Chronic Intermittent Intravenous Insulin Therapy (CIIIT) - CAM 20143

Category:	Therapy	**Last Reviewed:**	September 2023
Department:	Medical Affairs	**Next Review:**	September 2024
Original Date:	November 2001		

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.

For individuals who have type 1 diabetes who receive CIIIT, the evidence includes 2 randomized controlled trials (RCTs) and uncontrolled studies. 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 2 RCTs reported that CIIIT might moderate the progression of nephropathy or retinopathy. However, the published studies were small and reported improvements on intermediate outcomes only (i.e., changes in laboratory values). The clinical significance of the differences reported in these studies is uncertain. Additionally, most published evidence appeared between 1993 and 2000 and, as a result, does not account for recent improvements in diabetes care. The evidence is insufficient to determine the effects of the technology on health outcomes.

Background
GLUCOSE HOMEOSTASIS
Insulin-mediated glucose homeostasis involves three primary functions that occur at three 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 the liver production of glucose. However, after a glucose challenge, insulin binds to specific receptors on the hepatocyte to suppress glucose production. Without this inhibition, marked hyperglycemia would occur.

Medications 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).

The different classes of diabetic drug therapy target different aspects of glucose metabolism. Various insulin secretagogues (e.g., sulfonylureas) function by increasing the pancreatic secretion of insulin; thiazolidinediones (e.g., pioglitazone [Actos], rosiglitazone [Avandia]) function in part by increasing glucose uptake in the peripheral (principally skeletal) tissues; and biguanides (e.g., metformin) function by decreasing hepatic glucose production. While patients with type 2 diabetes may be treated with various combinations of all three 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 replacement therapy involves the use of subcutaneous injection to mimic a physiologic insulin profile. Intravenous insulin is used in the acute inpatient setting to manage hyperglycemic emergencies (e.g., diabetic ketoacidosis).

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

Related Policies
70141 Implantable Infusion Pump

Policy:
Chronic intermittent intravenous insulin therapy is investigational and/or unproven and therefore considered **NOT MEDICALLY NECESSARY.**

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

Coding
Please see the Codes table for details.

Benefit Application
BlueCard®/National Account Issues
State or federal mandates (e.g., Federal Employee Program) may dictate that certain U.S. Food and Drug Administration-approved devices, drugs, or biologics may not be considered investigational, and thus these devices may be assessed only by their medical necessity.

Chronic intermittent intravenous insulin therapy is typically offered in specialized clinics.

Rationale
This evidence review was created in November 2001 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through December 9, 2022.

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, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA [Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual]; Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Chronic Intermittent Intravenous Insulin Therapy for Type 1 Diabetes
Clinical Context and Therapy Purpose
The purpose of chronic intermittent intravenous insulin therapy (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 insulin therapies.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is patients with type 1 diabetes mellitus who need improved glycemic control.

Interventions
The therapy being considered is CIIIT. Several forms of CIIIT, 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 or more often in a pulsatile fashion using a specialized pump controlled by a computerized program that adjusts the doses based on frequent blood glucose monitoring.[1] CIIIT is principally designed to normalize the hepatic metabolism of glucose. Currently, no studies have been identified that have investigated the proposed mechanism 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.[2] The authors stated: "We reasoned that if the liver of an Insulin-Dependent Diabetes Mellitus [i.e., 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 directly into the portal vein to simulate the postprandial 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 normoglycemia 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.

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.

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

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- 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 qualitative or overlapping populations were excluded.

Review of Evidence
Glycemic Control
In 1993, Aoki et al. published a case series of 20 patients with "brittle" type 1 diabetes.[3] All patients received 4 daily injections of insulin (type of insulin not described); additional oral drug therapy, if any, was not described. Racial and ethnic demographics of study patients were 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 hemoglobin A1c (HbA1c) 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.[3,4]

In 1995, Aoki et al. also examined the effect of CIIIT with hypertensive medications in 26 patients with type 1 diabetes and associated hypertension and nephropathy.[5] The 26 patients were randomized to a control group (Group B) or a treatment group (Group A) for 3 months and then crossed over for an additional 3 months. Racial and ethnic demographics of study patients were noted as follows: Group A (n = 13), 85% White, 15% Hispanic/Latino; Group B (n = 13), 100% White. At baseline, all patients were being treated with 4 daily insulin injections and had achieved acceptable HbA1c levels of 7.4%. Patients also achieved acceptable baseline blood pressure control (< 140/90 mm Hg) with a variety of medications (i.e., 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.

Reductions in Diabetic End-Organ Damage
Weinrauch et al. (2010) published an RCT of the effects of CIIIT on the progression of nephropathy and retinopathy in 65 subjects with type 1 diabetes.[6] 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 HbA1c levels, and renal function (average creatinine, 1.59 mg/dL; average creatinine clearance [CrCl], 66.6 mL/min). Racial and ethnic demographics of study patients were not described. Primary endpoints were a progression of diabetic retinopathy and nephropathy. There was no significant difference in the 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; $p = .39$). 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; $p = .035$). While average CrCl fell less in the treatment group (-5.1 mL/min), the difference versus standard therapy was not significant (-9.9 mL/min; $p = .30$). Glycemic control did not vary significantly. The clinical significance of the difference in creatinine levels is uncertain.

Dailey et al. (2005) reported on a prospective, multicenter, controlled study evaluating the effects of CIIIT on the progression of diabetic nephropathy.[7] The authors assessed 49 patients with type 1 diabetes 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. Racial and ethnic demographics of study patients were not described. Both groups reported a significant decrease in HbA1c 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: Chronic Intermittent Intravenous Insulin Therapy for Type 1 Diabetes
One nonblinded RCT and 2 case series reporting on the effect of CIIIT on glycemic control in type 1 diabetes were identified. Both studies reported improvements: one in HbA1c 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 comparison group in the RCT limits the conclusions that can be drawn. 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.

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in "Supplemental Information" if they were issued by, or jointly by, a U.S. professional society, an international society with U.S. representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Diabetes Association
The 2022 American Diabetes Association "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.[8] There is no mention of chronic intermittent intravenous insulin therapy (CIIIT).

American Association of Clinical Endocrinology
In 2022, the American Association of Clinical Endocrinology updated its 2015 clinical practice guideline for developing a diabetes mellitus comprehensive care plan.[9] The guideline includes evidence-based recommendations for the comprehensive care of people with both type 1 and type 2 diabetes; recommendations are divided up into 4 sections: screening, diagnosis, targets, and monitoring; comorbidities and complications; management; education and new topics regarding diabetes. There is no mention of CIIIT.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Ongoing and Unpublished Clinical Trials
A search for active or recruiting clinical trials in December 2022 did not yield results for trials that might influence this review.

References:

1. American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2021. Diabetes Care. Jan 2021; 44(Suppl 1): S111-S124. PMID 33298420
2. Mirbolooki MR, Taylor GE, Knutzen VK, et al. Pulsatile intravenous insulin therapy: the best practice to reverse diabetes complications?. Med Hypotheses. Sep 2009; 73(3): 363-9. PMID 19446864
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4. Aoki TT, Grecu EO, Arcangeli MA. Chronic intermittent intravenous insulin therapy corrects orthostatic hypotension of diabetes. Am J Med Sci. Dec 1995; 99(6): 683-4. PMID 7503093
5. 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): 1260-5. PMID 8612440
6. Weinrauch LA, Suri J, Gleason RE, et al. Pulsatile intermittent intravenous insulin therapy for attenuation of retinopathy and nephropathy in type 1 diabetes mellitus. Metabolism. Oct 2010; 59(10): 1429-34. PMID 20189608
7. 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): 1491-5. PMID 11092517
8. Draznin B, Aroda VR, Bakris G, et al. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2022. Diabetes Care. Jan 01 2022; 45(Suppl 1): S125-S143. PMID 34964831
9. Blonde L, Umpierrez GE, Reddy SS, et al. American Association of Clinical Endocrinology Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan-2022 Update. Endocr Pract. Oct 2022; 28(10): 923-1049. PMID 35963508
10. 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=234. Accessed December 9, 2022.

Coding Section

Codes	Number	Description
CPT	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)
HCPCS	J7050	Infusion, normal saline solution, 250 cc
	J1817	Insulin for administration through dme (i.e., insulin pump) per 50 units
	G9147	Outpatient intravenous insulin treatment (oivit) either pushed 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
ICD-10-CM		Investigational for all relevant diagnoses
	E08.0-E13.9	Diabetes mellitus code range
ICD-10-PCS		ICD-10-PCS codes are only used for inpatient services. There are no specific ICD-10 PCS codes for this therapy.
	3E033VG, 3E033VG, 3E040VG, 3E043VG, 3E050VG, 3E053VG,3E060VG, 3E063VG	Administration, physiological systems and anatomical regions, introduction, hormone, insulin, codes for peripheral and central vein or artery and open or percutaneous approach
Type of Service	Medicine	
Place of Services	Physician's office	

Procedure and diagnosis codes on Medical Policy documents are included only as a general reference tool for each policy. **They may not be all-inclusive.**

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross Blue Shield Association technology assessment program (TEC) and other nonaffiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

History From 2016 Forward

09/12/2023 Annual review, no change to policy intent. Updating rationale and references.
09/01/2022 Annual review, no change to policy intent. Updating rationale and references.
09/01/2021 Annual review, no change to policy intent. Updating rationale and references.
09/01/2020 Annual review, no change to policy intent. Updating guidelines, coding, rationale and references.
09/03/2018 Annual review, no change to policy intent. Updating background, guidelines, benefit applications, rationale and references.
09/28/2018 Annual review, no change to policy intent. Updating background, rationale and references.
09/21/2017 Annual review, no change to policy intent. Updating background, description, rationale and references.
09/01/2016 Annual review, no change to policy intent. Updating rationale.
09/01/2016 Annual review, no change to policy intent. Updating rationale.
09/14/2015 Annual review, no change to policy intent. Updated background, description, rationale and references. Added related policy and guidelines.
09/07/2014 Annual review. Updated benefit applications, rationale and references. No change to policy intent.