Amino acids: the “forgotten” building blocks?

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Make today matter
Focus of presentation

- Adult critical illness
- Each amino acid
  - Protein synthesis properties
  - Evidence
  - Guidelines
  - Recommendations
Introduction

- ICU acquired weakness → impaired weaning from ventilator → increased mortality
- Altered amino acid (AA) metabolism contributing factor:
  - Gluconeogenesis
  - Acute phase protein synthesis
  - Non essential AA becomes conditionally essential AA
- Result: loss of lean body mass (LBM)
  - Muscle fibres: atrophy & degeneration
  - Decreased myofibrillar size

Gunst J 2018
Introduction

- Will increased AA administration prevent muscle weakness?
  - 3 RCT: absence of clear benefit
  - Possible reasons
    - Amino acid-induced suppression of autophagy (degree = amount)
    - Failure to counteract net catabolism
    - Wrong amino acid composition
      - Is EAA the key?
Specialised AA

Amino acids

- EAA
  - Leucine
- Conditionally EAA
  - Arginine
  - Glutamine
- Non EAA
  - Citrulline
  - Taurine
Specialised AA

Amino acids

- EAA
  - Leucine
- Conditionally EAA
- Non EAA
Leucine

- Functions
  - Insulin secretagogue
  - For protein synthesis = need activation of initiation factors
    - Act as neutraceutical to activate
    - Possibly assist with protein synthesis?
    - Inconsistent theory = availability of all EAA

Wolfe RR 2017
Leucine

- Interest in BCAA date back to 1980’s
  - Stimulate prot synth & ↓ muscle prot catabolism
  - Frank Cerra: BCAA-PN in surgical patients:
    - ↑ levels of plasma levels of BCAA and arginine
    - Improve N balance (promoting prot synth)
    - ↑ prelab levels
    - ↑ lymphocyte count

But what about clinical outcomes?

Moore FA 2017
Leucine

• Clinical outcomes
  – Did not demonstrate any effect on mortality or other parameters
  – Expensive

• Result: interest faded

Moore FA 2017
Recommendations

- ASPEN 2016
  - Based on expert consensus, we suggest that **standard enteral formulations** be used in ICU patients with **acute and chronic liver disease**. There is **no evidence** of further benefit of branched-chain amino acid formulations (BCAA) on coma grade in the ICU patient with encephalopathy who is already receiving first-line therapy with luminal-acting antibiotics and lactulose.
To supplement or not to supplement?

- Possible role
  - Elderly
  - Persistent inflammation, immunosuppression and catabolic syndrome (PICS)

- Problems
  - Lack of info on use (clinical setup and EN/PN)
Specialised AA

Amino acids

EAA

Conditionally EAA

Non EAA

Arginine
L-Arginine

- Promotes T-lymphocyte & fibroblast proliferation
- Intracellular substrate for NO production in macrophages
  - Improve bactericidal activity
- Secretagogue:
  - growth hormone
  - Prolactin
  - Somatostatin
  - Insulin
  - Glucagon

Moore FA 2017
Arginine metabolism

Trauma, Surgery, chronic infections

Sepsis

Myeloid cells

Limiting amino acid

Ochoa Gautier JB 2017
Pierre 2013

Polyamines

Ornithine

Glutamate

Citrulline

Aspartate

Arginosuccinate Synthase

Arginosuccinate Lyase

Arginase

P-5-C

iNOS

NO

Urea

Arginine
So what?

↑ arginine requirements → "sense"↓ home

Reduced protein synthesis

Dec wound healing

suppressed lymphocyte proliferation:

Dec immune function

Ochoa Gautier JB 2017
To supplement or not to supplement?

- Trauma, surgery, chronic infections
  - ↓ clinical infections & complications
  - ↓ LOS in hospital
  - ↓ ventilator days
  - x no effect on mortality

- PICS possibly

Moore FA 2017
Pierre 2013
Arginine metabolism

Trauma, Surgery, chronic infections

Sepsis

Ochoa Gautier JB 2017
Pierre 2013
To supplement or not to supplement?

- Upregulation of inducible nitric oxide (NO) synthase
  - ↓ Arg = suppresses lymphocyte proliferation
  - Citrulline, NO
  - Inc NO
    - Pathological vasodilation - amplifying shock
    - Physiologically possible but clinically unproven,
      - ? relevant

Moore FA 2017
Recommendations: EN

- ASPEN 2016
  - We suggest immune-modulating enteral formulations (arginine with other agents, including eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA], glutamine, and nucleic acid) should not be used routinely in the MICU.
  - Consideration for these formulations should be reserved for patients with TBI and perioperative patients in the SICU.

- Canadian, 2015
  - We do not recommend diets supplemented with arginine and other select nutrients be used for critically ill patients

Taylor 2016
Recommendations: EN

- ESPEN, 2006
  - Immune-modulating formulae (formulae enriched with arginine, nucleotides and x-3 fatty acids) are **superior to standard enteral formulae**:
    - in elective upper GI surgical patients
    - in patients with a mild sepsis
    - in patients with trauma
Glutamine

- Substrate for renal ammoniagenesis
- Precursor for glutathione (AOX)
- Major fuel for rapidly dividing cells
  - Enterocytes
  - Colonocytes = intestinal mucosa integrity
  - Immune cells
What happens with gln in crit illness?

• ↓ gln levels
  – surgical trauma, major injury, burns, infections, and pancreatitis
  – ↑ dysfunction

• Hypothetically it should help preserve muscles when supplemented?
  – BUT this is not the case
    • Proteolysis: Rather controlled by degree of inflammation
      – Not by glutamine levels
    • Additional amino acids are oxidised: limited synthesis

McCarthy 2018
Is it safe to use?

- Nu of trial last few years
  - Mortality
    - In hospital; 6 months post discharge
  - No benefit: infection

McCarthy 2018
What does the evidence say?

- Varying results from studies
- EN gln: Systematic review 2015, van Zanten
  - 1079 critically ill patients
  - No effect on
    - Hospital mortality
    - Infectious complications
    - ICU LoS
  - Significant reduction: hospital LoS

McCarthy 2018
What does the evidence say?

- EN & PN gln: Systematic review 2014 Tao et al
  - Moderate evidence
    - ↓ infectious complications
    - ↓ days mechanical ventilation
  - Low evidence: ↓ hospital LoS
  - Critically ill & surgical

Critically ill✓
Surgery✓

McCarthy 2018
What does the evidence say?

• Meta analysis, Oldani et al 2015
  – 30 RCT, 3696 ICU patients
  – Control vs experimental group
    • No difference in
      – Hospital mortality
      – ICU mortality
      – Infections

McCarthy 2018
What does the evidence say?

- Meta analysis: Stehle P 2017
  - PN gln-dipeptide administration
  - Inclusion:
    - critically ill patients
    - No hepatic / renal failure
    - Hemodynamically & metabolically stable
    - Adequate nutrition
    - Gln according to guidelines

↓ Hospital mortality
↓ Infectious complication
↓ Hospital LoS

Stehle P 2017
Recommendations: Enteral gln

• ASPEN, 2016
  – The addition of enteral glutamine to an EN regimen (not already containing supplemental glutamine) should be considered in burn, trauma, and mixed ICU patients (Grade B).

• Canadian, 2015
  – We recommend that enteral glutamine NOT be used in critically ill patients.
Recommendations: Enteral gln

- ESPEN, 2006
  - Glutamine **should be added** to standard enteral formula in:
    - **burned** patients
    - **trauma** patients
  - There are **not sufficient data** to support glutamine supplementation in surgical, heterogenous critically ill patients
Recommendations: Parenteral gIn

• ASPEN, 2016
  – We recommend that parenteral glutamine supplementation **NOT be used** routinely in the critical care setting. (moderate)

• Canadian, 2015
  – We recommend parenteral supplementation with glutamine **NOT be used**.
  – There **are insufficient data** to generate recommendations for intravenous glutamine in critically ill patients receiving enteral nutrition: **Do NOT use**
Recommendations: Parenteral gln

- ESPEN
  - 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).
Recommendations: PN & EN gln

• Canadian, 2015
  – We recommend that high dose combined parenteral and enteral glutamine supplementation NOT be used in critically ill patients.
  – There are insufficient data to make a recommendation on the use of enteral glutamine vs. parenteral dipeptide supplementation.
  – However given concerns of glutamine supplementation, we strongly recommend that glutamine supplementation NOT be used in critically ill patients, hence we do not recommend the use of enteral glutamine or parenteral dipeptides.
Specialised AA

Amino acids
- EAA
- Conditionally EAA
  - Citrulline
- Non EAA
Citrulline

- Arg & gln → citrulline → arginine → protein
- Intermediate of urea cycle
- Not incorporated into proteins
  - ? Regulate nitrogen homeostasis
- Other fx
  - Oxidant scavenging
  - Affects NO production
- ↓ levels: sepsis, ARDS

Gunst J 2018
To supplement or not to supplement?

- Possible role
  - Severe sepsis
  - ARDS

- Problems
  - Lack of info on application (clinical setup and EN/PN)

Gunst 2018
Specialised AA

Amino acids

- EAA
- Conditionally EAA
- Non EAA
- Taurine
Taurine

- Not incorporated into proteins

- Functions
  - Osmoregulation
  - Antioxidative
  - Anti-inflammatory

- ↓ levels: critically ill

Gunst J 2018
Taurine

- Enteral omega 3 fatty acid, alpha linolenic acid, and antioxidant supplementation in acute lung injury study (OMEGA study)
  - ↓ in ventilator free days
  - > days with organ failure
  - ↑ mortality

- Other immune enhancing components?

Gunst J 2018
To supplement or not to supplement?

- Possible role
  - Critical illness
  - ALI

- Problems
  - Lack of info on application

Gunst 2018
Specialised AA

- Amino acids
  - EAA
    - Arginine
  - Conditionally EAA
    - Glutamine
  - Non EAA
    - Citrulline
    - Taurine
What can we do?

- Arginine supplementation
  - Trauma, surgery, chronic infections

- Glutamine supplementation (TPN)
  - Critical illness

- Select an appropriate protein source
  - Whey protein >>>>> casein, soya
    - High in BCAA (leucine)
    - Higher in cysteine
    - Methionine:
      - Casein > whey > soya
Recommendations

- Timing, optimal dose, composition unclear
  - Supplement responsible

- Choose good quality protein source with all AA

- Adequately powered RCT showing benefit in critical illness
  - Not just physiological but also clinical outcomes
Thank You
References


References


References

