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Evidence Brief: Use of Intradialytic Parenteral Nutrition (IDPN) to Treat Malnutrition in Hemodialysis Patients

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PREFACE

The VA Evidence-based Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of particular importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. QUERI provides funding for four ESP Centers, and each Center has an active University affiliation. Center Directors are recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Centers. The ESP is governed by a Steering Committee comprised of participants from VHA Policy, Program, and Operations Offices, VISN leadership, field-based investigators, and others as designated appropriate by QUERI/HSR&D.

The ESP Centers generate evidence syntheses on important clinical practice topics. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The ESP disseminates these reports throughout VA and in the published literature; some evidence syntheses have informed the clinical guidelines of large professional organizations.

The ESP Coordinating Center (ESP CC), located in Portland, Oregon, was created in 2009 to expand the capacity of QUERI/HSR&D and is charged with oversight of national ESP program operations, program development and evaluation, and dissemination efforts. The ESP CC establishes standard operating procedures for the production of evidence synthesis reports; facilitates a national topic nomination, prioritization, and selection process; manages the research portfolio of each Center; facilitates editorial review processes; ensures methodological consistency and quality of products; produces “rapid response evidence briefs” at the request of VHA senior leadership; collaborates with HSR&D Center for Information Dissemination and Education Resources (CIDER) to develop a national dissemination strategy for all ESP products; and interfaces with stakeholders to effectively engage the program.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP CC Program Manager, at Nicole.Floyd@va.gov.

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EXECUTIVE SUMMARY

Chronic kidney disease (CKD) is a major public health concern, affecting 14.8% of US adults in 2011-2014, and was the 9th leading cause of death in the US in 2016. Progression of CKD leads to end-stage renal disease (ESRD), a total and permanent failure of kidney function requiring kidney transplant or maintenance hemodialysis. More than half (63.1%) of all prevalent ESRD cases receive hemodialysis, and despite its advantages, hemodialysis patients often suffer poor health outcomes, including substantially worse survival rates than the general population. Malnutrition affects 20-60% of hemodialysis patients and is one of the strongest predictors of mortality and morbidity in this population. A range of therapies exist for treatment of malnutrition in hemodialysis patients, and guidelines recommend nutritional counseling and oral nutrition supplements as first-line treatment for malnutrition in hemodialysis patients. If dietary counseling and oral nutrition supplements do not improve nutrition, guidelines recommend enteral tube feeding.

Parenteral nutrition is another option for patients who cannot tolerate oral or enteral routes, due to malfunction of the GI tract, chronic nausea, vomiting, or anorexia, or for patients with previous failed attempts with oral or enteral routes. Intradialytic parenteral nutrition (IDPN) is a form of partial parenteral nutrition administered during regularly scheduled dialysis sessions. Proponents of IDPN state that it is a safe and convenient way to supplement nutrient intake during a time when patients are already receiving treatment. However, IDPN therapy has a risk of harms (infection, fluid overload, chemical imbalance, *etc*) and increased costs compared to other therapies. Guidelines recommend use of IDPN only after nutritional counseling, oral, and/or enteral routes have been tried. However, barriers to following treatment recommendations (taste of oral supplements, nausea, lack of support, concerns about tube feeding, *etc*), ease of use, and potential profit have led to earlier pursuit of IDPN.

Background

The ESP Coordinating Center (ESP CC) is responding to a request from the Veterans Affairs Renal Field Advisory Committee for an evidence brief on the use of Intradialytic Parenteral Nutrition (IDPN) for the treatment of malnutrition among hemodialysis patients. Findings from this evidence brief will be used to develop recommendations on the use of IDPN in the treatment of Veteran hemodialysis patients with malnutrition.

Methods

To identify studies, we searched MEDLINE®, Cochrane Database of Systematic reviews, Cochrane Central Register of Controlled Trials, and other sources up to October 2017. We used prespecified criteria for study selection, data abstraction, and rating internal validity and strength of the evidence. See our PROSPERO protocol for our full methods.

IDPN does not appear to improve patient health or clinically important nutritional outcomes compared to the standard and recommended treatments of oral supplementation or dietary counseling (Executive Summary Table). For IDPN to best demonstrate a clinically important benefit over recommended treatment, ideally (1) it would significantly reduce the risk of mortality, (2) it would improve the functional status and quality of life of survivors, and (3) these benefits could be attributed specifically to IDPN and not differences between intervention and control groups in concomitant treatments, disease state, level of malnutrition, or other potentially confounding factors. However, primarily because detail about control group treatment regimens is inadequate to determine applicability to current practice, current evidence does not reliably demonstrate such benefits for IDPN. For example, in one of the most recent RCTs that compared IDPN to "standardized nutritional counseling", IDPN increased rates of a 15% improvement in serum

prealbumin at 4 weeks compared to control (41% IDPN vs 20.5% control, P = .0415). However, the meaningfulness and reliability of this finding is unclear because (1) the RCT lacked adequate information to determine what kind of intervention (if any) the control group received, and (2) although the 15% was noted to be a "relevant" increase, clinical justification for this threshold was not provided, data were not provided for this threshold at the end of the study (16 weeks), and this threshold was not pre-specified in the protocol. Compared with oral supplements, in the only RCT with an adequately described control group treatment regimen, IDPN did not improve mortality, hospitalization, or quality of life. Additionally, compared with "usual care", although studies demonstrated some benefits for IDPN, such as a mortality benefit seen for patients with lower baseline serum albumin levels (≤ 3.3 g/dL), inadequate detail about the control group treatment regimen similarly limits the usefulness of this evidence, and the clinical importance of the nutritional improvements is unclear as they were based on changes in mean scores and not clinically relevant thresholds. No study has compared IDPN to enteral tube feeding. Limited data are available regarding the adverse effects of IDPN. Commonly reported adverse events, including nausea, muscle pain, infections, and procedural complications, may be common in this patient population due to disease severity and comorbidities, and no differences between IDPN and control groups were reported.

Despite existing guidelines recommending IDPN only for hemodialysis patients with refractory malnutrition, IDPN is commonly being requested or used prior to other treatment options. However, current evidence is inadequate to demonstrate a benefit for IDPN over recommended treatments. Although IDPN has not been explicitly studied in hemodialysis patients who have failed adequate trials of or are unable to receive dietary counseling, oral, and/or enteral tube feeding due to malfunctioning GI tract or other issues, since evidence – albeit limited – has not raised concerns about IDPN safety, we agree with existing guidelines that it appears reasonable to consider use of IDPN in this population. Future research or coverage with evidence development efforts should focus on comparing IDPN with enteral tube feeding, as well as aiming for more clinically relevant outcome assessment, larger sample sizes, longer follow-up duration, and better-characterized control groups.

Executive Summary Table. Effect of IDPN on Patient Health and Nutritional Outcomes

	Patient Health Outcomes		Nutritional Indicators
	IDPN Compared to Oral Supplements		
≈	No improvement in mortality, hospitalization or quality of life ***Evidence:*** 1 fair-quality RCT[1]	↓↑	Variable effect with no improvement in nutritional indicators except serum albumin in a single study ***Evidence:*** 2 fair-quality RCTs[1,2] and 1 fair-quality cohort study[3]
	IDPN Compared to Dietary Counseling		
≈	No improvement in mortality, hospitalization, or quality of life ***Evidence:*** 1 fair-quality RCT[4]	↓↑	Variable effects on serum prealbumin No improvement in serum albumin or SGA ***Evidence:*** 1 fair-quality RCT[4]
	*IDPN Compared to Usual Care**		
↓↑	Variable effect on mortality; effect differs by baseline serum albumin level ***Evidence:*** 3 fair-quality cohort studies[5-7]	↓↑	Variable effect with improvement in at least one nutritional indicator ***Evidence:*** 2 fair-quality RCTs[8,9] and 3 fair-quality cohort studies[5,7,10]

≈ No improvement in quality of life
Evidence: 1 fair-quality RCT[9]

≈ No difference in outcomes; ↓↑ mixed effects on outcomes
Patient Health Outcomes=mortality, hospitalization, or quality of life/functional impairment
Nutritional Indicators=serum albumin, serum prealbumin, subjective global assessment, malnutrition inflammation score, body mass index, body weight, mid-arm circumference, triceps-skinfold thickness
*Usual care=following regular protocol of treatment; may include dietary counseling or oral supplements based on patient condition and physician recommendation

EVIDENCE BRIEF

INTRODUCTION

PURPOSE

The ESP Coordinating Center (ESP CC) is responding to a request from the Veterans Affairs Renal Field Advisory Committee for an evidence brief on the use of Intradialytic Parenteral Nutrition (IDPN) for the treatment of malnutrition among hemodialysis patients. Findings from this evidence brief will be used to develop recommendations on the use of IDPN in the treatment of Veteran hemodialysis patients with malnutrition.

BACKGROUND

Chronic kidney disease (CKD) is a major public health concern, affecting 14.8% of US adults in 2011-2014,[11] and was the 9th leading cause of death in the US in 2016.[12] The kidneys are responsible for filtering waste and extra fluid out of the blood stream. CKD is a gradual loss of this kidney function and can be caused by a wide range of factors, including diabetes, high blood pressure, kidney disease, and recurrent kidney infection. The Veteran population has high rates of certain comorbidities linked to CKD, including diabetes mellitus and hypertension. Thus, the prevalence of CKD in Veterans is estimated to be about 47%, substantially higher than in the general population.[13,14] Additionally, VHA patients have a lower rate of kidney transplantation and are more likely to die on the transplant waitlist compared to those with private insurance.[15] Progression of CKD can ultimately lead to end-stage renal disease (ESRD), a total and permanent failure of kidney function. When the kidneys can no longer remove waste and extra fluid from the blood stream, this can lead to swelling, exhaustion, seizures, coma, and ultimately death.[16] In 2014, the unadjusted prevalence of ESRD was 2,067 per million, an increase of 54.1% since 2000.[11] Patients with ESRD require kidney transplant or dialysis treatment to replace kidney function. The most common treatment for ESRD is hemodialysis, with more than half (63.1%) of all prevalent ESRD cases receiving hemodialysis. Hemodialysis filters a patient's blood outside of the body through a dialysis machine. Although hemodialysis is not a cure for kidney failure, it ameliorates the detrimental effects of kidney failure, and can greatly extend life expectancy.[17] Despite its advantages, hemodialysis patients often suffer poor health outcomes, including substantially worse survival than the general population (57% 3-year survival among hemodialysis patients vs 92% 3-year survival among age- and sex-matched general population) and higher mortality rates than kidney transplant patients (166 deaths vs 30 deaths per 1,000 patient years).[11]

One of the strongest predictors of morbidity and mortality among hemodialysis patients is malnutrition, affecting 20-60% of patients.[18-20] Malnutrition refers to deficiencies or adverse changes in nutritional or energy intake, and can lead to loss of body mass, poor wound healing, and organ failure. In the general population, malnutrition is usually caused by inadequate intake of energy or nutrients.[21] However, in hemodialysis patients, malnutrition is the result of a complex interplay between many factors, including inadequate food intake, chronic inflammation, blood loss, comorbid diseases, dietary restrictions, and renal and dialysis insufficiency.[20,22-24] The interaction between these factors and disease state results in losses in protein and energy stores and metabolic alterations, termed protein-energy wasting (PEW) or protein-energy malnutrition (PEM).[20,24] Clinical criteria to define malnutrition vary, and have

changed over time. Current guidelines for the treatment of malnutrition in hemodialysis patients (see Supplemental Materials Appendix A) generally include one or more clinical, anthropometric, or biochemical measures, and the European Society of Clinical Nutrition and Metabolism (ESPEN) recently provided a minimum set of criteria for diagnosing malnutrition (Figure 1).[25] One of the more notable changes in the recent ESPEN criteria is that serum protein levels (*eg*, serum albumin) are no longer included as a preferred marker of nutritional status, as they can commonly be reduced due to inflammation, and not necessarily malnutrition.[25]

Figure 1. Criteria for Diagnosing Malnutrition

Guidelines for Treatment of Malnutrition in Hemodialysis Patients

≥ 1 of the following characteristics*:

- Decreased serum albumin (< 3.4-3.8 g/dL)
- Weight loss (> 10% of body weight)
- Decreased dietary intake
- Low subjective global assessment score (SGA)

ESPEN Minimum Criteria

- BMI < 18.5 kg/m2

OR

- Unintentional weight loss (> 10% over indefinite amount of time or > 5% over the last 3 months)

In addition to:

- BMI < 20 kg/m2 if over 70 years of age, or < 22 kg/m2 if ≥ 70 years of age OR
- Fat free mass index < 15 and < 17 kg/m2 in men and women, respectively

*Specific characteristic for individual guidelines vary (see Supplemental Materials Appendix A for detailed criteria)

A range of therapies exist for treatment of malnutrition in hemodialysis patients. Guidelines recommend nutritional counseling as a first-line treatment for malnutrition in hemodialysis (see Supplemental Materials Appendix A). Nutritional counseling generally involves working with a registered dietician or nutritionist to assess patient- and disease-specific nutrient and energy needs, monitor intake and indicators of nutritional status, determine deficiencies, and educate patients on ways to improve or increase total energy or specific nutrient intake. Meal trays may also be provided during dialysis sessions. However, this is not commonly practiced in the US due to concerns of postprandial hypotension, choking and infection risks, and control of diabetes and phosphorus levels.[26] Guidelines commonly recommend oral supplementation to aide in improving nutrient and energy intake, often in conjunction with nutritional counseling, if patients are unable to meet energy and nutrient requirements through eating meals. Oral supplements typically include liquids, bars, or shakes, which may be standard nutritional supplements (*eg*, ZonePerfect®, Ensure®), or may be designed for patients on dialysis to meet specific nutritional needs and dietary restrictions (*eg*, Nepro®).[27,28] Oral supplements can be provided during dialysis sessions (intradialytic oral supplementation) or more frequently outside of dialysis sessions.[29] Oral nutrition supplementation has been shown to improve nutritional indicators (*ie*, serum albumin), but there are limited data on long-term clinical outcomes.[27] Common barriers to compliance and satisfaction with dietary counseling and oral nutrition supplements can include taste, nausea, diarrhea, and lack of support (*ie*, difficulty timing meals on dialysis days, limited food access, support for food preparation, finding foods/supplements meeting dietary restrictions, *etc*).

When dietary counseling and oral nutrition do not adequately improve nutritional status, guidelines recommend enteral tube feeding. This is when a small, flexible tube is surgically or endoscopically inserted into the nose (for short-term needs, generally < 3 months) or through the abdomen (for longer-term needs) to feed the gastrointestinal (GI) tract directly.[30,31] The frequency and composition of the feedings is prescribed by the patient's clinical and nutritional team and can be modified based on changes in nutritional status indicators to provide more or less of the required nutrition. Patients are encouraged to continue eating with a feeding tube in place, and feeding and maintenance of the tube can be done by the patient or caregiver at home. Although patients may be concerned about the appearance of the tube and the logistics of feeding and maintaining the tube at home, nutritionists particularly recommend oral and enteral supplementation because they maintain the usual physiological mechanisms of the GI tract.

Parenteral nutrition (PN) is another option for patients who cannot tolerate oral or enteral tube routes, due to malfunction of the GI tract, chronic nausea, vomiting, or anorexia, or for patients with previous failed attempts with oral and/or enteral tube routes. PN is the infusion of an intravenous nutritional formula into the blood stream, and is commonly used among hospitalized patients.[32] Intradialytic PN (IDPN) is a form of partial parenteral nutrition administered during regularly scheduled dialysis sessions as a supplement (commonly 3 times per week), and requires the patient to get some of their nutrients orally outside of dialysis time.[29,33-35] IDPN often consists of a mixture of amino acids, glucose, and lipids, which may be purchased as a commercially available standardized multi-chamber PN solution (*eg*, Kabiven®[36] or Clinimix®[37]) or may be compounded directly by hospital- or clinic-associated pharmacies. Commercially available standardized solutions may be being labor- and cost-saving compared to pharmacy compounding,[38] but the trade-off is that they cannot be tailored to meet individual patient's unique nutritional needs.

The estimated cost of IDPN therapy is ~$300/day per patient, compared to about $1 for each bar or shake of standard nutritional supplement (ZonePerfect®[39], Ensure®[40]), or $2-4 per can of disease-specific oral supplement (Nepro®[41]). Many insurers, including Medicare, Priority Health, and Blue Cross Blue Shield, typically only cover IDPN under specific eligibility criteria (*eg*, ≥ 10% sustained weight loss for at least 3 months, serum albumin ≤ 3.4 g/dL, AND failure to respond to oral or enteral nutrition treatment) (see Supplemental Materials Appendix B for full details). The current (2013) VHA Nutrition Therapy Handbook does not include guidelines for provision or coverage of IDPN, and use within VHA clinics and approval of requests from outside clinics varies among VHA sites.

Despite existing guidelines recommending IDPN only for hemodialysis patients with refractory malnutrition, IDPN is commonly being requested or used prior to other treatment options. For example, the VHA receives requests from community providers for IDPN for patients who have not tried oral or enteral tube nutrition therapies. These requests most commonly come from Fresenius and DaVita, which are for-profit companies that treated the largest percentage (69%) of hemodialysis patients in the US in 2014.[42] Interest in earlier initiation of IDPN may be due to multiple factors, including the barriers to oral or enteral tube nutrition described above, IDPN's non-invasive and passive nature, ease of use, profit, and/or clinical staffing (*eg*, lack of onsite nephrologists or dieticians). Proponents of IDPN state that it is a safe and convenient way to supplement nutrient intake during a time when patients are already receiving treatment. However, IDPN therapy has a potential for risk of harms (infection, fluid overload, chemical imbalance, hyperglycemia, *etc*) and increased costs compared to other therapies.[20,43]

Due to its higher cost, initiating IDPN prior to other treatment options would ideally be supported by improved patient health outcomes and nutritional status compared to other therapies. In hemodialysis patients, decreased serum albumin (< 3.5-4.0 g/dL) and prealbumin (< 20-30 mg/dL) levels are often cited as the strongest predictors of poor health outcome, including mortality.[1,18,19,44-46] However, more recently, protein levels are not recommended in the screening and outcome assessment of malnutrition.[25] Single nutritional indicators may be low for various reasons, including inflammation or stress, and thus cannot be used alone to assess overall nutrition status.[25] Clinical response to protein administration also may vary depending upon inflammation, oral intake, and the amount of protein in IDPN (which varies amongst IDPN solutions). Additionally, statistically significant *mean* improvements in biochemical markers do not always translate into clinically significant benefits. Therefore, full evaluation of IDPN's benefit-risk profile would ideally include achievement of a clinically-relevant improvement in *multiple* markers of nutritional status (biochemical, weight status and change, SGA score, *etc*), as well as improvements in quality of life and/or mortality without increasing the risk of important harms.

The most recent systematic review from 2010 concluded that data at that time were insufficient to definitively determine the benefit of IDPN.[47] However, since 2010, 3 new randomized controlled trials have emerged. The objective of this evidence brief is to synthesize the evidence regarding the effectiveness, harms, and cost-effectiveness of using intradialytic parenteral nutrition (IDPN) in hemodialysis patients with malnutrition.

KEY QUESTIONS

Key Question 1: What is the effectiveness of IDPN for the treatment of malnutrition in hemodialysis patients?

Key Question 2: What are the potential adverse effects of using IDPN for the treatment of malnutrition in hemodialysis patients?

Key Question 3: What is the cost-effectiveness of using IDPN for the treatment of malnutrition in hemodialysis patients?

Key Question 4: Do the effectiveness and potential adverse effects of IDPN differ per patient characteristics (*eg*, patient demographics, comorbidities, disease severity)?

ELIGIBILITY CRITERIA

The ESP included studies that met the following criteria:

- ***P****opulation*: Hemodialysis patients
- ***I****ntervention*: Intradialytic parenteral nutrition (IDPN)
- ***C****omparator*: Any other nutritional supplementation
- ***O****utcomes*:

- Clinically relevant improvement in individual indicators of nutrition status (*eg*, body weight, arm-muscle circumference, triceps-skinfold thickness, serum albumin, (*ie*, percent of patients reaching pre-specified threshold)), global nutrition status (*eg*, subjective global assessment, malnutrition inflammation score), mortality, morbidity, hospitalization, quality of life, cost-effectiveness

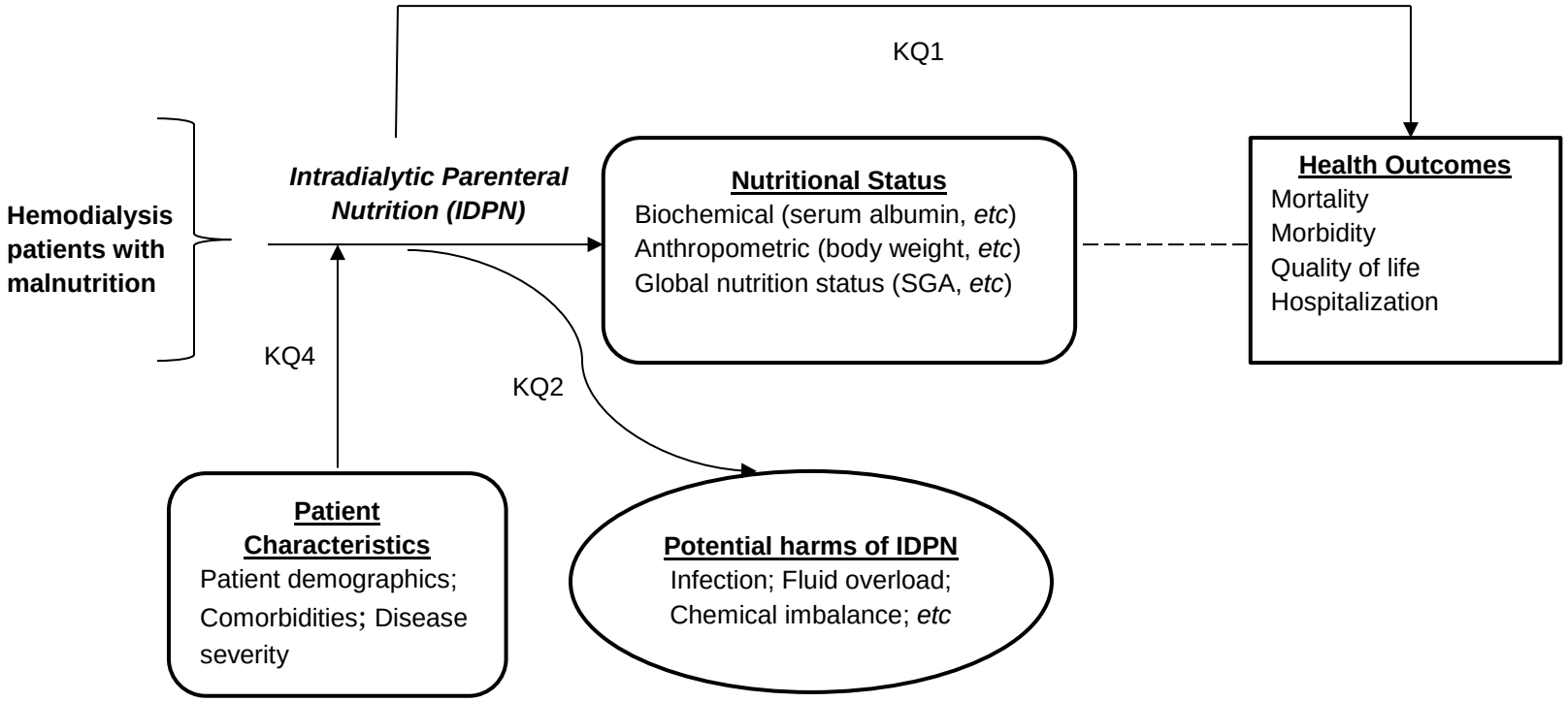
- Harms*:* Any (*eg*, unsafe increases in serum triglycerides, nausea, hypoglycemia, infections)

- ***T****iming:* Any
- ***S****etting:* Any
- ***S****tudy design*: Any, but may prioritize to accommodate timeline using a best-evidence approach

ANALYTIC FRAMEWORK

The analytic framework below (Figure 2) illustrates the Population, Interventions, Comparators, Outcomes, Timing, Setting, and Study design (PICOTSS) of interest that guided this review and their relationship to the key questions. This evidence brief evaluates the link between IDPN, health, and clinically significant outcomes (Key Question 1) and potential risks (Key Question 2). Key Question 4 examines whether the benefits and/or risks of IDPN differ per patient characteristics (eg, patient demographics, comorbidities, disease severity). Key Question 3 examines the cost-effectiveness of IDPN and is not included in the analytic framework.

Figure 2. Analytic Framework of IDPN for Malnutrition in Hemodialysis Patients

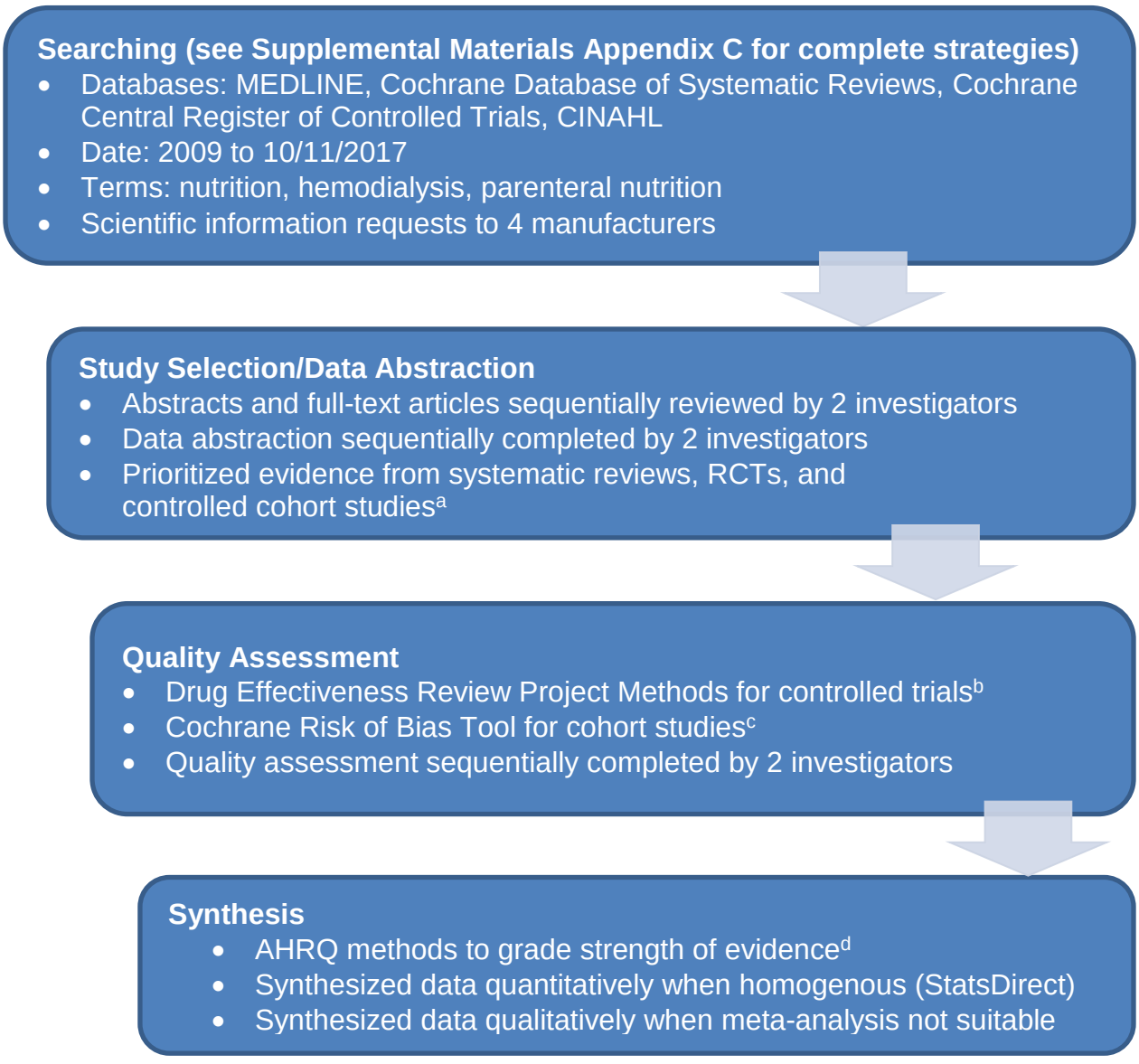


SGA=Subjective Global Assessment

METHODS

We followed the steps in the systematic review process outlined below. The complete description of our methods can be found on the PROSPERO international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO/; registration number CRD42017074001). A draft version of this report was reviewed by peer reviewers as well as clinical leadership (Supplemental Materials Appendix F).

Figure 3. Review Methods



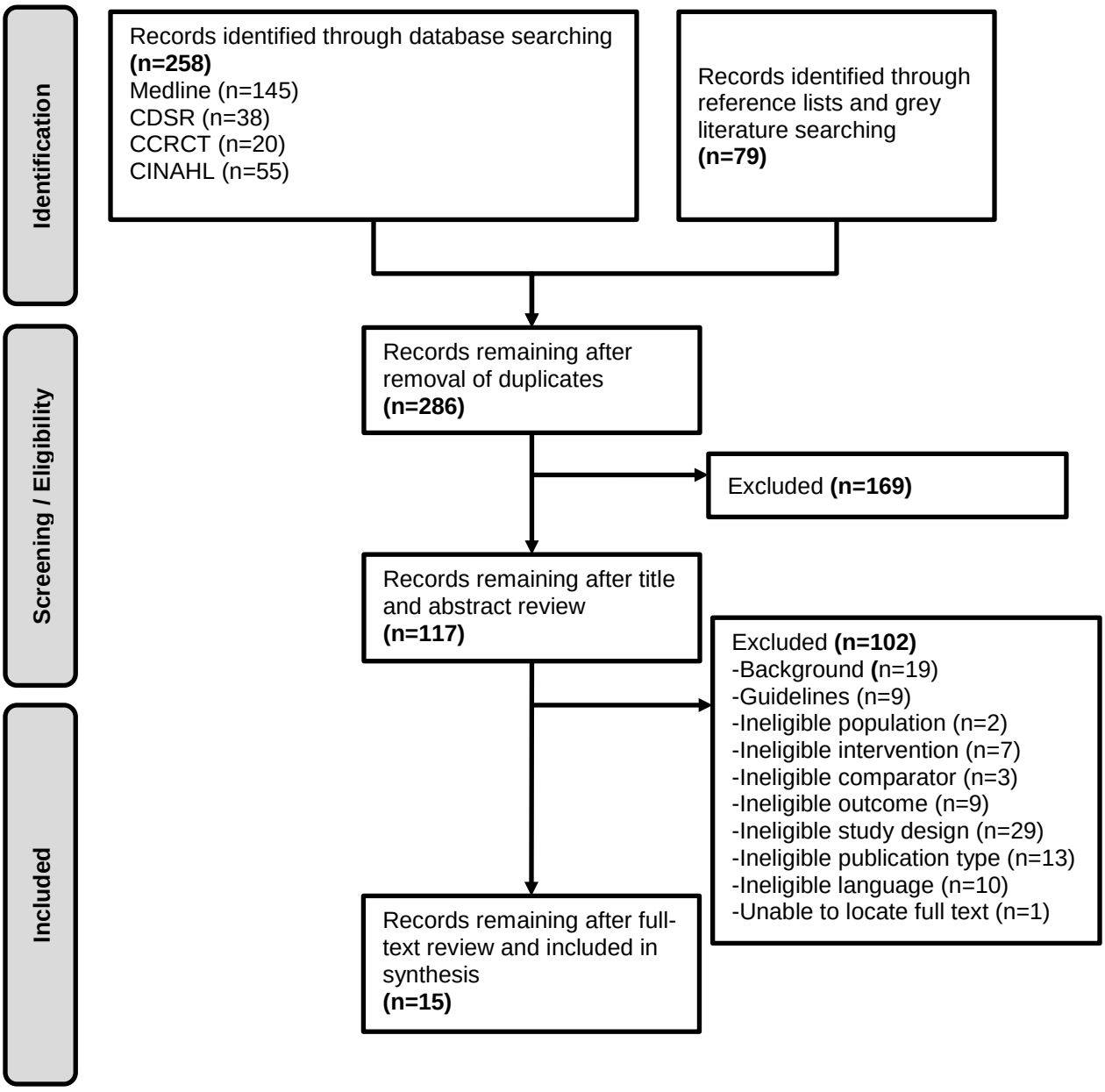
a: Effective Practice and Organization of Care. What study designs should be included in an EPOC review? 2013. **b:** McDonagh, et al. Methods for the drug effectiveness review project. *BMC Med Res Methodol*. 2012. **c:** Sterne J, et al. A Cochrane risk of bias assessment tool: For non-randomized studies of interventions (ACROBAT-NRSI). 2014. **d:** Berkman, et al. Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Agency for Healthcare Research and Quality;2013.

RESULTS

LITERATURE FLOW

The literature flow diagram (Figure 4) summarizes the results of the search and study selection processes (see Appendix D in supplemental materials for full list of excluded studies).

Figure 4. Literature Flowchart



Our search identified 286 unique, potentially relevant articles. We included 5 RCTs,[1,2,4,8,9] 6 cohort studies,[3,5-7,10,48] and 3 systematic reviews.[27,47,49] The 3 systematic reviews did not include formal assessment of individual study quality,[47,49] or did not find any studies for the key question relating to IDPN,[27] and were used only to identify relevant primary studies. We did not identify any comparative studies assessing cost-effectiveness outcomes, and to fill this gap we included one non-comparative before-after study reporting cost-effectiveness.[50]

Table 1 summarizes characteristics of the included RCT and cohort studies (see Supplemental Materials Appendix E for full evidence tables). Except for one large retrospective cohort,[6] most studies were small (sample size range 12-196) with follow-up ranging from 12 weeks to 2 years. Mean patient age was 65 years (range 37 to 80) with an even distribution of male to female patients (mean 50% male). All but 3 studies[5,6,48] were outside of the US, and no studies were specifically in a VA population. Patients were most often on chronic hemodialysis, with at least 6 months on dialysis prior to inclusion in the study. IDPN treatment varied among studies and was often ill-described. The majority of IDPN were standard solutions, but were not purchased premixed. Two studies[1,4] tailored IDPN solutions to patient characteristics. The most common comparison was to "usual recommended diet", but limited information was given on the details of the diet or if any nutritional counseling was provided. No studies compared IDPN to enteral tube nutrition support. Baseline nutritional status was commonly reported as serum albumin (mean=3.77 g/dL (range 3.02 to 3.8 g/dL)) or BMI (range 19.2 to 23.4 kg/m^2), and the criteria for malnutrition varied across studies, with most utilizing serum albumin of < 3.5 g/dL or < 4.0 g/dL along with at least one other predictor of malnutrition (weight loss, BMI, nutritional score or assessment, *etc*). All but 3 studies[3,7,48] were rated as fair quality, with common methodological limitations including unclear or high levels of nonadherence (*eg*, 19-26% discontinued oral supplementation and 24% discontinued IDPN[1]), unclear or between-group differences in attrition (*eg*, 17% control vs 0% IDPN[2]) among RCTs, lack of information about criteria for inclusion and exclusion of patients, and unclear handling of missing data. Three poor-quality studies had the additional methodological limitation of unadjusted baseline differences between intervention and control groups. We sent requests for scientific information to 4 commercial dialysis providers and/or IDPN manufacturers to identify additional published, unpublished, and supplemental data on published studies. We received responses from 2 dialysis providers and/or IDPN manufacturers, but no new material was identified.

Table 1. Characteristics of Included RCTs and Cohorts

Author, Year N	Study Design Follow-up	Mean age % male	Baseline mean SA (g/dL)	Baseline mean BMI/BW	Intervention	Comparator
Cano, 1990[8] N= 26	RCT 12 weeks	58 years 58% male	3.7	% BW: 88.8	IDPN 3x/week	Usual recommended diet
Cano, 2007 FineS[1] N=186	RCT 2 years	68 years 47% male	3.16	BMI: 22.8	IDPN + oral Per usual dialysis	Oral sup.
Capelli,1994[5] N=81	Retrospective Cohort 1 year	60 years 51% male	3.02	NR	IDPN 3x/week	Usual recommended diet +/- oral sup.

Chertow,1994[6] N=24,196	Retrospective Cohort 1 year	58 years 50% male	3.74	NR	IDPN Details NR	Usual recommended diet
Hiroshige,1998[7] N=28	Prospective cohort 6 months	77 years 57% male	3.41	BMI: 19.2	IDPN 3x/week	Usual recommended diet
Joannidis, 2008[10] N=12	Prospective cohort 6 months	80 years 50% male	3.57	BMI: 22.4	IDPN Per usual dialysis	Usual recommended diet
Liu, 2016[2] N=32	RCT 9 months	72 years 44% male	3.74	BMI: 21.4	AA+50% G OR 50% G 3x/week	Oral sup. + nutritional counseling
Marsen,2017[4] N=107	RCT 28 weeks	74 years 47% male	3.44	BMI: 22.6	IDPN 3x/week	Nutrition counseling
Oguz, 2001[3] N=20	Prospective cohort 4 months	NR NR	3.8	BMI: 23.4	AA only 3x/week	Oral amino acids + calcium
Piraino, 1981[48] N=46	Prospective cohort 20 weeks	NR NR	NR	NR	EAA + NEAA + G OR EAA + G 3-4x/week	Weight-stable chronic HD patients
Thabet, 2017[9] N=40	RCT 6 months	37 years 58% male	3.02	BMI: 19.4	IDPN + IV vitamins 3x/week	IV vitamins

Abbreviations: G=glucose; EAA=essential amino acids; NEAA=non-essential amino acids; RCT=randomized controlled trial; HD=hemodialysis; NR=not reported; BMI=body mass index; BW=body weight; SA=serum albumin; sup=supplements; FineS: French Intradialytic Nutrition Evaluation Study; IV=intravenous

KEY QUESTION 1: What is the effectiveness of IDPN for the treatment of malnutrition in hemodialysis patients?

IDPN Compared to Oral Supplements

IDPN does not appear to improve patient health or nutritional outcomes compared to oral supplementation (Table 2). One year of individualized IDPN treatment did not improve 2-year mortality, hospitalization rate, or quality of life in the French Intradialytic Nutrition Evaluation Study (FineS) RCT of 186 malnourished chronic hemodialysis patients.[1] Additionally, in 2 RCTs using IDPN[1] or amino acid plus glucose infusion[2], there were no differences in improvements in BMI, serum albumin, serum prealbumin, or subjective global assessment score (SGA) compared to oral supplements. This evidence is limited by small sample size and nonadherence (19-26% discontinued oral supplements and 24% discontinued IDPN)[1] or differences in attrition between groups (17% control vs 0% IDPN).[2] The only significant improvement in nutritional indicators was in a single, small (N = 20) prospective cohort from Turkey which reported significantly increased serum albumin after 4 months in patients receiving IDPN but not in patients receiving oral amino acid supplementation.[3] However, this study did not directly compare intervention and control groups, and is limited by lack of adherence (40% of patients transferred from oral

supplements to IDPN due to non-compliance) and no statistical adjustment for these potential confounding factors.

Table 2: Effect of IDPN versus Oral Supplements on Patient Health and Nutritional Outcomes

	Evidence	
	1 fair-quality RCT (N=186)[1]	1 fair-quality RCT (N=32)[2]
Patient Health Outcomes		
Mortality	≈ Mortality rate: 43% vs 39% (P = NS)	
Hospitalization	≈ # days hospitalized/days follow-up: 0.008 vs 0.06 (P = NS)	
QoL/ Functional Impairment	≈ No difference in Karnofsky score (data NR)	
Nutritional Outcomes*		
SA	≈	≈
PA	≈	≈
SGA		≈
BMI	≈	
MAC		
TSF		

*full data available in Supplemental Materials Appendix E; Data presented as intervention versus control
= data not reported
≈ = no difference in outcomes
Abbreviations: SA=serum albumin; NS=non-significant; NR=not reported; QoL=quality of life; PA=serum prealbumin; SGA=subjective global assessment; BMI=body mass index; MAC=mid-arm circumference; TSF=triceps-skinfold thickness; PC=prospective cohort

IDPN Compared to Dietary Counseling

A single RCT of 107 chronic hemodialysis patients funded and co-authored by an employee of Fresenius Kabi Germany GmbH compared 16 weeks of IDPN, "individually compounded according to official recommendations with products supplied by Fresenius Kabi Deutschland GmbH", to patients maintained on "regular food behavior".[4] All patients received nutritional counseling at baseline, but it is unclear what (if any) intervention the control group received throughout the study period. IDPN did not consistently improve patient health or nutritional outcomes. More patients receiving IDPN reached a 15% improvement in serum prealbumin at 4 weeks compared to control (41% IDPN vs 20.5% control, P = .0415). However, the

meaningfulness and reliability of this finding is unclear as (1) although the 15% threshold was noted to be a "relevant" increase, clinical justification for this threshold was not provided, data for this threshold were not provided at the end of the study (16 weeks), and this threshold was not pre-specified in the protocol; (2) the mean improvement in serum prealbumin (26.31 mg/L) at 16 weeks did not reach the threshold of > 30 mg/L found to be associated with a mortality reduction in Cano 2007; (3) it did not improve the % of patients who achieved the > 30 mg/L threshold (48.7% vs 31.8%, P = .1164); (4) it did not improve clinical outcomes of mortality (26.4% vs 12.9%, ESP calculated P = .09), hospitalization (hospitalization rate: 59% vs 43.2%, P = .15), or quality of life (change in SF-12 score: -2.74 vs 0.34, P = .1175); and (5) the study had the important limitations of small sample size, indirect outcomes, and lack of information on what kind of intervention (if any) the control group received and potential co-interventions.

IDPN Compared to Usual Care

IDPN generally reduced risk of mortality and improved mean scores on various nutritional outcomes compared to usual care (Table 3). However, usual care was not well-defined in these studies; it was commonly only reported as "usual recommended diet" making it difficult to assess applicability to specific clinical circumstances. Additionally, we do not have any information about the quality of life or functionality of the patients who survived. The largest non-randomized study[6] found that the effects of IDPN on 1-year mortality were dependent upon baseline serum albumin levels. Patients with lower baseline serum albumin (≤ 3.3 g/dL) had reduced odds of death with IDPN treatment (OR range 0.61 to 0.72, P < .01, estimated from Figure 2). Conversely, patients with higher baseline serum albumin (> 3.3 g/dL) had similar or increased odds of death compared to controls (OR range 0.85 (estimated from Figure 2), P = .10 to 2.6, P < .005). Although this study was large, interpretation of its findings is limited as we do not have details about what intervention or control patients received during the study period (including duration or specifics of IDPN treatment, receipt of other nutritional interventions, *etc)*, making it difficult to judge intervention adherence or potential co-interventions in this study. Additionally, we have no information on quality of life or function in the surviving patients. One smaller (N = 81) non-randomized study (baseline serum albumin 3.02 g/dL) also found improved survival with IDPN treatment, but it was small (N = 81) in addition to lacking of information on control group care.[5] Additionally, a single RCT of 40 chronic hemodialysis patients with refractory anemia reported no improvements in nutritionally related functional capacity with IDPN treatment or usual care.[9] Although several studies found improved mean scores on various nutritional outcomes compared to usual care, no study reported the proportion of patients reaching clinically meaningful improvements in nutritional outcomes. These studies are limited by small sample size (all but one N < 100), lack of information on intervention adherence, and limited statistical adjustment for potential confounders among non-randomized studies. Two studies with additional limitations (no adjustment for potential confounders)[7,48] reported similar findings.

Table 3: Effect of IDPN versus Usual Care on Patient Health and Nutritional Outcomes

	Evidence				
	1 fair-quality RCT (N=26)[8]	1 fair-quality RCT (N=40)[9]	1 fair-quality RC (N=81)[5]	1 fair-quality RC (N=24,196)[6]	1 fair-quality PC (N=12)[10]
Patient Health Outcomes					
Mortality			↑ RR survival = 1.34 (P < .01)	↓↑ OR death range 0.57† to 2.6 (P < .01)	
QoL/ Functional Impairment		≈ Functional capacity (data NR)			
Nutritional Outcomes*					
SA	↑	↑	≈		≈
PA	↑				
SGA/MIS		↑			
BMI		↑			↑
BW	↑		Survivors ↑ Non-survivors ≈		↑
MAC	↑				
TSF	≈				

= data not reported; ≈ No difference in outcomes, ↑=improvement in outcomes with IDPN; ↓↑=mixed effect on outcomes; Data presented as intervention versus control; †Estimated from Figure; *full data available in Supplemental Materials Appendix E

Abbreviations: SA=serum albumin; PA=serum prealbumin; SGA=subjective global assessment; MIS=malnutrition inflammation score; BMI=body mass index; BW=body weight; MAC=mid-arm circumference; TSF=triceps-skinfold thickness; RC=retrospective cohort; PC=prospective cohort

We are aware of 20 additional before-after studies with no non-IDPN control.[51-67 68-70] Most of these studies report significant increases in at least one nutritional or patient health indicator after IDPN treatment. However, these studies were not formally included in our synthesis due to inherent weaknesses in study design.[71]

KEY QUESTION 2: What are the potential adverse effects of using IDPN for the treatment of malnutrition in hemodialysis patients?

Limited data are available regarding the adverse effects of IDPN, with only 4 of the included studies reporting adverse events. Two RCTs[1,4] reported 12-14% of patients experiencing adverse events causing discontinuation of IDPN. Commonly reported adverse events included nausea, muscle pain, infections, hyperglycemia, and procedural complications. No differences in adverse events between intervention and control groups were reported, and some of these events may be common in this population due to disease state.[72] However, interpretation of these findings as consistent evidence of adverse effects is limited by (1) heterogeneity in outcomes, treatment duration, and follow-up duration; and (2) adverse events in these studies that may have been artificially underestimated due to more frequent laboratory monitoring and/or assessment.

KEY QUESTION 3: What is the cost-effectiveness of using IDPN for the treatment of malnutrition in hemodialysis patients?

A single study with no concurrent non-IDPN comparator reported a significant decrease in the average number of hospitalizations, cost of hospitalizations, and the length of stay ($P < .05$) after 6 months of IDPN therapy. However, when the cost of IDPN was taken into account, there were no overall cost savings for the 6 months of therapy.[50] This evidence is limited by a lack of comparison to a concurrent non-IDPN control group[71] and limited information on patient, dialysis, and IDPN characteristics.

KEY QUESTION 4: Do the effectiveness and potential adverse effects of IDPN differ per patient characteristics?

There is insufficient evidence to draw conclusions about the differential effectiveness of IDPN in subgroups. Although the effects of IDPN may be greater in patients with lower baseline serum albumin levels, our confidence in these findings is low as they must be considered taking into account the previously described limitations of serum protein levels in screening and outcome assessment of malnutrition. A single, large, non-randomized study reported mortality by baseline serum albumin level.[6] For patients with baseline serum albumin ≤ 3.3 g/dL there was reduced odds of death with IDPN treatment. However, for patients with baseline serum albumin ≤ 3.4 or 3.5 g/dL, there was no difference in mortality with IDPN treatment, and for patients with baseline serum albumin > 3.5 g/dL the odds of death were higher among IDPN-treated patients than control patients.

SUMMARY AND DISCUSSION

KEY FINDINGS AND CLINICAL IMPLICATIONS

The outcomes of untreated malnutrition are poor and associated costs are high. Therefore, treatment of malnutrition in hemodialysis patients is a priority, and early efforts to improve oral intake and the use of enteral nutrition supplements are important. IDPN has been proposed as a safe and convenient way to supplement nutrient intake to improve nutritional status and patient health outcomes for malnourished hemodialysis patients during a time when patients are already receiving treatment. Due to its higher cost, however, initiating IDPN prior to guideline-recommended first-line treatment options would ideally be supported by improved patient health outcomes and nutritional status compared to other therapies. For IDPN to best demonstrate a clinically important benefit over recommended treatment, ideally (1) it would significantly reduce the risk of mortality, (2) it would improve the functional status and quality of life of survivors, and (3) these benefits could be attributed specifically to IDPN and not to differences between intervention and control groups in concomitant treatments, disease state, level of malnutrition, or other potentially confounding factors. However, primarily because detail about control group treatment regimens is inadequate to determine applicability to current practice, current evidence does not reliably demonstrate such benefits for IDPN. IDPN has not significantly improved patient health or nutritional outcomes better than the current guideline-recommended treatments of dietary counseling and oral supplementation in any of 3 RCTs.[1,2,4] No studies have compared IDPN to enteral tube feeding. Compared to usual care, 2 RCTs[8,9] and 5 cohort studies[5-7,10,48] showed varied results on the effect of IDPN on patient health and nutritional outcomes, with improvements in single nutritional indicators commonly reported. However, single nutritional indicators are not sufficient to fully assess a patient's overall nutritional or clinical status as they may be low for various reasons, including inflammation or stress, and thus cannot be used alone to assess nutritional status. For example, clinical response to protein administration may vary depending upon inflammation, oral intake, and the amount of protein in IDPN (which varies amongst IDPN solutions). For these reasons, serum protein levels (*eg*, serum albumin, serum prealbumin) are more recently not recommended in the screening and outcome assessment of malnutrition.[25] Also, statistically significant *mean* improvements in biochemical markers do not always translate into clinically significant benefits. Therefore, full evaluation of IDPN's benefit-risk profile would ideally include achievement of a clinically relevant improvement in *multiple* markers of nutritional status (biochemical, weight status and change, SGA score, *etc*), as well as improvements in quality of life and/or mortality, without increasing the risk of important harms.

Limited data are available regarding the adverse effects of IDPN. Commonly reported adverse events included nausea, muscle pain, infections, hyperglycemia, and procedural complications, and no differences in adverse events between intervention and control groups were reported. However, interpretation of these findings as consistent evidence of adverse effects is limited by (1) heterogeneity in outcomes, treatment duration, and follow-up duration, and (2) adverse events in these studies may have been artificially underestimated due to more frequent laboratory monitoring and/or assessment.

Evidence on the cost-effectiveness of IDPN is limited to a single study with no concurrent non-IDPN comparator which reported a significant decrease in the average number of hospitalizations, cost of hospitalizations, and the length of stay ($P < .05$) after 6 months of IDPN

therapy, but no overall cost savings when the cost of IDPN was taken into account.[50] However, this study did not include comparison to a concurrent non-IDPN control group,[71] and provided limited details about patient, dialysis, and IDPN characteristics. Evidence is also limited on which patient subgroups may benefit the most from IDPN, with a single, large, non-randomized study reporting that patients with a lower baseline serum albumin level may be more likely to improve with IDPN.[6] Although this study was large, interpretation of its findings is limited as we do not have details about what intervention or control patients received during the study period, making it difficult to judge intervention adherence or potential co-interventions in this study.

Despite existing guidelines recommending IDPN only for hemodialysis patients with refractory malnutrition, IDPN is commonly being requested or used prior to other treatment options. However, IDPN has not been demonstrated to improve patient health or nutritional outcomes better than the current guideline recommended treatments of dietary counseling and oral supplementation. Due to the substantially higher cost of IDPN and unknown cost-effectiveness, broad usage of IDPN prior to other treatment options does not appear warranted. We agree with existing guidelines[35,73] which state that IDPN is a reasonable treatment option when confronted with patients who fail to respond to these initial treatments or are unable to receive these treatments due to malfunctioning gastrointestinal tract or other issues. There are no set recommendations for how long dietary counseling and/or oral supplementation should be tried before considering IDPN. However, chronic malnourishment for 3 to 6 months has been listed as indication that current treatments are not working.

LIMITATIONS

There are important limitations for the evidence in this review. Apart from one large retrospective cohort,[6] most studies were small (sample size range 12-196) with relatively short follow-up (range 12 weeks to 2 years). Measurement of clinically important outcomes such as quality of life, function, and cost-effectiveness was limited. Only a single study[4] included measurement of clinically relevant improvement in a nutritional indicator, but the meaningfulness and reliability of this finding is limited by small sample size, short follow-up duration, indirect outcomes, and lack of information on what kind of intervention (if any) the control group received and potential co-interventions. The published studies were heterogeneous and lacked sufficient detail to assess differences in outcome based on treatment duration, IDPN solution, dialysis regimen and modality, follow-up, patient characteristics (disease severity, comorbidities, *etc)* and outcome assessment. No studies compared IDPN to enteral tube feeding. Additionally, the majority of studies were compared to usual care, which was ill-defined, limiting the interpretation of the findings in specific clinical circumstances. Applicability to Veterans is likely low as only 3 studies were within the US[5,6,48] and no studies were specifically in a Veteran population. Although the mean patient age was likely applicable to Veterans (mean patient age was 65 years; median Veteran age was 64 years in 2015[74]) there was generally an even distribution of male to female patients (mean 50% male) in the studies, while Veterans are predominantly male (92%).[74] Additionally, some studies excluded patients with diabetes and the prevalence of diabetes in the Veteran population is about 20.5%.[75]

Limitations of our review methods include our literature search, our scope, and our use of sequential instead of independent dual assessment. For our literature search, we limited the timeframe and used existing systematic and narrative reviews to identify earlier studies. To meet our condensed timeframe, we focused on the most patient important health outcomes and did not

include all intermediate markers of nutritional status. Additionally, although widely used, sequential dual review has not been empirically compared to independent dual review and may increase the risk of error and bias.

FUTURE RESEARCH

The treatment pathway for malnourishment in hemodialysis patients is generally recommended as (1) dietary counseling, (2) oral supplementation, then (3) enteral tube feeding. In order to determine when IDPN should be used, comparisons to each treatment are needed. Further studies comparing IDPN to dietary counseling are warranted. The current best evidence is limited by sample size (N < 110), short follow-up duration (28 weeks), indirect outcomes, and lack of information on what kind of intervention (if any) the control group received and potential co-interventions.[4] Additional studies comparing IDPN to oral supplementation are also justified due to limitations in sample size (N < 200) and potentially follow-up duration (2 years).[1] Although RCTs can be preferred because of their greater methodological rigor, we recognize that they may not be feasible due to their higher cost. Additionally, large samples with high levels of adherence and long follow-up time may not be practical in this population due to disease severity and progression. Finally, no study has compared IDPN to enteral tube feeding. In order to justify initiation of IDPN prior to trying enteral tube feeding (for patients with functioning GI tracts), IDPN should be shown to improve patient health and/or nutritional status better than enteral tube feeding in adequately powered, methodologically sound RCTs.

CONCLUSIONS

IDPN has not been demonstrated to improve patient health or clinically important nutritional outcomes over the current guideline recommending treatments of dietary counseling and oral supplementation. Therefore, because of its higher cost, broad usage of IDPN prior to other treatment options does not appear warranted. However, because of its potential improvements in nutritional indicators, we agree with existing guidelines that IDPN is a reasonable treatment option when confronted with patients who fail to respond to these initial treatments or are unable to receive these treatments due to malfunctioning gastrointestinal tract or other issues. Limited data are available regarding the adverse effects of IDPN, but there does not appear to be significant differences in adverse events between IDPN and control groups. Future research should focus on comparing IDPN with enteral tube feeding, as well as further studies of IDPN compared to oral and/or dietary counseling with larger sample sizes, longer follow-up duration, and better-characterized control groups.

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