Nestlé Nutrition Institute

Controversies in Critical Care Nutrition

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Disclosure

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Objectives

- To understand the quality of evidence in the literature supporting early enteral feeding in critical illness.
- To learn the clinical impact from loss of gut barrier defenses, immune dysregulation, and progression from a commensal microbiome to a virulent pathobiome.
- To appreciate new ways by which nutritional therapy can support the intestinal microbiome and promote a clinical pattern of recovery in an ICU setting.

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Chaos in Critical Care Nutrition: How Important is Nutritional Rx?

PN

EN

"Recent large RCTs have not generated evidence that providing nutrition early in critical illness results in clinical benefits"

MP Casaer, G Van den Berghe (NEJM 2014;370:1227)

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Weakness in Scientific Method

Truth of research findings related to its reproducibility by subsequent research trials or its Positive Predictive Value (PPV)

JPA Ioannidis [PLoSMedicine 2005;2(8):e124]

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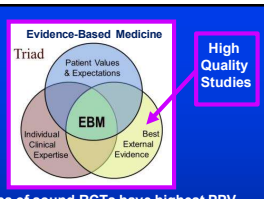
How Do We Trust Research Results?



- Large well-designed RCTs, appropriate meta-analyses of sound RCTs have highest PPV
  - 10% of large RCTs will be discounted by subsequent trials
  - 33% of good quality meta-analyses will be reversed
- Observational studies suffer from potential for confounding factors
  - 85% will be discounted by future studies
- Principles of clinical practice derived from all scientific information available
  - No study totally reliable at exclusion of all others
  - Incorporate findings if methodology sound, results plausible, supported by physiology

JPA Ioannidis [PLoSMedicine 2005;2(8):e124]

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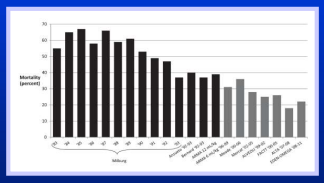
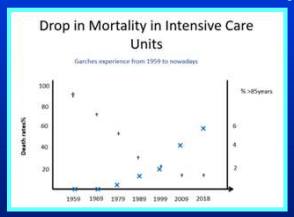
Documenting the Benefit of Nutritional Therapy

Recent large studies show no difference trophic vs full feeds, EN vs PN
Mortality of ARDSNet Controls has decreased 70% → < 20% over 30 yrs
As critical care improves, harder to tease out influence of each Rx modality





MJ Noto, AP Wheeler (Amer J Respir Crit Care Med 2013;188:128) Garches (Lancet Respir Med 2015)

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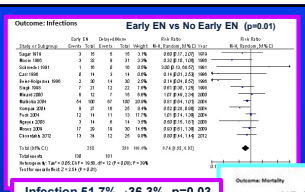
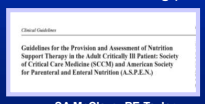
Nutrition Therapy Does Change Outcome

Early EN vs No Early EN

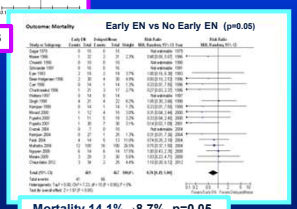


Infection 51.7%→36.3%, p=0.03

Controls: Intentional delay
Do nothing (STD)



SA McClave, BE Taylor
(JPEN 2016;40:159-211)



Mortality 14.1%→8.7%, p=0.05

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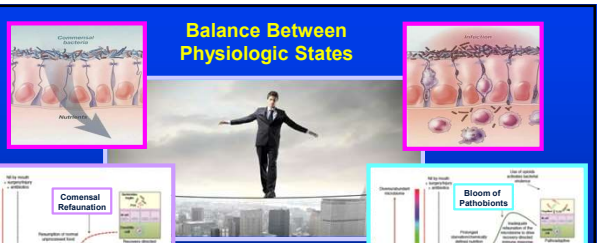
Balance Between Physiologic States



Comensal Refaunation

Bloom of Pathobionts

Pattern of Recovery
Barrier Function, Symbiosis, Homeostasis

Pattern of Gut Sepsis
Permeability, Dysbiosis, Immune Dysregulation

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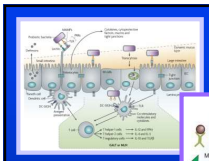
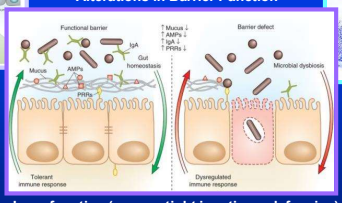
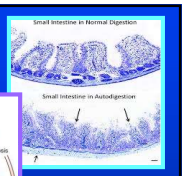
Gut Responses to Critical Illness

Alterations in Barrier Function

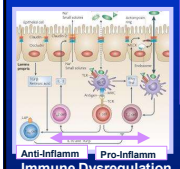


Commensal Signaling



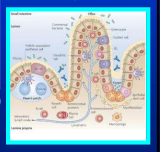


Autodigestion



Immune Dysregulation

Loss function (mucus, tight junctions, defensins)
Proinflammatory signaling (gut sepsis)
Penetration of pancreatic enzymes (MOF)
Emergence of virulent pathobiome



Toxic Lymph MOF[0]

MA Krezalek, JC Alverdy (Shock 2016;45:475) M Hayakawa (Dig Dis Sci 2011;56:2361)

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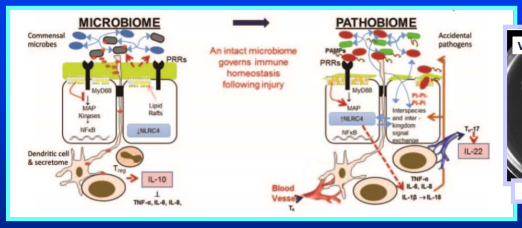
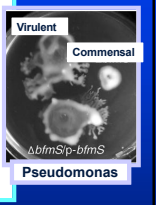
Progression from Microbiome to Pathobiome





Pseudomonas

- Disappearance of commensals, loss of biodiversity
- Emergence of virulent pathobiome
- Infectious morbidity, antibiotic resistance, anastomotic dehiscence

MA Krezalek, JC Alverdy (Shock 2016;45:475) M Hayakawa (Dig Dis Sci 2011;56:2361)

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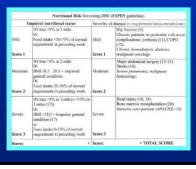
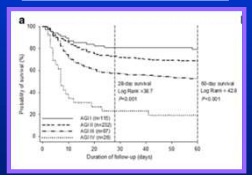
Calculating Nutritional Risk Gives Management Direction

- Nutrition risk – Two Aspects
  - Disease severity
  - Nutritional status
- Why assess nutrition risk?
  - Prognostic - Tolerance, difficulty Rx
  - May predict need to goal, benefit of Rx
  - Impact urgency, dose, need for supp PN



Age >70 yrs : Add 1 point

Score ≥3 Consider EN/PN
Score ≥5 High risk



[1] J Kondrup (Clin Nutr 2002) [2] B Hu (Crit Care 2017;21:188)

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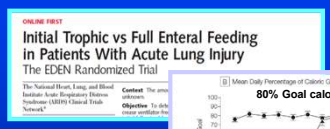
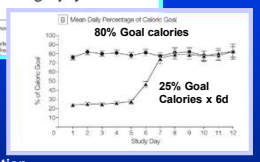
Is Trophic Underfeeding Effective ?





Eden Omega Trial ALI/ARDS patients on MV [1]
Trophic 20cc/hr (n=508) vs Full feeds (n=492)
No difference: Mortality, vent-free days, MOF, infection

PERMIT Trial Permissive Underfeeding in Mix ICU [2]
Underfeed 46% (n=894) vs Full feed 71% (n=446)
No difference: Infection, ICU LOS, ICU/Hosp mortality

[1] TW Rice (JAMA 2012;307:795) [2] YM Arabi (NEJM 2015;372:2398)

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Value of EN Due to Physiologic Response

Critical Care Medicine

- **Non-Nutrition benefits** – Seen in all patients
  - *Gastrointestinal responses*
    - Trophic on gut integrity
    - Commensal bacteria
    - Gut/lung axis of inflamm
    - Secretory IgA, GALT tissue
    - Reduced bact virulence
  - *Immune responses*
    - Modulate regulatory cells
    - Promote Th-2 >Th-1 lymphocytes
    - Maintain MALT tissue
  - *Metabolic responses*
    - Incretin to ↑ insulin sens
    - Reduce hyperglycemia (AGES)
- **Nutrition benefits** – Seen in high risk patients
  - Protein, calories
  - Micronutrients, anti-oxidants
  - Maintain LBM
  - Stimulate protein synthesis

Non-Nutritional: Trophic dose EN may be OK
Nutritional: Probably need full dose EN

S McClave, R Martindale, T Rice, D Heyland (CCM 2014;42:2600)

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Nutrirea-2 Trial: Impact of Aggressive EN

- Third largest PRCT in clinical nutrition (n=2400)
  - EN vs PN in MICU adults on MV in septic shock
  - Elderly (63 yrs), ICU LOS (9-10 days), high mortality rate (35%)
  - Groups got same calories (18-19 kcal/kg/d), protein (0.7-0.8 g/kg/d)
  - **Key issue** - EN start w/in 24 hrs of MV, advance to goal w/in 24 hrs
- Differences minimized by short duration of Rx in EN (6 days EN)
  - Crossover of PN group to EN after 3 days (aver 4 days PN)
- Results: No difference in outcomes
  - **Bowel Ischemia** in 19 EN pts vs 5 PN pts (p<0.05) J Reignier (Lancet 2018;391:133)

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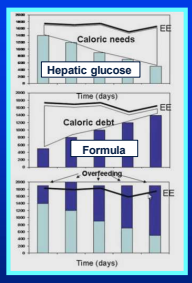
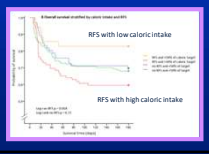
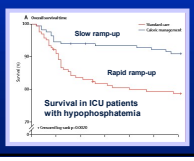
Five Reasons for Slow Ramp-up Over First Week

- Risk of bowel **ischemia** in pts with hemodynamic instability [1]
- **Overfeeding** in ICU pts can occur when formula is added to hepatic endogenous glucose production [2]
- Risk of **refeeding** syndrome in pts with hypophosphatemia [3]
- Underfeeding supports **Autophagy**
- Gauge **tolerance** as rate of infusion increased







[1] J Reignier (Lancet 2018;391:133)
[2] V Fraipont, JC Prieser (JPEN 2016;37:705-13)
[3] GS Doig (Lancet Respir Med 2015; 3: 943–52)

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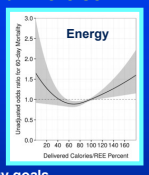
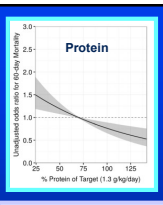
Pushing Protein: From Sarcopenia to Anabolic Resistance and Exercise





Reaching protein goals >> energy goals
Pushing dose to higher range 1.2-2.0 gm/kg/day

Important concept or jumping on a bandwagon?

MJ Allingstrup (Clin Nutr 2012;31:462)
Zusman (Crit Care 2016;20:367)

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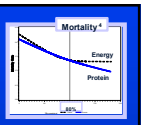
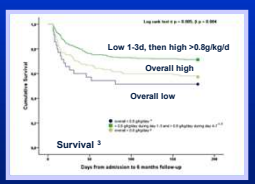
Pushing Protein

Is there a ceiling on protein incorporation into muscle?



Anabolic resistance [1]
- Splanchnic sequestration of AAs
- Availability of AAs to muscle, other organs
- Blunted anabolic response to AA provision
- Worsened by insulin resistence, inflammation, critical illness, age, # satellite cells, disuse
- ↑ Protein may overcome anabolic resistance



Elderly particularly susceptible: [2]
- ↑ Baseline loss musc mass
- ↓ Recovery musc fxn after disuse
- ↑ Anabolic resistence to AA
- ↑ Levels of protein needed for pos NB

[1]Shad (AmJPhysEndocrMetab 2016;311:E803) [2]Dickerson (JPEN 2015;39:759) [3]Koekkoek (ClinNutr 2018) [4] M Nicolo (JPEN 2016;40:45)

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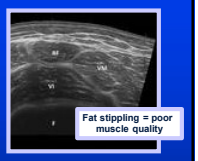
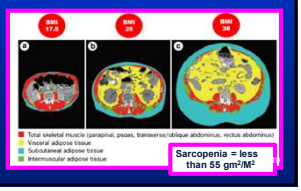
Pushing Protein

- Protein doses high enough? Intermittent > continuous?
- Importance of exercise - Start early in critical illness
  - Time exercise with protein provision
- Adjust for level of function
  - Awake alert – Safe ambulation
  - Debilitated - ↑Time in chair, passive range-of-motion exercises
  - Altered MS, shock - Continuous passive motion (CPM) device
  - Neuromuscular electrical stimulation (NIMES)
- What lessons can we learn from body builders?
  - BCAAs, HMB, Vit D, creatine, ALA, fish oil





Wischmeyer (Crit Care 2017;21:316) Hanna (JPEN 2015;39:273)

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Should We Provide Micronutrient Supplements?

Three schools of thought: Measure levels, correct deficiencies
Empirically provide physiologic doses
Provide supraphysiologic doses

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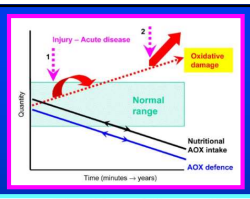
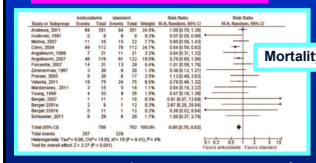
Micronutrient Supplementation





ASPEN/SCCM Empiric Rx [1]
ESPEN Crit Care: Empiric Rx, Measure Vit D [2]
CCPGs: Do not rec Empiric Rx (2015 reversed 2013 rec) [3]

[1] SA McClave (JPEN 2016;40:159) [2] M Berger (Clin Nutr online Jul 20, 2018 ESPEN 2018 Crit Care Guidelines)[3] D Heyland (criticalcarenutrition.com Dec 2016) [4] M Berger (Clin Nutr 2005;24:172)

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Should PN be Used More in the Hospital Setting?

- CALORIES Trial [1] EN vs PN x 5 days in 2400 mixed ICU pts (80% goal feeds)
  - No difference in outcomes
- NUTRIREA-2 Trial [2] EN vs PN x 5-6 days in 2410 MICU pts in septic shock
  - No difference in outcomes
- Impact: Under controlled conditions, high risk patients, PN can = EN
  - EN still preferred over PN, but should lower threshold to use PN

[1] SE Harvey [NEJM 2014; 371(18):1673] [2] J Reignier (Lancet 2017 Nov Online)

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Initiation of PN

SCCM
ASPEN

ESPEN
Critical Care Nutrition

- SCCM/ASPEN 2016:
  - Exclusive PN (Low Risk) – Withhold PN over first week
  - Exclusive PN (High Risk) – Initiate PN ASAP
  - Supplemental PN – Withhold supp PN for 7-10 days (all pts)
- Canadian CPGs 2015:
  - Exclusive PN (Low Risk) – Do not recommend PN
  - Exclusive PN (High Risk) – Consider PN esp if malnourished
  - Supplemental PN – Do not use in unselected patients
- ESPEN 2018:
  - Exclusive PN – Use delayed PN after 3-7 days if EN not feasible
    - Use early low dose PN in malnourished pts EN not feasible
  - Supplemental PN – Use case-by-case first week if EN < full dose
- Comment: Insufficient EN defined <60% goal requirements

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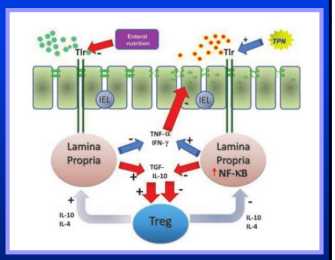
Does Current Nutritional Rx Support the Microbiome?

- EN less inflammation than PN [1,2]
  - Both result in relative nutrient deprivation
- Blenderized whole food formula vs polymeric (Mouse model) [3]
  - Reduced systemic inflammation (IL-6 levels)
  - Greater biodiversity
  - ↓Enterobacteriaceae, ↑Commensals
  - ↑Beneficial anti-inflamm (orgs) compounds
- Strategies to promote commensalism [4,5]
  - Judicious Abx, opioids, serum bovine IgG
  - Soluble fiber, PEG-phosphate
  - Fecal microbial transplant (FMT)



[1]Feng, Teitelbaum (Ann NY Acad Sci 2012;1258:71) [2]Ralls, Teitelbaum (Surg 2015;157:732) [3]Yeh, Morowitz (ASPEN CNW 2018 Abstr #2832646) [4]Morowitz (Surg Clin N Amer 2011;91:711) [5]Alverdy (CurrOpinClinNutrMetabCare 2005;8:205)

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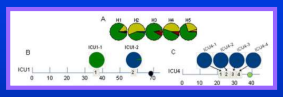
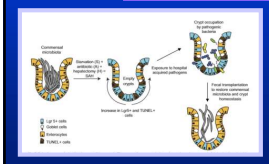
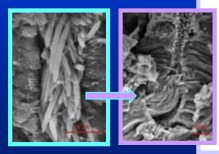
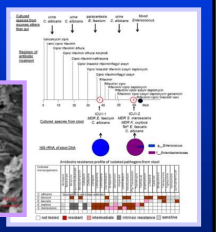
Rationale for FMT in ICU

- Clinical impact
  Lose 90% comensals in 6 hrs, loss of biodiversity, emergence of virulent pathobiome
  Antibiotic resistant orgs, sepsis, anastomotic dehiscence, toxic lymph, MOF









Krezalek, Alverdy (Shock 2016;45:475) Morowitz, Alverdy (Ann Surg 2011; 253:1094)
Zaborin, Alverdy (Am J Phys Gastroint Liver Physiol 2017;312:G112)

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FMT in ICU

- Delivery issues [1]
  Cecum > rectum 90 vs 63%
  Southern > Northern route (86 vs 74%)
  Second > first FMT (83 vs 62%)

- Comercial products from fully vetted donors [2]
  Stool studies (C+S, O+P, C Diff, VRE, MRSA, norovirus)
  Serology (HIV, RPR, Hep A/B/C, CMV, EBV)
  Clinical (no Abx, incarceration, illicit drugs, tattoos)

- Lyophilized powder vs sterile fecal filtrate transfer (FFT) [3]
  Bacterial components, bacterial phages, no live orgs
  Fresh/frozen vs lyophilized powder (83-100% vs 73-78%)

[1] ZD Jiang (Aliment Pharm Ther 2017;45:899) [2] CR Kelly (Gastro 2015;149:223) [3] PK Tosh (Clin Infect Dis 2012;54:707)

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Experience with FMT in the ICU

Patient	Presentation	Concomitant Rx	FMT	Recovery
16 y.o. Female[7]	Trauma, TBI, intractable diarrhea, AAA enterocolitis	Dexamethasone Antibiotics Probiotics	Day 72 Donor feces (Mother) Cecal infusion	2 Days ↓ Fever ↓ Diarrhea
29 y.o. Female[9]	SIRS, intractable diarrhea, septic shock (H/O UC, colectomy)	Antibiotics Probiotics	Day 20 Donor feces per NE tube	1 Day ↓ Fever ↓ Diarrhea
44 y.o. Female[5]	Septic shock, intractable diarrhea, s/p partial gastrectomy/vagotomy	Antibiotics Probiotics ECMO, CRRT	Day 30 Donor feces (Brother) per ND tube	2 Days ↓ Sepsis 7 Days ↓ Diarrhea
65 y.o. Male[8]	Cerebral hemorrhage, MODS, septic shock, intractable diarrhea	Antibiotics	Day 20 Donor feces (Grad student) Sterile-filtered pathogen-free feces per NG tube	1 Day ↓ Fever 7 Days ↓ Diarrhea
84 y.o. Male[8]	Cerebral infarct, MODS, septic shock, intractable diarrhea	Antibiotics Probiotics	Day 7 Donor feces (Grad student) Sterile-filtered pathogen-free feces per NG tube	1 Day ↓ Fever 7 Days ↓ Diarrhea

SA McClave (Curr Opin Crit Care 2018) Q Li (Crit Care 2015 ;19:37) (Am J Gastro 2014;109:1832)
Y Wei (Crit Care 2016;20:332) P Wurm (Crit Care Med 2017;45:e600)

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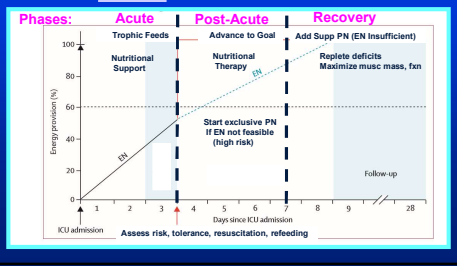
Phases of Critical Illness



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Questions?

Nutrition-related resources and tools
are available from Nestlé Nutrition Institute:
nestlenutrition-institute.org

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