Organ failure and artificial nutrition in patients with cancer in the ICU

Marianna Arvanitakis

Nutrition, soins intensifs et cancer

IJB 20/10/2012

PLAN

- Cancer patients in the ICU
- Impact of organ failure on outcome
- Nutritional support: How to do it
  - Acute Lung Injury, ARDS
  - Acute Renal Failure
  - Acute Liver Failure
- Glutamine

ICU ADMISSION OF PATIENTS WITH CANCER

Hôpital Erasme ULB

- Prospective, multicentric study (28 ICU)
- 753 (21%) admissions over a 2-month period of patients with cancer
- 93% of patients with solid tumours and 7% with haematological malignancies
- Admission:
  - Post-operative care (57%)
  - Sepsis (15%)
  - Respiratory failure (10%)
  - Others (neurological, renal….) (18%)

Soares et al, Crit Care Med 2010

MORTALITY

Hôpital Erasme | ULB

- Overall hospital mortality rate 30%
  - Medical complications (58%)
  - Emergency (37%)
  - Scheduled surgery (11%)

Comparable to ICU patients without cancer

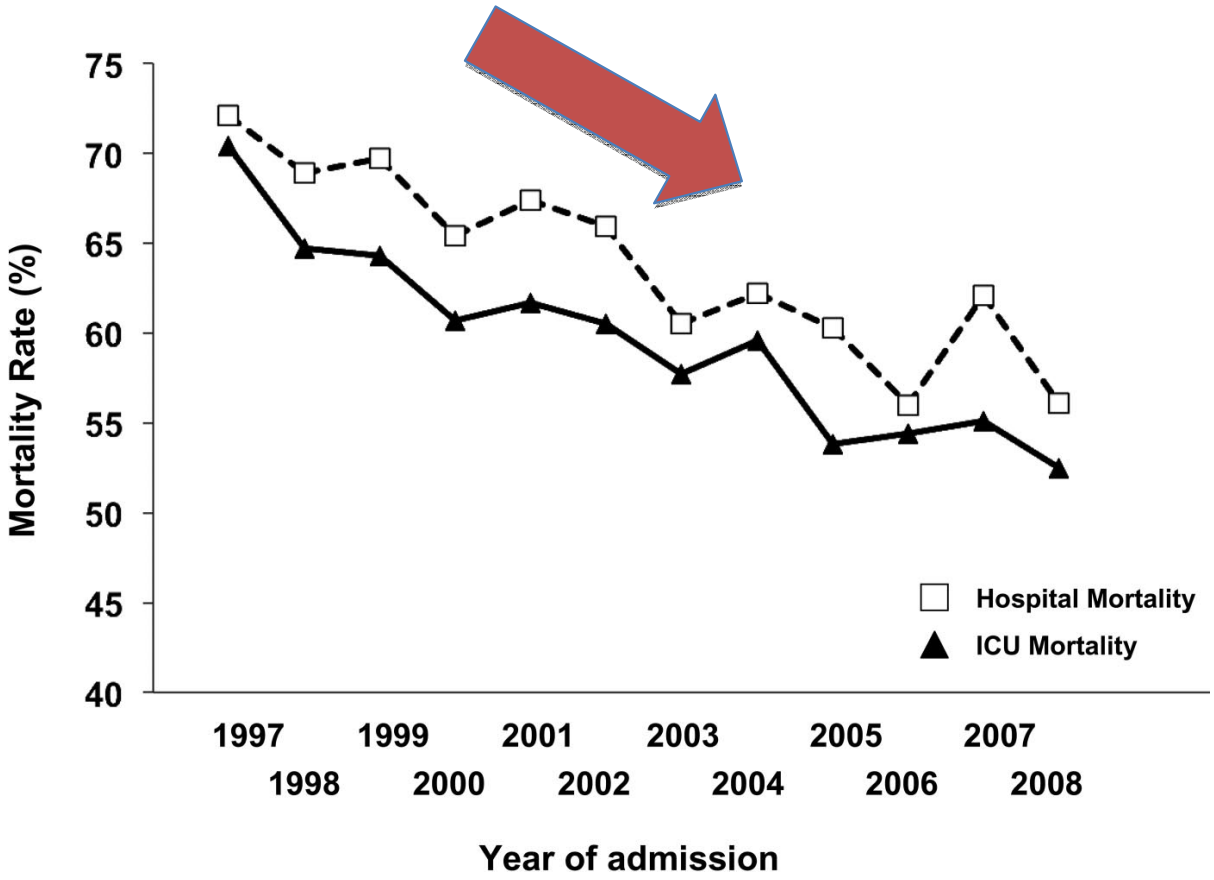
- Predictive factors (multivariate analysis)

	OR (95%CI)
Previous LOS before ICU admission (days)	1.18 (1.01-1.37)
Higher SOFA scores	1.25 (1.17-1.34)
Poor performance status	3.4 (2.19-5.26)
Need for mechanical ventilation	2.42 (1.51-3.87)
Progression or recurrence of malignancy	2.42 (1.51-3.87)

Soares et al, Crit Care Med 2010

ARE THINGS GETTING BETTER?

- Retrospective cohort study on prospectively collected data (period of 12 years)
- 3437 cancer patients with septic choc admitted in the ICU



Zuber et al, Crit Care Med 2012

CASE VOLUME IS IMPORTANT

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Predictive factors for in-hospital mortality

	OR (95%CI)
Medical cause for ICU admission	1.73 (1.29-2.32)
Higher SAPS II score	1.036 (1.03-1.04)
Invasive mechanical ventilation	5.52 (4.04-7.54)
Renal replacement therapy	1.74 (1.3-2.33)
Fungal infection	1.95 (1.18-3.21)
High case volume	0.63 (0.46-0.87)

Zuber et al, Crit Care Med 2012

TIME IS ALSO IMPORTANT….

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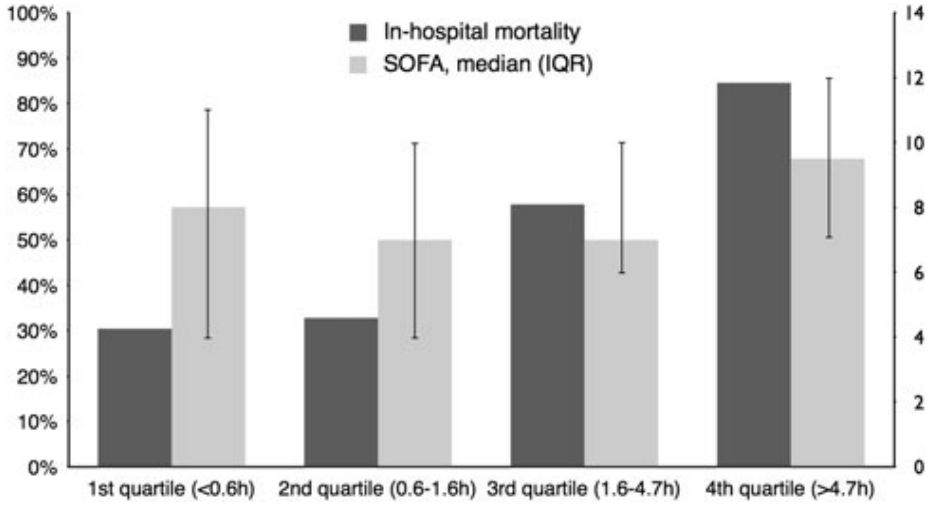
- Retrospective observational study with 199 critically ill cancer patients
- In hospital mortality 52%
- Time to intervention was shorter in survivors than in non-survivors (0.9 vs 3 h, p<0.001)
- Other confounding factors:
  - Severity of illness
  - PS
  - Haematological malignancy
  - Organ failure
  - Need for mechanical ventilation
  - Presence of infection



Song et al, Intensive Care Med 2012

HEAMATOLOGICAL MALIGNANCIES

- Retrospective study in a cohort of allogeneic hematopoietic stem-cell transplantation (HSCT) patients admitted from 1997-2003
- 209 patients requiring critical care

	Survival rates
In ICU	48.3%
In hospital	32.5%
6 months	27.2%
1 year	21%

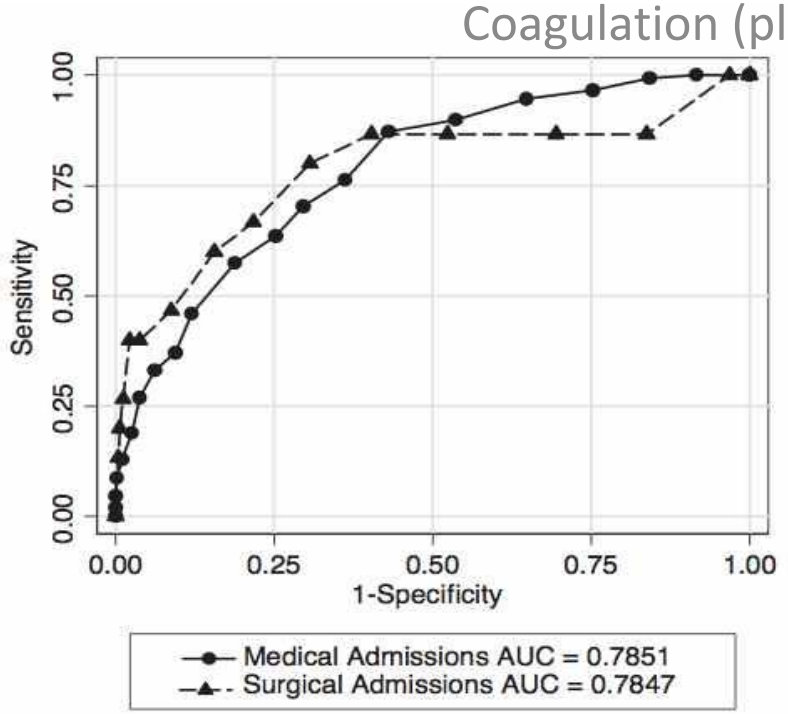
- Predictive factors for mortality:
  - Need for mechanical ventilation
  - Elevated bilirubin level

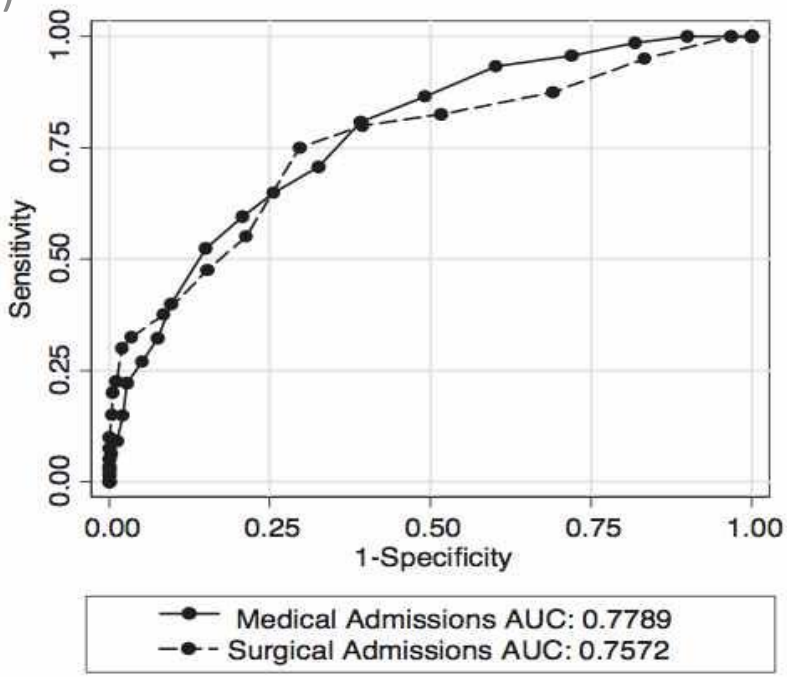
Pene et al, J Clin Oncol 2006

HOW TO PREDICT MORTALITY?

SOFA

Lungs (Pa02/Fi02)
Nervous system (Glasgow)
Cardiovascular system (MBP)
Liver (Bilirubin)
Renal (Creatinin)
Coagulation (plt)

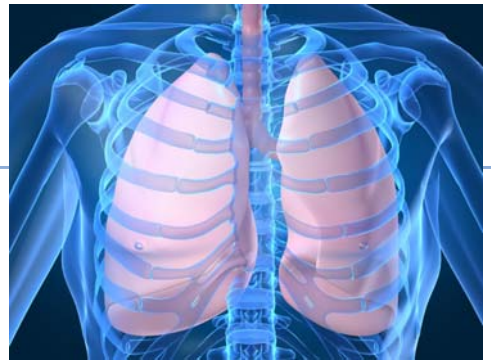




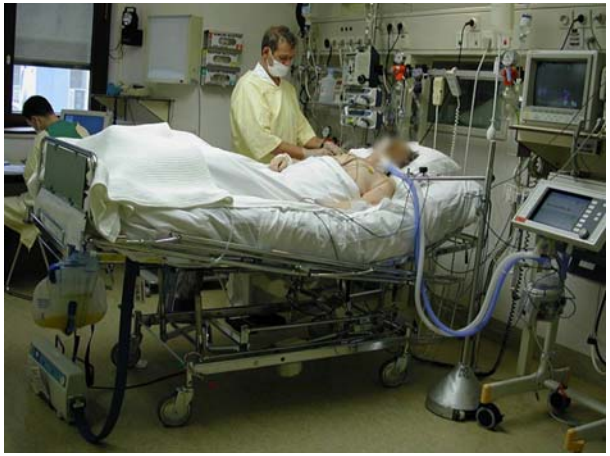
ICU mortality

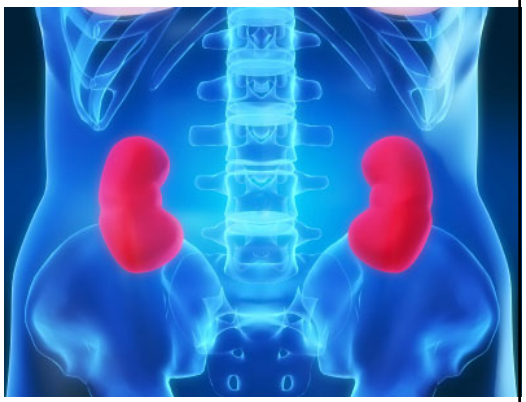
In-hospital mortality

Cardenas-Turanzas et al, J Crit Care 2012



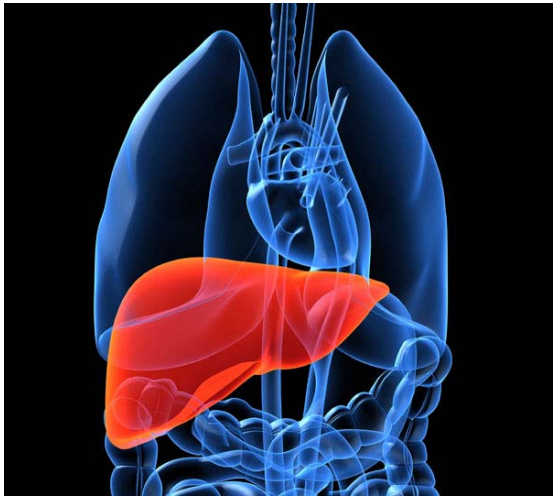
ARDS



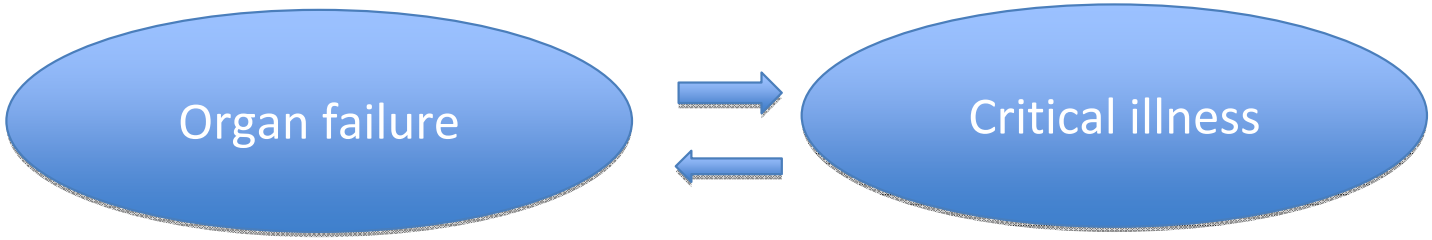


Acute renal failure

Acute liver failure

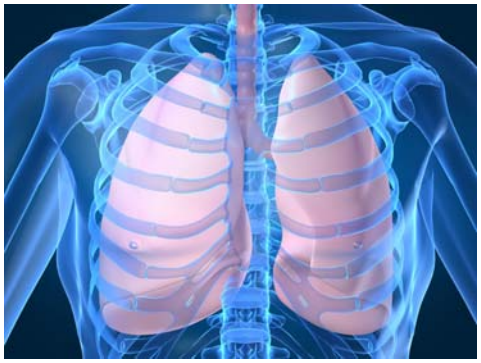


IMPACT OF ORGAN FAILURE

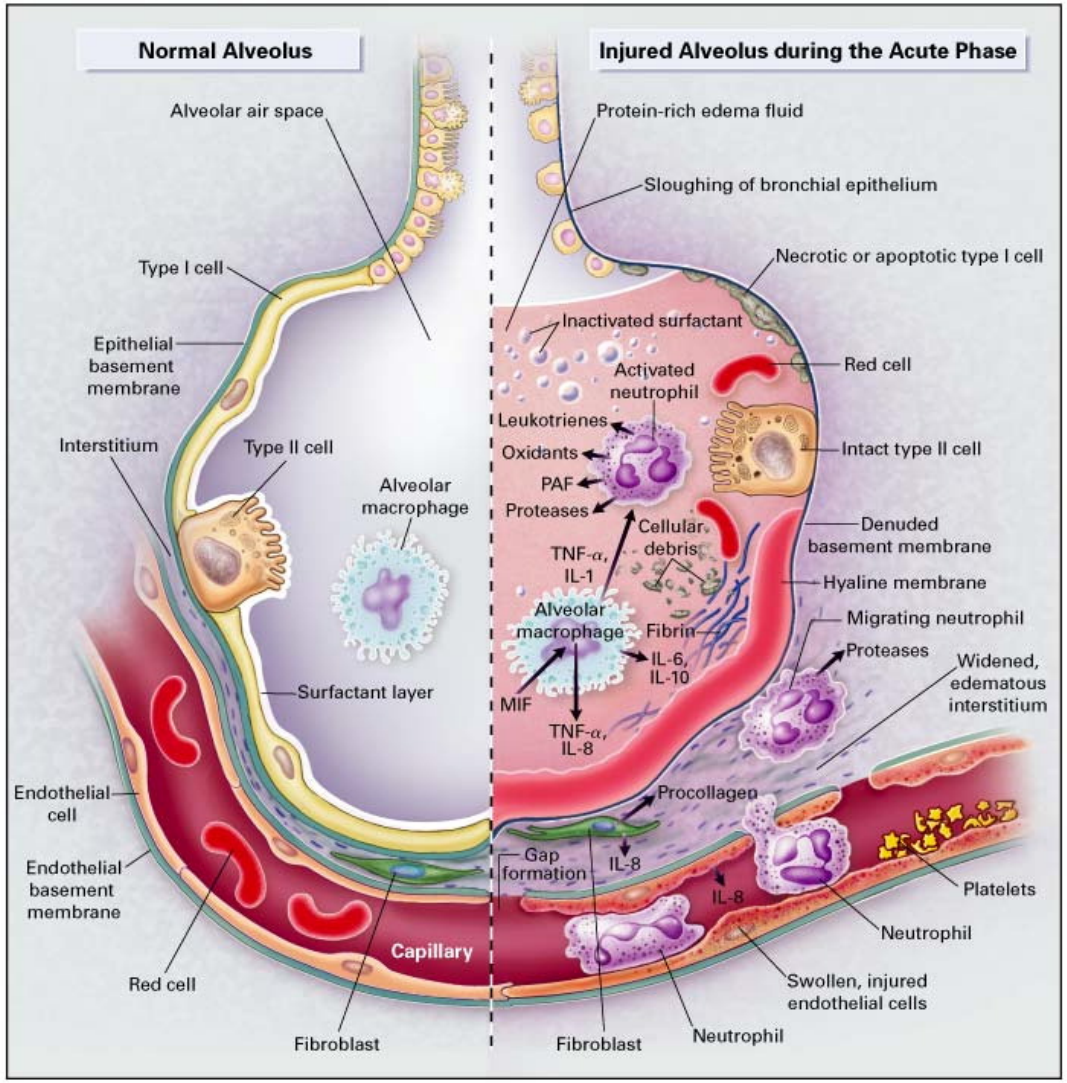


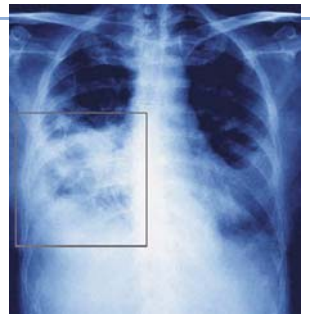
- Hypermetabolic state with EE proportional to stress
- Hyperglycemia and insulin resistance increase
- Protein catabolism and net negative nitrogen balance
- Insult leads to production of free radicals and oxidative stress

Acute respiratory distress syndrome

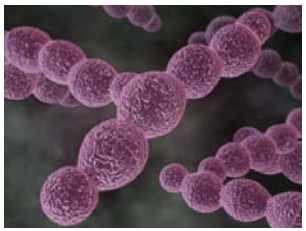


Acute onset of hypoxemia and bilateral pulmonary infiltrates without evidence of heart failure

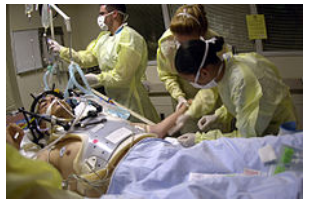




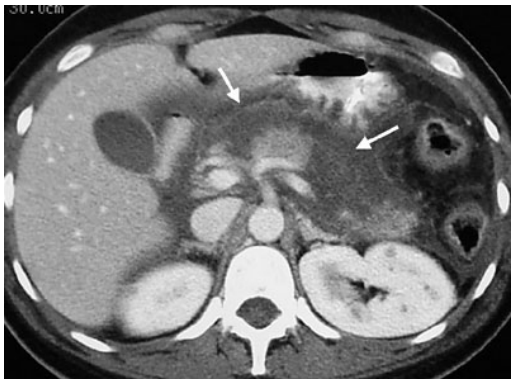
Pneumonia



Sepsis



Trauma



Severe acute pancreatitis

Ware et al, NEJM 2000

ARDS: NEW DEFINITION

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Table 3 The Berlin definition of ARDS (with permission from [22])

	Acute respiratory distress syndrome		
Timing	Within 1 week of a known clinical insult or new/worsening respiratory symptoms		
Chest imaging[a]	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules		
Origin of Edema	Respiratory failure not fully explained by cardiac failure or fluid overload; Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present		
	Mild	Moderate	Severe
Oxygenation[b]	$200 < PaO_2/FiO_2 \leq 300$ with PEEP or CPAP ≥ 5 cmH_2O[c]	$100 < PaO_2/FiO_2 \leq 200$ with PEEP ≥ 5 cmH_2O	$PaO_2/FiO2 \leq 100$ with PEEP ≥ 5 cmH_2O

Ferguson et al, Intensive Care Med 2012

GUIDELINES

Hôpital Erasme | ULB

ESPEN2006

10.5 *ARDS*:Patients with ARDS should receive EN enriched with ω-3 fatty acids and antioxidants (B).

ASPEN2009

E2. Patients with ARDS and severe acute lung injury (ALI) should be placed on an enteral formulation characterized by an anti-inflammatory lipid profile (ie, ω-3 fish oils, borage oil) and antioxidants. (Grade: A)

ASPEN2009

H1. Specialty high-lipid low-carbohydrate formulations designed to manipulate the respiratory quotient and reduce CO2 production are not recommended for routine use in ICU patients with acute respiratory failure. (Grade: E) (This is not to be confused with guideline E2 for ARDS/ALI).

ASPEN2009

H2. Fluid-restricted calorically dense formulations should be considered for patients with acute respiratory failure. (Grade: E)

Hôpital Erasme ULB

- Rationale: Reduce inflammatory response while increasing oxygen delivery and vasodilation

The Use of an Inflammation-Modulating Diet in Patients With Acute Lung Injury or Acute Respiratory Distress Syndrome: A Meta-Analysis of Outcome Data

Alessandro Pontes-Arruda, MD, MSc, PhD[1]; Stephen DeMichele, PhD[2]; Anand Seth, PhD[2]; and Pierre Singer, MD[3]

Journal of Parenteral and Enteral Nutrition
Volume 32 Number 6
November 2008 596-605

Pontes-Arruda et al, JPEN 2008

META-ANALYSIS OF 3 RCT

- 3 RCT comparing two types of EN

Table 1. Summary of the Clinical Studies Included in the Meta-analysis

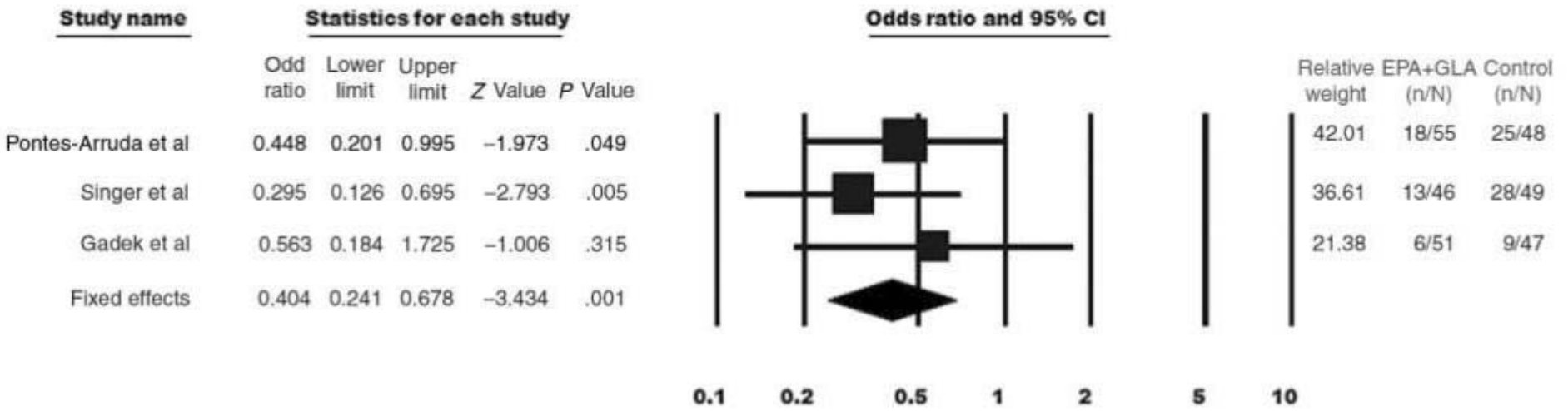
	Gadek et al[11]	Singer et al[12]	Pontes-Arruda et al[13]
Design	P, R, C, DB	P, R, C	P, R, C, DB
Setting	Multicenter—5 sites in the United States	Single center—Israel	Single center—Brazil
Patients	146 ARDS	100 ALI	165 Severe sepsis/septic shock
Interventions	EPA + GLA vs CD	EPA + GLA vs CD	EPA + GLA vs CD

EN (EPA/GLA)
Lip 55%
Ca/gr N: 150

EN
Lip 55%
Ca/gr N: 150

META-ANALYSIS OF 3 RCT

- Results: EPA + GLA
  - Decrease in in-hospital mortality
  - Increase in 28-day ventilation free days
  - Decrease in new organ dysfunction



Study name	Odd ratio	Lower limit	Upper limit	*Z* Value	*P* Value	Relative weight	EPA+GLA (n/N)	Control (n/N)
Pontes-Arruda et al	0.448	0.201	0.995	−1.973	.049	42.01	18/55	25/48
Singer et al	0.295	0.126	0.695	−2.793	.005	36.61	13/46	28/49
Gadek et al	0.563	0.184	1.725	−1.006	.315	21.38	6/51	9/47
Fixed effects	0.404	0.241	0.678	−3.434	.001			

BIAIS

- Control solution with high lipid content (55%) and low carbohydrate designed to reduce CO2 production (for COPD)

  → reason for poor outcome in control group?
- Timing of EN?
- Confounding effect of other therapeutic interventions? (prone position, low tidal volumes, steroids, NO)

Enteral Omega-3 Fatty Acid, γ-Linolenic Acid, and Antioxidant Supplementation in Acute Lung Injury

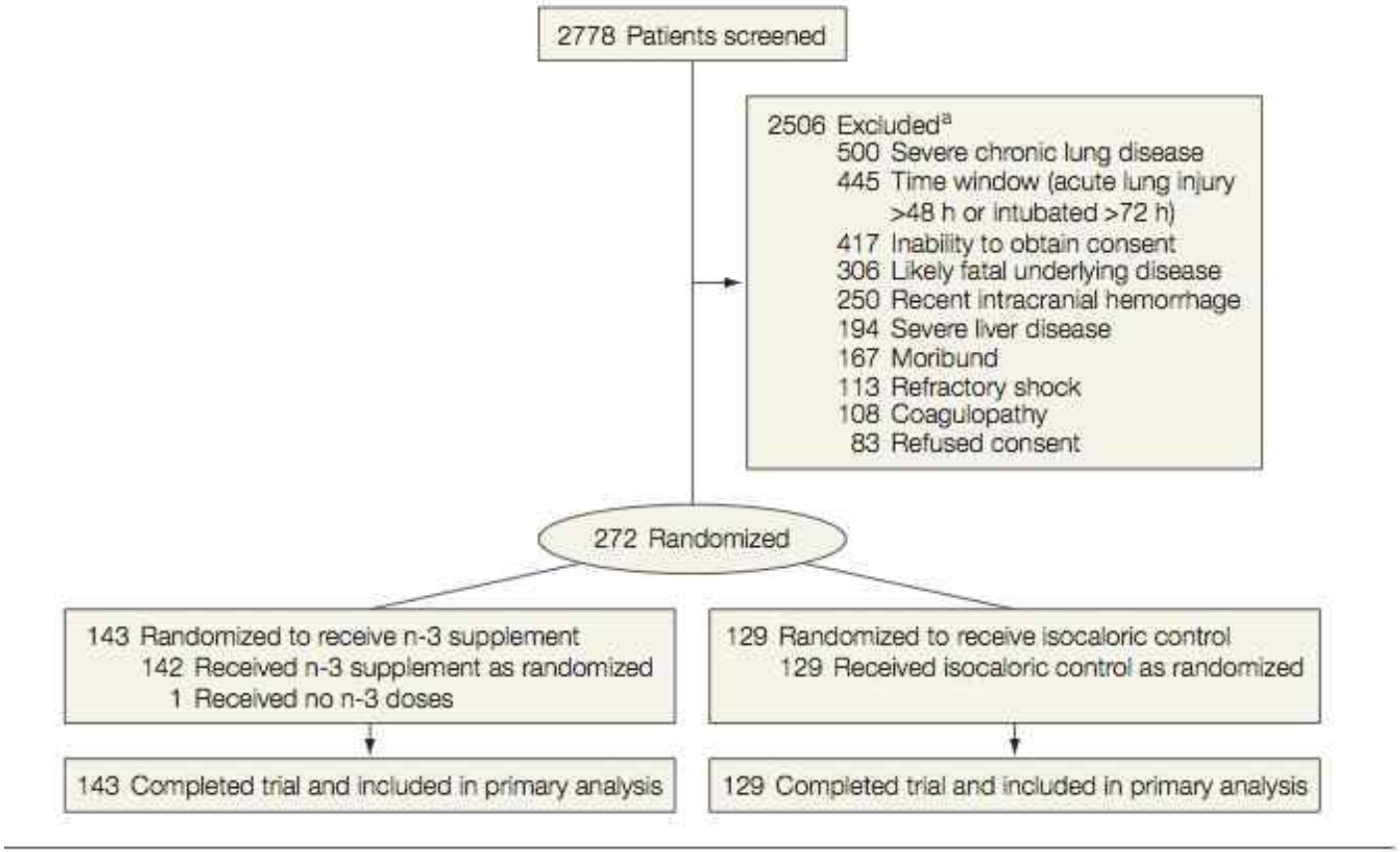


Table 1. Daily Nutrients in Omega-3 (n-3) vs Control Supplements

Nutrient	n-3 (240 mL)	Control (240 mL)
Energy, kcal	480	474
Protein, g	3.8	20
Carbohydrate, g	4.2	51.8
Fat, g	44.6	22
EPA	6.84	0
DHA	3.40	0
GLA	5.92	0
Vitamin C, mg	1000	76
All-natural vitamin E, IU	440	12
Beta-carotene, mg	4.8	0
Zinc, mg	24.2	5.6
Selenium, μg	85.2	18
L-Carnitine, mg	180	38
Taurine, mg	350	138

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GLA, γ-linolenic acid.

Rice et al, JAMA 2011

INCLUSION INTERRUPTED

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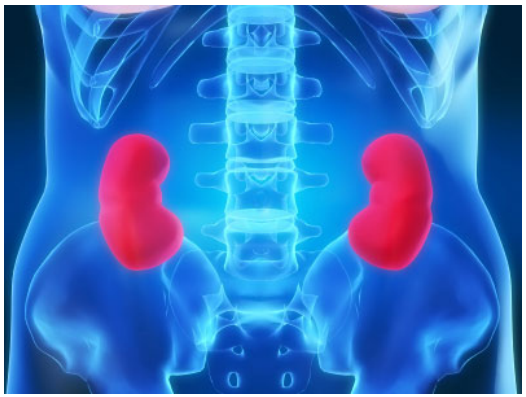
Table 3. Clinical Outcomes[a]

Outcome	Mean (SD) n-3 (n = 143)	Mean (SD) Control (n = 129)	Difference (95% CI)	*P* Value
Ventilator-free days from day 1 to day 28	14.0 (11.1)	17.2 (10.2)	−3.2 (−5.8 to −0.7)	.02
Death before discharge home, % (95% CI)				
Unadjusted	26.6 (19.3-33.8)	16.3 (9.9-22.7)	10.3 (0.7 to 19.9)	.054
Adjusted for differences in baseline covariates	25.1 (9.2-41.0)	17.6 (3.3-31.9)	7.5 (−3.1 to 18.1)	.11
No. of days not spent in an intensive care unit from day 1 to day 28	14.0 (10.5)	16.7 (9.5)	−2.7 (−5.1 to −0.3)	.04
No. of days without failure of circulatory, coagulation, hepatic, or renal organs from day 1 to day 28	12.3 (11.1)	15.5 (11.4)	−3.2 (−5.9 to −0.5)	.02

[a] Patients discharged from the hospital alive before 60 days are considered alive for all-cause 60-day hospital mortality. Mortality was adjusted for age, Acute Physiology and Chronic Health Evaluation III score, plateau pressure, missing plateau pressure, number of organ failures, and the alveolar-arterial difference in Pa_{O_2}.

Rice et al, JAMA 2011

Acute renal failure



ARF IN CRITICAL CARE CANCER PATIENTS

- 12%-49% critically ill cancer patients present with ARF
- 9%-32% require renal replacement therapy during ICU stay
- Mortality rates up to 85% when renal replacement therapy required

Causes of acute renal failure in cancer patients

Pre-renal failure	Sepsis
	Extracellular dehydration (diarrhoea, mucitis, vomiting)
	Sinusoidal obstruction syndrome (formerly called hepatic veno-occlusive disease)
	Drugs (e.g., calcineurin inhibitors, ACE inhibitors, NSAIDs)
	Capillary-leak syndrome (IL2)
Intrinsic failure	
Acute tubular necrosis	Ischaemia (shock, severe sepsis)
	Nephrotoxic agents (contrast agents, aminoglycosides, amphotericin, ifosfamide, cisplatin)
	Disseminated intravascular coagulation
	Intravascular haemolysis
Acute interstitial nephritis	Immuno-allergic nephritis
	Pyelonephritis
	Cancer infiltration (e.g., lymphoma, metastasis)
	Nephrocalcinosis
Vascular nephritis	Thrombotic microangiopathy
	Vascular obstruction
Glomerulonephritis	Amyloidosis (AL, myeloma; AA, renal carcinoma or Hodgkin's disease)
	Immunotactoid glomerulopathy
	Membranous glomerulonephritis (pulmonary, breast or gastric carcinoma)
	IgA glomerulonephritis, focal glomerulosclerosis
Post-renal failure	Intra-renal obstruction (e.g., urate crystals, light chain, acyclovir, methotrexate)
	Extrarenal obstruction (retroperitonal fibrosis, ureteral or bladder outlet obstruction)

Darmon et al, Critical Care 2006

IMPACT OF ARF ON METABOLISM

- The kidney plays a role in glucose homeostasis (up to 20% of glucose uptake) → ARF may aggravate critical illness hyperglycaemia
- ARF may increase protein catabolism
- Impaired lipid clearance with risk of hypertriglyceridemia
- Critical ill patients with ARF have increased oxidative stress
- Reduced clearance of K, Mg, P
- Water balance

Wiesen et al, JPEN 2011

GUIDELINES: ARF AND CONSERVATIVE THERAPY

Hôpital Erasme | ULB

ESPEN2006

Indication of artificial nutrition in ARF (EN) in case of undernutrition and when oral nutrition/ONS cannot reach requirements (grade C)

Protein requirements: 0.6-0.8 gr/Kg BW/day (up to 1 gr/Kg BW/d)

Standard EN formulas are adequate (grade C) but specific formulas might be necessary in case of electrolyte disturbances (grade C)

ESPEN2009

PN should be used in case the GI tract cannot be used for EN or if EN cannot reach nutritional goals (grade C)

ESPEN guidelines: EN and acute renal failure et al, Clinical Nutrition 2006

ESPEN guidelines: PN and acute renal failure et al, Clinical Nutrition 2009

CRRT: CONTINUOUS VENO-VENOUS HEMOFILTRATION (CVVH)

- CRRT is the choice of treatment in ARF (instead of IHD) in case of hemodynamic instability and fluid overload
- Overall nutrient balance: CRRT differs from conservative treatment
  - Loss of heat and increased EE
  - Loss of proteins (according to CVVH modalities and type of filter) → 6-15 gr/day of AA lost
  - Loss of water soluble vitamins
  - Electrolytes derangements (loss of K, P, Mg)

Wiesen et al, JPEN 2011

GUIDELINES: ARF AND CRRT

Hôpital Erasme ULB

ESPEN2006

Indication of artificial nutrition in ARF (EN) in case of undernutrition (BMI<20) and when oral nutrition/ONS cannot reach requirements (grade C)

ASPEN2010

Protein requirements: 1.0-1.5 gr/Kg BW/day (up to 1.7 gr/Kg BW/d)

Standard EN formulas are adequate (grade C) but specific formulas might be necessary in case of electrolyte disturbances (grade C)

Water soluble vitamins should be supplied (folic acid, vitamin C, thiamine, pyridoxin)(grade C)

ESPEN2009

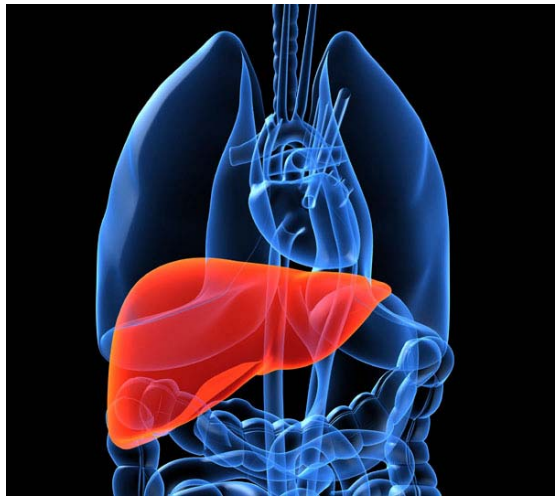
PN should be used in case the GI tract cannot be used for EN or if EN cannot reach nutritional goals (grade C)

ESPEN guidelines: EN and acute renal failure et al, Clinical Nutrition 2006

ESPEN guidelines: PN and acute renal failure et al, Clinical Nutrition 2009

ASPEN guidelines: acute and chronic renal failure et al, JPEN 2010

Acute Liver failure



CAUSES OF LIVER FAILURE IN PATIENTS WITH CANCER

- Acute viral hepatitis
  - Hepatitis B reactivation during chemotherapy (reappearance of HbsAg)
  - HSV and VZV
- Hypoxic hepatitis
  - In case of shock, respiratory failure…
- GVHD in allograft patients
- Neoplasic liver infiltration (lymphoma)
- HCC with cirrhosis
- Drug-induced
  - Paracetamol
  - Ampho B
  - Cyclophosphamide

MacDonald et al, Hepatology 2010

IMPACT OF ACUTE LIVER FAILURE ON METABOLISM

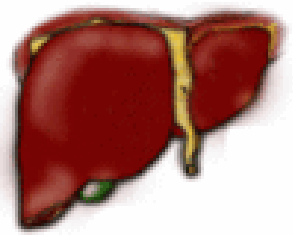
- Increased EE
  - Basal
  - Sepsis, respiratory failure…
- Increased proteolysis
- Altered glucose metabolism
  - Reduced ability of hepatocytes to store, synthetize and break down glycogen
  - Increased levels of neoglucogenesis from fat and proteins (alternate fuel source)
  - Insulin resistance with decreased peripheral glucose utilisation and hepatic glucose production

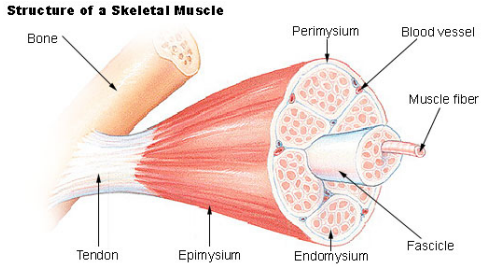
Cheung et al, Clin Gastro Hepatol 2012

HEPATIC ENCEPHALOPATHY

Aromatic AA (AAA)

Branched-chain AA (BCAA)





Decrease BCAA/AAA ratio

Decreased liver uptake because of hepatocellular failure

Increased muscle uptake used for energy substrate

Same blood-brain barrier transporter

Increased tryptophan brain uptake

Hepatic encephalopathy

Cheung et al, Clin Gastro Hepatol 2012

BCAA AND LIVER FAILURE

- 2 RCT in patients with cirrhosis

Nutritional Supplementation With Branched-Chain Amino Acids in Advanced Cirrhosis: A Double-Blind, Randomized Trial

GASTROENTEROLOGY 2003;124:1792–1801

Effects of Oral Branched-Chain Amino Acid Granules on Event-Free Survival in Patients With Liver Cirrhosis

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2005;3:705–713

Patients with BCAA supplementation had a decreased rate of decompensating episodes (ascites, encephalopathy)

Marchesini et al, Gastroenterology 2003

Muto et al, Clin Gastro Hepatol 2005

GUIDELINES: LIVER FAILURE

Hôpital Erasme ULB

ESPEN2006

Indication of artificial nutrition in acute liver failure (EN) in case of undernutrition and when oral nutrition/ONS cannot reach requirements (grade A)

Protein requirements: 1.2-1.5-0.8 gr/Kg BW/day
Energy requirements: 35-40 kcal/kg BW/day

Tube feeding may be used even in case of oesophageal varices

Standard EN formulas are adequate (grade C) except in case of hepatic encephalopathy where BCAA enriched formulas are recommended (grade A)

ESPEN2009

PN should be used in case the GI tract cannot be used for EN or if EN cannot reach nutritional goals (grade C)

Monitor and supplement with glucose if necessary, because of the risk for hypoglycaemia (grade C)

ESPEN guidelines: EN and liver disease, Clinical Nutrition 2006

ESPEN guidelines: PN and liver disease, Clinical Nutrition 2009

Glutamine

GLUTAMINE IN THE CRITICALLY ILL PATIENT:

- Not an essential AA but production is limited
- l with
- **16. Is there an indication for specific amino acids?**

  Recommendation: When PN is indicated in ICU patients the amino acid solution should contain 0.2–0.4 g/kg/day of L-glutamine (e.g. 0.3–0.6 g/kg/day alanyl-glutamine dipeptide) (Grade A).

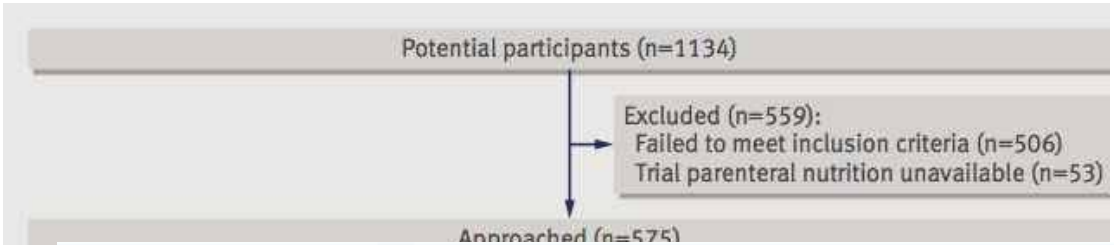
  - Preserves intestinal barrier function
  - Reduces morbidity and mortality
  - Attenuates hyperglycaemia and insulin resistance
- Already 3 meta-analysis up to now regarding Gln and PN
- Last meta-analysis grouping small trials with different treatment modalities (n=798 patients) showed a reduced mortality risk (RR:0.71, CI 0.55-0.92) and new infections (RR:0.76, CI 0.62-0.93)

Grau et al, Crit Care Med 2011

www.criticalcarenutrition.org

ESPEN Guidelines, Clinical Nutrition 2009

Randomised trial of glutamine, selenium, or both, to supplement parenteral nutrition for critically ill patients



	Trial parenteral nutrition formulations							
	Individual formulations				Combined groups			
Outcome	Glutamine (n=126)	Selenium (n=127)	Glutamine + selenium (n=124)	Neither (n=125)	Any glutamine (n=250)	Any non-glutamine (n=252)	Any selenium (n=251)	Any non-selenium (n=251)
New infections*								
All infections:	71 (56)	63 (50)	63 (51)	68 (54)	134 (54)	131 (52)	126 (50)	139 (55)
Odds ratio (95% CI)	—	—	—	—	1.07 (0.75 to 1.53)		0.81 (0.57 to 1.15)	
Confirmed infections†:	62 (49)	48 (38)	56 (45)	59 (47)	118 (47)	107 (42)	104 (41)	121 (48)
Odds ratio (95% CI)	—	—	—	—	1.23 (0.86 to 1.76)		0.75 (0.52 to 1.08)	
Mortality								
Within critical care or high dependency unit:	46 (37)	42 (33)	42 (34)	38 (30)	88 (35)	80 (32)	84 (33)	84 (33)
Odds ratio (95% CI)	—	—	—	—	1.17 (0.80 to 1.71)		1.004 (0.69 to 1.47)	
Within 6 months:	60 (48)	52 (41)	55 (44)	54 (43)	115 (46)	106 (42)	107 (43)	114 (45)
Odds ratio (95% CI)	—	—	—	—	1.18 (0.82 to 1.70)		0.89 (0.62 to 1.29)	

*Within 14 days after randomisation.
†Confirmed in accordance with Centers for Disease Control definition.

Andrews et al, BMJ 2011

GLUTAMINE: THE NEVER ENDING STORY

- New trial showing no effect of glutamine in PN
  - If data included in pre-existing meta-analyses
    - → RR: 0.67 changes to 0.80 (0.62-1.05) for mortality
    - → RR: 0.76 changes to 0.81 (0.67-0.98) for new infections

Challenge for current guidelines!!

- REDOXS trial comparing EN and PN supplementation with Gln and anti-oxydants…..n=1200 , no difference (unpublished results)

- In patients with exclusive PN?

Andrews et al, BMJ 2011

GLUTAMINE (IV) AND THE PERI-OPERATIVE SETTING

- 5 meta-analyses
  - Significant decrease in infectious complications
  - Decreased LOS
- Large RCT (n=428) with Gln supplementation in major abdominal surgery → no difference

More research is needed…

Gianotti et al, Annal Surg 2009

ASPEN paper on Glutamine, 2011

GLUTAMINE (IV) AND BONE MARROW TRANSPLANT PATIENTS

- 2 meta-analyses (Cochrane Review)
  - Decrease in number of positive blood cultures
  - No difference in mortality, infectious complications, mucositis, GVHD…

More research is needed…

Cochrane Review2008, 2009

ASPEN paper on Glutamine, 2011

CONCLUSIONS (1)

- Patients with cancer are increasingly admitted in the ICU for organ failure (mainly respiratory)
- In-hospital mortality rate is comparable to critically ill patients with other comorbidities (30%-50%)
- Similar approach to other critically ill patients regarding nutritional support
- Respiratory failure (ARDS):
  - Avoid EN with high lipids and low carbohydrate formulas

CONCLUSIONS (2)

- Acute renal failure:
  - Without CRRT
    - Restricted protein requirements (0.6-0.8 gr/kg/d)
    - Standard formulas but fluid and electrolytic imbalances may occur
  - With CRRT
    - Increased protein requirements (1-1.7 gr/kg/d)
    - Water soluble vitamin supplementation
- Acute Liver failure
  - Increased protein requirements (1.2-1.5 gr/kg/d)
  - Standard formula except in hepatic encephalopathy where BCAA formulas are recommended
- Glutamine
  - Can be useful in patients receiving exclusive PN in an critically ill setting


“La vie”, Chagall 1964