measurement in ICU survivorship research from 1970 to 2013: a scoping review of 425 publications. *Crit Care Med* 2016;44:1267–1277.
2. Abshire M, Dinglas VD, Cajita MIA, Eakin MN, Needham DM, Himmelfarb CD. Participant retention practices in longitudinal clinical research studies with high retention rates. *BMC Med Res Methodol* 2017;17:30.
3. Williamson PR, Altman DG, Blazeby JM, Clarke M, Devane D, Gargon E, Tugwell P. Developing core outcome sets for clinical trials: issues to consider. *Trials* 2012;13:132.
4. Tugwell P, Boers M, Brooks P, Simon L, Strand V, Idzerda L. OMERACT: an international initiative to improve outcome measurement in rheumatology. *Trials* 2007;8:38.
5. Schmitt J, Apfelbacher C, Spuls PI, Thomas KS, Simpson EL, Furue M, Chalmers J, Williams HC. The Harmonizing Outcome Measures for Eczema (HOME) roadmap: a methodological framework to develop core sets of outcome measurements in dermatology. *J Invest Dermatol* 2015;135:24–30.
6. Williamson P, Altman D, Blazeby J, Clarke M, Gargon E. Driving up the quality and relevance of research through the use of agreed core outcomes. *J Health Serv Res Policy* 2012;17:1–2.
7. Needham DM, Sepulveda KA, Dinglas VD, Chessare CM, Aronson Friedman L, Bingham III C, Turnbull AE. Core outcome measures for clinical research in acute respiratory failure survivors: an international modified Delphi consensus study. *Am J Respir Crit Care Med* 2017;196:1122–1130.
8. Turnbull AE, Sepulveda KA, Dinglas VD, Chessare CM, Bingham COI, Needham DM. Core domains for clinical research in acute respiratory failure survivors: an international modified Delphi consensus study. *Crit Care Med* 2017;45:1001–1010.
9. Williamson PR, Altman DG, Bagley H, Barnes KL, Blazeby JM, Brookes ST, Clarke M, Gargon E, Gorst S, Harman N, *et al*. The COMET handbook: version 1.0. *Trials* 2017;18:280.

Provision of Nutrients to the Acutely Ill
Introducing the "Baby Stomach" Concept

Recent major advances have profoundly changed our understanding of nutritional needs during a critical illness. Until recently, the concept of "more is better" was prevailing. Likewise, the use of high tidal volumes (10–12 ml/kg) was deemed appropriate in patients with acute respiratory distress syndrome two decades ago, based on a theoretical background. In the field of acute respiratory distress syndrome, the clear-cut results of large prospective, randomized, controlled, well executed, and adequately powered trials contradicted beliefs based on common sense. Similarly, the results of the EPaNIC (Early versus Late Parenteral Nutrition in Critically Ill Adults) trial (1) highlighted the risk of providing an excess of calories early during the course of a critical illness (2). Importantly, the patients included in the EPaNIC trial received the different categories of macronutrients (glucose, lipids, and amino acids) early or late in "all-in-one" parenteral solutions, precluding the identification of the differential effects of the three components. The team in Leuven, Belgium, further refined the analysis and took advantage of the variable proportions of macronutrients given to patients in the PEPaNIC (Early versus Late Parenteral Nutrition in the Pediatric Intensive Care Unit) trial (3). This *post hoc* analysis suggested that amino acids played a major role in the less favorable outcomes associated with early parenteral nutrition.

The detrimental effects of a high amount of nitrogen were further supported by findings of fat infiltration and a delayed recovery from weakness in patients randomized to the early parenteral nutrition arm of EPaNIC (4). These findings strikingly contradict the concept of a protective effect of a high protein intake, which is mainly suggested by retrospective data associating high protein intakes with a better outcome (5, 6). Hence, the optimal protein/nitrogen intake is a matter of controversy and can range from 0.8 to 2–2.5 g protein/kg/day (7, 8). This uncertainty highlights the weakness of the available evidence, mainly due to the lack of data from large prospective randomized controlled trials (8–10). The safety of a high dose of amino acids was suggested by Doig and colleagues (11), who reported data from a recent large phase II trial. In this trial, kidney function was not influenced by a daily dose of 100 g of intravenous amino acids as compared with standard care. Likewise, such safety was demonstrated by the unaltered amino acid oxidation observed during an enhanced provision of intravenous amino acids (1 g/kg/24 h) (12).

However, in this issue of the *Journal*, Thiessen and colleagues (pp. 1131–1143) (13) report the amplification of glucagon production by exogenous amino acids, together with the amplification of hepatic catabolism of amino acids by glucagon. In other words, amino acids provided during the catabolic phase of a critical illness could fuel the fire and aggravate nitrogen catabolism. As a result of these findings, future guidelines should be revised to differentiate between nitrogen intakes during the acute phase and the prolonged phase of a critical illness, where there are arguments to recommend a low protein intake initially. The final proof of the vicious circle involving glucagon and amino acids could be brought by the use of pharmacological glucagon agonists.

This line of investigation is a good example of how basic science needs to be fed with clinical data, thereby fueling research into novel pathophysiological mechanisms whose clinical relevance requires formal testing by appropriate studies. This constant dialog between bench and bedside is especially important for studying the metabolic response to critical illness, which is a very complex and varying sequence of adaptive events (2). From a clinical standpoint, the ability to build muscle proteins is probably elusive during the acute catabolic phase, where protein breakdown exceeds protein synthesis. In contrast, muscle protein synthesis could be boosted during the late and recovery phases of critical illness, and modulated by an individualized combination of proteins and physical activity. The optimal combination of the two strategies is presently unknown but is eagerly awaited (14).

The study by Thiessen and colleagues (13) is an excellent illustration of how basic and clinical research can be combined

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to help clinicians avoid mistakes due to "common-sense" beliefs based on associations reported in observational trials. These findings support the concept of low nutrient requirements during the acute phase, and potentially support a novel concept of "baby stomach" by analogy with the "baby lung" concept introduced by Gattinoni and Pesenti in 2005 (15). ■

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References

1. Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, Van Cromphaut S, Ingels C, Meersseman P, Muller J, *et al*. Early versus late parenteral nutrition in critically ill adults. *N Engl J Med* 2011;365: 506–517.
2. Preiser J-C, Ichai C, Orban J-C, Groeneveld ABJ. Metabolic response to the stress of critical illness. *Br J Anaesth* 2014;113:945–954.
3. Fivez T, Kerklaan D, Mesotten D, Verbruggen S, Wouters PJ, Vanhorebeek I, Debaveye Y, Vlasselaers D, Desmet L, Casaer MP, *et al*. Early versus late parenteral nutrition in critically ill children. *N Engl J Med* 2016;374: 1111–1122.
4. Hermans G, Casaer MP, Clerckx B, Güiza F, Vanhullebusch T, Derde S, Meersseman P, Derese I, Mesotten D, Wouters PJ, *et al*. Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial. *Lancet Respir Med* 2013;1:621–629.
5. Allingstrup MJ, Esmailzadeh N, Wilkens Knudsen A, Espersen K, Hartvig Jensen T, Wiis J, Perner A, Kondrup J. Provision of protein and energy in relation to measured requirements in intensive care patients. *Clin Nutr* 2012;31:462–468.
6. Nicolo M, Heyland DK, Chittams J, Sammarco T, Compher C. Clinical outcomes related to protein delivery in a critically ill population: a multicenter, multinational observation study. *JPEN J Parenter Enteral Nutr* 2016;40:45–51.
7. Hoffer LJ, Bistrian BR. Appropriate protein provision in critical illness: a systematic and narrative review. *Am J Clin Nutr* 2012;96:591–600.
8. Preiser J-C, van Zanten ARH, Berger MM, Biolo G, Casaer MP, Doig GS, Griffiths RD, Heyland DK, Hiesmayr M, Iapichino G, *et al*. Metabolic and nutritional support of critically ill patients: consensus and controversies. *Crit Care* 2015;19:35.
9. Hurt RT, McClave SA, Martindale RG, Ochoa Gautier JB, Coss-Bu JA, Dickerson RN, Heyland DK, Hoffer LJ, Moore FA, Morris CR, *et al*. Summary points and consensus recommendations from the International Protein Summit. *Nutr Clin Pract* 2017;32(1 Suppl):142S–151S.
10. Rooyackers O, Sundström Rehal M, Liebau F, Norberg Å, Wernerman J. High protein intake without concerns? *Crit Care* 2017;21:106.
11. Doig GS, Simpson F, Bellomo R, Heighes PT, Sweetman EA, Chesher D, Pollock C, Davies A, Botha J, Harrigan P, *et al*. Intravenous amino acid therapy for kidney function in critically ill patients: a randomized controlled trial. *Intensive Care Med* 2015;41: 1197–1208.
12. Liebau F, Sundström M, van Loon LJ, Wernerman J, Rooyackers O. Short-term amino acid infusion improves protein balance in critically ill patients. *Crit Care* 2015;19:106.
13. Thiessen SE, Derde S, Derese I, Dufour T, Vega CA, Langouche L, Goossens C, Peersman N, Vermeersch P, Vander Perre S, *et al*. Role of glucagon in catabolism and muscle wasting of critical illness and modulation by nutrition. *Am J Respir Crit Care Med* 2017;196:1131–1143.
14. Arabi YM, Casaer MP, Chapman M, Heyland DK, Ichai C, Marik PE, Martindale RG, McClave SA, Preiser JC, Reignier J, *et al*. The intensive care medicine research agenda in nutrition and metabolism. *Intensive Care Med* [online ahead of print] 3 Apr 2017; DOI: 10.1007/s00134-017-4711-6.
15. Gattinoni L, Pesenti A. The concept of "baby lung". *Intensive Care Med* 2005;31:776–784.

Early Intervention of Cystic Fibrosis Pulmonary Exacerbations Based on Home Monitoring

eICE through the Looking Glass

In this issue of the *Journal*, Lechtzin and colleagues (pp. 1144–1151) report a 52-week open study undertaken in 15 cystic fibrosis (CF) centers based in the United States over a 4-year period from June 2011 (1).

CF healthcare teams are faced with a dynamically evolving and ever-complex treatment landscape. The CF community must grapple with new challenges, including the emergence of "personalized" medicine and a growing desire for patients to maximize time spent at home and, for many, to engage with health professionals electronically through telemedicine (2). Ten top priorities for clinical research were recently highlighted by the international CF community using the James Lind Alliance methodology (3). Among the major identified priorities are: assessing "effective ways of simplifying the treatment burden of people with CF" (#1 priority) and developing "effective ways of motivation, support and technologies to help people with CF improve and sustain adherence to treatment" (#6 priority). Given these key questions and this shift in treatment focus, the study by Lechtzin and colleagues represents is timely investigation into the potential role of home monitoring in CF care (1).

"Through the Looking Glass"

Like Alice, the findings of this important study appear to be surprising and counterintuitive.

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