TUSCANY CRITICAL CARE

NUTRIZIONE ARTIFICIALE ED IMMUNONUTRIZIONE NEL PAZIENTE CRITICO

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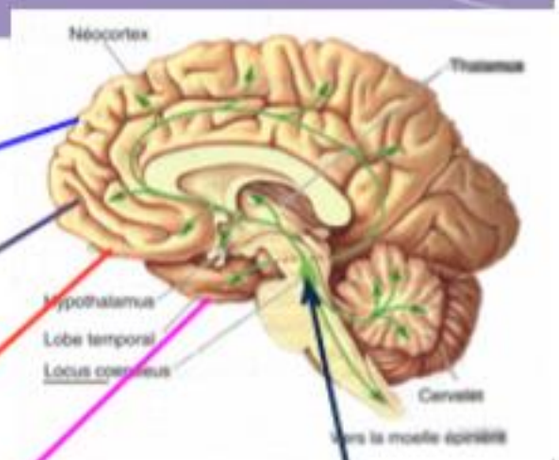
UCL

AZIENDA OSPEDALIERA SANTA MARIA TERNI

Typical course of the metabolic response to stress



Secondi minuti

Sistema nervoso simpatico
recettori adrenergici,
midollare surrenale

Ore

Asse ipotalamo ipofisario
ACTH,THS,GH,FSH,LH
Adiponectine (leptina, resistina, adiponectina)
Enteroormoni (peptide YY&CCK, ghrelina)

Fattore di stress

Giorni

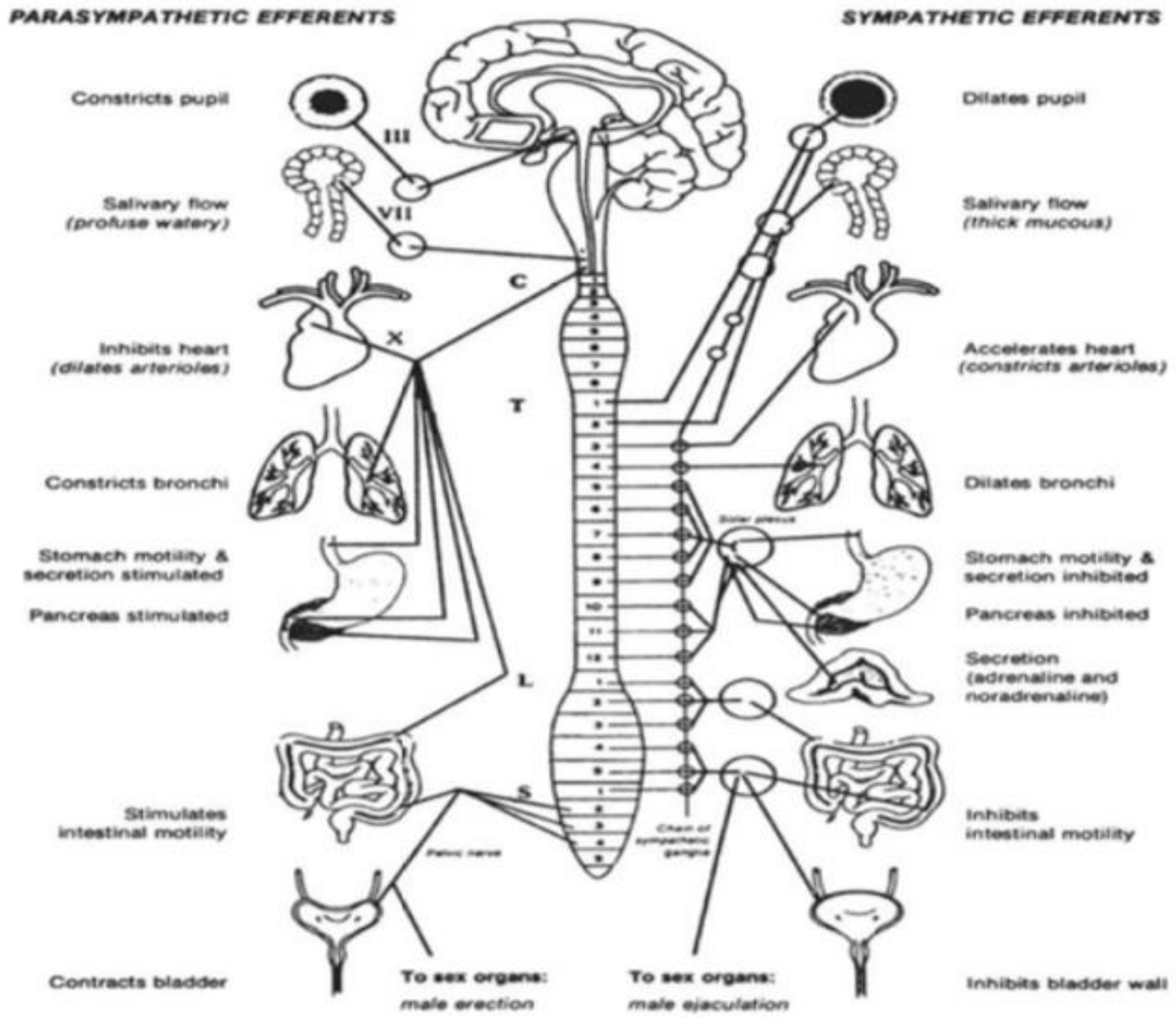
Infiammazione
Sistema immunitario
Citochine, mediatori
Stress ossidativo

Settimane /mesi

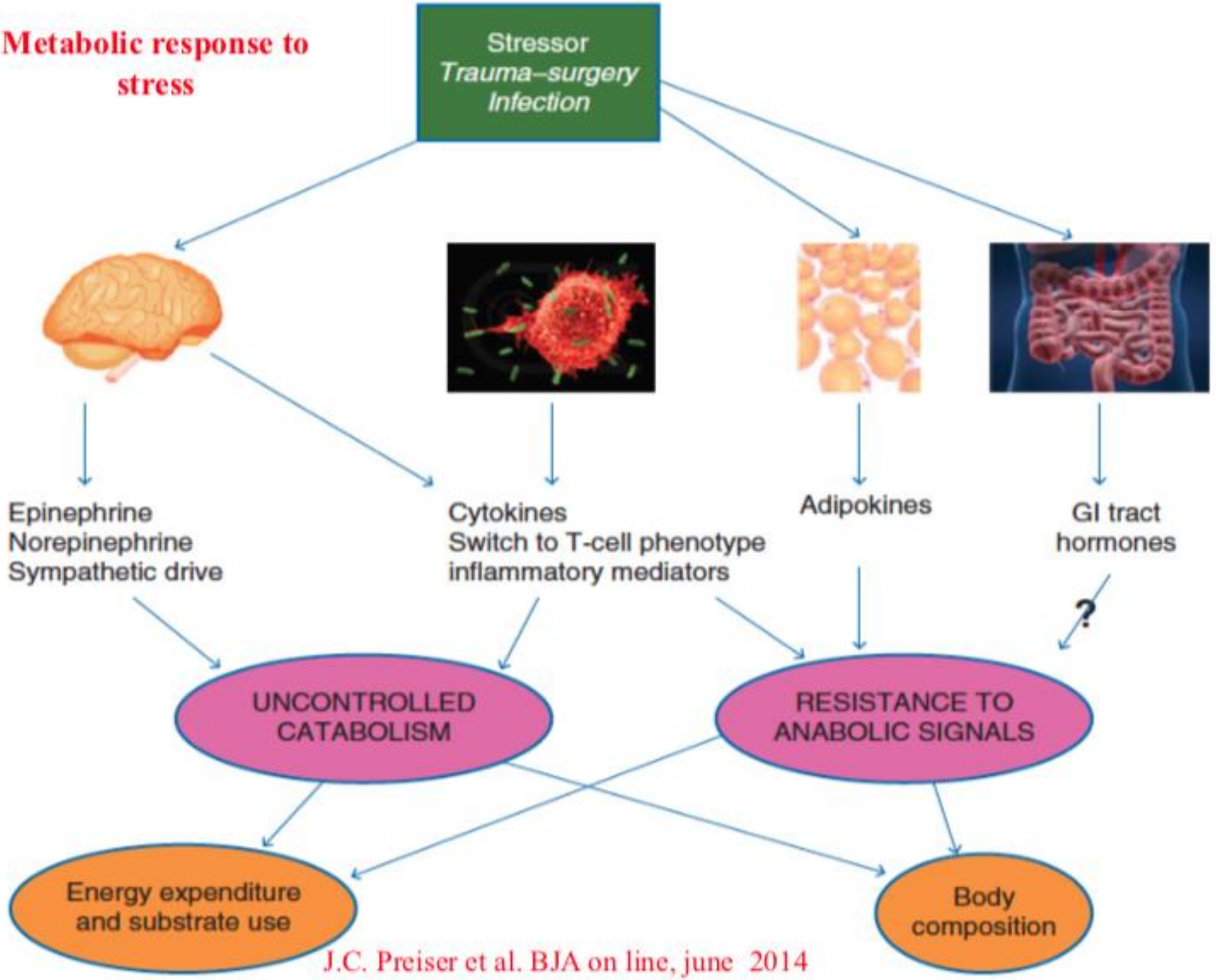
Comportamentale
Anoressia, prolungato

Table 2.4 Effects of adrenal medullary axis stimulation

Increased arterial blood pressure
Increase blood supply to brain (moderate)
Increased heart rate and cardiac output
Increased stimulation of skeletal muscles
Increase plasma free fatty acids, triglycerides, cholesterol
Increased release of endogenous opioids
Decreased blood flow to kidneys
Decreased blood flow to gastrointestinal system
Decreased blood flow to skin


PARASYMPATHETIC EFFERENTS
SYMPATHETIC EFFERENTS
Constricts pupil
Dilates pupil
III
Salivary flow
(profuse watery)
VII
Salivary flow
(thick mucous)
C
X
Inhibits heart
(dilates arterioles)
Accelerates heart
(constricts arterioles)
T
Constricts bronchi
Dilates bronchi
Stomach motility &
secretion stimulated
Stomach motility &
secretion inhibited
Pancreas stimulated
Pancreas inhibited
Secretion
(adrenaline and
noradrenaline)
L
S
Stimulates
intestinal motility
Inhibits
intestinal motility
Contracts bladder
To sex organs:
male erection
To sex organs:
male ejaculation
Inhibits bladder wall

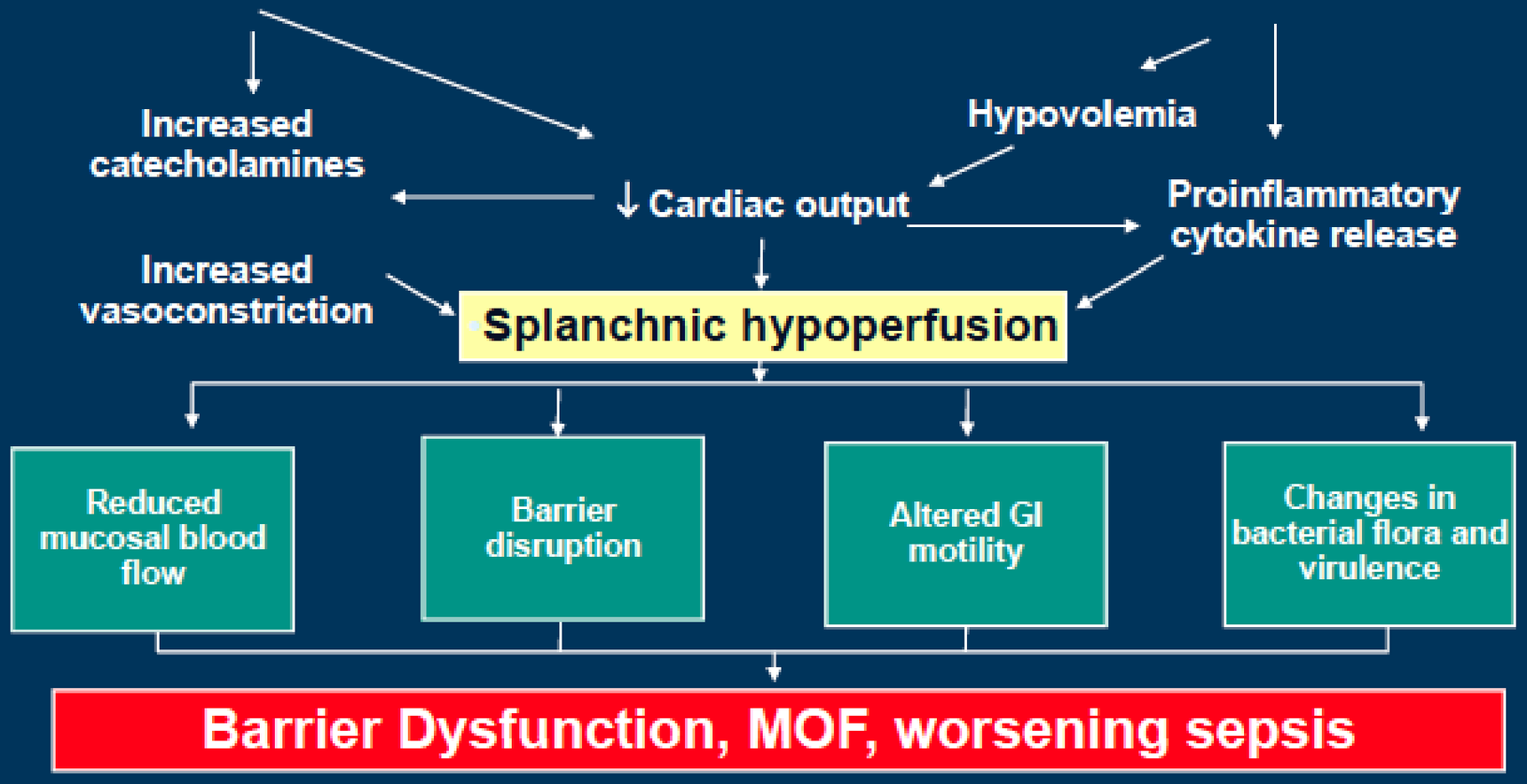
Metabolic response to stress



J.C. Preiser et al. BJA on line, june 2014

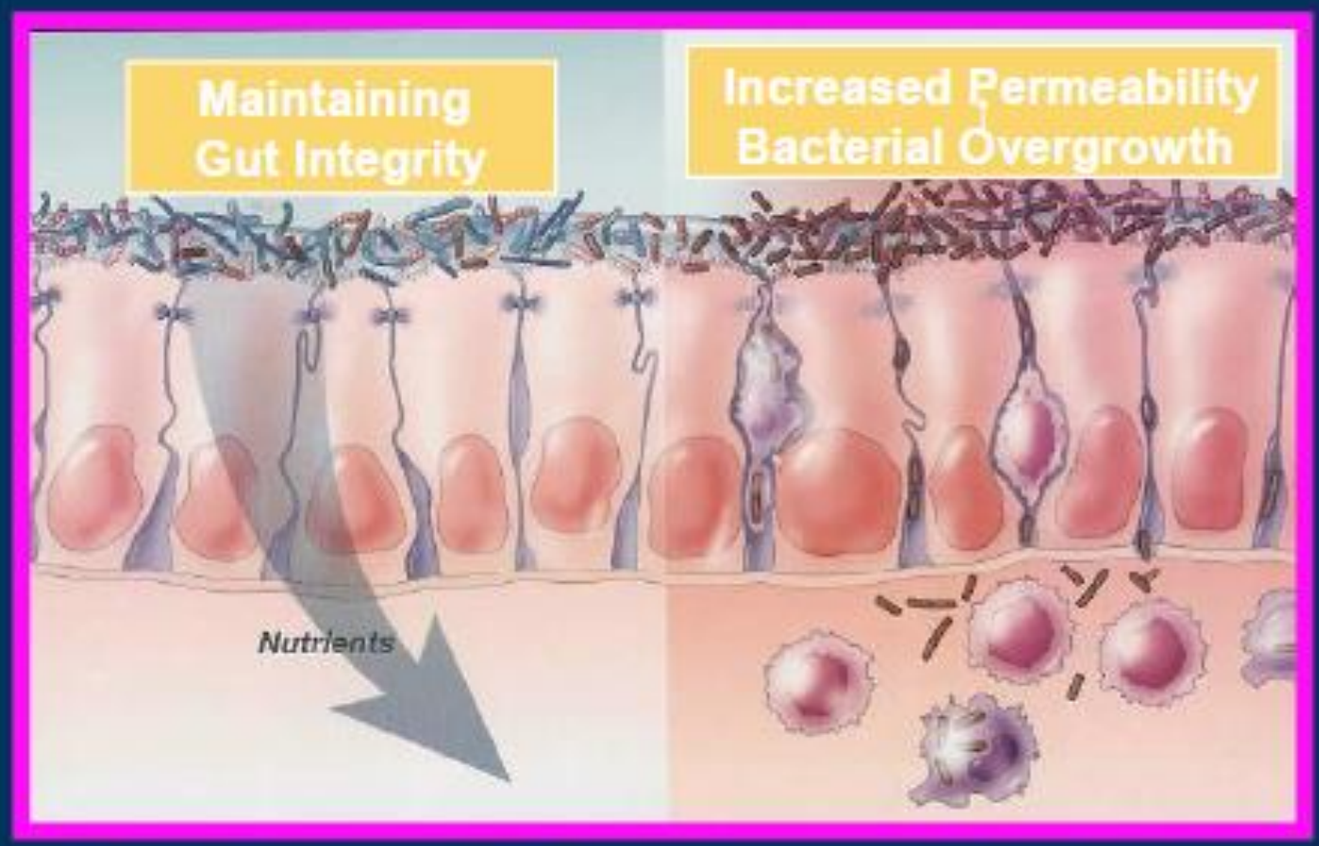
Pathophysiology of Splanchnic Hypoperfusion

ICU admission – sepsis- trauma- shock



•Schmidt H, Martindale R. *Curr Opin Nutr Metab Care*. 2003;6:587-591. Mutlu GM, et al. *Chest*. 2001;119:1222-1241.

Gut Integrity



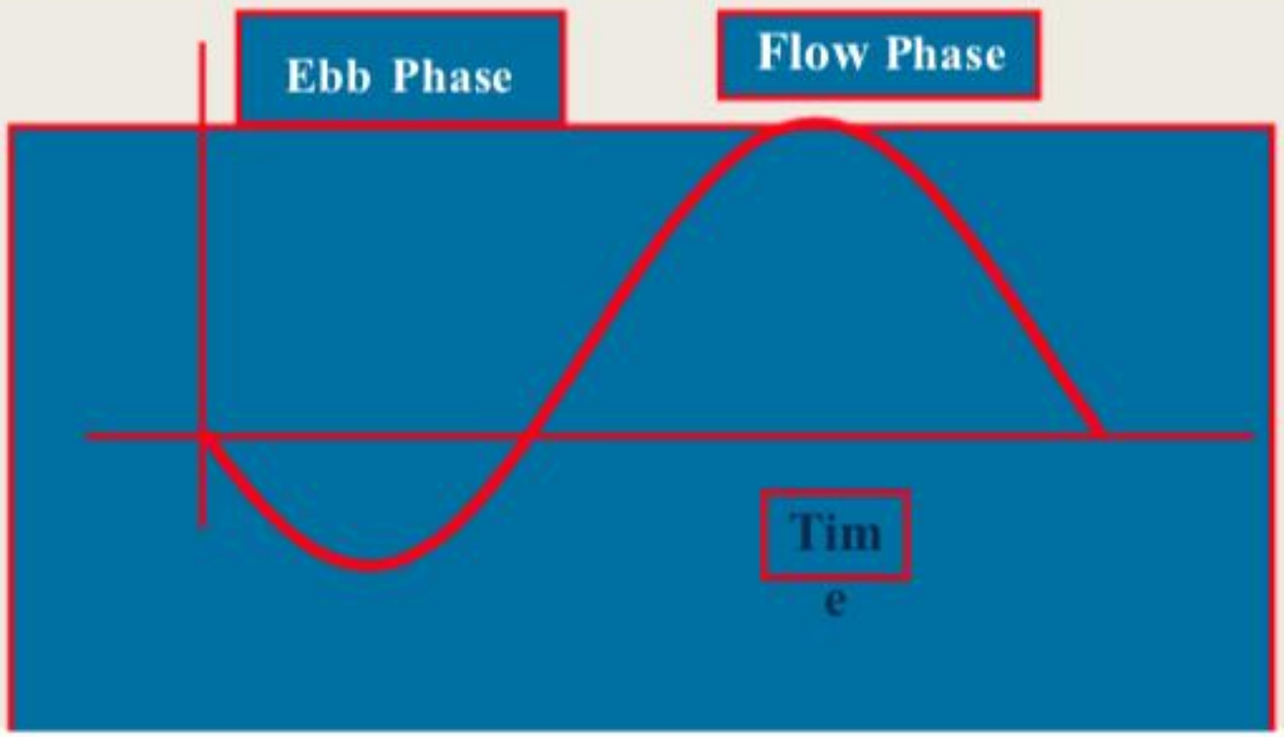
- Early EN maintains gut integrity, prevents bacterial overgrowth
- Increased gut permeability linked to MOF and disease severity [1]
- Bacterial translocation to MLNs, peritoneum, blood in sepsis [2]
- Sepsis dose Pseudomonas, Staph, E Coli : gut << IV [3]

[1] Ammori (J Gastrointest Surg 1999;3:252) [2] Ljungqvist (J Trauma 2000;48:314)
[3] Alverdy (J Leuko Biol 2008:83:461)

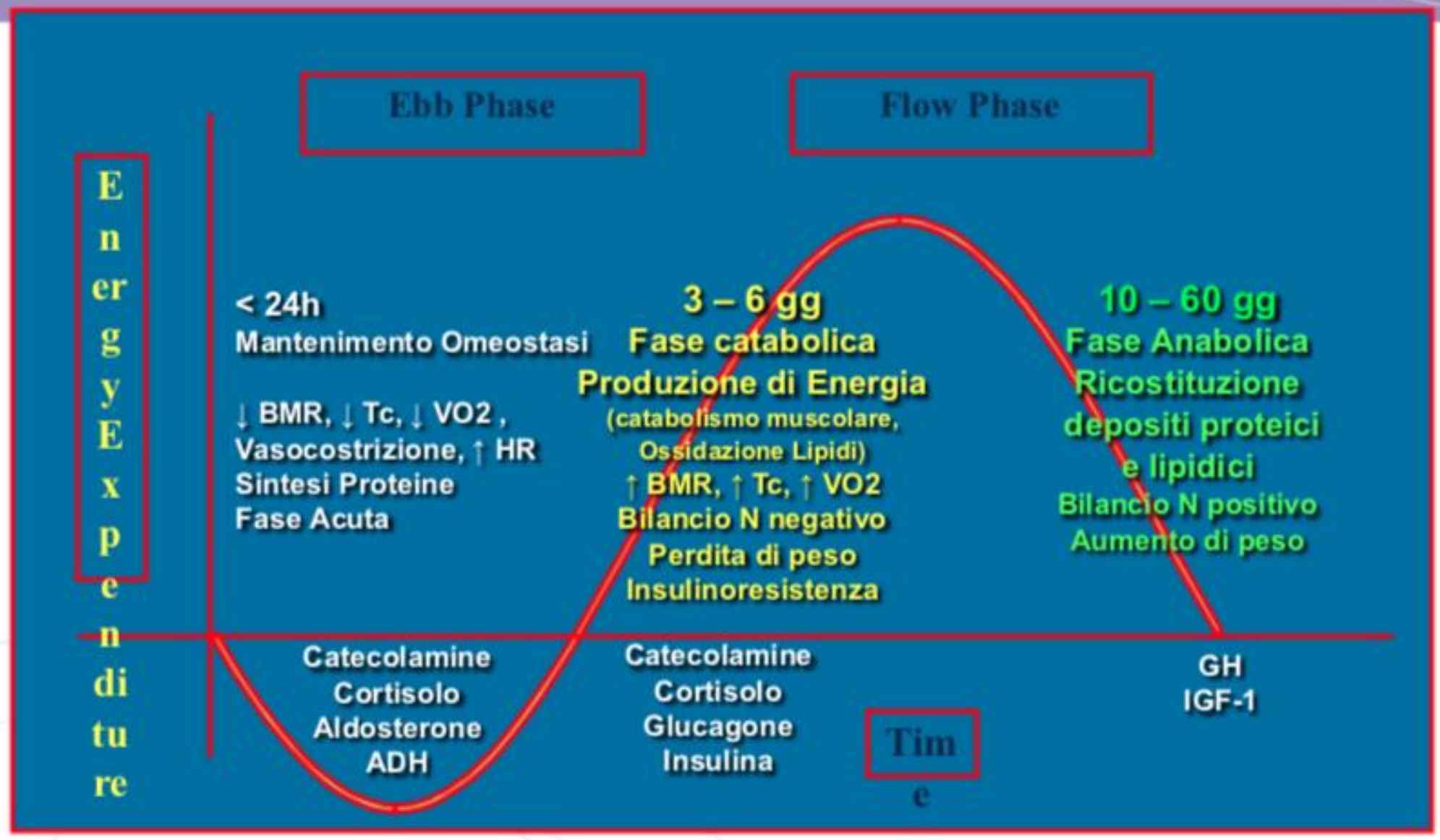
Sir David Cuthbertson

response to trauma, in particular its metabolic component

1. The ebb or early shock phase of decreased metabolism.
2. The flow or catabolic phase.
3. The convalescent or anabolic phase when resynthesis of lost tissue can take place.



Metabolic response to stress



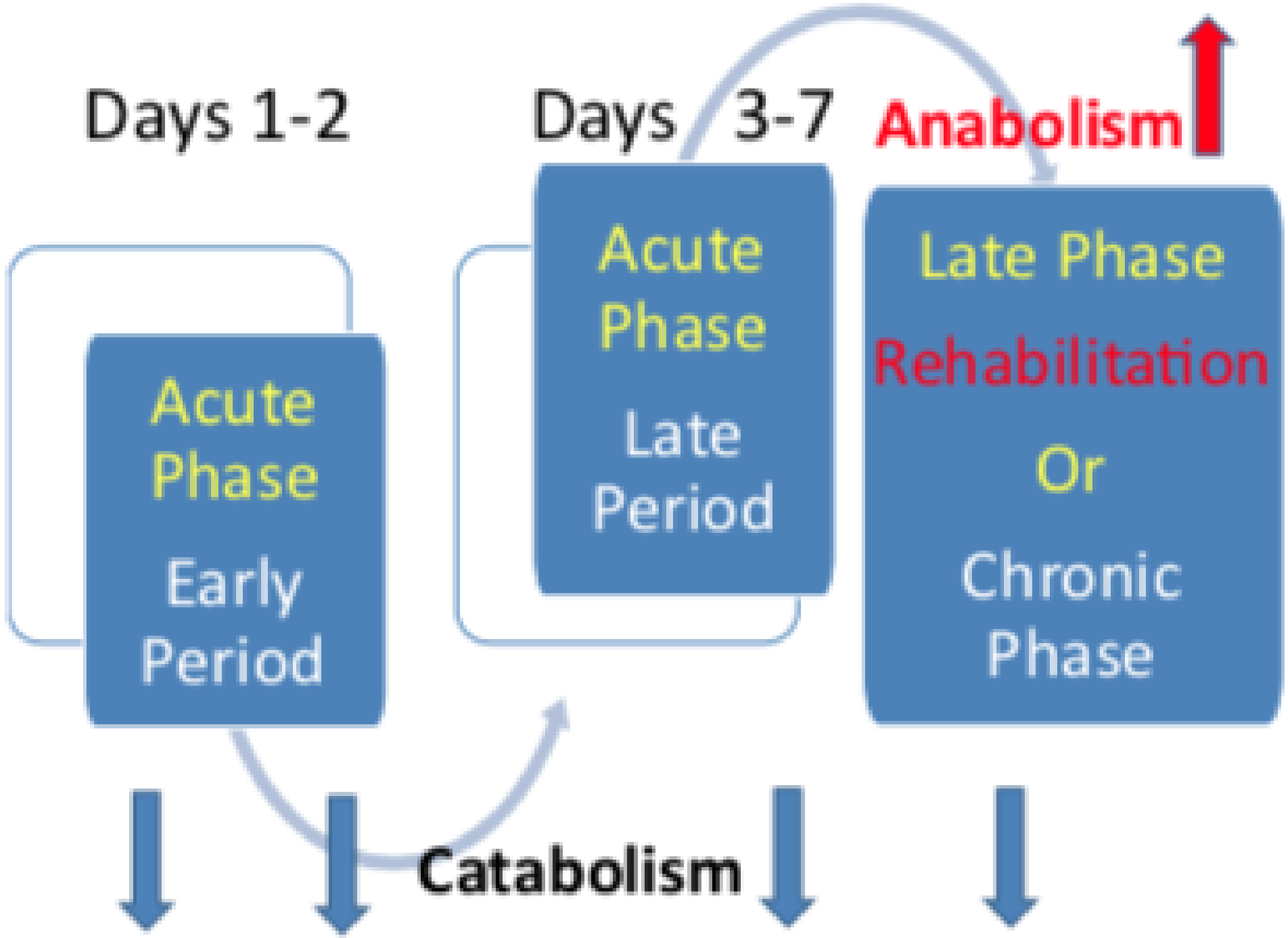
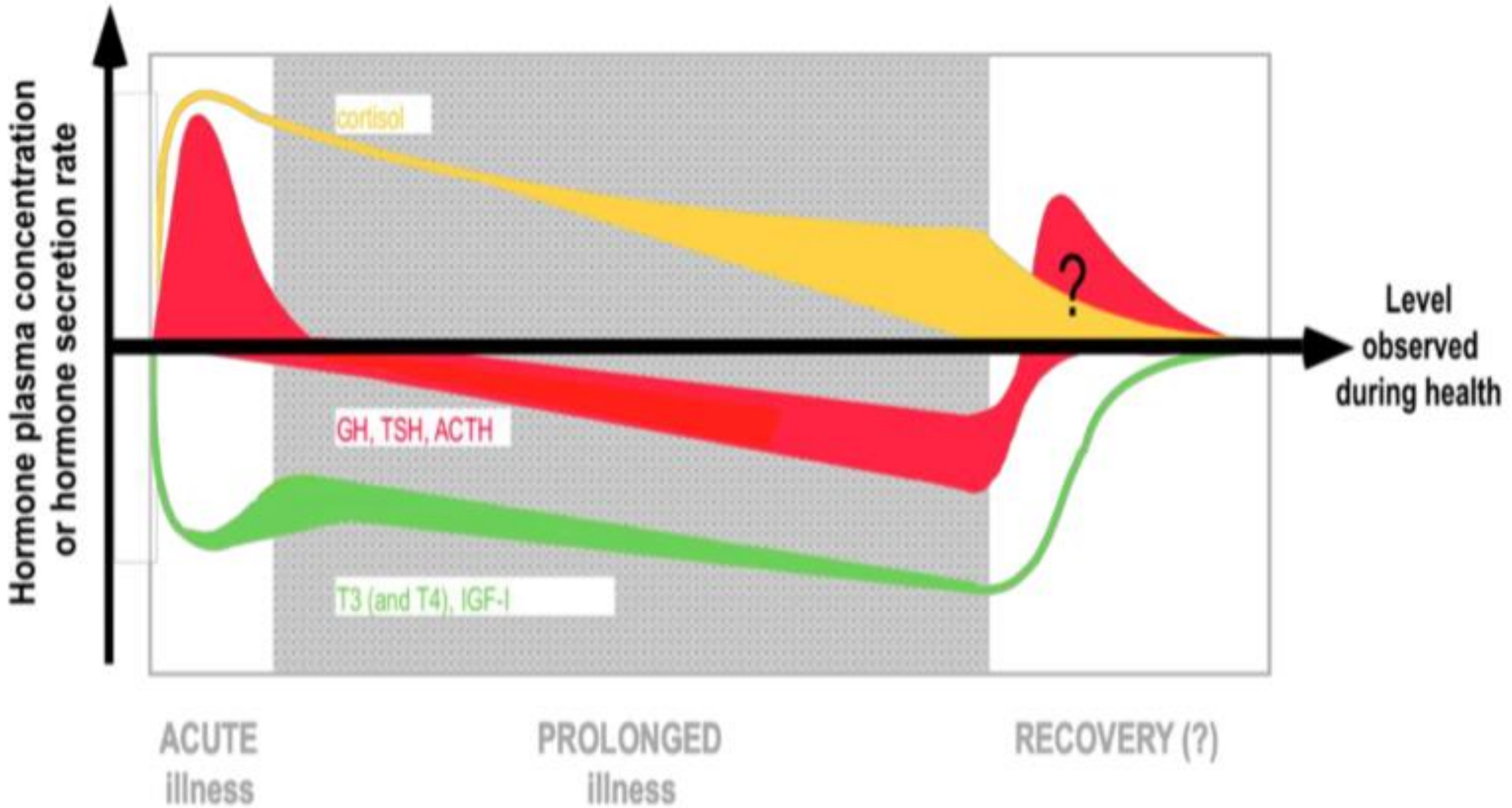


Fig. 2. Description of the acute and late phases following infection/stress/injury. After injury, the acute phase is composed of an early and a late period. Then the post-acute phase can be progressing to convalescence and rehabilitation or chronicity and Prolonged Inflammatory and Catabolic Syndrome (PICS).

PICS

1- DEPRESSIONE IMMUNITARIA ADATTATIVA
2- LIVELLO MINIMO MA PERSISTENTE DI INFIAMMAZIONE
3-APOPTOSI DIFFUSA
4-PERDITA DELLA MASSA MUSCOLARE
5- RITARDO NEL RIPRISTINO DELLA FUNZIONALITA’

Figure 4 Lean Body Mass Loss Over 20 days following surgery and critical illness (20 kg over 20 days = 1 kg lean body mass lost/day).


Hormone plasma concentration
or hormone secretion rate
cortisol
GH, TSH, ACTH
T3 (and T4), IGF-I
?
Level
observed
during health
ACUTE
illness
PROLONGED
illness
RECOVERY (?)

Contents lists available at ScienceDirect

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ESPEN Guideline

ESPEN guideline on clinical nutrition in the intensive care unit

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SUMMARY

Following the new ESPEN Standard Operating Procedures, the previous guidelines to provide best medical nutritional therapy to critically ill patients have been updated. These guidelines define who are the patients at risk, how to assess nutritional status of an ICU patient, how to define the amount of

3.3. Clinical question 3: How to screen for the risk of malnutrition during hospital stay?

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)

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.
Grade of recommendation: A – strong consensus (100% agreement)

Oral diet shall be preferred over EN or PN in critically ill patients who are able to eat.
Grade of recommendation: GPP – strong consensus (100% agreement)

Recommendation 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
Grade of recommendation: B – strong consensus (100% agreement)

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.
Grade of recommendation: GPP – strong consensus (96% agreement)

Recommendation 21

PN should not be started until all strategies to maximize EN tolerance have been attempted.
Grade of recommendation: GPP – strong consensus (95% agreement)

Recommendation 38

EN should be delayed

- **if shock is uncontrolled and hemodynamic and tissue perfusion goals are not reached, whereas low dose EN can be started as soon as shock is controlled with fluids and vasopressors/inotropes, while remaining vigilant for signs of bowel ischemia;**
- **in case of uncontrolled life-threatening hypoxemia, hypercapnia or acidosis, whereas EN can be started in patients with stable hypoxemia, and compensated or permissive hypercapnia and acidosis;**
- **in patients suffering from active upper GI bleeding, whereas EN can be started when the bleeding has stopped and no signs of re-bleeding are observed;**
- **in patients with overt bowel ischemia;**
- **in patients with high-output intestinal fistula if reliable feeding access distal to the fistula is not achievable;**
- **in patients with abdominal compartment syndrome; and**
- **if gastric aspirate volume is above 500 ml/6 h.**

Early EN should be performed

- **in patients receiving ECMO**
- **in patients with traumatic brain injury**
- **in patients with stroke (ischemic or hemorrhagic)**
- **in patients with spinal cord injury**
- **in patients with severe acute pancreatitis**
- **in patients after GI surgery**
- **in patients after abdominal aortic surgery**
- **in patients with abdominal trauma when the continuity of the GI tract is confirmed/restored**
- **in patients receiving neuromuscular blocking agents**
- **in patients managed in prone position**
- **in patients with open abdomen**
- **regardless of the presence of bowel sounds unless bowel ischemia or obstruction is suspected in patients with diarrhea**

Grade of recommendation: B – strong consensus (95.83% agreement)

Recommendation 22

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

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

Review

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

Association Between Malnutrition and Clinical Outcomes in the Intensive Care Unit: A Systematic Review

Charles Chin Han Lew, B Nutr Diet (Hons), APD, CNSC[1,2]; Rosalie Yandell, PhD, APD[1]; Robert J. L. Fraser, PhD, MBBS, FRACP[3]; Ai Ping Chua, MBBS, MMed[4]; Mary Foong Fong Chong, PhD, BSc (Hons)[5]; and Michelle Miller, PhD, Adv APD[1]

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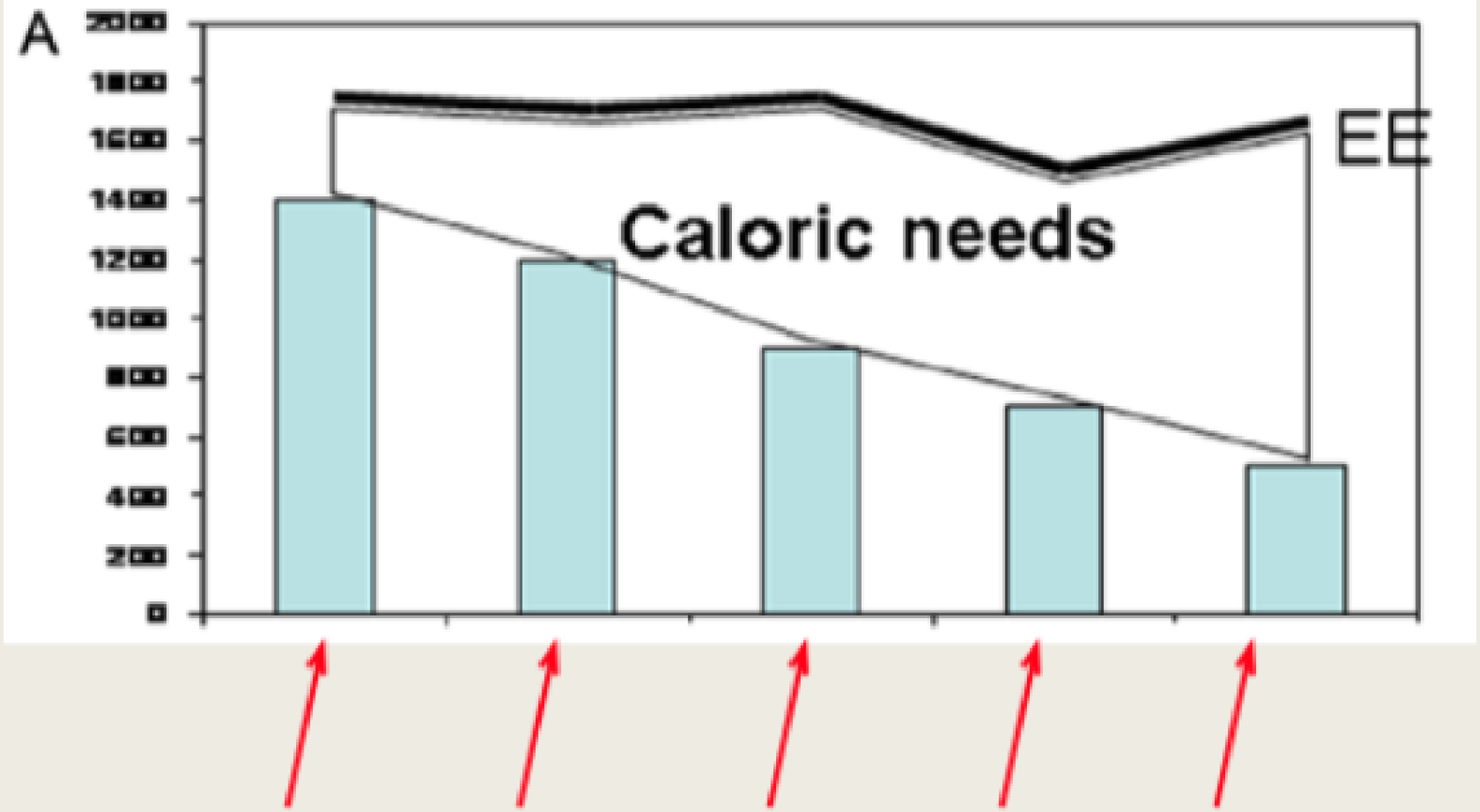
Table 3. Prevalence of Malnutrition.

Types of Patients in the ICU	Prevalence of Malnutrition
Heterogeneous group[8,20,21,23,26-32]	37.8%–78.1%
Elderly[34]	23.2%–34.4%
Cardiac surgery[22]	5.0%–20.0%
Liver transplantation[26,27]	52.6%
Acute kidney injury[39]	82.0%

ICU, intensive care unit.

Energy Estimation and Measurement in Critically Ill Patients



La produzione endogena di calorie, nei primi giorni, è pari al 50-75% della EE!!!!
(TappyL 1998)

Fraipont V, Preiser J.C. JPEN 2013

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Recommendation 17

Hypocaloric nutrition (not exceeding 70% of EE) should be administered in the early phase of acute illness.

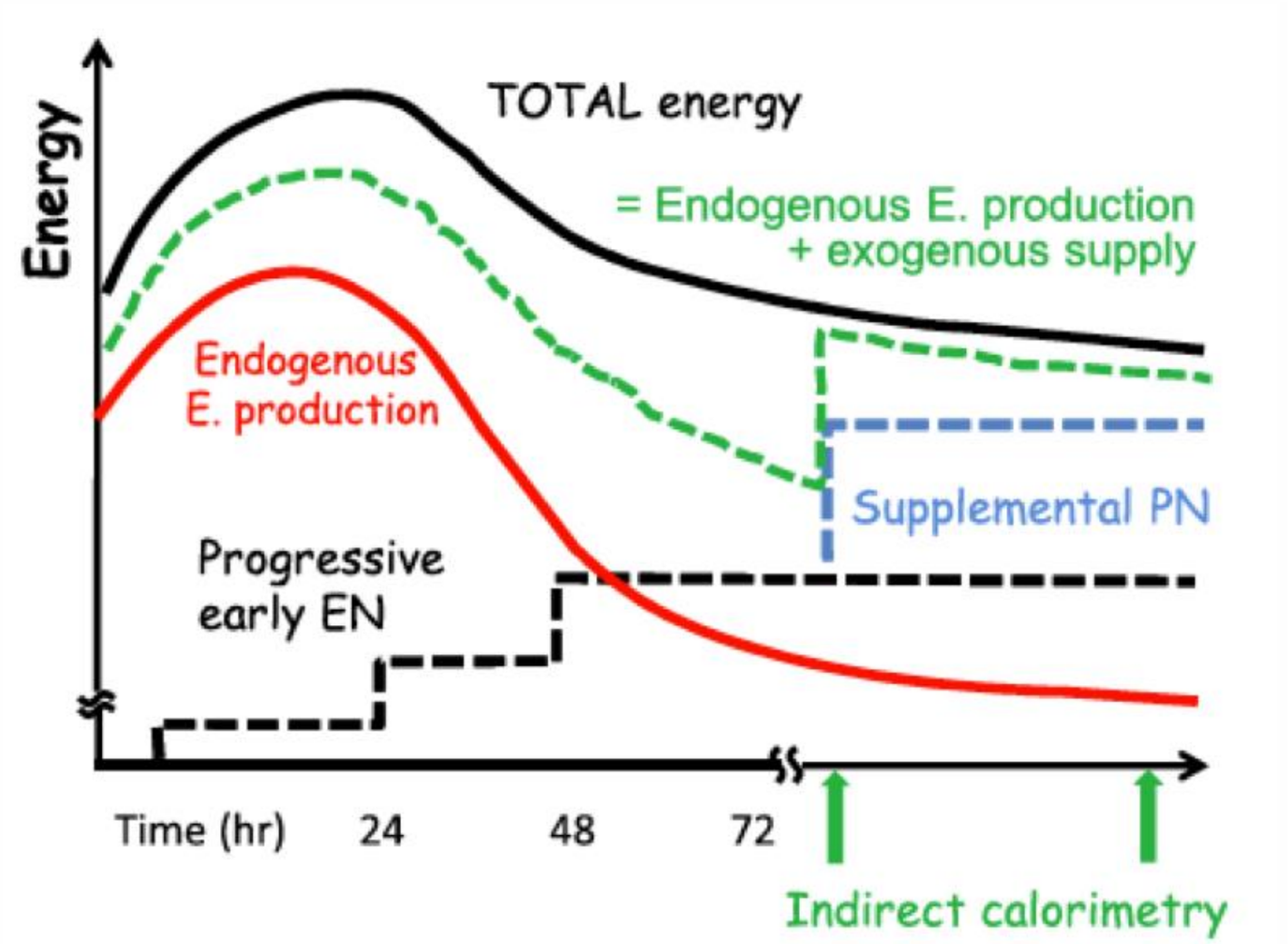
Grade of recommendation: B – strong consensus (100% agreement)

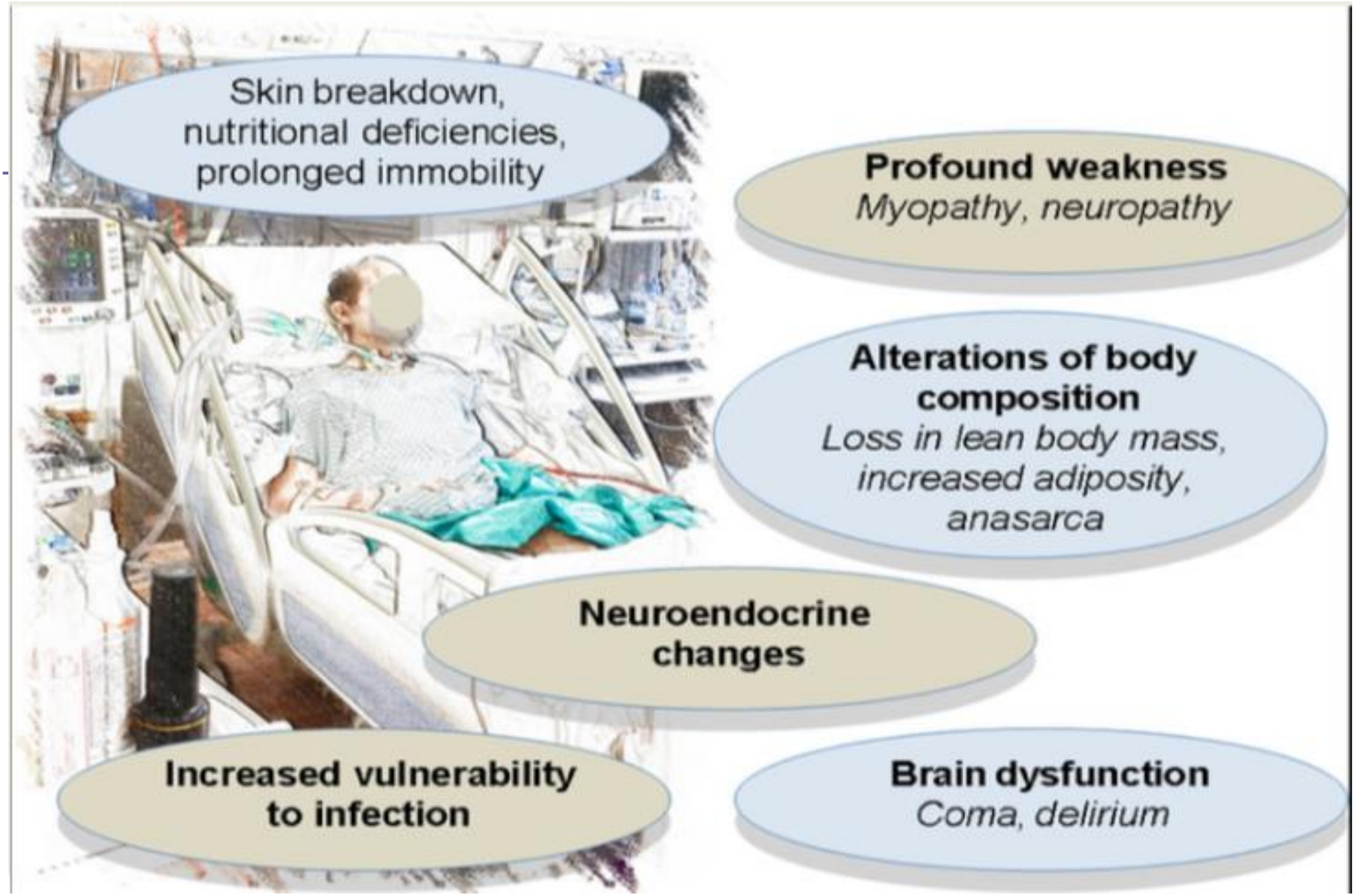
Recommendation 18

After day 3, caloric delivery can be increased up to 80-100% of measured EE.

Grade of recommendation: 0 – strong consensus (95% agreement)

Progressive feeding strategy that accommodated integrates endogenous energy provision




Skin breakdown, nutritional deficiencies, prolonged immobility
Profound weakness
Myopathy, neuropathy
Alterations of body composition
Loss in lean body mass, increased adiposity, anasarca
Neuroendocrine changes
Increased vulnerability to infection
Brain dysfunction
Coma, delirium

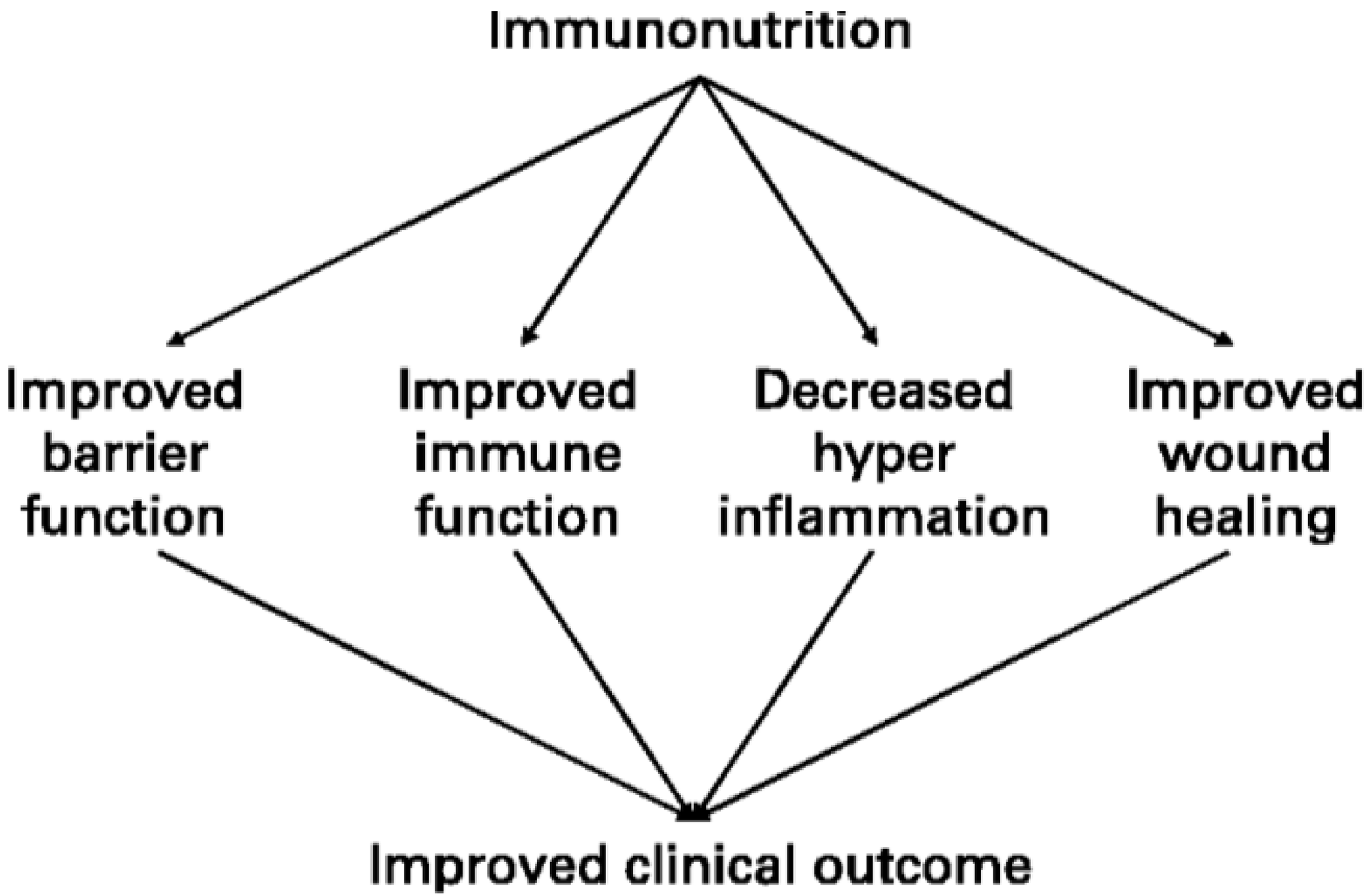
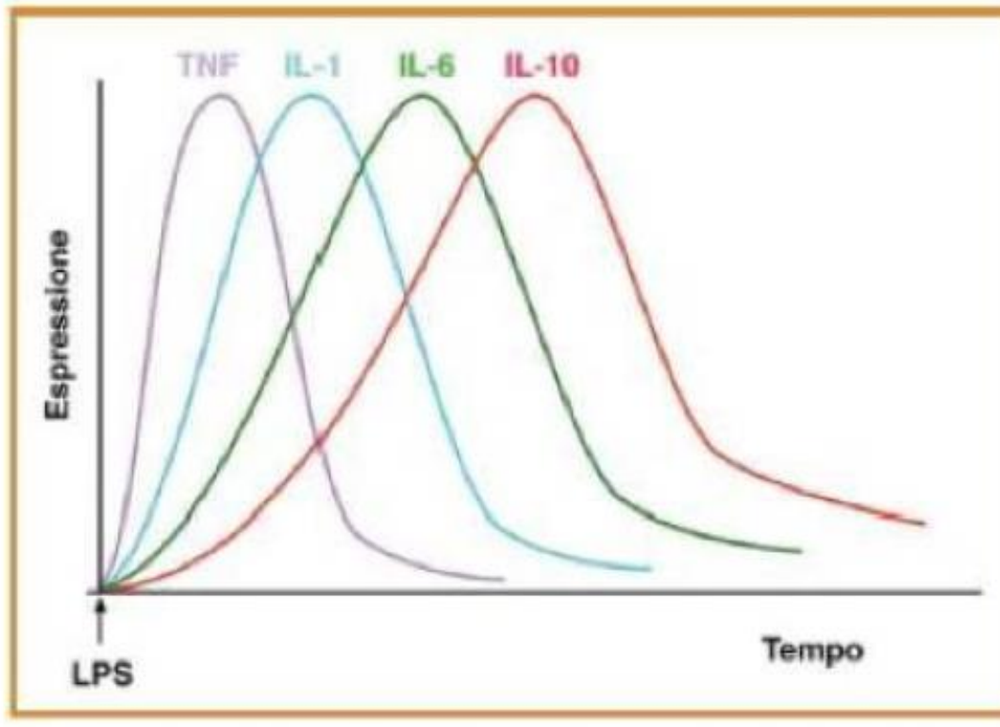


Fig. 2 The concept of immunonutrition in the context of surgical or critically ill patients.

Lo stato infiammatorio, il trauma, lo stato di infezione attivano la cascata dell’ infiammazione.

I macrofagi tissutali, i monociti, i mastociti, le piastrine rilasciano precocemente una molteplicità di citochine (TNF-a) ed interleuchina-1 (IL-1).

Il rilascio di IL-1 e TNF-a determinano il clivaggio dell’inibitore di nuclear factor-kB (NF kB) .
Una volta attivato NF-kB si attiva la produzione di(mRNA), che induce la produzione di altre citochine proinfiammatorie.



INFLAMMATION

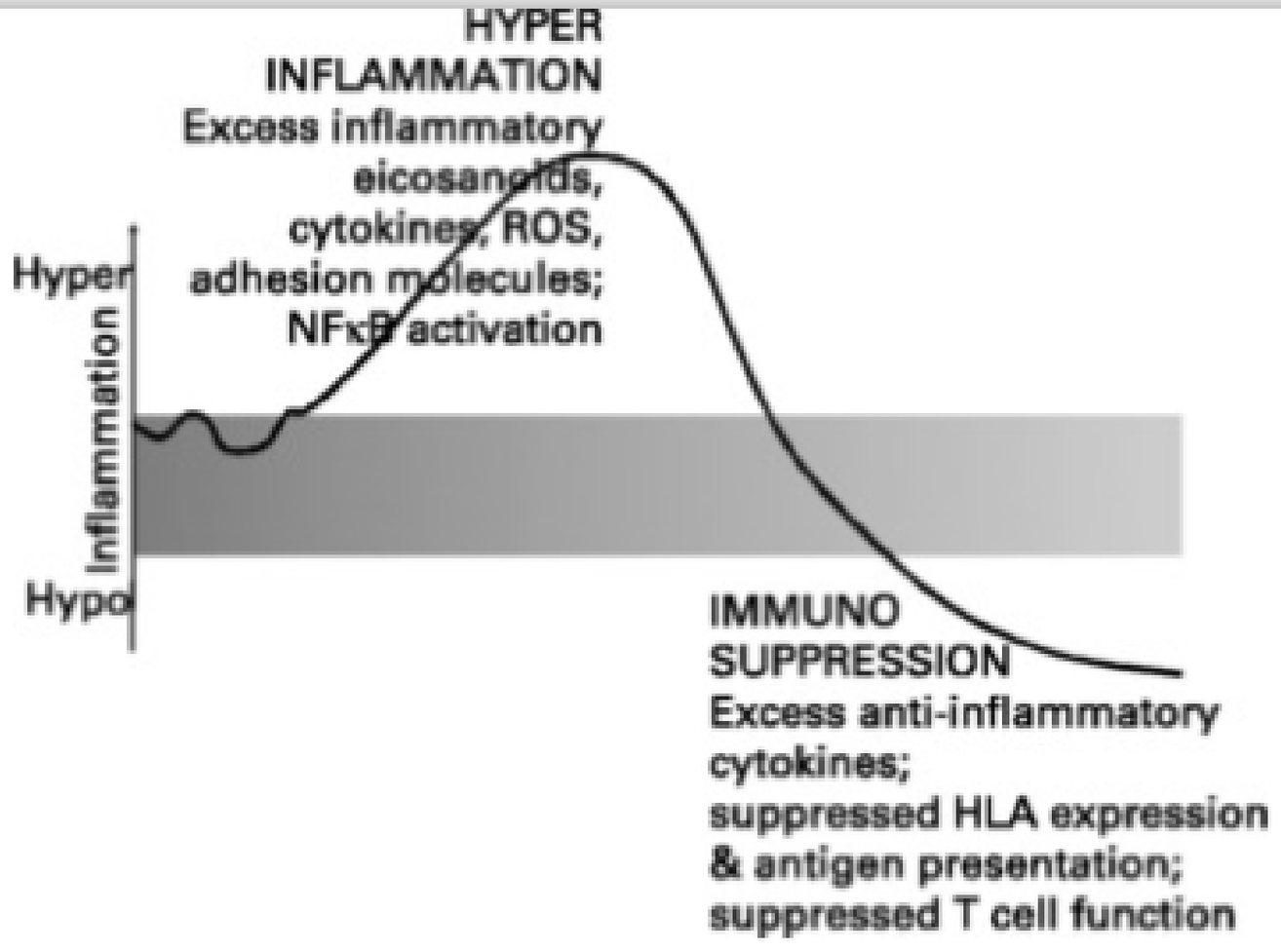
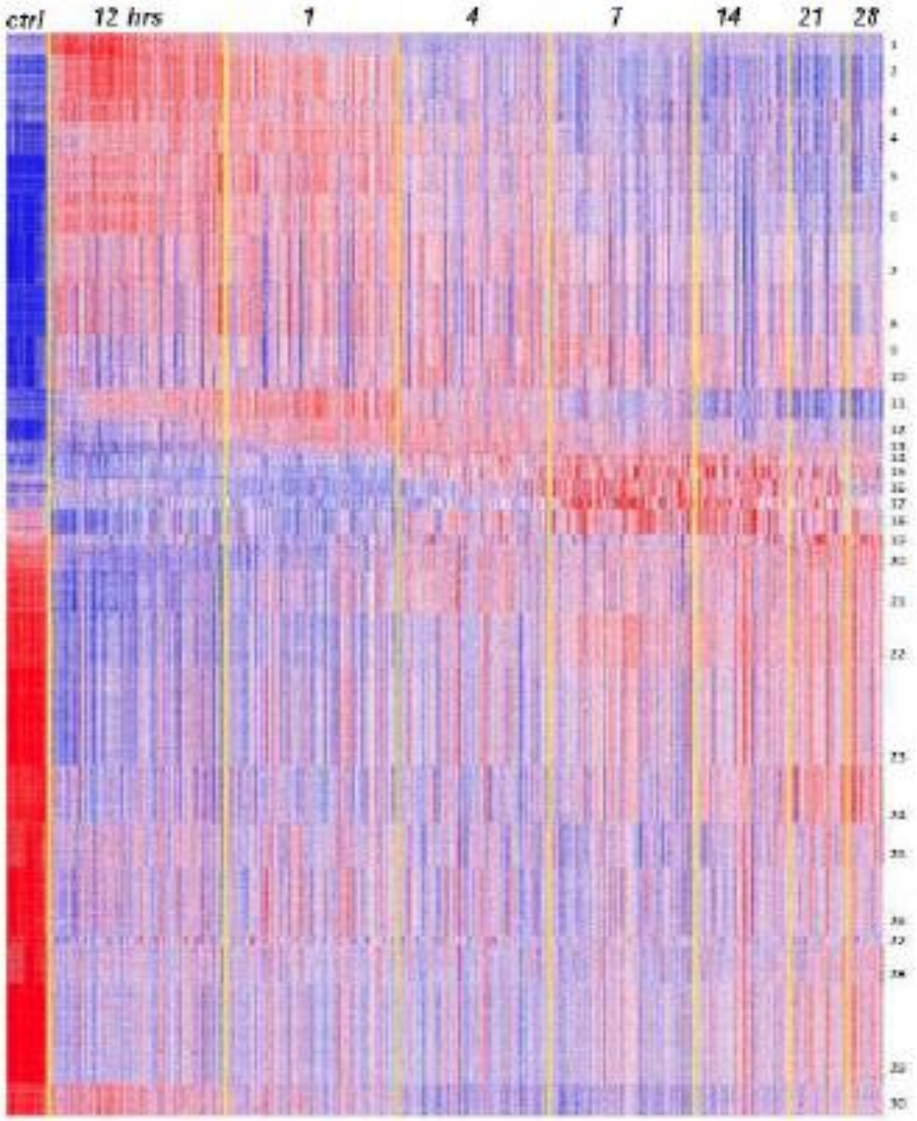


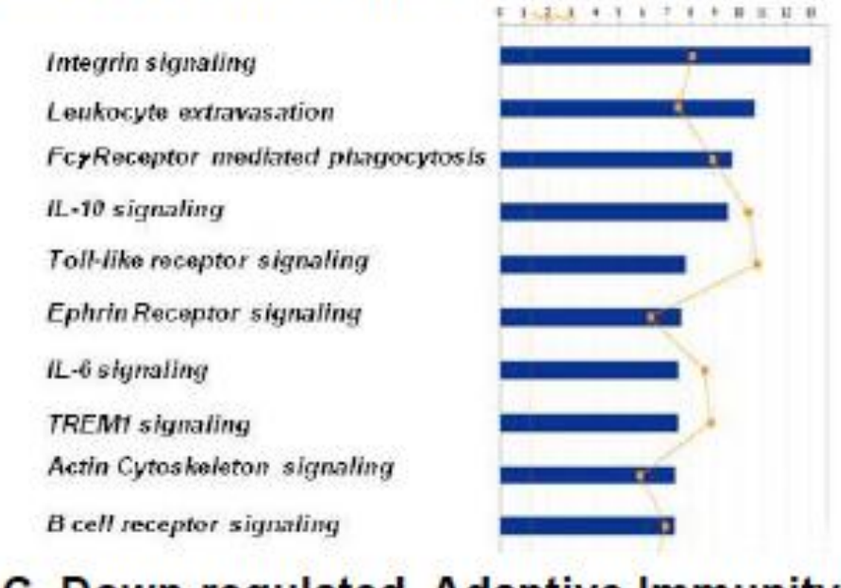
Fig. 1 Hypothetical biphasic immuno-inflammatory response to a traumatic insult. HLA, human leukocyte antigen; NFκB, nuclear factor κ B; ROS, reactive oxygen species. The grey area represents the physiological range.

A Genomic Storm – 75% of Genes Up or Down Regulated

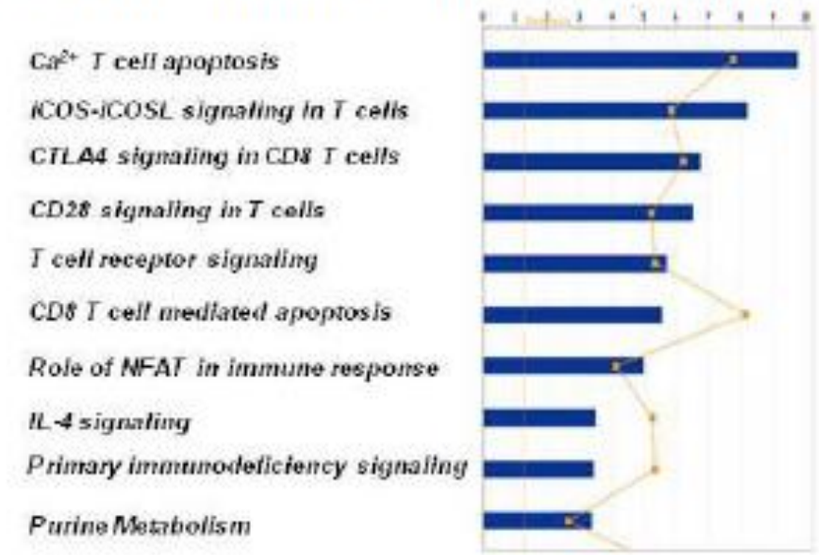
A. Gene expression After Severe Trauma



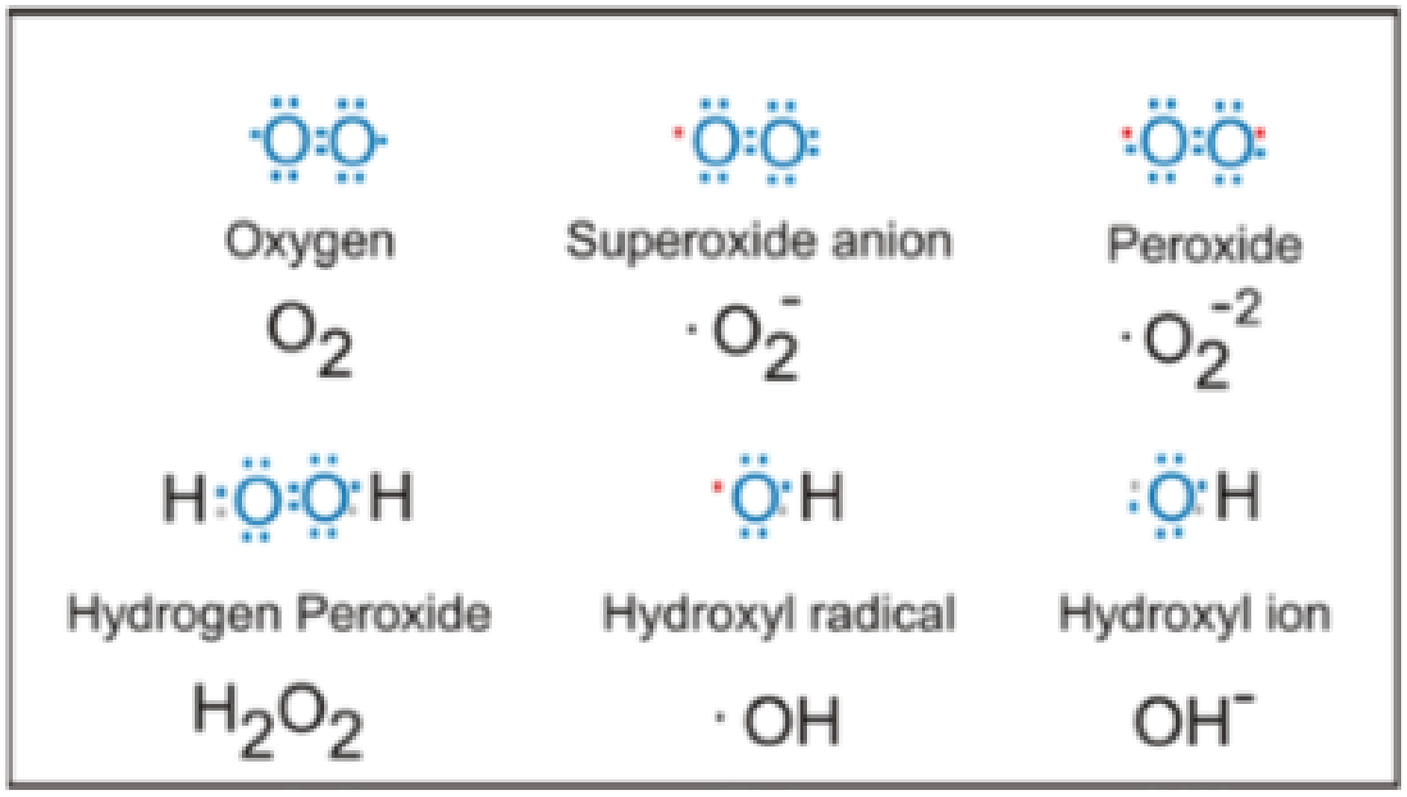
B. Up-regulated Innate Immunity



C. Down-regulated Adaptive Immunity



REACTIVE OXYGEN SPECIES



DEFENCE MECHANISMS

Detoxification of reactive oxygen species is paramount to the survival of all aerobic life forms. As such a number of defense mechanisms have evolved to meet this need and provide a balance between production and removal of ROS. An imbalance toward the pro-oxidative state is often referred to as “Oxidative stress”.

Cells have a variety of defense mechanisms to ameliorate the harmful effects of ROS. Superoxide dismutase (SOD) catalyzes the conversion of two superoxide anions into a molecule of hydrogen peroxide (H_2O_2) and oxygen (O_2) [3] (Eq. 1). In the peroxisomes of eukaryotic cells, the enzyme catalase converts H_2O_2 to water and oxygen, and thus completes the detoxification initiated by SOD (Eq. 2). Glutathione peroxidase is a group of enzymes containing selenium, which also catalyze the degradation of hydrogen peroxide, as well as organic peroxides to alcohols.

Eq. 1. $2\,O_2^{\cdot} + 2H^{+} \rightarrow H_2O_2 + O_2$

Eq. 2. $2\,H_2O_2 \rightarrow 2\,H_2O + O_2$

There are a number of non-enzymatic small molecule antioxidants that play a role in detoxification. Glutathione may be the most important intra-cellular defense against the deleterious effects of reactive oxygen species. This tripeptide (glutamyl-cysteinyl-glycine) provides an exposed sulphhydryl group, which serves as an abundant target for attack. Reactions with ROS molecules oxidize glutathione, but the reduced form is regenerated in a redox by an NADPH-dependent reductase. Vitamin C or ascorbic acid is a water soluble molecule capable of reducing ROS, while vitamin E (α-tocopherol) is a lipid soluble molecule that has been suggested as playing a similar role in membranes.

The ratio of the oxidized form of glutathione (GSSG) and the reduced form (GSH) is a dynamic indicator of the oxidative stress of an organism [2].

ORGANIC OXIDATION

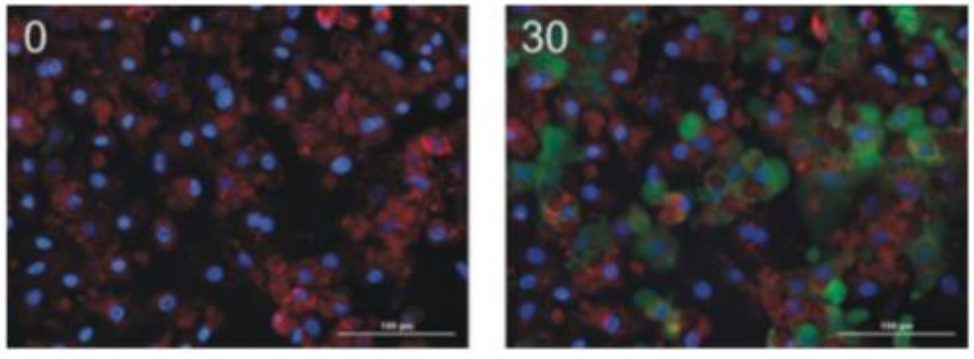


Figure 15. Oxidized DCF fluorescence in hepatocytes. Images of cultured hepatocytes captured after 0 and 30 minute treatments with 800 nM camptothecin. Cell nuclei were stained with Hoechst 33342 (blue), mitochondria were stained with MitoTracker® Red (Red); and oxidized DCF reagent is visualized in green [68]. Images were captured using Cytation™ 3 Imaging multimode microplate reader (BioTek Instruments) using a 20x objective.

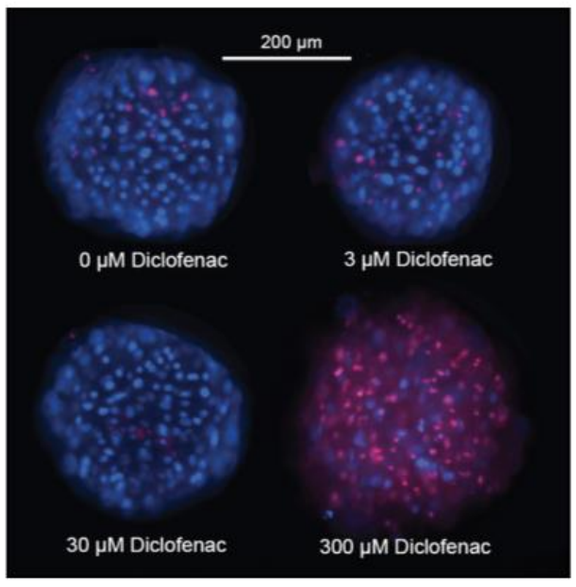


Figure 11. Mitochondrial Oxidative Stress Assessment Following a Three Day Diclofenac Dosing. Overlaid images of 3D liver microtissues, stained with Hoechst 33342 (blue) and MitoSOX™ Red (red); captured using the DAPI or RFP Cytation 3 imaging channels, respectively. Autofocus performed on DAPI stained cells [44].

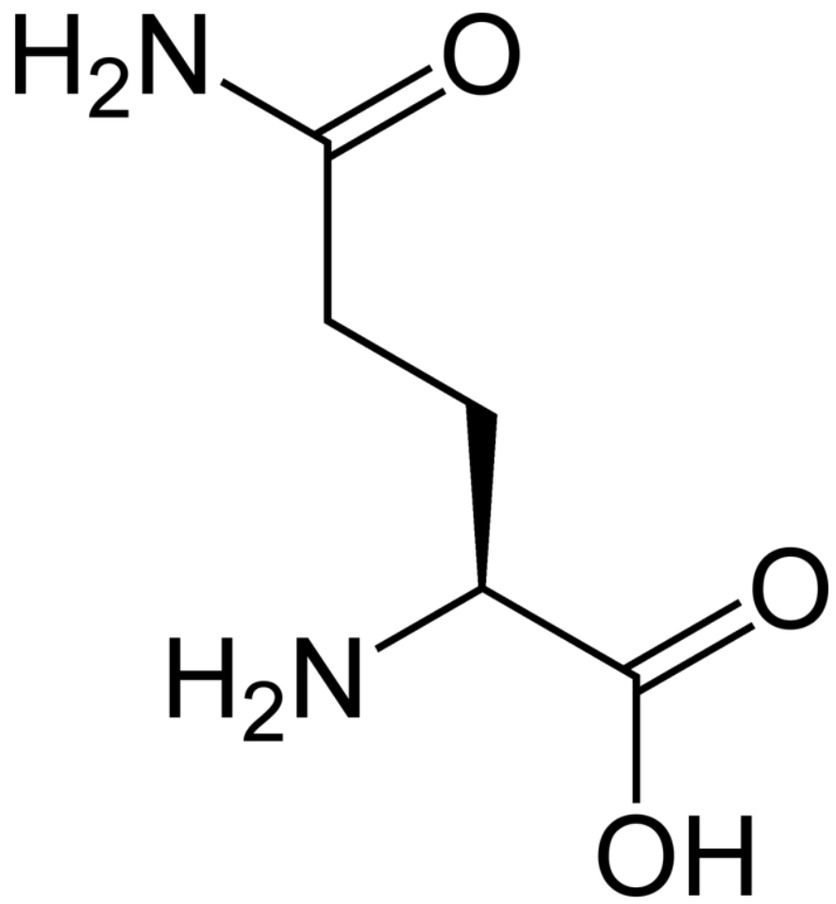
IMMUNONUTRIENTS

- The ω-3 fatty acids, have anti-inflammatory actions, which will help to reverse immunosuppression by down-regulating eicosanoid production.
- Sulphur amino acids enhance antioxidant status by maintaining concentrations of glutathione, one of the key anti-oxidants in the body.
- Glutamine is an important nutrient for rapidly dividing cells, such as those of the immune system and helps to improve gut carrier function. Glutamine also enhances glutathione production thereby improving anti-oxidant status.
- Arginine stimulates nitric oxide synthesis, and growth hormone production. It therefore has an anabolic effect, and also increases T helper cell numbers.
- Nucleotides currently have a less well defined role, but it is suspected that they have important effects upon T cell function.

Table 1
Nutrients, which influence immunity and their effects and mechanisms of action

Immunonutrient	Influence on inflammation and immune function	Possible mechanism(s)	Effects
Omega 3 polyunsaturated fatty acids	Inhibits inflammation, enhances T cell functions	Changes in membrane phospholipids	Changes in cytokine and lipid-derived mediator production
Sulphur amino acids and related compounds	Inhibits inflammation enhances T cell function	Suppression of oxidant effects and NFkB activation	Maintenance of glutathione status
Arginine	Enhances T cell function	Stimulation of growth hormone production	Altered nitric oxide production?
Glutamine	Stimulates T cell function, inhibits inflammation?	Stimulation of glutethione synthesis?	Enhances cell proliferation, increases

MACRONUTRIENTS (AMINO-ACIDS)

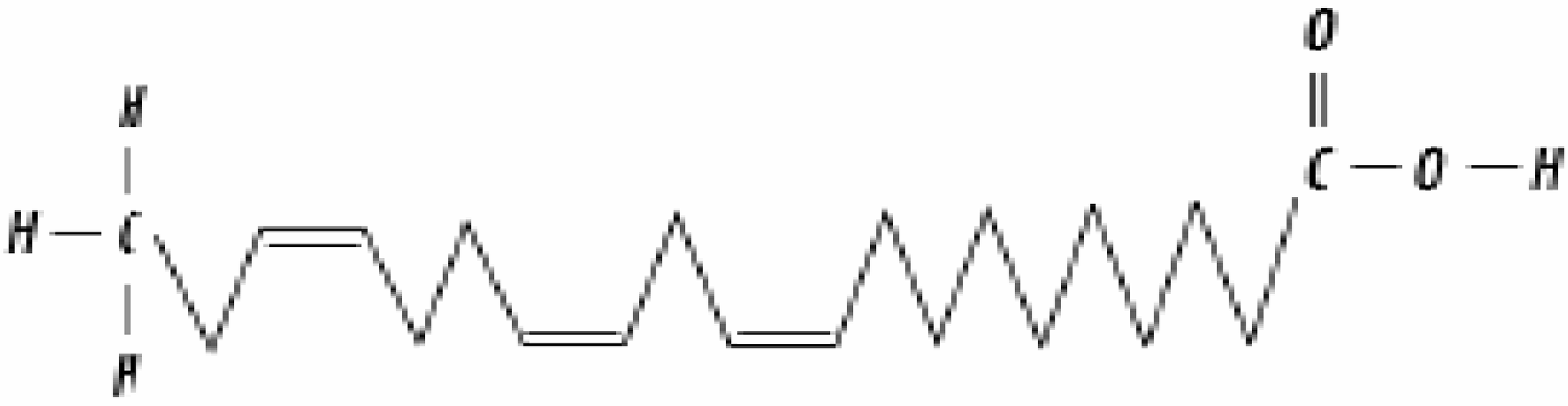


Acidi grassi omega-3

Definizione:

Gli omega-3 sono acidi grassi polinsaturi essenziali.

I loro metaboliti attivi EPA e DHA (acido eicosapentanoico e docosaesaenoico) modulano la funzionalità del sistema immunitario tramite meccanismi di tipo strutturale e biochimico.



Derivati degli acidi grassi omega-6 ed omega-3

ACIDO ARACHIDONICO

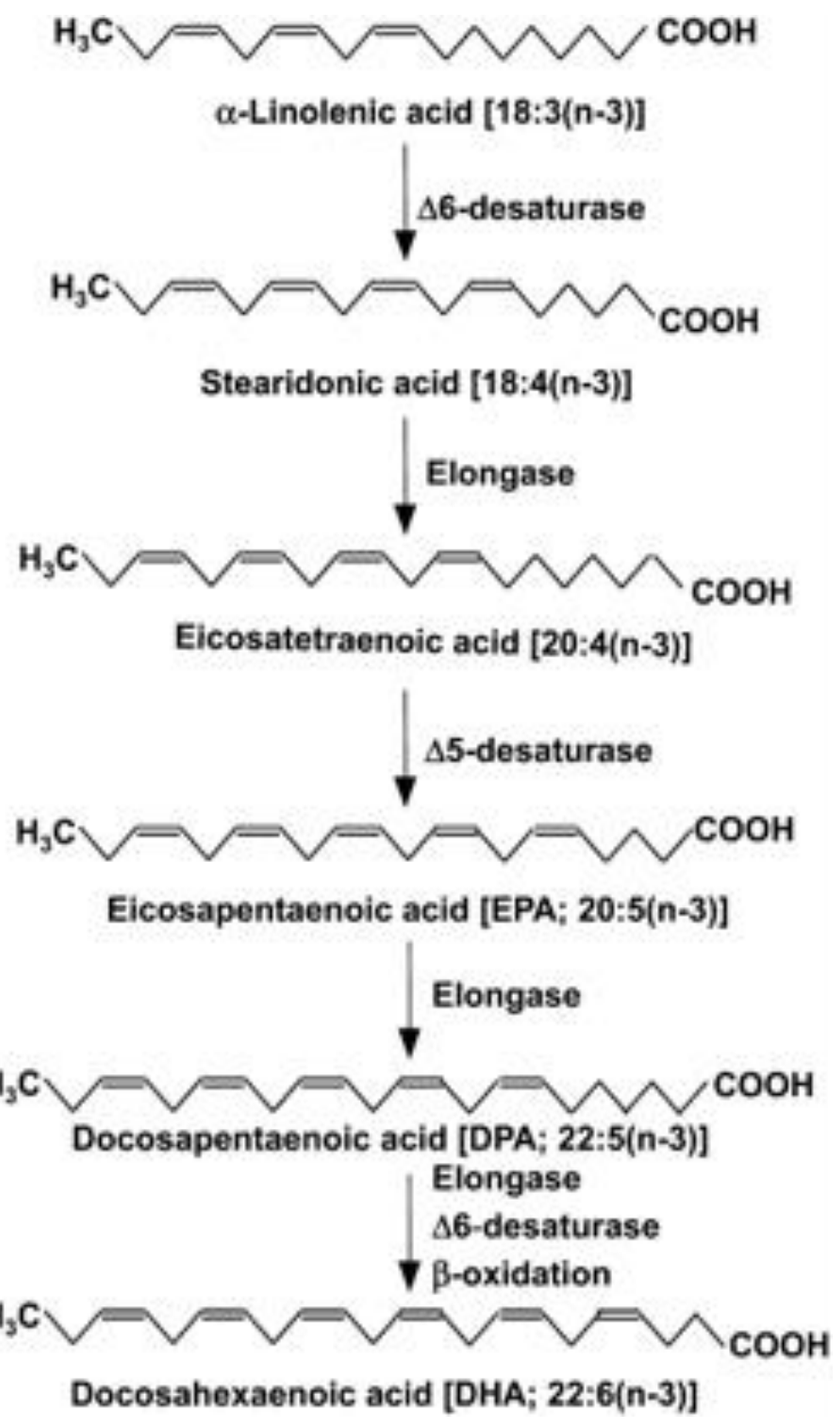
Eicosanoidi derivati dalla serie ω6

Immunosoppressori dal potere aggregante, vasocostrittore e proinfiammatorio

EPA/DHA

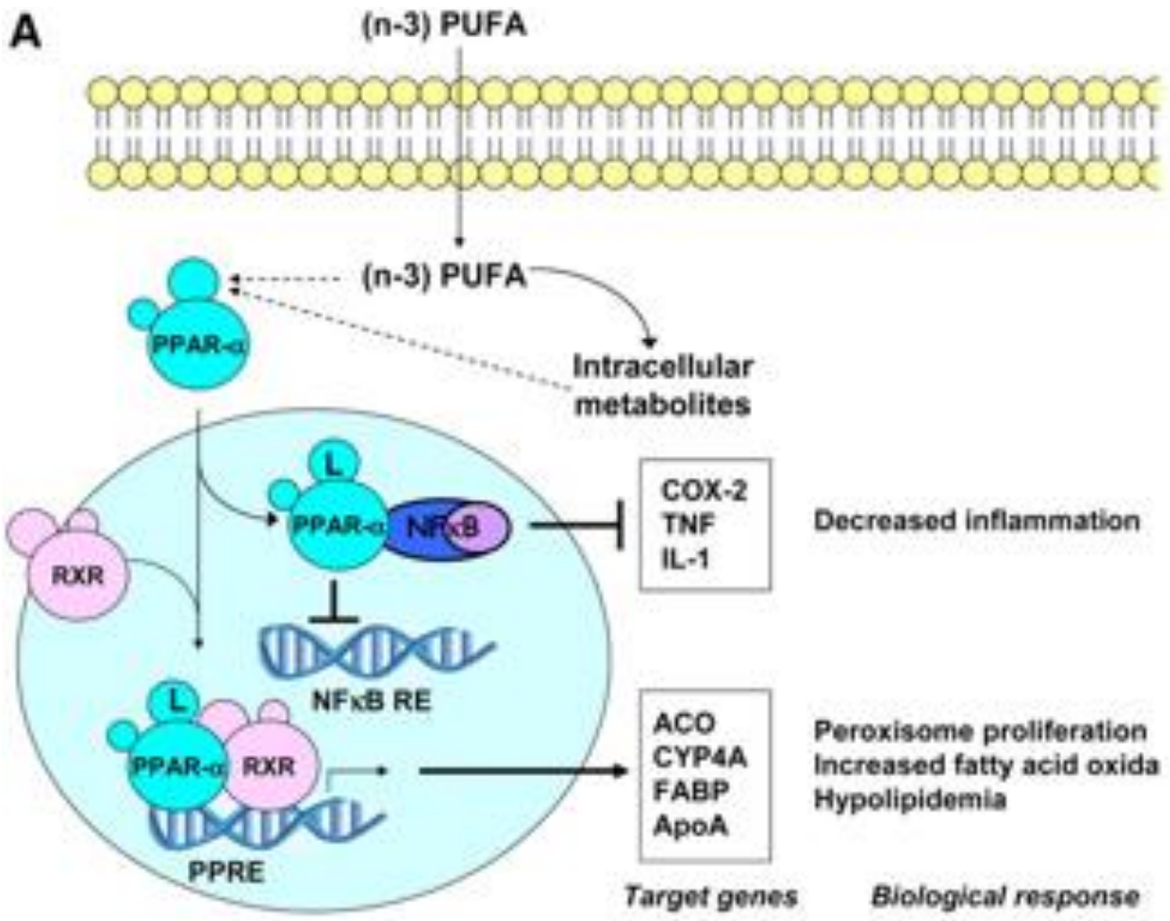
Eicosanoidi derivati dalla serie ω3

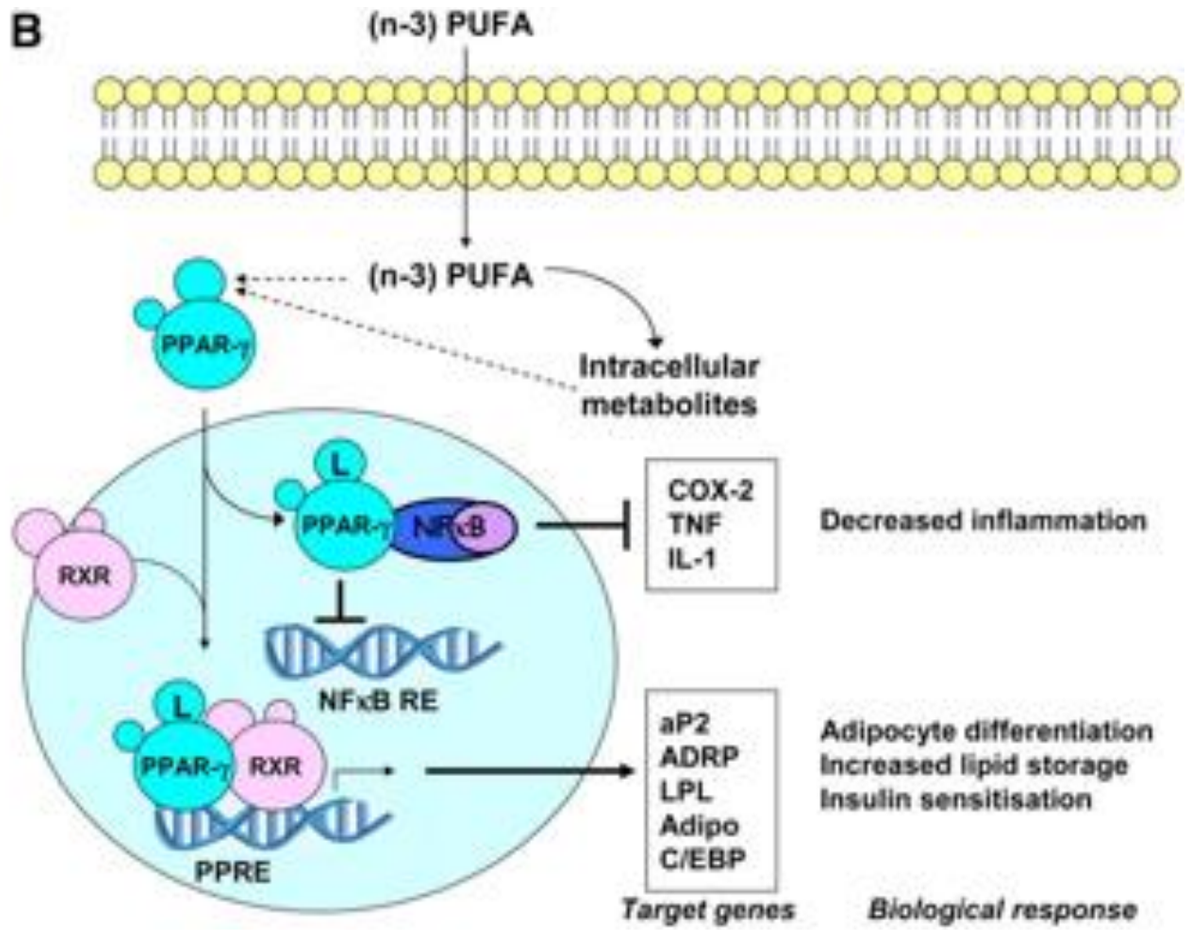
Immunostimolatori dal potere antiaggregante, vasodilatatore ed antinfiammatorio



(n-3) PUFA HANNO 4 MECCANISMI D'AZIONE ATTRAVERSO CUI CONTROLLANO MECCANISMI CELLULARI E TISSUTALI

1) (n-3) PUFA influenzano la concentrazione dei metaboliti ed ormonale
2) (n-3) PUFA sono coinvolti nello stress ossidativo e nell'ossidazione di LDL
3) agiscono direttamente o tramite recettori di superficie o intracellular
4) agiscono sui processi enzimatici e cellulari variando la composizione fosfolipidica della membrana cellulare


A
(n-3) PUFA
(n-3) PUFA
PPAR-α
Intracellular
metabolites
L
PPAR-α
NFκB
RXR
COX-2
TNF
IL-1
Decreased inflammation
NFκB RE
L
PPAR-α
RXR
PPRE
ACO
CYP4A
FABP
ApoA
Peroxisome proliferation
Increased fatty acid oxida
Hypolipidemia
Target genes
Biological response


B
(n-3) PUFA
(n-3) PUFA
PPAR-γ
Intracellular
metabolites
L
PPAR-γ
NFκB
RXR
COX-2
TNF
IL-1
Decreased inflammation
NFκB RE
L
PPAR-γ
RXR
PPRE
aP2
ADRP
LPL
Adipo
C/EBP
Adipocyte differentiation
Increased lipid storage
Insulin sensitisation
Target genes
Biological response

ENTERAL OMEGA 3 IN ARDS

- Reduced
  - Mortality
  - Rate of new organ failure
  - Length of ICU stay
  - Length of ventilation

- Faster improvement PaO_2/FiO_2

- Early administration of fish-oil based formula to ventilated patients exceptionally safe

- BAL reduced inflammatory markers

- Benefit lost if combined with arginine in medical ICU

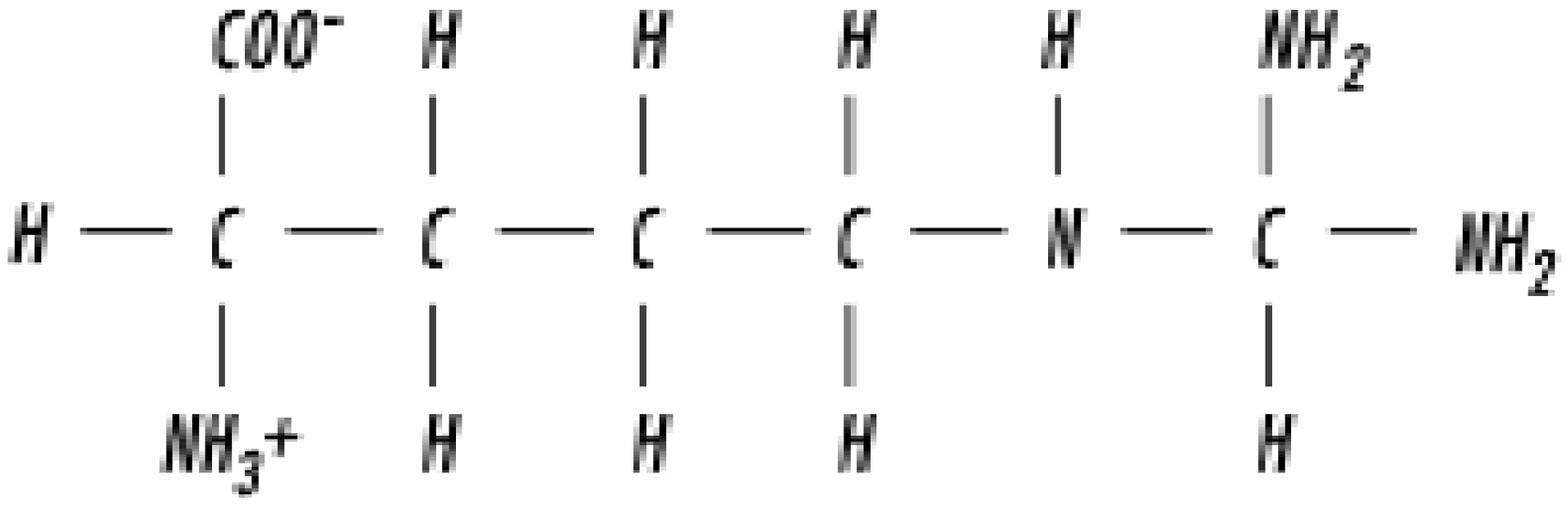
SEPSIS AND OMEGA 3 LIPIDS

- In animal models, fish oil has shown beneficial effects
- May increase bacterial killing
- Improves survival
- Maintains blood flow to intestine

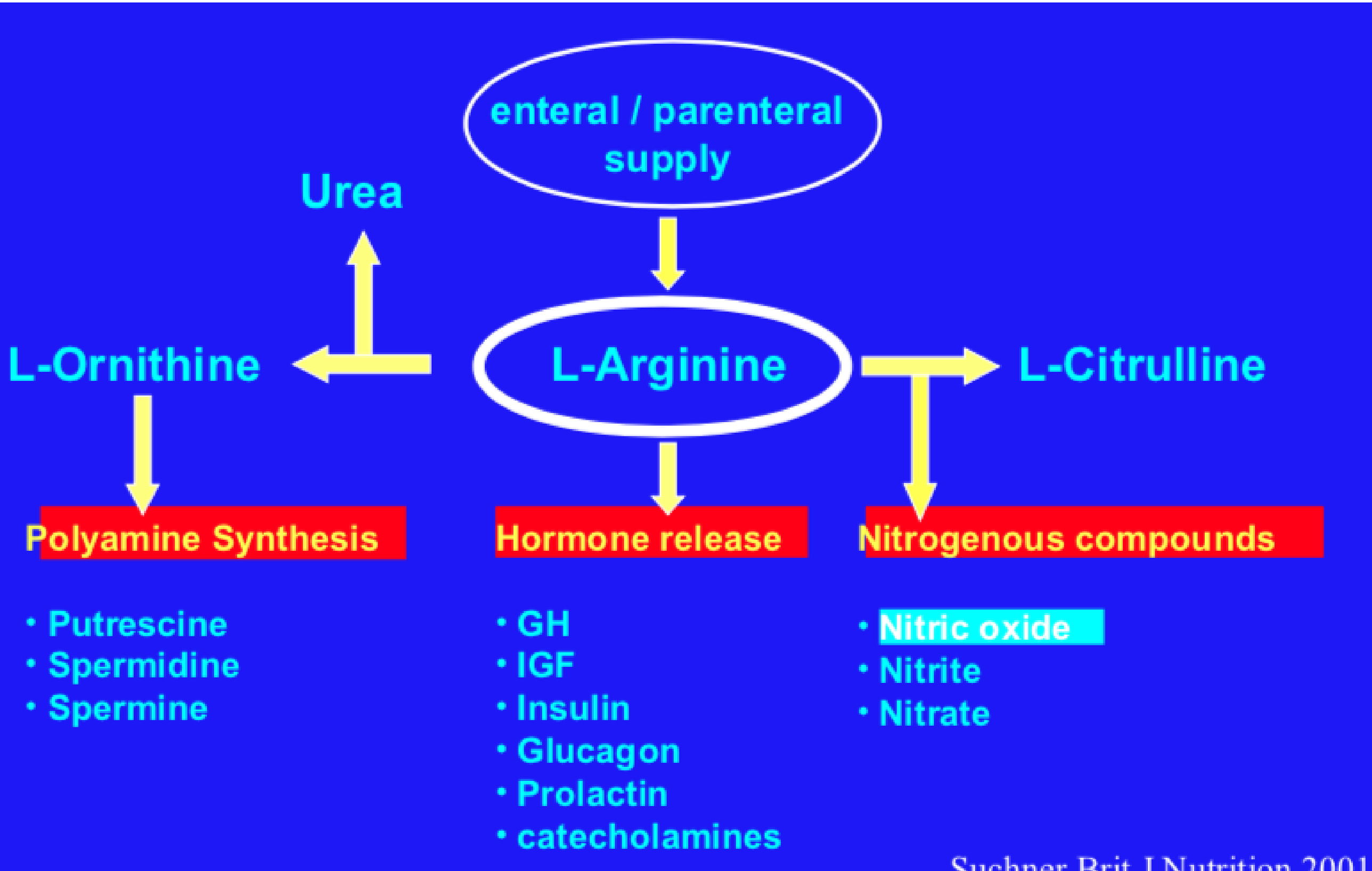
Arginina

Definizione:

Aminoacido semiessenziale nelle condizioni di stress e immunosoppressione

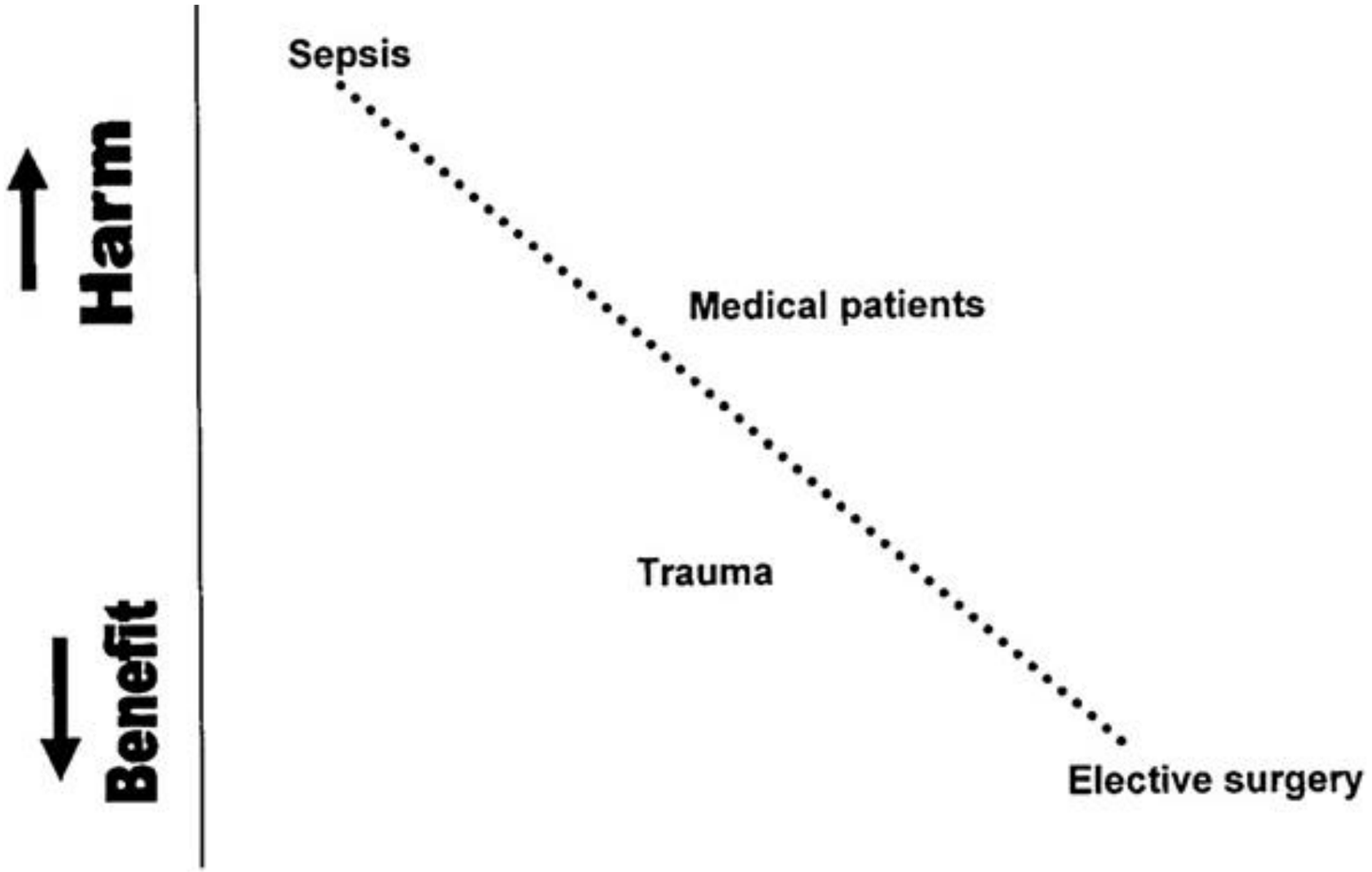


METABOLIC EFFECTS OF ARGININE

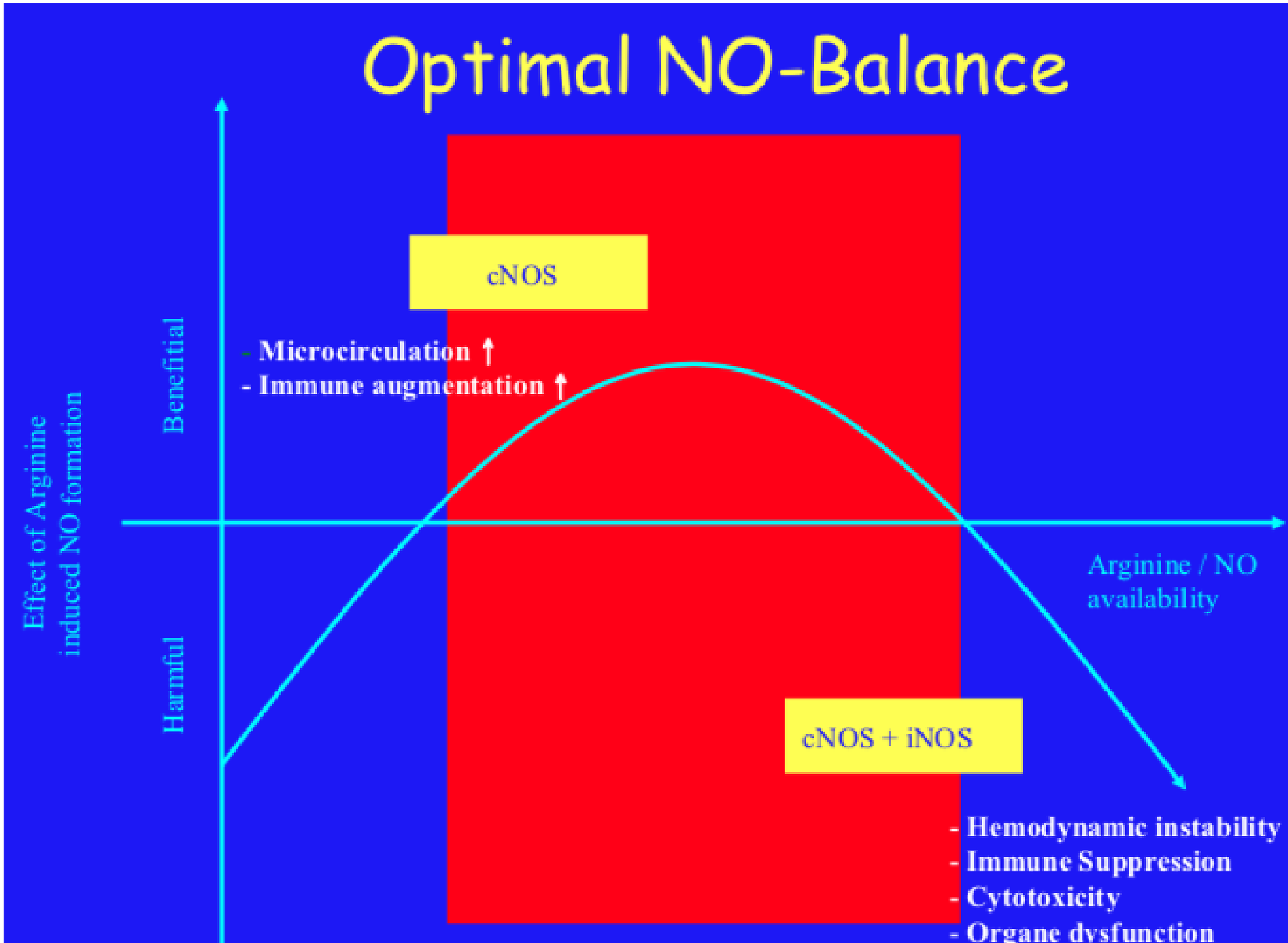


Suchner Brit J Nutrition 2001

RISK VS BENEFIT ARGININE



Optimal NO-Balance



Il ruolo metabolico dell’RNA (1)Substrato per duplicazione, maturazione e differenziazione cellulare (cellule a rapido turnover: linfocita, NK, enterocita, macrofago: incapace di sintetizzare RNA)

-Implicato nella sintesi di IL-2 e dei recettori macrofagici

-Substrato per la sintesi proteica

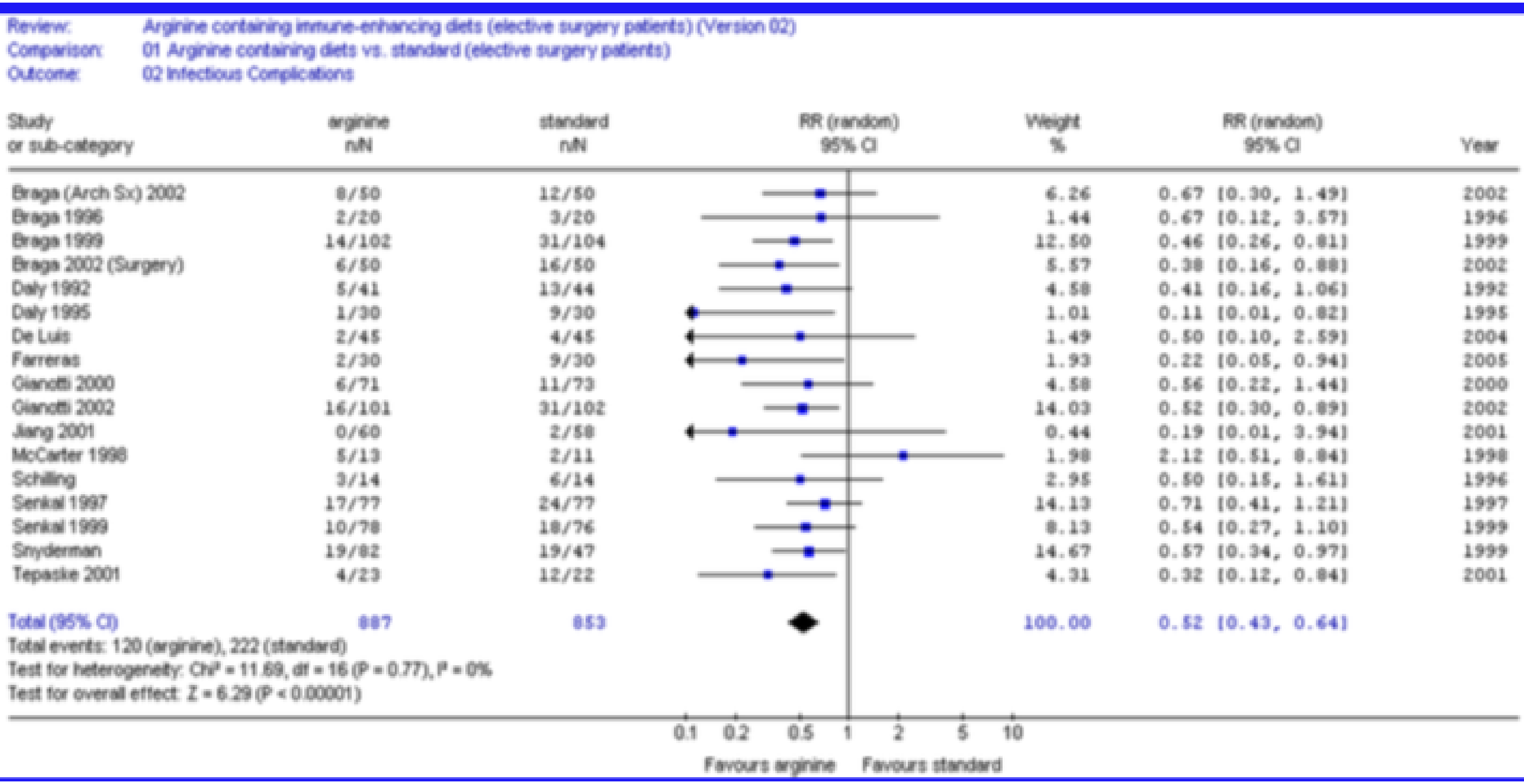
-Substrato per metabolismo energetico cellulare (coenzimi: NAD, FAD, ATP, ecc)

ELECTIVE SURGYCAL PATIENT

Cellular immune dysfunction
-T-cell
Decrease cytokine activation
- IL-2,IFN

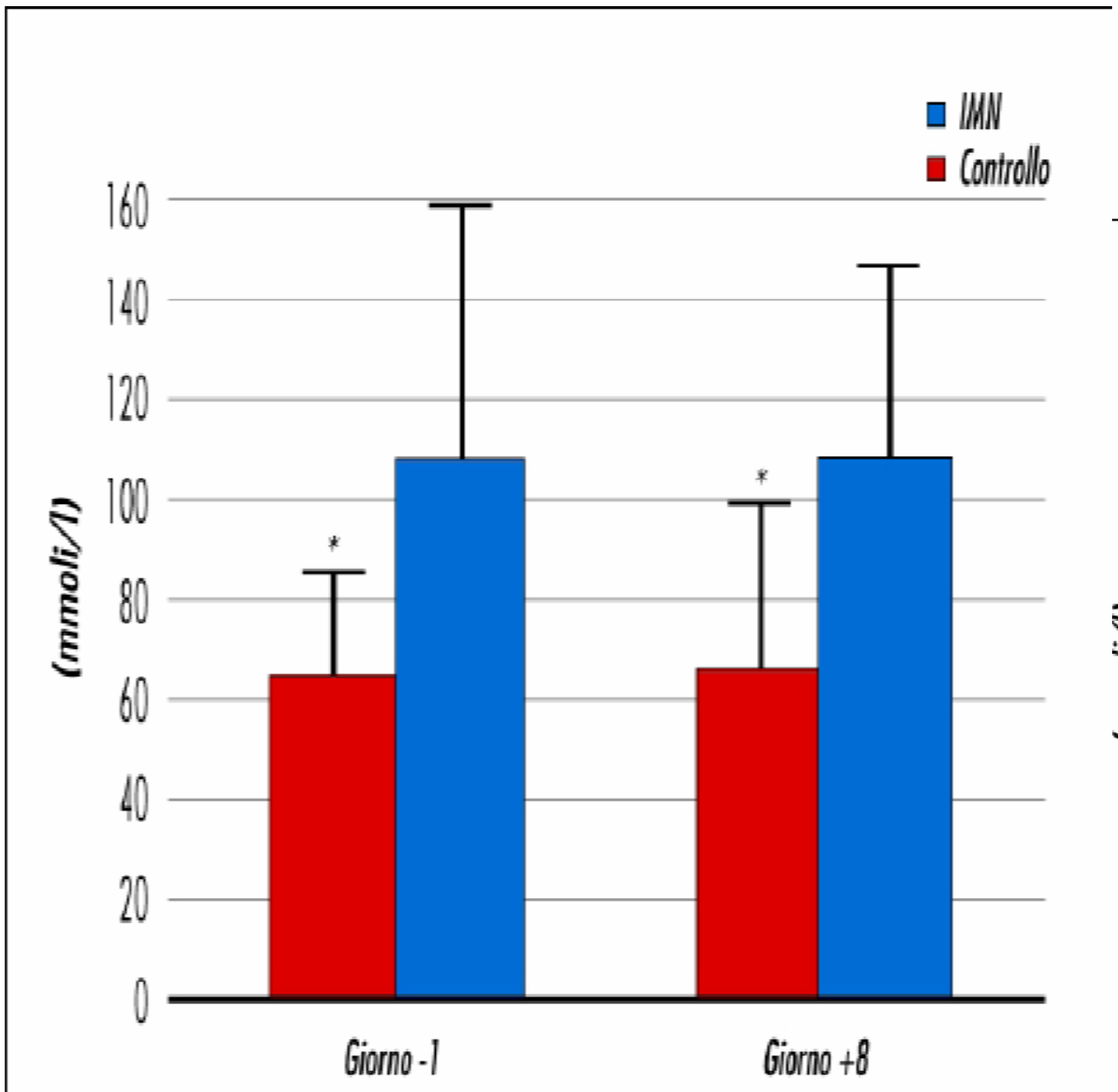
IMMUNONUTRITION IN SURGICAL PATIENTS

Review: Arginine containing immune-enhancing diets (elective surgery patients) (Version 02)
Comparison: 01 Arginine containing diets vs. standard (elective surgery patients)
Outcome: 02 Infectious Complications



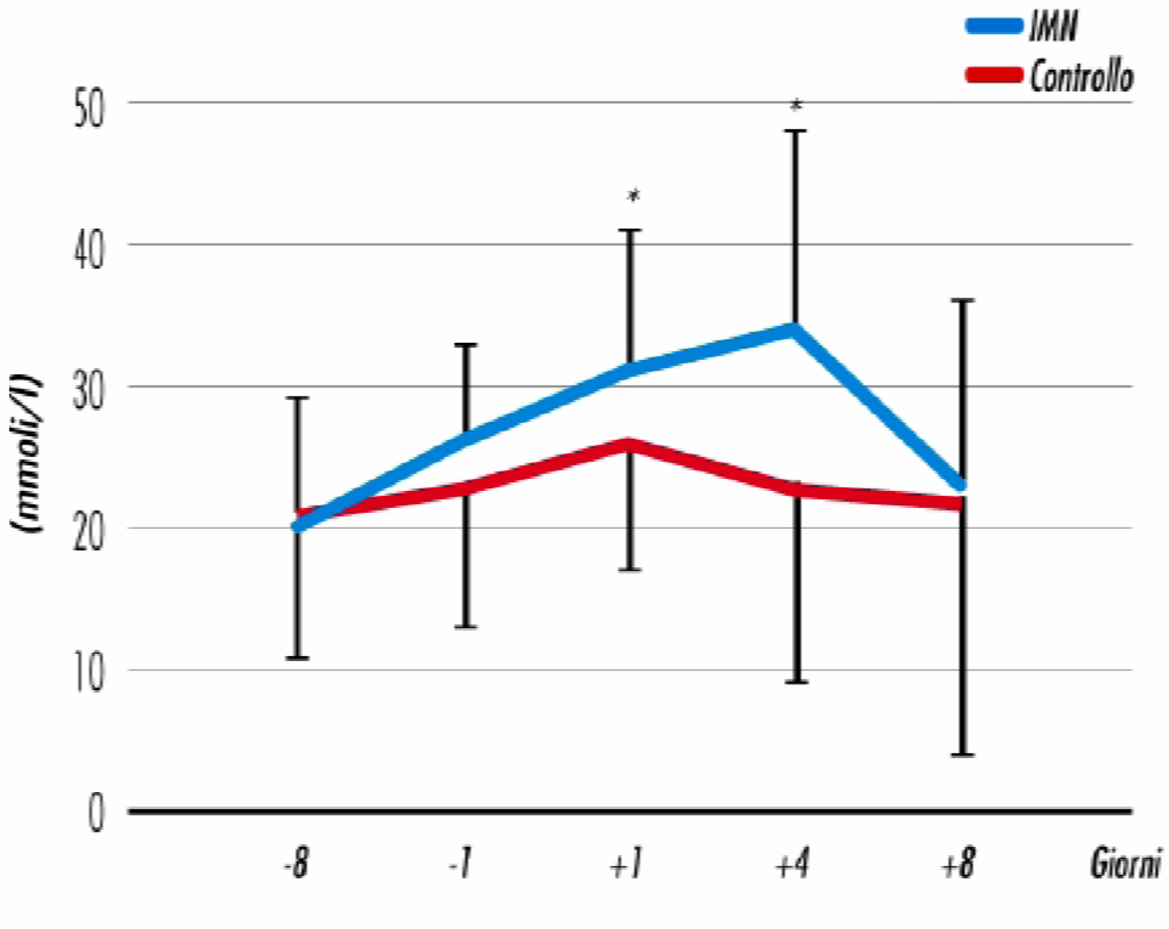
Risultati metabolici dell'immunonutrizione peri-operatoria (1)

Arginina plasmatica



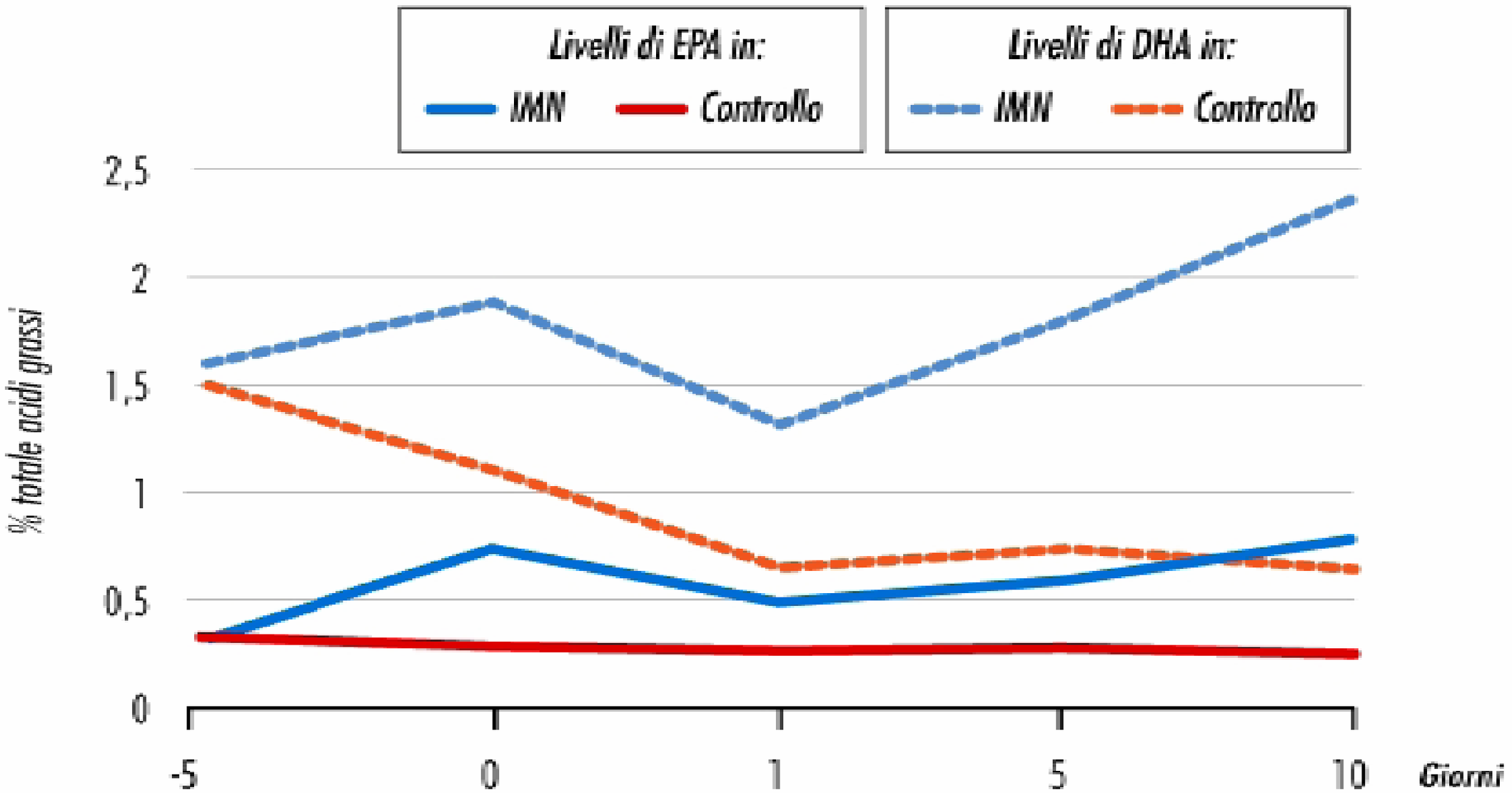
*p<0.05

Ossido nitrico plasmatico

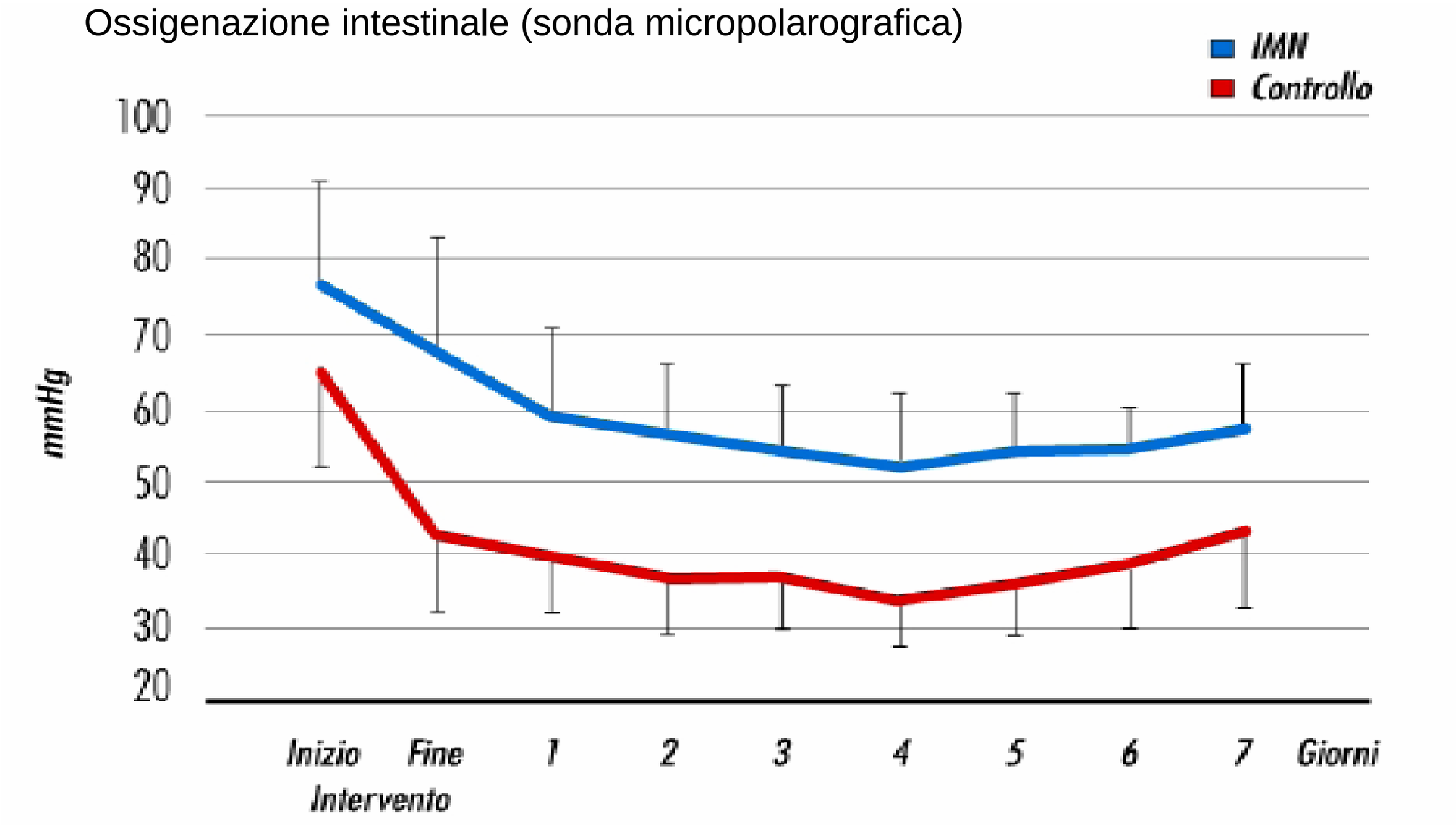


*p<0.05

Risultati metabolici dell'immunonutrizione peri-operatoria (2)



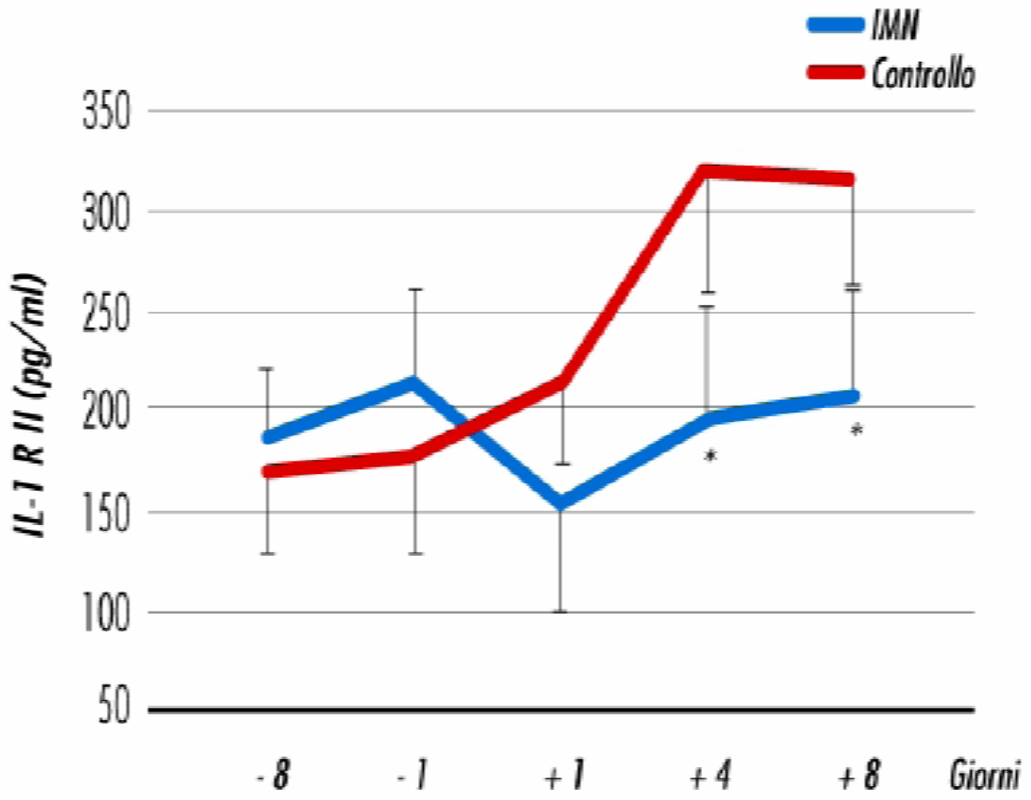
Risultati metabolici dell’immunonutrizione peri-operatoria (4)



P<0.05 a fine intervento e giorno post-operatorio 1,2,3,4,5,6,7.

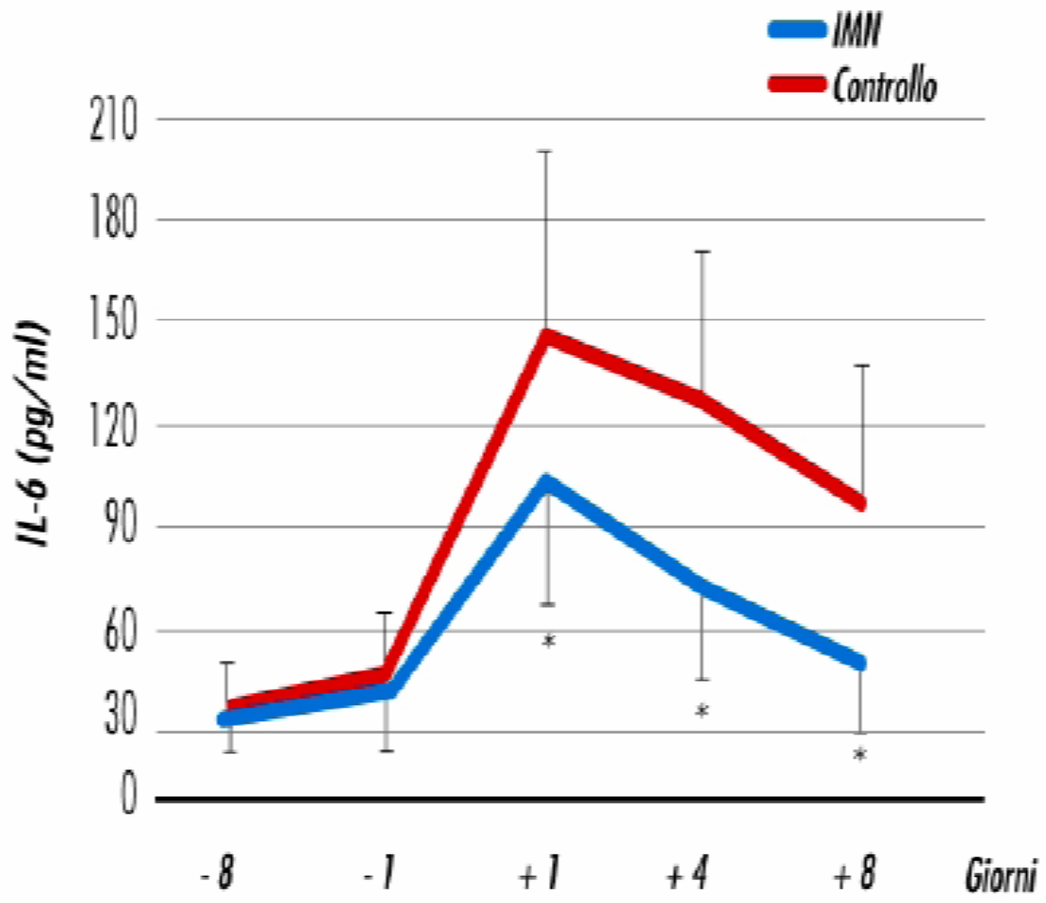
Risultati dell'immunonutrizione peri-operatoria (5)

Recettori solubili dell'interleuchina 1



*p<0.05

Interleuchina-6 plasmatica



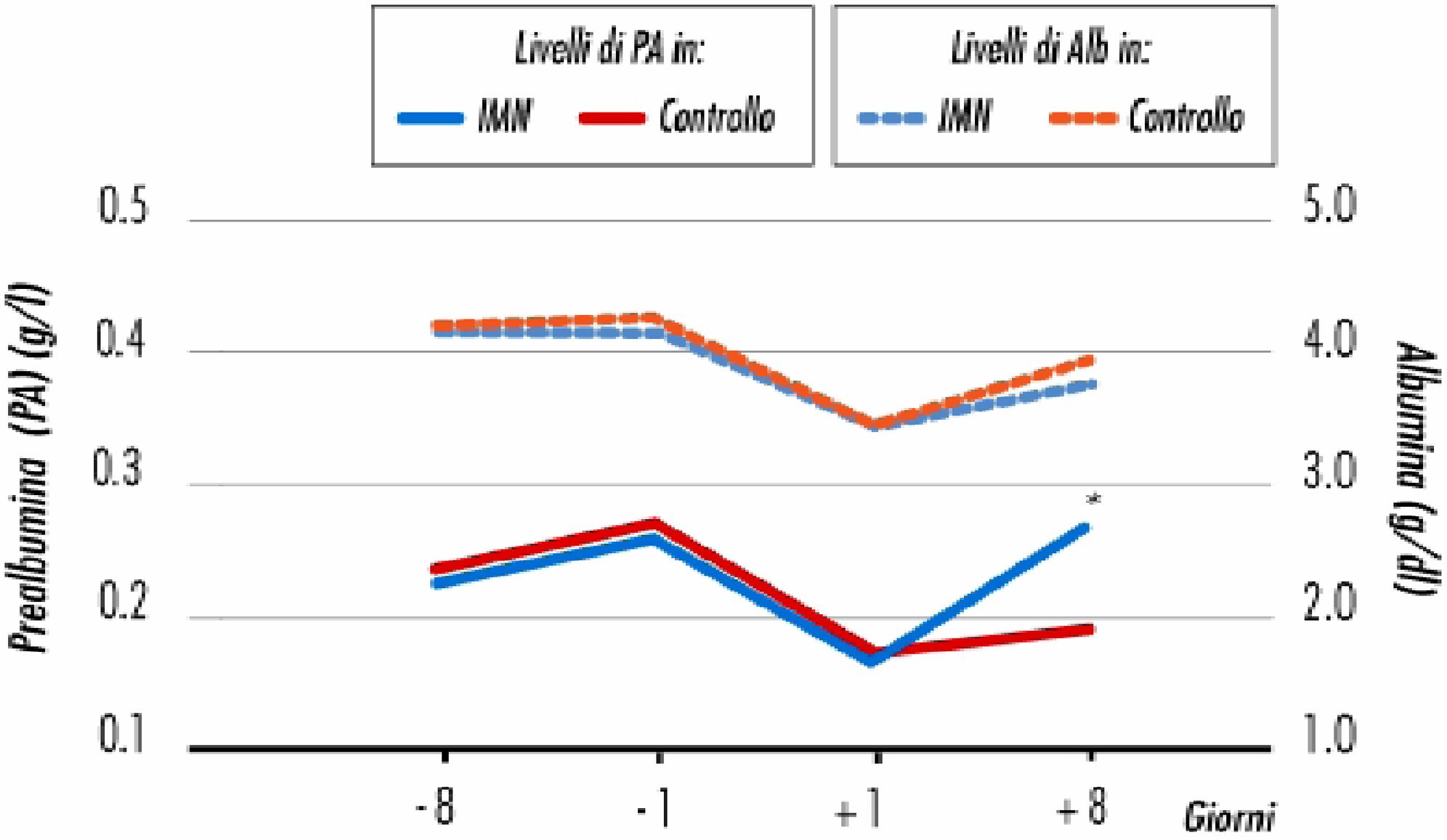
*p<0.05

Risultati metabolici dell'immunonutrizione peri-operatoria (8)

	IMN	Controllo
Linfociti tot.(n/mm^3)	1.353*	1.019
Linfociti T, %	75*	64
CD4, %	54*	41
CD8, %	18*	19
Rapporto CD4/CD8	2.9*	2.1
NK, %	16*	10
Linfociti B, %	13	12

Risultati metabolici dell’immunonutrizione peri-operatoria (10)

Parametri nutrizionali



*p<0.05

Immunonutrizione in pazienti sottoposti a chirurgia colo-rettale

	IMN peri-op (n=50)	IMN pre-op (n=50)	Controllo (n=50)	Convenzio e (n=50)
Decessi	1	0	0	1
Paz. Con compl. Infett.	5(a)	6(b)	16	15
Pz. Con compl. Non infett.	5	4	3	4
Deiscenza anastomotica	3	3	6	5
Terapia antibiotica* (gg±DS)	6.2±1.9 (c)	6.5±1.3(d)	8.8±2.0	8.4±1.8
Durata della degenza (gg±DS)	9.8±3.1(e)	9.5±1.3(f)	12.0±4.5	12.2±3.9

(a)p<0.02 vs controllo e convenzionale; (b)p<0.04 vs controllo e convenzionale; ©p<0.005 vs controllo e convenzionale; (d)p<0.004 vs controllo e convenzionale; (e)p<0.0001 vs controllo e convenzionale; (f)p<0.0005 vs controllo e convenzionale.
*Solo in pz con infezioni post-operatorie

(Braga, Surgery, 2002)

Immunonutrizione pre- e peri-operatoria

Conclusioni (1)

L’immunonutrizione (IMN) pre- o peri- operatoria consente al paziente di presentarsi all’intervento con un assetto immunometabolico ottimale.

Ciò si traduce in:

-incidenza di complicanze infettive: -50% rispetto ai controlli, e ridotta rispetto alla sola IMN post-operatria.

-Riduzione significativa (2-3gg) della degenza ospedaliera.

-Risparmio economico (-50% circa) sui costi di gestione globali.

Should Immunonutrition Become Routine in Critically Ill Patients?

A Systematic Review of the Evidence

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Frantisek Novak, MD
John W. Drover, MD, FRCSC
Minto Jain, MD, FRCSC
Xiangyao Su, PhD
Ulrich Suchner, MD

Context Several nutrients have been shown to influence immunologic and inflammatory responses in humans. Whether these effects translate into an improvement in clinical outcomes in critically ill patients remains unclear.

Objective To examine the relationship between enteral nutrition supplemented with immune-enhancing nutrients and infectious complications and mortality rates in critically ill patients.

Data Sources The databases of MEDLINE, EMBASE, Biosis, and CINAHL were searched for articles published from 1990 to 2000. Additional data sources included the Cochrane Controlled Trials Register from 1990 to 2000, personal files, abstract proceedings, and relevant reference lists of articles identified by database review.

Study Selection A total of 326 titles, abstracts, and articles were reviewed. Primary studies were included if they were randomized trials of critically ill or surgical patients that evaluated the effect of enteral nutrition supplemented with some combination of arginine, glutamine, nucleotides, and omega-3 fatty acids on infectious complication and mortality rates compared with standard enteral nutrition, and included clinically important outcomes, such as mortality.

Data Extraction Methodological quality of individual studies was scored and necessary data were abstracted in duplicate and independently.

Data Synthesis Twenty-two randomized trials with a total of 2419 patients compared the use of immunonutrition with standard enteral nutrition in surgical and critically ill patients. With respect to mortality, immunonutrition was associated with a pooled risk ratio (RR) of 1.10 (95% confidence interval [CI], 0.93-1.31). Immunonutrition was associated with lower infectious complications (RR, 0.66; 95% CI, 0.54-0.80). Since there was significant heterogeneity across studies, we examined several a priori subgroup analyses. We found that studies using commercial formulas with high arginine content were associated with a significant reduction in infectious complications and a trend toward a lower mortality rate compared with other immune-enhancing diets. Studies of surgical patients were associated with a significant reduction in infectious complication rates compared with studies of critically ill patients. In studies of critically ill patients, studies with a high-quality score were associated with increased mortality and a significant reduction in infectious complication rates compared with studies with a low-quality score.

Conclusion Immunonutrition may decrease infectious complication rates but it is not associated with an overall mortality advantage. However, the treatment effect varies depending on the intervention, the patient population, and the methodological quality of the study.

JAMA. 2001;286:944-953 www.jama.com

NOSOCOMIAL INFECTION IN critically ill patients is associated with higher morbidity and mortality, prolonged intensive care unit (ICU) and hospital stay, and increased health care costs.[1-3] Among seriously ill patients, malnutrition has been associated with increased infectious morbidity and prolonged hospital stay.[4] Providing nutrition support has become the standard of care for critically ill patients. Enteral nutrition is preferred to parenteral nutrition for meeting the nutritional needs of critically ill patients with functioning alimentary tracts.[5]

Several specific nutrients such as arginine, glutamine, nucleotides, and omega-3 fatty acids, either alone or in combination, have been shown in laboratory and clinical studies to influence nutritional, immunological, and inflammatory parameters.[6-11] To date, there have been several randomized trials that have evaluated the effect of these immunonutrients on clinically important outcomes. To our knowledge, 2 systematic reviews have already statistically aggregated the results of these randomized clinical trials in critically ill patients.[12,13] However, methodological limitations of

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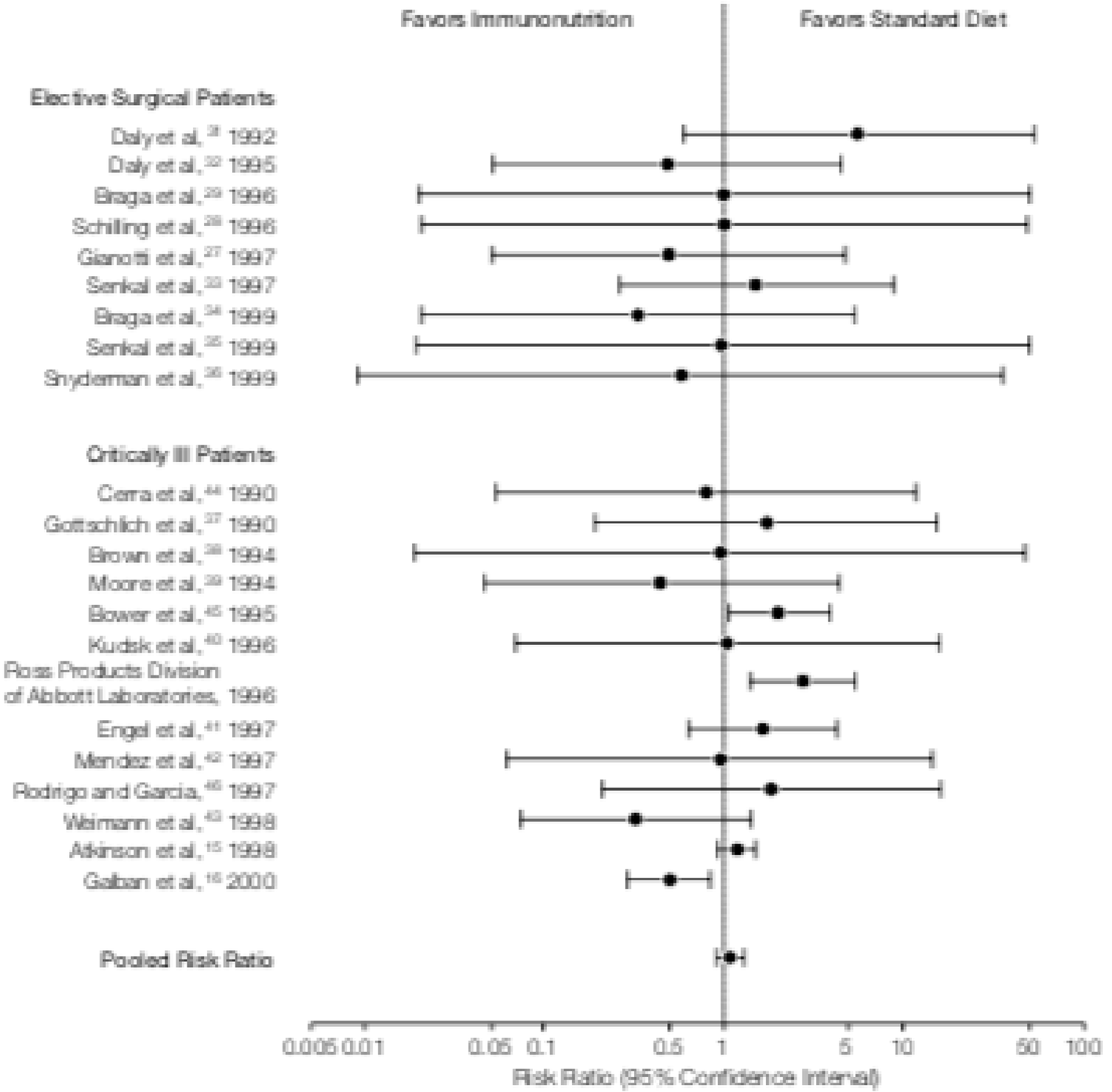
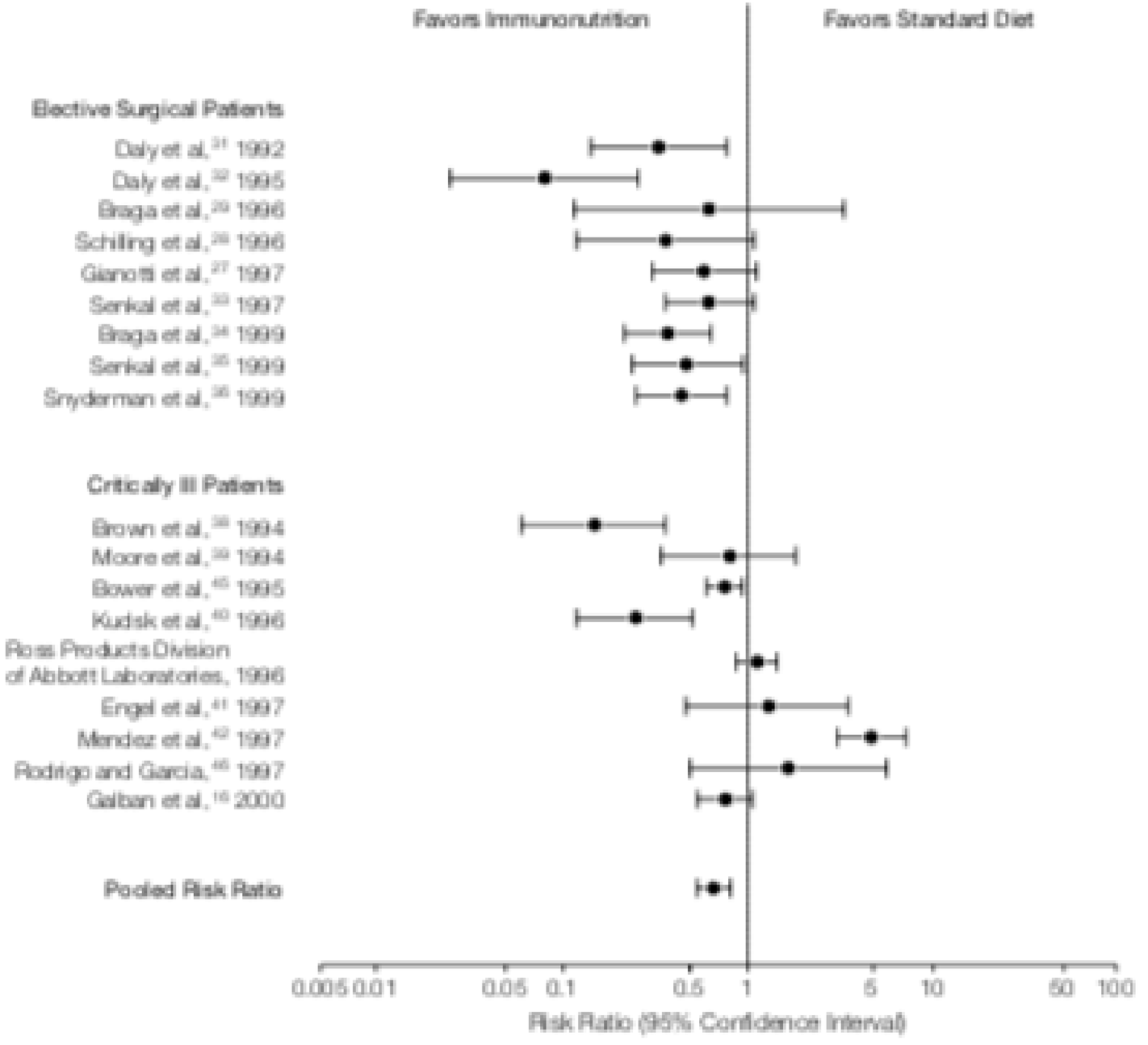
Caring for the Critically Ill Patient Section Editor: Deborah J. Cook, MD, Consulting Editor, *JAMA*.
Advisory Board: David Bihari, MD; Christian Brun-Buisson, MD; Timothy Evans, MD; John Heffner, MD; Norman Paradis, MD.

Figure 1. Effect of Immunonutrition on Mortality in 22 Trials



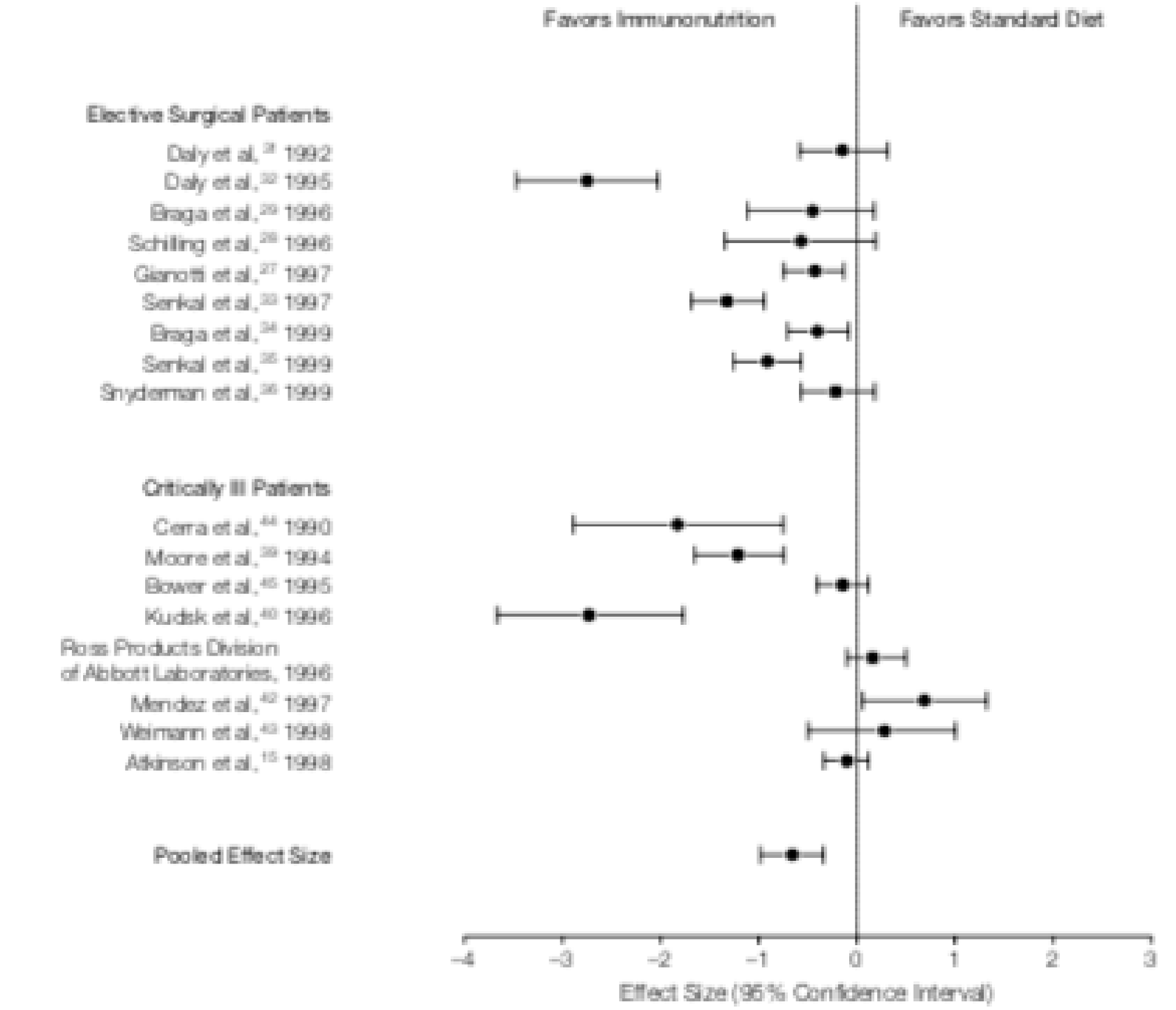
P value for homogeneity is .54. The study by the Ross Products Division of Abbott Laboratories has not been published.

Figure 2. Effect of Immunonutrition on Infectious Complications in 18 Trials



P value for homogeneity is <.001. The study by the Ross Products Division of Abbott Laboratories has not been published.

Figure 3. Effect of Immunonutrition on Length of Hospital Stay in 17 Trials



P value for homogeneity is <.001. The study by the Ross Products Division of Abbott Laboratories has not been published.

Table 2 – Recommendations on immunonutrition according to the international guidelines

Guidelines	Statement	Strength
2006 ESPEN guidelines (19)	*Glutamine should be added to standard enteral formula in burned patients and in trauma patients*	Grade A
Id.	*There are not sufficient data to support glutamine supplementation in surgical or heterogeneous critically ill patients*	
2009 ASPEN guidelines (10)	*Immune-modulating enteral formulations (supplemented with agents such as arginine, glutamine, nucleic acid, ω-3 fatty acids, and antioxidants) should be used for the appropriate patient population (major elective surgery, trauma, burns, head and neck cancer, and critically ill patients on mechanical ventilation), with caution in patients with severe sepsis*	Grade A (surgical ICU pts) Grade B (medical ICU pts)
2009 ESPEN guidelines (18)	*Fish oil enriched lipid emulsions probably decrease length of stay in critically ill patients*	Grade B
2009 CCP Guidelines (12)	*We recommend the use of an enteral formula with fish oils, borage oils and antioxidants in patients with Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS)*	
2013 CCP Guidelines (13)	*When PN is prescribed to critically ill patients, parenteral supplementation with glutamine **should** be considered. However, we strongly recommend that glutamine **NOT** be used in critically ill patients with shock and multi-organ failure. There are insufficient data to generate recommendations for IV glutamine in critically ill patients receiving EN*	
Id.	*The use of an enteral formula with fish oils, borage oils and antioxidants in patients with ALI and ARDS **should** be considered*	
Id.	*Based on 4 level 1 studies and 22 level 2 studies, we do not recommend diets supplemented with arginine and other select nutrients be used for critically ill patients*	
2013 SSC Guidelines (11)	*We suggest using nutrition with no specific immunomodulating supplementation in patients with severe sepsis*	Grade 2C

Which Nutrient for Which Population?

	Elective Surgery	Critically Ill				
		General	Septic	Trauma	Burns	Acute Lung Injury
Arginine	Benefit	**No benefit**	Harm(?)	**(Possible benefit)**	**No benefit**	**No benefit**
Glutamine	**Possible Benefit**	PN Beneficial **Recom-mend**	…	EN Possibly Beneficial: **Consider**	EN Possibly Beneficial: **Consider**	…
Omega 3 FFA	…	…	…	…	…	**Recom-mend**
Anti-oxidants	…	**Consider**	…	…	…	…

Canadian Clinical Practice Guidelines

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ESPEN Guideline

ESPEN guideline on clinical nutrition in the intensive care unit

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SUMMARY

Following the new ESPEN Standard Operating Procedures, the previous guidelines to provide best medical nutritional therapy to critically ill patients have been updated. These guidelines define who are the patients at risk, how to assess nutritional status of an ICU patient, how to define the amount of

3.13. Clinical question 13: Should we use additional enteral/parenteral glutamine (GLN) in the ICU?

Recommendation 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.

Grade of recommendation: B – strong consensus (95% agreement)

Recommendation 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.

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

Recommendation 28

In ICU patients except burn and trauma patients, additional enteral GLN should not be administered.

Grade of recommendation: B – strong consensus (92.31% agreement)

Recommendation 29

In unstable and complex ICU patients, particularly in those suffering from liver and renal failure, parenteral GLN-dipeptide shall not be administered.

Grade of recommendation: A – strong consensus (92.31% agreement)

3.14. Clinical question 14: Should we use enteral/parenteral EPA/DHA?

vRecommendation 30

High doses of omega-3-enriched EN formula should not be given by bolus administration.

Grade of recommendation: B – strong consensus (91% agreement)

Recommendation 31

EN enriched with omega-3 FA within nutritional doses can be administered.

Grade of recommendation: 0 – strong consensus (95% agreement)

Recommendation 32

High doses omega-3 enriched enteral formulas should not be given on a routine basis.

Grade of recommendation: B – consensus (90% agreement)

Recommendation 35

Antioxidants as high dose monotherapy should not be administered without proven deficiency.

Grade of recommendation: B – strong consensus (96% agreement)

Recommendation 33

Parenteral lipid emulsions enriched with EPA + DHA (Fish oil dose 0.1-0.2 g/kg/d) can be provided in patients receiving PN.

Grade of recommendation: 0 – strong consensus (100% agreement)

To enable substrate metabolism, micronutrients (i.e. trace elements and vitamins) should be provided daily with PN.

Grade of recommendation: B – strong consensus (100% agreement)

ONE SIZE DOES NOT FIT ALL

- Variation in degrees of acute phase response, protein loss, gut function and immune system alterations.
- 15-70% of hospitalised patients are undernourished or malnourished on admission, further complicating the provision of optimal nutrition therapy.
- A “one nutrition therapy regimen will fit all” approach is simplistic and unable to provide optimal therapeutic support.

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Thank You!