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Examining the Role of Nutrition Support and Outcomes for Hospitalized Patients: Putting Nutrition Back in the Study Design

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Abstract

For more than 40 years the use of nonvolitional feedings (ie, enteral nutrition [EN] and parenteral nutrition [PN]) has been a mainstay of the medical nutrition therapy that registered dietitians (RDs) utilize for their hospitalized patients with limited or no gastrointestinal function. To date, the use of this therapy remains somewhat controversial, and some clinicians dispute that its risks and costs outweigh its benefits. This commentary will explore the findings of prospective randomized clinical trials that compared PN or EN to standard care (ie, normal, volitional dietary intake), cite specific reasons why these findings may have occurred, and discuss the potential contribution the RD can provide to optimize study designs for these types of investigations.

THE ADVENT OF NUTRITION SUPPORT THERAPY FOR HOSPITAL MALNUTRITION

The association between malnutrition and adverse outcomes has been documented since 1936 (1); however, little recourse existed for its treatment in patients with inadequate gastrointestinal (GI) function until the successful use of PN reported by Dudrick and colleagues in 1968 (2). The simultaneous increase in availability of commercially prepared enteral products (3) enabled patients with limited or no GI function to obtain nutrition for indefinite periods of time and greatly expanded the role of clinical nutrition in medical care. The ability to deliver adequate nutrition to virtually all hospitalized patients resulted in substantial increases in the treatment of malnutrition and great gains in our knowledge about the morbidities associated with these specialized solutions. Simultaneously, these advances ignited research interest in the prevalence and treatment of malnutrition (4,5).

To date, the overall prevalence of malnutrition among hospitalized patients has not changed significantly, ranging from 10% to 55% (4,6). Malnourished patients tend to have longer lengths of hospitalization and higher morbidity, mortality, and costs of care than those who are well-nourished (7–9). Hospitalization can precipitate malnutrition fairly rapidly. For example, patients who remain in the intensive care unit for more than a few days experience

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profound deterioration of their skeletal muscle mass. These declines are estimated at 5% to 10% per week (10) and are associated with the onset of organ dysfunction and an overall poor prognosis (11).

IMPACT OF MALNUTRITION: ASSOCIATION VS CAUSALITY

The strong associations between malnutrition and poor outcomes have frequently led to inferences that this association is causative. However, the presence of an association does not establish causation. Distinguishing the severity of the underlying disease from malnutrition, and separating their independent effects on patient outcomes, has been one of the principal challenges that has faced the discipline of clinical nutrition (12). For malnutrition to be causally related to poorer outcomes it must be demonstrated that (a) it independently worsens clinical outcomes (ie, it is not simply a marker of greater disease burden), and (b) correcting the malnutrition independently results in improved clinical outcomes. Because underlying disease severity and malnutrition interact in a way that improvement or deterioration in one directly influences the course of the other, separating the independent effects on outcomes is extremely difficult and poses numerous methodological challenges.

Prospective randomized clinical trials that compare either PN or EN to standard care enable us to disentangle this complex disease/outcome interrelationship. Several meta-analyses have evaluated the prospective randomized clinical trials that have evaluated the impact of these feeding methods vs standard care on clinical outcomes (13–16). These authors found few benefits for both EN and PN. Two recent narrative reviews examined both prospective randomized clinical trials as well as other studies that used different designs (ie, prospective cohort or nonrandomized trials) to assess the impact of nonvolitional feedings compared with standard care and found similar results (17,18). This lack of robust causal evidence has resulted in proponents of evidence-based medicine questioning the use of nonvolitional feeding in hospitalized populations (19,20) and has been the focus of one or more keynote presentations and debates at the annual meeting of nutrition support professionals over the past decade (21,22).

POTENTIAL REASONS FOR FAILING TO DETECT AN IMPACT OF NONVOLITIONAL FEEDING

The trials included in the meta-analyses cited earlier (13–16) contain three major design elements that may have limited their ability to discern the influence of nutrition support therapy on outcomes. First, the prospective randomized clinical trials comparing PN or EN to standard care were largely comprised of populations with acute or sustained inflammation (ie, acute illness, diseases or conditions that compromise the GI tract, surgery, renal failure, or oncologic therapy). All of these conditions are characterized by varying levels of increased counterregulatory hormones, elevated proinflammatory cytokines, insulin resistance, and general catabolism. The type of malnutrition that accompanies this metabolic background has recently been discussed and differentiated by Jensen et al (23) (Figure). Broadly applied in the hospital setting, these terms can generally be characterized as a *chronic or acute disease-related or inflammation-associated malnutrition*. Nutrition support therapy provided to patients with this inflammation-related starvation does not prevent loss of lean body mass (24–26). In fact, repletion is not attainable until the disease-associated catabolism resolves (27,28). Thus, feedings provided during this interval are considered adjuvant therapy and are given with the assumption that they will minimize further exacerbation of existing malnutrition or delay its development in well-nourished patients. The impacts of adjuvant therapies typically are smaller in scale than primary treatments for disease.

The power of a study is defined as the probability of finding a significant difference if a difference really exists. When a study is inadequately powered it will fail to reject the null hypothesis (ie, concluding that there is no difference between the groups) when a true difference exists for the intervention being investigated. To have adequate power to detect significant differences in nonvolitional feeding trials that were provided exclusively during the catabolic interval likely requires a large number of participants in each group or physiologic outcomes that are more sensitive to nutrition intake provided during this interval. Unfortunately, almost all of the trials had very small sample sizes.

Second, evaluation of the nutritional therapy was limited to the fairly short interval of PN or EN support; however, many of the primary outcomes assessed, such as length of stay or total infections, occurred days or weeks after the nutrition support therapy exposure. Moreover, the average oral dietary intake in hospitalized patients, particularly in patients who require mechanical ventilation, is suboptimal (29–31); thus, participants randomly assigned to nutrition intervention were also exposed to standard care during their post-PN or -EN interval. The exposure of all participants to standard care after receiving PN or EN likely attenuated the differences between the groups for the outcomes examined. The nutrition provided can best be characterized as a “feast” via nonvolitional feedings (during the interval when repletion was not possible) followed by “famine” (when repletion was possible) approach.

Third, the conventional wisdom that feeding is always beneficial and withholding invasive nutritional support therapy in malnourished patients is unethical resulted in the exclusion of malnourished patients from the majority of the prospective randomized clinical trials comparing PN or EN to standard care. The failure to demonstrate a positive benefit of PN or EN may in part be due to the majority of participants being well-nourished, thereby less likely to have quantifiable benefit from this therapy yet being exposed to its associated risks. The ethical basis and need for inclusion of severely malnourished patients in future efficacy trials has recently been proposed (32).

PRINCIPLES OF STUDY DESIGN FOR NUTRITION INTERVENTIONS TARGETING INFLAMMATION-ASSOCIATED MALNUTRITION

The design of an intervention will vary depending on the type of disease and treatment being investigated. The prospective randomized clinical trials that have investigated the impact of PN or EN vs standard care have been designed most optimally to detect the impact of a medication for an acute infection (eg, vancomycin and *Escherichia coli*) rather than inflammation-associated malnutrition that is the predominant type of malnutrition found in hospitalized patients. Acute infections present with symptoms that occur with high frequency in those with the infection or disease and rarely in those without, they have a fairly short latent period and can typically be reversed within days following treatment with a medication. This often-held perception of EN as a medication was highlighted in a recent commentary that compared failure to administer the full amount of EN prescribed to suboptimal doses of prescribed antibiotics (33). Generally, an antibiotic has a required number of days for treatment of a specific strain of bacteria without further requirement after it is eliminated. Although levels of nutritional needs change throughout illness, the daily needs for nutrient intake remain until metabolism ceases (ie, death).

Medical nutrition therapy is a “marathon” not a “sprint.” If hospital-based malnutrition responded to EN or PN like an infection does to a specific antibiotic, or even like a single nutrient deficiency disease does when supplements for the nutrient are provided, the designs used may have had different results. Unfortunately, the chronic or acute disease– or injury-related starvation that constitutes the majority of the malnutrition in hospitalized populations

differs distinctly from this scenario. It has multiple causes that include not only nutritional intake but also the underlying chronic or acute disease or injury, which may act alone or in combination with nutrient intake. It may have a long latent period that results from cumulative exposure over many years (eg, individuals with chronic lung or cardiac diseases) or, in the case of trauma-induced starvation, may occur within days post-injury. The different latent periods produce physical symptoms that range from extreme depletion in those with long exposure to few or no symptoms in those with acute disease or injury-induced starvation. Further, this type of starvation is not reversible from nutrition intervention alone.

PUTTING NUTRITION BACK INTO THE STUDY DESIGN

None of the prospective randomized clinical trial studies included in the meta analyses cited earlier (13–16) provide any information on the broader, more informative question of how a comprehensive approach of intensive medical nutrition designed to optimize clinical nutrition care throughout hospitalization affects short- and long-term outcomes. In addition, several of the PN trials included populations that had a functional GI tract, and thus PN was not indicated. Professionals with formal training in nutrition know that nutritional status is acquired over long intervals (ie, months not days) and changing this status requires a prolonged period of consistent optimal intake using the most appropriate feeding modality. Evaluating the impact of the exposure of nonvolitional feedings provided for a short interval of hospital stay, which was not followed by intensive medical nutritional therapy tailored to provide optimal dietary intake, fails to recognize this critical continuum. In the prospective randomized clinical trials that evaluated the impact of nonvolitional feedings vs standard care, only four had an RD as the lead investigator (34–37). It is likely this lack of RD involvement contributed to the studies' lack of orientation for medical nutrition therapy.

CONCLUSION

The management of the PN and EN in hospitalized patients has traditionally been done by multidisciplinary nutrition support teams; however, in the mid 1990s cost constraints limited their financial support (38) and many of these teams were dissolved. Despite their diminished number, nonvolitional feedings continue to be an area that receives close attention from dietitians and other health care professionals, and several professional societies have developed clinical guidelines for its initiation and management (7,39).

Evidence-based medicine has been defined as “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients” (40). The practice of evidence-based medicine requires clinicians to integrate their clinical expertise with the best available evidence from the medical literature to provide the most optimal, cost-effective patient care. It may be that withholding nonvolitional nutrition during hospitalization in malnourished patients has no negative effect and the natural physiologic response, honed through thousands of years of evolution of not eating when ill, is beneficial, especially with a cytokine-producing disease or injury. Alternatively, it may be that optimizing the nutritional care provided throughout hospitalization improves outcomes. To discern this, well-designed feeding trials are paramount to advancing the fields of nutrition support therapy and clinical nutrition. This entails RDs becoming involved in the design, implementation, and interpretation of these studies.

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Terminology	Definition	Examples
Cachexia	Loss of body cell mass with an underlying sustained cytokine-mediated inflammatory disease or condition. Visceral proteins decline, but extracellular fluid may increase. Associated with chronic diseases or mild to moderate inflammation.	Organ failure Pancreatic cancer
Protein energy undernutrition	Considered a marasmus-kwashiorkor overlap syndrome. Visceral proteins are reduced. Extracellular fluid increases, which blurs weight/height, weight loss, and upper arm anthropometry. Driven by a moderate to severe proinflammatory state.	Major burns Surgery Sepsis Closed head injury
Marasmus	Loss of lean body mass without an underlying inflammatory condition. Characterized by pure starvation with reduced food intake and assimilation. Visceral proteins are preserved. Extracellular fluid is not increased.	Anorexia nervosa Hunger strike

Figure.

Consensus statements on malnutrition syndromes. Data from Jensen and colleagues (23).