# Medical Policy

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## Title: Chronic Intermittent Intravenous Insulin Therapy

**Professional**
Original Effective Date: December 9, 2016
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| Populations | Interventions | Comparators | Outcomes |
|---|---|---|---|
| Individuals:<br>• With type 1 diabetes | Interventions of interest are:<br>• Chronic intermittent intravenous insulin therapy | Comparators of interest are:<br>• Standard medical management | Relevant outcomes include:<br>• Symptoms<br>• Change in disease status<br>• Treatment-related morbidity |

## DESCRIPTION

Chronic intermittent intravenous insulin therapy (CIIIT) is a technique for delivering variable-dose insulin to diabetic patients with the goal of improved long-term glycemic control. Through an unknown mechanism, CIIIT is postulated to induce insulin-dependent hepatic enzymes to suppress glucose production.

## OBJECTIVE

The objective of this policy is to evaluate whether the use of chronic intermittent intravenous insulin therapy improves glycemic control and reduces end-organ damage outcomes for patients with type 1 diabetes, compared with standard insulin therapy.

## BACKGROUND

### Glucose Homeostasis

Insulin-mediated glucose homeostasis involves 3 primary functions which occur at 3 locations: (1) insulin secretion by the pancreas; (2) glucose uptake, primarily in the muscle, liver, gut, and fat; and (3) hepatic glucose production. In the fasting state, when insulin levels are low, most glucose uptake into cells is non-insulin-mediated. Glucose uptake is then balanced by liver production of glucose. However, after a glucose challenge, insulin binds to specific receptors on the hepatocyte to suppress glucose production. Without this inhibition, as can be seen in diabetic patients, marked hyperglycemia may result.

Medications Used for Glucose Homeostasis in Diabetes

Diabetes is characterized by elevated blood glucose levels due to inadequate or absent insulin production (type 1 diabetes) or due to increased hepatic glucose production, decreased peripheral glucose uptake, and decreased insulin secretion (type 2 diabetes).

Different classes of diabetic drug therapy target different aspects of glucose metabolism. Various insulin secretagogues (eg, sulfonylureas) function by increasing the pancreatic secretion of insulin; thiazolidinediones (eg, pioglitazone [Actos], rosiglitazone [Avandia]) function in part by increasing glucose uptake in the peripheral (principally skeletal) tissues; and biguanides (eg, metformin) function by decreasing hepatic glucose production. While patients with type 2 diabetes may be treated with various combinations of all 3 of these classes of drugs, with or without additional insulin, patients with type 1 diabetes, who have no baseline insulin secretion, receive exogenous insulin therapy. Standard insulin management involves use of subcutaneous injection to mimic a physiologic insulin profile. Intravenous insulin is used in the acute inpatient setting for the management of hyperglycemic emergencies (eg, diabetic ketoacidosis).

## REGULATORY STATUS

Any insulin infusion pump can be used for the purposes of chronic intermittent intravenous insulin therapy. Infusion pumps have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. FDA determined that this device was substantially equivalent to existing devices for the delivery of intravenous medications. FDA product code: lZG.

## POLICY

Chronic intermittent intravenous insulin therapy is considered **experimental / investigational**.

### Policy Guidelines

This policy does not apply to use of intravenous insulin infusions in the inpatient setting (ie, for the treatment of diabetic ketoacidosis or diabetic hyperosmolar coma).

## RATIONALE

This evidence review was conducted through January 26, 2019.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function - including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

### Chronic Intermittent Intravenous Insulin Therapy for Type 1 Diabetes

Clinical Context and Test Purpose

The purpose of CIIIT in patients who have Type 1 diabetes mellitus is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: does the use of CIIIT used to treat patients with Type 1 diabetes mellitus improve net health outcomes?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest are patients with Type 1 diabetes mellitus who need improved glycemic control.

Interventions
The therapy being considered is CIIT. Several forms of chronic intermittent insulin therapy, in which insulin is delivered intravenously or into the peritoneal space, have been evaluated.

CIIIT—also referred to as outpatient intravenous insulin therapy, pulsatile intravenous insulin therapy, hepatic activation therapy, or metabolic activation therapy—involves delivering insulin intravenously once weekly over several hours in a pulsatile fashion using a specialized pump controlled by a computerized program that adjusts the doses based on frequent blood glucose monitoring. CIIIT is principally designed to normalize the hepatic metabolism of glucose. Currently, no studies have been identified that have investigated the proposed mechanism of action of CIIIT in humans.

Aoki et al (1993) proposed that, in patients with type 1 diabetes, lower levels of insulin in the portal vein are associated with a decreased concentration of the liver enzymes required for hepatic metabolism of glucose.[1,] They stated: "We reasoned that if the liver of an IDDM [insulin-dependent diabetes mellitus; ie, type 1 diabetes] patient could be perfused with near-normal concentrations of insulin during meals, the organ could be reactivated," and proposed that intermittent intravenous pulsatile infusions of insulin administered once weekly while the patient ingests a carbohydrate meal would increase the portal vein concentrations of insulin, ultimately stimulating the synthesis of glucokinase and other insulin-dependent enzymes. The pulses are designed to deliver a higher, more physiologic concentration of insulin to the liver than is delivered by traditional subcutaneous injections. This higher level of insulin is thought to more closely mimic the body's natural levels of insulin because it is delivered to the liver. The goal of this outpatient therapy is improved glucose control through improved hepatic activation.

Comparators
The following therapies and practices are currently being used to make decisions about treatment to maintain normogylcemia in patients with Type 1 diabetes mellitus: guideline directed diabetic medical therapy including subcutaneous insulin as well as diabetes self-management with glucose monitoring, diet and exercise regimens.

Outcomes
The general outcomes of interest are symptomatic hyperglycemia and hypoglycemia, disease status changes such as the development of end-organ damage and treatment-related morbidity.

Timing
Patients with Type 1 diabetes mellitus require lifelong medical monitoring of glycemic control and end-organ status. Informal publication has indicated that patients have been treated with CIIIT for as long as 12 years.

Setting
Patients receive CIIIT in weekly outpatient treatment sessions.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

Studies with duplicative or overlapping populations were excluded.

Glycemic Control

Aoki et al (1993) published a case series of 20 patients with "brittle" type 1 diabetes.[1,] All patients received four daily injections of insulin (type of insulin not described); additional oral drug therapy, if any, was not described. Throughout the study, patients remained in close contact with the clinic (at least once a week), during which time appropriate adjustments in diet, insulin doses, and physical activity were made. While the study reported a decrease in the hemoglobin $A_{1c}$ ($HbA_{1c}$) levels, the lack of a control group limits the interpretation of the results. For example, the intense follow-up of the patients could have impacted results, regardless of any possible effects of the CIIIT.[1,2,]

Aoki et al (1995) also examined the effect of CIIIT with hypertensive medications in 26 patients with type 1 diabetes and associated hypertension and nephropathy.[3,] The 26 patients were randomized to a control group or a treatment group for 3 months and then crossed over for an additional 3 months. At baseline, all patients were being treated with four daily insulin injections and had achieved acceptable $HbA_{1c}$ levels of 7.4%. Patients also achieved acceptable baseline blood pressure control (<140/90 mm Hg) with a variety of medications (ie, angiotensin-converting enzyme inhibitors, calcium channel blockers, loop diuretics, alpha-2 agonists). The study was randomized, but not blinded, in that sham CIIIT procedures were not performed. Therefore, those patients receiving CIIIT received more intense follow-up during this period. During the treatment phase, patients reported a significant decrease in the dosage of antihypertensive medicines. No difference in glycemic control was noted. Because all patients had adequate blood pressure control at baseline, the clinical significance of the decrease in antihypertensive dosage requirement associated with CIIIT is uncertain.

*Section Summary: Glycemic Control*

One nonblinded RCT and a cases series reporting on the effect of CIIIT on glycemic control in type 1 diabetes were identified. Both studies reported improvements: one in $HbA_{1c}$ levels compared with baseline, and the other in a dose of antihypertensive medication in the treatment group compared with control. However, the lack of a blinded control comparator group in the RCT limits the conclusions that can be drawn.

**Reductions in Diabetic End-Organ Damage**

Weinrauch et al (2010) published an RCT of the effects of CIIIT on progression of nephropathy and retinopathy in 65 subjects with type 1 diabetes.[4] Patients were randomized to standard therapy of 3 to 4 daily subcutaneous insulin injections (n=29; control group) or standard therapy plus weekly CIIIT (n=36; treatment group). Baseline demographic characteristics were similar between the 2 groups, as were the age of onset, duration of diabetes, control of $HbA_{1c}$ levels, and renal function (average creatinine, 1.59 mg/dL; average creatinine clearance, 60.6 mL/min). Primary endpoints were a progression of diabetic retinopathy and nephropathy. There was no significant difference in progression of diabetic retinopathy. Progression was noted in 18.8% of 122 eyes adequately evaluated (17.9% of 67 treated eyes, 20.0% of 55 controls; p=0.39). On

average, serum creatinine increased in both groups; the increase was smaller in the treatment group (0.09 mg/dL) than in the control group (0.39 mg/dL; p=0.035). While average creatinine clearance fell less in the treatment group (-5.1 mL/min), the difference vs standard therapy was not significant (-9.9 mL/min; p=0.30). Glycemic control did not vary significantly. The clinical significance of the difference in creatinine levels is uncertain.

Dailey et al (2000) reported on a prospective, multicenter, controlled study evaluating the effects of CIIIT on the progression of diabetic nephropathy.[5,] They assessed 49 type 1 diabetes patients with nephropathy who were following the Diabetes Control and Complications Trial intensive therapy regimen. Of these, 26 were assigned to the control group, which continued intensive therapy, and 23 were assigned to the treatment group, which underwent weekly CIIIT plus intensive therapy. Both groups reported a significant decrease in $HbA_{1c}$ levels during the 18-month study period. Creatinine clearance declined in both groups as expected, but the rate of decline in the treatment group was significantly less than in the control group. The clinical significance of this finding is uncertain. Larger clinical trials that evaluate the endpoint of time to progression of renal failure are needed.

*Section Summary: Reductions in Diabetic End-Organ Damage*
Two controlled studies focusing on the efficacy of CIIIT for reducing diabetic end-organ complications were identified. Both reported significant improvements in intermediate measures of glycemic control in each group from pre- to post-intervention but did not consistently report differences in clinically meaningful outcomes from the beginning of the studies to the end. Similarly, there were no significant differences between treatment groups in the RCT.

## SUMMARY OF EVIDENCE

For individuals who have type 1 diabetes who receive CIIIT, the evidence includes two RCTs and several uncontrolled studies. The relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. A limited number of uncontrolled studies have suggested that CIIIT might improve glycemic control. The two randomized trials have reported that CIIIT might moderate the progression of nephropathy or retinopathy. However, the published studies were small and reported improvements on intermediate outcomes only (ie, changes in laboratory values). The clinical significance of the differences reported in these trials is uncertain. Additionally, most published evidence appeared between 1993 and 2010 and, as a result, does not account for improvements in diabetes care. The evidence is insufficient to determine the effects of the technology on health outcomes.

## PRACTICE GUIDELINES AND POSITION STATEMENTS

The American Diabetes Association (2019) "Standards of Medical Care in Diabetes" includes the American Diabetes Association's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate the quality of care. The pharmacologic approaches to glycemic treatment are summarized in chapter 9.[6,]

## U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

## ONGOING AND UNPUBLISHED CLINICAL TRIALS

A search for active or recruiting clinical trials in January 2019 did not yield results for trials that might influence this review.

## CODING

**The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.**

CPT/HCPCS

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| 82948 | Glucose; blood, reagent strip |
| 96365 | Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour |
| 96366 | Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure) |
| G9147 | Outpatient Intravenous Insulin Treatment (OIVIT) either pulsatile or continuous, by any means, guided by the results of measurements for: respiratory quotient; and/or, urine urea nitrogen (UUN); and/or, arterial, venous or capillary glucose; and/or potassium concentration |
| J1817 | Insulin for administration through DME (i.e., insulin pump) per 50 units |
| J7050 | Infusion, normal saline solution, 250 cc |

- There is no specific CPT code describing CIIIT. The series of CPT codes and HCPCS J codes above are used to describe the various components of CIIIT. Some codes, such as the code for glucose testing, may be used more than once during a single session of CIIIT.
- There is a HCPCS code specific to this therapy: G9147.

Diagnoses

Experimental / Investigational for all diagnoses related to this medical policy.

## REVISIONS

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| 12-09-2016 | Policy added to the bcbsks.com web site on 11-09-2016 with an effective date of 12-09-2016. |
| 03-15-2017 | Updated Description section. |
| | Updated Rationale section. |
| | In Coding section:<br>▪ Updated coding bullets. |
| | Updated References section. |
| 03-28-2018 | Updated Description section. |
| | Updated Rationale section. |
| | Updated References section. |
| 03-27-2019 | Updated Description section. |

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| | Updated Rationale section. |
| | In Coding section:<br>▪ Removed CPT codes: 94681, 99070, 99211. |
| | Updated References section. |

## REFERENCES


1. Aoki TT, Benbarka MM, Okimura MC, et al. Long-term intermittent intravenous insulin therapy and type 1 diabetes mellitus. Lancet. Aug 28 1993;342(8870):515-518. PMID 8102666
2. Aoki TT, Grecu EO, Arcangeli MA. Chronic intermittent intravenous insulin therapy corrects orthostatic hypotension of diabetes. Am J Med. Dec 1995;99(6):683-684. PMID 7503093
3. Aoki TT, Grecu EO, Prendergast JJ, et al. Effect of chronic intermittent intravenous insulin therapy on antihypertensive medication requirements in IDDM subjects with hypertension and nephropathy. Diabetes Care. Sep 1995;18(9):1260-1265. PMID 8612440
4. Weinrauch LA, Sun J, Gleason RE, et al. Pulsatile intermittent intravenous insulin therapy for attenuation of retinopathy and nephropathy in type 1 diabetes mellitus. Metabolism. Mar 1 2010;59(10):1429-1434. PMID 20189608
5. Dailey GE, Boden GH, Creech RH, et al. Effects of pulsatile intravenous insulin therapy on the progression of diabetic nephropathy. Metabolism. Nov 2000;49(11):1491-1495. PMID 11092517
6. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2019. Diabetes Care. Jan 2019;42(Suppl 1):S90-S102. PMID 30559235
7. Centers for Medicaid & Medicare Services. National Coverage Determination (NCD) for Outpatient Intravenous Insulin Treatment (40.7). 2009; https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=334&ncdver=1&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=intravenous+insulin&KeyWordLookUp=Title&KeyWordSearchType=And&bc=gAAAACAAAAAAAA%3d%3d&. Accessed January 26, 2019.