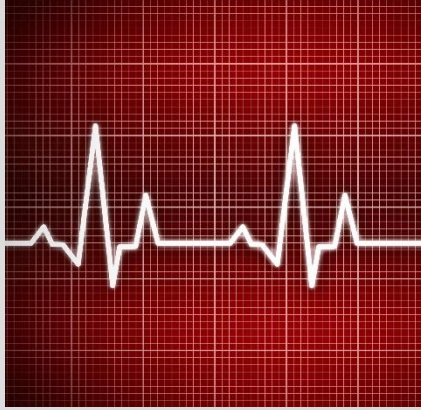

Malnutrition in ICU Sepsis

What, When and How to feed?

Meena Natesan, MS RD.

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Critical Care Sepsis

- Major health care problem – 30 million people per year worldwide and 6 million deaths (WHO, April 2018)
- Antibiotic treatment – change from exogenous endogenous bacterial source
- Specialized nutrition therapy
  - ❖ right time, right route and right substrate
  - ❖ significant influence on
    - endogenous microbial population,
    - virulence and
    - quantity

Sepsis Definition

Sepsis is:

- Systemic response to infection
- Life threatening condition characterized by Tachycardia, Tachypnea, Fever and Organ dysfunction often associated with a bacterial, viral or fungal infection
- SIRS - Tachycardia, Tachypnea, Fever, Dyspnea and Organ dysfunction

Sepsis:

Presence or presumed presence of an infectious source accompanied by SIRS

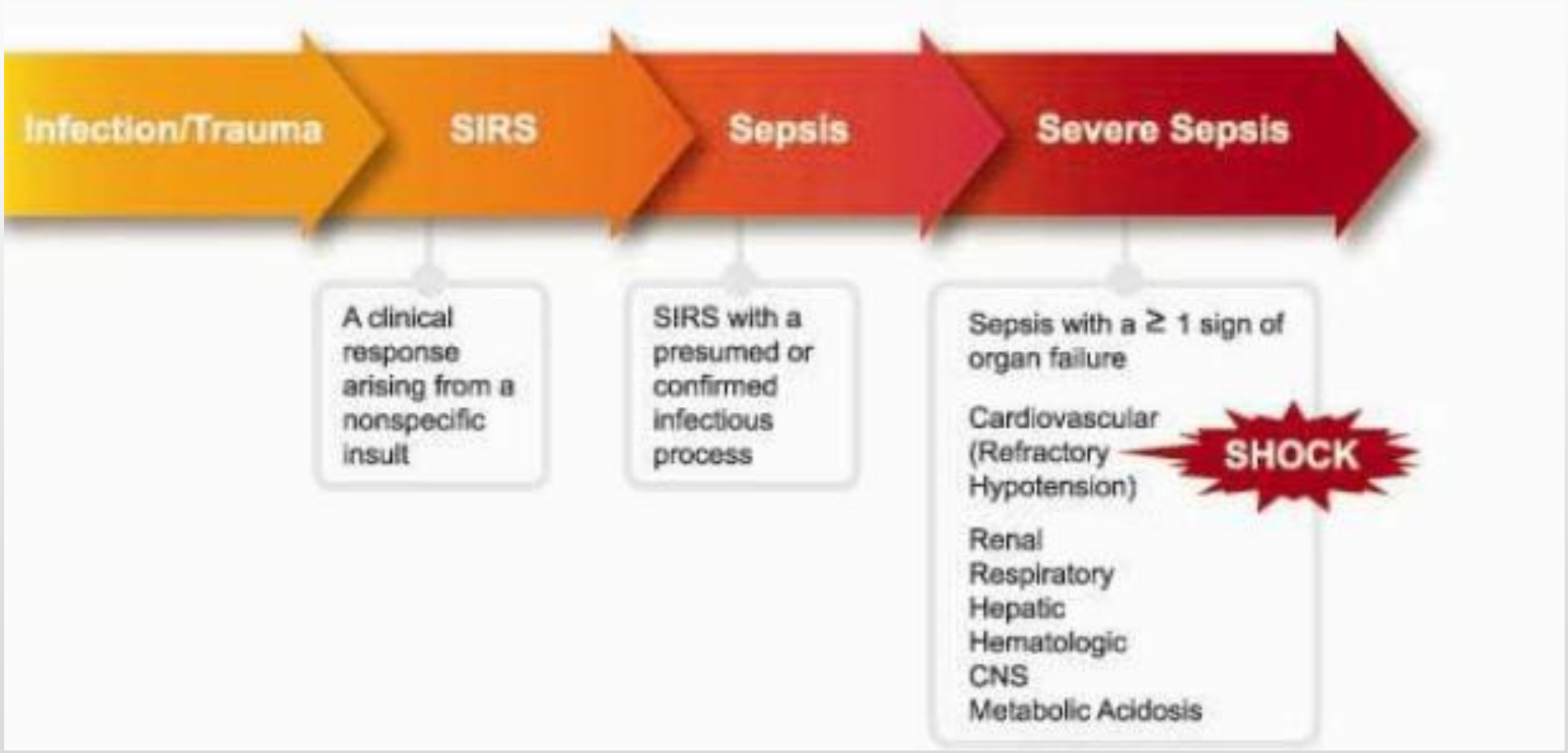
Severe Sepsis:

Presence of Sepsis with one or more organ dysfunction

Septic Shock:

Presence or Sepsis and hemodynamic instability

Sepsis

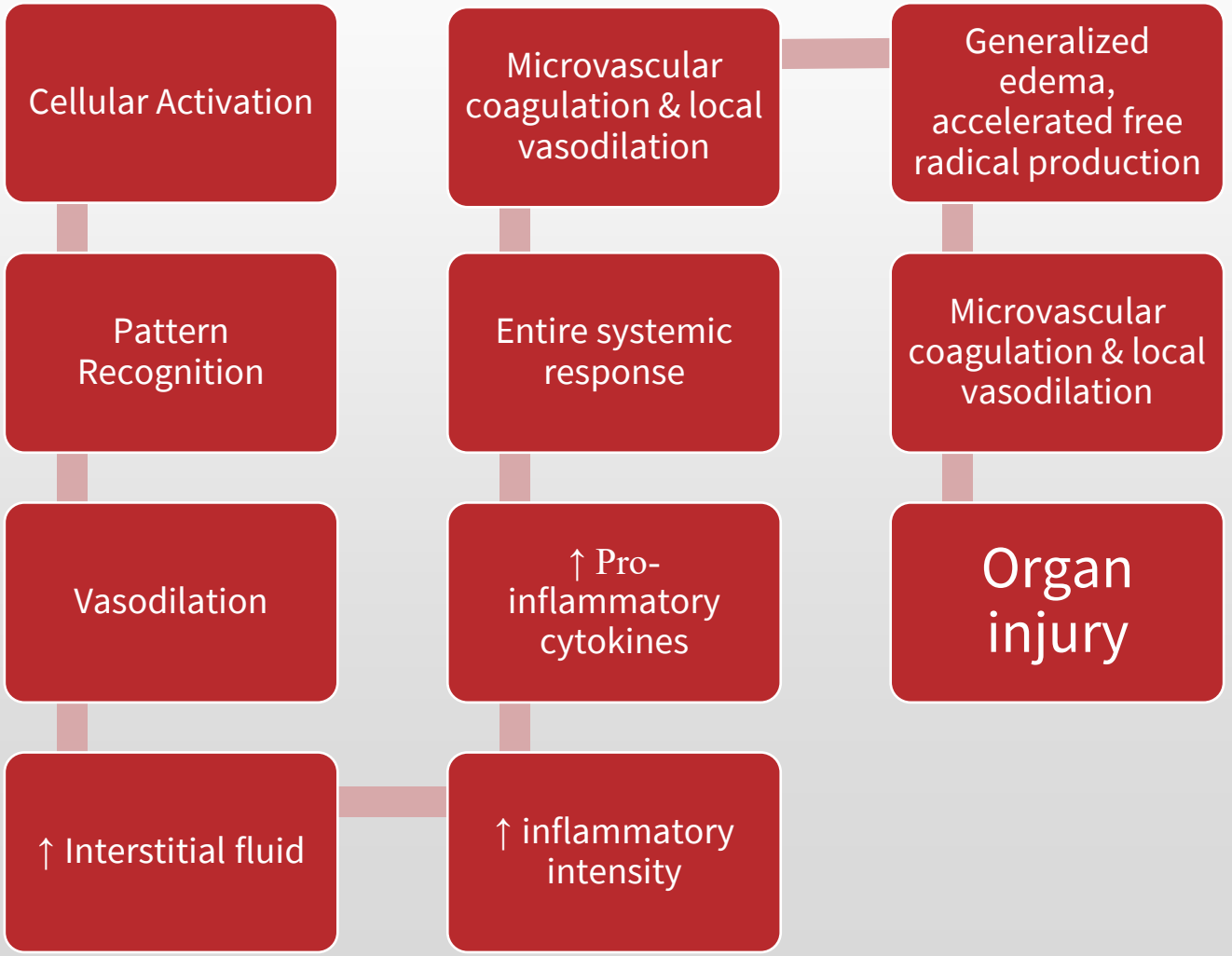

Infection/Trauma
SIRS
Sepsis
Severe Sepsis
A clinical response arising from a nonspecific insult
SIRS with a presumed or confirmed infectious process
Sepsis with a ≥ 1 sign of organ failure
Cardiovascular (Refractory Hypotension)
SHOCK
Renal
Respiratory
Hepatic
Hematologic
CNS
Metabolic Acidosis

Metabolism of Sepsis

- Increase in energy expenditure
- Protein catabolism
- Oxidation of stored lipids
- Significant alterations in body's ability to metabolize carbohydrates

Pathophysiology of Sepsis

Pro Inflammatory phase

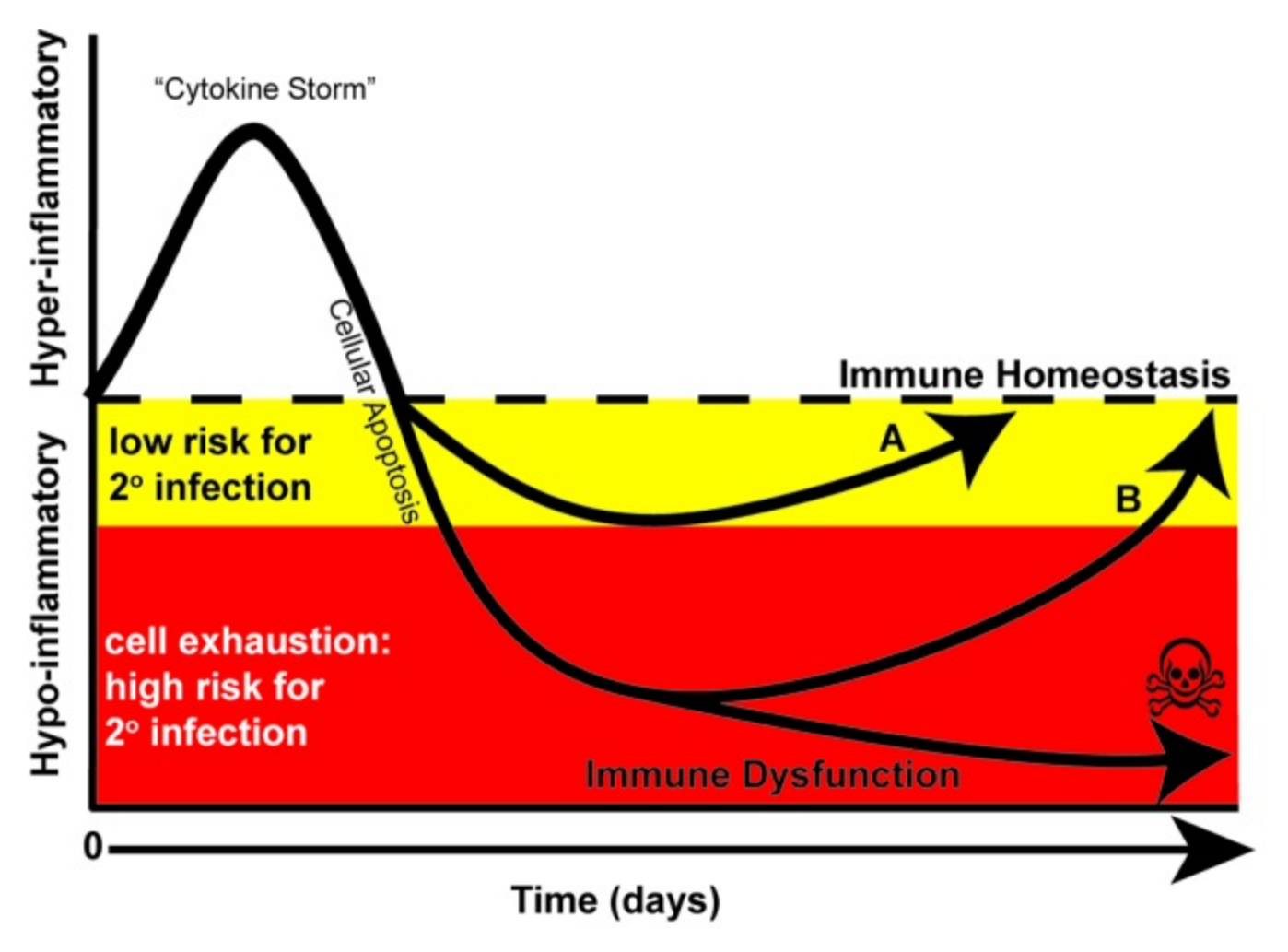


Pathophysiology of Sepsis (contd.)

Compensatory Anti-inflammatory phase

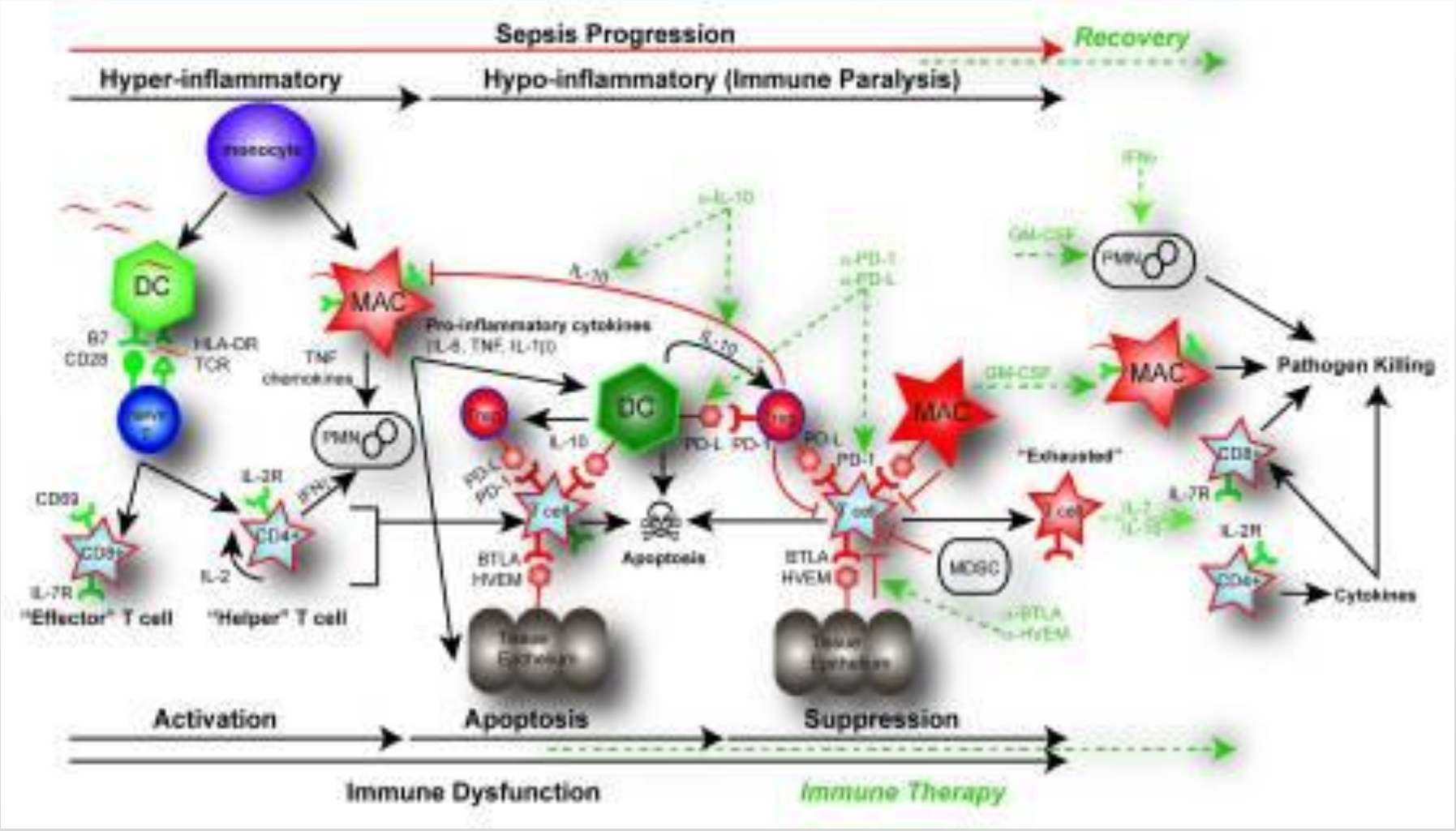
- In response to limit the overzealous inflammatory process in patients with SIRS
- Modification of the immune status that could favor the enhanced susceptibility of intensive care patients to nosocomial infections
- CARS may be considered as an adapted compartmentalized response with the aim to silence some acute proinflammatory genes, and to maintain the possible expression of certain genes involved in the anti-infectious process.

Pathophysiology of Sepsis (contd.)



The changing immune system in sepsis
Is individualized immuno-modulatory therapy the answer?
Jonathan S Boomer, [1,*] Jonathan M Green, [1] and Richard S Hotchkiss [2]

Pathophysiology of Sepsis (contd.)



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Pathophysiology of Sepsis (contd.)

In Conclusion

- Typically all major organs are involved but disruption in cardiac, pulmonary, renal and hepatic functions are most common
- First systemic response phase – not destructive but an effort to contain the infection
- Immune suppression phase – ideal target for nutritional intervention
- Appropriate nutrition therapy during sepsis helps
  - Maintain immune function
  - Modulate inflammatory response
  - Abrogate skeletal muscle catabolism
  - Improve wound healing
  - Maintain GI and Pulmonary mucosal barrier function

Metabolic Response During Sepsis

Carbohydrate Metabolism

- Glucose homeostasis regulated by several mechanisms
- In Sepsis – hyperglycemia and significant insulin resistance
- Pro-inflammatory Cytokines → release of catabolic hormones → gluconeogenesis & glycogenolysis to mobilize glucose
- Glycogen stores depleted within hours
- Lipid and protein become major energy substrate

Sepsis causes hyperglycemia due to

- Change in endogenous glucose production
- ↓ glucose uptake
- ↑ insulin resistance

Dahn & Colleagues showed 6 X greater hepatic glucose production in trauma and sepsis patients than in trauma alone

Metabolic Response During Sepsis (contd.)

Protein Metabolism

- Negative nitrogen balance occurs although ↑protein breakdown and synthesis
- ↑ Peripheral muscle breakdown + low amino acid uptake → ↑ ↑amino acid to the liver → ureagenesis ↑→ ↑ammonia, creatinine & uric acid production → losses through urine → ↑ N2 losses
- Hepatic uptake of AA & hepatic protein synthesis increased
- Provides substrate for gluconeogenesis ⟶ production of acute phase protein (which is not uniform) ⟶ ↑CRP & haptoglobulin and ↓ albumin & prealbumin
- Prolonged catabolism of skeletal muscle ⟶ compromised respiratory function, poor wound healing, ↑ immunosuppression, ↑ vent dependence and ↑ICU stay.

Metabolic Response During Sepsis (contd.)

Lipid Metabolism

- Lipolysis stimulated by catabolic hormones
- Stored triglycerides broken into free fatty acids and glycerol
- Intracellular transport metabolism affected
  - Long chain FFA accumulated in the cells
  - Intracellular acidosis
  - Accumulation of lactate and pyruvate
  - ↓ in aerobic respiration
- Impaired ketogenesis

Net Effect - Hyperlipidemia, hyperglycemia, hyperlactatemia, ↑ circulation of ß hydroxybutyrate

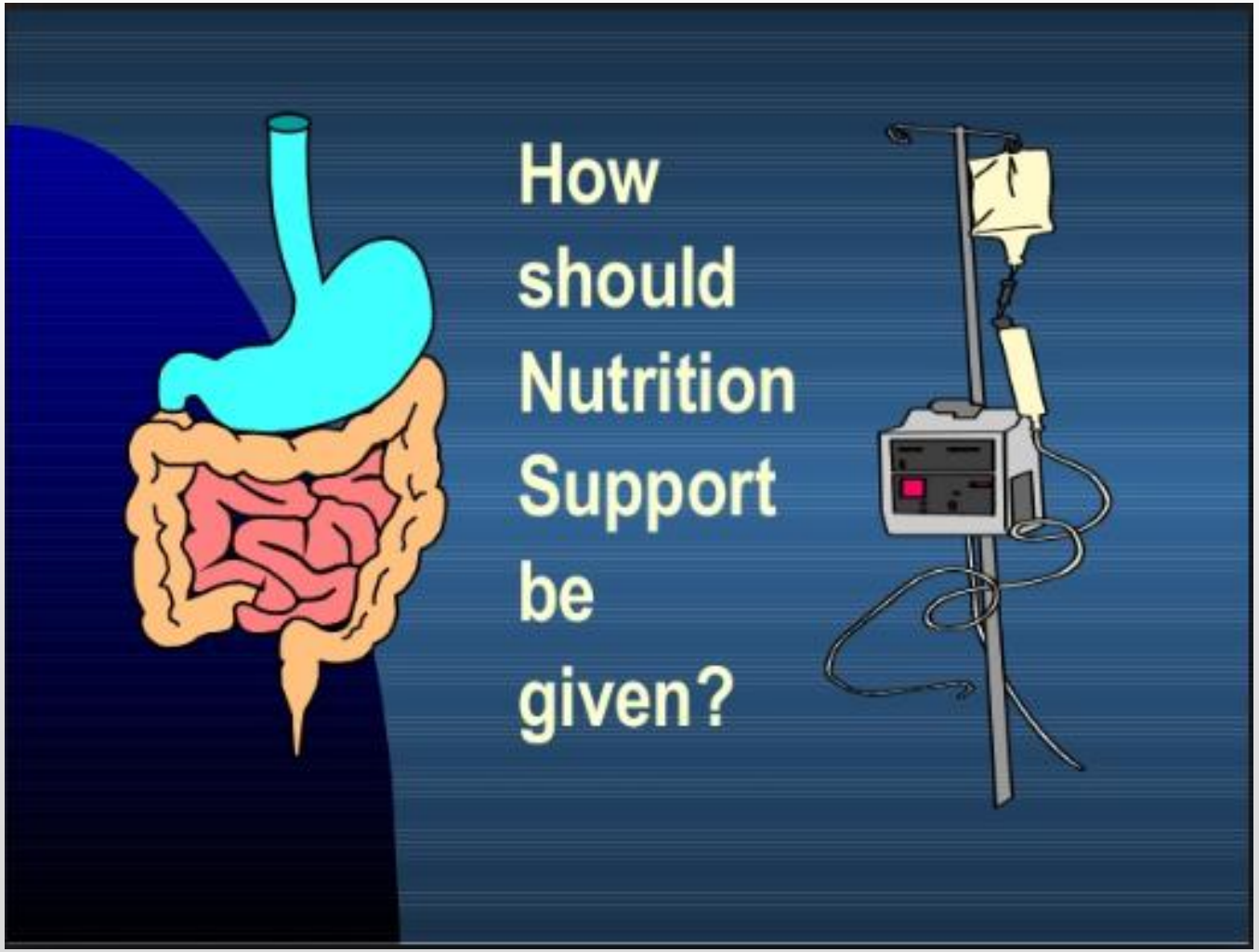
Nutrition Assessment in Sepsis and Critical Care

- Traditional methods not useful
  - Significant fluid shifts
  - Metabolic abnormalities due to inflammatory response
  - Biochemical and anthropometric measures unreliable
  - Inability to obtain nutrition history
- A thorough weight and diet history must often be pieced together from medical record and family history
- Evaluate
  - Weight and nutrition Hx PTA
  - Level of disease severity
  - GI function
  - Weight changes
  - Abdominal exam
  - Wounds
  - Lines, drain, tube placement
  - Vital signs
  - Vent settings
  - Hemodynamics
  - Labs

Energy Expenditure

- Significant increase in EE - estimated 20-60% above BEE
- Plank et al. showed an increase in REE over the first 7 days in patients with peritonitis and sepsis, which remained elevated for 21 days, even when sepsis had been treated
- Increase in EE due to ↑ protein muscle catabolism and usage of lipid source as oxidative fuel
- Initially beneficial to mobilize adequate endogenous substrate, but when prolonged becomes detrimental to host survival
- Adequate nutrition (EN and use of anti-inflammatory lipids like EPA and DHA) can attenuate metabolic stress
- Supplying substrates for enhanced acute-phase protein synthesis shown to improve enhance survival

Route of feeding



Route of feeding

- Early administration of EN beneficial in critical care population when compared to PN (Marik et al. and Heyland et al.)
- During sepsis, GI tract and liver susceptible to ischemia due to poor blood flow (Gut ischemia → Mitochondrial dysfunction → Mucosal acidosis → Progressive cell injury → Death)
- EN provides protection and even enhances perfusion during sepsis
- Khalid et al. reported that early enteral feeding decreased mortality in patients, requiring ventilation for over 48 hours and on vasopressors

Route of feeding (contd.)

- How to maximize gut function in sepsis and critical illness?
  - Maintain visceral perfusion by providing adequate resuscitation
  - Glycemic control
  - Correction of acidosis and electrolyte abnormalities
  - Minimize use of anti cholinergic medications, narcotics and other meds that reduce intestinal motility
  - Initiating EN at a low rate within first 24 to 48 hours of onset of sepsis
- Enterally feeding septic patients only after adequate volume resuscitation has proven to be beneficial
- Care and close monitoring necessary to prevent complications like bowel ischemia
- Zaloga et al. showed the foremost benefit of EN to be in the prevention of serious infections and not in its treatment

Route of feeding (contd.)

- Once sepsis has been well established, EN has no proven outcome over PN or even no nutrition (Eyer et al. showed starting EN 4-6 days after onset of sepsis did not prevent progression of multiple organ dysfunction or mortality risk)
- Challenges of providing EN during sepsis
  - Lack of access
  - GI dysfunction
- Challenges can be overcome by
  - Promotility agents
  - Timely tube placement
- PN should be used only when true GI intolerance/dysfunction prevents adequate EN delivery
- Even when PN used, low rate EN should be considered to maintain gut mucosal integrity and GALT

Timing of Nutrition Support

When is the best time?

Determined by

- Age
- Premorbid conditions
- Route of delivery
- Metabolic state
- Organ function

2016 Society of Critical Care Medicine (SCCM)/ American Society of Parenteral and Enteral Nutrition (A.S.P.E.N) Recommendations:

“We recommend that nutrition support therapy in the form of early EN be initiated within 24-48 hours in the critically ill patient who is unable to maintain volitional intake.”

Timing of Nutrition Support (contd)

Reported benefits of early Nutritional Intervention

- Prevention of adverse structural and functional alterations in the mucosal barrier
- Augmentation of visceral blood flow
- Enhancement of local and systemic immune response

Clinical benefits of early EN proven by three meta analysis studies show

- Decrease in infection,
- Decrease in hospital length of stay, and
- No increase in major morbidity

Marik PE, Zaloga GP, Early EN in acutely ill patients – a systemic review, Crit. Care Medicine (CCM) 2001,

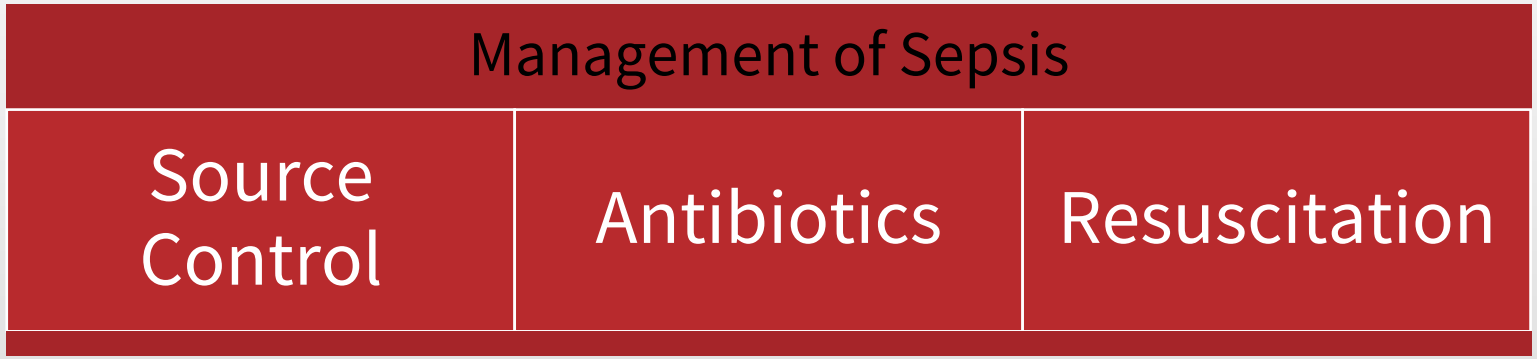
Heyland DK, Dhaliwal R. Early EN vs early PN – an irrelevant question for the critically ill, CCM 2005,

Osland E, Yunus RM, Khan S, Memon MA, Early vs trad. Postoperative feeding in patients undergoing resectional GI surgery – A meta analysis, J of Parenter Enteral Nutrition 2011,

Timing of Nutrition Support (contd)

Early EN Initiation – A Multidisciplinary approach

EN only after Resuscitation



Early and aggressive resuscitation or “Early Goal-Directed Therapy” very critical

Timing of Nutrition Support (contd)

Need for caution

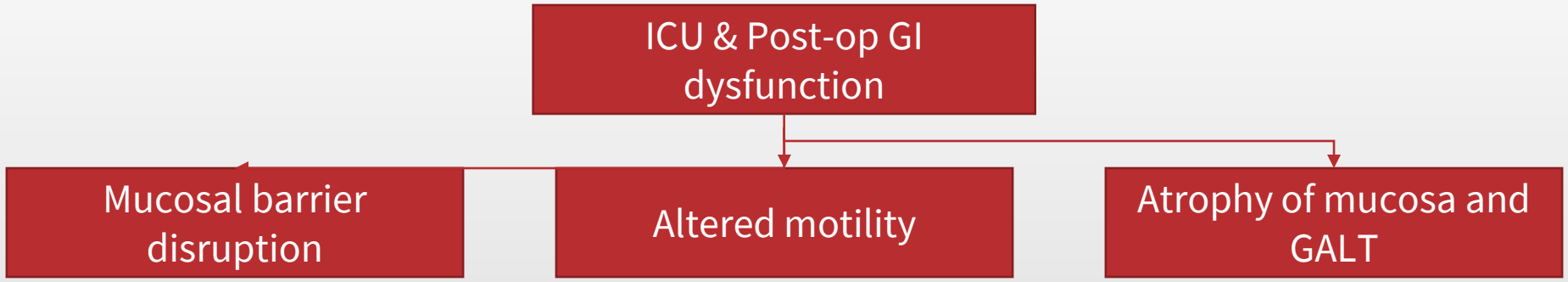
- Splanchnic circulation ↑ by 40 – 60 % when enterally fed
- This ↑ metabolic demand on the GI tract
- If supply < demand, rare but devastating complications
- NMI (Nonocclusive Mesenteric Ischemia) possible after early EN in the under resuscitated patient
- EN in the hemodynamically unstable patient should be done with extreme caution

2016 SCCM/A.S.P.E.N Recommendations:

"Based on expert consensus, we suggest that in the setting of hemodynamic compromise or instability, EN should be withheld until the patient is fully resuscitated and /or stable. Initiation/reinitiation of EN may be considered with caution in patients undergoing withdrawal of vasopressor support"

GI Dysfunction

GI dysfunction in the ICU range from 30 - 70 %



Ways to manage gut function in critical care and post-op state

- Maintenance of visceral perfusion
- Glycemic control
- Electrolyte correction
- Early enteral nutrition
- Reduce medications that alter GI function (anticholinergic agents, narcotics, vasopressors)

GI Dysfunction (contd.)

GI intolerance should be constantly re-assessed

- Abdominal distention
- ↑ gastric residuals or NG output
- Abdominal pain
- Diarrhea

Impaired gastric motility can be addressed by:

- Placement of post pyloric tubes
- Pro kinetic agent (erythromycin, metoclopramide, alvimopan)

Complications of Enteral Feeding in the ICU

- NMI
- GI Intolerance
- Aspiration
- Feeding tube misplacement
- NG tube – malpositioning of the tube in the respiratory tract
  - epistaxis
  - sinusitis
  - tube clogging

Complications of Parenteral Nutrition in the ICU

- Risk of infection
- Catheter related blood stream infections
- Electrolyte abnormalities
- Glucose intolerance
- TPN induced cholestasis

Nutritional Requirements

Energy

- Estimating energy requirements very difficult
- Energy expenditure 20-60% above BEE
- Body's ability to utilize calories in the early phase of sepsis is limited

Hypocaloric or permissive underfeeding vs. adequate feeding

- Several studies in critically ill patients have shown hypocaloric high protein feeding to be beneficial
- Extreme caloric restriction (<20 % calorie goal) is detrimental to critically ill
- Caloric delivery in the range of 20-30 cal/Kg is safe
- Heyland et al. showed lower mortality in patients that received a larger proportion of prescribed nutrition support in a large multi-institutional ICU study

Nutritional Requirements (contd.)

Carbohydrate

- 50-60% of the total energy requirements
  - Glucose oxidation ↑ in sepsis and can provide an appropriate route of disposal for exogenous glucose
  - Wolfe et al. concluded non protein caloric provision in septic patients should be largely in the form of carbohydrates with exogenous insulin added to stimulate cellular protein anabolism
- Glucose administration rate in excess of 4-6 mg/Kg/min causes ↑ lipogenesis and hyperglycemia.
- Excessive carbohydrate administration leads to poor glucose control
  - Van Den Berghe et al in a large prospective randomized trial showed ↓ ICU stay, ↓ mortality rate and fewer episodes of septicemia in patients that had strict blood glucose control (80 - 110mg/dl), vs in patients that had blood glucose levels between 180 – 200mg/dl
  - Significant hepatic mitochondrial abnormalities were also found in the control group that did not have tight blood glucose control

Nutritional Requirements (contd.)

Lipids

- An effective fuel source during sepsis
  - Energy dense 9 cal/g – beneficial in patients requiring fluid restriction
  - Respiratory quotient lower than carbohydrate, hence lower CO_2 production

- Source and make-up of lipid substrate is critical and a mixture of lipid fuels should be used when possible.

- Lipids should not exceed 1g/Kg/d when soybean oil is the only source of lipid.
  - 1g/Kg/d can be liberated when lipid sources contain omega 3 fatty acids, medium chain fatty acids and short chain fatty acids.

Nutritional Requirements (contd.)

Lipids - Type

- In sepsis there is reduced ability to transport long chain fatty acids across the mitochondrial membrane d/t alterations in the acylcarnitine carrier
- Medium chain fatty acids do not require carnitine for transport
- Sanderson et al and Bengmark et al showed the benefits of short chain fatty acids produced from bacterial oxidation of soluble fiber in the lumen
  - Helps maintain mucosal membrane integrity
  - Systemic enhancement of immune function via receptors on multiple cells including white blood cells.
- Omega 3 fatty acids when delivered as fish oils (DHA and EPA) shown to be beneficial in sepsis
  - modulates leukocyte function
  - regulation of cytokine release.
  - Enhances production of prostaglandin derivatives which improves resolution of the pro-inflammatory state
  - Abundant data reports influence of EPA and DHA on nuclear signaling and gene expression

Nutritional Requirements (contd.)

Lipids - Type

- Route of delivery of omega 3 fatty acids important
  - When fed enterally 2-3 days were required to achieve adequate levels
  - A clinically relevant response was achieved within 1-3 hours when fed parenterally
- Omega 3 fatty acids on Respiratory failure in sepsis
  - Prevents the loss of diaphragm function in sepsis
  - Enhances resistance to gram negative pathogens like pseudomonas
  - Multiple prospective trials showed ↑ mortality and lung related outcomes in ARDS &acute lung injury
  - EPA and DHA not only passively modulates the immune process but is also acutely involved in immune modulation
- Other benefits of lipids
  - Fat soluble vitamin carrier
  - Structural units in cell membrane
  - Precursor to eicosanoids
  - Cytokine production
  - Interaction with gene expression

Nutritional Requirements (contd.)

Omega 3 Fatty Acids

2016 SCCM/A.S.P.E.N. Recommendations

- “We cannot make a recommendation at this time regarding the routine use of an enteral formulation characterized by an anti-inflammatory lipid profile (e.g. Omega-3 fatty acids, borage oil) and antioxidants in patients with ARDS and severe ALI given conflicting data.”.

Nutritional Requirements (contd.)

Protein

- 1.5- 2 g/Kg/ day optimal in sepsis
- Higher in patients with excess N2 losses
- Increased in patients requiring tighter glycemic control
- But caution with patients with renal and hepatic failure
- Recent data supports the use of whey and casein in critically ill
  - BV, PER and NPU superior in whey and casein compared to soy

Arginine and Glutamine

ARGININE

Deficient in the critically ill and needs to be supplemented

- Critical in nitric oxide production pathway
- Arginine levels dramatically low in the septic state
- Nitric oxide reported to have numerous beneficial effects
  - ↑myocardial perfusion
  - ↓ hepatic and splanchnic injury following ischemic insult
  - Preventing endothelial damage

Toxic potentially

- Increasing arginine supplementation causes worsening hypotension and outcomes due to uncontrolled nitric oxide production
- Some studies showed ↑ mortality risk in arginine containing enteral feeding vs parenteral nutrition in sepsis

Overwhelming bulk of current literature suggest arginine containing tube feeds are safe and reduce complications

Arginine and Glutamine (contd.)

Glutamine

Sepsis → rapid and precipitous drop in plasma and muscle glutamine concentration

Benefits:

- Helps in acid base balance
- Provision of primary fuel for rapidly proliferating cells
- Integrity of GI mucosa
- Helps lower clinical infection and gram neg bacteremia
- Helps in synthesis of glutathione and arginine
- Lowers insulin resistance and inflammatory response
- Key substrate for gluconeogenesis
- Recent evidence shows glutamine can induce heat shock protein

Singleton et al showed that glutamine could lower lung injury and mortality in septic animals

Metaanalysis of glutamine use in the ICU showed ↓ hospital stay, ↓ infectious complications in surgical patients and improved mortality in the critically ill.

Arginine and Glutamine (contd.)

2016 SCCM/A.S.P.E.N Recommendations:

- “We suggest immune-modulating enteral formulations (arginine with other agents, including EPA, DHA, glutamine and nucleic acid) should not be routinely used in the MICU. Considerations for these formulations should be reserved in patients with TBI and perioperative patients in the SICU:
- “We suggest that immune-modulating formulas not be used routinely in patients with severe sepsis”
- “We suggest the routine use of an immune-modulating formula (containing both arginine and fish oils) in the SICU for the postoperative patient who requires EN therapy”

Antioxidants

- Sepsis increases production of ROS (reactive oxygen)
- Oxidant injury occurs with loss of balance between endogenous antioxidant defenses and cellular production of ROS
- ROS generated by phagocytic cells cause a host of signal transduction and gene activation events resulting in a proinflammatory state
- Free radicals injure cell membranes or may damage intracellular protein, nucleic acids and organelles → cell death
- Cellular injury → over production of ROS → overwhelms the hosts' ability to detoxify generated ROS

Benefits:

- Nathan et al in a large randomized trial of 595 ICU patients showed that addition of 3g IV Vitamin C /day and 3000IU Vitamin E lowered ventilator time and ICU stay
- Collier et al showed a modest mortality benefit after initiation of antioxidants
- Majority of several randomized prospective trials on various antioxidants in severely stressed and septic patients showed beneficial results
- No clear data on the duration of therapy

Immunity

- Malnutrition is linked to derangements in humoral and cellular immunity → increased susceptibility to infection
- Adequate nutrition needed to support a functional immune system and lower septic mortality and morbidity
- Inadequate nutrition support → gut failure → multi organ failure
- Bacterial translocation from intestinal lumen to gut lymphatics or the portal venous system is not clinically significant in the immune competent host. Destruction of the translocated bacteria depends on the immunity of the host. Early EN protects the mucosal barrier.
- Probiotics – proven beneficial in sepsis in the immuno compromised host

Maintenance of host immunity is the most valuable defense to lower septic complications and mortality. Nutrition support is one of the most effective ways to achieve this goal.

Case Study

- 24 year old male involved in a motor vehicle accident
- Diagnosed with brain Injury, multiple rib fractures, no other significant medical hx
- Admitted to the ER, dx with brain injury, bilateral rib fractures & pulmonary contusions
- No nutrition therapy started
- Required ventilation for hypoxia and worsening mental status
- After 48 hours of ventilatory support developed fevers and hypotension, chest X ray showed lower lobe infiltrates, started on vasopressors and antibiotics
- Nutrition consult ordered due to lack of nutrition delivery in the past 48 hours
- His height is 175 cm and weight is 80 Kg

Case Study (contd.)

In the ICU

- Day 1– Feeding was not initiated as patient was unstable
- Day 2 – Patient further resuscitated and vasopressor requirements ↓
- Tube feeds started at a low rate of 20ml/hour
- Day 3 -Tube feeds gradually increased 20ml/hour every 4 hours to goal of 80ml/hr
- Day 4 – Tube feeds advanced to goal rate
- Energy requirements - 2300 calories (Penn state equation)
- Protein requirements – 140g (1.8g/Kg)
- An immune- enhancing, low residue, lactose free formula was chosen given hx of trauma and sepsis
- Day 7 – Pt improving and transferred to the floor, but no improvement in mental status, still on the ventilator
- Day 10 – NG tube removed and PEG placed

Case Study (contd.)

- Week 3– Patient weaned off from the ventilator, still requiring T piece for airway protection
  - Patient more awake and following some commands
  - Rehabilitation therapy initiated including speech and swallow therapy
- Patient continued on tube feeds at goal rate, ice allowed for comfort
- Week 4– Patient passes bed-side swallow evaluation and pureed diet started
- Week 5 – Patient's po intake improved and tube feeds transitioned to nocturnal only
- Patient transferred to an acute rehabilitation facility for more intensive rehabilitation and decannulation

Conclusion

- Sepsis is a major health care problem
- Sepsis is a systemic response to infection
- Increased energy expenditure, protein catabolism and oxidation of stored lipids during sepsis
- Early nutrition assessment and intervention imperative in the treatment
- Early initiation of nutrition support very important after initial resuscitation has occurred
- Early enteral nutrition proven beneficial not only in the treatment but also in the prevention of serious infections
- Supplemental amino acids like arginine and glutamine, antioxidant and omega 3 fatty acids may be beneficial

Thank You!

ANY QUESTIONS?