16. Uhlig S, Yang Y, Waade J, Wittenberg C, Babendreyer A, Kuebler WM. Differential regulation of lung endothelial permeability in vitro and in situ. *Cell Physiol Biochem* 2014;34:1–19.
17. Warboys CM, Eric Berson R, Mann GE, Pearson JD, Weinberg PD. Acute and chronic exposure to shear stress have opposite effects on endothelial permeability to macromolecules. *Am J Physiol Heart Circ Physiol* 2010;298:H1850–H1856.
18. Kuebler WM, Borges J, Sckell A, Kuhnle GE, Bergh K, Messmer K, Goetz AE. Role of L-selectin in leukocyte sequestration in lung capillaries in a rabbit model of endotoxemia. *Am J Respir Crit Care Med* 2000;161:36–43.
19. Schmidt EP, Yang Y, Janssen WJ, Gandjeva A, Perez MJ, Barthel L, Zemans RL, Bowman JC, Koyanagi DE, Yunt ZX, *et al*. The pulmonary endothelial glycocalyx regulates neutrophil adhesion and lung injury during experimental sepsis. *Nat Med* 2012;18: 1217–1223.
20. Pries AR, Kuebler WM. Normal endothelium. *Handbook Exp Pharmacol* 2006;176:1–40.

Feeding the Critically Ill: More Questions Than Answers!

Over the last 5 years, a number of multicenter randomized controlled trials have evaluated various nutritional strategies in the critically ill patient (1–5). Rather than providing clear direction on how best to feed these patients, these studies have raised more questions, and the optimal approach to nutrition support in the critically ill is unclear. The prevailing dogma, which is reinforced by the updated Society of Critical Care Medicine/American Society for Parenteral and Enteral Nutrition clinical practice guidelines, suggests that critically ill patients should receive early enteral nutrition (within 24–48 h of intensive care unit [ICU] admission) targeting 80 to 100% of energy expenditure (normocaloric goals) as measured by indirect calorimetry or estimated using standard formula (6). In addition, these guidelines recommend "that enteral feeding protocols be designed and implemented to increase the overall percentage of goal calories provided [Quality of Evidence: Moderate to High]" (6). However, recent clinical trials and metaanalyses of these trials have been unable to demonstrate an outcome benefit of normocaloric enteral feeding over permissive underfeeding in heterogenous populations of ICU patients (7, 8). Furthermore, the results of the recently reported PYTHON (Pancreatitis, Very Early Compared with Selective Delayed Start of Enteral Feeding) trial dispels the notion that short-term starvation is harmful (3), and similarly the CALORIES trial suggests that short-term gut disuse is not harmful (4). In addition, the role of parenteral nutrition in critically ill patients is uncertain (4, 5). Consequently, the optimal time to initiate nutrition support, the optimal amount of calories and protein, the type of protein, and the means of delivering nutritional support in the critically ill patient all remain undefined. In addition, continuous tube feeding is profoundly unphysiologic; this mode of feeding does not support muscle anabolism and is associated with a myriad of metabolic complications (9). Previous small trials have suggested no safety concerns with intermittent compared with continuous enteral feeding in critically ill patients (10–12), and one suggested better tolerance (12). There is therefore an urgent need to perform a large randomized controlled trial comparing continuous versus intermittent tube feeding in critically ill and injured patients.

The timing of nutritional support appears to depend on a balance between the benefits of early starvation and the harm of prolonged starvation. Anorexia is an evolutionally preserved response that may be beneficial during acute illness (13). Complex and redundant pathways have evolved to ensure that the host becomes anorexic during acute illness. Folklore that dates back to the 1500s suggests that "fasting is a great remedy for fever" (14). Starvation promotes autophagy, and this may play a key role in promoting host defenses (15, 16). This adaptive mechanism occurs in response to stress and promotes the survival of the cell under these conditions (15–17). Autophagy contributes to the immune response against intracellular bacteria, parasites, and viruses (18). Autophagy plays a role in the degradation of both extracellular bacterial pathogens that invade the cell and true intracellular bacterial pathogens (19). From a teleological perspective, starvation would appear to be beneficial during the initial phase of acute illness, particularly bacterial sepsis. However, prolonged starvation of critically ill patients will lead to excess loss of lean body mass as well as immuno-paresis, metabolic dysfunction, and structural changes of the gastrointestinal tract. These data therefore suggest that an initial period of starvation until physiologic stability is achieved followed by a period of permissive underfeeding until the patient is transitioned to an oral diet or to normocaloric nutrition in the chronically critically ill may be a logical nutritional strategy. Based largely on observational data (20), it has been argued that this approach may be harmful in ICU patients at high nutrition risk (21). Furthermore, it has been claimed that patients at high nutrition risk, as assessed by the NUTRIC (Nutrition Risk in Critically Ill) score, benefit the most from nutrition therapy (21, 22). This specific issue was investigated by Arabi and colleagues (pp. 652–662) in a *post hoc* analysis of their PermiT (Permissive Underfeeding versus Target Enteral Feeding in Adult Critically Ill Patients) trial (2), reported in this issue of the *Journal* (23). In a very comprehensive analysis, the authors demonstrated that neither the NUTRIC score nor other baseline nutritional variables (except prealbumin) were able to identify populations of patients who could benefit from normocaloric nutritional goals. However, in this study, patients with a low baseline prealbumin level ($<$0.1 g/L) had a significantly lower 90-day mortality if they received permissive underfeeding as compared with normocaloric feeding. It is noteworthy that we have previously demonstrated that a prealbumin level less than 0.11 g/L was highly predictive of the refeeding syndrome (24).

The findings of the study by Arabi and colleagues have a number of important implications (23). The study does not support the notion that patients at nutritional risk are harmed by permissive underfeeding early in their ICU course; indeed, the opposite may be true. This finding is supported by the study of Doig and colleagues, who randomized malnourished patients with refeeding syndrome to permissive underfeeding or standard nutritional support (25). In this study, the hospital and 60-day

mortality were significantly greater in the normocaloric group. Second, although recommended in the updated Society of Critical Care Medicine/American Society for Parenteral and Enteral Nutrition clinical practice guidelines (based on expert consensus) (6), this analysis suggests that the NUTRIC score (22) should not be used for the purpose of identifying patients who may benefit from more aggressive early feeding. Because this is a *post hoc* analysis, a prospective trial randomizing patients with high NUTRIC scores to either hypocaloric or normocaloric feeds should be undertaken. Furthermore, although the updated guidelines do not recommend measuring a baseline prealbumin (6) or phosphorous once enteral feeding is initiated (25), these parameters may be useful in supporting the use of permissive underfeeding. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Paul E. Marik, M.D.
Division of Pulmonary and Critical Care Medicine
Eastern Virginia Medical School
Norfolk, Virginia

Todd W. Rice, M.D., M.Sc.
Division of Allergy, Pulmonary, and Critical Care Medicine
Vanderbilt University School of Medicine
Nashville, Tennessee

References

1. Rice TW, Wheeler AP, Thompson BT, Steingrub J, Hite RD, Moss M, Morris A, Dong N, Rock P; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. *JAMA* 2012;307:795–803.
2. Arabi YM, Aldawood AS, Haddad SH, Al-Dorzi HM, Tamim HM, Jones G, Mehta S, McIntyre L, Solaiman O, Sakkijha MH, *et al*.; PermiT Trial Group. Permissive underfeeding or standard enteral feeding in critically ill adults. *N Engl J Med* 2015;372:2398–2408.
3. Bakker OJ, van Brunschot S, van Santvoort HC, Besselink MG, Bollen TL, Boermeester MA, Dejong CH, van Goor H, Bosscha K, Ahmed Ali U, *et al*.; Dutch Pancreatitis Study Group. Early versus on-demand nasoenteric tube feeding in acute pancreatitis. *N Engl J Med* 2014;371:1983–1993.
4. Harvey SE, Parrott F, Harrison DA, Bear DE, Segaran E, Beale R, Bellingan G, Leonard R, Mythen MG, Rowan KM; CALORIES Trial Investigators. Trial of the route of early nutritional support in critically ill adults. *N Engl J Med* 2014;371:1673–1684.
5. 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.
6. Taylor BE, McClave SA, Martindale RG, Warren MM, Johnson DR, Braunschweig C, McCarthy MS, Davanos E, Rice TW, Cresci GA, *et al*.; Society of Critical Care Medicine; American Society of Parenteral and Enteral Nutrition. Guidelines for the provision and assessment of nutrition support therapy in adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society of Parenteral and Enteral Nutrition (ASPEN). *Crit Care Med* 2016;44:390–438.
7. Marik PE, Hooper MH. Normocaloric versus hypocaloric feeding on the outcomes of ICU patients: a systematic review and meta-analysis. *Intensive Care Med* 2016;42:316–323.
8. Tian F, Wang X, Gao X, Wan X, Wu C, Zhang L, Li N, Li J. Effect of initial calorie intake via enteral nutrition in critical illness: a meta-analysis of randomised controlled trials. *Crit Care* 2015;19:180.
9. Marik PE. Feeding critically ill patients the right 'whey': thinking outside of the box. A personal view. *Ann Intensive Care* 2015;5:51.
10. Bonten MJ, Gaillard CA, van der Hulst R, de Leeuw PW, van der Geest S, Stobberingh EE, Soeters PB. Intermittent enteral feeding: the influence on respiratory and digestive tract colonization in mechanically ventilated intensive-care-unit patients. *Am J Respir Crit Care Med* 1996;154:394–399.
11. Serpa LF, Kimura M, Faintuch J, Ceconello I. Effects of continuous versus bolus infusion of enteral nutrition in critical patients. *Rev Hosp Clin Fac Med Sao Paulo* 2003;58:9–14.
12. MacLeod JB, Lefton J, Houghton D, Roland C, Doherty J, Cohn SM, Barquist ES. Prospective randomized control trial of intermittent versus continuous gastric feeds for critically ill trauma patients. *J Trauma* 2007;63:57–61.
13. Marik PE. Is early starvation beneficial for the critically ill patient? *Curr Opin Clin Nutr Metab Care* 2016;19:155–160.
14. Wiktionary. Feed a cold, starve a fever. 2014 [accessed 2015 Jul 1]. Available from: https://en.wiktionary.org/wiki/feed_a_cold,_starve_a_fever
15. Choi AM, Ryter SW, Levine B. Autophagy in human health and disease. *N Engl J Med* 2013;368:651–662.
16. Levine B, Mizushima N, Virgin HW. Autophagy in immunity and inflammation. *Nature* 2011;469:323–335.
17. Fernández AF, López-Otín C. The functional and pathologic relevance of autophagy proteases. *J Clin Invest* 2015;125:33–41.
18. Rich KA, Burkett C, Webster P. Cytoplasmic bacteria can be targets for autophagy. *Cell Microbiol* 2003;5:455–468.
19. Xu Y, Eissa NT. Autophagy in innate and adaptive immunity. *Proc Am Thorac Soc* 2010;7:22–28.
20. Alberda C, Gramlich L, Jones N, Jeejeebhoy K, Day AG, Dhaliwal R, Heyland DK. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. *Intensive Care Med* 2009;35:1728–1737.
21. Wischmeyer PE. Ensuring optimal survival and post-ICU quality of life in high-risk ICU patients: permissive underfeeding is not safe! *Crit Care Med* 2015;43:1769–1772.
22. Heyland DK, Dhaliwal R, Jiang X, Day AG. Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. *Crit Care* 2011;15:R268.
23. Arabi YM, Aldawood AS, Al-Dorzi HM, Tamim HM, Haddad SH, Jones G, McIntyre L, Solaiman O, Sakkijha MH, Sadat M, *et al*.; PermiT trial group. Permissive underfeeding or standard enteral feeding in high– and low–nutritional-risk critically ill adults: *post hoc* analysis of the PermiT trial. *Am J Respir Crit Care Med* 2017;195:652–662.
24. Marik PE, Bedigian MK. Refeeding hypophosphatemia in critically ill patients in an intensive care unit: a prospective study. *Arch Surg* 1996;131:1043–1047.
25. Doig GS, Simpson F, Heighes PT, Bellomo R, Chesher D, Caterson ID, Reade MC, Harrigan PW; Refeeding Syndrome Trial Investigators Group. Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial. *Lancet Respir Med* 2015;3:943–952.