# Management of Non-Islet-Cell Tumor Hypoglycemia: A Clinical Review

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**Context:** Non-islet cell tumor hypoglycemia (NICTH) is a rare but serious paraneoplastic syndrome in which a tumor secretes high molecular weight IGF-II, causing hypoglycemia. Complete tumor resection is curative but is often delayed or unfeasible. There is no clear "standard of care" for managing these patients.

**Evidence Acquisition:** PubMed searches were conducted for: "non-islet-cell tumor hypoglycemia," "NICTH," "Doege-Potter," "Doege-Potter syndrome," "high molecular weight IGF-II," and "big IGF-II." Relevant articles were reviewed in detail. We limited our review to English-language articles, focusing on 1988–2013 (corresponding with the elucidation of the pathophysiology of NICTH).

**Evidence Synthesis:** The available literature exists as case reports or small case series, with a void of higher-order treatment studies. Thus, an evidence-based approach to data synthesis was difficult. Nevertheless, the available literature is presented objectively with an attempt to describe clinically useful trends and findings in the management of NICTH.

**Conclusions:** Appropriate identification of NICTH and prompt and complete tumor resection represents ideal management. However, when prompt resection is not feasible, iv glucose or dextrose often does not suffice to prevent hypoglycemia. In such cases, we suggest consideration of local antitumor therapies for disease control and trial of glucocorticoids alone or in combination with GH. Continuous glucagon infusion can be successful if the patient has a positive response to a glucagon stimulation test, and parenteral nutrition may allow higher glucose delivery, but both are limited by the need for continuous iv infusion. Diazoxide and octreotide have no role in NICTH. **(*J Clin Endocrinol Metab* 99: 713–722, 2014)**

Non-islet-cell tumor hypoglycemia (NICTH) is a rare paraneoplastic syndrome encountered in the setting of a wide variety of benign and malignant tumors (1). NICTH is eponymously known as Doege-Potter syndrome when the tumor is a fibrous tumor located in the thorax (2). This syndrome has been recognized for decades (3, 4) and was initially attributed to increased glucose utilization by large tumors (5). The true mechanism by which non-islet cell tumors cause hypoglycemia remained elusive into the 1970s and early 1980s when circulating insulin-like peptides were described (6, 7). In the 1980s and early 1990s, abnormal (incompletely processed) IGF-II was described (8, 9) and was ultimately characterized as a high molecular weight or "big" IGF-II (10, 11) with potent insulin-like activity causing hypoglycemia. This led to numerous reports describing a wide variety of management options. However, most of the available literature exists as case reports or small case series. The three largest series we identified reported on clinical features of NICTH but focused largely on epidemiology and diagnosis, with minimal comment on management (12–14). This review seeks to summarize the available literature on management of hypoglycemia in NICTH, with special focus on preoperative management and management in the setting of nonresectable disease.

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Abbreviations: ALS, acid-labile subunit; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; IGFBP-3, IGF-binding protein-3; NICTH, non-islet cell tumor hypoglycemia; rhGH, recombinant human GH; SFT, solitary fibrous tumor.

## Methods

PubMed searches were conducted for the following terms: "non-islet-cell tumor hypoglycemia," "NICTH," "Doege-Potter," "Doege-Potter syndrome," "high molecular weight IGF-II," and "big IGF-II." All articles identified by these searches were reviewed if the article text was available in English. Case reports and case series were included in our detailed review and summary if they were published between January 1, 1988, and August 15, 2013. This time period was chosen to correspond with the elucidation of the mechanism of NICTH. (In reading earlier published cases, it was more difficult to discern whether those cases were true cases of NICTH or whether the hypoglycemia was due to other etiologies). Additional articles were identified from the reference sections of articles found via the above searches, particularly from review articles.

## Epidemiology

NICTH is rare, with our own search revealing 98 case reports or small series (fewer than 10 patients) totaling 130 cases in the English language medical literature between January 1, 1988, and August 15, 2013. Additionally, there are several larger series providing more aggregate dates but fewer individual patient details. Tsuro et al (14), in addition to detailing a case report included in our summary, also reviewed details of 20 additional Japanese cases. Fukuda et al (12) summarized 78 patients with NICTH, Hizuka et al (13) reported on 44 cases, and Miraki-Moud et al (15) published 16 cases. Therefore, there are nearly 290 cases of NICTH reported in the English language medical literature in the past quarter century. We did not encounter familial cases or links with genetic tumor syndromes.

## Pathophysiology

The gene product of the IGF-II locus is a 180-amino acid residue molecule termed prepro-IGF-II. This molecule consists of an N-terminus 24-amino acid peptide, a 67-amino acid mature IGF-II, and an 89-amino acid C-terminus extension, defined as the E-domain. All pro-IGF-II-related molecules are designated as "big" IGF-II. The big IGF-II including amino acid residues 1–87 is associated with NICTH. Additional big IGF-II molecules have been described, such as the big IGF-II (amino acid residues 1–104), which is linked to the hepatitis C-associated osteosclerosis syndrome (16).

IGF-II is normally a 7.5-kDa peptide, but in cases of NICTH, most circulating IGF-II is a high molecular weight form in the 10- to 20-kDa range (8, 17). This big IGF-II is formed due to abnormal processing of an IGF-II precursor in tumors with aberrant IGF-II gene transcription and gene expression (18, 19). Although many reported cases of NICTH detail high IGF-II levels (9), low and normal IGF-II levels are also reported (20). It is thought that this discrepancy in reporting lies in assay variation in the ability of different laboratories to detect abnormal IGF-II forms (17). IGF-I and IGF-II are capable of lowering glucose levels but typically fail to do so because they are normally trapped within the vascular space in a high molecular weight protein complex. Under normal circumstances, 7.5-kDa IGF-II binds with 40-kDa IGF-binding protein-3 (IGFBP-3) to create a roughly 50-kDa binary complex. This complex then binds with 85-kDa acid-labile subunit (ALS) to create a roughly 140- to 150-kDa ternary complex. A normal subject would have approximately 20% of IGF-II in the binary complex and 80% in the ternary complex (16).

In NICTH, elevated total IGF-II leads to a greater concentration of free IGF-II. Additionally, the high molecular weight precursor big IGF-II tends to reside in the binary complex with IGFBP-3 (ALS is not able to bind due to steric hindrance with the altered IGF-II forms; ALS concentrations may also be lower). The ratio of binary:ternary complexes is typically reversed in NICTH, with 80% binary and 20% ternary (16). The big IGF-II:IGFBP-3 binary complex is approximately 60 kDa and is thought to be able to cross the endothelial barrier and exert hypoglycemic effects (17, 21, 22). Additionally, the activity of IGF-II suppresses both insulin and GH (with resultant low IGF-I). Low GH also leads to low ALS and IGFBP-3, allowing less binding of big IGF-II (16, 17).

In a similar fashion to insulin, IGF-II determines hypoglycemia by inhibiting glucose output from the liver and by enhancing glucose uptake by skeletal muscle. In particular, the activation of insulin receptors by IGF-II promotes continued glucose utilization mainly by the skeletal muscle and suppression of free fatty acid release by adipocytes. This also leads to inhibition of glucose release, glycogenolysis, gluconeogenesis, and ketogenesis in the liver (16). Furthermore, the release of the counter-regulatory hormones glucagon and GH is suppressed by IGF-II, which in turn magnifies the vulnerability to hypoglycemia in NICTH (23).

## Tumor Characteristics

Tumors of mesenchymal or hepatic origin are most commonly described with NICTH (24), although it is now

recognized that a wide variety of tumor types can result in production of big IGF-II (25). We found similar variability. Of the 288 total cases reviewed, solitary fibrous tumor (SFT) and/or mesothelioma was the histopathology reported in 64 cases (22%). In 38 of these cases, the pleura was the clear origin of the tumor, with retroperitoneum, abdomen, and pelvis also commonly reported, including a uterine SFT (26) and a bladder SFT (27). The next most common mesenchymal tumor type was hemangiopericytoma, with 19 of 288, or 7%. Hepatocellular carcinoma (HCC) was the most common nonmesenchymal tumor by far, with 50 cases out of 288, or 17%. Note that HCC is well-documented to produce IGF-II (ie, hypoglycemia in HCC cases is not only via hepatic failure of gluconeogenesis) (28). Other commonly reported tumor types include: adenocarcinomas (at least 20 cases—precise determination difficult due to sparse documentation in some reports), gastrointestinal stromal tumors (GISTs) (11 cases) (19, 29–34), various types of sarcomas, and renal cell carcinoma (35–37). Of interest to endocrinologists, NICTH has been reported with both adrenal cortical carcinoma (12, 38, 39) and thyroid cancer (40). Other unusual tumors reported include Burkitt's lymphoma (41), plasmacytoma (42), yolk cell tumor (43), Leydig cell tumor (44), and phyllodes tumor of the breast (45). Due to the predominance of pleural tumors and tumors of hepatic and gastric origin, the vast majority of reported cases of NICTH involve primary tumor origin from the chest, abdomen, or pelvis.

Note that even the most common tumor type and location, pleural SFT, does not typically result in NICTH. Of approximately 800 cases of pleural SFT reported as of 2009, only 5% are estimated to cause NICTH (46, 47). With other tumor types, given reports of only a handful of cases in the past quarter century, the rate of NICTH is likely to be much lower.

In the 288 cases we reviewed, we identified 192 (67%) that were reported as malignant. However, note that malignancy vs benignity was not described well in a large number of cases, and in a few cases it was difficult to even determine the tumor type from the published report.

Details on tumor size vary, but it is generally acknowledged that tumors must become quite large before hypoglycemia manifests (16, 24). Fukuda et al (12) found that tumor diameter was greater than 10 cm in 70% of their 78 cases, and Kalebi et al (48) reviewed 65 cases of pleural SFT and NICTH and reported a mean diameter of 20 cm.

## Patient Demographics

Of the 285 cases for which gender was reported, 131 were female (46%), implying either a slight male predominance, or more likely, no gender predilection. Reported ages ranged from 2–87 years, with at least four cases in the pediatric age range (ages 2, 5, 9, and 11— based on three pediatric case reports and the lower end of the age range in the largest series) (12, 41, 49, 50). Mean reported age could not be determined for the entire group of cases reviewed due to the lack of exact ages reported for all cases, but of the 128 cases for which exact ages were available, the mean age was 56.4 years.

## Presenting Symptoms

Fukuda et al (12) found that only 48% of the 65 cases presented with hypoglycemia as the initial manifestation of the tumor, whereas 52% had known tumors before the onset of hypoglycemia. Indeed, presentation with symptoms due to the tumor mass itself before the onset of hypoglycemia is well-described (51). Three cases documented dramatic improvement or complete resolution of pre-existing diabetes mellitus (42, 52, 53). One pregnant patient was described (54). Hypokalemia is also frequently described with NICTH and is attributed to the insulin-like activity of big IGF-II (12, 38, 55). In one case, subclinical Cushing syndrome was even described concomitantly with NICTH (56). Acromegaloid features have also been described in NICTH (16), with documented resolution after tumor resection (57). Dynkevich et al (16) postulate that neuroglycopenic symptoms are more commonly seen than autonomic symptoms due to repeated hypoglycemic events and insidious progression seen with NICTH.

## Diagnosis

NICTH should be suspected in any patient with hypoglycemia without clear etiology. Initial evaluation of hypoglycemia should proceed according to usual practice. The Endocrine Society Guidelines recommend investigation in patients in whom Whipple's triad is fulfilled (58). This includes evaluating and pursuing the possibilities of medication-induced hypoglycemia, critical illness, organ failure, and/or hormone deficiencies (eg, liver failure, kidney failure, adrenal insufficiency, GH deficiency), as well as endogenous hyperinsulinism (with differential diagnosis of insulinoma, post-gastric bypass hypoglycemia, insulin autoimmune hypoglycemia, and accidental or surreptitious insulin secretagogue ingestion). If there are clues to NICTH (eg, known malignancy, identification of large new mass), this can be pursued early. Otherwise, we would consider this rare diagnosis if the workup of the preceding causes was unrevealing. When performing laboratory in-

vestigation of hypoglycemia, it is imperative to draw a serum glucose level (not just a finger-stick capillary blood glucose level) to confirm hypoglycemia with simultaneous measurement of levels for insulin, proinsulin, C-peptide, β-hydroxybutyrate, and an oral hypoglycemic agent screen (58). Evaluation of liver and kidney function and a cosyntropin stimulation test round out the usual evaluation of hypoglycemia. Additional investigation when NICTH is suspected includes measurement of IGF-I, IGF-II, and GH levels. In a hypoglycemic patient with low insulin and C-peptide, a low β-hydroxybutyrate level suggests an agent mimicking insulin and is therefore an indication to measure IGF-I and IGF-II (59).

The typical pattern for NICTH on the above laboratory studies includes low glucose (serum glucose < 55 mg/dL) with simultaneous low insulin/proinsulin/C-peptide/β-hydroxybutyrate levels, and the absence of positive results on an oral hypoglycemic agent screen. Note that GH levels are typically low (unlike brief episodes of hypoglycemia that trigger a surge in GH). Depending on the specific IGF-II assay used, the IGF-II levels may or may not be elevated in NICTH (17, 25). Even if IGF-II levels are normal (approximate normal range, 275–750 ng/mL, depending on the laboratory used), the IGF-I levels are suppressed under 100 ng/mL (12), and therefore the IGF-II:IGF-I ratio is elevated (5) above the normal molar ratio of 3:1 (16) and often approaching or exceeding 10:1 (12). This ratio may be an important screening tool for NICTH in cases of hypoglycemia (13). For the initial laboratory studies above, we advocate using the cutoffs advocated by The Endocrine Society: insulin level < 3 μU/mL, proinsulin level < 5 pmol/L, C-peptide level < 0.2 nmol/L, and β-hydroxybutyrate level < 2.7 mmol/L (58).

To our knowledge, there is no commercially available assay for big IGF-II, and measurement of high molecular weight precursor forms of IGF-II must be done in a research laboratory setting at this time. Several such assays have been summarized previously (17). As a recent example, Miraki-Moud et al (15) detailed their rapid method for separating pro-IGF-II from mature IGF-II using tricine-SDS-PAGE, followed by IGF-II immunoblot. This method could be reproduced using their descriptions. Detection of a high percentage of IGF-II as pro-IGF-II (big IGF-II) would then allow for diagnosis of NICTH.

The lack of widely available measurement of big IGF-II is likely because NICTH, a very rare disease, is the only established clinical indication for testing big IGF-II (59). Nevertheless, a widely available assay would assist all practitioners, especially those without access to a research laboratory. As research on the clinical utility of IGF-II measurement in cancer screening, diagnosis, and monitoring evolves, we may see an expanded list of indications prompting further assay development (59).

In cases in which it is unclear whether hypoglycemia is due to IGF-II or another etiology (eg, liver failure due to metastatic disease with depleted glycogen stores), a glucagon-stimulation test can be employed. A rise in glucose suggests a hormonal cause of hypoglycemia, whereas the lack of appropriate rise suggests the absence of sufficient liver stores (41, 60).

As with evaluation of insulinoma, once you have the biochemical evidence, the next step is localization/visualization. If laboratory results suggest NICTH (eg, high IGF-II:IGF-I ratio and absence of evidence for hyperinsulinemia), a reasonable next step is cross-sectional imaging of the chest, abdomen, and pelvis to identify a tumor, given that the vast majority of reported cases of NICTH involve a tumor in one of these sites. If a tumor is identified, evaluation should proceed as one normally would proceed based on tumor location, imaging characteristics, and other patient characteristics. See Table 1 for comparison of laboratory test results in various etiologies of hypoglycemia.

## Management

Initial treatment of hypoglycemia is accomplished by oral glucose and/or iv glucose- or dextrose-containing fluids as

**Table 1.** Comparison of Laboratory Test Results for Various Etiologies of Hypoglycemia

| Diagnosis | Insulin | Proinsulin | C-Peptide | IGF-I | IGF-II | IGF-II:IGF-I Ratio | Pro-IGF-II | OHA Screen | Insulin Antibody |
|---|---|---|---|---|---|---|---|---|---|
| Exogenous insulin | High | Low | Low | Normal | Normal | Normal | Normal | − | − |
| Insulinoma, post-gastric bypass | High | High | High | Normal | Normal | Normal | Normal | − | − |
| OHA | High | High | High | Normal | Normal | Normal | Normal | + | − |
| Insulin autoimmune syndrome | High | High | High | Normal | Normal | Normal | Normal | − | + |
| IGF-mediated[a] | Low or low-normal | Low or low-normal | Low or low-normal | Low | High or normal | High | High | − | − |

Abbreviation: OHA, Oral hypoglycemic agent.

[a] In cases of NICTH, we expect the following laboratory values: insulin level < 3 μU/mL, proinsulin level < 5 pmol/L, C-peptide level < 0.2 nmol/L, IGF-I level < 100 ng/mL, IGF-II level > 275 ng/mL, and an IGF-II:IGF-I ratio > 3:1, with true cases of NICTH frequently having a ratio > 10:1.

necessary. In many cases, this suffices to avoid further hypoglycemia (47, 55, 61, 62). Once NICTH is identified and a primary tumor is found, the mainstay of treatment is surgical resection, which is curative for hypoglycemia if resection is complete (63–69). Resolution of hypoglycemia has also been described in cases of subtotal resection (70). In rare instances, hypoglycemia recurs with tumor recurrence after what was thought to be complete resection (71, 72). However, in many cases, total resection is either delayed or not feasible. Reasons for nonresectability include large tumor burden (73), widely metastatic disease (14, 74), compromised local structures necessitating subtotal resection (34, 75), physical characteristics of the tumor and/or its relationship to surrounding structures necessitating abortion of resection (76, 77), and patient preference (78, 79).

Often the hypoglycemia in NICTH is severe enough to require further treatment beyond iv glucose or dextrose, either in lieu of surgical resection or while awaiting surgical resection. Management in these cases has varied widely. An increase in oral food intake (whether in amount of food, caloric density, and/or frequency) is often tried in addition to iv glucose or dextrose, with mixed results (37, 57, 80, 81). Increases in calories and total carbohydrate delivery have sometimes been accomplished with iv nutrition (commonly known as partial parenteral nutrition or total parenteral nutrition) (82, 83). However, the use of partial parenteral nutrition or total parenteral nutrition is not a desirable long-term strategy given the necessity of long-term venous access with its inherent risks of complications and concomitant risks of bloodstream infections, liver toxicity, and electrolyte imbalances, not to mention cost (84).

Local antitumor therapy has been successful in selected cases, including resolution of NICTH due to HCC with two courses of intrahepatic adriamycin (85); resolution of NICTH due to GIST after selective use of embolization of a GIST before subtotal resection (34); preoperative glucose stabilization using a combination of selective embolization, chemotherapy, and radiation therapy (76); and resolution of NICTH with radiation therapy of a large leiomyosarcoma (despite untreated pulmonary metastases, although the patient later died due to tumor bleeding) (72). Meanwhile, systemic antitumor therapy has been reported with very limited success. Zachariah et al (22) described "multiple doses of chemotherapy" used for a 55-year-old man with NICTH due to a large retroperitoneal undifferentiated mesenchymal tumor, but noted that the patient "deteriorated and died" over the next few months; and Ishikura et al (39) reported failure of multiple chemotherapy regimens for NICTH due to adrenocortical carcinoma. However, Tsuro et al (14) detailed temporary improvement in hypoglycemia with chemotherapy, and Rosario et al (40) reported resolution of NICTH due to undifferentiated thyroid cancer after use of doxorubicin and cisplatin. Imatinib, a more targeted systemic therapy, has been used for GIST, with successful resolution of hypoglycemia (30). However, Hamberg et al (32) describe a case of NICTH due to GIST in which they suggest that imatinib worsened the hypoglycemia.

Glucagon via injection may ameliorate hypoglycemia in cases of NICTH, but the effect with this route is short-lived (81, 86) and is probably best reserved as an adjunctive therapy in the setting of acute hypoglycemia. However, continuous glucagon infusion (iv) has been tried in several cases, with success as monotherapy predicted by a positive glucagon stimulation test (41, 60). The effect may be limited (14, 87), however, especially as tumor burden increases in terminal patients (33, 88).

Diazoxide is a nondiuretic benzothiadiazine derivative initially introduced as an antihypertensive but found to have hyperglycemia as a side effect. Diazoxide has subsequently been used with moderate success in hypoglycemia due to insulinoma, thought due to reduction in insulin secretion by $\beta$-cells (89). Use in NICTH was not found to be successful in any case we reviewed (33, 36, 41, 53, 90). Additionally, use is often limited by fluid retention and edema (41).

Octreotide, a nonspecific somatostatin analog, has been used unsuccessfully in multiple cases (39, 91). Even tumor positivity on octreotide scintigraphy did not predict success, with reports of octreotide leading to blood glucose stabilizing "somewhat" allowing reduction in concomitant dexamethasone (77) and absolutely no resolution of hypoglycemia or suppression of big IGF-II with "maximal doses of octreotide" (92). The only case with any success reported "a slight reduction in the frequency of hypoglycemic episodes" (78).

Recombinant human GH (rhGH) at supraphysiological doses of 3–12 mg daily has been successful in many cases (43, 44, 92–96), including one pediatric case (49). Use of rhGH in NICTH is likely successful via multiple mechanisms. GH suppresses peripheral glucose uptake (96) and leads to increased levels of IGF-I, IGFBP-3, and ALS, with resultant promotion of the normal ternary-complexed IGF-II (17, 79, 94). This makes it a much more targeted therapy for NICTH despite continued high IGF-II levels (17) and perhaps increased IGF-II levels (25, 94). However, rhGH is not universally successful in resolving NICTH (36, 85), and even where successful, use may be limited by the need for high doses (25, 93) and resultant side effects of fluid retention (79), orthostatic hypotension, and others, especially in older patients (97). Additionally, we propose that cost could be a limiting factor, especially for long-term therapy. Finally, without the ben-

efit of randomized, controlled trial data, we cannot exclude the possibility that rhGH may stimulate the growth of tumor cells.

Glucocorticoids (including dexamethasone, hydrocortisone, prednisolone, and prednisone, typically in doses equivalent to prednisone 30–60 mg/d) are the most extensively described medical therapy for NICTH (98). High-dose glucocorticoid therapy has immediate beneficial effect on symptomatic hypoglycemia and, unlike other therapeutic regimens, can be effective in correcting the underlying biochemical dysfunction if long-term side effects do not occur. We found that 32 of 129 or 25% of individual cases reviewed (excluding the larger series and our own cases) included glucocorticoid therapy, and Tsuro et al (14) note 30% in their series of 20 Japanese patients with NICTH. Glucocorticoids have been successfully used as "bridge" therapy to resection (19, 98, 99). Complete freedom from iv glucose or dextrose using glucocorticoid monotherapy in nonresectable cases was also reported (14, 35, 73, 79, 90, 98), although in some cases hypoglycemia later recurred as tumor burden progressed (36, 51, 81). However, there are several cases where glucocorticoids failed as monotherapy (44, 87), even with extremely high doses (equivalent to > 200 mg prednisone daily) (43), and in combination therapy, although typically in cases of widespread disease/high tumor burden and imminent demise of the patient (29, 33, 100–102).

Unlike rhGH, glucocorticoids treat NICTH via reduction in IGF-II levels (79, 92, 98). Teale and Marks (25) demonstrated the biochemical differences between the therapies by measuring levels of glucose, insulin, C-peptide, GH, IGF-I, IGF-II, IGFBPs, and ALS before and after therapy in eight patients with NICTH, four of whom were treated with rhGH and four of whom were treated with glucocorticoids. Therapy with rhGH, while treating hypoglycemia largely via transition to ternary-complexed IGF-II, failed to produce normal insulin and C-peptide levels. This was thought to be due to a large remaining amount of unsequestered IGF-II with resultant ongoing activity at insulin receptors. Glucocorticoid therapy also led to hypoglycemia resolution, but did so via increased IGF-I and decreased big and total IGF-II (via suppressed production and/or increased clearance of big IGF-II), with resultant restoration of normal insulin and C-peptide levels. Glucocorticoids were more effective than rhGH in raising ALS levels but less effective in raising IGFBP-3 levels (25).

Combination therapy with glucocorticoids and rhGH may help minimize the doses and side effects of each (and mitigate some of the rhGH cost). Combination therapy was successful (including freedom from iv glucose or dextrose) in multiple cases where monotherapy with either failed (44, 92, 96), although one report suggested an antagonistic effect when the two were combined (98).

Although there are no randomized controlled trials to guide therapy, ample case reports and series are available in the literature over the past quarter century. For further review, Table 2 details the various treatment modalities utilized in the case reports and small case series reviewed. Additionally, Supplemental Table 1 (published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org) expands on the detail provided in Table 2. Total resection is curative for NICTH, but prompt and/or total resection is not always feasible. In this setting, there is no clear "standard of care." Nutritional approaches may provide relief from hypoglycemia but often do not suffice. Local or systemic targeted antitumor therapy may be an option for some patients and may be successful. In cases where this is not available or does not free the patient from hypoglycemia, the literature suggests the careful use of glucocorticoids. In certain cases, glucagon infusion and/or rhGH may be additive or glucocorticoid-sparing when side effects are unfavorable. Our management strategy is outlined in Figure 1.

**Table 2.** Treatment Modalities Utilized in the Case Reports/Series Reviewed

| Treatment Modalities | Refs. |
|---|---|
| Resection only | 1, 11, 18, 20, 21, 26, 28, 38, 45, 47, 48, 50, 52, 54, 55, 61–71, 98, 103–121 |
| Nutritional approaches (eg, hyperalimentation, enteral tube feeds, parenteral nutrition) | 8, 36, 37, 51, 57, 72, 82, 83, 91, 92, 102 |
| Local therapies (eg, embolization, radiation) | 34, 36, 60, 72, 76, 87, 102, 120 |
| Systemic therapies (eg, chemotherapy, targeted antitumor therapy such as imatinib) | 1, 22, 30–32, 36, 40, 76, 77, 85, 87 |
| Glucocorticoids | 1, 14, 19, 29, 33, 35, 36, 43, 44, 46, 51, 56, 73, 75, 77, 79, 81, 87, 90–92, 96, 98–102 |
| rhGH | 36, 43, 44, 49, 79, 85, 92–96, 98 |
| Glucagon | 14, 33, 41, 60, 81, 86–88 |
| Octreotide | 39, 77, 78, 91, 92 |
| Diazoxide or bendrofluazide | 33, 36, 41, 53, 90, 92 |

A more detailed representation of the information in Table 2 can be found in Supplemental Table 1.

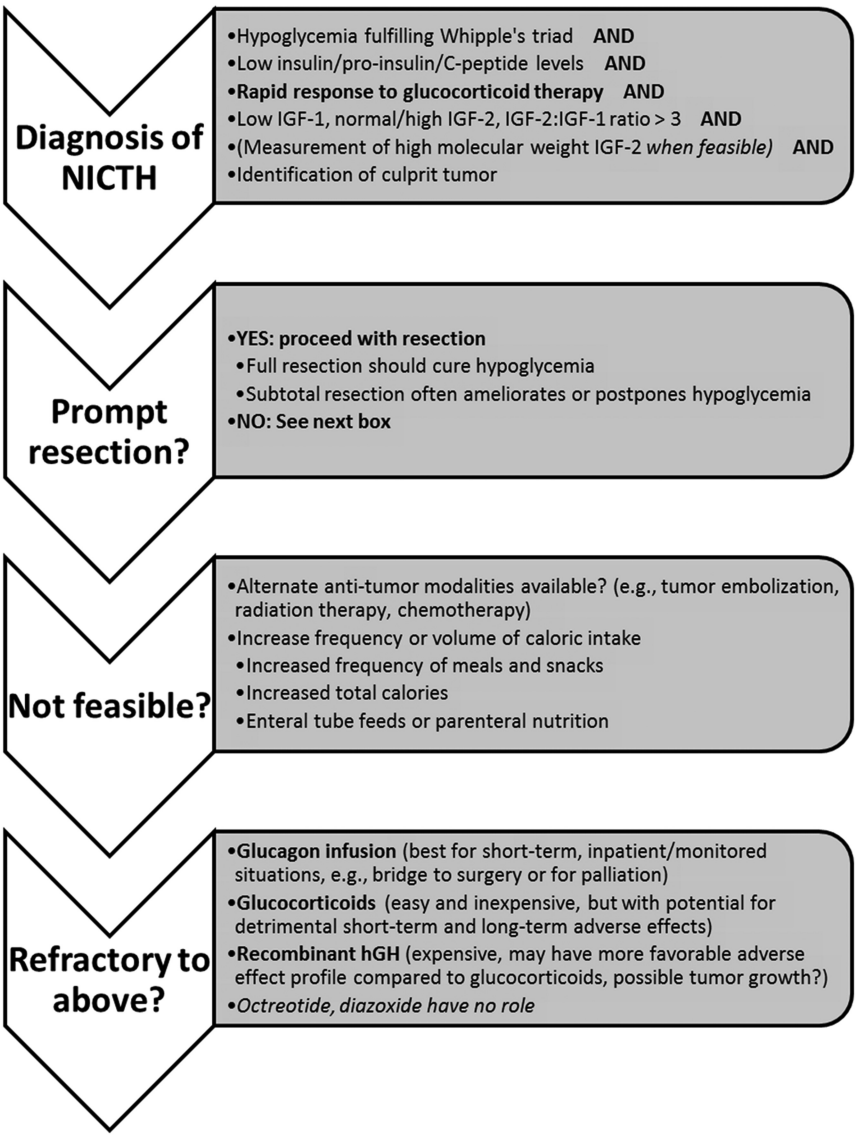


**Figure 1.** Management strategy for NICTH.

## Summary

NICTH is a rare but serious paraneoplastic syndrome involving progressive hypoglycemia in the setting of a wide variety of benign and malignant tumors, due to tumor production of high molecular weight IGF-II. A biochemical diagnosis is made when more common etiologies have been ruled out; hypoinsulinemic hypoglycemia is accompanied by an elevated IGF-II:IGF-I ratio (with low IGF-I and normal-to-high IGF-II). When possible, measurement of high molecular weight IGF-II further confirms the diagnosis. When a tumor is not previously known or readily apparent, imaging of the chest, abdomen, and pelvis is likely to be high yield. Prompt and complete surgical resection is curative, and subtotal resection and other local modalities such as radiation therapy may be successful. When resection is not feasible or is delayed, initial management of hypoglycemia involves increased caloric intake and frequency and/or iv glucose or dextrose. When conservative measures fail, medical therapy can be effective in alleviating hypoglycemia, although the degree of success likely correlates with overall tumor burden and progression. Based on the available literature, a trial of glucocorticoids at the lowest possible dose is a reasonable first step. Providers should anticipate the need to titrate to the equivalent of prednisone 30–60 mg per day, and even at these supraphysiological doses, success is not assured. When glucocorticoids fail to adequately control hypoglycemia or to reduce glucocorticoid exposure, addition of rhGH (again, at the lowest possible doses) to glucocorticoid therapy may provide greater therapeutic success with a more acceptable side effect profile than either agent alone. A reasonable alternative, acknowledging the limitations of continuous iv therapy, is continuous glucagon infusion. Octreotide and diazoxide have no role in NICTH.

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