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NARRATIVE REVIEW

Is There a Role for Intradialytic Parenteral Nutrition? A Review of the Evidence

Ramanath Dukkipati, MD,¹ Kamyar Kalantar-Zadeh, MD, PhD, MPH,¹ and Joel D. Kopple, MD^{1,2}

Protein-energy wasting (PEW) is highly prevalent in people with stages 4 and 5 chronic kidney disease, particularly in maintenance dialysis patients, and many indicators of PEW correlate strongly with mortality. Consequently, the causes, prevention, and treatment of PEW are active areas of investigation. A major cause of PEW is insufficient intake of nutrients, especially protein and energy (calories). Standard methods for increasing nutritional intake in patients with chronic kidney disease with PEW include dietary counseling and use of food supplements. If nutrient intake does not increase sufficiently, tube feeding and total parenteral nutrition may be considered. For maintenance hemodialysis patients, intradialytic parenteral nutrition (IDPN), an intravenous infusion of essential nutrients during hemodialysis treatments, may be used. Many studies have evaluated the effectiveness and safety of IDPN and show that IDPN has a good safety profile and also may improve protein-energy status. However, most studies have limitations in experimental design, such as small numbers of patients, lack of adequate controls, inclusion of patients without PEW, uncontrolled or unmonitored oral intake, nonrandomized design, or short duration. Additionally, most studies used nutritional or inflammatory indicators, rather than the more important outcomes of morbidity, mortality, or quality of life. Thus, although IDPN may partially satisfy the nutritional needs of maintenance hemodialysis patients who have or are at risk of PEW and who have substantial, but not adequate, protein and/or energy intake, longer term randomized prospective clinical trials with appropriate control groups are necessary to more definitively evaluate the clinical effectiveness and indications for IDPN.

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INDEX WORDS: Intradialytic parenteral nutrition; protein energy wasting.

There presently are ~400,000 people undergoing maintenance dialysis therapy in the United States and 1,000,000 people worldwide.¹ It is projected that by 2020, the maintenance dialysis population may be > 1 million in the United States and many more worldwide.² A major challenge facing maintenance dialysis patients is their high mortality rate, with current 5-year survival rates < 35%. Cardiovascular disease is the leading cause of mortality in maintenance dialysis patients. However, modification of traditional cardiovascular risk factors, includ-

ing cholesterol levels, does not seem to significantly improve mortality.³ Similarly, a modest increase in dialysis dose, evaluated in the Hemodialysis (HEMO) Trial, has not decreased mortality.⁴

Protein-energy wasting (PEW) is a common complication in people undergoing maintenance dialysis, and it is associated with higher morbidity and mortality. Indicators of PEW are among the strongest risk factors for mortality in maintenance dialysis patients.^{5,6} Indicators of PEW that correlate with increased mortality include decreased appetite, low protein intake, low serum albumin level, decreased body weight for height (ie, low body mass index), and decreased muscle mass. There are many causes of PEW in maintenance dialysis patients,⁷ with inadequate protein and energy intake and inflammatory disorders among the most common and dominant. These considerations are of particular importance because the prevalence of PEW in maintenance hemodialysis patients is increased in virtually all observational studies evaluating this topic, varying from 18%-75% across studies.⁸

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Box 1. Nutritional Components of a Typical IDPN

Standard IDPN	
Composition (final concentrations are 11% amino acids, 11.1% dextrose, 4.6% lipids)	
Protein: 97 g	
Carbohydrate: 98 g	
Fat: 41 g	
Nonprotein kcal: 743	
Total volume: 880 mL	
Infusion Regimen (goal is 275 mL/h [895 mL])	
Week 1: 105 mL/h (345 mL)	
Week 2: 210 mL/h (685 mL)	
Week 3: test for lipid; 125 mL/h × 30 min	
Carbohydrate-Control IDPN	
Composition (final concentrations are 11.6% amino acids, 8.9% dextrose, 4.6% lipids)	
Protein: 96 g	
Carbohydrate: 73.5 g	
Fat: 38 g	
Nonprotein kcal: 630	
Total volume: 825 mL	
Infusion Regimen (goal is 255 mL/h [825 mL])	
Week 1: 100 mL/h (325 mL)	
Week 2: 200 mL/h (650 mL)	
Week 3: test for lipid; 130 mL/h × 30 min	

Note: Possible formula additions include multivitamins, sodium phosphate, and magnesium sulfate.

Abbreviation: IDPN, intradialytic parenteral nutrition.

Inadequate nutritional intake is considered a common cause of PEW in maintenance dialysis patients^{7,9} which has given rise to several questions. (1) Can nutritional support prevent or ameliorate PEW? (2) In patients with PEW, will nutritional support improve quality of life or reduce morbidity or mortality? (3) Is nutritional support safe?

There are many techniques for providing nutrients to maintenance dialysis patients who have nutritionally inadequate food intake. These techniques include dietary counseling, food supplements, enteral tube feeding, intradialytic parenteral nutrition (IDPN), and total parenteral nutrition. The nutritional components of a typical IDPN solution are listed in Box 1, and examples of oral nutritional supplements are listed in Table 1. Provision of nutrients through both hemodialysate and peritoneal dialysate has been used.^{10,11} The former is still available only experimentally, and currently there are no Food and Drug Administration–approved amino-acid solutions available in the United States for intraperitoneal nutrition. Most nephrologists would agree that dietary counseling and food supplements should be the first approach for maintenance dialysis patients who are ingesting inadequate quantities of nutrients,^{8,12} and it is important to ensure that inadequate food intake is not caused by the lack of ability to purchase, prepare, or ingest foods; that illnesses that might prevent the digestion, absorption, or assimilation of nutrients are not present; and there are not correctible psychogenic causes for inadequate intake (eg, bipolar disorder or depressive states).¹³

In the opinion of the authors, enteral tube feeding is an effective method for providing nutrients to many maintenance dialysis patients with PEW. However, physicians often are hesitant to use this technique, and many patients are reluctant to accept this treatment. Thus, for malnourished maintenance hemodialysis patients who are unable to respond to dietary counseling or food supplements, IDPN may be the treatment of

Table 1. Nutritional Components of Select Oral Nutritional Supplements

	Nepro ^a (240 mL)	Nepro (1,000 mL)	Boost ^b Glucose Control (237 mL)	Boost Glucose Control (1,000 mL)	Boost (240 mL)
Total calories	425 kcal (1.8 kcal/mL)	1,800 kcal (1.8 kcal/mL)	250 kcal (1.06 kcal/mL)	1,060 kcal (1.06 kcal/mL)	240 kcal (1.0 kcal/mL)
Total protein (g)	19.1	81	14	58.2	10
Total carbohydrates (g)	39.4	166.8	20	84	41
Total fat (g)	22.7	96	12	49.4	4

^aManufactured by Abbott Laboratories (abbottnutrition.com).

^bManufactured by Nestle Inc (www.nestle-nutrition.com).

Box 2. Advantages and Disadvantages of IDPN**Advantages**

1. IDPN can be provided with each dialysis session (usually thrice weekly) through the blood tubing without the need for additional venopuncture or placement of a central catheter.
2. It provides nutritional support to patients independent of anorexia, appetite, willingness or ability to cooperate, or gastrointestinal function.
3. All needed nutrients can be provided through IDPN in contrast to nutrition provided through the dialysate.
4. The quantity and nutrient composition of the nutritional intake can be regulated.
5. Excess fluid and minerals and metabolic products can be removed during the course of dialysis; therefore, undesirable positive fluid or mineral balance or increased accrual of potentially toxic metabolites can be prevented.
6. It is a convenient way to provide supplemental nutrition with little or no effort by the patient and does not interfere with the patient's daily activities.

Disadvantages

1. The nutritional intake is given only during hemodialysis, which typically is provided for 3-4 hours thrice weekly or ~12 h/wk; therefore, IDPN is not very effective as the sole source of nutrition.
2. Nutrients given intravenously are cleared very rapidly from blood.
3. The short intense duration of intravenous feeding by IDPN is unphysiologic because normal nutrient-gut interactions are lacking and also because adult humans eating 3 or 4 meals daily spend most of their lives in the postprandial state, in contrast to the short intense duration of intravenous feeding by IDPN.
4. It often is expensive, although theoretically it does not have to be.
5. It requires time and effort from the nursing staff.
6. Microbial contamination with ensuing infection in the patient can occur.
7. There is a risk of reactive hypoglycemia, particularly if patients are infused with large quantities of D-glucose over short periods.

Abbreviation: IDPN, intradialytic parenteral nutrition.

choice. This treatment is not available for maintenance peritoneal dialysis patients. This review examines the published research concerning the effectiveness of IDPN, specifically with regard to whether IDPN offers a solution to the listed questions.

IDPN offers multiple potential advantages, listed in Box 2. These include easy administration through preexisting vascular access, ready regulation of nutritional content, prevention of net loss of amino acids and water-soluble vita-

mins during hemodialysis, and volume-neutral nutrition provision.

Disadvantages of IDPN include nutritional supplementation for only ~12 hours weekly, limiting its effectiveness as the sole source of nutrition; rapid clearance of nutrients from blood; and nonphysiologic circumvention of the normal nutrient-gut interactions. Additionally, IDPN is expensive and requires time and effort from the nursing staff. There are several potential adverse events that may occur with IDPN. These include bacterial contamination; reactive hypoglycemia, especially if the patient is given large amounts of glucose during IDPN (J.D. Kopple, unpublished observations, 2009); and a decrease in Kt/V, probably caused by increased urea generation from amino acids in the IDPN solution.¹⁴ Both published reports and personal experience indicate that these complications are uncommon.

PUBLISHED STUDIES

Most studies of IDPN are characterized by ≥ 1 of the limitations in experimental design listed in Box 3. In some studies, sample sizes were very small, study duration was short, and not all patients satisfied criteria for PEW or their protein-energy status was not well described. Often there was little or no description of comorbid illnesses or other confounding clinical characteristics of patients. Oral nutrient intake or use of oral supple-

Box 3. Common Errors or Limitations in the Experimental Design of Individual Studies of IDPN

1. Sample size too small to show benefits or lack of benefits
2. Retrospective
3. No control group
4. Criteria for the diagnosis of protein-energy wasting not indicated or inadequately described
5. Some patients did not have protein-energy wasting
6. Patients had heterogeneous comorbid conditions and other confounding factors
7. Other relevant clinical characteristics of patients not described
8. Dialysis dose not described or not standardized
9. Composition of IDPN solutions or dose of IDPN administered not standardized
10. Short study duration
11. Oral intake of nutrients uncontrolled and often not monitored
12. An oral nutritional supplement given to some patients

Abbreviation: IDPN, intradialytic parenteral nutrition.

ments generally was not controlled; hemodialysis treatments, including dialysis doses, were not standardized or were poorly described; and some studies were retrospective. Tables 2 and 3 summarize published reports of nonrandomized and randomized trials of IDPN, respectively. In general, only studies involving at least 10 patients are listed in the tables or discussed in the text.

Nonrandomized Studies of IDPN

There have been > 20 published nonrandomized observational studies of IDPN (Table 2). In general, these trials described an increase in various nutritional measures in association with the inauguration of IDPN, with increases observed most commonly for body weight, serum albumin level, and/or transferrin level. However, the lack of concurrent prospective randomized controls, the phenomenon of regression to the mean, the small number of patients studied, the short duration of many studies, and the lack of detail concerning clinical and protein-energy status of patients render these clinical trials difficult to evaluate. In the following section, we highlight several of the more notable observational studies and randomized trials of IDPN.

Heidland and Kult¹⁵ were the first to report the use of IDPN in maintenance hemodialysis patients. They evaluated 18 patients undergoing maintenance hemodialysis thrice weekly during a 60-week study period. Patients were given 16.7 g of essential amino acids, including histidine, and 250 mL of a mixture of D/L-malic acid, xylitol, and sorbitol during the last 90 minutes of each hemodialysis session. During the first 3 months, some nonessential amino acids were added to this mixture. In 13 patients, therapy was discontinued for 16 weeks. About 100 g of protein in foods was also prescribed during each dialysis treatment, although oral intake probably varied widely.¹⁵ After 30 weeks of IDPN, serum albumin and total protein levels had increased significantly, whereas discontinuation of IDPN for 16 weeks resulted in a significant decrease in serum transferrin levels, as well as levels of hemoglobin and several complement proteins.

Piraino et al¹⁶ reported 21 maintenance hemodialysis patients who received IDPN for 20 weeks. Of these, 16 patients who had lost at least 10% of their dry weight were treated with a solution providing an average of 400 mL of 8.5%

essential amino acids and nonessential amino acids with 400 mL of 50% glucose at each dialysis session. The remaining 5 patients, who had lost at least 15% of their dry weight, were treated with a solution providing essential amino acids and 50% glucose, although the volume of this solution is unclear. Dialysis dose was not reported, and comorbidity was not described in detail. Although neither patient group gained weight or had improved serum albumin levels, the subgroup of patients without hyperparathyroidism that received essential and nonessential amino acids experienced weight gain.

Bilbrey²⁰ reported experience with IDPN given for at least 3 months to 47 maintenance hemodialysis patients with a diagnosis of severe PEW in whom other attempts at treatment failed. Survivors showed a significant increase in serum albumin (3.30 ± 0.38 [SD] to 3.71 ± 0.30 g/dL; $P < 0.001$) and transferrin levels (165 ± 37 to 200 ± 62 ; $P < 0.001$; units presumably are in milligrams per deciliter). No increase in these serum protein levels was observed in nonsurvivors. Dialysis dosage, duration of IDPN therapy, prevalence of diabetes mellitus, and other clinical characteristics were not reported.

In a study not listed in Table 2, Schulman et al³⁵ treated 8 malnourished hemodialysis patients with IDPN and recombinant growth hormone. Six weeks after therapy with IDPN alone, serum transferrin concentrations increased; however, there was no significant change in the protein equivalent of total nitrogen appearance (PNA), insulin-like growth factor 1, serum albumin, or anthropometric measurement values. IDPN was continued for another 6 weeks, with 5 mg of growth hormone given at each hemodialysis session, and this was associated with a significant increase in serum albumin levels.

Capelli et al²² retrospectively described 81 patients with wasting who were undergoing maintenance hemodialysis; 50 received IDPN and 31 did not. All patients had low serum albumin levels; IDPN-treated patients had a body weight at least 10% less than desirable and/or at least 10% weight loss during 2 consecutive months. The untreated patients did not consistently have such low body weights or weight loss. Patients initially were given dietary counseling and/or oral nutritional supplements for 2 months. Those who did not respond were given IDPN. It is

Table 2. Nonrandomized Studies of IDPN

Study	Design	Treatment Duration	No. With PEW	Parameters Measured	Outcome
Heidland & Kult, ¹⁵ 1975	18 pts; 16.75 g of EAA, 100 kcal; no control	60 wk	Most did not	Alb, total protein, complement, transferrin	Increase in Alb, total protein, transferrin, complement after 16 wk therapy in 13 pts When therapy discontinued for 6 wk, decrease in complement levels, transferrin
Piriano et al, ¹⁶ 1981	16 pts: 16.5 g of EAA + 1 NEAA, 200 g of glucose 5 pts: 10.2 g of glucose/EAA only	20 wk	5 (in EAA group lost > 15% of usual BW)	BW	In EAA + NEAA group, 8 pts gained > 10% BW, other 8 lost weight Pts in EAA group gained weight if no acute illness
Powers & Piraino, ¹⁷ 1989	18 pts; 250 mL of 50% glucose, 250 mL of RenAmin ^a	46-165 infusions	All	Weight gain, Alb, TSF, MAMC	Weight gain (12.6 ± 4.9 lb) in 11/18 pts No change in Alb
Bilbrey & Cohen, ¹⁸ 1989	20 pts; 50 g of EAA + NEAA, 50 g of lipids, 125 g of glucose	90 d minimum	All	BW, MAMC	Only MAMC improved
Matthys & Ringoir, ¹⁹ 1991	10 pts; 16.75 g of EAA	3 mo	All	Quality of life, Hct, BW, degree of edema	BW increased starting from month 1 of therapy ($P < 0.01$) Scoring index of general condition increased ($P < 0.01$)
Bilbrey, ²⁰ 1993	47 pts; 400 mL of 15% AA, 150 mL of 70% glucose, 250 mL of 20% lipids	90 d minimum	All	Alb, transferrin, mortality	29 survived, 18 died Survivors had increase in Alb, transferrin No data for cause of death, dialysis dose
Chertow et al, ²¹ 1994	1,679 pts: 1.2 g of protein/kg, 15 kcal/kg 22,517 pts: no IDPN	12 mo or until death		Alb, URR, odds of death	Decrease in mortality in IDPN-treated pts who had Alb ≤ 3.3 g/dL

(Continued)

Table 2 (Cont'd). Nonrandomized Studies of IDPN

Study	Design	Treatment Duration	No. With PEW	Parameters Measured	Outcome
Capelli et al, ²² 1994	50 pts: 50 g of EAA, 50 g of lipids, 125 g of glucose, dietary suppl (discontinued when IDPN started) 31 pts: dietary suppl	9 mo	All had Alb < 3.5 g/dL, BW < 90% of desirable BW or BW loss > 10% over 2 mo	Alb, BW, mortality	32/50 treated pts & 16/31 untreated pts survived Weight gain in treated survivors, no weight gain in untreated survivors No weight gain in nonsurvivors in either group 6 mo of IDPN before change in weight or Alb
Foulks, ²³ 1994	72 pts; 0.64 g of N/kg, 3.78 kcal/kg as lipids, glucose	Mean, 159 d in responders, 222 d in nonresponders		Mortality, hosp rate	Decreased mortality and hosp rate in responders
Smolle et al, ²⁴ 1995	16 pts; 0.8 g/kg of EAA + NEAA	16 wk		Alb, skin test reactivity, WBC, SCr	NA ^b
Cranford, ²⁵ 1998	43 pts; 63 g of EAA + NEAA, 18.4 g of lipids, 92.5 g of carbohydrates	6 mo		Alb, BUN, hospitalizations	NA ^b
Hiroshige et al, ²⁶ 1998	10 pts: 200 mL of 50% glucose, 200 mL of 7% EAA, 200 mL of 20% lipids 18 pts: dietary counseling	12 mo	All	BW, BMI, TSF, MAMC, Alb, transferrin, plasma AA profile, mortality	All IDPN-treated pts survived, 5 pts without IDPN therapy died (3 of sepsis, 1 of GI bleed) during study period
Mortelmans et al, ²⁷ 1999	26 pts (16 pts completed study, 10 pts withdrew); 250 mL of 50% glucose, 250 mL of 20% lipids, 250 mL of 7% AA	9 mo	All	BW, MAMC, lean body mass, transferrin, serum preAlb	BW increased ($P < 0.05$); transferrin, Alb increased TSF increased ($P < 0.05$) No such change in pts who withdrew
Blondin & Ryan, ²⁸ 1999	45 pts ^c	6 mo	All had mean Alb < 3.2 ± 0.4 g/dL	Alb, BUN, morbidity, URR, hosp rate	Decrease in hosp rate ($P < 0.05$), increase in Alb ($P < 0.05$)

(Continued)

Table 2 (Cont'd). Nonrandomized Studies of IDPN

Study	Design	Treatment Duration	No. With PEW	Parameters Measured	Outcome
Cherry, ²⁹ 2002	24 pts; 250 or 500 mL of 10% AA, 250 mL of 50% glucose, 250 mL of 20% fat emulsion	4.3 mo (mean)	All	Alb, dry BW	Increase in dry BW, Alb

Note: Only studies with ≥ 10 total patients are listed. Conversion factors for units: serum creatinine in mg/dL to mmol/L, $\times 88.4$; serum urea nitrogen in mg/dl to mmol/L, $\times 0.357$.

Abbreviations and definitions: AA, amino acids; Alb, serum albumin; BUN, serum or plasma urea nitrogen; BW, body weight; EAA, essential amino acids; GI, gastrointestinal; Hct, hematocrit; Hosp rate, hospitalization rate; IDPN, intradialytic parenteral nutrition; MAMC, midarm muscle circumference; N, nitrogen; NA, not available; NEAA, nonessential amino acids; PEW, protein-energy wasting; pt, patient; SCr, serum creatinine; suppl, supplementation; TSF, triceps skin fold; URR, urea reduction ratio; WBC, white blood cell count.

^aRenAmin, a solution of essential and nonessential amino acids, is manufactured by Baxter (www.baxter.com).

^bPublication not accessible to authors.

^cIncomplete data provided.

unclear how the untreated patients were selected for study or why they did not receive IDPN. IDPN solutions were given for an average of 9 months and provided 50 g of essential amino acids per dialysis session, a 10% or 20% lipid emulsion (200-500 kcal/dialysis session), and an amount of D-glucose that varied by diabetic status. Mortality rates were 36% in IDPN-treated patients and 48% in untreated controls ($P > 0.05$). However, time to death in nonsurvivors was significantly longer in IDPN patients at 16.9 ± 7.9 (SD) versus 7.5 ± 4.2 months ($P < 0.01$).

Foulks²³ reported a nonrandomized study of 72 patients with PEW who were ingesting $< 75\%$ of their recommended diet and failed to respond to dietary counseling. After the start of IDPN therapy, patients were classified as responders if they showed an increase in dry body weight of at least 10% with IDPN or previously low serum albumin or total protein levels increased by 0.5 g/dL with IDPN. At baseline, responders had significantly lower serum albumin (2.2 ± 0.7 [SD] vs 3.0 ± 0.8 g/dL; $P < 0.0001$) and total protein levels (5.3 ± 1.0 vs 6.2 ± 1.3 g/dL; $P < 0.0001$), but similar body weight compared with nonresponders. During the 6 months before IDPN, responders had higher hospitalization rates ($P < 0.0001$). However, during IDPN, 52% of responders were hospitalized compared with 76% of nonresponders ($P < 0.0001$), with the hospitalization rate during IDPN decreasing significantly in only responders. The mortality rate also was significantly lower during IDPN in responders.

In the largest study to date, Chertow et al²¹ retrospectively compared 1,679 maintenance hemodialysis patients who had received IDPN with 22,517 control patients after adjustment for case mix and urea reduction ratios. For patients who had baseline serum albumin levels ≤ 3.3 g/dL, treatment with IDPN, after adjustment for case mix and predialysis serum creatinine levels, was associated with a reduction in the odds ratio of death at 1 year. In contrast, increased 1-year mortality was observed in patients receiving IDPN who had a serum albumin level ≥ 3.5 g/dL. The survival effect of IDPN was stronger in maintenance hemodialysis patients with baseline predialysis serum creatinine concentrations ≤ 8.0 mg/dL, potentially identifying individuals who had more to gain from IDPN.

Hiroshige et al²⁶ studied 28 maintenance hemodialysis patients > 70 years old with a diagnosis of protein-energy malnutrition. All patients were advised to receive IDPN, but 18 patients refused and were managed nutritionally using dietary counseling by a certified dietitian. The other 10 patients received IDPN for 1 year that provided 200 mL of 50% glucose, 200 mL of 20% lipid emulsion, and 200 mL of 7.1% essential amino acids per dialysis session. In this nonrandomized study, baseline nutritional measures in the 2 groups did not differ significantly. During IDPN treatment, there was a significant increase in serum albumin and transferrin levels, total lymphocyte count, body weight, triceps skinfold thickness, and midarm muscle circumference.

Table 3. Randomized Studies of IDPN

Study	Design	Treatment Duration	No. With PEW	Parameters Measured	Outcome
Toigo et al, ³⁰ 1989	11 pts: 26.5 g of modified EAA 10 pts: 24 g of EAA + NEAA	6 mo	None	Nerve conduction velocity, Alb	Decrease in Alb in EAA + NEAA group
Cano et al, ³¹ 1990	12 pts: 0.08 g of N/kg (/HD session) from EAA + NEAA, 1.6 g/kg (/HD session) lipids 14 pts: no intervention	3 mo	All	BW, appetite, MAMC	Increase in calorie (9 kcal/kg/d) and protein intake (0.25 g/kg/d) in IDPN-treated pts
McCann et al, ¹⁴ 1999	19 pts; 70% glucose, 15% AA, 20% lipids	11 wk	NA	Delivered Kt/V, URR	Decrease in delivered Kt/V in pts who received AA-containing IDPN
Navarro et al, ³² 2000	17 pts	3 mo			Positive net AA balance Increase in PCR, Alb, transferrin
Cano et al, ³³ 2006	17 pts: olive oil-based IV lipid emulsion 18 pts: soybean oil-based IV lipid emulsion	5 wk			Both groups showed similar improvement in nutritional status, plasma lipid, oxidative and inflammatory parameters
Cano et al, ³⁴ 2007	89 pts: IDPN 93 pts: control	12 mo	All	Primary end point, all-cause mortality; secondary end points, hosp rate, BW, Karnofsky score, BMI	No difference in hosp rate or mortality between 2 groups

Note: Only clinical trials with ≥ 10 patients are listed.

Abbreviations and definitions: AA, amino acids; Alb, serum albumin; BMI, body mass index; BW, body weight; EAA, essential amino acids; HD, hemodialysis; Hosp rate, hospitalization rate; IDPN, intradialytic parenteral nutrition; IV, intravenous; MAMC, midarm muscle circumference; N, nitrogen; NA, not available; NEAA, nonessential amino acids; PCR, protein catabolic rate; PEW, protein-energy wasting; pt, patient; URR, urea reduction ratio.

The group treated with dietary counseling without IDPN showed a significant decrease in all these parameters. Five patients died in the control group, whereas there were no deaths in IDPN patients ($P < 0.02$). Plasma levels of essential amino acids and some nonessential amino acids increased and 3-methylhistidine levels decreased in IDPN patients; the group not receiving IDPN showed a decrease in plasma essential amino acid levels.

Prospective Randomized Controlled Trials

Some of the larger randomized controlled trials of IDPN are listed in Table 3. In an early study not listed in Table 3, Guarnieri et al³⁶ randomly assigned 18 adults undergoing maintenance hemodialysis to 1 of 3 IDPN treatment groups: essential amino acids, a combination of

essential and nonessential amino acids, or an isocaloric infusion of 5% glucose alone. Patients received these infusions thrice weekly for only 2 months. The IDPN solutions provided very few calories. Most or all of the patients had PEW. The only significant change was an increase in body weight ($P < 0.05$) in patients receiving essential amino acids. No adverse effects were noted during or after the amino acid infusions, except for 1 patient who reported nausea. This same group of investigators later assigned 21 maintenance hemodialysis patients in random order to receive IDPN that provided as its nitrogen source either essential amino acids alone (11 patients) or a mixture of essential and nonessential amino acids (10 patients).³⁰ At baseline, mean serum albumin level was normal, average energy intake was low, and mean body weight

and protein intake were marginally decreased. During IDPN treatment, which was conducted for 6 months, the group given essential plus nonessential amino acids showed a significant decrease in serum albumin levels and nerve conduction velocities and an increase in normalized PNA (nPNA; also referred to as normalized protein catabolic rate [nPCR]). The group given essential amino acids showed an increase in nerve conduction velocities.

In a 12-week intervention study, Cano et al³¹ evaluated 26 patients with PEW who were undergoing maintenance hemodialysis. In the 12 patients receiving IDPN, there was a significant increase in body weight, midarm muscle circumference, serum albumin and prealbumin levels, creatinine appearance, skin test reactivity, plasma leucine level, and apolipoprotein A-I level, whereas none of these values increased in the control group not receiving IDPN. At baseline, individuals assigned to IDPN had nonsignificantly lower baseline values for many of these measurements, possibly contributing to the increase in values during IDPN. Although patients received fat, 1.6 g/kg, and nitrogen, 0.08 g/kg, from essential and nonessential amino acids and glycyl-tyrosine, plasma lipid levels did not change, except for the increase in plasma apolipoprotein A-I level. The authors concluded that this IDPN solution with high fat intake was effective and safe with regard to plasma lipids.

The French Intradialytic Nutrition Evaluation Study (FineS) is the largest and most carefully monitored prospective study of IDPN conducted to date.³⁴ A total of 186 adults aged 18-80 years who were undergoing maintenance hemodialysis for > 6 months were randomly assigned to receive (n = 93) or not receive (n = 93) IDPN at each hemodialysis session for 1 year. Both groups received oral nutritional supplements. To qualify for inclusion in the study, patients had at least 2 of the following indicators of PEW: (1) body mass index < 20 kg/m², (2) body weight loss > 10% within 6 months, (3) serum albumin level < 3.5 g/dL, and (4) serum prealbumin level < 30 mg/dL. Exclusion criteria were < 12 hours of weekly dialysis, single-pool weekly Kt/V < 1.2, parenteral nutrition received within the 3 months preceding the study, severe comorbid conditions that compromise 1-year survival, fasting serum

triglyceride level > 300 mg/dL, and hospitalization at the time of randomization.

Patients were followed up for 2 years, with nutritional intake from all sources and protein-energy status monitored at 0, 3, 6, 12, 18, and 24 months. At months 3, 6, and 12, IDPN provided the equivalent of 6.6 ± 2.6 (SD), 6.4 ± 2.1 , and 6.1 ± 2.2 kcal/kg/d and protein (given as amino acids) of 0.26 ± 0.08 , 0.25 ± 0.09 , and 0.24 ± 0.10 g/kg/d, respectively. This estimate divides the quantity of nutrients given by IDPN thrice weekly during hemodialysis by 7 to estimate the time-averaged daily dose. At 3, 6, and 12 months, oral supplements provided 5.9 ± 2.6 , 5.8 ± 2.5 , and 5.6 ± 2.7 kcal/kg/d and protein of 0.39 ± 0.18 , 0.38 ± 0.18 , and 0.37 ± 0.18 g/kg/d. Intake of nutrients from spontaneous eating, oral food supplements, and IDPN varied from center to center and patient to patient.

During the trial, both groups showed similar improvements in indicators of PEW, hospitalization rates, and mortality (no statistical difference between groups for each outcome). Karnofsky scores did not change from baseline in either group. Strictly speaking, there was no control group to compare the effectiveness of IDPN versus no nutritional support because both groups received oral nutritional supplements. The authors noted that FineS, although the largest randomized prospective trial of IDPN ever conducted, was underpowered to test the hypothesis of whether IDPN with oral nutritional supplements decreases mortality more than IDPN without oral nutritional supplements, with the improvement in nutritional status observed in both treatment groups potentially reflecting informative censoring due to death and/or drop out.

Does IDPN Improve Nutritional Status?

Some physicians questioned whether hemodialysis would remove an excessive amount of the amino acids infused during IDPN. Wolfson et al³⁷ examined this question in 8 clinically stable maintenance hemodialysis patients. Each patient was studied twice, while fasting and while they underwent their typical 5-hour hemodialysis treatments using low-flux dialyzer membranes. During 1 hemodialysis treatment, they received an infusion of 800 mL of normal saline, and during the other hemodialysis treatment, they received an infusion of an equal volume containing 39.5 g

of essential and nonessential amino acids and 200 g of D-glucose monohydrate. The order of administration of the 2 infusions with hemodialysis was determined randomly. Free amino acid losses into dialysate were 8.2 ± 3.1 g during the normal saline infusion and increased only slightly with the infusion of essential and nonessential amino acids and glucose to 12.6 ± 3.6 g, indicating that 79% of infused amino acids were retained. When patients underwent hemodialysis with the infusion of essential and nonessential amino acids and glucose, plasma amino acid concentrations increased by 20%, whereas during saline administration, plasma amino acid levels decreased by 33%.³⁷ If one compares the amino acids lost into dialysate with the magnitude of the decrease in plasma (and, hence, extracellular) amino acid levels, it is apparent that most amino acid losses in these fasting patients who did not receive IDPN came from the intracellular compartment. It is possible that these amino acid losses transiently alter cellular protein metabolism and may engender a catabolic state (discussed later).

Does IDPN Affect Protein Synthesis or Degradation?

Ikizler et al³⁸ and Pupim et al³⁹ examined this question in several studies. They first investigated the acute effects of hemodialysis on protein turnover in postabsorptive patients.³⁸ Total-body protein and forearm protein synthesis and degradation were measured in 11 clinically stable maintenance hemodialysis patients before, during, and for 2 hours after undergoing maintenance hemodialysis.³⁸ Patients fasted for at least 10 hours before the initiation of each study. They received a constant infusion of L-(1-¹³C) leucine and L-(ring-²H₅) phenylalanine starting 2 hours before the hemodialysis session and lasting until 2 hours afterward. During hemodialysis, total-body protein and forearm muscle protein degradation increased significantly and remained increased after dialysis. Protein synthesis in the forearm, but not the total body, also increased during hemodialysis, and protein synthesis in both compartments was increased postdialysis compared with baseline levels. Total-body net protein balance became significantly more negative during hemodialysis; during the postdialysis period, total-body protein balance decreased sig-

nificantly, but was still significantly more negative than baseline values. Net protein loss in the forearm also increased significantly during hemodialysis, but decreased to baseline levels during the postdialysis period.

These investigators then examined the acute metabolic response to IDPN.³⁹ Seven clinically stable patients who underwent maintenance hemodialysis with a single-pool Kt/V of at least 1.4 and no evidence of malnutrition or inflammation were studied during two 4-hour hemodialysis sessions, once while receiving IDPN and once while they were not. Each IDPN provided 300 mL of 15% essential and nonessential amino acids, 150 mL of 50% glucose, and 150 mL of 20% lipids. The order of the 2 treatments was determined randomly, and patients fasted for at least 10 hours before the initiation of each study. Patients again received a constant infusion of L-(1-¹³C) leucine and L-(ring-²H₅) phenylalanine starting 2 hours before the hemodialysis session until 2 hours afterward. During hemodialysis without IDPN in these fasting patients, net total-body protein and forearm protein balance were negative. During hemodialysis with IDPN compared with hemodialysis without IDPN, total-body protein and forearm protein synthesis were more positive and total-body protein degradation was decreased. Forearm muscle protein degradation was greater with IDPN, but not significantly so. Net total-body protein balance and forearm protein balance were substantially more positive with IDPN than without IDPN. The anabolic state induced by IDPN abated during the 2-hour period immediately after hemodialysis when intravenous nutrition was no longer given. These acute studies do not indicate whether the protein accrued during IDPN is retained throughout the subsequent interdialytic interval. Moreover, if patients received IDPN consistently, it is not known whether this anabolic response would continue, and if so, at what magnitude.

In a subsequent report, Pupim et al⁴⁰ compared the response of IDPN with intradialytic oral nutrition and no nutritional support during hemodialysis in 8 clinically stable maintenance hemodialysis patients. The oral nutrition provided 57 g of amino acids, 48 g of lipids, 109 g of carbohydrates, and 1,090 kcal and was administered in 3 equal feedings at 30, 90, and 150 minutes after the onset of the 4-hour hemodialy-

sis treatment. IDPN provided a slightly different nutritional mix with 59 g of amino acids, 26 g of lipids, 197 g of carbohydrates, and 752 kcal and was administered starting 30 minutes after the onset of the hemodialysis treatment until its termination. Results showed that with both IDPN and oral nutrition compared with no nutritional treatment, total-body protein synthesis was significantly increased, total-body protein degradation tended to be decreased, and net protein balance was significantly and dramatically more positive. During the 2 hours postdialysis, total-body protein synthesis was increased in only the oral nutrition patients; there were no differences between the 2 groups in proteolysis, but net total-body protein balance was significantly more negative in the oral nutrition group than in the IDPN or no nutritional treatment groups. In the forearm during IDPN and oral nutrition and for 2 hours postdialysis compared with no nutritional treatment, protein synthesis tended to be increased, although these trends were not significantly different. Forearm protein degradation was not different among the 3 groups during IDPN or oral nutrition or for 2 hours afterward. However, net forearm protein balance was significantly more positive during both IDPN and oral nutrition. During the 2 hours postdialysis, forearm protein balance was significantly more positive in the oral nutrition group compared with patients receiving IDPN or no nutritional treatment.

INDICATIONS FOR IDPN

Indications for IDPN are difficult to define because the benefits of this treatment to maintenance hemodialysis patients have never been clearly shown in randomized controlled clinical trials. There is a general consensus that patients who can eat or ingest food supplements should be nourished using these methods.³⁴ It is the opinion of the authors that people who cannot maintain adequate protein-energy status by ingestion of foods and nutritional supplements should be considered for tube feeding, which is effective, relatively safe, inexpensive, and more physiologic compared with intravenous feeding. Regrettably, many patients and physicians are reluctant to accept this nutritional therapy.

OBTAINING IDPN IN THE UNITED STATES

Patients with dual coverage with Medicare and Medicaid incur no out-of-pocket expenses for receiving IDPN, assuming that their plans will cover IDPN. For Medicaid-only patients, approval of IDPN is not uniform, although many states will pay for IDPN. For outpatients who have Medicare, Medicare Part D oversees reimbursement for IDPN, with the requirement that serum albumin level is ≤ 3.4 g/dL on a 3-month average or the patient has had a $> 5\%$ weight loss during 3 months and there have been attempts at oral nutrition and counseling. Some patients who have Medicare Part D or whose prescription medications are covered by private insurers have uneven coverage, and even among insurers who provide coverage, some costs may be required to be borne by the patient. IDPN generally is not approved by most health maintenance organizations. Pentec (www.pentechealth.com) and Nutrepletion (www.nutrepletion.com) are the 2 largest suppliers of IDPN in the United States. For hospitalized patients, IDPN is covered under Medicare part A.^{41,42} Both Medicare and most private insurance carriers recommend discontinuation of IDPN if serum albumin level is > 3.8 g/dL for > 3 consecutive months.

CONCLUSION

Notwithstanding the lack of data that definitively show either effectiveness or a lack of benefit of IDPN, intuitively it would seem that there is a role for IDPN in the nutritional support of maintenance hemodialysis patients. IDPN most commonly is recommended for patients who either have or are at high risk of developing PEW and for whom no other apparent methods for routine nutritional or non-nutritional treatment of their wasting have succeeded (eg, dietary counseling, psychotherapy, food supplements, attempts at tube feeding, and treatment of catabolic infections, other inflammatory conditions, or acidemia). Because IDPN as the sole source of nutrition given thrice weekly almost certainly will not maintain good protein-energy nutritional status or correct PEW, IDPN should be used only in concert with other sources of nutritional intake. These other sources of nutritional intake probably should provide at least 50%-80% of the patient's protein and energy needs. Occasionally,

a patient's nutritional intake is so low that it turns out not to be possible to nourish the patient using any oral or enteral technique. Such individuals may require total parenteral nutrition.

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