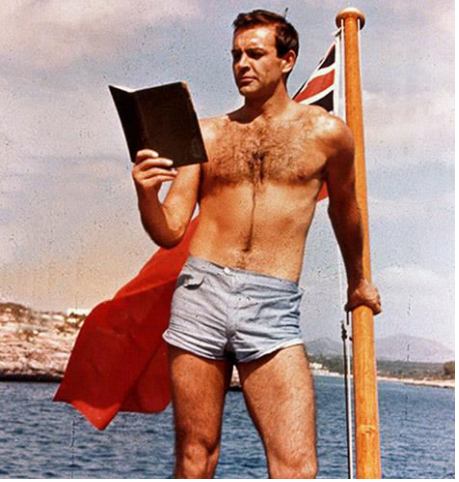
Giornate Catanesi di Nutrizione Clinica
10|11 Maggio 2019

«LA NUTRIZIONE E LA MALATTIA»

Farmaconutrizione nel paziente geriatrico immunodepresso

Pietro Vecchiarelli



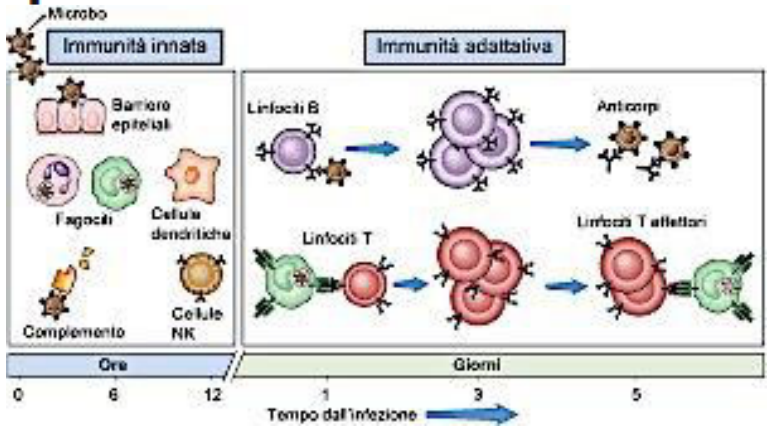
What is Aging?

Complex transition that includes a physiological and cognitive vulnerability making the individual more prone to diseases and acute medical events, leading to further decrease in reserve capacities of functional indipendency and ultimately to death

Guidet *et al. Ann. Intensive Care* (2018) 8:114

Immune-inflammatory responses in the elderly: an update

Giulia Accardi[1,2] and Calogero Caruso[1,2*]



Immunosenescence: age related decline in immune function at the cellular and serological level.

These changes lead to poor response to newly encountered microbial antigens, including vaccines, as well as to shift ot the immmune system towards an inflammatory, autoimmune profile.

This immune dysregulation provides the background for an increased susceptibility to autoimmune diseases, cancer, metabolic diseases, osteoporosis, neurological disorders, as well as allergic inflammation and infections.

Accardi and Caruso *Immunity & Ageing* (2018) 15:11
https://doi.org/10.1186/s12979-018-0117-8

Aging Clinical and Experimental Research
https://doi.org/10.1007/s40520-018-0936-7

ORIGINAL ARTICLE

Sicilian centenarian offspring are more resistant to immune ageing

Graziella Rubino[1,2] · Matteo Bulati[2] · Anna Aiello[2] · Stefano Aprile[2] · Caterina Maria Gambino[2] · Francesco Gervasi[3] · Calogero Caruso[2] · Giulia Accardi[2]

Received: 8 January 2018 / Accepted: 21 March 2018

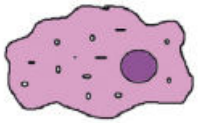
The whole present data confirm and extend the previous results showing that centenarian offspring retain more youthful immunological parameters and that the exhaustion of the immune system is less evident than in elderly without centenarian parents [15, 39–43].

Innate Immune Cells

Age-Associated Changes

Neutrophils 

- Decreased phagocytosis
- Decreased chemotaxis
- Defective apoptosis function

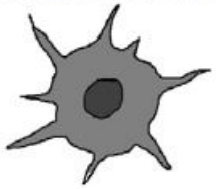
Macrophages 

- Decreased antigen presentation
- Decreased superoxide anion production
- Defective phagocytosis
- Decreased cytokine production

NK cells 

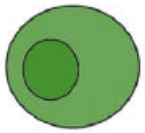
- Reduced cytolytic potential
- Decreased cytokine and chemokine production
- Reduced CD1 expression in NKT cells

Bridging innate and adaptive immunity

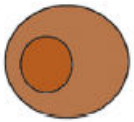
DC 

- Reduced IFN production
- Reduced expression of CD25 and ICAM-1 in mature MODCs
- Reduction in lymphocyte cytotoxicity and greater migratory capacity of monocyte-macrophage derived APCs.

Adaptive Immune Cells

T Cells 

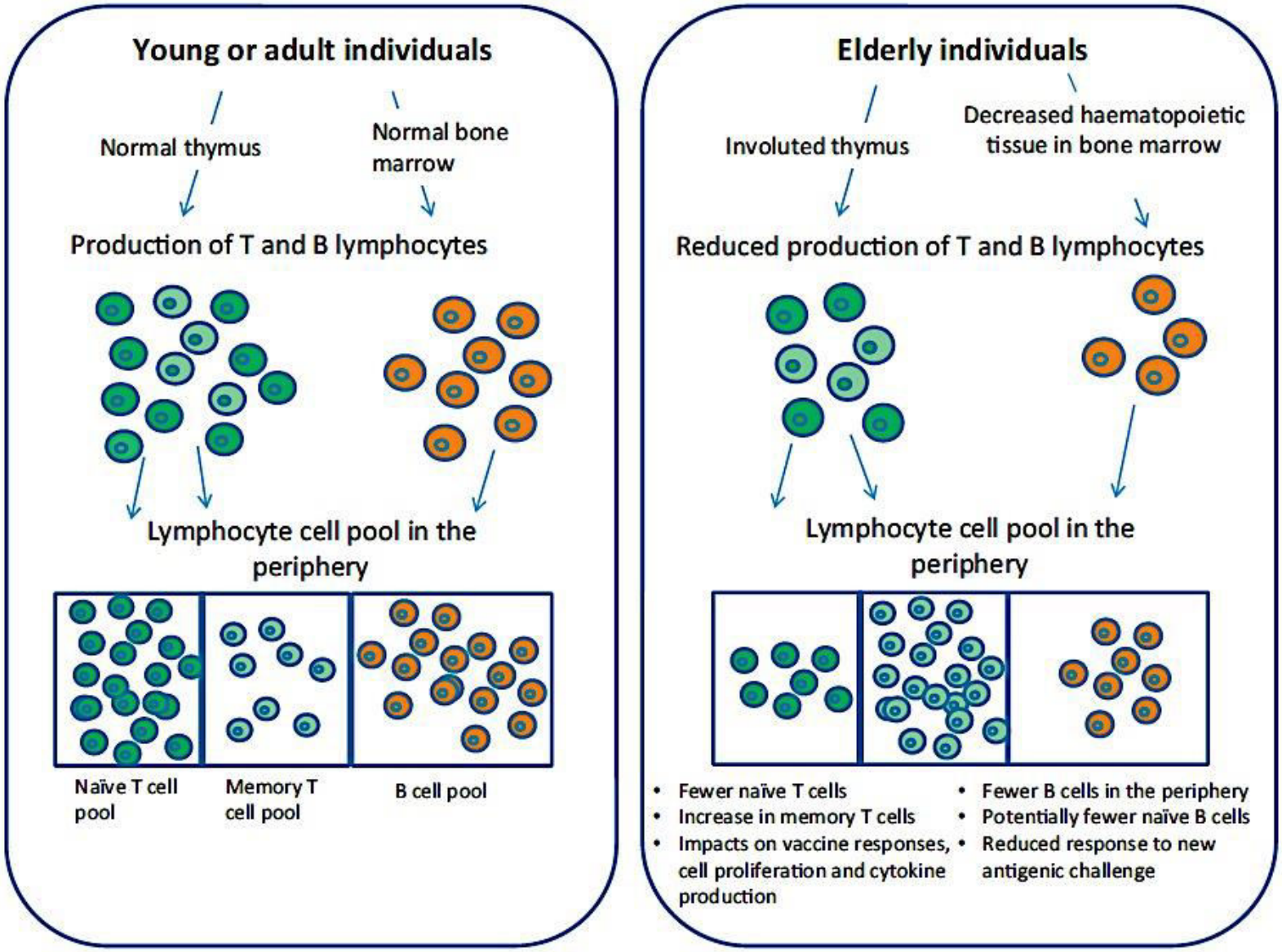
- Reduced development (Thymus atrophy). Reduced numbers of naïve $CD4^+/CD8^+$ T cells, and increased number of effector and memory $CD4^+/CD8^+$ T cells
- Decline in $CD8^+$ T cell cytotoxicity and proliferation
- Decline in CD4+ function, less generation of Th subsets (Th1 and Th2)

B cells 

- Reduced development. Reduced number of naïve B cells
- Decrease in B cell responses to new antigens
- Decreased diversity of B cell repertoires in elderly subjects

Maijo M.et al Mech Ageing Dev, 2014

Effect of age on the production and distribution of lynphocytes



Maijo M.et al Mech Ageing Dev, 2014

INFLAMM-AGING

Chronic, sterile, subclinical , low grade inflammation related to the ageing, produced as consequence of:

- Dysfunctional mitochondria;
- Defective autophagy;
- Endoplasmic reticulum stress;
- Activation of inflammasome by cells debris;
- Defective ubiquitin/proteasome system;
- Activation of DNA damage response;
- Senescent T cells;
- Age-related changes in the composition of microbiota (dysbiosis)

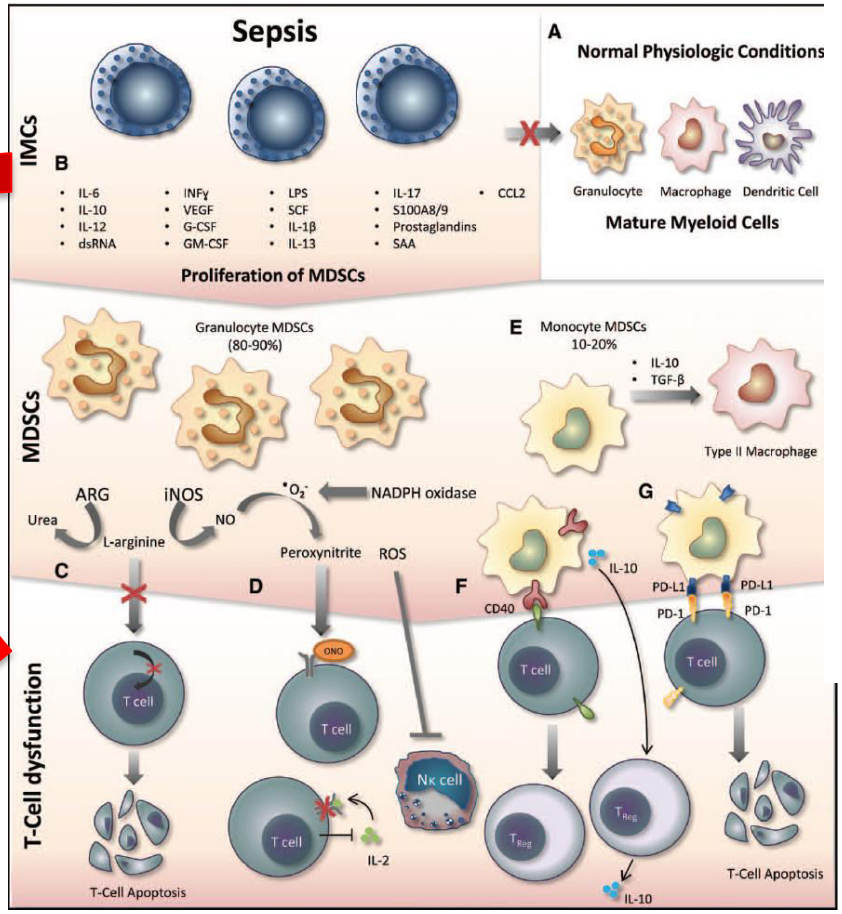
Fulop T.et al. Frontiers in Immunology, 2018

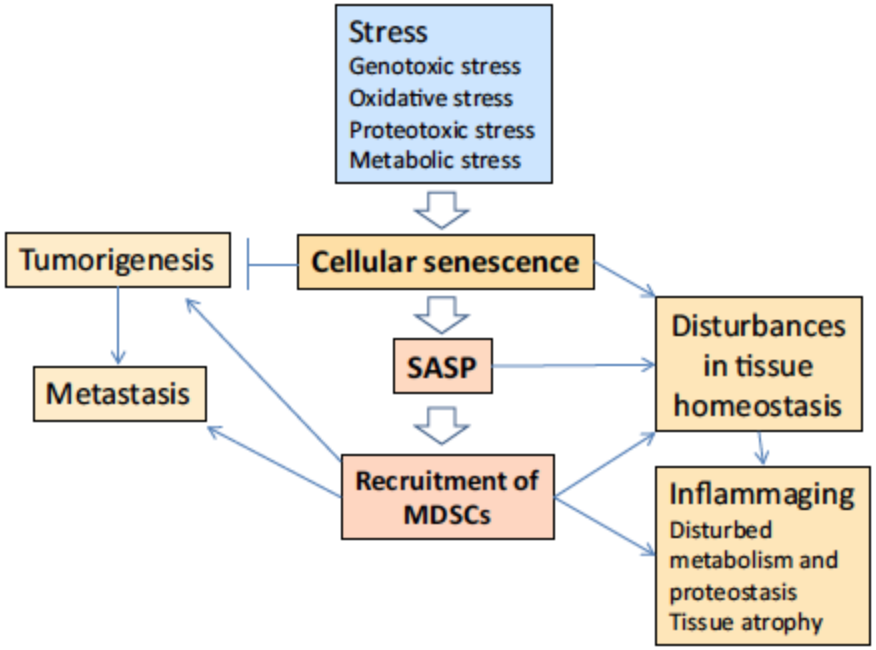
Expansion of myeloid-derived suppressor cells with aging in the bone marrow of mice through a NF-κB-dependent mechanism

Flores R et al. Aging Cell 2017

Although it has been demonstrated that the percent of MDSC as well as MDSC with NF-κB activation increases with accelerated and natural aging, the role of the MDSC, if any, in the aging process is unclear. It is also unclear whether the expansion of MDSCs drives aging or only is a consequence of aging. However, given that MDSCs accumulate in the spleen, peripheral lymph nodes, bone marrow, and blood of normal aged mice and are significantly increased in the circulation of aged individuals, it is likely that MDSCs contribute to age-associated immune dysfunction. Similarly, the increase in MDSCs with aging could contribute to the increased risk of cancer.

Role of MDSCs





IMC= Immature Myeloid Cells

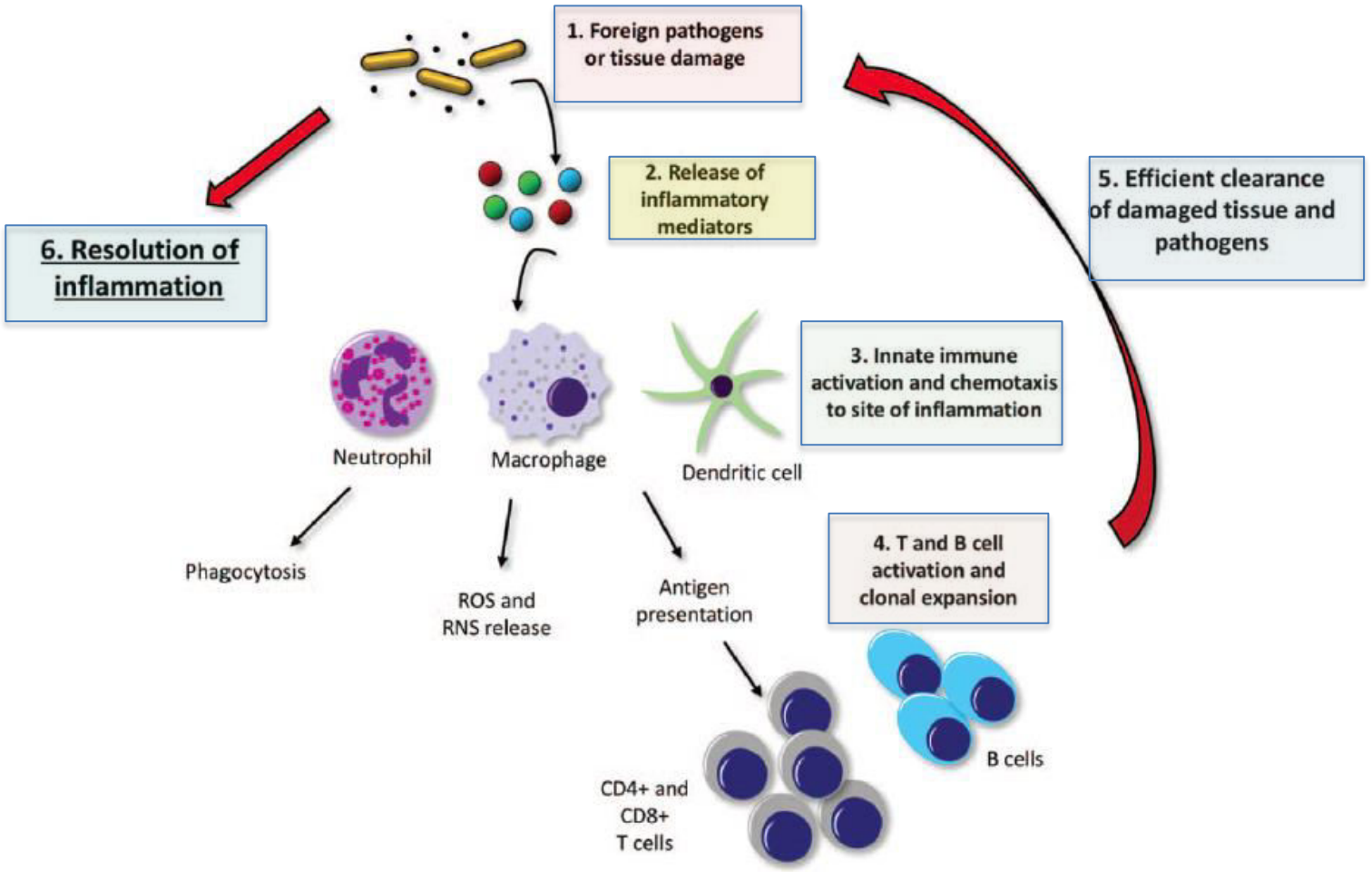
MDSCs= Myeloid Derived Suppressor Cells

SASP= Senescence Associated Secretory Phenothype

Mira JC et al. Crit Care Med 2017

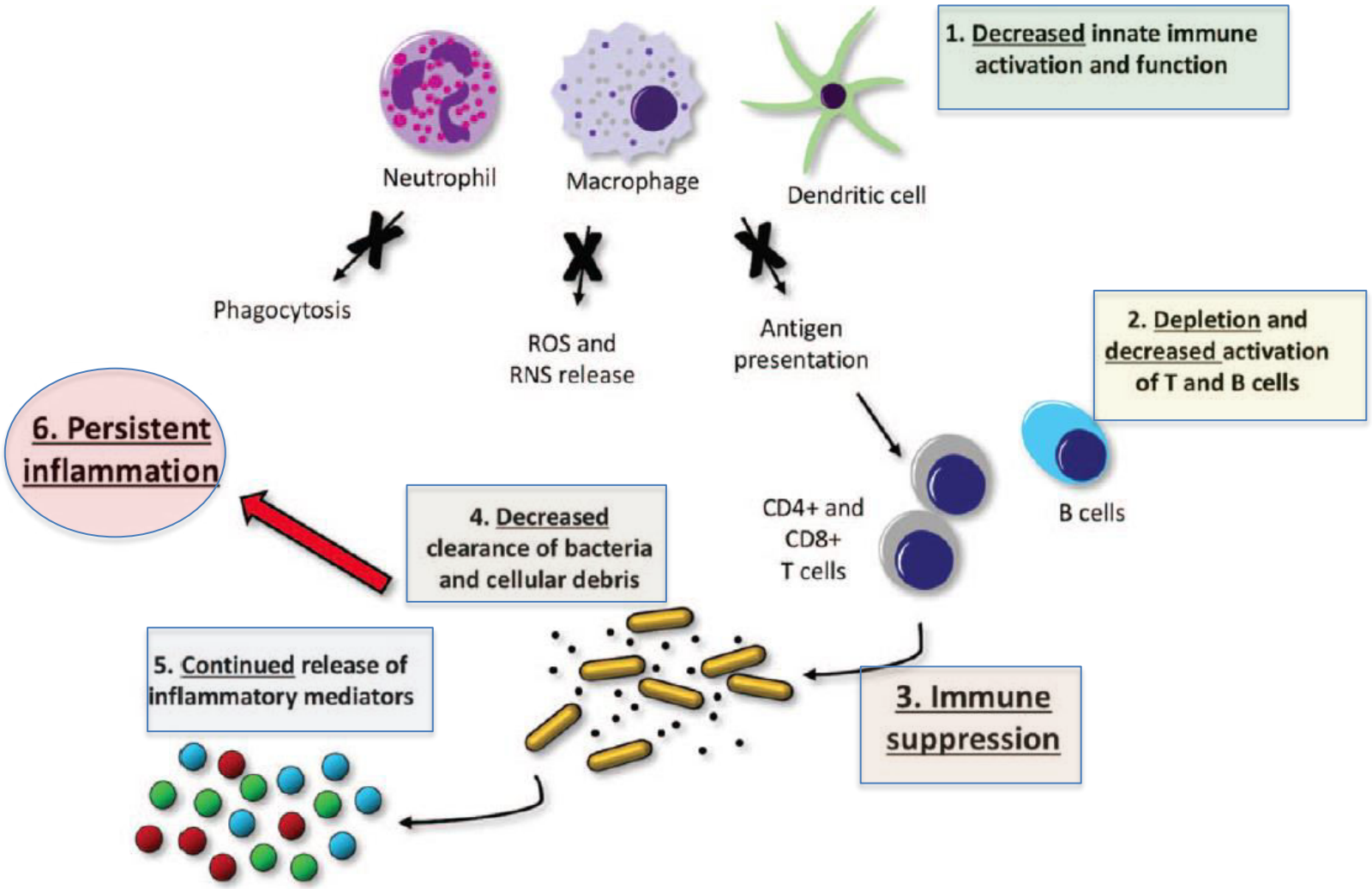
Salminen A et al Biogerontology, 2018

The host response to infection



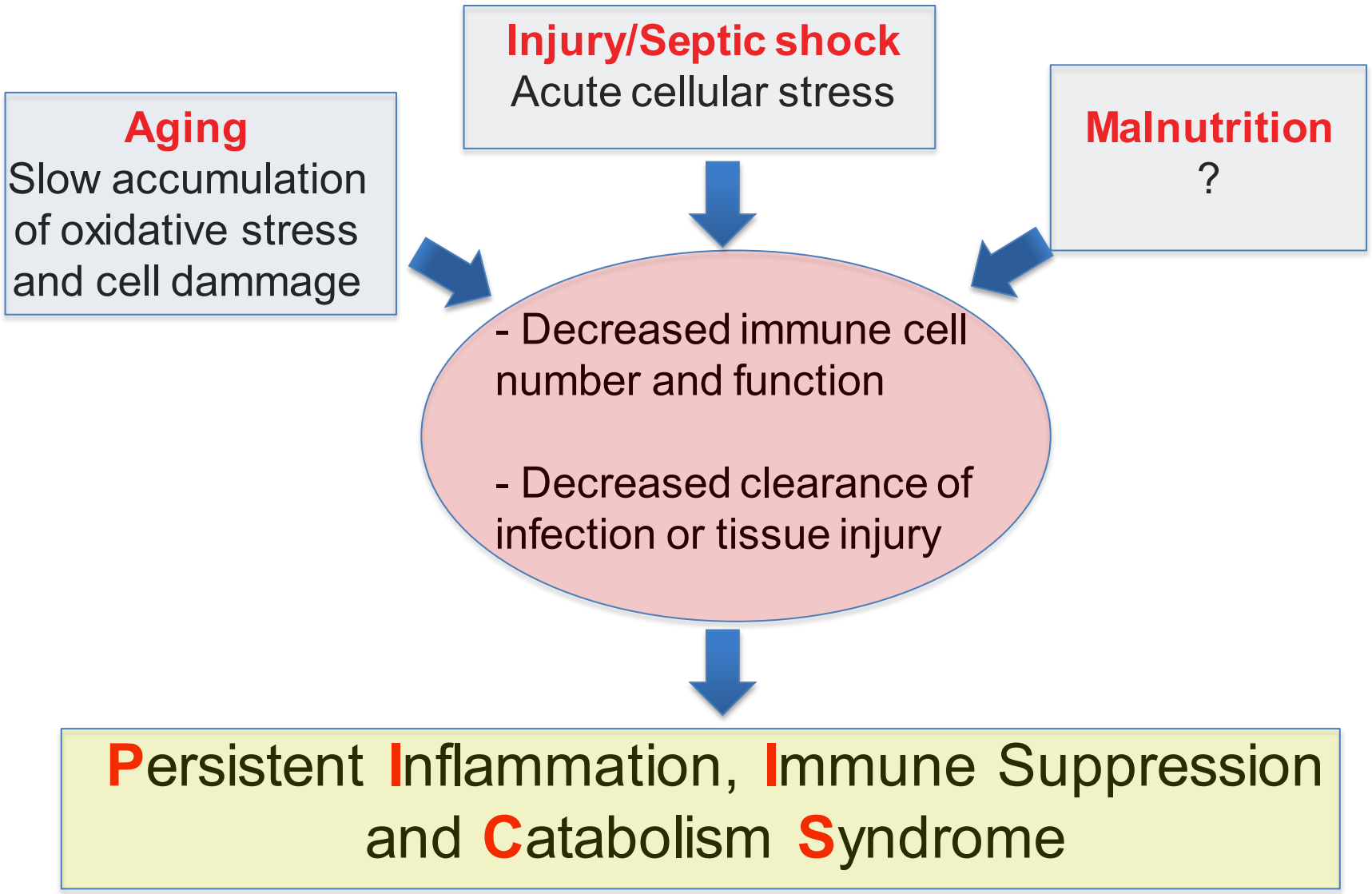
Nomellini V et al. Shock, 2018

The development of persistent inflammation and immunosuppression



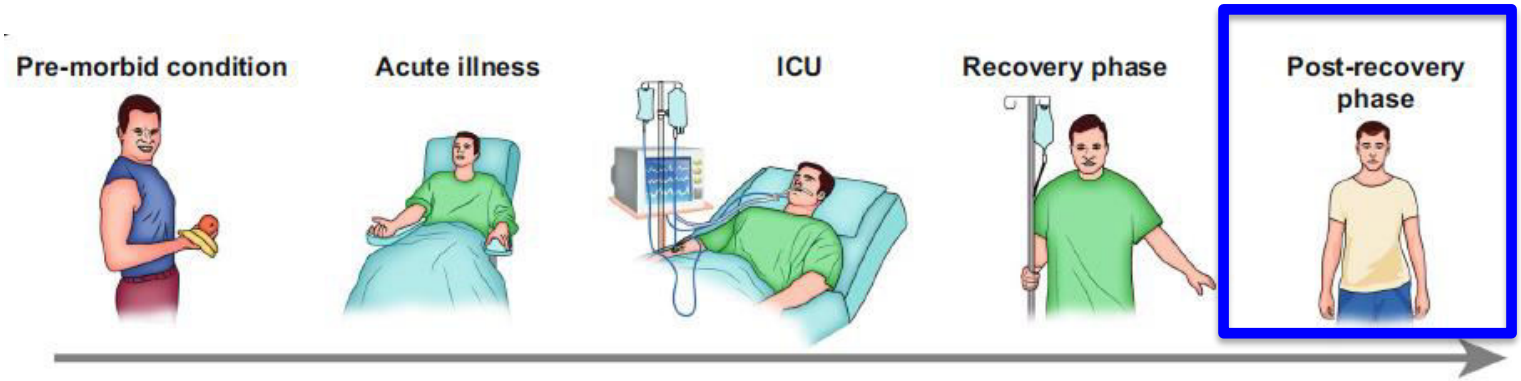
Nomellini V et al. Shock, 2018

The divergent yet similar pathways to develop PICS



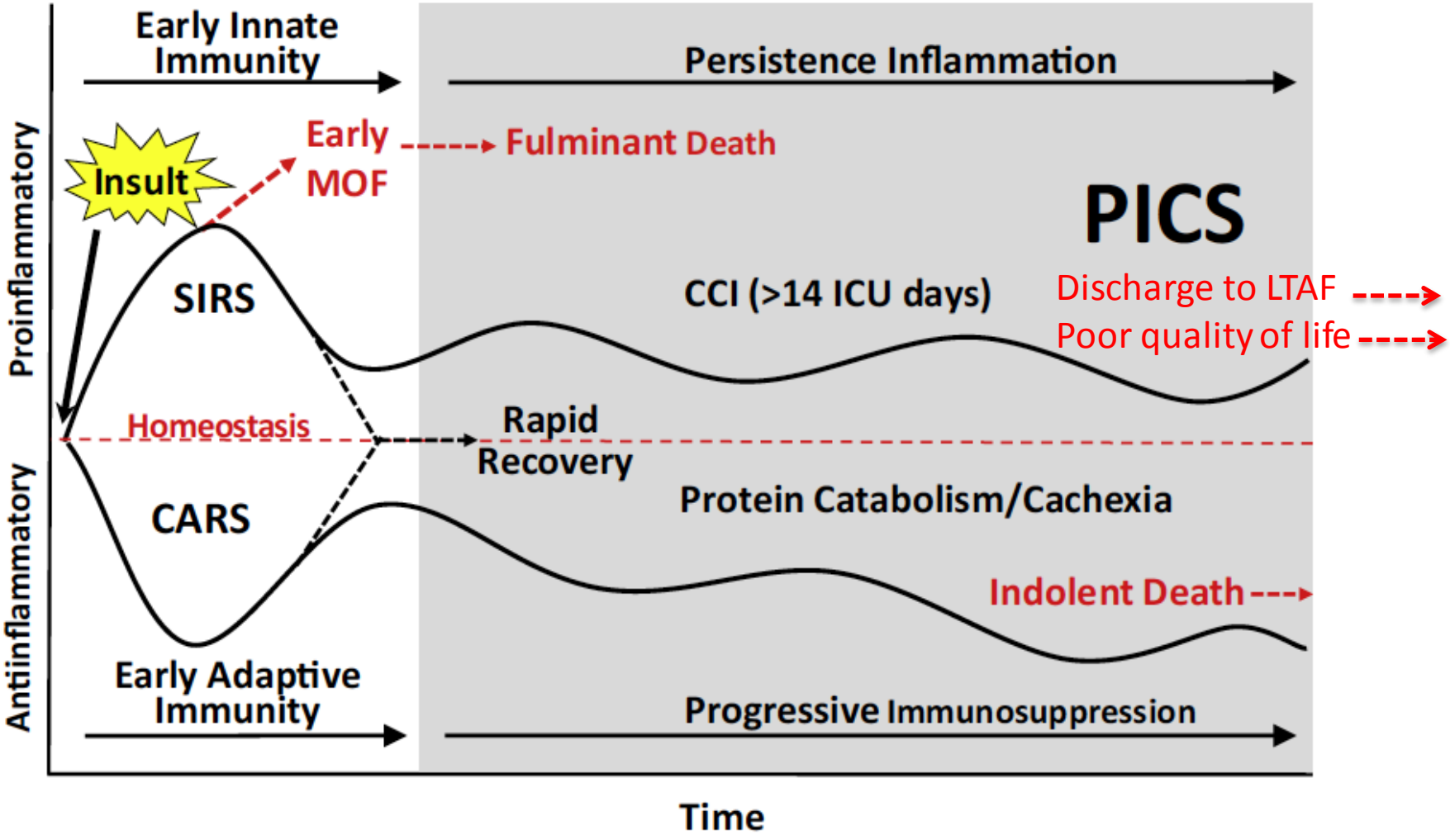
Nomellini V. et al Shock, 2018

Phases of critical illness: a guess!



Acute phase				
	Organ dysfunction	**Inflammation**	**Metabolic status**	**Days**
Early	Severe/progressive	Progressive	**Catabolic**	1-3
Late	Stable/regressive	Persistent/Regressive	**Catabolic-** Anabolic	2-4
Post acute phase				
Recovery	Reconstitution	Resolution of inflammation	Anabolic	> 7
Chronic	Persistent	Persistent Inflammation & Immunosuppression	**Catabolic**	> 7

The new paradigm of Persistent Inflammation, Immunosuppression and Catabolism Syndrome (PICS)



Mira J.C. et al Crit Care Clin, 2017

Markers used to idetify patients with/or a risk of PICS

PICS	Measurement
Critically ill patient	Admission to the ICU >14 d
Persistent inflammation	CRP >50 μg/dL
Persistent immunosuppression	Total lymphocyte count $<0.80 \times 10^9$/L
Catabolic state	Serum albumin <3.0 g/dL Prealbumin <10 mg/dL Creatinine height index <80% Weight loss >10% or BMI <18 during hospitalization

Mira J.C. et al Crit Care Clin, 2017

Research

Open Access

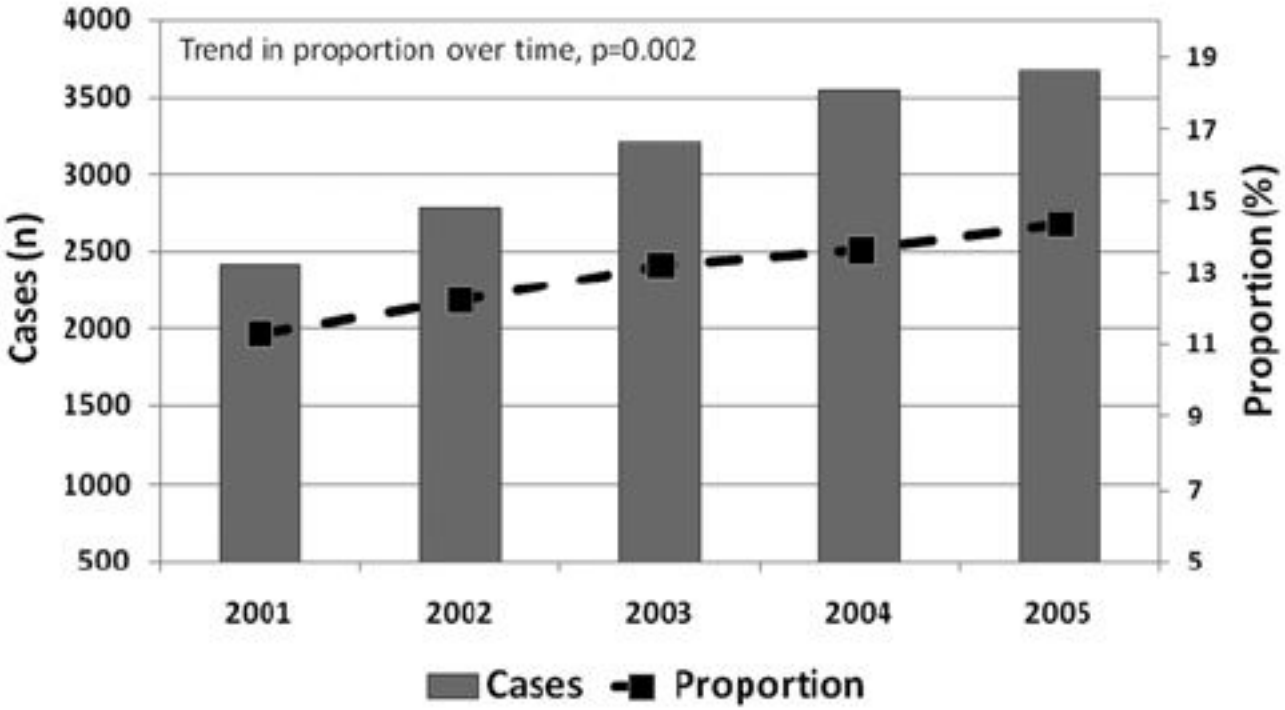
Very old patients admitted to intensive care in Australia and New Zealand: a multi-centre cohort analysis

Sean M Bagshaw[1,2], Steve AR Webb[3,4], Anthony Delaney[5], Carol George[6], David Pilcher[7], Graeme K Hart[1] and Rinaldo Bellomo[8]

Table 1

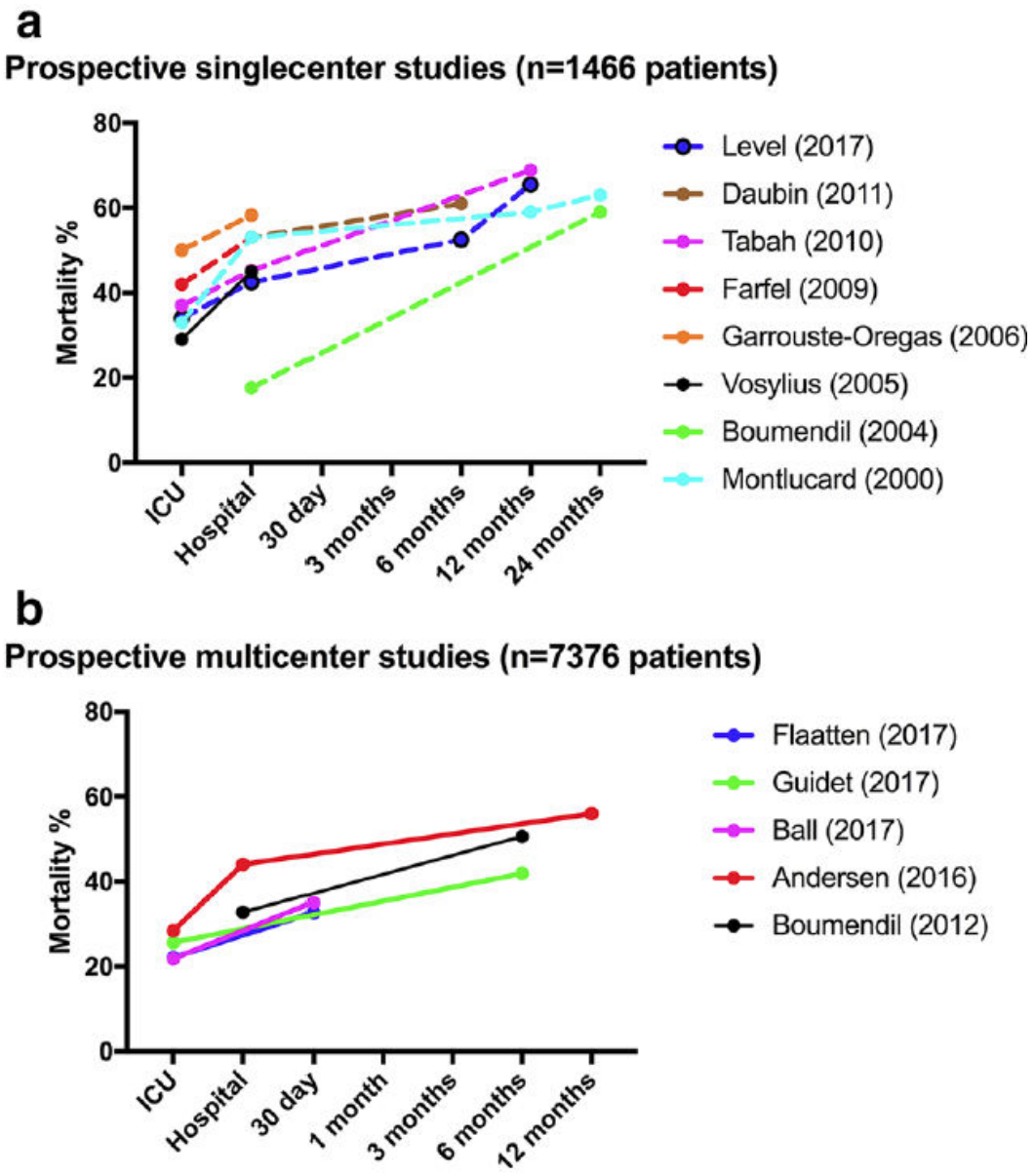
Summary of patient demographics, admission details and primary diagnoses by age strata

Characteristics						P value
					(n = 15,640)	
Age (years)						<0.0001
Male sex						<0.0001
Hospital admission sou						
Home						<0.001
Other acute care hospital						
Chronic care facility						
Other intensive care						
Co-morbid disease						



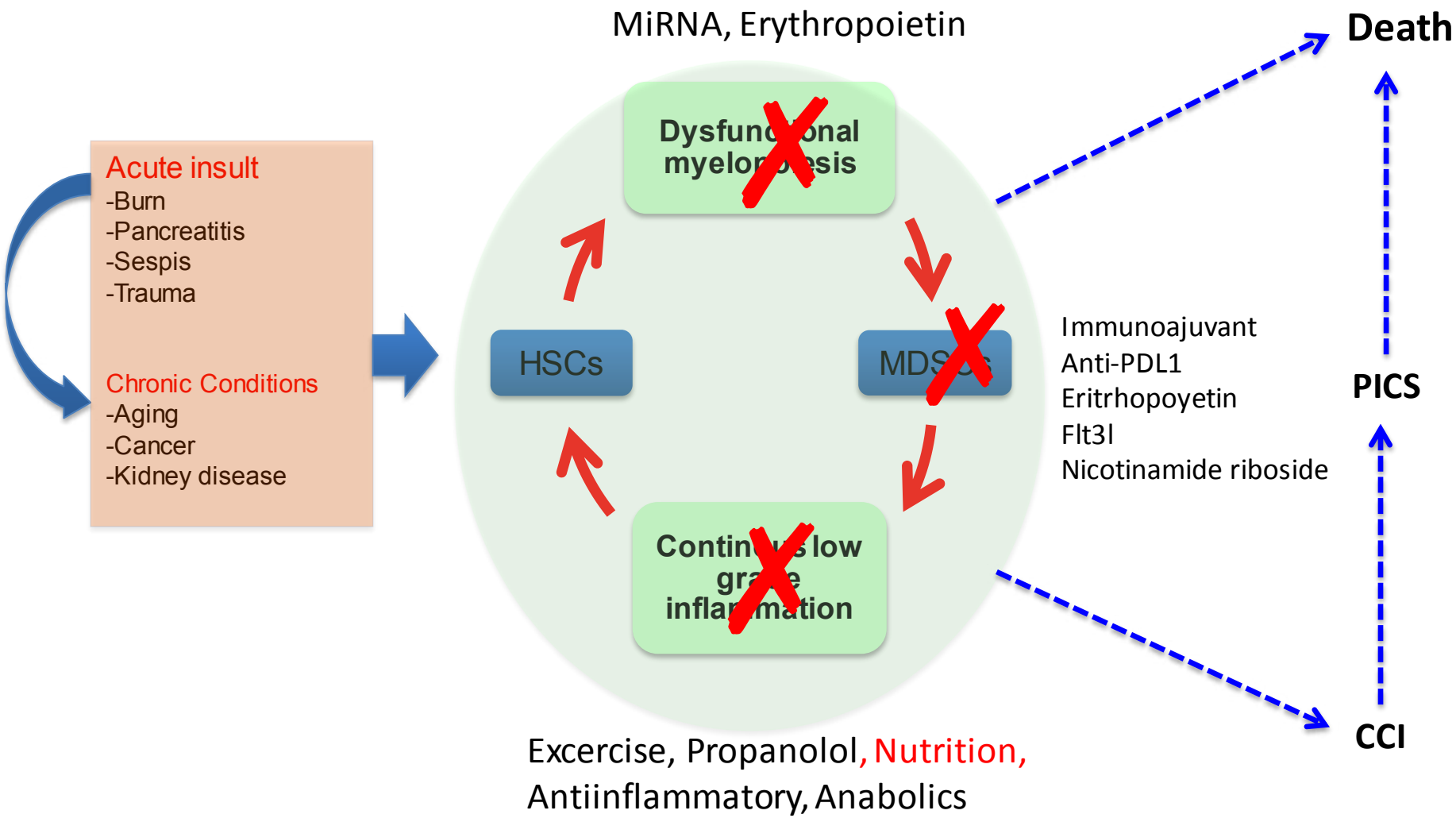
Critical Care 2009,

Mortality rates in elderly patients at ICU and hospital discharge



Guidet *et al. Ann. Intensive Care* (2018) 8:114

Can we interrupt this vicious cycle?



Efron P.A. et al. Annual Update In Intensive Care and Emergengy Medicine 2018. Springer

Farmaco-Nutrition

Proteins

Micronutrients

Vitamines

Aminoacids

Fatty Acids

Probiotics

Symbiotics

Antioxidants

Prebiotics

Nucleotides

Vitamin E ingestion improves several immune functions in elderly men and women

Free Radical Research, March 2008; 42(3): 272–280

MONICA DE LA FUENTE[1], ANGEL HERNANZ[2], NOELIA GUAYERBAS[1], VICTOR MANUEL VICTOR[1], & FRANCISCO ARNALICH[3]

- ✓ Contained in the membranes of the immune cells
- ✓ Strong antioxidant
- ✓ Enhance immune response + cell mediated immunity
- ✓ Icreases resistance to respiratory infections in nursing home residents
- ✓ Dose: 200 mg daily for 3 months is an optimal dose for improving T cell mediate functions in the elderly

ZINC

- ✓ Zinc deficiency affects multiple immune cells involved in both innate and adaptive immunity;
- ✓ The elderly often have a low serum Zinc level (inadequate intake, impaired metabolism, infection, inflammation…);
- ✓ Evidence from the literature indicates that the elderly might benefit from optimizing serum Zinc level trought adeguate intake;
- ✓ So far optimal Zinc intake is unknow;

Cossack 1989; Prasad 2003 and 2006; Bao 2003	45 mg of zinc/day for 6 months (zinc sulfonate)
Fortes 1998	25 mg/day for 3 months (Zinc sulfate)
Kahmann 2006; Metz 2007	10 mg of pure zinc (50 mg zinc-aspartate) per day for 48 days

Immunosenescence and nutrition: reviewing clinical evidence on pre-, pro- and synbiotics in aging

Renata Ramalho[1,2,3*]

J Allergy Immunol, 2017

Study / Reference	Design and Participants	Intervention	Outcomes	Results
Probiotics				
	• Randomized, placebo-			• Increase in NK cell activity, reduction

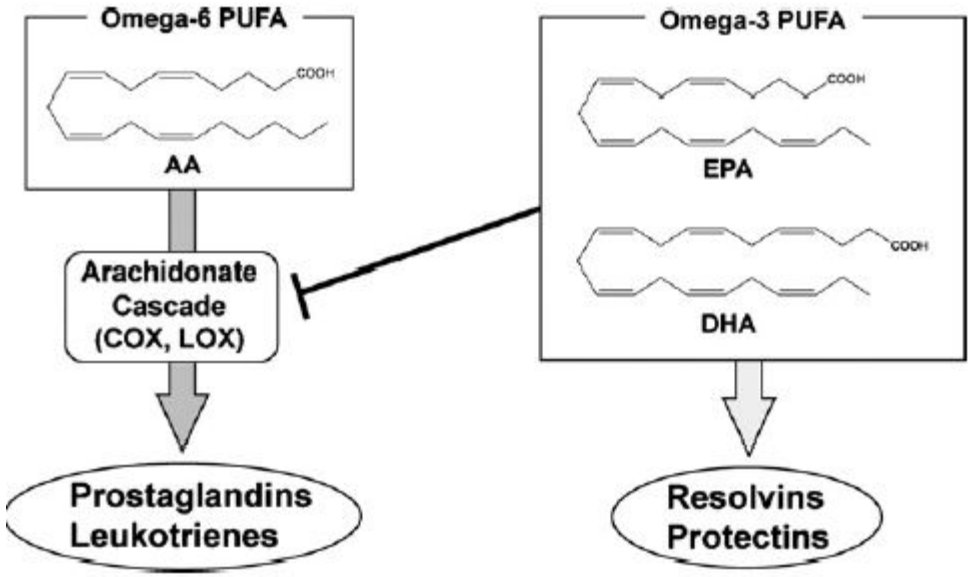
The evidence is scarse with reduced number of studies and including small group of partecipants…heterogeneity in design and type of interventions is an important limitation.

Despite this limitation, it seems that pre-, probiotics and synbiotics may represent a nutritional modulation for immunesenescence.

Synbiotics				
Macfarlane *et al.*, 2013 [116]	• Randomized, placebo-controlled, double-blinded cross-over study • 43 volunteers (22 females), 65-83 years-old	• 1 gelatin capsule *B. longum* ($2x10^{11}$ CFU)+6g Synergy I (Inulin+Oligofructose) twice a day for 2 weeks • Placebo: 1 capsule potato starch+6g Maltodextrose twice a day for 2 weeks	• Faecal microbiota • Inflammatory markers • Biochemical profiles	• Increase in number of faecal bifidobacteria (*Actinobacteria* and *Firmicutes*). • Reduction in faecal *Proteobacteria*. • Reduction in TNF-α.
Ouwehand *et al.*, 2009 [117]	• Randomized, placebo-controlled, double-blinded parallel study • 47 volunteers (35 females), > 65 years-old	• 1 sachet (5-5.5g) *L. acidophilus* NCFM ($2x10^{9}$ CFU)+Lactilol twice a day for 2 weeks • Placebo: 1 sachet (5g) Sucrose twice a day for 2 weeks	• Faecal microbiota • Mucosal immunity • SCFA production	• Increase in number of faecal *Bifidobacterium* • Increase in spermidine levels • Modest increase in PGE2 concentration in faeces

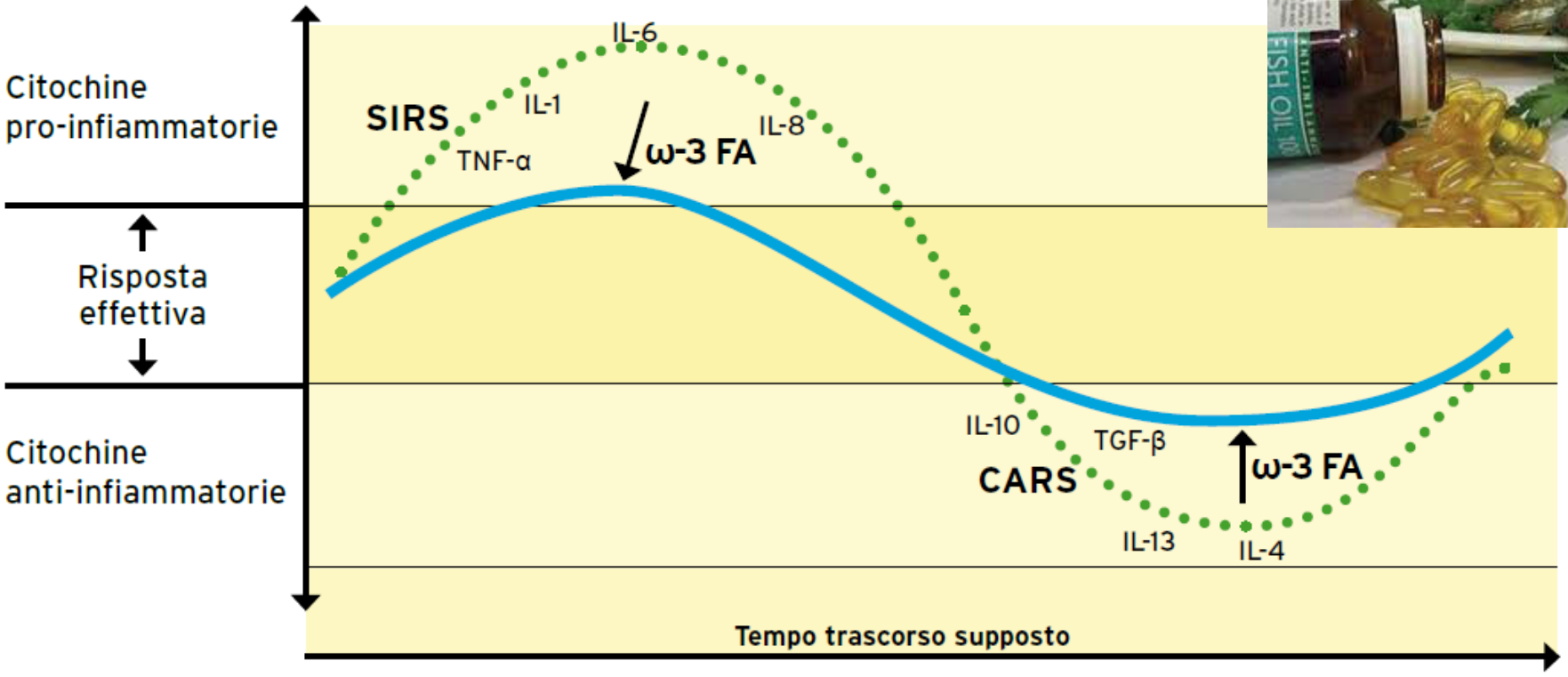
What is the role of ω-3 in inflammation?

Fig. 1. Possible mechanisms of omega-3 PUFA's anti-inflammatory actions. Omega-3 PUFAs are widely held to act via several possible mechanisms, such as preventing conversion of arachidonic acid (AA) into proinflammatory eicosanoids such as 4-series LTs and 2-series PGs via substrate competition, or serving as an alternative substrate to produce less potent 5-series LTs and 3-series PGs and thromboxanes. In addition, EPA and DHA are converted to bioactive metabolites such as resolvins and protectins with anti-inflammatory and pro-resolving properties.



Courtesy of M.Muscaritoli (modified)

Effetto degli ω-3 sulla risposta infiammatoria



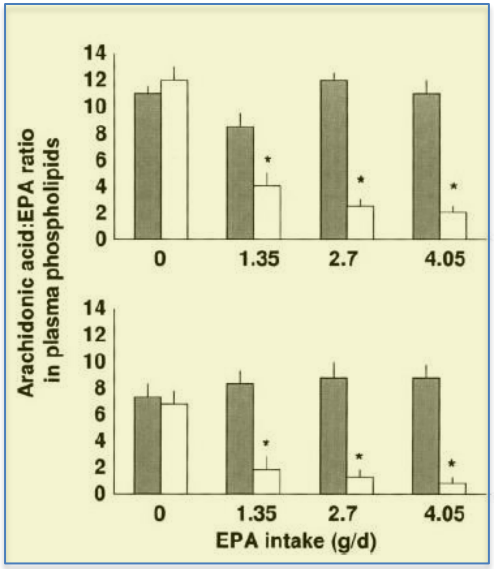
senza aggiunta di acidi grassi ω-3 da olio di pesce
con aggiunta di acidi grassi ω-3 da olio di pesce

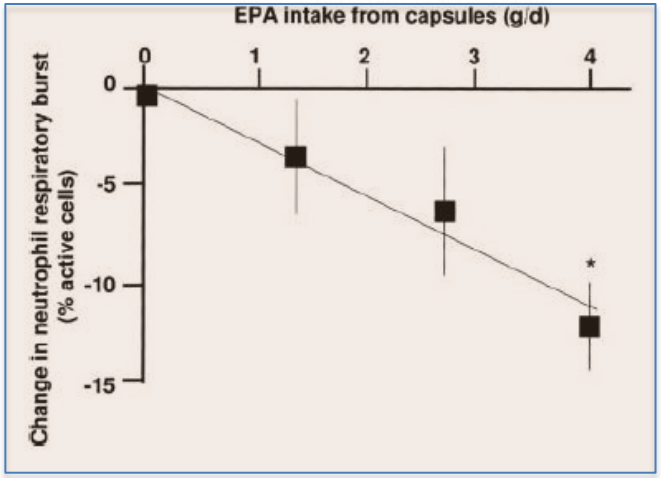
SIRS: Sindrome da Risposta Infiammatoria Sistemica;
CARS: Risposta Compensatoria Antinfiammatoria

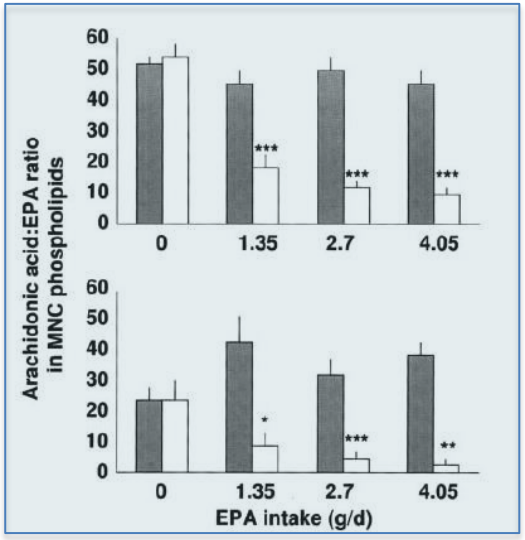
Dose-related effects of eicosapentaenoic acid on innate immune function in healthy humans: a comparison of young and older men[1–3]

Dinka Rees et al

Am J Clin Nutr 2006;83:331–42.







Conclusions

- The elderly can handle dietary long-chain-n-3 PUFAs in different way;
- The host innate immune functions remained unaffected in the elderly even with high intake of long-chain –n3 PUFAs (4.05 g EPA+0.9 g DHA/d);
- Hower at this intake, neutrophil superoxide production in response to E.Coli may be impaired by to 20%;
- An intake of 1.35 g EPA+0.3 gr DHA/d does not affect innate immune function in young or in the elderly

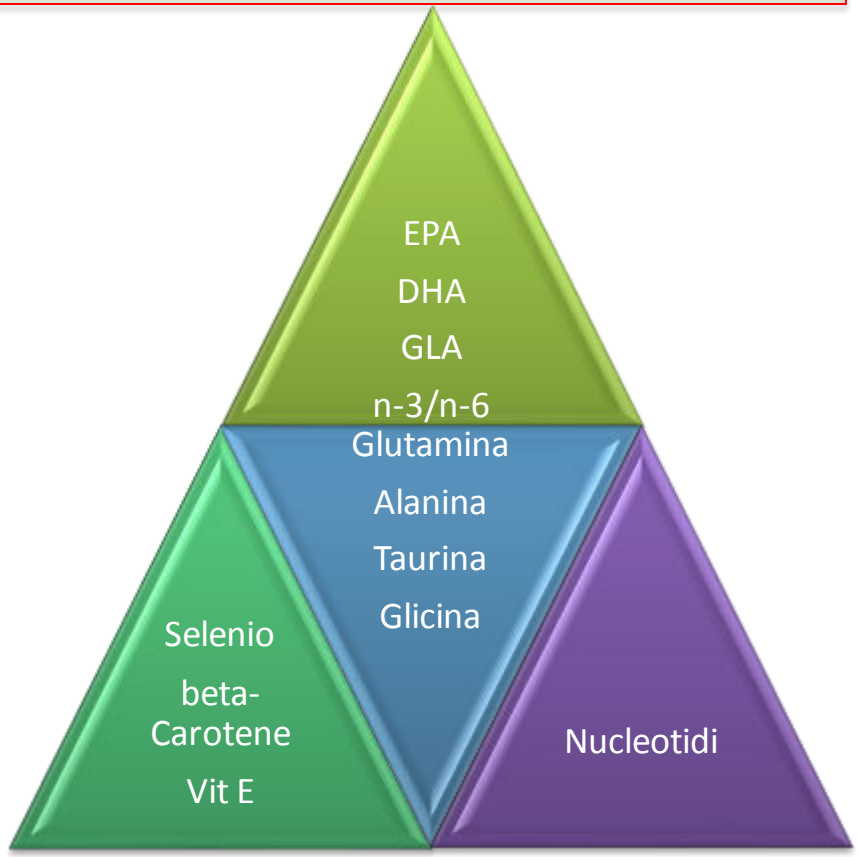
Fatty acids and the elderly

Cellular fatty acids impact on gene expression and act as precursors of prostaglandins, leukotriens, lipoxins and resolvins	Pae 2012	long chain *n*-3 PUFA (polyunsaturated fatty acids)	Improve cardiovascular, degenerative neurological, inflammatory and autoimmune diseases
	Galli 2009; Calder 2010	*n*-3 PUFA	Anti-inflammatory properties: inhibition formation of eicosanoids (Thromboxan A2) required for platelet aggregation; inhibition of proinflammatory cytokines IL-1β, TNFα, and IL-6. Reduction of IL-8, MCP-1, ROS, NOS and adhesion molecules (ICAM-1, VCAM-1 and selectins)
	Meydani 1991	*n*-3 PUFA (1.68 g EPA and 0.72 g DHA/day) for 3 months	Reduction in cytokine production, inhibition in mitogen-induced PBMC proliferation
	Bechoua 2003	low doses of PUFA (30 mg EPA and 150 mg DHA/day) for 6 weeks	Decrease in lymphocyte proliferation in response to mitogens. Reduction in the glutathione activity
	Bouwens 2009 and 2010	high doses of EPA (1.8 g) and DHA (1.8 g) equivalent to ten portions of oily fish per week for 26 weeks	Decrease plasma levels of free fatty acids and triglycerides, reduction in proinflammatory genes including NF-κB target genes, proinflammatory cytokines and genes involved in eicosanoid synthesis

Larbi A et al. Nutrition as a tool to reverse immnunosenescence? , 2018

Immunonutrizione

Miscele nutrizionali arricchite con specifici nutrienti attivi sul sistema immunitario, sul metabolismo e sulla struttura e funzione del tratto gastrointestinale.



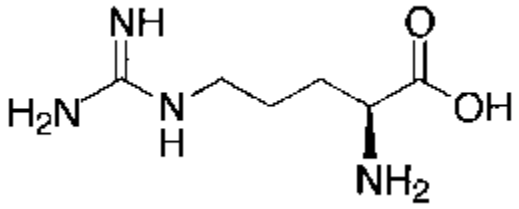
Diete arricchite con immunonutrienti

	Impact® Nestlé	Perative®Abbott	Stresson® Nutricia		AlitraQ® Abbott
Protéines % ($g \cdot L^{-1}$)	22 % (56)	20,5 % (66,6)	24 % (75)		21 %(52,5)
Glutamine ($g \cdot L^{-1}$)	0	0			15,5
Arginine ($g \cdot L^{-1}$)	13.0	6,5	6,7		4,5
Nucléotides ($g \cdot L^{-1}$)	1.0	0	0		0
Lipides % ($g \cdot L^{-1}$)	25 % (28)	25 % (37,4)	30 % (42)		13 % (15,5)
n-3 ($g \cdot L^{-1}$)	1,7	1,6	30 mg		0
Antioxydants	C, E, βcarotène, zn, se	A, C, βcarotène, zn, se	éléments-traces,A, C, E,		0
Taurine ($mg \cdot L^{-1}$)	0		0		oui
$kcal \cdot mL^{-1}$	1		1		1
Osmolalité($mOsm \cdot L^{-}$)	375	385	420		575

ARG e funzione immunologica

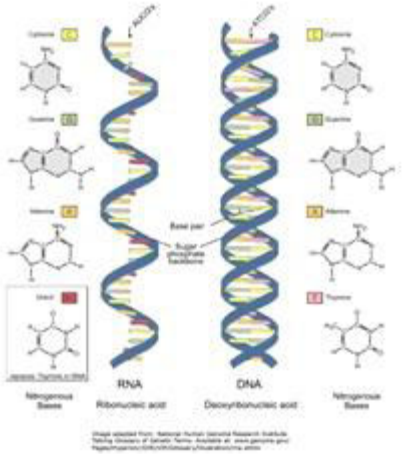
Aminoacido semiessenziale

necessario per:



- Proliferazione dei linfociti (Etron et al. 1991)
- Induzione delle funzioni dei T-linfociti (Etron e Barbul, 1998)
- Sintesi di NO (Nathan e Xle, 1994, Albina 1996)
- Aumento della fagocitosi PMN (Etron e Barbul, 1998)
- Aumento dell'attività delle cellule *Natural killer* (Etron e Barbul, 1998)

RNA



•Substrato essenziale per la replicazione, la maturazione e la differenziazione cellulare (cellule a rapido turnover: linfociti, Natural Killers, enterociti, macrofagi, che non sono in grado di sintetizzare l'RNA)

• Implicato nella sintesi dei recettori dell'IL-2 e dei macrofagi

• Substrato per la sintesi proteica

• Substrato per il metabolismo e l'energia cellulare (coenzimi: NAD, FAD, ATP, etc..)

Grimble GK, 2001, Hardy G, 2002

ARGININE / N-3 FATTY ACIDS INTERACTION

- ✓ Postoperative acquired arginine-deficient state which leads to substantial immune dysfunction
- ✓ Immature myeloid-derived suppressor cells accumulation early after surgery which express Arginase 1 (arginine depleting enzyme)
- ✓ N-3 fatty acids can blunt upregulation of immature cells and Arginase 1
- ✓ Arginine plus Omega-3 supplementation restores T-lymphocyte function including IL-2 production

Popovic, J Nutrit 2007

GLUTAMINE enteral supplementation

John C. Hall
Geoffrey Dobb
Jane Hall
Ruth de Sousa
Lisa Brennan
Rosalie McCauley

A prospective randomized trial of enteral glutamine in critical illness

OBJECTIVE: To assess the influence of **enteral glutamine** on the incidence of severe sepsis and death in critically ill patients.

DESIGN: This two-armed **clinical trial** was triple blind (patients, attending staff, research nurse).

SETTING: The 10 bed general ICU at Royal Perth Hospital, Western Australia.

PATIENTS: This **trial** evaluated 363 patients requiring mechanical ventilation (median APACHE II score=14); of these, 85 had trauma.

INTERVENTION: The intervention solution contained 20 g/l **glutamine** and the control solution was isojoulic and isonitrogenous.

CONCLUSION: This **clinical trial** did not support the use of **enteral glutamine** supplements in similar cohorts of critically ill patients.

Intensive Care Med (2003) 29:1710–1716

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American Society for Parenteral and Enteral Nutrition

Journal of Parenteral and Enteral Nutrition
Volume 37 Number 5
September 2013 566–567

DOI: 10.1177/0148607113495893
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REDOXs: Important Answers, Many More Questions Raised!

Jean-Charles Preiser, MD, PhD[1]; and Jan Wernerman, MD, PhD[2]

5. A broader unsolved issue is this: Which outcome should we use in the field of (pharmaco)nutrition? In a perfect world, we would select an outcome variable that will be meaningful (ie, an outcome directly influenced by the tested intervention), clinically relevant, and easily measurable. The survival rate is easily measurable and relevant, but how strong is the potential relation with a pharmaconutrient, especially when its mechanism of action is unknown? The infection rate is clearly relevant, and relatively easy to measure, but how can it be directly related to a pharmaconutrient that will influence much more systems than immunity?

> In terms of plausibility between glutamine supplementation and these outcome variable, we are left with several different options because of the lack of knowledge of the presumably beneficial mechanism. In general terms, the adequacy of (pharmaco)nutrition could be more precisely reflected by muscle mass or strength and/or functional autonomy, than by crude variables such as mortality or length of stay.

These questions clearly demonstrate that clinical research in nutrition remains in its infancy, at least in the field of critical care medicine. To expand our previous commentary, our cur-

2003: "Glutamine, a Life-Saving Nutrient, But Why?

2013: "Glutamine, a Potentially Toxic Nutrient, But Why, How, When, and in Which Patients?

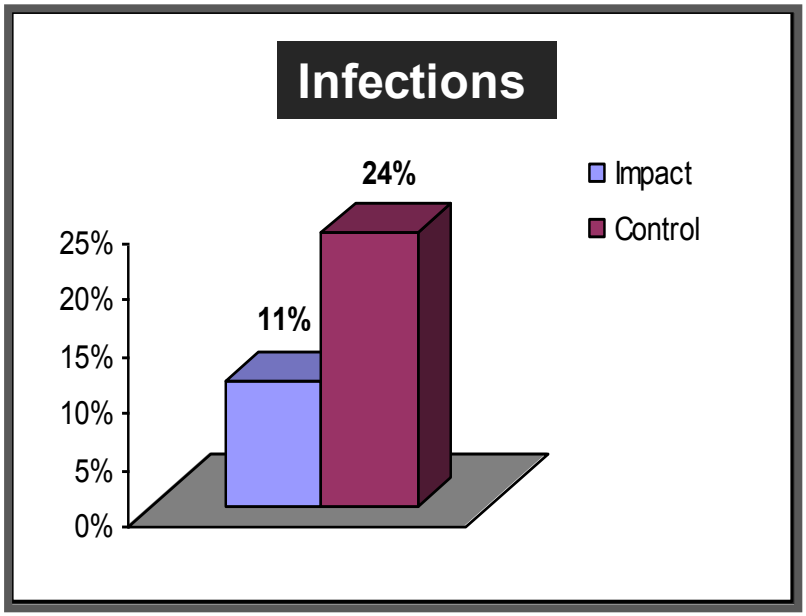
Perioperative Immunonutrition

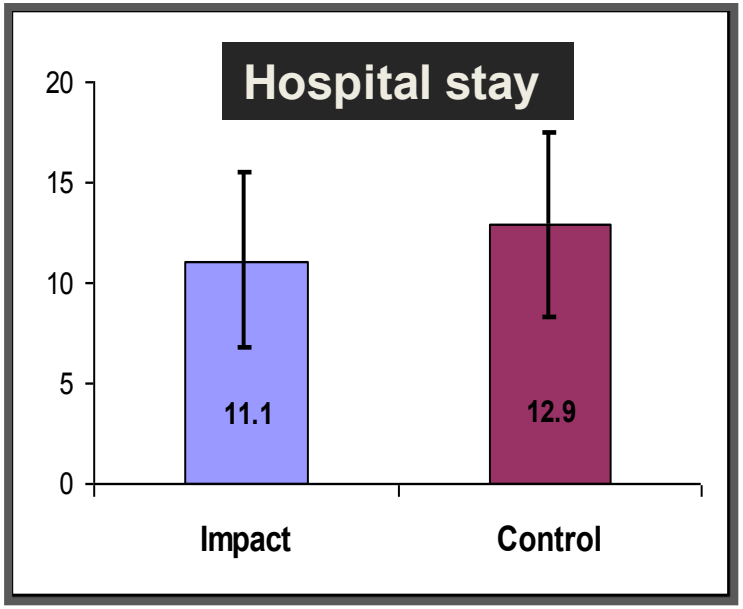
(cancer patients)

Braga M. et al. Arch Surg, 1999

206 patients (colon, stomach, pancreas) randomized trial 1l/d
Impact® or standard formula for 7 days preoperative

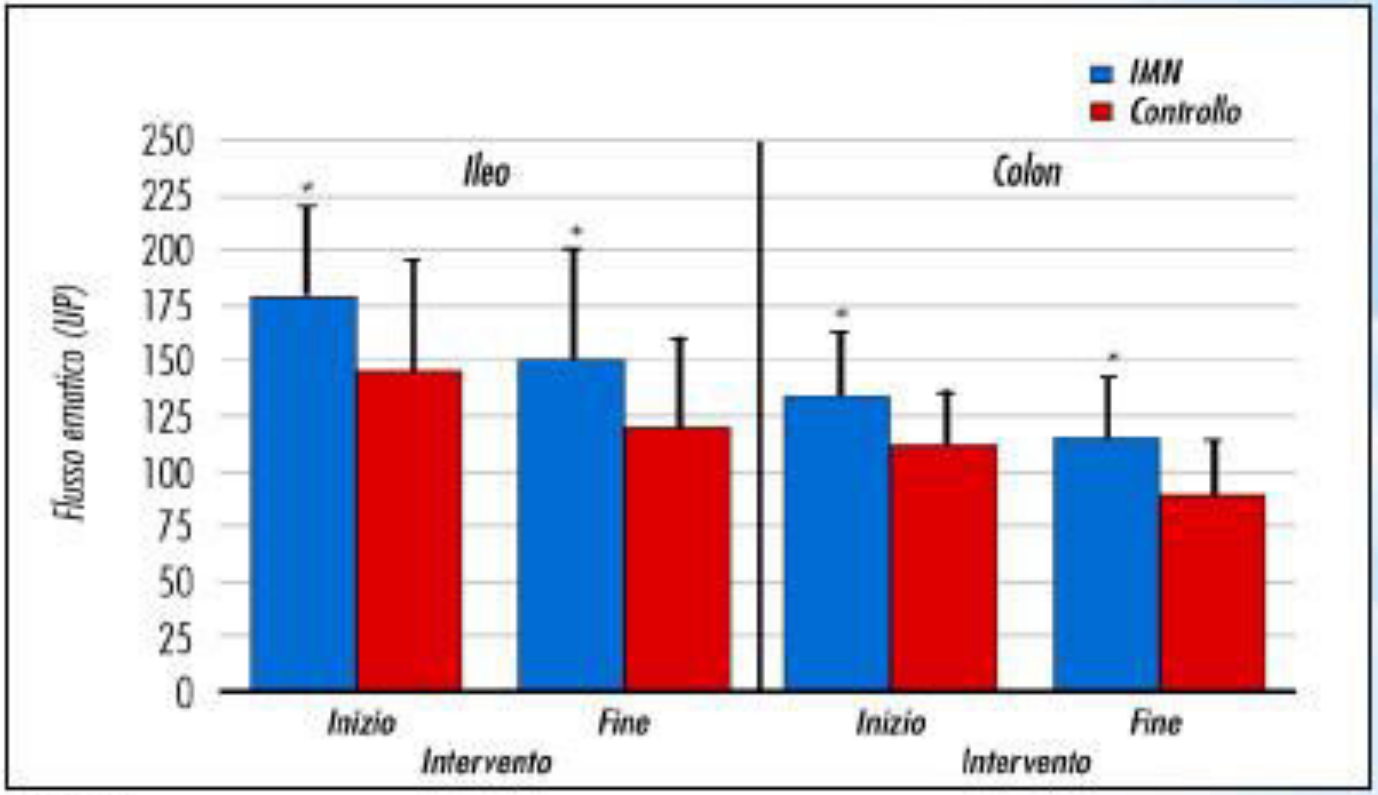
p<0.05 Impact vs. Control





Risposta metabolica: IMN vs. Std

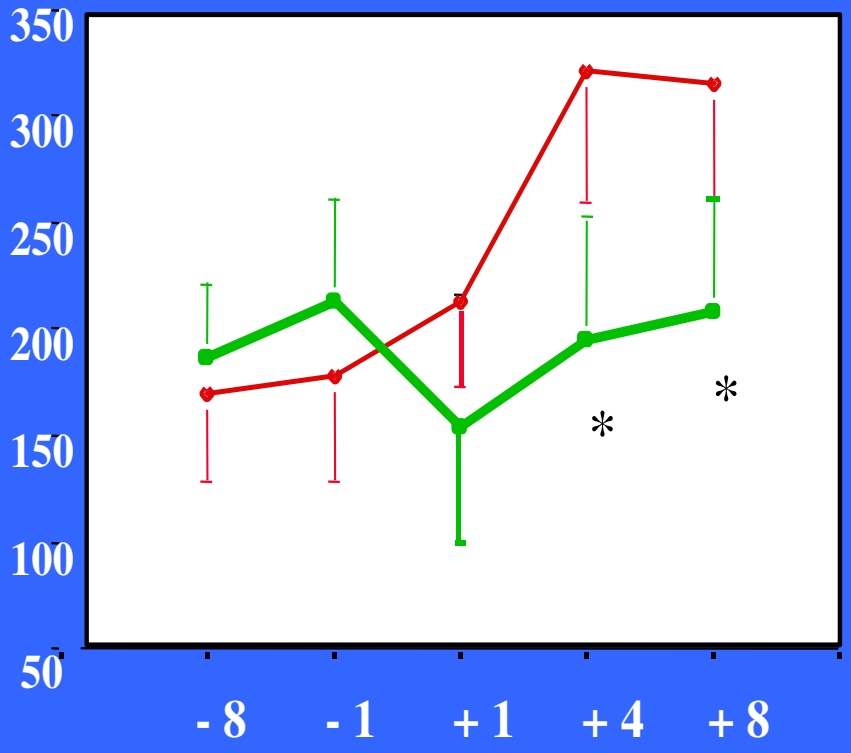
Microperfusione (Laser-Doppler)



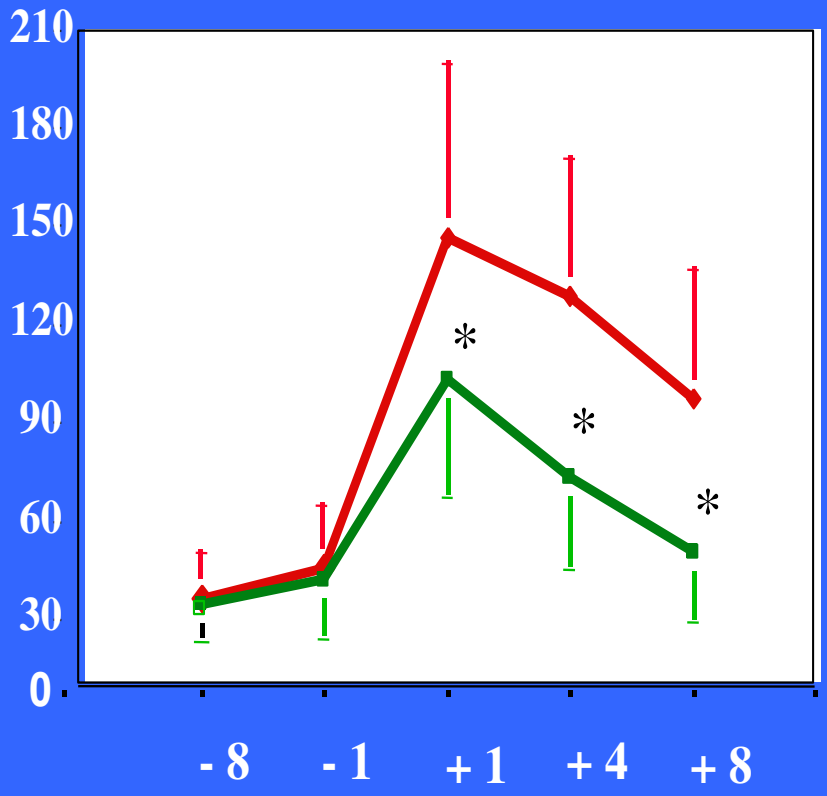
* p<0,05

(Braga, Arch Surg, 1996)

IL-1 R II (pg/mL)



IL-6 (pg/mL)



Supplemented

Control

Gianotti, JPEN 1999

World Journal of Surgery

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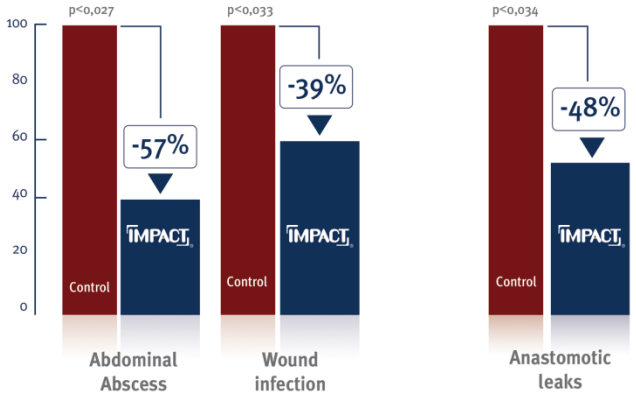
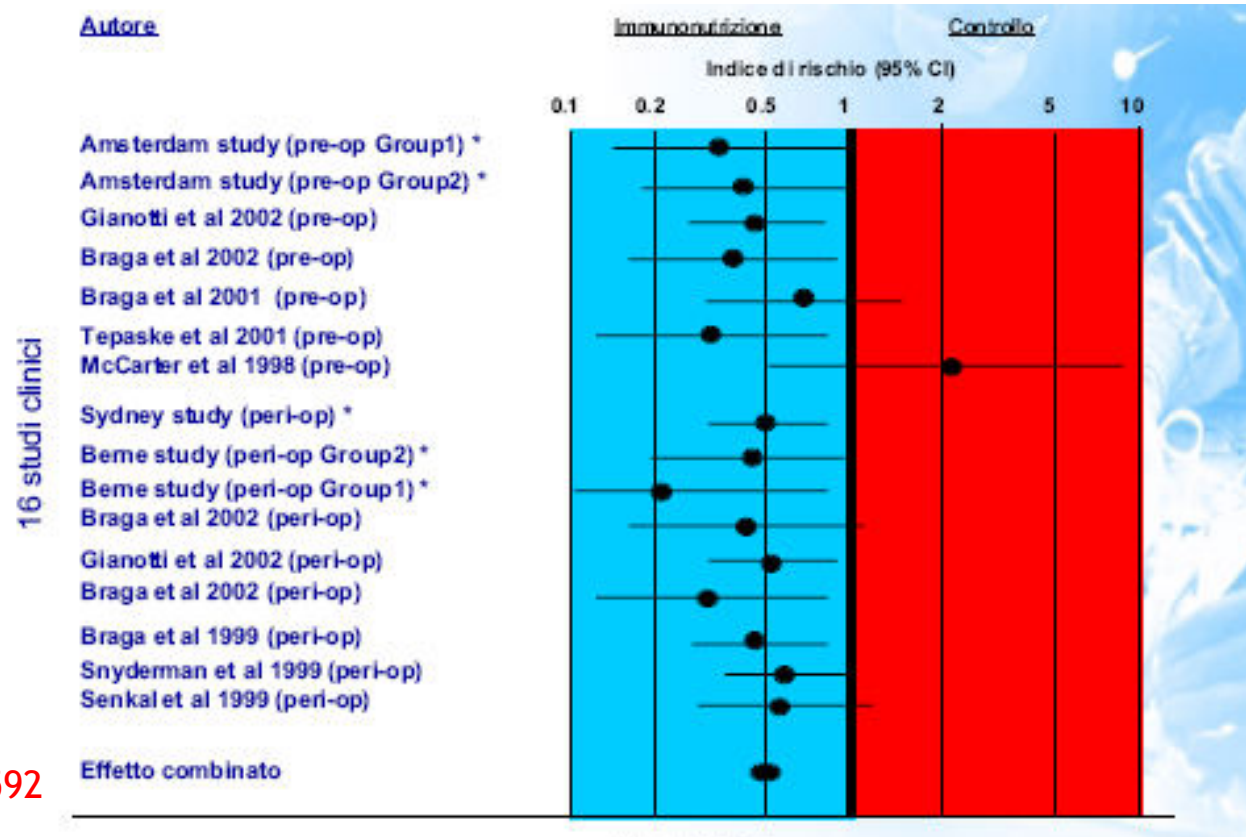
DOI: 10.1007/s00268-005-0657-x

Postsurgical Infections are Reduced with Specialized Nutrition Support

Dan L. Waitzberg, MD,[1] Hideaki Saito, MD,[2] Lindsay D. Plank, PhD,[3]





Waitzberg DL - World J Surg 2006, 30:1592

Conclusions

- Ageing is caracterized by immunosenescence and progressive decline in immunity;

- This complex process affects both innate and immune system

- Nutritional interventions have shown some promising results in targeting some of the impairements of the immune system observed with aging;

- Which molecular pathways of chronic inflammation (inflammaging) can be effectively targeted by a nutritional approach still needs to be determined;


Image hosted at Crazyprofile.com

Dieta mediterranea

Characterized by dietary patterns found in olive-growing regions of the Mediterranean: high consumption of olive oil, vegetable, fruits, nuts and cereals. Moderate intake of fish, poultry. Low intake of dairy product, red and processed meat (Gonzalez, 2000).	Osler 1997; Lasheras 2000; Trichopoulou 2003	MD	Association with a significant and substantial reduction in overall mortality
	Carluccio 2003; Cortes 2006; Dell'Agli 2006	Olive oil consumption in patients at risk of coronary heart disease	Reduced expression of ICAM-1, VCAM-1, and E-selectins Decrease plasma concentration of sICAM-1, sVCAM-1, sE-selectin, IL-6, and CRP
	Tangney 2011 Valls-Pedret 2012; Feart 2009 Scarmeas 2009	MD	Improved cognitive performances in dementia patients. MD associated with slower cognitive decline, reduction of mild cognitive impairment, reduction of neurodegenerative disorders such as Parkinson and Alzheimer
	Azzini 2011	MD	MD associated with down-regulation of CD49d and CD40 expression in monocytes. Reduced plasma expression of inflammatory markers such as sICAM-1, svCAM-1, CRP, IL-6, TNFα, IL-12. Higher levels of anti-inflammatory cytokine IL-10

Larbi A et al. Nutrition as a tool to reverse immnunosenescence? In Immunity and inflammation in health disease, 2018