Intradialytic Parenteral Nutrition

Policy # 00228
Original Effective Date: 02/20/2008
Current Effective Date: 02/15/2017

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Total Parenteral Nutrition and Enteral Nutrition in the Home is addressed in medical policy 00088.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:
- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider intradialytic parenteral nutrition (IDPN) as an adjunct to hemodialysis when it is offered as an alternative to a regularly scheduled regimen of total parenteral nutrition only in those patients who would be considered candidates for total parenteral nutrition (i.e., 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) to be eligible for coverage.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers intradialytic parenteral nutrition (IDPN) as an adjunct to hemodialysis in patients who would not otherwise be considered candidates for total parenteral nutrition (TPN) to be investigational.*

When Services Are Considered Not Medically Necessary
Based on review of available data, the Company considers intradialytic parenteral nutrition (IDPN) in patients who would be considered a candidate for total parenteral nutrition, but for whom the intradialytic parenteral nutrition is not offered as an alternative to total parenteral nutrition (TPN), but in addition to regularly scheduled infusions to total parenteral nutrition (TPN) to be not medically necessary.**

Background/Overview
Protein calorie malnutrition occurs in an estimated 25% to 40% of those undergoing dialysis. The cause of malnutrition in dialysis patients is often multifactorial and may include underdialysis, chronic inflammation, protein loss in the dialysate solution (particularly in peritoneal dialysis), untreated metabolic acidosis, and decreased oral intake.

The clinical evaluation of malnutrition is multifactorial but typically includes measurement of serum albumin. Serum albumin levels correlate with nutritional status but are imperfect measures of nutrition because they can be affected by multiple other disease states. Protein calorie malnutrition is associated with increased
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morbidity and mortality. For example, the risk of death is increased more than 10-fold in those whose serum albumin levels are less than 2.5 g/dL, and those with a serum albumin near the normal range (ie, 3.5-3.9 g/dL) have a mortality rate twice as high as those with albumin greater than 4.0 g/dL.

In patients receiving chronic dialysis, the National Kidney Foundation currently recommends a daily protein intake of 1.2 g/kg or more in patients undergoing hemodialysis and 1.3 g/kg or more in patients undergoing peritoneal dialysis. When malnutrition is present, a stepwise approach to treatment is generally used, beginning with dietary counseling and diet modifications, followed by oral nutritional supplements, and then by enteral nutrition supplements or parenteral nutritional supplements if needed.

IDPN, which refers to the infusion of hyperalimentation fluids at the time of either hemodialysis or peritoneal dialysis, has been investigated as a technique to treat protein calorie malnutrition in an effort to decrease the associated morbidity and mortality. In hemodialysis, the IDPN infusion is administered through the venous port of the dialysis tubing, typically, 30 minutes after dialysis has begun, and continued throughout the remainder of a dialysis session.

In peritoneal dialysis, sometimes referred to as intraperitoneal parenteral nutrition, amino acid intraperitoneal parenteral nutrition, or intraperitoneal nutrition, parenteral nutrition is provided by using a peritoneal dialysate solution with amino acids, instead of or in addition to glucose, as the osmotic agent.

**FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)  
TPN solutions are compounded by an individual pharmacy from individual ingredients (eg, dextrose, amino acids, trace elements) into a finished medication based on a prescription and are not required to have approval from the U.S. FDA through a new drug application process. Compounding pharmacies have historically been subject to regulation by state pharmacy boards, although FDA has increased its regulatory oversight with the Drug Quality and Security Act of 2013.

Peritoneal dialysis solutions are regulated as drugs by FDA. One amino acid-based peritoneal dialysate, Nutrineal™ PD4, 1.1% Amino Acid Peritoneal Dialysis Solution (Baxter Corp.) is available commercially outside of the United States, but has not been FDA approved.

Centers for Medicare and Medicaid Services (CMS)  
The coverage eligibility of IDPN for Medicare beneficiaries is summarized in a Health Care Financing Administration (HCFA) ruling from December 1996, which established that intradialytic nutrition would be considered eligible for coverage only if the patient would otherwise be a candidate for TPN. This ruling reads in part:

“Medicare coverage policies which apply to parenteral and enteral nutrition therapy items and services apply identically to intradialytic parenteral nutrition therapy items and services, because intradialytic parenteral nutrition therapy is a subset of parenteral and enteral nutrition therapy. Coverage of parenteral and enteral nutrition therapy is amplified in Medicare Coverage Issues manual section 65-10. Daily parenteral therapy is ‘considered reasonable and necessary for a patient with severe pathology of the alimentary tract which does not allow absorption of sufficient nutrients to
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Intradialytic parenteral nutrition therapy is administered to end stage renal disease (ESRD) patients while they are receiving dialysis. ESRD patients sometimes undergo parenteral therapy to replace fluids and nutrients lost during dialysis. ESRD patients must meet all of the parenteral nutrition therapy coverage requirements to receive intradialytic parenteral nutrition therapy. Those patients who do not meet all of the parenteral nutrition therapy coverage requirements are ineligible to receive Medicare coverage of intradialytic parenteral nutrition therapy under the prosthetic device benefit."

The HCFA ruling goes on to clarify the benefits for patients who would be considered candidates for tTPN and when the IDPN is designed to be offered in lieu of a regularly scheduled infusion of TPN.

"However, parenteral and enteral nutrition, including intradialytic parenteral nutrition therapy, services and items which are otherwise covered under section 1861(s)(8) can be denied under section 1862(a)(1) for lack of medical necessity: ... Example, if a Medicare beneficiary with ESRD, a dialysis patient who meets all of the requirements for coverage of parenteral nutrition therapy, receives intradialytic parenteral nutrition therapy during dialysis and also receives parenteral nutrition therapy on the other days of the week when the patient is not on dialysis, it may be determined that the patient is receiving an excessive number of lipids. A claim for Medicare payment that is denied because the patient, who qualifies for parenteral nutrition therapy coverage, is receiving an excessive number of lipids would be denied as not reasonable and necessary under section 1862(a)(1)(A) of the Act... Therefore the precise statutory basis for the coverage or denial of parenteral and enteral nutrition therapy, including intradialytic parenteral nutrition therapy, services and items is crucial and determinative as to whether or not limitation on liability protections can be applied."

**Rationale/Source**
The following is a summary of the key findings to date related to the use of IDPN as an adjunct to hemodialysis.

**Systematic Reviews**
While IDPN has been available for many years, there has never been a consensus regarding either its efficacy or patient selection criteria. In 1993, the Office of Health Technology Assessment, the technology assessment arm of Medicare, published a review concluding that studies of IDPN reported equivocal results, and the data did not validate its efficacy. Subsequently, in 1999, Foulks reported on an evidenced-based evaluation of IDPN. The analysis concluded that the overall quality of the literature was poor; only 3 randomized controlled trials (RCTs) were identified, and 1 was a feasibility study only; the other 2 had methodologic flaws or used types of IDPN that were not routinely used or were not available in the United States. The remaining literature consists of case series, which cannot control for the many variables in the renal dialysis population that may contribute to increased morbidity and mortality. According to Foulks' analysis, most case series had methodologic flaws including heterogeneity in study design, patient selection criteria, types of IDPN used, and adequacy of dialysis. Dukkipati et al conducted a systematic review of IDPN for the treatment of malnutrition in hemodialysis patients in 2010. The authors identified only 3 RCTs and found the data were insufficient to conduct a meta-analysis and to demonstrate net benefits in health outcomes with the use of IDPN. The authors concluded further clinical trials on IDPN are needed, and those
trials should measure survival, quality of life, and nutritional status. In 2010, Sigrist et al reported results from a systematic review of IDPN for patients with chronic kidney disease. The authors evaluated RCTs or systematic reviews of RCTs that specifically enrolled malnourished patients on hemodialysis who were randomized to either IDPN (including full IDPN or amino acids plus carbohydrates only) or any form of enteral or oral nutrition. Three studies met the authors’ inclusion criteria, only one of which reported mortality as an outcome. The data were insufficient to conduct a meta-analysis, and the authors concluded that evidence from clinical studies is insufficient to demonstrate either a net benefit or a net harm associated with the providing IDPN to malnourished hemodialysis patients.

**Randomized Controlled Trials**

An RCT of 186 malnourished hemodialysis patients from 38 treatment centers in France studied the effects of adding IDPN to oral supplementation compared with oral supplementation alone (1 year of treatment with 2-year follow-up). Based on intention-to-treat analysis, no differences were found in 2-year survival, hospitalizations, Karnofsky score, body mass index, or serum albumin and prealbumin levels between treatment groups. The study was powered to detect a 10% reduction in mortality with 78% power (5% α error). Meeting the stated nutritional goals (orally or parenterally) may have improved outcomes; an editorialist suggests that both groups had approximately 15% improved survival compared with historical controls.

**Nonrandomized Comparative Studies**

The largest study is a retrospective case series comparing the morbidity of 1679 IDPN-treated patients with that of 22,517 nontreated patients. This study found that dialysis patients with a serum albumin level of less than 3.4 g/dL who were treated with IDPN had significant increases in albumin and creatinine over time. In addition, these patients experienced a significant decrease in the odds ratio (OR) for death at 1 year compared with those who were not treated with IDPN. Interestingly, the OR for death increased for IDPN-treated patients who had an albumin level of greater than 3.4 mg/dL. Pupim et al performed a detailed analysis of protein metabolism in 7 patients receiving IDPN during hemodialysis. These patients would not have been considered candidates for IDPN on the basis of their nutritional status. While the administration of IDPN was associated with a sharp increase in protein anabolism, the effect was only transient.

A case series was published of 22 hemodialysis patients with acute illnesses (major surgery, infection) treated with IDPN for 1.5 to 48 months as nutritional supplementation (not support). IDPN was discontinued when the following were met: weight ceased to decline, stabilized, or increased; protein catabolic rate was greater than 1.0 g/kg/d; and serum albumin levels were greater than 3.8 g/dL. IDPN was well-tolerated and associated with improvements from baseline of several nutritional parameters. Without a comparison group, it is impossible to conclude that the effects were due to IDPN, and therefore this study does not affect the policy statement regarding patients who would otherwise not be candidates for total parenteral nutrition.

Predictors of IDPN response on hypoalbuminemia were examined in a study of 196 hypoalbuminemic patients receiving maintenance hemodialysis who underwent IDPN. The study suggested that IDPN treatment can improve hypoalbuminemia in patients receiving maintenance hemodialysis and that the likelihood and magnitude of response to IDPN in these patients is associated with the baseline severity of hypoalbuminemia. The authors suggest that this association may be useful in risk stratification of malnourished dialysis patients and recommend that their findings be confirmed through further controlled
trials. Also of potential future interest, Pupim et al reported that in a small series (N=8) of chronic hemodialysis patients, intradialytic oral nutrition or IDPN both led to highly positive whole-body net balance during hemodialysis.

Two other uncontrolled studies also suggest an improved outcome associated with IDPN. Because of the numerous biases inherent in any uncontrolled trial, these studies cannot validate whether IDPN is associated with an improved mortality. The observed treatment effect could be related to a selection bias in which very ill patients, ie, those expected to die, were not offered IDPN. In addition, IDPN administration may be associated with an increased attentiveness to dialysis parameters, counseling, and nutritional advice, etc. These studies suggest that being selected for IDPN may be associated with an improved mortality rate, but analysis of the direct contribution of IDPN will require controlled trials.

In 2012, results from a nonrandomized comparative study comparing changes in serum prealbumin level between hemodialysis patients treated with IDPN and controls were presented in abstract form, but no full-length published results were identified. Statistical calculation was undertaken for 32 patients per study group. IDPN was reported to lead to a significant increase of prealbumin during the 16-week course of treatment (26.31 mg/L), compared with the noninterventional control group (1.84 mg/L, p=0.02). Because of the small sample size, there was a lack of statistical power to evaluate responsiveness of the secondary end points in this study (eg, albumin, transferrin, quality of life).

Section Summary
The available evidence is inadequate to allow conclusions about whether the routine use of IDPN as an adjunct to hemodialysis improves patient outcomes. Although uncontrolled studies suggest that patients treated with IDPN may have improved biochemical markers of malnutrition and survival, controlled trials are needed to allow conclusions about whether IDPN is associated with improved outcomes. A small number of RCTs showed no significant improvements in health outcomes with IDPN as an adjunct to hemodialysis.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this policy are listed in Table 1.

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NCT: national clinical trial.

* Denotes industry-sponsored or cosponsored trial.

Summary of Evidence
Evidence demonstrating the efficacy of IDPN treatment in improving outcomes for patients undergoing hemodialysis is limited. The available evidence demonstrates improvements in intermediate outcomes such as increases in serum albumin and catabolic rate. However, long-term data on survival, quality of life, and other nutritional status outcomes are unavailable. TPN is accepted as a treatment for malnutrition in certain
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cases, and it would be reasonable to offer TPN concurrently with hemodialysis. Therefore, IDPN may only be considered medically necessary when it is offered as an alternative to a regularly scheduled regimen of total TPN in patients who would be considered candidates for TPN. IDPN is considered not medically necessary when added to regularly scheduled infusions of TPN and may be harmful due to the excess administration of lipids. Finally, due to the limited availability of data on IDPN in patients who would not otherwise be considered TPN candidates, the impact on net health outcome is not known. Therefore, IDPN is considered investigational in these patients.

References
7. Ikizler TA. Parenteral nutrition offers no benefit over oral supplementation in malnourished hemodialysis patients. Nephron. Feb 2008;107(2):76-77. PMID 17998928
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02/13/2008 Medical Director review
02/20/2008 Medical Policy Committee approval.
02/04/2009 Medical Director review
02/19/2009 Medical Policy Committee approval. No change to coverage eligibility.
02/04/2010 Medical Policy Committee approval
02/17/2010 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/03/2011 Medical Policy Committee review
02/16/2011 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/02/2012 Medical Policy Committee review
02/15/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/07/2013 Medical Policy Committee review
02/20/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/06/2014 Medical Policy Committee review
02/19/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/05/2015 Medical Policy Committee review
02/18/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/04/2016 Medical Policy Committee review
02/17/2016 Medical Policy Implementation Committee approval. Policy statements edited to clarify that they are intended to apply to parenteral nutrition administered during hemodialysis.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
02/02/2017 Medical Policy Committee review
02/15/2017 Medical Policy Implementation Committee approval. No change to coverage.
Next Scheduled Review Date: 02/2018

Coding
The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®), copyright 2016 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:
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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
   1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
   2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
   3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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