Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 5/1/12**
(See policy history boxes for previous effective dates)

Title: Chronic Intermittent Intravenous Insulin Therapy (CIIIT)

Description/Background

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

Background
There are 3 main sites of insulin-mediated glucose homeostasis that must function in a coordinated fashion to maintain euglycemia: 1) insulin secretion by the pancreas; 2) glucose uptake, primarily in the muscle, liver, gut, and fat; and 3) hepatic glucose production. For example, in the fasting state, when insulin levels are low, the majority of glucose uptake is non-insulin mediated. Glucose uptake is then balanced by liver production of glucose, critical to nourish vital organs, such as the brain. 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. Different classes of diabetic drug therapy target different aspects of glucose metabolism. Various insulin secretagogues (i.e., sulfonylureas) function by increasing the pancreatic secretion of insulin; thiazolidinediones (i.e., pioglitazone [Actos®] and rosiglitazone [Avandia®]) function in part by increasing glucose uptake in the peripheral (principally skeletal) tissues; and biguanides (i.e., metformin) function by decreasing hepatic glucose production. While patients with type 2 diabetes may be treated with various combinations of all 3 of the above classes of drugs, patients with type 1 diabetes, who have no baseline insulin secretion, receive exogenous insulin therapy, with or without additional drug therapy with thiazolidinediones or metformin. Large-scale randomized studies have established that tight glucose control is associated with a decreased incidence of microvascular complications of diabetes (i.e., nephropathy, neuropathy, and retinopathy). Currently, the American Diabetics Association recommends a target hemoglobin A1c (HbA1c) concentration of less than 7%.

Chronic intermittent intravenous insulin therapy (CIIIT) also referred to as outpatient intravenous insulin therapy (OIVIT), hepatic activation, or metabolic activation, involves delivering insulin intravenously over a 6- to 7-hour period in a pulsatile fashion using a specialized pump controlled by a computerized program that adjusts the dosages based on frequent blood glucose monitoring. 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 as they are delivered to the liver. It is hoped that this therapy ultimately results in improved glucose control through improved hepatic activation.

CIIIT is typically delivered once weekly as outpatient therapy.

Regulatory Status
Any insulin infusion pump can be used for the purposes of CIIIT. Infusion pumps have received U.S. Food and Drug Administration (FDA) marketing clearance through the 510(k) process, as they are determined to be substantially equivalent to predicate devices for the delivery of intravenous medications.

CPT / HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

G9147

Diagnoses / Medical Conditions

N/A

Medical Policy Statement

Chronic intermittent intravenous insulin therapy (CIIIT), either pulsatile or continuous, is experimental/investigational. It has not been scientifically demonstrated to be an effective adjunct to conventional treatment for diabetes mellitus.

Rationale

This policy was originally created in 2001 and was regularly updated with searches of the MEDLINE database through June 2011. Following is a key summary of the literature to date:

Does CIIIT improve the hepatic metabolism of glucose?
Chronic intermittent intravenous insulin therapy (CIIIT) therapy is principally designed to normalize the hepatic metabolism of glucose. Although the exact physiologic mechanism is unclear, Aoki, one of the principal investigators of the technique, et al. proposed that in diabetic patients, 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) Once weekly 6-hour intravenous pulsatile infusions of insulin while the patient ingests a carbohydrate meal are designed to increase the portal vein concentrations of insulin, ultimately stimulating the synthesis of glucokinase and other insulin-dependent enzymes. No studies were identified in a MEDLINE literature search that investigated the proposed scientific mechanism of CIIIT in humans.

Does CIIIT improve glycemic control in diabetic patients?
Because of the many variables associated with diabetic management, randomized controlled clinical trials are necessary to validate treatment effectiveness. A MEDLINE literature search did not identify any blinded randomized clinical trials focusing on the efficacy of CIIIT for glucose control.

In 1993, Aoki and colleagues published a case series of 20 patients with “brittle” type 1 diabetes. All patients received 4 daily injections of insulin (type of insulin not described); any 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 appropriate adjustments in diet, insulin therapy, and activity were made. While the study reported a decrease in the HbA1c levels, the lack of a control group limits the interpretation of 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. 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 randomly assigned to a control group or treatment group for 3 months and then crossed over to the opposite group for an additional 3 months. 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 (below 140/90 mm Hg) with a variety of medications (i.e., angiotensin-converting enzyme [ACE] inhibitors, calcium channel blockers, loop diuretics, and alpha-2 agonists). While the study was randomized, it was 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 dosage of antihypertensive medicines. No difference in glycemic control was noted. Since all patients had adequate blood pressure control at baseline, the clinical significance of the decrease in antihypertensive dosage requirement associated with CIIIT is uncertain.

Does CIIT reduce diabetic end-organ damage?
Because of the many variables associated with diabetic management, randomized controlled clinical trials are necessary to validate treatment effectiveness. A MEDLINE literature search identified two randomized clinical trials focusing on the efficacy of CIIIT for reducing diabetic end-organ complications..

In 2000, Dailey and colleagues reported on the effect of CIIIT on the progression of diabetic nephropathy. (4) A total of 49 patients with type 1 diabetes were included. Of these, 26 were assigned to the control group, and 23 were assigned to the treatment group that underwent

weekly CIIIT. Both groups reported a significant decrease in HbA1c during the 18-month study period. The creatinine clearance declined in both groups as expected, but the rate of decline in the treatment group was significantly less compared to the control group. Again, the clinical significance of this finding is uncertain; larger clinical trials that look at the endpoint of time to progression of renal failure are needed.

In 2010, Weinrauch and colleagues published a study of the effects of CIIIT on progression of nephropathy and retinopathy in 65 subjects with type I diabetes. (5) Patients were randomly allocated to standard therapy of 3-4 daily subcutaneous insulin injections (n=29) or standard therapy plus weekly CIIIT (n=36). Baseline demographic characteristics were similar between the 2 groups, as were age of onset, duration of diabetes, diabetic control and renal function (average creatinine 1.59 mg/dL, average creatinine clearance 60.6 mL/minute). Primary endpoints were 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 that were 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 less in the treatment group (0.09 mg/dL vs. 0.39 mg/dL, respectively; p=0.035). While average creatinine clearance fell less in the treatment group, the difference was not significant (-5.1 mL/minute vs. -9.9 mL/minute, respectively; p=0.30). Glycemic control did not vary significantly. The clinical significance of the difference in creatinine levels is unknown and requires further evaluation in trials involving a larger number of patients.

Ongoing Clinical Trials

A search of the online site ClinicalTrials.gov, in July 2011, found one ongoing non-randomized, Phase III trial. The “Effects of Intensive Bolus Intravenous Insulin Delivery on Metabolic Integrity in Type 1 and Type 2 Diabetes” trial is a multicenter trial to assess whether restoring metabolic integrity in 2,000 diabetic patients improves quality of life and complications associated with diabetes. (NCT01023165) This trial is expected to be completed in November 2015.

Summary

It is hypothesized that CIIIT improves hepatic glucose regulation. A limited number of uncontrolled studies suggest that chronic intermittent intravenous insulin therapy (CIIIT) may improve glycemic control. Two randomized trials report that CIIIT may moderate the progression of nephropathy. However, the published studies are small and report benefits on intermediate outcomes only, i.e., changes in laboratory values. This evidence does not permit definitive conclusions regarding the health benefits of CIIIT. Therefore, the technique is considered investigational.

Practice Guidelines and Position Statements

Clinical practice guidelines from professional associations, including the American Diabetes Association and the American Association of Clinical Endocrinologists, do not include CIIIT within each organization’s clinical practice guidelines for diabetes. (6,7)

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

N/A

Government Regulations

National:

"Effective for claims with dates of service on and after December 23, 2009, the Centers for Medicare and Medicaid Services (CMS) determines that the evidence is adequate to conclude that outpatient intravenous insulin therapy (OIVIT, i.e., CIIIT) does not improve health outcomes in Medicare beneficiaries. Therefore, CMS determines that OIVIT is not reasonable and necessary for any indication under section 1862(a)(1)(A) of the Social Security Act. Services comprising an Outpatient Intravenous Insulin Therapy regimen are nationally non-covered under Medicare when furnished pursuant to an OIVIT regimen (see subsection A. above)."

Local:

No local coverage determination on this topic. Not covered.

Michigan Department of Community Health:

No Medicaid policy on this topic. Not covered.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Intermittent (72 Hour) or Continuous Invasive Glucose Monitors
- Continuous Subcutaneous Insulin Infusion Pumps

References

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- United States National Institutes of Health, “Effects of pulsatile IV insulin delivery on diabetic retinopathy in patients with types 1 and 2 diabetes mellitus,” *Clinical Trials.gov*, Identifier NCT00287651, February 6, 2006, terminated 2009, < http://www.clinicaltrials.gov/ct2/show/NCT00287651?term=NCT00287651&rank=1 > accessed 3/29/10.
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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 11/28/11, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
9/1/10	7/22/10	6/15/10	Joint policy established
5/1/12	2/21/12	2/21/12	Routine maintenance; updated rationale, verified references.

Next Review Date: 1st Qtr, 2013

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN: N/A	Revised: N/A
BCBSM: N/A	Revised: N/A

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: CHRONIC INTERMITTENT INTRAVENOUS INSULIN THERAPY (CIIIT)

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered.
BCNA (Medicare Advantage)	Not covered
BCN65 (Medicare Complementary)	Not covered.
BlueCaid	Not covered.

II. Administrative Guidelines:

N/A