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

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TABLE OF CONTENTS

Appendix A: Guidelines for Treatment of Malnutrition in Hemodialysis 1
Appendix B: IDPN Insurance Coverage 5
Appendix C: Search Strategy 9
Appendix D: List of Excluded Studies 16
Appendix E: Evidence Tables 22
Data Abstraction of Included Primary Studies 22
Data Abstraction of Included Studies (IDPN vs Comparator) 22
Quality Assessment of Included Studies 26
Quality Assessment of Included RCTs 26
Quality Assessment of Included Observational Studies 28
Strength of Evidence For Included Studies 30
Appendix F: Peer Review 32
References 40

APPENDIX A: GUIDELINES FOR TREATMENT OF MALNUTRITION IN HEMODIALYSIS

Organization Year	Focus	Criteria for Malnutrition	Recommended First-line Treatment	Criteria for IDPN Initiation	Contraindications	Criteria for IDPN Discontinuation
American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) 2017[1]	Appropriateness of PN	Energy intake of ≤50% for 5-7 days Failure to achieve nutrition goals after 7 days	Oral or enteral	Malnourished and unable to tolerate adequate oral intake or EN	Diabetic patients who may experience hypoglycemia upon discontinuation of IDPN	NR
British Columbia IDPN Work Group 2014[2]	Provincial standards for IDPN	Patients must meet any 3 of the following criteria: 1) 3-month average SA <3.4 g/dL 2) Weight loss >10% of usual body weight or current weight <90% of ideal body weight 3) SGA score: B or C 4) Diet history showing a decreased intake 5) Documented diagnosis of GI disorder	"Standard nutrition intervention" – oral nutritional supplements or tube feeding	Malnourished *AND* the patient must demonstrate the following: 1) Failed attempts to increase nutritional status with oral nutritional supplements, 2) Not be a candidate for tube feeding, 3) Able to meet ≥50% of needs orally	Allergy to eggs, corn, or sulfites; Excessive, chronic fluid overload; Patient refusal to initiate IDPN; Patient is palliative with no anticipated increase in quality of life with IDPN	Patient must meet any 3 of the following criteria: 1) 3-month average SA >3.4 g/L 2) Increasing dry weight trend 3) Improved SGA score: A or B 4) Increased oral intake *OR* the patient demonstrates one of the following: 1) No benefit after 6 months of IDPN 2) Complications of/intolerance to IDPN
Department of Veterans Affairs, Veterans Health Administration Nutrition Therapy Handbook 2013[3]	ONS, EN, PN, any disease	≥ 2 of the following characteristics: 1) Insufficient energy intake: <75% estimated energy requirement for >7 days (acute injury or illness/chronic illness) or for ≥ 3 months (social, environmental circumstances)	Nutrition consult and trial of meeting nutrition with regular food and beverage items. ONS may be prescribed for malnourished patients after failure of food or diet management	IDPN not specified	NA	NA

Organization Year	Focus	Criteria for Malnutrition	Recommended First-line Treatment	Criteria for IDPN Initiation	Contraindications	Criteria for IDPN Discontinuation
		2) Weight loss, including (≥1-2% in 1 week, ≥5% in 1 month, ≥7.5%in 3 months, ≥10% in 6 months, or ≥20% in 1 year) 3) Mild to moderate loss of muscle mass 4) Mild to moderate loss of subcutaneous fat 5) Mild to moderate localized or generalized fluid accumulation - may mask weight loss 6) Diminished functional status (hand grip test)				
The European Society for Clinical Nutrition and Metabolism (E.S.P.E.N.), 2009[4]	Guidelines for adult parenteral nutrition	1) BMI <20kg/m^2 2) >10% weight loss over 6 months 3) SA < 3.5 g/dL 4) PA < 300 mg/L	Oral nutritional supplements	When nutritional counseling and oral nutritional supplements are unsuccessful in outpatients	NR	NR
German Medical Science, 2009[5]	Parenteral nutrition in patients with renal failure	1) Middle pre-dialysis SA 3 months 2) Middle pre-dialysis serum creatinine 3 months 3) Weight loss >10% of ideal body weight or >20% of normal body weight (no time limit) 4) Clinical examination indicates moderate to severe malnutrition 4) Dietary history indicating protein intake	Enteral nutrition and/or parenteral nutrition if state of renal failure requires more aggressive therapy – general recommendation to establish at least minimal enteral nutrition to enhance intestinal integrity even if	Malnourished *AND*: 1) Modifiable causes of malnutrition are excluded 2) enhanced oral or enteral supply is unsuccessful or cannot be carried out	NR	NR

Organization Year	Focus	Criteria for Malnutrition	Recommended First-line Treatment	Criteria for IDPN Initiation	Contraindications	Criteria for IDPN Discontinuation
		<0.8 g/kg, reduced calorie intake <25 kcal/kg 5) SGA score C	parenteral is indicated			
International Society of Renal Nutrition and Metabolism, 2013[6]	Consensus statement for the management of PEW Evidence, expert opinion	1) Poor appetite and/or poor oral intake 2) DPI<1.2 (CKD 5D) or <0.7 (CKD 3–4); DEI < 30 kcal/kg/day 3) SA < 3.8 g/dL or PA < 28 mg/dL 4) Unintentional weight loss: > 5% of IBW or EDW over 3 months 5) Worsening nutritional markers over time 6) SGA in PEW range	CKD-specific oral nutritional supplementation	Beneficial for individuals who cannot tolerate oral or enteral administration of nutrients with SA< 3g/dL		NR
National Kidney Foundation/Kidney Disease Outcomes Quality Initiative (KDOQI), 2000[7]	Clinical practice guideline for nutrition in chronic renal failure	Use of a broad panel of nutritional status markers for diagnosing PEW malnutrition and wasting: BMI, SGA, handgrip strength, waist circumference, SA, serum creatinine	Nutrition counseling with individualized care plan, updated at least quarterly	Must exhibit the following: 1) Evidence of protein or energy malnutrition and 2) Inadequate DPI or DEI 3) Inability to administer or tolerate adequate oral nutrition, including food supplements or tube feeding Combine IDPN with oral or enteral supplement		If combination of IDPN or Intraperitoneal Amino Acids does not meet protein and energy requirements, daily total or partial parenteral nutrition should be considered
Nottingham University Hospitals, 2016[8]	Clinical practice guideline	Spontaneous nutrition intake is < 29kcal/kg/IBW *and* < 0.8g protein/kg of IBW	Enteral and oral routes (food fortification advice and the use of oral	Malnourished AND 1) Enteral feeding and oral routes have failed	1) Allergy to eggs, corn and sulphites	NR

Organization Year	Focus	Criteria for Malnutrition	Recommended First-line Treatment	Criteria for IDPN Initiation	Contraindications	Criteria for IDPN Discontinuation
			nutritional supplements) with intense dietetic support	or are unsafe/not practical 2) Full dietetic assessment including risk of refeeding syndrome conducted by dietician	2) Palliative patient with no anticipated increase in QOL 3) Fluid overload (patient gains .4% dry weight) Uncontrolled diabetes (blood glucose above 20 mmol/l) 4) Receiving blood transfusion on the dialysis day 5) Deranged liver function tests 6) Septic patients and chronic infection (with elevated CRP)	
UK Renal Association, 2010[9]	Clinical practice guideline for nutrition in chronic kidney disease	1) BMI <18.5 kg/m^2 2) an unintentional weight loss >10% in 3-6 months 3) BMI <20 kg/m^2 AND unintentional weight loss >5% in 3-6 months	ONS first, EN if nutrient intake is still suboptimal despite ONS	IDPN suggested for select cases when tube feeding is declined or clinically inappropriate	NR	NR

Abbreviations: DEI=dietary energy intake, DPI=dietary protein intake, EN=enteral nutrition, EDW=estimated dry weight, IBW=ideal body weight, IDPN=intradialytic parenteral nutrition, NA=not applicable, N.I.C.E.=National Institute of Clinical Excellence, NR=not reported, PEW=protein energy wasting, ONS=oral nutrition supplements, PN=parenteral nutrition, SA=serum albumin, SGA= subjective global assessment (Grade A: well-nourished, B: mild to moderately malnourished, C: severely malnourished), PA=pre-serum albumin

APPENDIX B: IDPN INSURANCE COVERAGE

Agency Last Review Date	What's covered?	Coverage details	Conditions for coverage
Aetna 2017	IDPN	No. 0061 Parenteral nutrition may be either "self-mixed" (*ie*, the member or family caregiver is taught to prepare the nutrient solution aseptically) or "pre-mixed". The doctor must justify the need for pre-mixed parenteral nutritional solutions.	*ANY* of the following criteria: • Documentation of a failure of enteral (*ie*, oral or tube feeding) nutrition, as defined by *either* of the following: o A non-edematous or post-dialysis documented loss of greater than 10 % of body weight over a 3-month period; *or* o Total protein less then 6 g/dL or serum albumin less than 3.4 g/dL; • A condition in which it is necessary for the gastrointestinal tract to be totally non-functioning for a period of time; • Evidence of structural or functional bowel disease that makes oral and tube feedings inappropriate; • Hyperemesis gravidarum (only in cases of failed medical management or when used in a step-therapy program); • Member is peri-operative (regardless of disease state) and unable to tolerate oral or tube feedings. Parenteral nutrition is *not considered* medically necessary for members with a functioning gastrointestinal tract whose need for parenteral nutrition is only due to: • A physical disorder impairing food intake such as the dyspnea of severe pulmonary or cardiac disease; • A psychological disorder impairing food intake such as depression; • A side effect of a medication; • A swallowing disorder; • A temporary defect in gastric emptying such as a metabolic or electrolyte disorder; • Disorders inducing anorexia such as cancer; • Renal failure and/or dialysis* *Members receiving intra-dialytic parenteral nutrition must meet the criteria for total parenteral nutrition set forth above.

Blue Cross of Idaho 2014	IDPN	MP 8.01.44	Considered medically necessary when it is offered as an alternative to a regularly scheduled regimen of total parenteral nutrition only in patients who would be considered candidates for total parenteral nutrition (TPN)(*ie*, a severe pathology of the alimentary tract that does not allow absorption of sufficient nutrients to maintain weight and strength commensurate with the patient's general condition). Considered not medically necessary in patients who would be considered a candidate for TPN, but for whom the intradialytic parenteral nutrition is not offered as an alternative to TPN, but in addition to regularly scheduled infusions to TPN. Considered investigational in patients who would not otherwise be considered candidates for TPN.
Centers for Medicare and Medicaid Services (CMS) 2015	IDPN (solution only)	NCD Publication No. 100-3 Manual Section No. 180.2 PRM-1-2711.6 42 CFR 423.100 B3-2130, A3-3110.4, HO-228.4, A3-3111, HO-229 Covered under Part B if the therapy was being provided because of a non-functioning digestive tract. Otherwise it is covered under Part D.	Medication given by injection (parenterally) is not covered if standard medical practice indicates that the administration of the medication by mouth (orally) is effective and is an accepted or preferred method of administration. Physician's written order or prescription and sufficient medical documentation to permit an independent conclusion that the requirements of the benefit are met and that parenteral nutrition therapy is medically necessary. Coverage of parenteral nutrition therapy for this and any other condition must be approved on an individual, case-by-case basis initially and at periodic intervals of no more than three months by the Medicare Administrative Contractor (A/B MAC (B)) medical consultant or specially trained staff, relying on such medical and other documentation as the A/B MAC (B) may require.
Cigna 2017	IDPN	Medical Coverage Policy: 0136	The individual is on chronic hemodialysis *AND* the individual is a candidate for total parenteral nutrition (*ie*, nutritional status cannot be adequately maintained on oral or enteral feedings).
Priority Health 2016	IDPN	Medical Policy No. 91517-R4 Clinical re-evaluation after 6 months for consideration of continued treatment	SA < 3.4 g/dL or protein < 6 g/dL *AND* one of the following: • BMI < 18.5 kg/m^2 • Unintentional weight loss > 10% within the last 6 months

			• BMI < 20 kg/m^2 and unintentional weight loss > 5% within the last 3-6 months
United Healthcare 2017	IDPN, infusion pumps, supply kit, administration kit	Policy Number: N-001 Covered in accordance with Medicare coverage criteria.	Documentation must be clear and precise to verify that the patient suffers from a permanently impaired gastrointestinal tract and that there is insufficient absorption of nutrients to maintain adequate strength and weight. Records should document that the patient cannot be maintained on oral or enteral feedings and that due to severe pathology of the alimentary tract, the patient must be intravenously infused with nutrients. Infusions must be vital to the nutritional stability of the patient and not supplemental to a deficient diet or deficiencies caused by dialysis. Physical signs, symptoms and test results indicating severe pathology of the alimentary tract must be clearly evident in any documentation submitted.
Health Net/ Centene Corporation 2017	IDPN	CP.PHAR.205 Initial approval duration for IDPN is for 3 months. Continued approval duration is 6 months, given that the member has no evidence of unacceptable complications from treatment and documentation supports positive response to therapy.	Documented failure of enteral nutrition as shown by *ANY* of the following: • Weight loss > 10% of ideal body weight in 3 months or > 20% of usual body weight • Total protein < 6 g/dL in past 4 weeks • SA < 3.4 g/dL in past 4 weeks *AND* evidence of structural or functional bowel disease that makes oral or tube feedings inappropriate, or a condition in which the gastrointestinal tract is non-functioning for a period of time *AND* • Patient has ESRD • Patient is undergoing hemodialysis • IDPN is offered as an alternative to regularly scheduled TPN.
Independence Blue Cross 2017	IDPN	Policy No. 08.00.17g After an initial 3-month trial, continued coverage will depend on the degree of improvement in nutritional status, taking into consideration the individual's serum albumin levels.	When it is infused as an alternative to a regularly scheduled regimen of TPN in individuals who meet the medical necessity criteria for TPN, *OR* In individuals with a functional gastrointestinal tract when *all* of the following criteria are met: • The individual has a documented comprehensive nutritional assessment and dietary counseling • In spite of enteral nutrition via tube feeding, or adequate oral nutrition, the individual has evidence of protein or energy malnutrition as defined by any of the following:

	○ Evidence of protein intake <1.2g/Kg or calories<25 Kcal/Kg ○ Evidence of weight loss 10-20% of usual body weight within 3-6 months ○ Serum Albumin Levels <3.4 g/l (3 months average) • The individual has evidence of adequate dialysis therapy

Abbreviations: BMI=body mass index, ESRD=end stage renal disease, IDPN=intradialytic parenteral nutrition, TPN=total parenteral nutrition

APPENDIX C: SEARCH STRATEGY

1. Search for current systematic reviews **Date Searched: 10/11/17**	
Source:	**Evidence:**
AHRQ	Search: Hemodialysis; Haemodialysis; Parenteral Nutrition Relevant Results: None
CADTH	Search: Hemodialysis; Haemodialysis; Parenteral Nutrition Relevant Results: None
NHS Evidence (NICE)	Search: Hemodialysis and nutrition; Hemodialysis and oral supplement; haemodialysis and nutrition; haemodialysis and oral supplement; Hemodialysis and Parenteral Nutrition; Haemodialysis and Parenteral Nutrition Relevant Results: UK Renal Association. "Nutrition in CKD 5th Edition" (2010)
National Library of Medicine	Search: Hemodialysis and nutrition; Hemodialysis and oral supplement; haemodialysis and nutrition; haemodialysis and oral supplement; Hemodialysis and Parenteral Nutrition; Haemodialysis and Parenteral Nutrition Relevant Results: None
ECRI Institute	Search: Hemodialysis; Hemodialysis Relevant Results: None
Cochrane Database of Systematic Reviews (CDSR)	Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to October 5, 2017> Search Strategy: --- 1 (hemodialysis or haemodialysis).mp. [mp=title, abstract, full text, keywords, caption text] (201) 2 (hemodiafiltration or haemodiafiltration).mp. [mp=title, abstract, full text, keywords, caption text] (24) 3 (hemofiltration or haemofiltration).mp. [mp=title, abstract, full text, keywords, caption text] (33) 4 1 or 2 or 3 (211) 5 malnutrition.mp. [mp=title, abstract, full text, keywords, caption text] (294) 6 nutritional supplementation.mp. [mp=title, abstract, full text, keywords, caption text] (65) 7 Nutritional Status.mp. [mp=title, abstract, full text, keywords, caption text] (256) 8 oral nutrition*.mp. [mp=title, abstract, full text, keywords, caption text] (37) 9 Enteral nutrition*.mp. [mp=title, abstract, full text, keywords, caption text] (141) 10 parenteral nutrition*.mp. [mp=title, abstract, full text, keywords, caption text] (207) 11 5 or 6 or 7 or 8 or 9 or 10 (665) 12 4 and 11 (38) **********

MEDLINE: Systematic Reviews	Database: Ovid MEDLINE(R) <1946 to September Week 4 2017>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <October 10, 2017> Search Strategy: --- 1 (hemodialysis or haemodialysis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (72847) 2 (hemodiafiltration or haemodiafiltration).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3362) 3 (hemofiltration or haemofiltration).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (6721) 4 exp Renal Dialysis/ (108964) 5 1 or 2 or 3 or 4 (131024) 6 exp Protein-Energy Malnutrition/ (7509) 7 malnutrition.mp. or exp Malnutrition/ (140928) 8 exp Nutritional Support/ (45694) 9 nutritional supplementation.mp. (1796) 10 Nutritional Status.mp. or exp Nutritional Status/ (55534) 11 oral nutrition*.mp. (1266) 12 exp Enteral Nutrition/ or Enteral nutrition*.mp. (22351) 13 exp Parenteral Nutrition, Total/ or exp Parenteral Nutrition/ or parenteral nutrition*.mp. (32162) 14 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (230196) 15 5 and 14 (6749) 16 11 or 12 or 13 (49606) 17 15 and 16 (818) 18 11 and 13 and 15 (23) 19 meta-analysis.pt. (91059) 20 meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ (117580) 21 ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab. (125288) 22 ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab. (8406) 23 ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab. (19859) 24 (data synthes* or data extraction* or data abstraction*).ti,ab. (20899) 25 (handsearch* or hand search*).ti,ab. (7967) 26 (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab. (21439) 27 (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. (217048) 28 (meta regression* or metaregression*).ti,ab. (5902) 29 (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. (217048) 30 (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw. (160185) 31 (cochrane or (health adj2 technology assessment) or evidence report).jw. (18591) 32 (meta-analysis or systematic review).ti,ab. (169828) 33 (comparative adj3 (efficacy or effectiveness)).ti,ab. (10451) 34 (outcomes research or relative effectiveness).ti,ab. (6770)

	35 ((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab. (1644) 36 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 (353175) 37 17 and 36 (14) **********
VA Products - VATAP, PBM and HSR&D publications, VA ART database (Captures HSR&D funded projects)	A. http://www.hsrd.research.va.gov/research/default.cfm Search: Hemodialysis; Haemodialysis Relevant Results: Hynes DM, Stroupe KT, Fischer MJ, Reda DJ, Manning W, Browning MM, Huo Z, Saban K, Kaufman JS, for ESRD Cost Study Group. Comparing VA and private sector healthcare costs for end-stage renal disease. Medical care. 2012 Feb 1; 50(2):161-70. B. http://www.research.va.gov/research_topics/ Relevant Results: None C. http://art.puget-sound.med.va.gov/default.cfm Search: Hemodialysis; Haemodialysis; haemodialysis and nutrition; haemodialysis and oral supplement Relevant Results: None

2. Search for systematic reviews currently under development (includes forthcoming reviews & protocols) **Date Searched: 10/11/17**	
Source:	**Evidence:**
AHRQ topics in development (EPC Status Report)	https://www.epc-src.org/src/logon.cfm Emailed Robin.Paynter@va.gov and she reported no future, ongoing, or completed AHRQ Effective Health Care program reviews on this topic.
PROSPERO (SR registry)	http://www.crd.york.ac.uk/PROSPERO/ Search: Hemodialysis; haemodialysis Relevant Results: Rana Rizk, Silvia Evers, Mickael Hiligsmann, Mirey Karavetian. Economic evaluations of interventions to manage hyperphosphatemia in adult hemodialysis patients: a systematic review. PROSPERO 2014:CRD42014014631 Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014014631
DoPHER (SR Protocols)	http://eppi.ioe.ac.uk/webdatabases4/Intro.aspx?ID=9 Search: Hemodialysis; haemodialysis Relevant Results: None
Cochrane Methodology Register	Database: EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012> Search Strategy: --- 1 (hemodialysis or haemodialysis).mp. [mp=title, abstract, subject heading word] (12) 2 (hemodiafiltration or haemodiafiltration).mp. [mp=title, abstract, subject heading word] (0)

	3 (hemofiltration or haemofiltration).mp. [mp=title, abstract, subject heading word] (0) 4 1 or 2 or 3 (12) 5 malnutrition.mp. [mp=title, abstract, subject heading word] (3) 6 nutritional supplementation.mp. [mp=title, abstract, subject heading word] (4) 7 Nutritional Status.mp. [mp=title, abstract, subject heading word] (1) 8 oral nutrition*.mp. [mp=title, abstract, subject heading word] (1) 9 Enteral nutrition*.mp. [mp=title, abstract, subject heading word] (2) 10 parenteral nutrition*.mp. [mp=title, abstract, subject heading word] (3) 11 5 or 6 or 7 or 8 or 9 or 10 (11) 12 4 and 11 (0) **********

3. Current Guidelines **Date Searched: 9/11/17**	
Source:	**Evidence:**
National Guideline Clearinghouse	Search: Hemodialysis; haemodialysis Relevant Results: McClave, Stephen A., et al. "Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN)." Journal of Parenteral and Enteral Nutrition 40.2 (2016): 159-211.
VA/DOD Clinical Practice Guidelines	Relevant Results: The Management of Chronic Kidney Disease Working Group (2014). "VA/DoD clinical practice guideline for the management of chronic kidney disease in primary care."
The Renal Association	Relevant Results: None
Google Scholar	Search: IDPN guideline; intradialytic parenteral nutrition guideline; Hemodialysis and parenteral nutrition; Haemodialysis and parenteral nutrition Relevant Results: Cano, N. J., et al. (2007). "Intradialytic parenteral nutrition does not improve survival in malnourished hemodialysis patients: a 2-year multicenter, prospective, randomized study." J Am Soc Nephrol **18**(9): 2583-2591. Carrero, J. J., et al. (2013). "Etiology of the protein-energy wasting syndrome in chronic kidney disease: a consensus statement from the International Society of Renal Nutrition and Metabolism (ISRNM)." J Ren Nutr 23(2): 77-90. Corbello, Jesse, and Mitchell H. Rosner. "Intradialytic total parenteral nutrition (IDPN): evidence-based recommendations." Practical gastroenterology (2009): 13. Cranford, W. "Cost effectiveness of IDPN therapy measured by hospitalizations and length of stay." *Nephrology news & issues*12.9 (1998): 33-5.
Google	Search: IDPN guideline; intradialytic parenteral nutrition guideline; Hemodialysis and parenteral nutrition; Haemodialysis and parenteral nutrition Relevant Results: Brown RO, Compher C, Parenteral ASf, Directors ENBo. ASPEN clinical guidelines: nutrition support in adult acute and chronic renal failure. Journal of Parenteral and Enteral Nutrition. 2010;34(4):366-377.

	Department of Veterans Affairs. VHA Handbook 1109.05: Nutrition Therapy. In: Administration VH, ed. Washington D.C.: Department of Veterans Affairs; 2013. Nottingham University Hospitals, Mafrici B. Guideline for the use and administration of intradialytic parenteral nutrition (IDPN) in adult haemodialysis patients. In: Hospitals NU, ed: Nottingham University; 2016. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI). KDOQI Clinical Practice Guidelines for Nutrition in Chronic Renal Failure Guideline 19: Indications for Nutritional Support. In:2000. Worthington P, Balint J, Bechtold M, et al. When Is Parenteral Nutrition Appropriate? Journal of Parenteral and Enteral Nutrition. 2017;41(3):324-377.

4. Search for current primary literature (limited to 2009 forward) **Date Searched: 10/11/17**	
Source:	**Evidence:**
MEDLINE	Database: Ovid MEDLINE(R) <1946 to September Week 4 2017>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <October 10, 2017> Search Strategy: ---------- 1 (hemodialysis or haemodialysis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (72847) 2 (hemodiafiltration or haemodiafiltration).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3362) 3 (hemofiltration or haemofiltration).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (6721) 4 exp Renal Dialysis/ (108964) 5 1 or 2 or 3 or 4 (131024) 6 exp Protein-Energy Malnutrition/ (7509) 7 malnutrition.mp. or exp Malnutrition/ (140928) 8 exp Nutritional Support/ (45694) 9 nutritional supplementation.mp. (1796) 10 Nutritional Status.mp. or exp Nutritional Status/ (55534) 11 oral nutrition*.mp. (1266) 12 exp Enteral Nutrition/ or Enteral nutrition*.mp. (22351) 13 exp Parenteral Nutrition, Total/ or exp Parenteral Nutrition/ or parenteral nutrition*.mp. (32162) 14 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (230196) 15 5 and 14 (6749) 16 11 or 12 or 13 (49606) 17 15 and 16 (818) 18 limit 17 to yr="2009 -Current" (188) 19 limit 18 to humans (167) 20 limit 19 to english language (144) 21 remove duplicates from 20 (131) **********
CCRCT	Database: EBM Reviews - Cochrane Central Register of Controlled Trials <September 2017> Search Strategy:

	---------- 1 (hemodialysis or haemodialysis).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (7053) 2 (hemodiafiltration or haemodiafiltration).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (463) 3 (hemofiltration or haemofiltration).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (651) 4 exp Renal Dialysis/ (4567) 5 1 or 2 or 3 or 4 (8873) 6 exp Protein-Energy Malnutrition/ (235) 7 malnutrition.mp. or exp Malnutrition/ (3945) 8 exp Nutritional Support/ (2945) 9 nutritional supplementation.mp. (540) 10 Nutritional Status.mp. or exp Nutritional Status/ (3955) 11 oral nutrition*.mp. (389) 12 exp Enteral Nutrition/ or Enteral nutrition*.mp. (3155) 13 exp Parenteral Nutrition, Total/ or exp Parenteral Nutrition/ or parenteral nutrition*.mp. (2987) 14 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (12223) 15 5 and 14 (538) 16 11 or 12 or 13 (5747) 17 15 and 16 (65) 18 limit 17 to yr="2009 -Current" (24) 19 limit 18 to humans [Limit not valid; records were retained] (24) 20 limit 19 to english language (21) 21 remove duplicates from 20 (20) **********
CINAHL	Database: EBSCOhost CINAHL Plus with Full Text Search Strategy: ---------- 1 (MH "Hemodialysis+") OR "hemodialysis or haemodialysis" (12152) 2 (MH "Hemodiafiltration") OR "hemodiafiltration or haemodiafiltration" (258) 3 hemofiltration or haemofiltration (932) 4 (MH "Dialysis Patients") OR "Renal Dialysis" (3800) 5 1 or 2 or 3 or 4 (15223) 6 (MH "Protein-Energy Malnutrition+") (837) 7 (MH "Malnutrition") OR "Malnutrition" (10550) 8 (MH "Nutritional Support+") OR "Nutritional Support" (27967) 9 nutritional supplementation (544) 10 (MH "Nutritional Status") OR "Nutritional Status" (13633) 11 "oral nutrition*" (513) 12 (MH "Enteral Nutrition") OR "Enteral nutrition*" (8129) 13 (MH "Parenteral Nutrition+") OR (MH "Peripheral Parenteral Nutrition") OR "parenteral nutrition*" OR (MH "Intradialytic Parenteral Nutrition") (6596) 14 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (48508) 15 5 and 14 (776) 16 11 or 12 or 13 (13387) 17 15 and 16 (130) 18 limit 17 to yr="2009 -Current" (55) **********

5. Search for ongoing primary research **Date Searched: 10/11/17**	
Source:	**Evidence:**

Clinicaltrials.gov	Search: Hemodialysis and nutrition; Haemodialysis and nutrition; hemodialysis AND parenteral; haemodialysis AND parenteral Results: Lacson, Eduardo, et al. "Potential impact of nutritional intervention on end-stage renal disease hospitalization, death, and treatment costs." Journal of Renal Nutrition 17.6 (2007): 363-371. Marsen, Tobias A., et al. "Intradialytic parenteral nutrition in maintenance hemodialysis patients suffering from protein-energy wasting. Results of a multicenter, open, prospective, randomized trial." Clinical Nutrition (2015). Effects of Nutritional Supplementation on Protein and Energy Homeostasis in Malnourished Chronic Hemodialysis Patients. NCT00244075. (Completed, no results)
HSRProj (Health Services Research Projects in Progress)	Search: Hemodialysis; Haemodialysis Results: None

APPENDIX D: LIST OF EXCLUDED STUDIES

Exclude reasons: B=Relevant for background information only, 1=Ineligible population, 2=Ineligible intervention, 3=Ineligible comparator, 4=Ineligible outcome, 5=Ineligible timing, 6=Ineligible study design, 7=Ineligible publication type 8=Outdated or ineligible systematic review, 9=non-English language, 10=Full text not available

#	Citation	Exclude reason
1.	Intradialytic Parenteral Nutrition (IDPN) for End-Stage Renal Disease in Adults. *Hayes Brief.* 2008.	B
2.	Intradialytic Parenteral Nutrition (IDPN) for End-Stage Renal Disease in Adults. *Hayes Annual Review.* 2010.	B
3.	Intradialytic Parenteral Nutrition for End-Stage Renal Disease in Adults. *Hayes Search & Summary.* 2017.	B
4.	Ash S, Campbell KL, Bogard J, Millichamp A. Nutrition prescription to achieve positive outcomes in chronic kidney disease: a systematic review. *Nutrients.* 2014;6(1):416-451.	B
5.	Avery-Lynch M. Intradialytic parenteral nutrition in hemodialysis patients: Acute and chronic intervention. *CANNT journal = Journal ACITN.* 2006;16(2):30-33.	E6
6.	Baltz PS, Shuster M. Intradialytic parenteral nutrition as a therapy for malnourished hemodialysis patients. *ANNA journal.* 1992;19(1):72-73.	E6
7.	Basic-Jukic N, Racki S, Kes P, et al. [How to prevent protein-energy wasting in patients with chronic kidney disease--position statement of the Croatian Society of Nephrology, Dialysis and Transplantation]. *Acta Medica Croatica.* 2014;68(2):191-199.	E9
8.	Basic-Jukic N, Radic J, Klaric D, et al. [Croatian guidelines for screening, prevention and treatment of protein-energy wasting in chronic kidney disease patients]. *Lijecnicki Vjesnik.* 2015;137(1-2):1-8.	E9
9.	Berneis K, Iseli-Schaub J, Garbani E, Meier R, Kiss D. Effects of intradialytic parenteral nutrition in chronic haemodialysis patients with malnutrition: a pilot study. *Wiener klinische Wochenschrift.* 1999;111(21):876-881.	E6
10.	Bilbrey G. Is intradialytic parenteral nutrition of benefit in hemodialysis patients? *Semin Dialysis.* 1993;6:168-170.	E6
11.	Bilbrey G, Cohen T. Identification and treatment of protein calorie malnutrition in chronic hemodialysis patients. *Dialysis & transplantation.* 1989;18(12):669-700.	E6
12.	Bossola M, Giungi S, Luciani G, Tazza L. Interventions to counteract anorexia in dialysis patients. *Journal of Renal Nutrition.* 2011;21(1):16-19.	E7
13.	Bossola M, Tazza L, Giungi S, Rosa F, Luciani G. Artificial nutritional support in chronic hemodialysis patients: a narrative review. *Journal of Renal Nutrition.* 2010;20(4):213-223.	B
14.	Bossola M, Tazza L, Vulpio C, et al. [Malnutrition in patients on chronic hemodialysis: prevalence, pathogenesis, and treatment]. *Giornale Italiano di Nefrologia.* 2009;26(2):201-214.	E9
15.	Bozzoli L, Sabatino A, Regolisti G, et al. [Protein-energy wasting and nutritional supplementation in chronic hemodialysis]. *Giornale Italiano di Nefrologia.* 2015;32(5):Sep-Oct.	E9
16.	Brown RO, Compher C, Parenteral ASf, Directors ENBo. ASPEN clinical guidelines: nutrition support in adult acute and chronic renal failure. *Journal of Parenteral and Enteral Nutrition.* 2010;34(4):366-377.	G
17.	CADTH. Guidelines for Renal Care and Dialysis for Adults with Renal Disease. 2007.	E7
18.	Cano NJ, Aparicio M, Brunori G, et al. ESPEN Guidelines on Parenteral Nutrition: adult	G

	renal failure. *Clinical Nutrition.* 2009;28(4):401-414.	
19.	Cano NJ, Saingra Y, Dupuy AM, et al. Intradialytic parenteral nutrition: comparison of olive oil versus soybean oil-based lipid emulsions. *The British journal of nutrition.* 2006;95(1):152-159.	E3
20.	Carrero JJ, Stenvinkel P, Cuppari L, et al. Etiology of the protein-energy wasting syndrome in chronic kidney disease: a consensus statement from the International Society of Renal Nutrition and Metabolism (ISRNM). *J Ren Nutr.* 2013;23(2):77-90.	B
21.	Cheenam B, Leena P. Dietary intervention and protein supplementation in chronic kidney disease patients undergoing hemodialysis. *Asian Journal of Pharmaceutical and Clinical Research.* 2015;8(4):230-232.	E2
22.	Cherry N, Shalansky K. Efficacy of intradialytic parenteral nutrition in malnourished hemodialysis patients. *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists.* 2002;59(18):1736-1741.	E6
23.	Cheu C, Pearson J, Dahlerus C, et al. Association between oral nutritional supplementation and clinical outcomes among patients with ESRD. *Clinical Journal of The American Society of Nephrology: CJASN.* 2013;8(1):100-107.	E2
24.	Corbello J, Rosner MH. Intradialytic total parenteral nutrition (IDPN): evidence-based recommendations. *Practical gastroenterology.* 2009:13.	B
25.	Czekalski S, Hozejowski R. Intradialytic amino acids supplementation in hemodialysis patients with malnutrition: results of a multicenter cohort study. *J Ren Nutr.* 2004;14(2):82-88.	E6
26.	Dahlan R, Biyani M, McCormick BB. High mortality following gastrostomy tube insertion in adult peritoneal dialysis patients: case report and literature review. *Endoscopy.* 2013;45 Suppl 2 UCTN:E313-314.	E1
27.	Department of Veterans Affairs. VHA Handbook 1109.05: Nutrition Therapy. In: Administration VH, ed. Washington D.C.: Department of Veterans Affairs; 2013.	G
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29.	Downs J. Nutritional management of acute kidney injury in the critically ill: a focus on enteral feeding. *South African Journal of Clinical Nutrition.* 2014;27(4):187-193.	E7
30.	Druml W, Kierdorf HP, Working group for developing the guidelines for parenteral nutrition of The German Association for Nutritional M. Parenteral nutrition in patients with renal failure - Guidelines on Parenteral Nutrition, Chapter 17. *German Medical Science.* 2009;7:Doc11.	G
31.	Dukkipati R, Kalantar-Zadeh K, Kopple JD. Is there a role for intradialytic parenteral nutrition? A review of the evidence. *American Journal of Kidney Diseases.* 2010;55(2):352-364.	E7
32.	Fausz C, Sostaric B. Diabetic ESRD patient supported with intradialytic parenteral nutrition. *ANNA journal.* 1992;19(5):485-486.	E6
33.	Fernandez-Reyes MJ, Sanchez R, Garcia L, et al. Acute responses of gastrointestinal hormones to both oral and parenteral intradialytic nutrition. *American Journal of Nephrology.* 2010;32(3):272-278.	E4
34.	Fleet M, Osman F, Komaragiri R, Fritz A. Protein catabolism in advanced renal disease: role of cytokines. *Clinical Nephrology.* 2008;70(2):91-100.	E4
35	Fuhrman MP. Intradialytic parenteral nutrition and intraperitoneal nutrition. *Nutrition in Clinical Practice.* 2009;24(4):470-480.	E7
36.	Foulks CJ. The effect of intradialytic parenteral nutrition on hospitalization rate and mortality in malnourished hemodialysis patients. Journal of Renal Nutrition. 1994;4(1):5-10.	E6
37.	Fuhrman T, Parker M. Intradialytic Parenteral Nutrition. *Support Line.* 2015;37(1):3-7.	B
38.	Garcia de Lorenzo A, Arrieta J, Ayucar A, et al. [Intra-dialysis parenteral nutrition in	E9

	chronic renal patients: consensus SEN-SENPE]. *Nutricion Hospitalaria.* 2010;25(3):375-377.	
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46.	Ikizler TA. Optimal nutrition in hemodialysis patients. *Advances in Chronic Kidney Disease.* 2013;20(2):181-189.	E6
47.	Ikizler TA, Cano NJ, Franch H, et al. Prevention and treatment of protein energy wasting in chronic kidney disease patients: a consensus statement by the International Society of Renal Nutrition and Metabolism. *Kidney International.* 2013;84(6):1096-1107.	G
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76.	Polidoro M. [IDPN: effects on the treatment of CKD-MBD]. *Giornale Italiano di Nefrologia.* 2015;32(4):Jul-Aug.	E9
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	chronic hemodialysis patients with an amino acid solution (RenAmin Amino Acid Injection) formulated for renal failure. *Perspectives in Clinical Nutrition Baltimore, MD: Urban & Schwarzenberg.* 1989:191-205.	
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96.	Weiner DE, Kapoian T, Johnson DS. Nutrition, vitamin D, and health outcomes in hemodialysis: time for a feeding frenzy? *Current Opinion in Nephrology & Hypertension.* 2015;24(6):546-556.	B
97.	Weiner DE, Tighiouart H, Ladik V, Meyer KB, Zager PG, Johnson DS. Oral intradialytic nutritional supplement use and mortality in hemodialysis patients. *American Journal of Kidney Diseases.* 2014;63(2):276-285.	B
98.	Wolfson M. Use of intradialytic parenteral nutrition in hemodialysis patients. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 1994;23(6):856-858.	E6
99.	Wolfson M, Jones MR, Kopple JD. Amino acid losses during hemodialysis with infusion of amino acids and glucose. *Kidney Int.* 1982;21(3):500-506.	E4
100.	Wong P, Smith P, Rodger D. The use of intradialytic parenteral nutrition to treat malnutrition: a case study. *CANNT journal = Journal ACITN.* 2003;13(2):31-46; quiz 37-39,46-38.	E6
101.	Worthington P, Balint J, Bechtold M, et al. When Is Parenteral Nutrition Appropriate? *Journal of Parenteral and Enteral Nutrition.* 2017;41(3):324-377.	G
102.	Wright M, Jones C. *Nutrition in CKD 5th Edition.* UK Renal Association, 2010.; 2010.	G

APPENDIX E: EVIDENCE TABLES

DATA ABSTRACTION OF INCLUDED PRIMARY STUDIES

Data Abstraction of Included Studies (IDPN vs Comparator)

Author Year N	Study Design, Setting, Follow-up Duration	Baseline patient characteristics	IDPN characteristics Dialysis timing and duration of treatment Comparator	Criteria for malnutrition	Patient Health Outcomes	Biochemical Outcomes	Anthropometric Outcomes	Nutritional Score Outcomes
Cano 1990[10] N= 26	RCT, Single center, 12 wks	Mean age: 58 yr %male: 58% %white: NR BW (%): 88.7% SA (g/dL): 3.7 SGA: NR	IDPN (Lipid/AA) Dialysis 3x/wk 12 wks Usual recommended diet	PA < 300 mg/L	NR	Mean change: SA (g/L):0.95 vs -0.43, P < .05 PA (mg/L): 20 vs -18, P < .05	Mean change: BW (%): 2.0 vs -1.5, P < .01 MAC: 3.67 vs -0.36, P < .025 TSF: 2.00 vs -3.14, P = NS	NR
Cano 2007[11] N= 186	RCT, Multicenter, 2 years	Mean age: 68 yr %male: 47% %white: NR BMI: 22.8 SA (g/dL): 3.16 SGA: NR Karnofsky score: 65.5	IDPN (Protein/Lipid/Glucose/AA) + oral supplements Dialysis timing per patient usual dialysis schedule Treatment over 1 yr Oral supplements	2 of the following: BMI < 20, BW loss > 10%, SA < 3.5 g/dL, PA < 300 mg/L	Mortality: 43% vs 39%, P = NS Hospitalization rate (#days hosp./days follow-up): 0.08 vs 0.06 (month 12 to 24) P = NS No change in Karnofsy score in either group	No difference in change in SA or PA (data NR)	No difference in change in BMI (data NR)	NR
Capelli 1994[12] N= 81	RC, Single center, 1 yr	Mean age: 60 yr %male: 51% %white: 42% BW/BMI: NR SA (g/dL): 3.02 SGA: NR	IDPN (Protien/Lipid/Dextrose) Dialysis 3x/wk for 9 months (avg.) Usual recommended diet + oral supplements (dependent on SA)	SA < 3.5 g/dL and BW < 10% of ideal or > 10% weight loss	Survival: RR = 1.34, P < .01 (Cox) Time to death (mo) for non-survivors: 16.9 vs 7.5, P < .01	Mean change: SA (g/dL) Survivors: 0.53 (P = NS) vs 0.57 (P = NS) Nonsurvivors: -0.11 (P = NS) vs 0.22 (P = NS)	Mean change: BW (lb) Survivors: 26 (P = .01) vs -2 (P = NS) Nonsurvivors: 6.1 (P = NS) vs 1.3 (P = NS)	NR

Author Year N	Study Design, Setting, Follow-up Duration	Baseline patient characteristics	IDPN characteristics Dialysis timing and duration of treatment Comparator	Criteria for malnutrition	Patient Health Outcomes	Biochemical Outcomes	Anthropometric Outcomes	Nutritional Score Outcomes
Chertow 1994[13] N= 24,196	RC, Multicenter, 1 yr	Mean age: 58 yr %male: 49% %white: 48% BW.BMI: NR SA (g/dL): 3.74 SGA: NR	IDPN (details NR) Usual recommended diet	NR	OR death: (SA ≥ 4.0 g/dL & CRE > 8.0 mg/dL) = 2.6 (95% CI 1.34 - 5.04) SA ≤ 3.3 =0.72* (P < .01) SA ≤ 3.0 g/dL = 0.57 (95% CI 0.44 - 0.77)	NR	NR	NR
Hiroshige 1998[14] N= 28	PC, Single center, 1 yr	Mean age: 77 yr %male: 57% %white: NR BMI: 19.2 SA (g/dL): 3.41 SGA: NR	IDPN (Dextrose/Lipids/AA) Dialysis 3x/wk for 1 yr Usual recommended diet	Nutritional assessment (details NR)	Mortality: 0% vs 27.8%, (P < .02)	Mean change: SA (g/dL) 0.2 (P < .01) vs -0.2 (P < .01)*	Mean change: BMI (kg/m2): 1.0 (P < .05) vs -1.5 (P < .05)* BW (kg): 3 (P < .05) vs -2.5 (P < .05)* MAC: -0.06 (P < 0.05) vs 0.07 (P < .05) TSF: -0.05 (P < 0.05) vs 0.2 (P < .01)*	NR
Joannidis 2008[15] N= 12	PC, Multicenter, 6 months	Mean age: 80 yr %male: 50% %white: NR BMI: 22.4 SA (g/dL): 3.57 SGA: NR	IDPN (AA/Glucose/Lipids) During normal dialysis schedule for 6 mo Usual recommended diet	nPCR < 1g/kg/day, hs-CRP ≥ 0.5mg, SA ≤ 4 g/dL and BMI < 26	Mortality: 0% vs 17% (P NR)	Mean change: SA (g/dL): -0.02 (P = NS) vs 0.23 (P = .03)	Mean change: BW (kg) 1.2 (P = 0.03) vs 0 (P = NS) BMI: 0.9 (P = 0.03) vs 0 (P = NS	NR

Author Year N	Study Design, Setting, Follow-up Duration	Baseline patient characteristics	IDPN characteristics Dialysis timing and duration of treatment Comparator	Criteria for malnutrition	Patient Health Outcomes	Biochemical Outcomes	Anthropometric Outcomes	Nutritional Score Outcomes
Liu 2016[16] N= 32	RCT, Single center, 9 months	Mean age: 72 % male: 44 % white: 0% BMI: 21.4 SA (g/dL): 3.74 SGA: Grade B=31.3%, Grade C=0.09%	IDPN (AA+glucose OR glucose only) Dialysis 3x/wk for 9 mo Nutrition counseling and oral supplements	1 or more of: SA < 3.5 g/dL, PA < 200 mg/dL, PCR 1.1 g/kg/day	NR	Mean change: SA (g/L): AA Group = -0.30 vs Glucose Group = -2.25 vs Control = -1.45 P = 0.554 PA (mg/L): AA group = 9.25 vs Glucose Group = 32.5 vs Control = -13.30 P = 0.427	NR	Mean change: SGA (level B) AA Group = -8.3% vs Glucose Group = 0% vs Control = 20%, P value NR; (level C): AA Group = 0% vs Glucose Group = -10% vs Control = 0%, P value NR
Marsen 2017[17] N= 107	RCT, Multicenter, 28 weeks	Mean age: 74 % male: 47% %white: NR BMI: 22.6 SA(g/dL): 3.44 SGA: Grade B= 75.9%; Grade C= 24%	IDPN Dialysis 3x/wk for 16 wks Nutritional counseling	SA < 3.5 g/dL, PA < 250 mg/dL, SGA level B or C	Mortality: 26.4% (14/53) vs 12.9% (7/54) (P = NR) Hospitalization: 59.0% vs 43.2%, P = .1509 Health related QoL (SF-12) score change from baseline at 16 wks. -2.74 vs 0.34, P = .1175	Positive response to IDPN (≥ 30mg/L increase in PA) 48.7% vs 31.8% at week 16 (P = .1164) Patients achieving > 15% increase from baseline at week 4, PA (mg/L): 41% vs 20.5%, P = .0415	NR	Improved SGA score by one grade: 20.5% vs 13.6%, P = .4037

Author Year N	Study Design, Setting, Follow-up Duration	Baseline patient characteristics	IDPN characteristics Dialysis timing and duration of treatment Comparator	Criteria for malnutrition	Patient Health Outcomes	Biochemical Outcomes	Anthropometric Outcomes	Nutritional Score Outcomes
Oguz 2001[18] N= 20	PC, Single center, 4 months	Mean age: NR %male: NR %white: NR BMI: 23.4 SA (g/dL): 3.8 SGA: NR	AA only Dialysis 3x/wk for 4 mo Oral AA	SA < 4 g/dL, total cholesterol < 150 mg/dL, PA < 200 mg/dL	NR	Mean change: SA (g/dl): 0.18 (P = .048) vs 0.28 (P = .17)	Mean change: BMI: -0.10 (P = 0.87) vs -0.10 (P = .69) MAC: -1 (P = .09) vs 0.47 (P = .35) TSF: -0.43 (P = 0.5) vs 0.42 (P = .66)	NR
Piraino 1981[19] N= 46	PC, Single center, 20 weeks	NR	IDPN (EAA + NEAA + glucose OR EAA + glucose) Dialysis 3-4x/wk for 20 weeks Weight stable chronic HD patients	≥ 10 or 15% loss of dry weight	NR	No significant difference in SA before or after treatment compared to control (data NR)	NR	NR
Thabet 2017[20] N= 40	RCT, Single center, 6 months	Mean age: 37 yr %male: 58% %white: NR BMI: 19.41 SA (g/dL): 3.02 SGA: NR	IDPN + erythropoietin + IV iron dextran + folic acid + vitamin B12 3x/wk for 6 mo Usual care + erythropoietin + IV iron dextran + folic acid + vitamin B12	BMI < 23, positive MIS, SA < 3.5 g/dL	No improvement in functional capacity (data NR)	Mean change: SA (g/dL) 0.93 (P = .001) vs -0.14 (P = 0.316)	Mean change: BMI 2.8 (P = .001) vs 0.03 (P = .981)	Mean change: MIS -8.75 (P = .001) vs 0.25 (P = .716)_

*Estimated from Figure; Table does not include Cranford 1998, only included for cost-effectiveness outcomes

Abbreviations: AA=amino acids, MAC=mid-arm circumference, BMI=body mass index, BW=body weight, CRE=creatinine, EAA=essential amino acids, IDPN=intradialytic parenteral nutrition, NEAA=non-essential amino acids, NS=not significant, NR=not reported, PA=serum pre-albumin, SA=serum albumin, SGA=subjective global assessment (Grade A: well-nourished, B: mild to moderately malnourished, C: severely malnourished), TSF=triceps skinfold, RC=retrospective cohor,; PC=prospective cohort; MIS=malnutrition inflammation score, nPCR=normalized protein catabolic rate, hs-CRP=high-sensitive C-reactive protein

QUALITY ASSESSMENT OF INCLUDED STUDIES

Quality Assessment of Included RCTs

Author Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Masked outcome assessor, Care provider, Patient?	Outcome measurement equal, reliable, and valid?	Intention-to-treat (ITT) analysis	Acceptable levels of crossovers, adherence, and contamination?	Acceptable levels of overall attrition and between-group differences in attrition?	Quality Rating (Good, Fair, Poor)
Cano 1990[10]	Unclear	Unclear	Yes NS differences in demographic or nutritional information	Unclear No No	Yes	Unclear No mention of missing data or crossovers	Unclear No mention of missing data or crossovers	Unclear No mention of missing data or crossovers	Fair
Cano 2007[11]	Unclear Sequence generation not described	No Opaque sealed envelopes; QA guidance states opaque envelopes as an inadequate approach	Yes NS differences in demographic, nutritional indices at baseline	Unclear No No	Yes	Yes	No IDPN group: 26% discont. oral supp, 24% discont. IDPN Control: 19% discont. oral supp	Yes No patients lost to follow-up	Fair
Liu 2016[16]	Yes Used random numbers table	Unclear	Yes NS differences in demographic or nutrition information	Unclear No No	Yes	No 11% (4/36) of study population were not included in the final analysis due to transfer to another hospital	Yes	No Attrition: 17% control vs 17% glucose vs 0% AA; < 20%, but >10% difference between groups.	Fair
Marsen 2017[17]	Unclear Consecutively randomized in	Yes Contract	Yes NS differences in	Unclear No	Yes	No 16% (17/107) of	Yes 14% (15/107,	Yes 17% vs 15%	Fair

Author Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Masked outcome assessor, Care provider, Patient?	Outcome measurement equal, reliable, and valid?	Intention-to-treat (ITT) analysis	Acceptable levels of crossovers, adherence, and contamination?	Acceptable levels of overall attrition and between-group differences in attrition?	Quality Rating (Good, Fair, Poor)
	blocks of 4 based on a generated randomization schedule; cannot verify comparability at baseline of randomized group	research organization controlled randomization; "centralized" randomization	demographic information; report analyzed groups but not randomized groups	No		the study population were not included in the final ITT analysis due to missing data	excluding deaths) discontinued therapy overall, only one crossover and no contamination reported.		
Thabet 2017[20]	Unclear Sequence generation not described; randomized in blocks of 4 as determined by researcher	Unclear Not described	No Intervention group had significantly lower baseline BMI and creatinine, higher MIS score	Unclear No No	Yes	Yes No dropout	Unclear Adherence not described	Yes No dropout	Fair

Abbreviations: AA=amino acids, BMI=body mass index, discont=discontinued, IDPN=intradialytic parenteral nutrition, NS=not significant, QA=quality analysis, sup.=supplement

Quality Assessment of Included Observational Studies

Author Year	Risk of selection bias? (yes/no/unclear)	Risk of performance bias? (yes/no/unclear)	Risk of detection bias? (yes/no/unclear)	Risk of bias due to confounding? (yes/no/unclear)	Risk of Attrition bias? (yes/no/unclear)	Risk of reporting bias? (yes/no/unclear)	Overall Quality (Good/Fair/Poor)
Capelli 1994[12]	Unclear No information about number of exclusions	No All patients followed same algorithm for treatment protocol	No Objective outcomes	Unclear Patients similar at baseline, but did not include serum albumin, weight, etcetera, which may have been unbalanced (Table 5). Adjusted for demographic and dialysis factors, potential for residual confounding if IDPN group was more malnourished	Unclear No description of handling of missing data	Unclear	Fair
Chertow 1994[13]	No Every patient in a national database receiving hemodialysis at the centers during the study period were included	Unclear No info on other interventions received in IDPN or control groups	No Objective outcomes	Unclear Differences at baseline (serum albumin, creatinine, urea reduction ratio, *etc*), adjusted for differences, potential for residual confounding if IDPN group was more malnourished (*ie*, higher weight loss)	Unclear No description of handling of missing data	Unclear	Fair
Hiroshige 1998[14]	Unclear No information about number of exclusions	No All patients prescribed renal diet, followed same treatment protocol	No Objective outcomes	Unclear Control group consisted of those refusing IDPN (reasons not given – potentially related to disease status). IDPN group significantly older (81 vs 74 yrs) at baseline. No adjustment for potential confounders.	Unclear No description of handling of missing data	Unclear	Poor

Author Year	Risk of selection bias? (yes/no/unclear)	Risk of performance bias? (yes/no/unclear)	Risk of detection bias? (yes/no/unclear)	Risk of bias due to confounding? (yes/no/unclear)	Risk of Attrition bias? (yes/no/unclear)	Risk of reporting bias? (yes/no/unclear)	Overall Quality (Good/Fair/Poor)
Joannidis 2008[15]	Unclear No information about number of exclusions	No	No	Unclear Controls matched for age, sex, BMI, and comorbidity. Similar at baseline except nPCR significantly lower in controls, no adjustment	No	Unclear	Fair
Oguz 2001[18]	Unclear Unclear how intervention and control groups were chosen	Unclear 40% transferred from oral group to IDPN due to non-compliance and did not get first week of IDPN	No	Unclear State no differences between groups, but no data given and do not mention nutritional indicators (serum albumin, *etc*). No adjustment for potential confounders.	No	Unclear	Poor
Piraino 1981[19]	Yes No information on exclusions; unclear how different intervention groups were chosen, unclear if there were other groups (4-13?) not included in analysis	Unclear Treatment unbalanced between intervention groups; no information on control group	No	Yes Group 2 (combined amino acid and glucose solution) may have had worse prognosis due to hyperparathyroidism and related issues; no information on demographics or comorbidities at baseline. No adjustment for potential confounders	No	Unclear Potential suppression of patient groups 4 to 13	Poor

Abbreviations: BMI=body mass index, IDPN=intradialytic parenteral nutrition, nPCR=normalized Protein Catabolic Rate

STRENGTH OF EVIDENCE FOR INCLUDED STUDIES

SOE Grade (High, moderate, low)	No. Studies Study Design (N)	Study Limitations (High, medium, low)	Directness (Direct or indirect)	Consistency (Consistent, inconsistent, unknown for single study)	Precision (precise or imprecise)	Reporting Bias (Suspected, undetected)	Other Issues (None or describe)	Finding (Results – describe direction in words (greater or lower risk or no difference) and provide data
Mortality								
IDPN vs oral supplements: Low	1 RCT[11] (186)	Medium	Direct	Unknown	Imprecise	Undetected	None	No difference in mortality: 43% (IDPN) vs 39% (control) (P = NS)
IDPN vs dietary counseling: Insufficient	1 RCT[17] (107)	Medium	Indirect	Unknown	Imprecise	Suspected: Main threshold outcome not listed in protocol	None	26.4% (IDPN) vs 15.9% (control) (P = NR)
IDPN vs usual care*: SA ≤ 3.3 g/dL Low	2 Cohorts[12,13] (24,277)	Medium	Indirect	Consistent	Precise	Undetected	None	Lower mortality/improved survival with IDPN (OR death range 0.57** to 0.72**, P < .01),[13] RR survival = 1.34 (P < .01)[12]
IDPN vs usual care*: SA > 3.3 g/dL Low	3 Cohorts[13,14] (24,224)	Medium	Indirect	Inconsistent	Precise	Undetected	None	Higher mortality with IDPN in subgroup of patients with SA ≥ 3.5 g/dL (OR death for SA ≥ 4.0 g/dl and CRE ≥ 8 mg/dL = 2.6 (1.34 to 5.04)).[13] No difference in mortality with IDPN in subgroup of patients with SA ≤ 3.5 (OR = 1.0**) or SA ≤ 3.4 (OR = 0.86**)[13] With baseline SA = 3.41 lower mortality with IDPN 0% vs 28% (P < .02)[14]
Hospitalization								
IDPN vs oral supplements: Low	1 RCT[11] (186)	Medium	Direct	Unknown	Imprecise	Undetected	None	No difference in hospitalization rate (# days hospitalization/ follow-up):

SOE Grade (High, moderate, low)	No. Studies Study Design (N)	Study Limitations (High, medium, low)	Directness (Direct or indirect)	Consistency (Consistent, inconsistent, unknown for single study)	Precision (precise or imprecise)	Reporting Bias (Suspected, undetected)	Other Issues (None or describe)	Finding (Results – describe direction in words (greater or lower risk or no difference) and provide data
Mortality								
								.008 (IDPN) vs 0.06 (control) (P = NS)
IDPN vs dietary counseling: Insufficient	1 RCT[17] (107)	Medium	Indirect	Unknown	Imprecise	Suspected: Main threshold outcome not listed in protocol	None	No difference in hospitalization: 59% (IDPN) vs 43.2% (control) (P = .15)
Quality of Life/Functional Impairment								
IDPN vs oral supplements: Low	1 RCT[11] (186)	Medium	Direct	Unknown	Imprecise	Undetected	None	No difference in function as measured by Karnofsky score (data NR)
IDPN vs dietary counseling: Insufficient	1 RCT[17] (107)	Medium	Indirect	Unknown	Imprecise	Suspected: Main threshold outcome not listed in protocol	None	No difference QoL as measured by SF-12:- 2.74 (IDPN) vs 0.34 (control), P = .1175
IDPN vs usual care*: Low	1 RCT[20] (40)	Medium	Indirect	Unknown	Imprecise	Undetected	None	No improvement in functional capacity in either group (data NR)
% meeting threshold for nutritional improvement								
IDPN vs dietary counseling: Insufficient	1 RCT[17] (107)	Medium	Indirect	Unknown	Imprecise	Suspected: Main threshold outcome not listed in protocol	None	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)

Abbreviations: IDPN=intradialytic parenteral nutrition, NR=not reported, NS=not significant, SA=serum albumin, QoL=quality of life; CRE=creatinine

APPENDIX F: PEER REVIEW

Comment Number	Reviewer Number	Comment	Author Response
Are the objectives, scope, and methods for this review clearly described?			
1.	1	Yes	None
2.	2	Yes	None
3.	3	Yes	None
4.	4	Yes	None
5.	5	Yes	None
6.	6	Yes	None
Is there any indication of bias in our synthesis of the evidence?			
7.	1	No	None
8.	2	Yes - Portland VA Health Care prpares for VHA and clearly has intenion to reduce costs due to early therapy application	The ESP CC's purpose in developing this evidence brief is to aid the VA Renal Field Advisory Committee in understanding the effectiveness and harms of IDPN for malnourished hemodialysis patients so they may establish national recommendations for its use in VA. Just because something is expensive, doesn't mean that an investigation of its benefits and harms are inherently biased. We investigate a wide range of health care topics with a wide range of costs. We use the same prespecified, transparent, and reproducible methods to critically evaluate all topics regardless of their cost.
9.	3	No	None
10.	4	No	None
11.	5	No	None
12.	6	No	None
Are there any published or unpublished studies that we may have overlooked?			
13.	1	No	None
14.	2	No	None
15.	3	No	None
16.	4	No	None

17.	5	No	None
18.	6	No	None
Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.			
19.	2	The review strives to develop a chain of evidence from the very heterogeneous and sparse literature of only 11 RCTs and cohort studies on the subject of IDPN and to ultimately take a position on whether its use is justified and when it should be started in this population. The reviewers come to completely contrary results compared to the ESPEN recommendation on IDPN in adult renal failure, published in Clin Nutr 2009. This is especially surprising in view of the fact that since 2009 only 3 additional studies on the subject, all of them are RCTs, have been published, and which have found their way into the review process. Of these 3 RCTs, one did not administer IDPN but Aminoacids alone or in addition with Glucose, one made the comparison to vitamins as controls and none addressed the issue of survival. It is therefore surprising that the vote in this review comes to a completely different conclusion about the benefits of IDPN and therefore is more than questionable.	We disagree with this reviewer that our report comes to a different conclusion than the 2009 ESPEN or the 2017 ASPEN guidelines. We state that IDPN may be used for hemodialysis patients who do not respond to dietary counseling, oral, and/or enteral supplementation. The 2009 ESPEN guidelines recommend IDPN "…if nutritional counseling and oral nutritional supplements (ONS) are unsuccessful" (pg. 409)[4] Additionally, the 2017 American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines recommend use of IDPN for patients who are "unable to tolerate adequate oral intake or [enteral nutrition]" (pg. 327)[1] which agree with the findings of our report. We have added clarification that we agree with these existing guidelines to our discussion and conclusion. We agree that the published literature is heterogeneous in nature and have added further discussion of this to the limitations section of the report.
20.	2	One major problem of a general recommendation on the use of IDPN begins with the population being studied. In this VHA population malnutrition is not the consequence of ESRD, i.e. to be assigned to a single cause, but multifactorial and has to be discriminated from the different underlying diseases, the various secondary diseases, the diverse dialysis therapy modalities etc. Accordingly, an evaluation may only come to a general recommendation, if all these causes are excluded or standardized. To my knowledge, this has not been ensured in any of the studies conducted, even if the most recent investigation has endeavored to do so [4].	We agree that the causes of malnutrition are multifactorial. We attempted to explore whether IDPN has differential effects in subgroups of patients based on patient characteristics (disease severity, comorbidities, *etc*), but were unable to due to limitations of the evidence (heterogeneity, lack of sufficient detail on patient characteristics, *etc*). We agree that this is a limitation of the evidence and have added further detail on this to the discussion section.
21.	2	Additionally, the dialysis treatment itself is so heterogeneous that it can affect outcome to varying degrees (fully synthetic vs polysulfone dialyzers, ultra pure dialysate vs. normal dialysate, HDF vs HD). Non of the studies cited has done so.	We agree that dialysis treatment regimen may affect outcome. Studies lacked sufficient detail to assess the differential effect of IDPN based on these differences and we have added discussion of this to our limitations section.
22.	2	IDPN therapy is at minimum able to improve nutritional parameters and is reported cost neutral compared to the alternative hospitalization and hospital costs.	We agree with this chain of logic, but available evidence is yet insufficient to support this.

		Assuming that nutritional parameters predict morbidity and /or mortality, it seems reasonable to speak of not-inferiority of IDPN. Therefore, in the individual case, it should be left to the discretion of the physician to initiate such therapy.	Although studies have shown improvement in mean changes in some nutritional parameters, mean improvements in biochemical markers do not always translate into clinically significant benefits. A single study reported % of patients reaching a threshold of improvement in a single biochemical parameter (15% improvement in serum prealbumin)[17], but the meaningfulness of this improvement is unclear as clinical justification for the threshold was not provided, and we are not aware of evidence linking this threshold to reduced mortality. IDPN resulted in no improvement in a separate clinically-relevant threshold directly linked to mortality (> 30 mg/L improvement in serum prealbumin).[11] Further, our confidence is low in the evidence supporting this reviewer's statement that IDPN is "cost-neutral" due to its imprecision (N=45), indirectness (outdated, lack of information on patient characteristics, dialysis type, and IDPN characteristics), unknown consistency (single study) and methodological limitations (no concurrent non-IDPN comparator)
23.	2	The authors use the title of an "evidence brief", which is misleading and not justified, if any it should be avoided.	Because there is no widely-agreed definition for "evidence brief" and this reviewer did not suggest an alternative, we are unclear of this reviewer's intentions with suggesting avoiding use of the title. Because this reviewer made this statement in introduction to comments 25-31, which include claims that we have misinterpreted the evidence, we can only assume this reviewer made this suggestion in relation to these claims. Below we have provided detailed responses refuting each of this reviewer's claims that we have misinterpreted the evidence.
24.	2	The authors do not mention the problem of comparability in relation to the age of the population studied in the RCTs, which varies from a mean of 37 to a mean of 80 years. In their review the authors either intentionally or forgetfully omit data about the age of the VHA population for which the review is created and which should ultimately serve as a comparison. It must be assumed that the VHA population is over 65 years old, this however would exclude several RCTs for comparison.	We disagree as the overall mean patient age of the included studies was 65 years, which is comparable to the median Veteran age in 2015 of 64 years.[21] We discuss the comparability of the age of the studied patient populations to the Veteran population in our "Limitations" section on page 19 of our report. Although mean patient age

			varied among studies, the majority of studies had mean patient age between 58 and 80 years (with one study reporting a mean patient age of 37 years).
25.	2	The authors come to a recommendation for the non-superority of IDPN versus ONS by regard of three RCTs in their review. However, one of which examined 2-year mortality, hospitalization and quality of life, a second one BMI, albumin, prealbumin and SGA, and a third only improvement in albumin. The attempt to compare these RCTs must be regarded as questionable, since the incomparable of the study structures excludes a similarity in principle. Therefore the concluision on page 18 lines21-24 is incorrect.	We disagree that we are incorrect to conclude that IDPN has not been shown to improve clinically important outcomes overall oral supplements, which agrees with the current ASPEN guidelines.[1] We include two RCTs and one prospective cohort study compared to oral supplements. Regardless of the numerous types of outcomes measured, none found a clinically important benefit with IDPN. We discuss the heterogeneity of the studies a limitation of the evidence.
26.	2	Comparison of IDPN vs dietary counselling was investigated for changes in prealbumin in yet another RCT cited. The results demonstrate significant improvement of prealbumin, a surrogate marker for outcome and survival in hemodialysis patients suffering from PEW. It remains unclear why the authors of this review claim that " IDPN has not demonstrated to improve …. nutritional outcomes" (page 18 line 22). Today several parameters are defined as markers for and discriminate on malnutrition. None of them is superior to the other therefore the data is to be interpreted as a clear advantage of IDPN over dietary counselling.	As we prespecified, our review sought the evidence that would best demonstrate a clinically important benefit of IDPN over recommended treatment, which would be direct evidence of how IDPN compared to other treatments on "clinically-relevant" nutritional status indicators and health outcomes (http://www.crd.york.ac.uk/PROSPERO/; registration number CRD42017074001). We identified the threshold of > 30mg/L increase in serum prealbumin as the strongest nutritional marker because it is the only marker that is supported by prospectively measured nutritional data with identification of a threshold of improvement associated with mortality.[11] On page 18 line 22 we concluded that IDPN has not been demonstrated to improve patient health or nutritional outcomes better than current guideline recommended treatment, including dietary counseling, because a single small RCT (Marsen 2017) provided preliminary evidence that IDPN does not significantly increase > 30mg/L improvements. Although we agree that in Marsen 2017, IDPN improved the percentage of patients reaching a 15% improvement in serum prealbumin at 4 weeks, no clinical justification was given for this threshold and we are not aware of evidence

			linking this threshold to reduced mortality. For this and other reasons outlined in the report, we disagree that demonstration of IDPN improving a single nutritional marker with unknown clinical significance, shows a “clear advantage” of IDPN.
27.	2	The comparison of IDPN vs usual care improperly attempts an argumentative weakening of IDPN by mentioning that “usual recommended diet… may have included dietary recommendations and/or oral supplementation” (page 15, line 20-21), which is purely speculative by the authors and misleadingly weakens the comparator. Such personal speculation should be omitted.	Our discussion of the insufficient characterization of “usual care” is not meant to weaken IDPN. We discuss this lack of detail to point out the limited applicability of these studies and difficulty in assessing applicability to specific clinical circumstances. We have removed the language that usual care may have included dietary recommendations and/or oral supplementation, as we agree it is unclear and not crucial to our main point.
28.	2	Moreover the review misstates results from three essential RCTs. In the Chertow publication Albumin is discriminated at ≤3.4g/dl. The fact that patients with Alb> 3.4g/dl received IDPN should be mentioned with all due caution and may not be interpreted in this context, as Alb cut-off for malnutrition is 3,5g/dl. These patients therefor cannot be considered to be malnourished without additional parameters specific for PEW, eg. BMI or prealbumin.	We agree that patients with higher baseline serum albumin levels may not have been considered malnourished and the findings should be interpreted with caution. Since this cohort study (Chertow 1994) used a large retrospective database and assigned intervention and control groups based on receipt of IDPN alone, we do not have information about why patients with serum albumin above 3.5 were treated with IDPN and if they had other nutritional parameters of malnutrition. This lack of information about the intervention and control groups is discussed as a limitation of these findings. We include 2 RCTs compared to oral supplements and 1 RCT compared to dietary counseling. Please see our responses to comments #26 and #27 for our detailed rebuttal about the misstated results from the “three essential RCTs”.
29.	2	Furthermore the results should not be weakened just because there is a lack of information on control interventions, quality of life etc. Undoubtedly, as well as for the Capelli study [5], a survival advantage for IDPN could be shown.	We disagree and believe the lack of information on control group does limit the interpretation of findings. Without this information, we cannot judge intervention adherence or potential co-interventions in this study and thus cannot determine if the mortality benefit observed can 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. Additionally, for a treatment to best demonstrate a clinically-important benefit over recommended treatments, it should not only reduce the risk of mortality, but also improve the functional status and quality of life of the survivors.
30.	2	Furthermore, it remains unclear why the authors conclude with regard to Thabet's work that “nutritionally related functional capacity is not improved”, as both BMI and Alb increase.	We concluded that “nutritionally related functional capacity is not improved” based on the finding of “no patient had improvement of functional capacity [nutritionally related functional impairment]”(pg 187).[20] We agree with and reported that BMI and serum albumin increased, but those are not measures of functional capacity.
31.	2	It is speculative if RCTs analyzed will be suitable to answer questions on survival benefit. It seems inappropriate, considering the duration of RCTs between 12 weeks and 1 year, to address this question of a survival benefit compared to a usual diet or diatetic counseling. Even 2 years may be still too short to measure for a survival advantage.	We agree that longer follow-up duration is ideal. However, as hemodialysis patients currently only have 57% 3-year survival,[22] improvement in 2-year survival would be a substantial benefit.
32.	2	Of course, tube feeding would be the most efficient measure apart from TPN, but for a population that is ambulatory, tube feeding is closer to non-ambulatory therapy than IDPN or ONS. Therefore the recommendation to comply IDPN with tube feeding fails because of the acceptance.	We agree that appearance and logistics of tube feeding may be barriers to acceptance, as discussed in the introduction section. Despite this, ambulatory feeding tubes are available and thus a comparison of IDPN to enteral tube feeding is feasible.
33.	2	Last but not least, longer study duration is not feasible considering the study costs, sponsors from the industry will not approve for funding because of missing innovation and patent protection. It remains only the longitudinal observation and to burden the health insurance companies as payers themselves.	We have modified our recommendations to not be limited to RCTs due to their higher cost.
34.	2	An additional Key Question 1.1 is missing and should be addressed. Despite speculation on IDPN in non-diabetics, ineffectiveness of IDPN in diabetics with ESRD has been proven on various times but is not mentioned [1,4,5].	We attempted to address diabetics (and other subgroups) with Key Question 4, but the evidence was insufficient as subgroup analysis by diabetes status was only reported in a single, small, non-randomized, retrospective study.[12]
35.	3	This is an excellent report. Very well conducted, comprehensive and the conclusions and recommendations are fair and appropriate.	Thank you.
36.	4	P.1; Lines 31-33: "Intradialytic parenteral nutrition (IDPN) is the infusion of an intravenous nutritional formula during regularly scheduled dialysis sessions.". Suggest to modify the statement so that non-specialists would not misinterpret the	The sentence has been modified as suggested for clarity.

		sentences. Suggested revision "Intradialytic PN (IDPN) is a form of partial parenteral nutrition administered during hemodialysis session. It is not intended to provide the total daily nutrient requirements for the patient."	
37.	4	p.4 line 60 - p.5 line: Consider replacing the definition of malnutrition. Reference 25 is an outdated paper. There is currently an international workgroup comprising researchers and policy makers from Asia, Europe, US, Canada, South American, and Australia to come up with a standardized definition of malnutrition. This workgroup has been meeting for 5 years and the initial report in due to be published. Consider reviewing (and including) these 2 papers in this document as they are the basis and framework for revise definition. It is important to point out that serum protein is not a preferred marker of nutritional status. (Cederholm T et al, Clin Nutr 2015 Jun;34(3):335-4; Malone A, Hamilton C. Nutr Clin Pract. 2013 Dec;28(6):639-50)	We added a figure detailing the new ASPEN consensus recommendations for diagnosing malnutrition in addition to the discussion of the varying diagnostic criteria in current guidelines for treatment of malnutrition in hemodialysis patients. We have also added a discussion around serum protein levels no longer being a preferred marker of nutritional status.
38.	4	p.5 line 21: There seems to be an over-emphasis of the use of specialized oral nutritional supplement (i.e., Nepro). It may be misleading as patients on HD receiving a potassium-restricted diet may also tolerate standard nutritional supplement. And there is no published data to my knowledge that showed better clinical outcomes with specialized oral supplement (e.g., Nepro) over standard supplemental products. This may also affect the cost-estimation on p.6	We mentioned Nepro as it used in the VA, but reference to standard nutritional supplements has been added to this section as well as information on cost of standard nutritional supplements on page 6.
39.	4	p.5. Lines 53-54: Total parenteral nutrition (TPN) is an old term. Currently, we call it parenteral nutrition (PN). This is especially important because IDPN is a form of PN, but not TPN as it only provide PARTIAL nutrition but not total daily needs. Please refer to ASPEN and ESPEN documents for details.	We have removed the reference to TPN and revised this paragraph to discuss PN overall and IDPN as partial PN. “PN is the infusion of an intravenous nutritional formula into the blood stream, and is commonly used among hospitalized patients. 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”
40.	4	p.5 line 60: Please change "i.e." to "e.g.," it is important the ingredients in the brand name products may change over time. So, it would be potentially misleading to use the term Kabiven and premixed solution interchangeably. I would suggest to call these product "commercially available standardized multichamber PN solution" (see https://www.nutritioncare.org/Guidelines_and_Clinical_Resources/Toolkits/Parenteral_Nutrition_Safety_Toolkit/Multi-Chamber_PN__Standardized,_Commercial_Products_Tools_and_Resources/)	Wording has been changed from *ie* to *eg*, and the wording around the products has been changed as suggested to “commercially available standardized multi-chamber PN solution”. The reference to NutriRite has been removed to avoid confusion as it is an individualized solution. A reference to a systematic review of multi-chamber bags has been added to this section from the listed resources.
41.	4	p.17- Key Question 2- It is also worth mentioning that the goal for the "treatment of malnutrition" varied significantly amongst the published studies. Therefore, it is	A discussion of the limitations in the evidence of adverse effects has been expanded under Key

		almost impossible to objectively compare the treatment outcomes and the adverse effect associated with IDPN. There is also a potential treatment bias - patients receiving IDPNs likely have received more frequent laboratory monitoring and symptomatic assessment for fluid and electrolyte disoders. Thus, the actual incidence of adverse events might have been artificially lowered.	Question 2 and in the discussion, including a discussion of the potential for lower adverse events amongst patients receiving IDPN due to increased monitoring.
42.	4	p.17, Key Question 4- I am concerned about the conclusion anchoring lower serum albumin as a the "potential best candidates for IDPN". As mentioned, as a field, we are moving away from using serum albumas a sole indicator for nutritional intervention or assessment of treatment efficiacy. The paper (ref .6) cited is based on older concept. More importantly, the clinical response to protein provision depends on the patient's inflammatory status, concurrent oral intake, as well as the amount of protein provision in the IDPN. The range of protein provision in published studies using IDP varies and the oral nitrogen/protein intake is rarely characterized. Therefore, I think using the serum albumin as a screening criterion or treatment outcome assessment can be very misleading.	We have reframed this section to highlight that we cannot draw conclusions based on the evidence available. We have added discussion of the limitations of serum protein levels in screening and outcome assessment of malnutrition to this section as well as to the introduction and discussion sections.
43.	4	p.19- Lines 26-27: Please revise to "No studies compared IDPN to patient receiving enteral nutrition or enteral tube feeding". Note that orally administered nutritional supplements such as Ensure or Nepro are, indeed, enteral supplements. So, the original statement is incorrect.	We have revised this wording to “no studies compared IDPN to enteral tube feeding” for clarification.
44.	4	Finally, it is worth mentioning that the outcomes of untreated malnutrition is poor and costs associated with subsequent hospitalization for managing malnutrition is high. Therefore, the priority should be on improving/reversing malnutrition in patients with CKD requiring HD. Every attempt should be made to first increase oral intake or the use of enteral nutrition in reversing malnutrition in patients with CKD.	We have added this context to the beginning of the discussion section to highlight the need for treatment of malnutrition in hemodialysis patients.
45.	5	Page 6 Evidence Brief: 2nd paragraph potential for risk for harms (infection, fluid overload, chemical imbalance,.....add hyperglycemia).	We have added hyperglycemia as a potential harm, and also listed it in the adverse events section of the results. As hyperglycemia is a concern among diabetic patients, we have added a discussion of the prevalence of diabetes among Veterans as a potential limitation in the applicability of the studies.

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