JUMP START

Energize your Research in Parenteral Nutrition

JUMPstart Virtual Meeting

Advanced module JUMPstart 2021: Day 1 Presentation slides

March 27, 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 Saturday March 27th. 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.

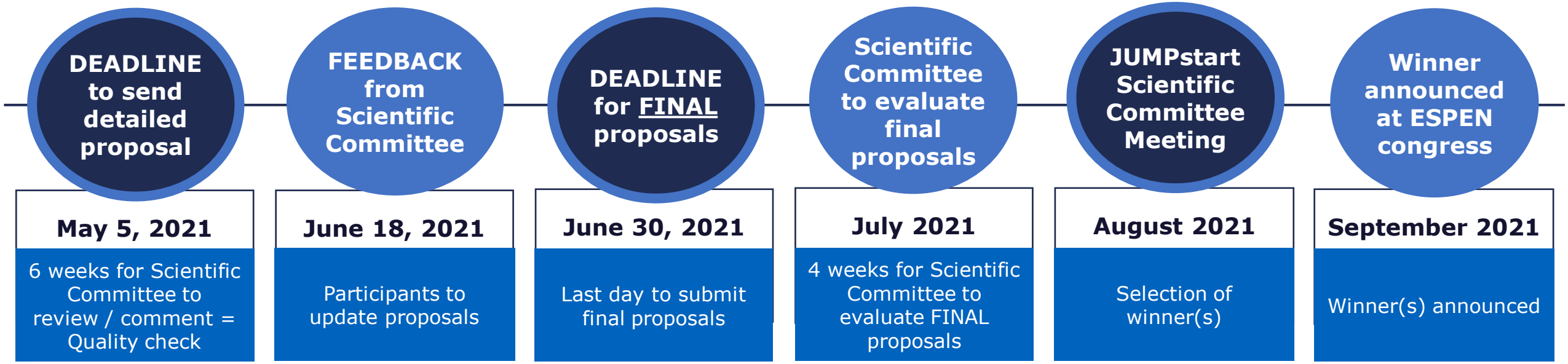
Please feel free to use this document to take notes and refer back to.

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: Saturday, Mar 27, Part I

Time (GMT)	Session	Lead
Part I: Exclamation marks and question marks: State of the art in parenteral nutrition		
14:00	Welcome	Prof. Mette Berger Dr. Anke Wenn
14:10	Disaster control I: Energy and protein	Prof. Olav Rooyackers
14:25	Disaster control II: Monitoring clinical nutrition	Prof. Mette Berger
14:45	Discussion	Prof. Olav Rooyackers Prof. Mette Berger
14:55	Feeding the hungry I: Identifying and feeding patients at risk of malnutrition	Prof. Mette Berger
15:10	Feeding the hungry II: Parenteral nutrition: When and how to?	Prof. Bob Martindale
15:25	Discussion	Prof. Bob Martindale Prof. Mette Berger Prof. Olav Rooyackers Prof. Tim Friede
15:35	**Break (20 minutes)**	

Meeting agenda: Saturday, Mar 27, Part II

Time (GMT)	Session	Lead
15:55	Welcome back	Prof. Mette Berger Dr. Anke Wenn
16:00	**Bubble discussions**	All
Part II: Counting peas: Methods in nutrition research		
16:15	Reviewing nutrition studies: How do we keep from falling into traps?	Prof. Bob Martindale
16:35	Tiny details: Isotopes and metabolomics	Prof. Olav Rooyackers
16:55	Discussion	Prof. Bob Martindale Prof. Olav Rooyackers
17:05	Wrapping up statistics	Prof. Tim Friede
17:25	Discussion	All
17:35	Applying for the JUMPstart research grant	Prof. Mette Berger Dr. Anke Wenn
17:45	Q&A	All
17:55	Outlook Day 2	Prof. Mette Berger

Contents: Day 1

Part I: Exclamation marks and question marks: State of the art in parenteral nutrition

- Disaster control (part I) – Prof. Olav Rooyackers
- Disaster control (part II) – Prof. Mette Berger
- Feeding the hungry (part I) – Prof. Mette Berger
- Feeding the hungry (part II) – Prof. Bob Martindale

Part II: Counting peas: Methods in nutrition research

- Reviewing nutrition studies – Prof. Bob Martindale
- Tiny details – Prof. Olav Rooyackers
- Wrapping up statistics – Prof. Tim Friede
- Applying for the JUMPstart research grant – Prof. Mette Berger

Part I

Exclamation marks and question marks: State of the art in parenteral nutrition

Disaster control I: Energy and protein

Prof. Olav Rooyackers

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Disaster Control 1:
Energy and protein requirements in catabolic and anabolic phase

Prof. Olav Rooyackers

Advanced module, Day 1, Part I: Confounding factors in the ICU

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. Clin Nutr 2019

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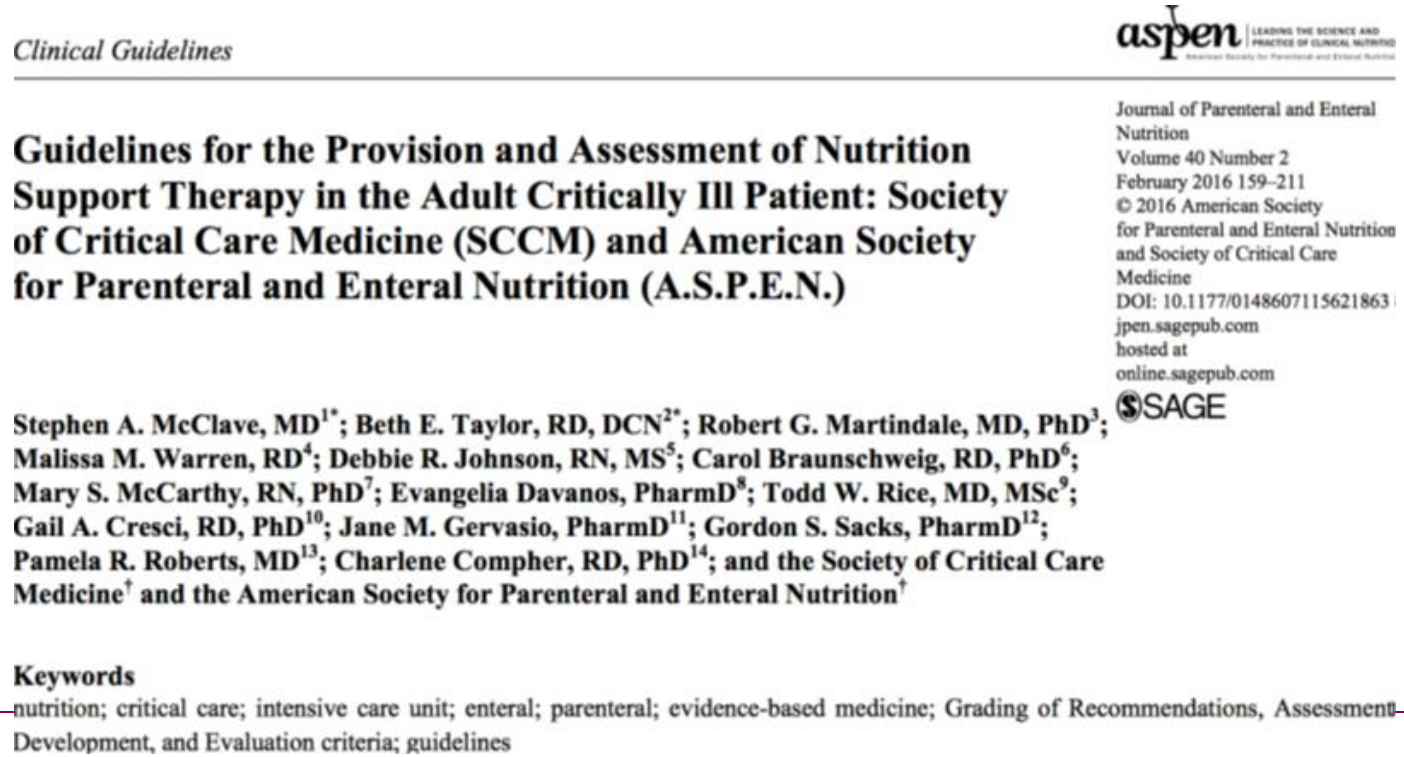

Clinical Guidelines

aspen LEADING THE SCIENCE AND PRACTICE OF CLINICAL 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
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Keywords
nutrition; critical care; intensive care unit; enteral; parenteral; evidence-based medicine; Grading of Recommendations, Assessment, Development, and Evaluation criteria; guidelines

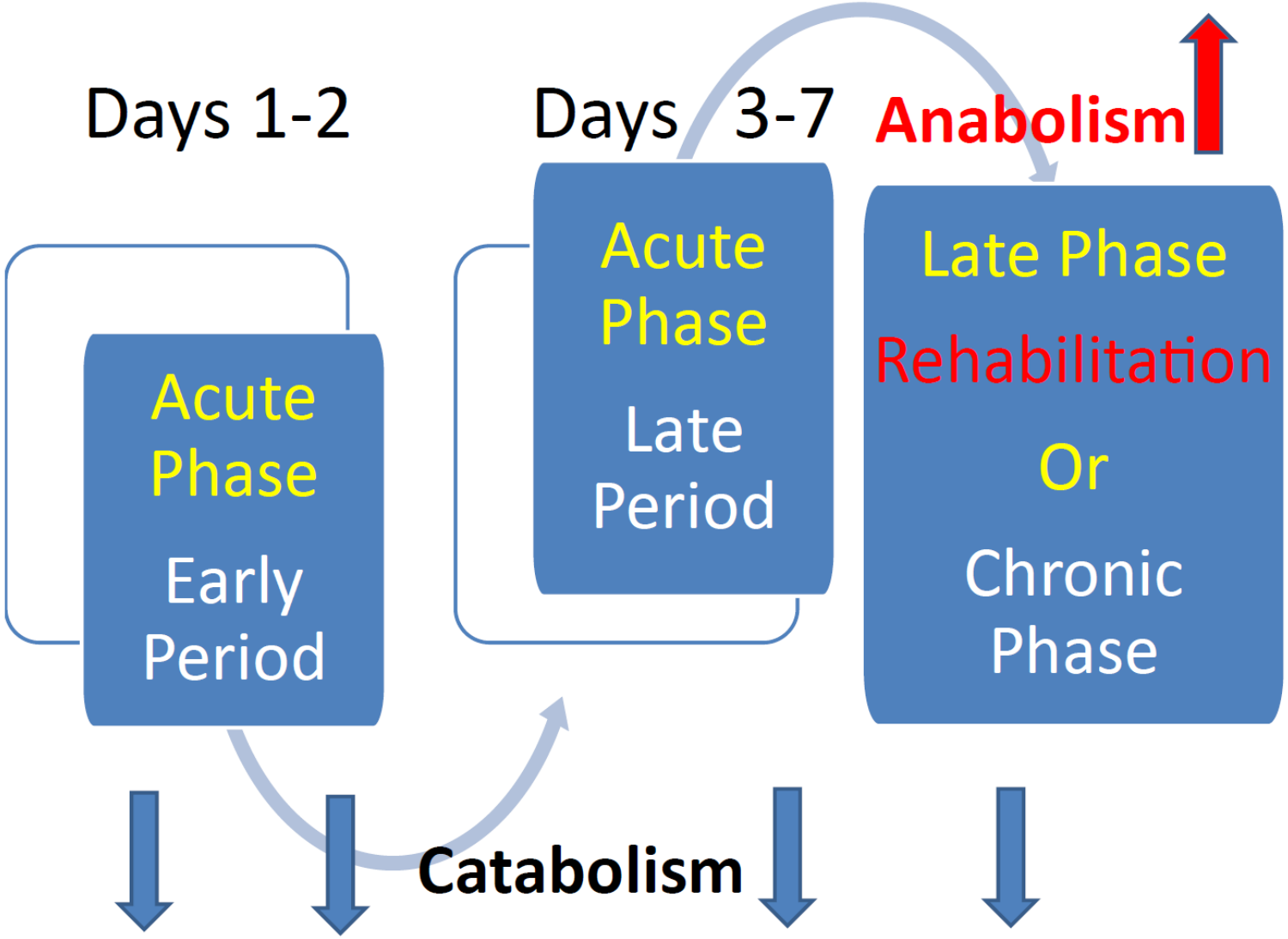

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Table 2
Levels of evidence [3].

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

Table 3
Grades and forms of recommendations (SIGN) [3].

a) Grades of recommendation	
A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population; or A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results: or extrapolated evidence from studies rated as 1++ or 1+.
0	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2++ or 2+
GPP	Good practice points. Recommended best practice based on the clinical experience of the guideline development group

ESPEN Guidelines 2018 - GENERAL

No:	Recommendation	Grade	Consensus
1	Medical nutrition therapy shall be considered for all patients staying in the ICU, mainly for more than 48 h	GPP	100%
3	Oral diet shall be preferred over EN or PN in critically ill patients who are able to eat.	GPP	100%
4	If oral intake is not possible, early EN (within 48 h) in critically ill adult patients should be performed/initiated rather than delaying EN	B	100%
5	If oral intake is not possible, early EN (within 48 h) shall be performed/initiated in critically ill adult patients rather than early PN	A	100%
6	In case of contraindications to oral and EN, PN should be implemented within three to seven days	B	89%
7	Early and progressive PN can be provided instead of no nutrition in case of contraindications for EN in severely malnourished patients.	0	95%
8	To avoid overfeeding, early full EN and PN shall not be used in critically ill patients but shall be prescribed within three to seven days.	A	100%

Singer P et al. Clin Nutr 2019

ESPEN Guidelines 2018 - ENERGY

No:	Recommendation	Grade	Consensus
15	In critically ill mechanically ventilated patients, EE should be determined by using indirect calorimetry.	B	100%
	If calorimetry is not available, using VO2 (oxygen consumption) from pulmonary arterial catheter or VCO2 (carbon dioxide production) derived from the ventilator will give a better evaluation on EE than predictive equations.		82%
16	If indirect calorimetry is used, isocaloric nutrition rather than hypocaloric nutrition can be progressively implemented after the early phase of acute illness	0	95%
17	Hypocaloric nutrition (not exceeding 70% of EE) should be administered in the early phase of acute illness.	B	100%
18	After day 3, caloric delivery can be increased up to 80-100% of measured EE.	0	95%
19	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.	B	95%

Singer P et al. Clin Nutr 2019

ESPEN Guidelines 2018- PROTEIN + GLUTAMINE

No:	Recommendation	Grade	Consensus
22	During critical illness, 1.3 g/kg protein equivalents per day can be delivered progressively	0	91%
26	In patients with burns > 20% body surface area, additional enteral doses of GLN (0.3-0.5 g/kg/d) should be administered for 10-15 days as soon as EN is commenced.	B	95%
27	In critically ill trauma, additional EN doses of GLN (0.2-0.3 g/ kg/d) can be administered for the first five days with EN. In case of complicated wound healing it can be administered for a longer period of ten to 15 days.	0	91%
28	In ICU patients except burn and trauma patients, additional enteral GLN should not be administered.	B	92.31%
29	In unstable and complex ICU patients, particularly in those suffering from liver and renal failure, parenteral GLN –dipeptide shall not be administered.	A	92.31%

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Table 3
Grades and forms of recommendations (SIGN) [3].

a) Grades of recommendation				
A	**3**	**18%**		At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	**7**	**41%**		A body of evidence including studies rated as 2++, directly applicable to the target population; or A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results: or extrapolated evidence from studies rated as 1++ or 1+.
0	**5**	**29%**	**41%**	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2++ or 2+
GPP	**2**	**12%**		Good practice points. Recommended best practice based on the clinical experience of the guideline development group

Singer P et al. Clin Nutr 2019

ESPEN versus ASPEN

	ESPEN (2019)	ASPEN (2016)
Energy	In critically ill mechanically ventilated patients, EE should be determined by using indirect calorimetry. (grade B) Hypocaloric nutrition (not exceeding 70% of EE) should be administered in the early phase of acute illness. (grade B) After day 3, caloric delivery can be increased up to 80-100% of measured EE. (grade 0)	We suggest that indirect calorimetry (IC) be used to determine energy requirements, when available and in the absence of variables that affect the accuracy of measurement. [Quality of Evidence: Very Low] Based on expert consensus, in the absence of IC, we suggest that a published predictive equation or a simplistic weight-based equation (25–30 kcal/kg/d) be used to determine energy requirements.
Protein	During critical illness, 1.3 g/kg protein equivalents per day can be delivered progressively. (grade 0)	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 [Quality of Evidence: Very Low]

ESPEN Guidelines 2018 - GAPS

No:	Recommendation	Grade	Consensus
1	Medical nutrition therapy shall be considered for all patients staying in the ICU, mainly for more than 48 h	GPP	100%
3	Oral diet shall be preferred over EN or PN in critically ill patients who are able to eat.	GPP	100%
7	Early and progressive PN can be provided instead of no nutrition in case of contraindications for EN in severely malnourished patients.	0	95%
16	If indirect calorimetry is used, isocaloric nutrition rather than hypocaloric nutrition can be progressively implemented after the early phase of acute illness	0	95%
18	After day 3, caloric delivery can be increased up to 80-100% of measured EE.	0	95%
22	During critical illness, 1.3 g/kg protein equivalents per day can be delivered progressively	0	91%
27	In critically ill trauma, additional EN doses of GLN (0.2-0.3 g/ kg/d) can be administered for the first five days with EN. In case of complicated wound healing it can be administered for a longer period of ten to 15 days.	0	91%

Singer P et al. Clin Nutr 2019

My most burning questions

- Are acutely critically ill patients not able to suppress endogenous energy supply AND if so which patients are these?
- Why do acutely critically ill patients die when overfed and we don’t?
- Should we give adequate protein (1.3 gram/kg/day) from admission?
- How can we identify the individual patient’s trajectory and how do we monitor and adjust the individual patient’s nutrition accordingly?

Disaster control II: Monitoring clinical nutrition

Prof. Mette Berger

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Disaster control II:

Monitoring clinical nutrition

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

Advanced module, Day 1, Part I: Exclamation marks and questions marks: State of the Art in Parenteral Nutrition

Monitoring nutrition – take home message

- Any therapy has potential side effects: so has nutrition – too little/too much equally bad
- Main causes of complications
  - inexact appreciation of energy requirements – they change over time
  - Absence of systematic monitoring approach
- Monitoring delivery to ensure reaching prescribed goals – macro & micronutrients
- Monitoring metabolic response reduces complications (glycemia, insulin requirements, liver tests, prealbumin, weight)

But to monitor …

You need to decide where you want to go

1st GOAL?

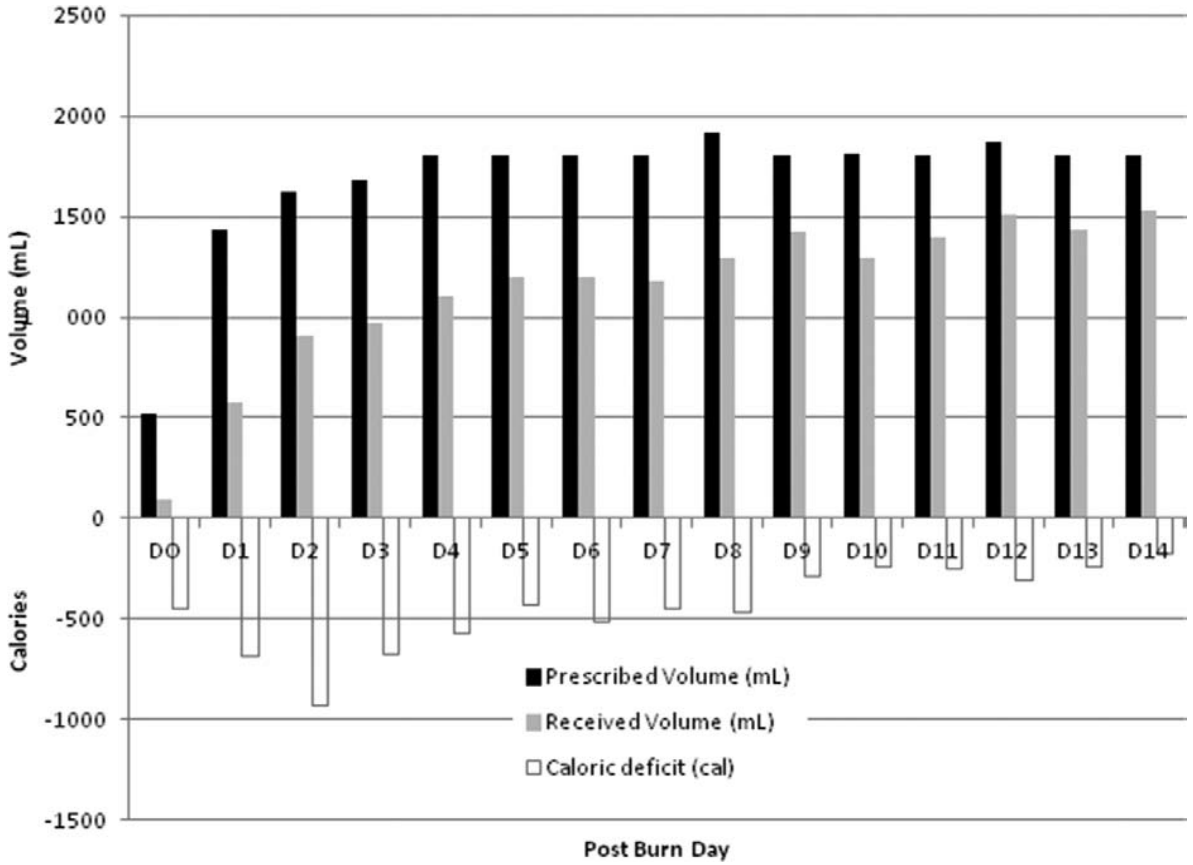
ENERGY TARGET

Which needs to be

MEASURED

Enteral Nutrition: What the Dietitian Prescribes Is Not What The Burn Patient Gets!

Sudenis et al, JBCR 2015; 36:297–305

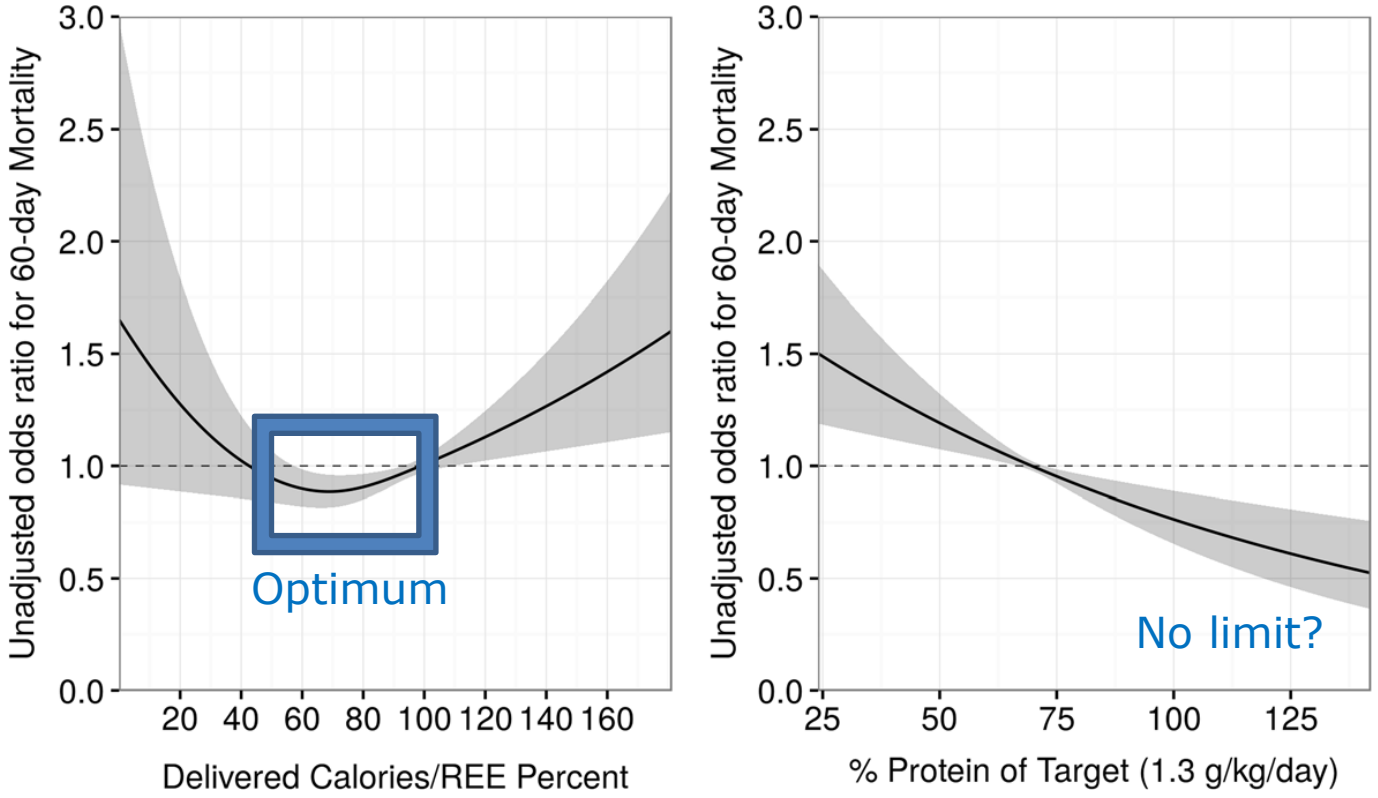


Toronto
n=90
age 47 ± 18 years
TBSA 28%

median prescribed and median received enteral feed volume (y axis) and the median caloric deficit

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

Zusman et al, Crit Care 2016

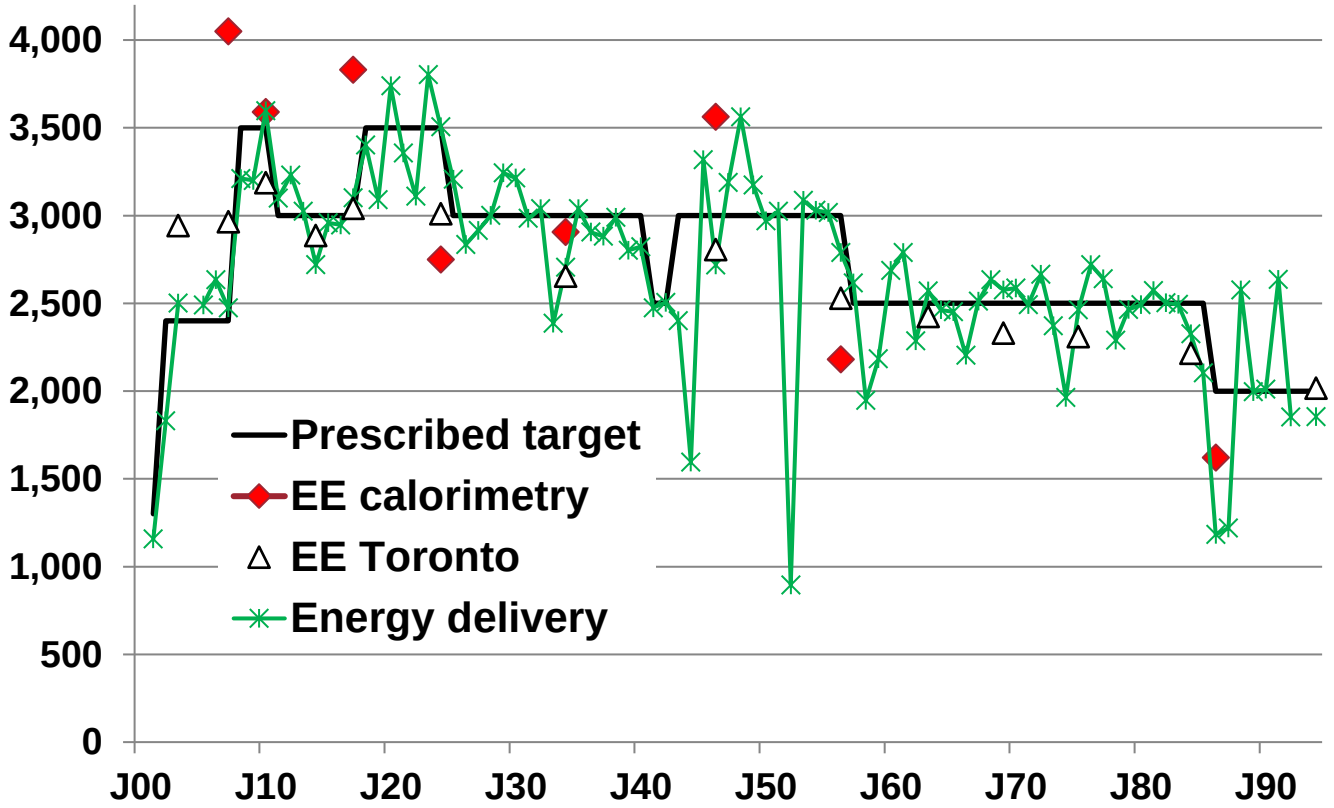


Association of administered calories/resting EE (Adcal/REE) % with 60-day mortality (left), and protein intake by daily requirement (1.3 g/kg/d) with 60-day mortality (right)

5'100 IC studies in 1'050 patients

Nutritional follow up

male 28 years, admission weight 75 kg, burns 72% TBSA

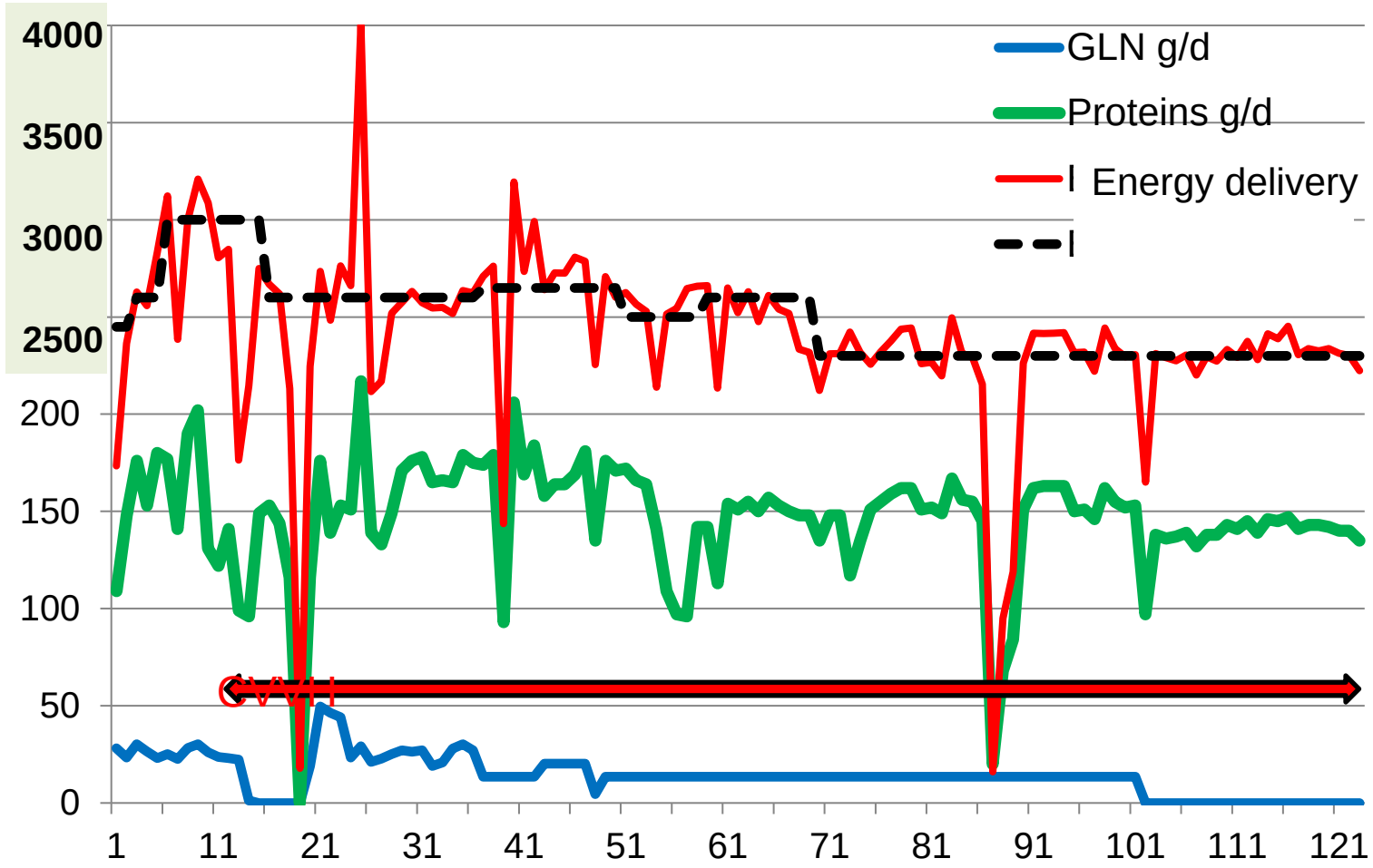


Berger, Springer 2013

What should we monitor?

- Energy requirement evolution? IC
- Energy balance (daily, cumulated)
  - i.e. under- or over-feeding
- Substrate delivery
  - Protein intakes (1.2-1.5 g/kg)
  - Fat intakes
- Response to feeding
  - Changes in prealbumin (protein adequacy)
  - Blood glucose, insulin requirements
  - Liver tests, Triglycerides
  - Weight, Testosterone
- Impact of therapy
  - Trace elements, Glutamine (CRRT)
  - Vitamin D3, C, other?

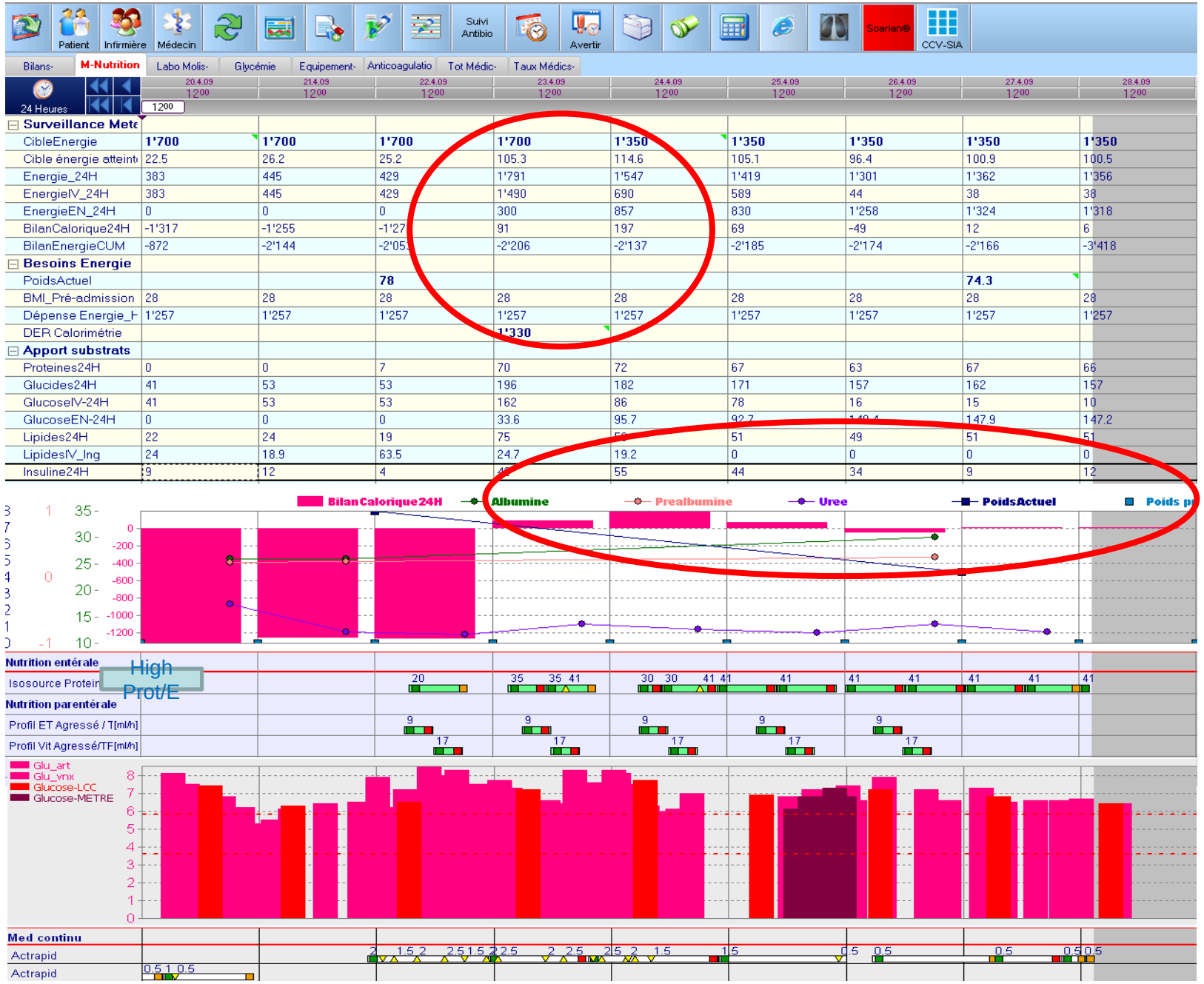
M, 51 years, burned 60% BSA, weight 97 kg (85kg by day 120)



Glutamine Enteral

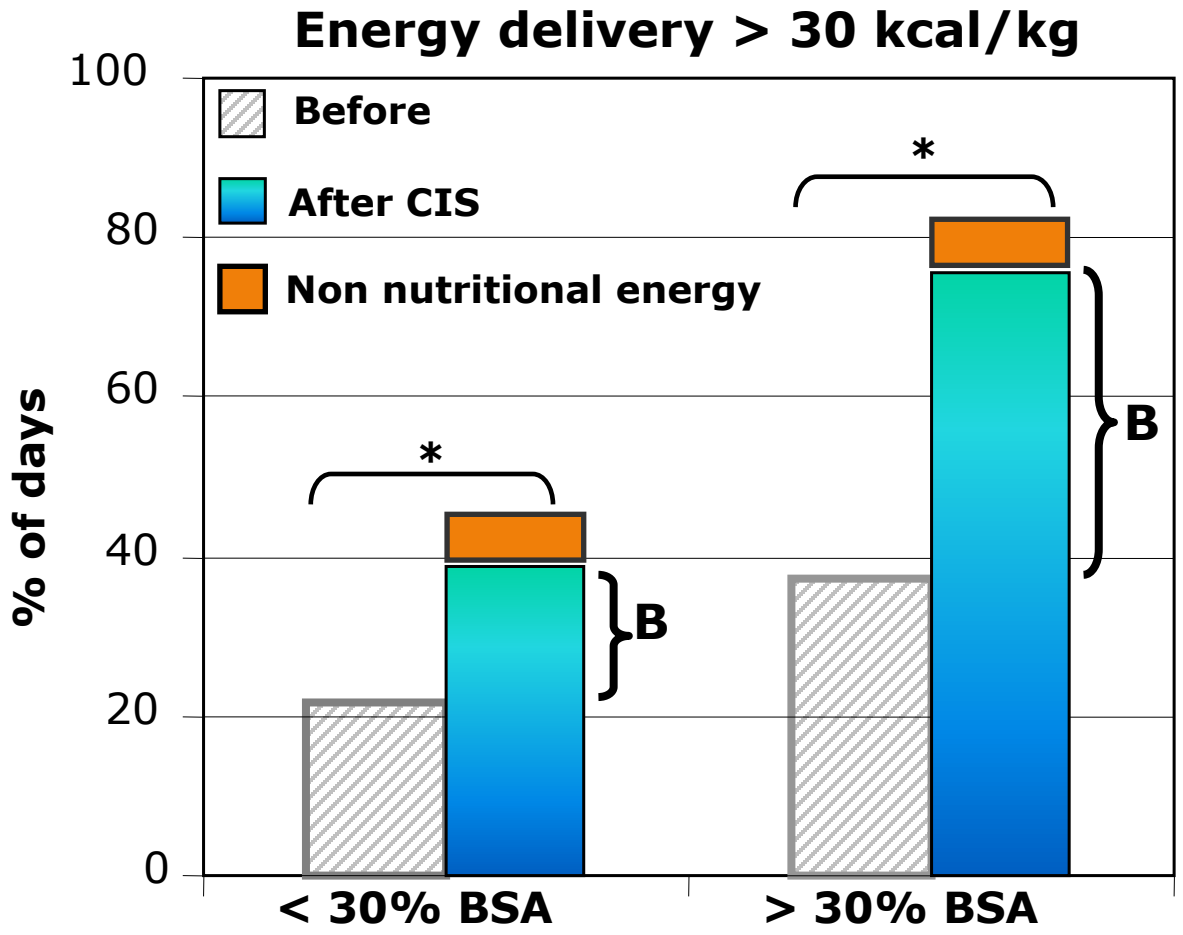
IV

N°
202
F
70kg



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

Berger et al, Nutrition 22 (2006) 221



Monitoring nutrition in the ICU

Singer et al Clin Nutr 2018 e-pub

1. Introduction
2. Standard operating procedures (SOPs)

   SOPs are a set of step-by-step instructions that aim to deliver care efficiently and reduce the risk of an undesirable event. ….. SOPs are particularly important in the field of nutrition therapy, as several categories of healthcare professionals are involved. SOPs must be adapted to local possibilities, and should be established, followed, and audited in each department to avoid complications of nutrition.
3. Clinical monitoring
   - 3.1. Gastro-intestinal symptoms: GRV, IAP, dysphagia…
   - 3.2. Delivery of nutrients: volumes, energy and proteins
4. Laboratory variables
5. Energy expenditure & body composition

Clinical Nutrition xxx (2018) 1–10

Contents lists available at ScienceDirect

Clinical Nutrition

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

Review

Monitoring nutrition in the ICU

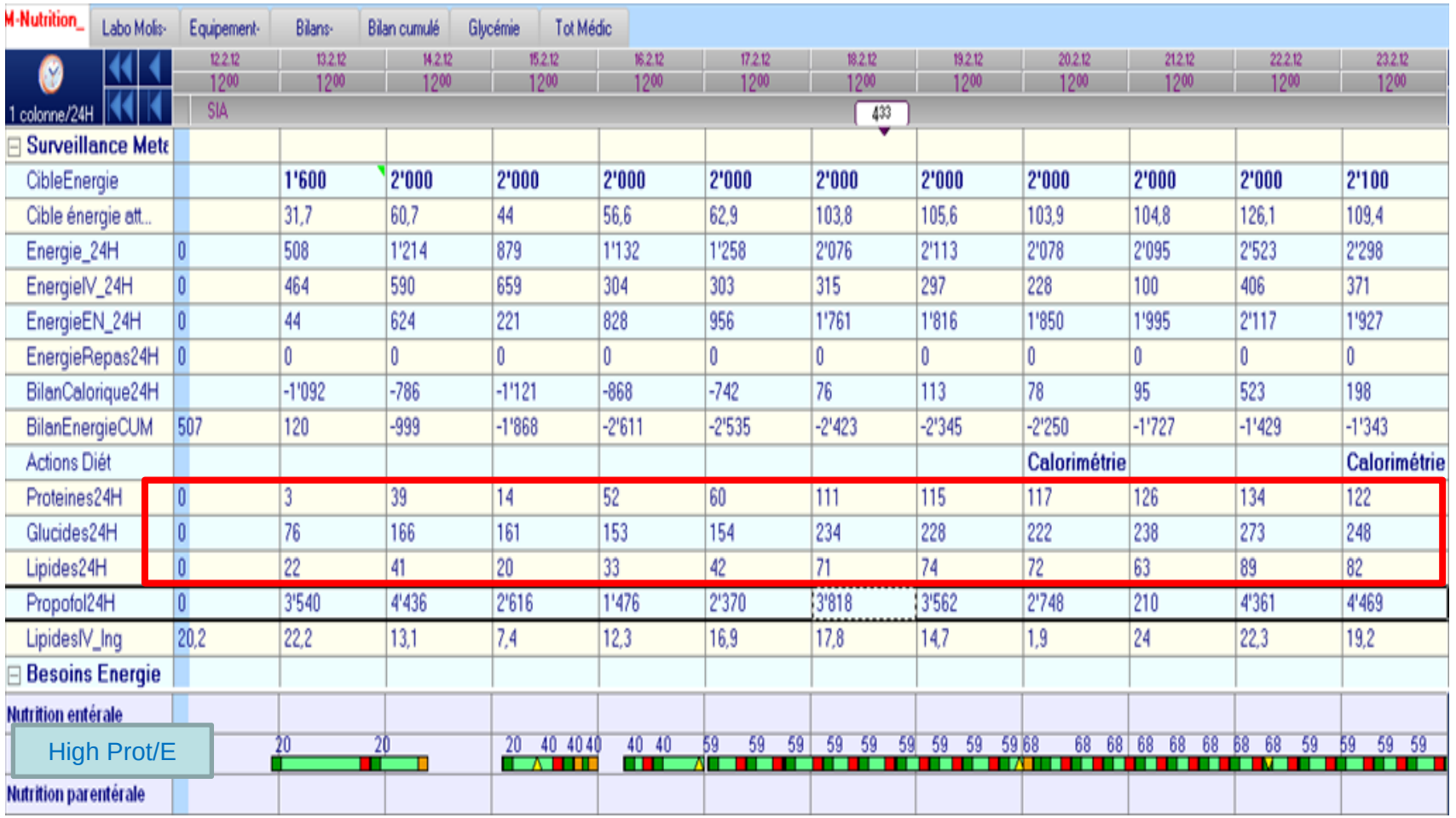
Mette M. Berger [a, *], Annika Reintam-Blaser [b, c], Philip C. Calder [d, e], Michael Casaer [f], Michael J. Hiesmayr [g], Konstantin Mayer [h], Juan Carlos Montejo [i, j], Claude Pichard [k], Jean-Charles Preiser [l], Arthur R.H. van Zanten [m], Stephan C. Bischoff [n], Pierre Singer [o]

This position paper summarizes theoretical and practical aspects of the monitoring of artificial nutrition and metabolism in critically ill patients, thereby completing ESPEN guidelines on intensive care unit (ICU) nutrition.

Methods: Available literature and personal clinical experience on monitoring of nutrition and metabolism was systematically reviewed by the ESPEN group for ICU nutrition guidelines.

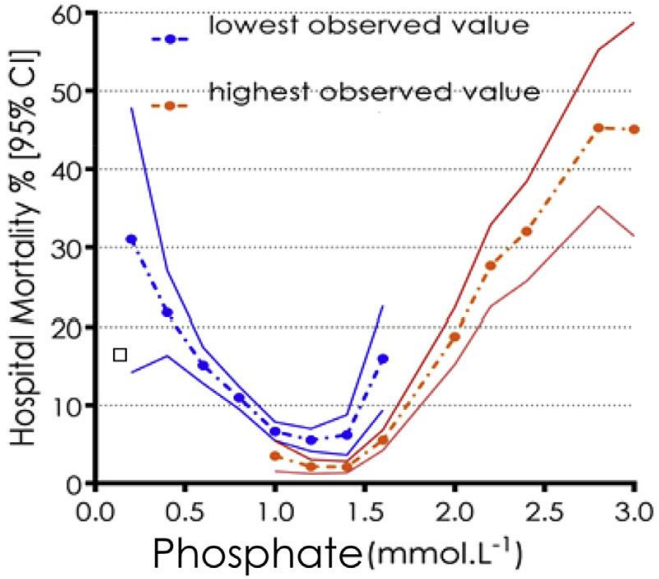
Results: We did not identify any studies comparing outcomes with monitoring versus not monitoring nutrition therapy. The potential for abnormal values to be associated with harm was clearly recognized. The necessity to create locally adapted standard operating procedures (SOPs) for follow up of enteral and parenteral nutrition is emphasised. Clinical observations, laboratory parameters (including blood glucose, electrolytes, triglycerides, liver tests), and monitoring of energy expenditure and body composition are addressed, focusing on prevention, and early detection of nutrition-related complications.

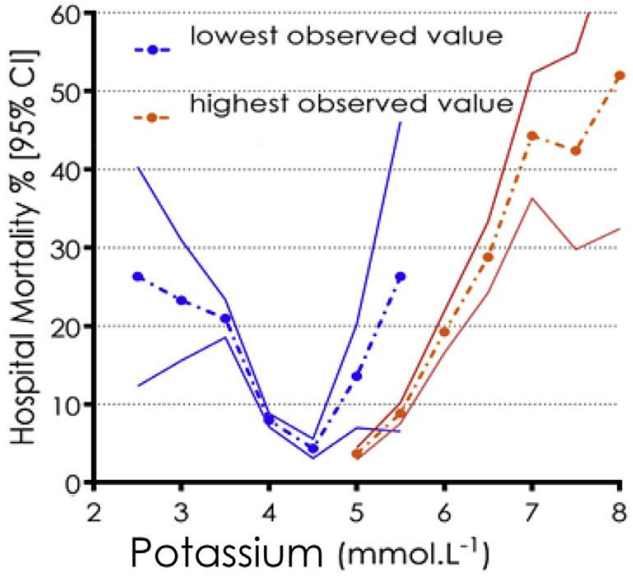
Conclusion: Understanding and defining risks and developing local SOPs are critical to reduce specific risks.

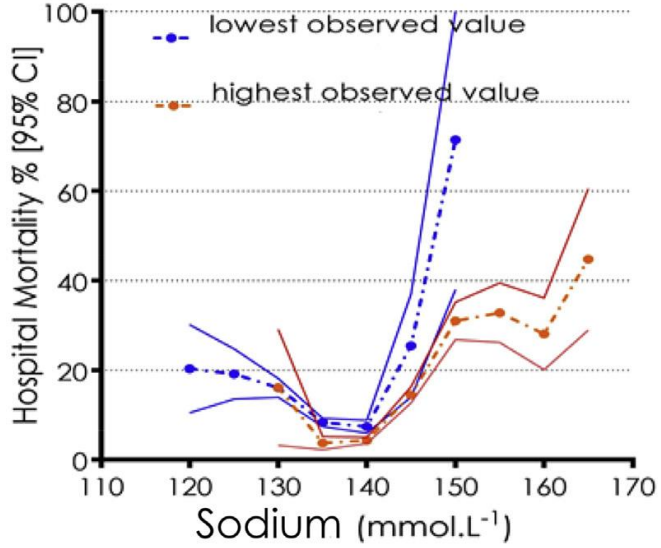

M-Nutrition_
Labo Molis-
Equipement-
Bilans-
Bilan cumulé
Glycémie
Tot Médic
1 colonne/24H
SIA
Surveillance Mete
CibleEnergie
Cible énergie att...
Energie_24H
EnergieIV_24H
EnergieEN_24H
EnergieRepas24H
BilanCalorique24H
BilanEnergieCUM
Actions Diét
Proteines24H
Glucides24H
Lipides24H
Propofol24H
LipidesIV_Ing
Besoins Energie
Nutrition entérale
Nutrition parentérale
High Prot/E

Monitoring nutrition in the ICU.

Clin Nutr, 2018 e-pub







Association between minimum (blue) and maximum (red) serum electrolyte concentrations during the ICU stay and hospital mortality in 6323 patients after major cardiothoracic surgery

Monitoring nutrition in the ICU

Clin Nutr, 2019;38(2):584-593

Recommended blood and urinary laboratory determinations, proposed frequency, cost, and relative cost

Variable	Frequency	Relative cost index
Glucose	First 24 h of ICU admission/feeding: every 4–6 h Later: at least 2 times daily	0.6‰
Phosphate	Within first 6–12 h of admission Later: once a day	0.8‰
Potassium	First 24 h of ICU admission/feeding: every 6 h with blood gases	0.7‰
Sodium, Chloride, Magnesium	Once daily	0.6 and 2.1‰
Liver tests: AST, ALT	Twice weekly	2‰
Triglycerides [65]	Twice weekly	0.7‰
Prealbumin	Once weekly	5‰
Glutamine	In selected cases (renal replacement therapy, burns, PN without glutamine)	3‰
Trace elements: Cu, Se, Zn	In selected cases (such as e.g. burns, addressed in the text)	11, 26 and 17‰
Urea – blood	3 times weekly	0.6‰
Urea – urine	6-hr urine collection once weekly in absence of renal failure	0.7‰
Ammonium	In case of unexplained worsening of consciousness state [43]	10‰
Carnitine	Considering the limited availability and cost, to be done only in presence of unexplained rapid muscle catabolism and hyperlactatemia [79] with adequate protein supply	51‰

Based on Swiss prices [103] on 1.1.2018 (1 CHF ¼ 0.85 V).
a An approach comparable to the "Big Mac Index"

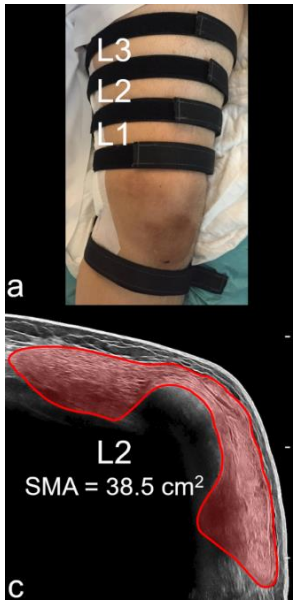
Monitoring Nutrition in Critical Illness: What Can We Use?

Ferrie & Tsang NCP 2018 Feb;33(1):133-146

Literature search: The most recent 200 articles were examined to quantify the number of occurrences for each indicator.
Results: 53 parameters were found, including the 15 already identified as commonly used; 27 were used in ≥3 recent studies.
Less-well-established nutrition indicators with potential for use in the ICU (moderate or high feasibility and availability) included **ultrasound measurement of arm or leg muscle thickness**, **fatigue scoring** with the Chalder scale, urinary creatinine assay, and serum insulin-like growth factor 1 level.

Berger MM et al
Based on our most recent SPN2 and HMB research, add:

- Muscle ultrasound
- Phase angle (bioimpedance)
- SF-12 score at 60 or 90 day

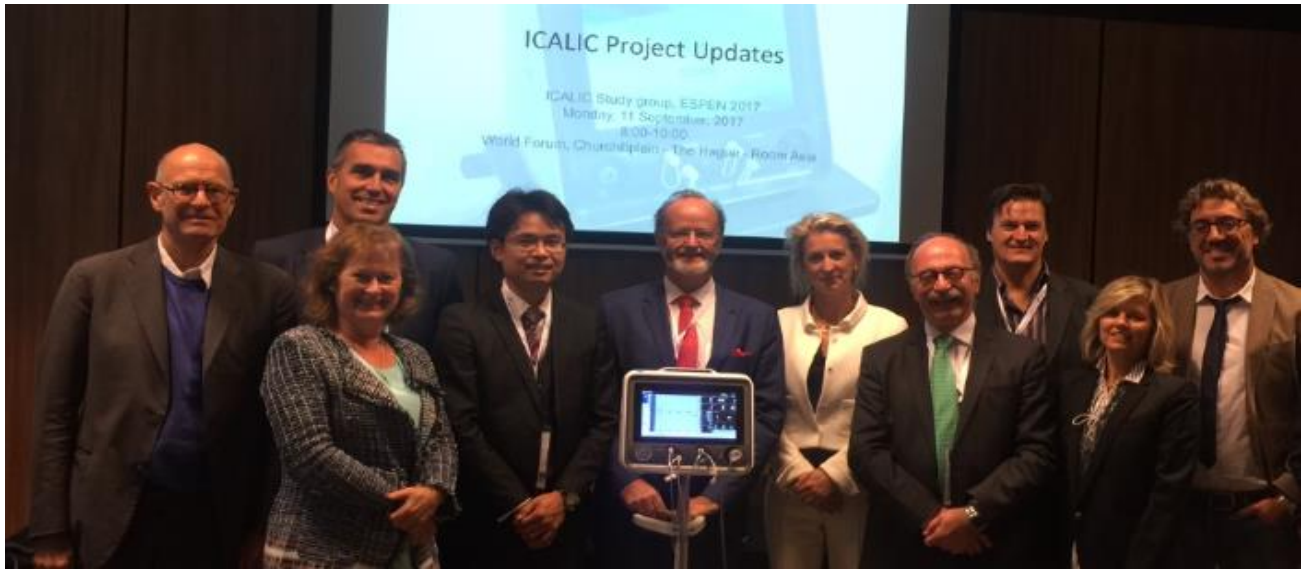


Study Failure Prevention?

- Absence of monitoring exposes to
  - Not detecting protocol deviations
  - Not detecting inappropriate feed/nutrient delivery
    → conclusion by ITT might be wrong

    e.g.: delivering 0.7 g/protein instead of 1.3 g/kg

    e.g.: excessive energy ← propofol, Glucose, when iso-caloric is the objective aimed
  - Not detecting complications, such as hypoP in refeeding, or overfeeding …



ICALIC project group

11.09.2017

Taku Oshima **Japan**, Mette M. Berger **CH**, Elisabeth De Waele**, Belgium**, Claudia-Paula Heidegger **CH**, Michael Hiesmayr **Austria**, Pierre Singer, **Israel,** Jan Wernerman **Sweden**, Claude Pichard **CH**

Q-NRG® – Indirect calorimeter on market since 2019
< 3 kg, 15000 €

Monitor energy expenditure

Feeding the hungry I: Identifying and feeding patients at risk of malnutrition

Prof. Mette Berger

FRESENIUS KABI
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JUMPstart Training Program

Feeding the hungry I:

Identifying and Feeding patients at risk of malnutrition

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

Advanced module, Day 1, Part I: Exclamation marks and questions marks: State of the Art in Parenteral Nutrition

Content

1. Why Screen and Assess ?
2. Available tools:
   - NRS
   - SGA
   - Frailty score
   - Bioimpedance – phase angle
   - Muscle mass and function
   - Indirect calorimetry
   - Comorbidity
   - Nutric Score
   - Additional tools (Lab parameters)
3. GLIM
4. Perioperative Care
5. Conclusions

Why screen and evaluate?

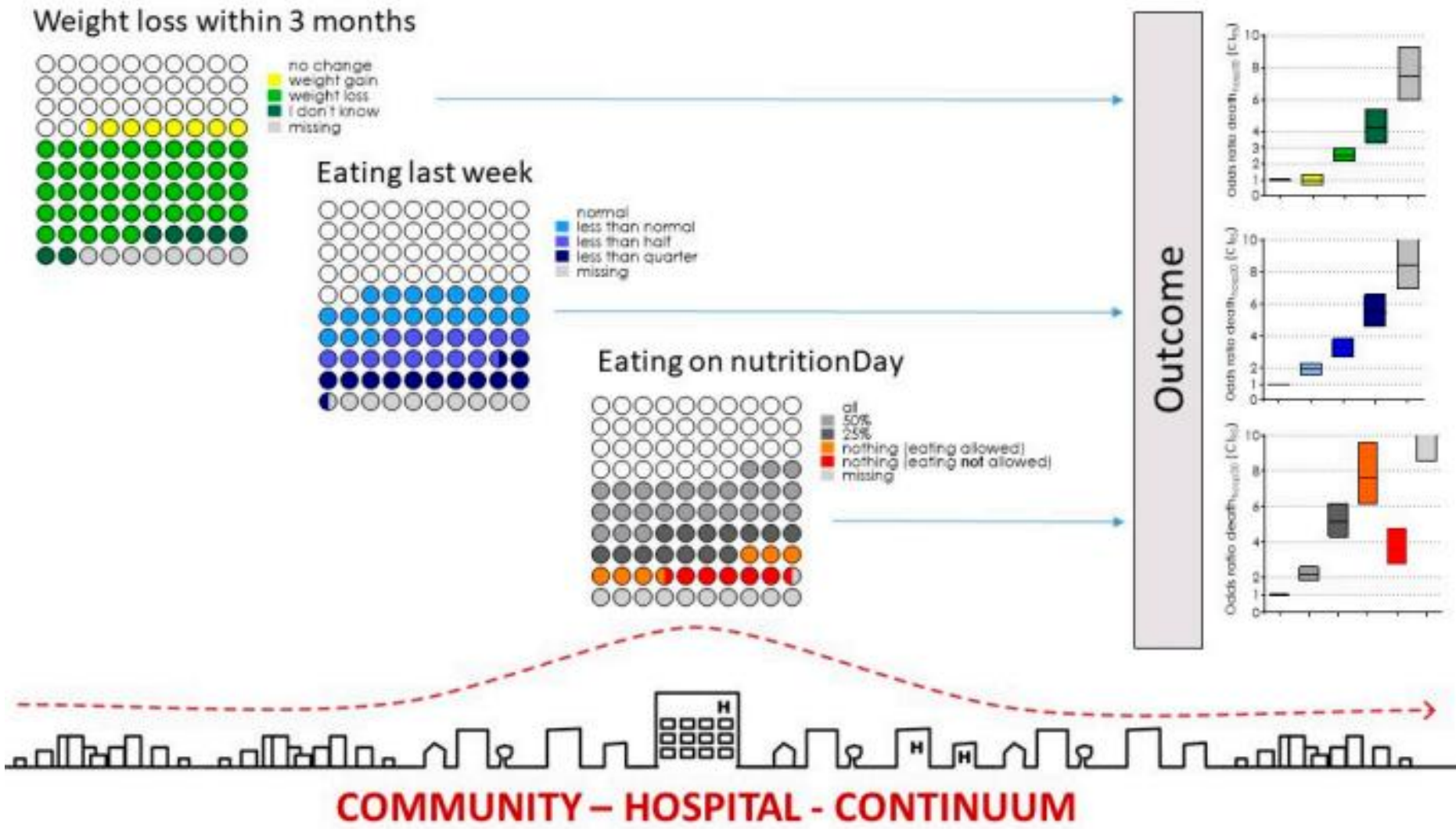
Because you will pick the population

on which to invest,

on which therapy will work

Hospital Malnutrition, a Call for Political Action: A Public Health and Nutrition Day Perspective

Hiesmayr M et al, J. Clin. Med. 2019, 8, 2048



Malnutrition in Hospitalized Patients

Primary Malnutrition (arising in the absence of disease)

+

Disease-related Malnutrition

+

Iatrogenic Malnutrition

→

Malnutrition resulting from medical treatment

- Negligence of medical personnel to give enough nutrition during hospital stay
- Complications of surgery or medications
- Drug, nutrient shortages

[1]Iwuoha OI, IOSR-JNHS 2014
[2]Chan LN, JPEN 2013

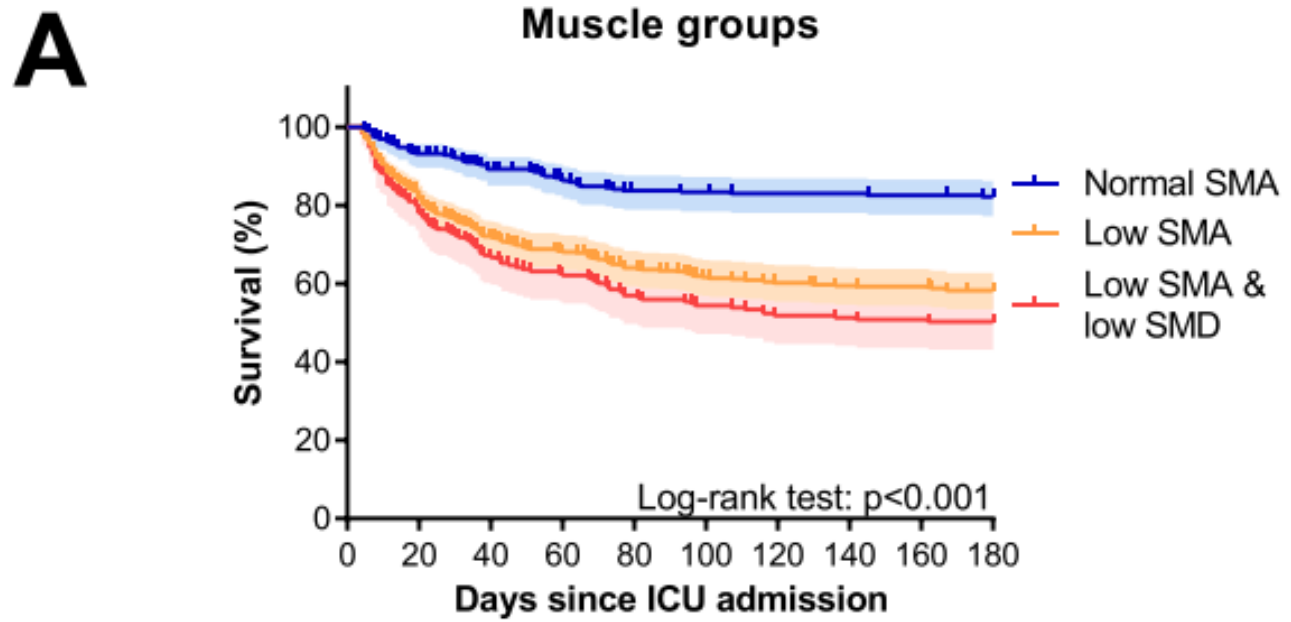
Early high protein intake and mortality in critically ill ICU patients with low skeletal muscle area and –density

Looijaard et al Clin Nutr 2020

abdominal CT-scans at L3
N= 739: mean age 58 years, 65% male, APACHE II score 23

Of 739 included patients

- 294 (40%) with normal skeletal muscle area
- 445 (60%) with low skeletal muscle area.
- 200 (45% of the low SMA group) had combined low skeletal muscle area and density.



Number at risk						
Normal SMA	293	252	225	222	221	218
Low SMA	444	306	271	252	248	242
Low SMA & low SMD	200	131	113	102	100	98

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

Looijaard et al Clin Nutr 2020

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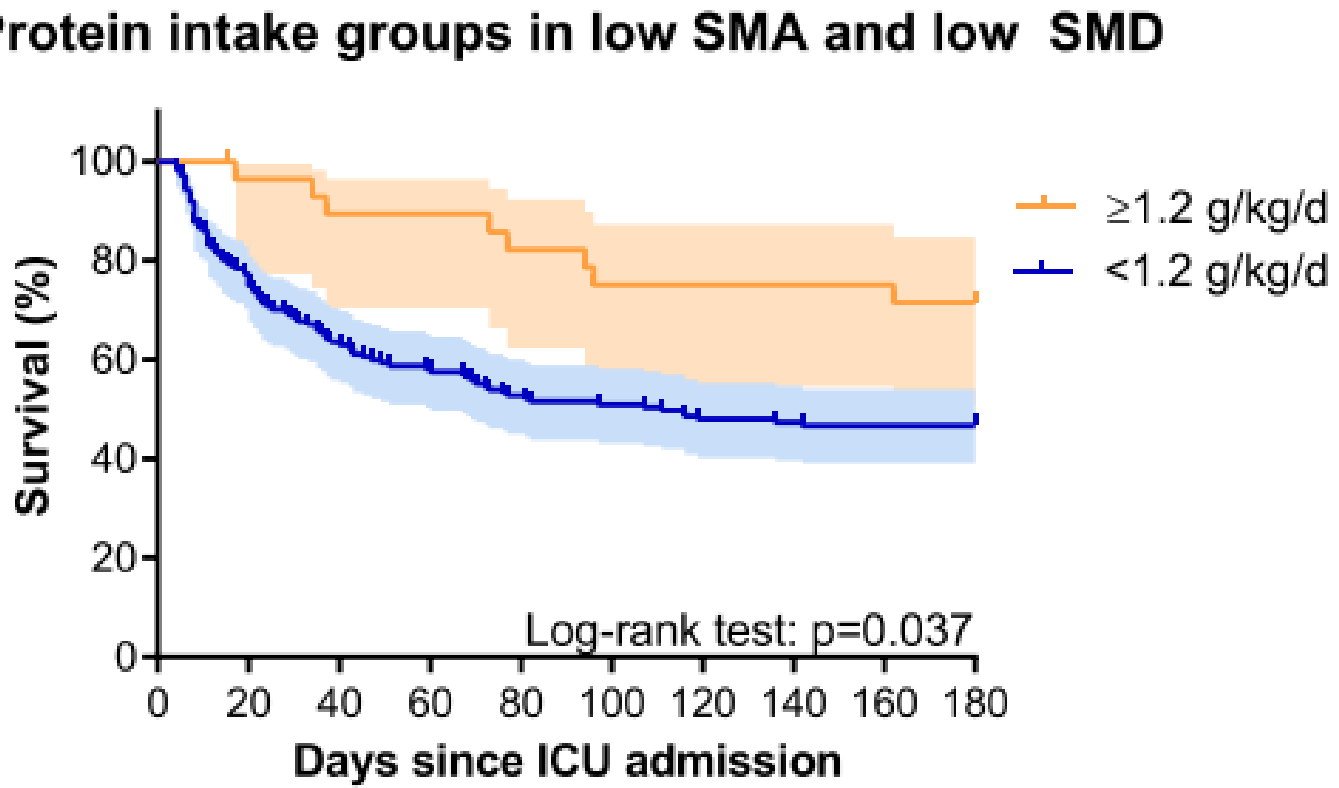


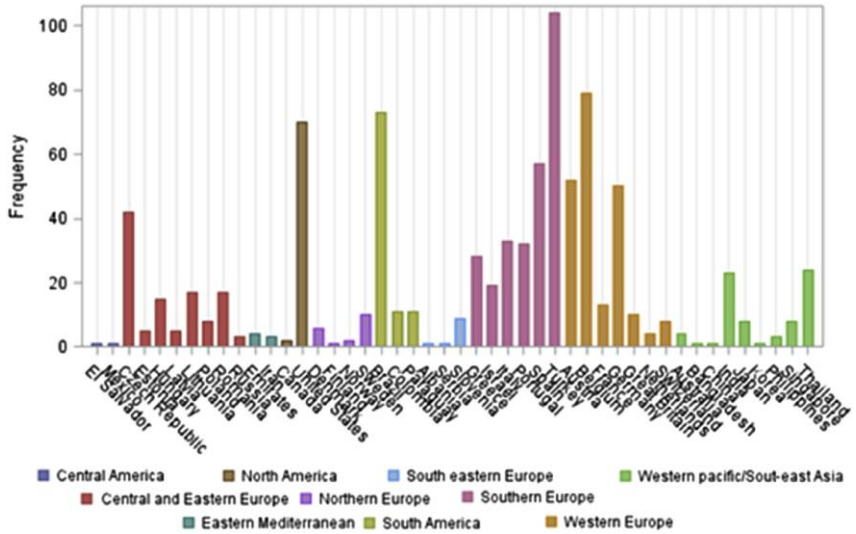
Number at risk

Low protein	171	106	89	81	80	78
High protein	29	26	24	22	22	20

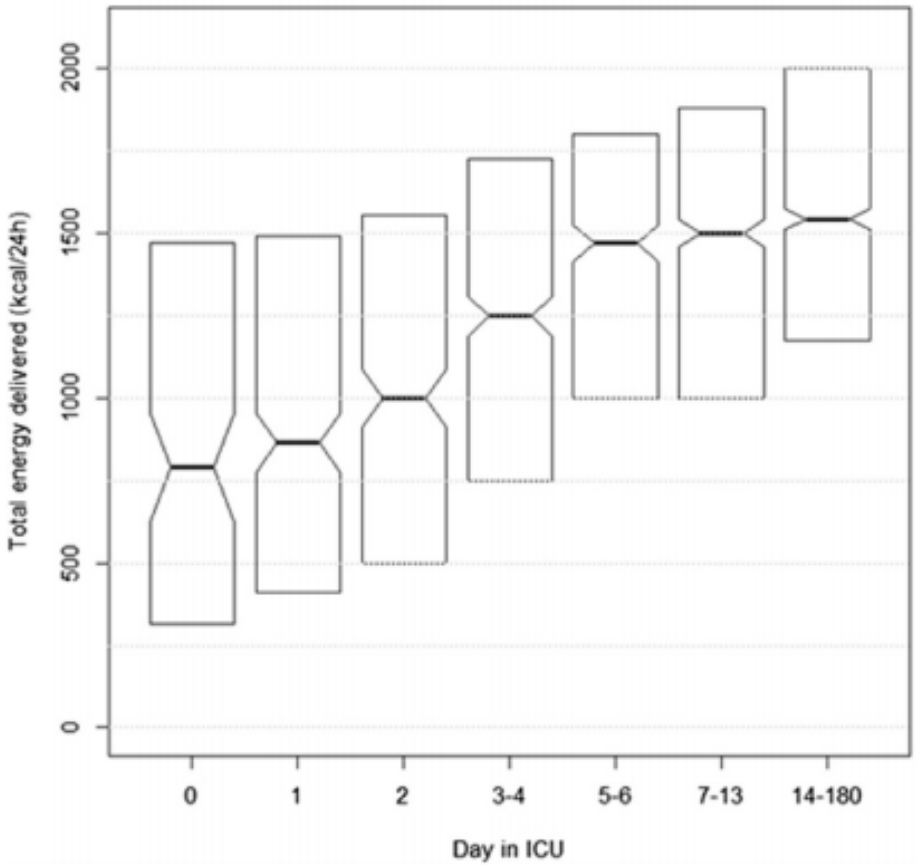
Early high protein intake is associated with lower mortality in critically ill patients with low skeletal muscle area and -density, but not in patients with normal skeletal muscle area on admission.

NutritionDay ICU: A 7 year worldwide prevalence study of nutrition practice in intensive care

Itai Bendavid [a], Pierre Singer [a, *], Miriam Theilla [a], Michael Themessl-Huber [b], Isabella Sulz [b], Mohamed Mouhieddine [c], Christian Schuh [b], Bruno Mora [c], Michael Hiesmayr [c]



Number of units participating to nutrition Day ICU according to countries



- NutritionDay-ICU showed that most of the patients are underfed during their ICU stay
- Nutritional support is slow to start and never reaches the recommended targets.
- Administration of calories did not appear to be related to actual or ideal body weight within all BMI groups. Patients with a BMI 40 received slightly less calories than all other.
- Parenteral nutrition prescription reaches only 20% of the study population
- These observations are showing the poor observance to guidelines.

Wischmeyer et al. Critical Care (2017) 21:142
DOI 10.1186/s13054-017-1736-8

Critical Care

RESEARCH Open Access

A randomized trial of supplemental parenteral nutrition in underweight and overweight critically ill patients: the TOP-UP pilot trial

Paul E. Wischmeyer[1*], Michel Hasselmann[2], Christine Kummerlen[2], Rosemary Kozar[3], Demetrios James Kutsogiannis[4], Constantine J. Karvellas[5], Beth Besecker[6], David K. Evans[7], Jean-Charles Preiser[8], Leah Gramlich[9], Khursheed Jeejeebhoy[10], Rupinder Dhaliwal[11], Xuran Jiang[11], Andrew G. Day[11] and Daren K. Heyland[11,12,13]

Pilot study: trends toward reduced ICU and hospital mortality were observed only in the BMI <25 subgroup of the SPN + EN arm
No effect in the BMI >35 subgroup.

Journal of Clinical Medicine

MDPI

Article

Protein Intake, Nutritional Status and Outcomes in ICU Survivors: A Single Center Cohort Study

Peter J.M. Weijs [1,2], Kris M. Mogensen [3], James D. Rawn [4] and Kenneth B. Christopher [5,*]

Received: 16 December 2018; Accepted: 31 December 2018; Published: 4 January 2019

Patients diagnosed with malnutrition, the 90- day Post Discharge Mortality was 30% less for each additional 1g protein/kg/day of protein supply.

Wischmeyer et al. Critical Care (2017); Peter Weijs, Mogensenet al. J. Clin. Med. 2019

ESPEN

THE EUROPEAN SOCIETY FOR CLINICAL NUTRITION AND METABOLISM

ESPEN 2019 ICU Guidelines

Statement 1:
Every critically ill patient staying **for more than 48 h** in the ICU should be considered **at risk for malnutrition**. Strong consensus (96% agreement)

Singer et al. Clin Nutr. 2019

ICU - ESPEN-ASPEN – any difference?

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ESPEN 2019 → A general clinical assessment should be performed to assess malnutrition in the ICU, until a specific tool has been validated.

ASPEN2016 SCCM → Patients at higher nutrition risk in an ICU setting require a full nutrition assessment. NRS 2002 and the NUTRIC score determine both nutrition status and disease severity

Singer P, Blaser AR, Berger MM et al., ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr. 2019
Mc Clave, Taylor B, Martindale R, et al. 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, 2016

Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials

NRS 2002

JENS KONDRUP,* HENRIK HØJGAARD RASMUSSEN,† OLE HAMBERG,‡ ZENO STANGA§ AND AN AD HOC ESPEN WORKING GROUP[1]

Clinical Nutrition (2003) **22(3)**: 321–336

Nutritional status alteration		Severity of condition	
Absent Score 0	Normal status	**Absent** Score 0	
Light Score 1	- Weight loss > 5% in 3 months - Ingesta < 50 % usual intakes	**Mild** Score 1	Femoral Fracture COPD, Diabetes dialysis
Moderate Score 2	- Weight loss > 5% in 2 months - BMI 18,5 to 20,5 - Ingesta: 25 - 50% of usual intakes	**Moderate** Score 2	Severe pneumonia Major digestive surgery
Severe Score 3	- Weight loss> 5% in 2 months - BMI < 18,5 - Ingesta < 25% usual intakes	**Severe** Score 3	ICU patients
		Age Score 0 Score 1	< 70 years ≥ 70 years

Hospital NRS > 3 → risk of malnutrition related complications
ICU NRS ≥5 → High risk of complications

NRS-2002: Classification of patients

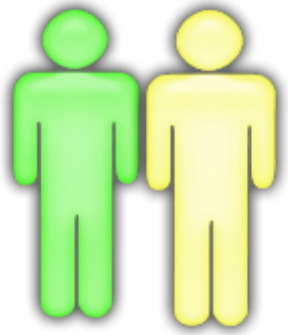
Hospital

- **Score ≥ 3:** the patient is nutritionally at risk and a nutritional care plan is initiated

Critically ill

- **Score ≥ 5:** High risk Mortality increases

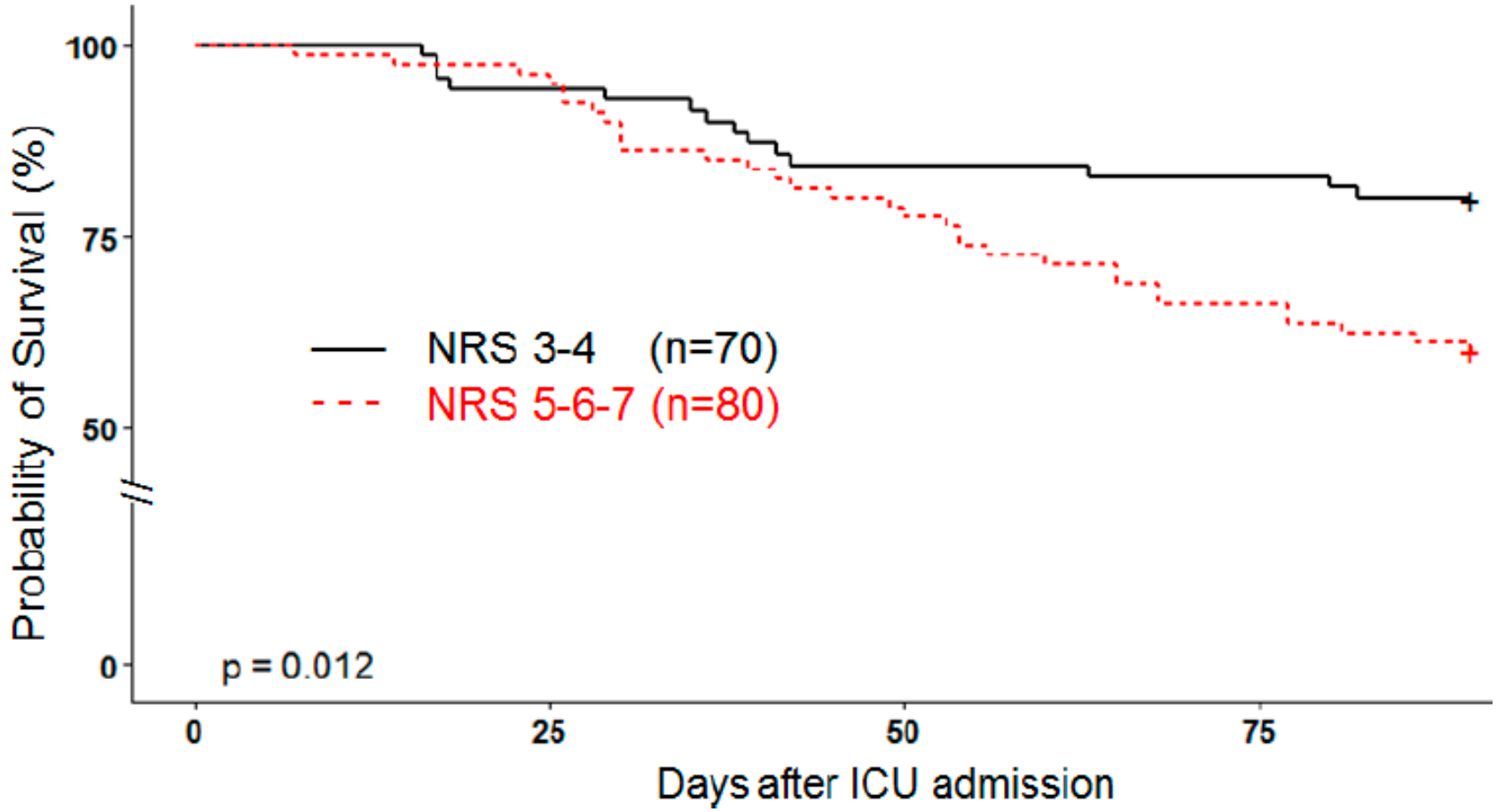
- **Score < 3:** weekly rescreening of the patient. If the patient e.g. is scheduled for a major operation, a preventive nutritional care plan is considered to avoid associated risk status



- **Score < 5:** Apply SOP and start EN if on mechanical ventilation

Metabolic and Nutritional Characteristics of Long-Stay Critically Ill Patients

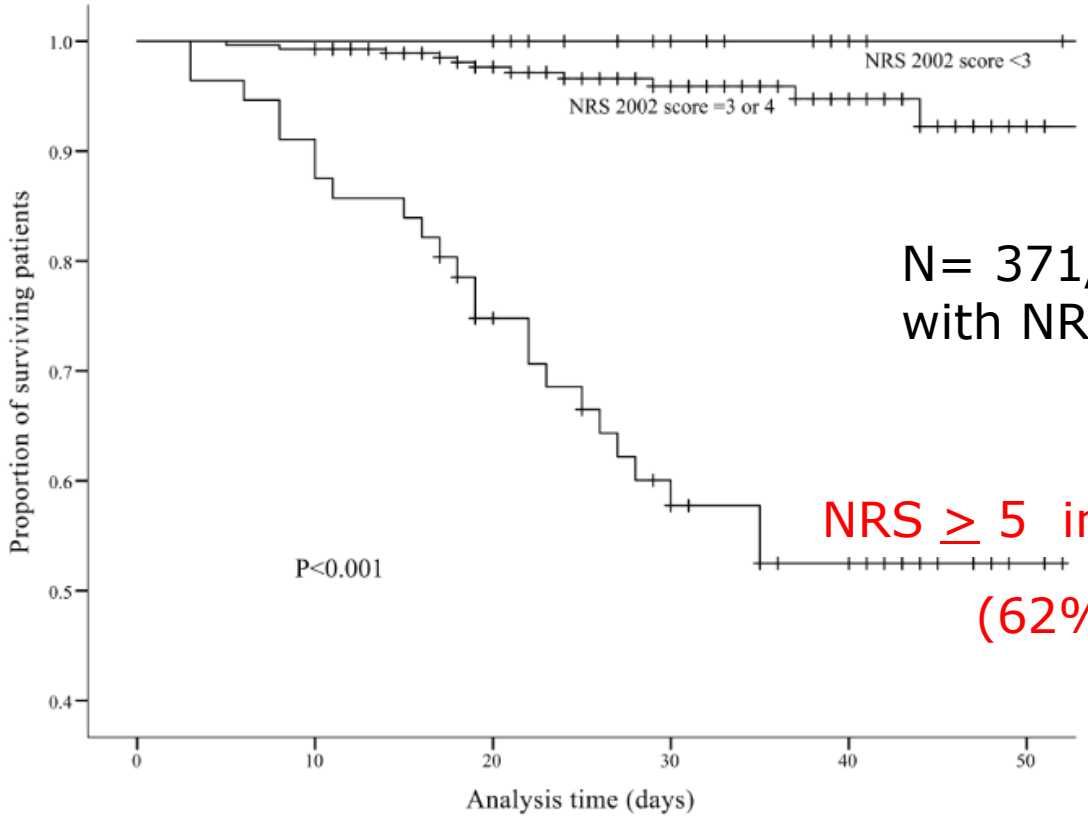
Viana MV et al, J Clin Med, 2019, 8, 985



Kaplan–Meier analysis comparing elevated and low NRS scores

NRS>5 & COVID mortality - Wuhan

Survival of severe and critically ill patients with COVID-19 stratified by the NRS score.
Zhao X, Li Y, Ge Y et al, JPEN 2020 In preparation



8% of patients - 0 died

76% of patients – 4% died

N= 371/ 413 patients with NRS

NRS ≥ 5 in 16% of patients – 43% died

(62% of ICU, 7% of severe cases)

25% of patients were fed

Subjective global assessment (SGA)

- weight loss
- dietary intake
- GI symptoms
- functional capacity
- disease-related effects
- physical signs of malnutrition (loss of subcutaneous fat or muscle mass, oedema, ascites)

SGA Rating:

SGA A:
well nourished

SGA B:
Moderately malnourished

SGA C:
severely malnourished

Detsky et al., JPEN (1987) 11: 8-13

2014 Jul;149(7):633-40.

Research

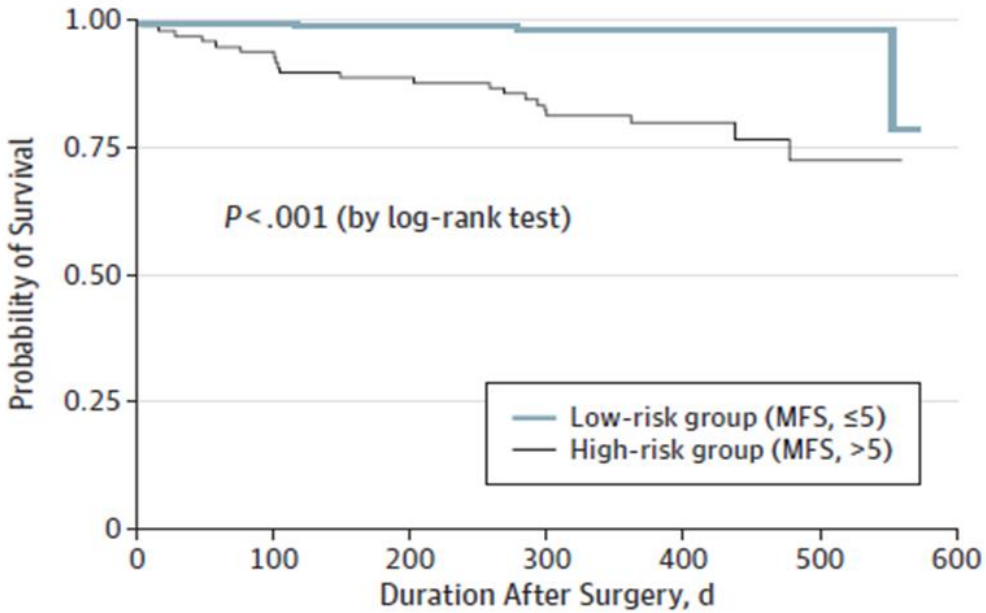
Original Investigation | SURGICAL CARE OF THE AGING POPULATION

Multidimensional Frailty Score for the Prediction of Postoperative Mortality Risk

Sun-wook Kim, MD; Ho-Seong Han, MD, PhD; Hee-won Jung, MD; Kwang-il Kim, MD, PhD; Dae Wook Hwang, MD, PhD; Sung-Bum Kang, MD, PhD; Cheol-Ho Kim, MD, PhD

JAMA Surg 2014; 149:633

Figure 4. Cumulative All-Cause Mortality Rate According to Risk Stratification Based on Multidimensional Frailty Score (MFS)



No. at Risk						
Low-risk group	177	176	175	172	99	38
High risk group	98	92	87	80	37	9

Nutric Score

Canadian Score designed to quantify the risk of critically ill patients developing adverse events that may be modified by "aggressive" nutrition therapy.

Table 1: NUTRIC Score variables

Variable	Range	Points
Age	<50	0
	50 - <75	1
	≥75	2
APACHE II	<15	0
	15 - <20	1
	20-28	2
	≥28	3
SOFA	<6	0
	6 - <10	1
	≥10	2
Number of Co-morbidities	0-1	0
	≥2	1
Days from hospital to ICU admission	0 - <1	0
	≥1	1
IL-6	0 - <400	0
	≥ 400	1

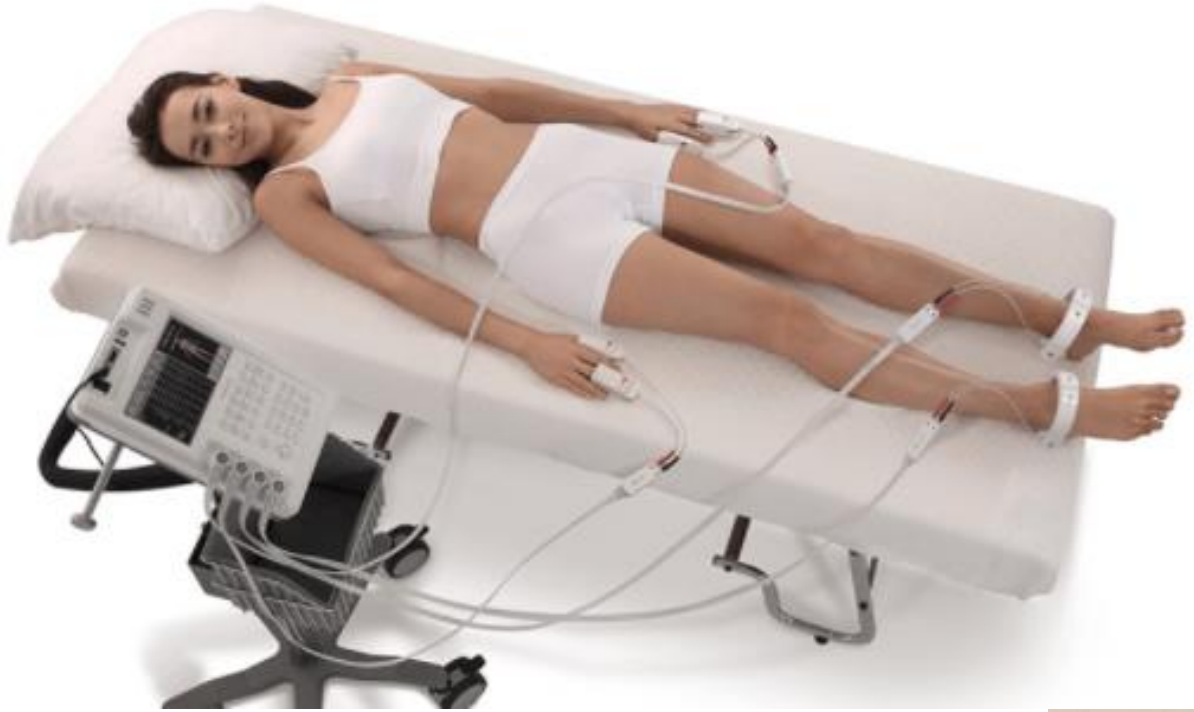
Table 3. NUTRIC Score scoring system: If no IL-6 available*

Sum of points	Category	Explanation
5-9	High Score	➢ Associated with worse clinical outcomes (mortality, ventilation). ➢ These patients are the most likely to benefit from aggressive nutrition therapy.
0-4	Low Score	➢ These patients have a low malnutrition risk.

Heyland DK, Clin Nutr 2015

BIA

Bioelectrical impedance analysis



Easy to use
Non-invasive
Repeatable
Low cost,

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

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*

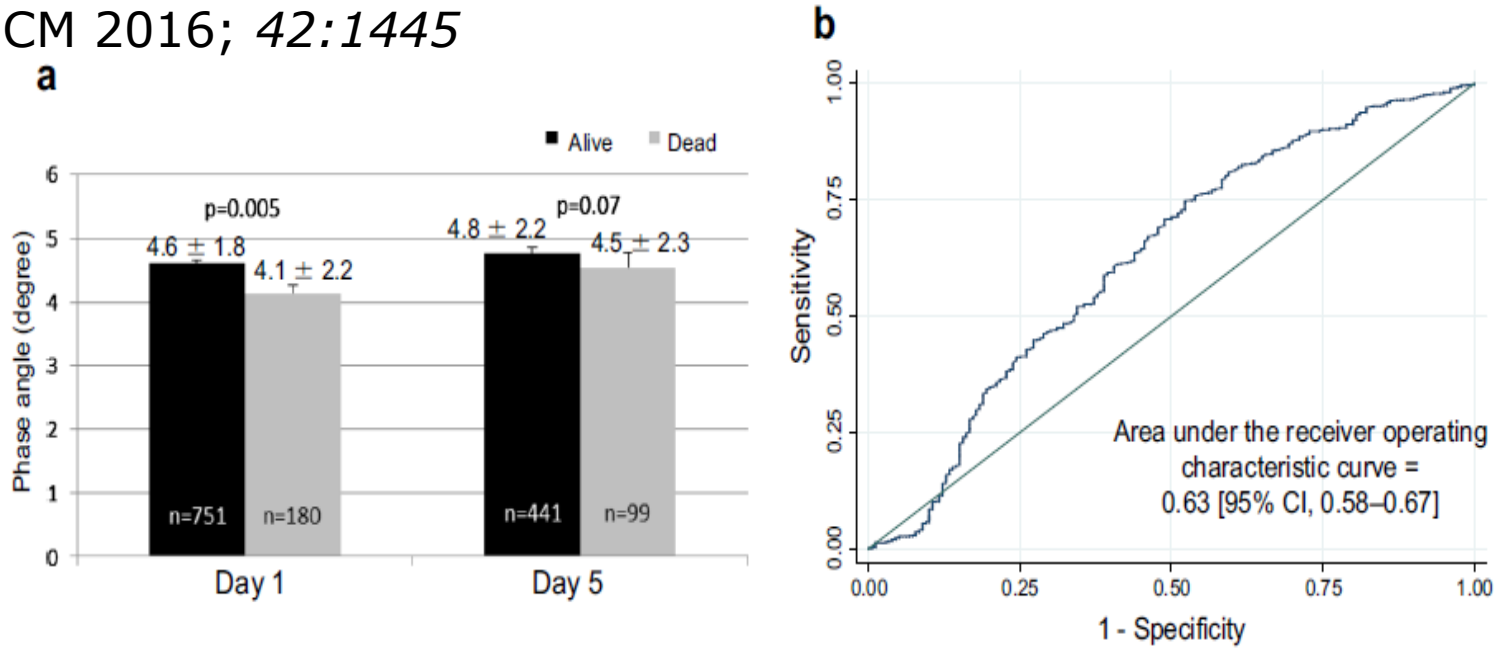
Fat-free mass was assessed by measurement of the 50-kHz phase angle at admission.

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*



Predictive value of fat-free mass as measured by BIA-derived phase angle at ICU admission on 28-day mortality.

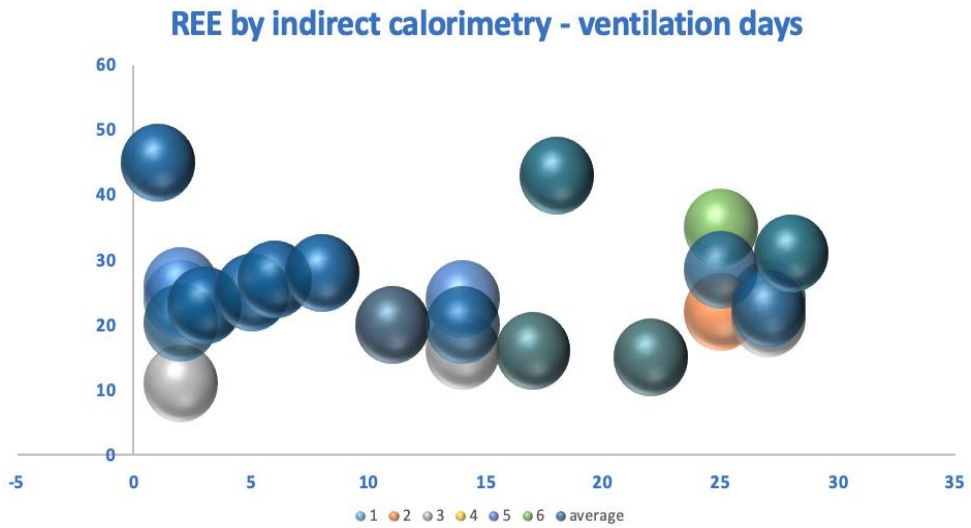
a. 28-day mortality according to phase angle values on day 1 and day 5. in 931 patients, and on day 5 in the 540 patients remaining in the ICU.

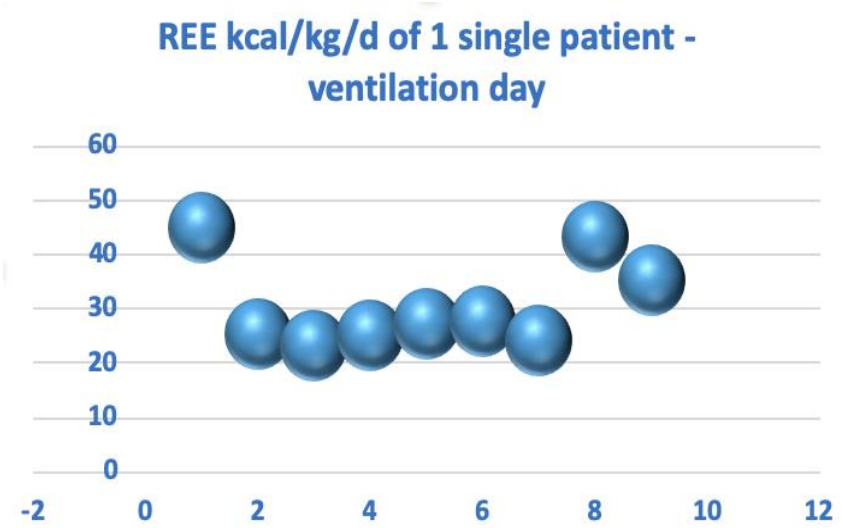
b. Area under the receiver operating characteristic curve (AUC) assessing 28-day mortality prediction by **day 1 phase angle** (*n* = 931).

Take nutritional therapy seriously: it will increase efficiency of other ttt (?)

Prof. E. De Waele

Mean Energy Expenditure of ventilated COVID19 patients measured by indirect calorimetry: **21 kcal/kg/day**





6 COVID-19 patients on mechanical ventilation
Median age 63 yrs, 95 kg, BMI 30.3, mortality 33%

Practical guidance for the use of indirect calorimetry during COVID 19 pandemic. Singer P, Pichard C, De Waele E. Clin Nutr Exper 2020; 33:18

Energy delivery guided by indirect calorimetry in critically ill patients: a systematic review and meta-analysis

Duan JY et al, Crit Care 2121 in press

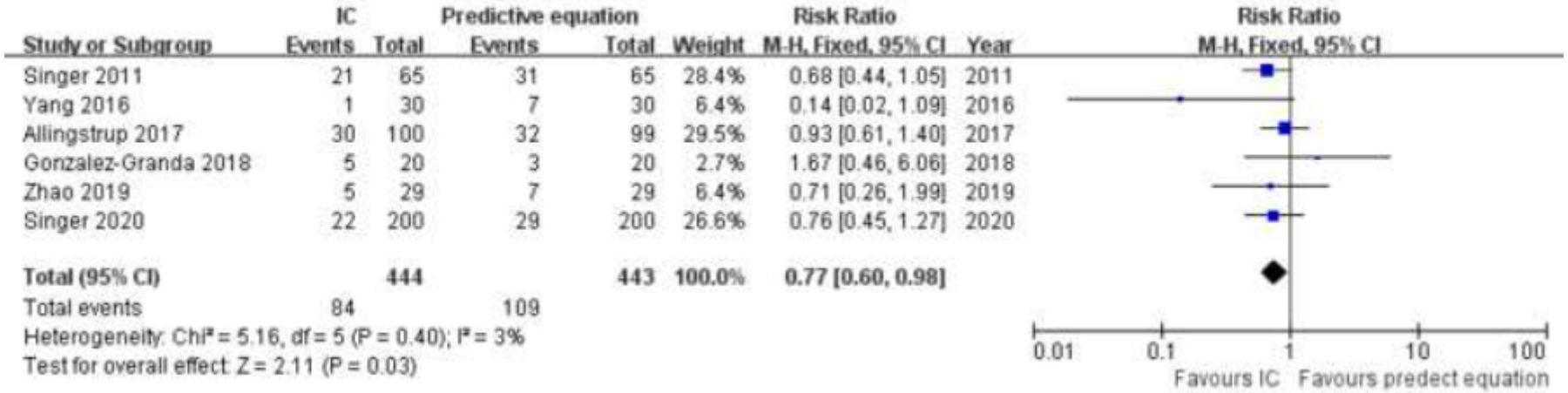
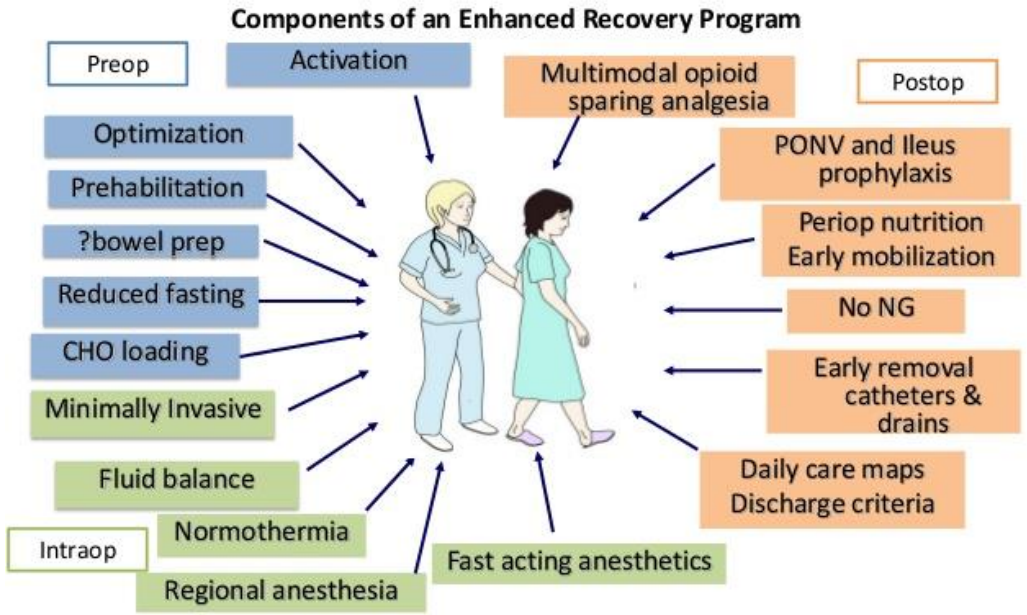


Figure 2. Forest plot showing the effects of energy delivery guided by indirect calorimetry on short-term mortality rate in critically ill patients

(RCTs) were included if they focused on energy
delivery guided by either IC or predictive equations in critically ill adults
Eight RCTs with 991 adults met the inclusion criteria

Conclusions: This meta-analysis indicates that IC-guided energy delivery significantly reduces short-term mortality in critically ill patients. This finding encourages the use of IC-guided energy delivery during critical nutrition support. But more high-quality 33studies are still needed to confirm these findings.

Nutrition in Surgery -- ERAS



ESPEN guideline: Clinical nutrition in surgery

Weimann A et al, ClNu 2017; 36:623

- Integration of nutrition into the overall management of the patient
- Avoidance of long periods of preoperative fasting
- Re-establishment of oral feeding as early as possible after surgery
- Start of nutritional therapy early, as soon as a nutritional risk becomes apparent
- Metabolic control e.g. of blood glucose
- Reduction of factors which exacerbate stress-related catabolism or impair GI function
- Minimize time on paralytic agents for ventilator management in the postoperative period
- Early mobilisation to facilitate protein synthesis and muscle function.

Screening leads to nutritional care

Conclusions

- Disease-related malnutrition is a problem in hospitalized patients all over the world
- Impaired nutritional status is associated with reduced quality of life, increased complications and cost and lower survival rates
- The risk of malnutrition is common and significant among hospitalized patients, requiring a systematic diagnostic approach for early detection, with subsequent adequate therapeutic treatment
- Nutrition screening and frequent reassessments are key components of patient care

Feeding the hungry II: Parenteral nutrition: When and how to?

Prof. Bob Martindale

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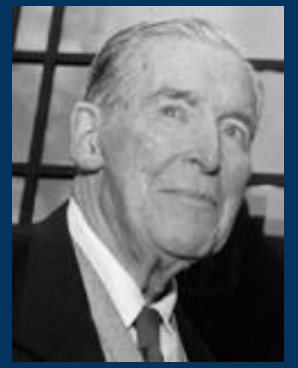
JUMPstart Training Program

Feeding the hungry II: PN: when and how to?

Prof. Bob G. Martindale, MD, PhD

Modern History of PN

- 1966 Sustained normal growth of puppy
- 1968 Sustained normal growth of human infant
  - Lawson LJ gave PN in mid 1960's to adults in the UK
- 1930 to 1970
  - Venous access methods
    - Korean War yielded subclavian access techniques
- 1960 to 1970's PN as we know it today
  - IV lipid emulsions developed
  - Protein hydrolysate transition to crystalline AA
- 1970's
  - Trace minerals



were given. Overall nitrogen balance was improved in these cases and weight loss reduced to a minimum (Fig. 2). Parenteral nutritional therapy has also been

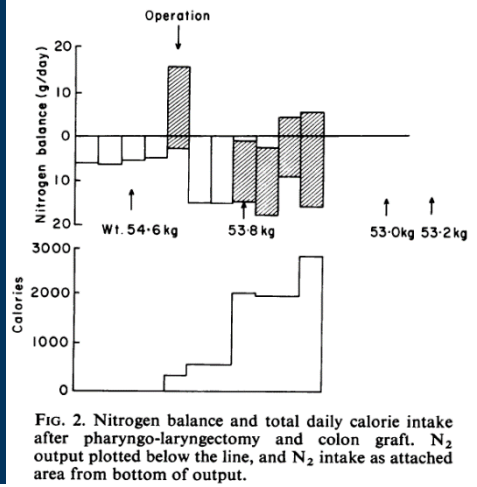
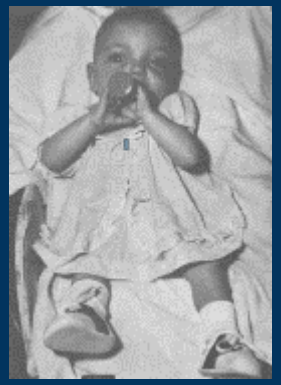
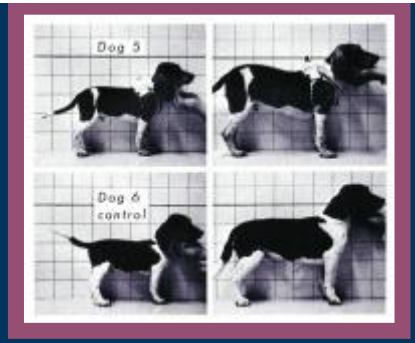


FIG. 2. Nitrogen balance and total daily calorie intake after pharyngo-laryngectomy and colon graft. N_2 output plotted below the line, and N_2 intake as attached area from bottom of output.

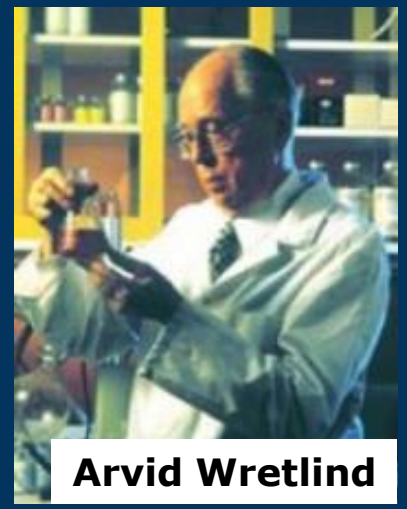
Lawson LJ Postgraduate Medicine 1967



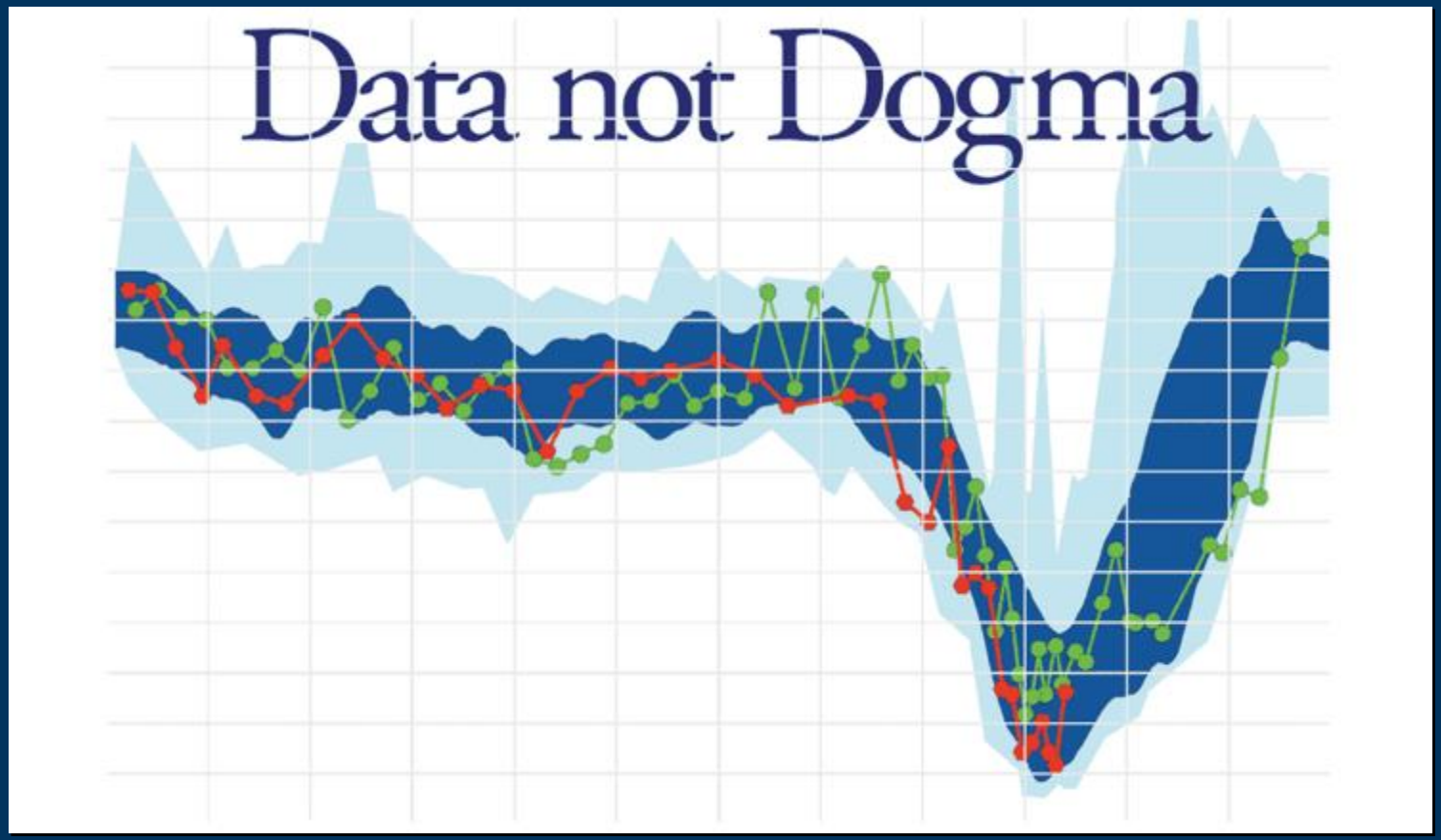


Evolution of Lipid Emulsions: "the good, the bad and the ugly"

- Milk infusions
  - Hodder in Canada 1873 during cholera epidemic
  - Essentially 100% fatal
- 1920 to 1960
  - Multiple attempts lipid infusions Japan and USA without consistent success
    - 1944 olive oil / lecithin emulsion given to child that survived
- 1950's Cottonseed oil approved for use in USA
  - Rapid development fever, nausea, headache, coagulopathy etc.
    - "fat overloading syndrome"
  - Pulled from the market 1957
- 1961 Soy based product
  - Arvid Wretlind
    - Mixture of SO, egg yolk emulsifier (lecithin), glycerin
      - NaOH to keep pH in range (ph 8.0)



Arvid Wretlind



What is the data to support our choice of EN or PN ?

In 2020 is the optimal route of nutrient delivery again in question ?

- Historical perspective
  - PN was "King" 1970's to 1980's
    - Perception was that caloric/energy delivery was key
    - "We" knew better than mother nature on where calories are delivered
  - EN 1980's to 2010
    - Better understanding of metabolic and non-nutritional benefits of EN
  - Since 2010 - Driven by individual patient metabolism, EN or PN
    - Glycemic control
    - Protein delivery
    - More balanced PN IVLE
    - Mitochondria focused nutrition ?
    - Autophagy ?

Berger MM et al Curr Opin Critical Care 2019

Critical Care Nutrition Continues to Evolve

Nutrition Support

1960-1982

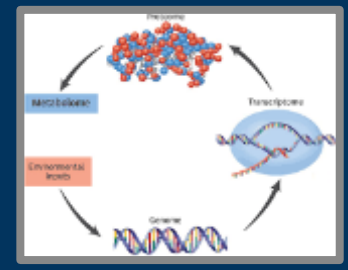
- "Skeletons in the Closet"
- PEM in 50% pts US hospitals
- Support to prevent PEM
- PN-based

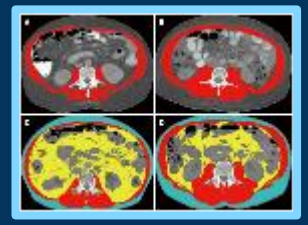
Nutrition Therapy

1982-2014

- EN for macronutrients
- EN for non-nutritional benefits
  - Immune/metabolic-modulation
  - Attenuates inflammation
  - Maintains gut integrity
  - Maintaining the microbiome
- Increase protein delivery
- Immunonutrition – surgery, critical care

2015-?

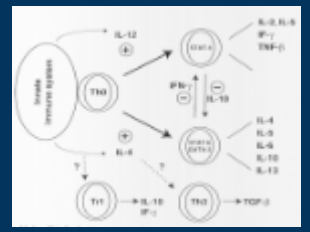


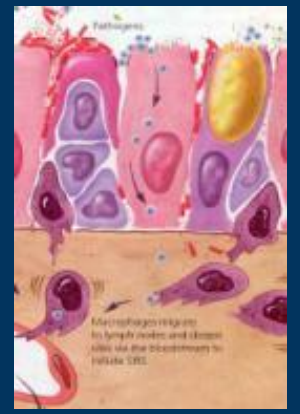


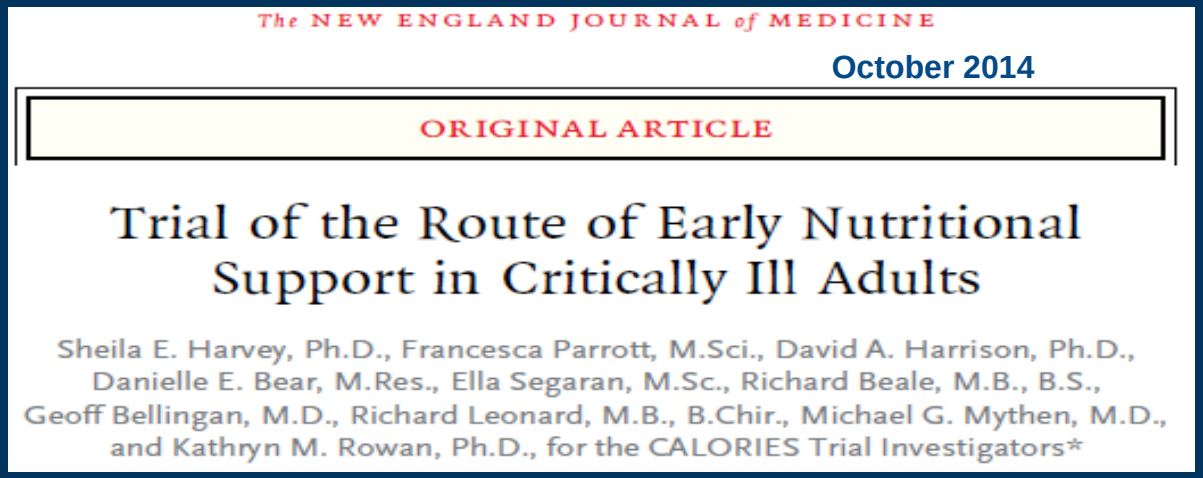
- EN remains 1st choice
- PN new awakening
- Better understanding of physiology of IMN
  - Arginine, FO, Gln, nucleic acids
    - SPM's as endogenously produced end products of FO
- Altering the Microbiome
  Metabolomics—"omics"
- Resistance exercise
- Nutrition focus on the mitochondria

Reasons why PN use was dramatically decreased between 1980 and 2014: Benefits of Early Enteral Feeding

- Attenuates inflammatory response to stress
- Prevents mucosal atrophy, loss of gut barrier
- Luminal delivery maintains GALT and MALT
- Systemic immune support – decrease BSI, Pneumonia
- Helps maintain "normal" gut microbiome
- Less insulin resistance, hyperglycemia less common
- Maintains vagal mediated anti-inflammatory reflex
- Portal nutrient delivery allows for first pass effect
- More balanced nutrient delivery possible







The NEW ENGLAND JOURNAL of MEDICINE

October 2014

ORIGINAL ARTICLE

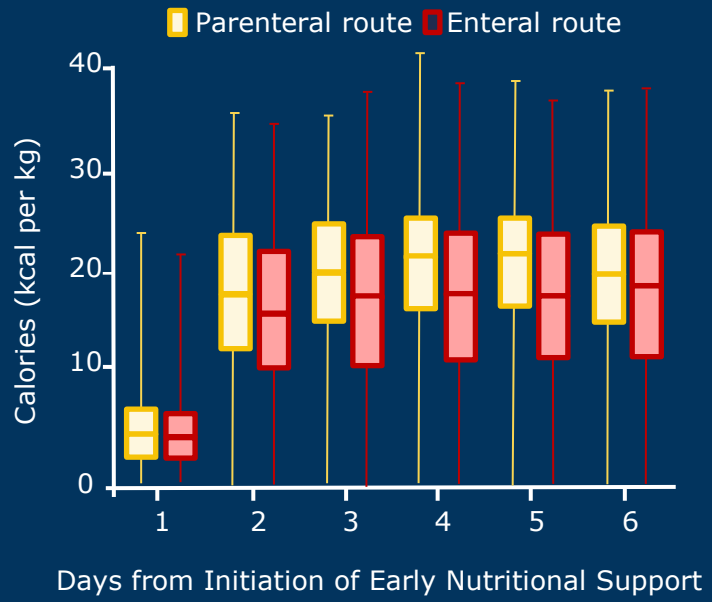
Trial of the Route of Early Nutritional Support in Critically Ill Adults

Sheila E. Harvey, Ph.D., Francesca Parrott, M.Sci., David A. Harrison, Ph.D., Danielle E. Bear, M.Res., Ella Segaran, M.Sc., Richard Beale, M.B., B.S., Geoff Bellingan, M.D., Richard Leonard, M.B., B.Chir., Michael G. Mythen, M.D., and Kathryn M. Rowan, Ph.D., for the CALORIES Trial Investigators*

- **N= 2388 collected data (1191 PN and 1197 EN)**
  - **Pragmatic PCT 33 ICU's in England**
  - **EN v PN started within 36h, > 5 days of nutrition**
  - **Evenly matched for co-morbidity, demographics etc**
  - **Mortality primary outcome with 14 other secondary outcomes**
  - **Minimal differences: hypoglycemia and emesis**
  - **NO significant differences in Mortality or other 14 parameters (mortality 33% PN vs 34% EN)**

Comparing Outcomes in PN versus EN

Caloric intake



Protein Delivered: EN 0.7 gm/kg
PN 1.0 gm/kg

- **No difference in:**
  - **30 day mortality**
  - **90 day mortality**
    - **Infections**
  - **14 other parameters**

Some issues with study design:
i.e. Suboptimal method of determining infection

Harvey SE et al. *N Engl J Med*. 2014;371:1673-1684.

Examining the Route of Early Feeding in Critically Ill Septic Patients

Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2)

Jean Reignier, Julie Boisramé-Helms, Laurent Brisard, Jean-Baptiste Lascarrou, Ali Ait Hssain, Nadia Anguel, Laurent Argaud, Karim Asehnoune, Pierre Asfar, Frédéric Bellec, Vlad Botoc, Anne Bretagnol, Hoang-Nam Bui, Emmanuel Canet, Daniel Da Silva, Michael Darmon, Vincent Das, Jérôme Devaquet, Michel Djibre, Frédérique Ganster, Maité Garrouste-Orgeas, Stéphane Gaudry, Olivier Gontier, Claude Guérin, Bertrand Guidet, Christophe Guitton, Jean-Etienne Herbrecht, Jean-Claude Lacherade, Philippe Letocart, Frédéric Martino, Virginie Maxime, Emmanuelle Mercier, Jean-Paul Mira, Saad Nseir, Gael Piton, Jean-Pierre Quenot, Jack Richecoeur, Jean-Philippe Rigaud, René Robert, Nathalie Rolin, Carole Schwebel, Michel Sirodot, François Tinturier, Didier Thévenin, Bruno Giraudeau, Amélie Le Gouge, for the NUTRIREA-2 Trial Investigators and the Clinical Research in Intensive Care and Sepsis (CRICS) group

Reignier J, et al. *The Lancet.* 2018.

Nutricea-2 Trial

- 3rd largest PRCT in clinical nutrition (n=2400)
- Pts meet strict criteria for sepsis within 24 hours
- Data collected

ICU stay 9-10 days	mean age 63
SOFA 11	high mortality 53%
Ventilated	93% medical dx

- Similar calories to both groups
- Protein gm/kg/d 0.7 EN vs 0.8 PN
- No difference in major outcomes
  - small bowel ischemia 19 EN v 5 PN
  - Vomiting, diarrhea increase in EN

Reignier J et al Lancet 2018

What has changed in PN therapy to potentially support considering changing practice ?

- Better understanding of the importance of glycemic control and physiology of insulin resistance
- More physiologic PN solutions
  - Wider variety of lipid emulsions available
    - SMOF, Olive oil, fish oil, MCT
      - SMOF lipid now approved in USA (2016)
      - Omegaven (2018 for pediatrics)
  - Improved AA solutions
    - Gln dipeptide, taurine, carnitine
    - PN still not a very physiologic AA ratio
  - Trace minerals / antioxidants
      - Quantity and timing still controversial
- Increase in the use of trophic or supplemental nutrition ***with*** PN

Use of Parenteral Nutrition SCCM and ASPEN Guidelines 2016

- Previous major differences noted between EN and PN are decreasing
- Withhold PN in low risk
  - If EN not feasible (NRS 2002 ≤ 3 or Nutric Score ≤5)
- Initiate exclusive PN ASAP in high risk or severely malnourished pt if EN not feasible
- (NRS 2002 ≥5, Nutric Score ≥6)
- Add supplement PN after 7-10 days if EN < 60% goal high or low risk [1]
- Maximize efficacy of PN
  - Use Nutrition Teams, protocols
  - Do not use parenteral glutamine [2]
  - Hypocaloric dosing (80%) first week [3]
  - Withhold soy-based lipids first week
  - Moderate glucose control (140-180 mg/dL)
  - Transition off PN when EN provides > 60% goal

- [1]Heiddeger (Lancet 2012 Dec 3)
- [2] Heyland REDOXS Trial (NEJM2013; 368:1489)
- [3]Jiang (Clin Nutrit 2011;30:730)

Fuel utilization during metabolic stress !

Calories 20-35 Kcal / Kg / D

Carbohydrates 3-6 mg / kg / min
250 – 350 gm / D

Protein 1.25 – 2.0 gm / Kg / D
80 – 150 gm / D

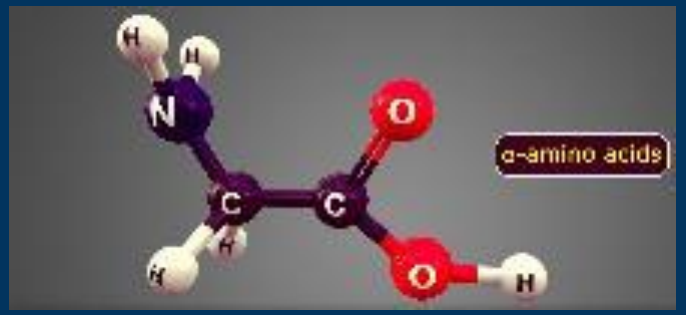
Lipids 10 – 30 % of total calories
Variable based on source

Vitamins / minerals / trace minerals
Variable dependent on oxidant load

Carbohydrates in the hypermetabolic host

- **Endogenous glucose production increased 150 to 200 %**
  - **Enhanced glycolytic pathways with decrease ability to use beta-oxidation (Kreb's cycle)**
  - **Altered mitochondrial biogenesis**
- **Obligate requirement for 100gm/d for CNS and other tissue requiring glucose**
  - **Gluconeogenesis poorly suppressed with exogenous glucose**
  - **Goal: deliver maximum CHO for protein sparing without hyperglycemia**
- **Maximum utilization of exogenous CHO during stress**
  - **3 to 6 mg/kg/min (250 – 300 gm day or 70 kg man)**
- **Limited if any benefit for alternate EN or PN CHO sources**
  - **Fructose, Glycerol etc**

Amino Acid Supply in PN

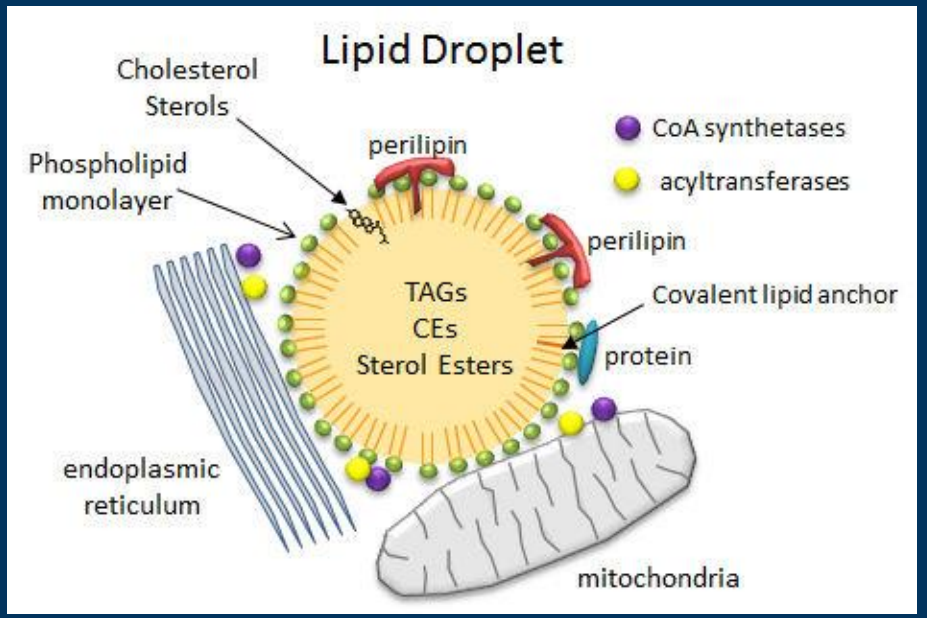


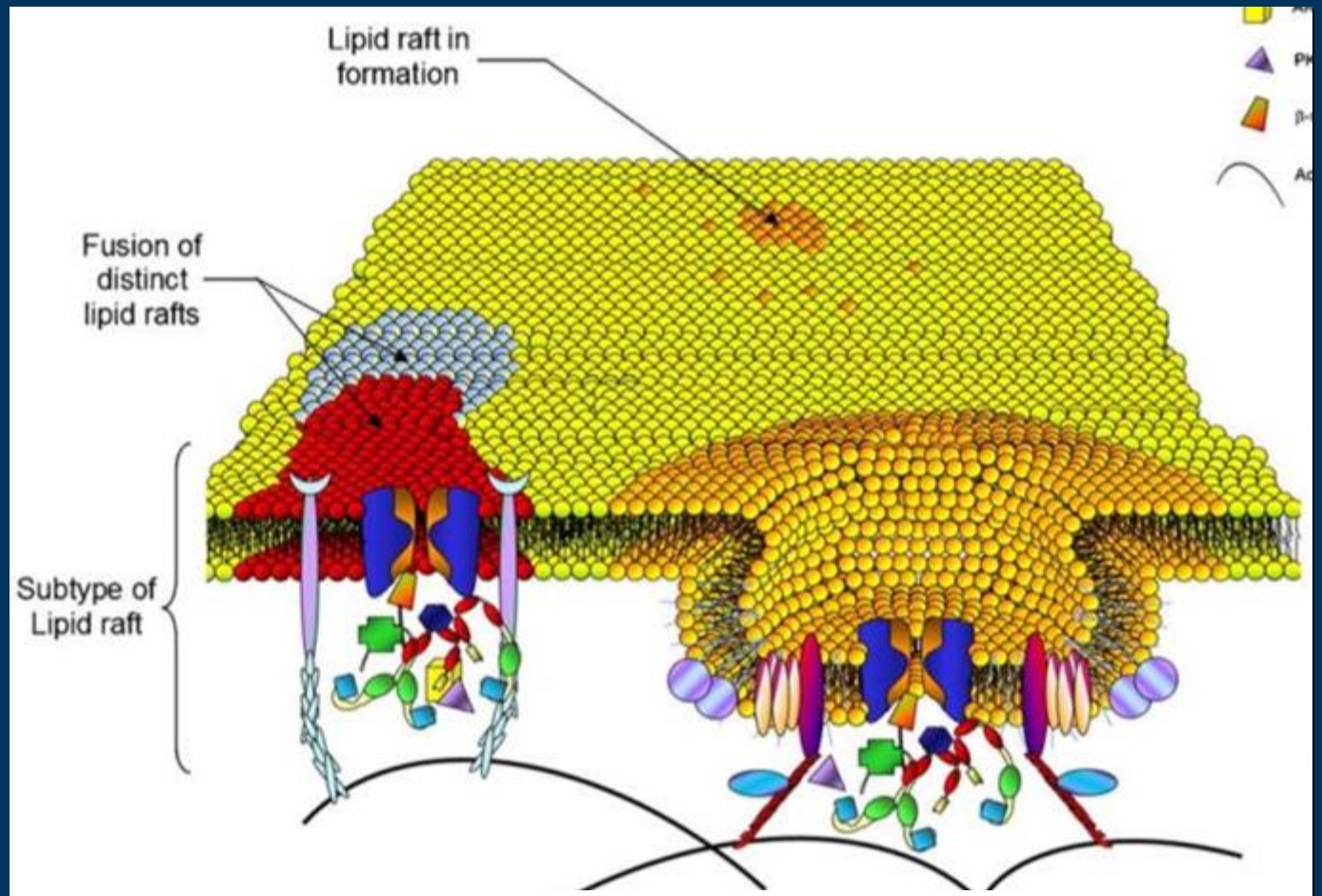
- Protein metabolism
  - 2.5 to 3 % per day turnover in normal setting
    - 50% for digestive function
  - Increased dramatically in major stress and sepsis
- Crystalline Amino Acids
- Trend for increase in Amino Acid
  - 2009 1.0 to 1.5gm.kg/d
  - 2016 1.5 to 2.0 gm/kg/d
- Specific Amino Acids
  - leucine, glutamine, arginine, etc
- Organ Specific PN ?
  - Renal
  - Hepatic
  - Pulmonary
  - Stress
  - Cancer
  - Immune modulation

Lipids in Nutritional Support:

- Traditional view of lipids
  - Nutrients (calories)
    - » 9 Kcal per gram
  - Essential Fatty Acids
    - » EFA = linoleic and linolenic acids
    - » Should be between 2-4% of total calorie
  - Enterally micelle formation required for LC FA absorption
    - » fat soluble vitamin absorption

- Current view (in addition to above)
  - Membrane receptor function and activity
  - Membrane fluidity
  - Eicosanoid metabolism
  - Modulate cytokine production
  - Regulation of intracellular signaling pathways
  - Transcription factor activity
  - SPMs -inflammation resolution
  - Gene expression





Data or Dogma:
Lipids are primarily for energy and EFA:

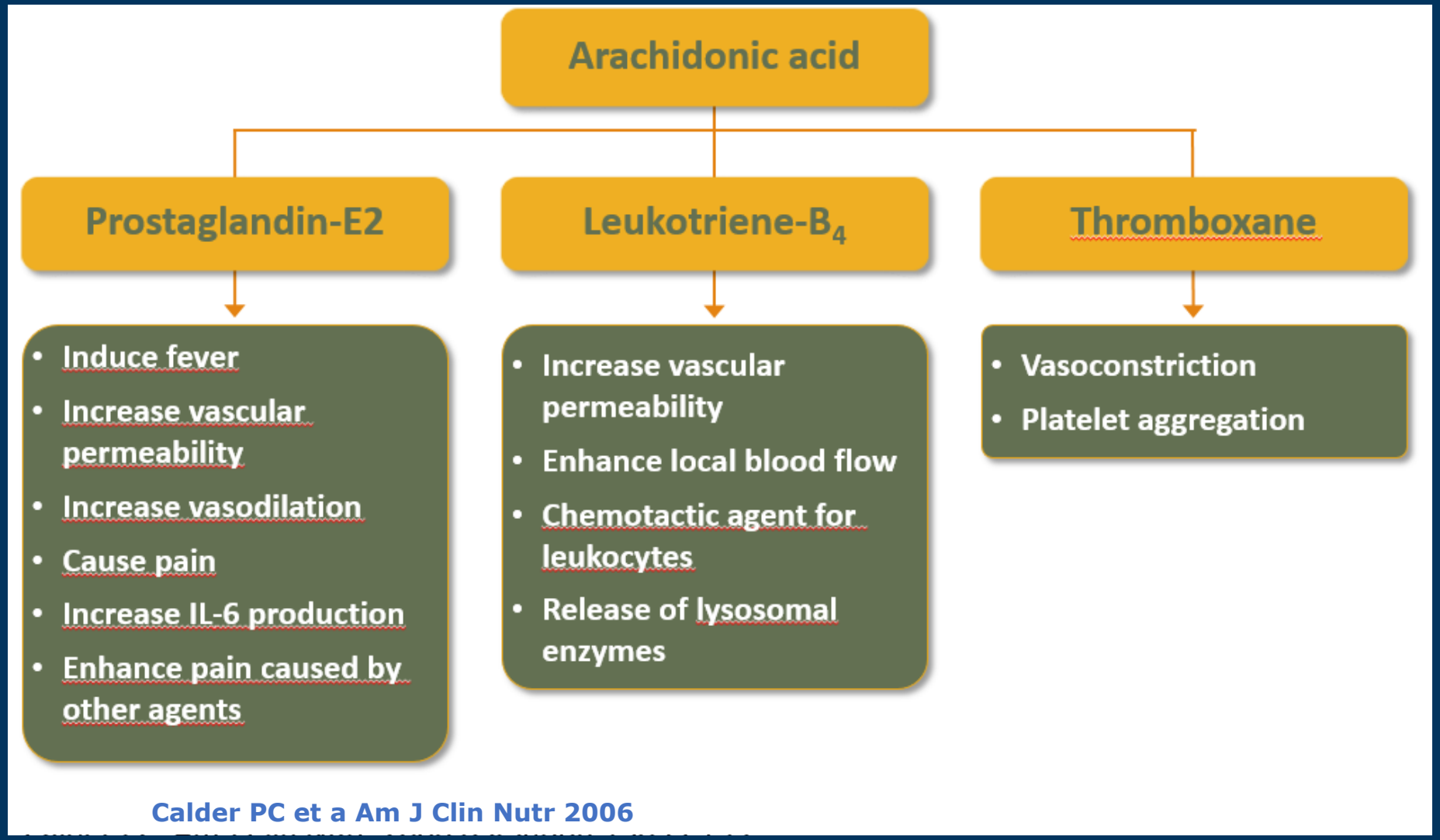
Lipids regulate as many genes as cortisol and thyroid hormones

Biological activities grouped into:

- Regulation of membrane structure and function
- Membrane fluidity – concepts of lipid rafts
- Regulation of bioactive mediators –Gene regulation
  - example NFKB
- Specific FA receptors – G protein coupled receptors

Calder P Biochimica Biophysica Acta 2015
Calder P JPEN 2015

Pro-inflammatory Effects of Eicosanoids Derived from ω-6 PUFAs



Calder PC et a Am J Clin Nutr 2006

Relative Range of Inflammatory Effects from Different Lipid Sources -

More inflammatory

Less inflammatory

Anti-inflammatory

Safflower oil

Soybean oil

- Medium chain triglyceride oil

Olive oil

Fish oil

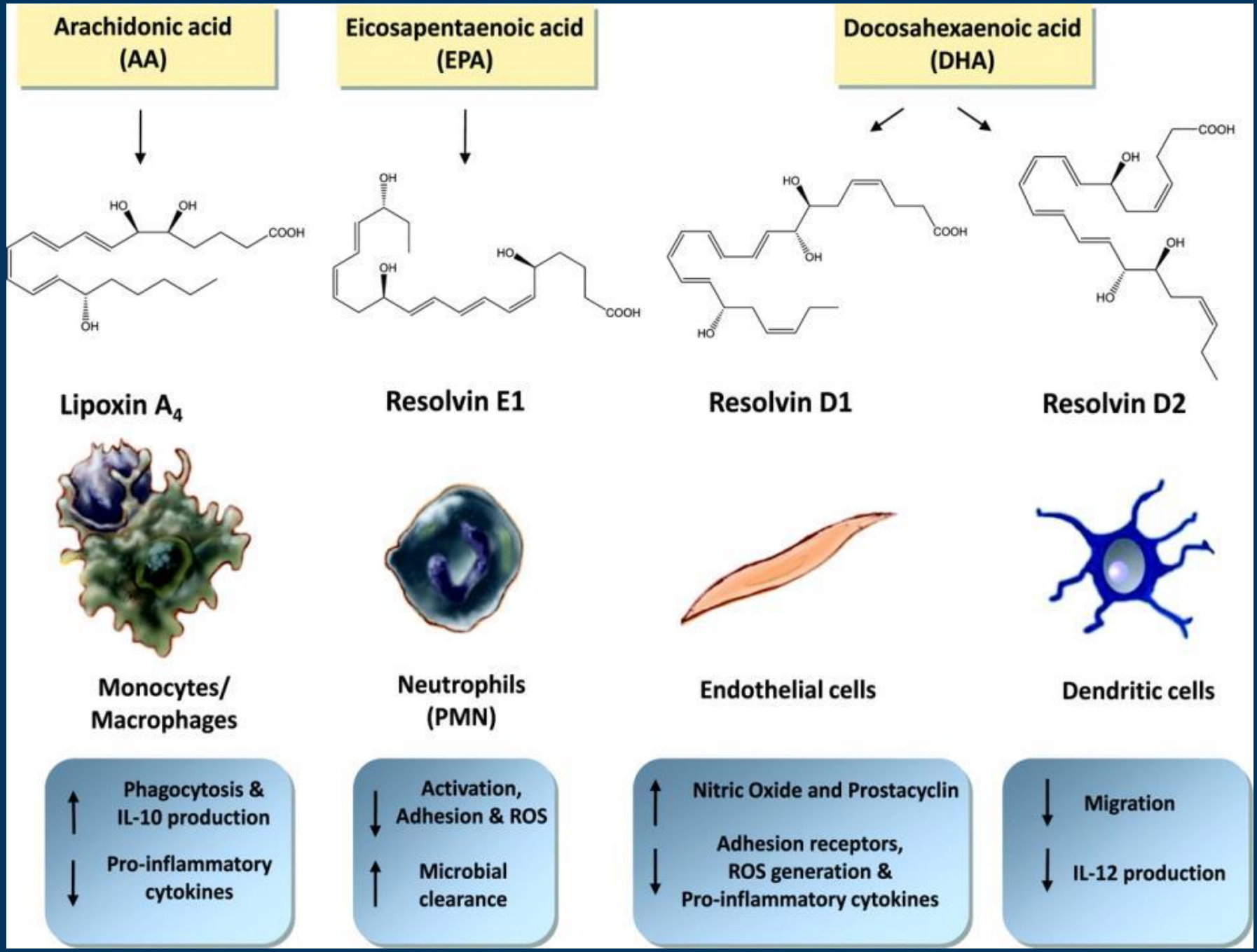
SCFA (Butyrate)

SPM's
Inflammation Resolution

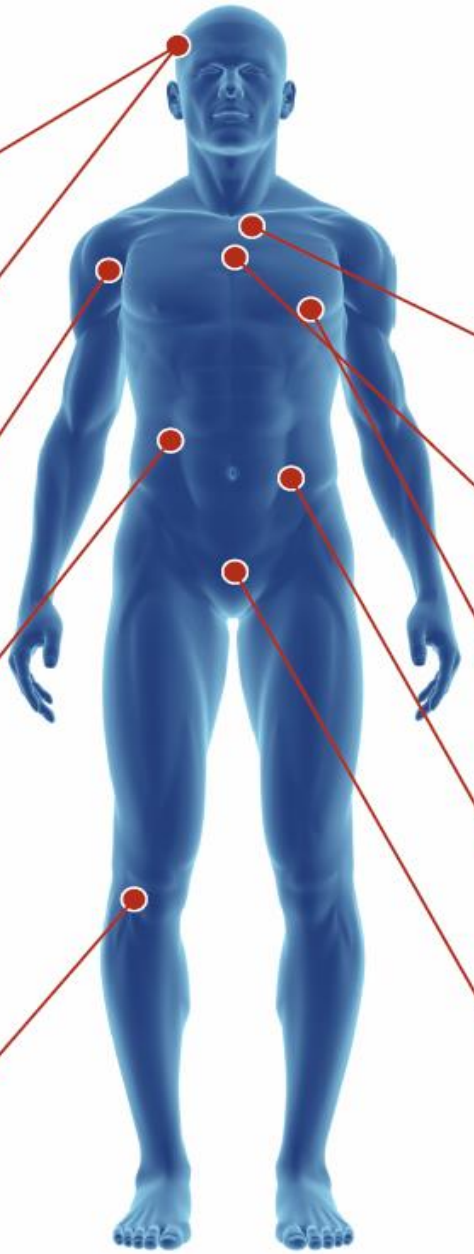
Calder PC et al JPEN 2020
Martindale RG et al JPEN 2020
Vanek VW et al Nutr Clin Pract 2012

Inflammation has two phases: initiation and resolution

Biological on / off systems


Arachidonic acid (AA)
Eicosapentaenoic acid (EPA)
Docosahexaenoic acid (DHA)
Lipoxin A4
Resolvin E1
Resolvin D1
Resolvin D2
Monocytes/ Macrophages
Neutrophils (PMN)
Endothelial cells
Dendritic cells
Phagocytosis & IL-10 production
Pro-inflammatory cytokines
Activation, Adhesion & ROS
Microbial clearance
Nitric Oxide and Prostacyclin
Adhesion receptors, ROS generation & Pro-inflammatory cytokines
Migration
IL-12 production

Identification of SPM
at Bioactive Levels in Humans



Brain
380-1800 pg/mg protein
Lukiv et al., 2005; Wang et al., 2015; Zhu et al., 2015

Cerebrospinal Fluid
11-390 pM
Pruss et al., 2013

Lymph Nodes
3-112 pg/100 mg
Colas et al., 2014

Adipose Tissues
2-3 pg/106 cells
Clària et al., 2012

Placenta
1-8 pg/mg
Keelan et al., 2015

Synovial Fluid
0.2-0.7 nM
Giera et al., 2012

Exhaled Breath Condensate
6 nM
Levy et al., 2007

Sputum (Cystic Fibrosis)
17-365 pg/mg protein
Yang et al. 2012

Plasma
3-30 pM
Colas et al., 2014; Mas et al., 2012; Arita et al., 2005

Serum
14 pM-6 nM
Colas et al., 2014; Mas et al., 2012; Psychogios et al., 2011

Breast Milk
10 pM-27 nM
Weiss et al., 2013; Arnardottir et al., 2016

Spleen
1-112 pg/100 mg
Colas et al., 2014

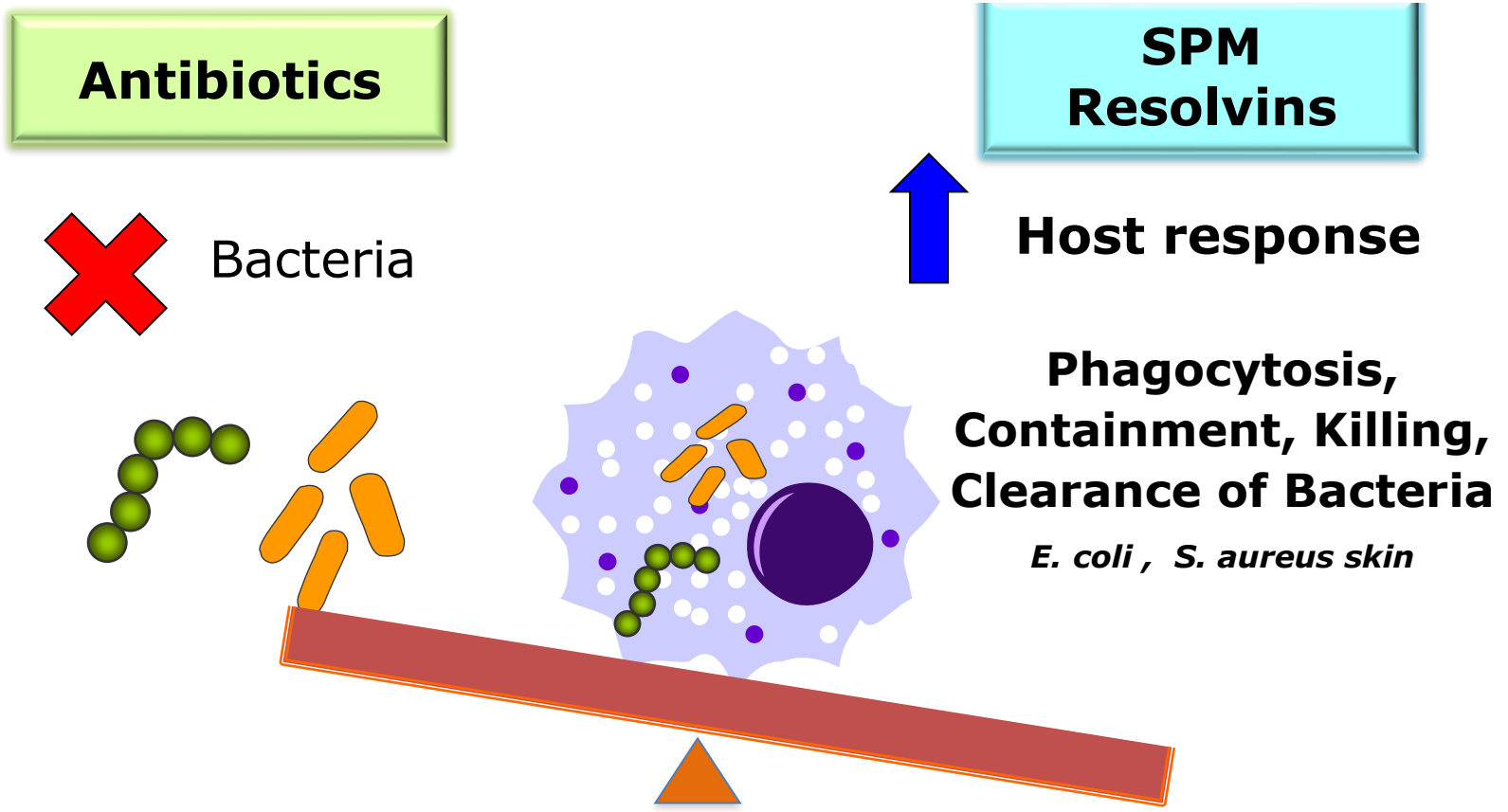
Urine
12-330 pM
Sasaki et al., 2015

Sirhan CN Molecular Aspects of Medicine 2017

Infection regulates pro-resolving mediators that lower antibiotic requirements

Nature 2012

Nan Chiang[1], Gabrielle Fredman[1], Fredrik Bäckhed[2], Sungwhan F. Oh[1], Thad Vickery[1], Birgitta A. Schmidt[1] & Charles N. Serhan[1]



SPM's accelerate resolution of infections

Enhance bacterial killing , reduce inflammation

Treating the host with SPM *lowers* the required antibiotic doses

What is the evidence that FO and SPM's are relevant to human disease?

- **Evolutionarily conserved (function at nanogram to picogram levels)**

- **SPM serum profiles correlated with outcome**
  - **Sepsis: Increased levels – associated with 28 day decreased mortality**
  - **TBI: improved outcomes**
  - **Surgical infections- less antibiotics required**
  - **CF – improved P. aeruginosa clearance**
  - **TB – disease activity associated with SPM serum level**
  - **Ca therapy- alters angiogenesis, tumor microenvironment**
  - **Herpes eye infection: increased vision , viral clearance**
  - **In-vitro healthy vol: WBC improved bacterial clearance**
  - **Post-op Hepatobiliary surgery decrease inflammation, infections**
    - » **Resolvin E1 correlates with inflammation**

Dalli J Molecular Biol 2017
Dalli J et al Crit Care Med 2017
Serhan CN FEBS 2017
Uno H et al Surgery 2016

10 recent meta-analyses investigated the clinical benefits of omega-3 FA containing IVLE compared to standard IVLE without fish oil:*

Included adult patient populations:
- **Surgical patients[1-4,7]**
- **Intensive care unit (ICU) [5,6] and/or critically ill patients[5]**
- **Non-ICU patients[6]**

- **Clinical outcomes shown:**
  - **Infectious complications were significantly reduced in non-ICU patients[1,2,4,6,7] and ICU patients[5,7]**
  - **Hospital length of stay (LOS) was significantly shorter in ICU and non-ICU patients[2,4,6,7]**
  - **Hospital LOS showed a tendency to be reduced in surgical and critically ill patients[1,5]**
  - **ICU length of stay was significantly reduced in surgical and critically ill patients[1,2,6]**

1. Wei C, Hua J, Bin C et al. Impact of lipid emulsion containing fish oil on outcomes of surgical patients: systematic review of randomized controlled trials from Europe and Asia. Nutr 2010;26:474-481.
2. Chen B, Zhou Y, Yang P et al. Safety and efficacy of fish oil-enriched parenteral nutrition regimen on postoperative patients undergoing major abdominal surgery: a meta-analysis of randomized controlled trials. J Parenter Enteral Nutr 2010;34:387-394.
3. Tian H, Yao X, Zeng R et al. Safety and efficacy of a new parenteral lipid emulsion (SMOF) for surgical patients: a systematic review and meta-analysis of randomized controlled trials. Nutr Rev 2013;71:815-821.
4. Li NN, Zhou Y, Qin XP et al. Does intravenous fish oil benefit patients post-surgery? A meta-analysis of randomised controlled trials. Clin Nutr 2014;33:226-239.
5. Manzanares W, Langlois PL, Dhaliwal R et al. Intravenous fish oil lipid emulsions in critically ill patients: an updated systematic review and meta-analysis. Crit Care 2015;19(1):167.
6. Pradelli L, Mayer K, Muscaritoli M, Heller AR. n-3 fatty acid-enriched parenteral nutrition regimens in elective surgical and ICU patients: a meta-analysis. Crit Care 2012;16:R184 & Correction: Pradelli et al. Crit Care 2013;17(1):405
7. Bae HJ, Lee GY, Seong JM, Gwak HS. Outcomes with perioperative fat emulsions containing omega-3 fatty acid: A meta-analysis of randomized controlled trials. Am J Health Syst Pharm 2017; 74: 904–18.

Lipids in the intensive care unit: Recommendations from the ESPEN Expert Group☆

Philip C. Calder [a, b, *], Michael Adolph [c], Nicolaas E. Deutz [d], Teodoro Grau [e], Jacqueline K. Innes [a], Stanislaw Klek [f], Shaul Lev [g], Konstantin Mayer [h], Adina T. Michael-Titus [i], Lorenzo Pradelli [j], Mark Puder [k], Hester Vlaardingerbroek [l], Pierre Singer [g]

Clinical Nutrition 37(2018) 1-18

- **EN remains first choice for route of delivery of nutrients/lipids**
- **EN and PN containing FO's are well tolerated and have shown significant clinical benefits;**
  - **Anti-inflammatory and immune-modulating effects**
  - **Consistent decrease in complications**
    - **Decrease infections, LOS in ICU and total hospital stay**
- **Dosing**
  - **Between 0.1 gm and 0.2 gm/kg/d fish oil needed to show benefits**
    - **Survival, infection, LOS**
    - **Lower antibiotic requirements shown at 0.15 and 0.20 gm/kg/d**
- **Safe**
  - **No increase in bleeding abnormality**
- **Cost Effective: Treatment cost of FO containing LE are completely offset by decrease ICU stay and decrease use of antibiotics**

For the clinical setting what are the risks of additional EPA and DHA (fish oils)

- **Concern that fish oils may inhibit thrombosis:**
  - **Patients on other forms of anti-coagulation**
    - **ASA, Clopidogrel, coumadin, Dipyridamole**
  - **Patients at high risk of bleeding in the post-op period**
  - **Patients with traumatic brain injury**
- **RISK: In the clinical setting with fish oil containing formula EN or PN: essentially *NONE***
  - **No clinically significant effect on platelet aggregation (up to 20gm/d)**
  - **No reported ill effects of fish oils in ICU settings**

Jeansen S et al Clinical Nutrition 2017, Watson PD J. Am. Coll Cardio. 2009
Balk E, et al 2004 Evidence report AHRQ publication # 04-010-2
Bays HE; Am J Cardiology 2007 , Mousa SA Methods Mole Bio 2010

Soy vs Mixed ILE
Data or Dogma?

VS

PN Multivitamin for injection (MVI) and trace elements

Table 4. Multivitamin Injection Formulations, 2000

Ingredient	Amount/Unit
Fat-soluble vitamins	
A (retinol)	1 mg
D (ergocalciferol or cholecalciferol)	5 mcg
E (α-tocopherol)	10 mg
K (phylloquinone)	150 mcg
Water-soluble vitamins	
C (ascorbic acid)	200 mg
B_1 (thiamine)	6 mg
B_2 (riboflavin)	3.6 mg
B_6 (pyridoxine)	6 mg
B_{12} (cyanocobalamin)	5 mcg
Folic acid	600 mcg
Niacin	40 mg
Pantothenic acid	15 mg
Biotin	60 mcg

Table 5. Adult Multiple Trace Element Injections (Concentration/mL)[5]

	MTE-4	MTE-4 Concentrate	MTE-5	MTE-5 Concentrate
Chromium, mcg	4	10	4	10
Copper, mcg	0.4	1	0.4	1
Manganese, mg	0.1	0.5	0.1	0.5
Zinc, mg	1	5	1	5
Selenium, mcg	0	0	20	60

Multiple trace element injections are from American Regent, Inc (Shirley, NY). Single trace element injections are also available for chromium, copper, manganese, zinc, and selenium.

Continuous vs Cycling PN

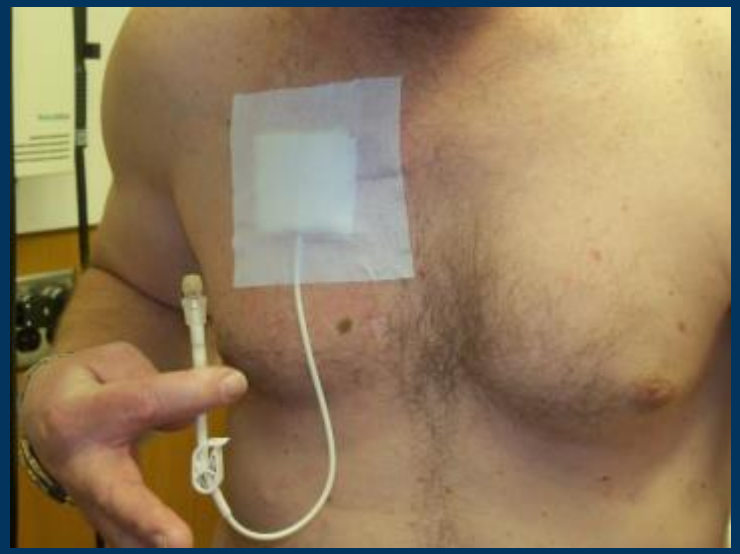
- Most hospitals and ICUs run TPN 24 hours until patient is stable then transition to intermittent
- Most patients can be safely cycled down to 12 hours
- Decrease by blocks of 4-6 hours daily
  - 24 → 20 → 16 → 12
  - DM higher risk of problems
- Monitor for refeeding when cycling in high risk patients

Choices in delivery?

- **Choices:**
  - **Premixed**
  - **Made to order**
  - **3:1 vs piggy back**

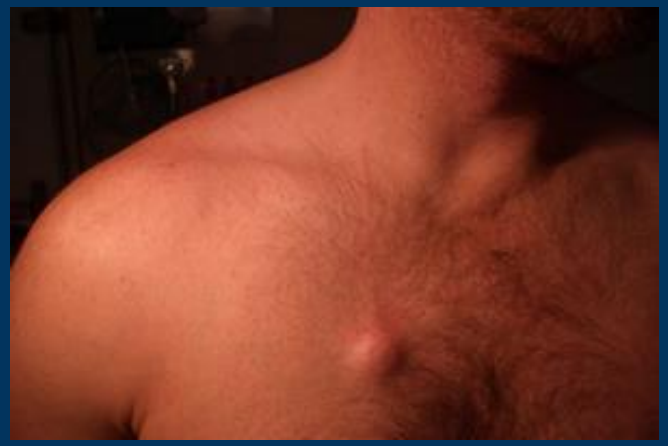
PN Lines

Tunneled

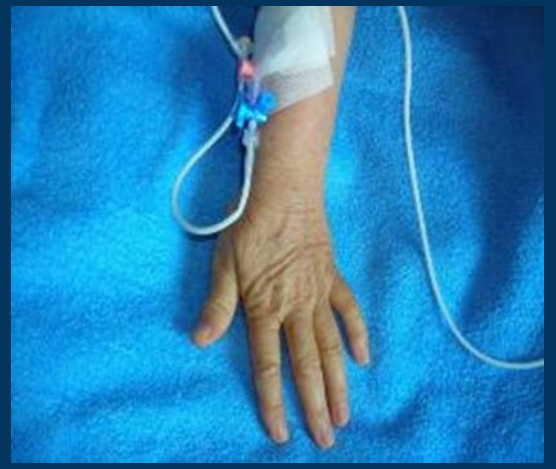


PICC

Port



Peripheral



Number of lumens vs infection

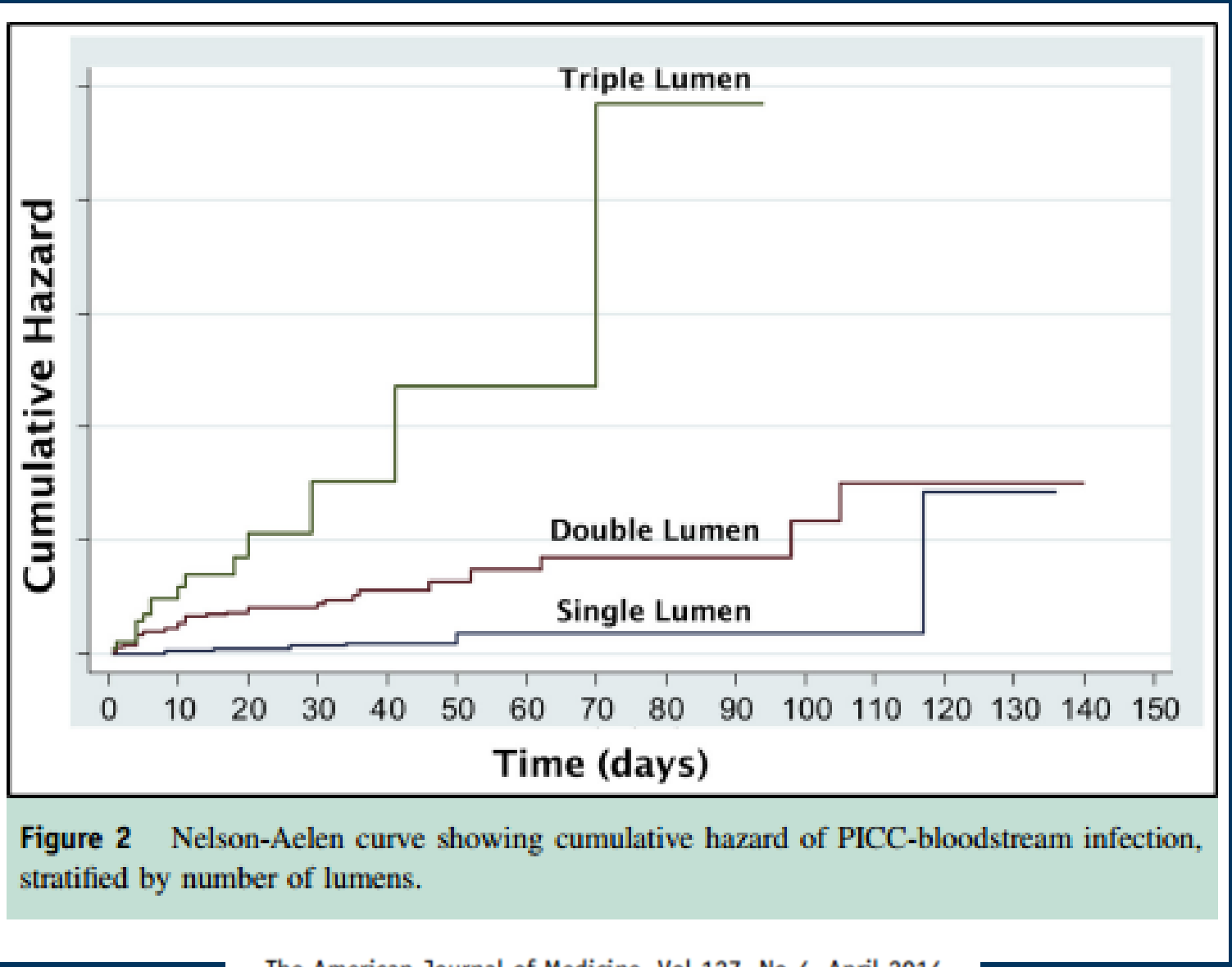


Figure 2 Nelson-Aelen curve showing cumulative hazard of PICC-bloodstream infection, stratified by number of lumens.

The American Journal of Medicine, Vol 127, No 4, April 2014

Use of Parenteral Nutrition in Critical Care 2016 Guidelines

- **Withhold PN ~ 7 days for low risk patients if EN not feasible**
  - **(NRS 2002 ≤ 3 or Nutric Score ≤5)**

- **if EN not feasible initiate exclusive PN ASAP in high risk or severely malnourished pt (NRS 2002 ≥5, Nutric Score ≥6)**

- **Add supplemental PN after 7-10 days if EN providing > 60% goal**

- **Maximize efficacy of PN**
  - **Use protocols – Do not use parenteral glutamine**
  - **Hypocaloric dosing (80%) first week**
  - **Moderate glucose control (140-180 mg/dL)**
  - **Transition off PN when EN provides > 60% goal**
  - **In hyperdynamic and septic patients withhold soy-based lipids first week (consider alternative IVLE)**

McClave S, Taylor B, Martindale R et al SCCM / ASPEN Critical Care Guidelines 2016 CCM / JPEN

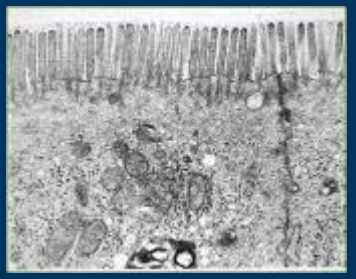
Guidelines for PN in Critical Care

	SCCM / ASPEN[1]	SCCM/ASPEN[1]	ESPEN[2]	CCPG[3]
Patients	**Low Nutrition Risk (eg. NRS < 3 or Nutric score <5)**	**High Nutritional Risk (eg. NRS 2002>5, Nutric Score >5) or severely malnourished**	**In case of contraindications to oral and/or EN and in case of intolerance to EN delayed PN (after 3 to 7 days) should be used.**	**In critically ill pts with intact GI tract, we recommend that PN not be used routinely, but early PN should be considered in nutritionally high risk patients with a relative contraindication to early EN**
Initiation of PN	**Exclusive PN be withheld over the first 7 days following ICU admission if the patient cannot maintain volitional intake and if early EN not feasible** **Evidence Quality: very low**	**Initiate PN as soon as possible following resuscitation (when EN not possible)**	**Early low-dose PN can be considered over no nutrition in case of contraindications for EN in severely malnourished pts.** **In patients who do not tolerate full dose EN during the first week in the ICU, the safety and benefits of initiating PN should be weighed on a case-by-case basis.** **PN should not be started until all strategies to maximize EN tolerance are tried out.** **OR** **PN should be started after enteral nutrition has failed to reach the calorie target.**	**In pts who are not tolerating adequate EN, there is *insufficient data* to recommend when PN should be initiated. Practitioners will have to weigh the safety and benefits of initiating PN in pts not tolerating EN on a case by case basis**

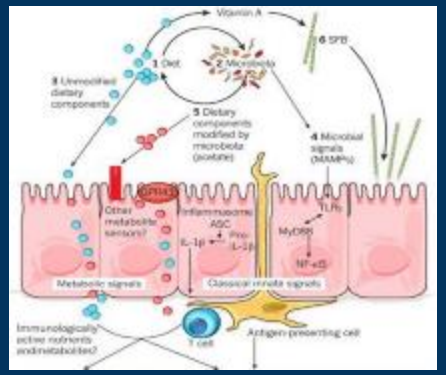
1.McClave SA et al. *JPEN* 2016
2.Singer P, et al. *Clin Nutr* 2019
3.Canadian Clinical Practice Guidelines 2015. www.criticalcarenutrition.com.

Basic Tenants of PN Nutrition 2020
Enteral Nutrition Remains First Choice When Possible

- **Concept of early enteral feeding yielding nutritional and non-nutritional benefits**
  - **Maintaining GI mucosal barrier**
  - **Delivery of early enteral feeding to attenuate the metabolic response to stress**
  - **Immune and metabolic modulation**
  - **Helps maintain lean body mass and function**



- **"Reawakening" of the use of PN**
  - **Better macronutrient choices**
    - **Increase protein**
    - **IVLE- mixed oils**
  - **Better understanding of insulin resistance**
  - **Expanded understanding on lipid physiology**
    - **FO--SPM's, FFA receptors**



McClave, Martindale, Rice, Heyland CCM 2014
Rosenthal M, Martindale R, Moore F Curr Prob Surgery 2015

Part II

Counting peas: Methods in nutrition research

Reviewing nutrition studies: How do we keep from falling into traps?

Prof. Bob Martindale

FRESENIUS KABI
caring for life

JUMPstart Training Program

Reviewing Nutrition Studies: How do we keep from falling into traps?
Staying out of rabbit holes!

Prof. Bob G. Martindale, MD, PhD

Advanced Module, Day 1, Part II: Counting peas: Methods in nutrition research

Questions to ask yourself before beginning a study

- **What is the specific focus: basic science or clinical science ?**

- **Do you have a true interest in the question being evaluated ?**
  - **Doomed if not: complacency, poor techniques, cutting corners**

- **Does your research question add to the knowledge in the field?**
  - **Does it educate?**
- **Does the concept work within current concepts or challenge the current dogma?**

For clinical studies

- **Will the research project change current clinical practice?**

- **Does it support or challenge current clinical practice?**

Recent literature has changed the way we think about nutritional intervention in trauma / surgery !

- **Early vs Late PN / Nutrition -Van den Berghe G (NEJM 2011)**
  - **EPNic Trial: Nutritional intervention shuts off "autophagy" ?**
- **Trophic vs full feeds - Rice T (JAMA 2012)**
  - **How much is enough**
- **Redox trial - Heyland DK (NEJM 2013)**
  - **Intervention with high dose GLN is harmful in "real sick" people ?**
- **Supplemental PN- Heidigger (Lancet 2013)**
  - **Supplemental PN "may" benefit**
- **Resolving inflammation vs blocking it- Serhan (Nature 2014, JCI 2018)**
  - **Resolvins, Protectins, Maresins**
- **PN = EN ? Harvey S (NEJM 2014)**
  - **No benefit of EN over PN**
- **PN better than EN ?- Reignier (Lancet 2018)**
  - **Nutrirea 2 : Less bowel ischemia, vomiting**
- **The science behind the "microbiome" Alverdy (JACS 2018)**
  - **Microbiome converts to pathobiome**
- **Full vs reduced calories in the ICU (ANZICs NEJM 2018)**
- **Autophagy is protective in sepsis / trauma (Microbial Path 2019)**

What changes practice ?

- **Opportunity**
  - **Environmental context, resources, social influences**
- **Capability**
  - **Knowledge, skills**
- **Motivation**
  - **Beliefs about consequences, reinforcement**
- **Optimism**
  - **Confidence you finding will improve outcome**

Arroyo NA et al Ann Surg 2021

Example of how useful is the research: Picking the an appropriate research question.

- **Cancer biomarkers**
  - **In 2005, 1575 articles detailing or studying biomarkers of cancer**
  - **1509 (essentially 96%) reported at least one "significant" biomarker in cancer**

  - **Few (<5%) have entered routine clinical practice**

Example of how useful is the research

- **Cancer biomarkers**
  - **In 2005, 1575 articles detailing or studying biomarkers of cancer**
  - **1509 (essentially 96%) reported at least one "significant" biomarker in cancer**
  - **Few (<5%) have entered routine clinical practice**
  - **Why:**
    - **Inadequate review of the literature before doing the study**
    - **Inadequate use of resources i.e. core labs, other investigators at institution, sharing of concepts and knowledge**
    - **Wrong motivation – economics does not work as well and other drivers of research**
    - **"better to be first than right"**
      - **When hypothesis is wrong and the study is negative almost no one tries to publish negative results**
      - **Concern for "publish or perish"**

Anderson NL et al Clin Chem 2010
MacLeod MR et al Lancet 2014

Example of how useful is the research

- **Nutritional biomarkers**
  - **1975 – albumin named at "risk factor"**
  - **1975-2000 Visceral proteins become the "gold standard" for nutrition biomarkers**
    - **796 papers extolling the benefits of visceral proteins as nutritional biomarkers**
    - **31 questioning the value**
  - **2000 beginning to question: "are they nutrition biomarkers or are they risk predictors"**
    - **NRS 2002, NUTRIC score**
  - **2021**

NCP Nutrition in Clinical Practice | aspen

Position Paper | Free Access

The Use of Visceral Proteins as Nutrition Markers: An ASPEN Position Paper

David C. Evans MD, FACS, PNS, Mark R. Corkins MD, CNSC, FASPEN, AGAF, FAAP, Ainsley Malone MS, RD, LD, CNSC, FAND, FASPEN, Sarah Miller PharmD, BCNSP ... See all authors

Advertisement

NCP February 2021 pages 22-28

Other Rabbit Holes “We” Have Entered

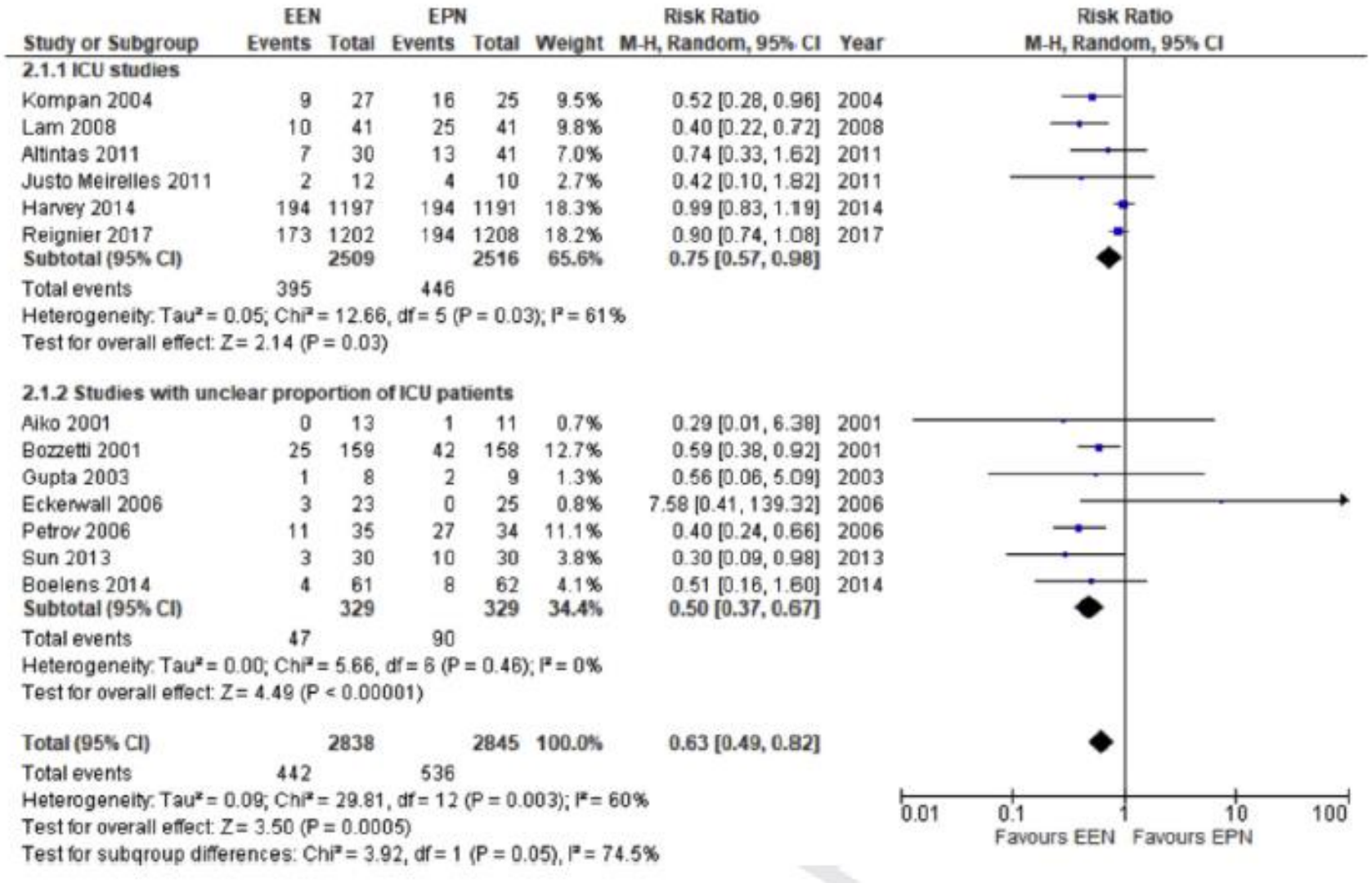
- **Disease specific formulas**
  - **Renal, Pulmonary, Stress**
- **EN v PN**
- **EN + PN**
- **Getting to goal calories as soon as possible**
- **Probiotics in clinical practice**

What happened to TPN ?
The disappearance of PN in the Trauma ICU

- **Retrospective analysis of all Level 1 TICU admissions over 6 year period**
  - **Comparative cohorts matched case-control approaches**
  - **Logistic regression analysis adjusting for significant risk factors**
- **2,964 patients admitted**
  - **464 received TPN**
- **Results:**
  - **TPN used decreased from 26% in 2000 to 3 % in 2005**
  - **Mortality in the higher TPN group higher (5.4% vs 10.2%)**
  - **Complications higher in the TPN group**
  - **Decrease resource utilization with enteral**

Rhee RJ et al J Trauma 2007;63:1215-1222

Early EN vs Early PN in ICU Infections



Study or Subgroup	EEN Events	EEN Total	EPN Events	EPN Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
2.1.1 ICU studies							
Kompan 2004	9	27	16	25	9.5%	0.52 [0.28, 0.96]	2004
Lam 2008	10	41	25	41	9.8%	0.40 [0.22, 0.72]	2008
Altintas 2011	7	30	13	41	7.0%	0.74 [0.33, 1.62]	2011
Justo Meirelles 2011	2	12	4	10	2.7%	0.42 [0.10, 1.82]	2011
Harvey 2014	194	1197	194	1191	18.3%	0.99 [0.83, 1.19]	2014
Reignier 2017	173	1202	194	1208	18.2%	0.90 [0.74, 1.08]	2017
Subtotal (95% CI)		**2509**		**2516**	**65.6%**	**0.75 [0.57, 0.98]**	
Total events	395		446				
Heterogeneity: Tau² = 0.05; Chi² = 12.66, df = 5 (P = 0.03); I² = 61%							
Test for overall effect: Z = 2.14 (P = 0.03)							
2.1.2 Studies with unclear proportion of ICU patients							
Aiko 2001	0	13	1	11	0.7%	0.29 [0.01, 6.38]	2001
Bozzetti 2001	25	159	42	158	12.7%	0.59 [0.38, 0.92]	2001
Gupta 2003	1	8	2	9	1.3%	0.56 [0.06, 5.09]	2003
Eckerwall 2006	3	23	0	25	0.8%	7.58 [0.41, 139.32]	2006
Petrov 2006	11	35	27	34	11.1%	0.40 [0.24, 0.66]	2006
Sun 2013	3	30	10	30	3.8%	0.30 [0.09, 0.98]	2013
Boelens 2014	4	61	8	62	4.1%	0.51 [0.16, 1.60]	2014
Subtotal (95% CI)		**329**		**329**	**34.4%**	**0.50 [0.37, 0.67]**	
Total events	47		90				
Heterogeneity: Tau² = 0.00; Chi² = 5.66, df = 6 (P = 0.46); I² = 0%							
Test for overall effect: Z = 4.49 (P < 0.00001)							
Total (95% CI)		**2838**		**2845**	**100.0%**	**0.63 [0.49, 0.82]**	
Total events	442		536				
Heterogeneity: Tau² = 0.09; Chi² = 29.81, df = 12 (P = 0.003); I² = 60%							
Test for overall effect: Z = 3.50 (P = 0.0005)							
Test for subgroup differences: Chi² = 3.92, df = 1 (P = 0.05), I² = 74.5%							

Singer P et al ESPEN 2018 (ESPEN ICU Guidelines)

Were we wrong about PN ?

Support in Critically Ill Adults

Sheila E. Harvey, Ph.D., Francesca Parrott, M.Sci., David A. Harrison, Ph.D., Danielle E. Bear, M.Res., Ella Segaran, M.Sc., Richard Beale, M.B., B.S., Geoff Bellingan, M.D., Richard Leonard, M.B., B.Chir., Michael G. Mythen, M.D., and Kathryn M. Rowan, Ph.D., for the CALORIES Trial Investigators*

- **N= 2388 collected data (1191 PN and 1197 EN)**
  - **Pragmatic PCT 33 ICU's in England**
  - **EN v PN started within 36h, > 5 days of nutrition**
  - **Evenly matched for co-morbidity, demographics etc**
  - **Mortality primary outcome with 14 other secondary outcomes**
  - **Minimal differences: hypoglycemia and emesis**
  - ***NO significant differences in:***
    - **Mortality at 30 days or 90 days**
      - **mortality 33% PN vs 34% EN at 30 days**
    - **14 other parameters no difference**

Harvey SE et al. *N Engl J Med*. 2014;371:1673-1684.

Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2)

Jean Reignier, Julie Boisramé-Helms, Laurent Brisard, Jean-Baptiste Lascarrou, Ali Ait Hssain, Nadia Anguel, Laurent Argaud, Karim Asehnoune, Pierre Asfar, Frédéric Bellec, Vlad Botoc, Anne Bretagnol, Hoang-Nam Bui, Emmanuel Canet, Daniel Da Silva, Michael Darmon, Vincent Das, Jérôme Devaquet, Michel Djibre, Frédérique Ganster, Maité Garrouste-Orgeas, Stéphane Gaudry, Olivier Gontier, Claude Guérin, Bertrand Guidet, Christophe Guitton, Jean-Etienne Herbrecht, Jean-Claude Lacherade, Philippe Letocart, Frédéric Martino, Virginie Maxime, Emmanuelle Mercier, Jean-Paul Mira, Saad Nseir, Gael Piton, Jean-Pierre Quenot, Jack Richecoeur, Jean-Philippe Rigaud, René Robert, Nathalie Rolin, Carole Schwebel, Michel Sirodot, François Tinturier, Didier Thévenin, Bruno Giraudeau, Amélie Le Gouge, for the NUTRIREA-2 Trial Investigators and the Clinical Research in Intensive Care and Sepsis (CRICS) group

Large PRCT ICUs in France (n=2400)

Pts met strict criteria for sepsis within 24 hours

Data collected

Similar calories to both groups

Protein gm/kg/d 0.7 EN vs 0.8 PN

No difference in major outcomes

Enteral group:

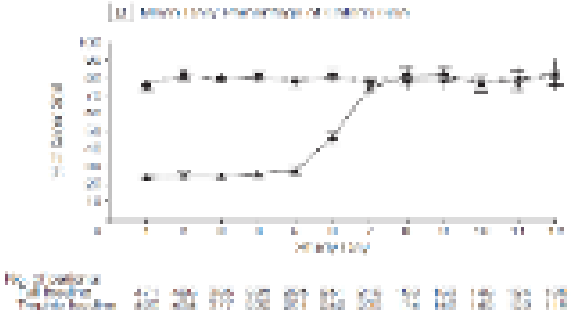
ischemia 19 EN v 5 PN

EN had increase in vomiting, diarrhea

Reignier J, et al. *The Lancet* 2018;391:133-143.

"Trophic" or Permissive Under Feeding vs Goal Feeding

- **Rice T et al: RCT Trophic vs full enteral feeding with ALI**
  - **JAMA 2012 N=1000**
  - **No difference in;**
    - **Mortality, ventilator free days, MOF, infection**
- **Choi EY et al: Meta-analysis 4 studies**
  - **JPEN 2014 n=1540**
  - **No difference in;**
    - **Mortality, LOS**
- **Charles E et al : RCT Surgical ICU**
  - **AJCN 2014 N=83**
  - **No difference in;**
    - **Mortality, LOS, Infection**
  - **? of type 2 error**
- **Arabi YM et al RCT 7 centers med/surg ICU**
  - **NEJM 2015 PERMIT Trial N=894**
  - **Isonitrogenous**
  - **No difference in mortality**
- **Anzics trial**
  - **NEJM 2018 MCRCT**
  - **No difference in outcomes**



The NEW ENGLAND JOURNAL of MEDICINE

Energy-Dense versus Routine Enteral Nutrition in the Critically Ill

The TARGET Investigators, for the ANZICS Clinical Trials Group*

Critical Care Nutrition

Where's the Evidence?

Jayshil J. Patel, MD[a], Ryan T. Hurt, MD, PhD[b], Stephen A. McClave, MD[c], Robert G. Martindale, MD, PhD[d,*]

Critical Care Clinics 2017

Each study has potential confounding factors

Table 1
Studies that showed improved outcomes with permissive underfeeding, as compared with full enteral feeding

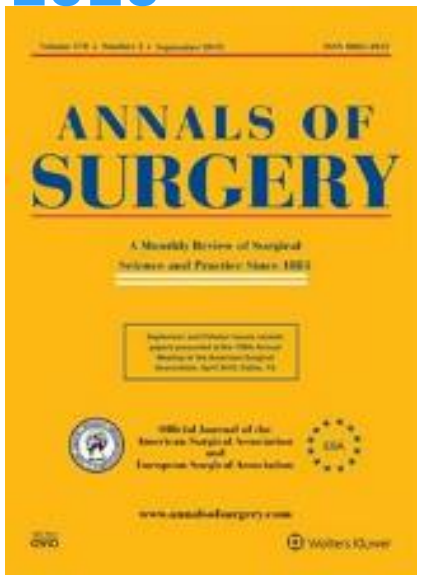
Author, Year	Study Design	Study Population	No. of Patients	Comments
Ibrahim et al,[34] 2002	Single-center RCT	Medical ICU	150	Target caloric intake was not achieved and high incidence of VAP in full EN group; bolus feeding likely contributed to both
Krishnan et al,[35] 2003	Observational	Medical ICU	187	Different feeding delivery in each quartile, leading to dissimilar group comparisons
Ash et al,[36] 2005	Retrospective	Trauma ICU	120	Different feeding delivery in each quartile, leading to dissimilar group comparisons
Arabi et al,[37] 2010	Observational	Mixed ICU	523	Oral diet inclusion confounded study outcome analysis
Arabi et al,[38] 2011	Single-center RCT	Mixed ICU	240	High likelihood for type 1 error (improbable that a 12% difference in calories accounted for significant difference in mortality)
Casaer et al,[39] 2013	Multicenter RCT	Mixed ICU	4640	Post-hoc analysis showed no difference in EN between 2 groups and late PN group without suggestion of mortality by increasing percentage calories at days 3, 5, 7
Braunschweig et al,[40] 2015	Multicenter RCT	Mixed ICU	78	High likelihood for type 1 error as high death rate in full EN group limited enrollment

Perioperative Probiotics or Synbiotics in Adults Undergoing Elective Abdominal Surgery

A Systematic Review and Meta-analysis of Randomized Controlled Trials

Abeed H. Chowdhury, PhD, FRCS, Alfred Adiamah, MRCS,* Anisa Kushairi, BMedSci, BM BS,* Krishna K. Varadhan, PhD, MRCS,* Zeljko Krznaric, MD, PhD,† Anil D. Kulkarni, MSc, PhD,‡ Keith R. Neal, DM, FRCP,§ and Dileep N. Lobo, DM, FRCS, FACS, FRCPE*¶*

2020



34 RCT n=2753

1354 treated with Synbiotics or Probiotics

1369 control

Synbiotics and Probiotics decrease risk of infections 56% p<0.00001

Synbiotics > than probiotics p<0.00001

Conclusions:

1) **Probiotics and synbiotics decrease infections, LOS**
   - **No adverse effects**
2) **No change in mortality**

A randomized synbiotic trial to prevent sepsis among infants in rural India

Pinaki Panigrahi[1,2], Sailajanandan Parida[3], Nimai C. Nanda[4], Radhanath Satpathy[5], Lingaraj Pradhan[6], Dinesh S. Chandel[7], Lorena Baccaglini[1], Arjit Mohapatra[5], Subhranshu S. Mohapatra[5], Pravas R. Misra[5], Rama Chaudhry[8], Hegang H. Chen[9], Judith A. Johnson[10], J. Glenn Morris Jr[10], Nigel Paneth[11] & Ira H. Gewolb[12]

nature
International journal of science

2017

- **RDBPCT of L. plantarum + FOS n=4,556 infants >2,000gm, 35wk gestation**
- **WHO criteria for sepsis 42% reduction in sepsis 1 week of tx $1**

Table 2 | Effect of synbiotic treatment on sepsis and other morbidities in the first 60 days of life

Outcome variables	Control $n=2,278$ (%)	Synbiotic $n=2,278$ (%)	RR (95% CI)	NNT (95% CI)	*P* value
Death and sepsis (primary outcome)	206 (9.0)	123 (5.4)	0.60 (0.48, 0.74)	27 (19, 47)	<0.001
Deaths	4 (0.2)	6 (0.3)	1.50 (0.42, 5.31)	NA*	0.526†
Sepsis (A + B + C)	202 (8.9)	117 (5.1)	0.58 (0.46, 0.72)	27 (19, 44)	<0.001
A. Sepsis/pSBI—culture-positive septicaemia	27 (1.2)	6 (0.3)	0.22 (0.09, 0.53)	108 (71, 232)	<0.001
Gram-negative sepsis	16 (0.7)	4 (0.2)	0.25 (0.08, 0.75)	190 (110, 699)	0.007
Gram-positive sepsis	11 (0.5)	2 (0.1)	0.18 (0.04, 0.82)	253 (142,1,169)	0.012
B. Sepsis/pSBI— culture-negative sepsis (Culture-negative clinical sepsis warranting hospitalization and IV antibiotics)	36 (1.6)	19 (0.8)	0.53 (0.30, 0.92)	134 (72, 890)	0.021
C. Sepsis/pSBI—LRTI (LRTIs requiring antibiotic therapy)	139 (6.1)	92 (4.0)	0.66 (0.51, 0.88)	48 (30, 126)	0.002
Diarrhoea	59 (2.6)	12 (0.5)	0.20 (0.11, 0.38)	48 (36, 74)	<0.001
Local infections (including >10 pustules, oral thrush, conjunctivitis)	33 (1.5)	16 (0.7)	0.48 (0.27, 0.88)	134 (74, 677)	0.015
Abscess/ otitis media	11 (0.5)	5 (0.2)	0.45 (0.16, 1.33)	NA*	0.133*
Omphalitis	13 (0.6)	3 (0.1)	0.23 (0.07, 0.81)	228 (128,1,045)	0.014

Gastroenterology 2020;159:697–705

CLINICAL PRACTICE GUIDELINES

AGA Clinical Practice Guidelines on the Role of Probiotics in the Management of Gastrointestinal Disorders

Grace L. Su,[1,2] Cynthia W. Ko,[3] Premysl Bercik,[4] Yngve Falck-Ytter,[5,6] Shahnaz Sultan,[7] Adam V. Weizman,[8] and Rebecca L. Morgan[9]

[1]Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, Michigan; [2]Gastroenterology Section, Veterans Administration Ann Arbor Healthcare System, Ann Arbor, Michigan; [3]Division of Gastroenterology, University of Washington Medical School, Seattle, Washington; [4]Division of Gastroenterology, McMaster University, Hamilton, Ontario, Canada; [5]Division of Gastroenterology, Case Western Reserve University, Cleveland, Ohio; [6]Louis Stokes Veterans Affairs Medical Center, Cleveland, Ohio; [7]Division of Gastroenterology, University of Minnesota, Minneapolis, Minnesota; [8]Division of Gastroenterology, Mount Sinai Hospital, Department of Medicine, University of Toronto, Toronto, Ontario, Canada; and [9]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada

Knowledge gaps
Significant heterogeneity
Lack of consistent harms reporting
Lack of manufacturing details make true comparison impossible

Why have probiotics been ignored by most nutrition communities ?

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Original article

Why do current strategies for optimal nutritional therapy neglect the microbiome?

Stephen A. McClave M.D. [a,*], Robert Martindale M.D., Ph.D. [b]

- **Widely variable literature**
- **Numerous genus, species, and even strains make very confusing**
- **Lack of understanding of effects and research tools to investigate**
  - **Rapid introduction of new biological measurements, methods involving genomes, gene products, complex analysis tools and methods**
  - **Metabolomics**
  - **Conversion of microbiome to pathobiome (phenotypic changes)**

What are “we” doing wrong ?

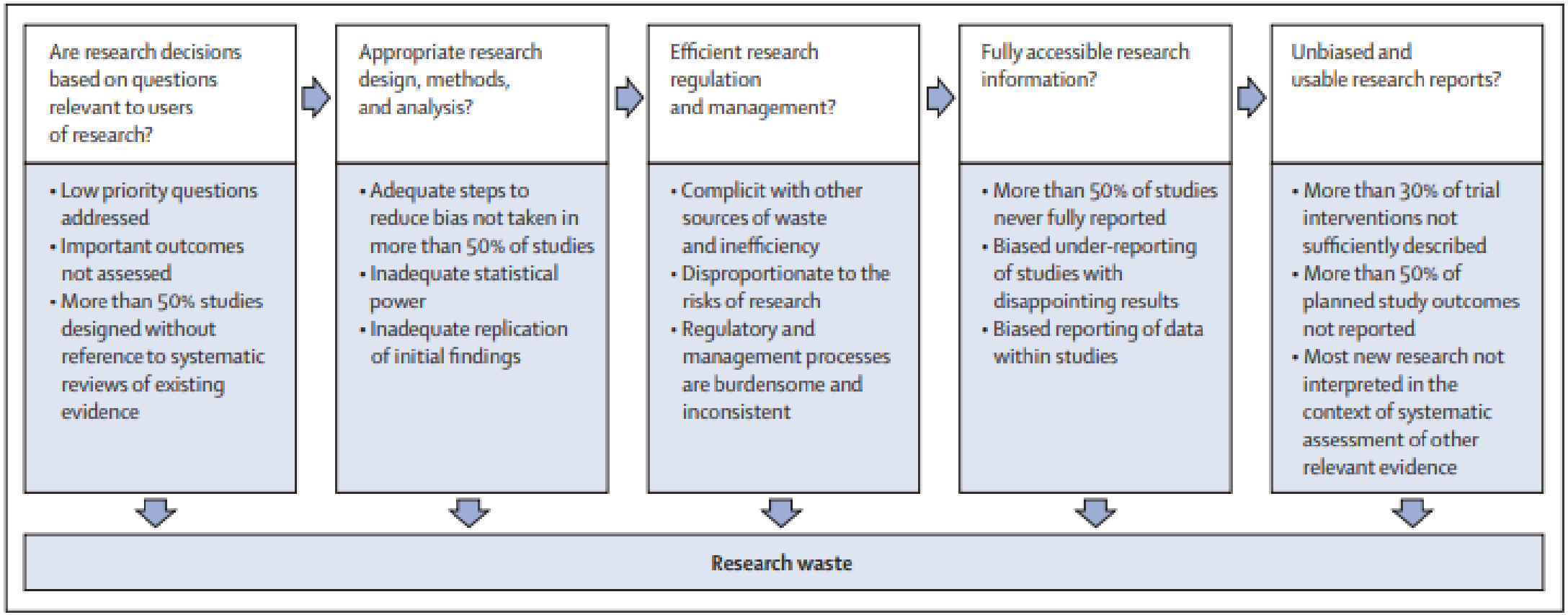


Figure: Avoidable waste or inefficiency in biomedical research

MacLeod MR et al Lancet 2014

Summary: Picking our study type to make a difference and stay out of rabbit holes

- **To change practice we must align the outcome with evidence**
  - **Many types of data is required**
    - **RCT's**
    - **Meta-analysis**
    - **Observational studies**
    - **Theoretical and concept confirmation data**

The most dangerous phrase in the English language is;

"We've always done it this way!"

Grace Murray Hopper

Tiny details: Isotopes and metabolomics

Prof. Olav Rooyackers

FRESENIUS KABI
caring for life

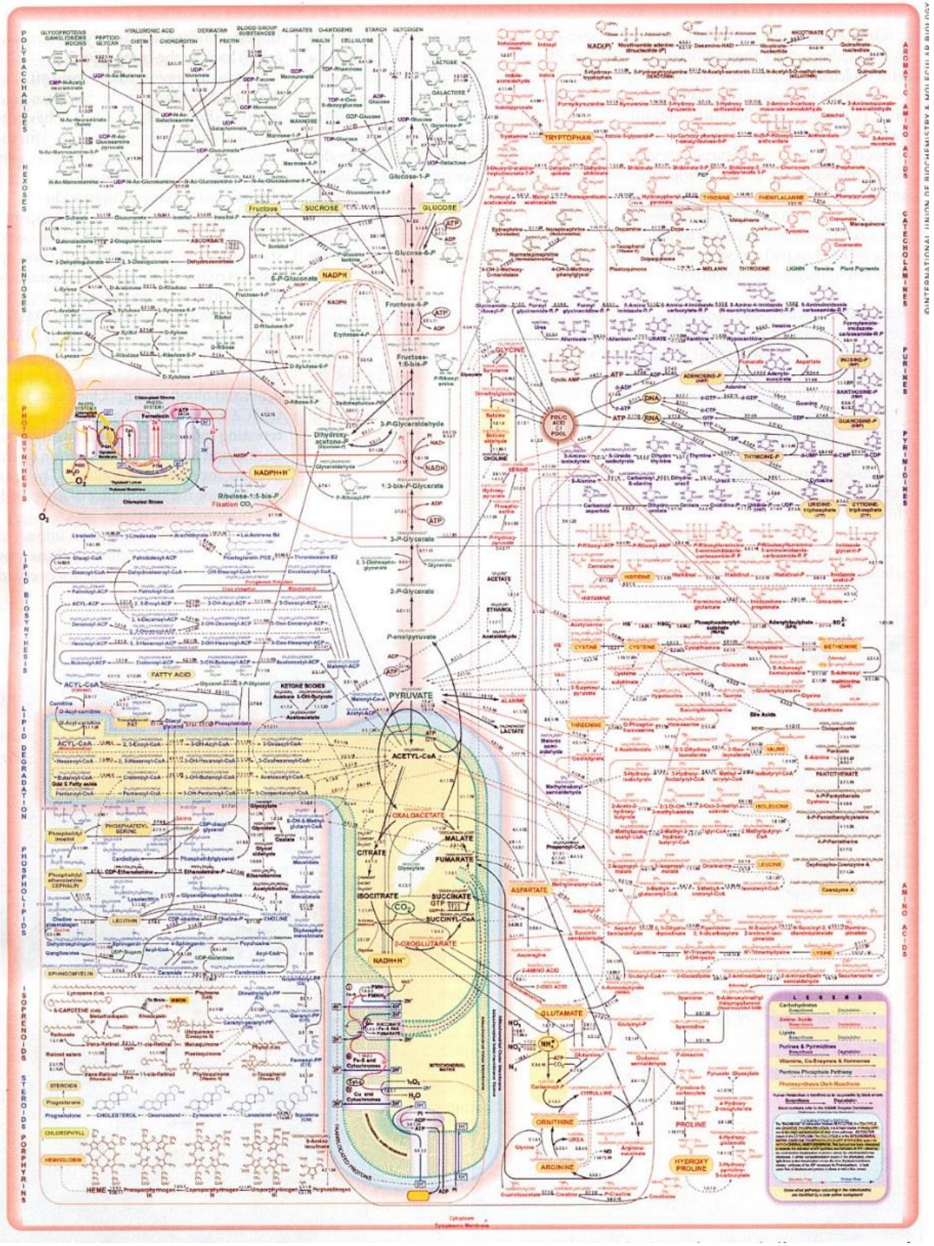
JUMPstart Training Program

Tiny details:

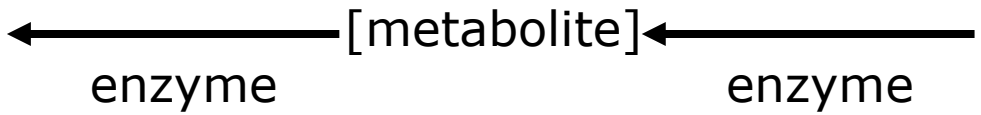
From GENES to FLUXES

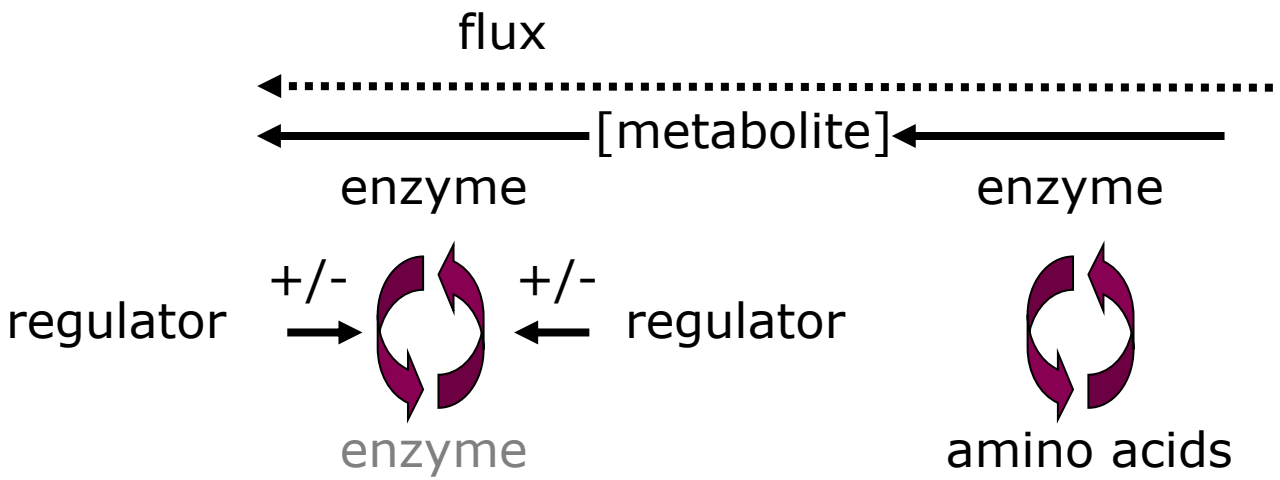
Olav Rooyackers

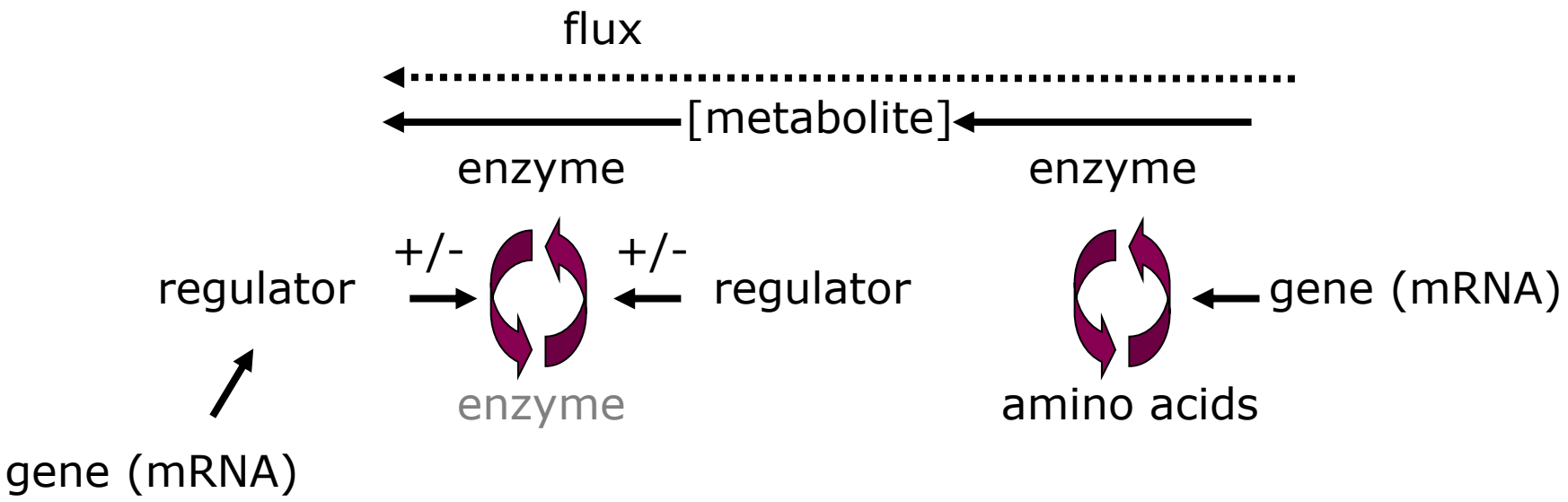
Advanced Module, Day 1, Part II: Counting peas: Methods in nutrition research



[metabolite]



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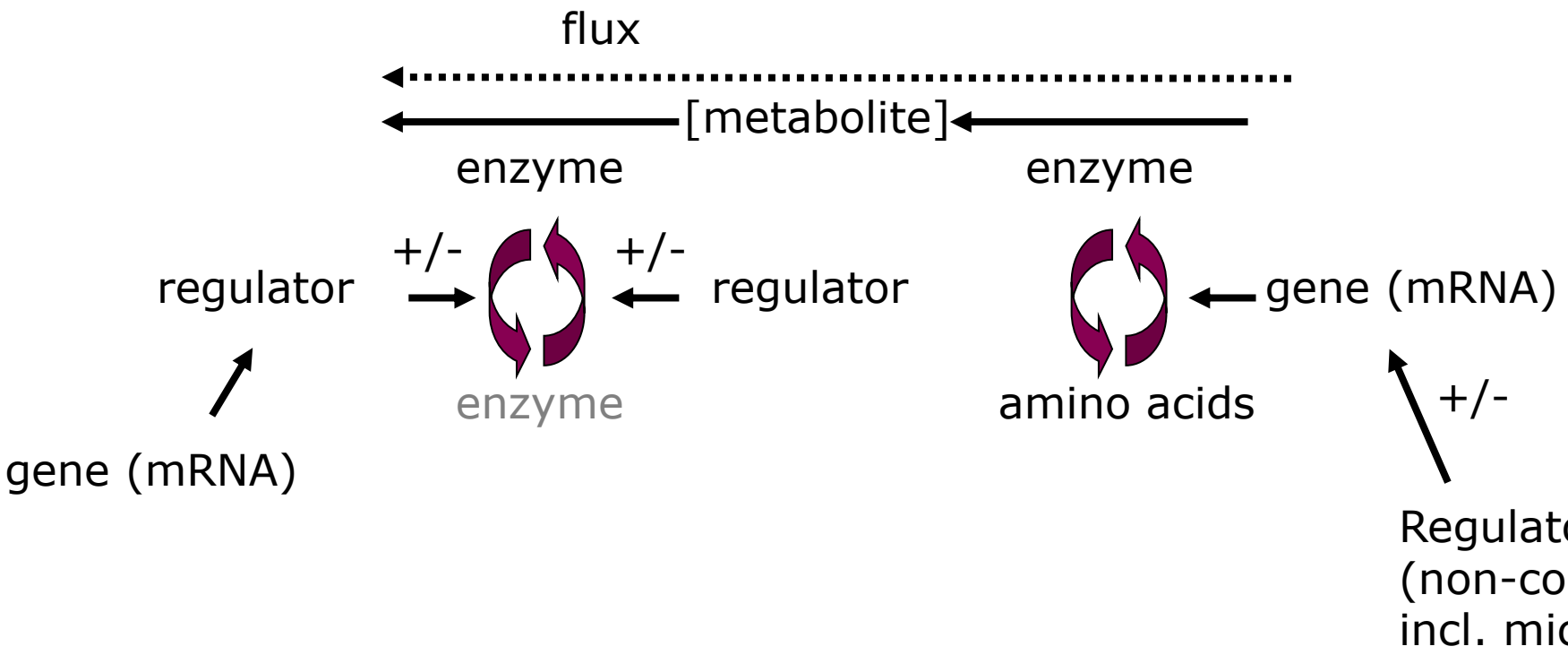
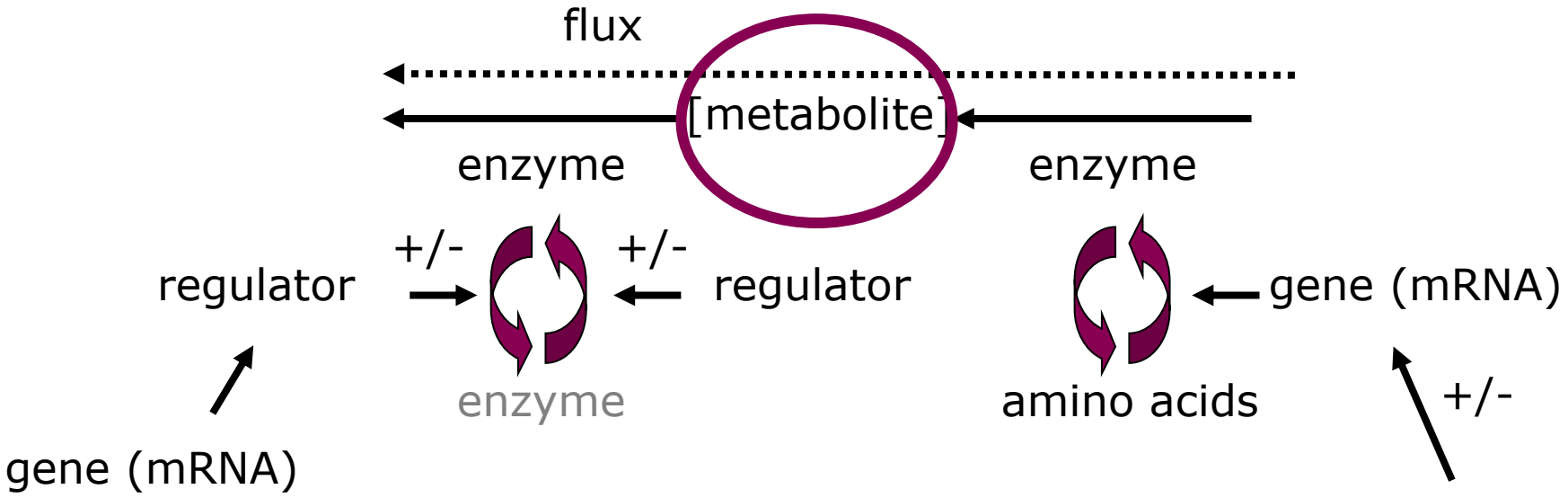
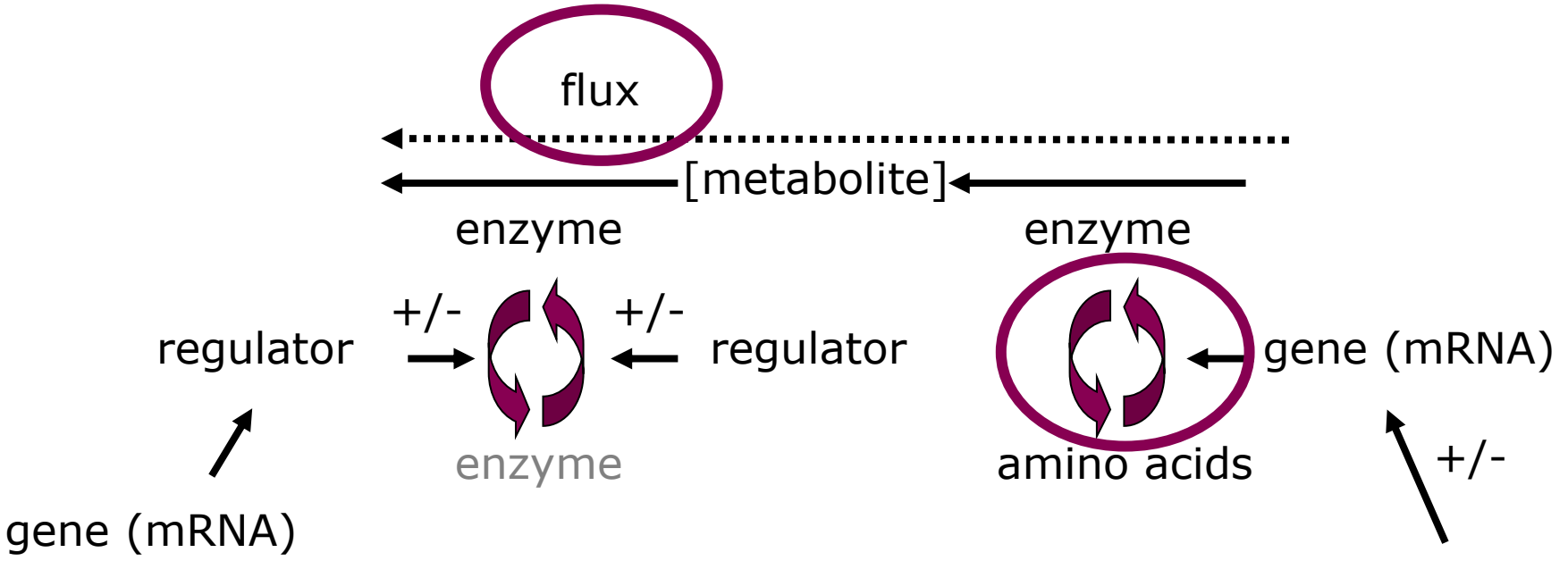




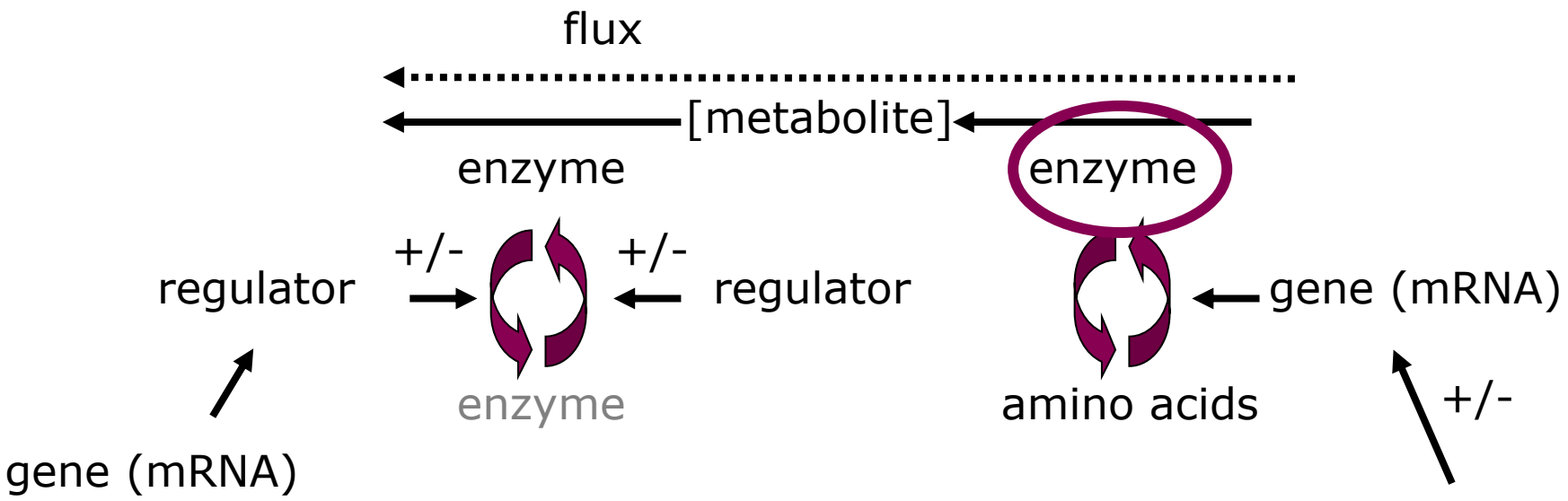
Methods/techniques:

- HPLC
- Enzymatic or colorimetric methods
- Metabolomics (mass spec)



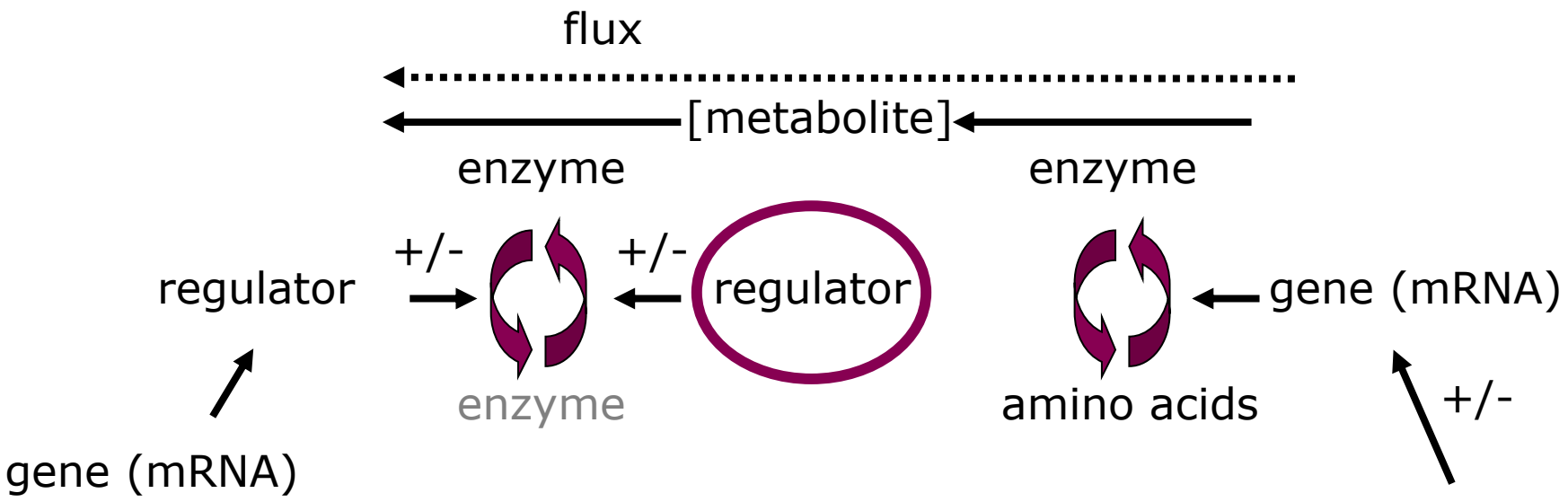
Methods/techniques:

- Tracer methods (stable or radio-active)
- Fluxomics



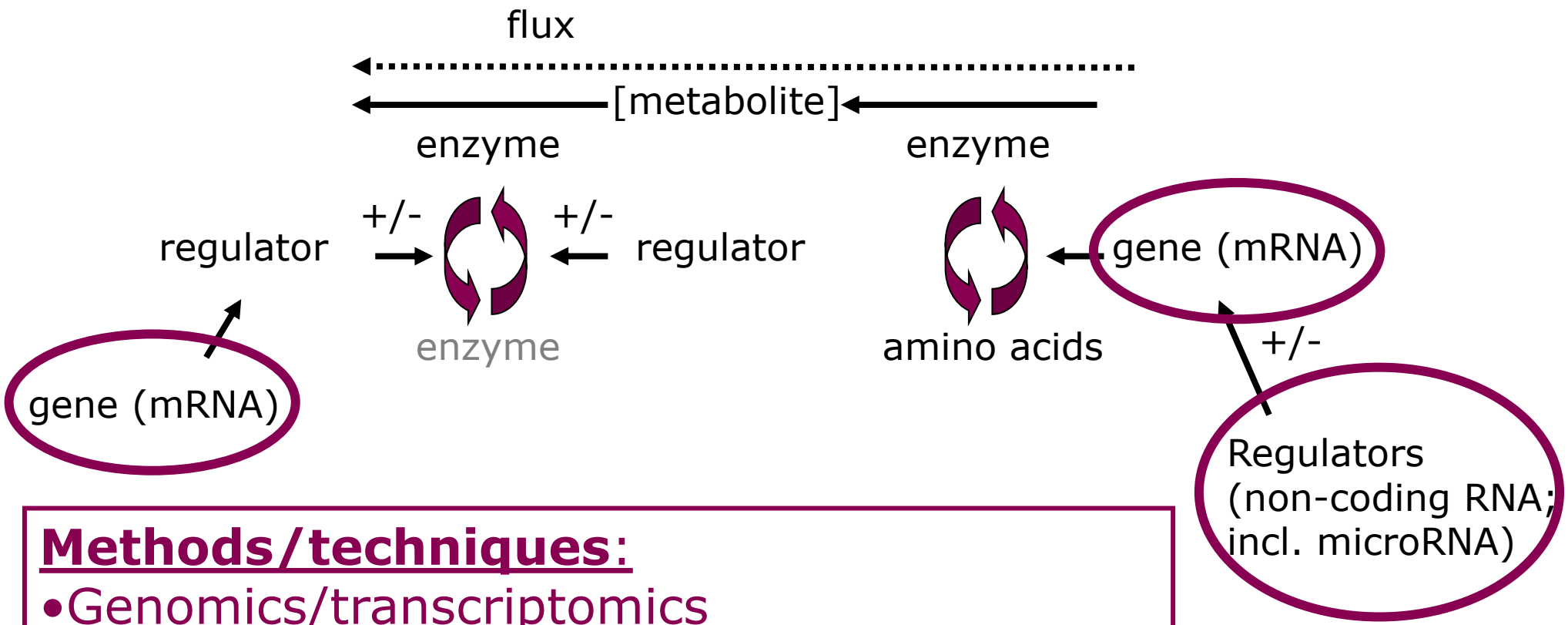
Methods/techniques:

- Enzymatic methods
  - Maximal activities
  - Kinetic measurements
- Western blot



Methods/techniques:

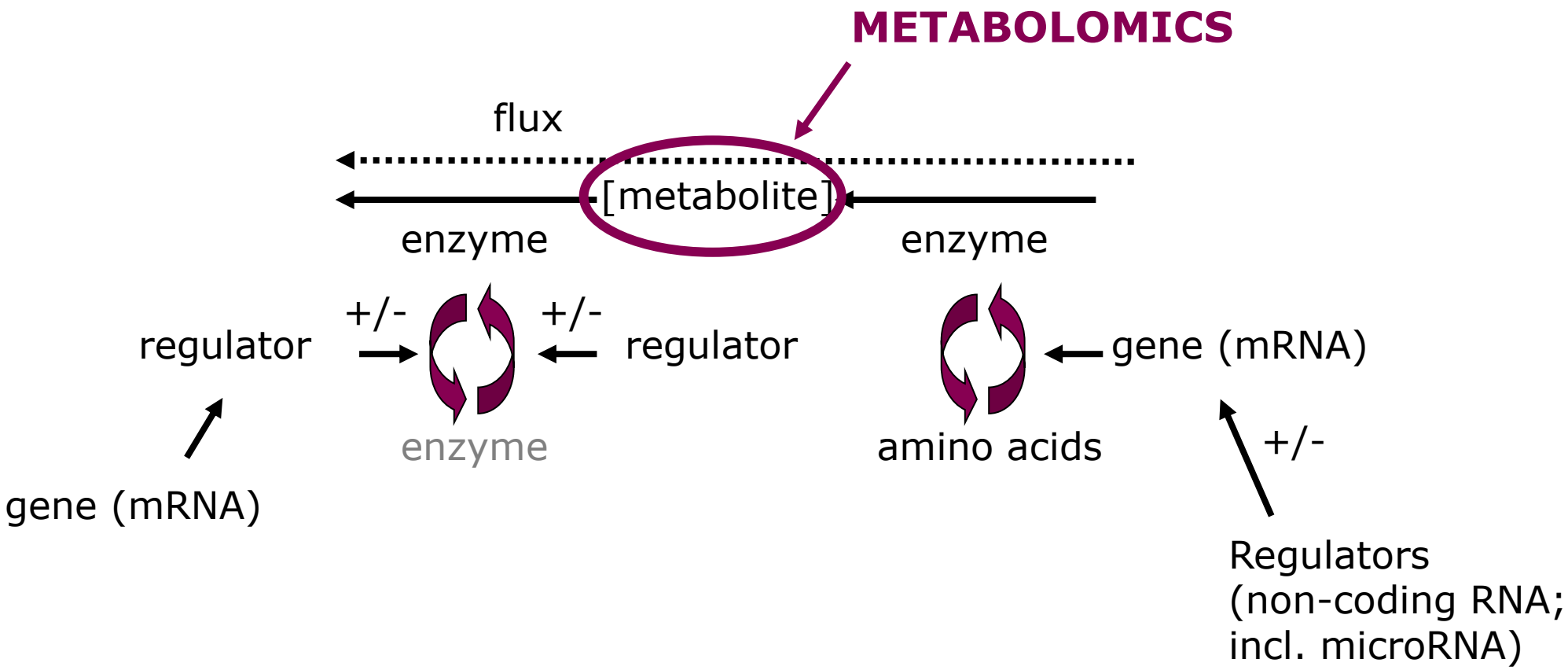
- Western blot (incl. posttranslational modifications)
- Proteomics



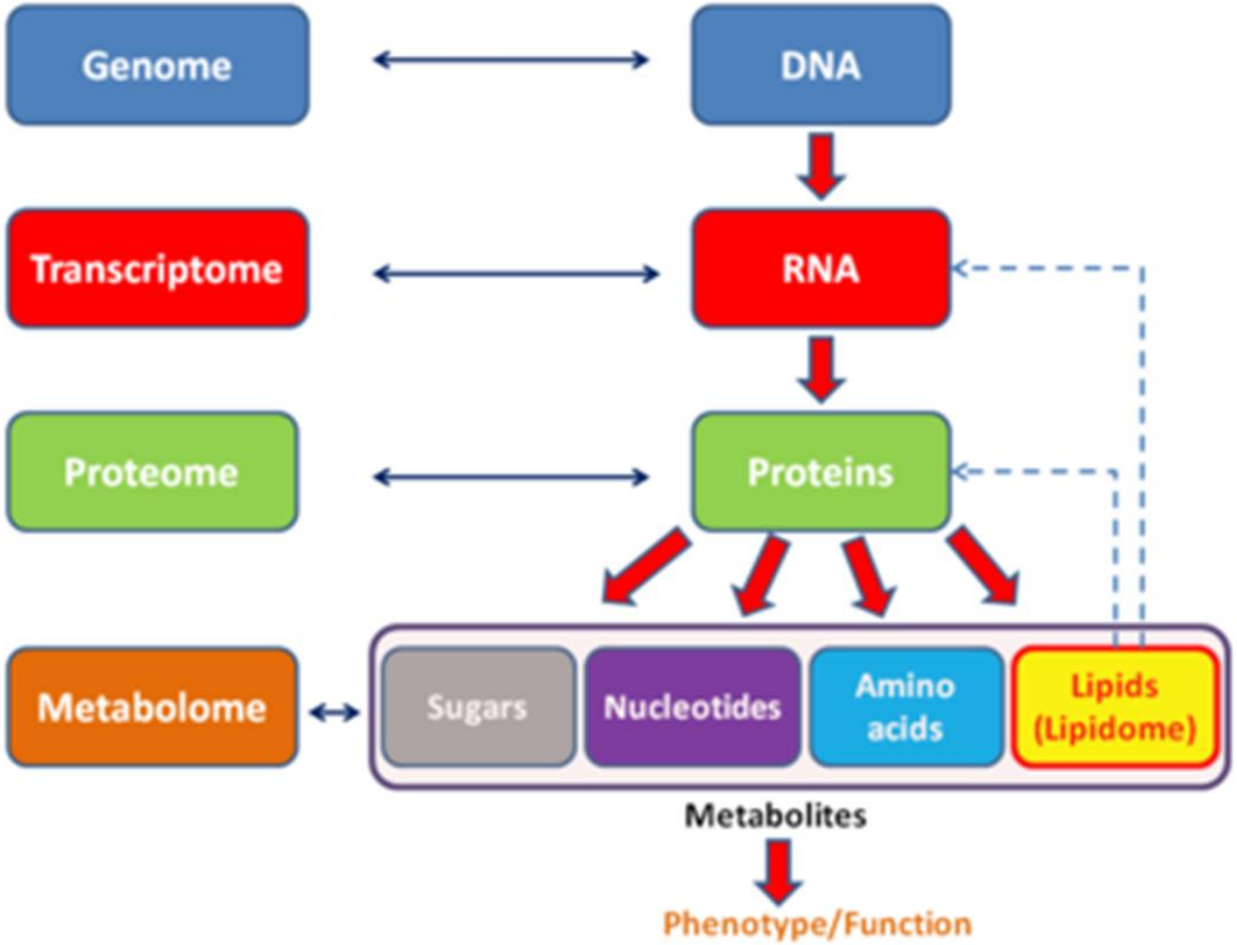
Methods/techniques:

- Genomics/transcriptomics
  - Northern blot, Quantitative PCR
  - Micro-array platforms/RNA sequencing
  - Modification (DNA methylation)
  - Multiplex miRNA profiling

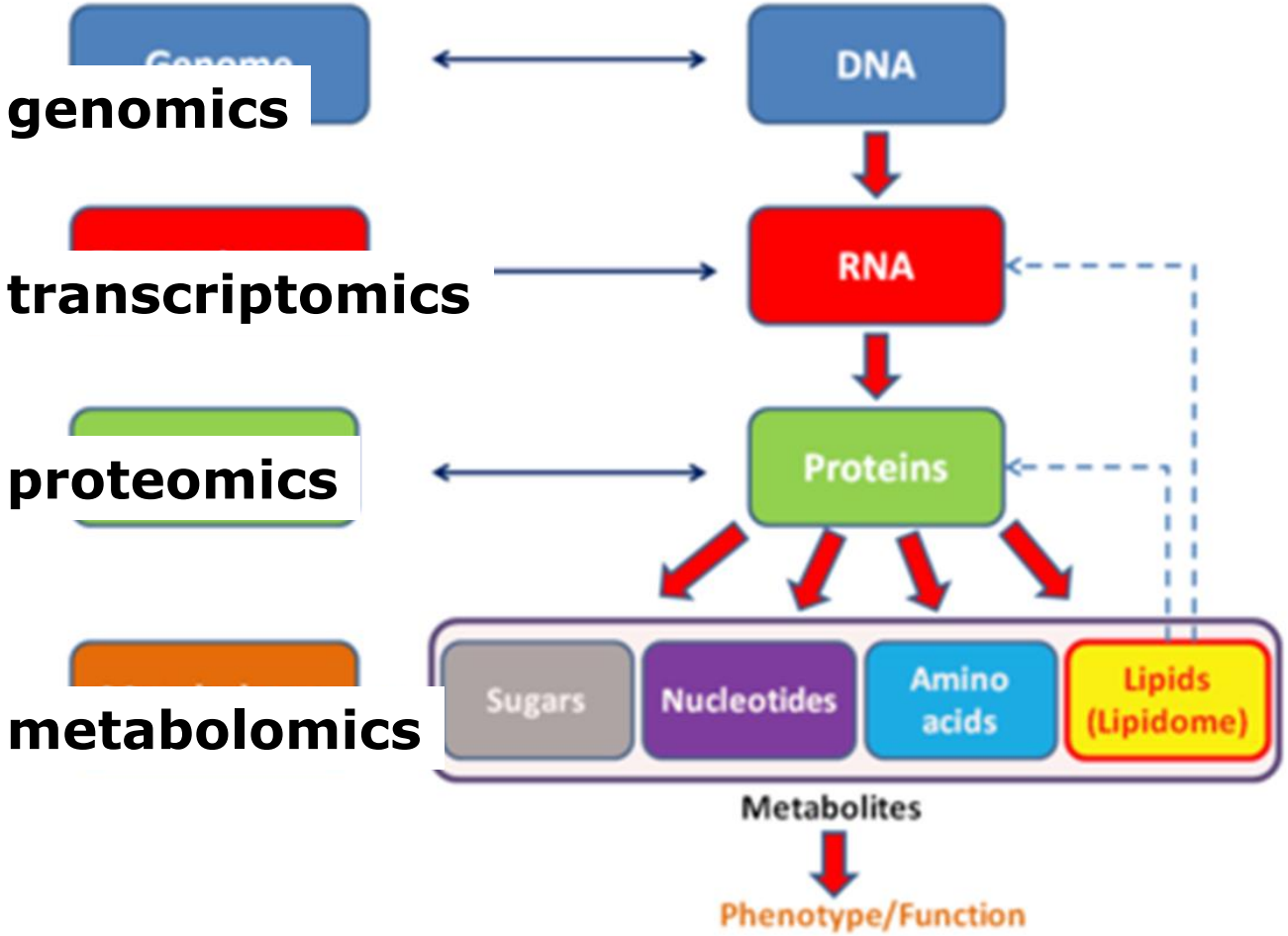
Examples

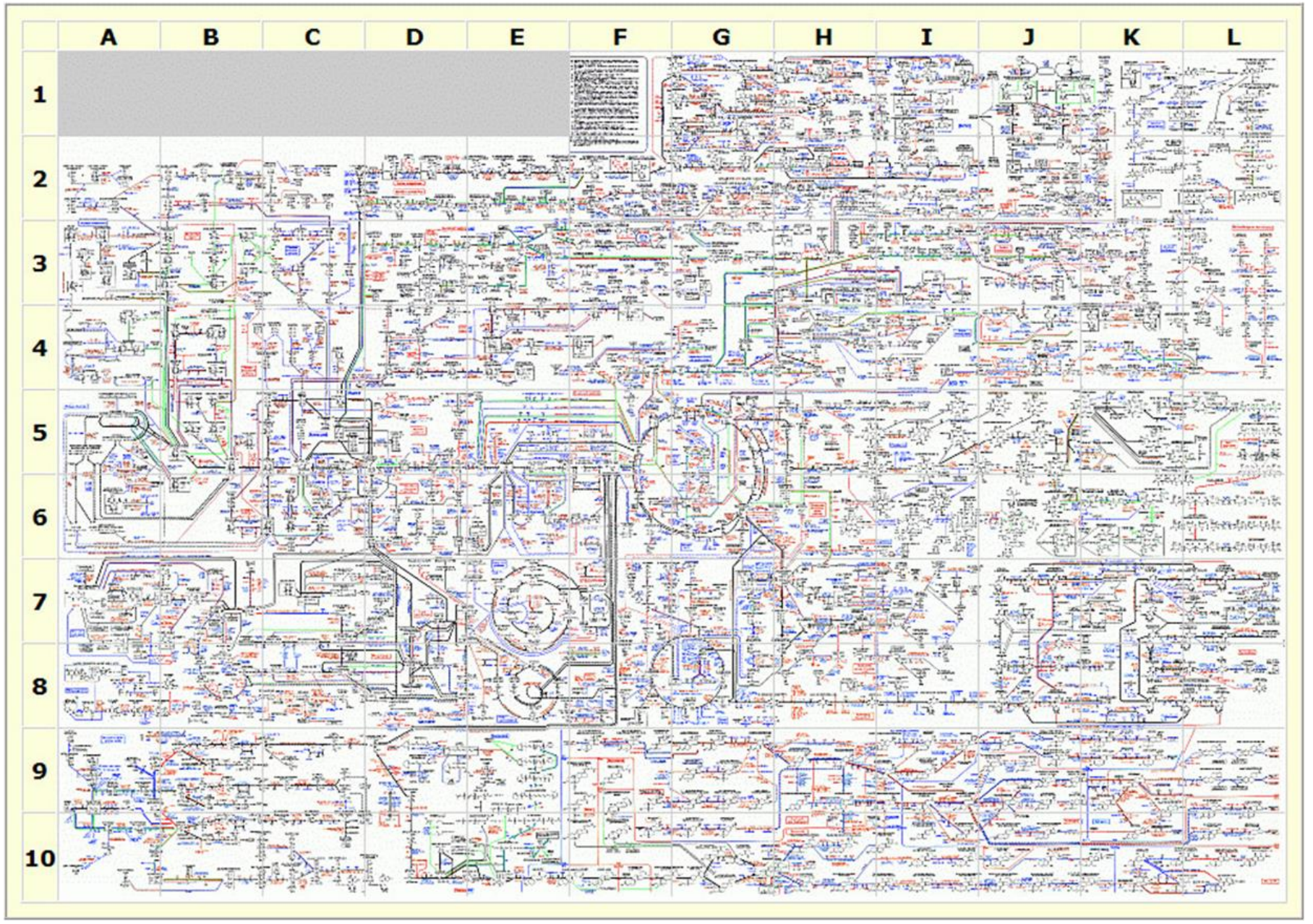


Omics
From Wikipedia



Omics
From Wikipedia

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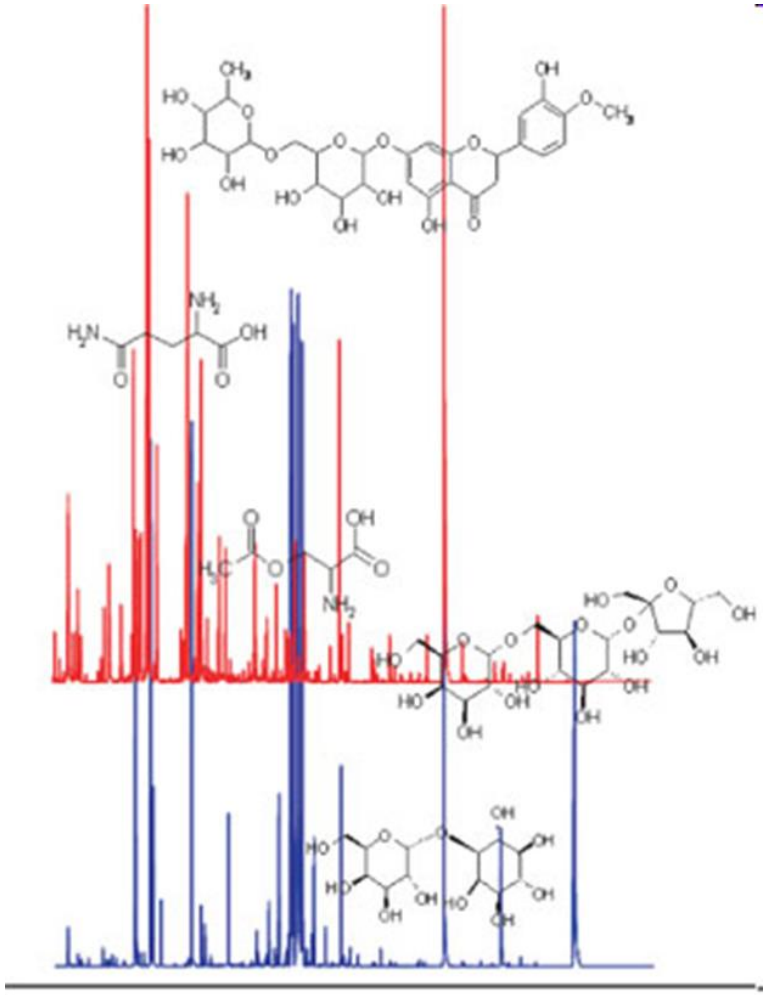
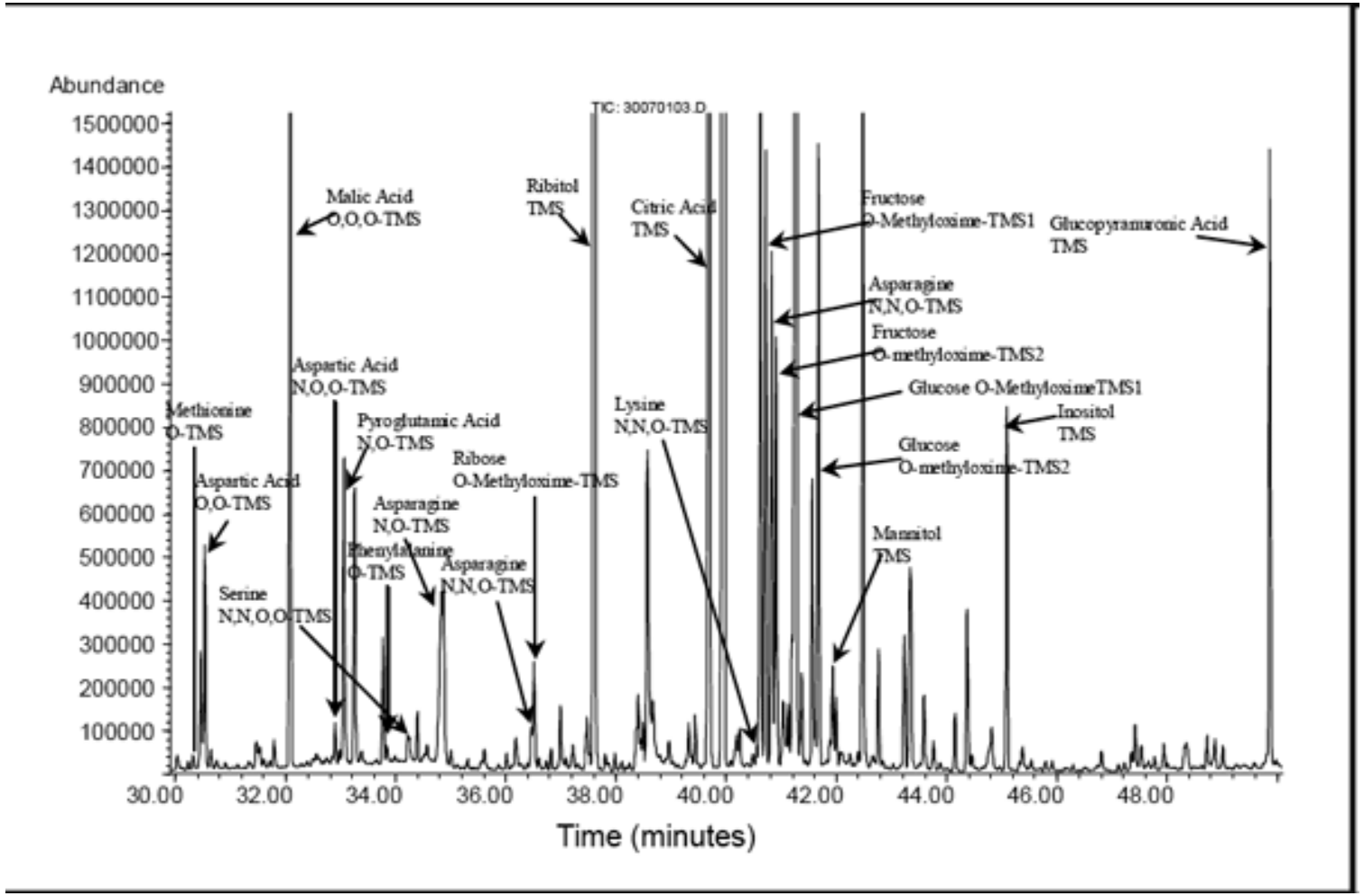
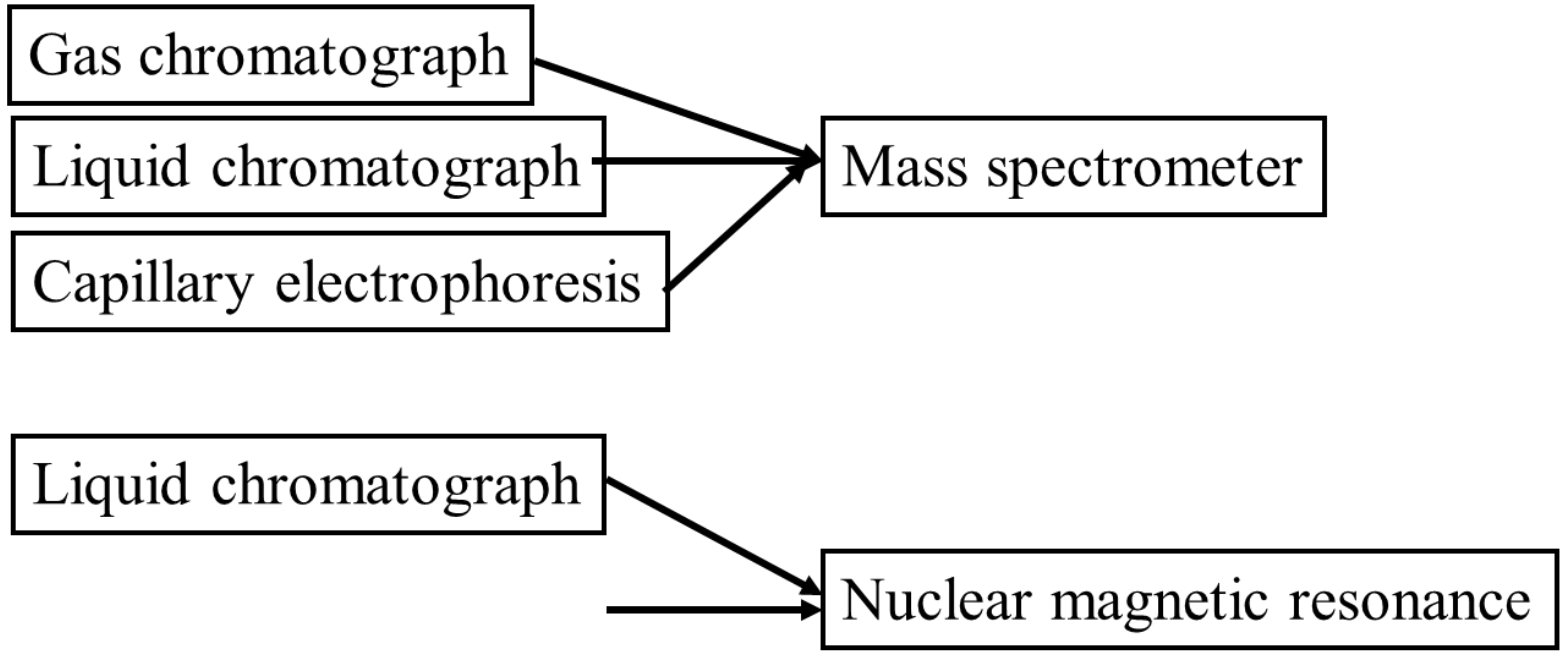
Discovery metabolomics/lipidomics fingerprinting



Targeted metabolomics/lipidomics profiling



Analytical tools



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Bioanalysis

Analytical pitfalls and challenges in clinical metabolomics

Isabelle Kohler[1],
Aswin Verhoeven[1],
Rico JE Derks[1]
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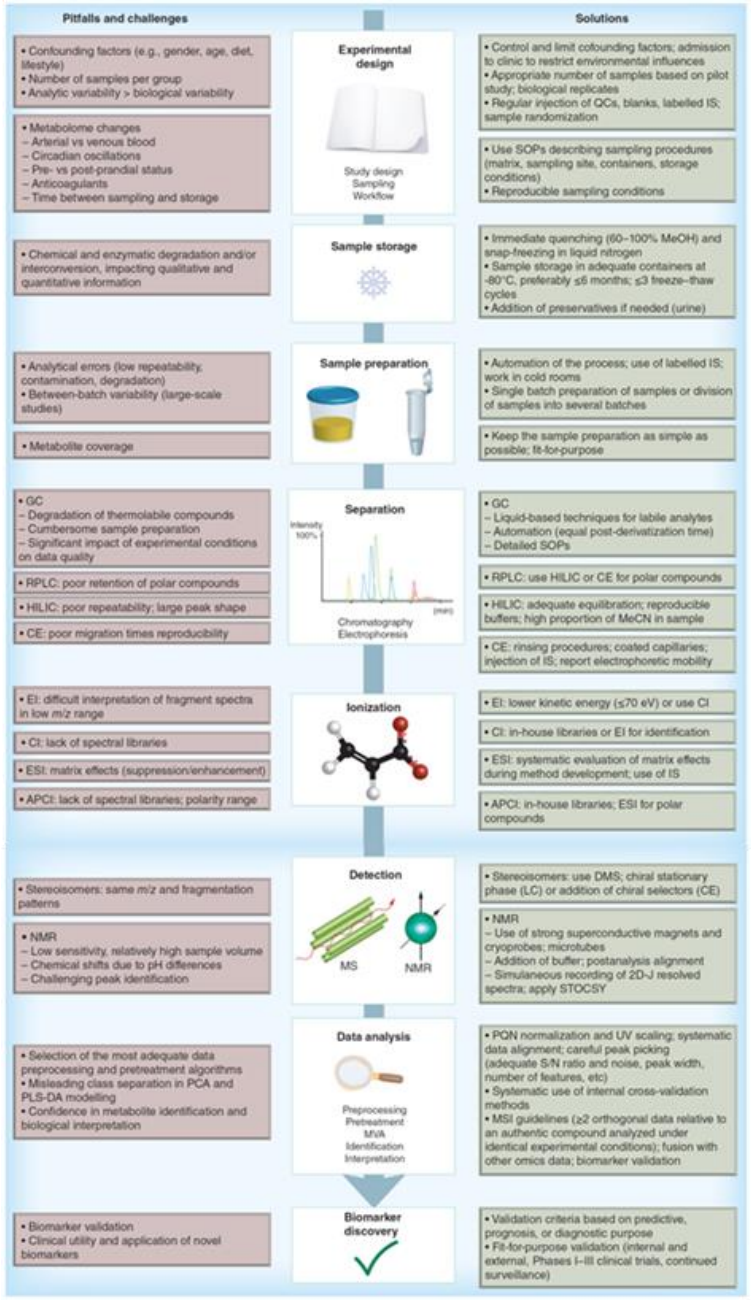
Pitfalls and challenges
Solutions
Experimental design
• Confounding factors (e.g., gender, age, diet, lifestyle)
• Number of samples per group
• Analytic variability > biological variability
• Control and limit cofounding factors; admission to clinic to restrict environmental influences
• Appropriate number of samples based on pilot study; biological replicates
• Regular injection of QCs, blanks, labelled IS; sample randomization
Study design
Sampling
Workflow
• Metabolome changes
– Arterial vs venous blood
– Circadian oscillations
– Pre- vs post-prandial status
– Anticoagulants
– Time between sampling and storage
• Use SOPs describing sampling procedures (matrix, sampling site, containers, storage conditions)
• Reproducible sampling conditions
Sample storage
• Chemical and enzymatic degradation and/or interconversion, impacting qualitative and quantitative information
• Immediate quenching (60–100% MeOH) and snap-freezing in liquid nitrogen
• Sample storage in adequate containers at -80°C, preferably ≤6 months; ≤3 freeze–thaw cycles
• Addition of preservatives if needed (urine)
Sample preparation
• Analytical errors (low repeatability, contamination, degradation)
• Between-batch variability (large-scale studies)
• Automation of the process; use of labelled IS; work in cold rooms
• Single batch preparation of samples or division of samples into several batches
• Metabolite coverage
• Keep the sample preparation as simple as possible; fit-for-purpose
Separation
• GC
– Degradation of thermolabile compounds
– Cumbersome sample preparation
– Significant impact of experimental conditions on data quality
• GC
– Liquid-based techniques for labile analytes
– Automation (equal post-derivatization time)
– Detailed SOPs
Intensity
100%
t (min)
Chromatography
Electrophoresis
• RPLC: poor retention of polar compounds
• RPLC: use HILIC or CE for polar compounds
• HILIC: poor repeatability; large peak shape
• HILIC: adequate equilibration; reproducible buffers; high proportion of MeCN in sample
• CE: poor migration times reproducibility
• CE: rinsing procedures; coated capillaries; injection of IS; report electrophoretic mobility
Ionization
• EI: difficult interpretation of fragment spectra in low m/z range
• EI: lower kinetic energy (≤70 eV) or use CI
• CI: lack of spectral libraries
• CI: in-house libraries or EI for identification
• ESI: matrix effects (suppression/enhancement)
• ESI: systematic evaluation of matrix effects during method development; use of IS
• APCI: lack of spectral libraries; polarity range
• APCI: in-house libraries; ESI for polar compounds
Detection
• Stereoisomers: same m/z and fragmentation patterns
• Stereoisomers: use DMS; chiral stationary phase (LC) or addition of chiral selectors (CE)
• NMR
– Low sensitivity, relatively high sample volume
– Chemical shifts due to pH differences
– Challenging peak identification
MS
NMR
• NMR
– Use of strong superconductive magnets and cryoprobes; microtubes
– Addition of buffer; postanalysis alignment
– Simultaneous recording of 2D-J resolved spectra; apply STOCSY
Data analysis
• Selection of the most adequate data preprocessing and pretreatment algorithms
• Misleading class separation in PCA and PLS-DA modelling
• Confidence in metabolite identification and biological interpretation
Preprocessing
Pretreatment
MVA
Identification
Interpretation
• PQN normalization and UV scaling; systematic data alignment; careful peak picking (adequate S/N ratio and noise, peak width, number of features, etc)
• Systematic use of internal cross-validation methods
• MSI guidelines (≥2 orthogonal data relative to an authentic compound analyzed under identical experimental conditions); fusion with other omics data; biomarker validation
Biomarker discovery
• Biomarker validation
• Clinical utility and application of novel biomarkers
• Validation criteria based on predictive, prognosis, or diagnostic purpose
• Fit-for-purpose validation (internal and external, Phases I–III clinical trials, continued surveillance)

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Characteristic	Malnutrition Absent (n = 53)	Malnutrition Present (n = 32)
Age, mean ± SD, y	53.4 ± 13.2	58.9 ± 14.9
Male sex, No. (%)	27 (51)	21 (66)
White race, No. (%)	39 (74)	29 (91)
APACHE II score, mean ± SD	25.1 ± 10.2	28.6 ± 8.3
Peak creatinine, mean ± SD, mg/dL	2.1 ± 2.0	2.3 ± 2.1
Malignancy, No. (%)	16 (30)	17 (53)
Chronic kidney disease, No. (%)	28 (53)	20 (63)
Sepsis, No. (%)	34 (64)	24 (75)
28-Day mortality, No. (%)	12 (23)	18 (56)

281 metabolites

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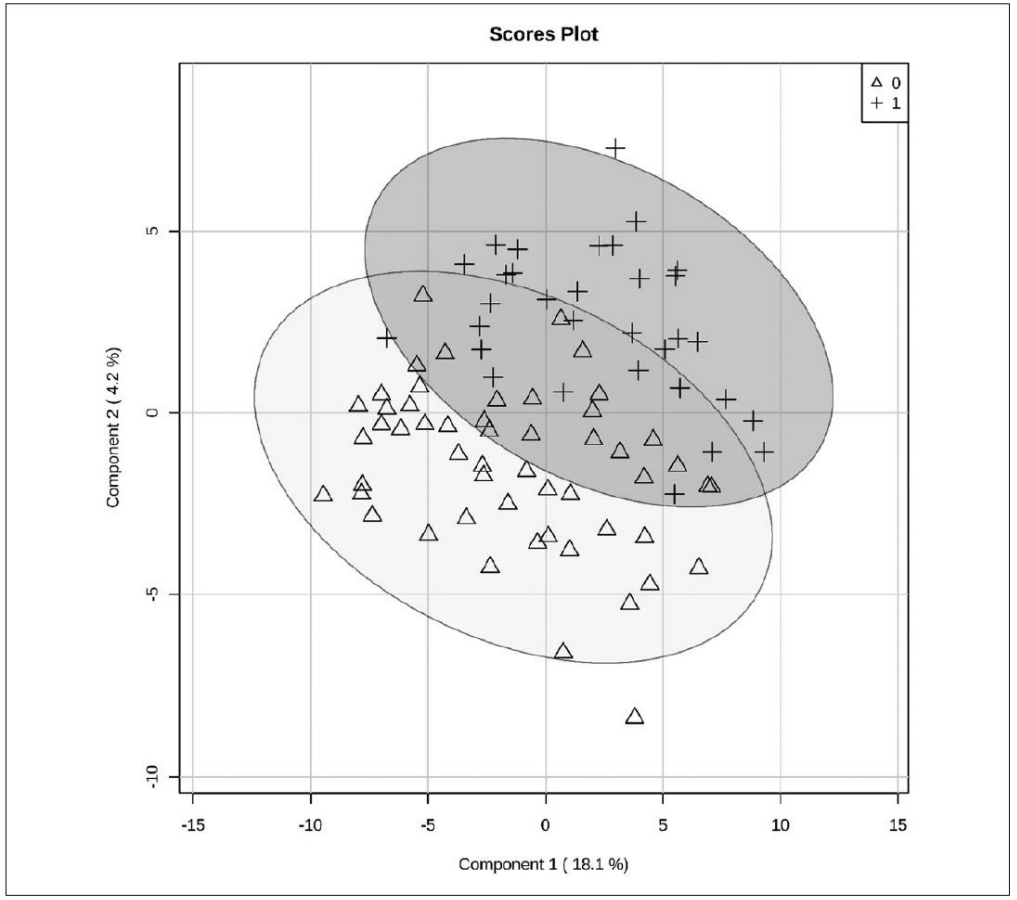

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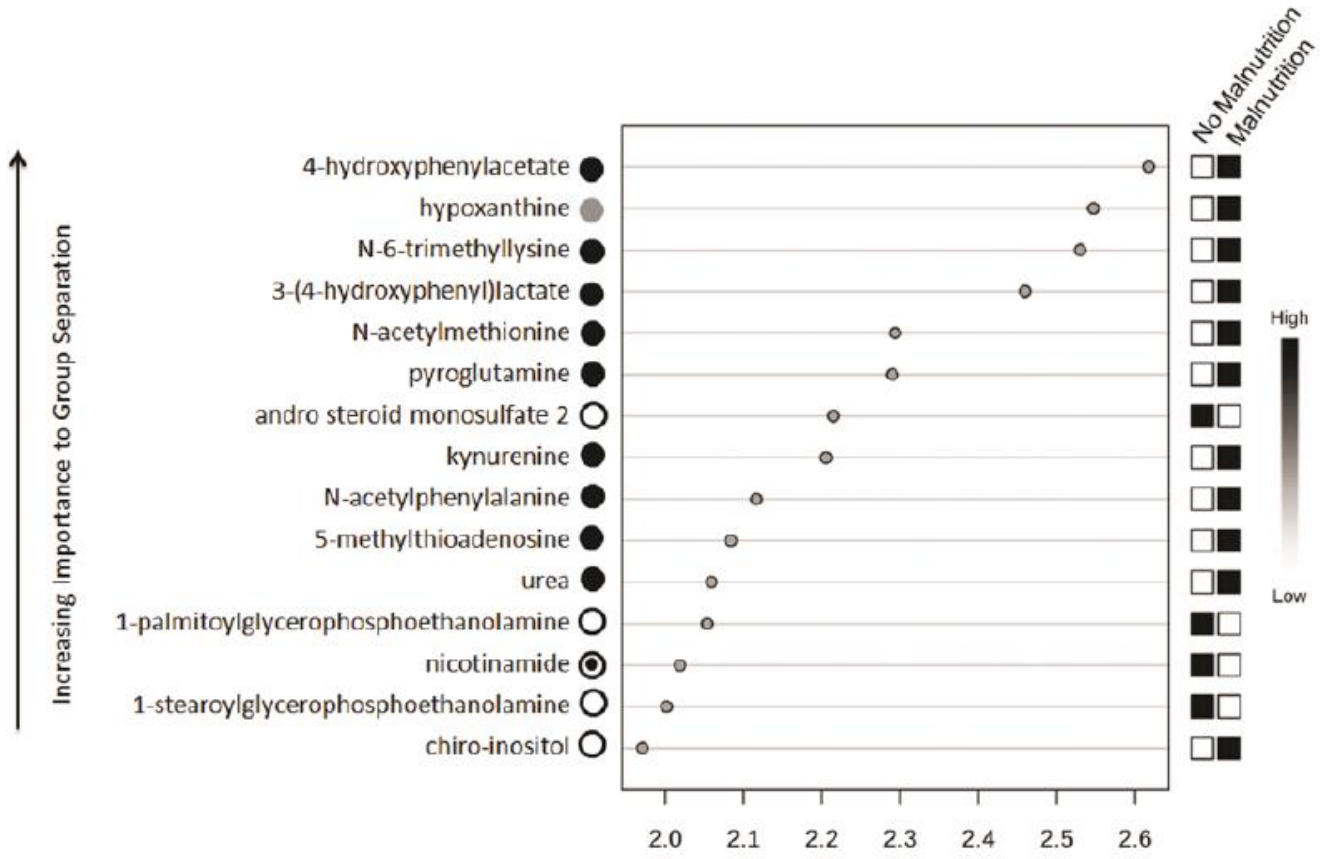

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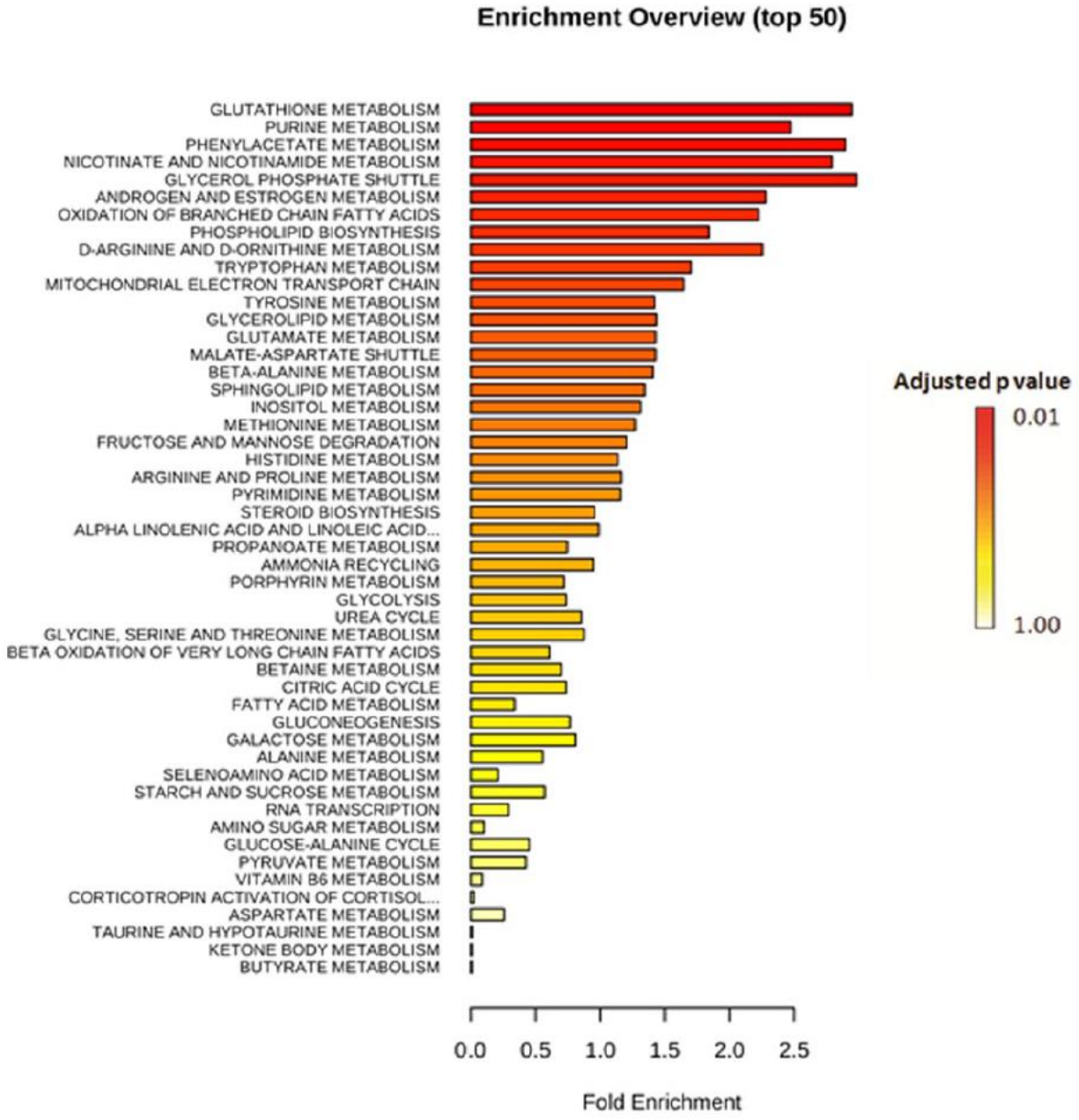
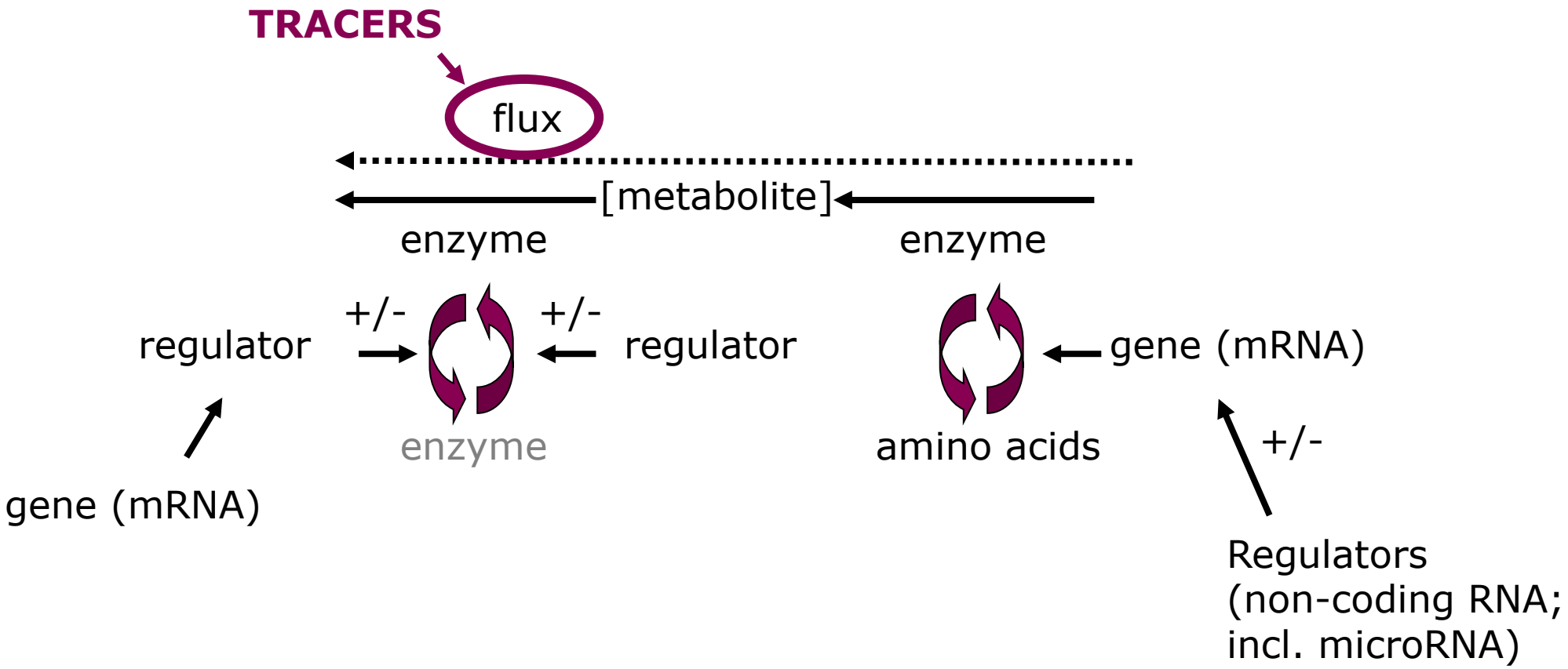
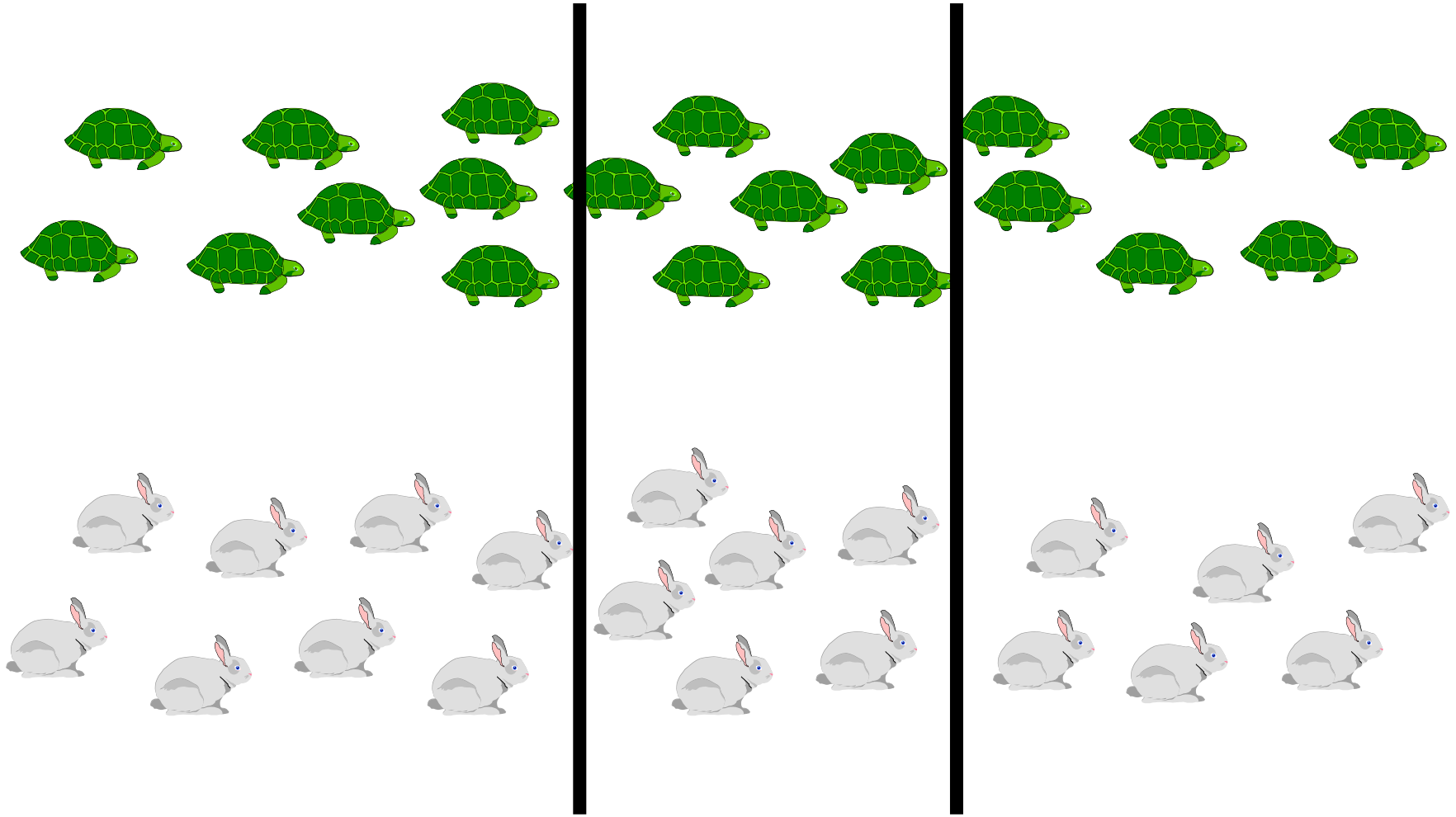


Examples



Flux - Concentration



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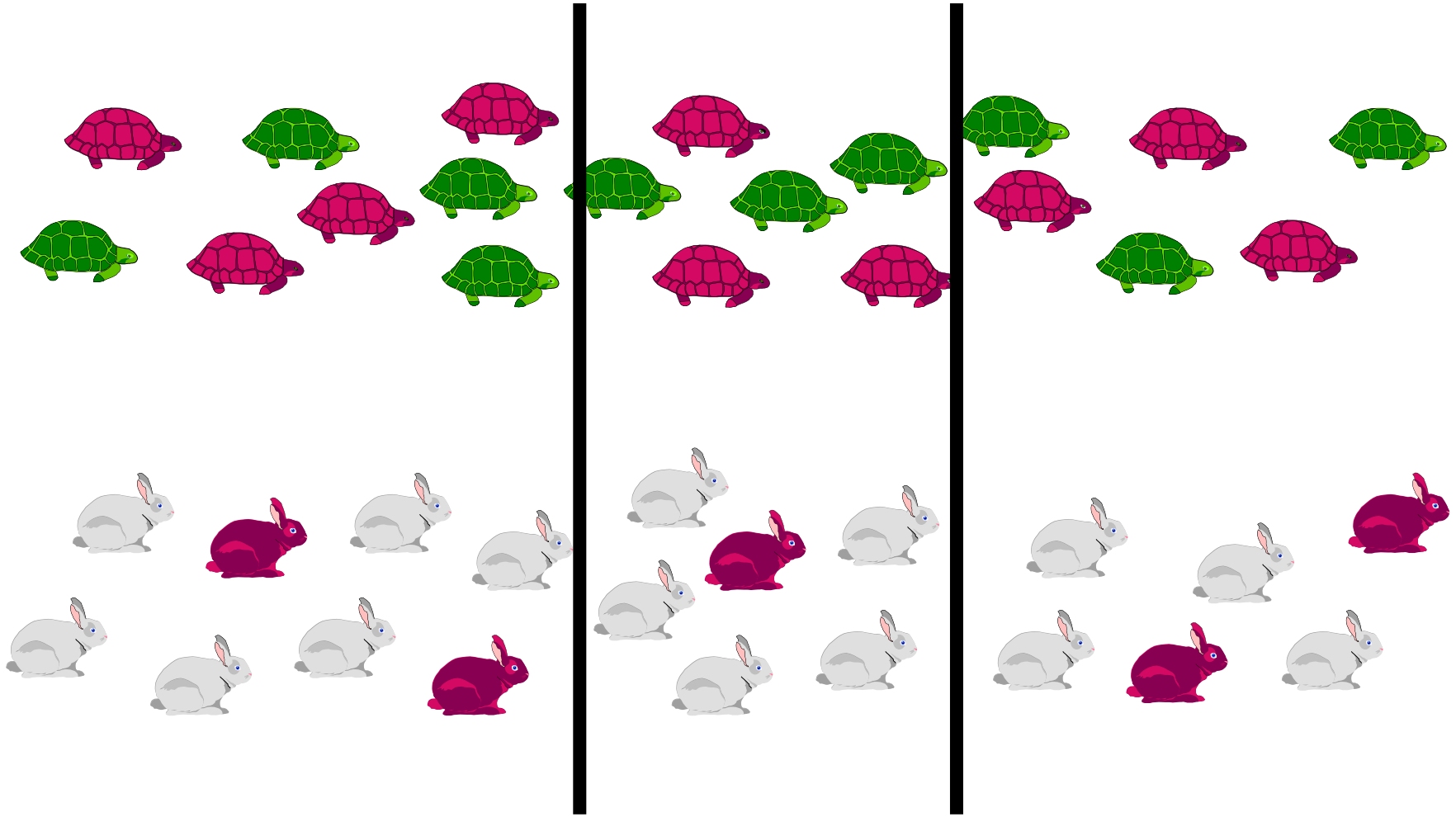
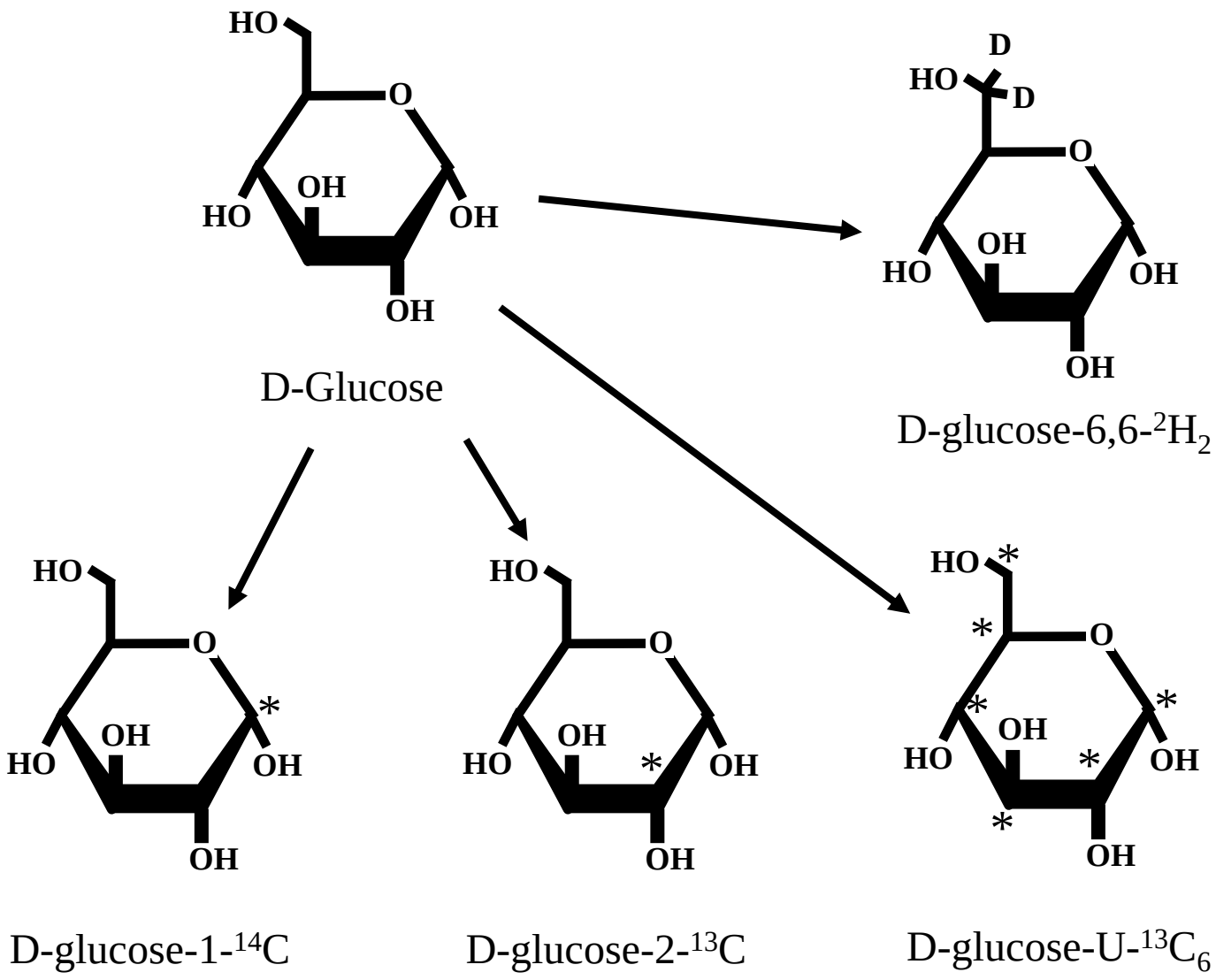
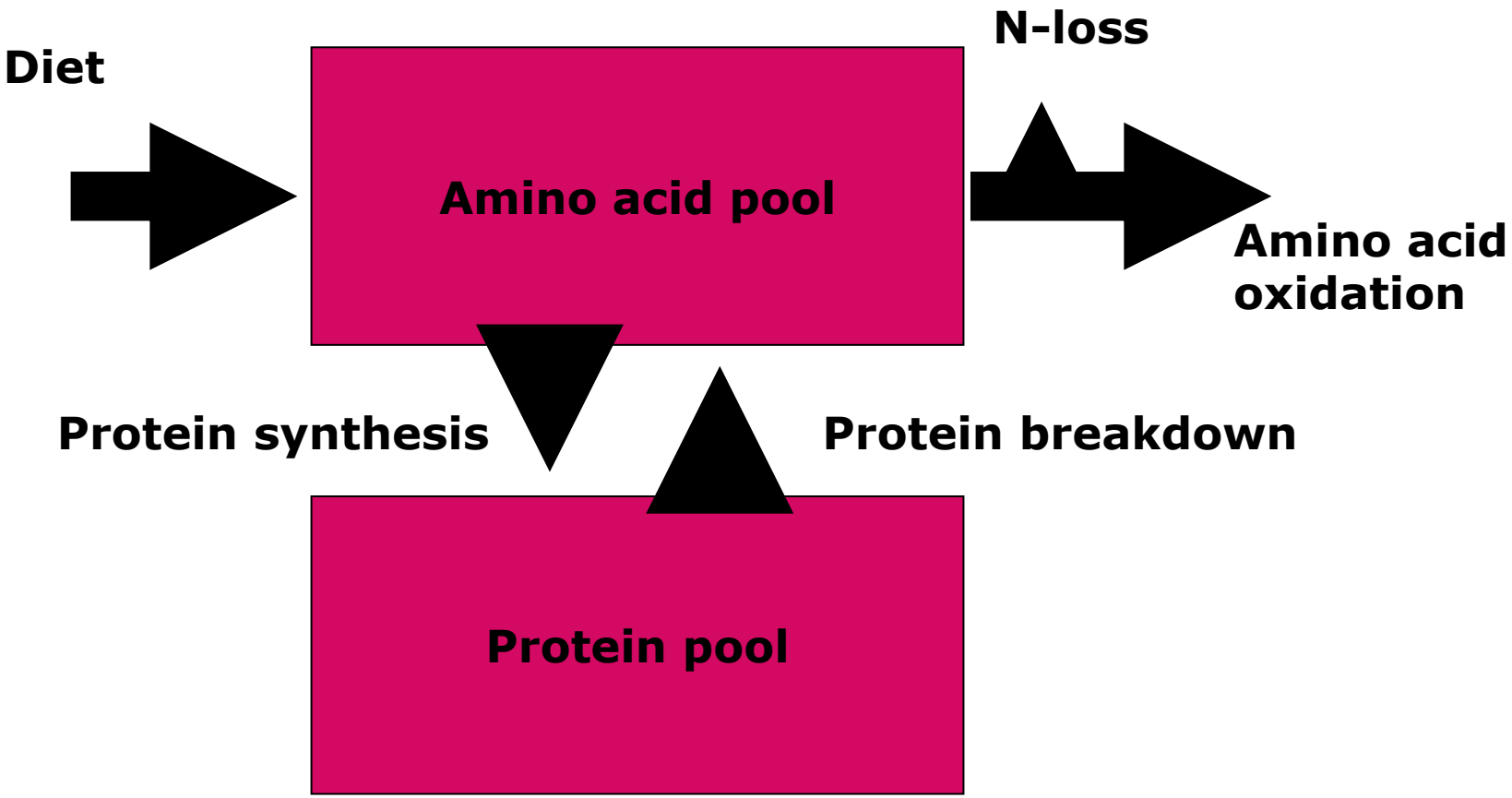


Examples

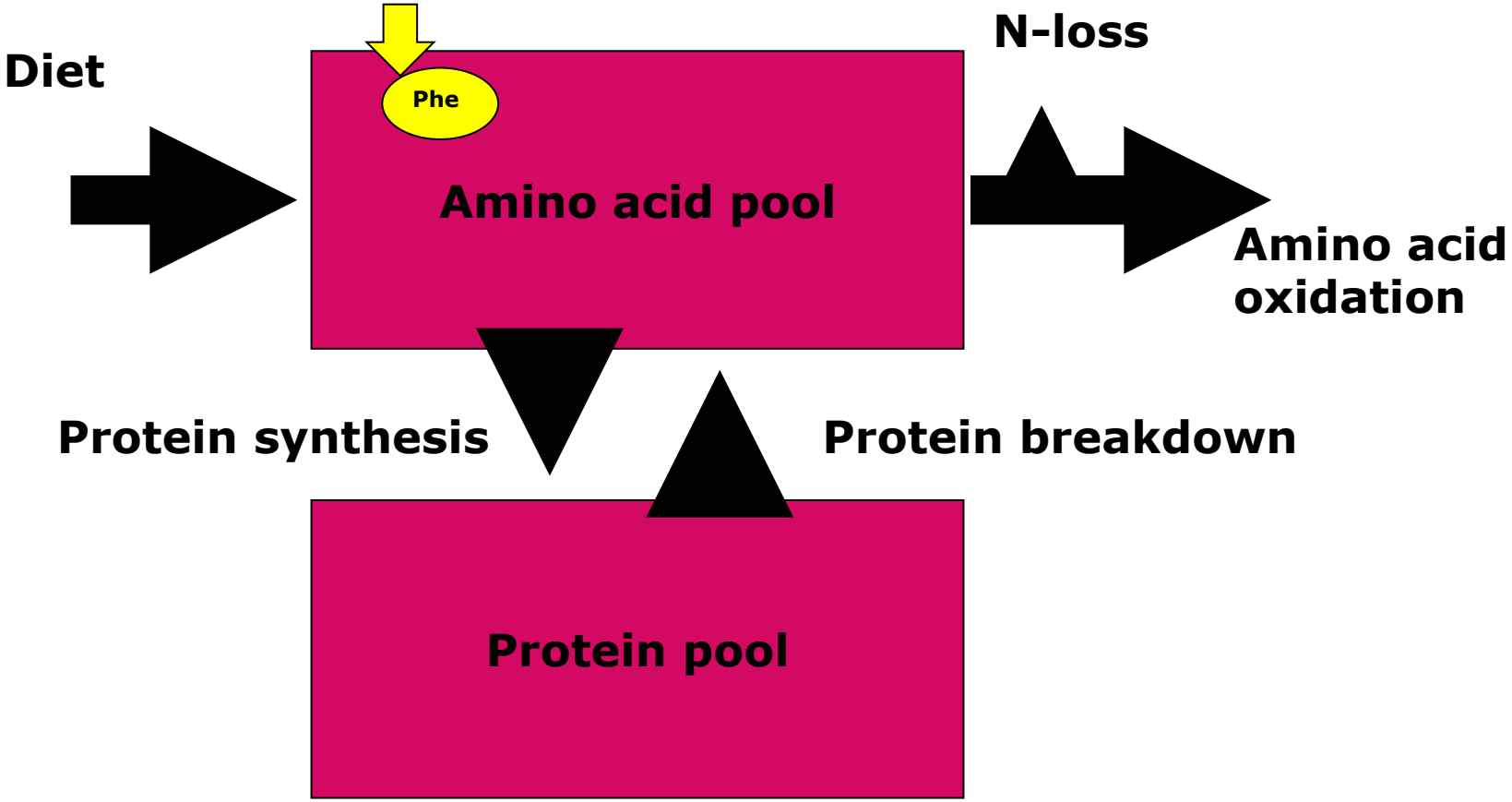
- Glucose production rates
- Gluconeogenesis rates
- Lipolysis rates
- Protein synthesis rates
- Daily energy expenditure
- NO synthesis rates
- DNA synthesis rates



Protein Turnover



Protein Turnover Measurements



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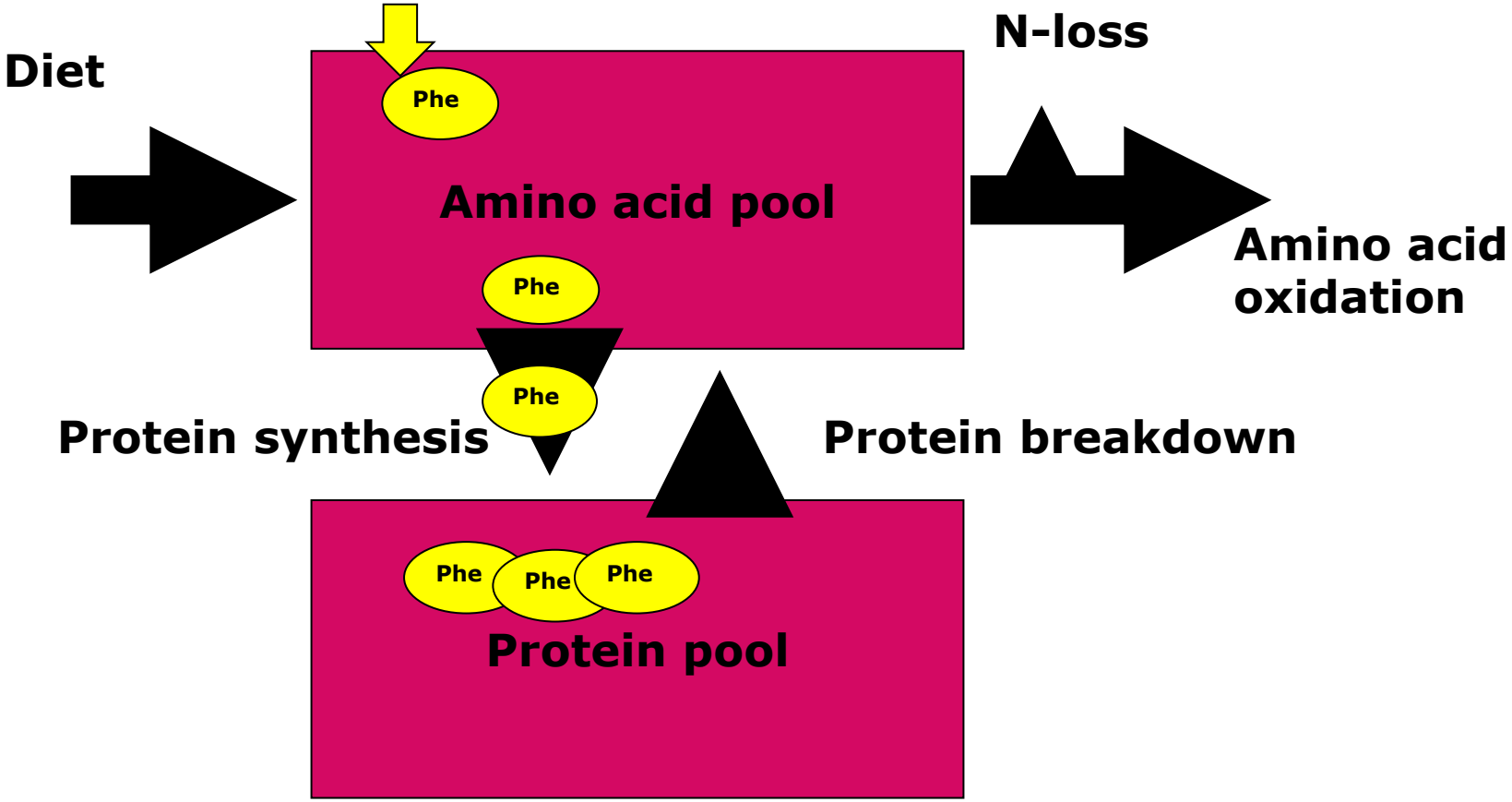

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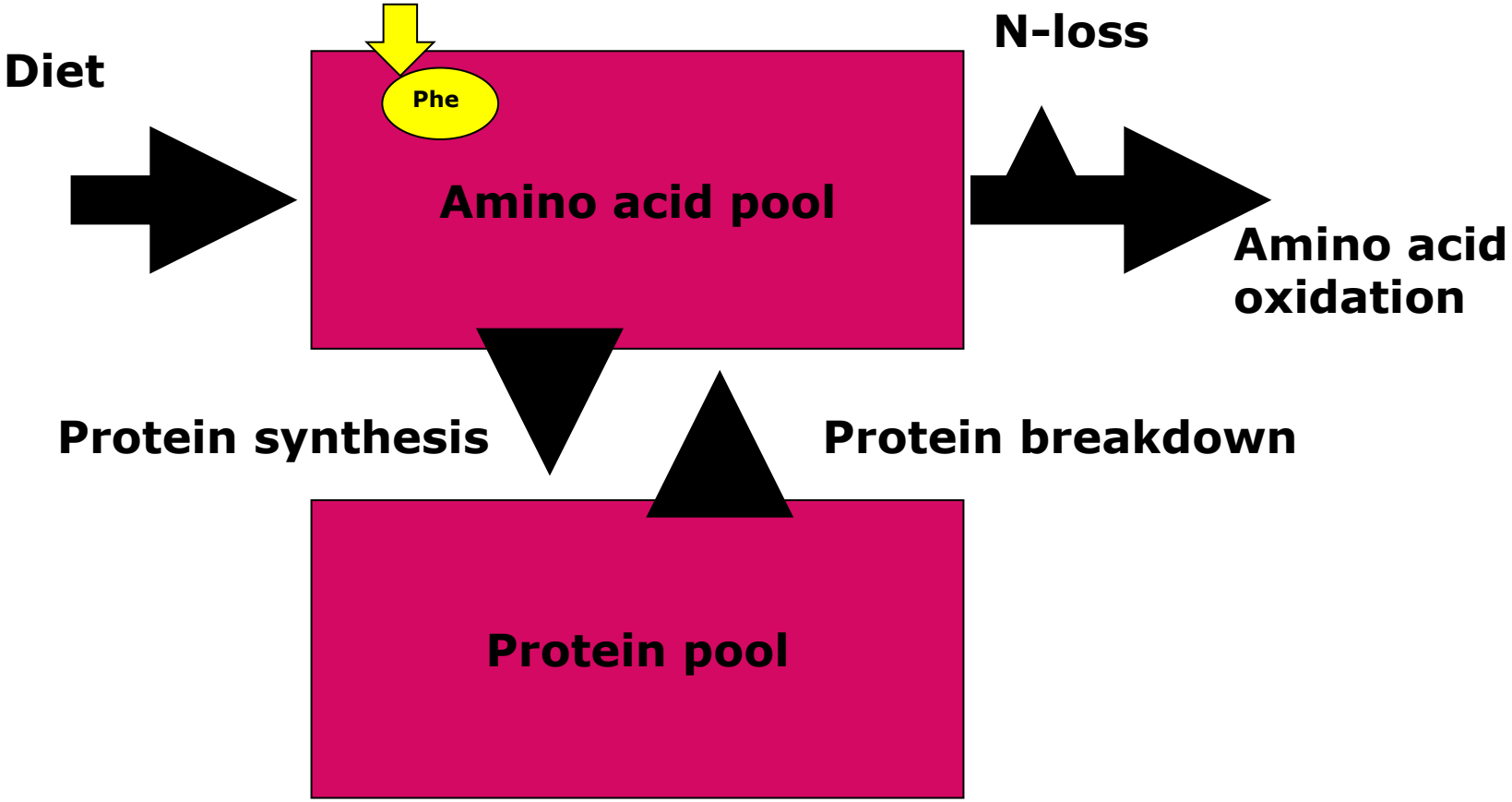

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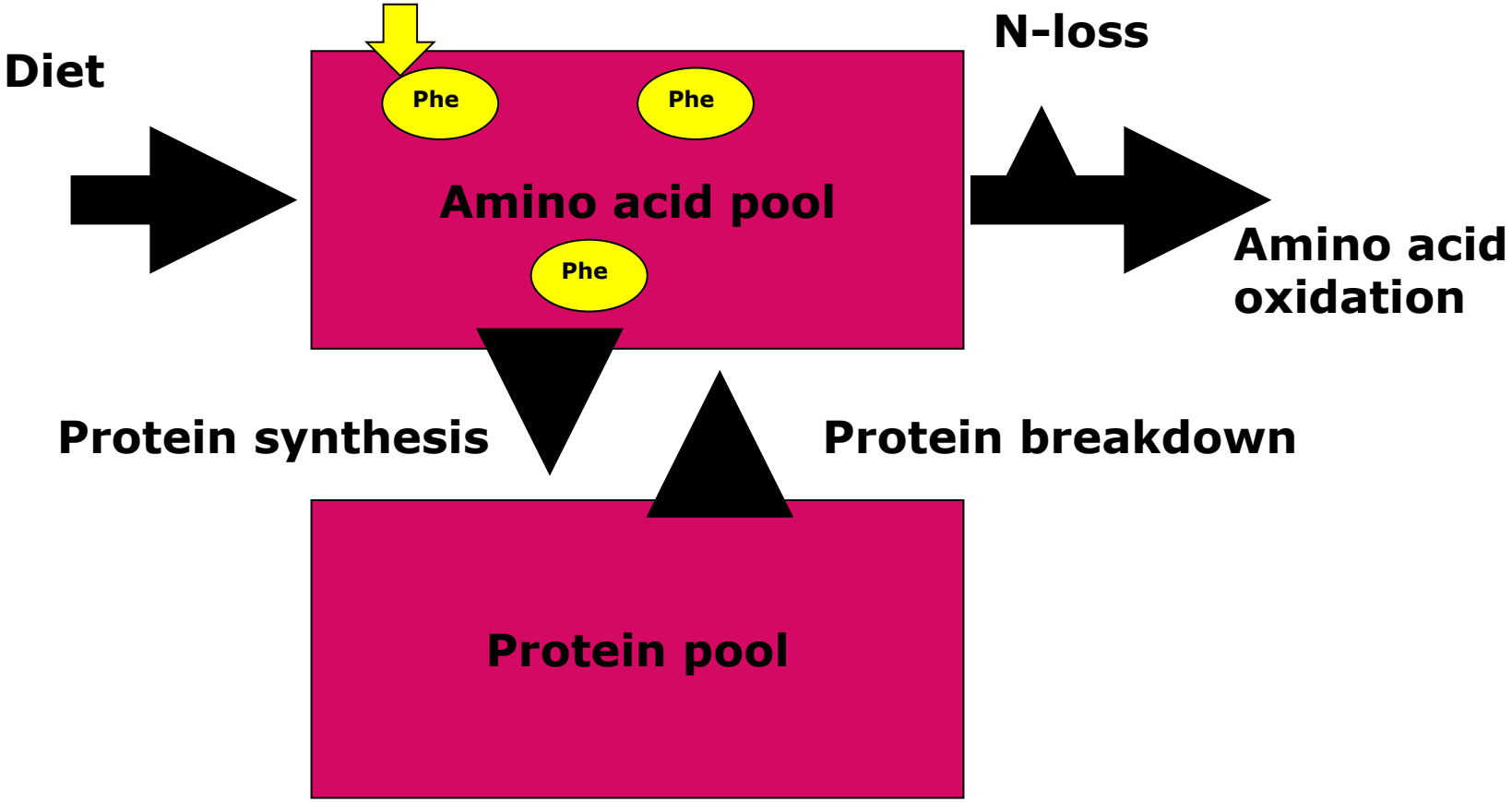

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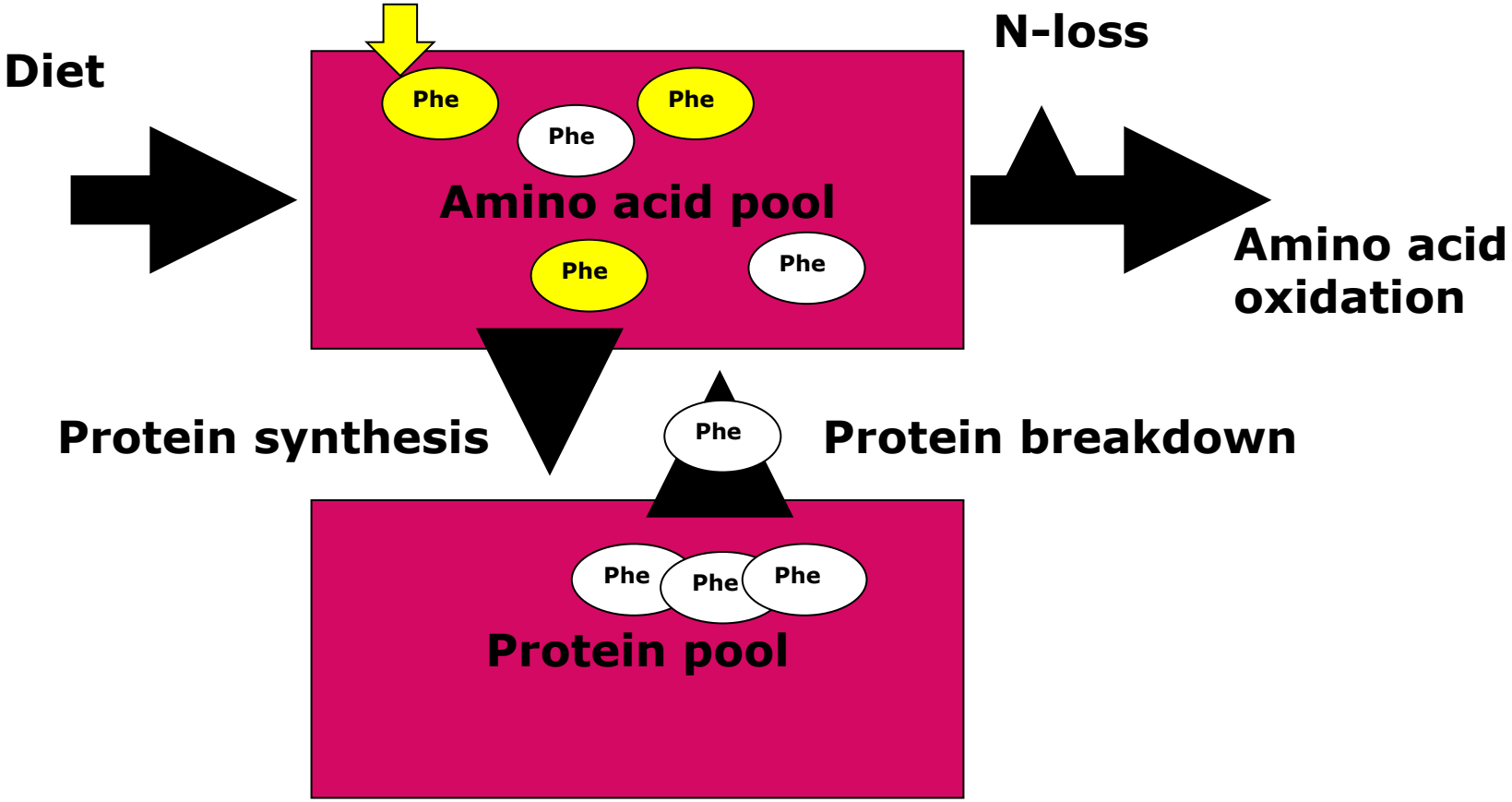
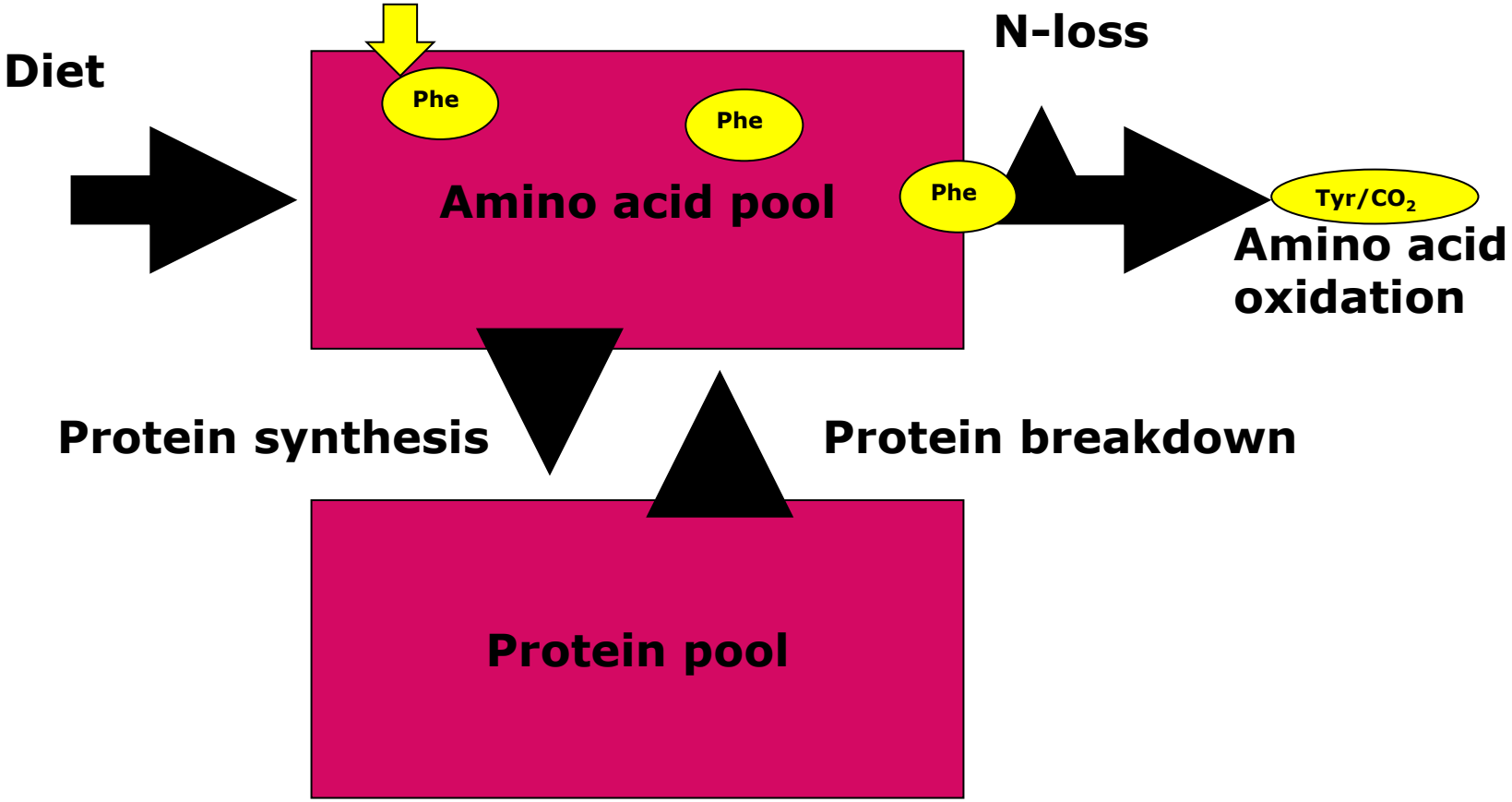
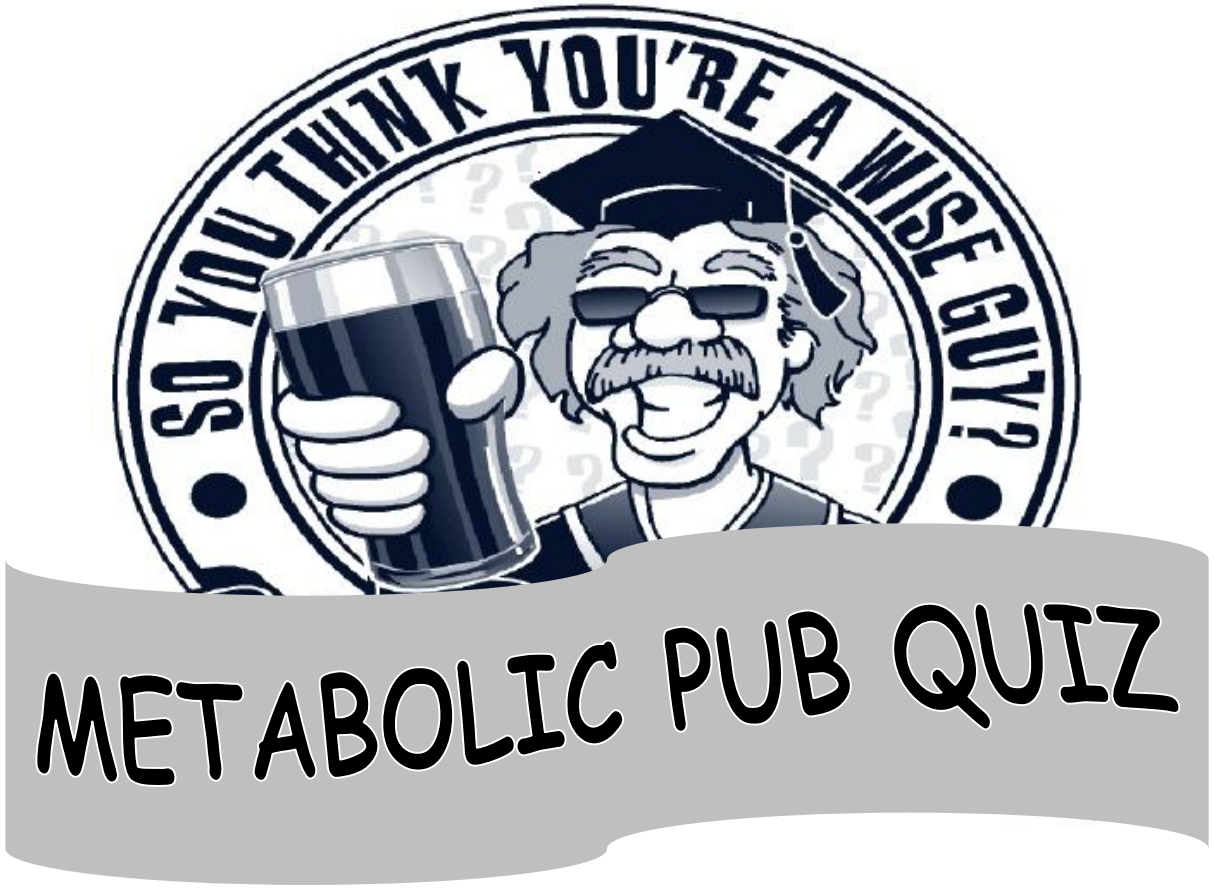
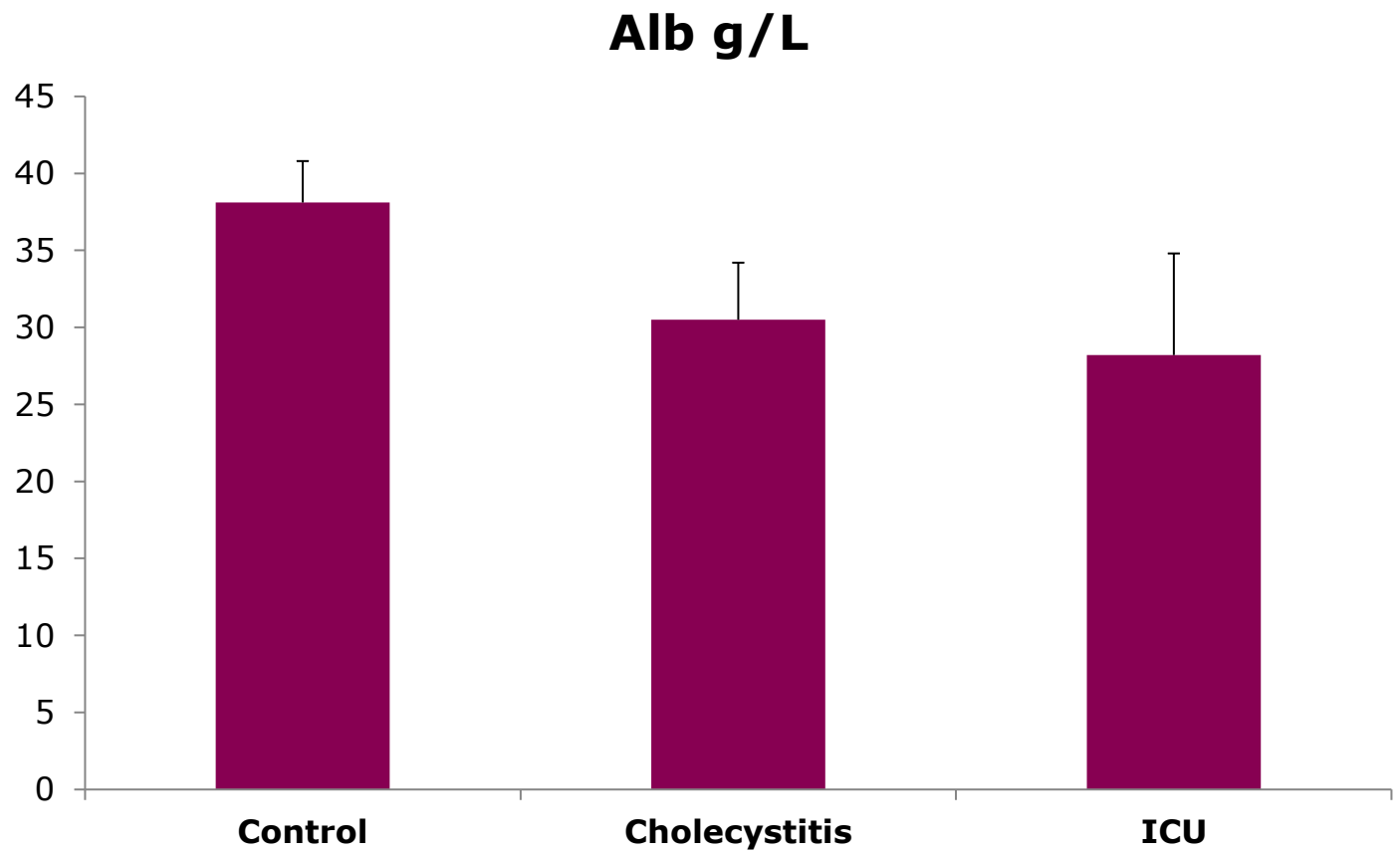


Protein Turnover Measurements




SO YOU THINK YOU'RE A WISE GUY?
METABOLIC PUB QUIZ

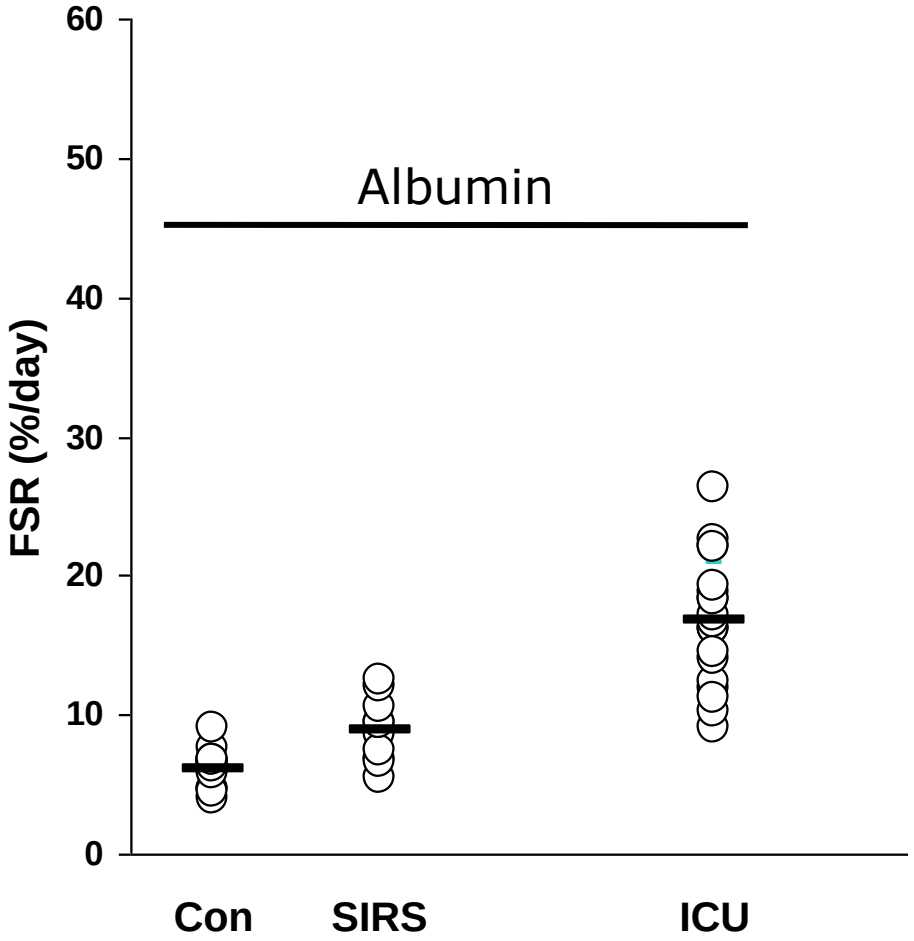
1. Albumin and inflammation



From: Barle et al ClinSci 2006;
Barle et al ICM 2001

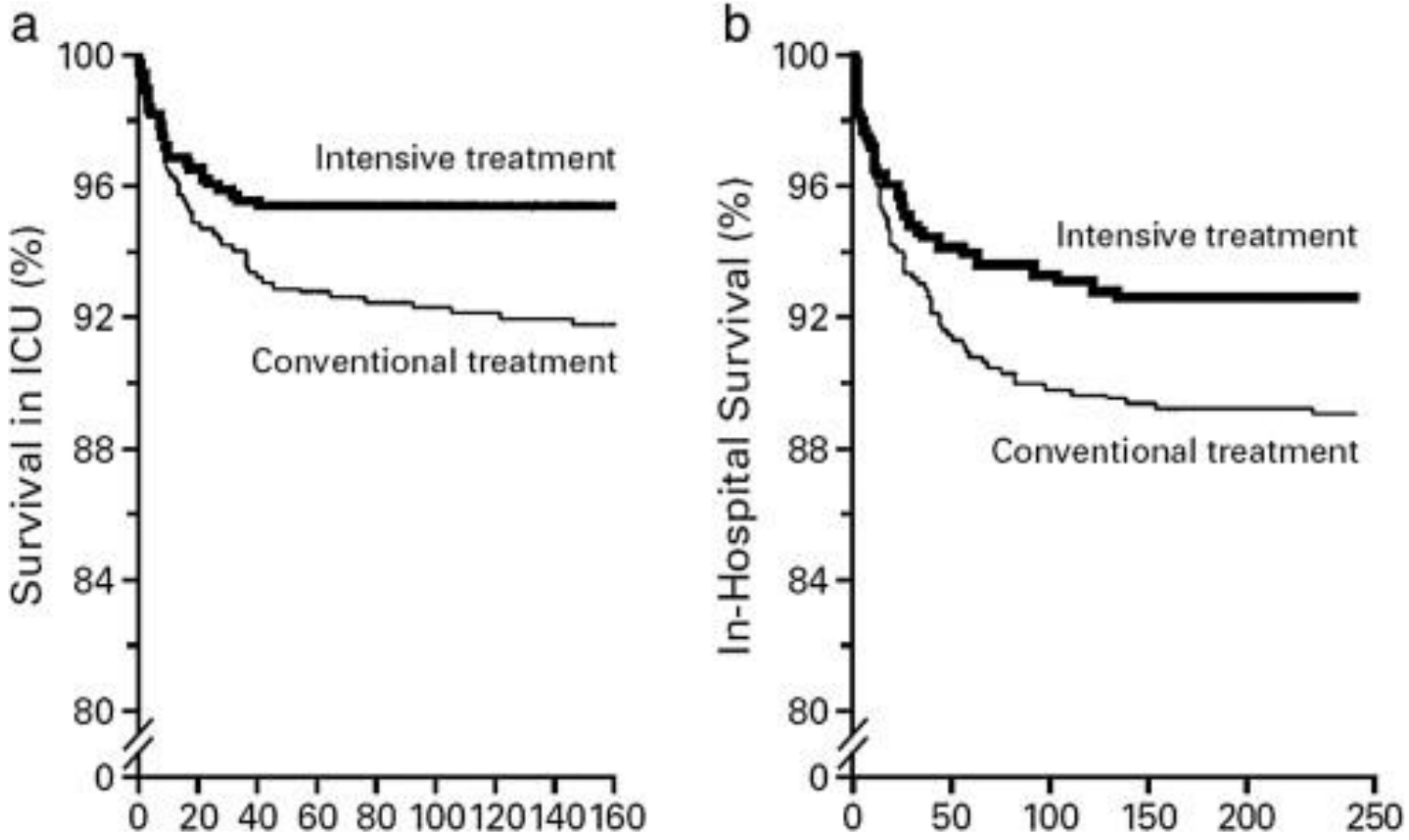
VEVOX QUESTION 1

- Low albumin levels during inflammation are the result of a decreased albumin synthesis?
  → YES
  → NO



From: Barle et al ICM 2001, Clin Sci 2006

2. Intensive insulin treatment in the ICU



From: VanderBerghe et al. NEJM 2001

VEVOX QUESTION 2

- Intensive insulin treatment in the ICU lowers glucose levels by increasing glucose uptake in muscle?
  → YES
  → NO

0021-972X/04/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 89(11):5382–5386

doi: 10.1210/jc.2004-1118

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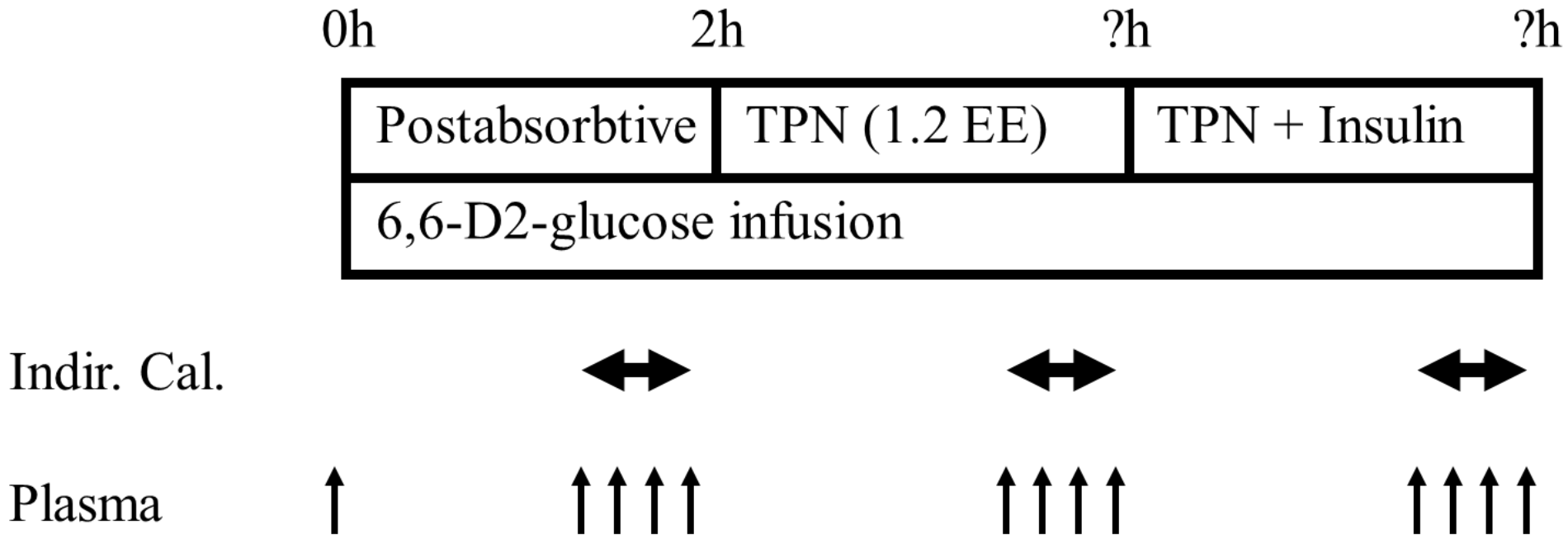

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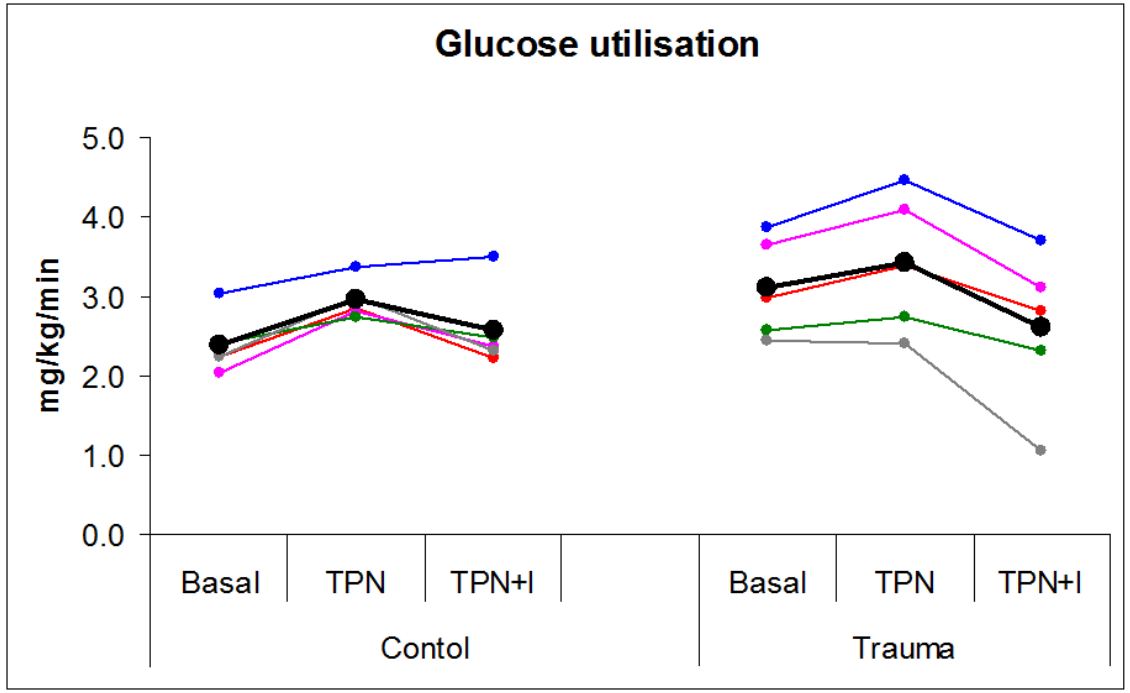
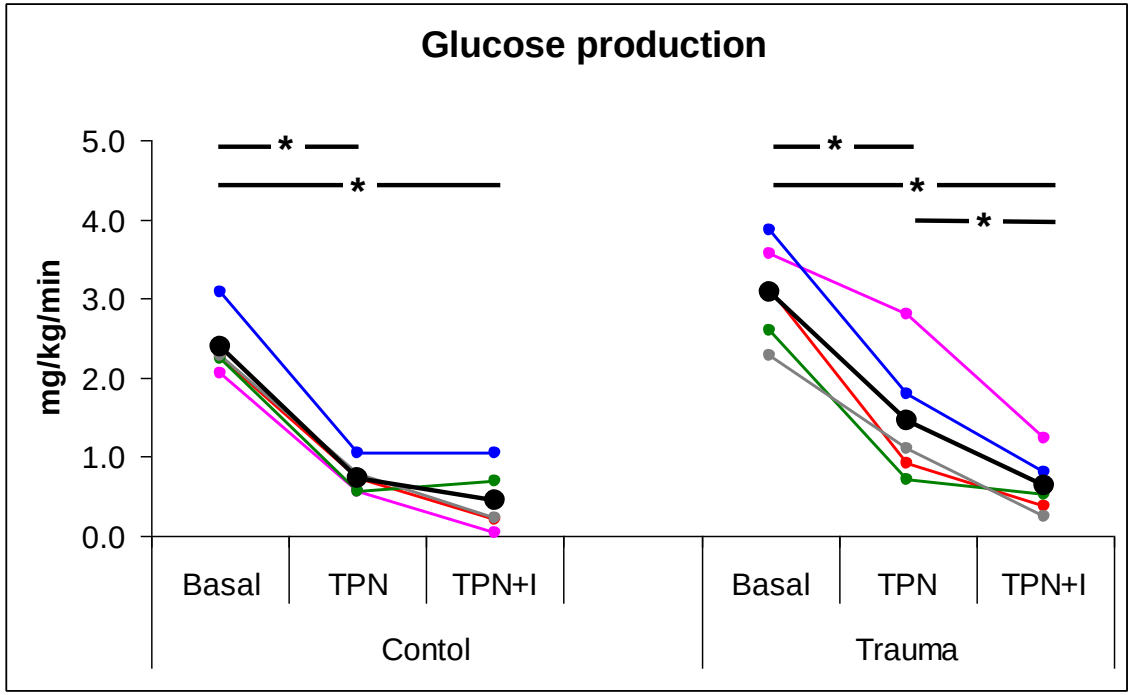
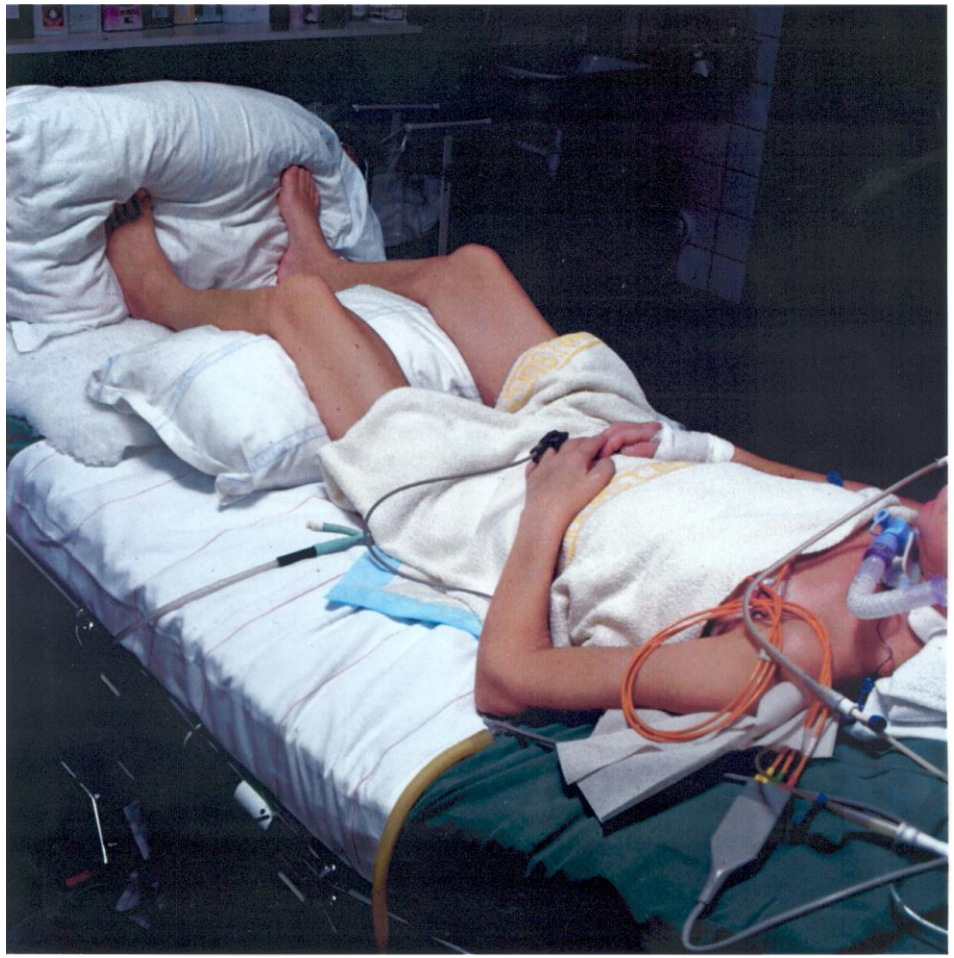
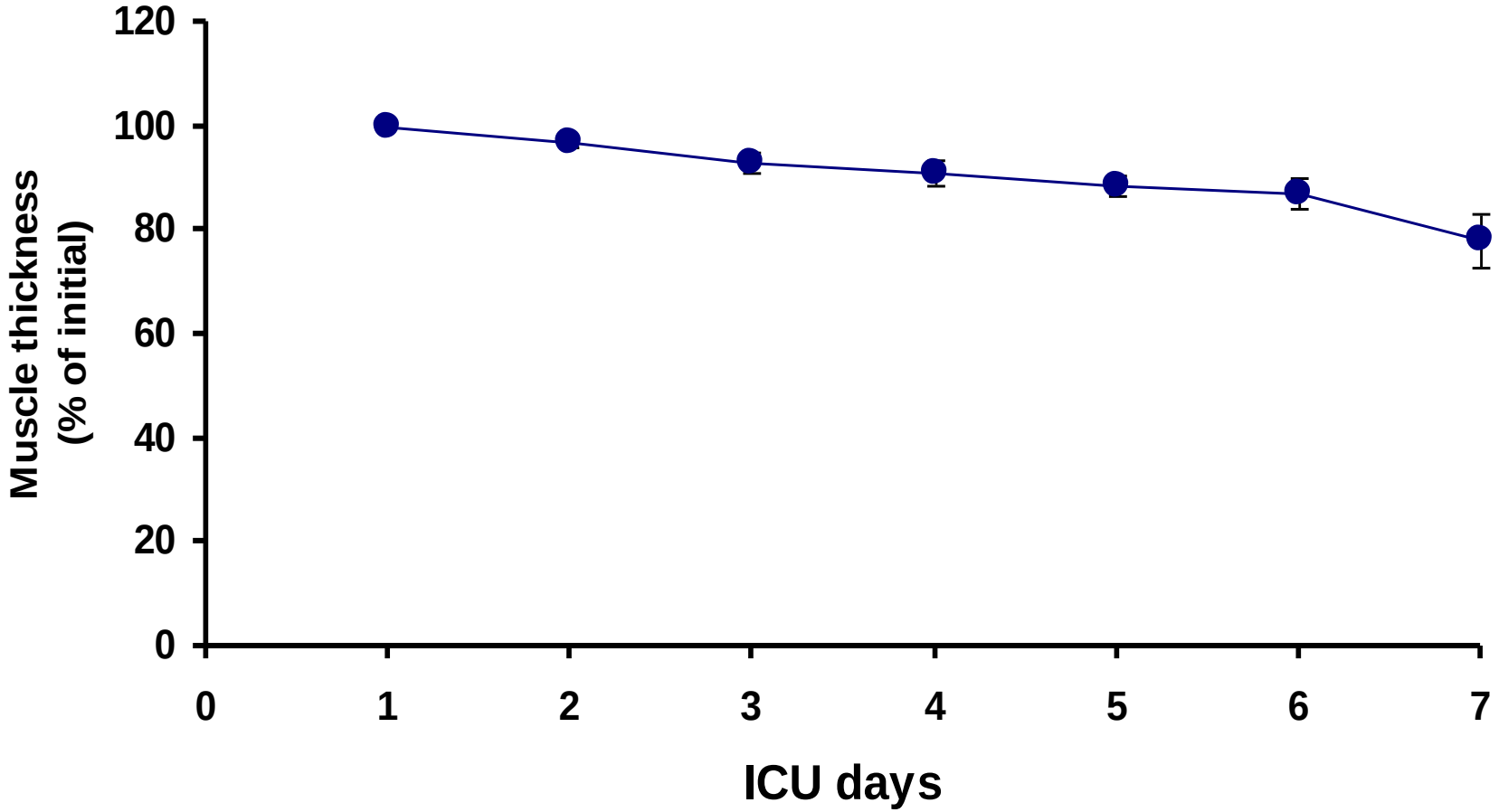




2. Muscle wasting during critical illness

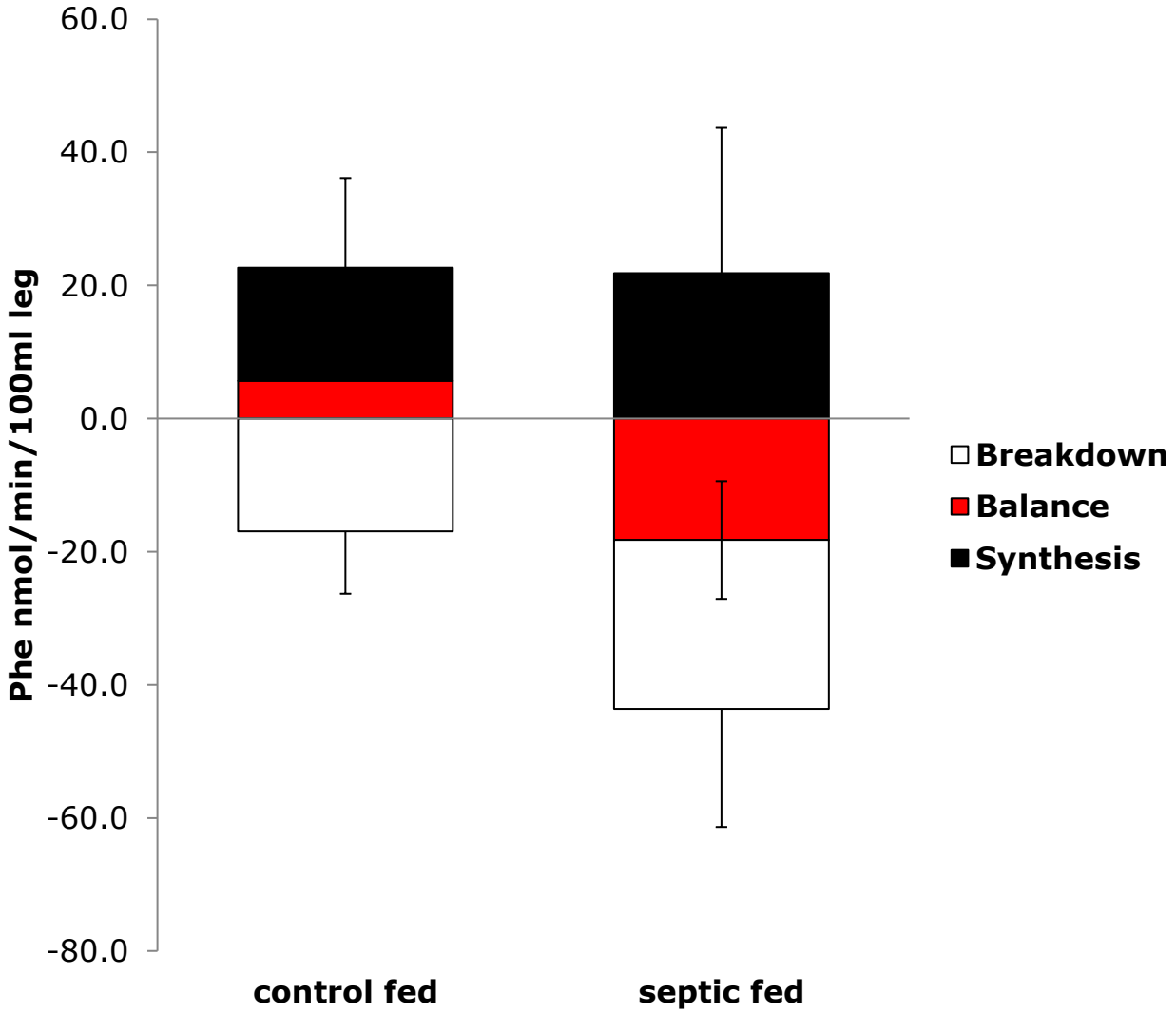




From: Reid et al, Clin Nutr 2004

VEVOX QUESTION 3

- Muscle wasting in ICU patients is due to a decreased protein synthesis?
  → YES
  → NO



From: Klaude et al Clin Sci 2011

Take home on Tiny Details.

- Pick the method most likely to answer your question
- Metabolomics is a growing field with lots of potential to predict outcome and find new pathways BUT be aware of the pitfalls
- Tracer methodology is the only way to quantify metabolic pathways in vivo BUT is expensive, needs specialised expertise and is limited to smaller studies

Wrapping up statistics

Prof. Tim Friede

FRESENIUS KABI
caring for life

JUMPstart Training Program

Statistics in planning and evaluating clinical trials: Wrapping up

Prof. Tim Friede

What happened so far … (what's next)

- **Some statistical concepts**
  - e.g. confidence intervals; hypothesis tests; hypothesis tests: multiple testing; stratification
- **Some concepts in clinical trials**
  - Randomization and treatment blinding
  - Cluster randomized trials
  - Sample size calculation and recalculation
  - Adaptive designs
  - Competing events

What’s next

- **Some (additional thoughts on) statistical concepts**
  - e.g. hypothesis tests: multiple testing; stratification
- **Some concepts in clinical trials**
  - Cluster randomized trials
  - Competing events

Hypothesis tests

- Null hypothesis H_0, e.g. no difference between two treatment groups (mean difference = 0, relative risk = 1, hazard ratio = 1, …)
- Error rates: Types I und II

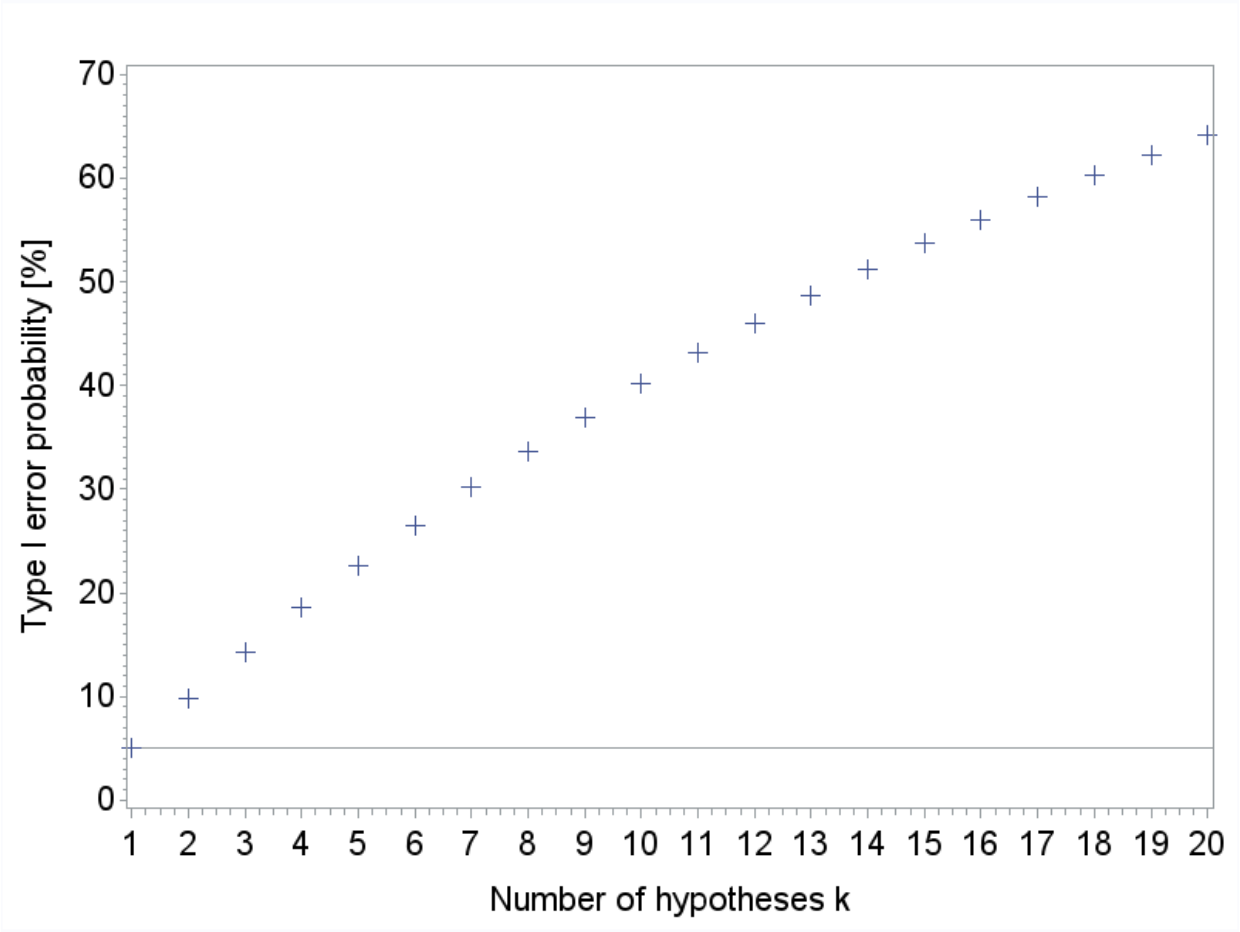
		Test decision	
		Do not reject	Reject
Truth (unknown)	H_0 true	Correct ✓	Type I error ✗
	H_0 false	Type II error ✗	Correct ✓

Why do we focus (usually) on a single primary outcome? Some comments on multiple testing

- Usual two-sided significance level $\alpha = 5\%$
- With several (k) independent hypothesis tests the acutual level increases (without appropriate adjustments) to

$$\alpha_{FWER} = 1 - (1 - \alpha)^k$$

- Methods for Type I error rate adjustments: Bonferroni, Benjamini-Hochberg, closed testing procedure, …



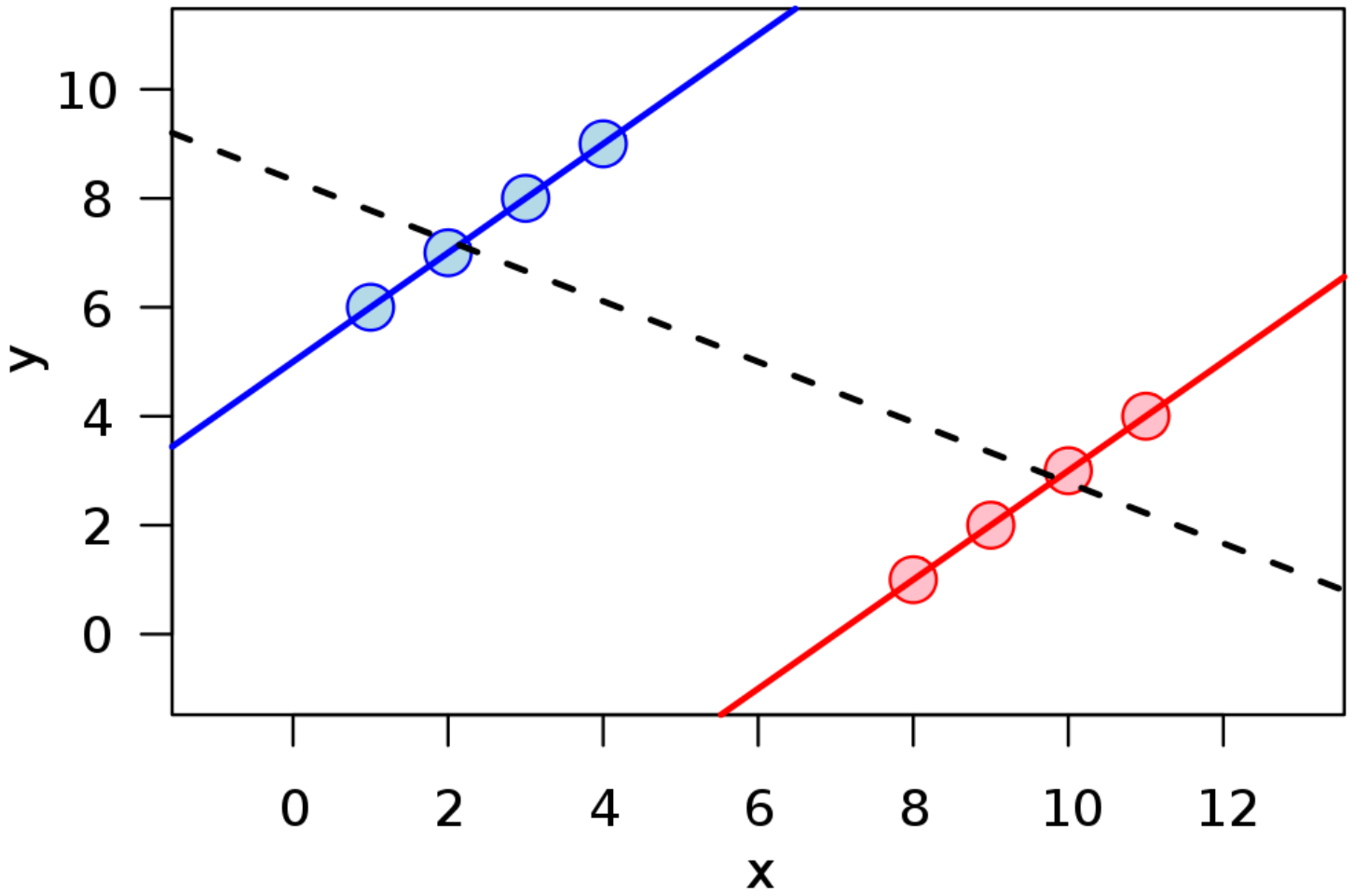
Bonferroni method

- **Applying the Bonferroni method**
  - The individual null hypotheses will be tested to an adjusted level of α/k, e.g. 1% with $\alpha = 5\%$ and $k = 5$ comparisons.
- **Properties of the Bonferroni method**
  - The probability that at least one null hypothesis is rejected erroneously is controlled at level α for any constellation of null hypotheses.
  - With many comparisons (large k) and correlated test statistics the Bonferroni method is conservative, i.e. the error probability above is much smaller than the nominal level α. Therefore, the statistical power is reduced.

Question to Audience

- We just said the Bonferroni method is conservative for large number of comparisons and correlated test statistics. Could you describe a situation with correlated test statistics?
  - (open question)

Simpson’s paradox



http://en.wikipedia.org/wiki/Simpson%27s_paradox

Key points so far

- **With several comparisons** the (familywise) type I error rate increases
- ***Methods for type I error rate adjustments*** including Bonferroni, Benjamini-Hochberg, closed testing procedure
- **Simpson's paradox** implies stratification of analyses (and also randomization in RCT)
- Typical situations for **stratification** include stratification for centre in multi-centre clinical trials or more generally important prognostic factors

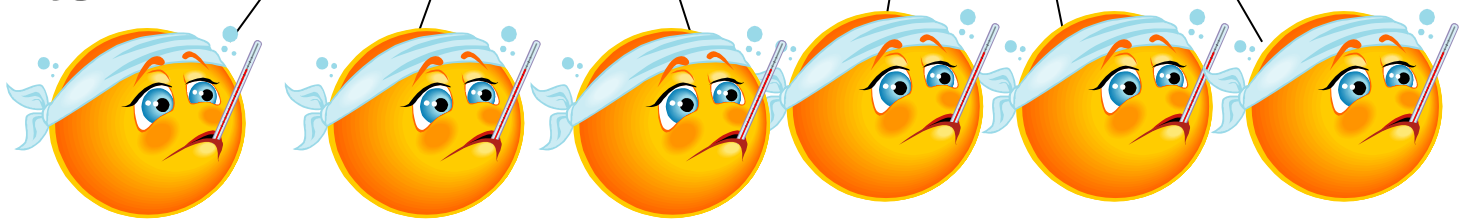
What’s next (outline)

- **Some statistical concepts**
  - e.g. confidence intervals, hypothesis tests
- **Some concepts in clinical trials**
  - Cluster randomized trials
  - Competing events

Cluster randomized trials

Care facility

Patients



...

Cluster randomized trials

- **Randomization of clusters** such as hospitals, wards, practices (and not subjects / patients)
- **Note:** all patients within the same cluster receive the same intervention
- Mainly two **reasons for cluster randomized trials**
  - Intervention on cluster level: health care research, e.g. training programme for health care processionals
  - To avoid “contamination”
- Reference: see e.g. Bland and Kerry (1997) BMJ https://doi.org/10.1136/bmj.315.7108.600

Cluster randomized trials: Consequences for design and analysis

- **Statistical analysis**
  - Hierarchical models (also known as multi-level models or mixed-effects models)
  - To account for correlation between observations within the same cluster
- **Sample size calculation**
  - Sample size ($n_{cluster}$) required in cluster randomized trial larger than sample size (n_{ind}) in trial with randomization of individual subjects

$$n_{cluster} = DE \times n_{ind}$$

  - ***Design effect*** (*DE*): depends on cluster size (*m*) and correlation (*rho*) between observations within the same cluster

$$DE = 1 + (m-1) \times rho$$

- Reference: see e.g. Kerry and Bland (1998) BMJ https://doi.org/10.1136/bmj.316.7130.549

Competing events

- **Event of interest:** aim to assess the risk (probability) of the occurence of a particular event (e.g. adverse event)
- **Competing event**: events that preclude the occurrence of the event of interest
- **Example**: Estimating the probability of headache, patients who die without prior headache report will never report headache. Therefore, death is a competing event with respect to the occurrence of headache.
- Reference: see e.g. Stegherr et al (2021) Biometrical Journal https://doi.org/10.1002/bimj.201900347

Assessing (adverse) event probabilities in the presence of varying follow-up times and competing events

- **Incidence proportion** (# patients with AE within time t / n)
  - Useful with identical follow-up times
  - Underestimates AE probability in the presence of censoring with varying follow-up times
- **1 - Kaplan-Meier** (censoring competing events)
  - Overestimates AE probability
  - 1-KM approximates a distribution function, i.e. assuming that eventually all patients experience the adverse event
- Reference: see e.g. Unkel et al (2019) Pharmaceutical Statistics https://doi.org/10.1002/pst.1915

Assessing adverse event probabilities in the presence of varying follow-up times and competing events

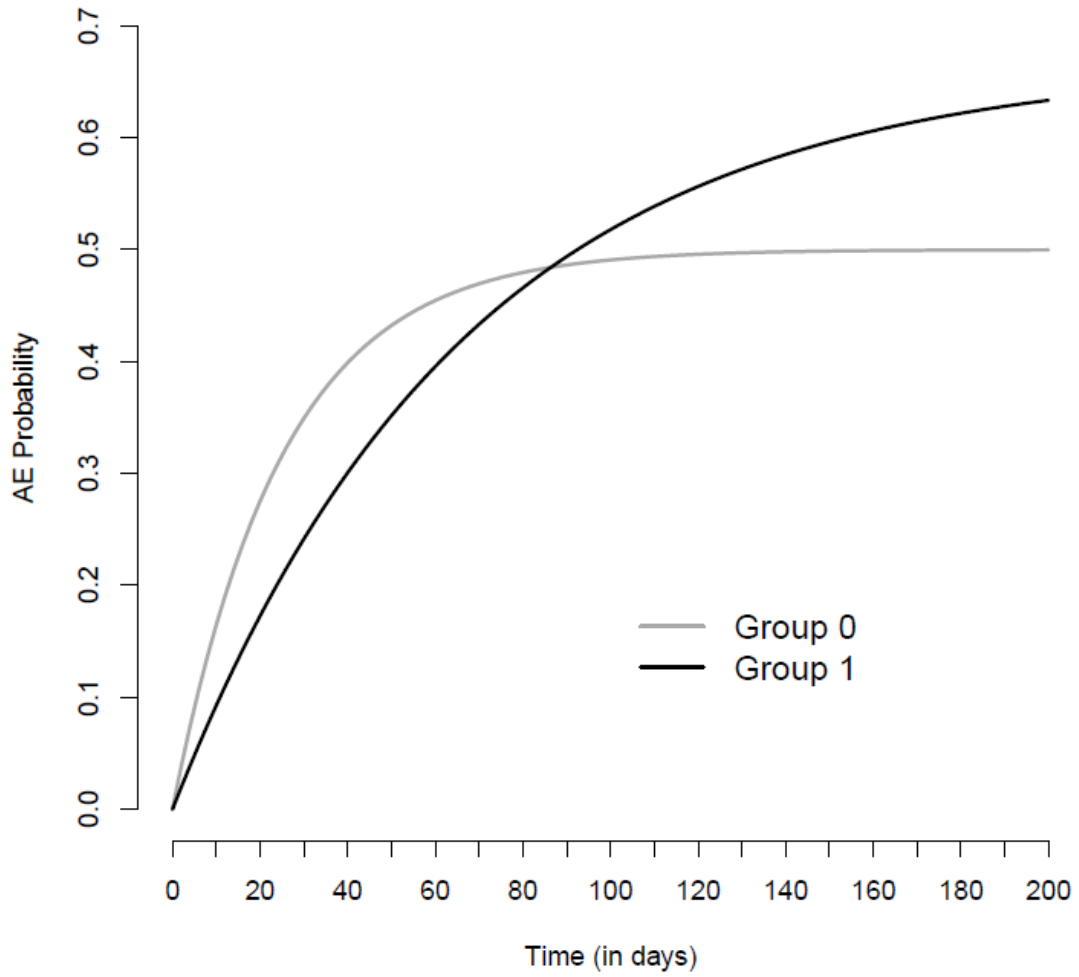


Figure 3 from Unkel et al (2019)

- In **group 0**, AE and competing event hazard rates set to 0.02 events per day, eventually leading to an AE probability of 1/2
- In **group 1**, the AE and competing event hazards reduced by factor of 0.5 and 0.25, respectively
- Although AE hazard in group 1 lower compared to group 0, the cumulative AE probability in group 1 is eventually greater than in group 0
- **Conclusion: need to model all events**

Summary points

- **Multiple testing**
  - **With several comparisons** the (familywise) type I error rate increases
  - ***Methods for type I error rate adjustments*** such as Bonferroni procedure
- **Stratification**
  - **Simpson's paradox** implies stratification of analyses (and also randomization in RCT)
  - Typical situations for **stratification** include stratification for centre in multi-centre clinical trials or more generally important prognostic factors
- **Cluster randomized trials**
  - Sometimes clusters need to be randomized rather than individuals
  - Implications for design and analysis due to **correlation between observations from the same cluster**
- **Competing events**
  - Need to be considered in the analysis of event probabilities
  - Ignoring competing events is likely to result in biased results

Applying for the JUMPstart research grant

Prof. Mette Berger
Dr. Anke Wenn

FRESENIUS KABI
caring for life

JUMPstart Program Advanced Module

Applying for the Research Grant

Explanation of research proposal requirements

Prof. Mette Berger & Dr. Anke Wenn

Applying for the JUMPstart research grant

- Scope of the JUMPSTART research grant
- Template for detailed research proposals
- Rating scheme
- Process and timelines
- Q&A session

SCOPE of the JUMPstart research grant

Terms and conditions for the JUMPSTART Research Grant

The research proposals should be aimed at developing new knowledge related to parenteral nutrition in critically in critically ill/ major surgery patients. They are to be centered on the evaluation of parenteral nutrition concepts to improve guidance to nutrition care these patient group.

Research proposals can come from the following areas:

- Basic research
- Translational research
- Clinical research

Applications to use PN in sensitive populations, e.g. children or pregnant women, are excluded.

Participation in both basic and advanced training module is a prerequisite for application to the research grant. The research proposal is to be submitted as a study synopsis by June 30th, 2021 and needs to contain the following contents.

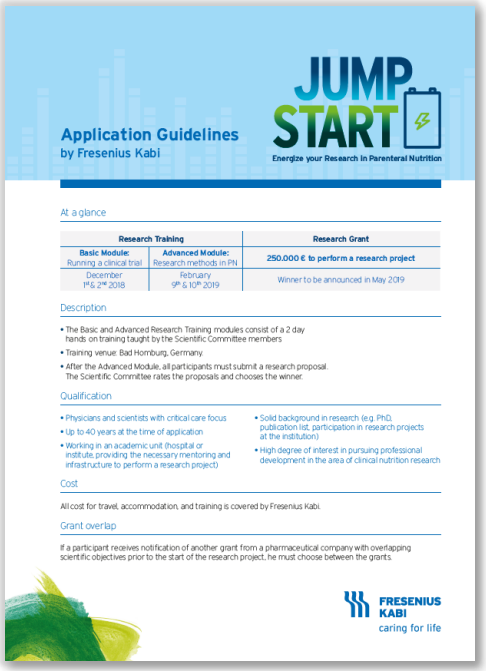
A Clear study hypothesis/research question

B Rationale and clinical significance of the hypothesis/research question, including references

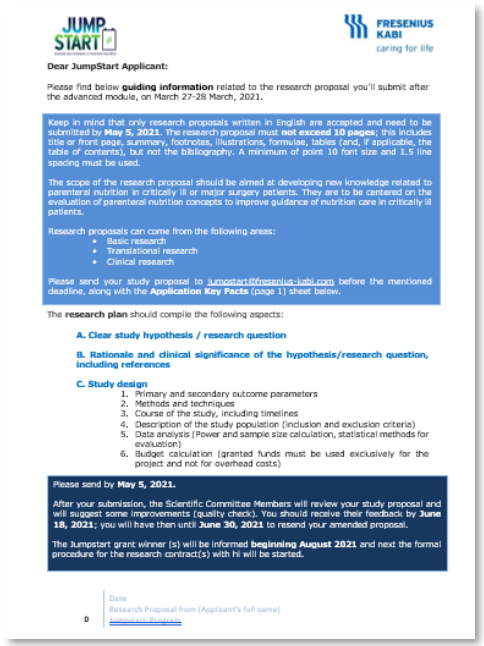
C Study design

- Primary and secondary outcome parameters
- Methods and techniques
- Course of the study, including timelines
- Description of the study population (inclusion- and exclusion criteria)
- Data analysis (Power and sample size calculation, statistical methods for evaluation)
- Budget calculation (granted funds must be used exclusively for the project and not for overhead costs)

JUMPstart Application guidelines



Template for Detailed Research Proposals (May 5, 2021)



JUMP START

FRESENIUS KABI
caring for life

Dear JumpStart Applicant:

Please find below **guiding information** related to the research proposal you'll submit after the advanced module, on March 27-28 March, 2021.

Keep in mind that only research proposals written in English are accepted and need to be submitted by **May 5, 2021**. The research proposal must **not exceed 10 pages**; this includes title or front page, summary, footnotes, illustrations, formulae, tables (and, if applicable, the table of contents), but not the bibliography. A minimum of point 10 font size and 1.5 line spacing must be used.

The scope of the research proposal should be aimed at developing new knowledge related to parenteral nutrition in critically ill or major surgery patients. They are to be centered on the evaluation of parenteral nutrition concepts to improve guidance of nutrition care in critically ill patients.

Research proposals can come from the following areas:

- Basic research
- Translational research
- Clinical research

Please send your study proposal to Jumpstart@fresenius-kabi.com before the mentioned deadline, along with the **Application Key Facts** (page 1) sheet below.

The **research plan** should compile the following aspects:

A. Clear study hypothesis / research question

B. Rationale and clinical significance of the hypothesis/research question, including references

C. Study design

1. Primary and secondary outcome parameters
2. Methods and techniques
3. Course of the study, including timelines
4. Description of the study population (inclusion and exclusion criteria)
5. Data analysis (Power and sample size calculation, statistical methods for evaluation)
6. Budget calculation (granted funds must be used exclusively for the project and not for overhead costs)

Please send by **May 5, 2021.**

After your submission, the Scientific Committee Members will review your study proposal and will suggest some improvements (quality check). You should receive their feedback by **June 18, 2021**; you will have then until **June 30, 2021** to resend your amended proposal.

The Jumpstart grant winner (s) will be informed **beginning August 2021** and next the formal procedure for the research contract(s) with hi will be started.

Date

Research Proposal from (Applicant's full name)

Appendix: Biography

- ✓ Guiding instructions
- ✓ **Page 1 Application Key Facts (1 pager)**
- ✓ **Page 2 Detailed Research Plan (max 10 pages)**

Detailed Research Proposals
Guiding Instructions

Only English applications accepted

Keep in mind that only research proposals written in English are accepted and need to be submitted by **May 5, 2021**. The research proposal must **not exceed 10 pages**; this includes title or front page, summary, footnotes, illustrations, formulae, tables (and, if applicable, the table of contents), but not the bibliography. A minimum of point 10 font size and 1.5 line spacing must be used.

1 Pager: application key facts

The scope of the research proposal should be aimed at developing new knowledge related to parenteral nutrition in critically ill or major surgery patients. They are to be centered on the evaluation of parenteral nutrition concepts to improve guidance of nutrition care in critically ill patients.

Max 10 pages, FONT size 10 + references

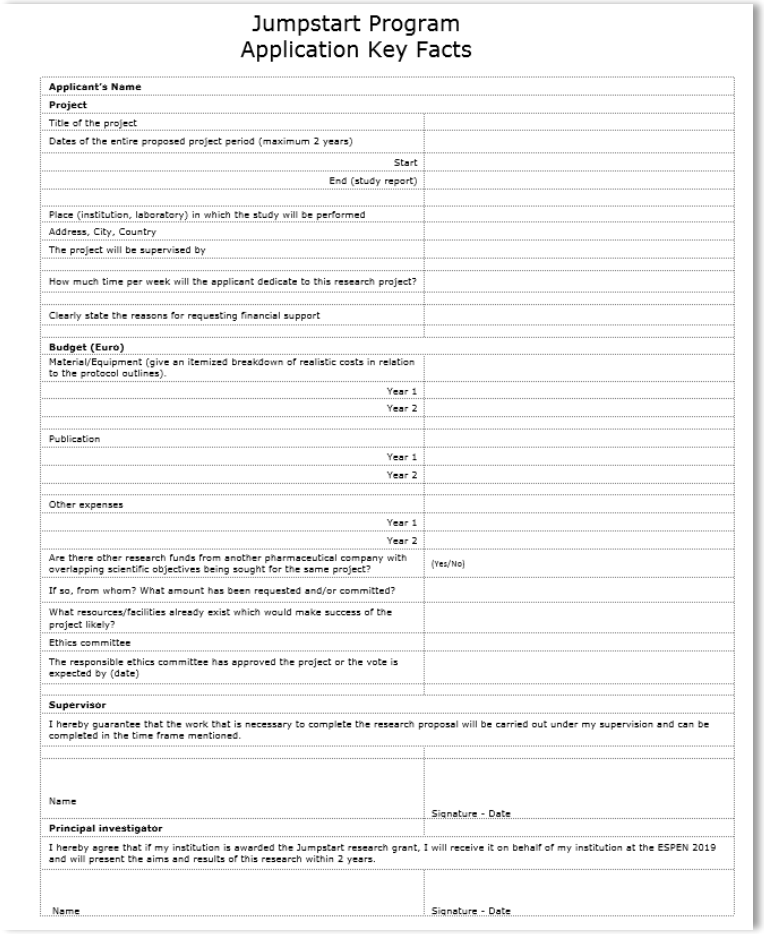
Research proposals can come from the following areas:

- Basic research
- Translational research
- Clinical research

Please send your study proposal to jumpstart@fresenius-kabi.com before the mentioned deadline, along with the **Application Key Facts** (page 1) sheet below.

Detailed Research Proposal

Application Key Facts (1 pager)



Jumpstart Program
Application Key Facts

Applicant's Name	
Project	
Title of the project	
Dates of the entire proposed project period (maximum 2 years)	
Start	
End (study report)	
Place (institution, laboratory) in which the study will be performed	
Address, City, Country	
The project will be supervised by	
How much time per week will the applicant dedicate to this research project?	
Clearly state the reasons for requesting financial support	
Budget (Euro)	
Material/Equipment (give an itemized breakdown of realistic costs in relation to the protocol outlines)	
Year 1	
Year 2	
Publication	
Year 1	
Year 2	
Other expenses	
Year 1	
Year 2	
Are there other research funds from another pharmaceutical company with overlapping scientific objectives being sought for the same project?	(Yes/No)
If so, from whom? What amount has been requested and/or committed?	
What resources/facilities already exist which would make success of the project likely?	
Ethics committee	
The responsible ethics committee has approved the project or the vote is expected by (date)	
Supervisor	
I hereby guarantee that the work that is necessary to complete the research proposal will be carried out under my supervision and can be completed in the time frame mentioned.	
Name	Signature - Date
Principal investigator	
I hereby agree that if my institution is awarded the Jumpstart research grant, I will receive it on behalf of my institution at the ESPEN 2019 and will present the aims and results of this research within 2 years.	
Name	Signature - Date

1 Pager:
application key facts

- Name
- Project
- Budget & timelines
- Supervisor
- Investigator
- Signatures

Detailed Research Plans

Content of research plan (Max 10 pages)

My detailed Research Plan
max 10 pages +
references

The **research plan** should compile the following aspects:

A. Clear study hypothesis / research question

B. Rationale and clinical significance of the hypothesis/research question, including references

C. Study design

1. Primary and secondary outcome parameters
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Applying for the JUMPstart research grant

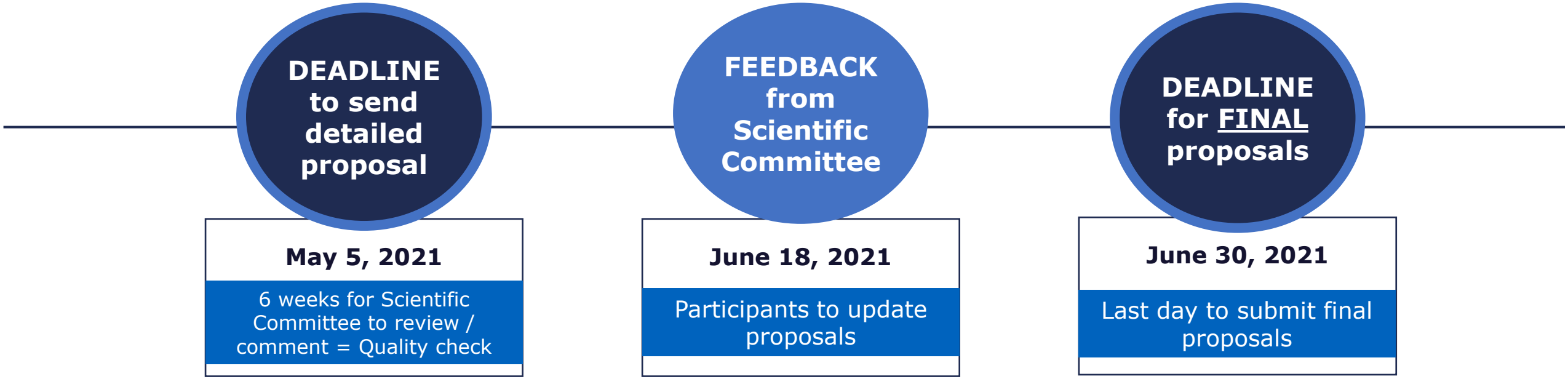
- Scope of the JUMPSTART research grant
- Template for detailed research proposals
- **Rating scheme**
- **Process and timelines**
- Q&A session

Evaluation grid used by the Scientific Committee

Project content assessment criteria	Evaluation				
Originality	20%				
The study idea is innovative and original.	2	4	6	8	10
The proposal approaches the research question in a clever and pragmatic way.	2	4	6	8	10
Scientific validity and feasibility	40%				
The hypothesis and objectives are clearly defined	2	4	6	8	10
The study design approaches the research question in an appropriate way.	2	4	6	8	10
The methods and techniques are clearly defined and appropriate.	2	4	6	8	10
The sample size is determined based on an adequate formula	2	4	6	8	10
The described patient population obtains a sufficient homogeneity	2	4	6	8	10
The described patient population seems feasibly to recruit within the time frame planned.	2	4	6	8	10
Anticipated statics tests are suitable	2	4	6	8	10
The budget calculations seem complete and realistic.	2	4	6	8	10
Clinical impact	40%				
The study is relevant for a large patient population.	2	4	6	8	10
The study addresses relevant clinical endpoints.	2	4	6	8	10
The study may impact clinical decision making.	2	4	6	8	10
The study is easy to implement in clinical practice.	2	4	6	8	10

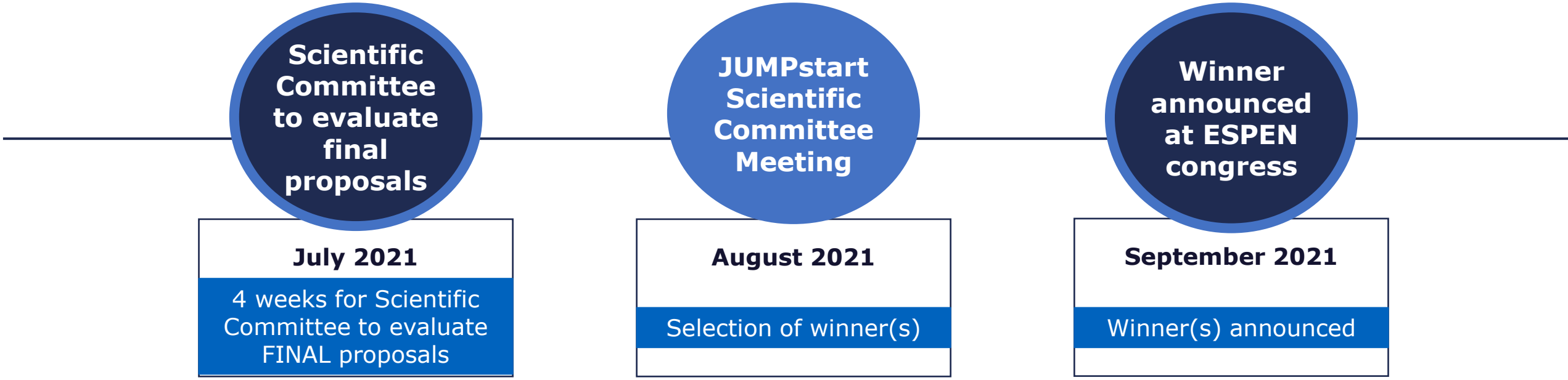
TIMELINES & PROCESS for review of Research Proposals

Submisson of 'Detailed Research Proposals'



TIMELINES & PROCESS after the final submissions

Final evaluation of proposals & selection of GRANT winner(s)



Important documents