New Types of Evidence and Product Innovation: From Patient Needs to Product Design and Development

MEDICAL FOODS WORKSHOP:
Science, Regulation and Practical Aspects

AUGUST 13–14, 2019 WASHINGTON, DC

Research and Evidence Development

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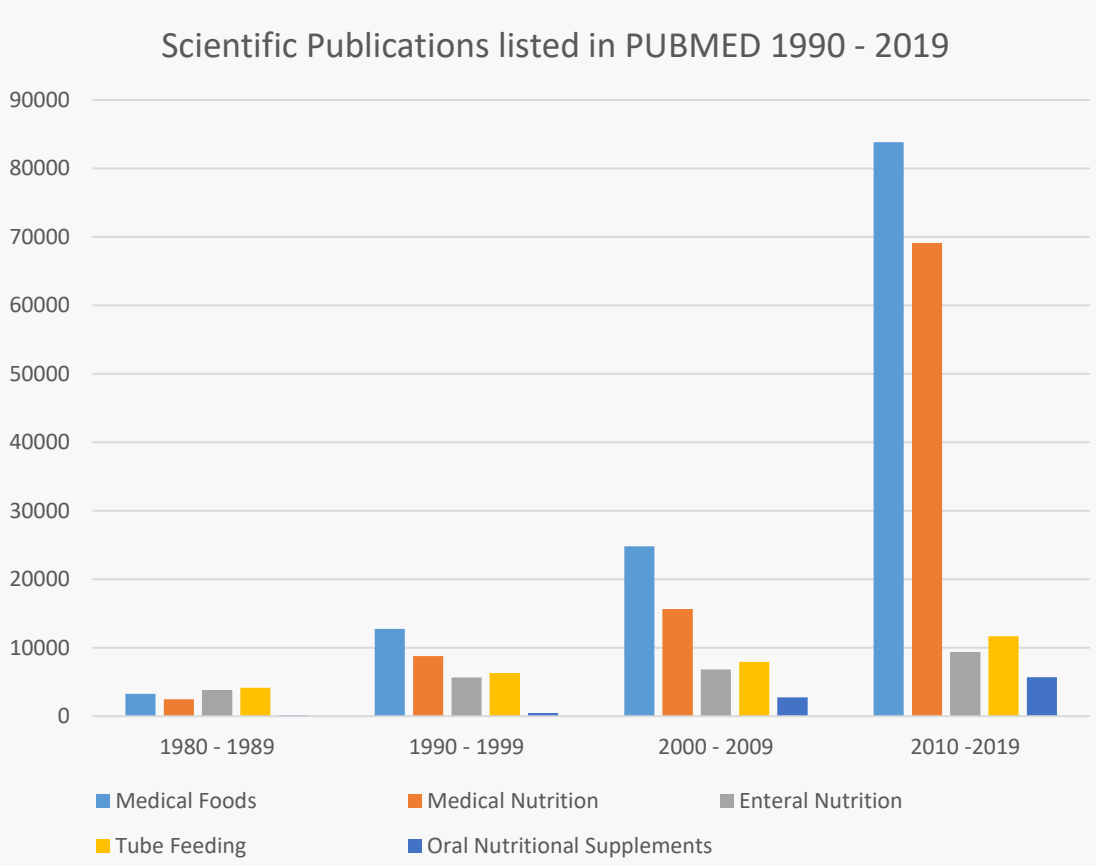
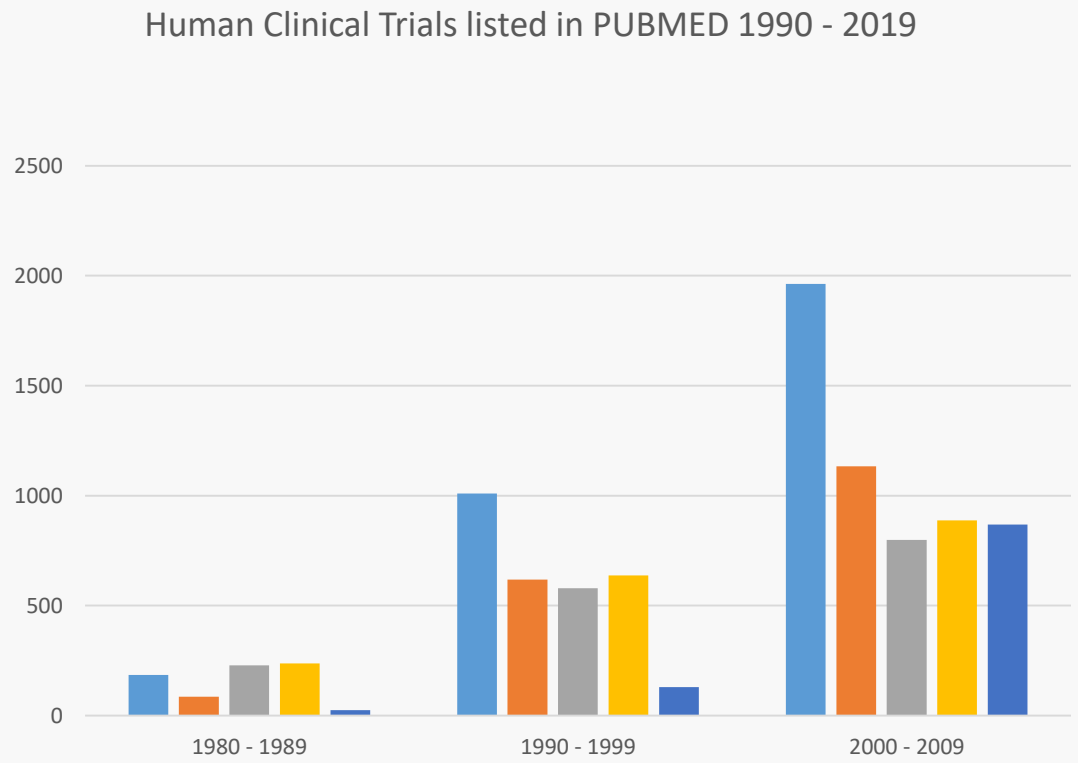
There is a **significant body of evidence** for Medical Foods, Medical Nutrition, Enteral Nutrition, TF and ONS

		Medical Foods	Medical Nutrition	Enteral Nutrition	Tube Feeding	Oral Nutritional Supplements
1980 - 1989	Publications	3269	2491	3833	4166	151
	Human CT's	185	86	228	237	25
1990 - 1999	Publications	12742	8774	5649	6318	464
	Human CT's	1009	619	579	637	130
2000 - 2009	Publications	24782	15665	6807	7954	2769
	Human CT's	1963	1133	798	888	868
2010 -2019	Publications	83815	69115	9397	11686	5676
	Human CT's	**6156**	**4985**	**878**	**984**	**1590**

Total number of publications and of human clinical trials has increased in the last 40 years





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Globally, a significant number of studies focus on raising awareness and burden of disease

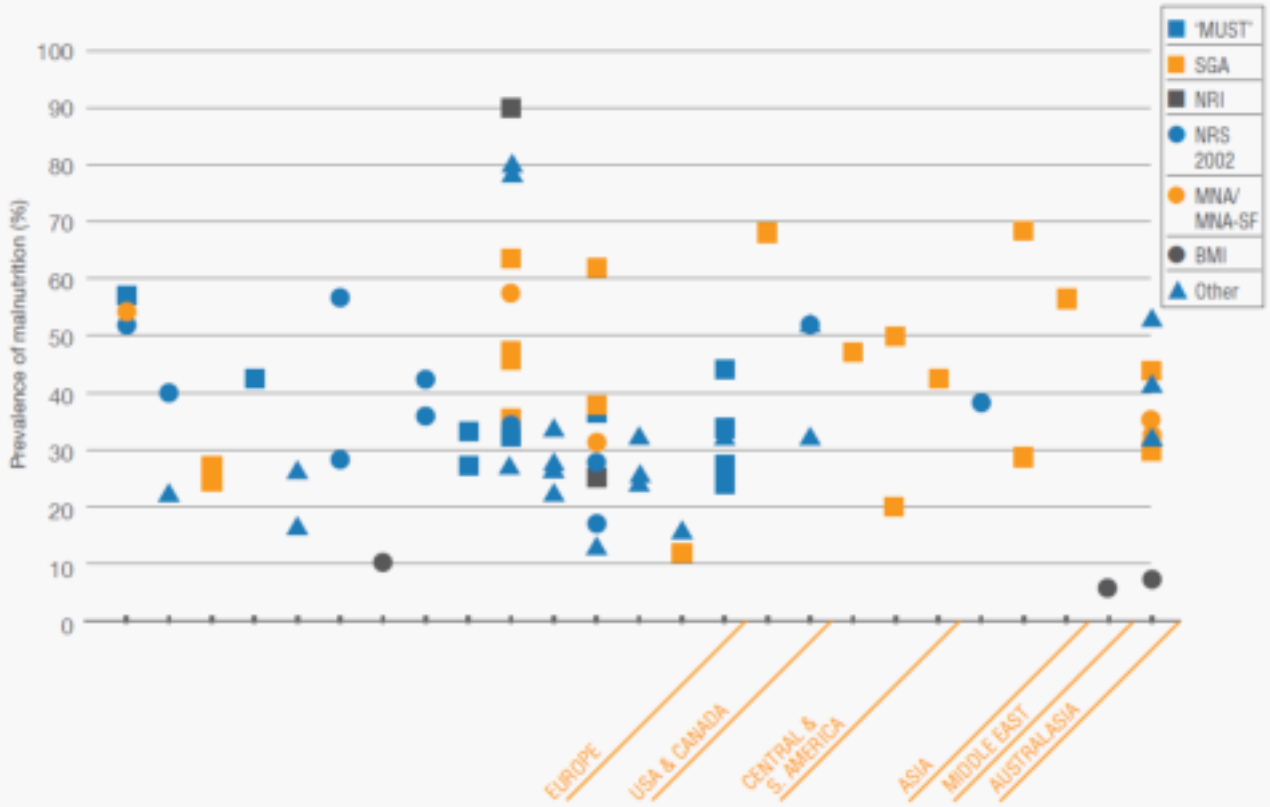


Figure 1.8 Prevalence of malnutrition risk in adult hospital patients using different screening methods by country and world region

Better care through better nutrition: Value and effects of Medical Nutrition. A Summary of the Evidence Base. Medical Nutrition International Industry. Fourth version 2018. Available at: https://medicalnutritionindustry.com/files/user_upload/documents/medical_nutrition/2018_MNI_Dossier_Final_web.pdf. Last accessed: 08/07/2019.

In identifying populations at risk

- Increasing age is associated with an increasing risk of malnutrition[1-3]
- Elderly, Oncology, Respiratory, Endocrine and GI wards show a higher prevalence of malnutrition in the hospital setting [1,3,4-5]
- Chronic conditions as COPD, diabetes, gastrointestinal and cancer are associated to a higher risk of malnutrition [1,6]

1. Russell C, Elia M. Nutrition Screening Week in the UK and Republic of Ireland in 2011. Hospitals, care homes and mental health units. Redditch, BAPEN. 2012. Ref Type: Report **2.** Cuervo M, Garcia A, Ansorena D, et al. Nutritional assessment interpretation on 22,007 Spanish community dwelling elders through the Mini Nutritional Assessment test. Public Health Nutr 2009; 12(1):82-90. **3.** Pirlich M, Schutz T, Norman K, et al. The German hospital malnutrition study. Clin Nutr 2006; 25(4):563-572. **4.** Agarwal E, Ferguson M, Banks M, et al. Nutritional status and dietary intake of acute care patients: results from the Nutrition Care Day Survey 2010. Clin Nutr 2012; 31(1):41-47. **5.** 51. Lim SL, Ong KC, Chan YH, et al. Malnutrition and its impact on cost of hospitalization, length of stay, readmission and 3-year mortality. Clin Nutr 2012; 31(3):345-350. **6.** Meijers JM, Schols JM, van Bokhorst-de van der Schueren MA, Dassen T, Janssen MA, Halfens RJ. Malnutrition prevalence in The Netherlands: results of the annual Dutch national prevalence measurement of care problems. Br J Nutr 2009; 101(3):417-423

… Identifying gaps in current clinical practice and areas of improvement, that may lead to QIP

Prevalence of malnutrition and risk of malnutrition in older people on hospital admission and discharge (adapted from Cansado et al. 2009)

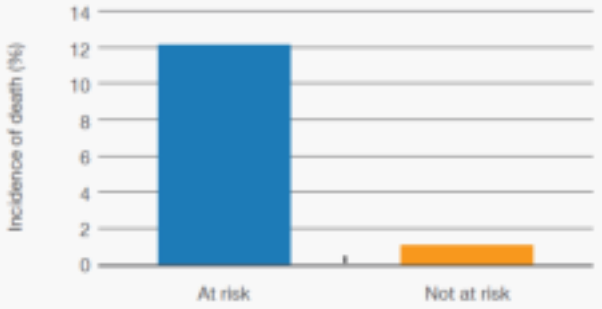
	Surgical patients (*n* = 341)			Medical patients (*n* = 190)		
MNA Category	Admission (%)	Discharge (%)	*p**	Admission (%)	Discharge (%)	*p***
Normal	21.9	22.8	NS***	8.4	4.2	0.05
Risk of malnutrition	51.3	43.4	0.05	48.9	44.7	0.07***
Malnourished	26.6	33.7	0.003	42.6	51.0	0.002

*p** indicates statistical differences for surgical patients on admission vs discharge
*p*** indicates statistical differences for medical patients on admission vs discharge
***NS: Not Significant

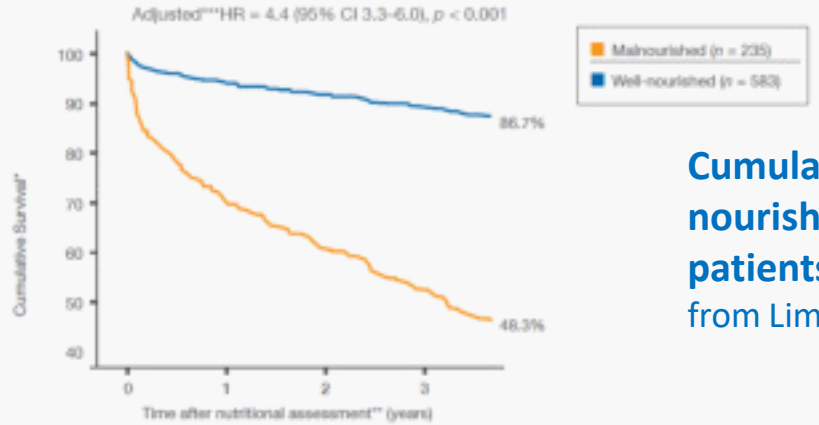
Cansado P, Ravasco P, Camilo M. A longitudinal study of hospital undernutrition in the elderly: comparison of four validated methods. J Nutr Health Aging 2009; 13(2):159-164.

.. And showing the consequences

- Decreased muscle function and impaired functional status in older people 1
- Impaired function in children and adults with cystic fibrosis 2
- Impaired quality of life (QOL) in patients with cancer, hip fracture and COPD 3
- Malnutrition is associated with increased mortality vs. non-malnourished 4,5



Increased frequency of death in at risk patients vs not at risk patients (p < 0.001) (adapted from Sorensen et al. 2008)



Cumulative survival in well-nourished and malnourished patients (n = 818) (adapted from Lim et al. 2012)

1. Humphreys J, de la Maza P, Hirsch S, Barrera G, Gattas V, Bunout D. Muscle strength as a predictor of loss of functional status in hospitalized patients. Nutrition 2002; 18(7-8):616-620.t **2.** Steinkamp G, Wiedemann B, on behalf of the German CFQA Group. Relationship between nutritional status and lung function in cystic fibrosis: cross sectional and longitudinal analyses from the German CF quality assurance (CFQA) project. Thorax 2002; 57:596-601. **3.** Stratton RJ, Green CJ, Elia M. Disease-related malnutrition: an evidence based approach to treatment. Wallingford: CABI Publishing; 2003. **4.** Sorensen J, Kondrup J, Prokopowicz J, Schiesser M, Krahenbuhl L, Meier R et al. EuroOOPS: an international, multicentre study to implement nutritional risk screening and evaluate clinical outcome. Clin Nutr 2008; 27(3):340- 349.**5.** Lim SL, Ong KC, Chan YH, Loke WC, Ferguson M, Daniels L. Malnutrition and its impact on cost of hospitalization, length of stay, readmission and 3-year mortality. Clin Nutr 2012; 31(3):345-350.

Significant $ are invested in highlighting the problem and consequences of DRM

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Evidence is incorporated every step of the way

Patients and Clinicians insights

Unmet needs

Clinical Guidelines

Dietary & Nutritional Recommendations

Expert feedback

Trial test

Produce & test

Quality assessment

Organoleptic, Stability

Clinical Outcomes

Nutritional adequacy

GI tolerance

Functional benefits (muscle mass, glycemic control)

Reduced morbidity, complications & mortality

HE (LOS, cost of care)

PRO (QoL, preference, satisfaction)

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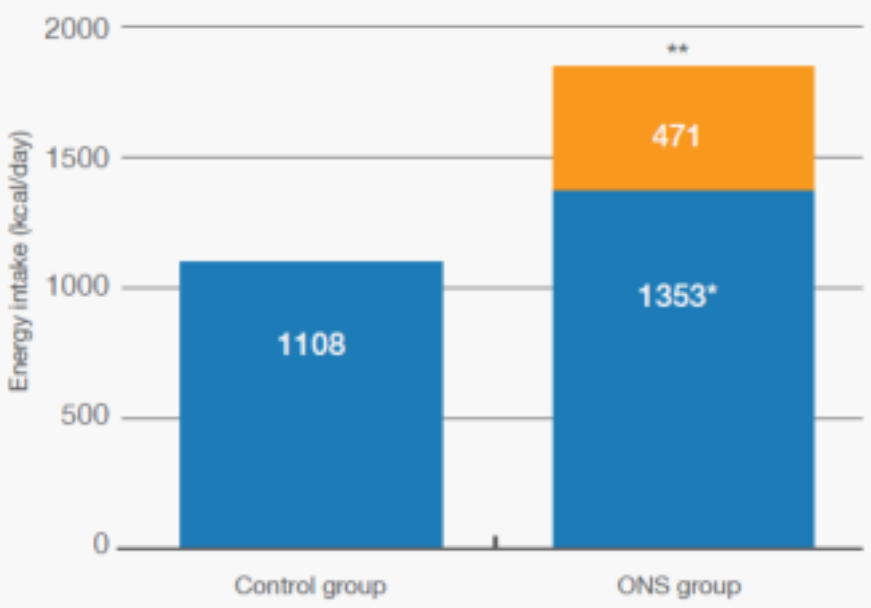
Nutritional efficacy: increasing nutritional intake

- A comprehensive SR of trials in the hospital setting (58 trials, 34 RCTs of which 25 [74% of all RCTs] assessed intake with ONS) showed **efficacy of ONS in increasing total energy intake** in patients with COPD, elderly, post-surgical, orthopedic, patients with liver disease, and patients with cancer.[1]



Higher total food and energy intake in hospitalized post-surgical patients with ONS (adapted from Rana et al. 1992)[2]
Significant increase in total energy intake, $p < 0.0001$; significant increase in intake from ward diet, $p < 0.02$.

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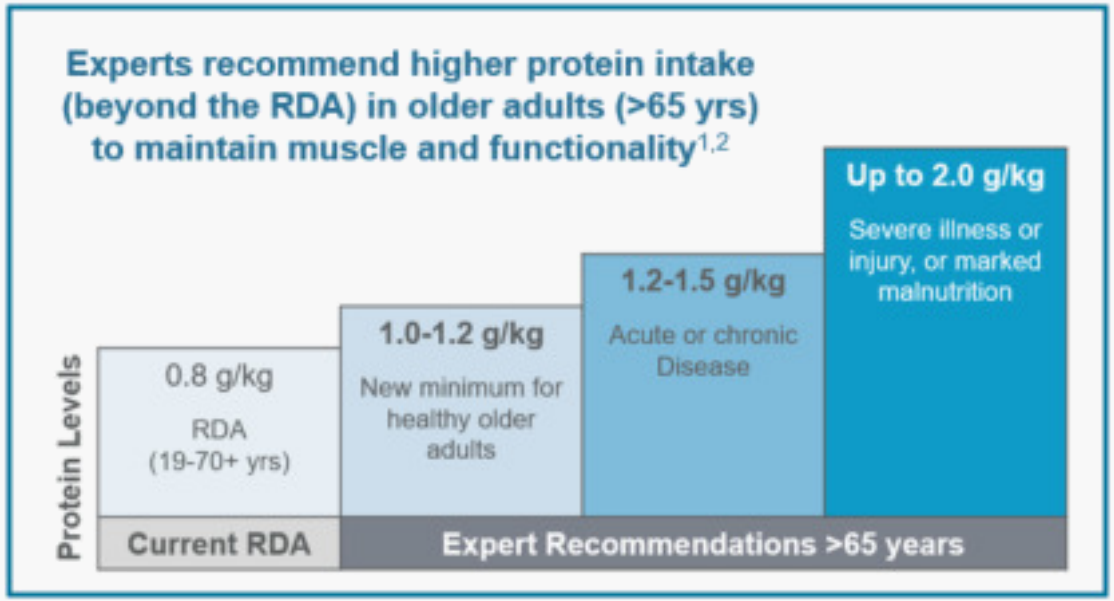
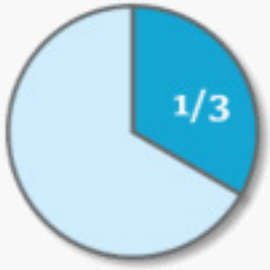
1. Stratton RJ, Green CJ, Elia M. Disease-related malnutrition: an evidence based approach to treatment. 2003. Wallingford: CABI Publishing. **2.** Rana SK, Bray J, Menzies-Gow N et al. Short term benefits of post-operative oral dietary supplements in surgical patients. Clin Nutr. 1992; 11:337-344.

Higher protein intake is required to support muscle mass and physical function in older adults





More than **1 in 3 adults** ages 51+ years do not meet minimum recommendations for protein intake[3]

(Consume less than the RDA for protein: 0.8 g/kg/d)

40%
95% CI
(0.43 to 0.82)

Less likely to become dependent in ≥1 functional tasks[4] (walking ½ mile, climbing stairs, kneeling, lifting objects)

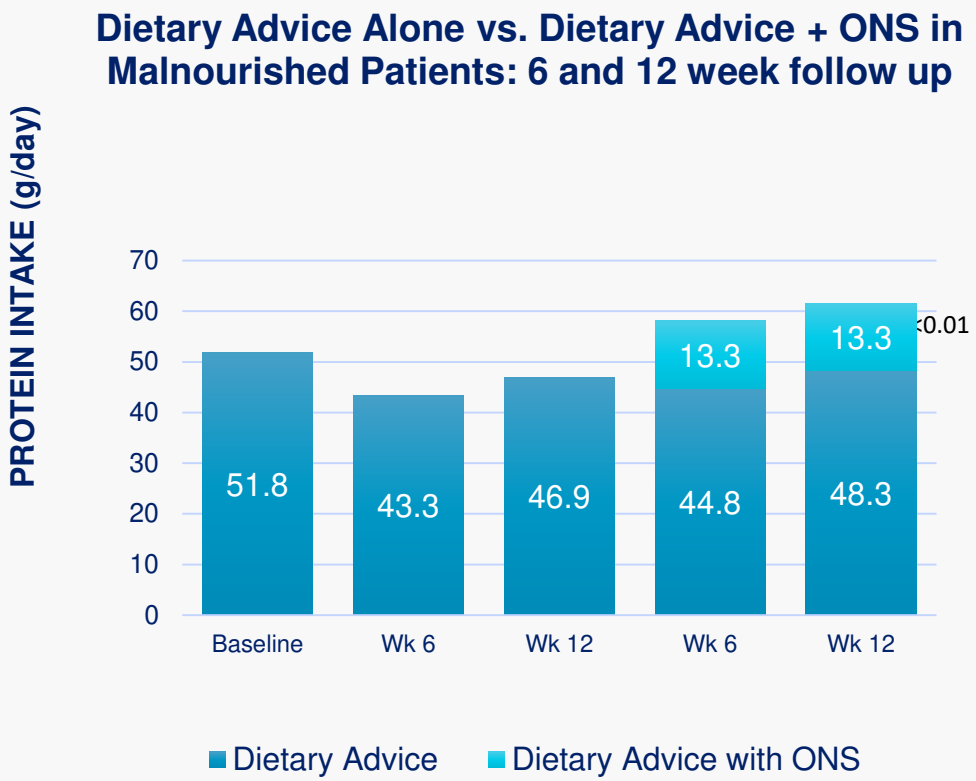
Higher protein intake linked to maintenance of **functional independence** in older adults[4]

(Daily protein intake ≥1.2 g/kg vs. <0.8 g/kg; US adults ages 50+, over 12 year period)

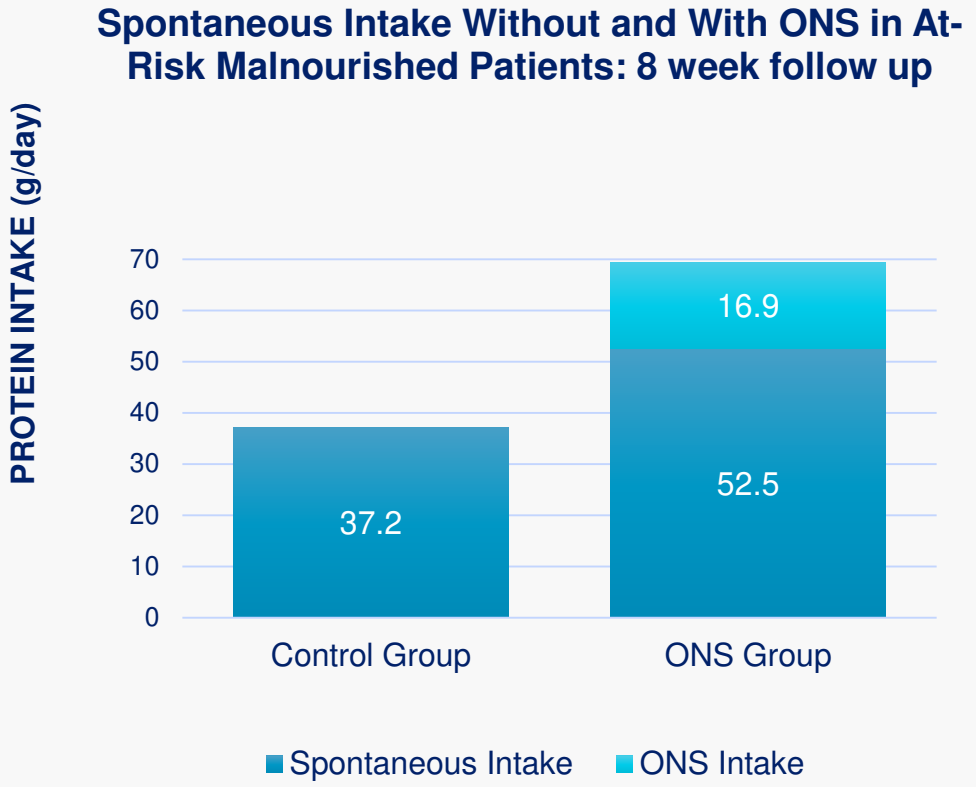
1. Bauer 2013; 2. Deutz 2014; 3. Krok-Schoen 2018; 4. Mustafa 2018

Higher protein intake seen with normal diet plus ONS vs. normal diet alone

Higher protein intake seen with normal food + ONS compared to voluntary food intake alone in malnourished / at risk patients



Adapted from Parsons 2017.



Adapted from Gazzotti et al 2013.

Evidence Based Outcomes: Drover Meta-Analysis in immunonutrition

- **35 RCTs in major elective surgery (n= 3438)**
  - 25/35 studies in elective GI surgery
- **Evaluated pre-, peri- and post-operative use of arginine-supplemented diets (IM) on outcomes:**

Primary Outcome
Infectious complications reduced by 41%

(p<0.00001)

Reduced 41%

Secondary Outcomes
Hospital LOS reduced WMD 2.38 days (p<0.00001)

Mortality: No change

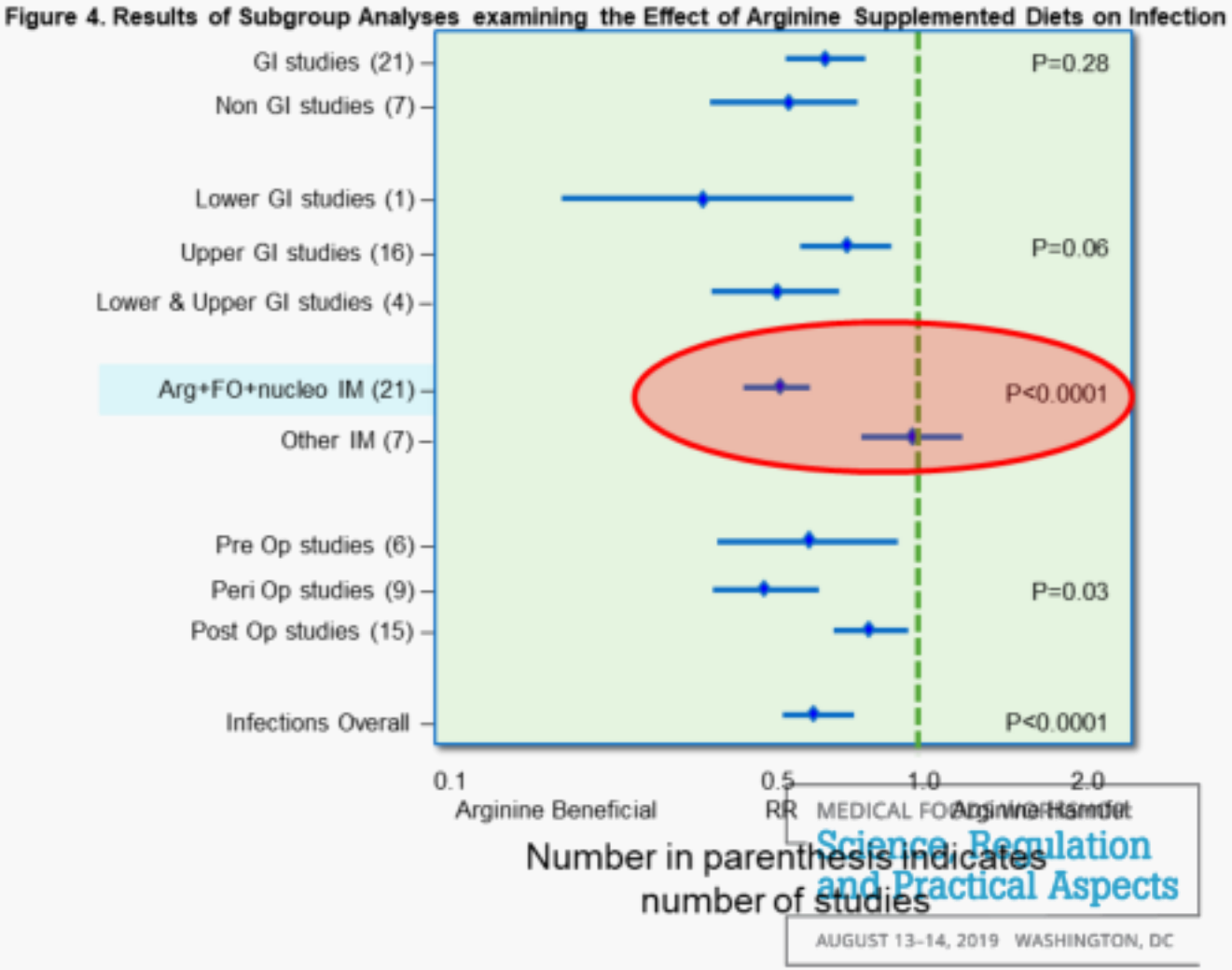
Reduced 2.38 Days

Various sub-analyses

Drover et al. *J Am Coll Surg* 2011;212(3):385-399.

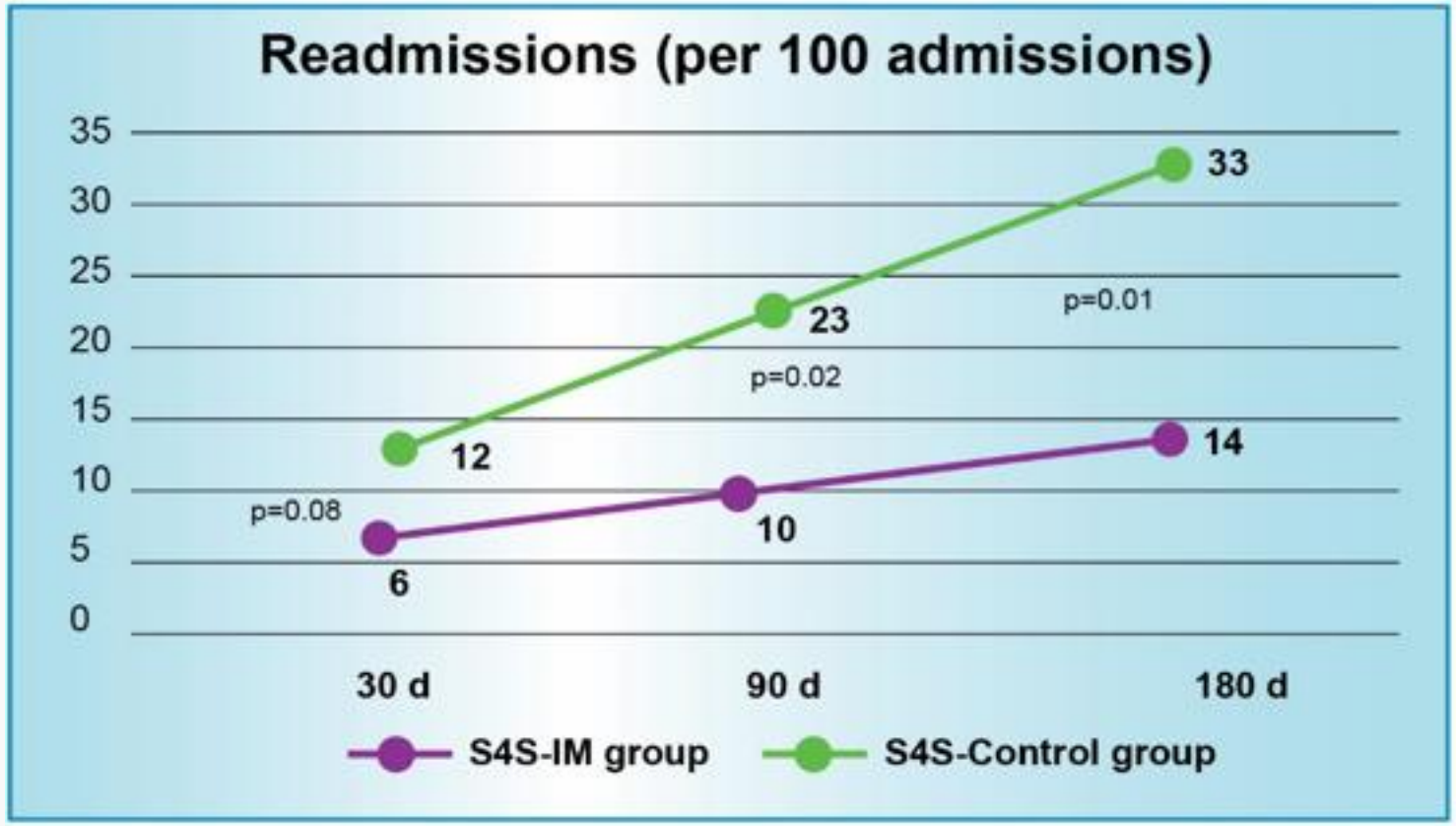
Sub-analyses of Immunonutrition Formulas on Infection

- Same benefit shown for GI surgery vs. non GI surgery
- Same benefit shown for Upper and Lower GI surgeries
- **Only Arg-n3-nucleotide formula showed statistically significant benefit when compared with other arginine supplemented (IM) formulas (p<0.0001)**
- Peri-operative use showed greatest benefit (p= 0.03)



Drover et al. *J Am Coll Surg* 2011;212(3):385-399.

Effects of arginine-based immunonutrition on inpatient total costs and hospitalization outcomes for patients undergoing colorectal surgery

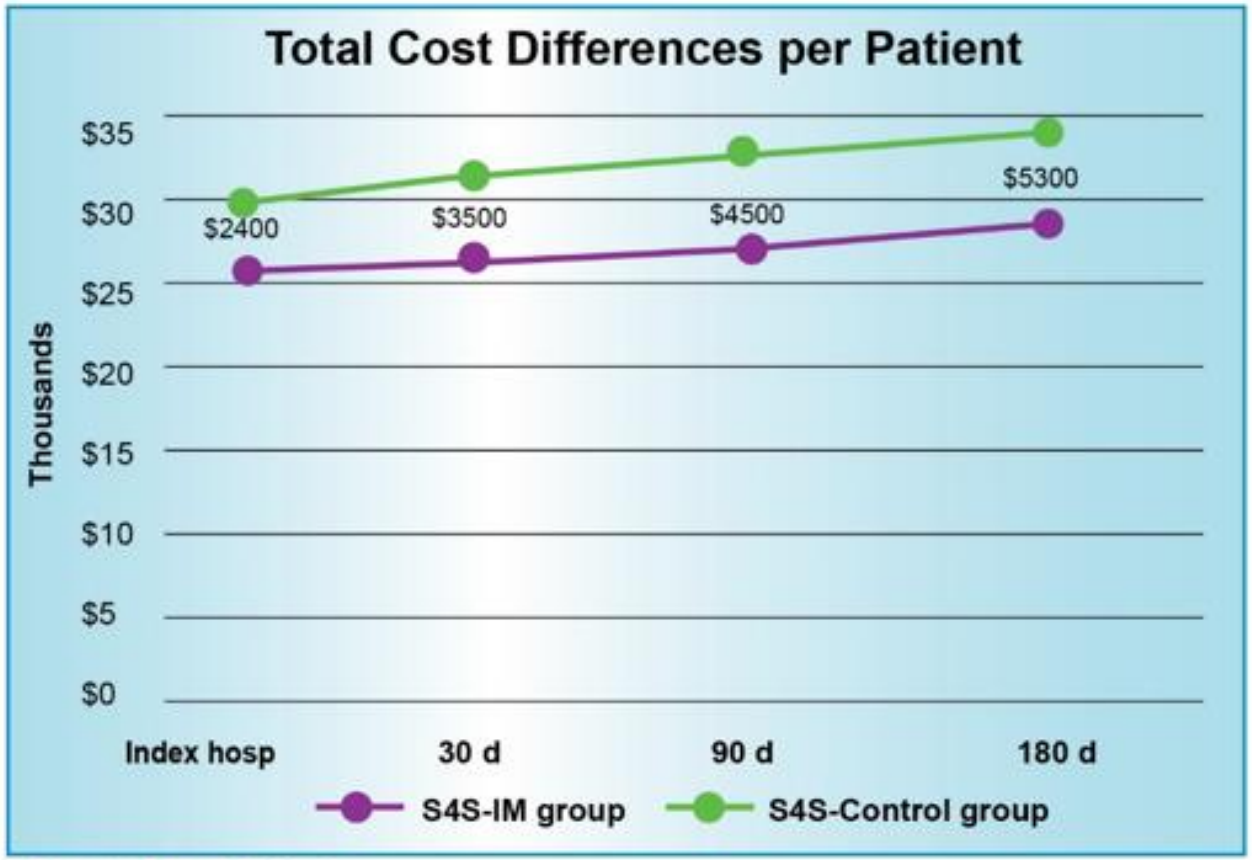


Adapted fom Table 4

- n= 716 colorectal surgery patients
- **Strong for Surgery** (S4S) study group- Provided with preop IM containing supplemental arginine, n-3 fatty acids and nucleotides
- Clinical Outcomes
  - Readmission decreased 50-58%
  - Decreased risk of SSI (0% vs 2.65%; p=0.04)
  - Decreased risk of thromboembolism (1.3% vs. 5%; p=0.05)

Banerjee et al. Nutr 2017;42:106-13.
Strong for Surgery is a Quality Program of the American College of Surgeons

Effects of arginine-based immunonutrition on inpatient total costs and hospitalization outcomes for patients undergoing colorectal surgery



Adapted fom Table 2

- From Index Hospitalization to 180 days post-discharge, mean cost of care was $5300 less for the **Strong for Surgery** (S4S)-IM group vs. (S4S)-control group.

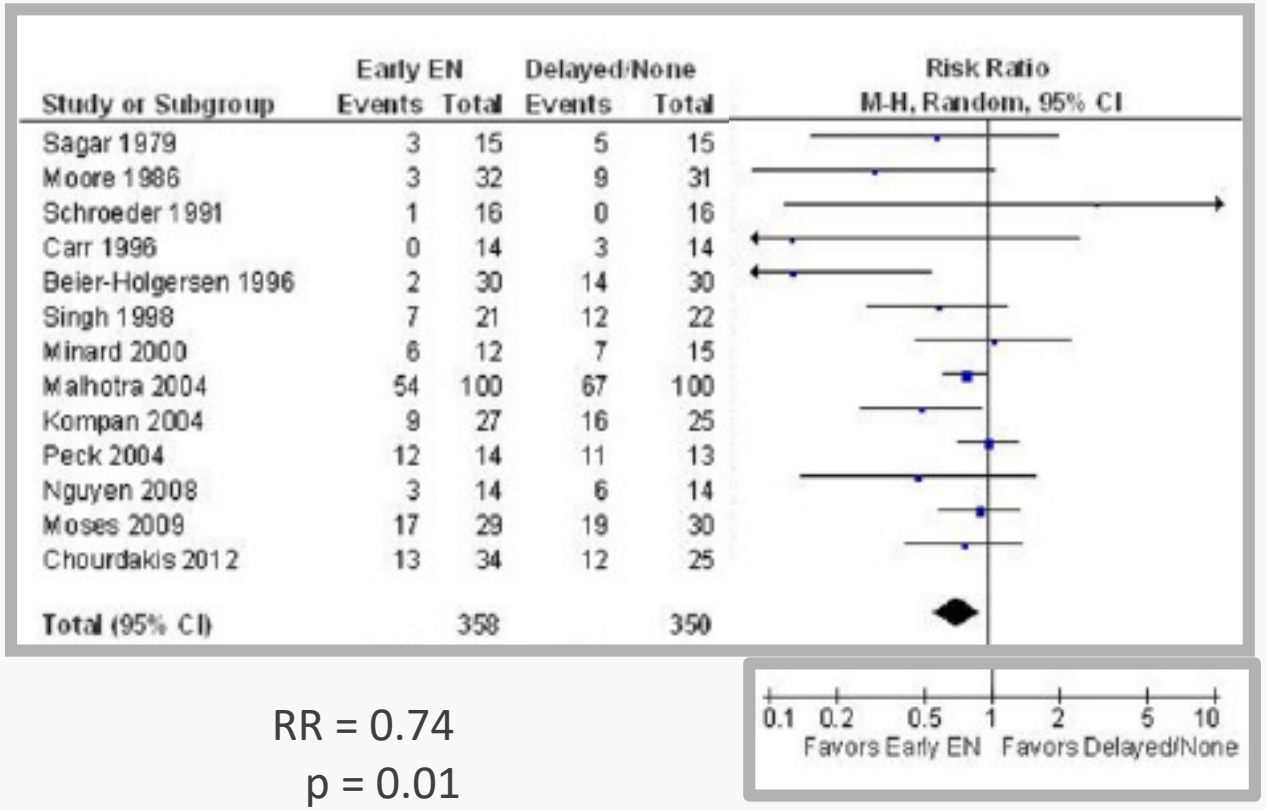
Banerjee et al. Nutr 2017; 42: 106-13. Strong for Surgery is a Quality Program of the American College of Surgeons

Clinical Guidelines guide practice and innovation

- Assess patients on admission to the ICU for nutrition risk, and calculate both energy and protein requirements to determine goals of nutrition therapy.
- Initiate EN within 24-48 hours following the onset of critical illness and admission to the ICU and increase to goals over the first week of ICU stay.
- Take steps as needed to Reduce Risk of aspiration or improve tolerance to gastric feeding (use pro-kinetic agent, continuous infusion, chlorhexidine mouthwash, elevate the head of bed and divert level of feeding in the GI tract).
- Implement enteral feeding Protocols with institution-specific strategies to promote delivery of EN.
- Do not use gastric residual volumes as part of routine care to monitor ICU patients on EN.
- Start PN early when EN is not feasible or sufficient in high risk or poorly nourished patients.

McClave SA[1], Taylor BE[2], Martindale RG[3], Warren MM[4], Johnson DR[5], Braunschweig C[6], McCarthy MS[7], Davanos E[8], Rice TW[9], Cresci GA[10], Gervasio JM[11], Sacks GS[12], Roberts PR[13], Compher C[14]; Society of Critical Care Medicine; American Society for Parenteral and Enteral Nutrition. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2016 Feb;40(2):159-211. doi: 10.1177/0148607115621863.

ASPEN CC Nutrition guidelines: Early vs Delayed/No EN and infectious morbidity

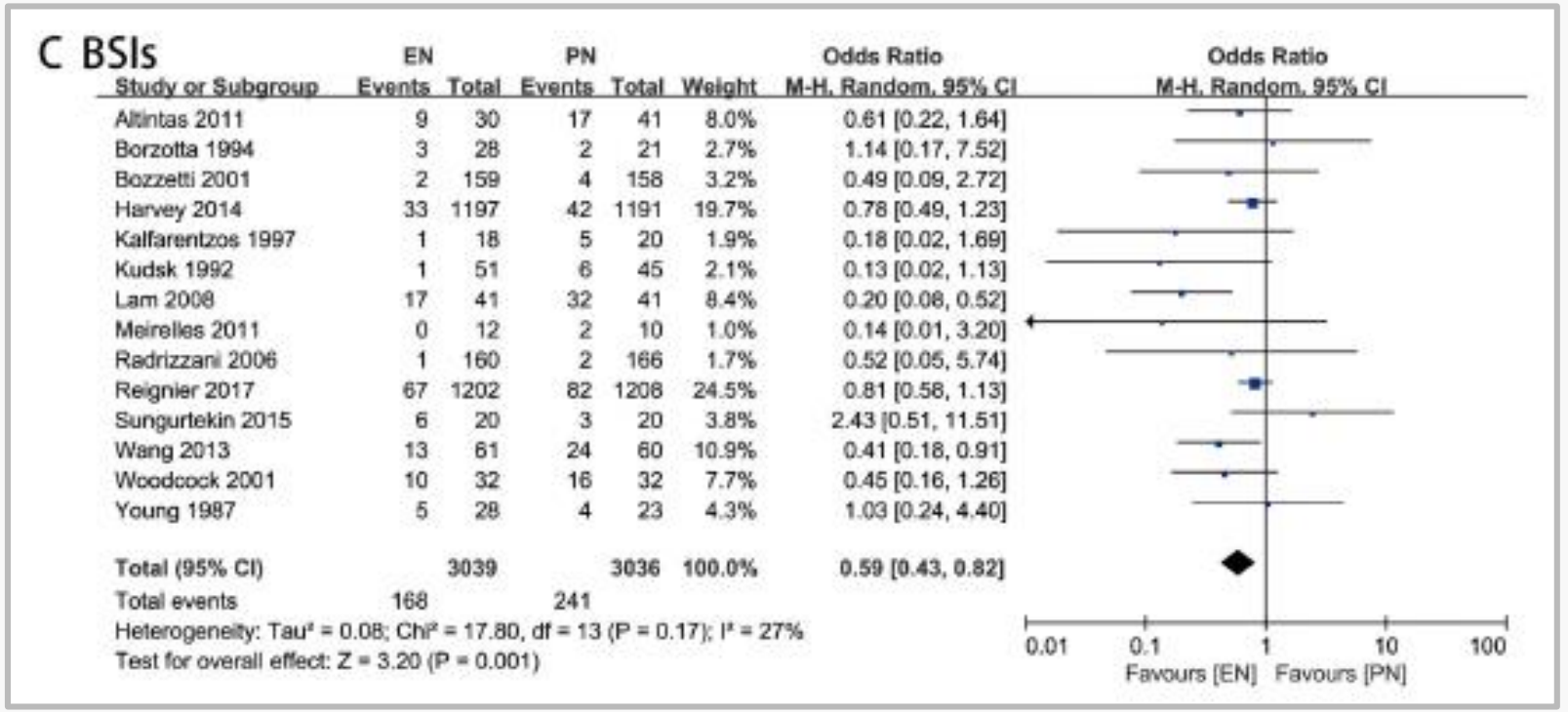


RR = 0.74

p = 0.01

McClave SA1, Taylor BE2, Martindale RG3, Warren MM4, Johnson DR5, Braunschweig C6, McCarthy MS7, Davanos E8, Rice TW9, Cresci GA10, Gervasio JM11, Sacks GS12, Roberts PR13, Compher C14; Society of Critical Care Medicine; American Society for Parenteral and Enteral Nutrition. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2016 Feb;40(2):159-211. doi: 10.1177/0148607115621863.

EN vs PN in Critical Illness-2018



- Systematic review and meta-analysis of RCTs in ICU
- 23 Trials, 6478 patients
- Outcomes Searched: Mortality, Organ failure, BSI, Hospital LOS

Findings: EN vs PN with no effect on mortality; EN could decrease Blood Stream Infections (BSI), incidence of organ failure & reduce hospital LOS

Zhang G, et al. J Clin **Anesthesia** 2018;51:62-69

Hypocaloric High-Protein Enteral Nutrition Improves Glucose Management in Critically Ill Patients

Study Results-102 patients ITT Analysis

- Use of a high protein, low carbohydrate, enzymatically hydrolyzed 100% whey protein tube-feeding formula as part of a hypocaloric feeding regimen is associated with:
  - Decrease of 10.8% in average blood glucose (126 Mg/dL [114, 143] vs. 138 Mg/dL [125, 158]; (p = 0.004)
  - Decrease in mean rate of glucose > 150 mg/dL (p=0.015)
  - Increase in events with normal blood glucose 80-110 mg/dL (p=0.0007)
  - No significant difference in glycemic events $\leq$ 80 mg/dL
  - 10.9% decrease (p=0.048) in number of times insulin administered
  - Increase in serum Alkaline Phosphatase in the control group (p<0.05)
  - Increase in serum Carbon Dioxide in the control group (<0.05)

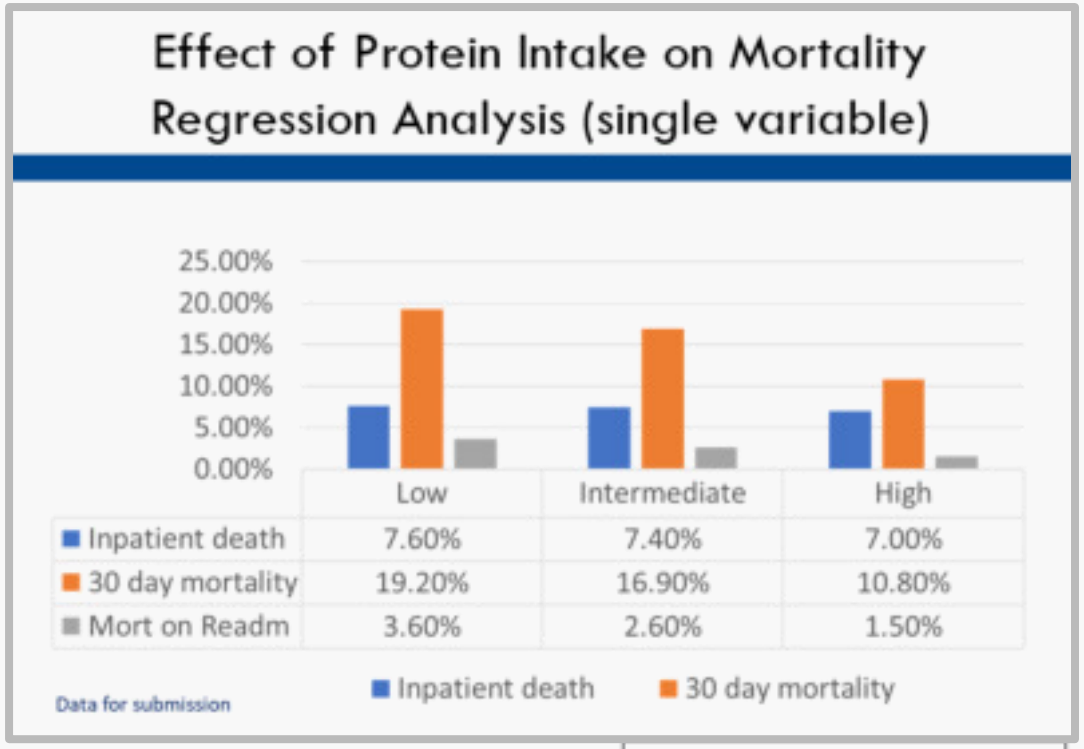
Rice TW et al. JPEN 2018; DOI:10.1002/jpen.1447

Rice TW et al. JPEN 2018; DOI:10.1002/jpen.1447

Should Hypocaloric Hyperproteic Nutrition Become the Standard of Care in Critically Ill Patients?

Objective: Determine demographics of today's ICU and describe most appropriate EN delivery in this population of patients

- Restrospective analysis of 2000 patient encounters
- Geisinger Health System
- Critically ill and mechanically ventilated
- 62 y/o
- BMI 28: 70% overweight or obese
- 45% female



Conclusion: Higher protein along with lower carbohydrate intake appears to generate the best outcomes for critically ill patients; lowest mortality with VHPLC feeding.

Hussein et al. ASPEN 2019, Phoenix, AZ

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Guidelines continue to emerge based on evidence for specific diseases and outcomes

ESPEN Guideline

ESPEN guideline on clinical nutrition and hydration in geriatrics

Dorothee Volkert [a, *], Anne Marie Beck [b], Tommy Cederholm [c], Alfonso Cruz-

ESPEN guideline clinical nutrition in neurology

Rosa Burgos [a, *], Irene Bretón [b], Emanuele Cereda [c, d], Jean Claude Desp
Rainer Dziewas [f], Laurence Genton [g], Filomena Gomes [h], Pierre Jésus [e],
Andreas Leischker [i], Maurizio Muscaritoli [j], Kalliopi-Anna Poulia [k], Jean

ESPEN guideline on clinical nutrition in liver diseas

Mathias Pl
Lindsay D.

Clinical Guidelines

aspen

Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Pediatric Critically Ill Patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition

Journal of Parenteral and Enteral Nutrition
Volume 41 Number 5
July 2017 706–742

DOI: 10.1177/0148607117711387
journals.sagepub.com/home/pen
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Nilesh M. Mehta, MD[1]; Heather E. Skillman, MS, RD, CSP, CNSC[2]; Sharon Y. Irving, PhD, CRNP, FCCM, FAAN[3]; Jorge A. Coss-Bu, MD[4]; Sarah Vermilyea, MS, RD, CSP, LD, CNSC[5]; Elizabeth Anne Farrington, PharmD, FCCP, FCCM, FPPAG, BCPS[6]; Liam McKeever, MS, RDN[7]; Amber M. Hall, MS[8]; Praveen S. Goday, MBBS, CNSC[9]; and Carol Braunschweig, PhD, RD[10]

JPEN J Parenter Enteral Nutr. 2016 Feb;40(2):159-211. doi: 10.1177/0148607115621863.

Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.).

McClave SA[1], Taylor BE[2], Martindale RG[3], Warren MM[4], Johnson DR[5], Braunschweig C[6], McCarthy MS[7], Davanos E[8], Rice TW[9], Cresci GA[10], Gervasio JM[11], Sacks GS[12], Roberts PR[13], Compher C[14]; Society of Critical Care Medicine; American Society for Parenteral and Enteral Nutrition.

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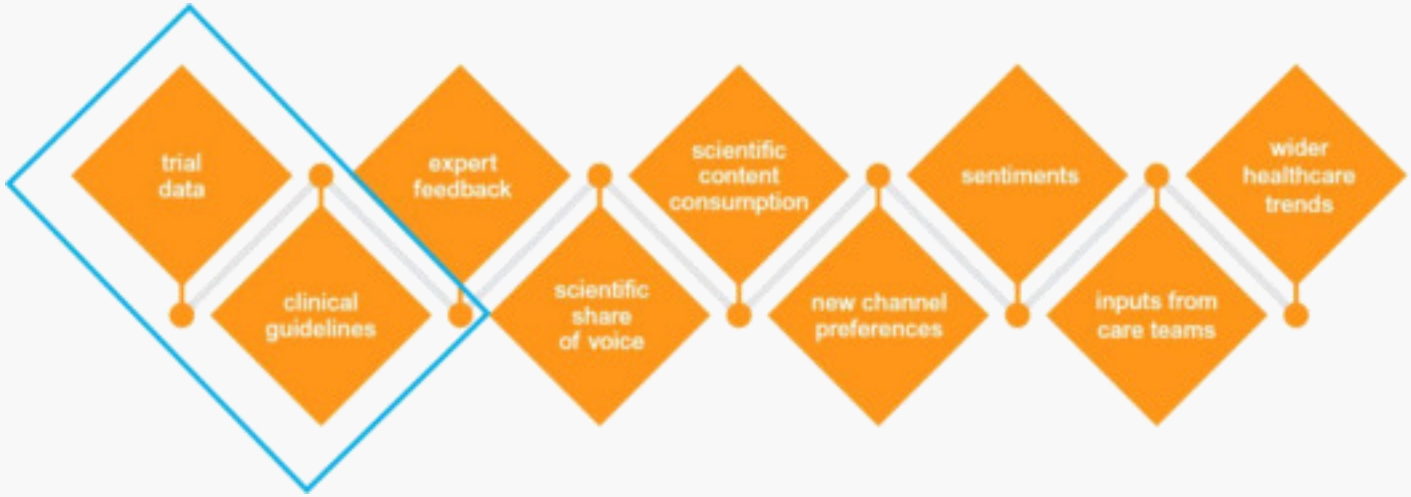
In summary

- There is a significant body of evidence in clinical nutrition
- This is captured in Clinical Guidelines which influences innovation
- After products are available, there continues to be evidence generated to show outcomes improvements and patient reported outcomes



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Thank you!

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