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Intradialytic Total Parenteral Nutrition (IDPN): Evidence-Based Recommendations

by Jesse Corbello, Mitchell H. Rosner

Patients with end-stage renal disease on chronic hemodialysis have a high incidence of protein-energy malnutrition (PEM). The reasons for this are multi-factorial and include: inadequate food intake, a catabolic response to systemic illness or chronic inflammation, loss of nutrients through the dialysis procedure, as well as systemic effects of the uremic milieu. Intradialytic parenteral nutrition (IDPN) has been advocated for the management of malnutrition in hemodialysis patients. The rationale for its use is that patients are unable to increase oral intake to meet their nutritional needs or that the oral or enteral route is not effective in managing malnutrition in this group of patients. However, numerous studies using IDPN have failed to demonstrate efficacy conclusively with this very costly mode of treatment. This article reviews the literature evaluating the use of IDPN in the maintenance of hemodialysis patients and summarizes the existing recommendations and reimbursement guidelines for this therapy.

INTRODUCTION

Protein-energy malnutrition (PEM) is very common among patients with end-stage renal disease (ESRD) undergoing maintenance hemodialysis therapy (note: the term ESRD here is used to refer specifically to patients undergoing thrice weekly chronic hemodialysis) (1). Owing to different definitions of PEM and different patient populations that have been studied, the prevalence of PEM in the ESRD population varies between 18–70% (1). Most importantly, the presence of PEM is one of the strongest predictors of mortality and morbidity in this population and thus has been a target of intense interest for clinicians. Typically, most studies of PEM and its link to outcomes have focused on traditional markers of poor nutritional status including albumin, body mass index (BMI), and serum creatinine (2,3). In all cases, lower levels of these parameters were associated with increased mortality (1–3). Based upon findings such as these, the National Kidney Foundation (NKF) Kidney Dialysis Outcome Quality Initiative (K/DOQI) recommended that all ESRD patients undergo routine and continuous monitoring of nutritional parameters that include the following: predialysis serum albumin, percent of usual body weight, percent of standard (NHANES II) body weight, subjective global assessment, dietary interviews and measurement of a normalized protein equivalent of total nitrogen appearance (nPNA) (1). The combination of these measurements provides a global assessment of nutrition including visceral and somatic protein pools, body weight and hence fat mass and nutrient intake. Furthermore, it is hoped that by maintaining a focus on nutritional parameters, those patients that are failing to achieve goals will be quickly indentified and intervened upon.

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Table 1.
Causes of Protein Energy Malnutrition in ESRD Patients

1. Inadequate food intake
   a. Anorexia caused by the uremic state
   b. Altered taste sensation
   c. Intercurrent illness and hospitalizations
   d. Emotional distress or illness
   e. Impaired ability to procure, prepare or mechanically ingest foods
   f. Unpalatable prescribed diets
2. Catabolic response to superimposed illnesses
3. Dialysis procedure
   a. Removal of nutrients by dialysis*
   b. Promotion of catabolic state due to inflammatory stimuli (dialysis membrane)
4. Chronic inflammation with hypercatabolism and anorexia
5. Blood loss (gastrointestinal bleeding, frequent blood sampling, blood loss during dialysis)
6. Endocrine disorders of uremia (insulin and insulin-like growth factor-1 resistance)
7. Possibly the accumulation of uremic toxins
8. Socioeconomic factors
9. Undetected and untreated gastroparesis
10. Untreated constipation
11. Mobility limitations

*Dialytic removal of amino acids averages 10–12 grams per hemodialysis treatment as well as low amounts of protein (<1 to 3 grams per session) (43).
Adapted from reference 1.

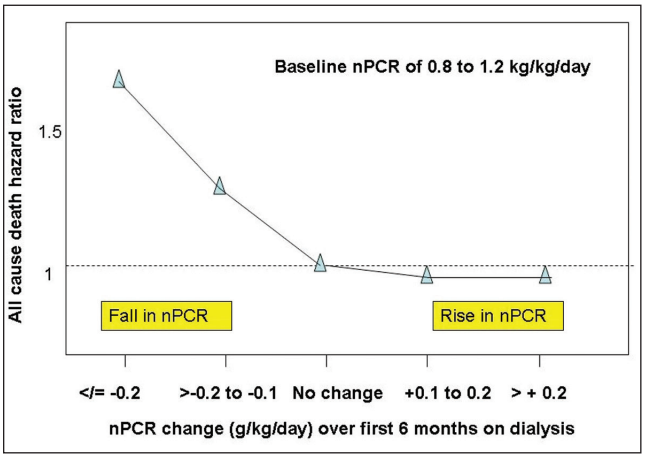

Figure 1: Change in mortality rate associated with increases in nPCR (adapted from reference 33).

The causes of PEM in ESRD patients are multiple (Table 1) and interventions to improve the nutritional status of an individual patient necessarily require a close examination of potential etiologies. This review focuses on those patients with severe PEM, where consideration of giving intradialytic (during the dialysis session) total parenteral nutrition (IDPN) is being contemplated. The review discusses the overall management of protein and energy intake in ESRD patients, the role of inflammation in leading to PEM and summarizes the evidence for the use of IDPN in selected patients.

DIETARY PROTEIN INTAKE IN ESRD PATIENTS

Dietary Protein Intake (DPI) is reported to be low in ESRD patients with mean levels of DPI varying from 0.94 to 1.0 grams protein/kg/day (4,5). This means that half of ESRD patients will ingest less than this amount of protein. This begs the important question as to what the optimal DPI should be in ESRD patients. There are no long-term prospective clinical trials that randomize ESRD patients to different DPIs with assessment of outcome measures such as mortality, morbidity and quality of life. However, several small studies have examined the effects of varying DPI on nutritional status (4–7). The results of these studies indicate that a DPI of 1.2 grams/kg/day is necessary to ensure neutral or positive nitrogen balance in stable ESRD patients. Furthermore, retrospective studies which have analyzed the relationship between DPI and outcome measures such as nutritional status (8), or mortality and morbidity (9–11) have been conducted. In interpreting these studies, it is important to look at the assessment methodology for DPI. The most common methods for estimating intake in ESRD patients are dietary recalls, dietary diaries and determination of the nPNA. While dietary recalls and diaries are simple, they tend to be crude and the validity and reliability of the data is dependent upon the patient's ability to provide accurate data (12). Thus, the use of nPNA is the most commonly used quantitative measurement of DPI.

The nPNA is based upon the concept that ingested nitrogen is equal to total nitrogen excretion if there is no change in body nitrogen pool (13). Ingested protein

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plus the products arising from endogenous protein are metabolized to several nitrogenous products (urea, amino acids, peptides, etc). If nitrogen balance is neutral, the nitrogenous products that are removed from the body through urine, stool and skin plus any change in the body's urea nitrogen pool are equal to the nitrogen intake. Because urea is a principal nitrogen waste product, protein intake in stable patients can be estimated from the urea appearance rate in urine (13). For patients with ESRD, who may not have significant urine output, the change in blood urea nitrogen between dialysis treatments is used to calculate the nPNA (also termed the protein catabolic rate [PCR]). It is important to recognize that there are important limitations in interpreting urea-derived estimates of DPI. In catabolic states, endogenous protein breakdown can increase urea appearance giving a falsely higher PNA than actual protein intake. Secondly, a single PNA will not reflect more long-term DPI and this value can change rapidly from day-to-day.

Three retrospective studies of ESRD patients demonstrated that at DPIs lower than 1.2 grams/kg/day there were lower albumin levels and higher mortality (9,14,15). On the other hand, not every epidemiological study found a significant relationship between mortality or morbidity and nPNA (10,11). This may be due to the confounding issues associated with the use of nPNA and the role of chronic inflammation (discussed next). A recent study has also demonstrated that changes in protein intake during a 6-month period at the initiation of dialysis are predictive of prospective mortality independent of baseline nPNA. A decrease in nPNA over time correlated with incremental death risk independent of demographic, clinical, or other laboratory characteristics, whereas an increase in protein intake over time indicated a trend toward better survival (Figure 1) (15).

Based upon this limited database, the NKF K/DOQI guidelines made a (evidence and opinion-based) recommendation that the recommended DPI for clinically stable ESRD patients is 1.2 grams/kg/day (1). However, it will be difficult for many ESRD patients to meet this recommendation. The difficulty in attaining this goal may require food supplements, tube feeding or intravenous nutrition. It is this last option that is the focus of this article.

THE ROLE OF INFLAMMATION IN DPI AND NUTRITIONAL STATUS

While the term *malnutrition* implies that this condition can simply be cured by increasing nutritional intake, this is clearly not the case. While the evidence does show that many ESRD patients have decreased body weights and subnormal values of serum proteins (16,17), the mechanisms for these abnormalities are complex (Table 1) and assigning their cause to protein-energy malnutrition alone is misleading. Furthermore, simply supplying more food or altering the composition of the diet is not uniformly successful in improving nutritional parameters. For instance, much has been made of low serum albumin being an index of malnutrition and indeed, a low serum albumin is the strongest independent predictor of total and cardiovascular mortality in ESRD patients (17). In fact, a recent analysis of a large cohort of chronic dialysis patients found that not only was an albumin concentration

Table 2.
Sample intradialytic parenteral nutrition prescription

Initiated after 30 minutes into the dialysis session, through the venous port of the dialysis tubing and given for the duration of the hemodialysis procedure (3.5 hours) at a rate of 150 ml/hour.

Solution:

1. **Amino acids:** 300 mL of a 15% solution of amino acids (15% Clinisol®; Baxter Healthcare Corp., Deerfield, Illinois, USA) consisted of nine essential AAs (lysine, 1.18 g; leucine, 1.04 g; phenylalanine, 1.04 g; valine, 960 mg; histidine, 894 mg; isoleucine, 749 mg; methionine, 749 mg; threonine, 749 mg; thryptophan, 250 mg) and eight nonessential AAs (alanine, 2.17 g; arginine, 1.47 g; glycine, 1.04 g; proline, 894 mg; glutamate, 749 mg; serine, 592 mg; aspartate, 434 mg; tyrosine, 39 mg).
2. **Dextrose:** 150 mL of dextrose at a concentration of 50%
3. **Lipids:** 150 mL of lipids at a concentration of 20%

This solution provides 188 kcal/hour or 3.5 kcal/kg fat-free mass per hour for a total of: 45 g of protein and 735 total kcal in 600 mL.

Table 3.
Selected Studies of Intradialytic Parenteral Nutrition

Author	*Design*	*N*	*IDPN Composition*
Heidland (34) (1975)	Nonrandomized	18	15.5 g EAA+ histidine + 100 g oral protein as "curds and steak"
Thunberg (35) (1980)	Nonrandomized	4	10–50% hypertonic glucose, 5.5–8.5% amino acids, and 10% lipids
Wolfson (36) (1982)	Randomized	8	Group1: 800 ml NS infusion Group 2: 800 ml 39.5 g EAA + NEAA + 200 g d-Glucose
Madigan (44) (1990)	Nonrandomized	9	Varied: 6 given 1L with 8.5% AA/50% dextrose, 3 given 1L with 10% AA/50% dextrose, 3 also given 10% lipids
Capelli (30) (1994)	Nonrandomized, retrospective	81 Total: 50-IDPN 31-no intervention	50 g AA/50% dextrose/10–20% lipids Diabetics: 50 g AA/20% Dextrose/10–20% lipids
Chertow (33) (1994)	Nonrandomized, retrospective	IDPN: 1,679 Control: 22,517	Not reported
Mortelmans (45) (1999)	Nonrandomized, prospective	16	250 mL 50% glucose, 250 mL 20% lipids, 250 mL 7% AA (60% EAA + 40% NEAA) And an additional 250 ml 7% AA at end of dialysis session
Cherry (40) (2002)	Nonrandomized, partially prospective	24	750 mL containing 250 mL 10% AA/250 mL 50% Dextrose/ 250 mL 20% Fat emulsion or 1000 mL containing 500 mL 10% AA/250 mL 50% Dextrose/250 mL 20% Fat emulsion
Pupim (46) (2002)	Randomized, crossover	7	300 mL 15% AA, 150 mL 50% dextrose 150 mL 20% Lipids
Goldstein (47) (2002)	Nonrandomized, retrospective	3 (pediatrics)	70% Dextrose, 15% AA, 20% Lipids (total volume ranged from 478 mL to 597 mL)
Pupim (48) (2004)	Randomized, crossover	6	Group1: IDPN alone Group2: IDPN plus exercise during dialysis IDPN: 300 mL 15% AA, 150 mL 50% dextrose, 150 mL 20% Lipids
Pupim (27) (2006)	Randomized, prospective, crossover	8	Group 1: IDPN: 300 mL 15% AA, 150 mL 50% dextrose 150 mL 20% Lipids Group 2: 2 cans NEPRO, 5 spoons protein powder given during dialysis Group 3: no nutrition supplements

AA: amino acids; EAA: essential amino acids; NEAA: non-essential amino acids; CRP: C-reactive protein; nPCR: normalized protein catabolic rate; HD: hemodialysis

Duration and Administration	*Results*	*Comments*
60 weeks, last 90 minutes of dialysis	• Significant increase in albumin • No change in body weight	Study group given high protein oral diet
6 months	• Significant increases in albumin and arm muscle circumference ($p < 0.02$)	Improvement in protein and caloric intake ($p < 0.01$)
2 treatments during 5 hour dialysis, infusion begun at start of dialysis	• Significantly higher postdialysis plasma AA in group 2 ($p < 0.001$)	Group 1 found to lose 8 g of AA in dialysate
2 months	• Significant increase in albumin	4 pts lost weight Small number of patients All patients diabetic
9 months	• Significant weight gains in survivors both non-diabetic and diabetic ($p < 0.01$) • No significant change in albumin • Significant increase in survival with use of IDPN (RR = 1.34, $p < 0.01$)	All patients had 2 month trial of increased oral intake/supplements
Followed for 1 year or until death	• Suggested a treatment advantage in terms of Odds ratio for death in patients with Alb″ 3 g/dL regardless of Cr vs. controls	No data regarding prescription or frequency of IDPN Unblinded
9 months, infusion given during entire dialysis procedure plus additional 250 mL AA at end of procedure	• Significant increases in body weight (at both 6 and 9 months, $p < 0.05$ for both time points), prealbumin, and transferrin	No change in serum albumin. No significant change in total bone densitometry measurements.
Mean of 4.3 months	• Significant increase in body weight at 9 and 12 months ($p < 0.05$ and $p < 0.003$, respectively) and significant increase in albumin at 3 and 9 months ($p < 0.05$)	Small number of patients with many lost to follow-up/died during study
2 dialysis sessions	• Whole-body protein synthesis, and net protein balance increased significantly during HD ($p < 0.05$)	No differences in post dialysis protein synthesis or net protein balance
Variable	• Significant increase in %Wt change, %BMI change, nPCR ($p < 0.02$, $p < 0.02$, $p < 0.05$ respectively)	No significant change in albumin Very small sample size
2 dialysis sessions	• Significant increase in net forearm muscle protein balance with IDPN + exercise	No change in whole body protein homeostasis and energy expenditure
3 dialysis sessions, 4 weeks apart	• Net whole-body protein synthesis was significantly increased post-HD for oral group versus control ($p < 0.05$) and IDPN ($p < 0.05$)	Effects of whole body protein synthesis dissipated post HD in IDPN group

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Table 3 (continued).
Selected Studies of Intradialytic Parenteral Nutrition

Author	*Design*	*N*	*IDPN Composition*
Cano (49) (2006)	Prospective, controlled, and randomized	35	Group 1: 50 g AA, 125 g glucose and Clinoleic® 20% (40 g/l soybean oil and 160 g/l Olive oil) Group 2: 50 g AA, 125 g glucose and Ivelip® 20% (200 gl soybean oil)
Avery-Lynch (50) (2006)	Retrospective, nonrandomized	8	5% AA, 25% Dextrose or 5% AA, 16.6% Dextrose
Cano (39) (2007)	Prospective, randomized	186	Study group: Oral supplements consisting of 500 kcal/d and 25 g/d protein and IDPN to fulfill the difference between oral and recommended intake
Joannidis (51) (2008)	Prospective cohort	12 IDPN in 6, 6 matched controls	500 mL Aminomel Nephro, 100 ml 60% glucose, 100 mL Elolipid, 0.5 g l-carnitine
Korzets (52) (2008)	Retrospective, nonrandomized	22	Variable, 10% AA 50–85 g, 50% Dextrose 125–185 g, Clinoleic® 20% (olive oil based lipid)

AA: amino acids; EAA: essential amino acids; NEAA: non-essential amino acids; CRP: C-reactive protein; nPCR: normalized protein catabolic rate; HD: hemodialysis

≤3.5g/dL a predictor of death versus those with albumin of 4 g/dL, but that if 50% of the US dialysis population had their albumin increase by 0.2 g/dL a Medicare cost savings of ~$36 million would be achievable (18). However, there are several other causes outside of poor nutritional intake that can account for a low serum albumin. The serum albumin concentration is influenced by age, fluid overload, capillary leakage and inflammation in addition to the amount of dietary protein consumed (19,20).

Indeed, when comparative analysis of predictors of outcome in ESRD patients was studied, no significant difference in serum albumin levels was found between malnourished and well-nourished ESRD patients (21).

Chronic inflammation is clearly one of the major driving forces altering nutritional markers. In a study of incident dialysis patients studied prospectively, malnutrition as assessed by means of Subjective Global Assessment is best predicted by inflammatory markers such as C-reactive protein and interleukin (IL)-6, but not by serum albumin (22). In dialysis patients, albumin generation and serum albumin levels are negatively correlated with markers or inflammation, including C-reactive protein, fibrinogen, and interleukin-6 (23). Indeed, the common thread in most chronic inflammatory conditions is activation of protein breakdown and loss of muscle mass. Thus, inflammation, mediated by pro-inflammatory cytokines, can lead to hypoalbuminemia, and loss of lean muscle mass. This link between inflammation, nutritional parameters and morbidity and mortality has led to the term "malnutrition-inflammation complex syndrome" in order to heighten awareness and study of this causal link (24). The interpretation of nutritional parameters (especially, serum albumin) must be done cautiously and take these inflammatory influences into consideration. Furthermore, intervention strategies that focus solely on nutritional supplementation and ignore the inflammatory component may not be successful in achieving significant impact on nutritional parameters.

Duration and Administration	*Results*	*Comments*
5 weeks (15 dialysis sessions)	• Significant increases in both groups in albumin, nPCR, Kt/V urea ($p < 0.01$)	No difference between the two groups
1.5 to 16 months depending on the patients protein calorie malnutrition state	• Average weight change of 1.13 kg, average nPNA change of 0.65	Small observational sample
1 year of therapy, 2 year follow-up	• No difference in all-cause mortality between groups. • No difference in hospitalization rate, BMI, Karnofsky score, nutritional markers between groups	Both groups showed an increase in serum albumin at months 3, 6, 12, 18 ($p < 0.01$) and prealbumin at months 3 to 24 ($p < 0.02$). Multivariate analysis showed serum prealbumin increase >30 mg/L from day 0 to month 3 (or 0.46; 95% CI 0.27–0.79)
6 months	• Significantly increased dry body weight, did not affect markers of inflammation	Very small sample size
1.5 to 48 months (18 patients received IDPN less than 6 months)	• Significant increases in nPCR, albumin, prealbumin ($p < 0.05$)	Significant decrease in CRP ($p < 0.05$). All acutely ill dialysis patients.

INDICATIONS FOR NUTRITIONAL SUPPORT

As mentioned above, it is difficult for dialysis patients to meet the goal dietary intake of 1.2 grams/kg/day. Furthermore, the recommendation to increase DPI may be at odds with other nutritional recommendations (for instance, increasing protein intake will invariably lead to increases in phosphorus and acid production) and require careful monitoring of laboratory values, nutritionist input and in some cases alteration of the dialysis prescription or medications. Thus, careful nutritional monitoring is essential and the NKF K/DOQI guidelines recommend that every ESRD patient should receive intensive nutritional counseling with development of an individualized care plan which is reviewed and modified at least quarterly (1). The goals of this monitoring are multiple: (1) assess nutritional status using a global assessment strategy (2), counsel patients on adequate nutritional intake (including those foods to avoid), and (3) to detect changes in nutritional status that require intervention.

However, even when counseled by an experienced renal dietician, many dialysis patients consume less than 80% of their recommended intake (25). As indicated in Table 1, there are many reasons for this and any recommendations for increasing nutritional intake must begin with a careful assessment of reversible causes for the nutritional deterioration. Only after these measures have been addressed should nutritional support be instituted, enteral being considered first. Specific indications for nutritional support are not available and thus, individualized patient decisions that factor in a global assessment of the patient's medical and social situation need to be made.

After identification of the "nutritionally at risk" patient, the first step would be intensive dietary counseling to attempt to increase dietary protein and energy intake. During this stage, patients should be closely monitored to assess whether nPNA is increasing along with regular global assessments. If these conservative measures fail, the next step would be the prescription

of enteral nutritional supplements (such as protein-rich drinks such as Nepro© which contains 19.1 grams of protein and 425 calories per 8 fluid ounces (cost $3.50). If the intestinal tract is functional, enteral tube feeding can be considered as the first line of therapy in those patients who are unable to eat adequately (often true for hospitalized patients and patients recovering from serious illness).

Evaluation of the potential value of nutritional therapies to improve clinical outcome is hampered because there are few prospective, randomized studies of nutritional therapy. Those randomized, prospective studies that have been conducted have generally used nutritional parameters, rather than morbidity or mortality, as the key outcome measures, often have had underpowered sample sizes, and have sometimes not been restricted to patients with documented PEM. Moreover, most studies have not compared different modalities of nutritional therapy. Much of the rationale for using nutritional therapies comes from studies in other patient populations and using the logic that there would be no reason to suspect that malnourished ESRD patients would differ in response to enteral feedings (1).

Table 4.
Medicare Intermediary Criteria (2009) for Initiating Intra-Dialytic Parenteral Nutrition in the Presence of a Functional Gastrointestinal Tract (adapted from reference 42)

1. Evidence of protein or energy malnutrition and inadequate dietary protein and/or energy intake (for instance: dietary history of decreased intake: protein <0.8 g/kg and/or calories <25 kcal/kg and subjective global assessment (SGA): "C" rating [severe malnutrition])
2. Weight loss greater than 10% of ideal body weight or 20% of usual body weight (no time constraints)
3. Serum albumin <3.4 g/dL (3 month rolling average)
4. Evidence of a comprehensive nutritional assessment and dietary counseling
5. Inability to administer or tolerate adequate oral nutrition, including food supplements or tube feeding
6. Evidence that patient was intolerant of enteral nutrition, or could not meet the individual's nutritional needs or is not feasible (3 month trial)
7. Evidence that the individual has had the following conditions ruled out or previously addressed:
   - Anorexia caused by the uremic state
   - Altered taste sensation
   - Intercurrent (limited) illness
   - Emotional distress or illness
   - Impaired ability to procure, prepare or mechanically ingest foods
   - Unpalatable prescribed diets
   - Catabolic response to a superimposed (limited) illness
   - Inadequate dialysis/uremic state
   - Gastroparesis
   - Constipation

ORAL OR ENTERAL NUTRITIONAL SUPPORT

The potential advantages of oral or enteral feeding include: (1) the ability to provide a patient's total nutritional needs chronically on a daily basis; (2) the ability to provide balance nutrients that can be tailored to a disease-specific state; (3) the ability to provide nutrients in a smaller fluid volume than parenteral nutrition; (4) lower infection risk than parenteral nutrition and (5) considerably less expensive than parenteral nutrition. Stratton et al published a systematic review and meta-analysis looking at the effects of multinutrient oral supplements and tube feeding in maintenance dialysis patients (26). The authors reviewed 18 studies (5 of which were randomized controlled trials) with a total of 541 patients. In the majority of the studies, supplementation was done with the equivalent of one can per day (or only on dialysis days) of a formula similar to Nepro©. These studies suggested that total energy and protein intakes can be increased by 20–50% with either oral or enteral nutritional support. As compared with routine care, nutritional support resulted in significantly greater serum albumin concentration (0.227 g/dL; 95% confidence interval, 0.037 to 0.418 g/dL). Interestingly, there were no adverse effects of nutritional supplementation on electrolyte or volume status. The meta-analysis also concluded that there was insufficient data to assess mortality, morbidity or change in quality of life from the available studies. There was also a notable lack of information on the effects of oral supplements and enteral tube feeding on infective, cardiovascular and skeletal complications.

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In some cases, oral or enteral supplements may not be appropriate. Some patients may complain of palatability problems or poor appetite and refuse to take supplements. In other cases, fluid overload due to increased intake may become an issue (although this can usually be managed with alteration of the dialysis prescription). More compelling problems that would limit the use of enteral feeding include: (1) severe malnutrition where oral nutrition is not meeting nutritional demands; (2) inability to utilize the gastrointestinal tract due to severe disease (massive bowel resection, short bowel syndrome, complete mechanical obstruction where surgery is not an option, or enteritis requiring greater than 3 months of bowel rest); or (3) disability that limits oral intake and makes the use of enteral feeding difficult. In these limited circumstances, IDPN may be an option.

INTRADIALYTIC PARENTERAL NUTRITION

Intradialytic parenteral nutrition (IDPN) has the advantage of overcoming limitations in oral intake; it can be given during the dialysis procedure thus ensuring compliance as well as maintenance of fluid balance, and can provide a reasonably large amount of supplementation in a short period of time. IDPN is not designed to supply all of the protein and energy requirements required by a patient since it is only give thrice weekly when the patient is on dialysis. Indeed, Pupim et al studied 8 patients comparing oral supplementation, IDPN, and no supplementation as it relates to protein homeostasis (27). In this study, net whole-body protein synthesis was significantly increased post-dialysis for both the oral and IDPN group. However, the effect of supplementation on whole body protein synthesis dissipated in the post dialysis period in the IDPN group, but persisted in the oral supplementation group. Thus, other means outside of IDPN must be utilized to maintain protein and energy intake (such as supplemental enteral feeding or total parenteral nutrition). Furthermore, IDPN should not be thought of as a long-term support modality, but as a therapy to increase protein-energy balance in those patients requiring "resuscitation" (i.e., those patients who might be expected to be able to regain nutritional balance and then transition back to oral feeding). Traditionally, IDPN formulations contain amino acids including both essential and non-essential amino acids as well as dextrose and lipids (see Table 2).

Several reports (Table 3) suggested a benefit from IDPN, mainly in leading to rises in serum albumin levels (28–36). However, in 1993, the Office of Health Technology Assessment summarized the existing data in a review concluding that studies of IDPN reported equivocal results and the data did not validate its efficacy (37). More recently, Foulks reported on an evidence-based evaluation of IDPN (38). The analysis concluded that the overall quality of the literature was poor; only three randomized studies were identified, but one was a feasibility study only and the other two had methodological flaws or used types of IDPN that were not routinely used or not available in the United States. The remaining literature consists of case series, which cannot control for the many variables in the dialysis population that may contribute to mortality and morbidity outcomes. According to Foulks' analysis, the majority of the case series had methodological flaws including heterogeneity in study design, patient selection criteria, types of IDPN used and the adequacy of dialysis.

The largest study reported on the effects of IDPN is a retrospective case series comparing the morbidity of 1679 IDPN-treated patients with that of 22,517 non-treated patients (33). This study found that dialysis patients with a serum albumin of <3.4 g/dL who were treated with IDPN had significant increases in albumin and creatinine (marker of muscle mass) over time. Additionally, these patients experience a significant decrease in the odds ratio for death at one year compared to those who were not treated with IDPN. Due to the numerous biases inherent in any uncontrolled trials, these studies cannot validate whether IDPN is associated with decreased mortality. The observed treatment effect could be related to a selection bias in which very ill patients (i.e. those expected to die) were not offered IDPN. In addition, IDPN administration may be associated with an increased attentiveness to dialysis parameters, counseling and nutritional advice. These uncontrolled studies do suggest that being selected for IDPN may be associated with a decreased mortality rate, but analysis of the direct contribution of IDPN requires controlled prospective trials.

Cano et al in 2007 published the French Intradialytic Nutrition Evaluation study (FineS) (39). The FineS was the first prospective, randomized, controlled trial evaluating the effects of IDPN on mortality outcomes. In this study, 186 chronic dialysis patients who had two markers of malnutrition including: BMI <20 kg/m^2, body weight loss within 6 months >10%, serum albumin <3.5 g/dL, and serum prealbumin <30.0 mg/dL were randomized into one of two arms. One therapeutic group received oral supplements consisting of 500 kcal/day and 25 g/day of protein, while the other therapeutic arm received the same oral supplementation plus IDPN to fulfill the difference between oral and recommended intake. The groups were given this supplementation for 1 year and followed for a total of 2 years. The primary outcome was 2-year mortality and was similar between the two groups, 39% in the control group and 43% in the IDPN group. Both groups showed increases in albumin and prealbumin. Thus, as compared to oral supplementation, IDPN offered no additional survival advantage.

Based upon these data, the current recommendations for the use of IDPN have focused on those patients that cannot meet their nutrient needs orally after an exhaustive search for reversible causes and/or those who are not candidates for enteral nutrition because of gastrointestinal intolerance or for full parenteral nutrition due to venous access problems (40,41). Based upon the existing data as well as expert opinion, Table 4 lists criteria that at least one Medicare Advantage coordinated care plan utilizes for considering the use of IDPN in those patients that have a *functional* gastrointestinal tract (40–42). In those whose gastrointestinal tract is *not functional*, a time limited trial of IDPN may be warranted, but more than likely full parenteral nutrition is indicated. Given the expense of IDPN, as well as the limited dataset supporting its use, the requirements are appropriately stringent.

SUMMARY

Practitioners involved in the care of patients with ESRD continue to look for methods to decrease the morbidity and mortality of this population. Clearly, malnutrition and inflammation contribute to the mortality risk. However, the use of supplemental nutrition in the form of IDPN has not been shown to positively impact outcomes, although it can increase serum albumin levels. Studies to date are limited, non-randomized, non-prospective and use surrogate endpoints. According to the K/DOQI Nutrition guidelines, IDPN may be beneficial in patients who are malnourished or unable to consume adequate energy and protein to meet nutritional requirements, who are unable to tolerate oral or tube feedings, and who are able to meet their needs with the combination of oral diet or tube feedings plus IDPN (1). Medicare part D now covers IDPN for those patients meeting stringent requirements, but usually at a substantial cost to the patient secondary to co-payments or co-insurance costs (32).

Thus IDPN should be limited to those with the most profound nutritional supplementation needs, those patients with a serum albumin less than 3.4 g/dL, and only after aggressive attempts at enteral supplementation. It is also important to carefully investigate the many factors that contribute to malnutrition in the ESRD population and target a broad array of interventions. In the end, well-designed, prospective, randomized intervention studies are needed to evaluate mortality differences among the different nutritional therapies. ■

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