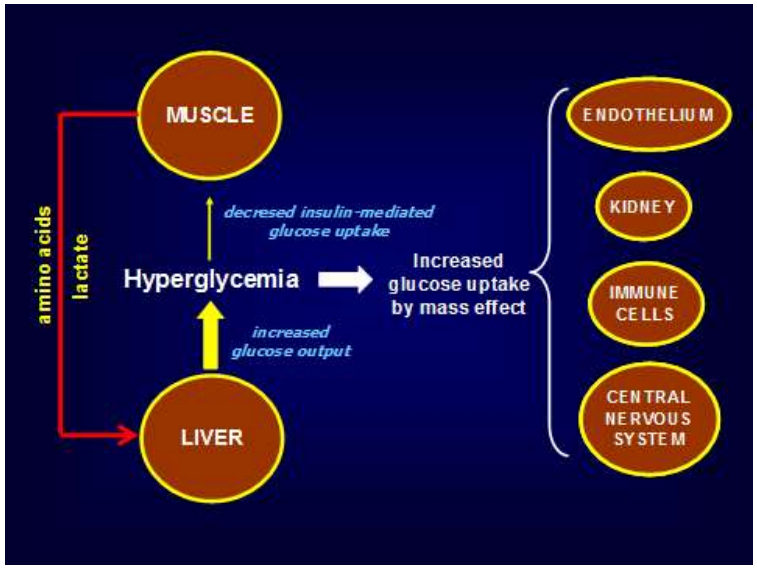
- **Insulin shall be administered, when glucose levels exceed 10 mmol/L (180 mg/dl).**

Grade of recommendation: A - strong consensus (93% agreement)

ESPEN guideline on clinical nutrition in the intensive care unit
Clinical Nutrition 38 (2019) 48-79

- Strong association between **dysglycemia** [i.e severe hyperglycemia (>180 mg/dl, >10 mmol/L), marked glycemic variability (coefficient of variation > 20%), mild hypoglycemia (<70 mg/dl)] and increased mortality.
- **Glycemic target** associated with best outcome and lowest risk of hypoglycemia: **144-180 mg/dl** (6-10 mmol/L) [JAMA 2017;42:16-28.]
- **Process of glycemic control in ICU to avoid dysglycemia**:
  - **Blood draw**: preferentially central venous or arterial. Avoid capillary pricks in critically ill patients
  - **Glucose** meter: the point-of-care devices are not validated for use in the critically ill, as several sources of interference are likely. The use of blood gas analyzer or central laboratory analyzers (hexokinase-based) is essential.
  - **Insulin**: **intravenous and continuous** in case of ongoing nutrition support (enteral or parenteral) using an electric syringe.
  - Insulin algorithm: **dynamic scale** rather than sliding scales
  - Hyperglycemia can be managed with increased insulin doses, but **adequacy of carbohydrate administration** should always be considered when high insulin is required (> 6 U/hr).



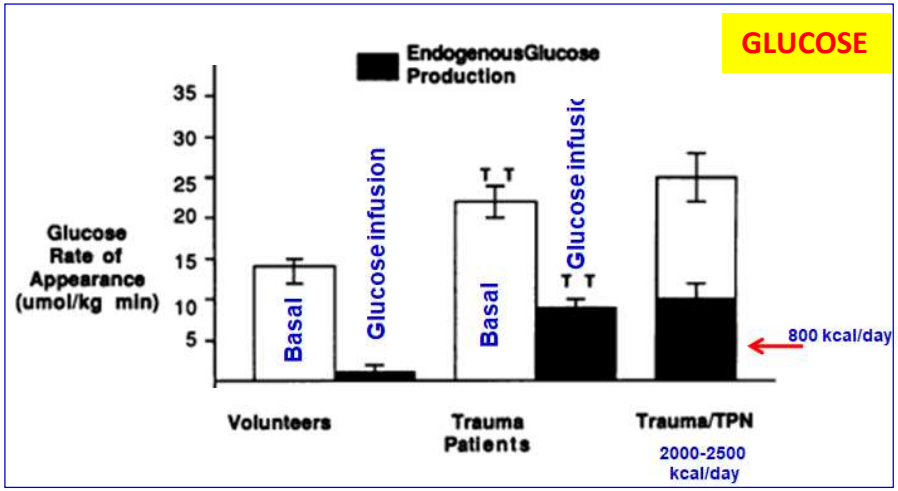


The early phase of critical illness is associated with relevant endogenous energy production

An Integrated Analysis of Glucose, Fat, and Protein Metabolism in Severely Traumatized Patients

Studies in the Basal State and the Response to Total Parenteral Nutrition

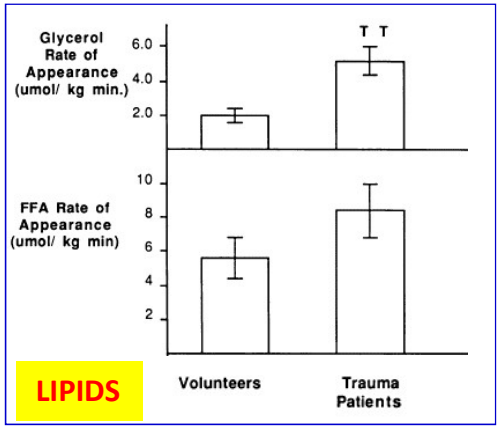
Ann. Surg. • January 1989

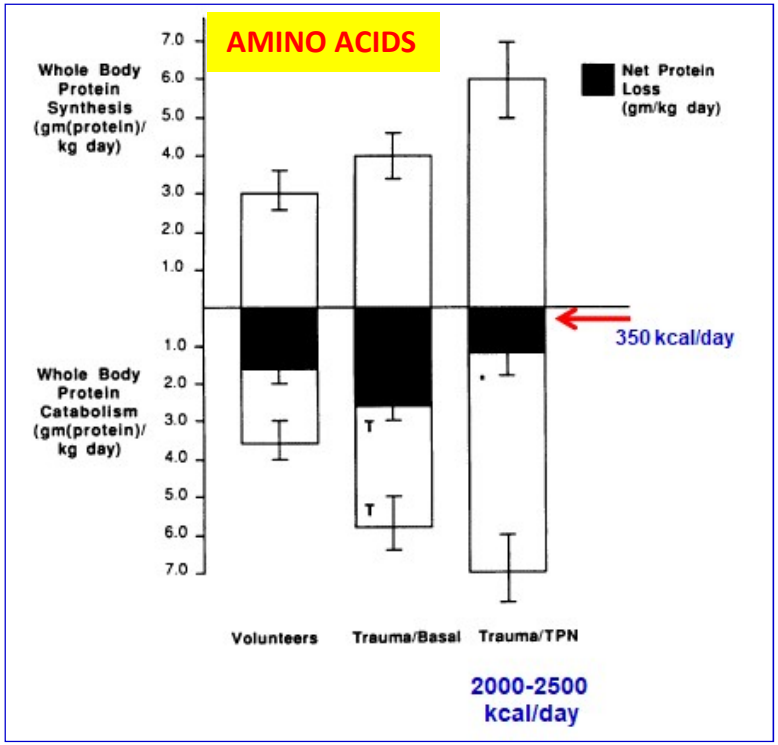


Fasting glucose production
Volunt: 250 g/day
Trauma: 400 g/day
1500 kcal/day

Glucose infusion (250 g/day)
Endogenous production
Volunt: <10 g/day
Trauma: 180 g/day

Kcal/day in trauma patients
Exogenous: 1500
Endogenous: 750



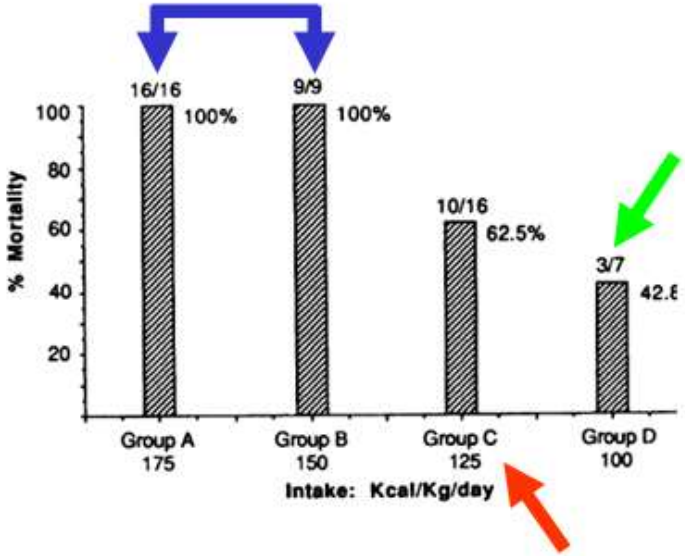


A New Model for Studying Nutrition in Peritonitis

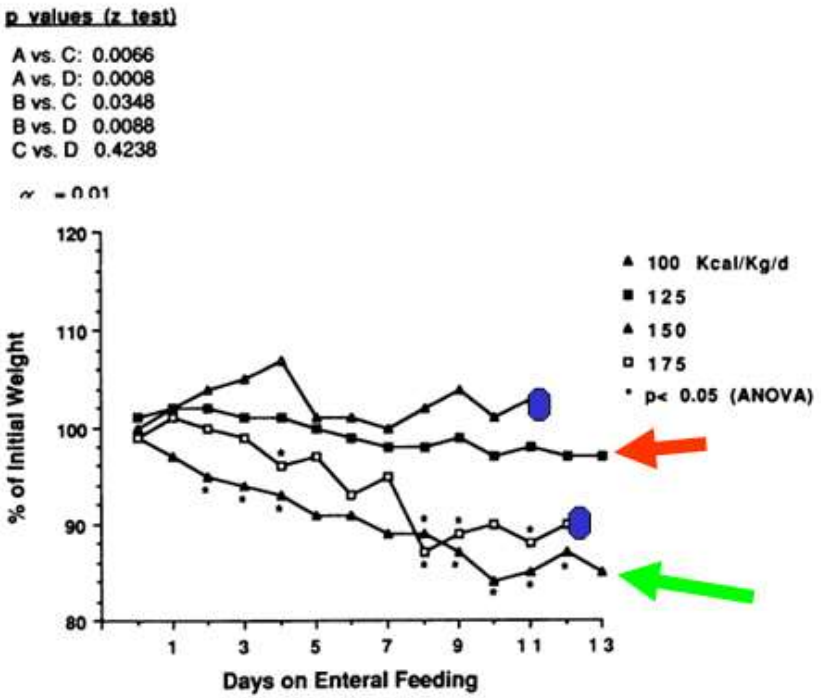
The Adverse Effect of Overfeeding

J. WESLEY ALEXANDER, M.D., Sc.D., SARA J. GONCE, B.A., B.S., PHILLIP W. MISKELL, B.A., B.S., MICHAEL D. PECK, M.D., and HARRY SAX, M.D.

Ann. Surg. • March 1989



125 kcal/kg/day diet was found to be optimal for burned guinea pigs



Weight changes in the four groups of animals given different amounts of food, beginning the day enteral nutrition was started. Gastrostomy feedings were begun on the third day after peritoneal pump placement.

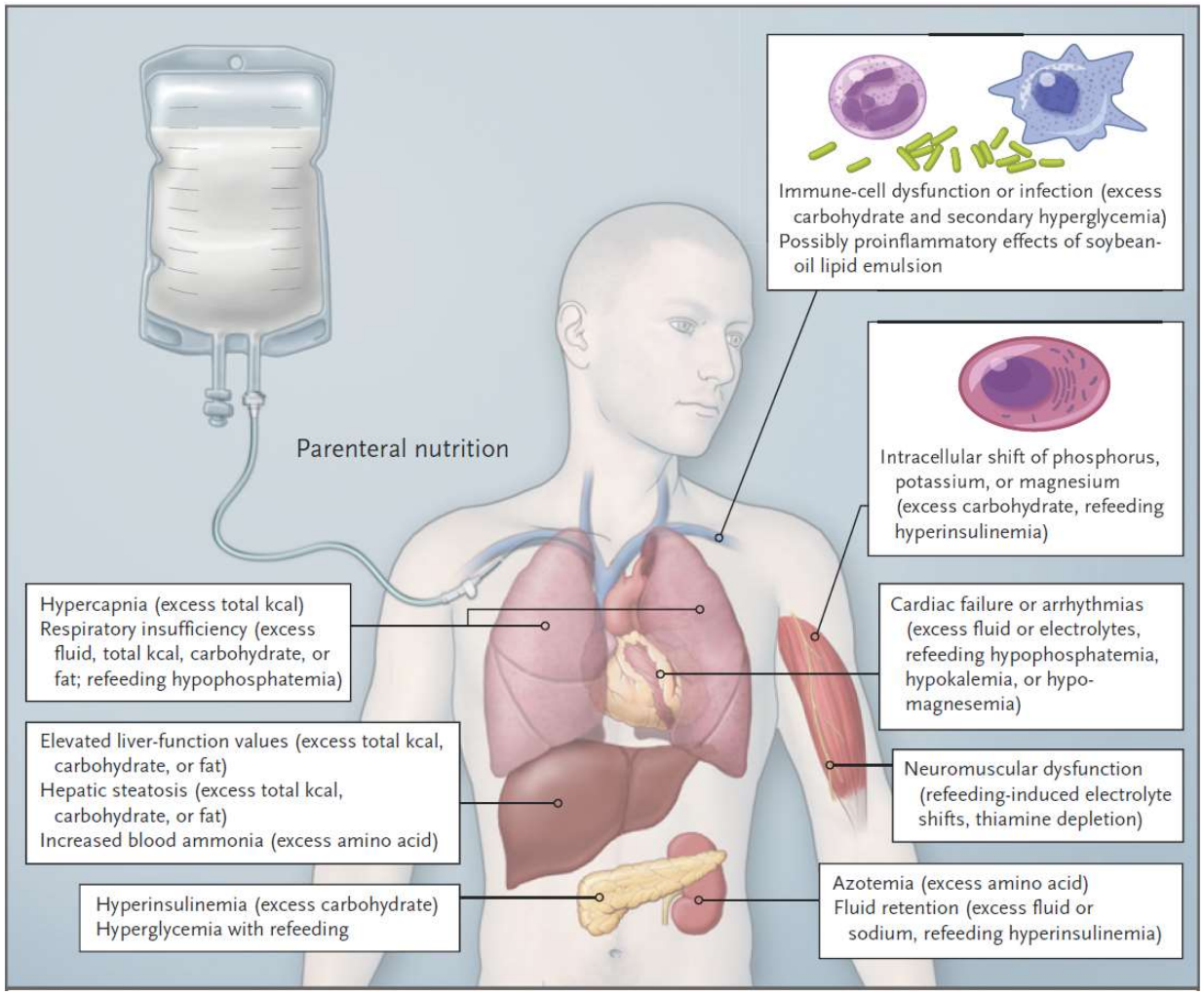
The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL THERAPEUTICS

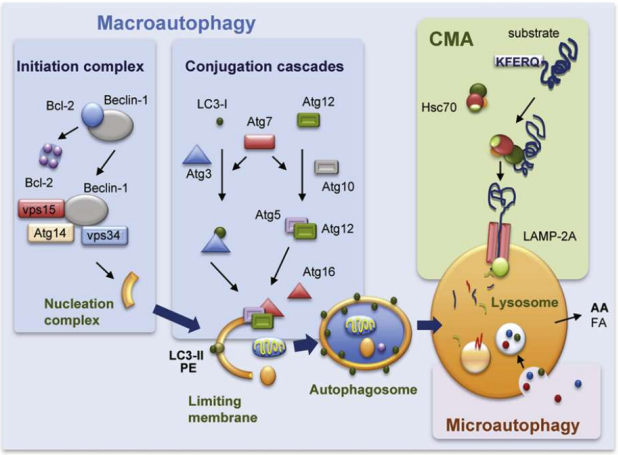
Parenteral Nutrition in the Critically Ill Patient

Thomas R. Ziegler, M.D.

N Engl J Med 2009;361:1088-97.



Potential Metabolic and Clinical Consequences of Overfeeding and the **Refeeding Syndrome** during Administration of Central Venous Parenteral Nutrition in Patients with Critical Illness. Hypertriglyceridemia can occur with excess administration of carbohydrates or fat emulsion; excess administration of specific electrolytes in a variety of clinical conditions (e.g., acute kidney injury) can lead to elevated blood levels, whereas inadequate administration, especially during refeeding, can lead to decreased blood levels. Inadequate energy provision in relation to the dose of amino acids can contribute to azotemia

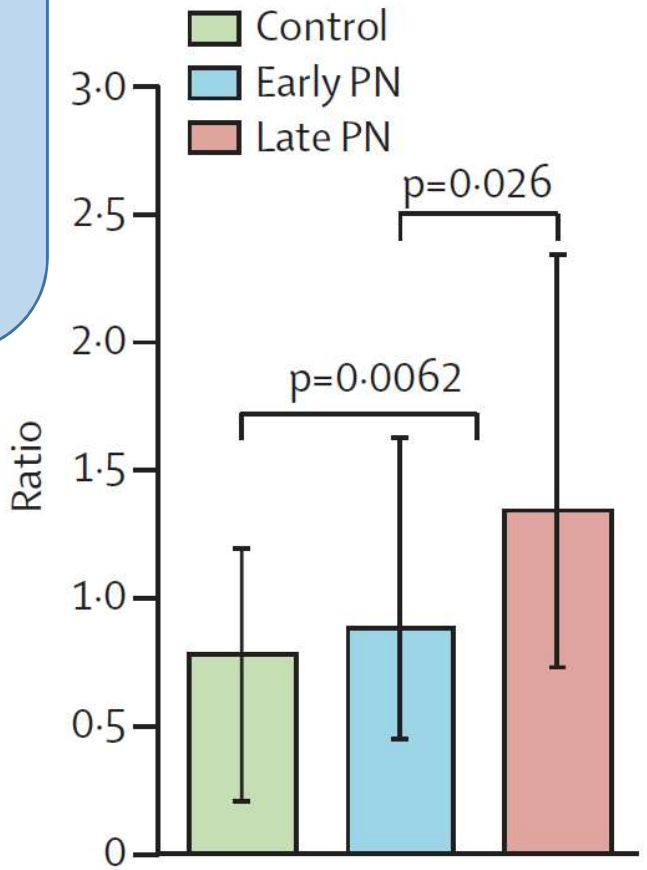


Cell Metabolism 13, May 4, 2011

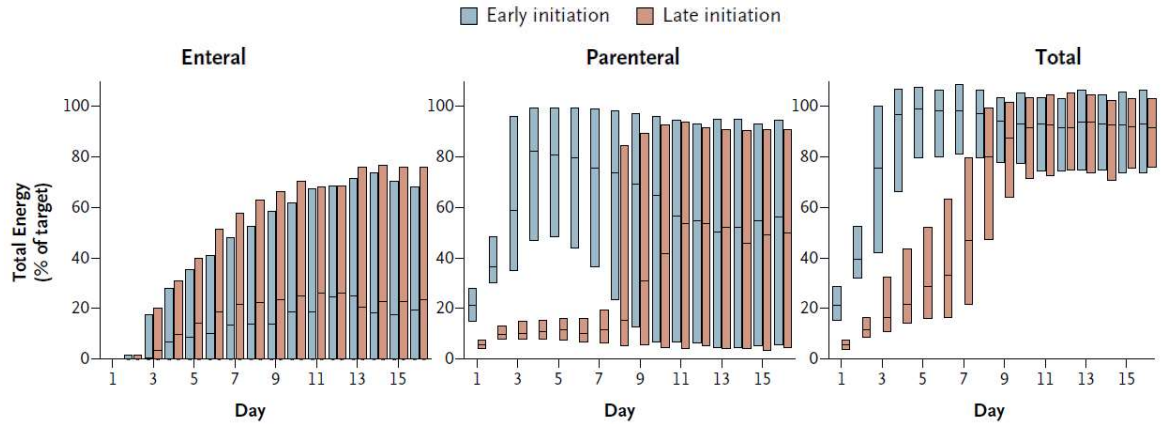
NUTRIENT-INDUCED SUPPRESSION OF AUTOPHAGY

- **Autophagy is a crucial cellular repair process that removes damaged organelles, toxic protein aggregates, and intracellular or macrophage-engulfed microorganisms. It is the only clearance mechanism for damaged mitochondria**
- **The harmful impact of early nutrition may be attributed to nutrient-induced suppression of autophagy.**
- **However, restricting macronutrient intake may only be tolerated for a limited period of time.**
- **The optimal timing when parenteral nutrition can be initiated safely and effectively remains unclear.**

Microtubule-associated protein light chain 3(LC3)
LC3 II to LC3I ratio, related to autophagosome formation



Hermans et al. Subanalysis of the EPaNIC trial Lancet Respir Med 2013; 1: 621–29



Early versus Late Parenteral Nutrition in Critically Ill Adults. EPaNIC study.
Casaer et al. N Engl J Med 2011;365:506-17.

Primary outcome	Late-Initiation Group (N=2328)	Early-Initiation Group (N=2312)	P Value
Duration of stay in ICU§			
Median (interquartile range) — days	3 (2–7)	4 (2–9)	0.02
Secondary outcome			
New infection — no. (%)			
Any	531 (22.8)	605 (26.2)	0.008

Zusman *et al. Critical Care* (2016) 20:367
DOI 10.1186/s13054-016-1538-4

Critical Care

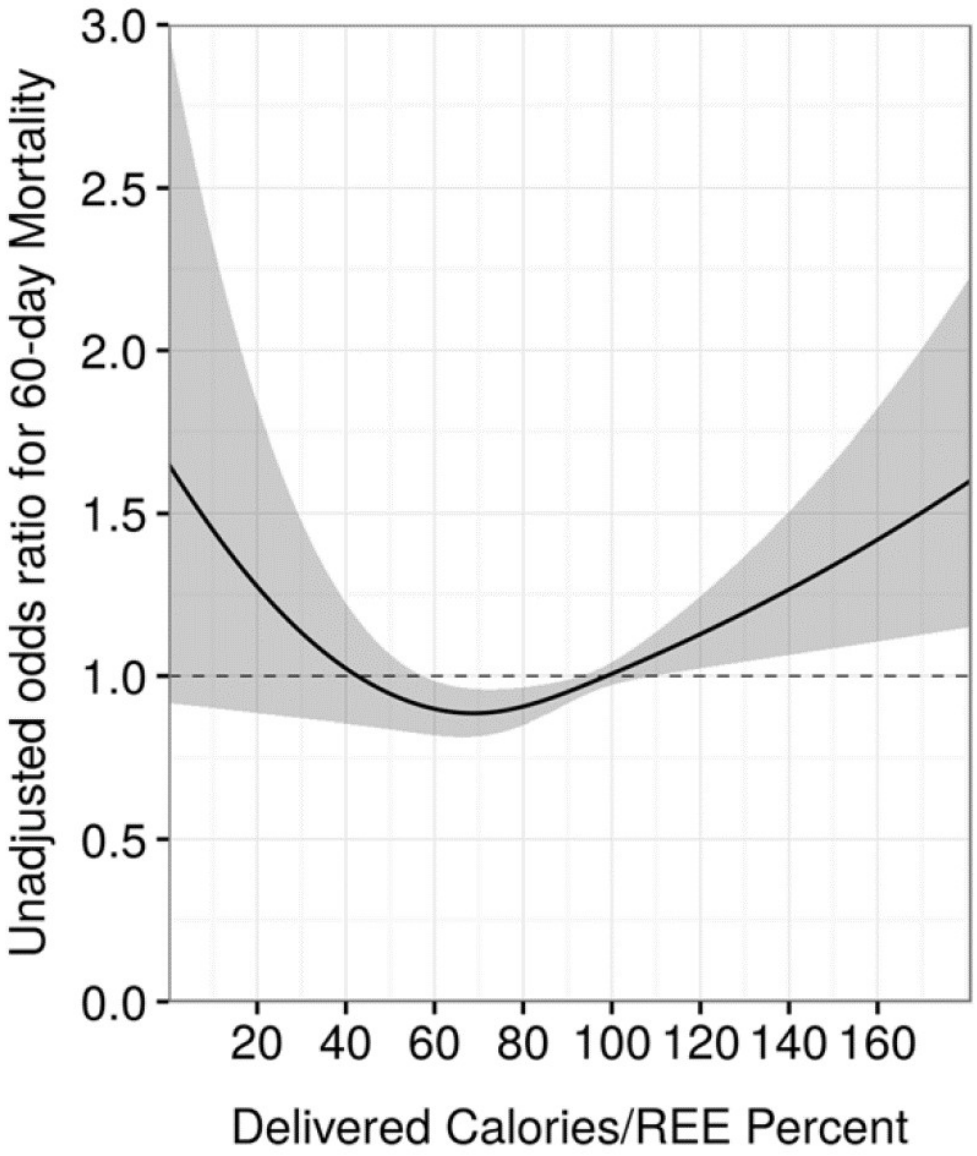
RESEARCH Open Access

Resting energy expenditure, calorie and protein consumption in critically ill patients: a retrospective cohort study

Oren Zusman[1*], Miriam Theilla[2,3], Jonathan Cohen[2,4], Ilya Kagan[2], Itai Bendavid[2] and Pierre Singer[2,4]

- Retrospective study on 1171 mechanically ventilated ICU patients
- Association of administered calories/REE obtained by indirect calorimetry with 60-day mortality by odds ratio.

➢**The therapeutic window of energy delivery in ICU is narrow**



Clinical Nutrition 38 (2019) 1206–1210

Contents lists available at ScienceDirect

Clinical Nutrition

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

Original article

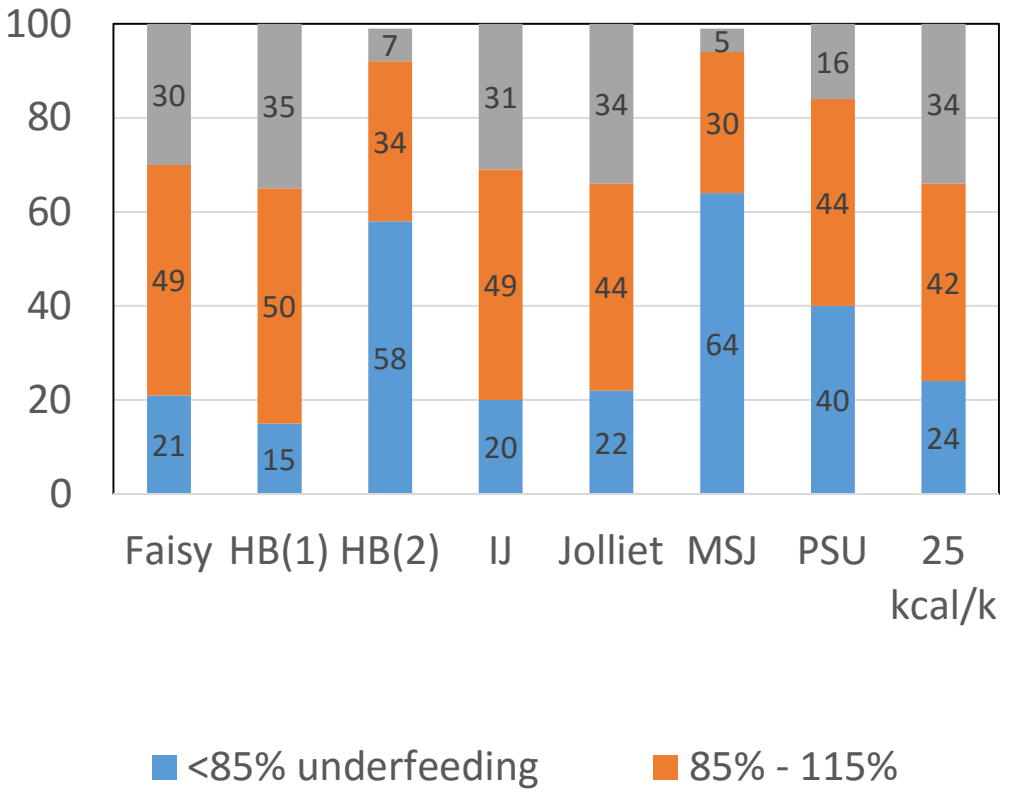
Predictive equations versus measured energy expenditure by indirect calorimetry: A retrospective validation

Oren Zusman [a, b, *], Ilya Kagan [b, c], Itai Bendavid [b, c], Miriam Theilla [c, d], Jonathan Cohen [b, c], Pierre Singer [b, c]

[a] Department of Cardiology, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel
[b] Sackler School of Medicine, Tel Aviv University, Israel
[c] Department of General Intensive Care and Institute for Nutrition Research, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel
[d] Nursing Department, Steyer School of Health Professions, Sackler School of Medicine, Tel Aviv University, Israel

- **Patients hospitalized from 2003 to 2015 in a 16-bed ICU**
- **Total of 3573 resting energy expenditure (REE) measurements via indirect calorimetry (IC) in 1440 patients**
- **A total of 8 equations were examined.**
- **Agreement was defined as a measurement within 85% and 115% of measured REE**

Agreement of equations with measured REE



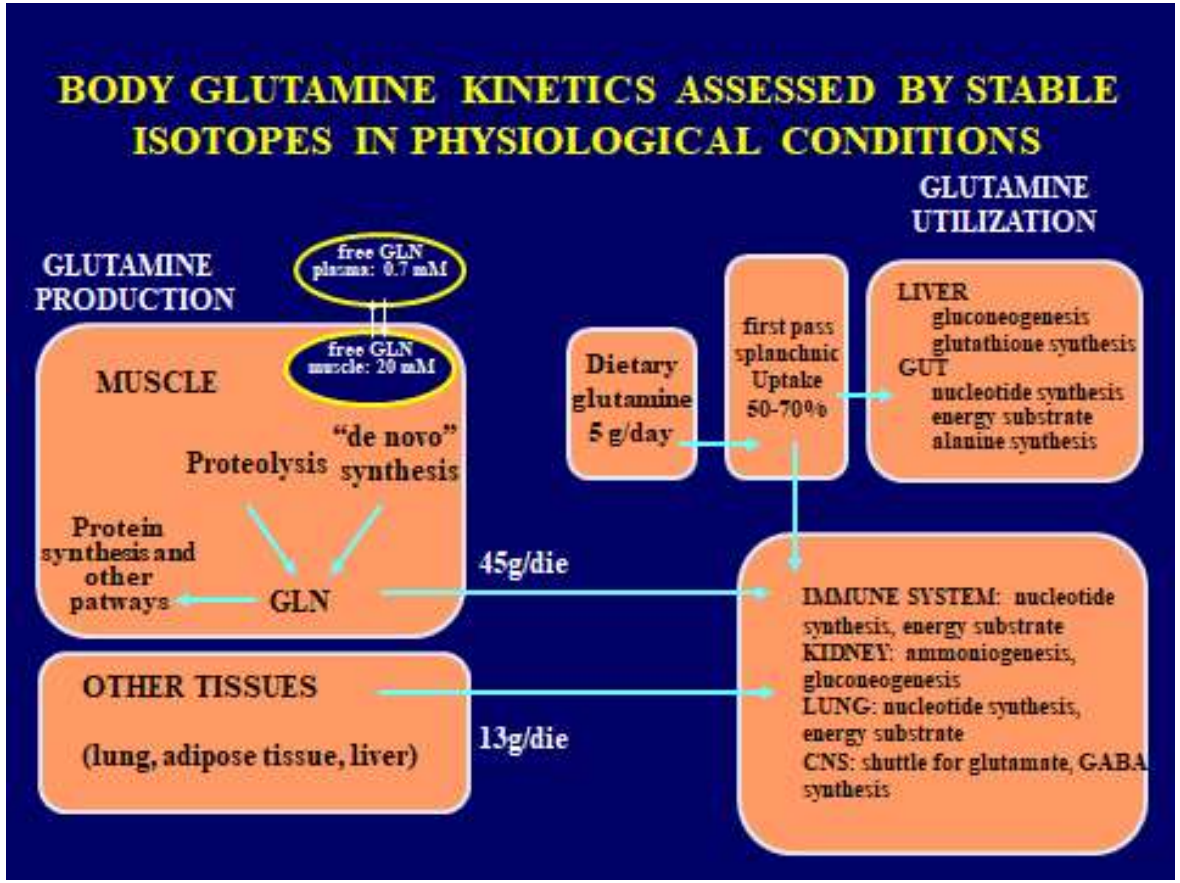
EQUATIONS		
•	Faisy 2003	8*(wt)þ 14*(ht) +42* minute ventilation (m) þ 94*(daily maximal temperature)-4834
•	HB(2) Harris Benedict 1918	Males: 13.75*(ht) + 5*(wt) 6.8*(age) +66 Females: 1.8*(ht) +9.6*(wt) 4.7*(age) +655
•	HB(1)	HB(1) * 1.3
•	IJ Ireton-Jones 1997	1784 þ 5*(wt) 11*(age) þ 244*(male) + 239*(trauma) + 804*(burns)
•	Jolliet 1998	Males, age >60: 25*(wt) Males, age <60: 30*(wt) Females, age >60, 20*(wt) Females, age <60, 25*(wt)
•	MSJ Mifflin-St. Jeor 1990	Males: 10*(wt) þ6.25*(ht) 5*(age) +5 Females: 10*(wt) þ 6.25*(ht) 5*(age) 161
•	PSU Penn State 2003	0.96*(MSJ) + 167*(daily maximal temperature) + 31* minute ventilation (ml) 6212

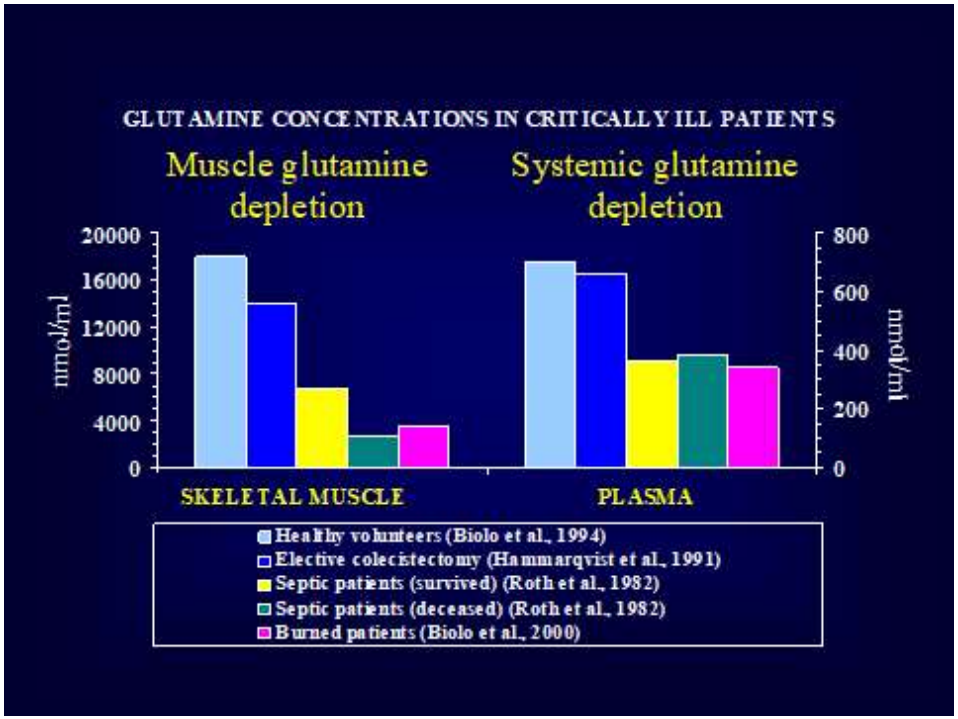
2018 ESPEN guideline on clinical nutrition in the intensive care unit. Singer et al. Clin Nutr 2018

If oral intake is not possible, early EN (within 48 hours) shall be performed/initiated in 402 critically ill adult patients rather than early PN
Grade of recommendation: A – strong consensus (100 % agreement)

Hypocaloric nutrition (not exceeding 70% of EE) should be administered in the early phase of acute illness.
Grade of recommendation: B – strong consensus (100 % agreement)

If predictive equations are used to estimate the energy need, hypocaloric nutrition (below 70 % estimated needs) should be preferred over isocaloric nutrition for the first week of ICU stay.
Grade of recommendation B – strong consensus (95 % agreement)


BODY GLUTAMINE KINETICS ASSESSED BY STABLE ISOTOPES IN PHYSIOLOGICAL CONDITIONS
GLUTAMINE UTILIZATION
GLUTAMINE PRODUCTION
free GLN plasma: 0.7 mM
free GLN muscle: 20 mM
MUSCLE
Proteolysis
"de novo" synthesis
Protein synthesis and other patways
GLN
45g/die
Dietary glutamine 5 g/day
first pass splanchnic Uptake 50-70%
LIVER
gluconeogenesis
glutathione synthesis
GUT
nucleotide synthesis
energy substrate
alanine synthesis
IMMUNE SYSTEM: nucleotide synthesis, energy substrate
KIDNEY: ammoniogenesis, gluconeogenesis
LUNG: nucleotide synthesis, energy substrate
CNS: shuttle for glutamate, GABA synthesis
OTHER TISSUES
(lung, adipose tissue, liver)
13g/die


GLUTAMINE CONCENTRATIONS IN CRITICALLY ILL PATIENTS
Muscle glutamine depletion
Systemic glutamine depletion
nmol/ml
20000
16000
12000
8000
4000
0
800
600
400
200
0
SKELETAL MUSCLE
PLASMA
Healthy volunteers (Biolo et al., 1994)
Elective colecistectomy (Hammarqvist et al., 1991)
Septic patients (survived) (Roth et al., 1982)
Septic patients (deceased) (Roth et al., 1982)
Burned patients (Biolo et al., 2000)

A Randomized Trial of Glutamine and Antioxidants in Critically Ill Patients

Daren Heyland, M.D., John Muscedere, M.D., Paul E. Wischmeyer, M.D., Deborah Cook, M.D., Gwynne Jones, M.D., Martin Albert, M.D., Gunnar Elke, M.D., Mette M. Berger, M.D., Ph.D., and Andrew G. Day, M.Sc., for the Canadian Critical Care Trials Group

N Engl J Med 2013;368:1489-97.

GLUTAMINE SUPPLEMENTATION

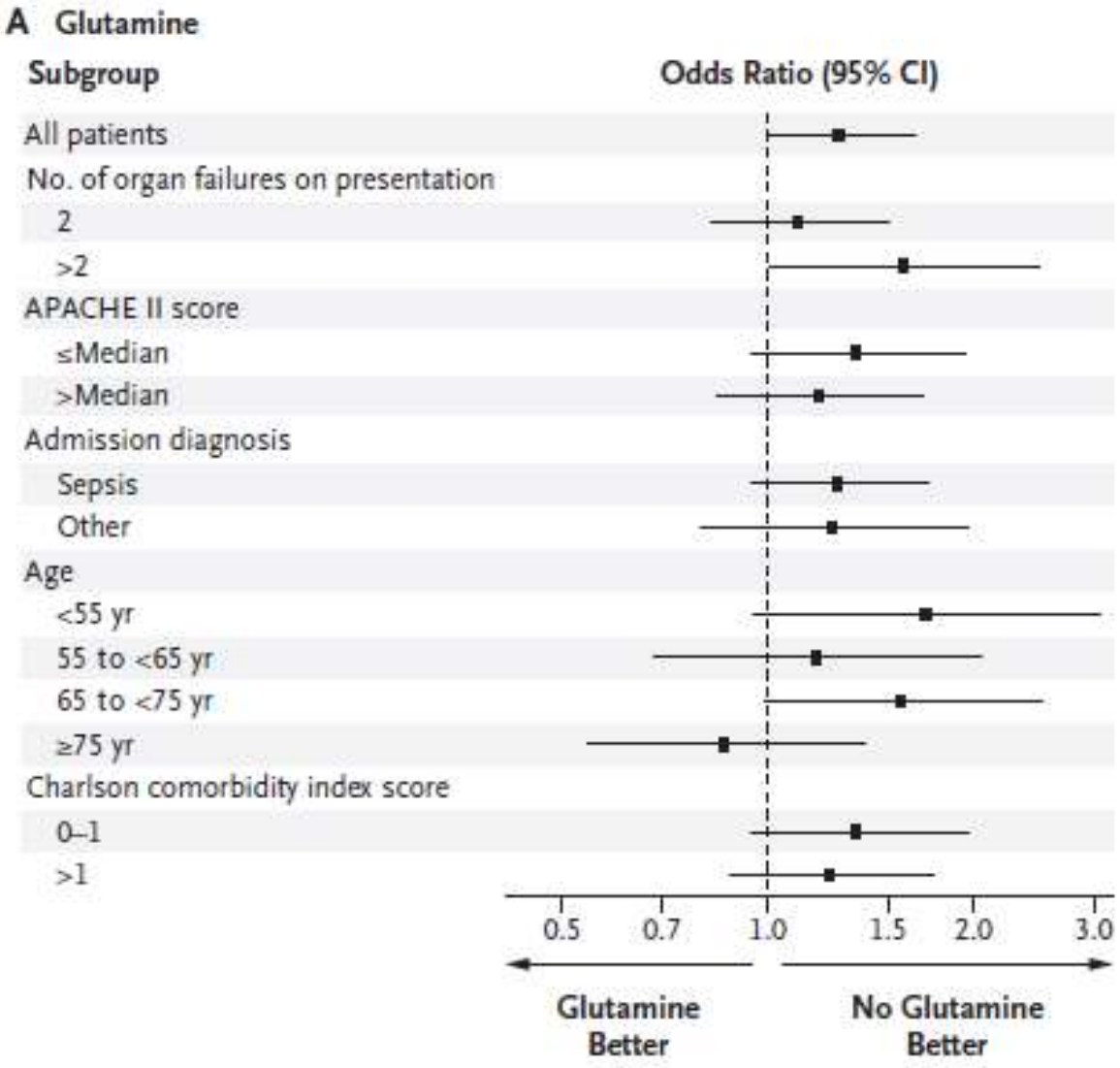
- within 24 hrs ICU admission
- ≈ 60 g/day
- intravenous and enteral

Inclusion Criteria

Mechanically ventilated adult patients admitted to ICU, 2 or more of the following organ failures:

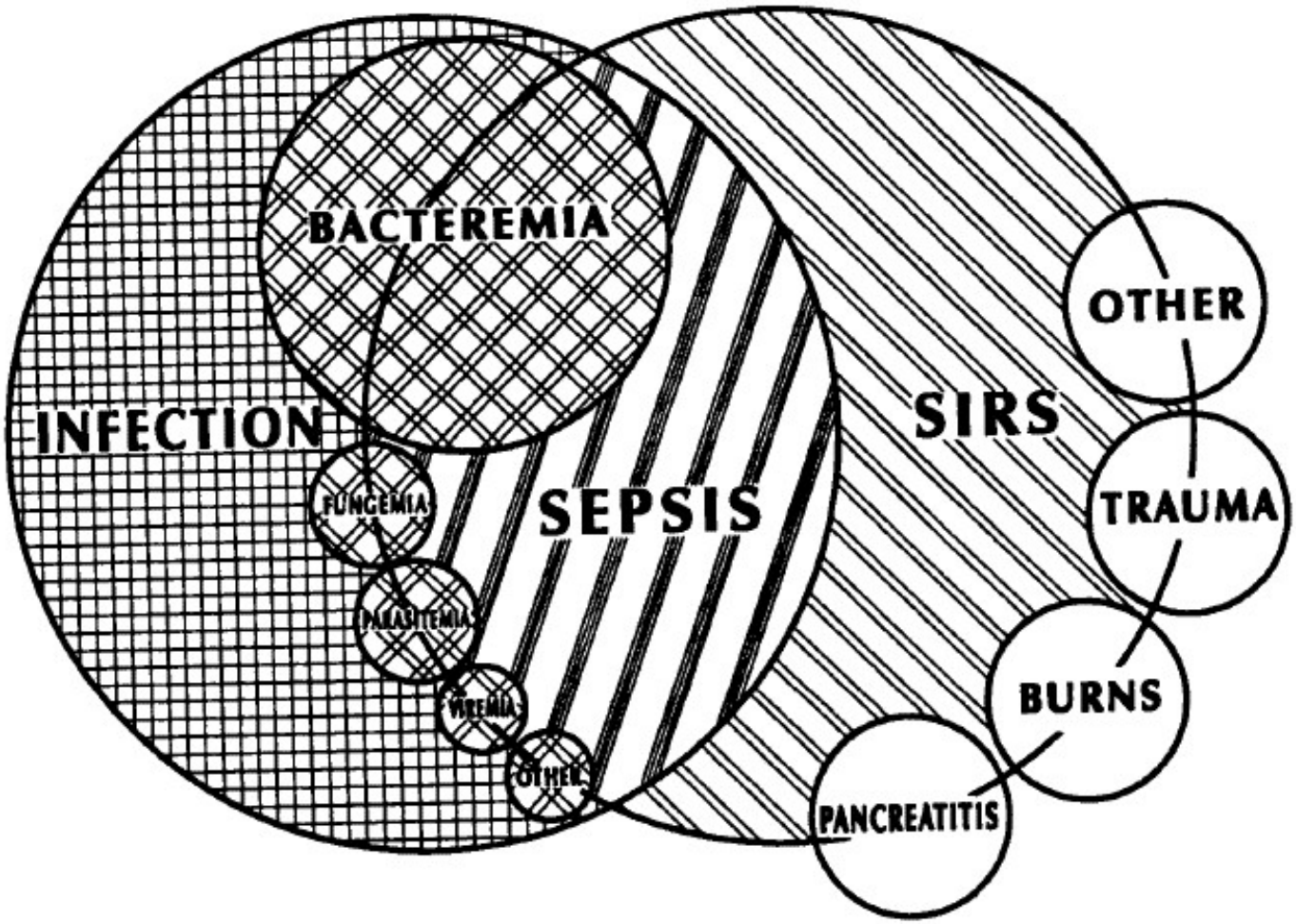
1) A PaO2/FiO2 ratio of <300;
2) Hypoperfusion defined as the need for vasopressor agents
3) Renal dysfunction defined as a serum creatinine >171 micromol/L or a urine output of less than 500 ml/last 24 hours
4) A platelet count of < 50 x109/L.

GLUTAMINE
28-day mortality



Diagnosis and Prognosis

The interrelationship between systemic inflammatory response syndrome (SIRS), sepsis, and infection



SIRS = the systemic inflammatory response to a variety of severe clinical insults. The response is manifested by two or more of the following conditions:

(1) temperature >38°C or <36°C;

(2) heart rate >90 beats per minute;

(3) respiratory rate >20 breaths per minute or PaC02 <32 mm Hg;

(4) white blood cell count>12,OOOIcu mm, <4,OOO/cu mm, or > 10% immature (band) forms

accp/sccm consensus conference

Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis

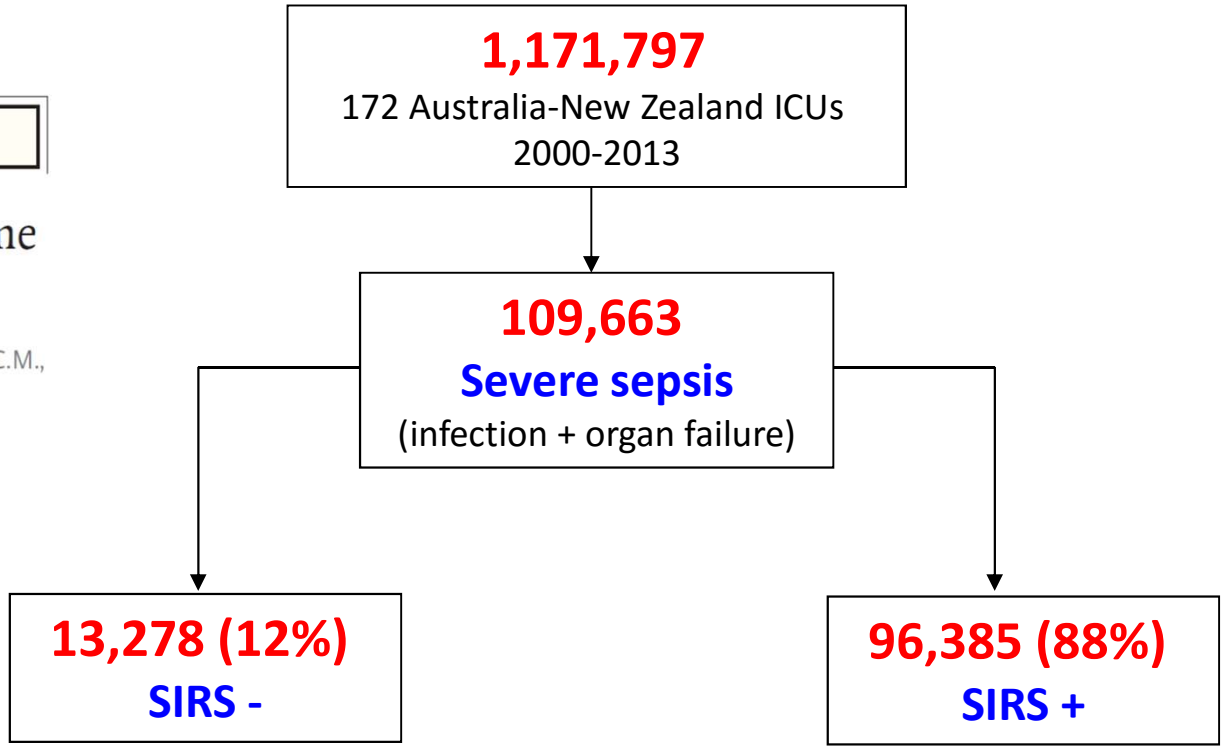
Bone et al., Chest 1992; 101:1644-55

The NEW ENGLAND JOURNAL of MEDICINE
N ENGL J MED 372;17 NEJM.ORG APRIL 23, 2015

ORIGINAL ARTICLE

Systemic Inflammatory Response Syndrome Criteria in Defining Severe Sepsis

Kirsi-Maija Kaukonen, M.D., Ph.D., Michael Bailey, Ph.D., David Pilcher, F.C.I.C.M., D. Jamie Cooper, M.D., Ph.D., and Rinaldo Bellomo, M.D., Ph.D.

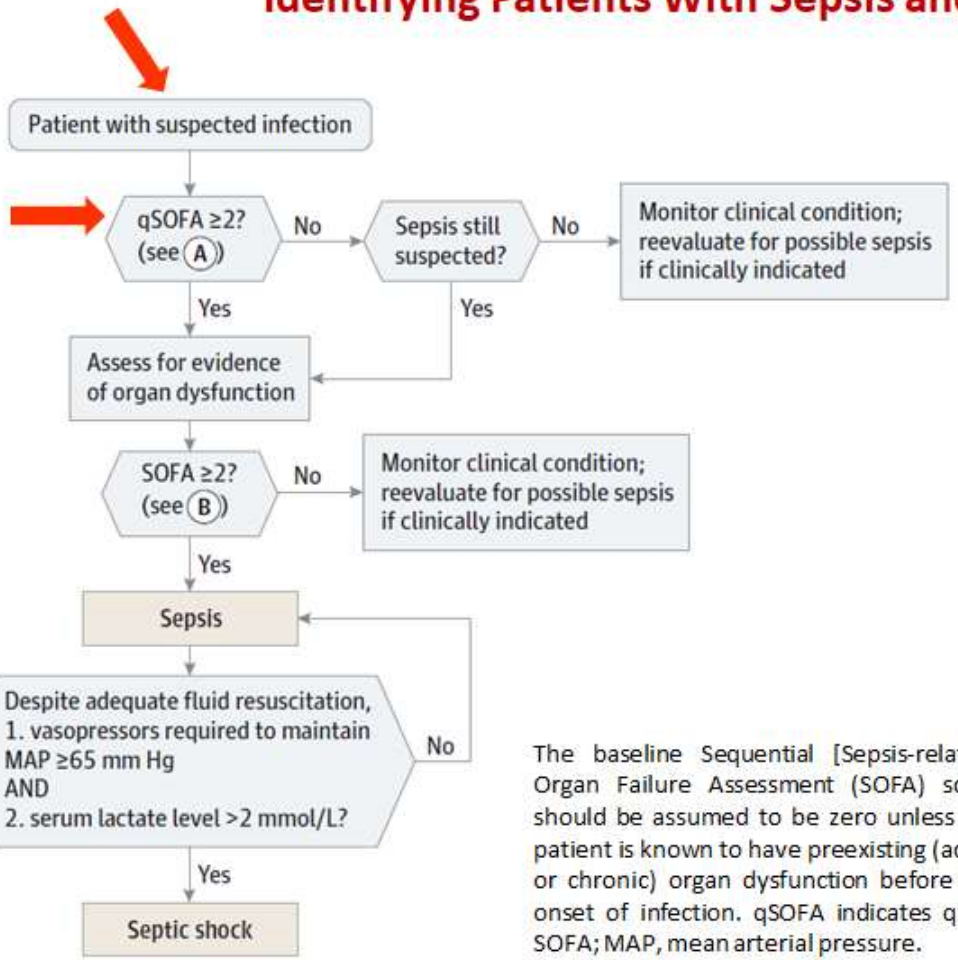


Characteristics	1991 Definition		
	Sensitivity (%)	Specificity (%)	Area Under Receiver Operating Characteristic
Unit stay level	94.6	61.0	0.778

[a]Adjudication outcome: 353 sepsis cases (37%), 607 of nonsepsis cases;

Crit Care Med 2012 Vol. 40, No. 6

Operationalization of Clinical Criteria Identifying Patients With Sepsis and Septic Shock



The baseline Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score should be assumed to be zero unless the patient is known to have preexisting (acute or chronic) organ dysfunction before the onset of infection. qSOFA indicates quick SOFA; MAP, mean arterial pressure.

A qSOFA Variables
- Respiratory rate
- Mental status
- Systolic blood pressure

B SOFA Variables
- PaO_2/FiO_2 ratio
- Glasgow Coma Scale score
- Mean arterial pressure
- Administration of vasopressors with type and dose rate of infusion
- Serum creatinine or urine output
- Bilirubin
- Platelet count

Singer, M. et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 315, 801–810 (2016).

Initial evaluation of common sources of sepsis

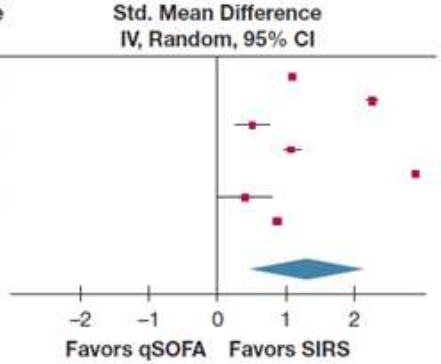
Up to Date 2018

Suspected site	Symptoms/signs (fever is frequently seen with all conditions)	Initial microbiologic evaluation
Upper respiratory tract	Pharyngeal inflammation plus exudate ± swelling and lymphadenopathy	Throat swab for aerobic culture
Lower respiratory tract	Productive cough, pleuritic chest pain, consolidative auscultatory findings	Sputum of good quality, rapid influenza testing, urinary antigen testing (eg, pneumococcus, legionella; not recommended in children), quantitative culture of protected brush or bronchoalveolar lavage
Urinary tract	Urgency, dysuria, loin, or back pain	Urine culture and microscopy showing pyuria
Vascular catheters: arterial, central venous	Redness or drainage at insertion site	Culture of blood (from the catheter and a peripheral site), culture catheter tip (if removed)
Indwelling pleural catheter	Redness or drainage at insertion site	Culture of pleural fluid (through catheter), culture of catheter tip (if removed)
Wound or burn	Inflammation, edema, erythema, discharge of pus	Gram stain and culture of draining pus, wound culture not reliable
Skin/soft tissue	Erythema, edema, lymphangitis	Culture blister fluid or draining pus; role of tissue aspirates not proven
Central nervous system	Signs of meningeal irritation	CSF cell count, protein, glucose, Gram stain, and culture[Δ]
Gastrointestinal	Abdominal pain, distension, diarrhea, and vomiting	Stool culture for Salmonella, Shigella, Campylobacter, and Clostridium difficile
Intra-abdominal	Specific abdominal symptoms/signs	Aerobic and anaerobic culture of percutaneously or surgically drained abdominal fluid collections
Peritoneal dialysis (PD) catheter	Cloudy PD fluid, abdominal pain	Cell count and culture of PD fluid
Genital tract	Women: Low abdominal pain, vaginal discharge Men: Dysuria, frequency, urgency, urge incontinence, cloudy urine, prostatic tenderness	Women: Endocervical and high vaginal swabs onto selective media Men: Urine Gram stain and culture
Bone	Pain, warmth, swelling, decreased use	Blood cultures, MRI, bone cultures at surgery or by interventional radiology
Joint	Pain, warmth, swelling, decreased range of motion	Arthrocentesis with cell counts, Gram stain, and culture

DIAGNOSIS

Study or Subgroup	SIRS Mean	SIRS SD	SIRS Total	qSOFA Mean	qSOFA SD	qSOFA Total	Weight	Std. Mean Difference IV, Random, 95% CI
Churpek, 2017	0.88	0.45	30,677	0.38	0.45	30,677	14.4%	1.11 (1.09 to 1.13)
Donnelly, 2017	0.54	0.02	2,593	0.12	0.26	2,593	14.3%	2.28 (2.21 to 2.35)
Dorsett, 2017	0.39	0.5	152	0.16	0.38	152	14.2%	0.52 (0.29 to 0.75)
Freund, 2017	0.74	0.45	879	0.25	0.45	879	14.3%	1.09 (0.99 to 1.19)
Raith, 2017	0.86	0.11	184,875	0.54	0.11	184,875	14.4%	2.91 (2.90 to 2.92)
Siddiqui, 2017	0.62	0.47	58	0.42	0.51	58	14.0%	0.41 (0.04 to 0.77)
Williams, 2017	0.47	0.48	8,871	0.1	0.34	8,871	14.4%	0.89 (0.86 to 0.92)
Total (95% CI)			**228,105**			**228,105**	**100.0%**	**1.32 (0.40 to 2.24)**

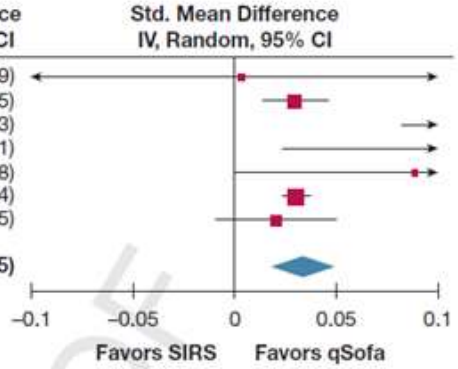
Heterogeneity: $Tau^2 = 1.53$; $Chi^2 = 43948.08$, df = 6 ($P < .00001$); $I^2 = 100\%$
Test for overall effect: Z = 2.81 ($P = .005$)



PROGNOSIS

Study or Subgroup	qSOFA Mean	qSOFA SD	qSOFA Total	SIRS Mean	SIRS SD	SIRS Total	Weight	Std. Mean Difference IV, Random, 95% CI
April, 2017	0.66	2.61	214	0.65	2.61	214	0.7%	0.00 (−0.19 to 0.19)
Churpek, 2017	0.69	1.34	30,677	0.65	1.34	30,677	31.9%	0.03 (0.01 to 0.05)
Finkelsztein, 2017	0.74	0.47	152	0.59	0.5	152	0.5%	0.31 (0.08 to 0.53)
Freund, 2017	0.8	1.59	879	0.65	0.83	879	2.8%	0.12 (0.02 to 0.21)
Park, 2017	0.733	1.54	1,009	0.599	1.46	1,009	3.2%	0.09 (0.00 to 0.18)
Raith, 2017	0.607	0.88	184,875	0.58	0.88	184,875	42.6%	0.03 (0.02 to 0.04)
Williams, 2017	0.73	0.48	8,871	0.72	0.48	8,871	18.3%	0.02 (−0.01 to 0.05)
Total (95% CI)			**226,677**			**226,677**	**100.0%**	**0.03 (0.02 to 0.05)**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 11.39$, df = 6 ($P = .08$); $I^2 = 47\%$
Test for overall effect: Z = 4.12 ($P < .0001$)



A Comparison of the Quick-SOFA and Systemic Inflammatory Response Syndrome Criteria for the Diagnosis of Sepsis and Prediction of Mortality

A Systematic Review and Meta-Analysis

CHEST 2018; 153(3):646-655

AMERICAN COLLEGE OF CHEST PHYSICIANS

Etiology of Illness in Patients with Severe Sepsis Admitted to the Hospital from the Emergency Department

Alan C. Heffner,[1,3] James M. Horton,[2] Michael R. Marchick,[3] and Alan E. Jones[3]

Divisions of [1]Critical Care Medicine and [2]Infectious Diseases, Department of Internal Medicine, and [3]Department of Emergency Medicine, Carolinas Medical Center, Charlotte, North Carolina

Clinical Infectious Diseases

2010; 50:814–820

PATIENTS

45% had positive culture results

55% had negative culture results.

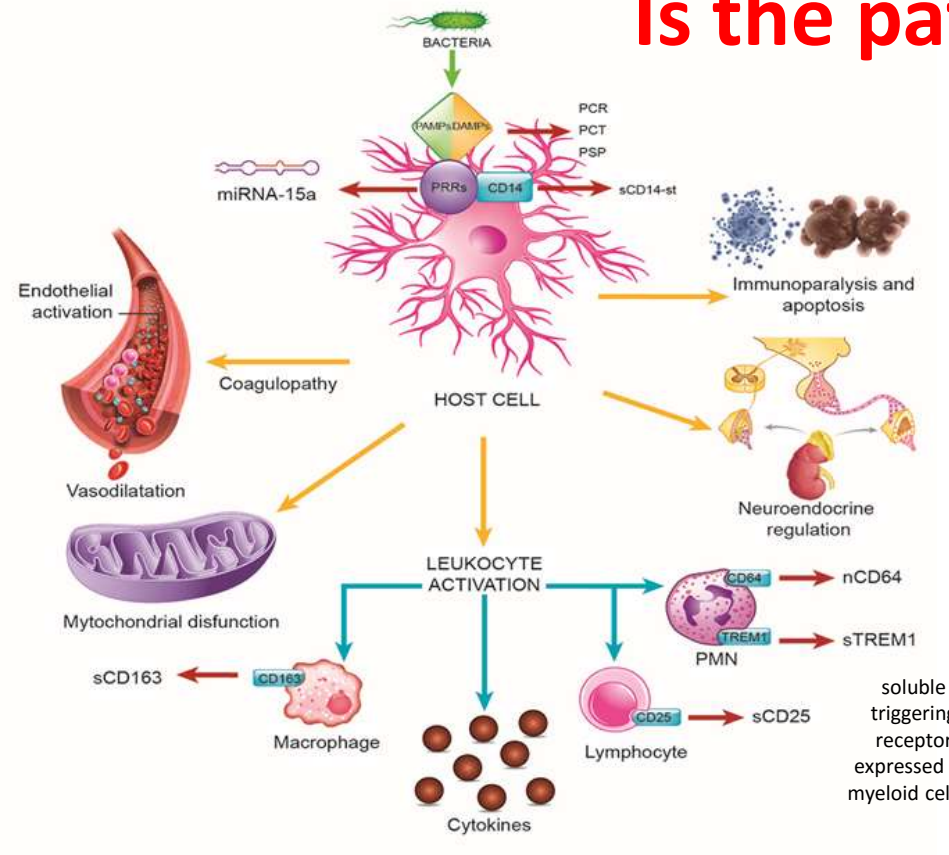
- **24% had clinical infections**
- **4% had atypical infections**
- **18% had noninfectious mimics**
- **9% had an illness of indeterminate etiology**

- **Aspiration**
- **Anaphylaxis**
- **Adrenal insufficency**
- **Bowel obstruction**
- **Diabetic ketoacidosis**
- **Heat emergency**
- **Hypovolemia**
- **Pulmonary Embolism**
- **Pancreatitis**
- **Heat emergency**
- **Intestinal ischemia**
- **Tyroid disease**
- **Toxic ingestion/overdose**
- **Withdrawl state**
- **Spinal cord injury**
- **Cancer**

Prevalence of infection ~ 5:1

- **Missed or delayed antibiotic therapy**
- **Inappropriate antibiotic therapy**

Is the patient infected? Sepsis Biomarkers!



Phospholipase A_2

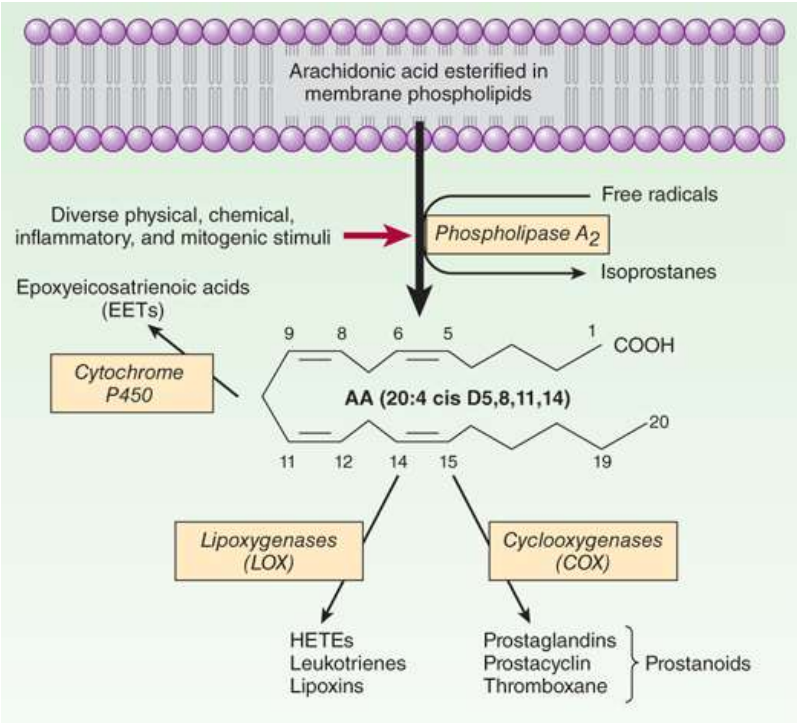


Table 4 Diagnostic performance of biomarkers in distinguishing sepsis from non-infective SIRS in patients with organ dysfunction.

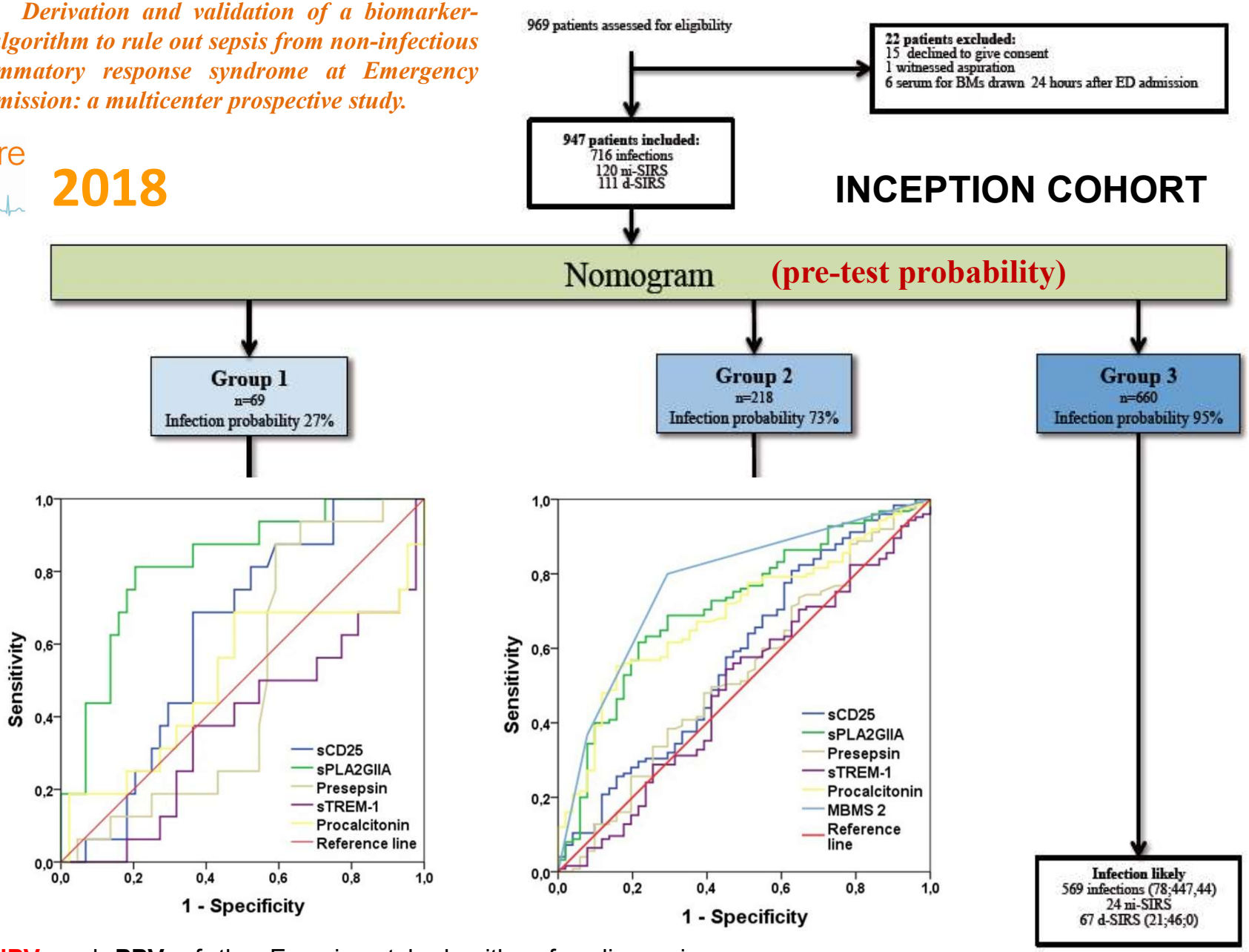
Marker		AUC (95% CI)	Cut off	Sensitivity	Specificity	PPV	NPV
PCT		0.84 (0.77 to 0.91)	1.0 ng/ml	74%	81%	86%	67%
PSP	pancreatic stone protein	0.91 (0.86 to 0.96)	30 ng/ml	88%	78%	86%	81%
sCD25		0.87 (0.81 to 0.93)	2.5 ng/ml	80%	78%	85%	72%
HBP	heparin binding protein	0.58 (0.48 to 0.68)	50 ng/ml	78%	38%	66%	53%
IL6		0.82 (0.74 to 0.89)	200 pg/ml	71%	66%	76%	60%
IL8		0.76 (0.68 to 0.84)	80 pg/ml	82%	58%	75%	67%
IL1β		0.77 (0.69 to 0.85)	1.0 pg/ml	65%	88%	89%	62%

Biomarker performance is shown for 76 patients with severe sepsis and 50 patients with non-infective SIRS and organ dysfunction. Data for GMCSF and TNFα are not shown as only a minority of patients had detectable levels of these markers.

Llewelyn *et al. Critical Care* 2013, **17**:R60
http://ccforum.com/content/17/2/R60

Mearelli et al. Derivation and validation of a biomarker-based clinical algorithm to rule out sepsis from non-infectious systemic inflammatory response syndrome at Emergency Department admission: a multicenter prospective study.

Critical Care Medicine **2018**



The **NPV** and **PPV** of the Experimental algorithm for diagnosing infection in the full spectrum of severity were 71% and 93%, respectively. The corresponding figure for the **diagnosis of S/SS** were **93%** and 92%, respectively.

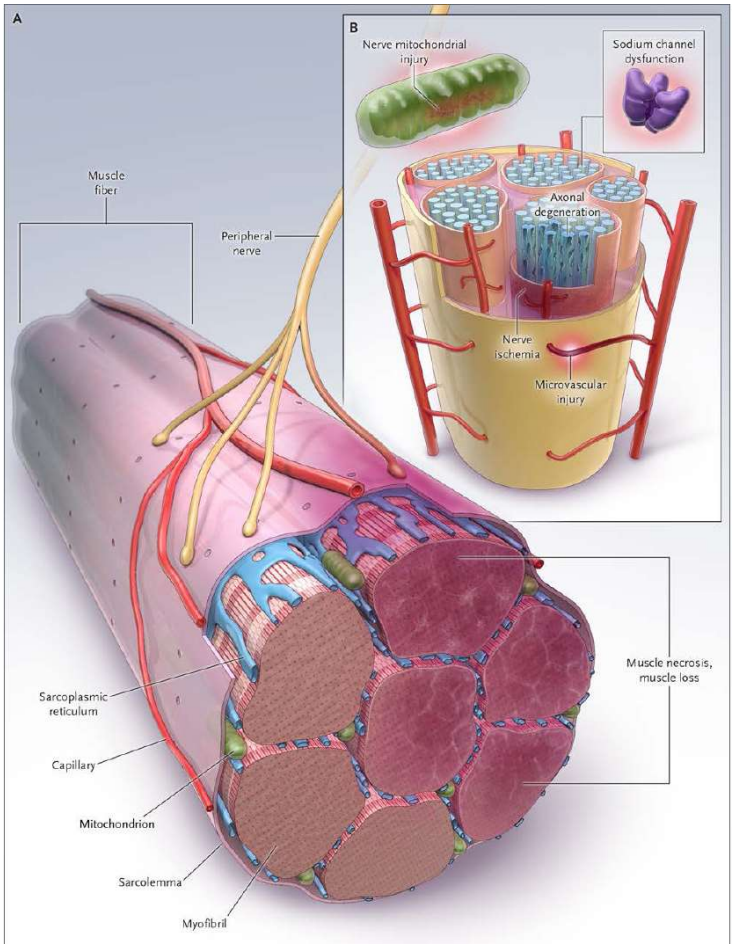
In the whole population (1161 patients with SIRS, inception + validation coorts), **only 5 (0.7%) patients with S/SS were misclassified**

The NEW ENGLAND JOURNAL of MEDICINE

CRITICAL CARE MEDICINE

ICU-Acquired Weakness and Recovery from Critical Illness

N ENGL J MED 370;17 NEJM.ORG APRIL 24, 2014



MUSCLE WEAKNESS OF CRITICAL ILLNESS

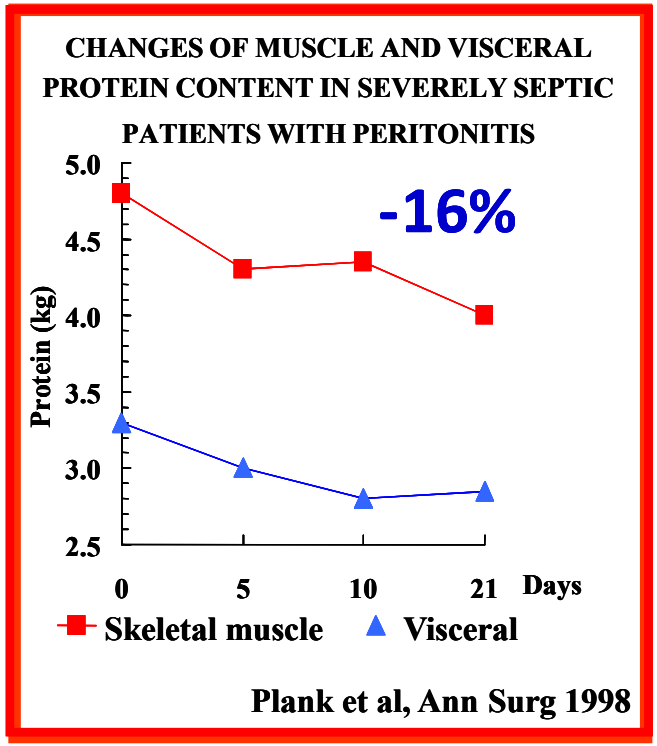
CONSEQUENCES

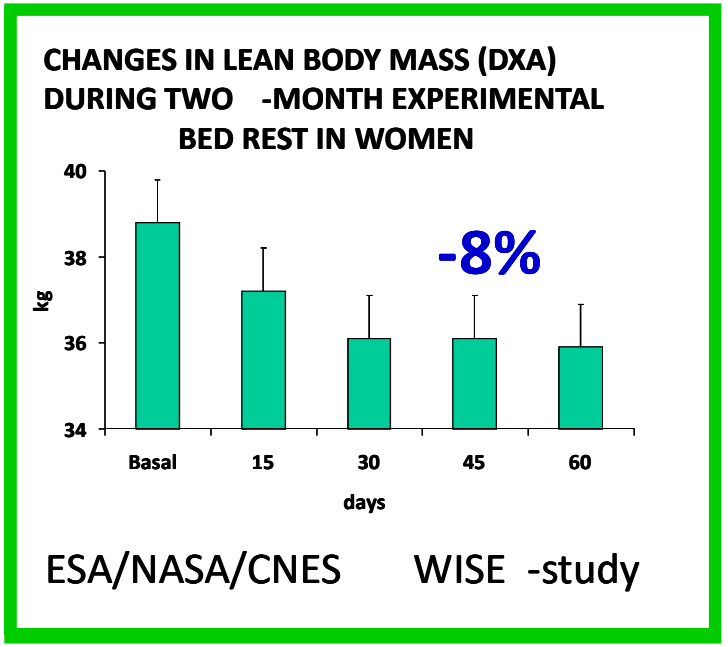
- increased morbidity
- increased hospital mortality
- prolonged hospitalization
- ventilatory impairment
- prolonged mechanical ventilation
- prolonged rehabilitation
- chronic disability in survivors

MECHANISMS

- **Skeletal-muscle wasting**. Possible mechanisms include microvascular ischemia, catabolism, and immobility.
- **Polyneuropathy** with axonal degeneration. Possible mechanisms include microvascular injury with resulting nerve ischemia, dysfunction of sodium channels, and injury to nerve mitochondria.

Muscle Catabolism in Sepsis and Inactivity





Sepsis

Bed rest

Recommendation 15

- **During critical illness, 1.3 g/kg protein equivalents per day can be delivered progressively**

Grade of recommendation: 0 - strong consensus (91% agreement)

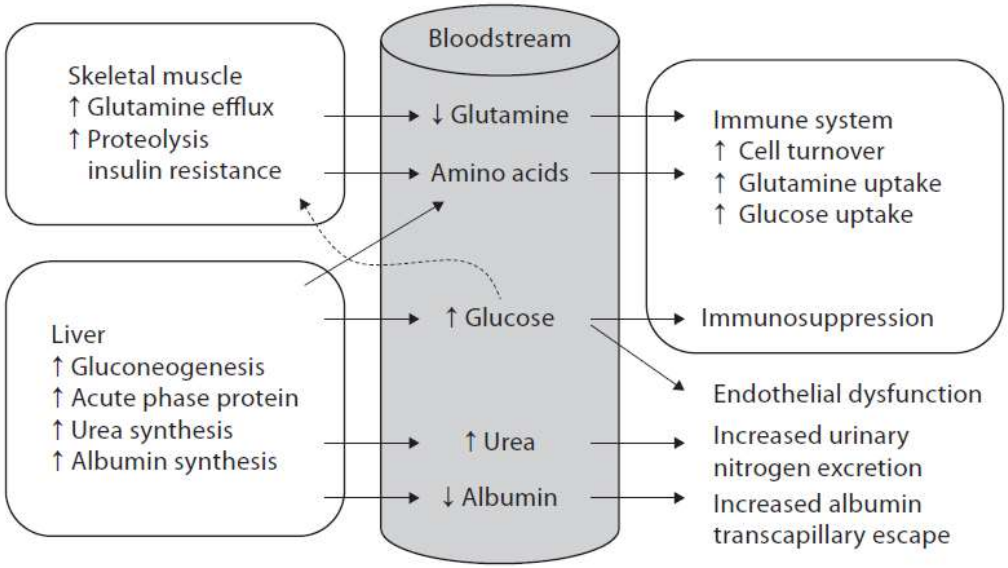
Statement 3

- **Physical activity may improve the beneficial effects of nutritional therapy**

Consensus (86% agreement)

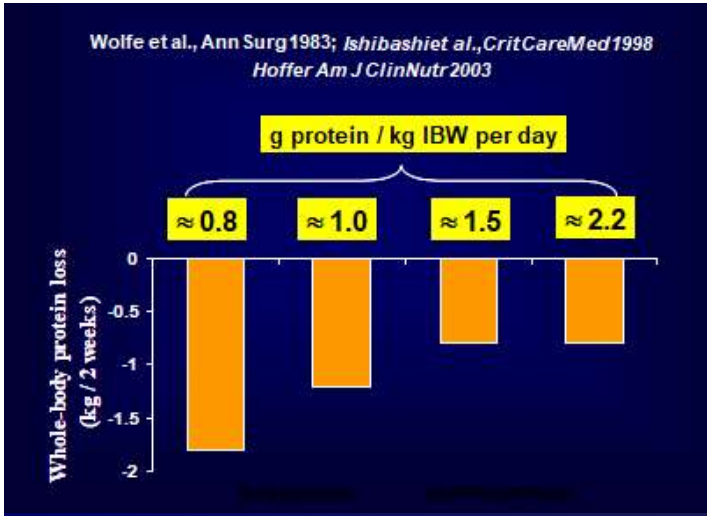
ESPEN guideline on clinical nutrition in the intensive care unit
Clinical Nutrition 38 (2019) 48-79

Mechanisms of muscle wasting, glutamine depletion, hyperglycemia, and hypoalbuminemia in critical illness.



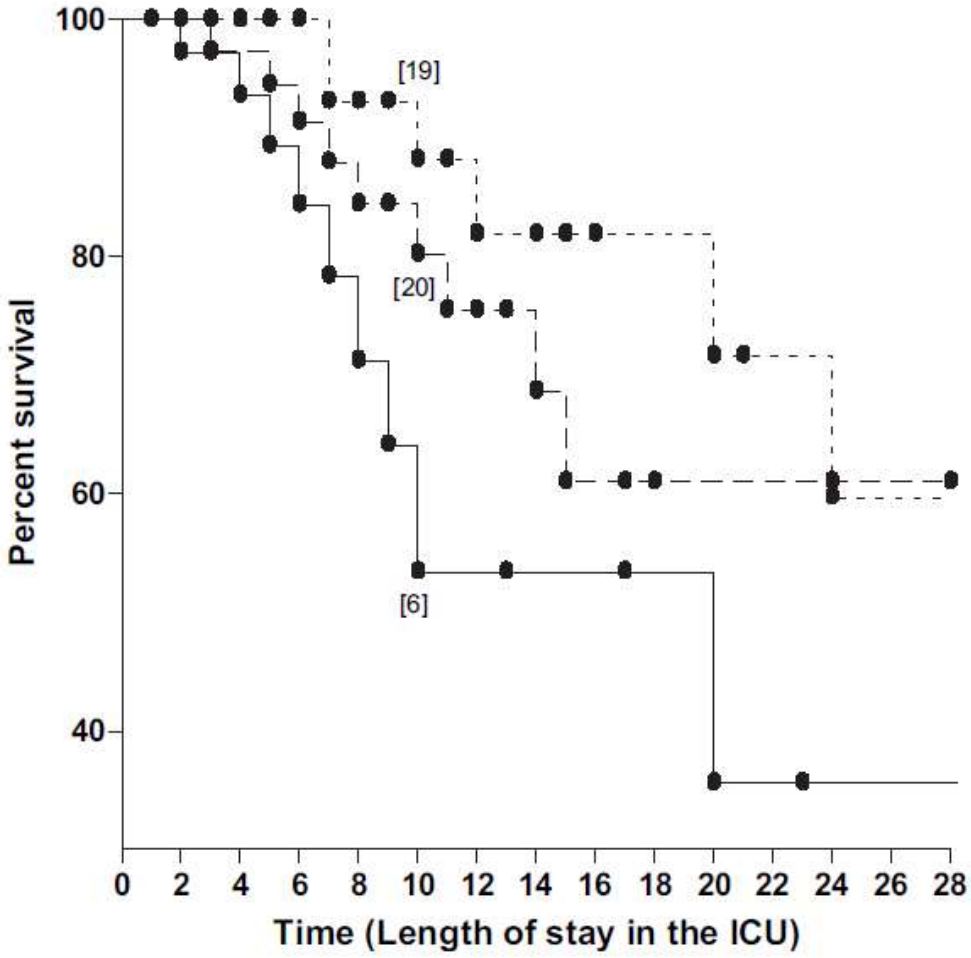
Protein Metabolism and Requirements. Biolo G. Singer P (ed): Nutrition in Intensive Care Medicine: Beyond Physiology. World Rev Nutr Diet. Basel, Karger, 2013, vol 105, pp 12–20

A higher protein intake and physical activity might be needed to overcome anabolic resistance associated with older age, immobility and critical illness (100 g protein = 83 g amino acids)



Improvement in nitrogen balance in critical illness at adequate energy intake

Prospective observational cohort study of 113 ICU patients



Comparison of curves for all patients: Mantel logrank P < 0.021; BresloweGehan: P < 0.027. Log-rank test for trend: P < 0.011.

Clinical Nutrition 31 (2012) 462–468

Contents lists available at SciVerse ScienceDirect

Clinical Nutrition

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

Original article

Provision of protein and energy in relation to measured requirements in intensive care patients

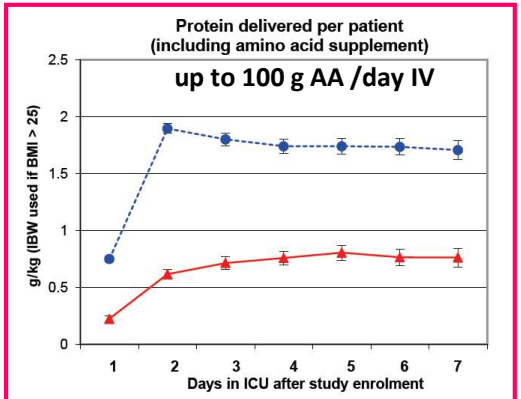
Matilde Jo Allingstrup [a,*], Negar Esmailzadeh [a], Anne Wilkens Knudsen [a], Kurt Espersen [a], Tom Hartvig Jensen [a], Jørgen Wiis [a], Anders Perner [a], Jens Kondrup [b]

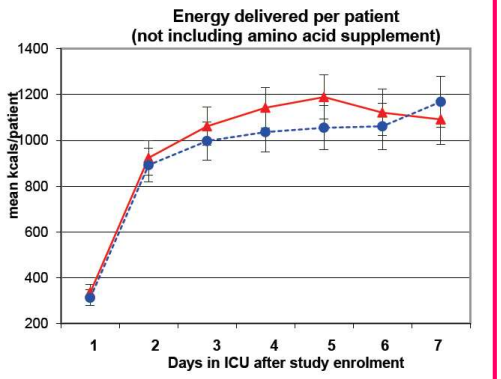
[a] Department of Intensive Care 4131, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark
[b] Department of Human Nutrition, Faculty of Life Sciences, University of Copenhagen & Clinical Nutrition Unit, Copenhagen University Hospital, Rigshospitalet, Denmark

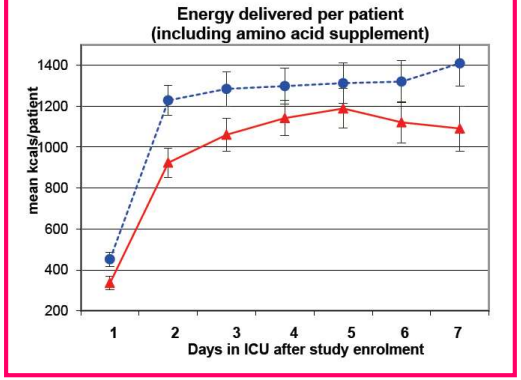
High protein & AA
Medium protein & AA
Low protein & AA

Protein provision g/kg/day	Energy provision Kcal/kg/day
1.46 ± 0.29	**27.2 ± 6.7**
1.06 ± 0.23	**24.7± 5.7**
0.79±0.29	**21.7 ± 6.7**
L vs. M: <0.001	L vs. H: <0.001
L vs. H: <0.001	
M vs. H: <0.001	

Death occurred earlier in the tertile of patients with the lowest provision of protein and amino acids. The results were confirmed in Cox regression analyses which showed a **significantly decreased hazard ratio of death with increased protein provision**, also when adjusted for baseline prognostic variables (APACHE II, SOFA scores and age). **Provision of energy was not related to mortality.**



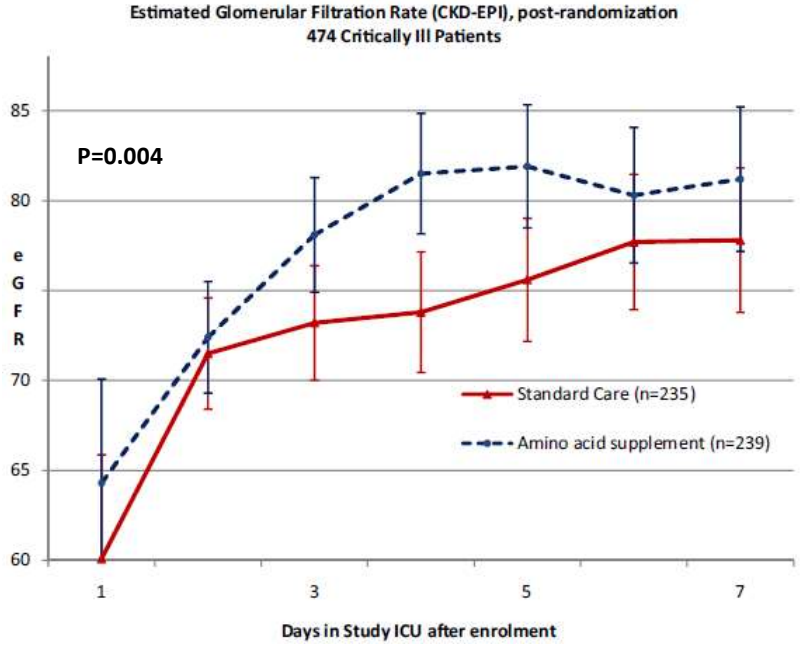




Intravenous amino acid therapy for kidney function in critically ill patients: a randomized controlled trial

Intensive Care Med (2015) 41:1197–1208
DOI 10.1007/s00134-015-3827-9

Gordon S. Doig
Fiona Simpson
Rinaldo Bellomo
Philippa T. Heighes
Elizabeth A. Sweetman
Douglas Chesher
Carol Pollock
Andrew Davies
John Botha
Peter Harrigan
Michael C. Reade



The Effect of IV Amino Acid Supplementation on Mortality in ICU Patients May Be Dependent on Kidney Function: Post Hoc Subgroup Analyses of a Multicenter Randomized Trial

Ran Zhu, MD[1]; Matilde J. Allingstrup, PhD[1,2]; Anders Perner, PhD[2]; Gordon S. Doig, PhD[1]; for the Nephro-Protective Trial Investigators Group

(*Crit Care Med* 2018; 46:1293–1301)

Outcome	Standard Care	Amino Acid Supplement	Difference (95% CI)	*p*
Subgroup with "no" baseline kidney dysfunction and "no" baseline risk of progression of AKI				
	189 patients	179 patients		
Deaths before study day 90, % (*n*/*N*)	21.2% (40/189)	14.2% (25/176)[a]	−7.9% (−15.1 to −0.7)	0.0341[b]
Subgroup "with" baseline kidney dysfunction "or" baseline risk of progression of AKI				
	46 patients	60 patients		
Deaths before study day 90, % (*n*/*N*)	15.2% (7/46)	28.3% (17/60)	−0.6%[b] (−16.2 to 15.2)	0.945[d]

CONCLUSIONS

- Metabolic changes contribute to organ dysfunction of sepsis
- Hyperglycemia (<180 mg/dl) and glucose variability should be avoided in sepsis
- Permissive underfeeding should be implemented in the acute phase of sepsis
- Endocrine and metabolic biomarkers may contribute to diagnosis and prognosis definition of sepsis
- Increased protein intake and early reabilitation may reduce skeletal muscle wasting and weakness in sepsis