

## Original Article

# Clinical practice guidelines for congenital hyperinsulinism

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**Abstract.** Congenital hyperinsulinism is a rare condition, and following recent advances in diagnosis and treatment, it was considered necessary to formulate evidence-based clinical practice guidelines reflecting the most recent progress, to guide the practice of neonatologists, pediatric endocrinologists, general pediatricians, and pediatric surgeons. These guidelines cover a range of aspects, including general features of congenital hyperinsulinism, diagnostic criteria and tools for diagnosis, first- and second-line medical treatment, criteria for and details of surgical treatment, and future perspectives. These guidelines were generated as a collaborative effort between The Japanese Society for Pediatric Endocrinology and The Japanese Society of Pediatric Surgeons, and followed the official procedures of guideline generation to identify important clinical questions, perform a systematic literature review (April 2016), assess the evidence level of each paper, formulate the guidelines, and obtain public comments.

**Key words:** congenital hyperinsulinism, hypoglycemia, guidelines

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## I Introduction

### A Guideline target population

- 1 Patients < 18 yr with congenital hyperinsulinism (congenital hyperinsulinemic hypoglycemia)
  - a Includes both syndromic and nonsyndromic form (Table 1)
- 2 Patients not covered by this guideline
  - a Patients with insulinomas
  - b Patients with drug-induced hyperinsulinemic hypoglycemia
  - c Patients diagnosed with hypoglycemia other than congenital hyperinsulinism
  - d Patients with adult-onset hyperinsulinemic hypoglycemia
  - e Patients with hyperinsulinemia associated with insulin resistance

### B Objectives

To improve the following outcomes:

- 1 Neurological sequelae (developmental delay, epilepsy)
- 2 Development of postsurgical diabetes mellitus
  - These guidelines aim to present general principles. Each patient, therefore, may be treated on a case-by-case basis, according to the conditions specific to the patient.

### C Intended users

- 1 General pediatricians and neonatologists
- 2 Pediatric endocrinologists
- 3 Pediatric surgeons

### D Outline of the disorder

- Congenital hyperinsulinism (CHI) is a group of disorders causing persistent hypoglycemia, due to congenital over-secretion of insulin, and does not include acquired conditions, such as insulinoma, iatrogenic hyperinsulinemia, or dumping syndrome. It is the most common cause of persistent hypoglycemia in neonates and infants, and was previously referred to as “nesidioblastosis” or “persistent hyperinsulinemic hypoglycemia in infancy

(PHHI)”. However, these terms are not appropriate as “nesidioblastosis” is a histopathological condition that can be observed in normal newborns and patients with CHI can develop hypoglycemia beyond infancy (1, 2).

- There are two forms of CHI: a transient form, which develops soon after birth and generally resolves by 3–4 mo of age, and a persistent form, with a more protracted duration. In some cases, the symptoms of persistent CHI may manifest after infancy. According to the 2009–2010 National Survey in Japan, the incidence of transient CHI is estimated at 1 in 17,000 births and that of persistent CHI at 1 in 35,400 births (3).
- Hypoglycemia may manifest loss of consciousness or convulsions and, most importantly, recurrent or persistent hypoglycemia may result in severe neurological sequelae, such as epilepsy or developmental delay. Optimal control of blood glucose, therefore, is of crucial importance (4, 5).
- Medical treatment for CHI includes nutritional support by hypertonic glucose infusion, continuous feeding through gastrostomy or nasogastric tube, or the use of cornstarch or formula for glycogen storage diseases. Furthermore, oral administration of diazoxide, a pancreatic  $\beta$  cells  $K_{ATP}$  channel opener, has been approved for the treatment of CHI. For patients with diazoxide unresponsive CHI, the following therapies have been attempted: off-label use of octreotide, as multiple daily injections or continuous infusion; glucagon, as a continuous infusion; intravenous injection of glucocorticoids; or oral administration of nifedipine (6–16).
- When euglycemia cannot be maintained by medical treatment, pancreatectomy has been performed to avoid neurological sequelae. However, the majority of patients who underwent subtotal pancreatectomy developed postsurgical insulin-dependent diabetes

**Table 1.** Known causes of pediatric hyperinsulinemic hypoglycemia (including acquired causes) (6–16).

Congenital or acquired	Type	Causes	Inheritance
Congenital (CHI)	Persistent (non-syndromic)	K <sub>ATP</sub> channel mutation SUR1 ( <i>ABCC8</i> ) Kir6.2 ( <i>KCNJ11</i> )	AR, AD, Paternally-inherited monoallelic mutation + loss of maternal allele (focal form)
		Glutamate dehydrogenase ( <i>GLUD1</i> ) mutation	AD
		<i>HNF4A</i> mutation	AD
		Glucokinase ( <i>GCK</i> ) mutation	AD
		<i>HADH</i> (hydroxyacyl-CoA dehydrogenase)	AR
		<i>UCP2</i> mutation	AD
		Insulin receptor mutation	AD
		Exercise induced ( <i>SLC16A1</i> mutation)	AD
		6q24-TNDM (post remission)	
		Persistent or transient (syndromic)	
Congenital disorder of glycosylation 1a, 1b, 1t			
Sotos syndrome			
Mosaic Turner syndrome Kabuki syndrome			
Transient		Infant of diabetic mother	
		Small-for-gestational age (SGA)	
		Stress-induced hyperinsulinemia	
		Maternal use of Ritodrine	
		<i>HNF4A</i> mutation	
		<i>HNF1A</i> mutation	
Acquired		Insulin overdose	
		Insulinoma	
		Insulin autoimmune syndrome (Hirata disease)	
		Noninsulinoma hypoglycemia syndrome (NIPHS)	
		Post-gastric bypass Post-fundoplication for gastro-esophageal reflux	

AD, autosomal dominant; AR, autosomal recessive.

mellitus. This is consistent with the study showing that, after 11 yr of operation, diabetes mellitus developed in 96% of 45 patients who underwent > 95% pancreatectomy (17). A further study reported that, after 14 yr, glucose intolerance and insulin-dependent diabetes mellitus developed in 100% and 91% of 58 patients who underwent subtotal pancreatectomy for the diffuse form of CHI, respectively (18). In individuals with a paternally-inherited monoallelic mutation in one of the K<sub>ATP</sub> channel genes, the focal

form of CHI can develop as a consequence of the somatic loss of the maternal allele in a developing pancreatic  $\beta$  cell. The focal form of CHI can be diagnosed by mutational analysis and an <sup>18</sup>F-DOPA PET scan (19–24). When a focal lesion is successfully resected by partial pancreatectomy, the patient can be cured without postsurgical sequelae. However, the resection should be performed with caution, particularly when the focal lesion is located in the head of the pancreas, as these lesions are in close proximity to the common bile

duct and the main pancreatic duct. Resection of the head of the pancreas and distal pancreateojejunostomy using a Roux-en-Y loop have been proposed as treatment for lesions in the head of the pancreas that cannot be enucleated (25). Mechanisms other than the paternally-inherited monoallelic mutation of the  $K_{ATP}$  channel genes cause a diffuse form of CHI. However, atypical cases with scattered patchy clusters of abnormal  $\beta$  cells have been reported (atypical CHI) (26–28). Furthermore, reports have described a case of Costello syndrome, with a mutation in the *HRAS* gene, presenting with a typical focal lesion indistinguishable from that caused by  $K_{ATP}$  channel mutations (29, 30).

- Even in patients with persistent CHI, the severity of hypoglycemia tends to improve over time and patients often achieve spontaneous remission without the need for medical treatment (31). Diabetes mellitus can develop after medical treatment (32), although the incidence is much lower compared with that observed in patients following subtotal pancreatectomy (5).

## II Etiology • Pathophysiology • Diagnosis

### A Etiology • Pathophysiology (Table 1)

#### 1 Pathophysiology

CHI is a group of disorders that causes persistent hypoglycemia due to congenital over-secretion of insulin. The transient form of CHI develops soon after birth and generally resolves by 3–4 months of age, while the persistent form has a longer duration. The symptoms of persistent CHI may manifest after infancy.

#### 2 Etiology

Transient CHI often develops in infants of diabetic mothers, neonates classified as small for gestational age (SGA), or neonates with cardiorespiratory problems. Excluding mutations in *HNF4A* or *HNF1A*, or syndromic hypoglycemia, the causes of transient CHI are largely non-genetic. Conversely, it has also

been postulated that the causes of persistent CHI are largely genetic. A number of different causative gene mutations have recently been identified, although there remain a number of patients whose genetic backgrounds are not known (6–16).

- 3 Diagnosis is based on the finding of inappropriate relative hyperinsulinemia in the context of hypoglycemia. However, the insulin cutoff values for the different levels of hypoglycemia are not clear, and at times, it may be challenging to demonstrate elevated insulin levels of the hypoglycemic critical samples.

### B Clinical question (CQ) pertaining to diagnosis. (Fig. 1)

- 1 CQ1: Tests and clinical findings for the diagnosis of hyperinsulinemic hypoglycemia?

- Recommendation

- Obtain hypoglycemic critical samples “before” treatment in order to perform the tests shown in Table 2. [Recommendation level 1, Evidence level A]

- When hypoglycemic critical samples are not obtained, the controlled fasting test is useful to induce a hypoglycemic state and obtain critical samples. The fasting test can also be used to assess the patient’s glycemic response to glucagon. Before performing the fasting test, fatty acid oxidation disorders or defects in carnitine metabolism should be excluded by screening for serum acylcarnitine profiles. [Recommendation level 2, Evidence level A]
- Diagnostic criteria for hyperinsulinemic hypoglycemia based on the critical samples obtained at hypoglycemia (blood glucose < 50 mg/dL).

- (1) Definite

Fulfills  $\geq 2$  of the criteria in Table 3, or

Fulfills one of the criteria + either identification of the presence of the causes of acquired hyperinsulinemic hypoglycemia in Table 1, or identification of a mutation in one of the known causative genes.

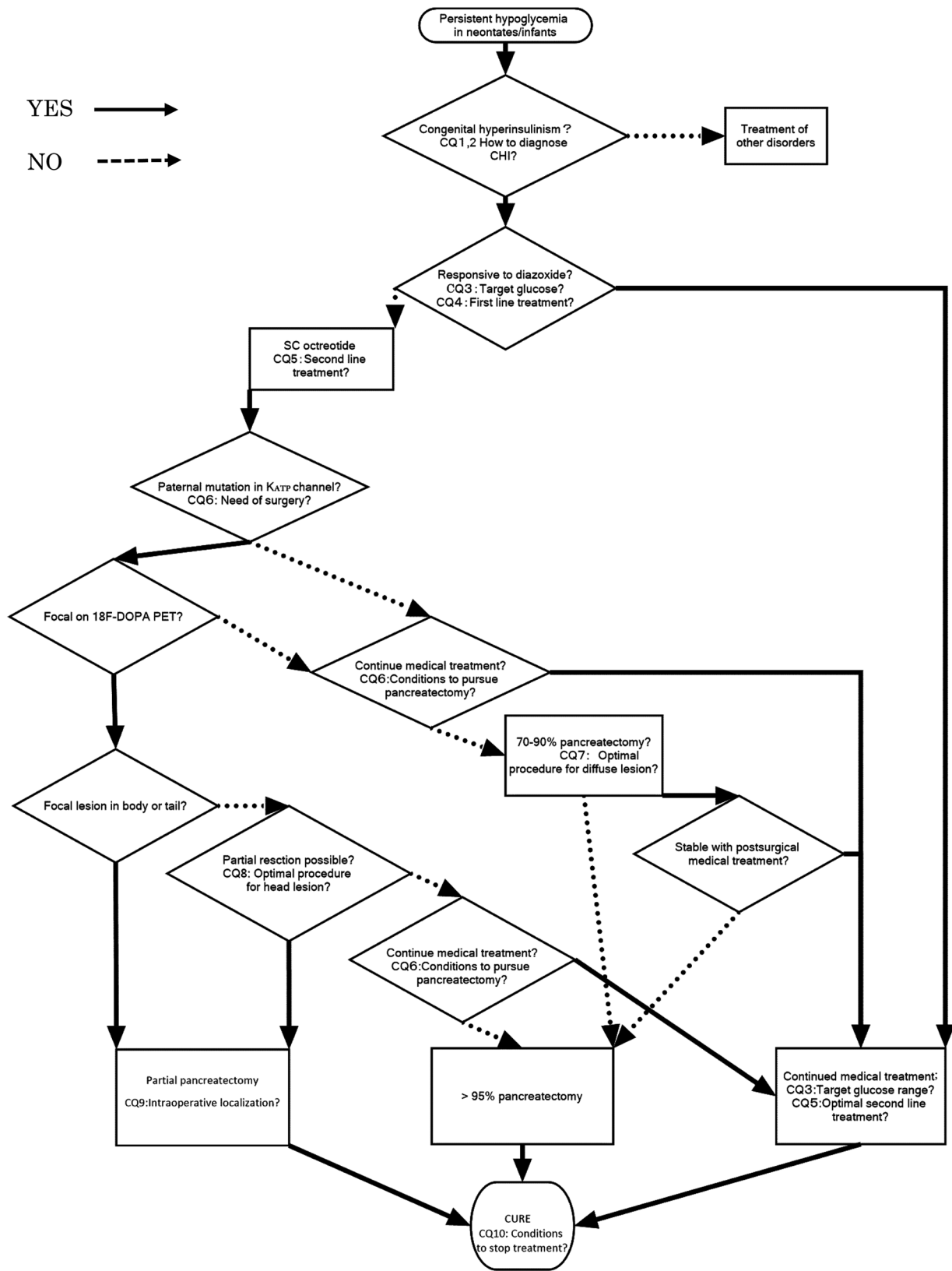


Fig. 1. Flow chart for the management of congenital hyperinsulinism.

**Table 2.** Laboratory tests for hypoglycemic critical samples

Source	Tests
Blood	CBC, CRP, Blood chemistry, Electrolytes Blood glucose*. ** Insulin* • C-peptide Blood gas analysis* Free fatty acids Ammonia* Ketone bodies ( $\beta$ -hydroxybutyrate)* Lactate • pyruvate ACTH • cortisol FT4 • TSH GH • IGF-1 Serum acylcarnitine profile (tandem mass spectrometry) Serum stored frozen*
Urine	Urinalysis* Urine organic acids (gas chromatography-mass spectrometry) Urine stored frozen*

\* Mandatory. \*\* Blood glucose is better measured by using a tube with fluoride than by a point-of-care glucometer.

**Table 3.** Diagnostic criteria of hyperinsulinemic hypoglycemia (at blood glucose < 50 mg/dL)

1. Blood insulin	> 1 $\mu$ U/mL
2. Glycemic response by 0.5–1 mg glucagon (IM, IV)*	> 30 mg/dL (15–45 min)
3. Glucose infusion rate to maintain euglycemia (mg/kg/min)	> 7 (before 6 mo) 3–7 (after 6 mo) > 3 (adult)
[Supportive findings]	
Blood $\beta$ -hydroxybutyrate (BHB)**	< 2 mmol/L (2000 $\mu$ mol/L)
Blood free fatty acids (FFA, NEFA)**	< 1.5 mmol/L (1.5 mEq/L)

\* Glucagon may be given intravenously at 0.03 mg/kg. \*\* When  $\beta$ -hydroxybutyrate (BHB) is low and free fatty acids (FFA) are high, disorders of fatty acid oxidation or defects in carnitine metabolism should be excluded. Within 48 h of birth, BHB and FFA are difficult to assess because of the physiological hyperinsulinemic state. In some cases, hyperinsulinemia may not be the only cause of hypoglycemia and other co-morbidities should be considered.

## (2) Possible

Fulfills one of the criteria in Table 3.

[Recommendation level 1, Evidence level B]

### ● NOTES

- While the majority of cases of persistent hypoglycemia in adults are caused by iatrogenic insulin overdose, insulinoma, or dumping syndrome, there are a range of causes in pediatric patients, including congenital

hyperinsulinism, endocrine abnormalities, or inborn errors of metabolism. Some of these conditions can only be identified by abnormal results of tests taken during hypoglycemia. Therefore, it is important to obtain hypoglycemic critical samples before treatment while the patient is still in the hypoglycemic state (< 50 mg/dL).

- When hypoglycemic critical samples are not available, the controlled fasting test is a useful alternative to



induce hypoglycemia (33); however the test should be performed in an experienced center under strict monitoring. In patients with disorders of fatty acid oxidation or with defects in carnitine metabolism, the fasting test could induce fatal arrhythmia. Therefore, before the test, a serum acylcarnitine profile by tandem mass spectrometry should be obtained, as this can identify most of these disorders, even in the non-fasting state.

- In neonates, there is a physiological decline of fasting blood glucose within the first 1–2 h, followed by a gradual increase and stabilization at approximately 80 mg/dL by 72 h after birth (34). After 48 h, the threshold for the counter-regulatory reaction against hypoglycemia is the same as that of adults. However, children tend to develop hypoglycemia with blood glucose < 70 mg/dL due to limited glycogen reserves or the source for gluconeogenesis (33). After 72 h, the response of glucose stimulated insulin secretion is also the same as that of older children (33). Physiological transient hypoglycemia after birth is likely to be caused by relative hyperinsulinemia at this stage in life (35), and the decline could be significant in low birth weight neonates or in preterm neonates, causing transient CHI hypoglycemia.
- By definition, hyperinsulinemic hypoglycemia is hypoglycemia resulting from an over-secretion of insulin. The definition of hypoglycemia, therefore, is a starting point to diagnose hyperinsulinemic hypoglycemia. Considering the physiological fluctuation of blood glucose after birth, hypoglycemia can be defined as blood glucose < 60 mg/dL beyond 48 h after birth (33) or blood glucose < 50 mg/dL for up to 48 h after birth. However, normal blood glucose is affected by a number of factors, including birth weight or gestational age. Therefore, the diagnosis of hypoglycemia could be extended until after 48 h of birth.
- The definition of “over-secretion” of insulin during hypoglycemia is controversial. Some reports have stated that any detectable level of insulin during hypoglycemia is abnormal (6) while others set a higher threshold for insulin levels during hypoglycemia (11, 36). While measurable insulin levels during hypoglycemia are generally indicative of hyperinsulinemic hypoglycemia, in some cases, patients presenting with measurable insulin levels during hypoglycemia were diagnosed with other hypoglycemic disorders (11). Insulin levels > 3  $\mu$ U/mL during hypoglycemia were associated with a sensitivity of 93% and specificity of 95% for the diagnosis of insulinoma (37). Other proposed indices for the diagnosis of insulinoma include insulin (pmol/L) / (blood glucose (mmol/L)–1.7) > 53.6, with a sensitivity and specificity of 98%; C-peptide (nmol/L) / (blood glucose (mmol/L)–1.7) > 0.61, with a sensitivity of 95% and a specificity of 94%; or insulin /  $\beta$ -hydroxybutyrate < 2.7 mmol/L, with a sensitivity and a specificity of 100% (38). In cases of congenital hyperinsulinism, it has been suggested that C-peptide > 0.5 ng/mL is a better index than insulin (39). However, this guideline uses insulin as a diagnostic test, as C-peptide or proinsulin are not routinely measured in hypoglycemia in many emergency care centers.
- Similarly, different cut-off values for ketone bodies and free fatty acids (FFA) in hypoglycemia have been proposed, including  $\beta$ -hydroxybutyrate (BHB) < 1.5 mmol/L and FFA < 1–1.5 mmol/L (33); BHB < 0.5 mmol/L and FFA < 0.5 mmol/L (36); BHB < 1.8 mmol/L and FFA < 1.7 mmol/L (39); or BHB < 2.0 mmol/L and FFA < 1.5 mmol/L (40). In cases of adult insulinoma, it was found that BHB < 2.7 mmol/L with a blood glucose < 60 mg/dL has a sensitivity and a specificity of 100% (37). Van Veen *et al.* (41) reported BHB levels of 0.91–3.31 mmol/L (mean 2.23) and FFA levels of 1.03–3.24 mmol/L (mean 2.15) in normal infants < 2 yr of age after 20 h of fasting. We therefore set the criteria of BHB and FFA accordingly.
- Conversely, undetectable insulin at hypoglycemia does not necessarily exclude a diagnosis of CHI (36, 42). Secretion of insulin could be episodic and insulin has a short half-life (2%/min) in the blood. Compared with insulin, C-peptide has a longer half-life and is more suitable for diagnosis although it is not measured routinely in the emergency setting. Glycemic response by the glucagon test is another useful index. Glycemic response > 30 mg/dL during hypoglycemia by the glucagon test strongly suggests the diagnosis of CHI (6, 33, 36, 43).
- The glucose infusion rate (GIR) to maintain euglycemia matches the rate of gluconeogenesis at the age of the patient. GIR is 4–6 mg/kg/min in neonates, and 1–2 mg/kg/min in adults. The values applicable to children are in between these values. Patients with CHI could develop symptoms after infancy; therefore, GIR cutoffs of 8–10 mg/kg/min for neonates cannot be applied to older children (6, 11). We therefore set age specific cutoffs for GIR.
- Laboratory test standardization between centers is insufficient; therefore, it is important to make a diagnosis of hyperinsulinemic hypoglycemia taking the clinical findings into account and not to stick to the cutoffs too rigorously.

2 CQ 2: How congenital hyperinsulinism is diagnosed in patients with hyperinsulinemic hypoglycemia ?

● Recommendation

- When the diagnosis of hyperinsulinemic hypoglycemia is made, acquired hyperinsulinemia should be excluded by the followings: [Recommendation level 1, Evidence level A]
- History of gastric bypass, fundoplication for gastroesophageal reflux, use of insulin or oral hypoglycemia agents for diabetes mellitus.
- Blood insulin/C-peptide ratio, anti-insulin antibody, imaging studies of the pancreas (contrast enhanced CT, contrast enhanced MRI, endoscopic ultrasound)

● NOTES

- To diagnose congenital hyperinsulinism, it is important to exclude acquired causes of hyperinsulinemic hypoglycemia (Table 1). These include insulin overdose for diabetes, insulinoma, insulin autoimmune syndrome (Hirata disease), noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS), post-gastric bypass, post-fundoplication for gastroesophageal reflux, or dumping syndrome with postprandial hypoglycemia (10).
- Therefore, in addition to meticulous history taking, the following tests and investigations are useful: exogenous insulin, measured by the inconsistent insulin/C-peptide ratio; imaging studies of the pancreas, including CT, MRI, and endoscopic ultrasound; or anti-insulin antibody tests.

### III Treatment Goals • First Line Treatment (Fig. 1)

#### A CQs pertaining to treatment goals and the first line treatment.

1 CQ 3: What is the target blood glucose for congenital hyperinsulinism ?

● Recommendation

- Treatment goals should be set at blood glucose > 70 mg/dL for CHI. [Recommendation level 1, Evidence level B]
- The threshold of blood glucose to circumvent

neurological sequelae cannot be set because it is patient specific. [Recommendation level 1, Evidence level A]

● NOTES

- In hyperinsulinemic hypoglycemia, glycogenolysis and gluconeogenesis are suppressed and patients tend to develop profound hypoglycemia, compared with hypoglycemia from other causes. Therefore, blood glucose should be maintained above 70 mg/dL, which corresponds to the level at which physiological secretion of counter-regulatory hormones normally starts (33, 44, 45).
- There is no evidence-based blood glucose threshold for the prevention of hypoglycemic neurological sequelae (33). In addition to blood glucose levels, a number of factors affect neurological outcome in hypoglycemia, including patient age; presence or absence of convulsions or loss of consciousness; and co-morbidities, such as infection, fever, hypoxemia, or ischemia (46). Repeated exposure to mild hypoglycemia, slightly below 45 mg/dL, could cause significant developmental delay (47). On the contrary, in normal term-late preterm neonates, maintaining blood glucose above 47 mg/dL was not associated with neurological sequelae at 2 yr of age (48). The recommended blood glucose target of > 70 mg/dL has a “margin of safety” such that inability to achieve the target level does not necessarily cause neurological sequelae.

2 CQ4: What is the recommended first line treatment?

● Recommendation

- Maintain blood glucose above the target range by continuous glucose infusion. [Recommendation level 1, Evidence level A]
- When blood glucose is successfully maintained by continuous glucose infusion, nutritional support by frequent feeding, continuous feeding, cornstarch (after 9 mo), or formula for glycogen storage diseases should be attempted. [Recommendation level 1, Evidence level A]
- When blood glucose is not maintained by continuous glucose infusion, or when it is difficult to withdraw glucose infusion for an extended period, a 5 d trial of oral diazoxide,



in 2–3 divided doses, at 5–15 mg/kg/d should be attempted, unless contraindicated by cardiac failure or pulmonary hypertension. [Recommendation level 1, Evidence level A]

- When diazoxide is effective in stabilizing blood glucose levels, intravenous glucose infusion should be withdrawn and transfer to nutritional support (frequent feeding, continuous feeding, or cornstarch formula for glycogen storage diseases) should be attempted. [Recommendation level 1, Evidence level A]
- While on diazoxide, the patient should be on a glucose self-monitoring regimen to detect episodes of hypoglycemia. Furthermore, CBC, blood chemistry, and physical examination should be performed to detect frequent adverse events, such as hypertrichosis, tachycardia, or edema. [Recommendation level 1, Evidence level B]
- When euglycemia is not achieved by the first line treatment and continuous glucose infusion cannot be withdrawn, the second line treatment should be initiated. [Recommendation level 1, Evidence level A]

#### • NOTES

- The brain can use glucose, ketone bodies, and lactate for ATP sources but not fatty acids. Under normal conditions, the main source of ATP is glucose (49). Therefore, the aim should be to achieve blood glucose levels > 70 mg/dL by continuous glucose infusion. Blood glucose < 45 mg/dL should be avoided, even temporarily (47, 48).
- Generally, a central venous catheter is required when continuous glucose infusion above 7 mg/kg/min is necessary.
- Continuous glucose infusion may result in hypoglycemia caused by an incidental infusion problem. Furthermore, administration through a central venous catheter, poses additional risks of septicemia or thrombosis and it would be more difficult to care for the patients at home. Therefore, after stabilization of glycemic control, early transition to enteral nutritional treatment, including frequent feeding, use of cornstarch or formula for glycogen storage diseases, continuous feeding through nasogastric tube or gastrostomy is required (9, 50). In patients with glycogen storage disease type 1, cornstarch is reported to be more effective in preventing

nocturnal hypoglycemia than continuous feeding (51). The efficacy of cornstarch for severely affected CHI is limited, but is used frequently for patients with CHI after 9–12 mo of age (50, 52–55). Similarly, the formula for glycogen storage diseases, especially the night-time formula mostly composed of carbohydrates (GSD-N), (50, 52–55) is often used for younger infants with CHI. The use of cornstarch and formula for glycogen storage diseases is described in detail in reference (56).

- Diazoxide is a  $K_{ATP}$  channel opener and is effective against the causes of CHI, except for those mutations in the  $K_{ATP}$  channel genes, glucokinase gene, and *SLC16A1* gene. Unfortunately, the majority of cases of neonatal onset persistent CHI are caused by mutations in the  $K_{ATP}$  channel genes; therefore, diazoxide is often ineffective in these patients (6–16). Even when good glycemic response is achieved, the effect could be transient, reverting to pretreatment levels within a few days. Since the half-life of diazoxide is 9.5–24 h in pediatric patients (52), the efficacy of diazoxide should be assessed after at least 5 d from initiation. Patients with no response to doses of 15 mg/kg/d are considered unresponsive to diazoxide (6, 9–12, 31, 50, 52). Major side effects of diazoxide are hypertrichosis and water retention with long-term use. Other reported side effects include neutropenia (57), pulmonary hypertension (57, 58), or paradoxical hypoglycemia (59). The most serious side effects are tachycardia, cardiac failure, or reopening of patent ductus arteriosus caused by water retention (57, 58, 60). Therefore, care should be taken when administering diazoxide to low birth weight infants, and it is desirable to prescribe diazoxide along with diuretics. As diuretics, thiazides are preferred over loop diuretics (9).

## IV Second Line Treatment

### A CQs pertaining to second line treatment (Fig. 1)

- 1 CQ 5: What are the optimal second line treatments for diazoxide unresponsive CHI?
  - Recommendation
    - In patients unresponsive to diazoxide, subcutaneous octreotide, intravenous glucagon, or oral calcium antagonist should be sequentially attempted as second line therapies. [Recommendation level 1, Evidence level A]
    - Glucocorticoid is not recommended as a

**Table 4.** Second line treatment

Nutritional therapy	IV glucose infusion Cornstarch, formula for glycogen storage diseases Frequent feeding, continuous feeding through nasogastric tube or gastrostomy
Medication	Octreotide 5–25 µg/kg/day, SC in 3–4 divided doses or by continuous SC infusion. Glucagon 1–20 µg/kg/h, continuous IV. Nifedipine Oral administration of 0.25–2.5 mg/kg/day, divided into 3 doses. (Hydrocortisone) (2.5 mg/kg/dose, IV 2–3 times a day)

\* SC, subcutaneous; IV, intravenous. \* Start from the lowest dosage and titrate according to the response.

\* Hydrocortisone is no longer recommended.

second line therapy. [Recommendation level 2, Evidence level B]

- In patients unresponsive to diazoxide, etiological diagnosis should be performed. [Recommendation level 1, Evidence level A]
- In patients unresponsive to diazoxide, mutational analysis of the  $K_{ATP}$  channel genes (*ABCC8*, *KCNJ11*) should be performed. [Recommendation level 1, Evidence level B]
- In patients unresponsive to diazoxide, a  $^{18}\text{F}$ -DOPA PET scan should be performed. [Recommendation level 1, Evidence level A]

#### ● NOTES

- When the patient is unresponsive to diazoxide, and blood glucose cannot be stabilized by the first line treatment, second line treatment should be initiated promptly to establish stable blood glucose control and avoid long-term hospitalization.
- When the patient is responsive to diazoxide, the treatment should be continued and supplemented by nutritional therapy, if required. If the patient responds well to nutritional therapy, diazoxide can be gradually decreased and eventually withdrawn (CQ10).
- In patients with diazoxide unresponsive CHI whose blood glucose cannot be stabilized by the first line treatment, second line treatments should be initiated without delay (Table 4). While stabilizing blood glucose levels, mutational analysis and  $^{18}\text{F}$ -DOPA PET scans should be performed to explore the possibility of cure by partial pancreatectomy. Currently, none of the medication for the second line therapy is approved in Japan for this indication.

- $^{18}\text{F}$ -DOPA PET scans are available only at limited centers at the time of writing these guidelines.
- Octreotide is a long acting somatostatin analog acting through somatostatin receptors 2 and 5 to suppress secretion of insulin from the  $\beta$  cells. Octreotide is the most commonly used second line treatment. Its efficacy for congenital hyperinsulinism has been reported since the 1990s (31, 61, 62). Yorifuji *et al.* reported that continuous infusion of octreotide was effective in all patients ( $n = 13$ ) with biallelic or paternally-inherited monoallelic mutation in the  $K_{ATP}$  channel genes (63). Similarly, Demirbilek *et al.* (64) reported the efficacy of octreotide in 28 patients with diazoxide unresponsive CHI. In their series, octreotide was effective in 42.8% of the patients and, in 12 patients with long term treatment, liver dysfunction, cholelithiasis, and cholecystitis were the major adverse events.
- The half-life of octreotide is 100–105 min; therefore, multiple daily subcutaneous injections or continuous subcutaneous infusion is necessary to control hypoglycemia. Because of the relatively short half-life, titration of octreotide is possible within a short period of time.
- Common side effects of octreotide include gastrointestinal symptoms, such as whitish-colored stools, abdominal discomfort, formation of gall stone or biliary sludge, and hypotension (12%, most common adverse effect) (31, 64, 65). Furthermore, rare but more severe side effects include liver dysfunction (66–68), thrombocytopenia, hyperkalemia, leukocytosis, elongation of the QT interval on ECG (69), necrotizing enterocolitis (70), and growth deceleration after prolonged use (63). The most important of these adverse effects is necrotizing enterocolitis, which can be fatal (65). To date, most cases

of necrotizing enterocolitis were reported in patients receiving octreotide up to 30 d following birth, although a case involving a child has also been reported (71). Therefore, the use of octreotide in neonates should be approached with particular care (9) and physicians should be alerted by abdominal symptoms, even beyond infancy. Other problems include attenuating efficacy after extended period of administration (tachyphylaxis) or paradoxical hypoglycemia (72). Physicians should be aware of these side effects and look for signs of the side effects at each visit.

- Glucagon is counter-regulatory to the effect of insulin and causes elevation of blood glucose by promoting hepatic glycogenolysis and gluconeogenesis. Intramuscular or subcutaneous injection of 0.5–1 mg is commonly used for the treatment of hyperinsulinemic hypoglycemia. In addition, continuous IV infusion of glucagon is often used for the glycemic control of CHI, alone or along with octreotide (31). There are reports of successful glycemic control of CHI by continuous subcutaneous infusion of glucagon (73, 74). However, currently available preparations of glucagon tend to precipitate in the infusion tube making long term treatment impractical (9).
- Nifedipine is a calcium antagonist, which is thought to act by blocking the influx of calcium into the pancreatic  $\beta$  cells (31). The efficacy is usually limited but successful glycemic control for residual hypoglycemia after pancreatectomy has been reported (75–77).
- Approximately 90% of patients with diazoxide unresponsive CHI have mutations in the  $K_{ATP}$  channel genes, *ABCC8* or *KCNJ11* (78, 79). Patients with paternally-inherited monoallelic mutations in the  $K_{ATP}$  channel genes may have a focal lesion, potentially amenable to cure by partial pancreatectomy without postsurgical sequelae. Therefore, it is important to identify focal lesions in patients who still require glucose infusion or whose blood glucose cannot be stabilized after the initiation of second line treatment (6–16, 80). Some patients with a paternally-inherited monoallelic mutation are known to have a diffuse lesion, but the possibility of a focal lesion is at least 50% (9). Furthermore, 84.2% of Japanese patients with  $K_{ATP}$  channel mutations were reported to have a paternally-inherited monoallelic mutation (81).
- Unlike tumors, focal lesions do not have a mass effect to compress surrounding structures. Therefore, they are rarely identified by conventional imaging studies including CT, MRI, or angiography. 18-Fluorodihydroxy phenylalanine ( $^{18}\text{F}$ -DOPA) is known to be selectively incorporated into the pancreatic  $\beta$  cells.

The  $^{18}\text{F}$ -DOPA PET scan has been demonstrated to be superior to arterial stimulation venous sampling (ASVS) or transhepatic selective venous sampling in identifying focal lesions, and is currently the first choice for the localization of focal lesions (19, 22, 82–88). Although highly accurate and specific, a weakness of  $^{18}\text{F}$ -DOPA PET scans is the identification of a focal lesion in the head of the pancreas, where artifact uptakes are commonly observed. Furthermore,  $^{18}\text{F}$ -DOPA PET scans cannot easily identify a large focal lesion (89) or a small lesion without strong uptakes (90).

## 2 CQ 6-1: When pancreatectomy should be considered for a focal lesion?

### • Recommendation

- Partial pancreatectomy should be performed when a focal lesion in the body-tail of the pancreas is identified by  $^{18}\text{F}$ -DOPA-PET scan and blood glucose cannot be stabilized by nutritional support and diazoxide. [Recommendation level 1, Evidence level A]
- Partial pancreatectomy should be considered when a focal lesion in the head of the pancreas is identified by  $^{18}\text{F}$ -DOPA-PET scan and blood glucose cannot be stabilized by nutritional support and diazoxide. [Recommendation level 1, Evidence level A]

### • NOTES

- Patients with a focal lesion can be cured by partial pancreatectomy without development of postsurgical diabetes mellitus (6–16). In patients with inadequate glycemic control by medical treatment, the possibility of surgical treatment should be considered by weighing the risks of postsurgical complication against the risks of hypoglycemic neurological sequelae and the burden of continued medical treatment itself.
- The pooled accuracy of  $^{18}\text{F}$ -DOPA PET scans by meta-analysis has been reported as 82% (22). Furthermore, according to a standardized protocol for  $^{18}\text{F}$ -DOPA PET/CT published in 2005, a focal lesion could be accurately localized (sensitivity 94%, specificity 100%) (84). It is hypothesized that the specificity of  $^{18}\text{F}$ -DOPA PET scan is very high for a focal lesion in the body and the tail, where artifact uptake usually does not pose difficulties.
- For a focal lesion in the body and the tail, the risk of damage to the main pancreatic duct or the bile duct is low. Even when the focal lesion cannot be identified intraoperatively, the patient can be cured by resection of the pancreas distal to the area identified by  $^{18}\text{F}$ -DOPA

PET scan.

- On the contrary, for a focal lesion in the head of the pancreas, enucleation could be difficult because of the risks of damaging the main pancreatic duct or the bile duct during surgery. Particularly in neonates, damage to the main pancreatic duct can only be known when it is damaged (91), and leak of pancreatic juice cannot be prevented intraoperatively. For these patients, resection of the head of the pancreas and distal pancreateojejunostomy using the Roux-en-Y loop is recommended (25). Since the surgical stress associated with this operation is considerable, a therapeutic strategy should be planned, carefully weighing the risks of the surgery against the risks of continued medical treatment until spontaneous remission (92) by a multidisciplinary team including pediatric surgeons.
- There have been reports of laparoscopic pancreatectomy for CHI (93–96). Although the evidence is limited, laparoscopic pancreatectomy can be considered in experienced centers.

### 3 CQ6-2: When should pancreatectomy be considered for the diffuse form of CHI?

- Recommendation
  - Consider pancreatectomy for a diffuse lesion diagnosed by mutational analysis or by <sup>18</sup>F-DOPA-PET scan that is resistant to medical treatment, including second line treatments. [Recommendation level 1, Evidence level B]
  - It is desirable to avoid > 95% pancreatectomy. [Recommendation level 2, Evidence level B]
- NOTES
  - Definitions of the extent of partial pancreatectomy is shown in the NOTE in CQ7.
  - Even after > 95% pancreatectomy, residual hypoglycemia is commonly observed. The incidence of postsurgical insulin dependent diabetes mellitus is also high and euglycemia is achieved in only the minority of the patients (17, 18, 91). In a report by Beltrand *et al.* (18), out of 105 patients who underwent subtotal pancreatectomy, hypoglycemia remained in 59%, hyperglycemia immediately after surgery in 53%, hyperglycemia after 13 years in 100%, and insulin dependent diabetes mellitus after 14 yr in 91%. Similarly, Arya *et al.* (17) reported the incidence of diabetes mellitus after 11 years as 96% among 45 patients who underwent 95% pancreatectomy.
  - Hypoglycemia in CHI tends to reach remission with age, and often patients reach complete remission after

a long period of medical treatment (54, 63, 97). Post treatment diabetes mellitus is reported in patients who were treated by medical treatment alone. The incidence of diabetes, however, is much higher in patients who underwent pancreatectomy (98). Furthermore, it has been reported that neurological prognosis did not differ between patients who underwent pancreatectomy and those treated only by medical treatment (5, 99).

- Some investigators recommend performing 50–75% pancreatectomy for patients whose glycemic control is not satisfactory after introduction of the second line treatment to make the medical management easier (9, 91). No data exist on the risk of future diabetes mellitus as it relates to the extent of pancreatectomy.

## V Surgical Treatment (Fig. 1)

### 1 CQ 7: What is the optimal surgical procedure for a diffuse lesion resistant to medical treatment?

- Recommendation
  - Optimal extent of pancreatectomy for a diffuse lesion has not been established. [Recommendation level 0, Evidence level C]
- NOTES
  - By definition, 85% pancreatectomy is a resection of the distal pancreas at the right margin of the superior mesenteric vein; 95% pancreatectomy is a resection at the left margin of the common bile duct, removing most of the head, uncus, body, and tail of the pancreas; and 98% pancreatectomy is a resection of most of the pancreas, leaving only the pancreatic tissues surrounding the pancreaticoduodenal arteries (100).
  - After near total (98%) pancreatectomy, euglycemia is achieved in only 7–50% of patients, while hypoglycemia remains in 17–59% of patients and hyperglycemia in 17–100%. Postsurgical glycemic control after near total/subtotal pancreatectomy is difficult to predict before surgery (18, 100–102). Furthermore, it has been reported that, after prolonged follow up until puberty, 100% of the patients developed diabetes mellitus with 91% of them being insulin dependent (18).
  - Lord *et al.* reviewed 97 children with diffuse CHI who underwent near-total pancreatectomy (median extent: 98%), and found that only 23% of them were discharged with euglycemia, 51% (40 cases) required additional medical treatment for residual hypoglycemia, and 36% (35 cases) required treatment for hyperglycemia at discharge (103).



- Research on patients who underwent 95% pancreatectomy, found that 60% had residual hypoglycemia, which was comparable to the cases of 98% pancreatectomy. After a long interval between 7.3 and 13 yr of age, diabetes mellitus developed in 45–100% of patients (17, 104–106).
- A study on 45 patients who underwent 95% pancreatectomy found that 22 (49%) developed hyperglycemia requiring insulin. Ten of these required insulin immediately after surgery, although insulin was only transiently required in 4 patients. The proportion of patients requiring insulin was 77% after 7 yr and 96% after 11 yr (17).
- A meta-analysis of 422 cases from 12 reports between 1997 and 2009 identified 103 cases of diffuse CHI. Of these, 36% had residual hypoglycemia and 31% had hyperglycemia or diabetes mellitus following 80–98% pancreatectomy (107).
- A report from a single-center experience involving 250 cases after pancreatectomy of diffuse CHI, found that 50% of patients had residual hypoglycemia, 25% required insulin for hyperglycemia, and only 25% had euglycemia. However, glycemic control was easier following pancreatectomy (108).
- In a further report on 10 cases of diffuse CHI, all patients who underwent 95% pancreatectomy developed diabetes mellitus, three of them immediately following surgery and seven after a median of 8 yr (106).
- The most common postsurgical complication was bleeding. Bile ducts damage was more common after 95% pancreatectomy or redo-operation than after subtotal pancreatectomy <80% (11.9–22.2%) (109).
- After 95% pancreatectomy, abnormalities of exocrine function were common, with abnormalities of fecal elastase I in 72% of patients and symptomatic exocrine insufficiency in 49% (17).
- For patients resistant to medical treatment, > 95% pancreatectomy is useful for the control of hypoglycemia. However, extremely high incidence of postsurgical diabetes mellitus has also been reported. Considering the self-remitting nature of CHI, some investigators recommend avoiding > 95% pancreatectomy as far as possible. Furthermore, the optimal extent of resection has not been established; therefore, no recommendation can be made at the moment.

## 2 CQ 8: What is the optimal surgical procedure for a focal lesion in the head of the pancreas?

### • Recommendation

- For a focal lesion in the head of the pancreas, total removal of the lesion by resection of

the head of the pancreas or enucleation of the focal lesion should be considered. [Recommendation level 1, Evidence level C]

- For resection of the head of the pancreas, distal pancreateojejunostomy using a Roux-en-Y loop should be performed to preserve the normal pancreas. [Recommendation level 1, Evidence level C]

### • NOTES

- A focal lesion in the head of the pancreas should be completely removed either by pancreas head resection or by enucleation. These procedures allow optimal control of euglycemia without the need for intravenous glucose, and can be achieved without major postsurgical complications (25, 110, 111).
- The majority of the focal lesions have a diameter of < 1 cm and 50% of them are located in the head of the pancreas (25, 107).
- Pre- and intra-operative localization of a focal lesion is extremely important (108). A focal lesion may have tentacles of diseased tissue, extending to form a large lesion. Therefore, intraoperative pathological evaluations are important to determine the extent of resection. Laparoscopic surgery is not recommended for a focal lesion in the head of the pancreas (112).
- In patients with diazoxide-unresponsive CHI and a paternally-inherited monoallelic mutation in one of the  $K_{ATP}$  channel genes, detected by molecular analysis, the possibility of a focal lesion should be considered and an  $^{18}F$ -DOPA PET scan should be performed.
- Previously, arterial stimulation venous sampling (ASVS) was performed to detect a focal lesion (113).
- However,  $^{18}F$ -DOPA PET/CT scan is superior to ASVS and is the first choice for the detection of a focal lesion (114, 115). The pooled accuracy of  $^{18}F$ -DOPA PET scan by meta-analysis has been reported as 82% (22). Furthermore, according to a standardized protocol of  $^{18}F$ -DOPA PET/CT published in 2005, a focal lesion could be accurately localized with a sensitivity of 94% and a specificity of 100% (84). Conversely, it has been reported that focal lesions in the head of the pancreas could be accurately diagnosed by  $^{18}F$ -DOPA PET/CT in 70–75% of cases (88, 115).
- Palladino *et al.* reported that approximately 2/3 of the focal form of CHI could be identified by visual inspection or by palpation (108). Similarly, Adzick *et al.* reported that 24 out of 38 cases with a focal lesion could be visually identified and that the chances of visual identification were higher with increasing experiences of the surgeons, highlighting the need for



greater surgical expertise (111).

- Von Rohden *et al.* reported the usefulness of intraoperative ultrasound showing that in 3 out of 5 cases of the focal form CHI, the findings obtained by ultrasound were almost identical to those obtained by preoperative <sup>18</sup>F-DOPA PET scans (116). In some of the patients, ultrasound detected a lesion which could not be identified by <sup>18</sup>F-DOPA PET scans. Furthermore, important structures, such as the pancreatic duct or bile duct, could also be identified by intraoperative ultrasound, providing useful information for surgery. The authors also highlighted the weakness of ultrasound in detecting a large segmental lesions. Generally, focal lesions are characterized by hypoechogenicity relative to the surrounding normal pancreas (116).
- When a focal lesion cannot be identified by intraoperative visual inspection, palpation, or ultrasound, the extent of the resection can only be determined by intraoperative pathological diagnosis of multiple biopsies taken from each part of the pancreas (102).
- In summary, for surgical treatment, it is important to localize a focal lesion by combining the information of preoperative imaging studies by <sup>18</sup>F-DOPA PET scan with intraoperative visual inspection, palpation, ultrasound, and pathological diagnosis.
- When a patient has a large focal lesion in the head of the pancreas or has a focal lesion close to the pancreatic duct or the bile duct, resection of the head of the pancreas in association with distal pancreateojejunostomy using a Roux-en-Y loop is recommended. Pancreaticoduodenectomy has not been reported for a focal lesion in the head.
- No clear evidence exists on the ideal timing for the resection of the head of the pancreas with distal pancreateojejunostomy. However, when medical treatment cannot maintain normoglycemia, the procedure can be performed at any age. Since the procedure has a substantial risk for neonates and infants, the decision should be made by close communication between neonatologists, pediatric endocrinologists, and pediatric surgeons.
- Adzick *et al.* performed resection of the head of the pancreas with distal pancreateojejunostomy in 19 out of 38 patients with focal CHI (111). For this procedure, it is important to avoid damaging the bile ducts and to preserve blood supply to the duodenum from the superior pancreatic arteries. Fekete *et al.* (110) reported their experience of a similar procedure in 19 patients with a focal lesion in the head of the pancreas. Hypoglycemia improved in all cases. However, after surgery, 2 patients had stenosis of the common bile

duct, 1 developed chylous ascites, and another had anastomotic stenosis of the pancreatic duct. Conversely, Laje *et al.* (25) reported their experience of near-total pancreatic head resection and pylorus-preserving pancreaticoduodenectomy for focal CHI in the head of the pancreas in 21 and 2 cases, respectively, reporting the achievement of euglycemia in all cases without postsurgical complications.

### 3 CQ 9: What are the useful procedures to identify a focal lesion intraoperatively?

#### ● Recommendation

- The pancreas should be visually inspected and palpated to identify a focal lesion. [Recommendation level 1, Evidence level C]
- Intraoperative ultrasound can be useful to identify a focal lesion. [Recommendation level 2, Evidence level C]
- When a focal lesion cannot be identified by visual inspection or by palpation, intraoperative biopsies should be taken from multiple parts of the pancreas for rapid diagnosis by frozen section. [Recommendation level 1, Evidence level B]

#### ● NOTES

- Palladino *et al.* reported that approximately 2/3 of the focal form of CHI could be identified by visual inspection or by palpation (108). Similarly, Adzick *et al.* reported that 24 out of 38 cases with a focal lesion could be visually identified. They also stated that the chances of visual identification rose with increasing experiences of the surgeons stressing the need to have more experiences of surgery (111).
- Intraoperative pathological diagnosis is almost mandatory when a focal lesion cannot be identified by visual inspection or palpation. Biopsy samples of 3–5 mm in diameter should be taken from the head, body, and tail of the pancreas (111). Pathological diagnosis should be performed by experienced pathologists (114).
- Von Rohden *et al.* reported on the usefulness of intraoperative ultrasound showing that in 3 out of 5 cases of the focal form CHI, the findings obtained by ultrasound were almost identical to those obtained by preoperative <sup>18</sup>F-DOPA PET scans (116). In some of the patients, ultrasound detected a lesion which could not be identified by <sup>18</sup>F-DOPA PET scans. Furthermore, important structures, such as the pancreatic duct or bile duct could also be identified by intraoperative ultrasound providing useful information for surgery. The authors also highlighted the weakness of ultrasound

in detecting a large segmental lesion. Generally, focal lesions are characterized by hypoechogenicity relative to the surrounding normal pancreas (116).

- To summarize, pancreatectomy should be guided by preoperative imaging studies and intraoperative visual inspection, palpation, ultrasound, and pathological diagnosis. Intraoperative pathological diagnosis is particularly important and an experienced pathologist, who can make an accurate intraoperative diagnosis by frozen section samples, is indispensable to the treatment team.

## VI End of Treatment (Fig. 1)

1 CQ 10: What are the conditions to withdraw from medical treatment?

- **Recommendation**
  - The dosage of diazoxide can be gradually decreased unless hypoglycemia does not recur, and withdrawal can be attempted when the dosage is below 1 mg/kg/d. [Recommendation level 2, Evidence level C]
  - Reduction in the dosage of diazoxide should be attempted based on monitoring of blood glucose. However, when the patient has a history suggestive of transient CHI, such as maternal diabetes mellitus or SGA birth, dose reduction can be attempted every 2 wk–1 mo, as long as blood glucose levels are stable. [Recommendation level 2, Evidence level C]
  - After withdrawal from diazoxide, relapse of hypoglycemia should be monitored either by frequent blood glucose monitoring or by continuous blood glucose monitoring for 7 d. [Recommendation level 2, Evidence level C]
  - After withdrawal from diazoxide, fasting tolerance should be tested by 8–18 h (could be shorter for infants below 6 mo) of fasting tests according to the age of the patient. [Recommendation level 2, Evidence level C]
  - After withdrawal from nutritional therapy, relapse of hypoglycemia should be monitored either by frequent blood glucose monitoring or by continuous blood glucose monitoring for 7 d. Furthermore, fasting tolerance should be tested by 8–18 h of fasting tests, according

to the age of the patient. [Recommendation level 2, Evidence level C]

### • NOTES

- In many patients with CHI, even those with persistent CHI, hypoglycemia gradually resolves and patients no longer require medication (7, 10, 52). However, remission may require several months to several years, and some patients still require treatment after adulthood. The decision to discontinue medical treatment is a 2-step process, considering (1) whether medication could be discontinued and (2) whether nutritional therapy could be discontinued. It is important to carefully assess whether each therapy can be discontinued without increasing episodes of hypoglycemia.
- Some investigators propose that diazoxide could be discontinued when the dosage is below 5 mg/kg/d (117). However, we are aware of patients who developed hypoglycemia upon withdrawal of diazoxide when the dosage was decreased to 2 mg/kg/d. We therefore set the dosage of diazoxide at 1 mg/kg/d as the threshold to consider discontinuation of therapy. As in the majority of cases, relapse of hypoglycemia occurs within 7 d of diazoxide withdrawal (118), careful monitoring of blood glucose should be performed during the 7 d period.
- It is impossible to diagnose transient CHI by laboratory test results alone. A history of maternal diabetes mellitus or SGA birth weight strongly suggests transient CHI (3).

## VII Future Perspectives

Novel therapies for CHI include long-acting octreotides (119), GLP1 receptor antagonists (120), Lanreotide (121, 122), insulin receptor antagonists (123), Pasireotide (124),  $\omega$ 3 unsaturated fatty acids (125), or mTOR inhibitors (126). In addition, water soluble glucagon is under development. These guidelines may require further revision in the near future to incorporate these advances in the treatment.

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## Process of guideline generation

### A. Process of guideline generation

As CHI is a rare disorder affecting neonates and infants, few clinical trials have been performed. Therefore, clinical practice has been guided by expert opinions, which vary from center to center. The latest guidelines were issued in 2006 by the Japanese Society for Pediatric Endocrinology. These guidelines are intended to replace the existing guidelines, incorporating surgical aspects of CHI treatment and other recent advances, as a collaborative effort between the Japanese Society for Pediatric Endocrinology and the Japanese Society of Pediatric Surgeons. These guidelines were generated as a part of the research funded by a grant-in-aid for scientific research from the Ministry of Health, Labour, and Welfare of Japan (Principle investigator, Masaki Nio).

### B. Members of the committee

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## [Conflict of Interests]

The members of the guideline committee have no conflict of interests to declare.

**C. Funding source**

The funding source of this guideline was a grant-in-aid for scientific research from the Ministry of Health, Labour, and Welfare of Japan (Research on Measures for Intractable Diseases, No. 2016-021, Principle Investigator, Masaki Nio).

**D. Process of generation**

## 1. Understanding of the current situation

Understanding of the current situation was based on the results of the National Survey conducted in 2008-2009 by a research grant from the Ministry of Health, Labour, and Welfare of Japan to T.Y. (Research on Measures for Intractable Diseases, No. 2013-070).

## 2. Systematic review and generation of recommendation

## (1) Systematic review

## a. Pubmed (before March 31, 2016)

Out of the 1698 references identified by a search of ((congenital) AND hyperinsulinism) OR ((hyperinsulinemic) AND hypoglycemia), non-English literature, review article before 2005, articles on different topics (e.g., lipodystrophy, diabetes mellitus, non-human, insulin resistance) were excluded and the remaining 718 papers were reviewed by the committee members.

## b. Igakyo Chuo Zasshi (Japan's largest medical literature database)

Out of the 254 references screened by (congenital hyperinsulinism), meeting abstracts were excluded. The remaining 95 papers were reviewed by the committee members.

## c. Literature added by the committee members (especially those published after March

- 31, 2016 before completion of the guideline generation).
- (2) Evidence level of references
    1. (HIGH) Systematic review (SR), Meta-analysis(MA), Randomized controlled trial (RCT)
    2. (MEDIUM) Observational study (OS), Cohort study, Case-control study
    3. (LOW) Case series (CS), Case report, Expert opinion (EO)
  - (3) Strength of Evidences
    1. Level A (strong):Strongly confident in the conclusion.
    2. Level B (medium):Moderately confident in the conclusion.
    3. Level C (weak):Weakly confident in the conclusion.
    4. Level D (very weak):No confidence in the conclusion.
  - (4) Strength of Recommendation
    1. Level 1 (Strong Recommendation)
    2. Level 2 (Weak Recommendation)
    3. Level 0 (No Recommendation)
  3. External reviews
    - a. Review in the board of directors, The Japanese Society for Pediatric Endocrinology (July 5–15, 2016)
    - b. Approved in the Board of Directors, The Japanese Society for Pediatric Endocrinology (July 16, 2016)
    - c. Public comment, The Japanese Society for Pediatric Endocrinology (July 19–31, 2016)
    - d. Assessment in the Guideline Committee, The Japanese Society for Pediatric Endocrinology guideline (July 19–31, 2016)
    - e. Public comment, The Japanese Society of Pediatric Surgeons (August 1–15, 2016)
    - f. Assessment in the Academic Survey and Advanced Medical Science Committee, The Japanese Society of Pediatric Surgeons (August 15–September 4, 2016)
    - g. Review in the Board of Directors, The Japanese Society of Pediatric Surgeons (September 5–12, 2016)
    - h. Approved in The Japanese Society of Pediatric Surgeons (September 13, 2016)

## E. Revision

These guidelines will be revised within 5 years of release. Members of the revision committee will be appointed by the board of directors of the Japanese Society for Pediatric Endocrinology and the Japanese Society of Pediatric Surgeons. The revision committee could include other multidisciplinary health care professionals from outside the Societies. When a novel finding emerges that could affect the content of these guidelines, minor-revisions may be performed, with the approval of the board of directors of both Societies.



## References

1. Stanley CA. Advances in diagnosis and treatment of hyperinsulinism in infants and children. *J Clin Endocrinol Metab* 2002;87: 4857–9 (HIGH). [[Medline](#)] [[CrossRef](#)]
2. De León DD, Stanley CA. Mechanisms of Disease: advances in diagnosis and treatment of hyperinsulinism in neonates. *Nat Clin Pract Endocrinol Metab* 2007;3: 57–68 (HIGH). [[Medline](#)] [[CrossRef](#)]
3. Kawakita R, Sugimine H, Nagai S, Kawai M, Kusuda S, Yorifuji T. Clinical Characteristics of Congenital Hyperinsulinemic Hypoglycemia in Infant: A Nationwide Epidemiological Survey in Japan. *J Jpn Pediatr Soc* 2011;115: 563–9 (in Japanese). (MEDIUM).
4. Menni F, de Lonlay P, Sevin C, Touati G, Peigné C, Barbier V, *et al.* Neurologic outcomes of 90 neonates and infants with persistent hyperinsulinemic hypoglycemia. *Pediatrics* 2001;107: 476–9 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
5. Ludwig A, Ziegenhorn K, Empting S, Meissner T, Marquard J, Holl R, *et al.* Diabetes Patienten-Verlaufsdokumentationssystem (DPV) Group Glucose metabolism and neurological outcome in congenital hyperinsulinism. *Semin Pediatr Surg* 2011;20: 45–9 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
6. Arnoux JB, Verkarre V, Saint-Martin C, Montravers F, Brassier A, Valayannopoulos V, *et al.* Congenital hyperinsulinism: current trends in diagnosis and therapy. *Orphanet J Rare Dis* 2011;6: 63 (HIGH). [[Medline](#)] [[CrossRef](#)]
7. Senniappan S, Shanti B, James C, Hussain K. Hyperinsulinaemic hypoglycaemia: genetic mechanisms, diagnosis and management. *J Inherit Metab Dis* 2012;35: 589–601 (HIGH). [[Medline](#)] [[CrossRef](#)]
8. Sweet CB, Grayson S, Polak M. Management strategies for neonatal hypoglycemia. *J Pediatr Pharmacol Ther* 2013;18: 199–208 (HIGH). [[Medline](#)]
9. Lord K, De León DD. Monogenic hyperinsulinemic hypoglycemia: current insights into the pathogenesis and management. *Int J Pediatr Endocrinol* 2013;2013:3. (HIGH).
10. Arya VB, Mohammed Z, Blankenstein O, De Lonlay P, Hussain K. Hyperinsulinaemic hypoglycaemia. *Horm Metab Res* 2014;46: 157–70 (HIGH). [[Medline](#)] [[CrossRef](#)]
11. Yorifuji T. Congenital hyperinsulinism: current status and future perspectives. *Ann Pediatr Endocrinol Metab* 2014;19: 57–68 (HIGH). [[Medline](#)] [[CrossRef](#)]
12. Yorifuji T, Masue M, Nishibori H. Congenital hyperinsulinism: global and Japanese perspectives. *Pediatr Int* 2014;56: 467–76 (HIGH). [[Medline](#)] [[CrossRef](#)]
13. Shah P, Demirbilek H, Hussain K. Persistent hyperinsulinaemic hypoglycaemia in infancy. *Semin Pediatr Surg* 2014;23: 76–82 (HIGH). [[Medline](#)] [[CrossRef](#)]
14. Güemes M, Hussain K. Hyperinsulinemic Hypoglycemia. *Pediatr Clin North Am* 2015;62: 1017–36 (HIGH). [[Medline](#)] [[CrossRef](#)]
15. Vora S, Chandran S, Rajadurai VS, Hussain K. Hyperinsulinemic hypoglycemia in infancy: current concepts in diagnosis and management. *Indian Pediatr* 2015;52: 1051–9 (HIGH). [[Medline](#)] [[CrossRef](#)]
16. Stanley CA. Perspective on the genetics and diagnosis of congenital hyperinsulinism disorders. *J Clin Endocrinol Metab* 2016;101: 815–26 (HIGH). [[Medline](#)] [[CrossRef](#)]
17. Arya VB, Senniappan S, Demirbilek H, Alam S, Flanagan SE, Ellard S, *et al.* Pancreatic endocrine and exocrine function in children following near-total pancreatectomy for diffuse congenital hyperinsulinism. *PLoS ONE* 2014;9: e98054 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
18. Beltrand J, Caquard M, Arnoux JB, Laborde K, Velho G, Verkarre V, *et al.* Glucose metabolism in 105 children and adolescents after pancreatectomy for congenital hyperinsulinism. *Diabetes Care* 2012;35: 198–203 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
19. Gopal-Kothandapani JS, Hussain K. Congenital hyperinsulinism: Role of fluorine-18L-3, 4 hydroxyphenylalanine positron emission tomography scanning. *World J Radiol* 2014;6: 252–60 (HIGH). [[Medline](#)] [[CrossRef](#)]
20. Yang J, Hao R, Zhu X. Diagnostic role of 18F-dihydroxyphenylalanine positron emission

- tomography in patients with congenital hyperinsulinism: a meta-analysis. *Nucl Med Commun* 2013;34: 347–53 (HIGH). [[Medline](#)] [[CrossRef](#)]
21. Treglia G, Mirk P, Giordano A, Rufini V. Diagnostic performance of fluorine-18-dihydroxyphenylalanine positron emission tomography in diagnosing and localizing the focal form of congenital hyperinsulinism: a meta-analysis. *Pediatr Radiol* 2012;42: 1372–9 (HIGH). [[Medline](#)] [[CrossRef](#)]
  22. Blomberg BA, Moghbel MC, Saboury B, Stanley CA, Alavi A. The value of radiologic interventions and (18)F-DOPA PET in diagnosing and localizing focal congenital hyperinsulinism: systematic review and meta-analysis. *Mol Imaging Biol* 2013;15: 97–105 (HIGH). [[Medline](#)] [[CrossRef](#)]
  23. Banerjee I, Skae M, Flanagan SE, Rigby L, Patel L, Didi M, *et al.* The contribution of rapid  $K_{ATP}$  channel gene mutation analysis to the clinical management of children with congenital hyperinsulinism. *Eur J Endocrinol* 2011;164: 733–40 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
  24. Banerjee I, Avatapalle B, Padidela R, Stevens A, Cosgrove KE, Clayton PE, *et al.* Integrating genetic and imaging investigations into the clinical management of congenital hyperinsulinism. *Clin Endocrinol (Oxf)* 2013;78: 803–13 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
  25. Laje P, Stanley CA, Palladino AA, Becker SA, Adzick NS. Pancreatic head resection and Roux-en-Y pancreaticojejunostomy for the treatment of the focal form of congenital hyperinsulinism. *J Pediatr Surg* 2012;47: 130–5 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
  26. Rahman SA, Nessa A, Hussain K. Molecular mechanisms of congenital hyperinsulinism. *J Mol Endocrinol* 2015;54: R119–29 (LOW). [[Medline](#)] [[CrossRef](#)]
  27. Sempoux C, Capito C, Bellanné-Chantelot C, Verkarre V, de Lonlay P, Aigrain Y, *et al.* Morphological mosaicism of the pancreatic islets: a novel anatomopathological form of persistent hyperinsulinemic hypoglycemia of infancy. *J Clin Endocrinol Metab* 2011;96: 3785–93 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
  28. Hussain K, Flanagan SE, Smith VV, Ashworth M, Day M, Pierro A, *et al.* An ABCC8 gene mutation and mosaic uniparental isodisomy resulting in atypical diffuse congenital hyperinsulinism. *Diabetes* 2008;57: 259–63 (LOW). [[Medline](#)] [[CrossRef](#)]
  29. Sheffield BS, Yip S, Ruchelli ED, Dunham CP, Sherwin E, Brooks PA, *et al.* Fatal congenital hypertrophic cardiomyopathy and a pancreatic nodule morphologically identical to focal lesion of congenital hyperinsulinism in an infant with Costello syndrome: case report and review of the literature. *Pediatr Dev Pathol* 2015;18: 237–44 (LOW). [[Medline](#)] [[CrossRef](#)]
  30. Gripp KW, Robbins KM, Sheffield BS, Lee AF, Patel MS, Yip S, *et al.* Paternal uniparental disomy 11p15.5 in the pancreatic nodule of an infant with Costello syndrome: Shared mechanism for hyperinsulinemic hypoglycemia in neonates with Costello and Beckwith-Wiedemann syndrome and somatic loss of heterozygosity in Costello syndrome driving clonal expansion. *Am J Med Genet A* 2016;170: 559–64 (LOW). [[Medline](#)] [[CrossRef](#)]
  31. Welters A, Lerch C, Kummer S, Marquard J, Salgin B, Mayatepek E, *et al.* Long-term medical treatment in congenital hyperinsulinism: a descriptive analysis in a large cohort of patients from different clinical centers. *Orphanet J Rare Dis* 2015;10: 150 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
  32. Gussinyer M, Clemente M, Cebrián R, Yeste D, Albusu M, Carrascosa A. Glucose intolerance and diabetes are observed in the long-term follow-up of nonpancreatectomized patients with persistent hyperinsulinemic hypoglycemia of infancy due to mutations in the ABCC8 gene. *Diabetes Care* 2008;31: 1257–9 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
  33. Thornton PS, Stanley CA, De León DD, Harris D, Haymond MW, Hussain K, *et al.* Pediatric Endocrine Society. Recommendations from the pediatric endocrine society for evaluation and management of persistent hypoglycemia in neonates, infants, and children. *J Pediatr* 2015;167: 238–45 (HIGH). [[Medline](#)] [[CrossRef](#)]
  34. Srinivasan G, Pildes RS, Cattamanchi G, Voora S, Lilien LD. Plasma glucose values in normal neonates: a new look. *J Pediatr* 1986;109: 114–7

- (MEDIUM). [\[Medline\]](#) [\[CrossRef\]](#)
35. Stanley CA, Rozance PJ, Thornton PS, De León DD, Harris D, Haymond MW, *et al.* Re-evaluating transitional neonatal hypoglycemia: mechanism and implications for management. *J Pediatr* 2015;166: 1520–5.e1 (MEDIUM). [\[Medline\]](#) [\[CrossRef\]](#)
  36. De León DD, Stanley CA. Determination of insulin for the diagnosis of hyperinsulinemic hypoglycemia. *Best Pract Res Clin Endocrinol Metab* 2013;27: 763–9 (HIGH). [\[Medline\]](#) [\[CrossRef\]](#)
  37. Placzkowski KA, Vella A, Thompson GB, Grant CS, Reading CC, Charboneau JW, *et al.* Secular trends in the presentation and management of functioning insulinoma at the Mayo Clinic, 1987–2007. *J Clin Endocrinol Metab* 2009;94: 1069–73 (MEDIUM). [\[Medline\]](#) [\[CrossRef\]](#)
  38. Nauck MA, Meier JJ. Diagnostic accuracy of an amended insulin-glucose ratio for the biochemical diagnosis of insulinomas. *Ann Intern Med* 2012;157: 767–75 (MEDIUM). [\[Medline\]](#) [\[CrossRef\]](#)
  39. Ferrara C, Patel P, Becker S, Stanley CA, Kelly A. Biomarkers of Insulin for the Diagnosis of Hyperinsulinemic Hypoglycemia in Infants and Children. *J Pediatr* 2016;168: 212–9 (MEDIUM). [\[Medline\]](#) [\[CrossRef\]](#)
  40. The Japanese Society for Pediatric Endocrinology, Committee on Pharmaceutical Affairs. Guideline for diagnosis and treatment of hyperinsulinemic hypoglycemic hypoglycemia. *J Pediatr Soc* 2006; 110: 1472–4. (in Japanese) (HIGH).
  41. van Veen MR, van Hasselt PM, de Sain-van der Velden MG, Verhoeven N, Hofstede FC, de Koning TJ, *et al.* Metabolic profiles in children during fasting. *Pediatrics* 2011;127: e1021–7 (MEDIUM). [\[Medline\]](#) [\[CrossRef\]](#)
  42. Brady C, Palladino AA, Gutmark-Little I. A novel case of compound heterozygous congenital hyperinsulinism without high insulin levels. *Int J Pediatr Endocrinol* 2015; 2015: 16. (LOW).
  43. Finegold DN, Stanley CA, Baker L. Glycemic response to glucagon during fasting hypoglycemia: an aid in the diagnosis of hyperinsulinism. *J Pediatr* 1980;96: 257–9 (MEDIUM). [\[Medline\]](#) [\[CrossRef\]](#)
  44. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, *et al.* Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care* 2013;36: 1384–95 (HIGH). [\[Medline\]](#) [\[CrossRef\]](#)
  45. Ly TT, Maahs DM, Rewers A, Dunger D, Oduwole A, Jones TW, International Society for Pediatric and Adolescent Diabetes. ISPAD Clinical Practice Consensus Guidelines 2014. Assessment and management of hypoglycemia in children and adolescents with diabetes. *Pediatr Diabetes* 2014;15(Suppl 20): 180–92 (HIGH). [\[Medline\]](#) [\[CrossRef\]](#)
  46. Gataullina S, Dellatolas G, Perdry H, Robert JJ, Valayannopoulos V, Touati G, *et al.* Comorbidity and metabolic context are crucial factors determining neurological sequelae of hypoglycaemia. *Dev Med Child Neurol* 2012;54: 1012–7 (MEDIUM). [\[Medline\]](#) [\[CrossRef\]](#)
  47. Lucas A, Morley R, Cole TJ. Adverse neurodevelopmental outcome of moderate neonatal hypoglycaemia. *BMJ* 1988;297: 1304–8 (MEDIUM). [\[Medline\]](#) [\[CrossRef\]](#)
  48. McKinlay CJ, Alsweiler JM, Ansell JM, Anstice NS, Chase JG, Gamble GD, *et al.* CHYLD Study Group Neonatal Glycemia and Neurodevelopmental Outcomes at 2 Years. *N Engl J Med* 2015;373: 1507–18 (HIGH). [\[Medline\]](#) [\[CrossRef\]](#)
  49. Vannucci RC, Vannucci SJ. Glucose metabolism in the developing brain. *Semin Perinatol* 2000;24: 107–15 (HIGH). [\[Medline\]](#) [\[CrossRef\]](#)
  50. Arnoux JB, de Lonlay P, Ribeiro MJ, Hussain K, Blankenstein O, Mohnike K, *et al.* Congenital hyperinsulinism. *Early Hum Dev* 2010;86: 287–94 (HIGH). [\[Medline\]](#) [\[CrossRef\]](#)
  51. Shah KK, Odell SD. Effect of dietary interventions in the maintenance of normoglycaemia in glycogen storage disease type 1a: a systematic review and meta-analysis. *J Hum Nutr Diet* 2013;26: 329–39 (HIGH). [\[Medline\]](#) [\[CrossRef\]](#)
  52. Mohamed Z, Arya VB, Hussain K. Hyperinsulinaemic hypoglycaemia: genetic mechanisms, diagnosis and management. *J Clin Res Pediatr Endocrinol* 2012;4: 169–81 (HIGH). [\[Medline\]](#) [\[CrossRef\]](#)

53. Iwasaki Y, Kamoda T, Takizawa F, Ono T, Ohkubo K, Matsui A. A case of persistent hyperinsulinemic hypoglycemia of infancy treated with diazoxide and cornstarch. *Clin Endocrinol (Oxf)* 2006;54: 1037–41 (in Japanese) (LOW).
54. Matsubara K, Wada T, Yorifuji T, Masue M, Nishibori H, Isono K, *et al.* Three-year treatment with continuous subcutaneous infusion of octreotide successfully managed in a patient with congenital hyperinsulinism without pancreatectomy. *J Jpn Pediatr Soc* 2011; 115: 1445–50. (In Japanese) (LOW).
55. Froissart R, Piraud M, Boudjemline AM, Vianey-Saban C, Petit F, Hubert-Buron A, *et al.* Glucose-6-phosphatase deficiency. *Orphanet J Rare Dis* 2011;6: 27 (HIGH). [[Medline](#)] [[CrossRef](#)]
56. Imperial Gift Foundation Boshi-Aiiku-Kai “Wakariyasui Kangata-togenbyo shokuji ryohou” 2013 (<http://www.boshiaiikukai.jp/img/milk/kangata-togenbyo.pdf>) (in Japanese).
57. Yildizdas D, Erdem S, Küçükosmanoglu O, Yilmaz M, Yüksel B. Pulmonary hypertension, heart failure and neutropenia due to diazoxide therapy. *Adv Ther* 2008;25: 515–9 (LOW). [[Medline](#)] [[CrossRef](#)]
58. Demirel F, Unal S, Çetin II, Esen I, Arasli A. Pulmonary hypertension and reopening of the ductus arteriosus in an infant treated with diazoxide. *J Pediatr Endocrinol Metab* 2011;24: 603–5 (LOW). [[Medline](#)] [[CrossRef](#)]
59. Ponmani C, Gannon H, Hussain K, Senniappan S. Paradoxical hypoglycaemia associated with diazoxide therapy for hyperinsulinaemic hypoglycaemia. *Horm Res Paediatr* 2013;80: 129–33 (LOW). [[Medline](#)] [[CrossRef](#)]
60. Yoshida K, Kawai M, Marumo C, Kanazawa H, Matsukura T, Kusuda S, *et al.* High prevalence of severe circulatory complications with diazoxide in premature infants. *Neonatology* 2014;105: 166–71 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
61. Glaser B, Hirsch HJ, Landau H. Persistent hyperinsulinemic hypoglycemia of infancy: long-term octreotide treatment without pancreatectomy. *J Pediatr* 1993;123: 644–50 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
62. Thornton PS, Alter CA, Katz LE, Baker L, Stanley CA. Short- and long-term use of octreotide in the treatment of congenital hyperinsulinism. *J Pediatr* 1993;123: 637–43 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
63. Yorifuji T, Kawakita R, Hosokawa Y, Fujimaru R, Matsubara K, Aizu K, *et al.* Efficacy and safety of long-term, continuous subcutaneous octreotide infusion for patients with different subtypes of KATP-channel hyperinsulinism. *Clin Endocrinol (Oxf)* 2013;78: 891–7 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
64. Demirbilek H, Shah P, Arya VB, Hinchey L, Flanagan SE, Ellard S, *et al.* Long-term follow-up of children with congenital hyperinsulinism on octreotide therapy. *J Clin Endocrinol Metab* 2014;99: 3660–7 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
65. Testoni D, Hornik CP, Neely ML, Yang Q, McMahon AW, Clark RH, *et al.* Best Pharmaceuticals for Children Act — Pediatric Trials Network Administrative Core Committee. Safety of octreotide in hospitalized infants. *Early Hum Dev* 2015;91: 387–92 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
66. Avatapalle B, Padidela R, Randell T, Banerjee I. Drug-induced hepatitis following use of octreotide for long-term treatment of congenital hyperinsulinism. *BMJ Case Rep* 2012;2012. (LOW).
67. Ben-Ari J, Greenberg M, Nemet D, Edelstein E, Eliakim A. Octreotide-induced hepatitis in a child with persistent hyperinsulinemia hypoglycemia of infancy. *J Pediatr Endocrinol Metab* 2013;26: 179–82 (LOW). [[Medline](#)] [[CrossRef](#)]
68. Koren I, Riskin A, Barthlen W, Gillis D. Hepatitis in an infant treated with octreotide for congenital hyperinsulinism. *J Pediatr Endocrinol Metab* 2013;26: 183–5 (LOW). [[Medline](#)] [[CrossRef](#)]
69. Celik N, Cinaz P, Emeksiz HC, Hussain K, Çamurdan O, Bideci A, *et al.* Octreotide-induced long QT syndrome in a child with congenital hyperinsulinemia and a novel missense mutation (p.Met115Val) in the ABCC8 gene. *Horm Res Paediatr* 2013;80: 299–303 (LOW). [[Medline](#)] [[CrossRef](#)]



70. Laje P, Halaby L, Adzick NS, Stanley CA. Necrotizing enterocolitis in neonates receiving octreotide for the management of congenital hyperinsulinism. *Pediatr Diabetes* 2010;11: 142–7 (LOW). [[Medline](#)] [[CrossRef](#)]
71. Hawkes CP, Adzick NS, Palladino AA, De León DD. Late presentation of fulminant necrotizing enterocolitis in a child with hyperinsulinism on octreotide therapy. *Horm Res Paediatr* 2016;86: 131–6 (LOW). [[Medline](#)] [[CrossRef](#)]
72. Abell SK, Teng J, Dowling A, Hofman MS, MacIsaac RJ, Sachithanandan N. Prolonged life-threatening hypoglycaemia following dose escalation of octreotide LAR in a patient with malignant polysecreting pancreatic neuroendocrine tumour. *Endocrinol Diabetes Metab Case Rep* 2015:140097. (LOW).
73. Neylon OM, Moran MM, Pellicano A, Nightingale M, OConnell MA. Successful subcutaneous glucagon use for persistent hypoglycaemia in congenital hyperinsulinism. *J Pediatr Endocrinol Metab* 2013;26: 1157–61 (LOW). [[Medline](#)] [[CrossRef](#)]
74. Mohnike K, Blankenstein O, Pfuetzner A, Pötzsch S, Schober E, Steiner S, *et al.* Long-term non-surgical therapy of severe persistent congenital hyperinsulinism with glucagon. *Horm Res* 2008;70: 59–64 (LOW). [[Medline](#)] [[CrossRef](#)]
75. Baş F, Darendeliler F, Demirkol D, Bundak R, Saka N, Günöz H. Successful therapy with calcium channel blocker (nifedipine) in persistent neonatal hyperinsulinemic hypoglycemia of infancy. *J Pediatr Endocrinol Metab* 1999;12: 873–8 (LOW). [[Medline](#)] [[CrossRef](#)]
76. Durmaz E, Flanagan SE, Parlak M, Ellard S, Akcurin S, Bircan I. A combination of nifedipine and octreotide treatment in an hyperinsulinemic hypoglycemic infant. *J Clin Res Pediatr Endocrinol* 2014;6: 119–21 (LOW). [[Medline](#)] [[CrossRef](#)]
77. Koklu E, Ozkan KU, Sayar H, Koklu S, Keskin M. Treatment of hyperinsulinemic hypoglycemia because of diffuse nesidioblastosis with nifedipine after surgical therapies in a newborn. *J Pediatr Endocrinol Metab* 2013;26: 1153–6 (LOW). [[Medline](#)] [[CrossRef](#)]
78. Snider KE, Becker S, Boyajian L, Shyng SL, MacMullen C, Hughes N, *et al.* Genotype and phenotype correlations in 417 children with congenital hyperinsulinism. *J Clin Endocrinol Metab* 2013;98: E355–63 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
79. Kapoor RR, Flanagan SE, Arya VB, Shield JP, Ellard S, Hussain K. Clinical and molecular characterisation of 300 patients with congenital hyperinsulinism. *Eur J Endocrinol* 2013;168: 557–64 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
80. Nagai S, Yorifuji T, Doi H, Kawai M, Momoi T, Okamoto S, *et al.* Successful Treatment of Congenital Hyperinsulinism by Enucleation of a Focal Islet-cell Hyperplasia of the Pancreas. *J Jpn Pediatr Soc* 2009;113: 838–49 (in Japanese) (LOW).
81. Yorifuji T, Kawakita R, Nagai S, Sugimine A, Doi H, Nomura A, *et al.* Molecular and clinical analysis of Japanese patients with persistent congenital hyperinsulinism: predominance of paternally inherited monoallelic mutations in the KATP channel genes. *J Clin Endocrinol Metab* 2011;96: E141–5 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
82. Ismail D, Hussain K. Role of 18F-DOPA PET/CT imaging in congenital hyperinsulinism. *Rev Endocr Metab Disord* 2010;11: 165–9 (HIGH). [[Medline](#)] [[CrossRef](#)]
83. Capito C, Khen-Dunlop N, Ribeiro MJ, Brunelle F, Aigrain Y, Crétolle C, *et al.* Value of 18F-fluoro-L-dopa PET in the preoperative localization of focal lesions in congenital hyperinsulinism. *Radiology* 2009;253: 216–22 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
84. Mohnike K, Blankenstein O, Christesen HT, De Lonlay J, Hussain K, Koopmans KP, *et al.* Proposal for a standardized protocol for 18F-DOPA-PET (PET/CT) in congenital hyperinsulinism. *Horm Res* 2006;66: 40–2 (MEDIUM). [[Medline](#)]
85. Mohnike K, Blankenstein O, Minn H, Mohnike W, Fuchtnner F, Otonkoski T. [18F]-DOPA positron emission tomography for preoperative localization in congenital hyperinsulinism. *Horm Res* 2008;70: 65–72 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
86. Barthlen W, Blankenstein O, Mau H, Koch M,



- Höhne C, Mohnike W, *et al.* Evaluation of [18F] fluoro-L-DOPA positron emission tomography-computed tomography for surgery in focal congenital hyperinsulinism. *J Clin Endocrinol Metab* 2008;93: 869–75 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
87. Ribeiro MJ, Boddaert N, Delzescaux T, Valayannopoulos V, Bellanné-Chantelot C, Jaubert F, *et al.* Functional imaging of the pancreas: the role of [18F]fluoro-L-DOPA PET in the diagnosis of hyperinsulinism of infancy. *Endocr Dev* 2007;12: 55–66 (MEDIUM). [[Medline](#)]
88. Hardy OT, Hernandez-Pampaloni M, Saffer JR, Scheuermann JS, Ernst LM, Freifelder R, *et al.* Accuracy of [18F]fluorodopa positron emission tomography for diagnosing and localizing focal congenital hyperinsulinism. *J Clin Endocrinol Metab* 2007;92: 4706–11 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
89. Kühnen P, Matthae R, Arya V, Hauptmann K, Rothe K, Wächter S, *et al.* Occurrence of giant focal forms of congenital hyperinsulinism with incorrect visualization by (18) F DOPA-PET/CT scanning. *Clin Endocrinol (Oxf)* 2014;81: 847–54 (LOW). [[Medline](#)] [[CrossRef](#)]
90. Masue M, Nishibori H, Fukuyama S, Yoshizawa A, Okamoto S, Doi R, *et al.* Diagnostic accuracy of [<sup>18</sup>F]-fluoro-L-dihydroxyphenylalanine positron emission tomography scan for persistent congenital hyperinsulinism in Japan. *Clin Endocrinol (Oxf)* 2011;75: 342–6 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
91. Barthlen W, Mohnike W, Mohnike K. Techniques in pediatric surgery: congenital hyperinsulinism. *Horm Res Paediatr* 2011;75: 304–10 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
92. Masue M, Nishibori H, Takada I, Yorifuji T. Diagnostic accuracy of 18F-DOPA PET to localize KATP-channel hyperinsulinism and post-treatment prognosis. *J Jpn Pediatr Soc* 2014; 118: 1342–9. (MEDIUM).
93. Soheilipour F, Jesmi F, Ahmadi M, Pazouki A, Alibeigi P, Abdolhosseini M. Minimally invasive surgical interventions in the treatment of primary persistent hyperinsulinemic hypoglycemia of infancy. *Arch Endocrinol Metab* 2015;59: 466–9 (LOW). [[Medline](#)] [[CrossRef](#)]
94. Liem NT, Son TN, Hoan NT. Laparoscopic near-total pancreatectomy for persistent hyperinsulinemic hypoglycemia of infancy: report of two cases. *J Laparoendosc Adv Surg Tech A* 2010;20: 115–7 (LOW). [[Medline](#)] [[CrossRef](#)]
95. Blakely ML, Lobe TE, Cohen J, Burghen GA. Laparoscopic pancreatectomy for persistent hyperinsulinemic hypoglycemia of infancy. *Surg Endosc* 2001;15: 897–8 (LOW). [[Medline](#)] [[CrossRef](#)]
96. Al-Shanafey S. Laparoscopic vs open pancreatectomy for persistent hyperinsulinemic hypoglycemia of infancy. *J Pediatr Surg* 2009;44: 957–61 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
97. Murakami M, Mushiake S, Kashiwagi H, Etani Y, Miyoshi Y, Ozono K. A case of persistent hyperinsulinemic hypoglycemia of infancy successfully managed with subcutaneous octreotide injection and nocturnal intravenous glucose supply. *Clin Pediatr Endocrinol* 2007;16: 75–80 (LOW). [[Medline](#)] [[CrossRef](#)]
98. Mazor-Aronovitch K, Landau H, Gillis D. Surgical versus non-surgical treatment of congenital hyperinsulinism. *Pediatr Endocrinol Rev* 2009;6: 424–30 (LOW). [[Medline](#)]
99. Mazor-Aronovitch K, Gillis D, Lobel D, Hirsch HJ, Pinhas-Hamiel O, Modan-Moses D, *et al.* Long-term neurodevelopmental outcome in conservatively treated congenital hyperinsulinism. *Eur J Endocrinol* 2007;157: 491–7 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
100. Lovvorn HN 3rd, Nance ML, Ferry RJ Jr, Stolte L, Baker L, O'Neill JA Jr, *et al.* Congenital hyperinsulinism and the surgeon: lessons learned over 35 years. *J Pediatr Surg* 1999;34: 786–92, discussion 792–3 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
101. de Lonlay-Debeney P, Poggi-Travert F, Fournet JC, Sempoux C, Dionisi Vici C, Brunelle F, *et al.* Clinical features of 52 neonates with hyperinsulinism. *N Engl J Med* 1999;340: 1169–75 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
102. Suchi M, Thornton PS, Adzick NS, MacMullen C, Ganguly A, Stanley CA, *et al.* Congenital hyperinsulinism: intraoperative biopsy interpretation can direct the extent of

- pancreatectomy. *Am J Surg Pathol* 2004;28: 1326–35 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
103. Lord K, Dzata E, Snider KE, Gallagher PR, De León DD. Clinical presentation and management of children with diffuse and focal hyperinsulinism: a review of 223 cases. *J Clin Endocrinol Metab* 2013;98: E1786–9 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
  104. Leibowitz G, Glaser B, Higazi AA, Salameh M, Cerasi E, Landau H. Hyperinsulinemic hypoglycemia of infancy (nesidioblastosis) in clinical remission: high incidence of diabetes mellitus and persistent beta-cell dysfunction at long-term follow-up. *J Clin Endocrinol Metab* 1995;80: 386–92 (MEDIUM). [[Medline](#)]
  105. Shilyansky J, Fisher S, Cutz E, Perlman K, Filler RM. Is 95% pancreatectomy the procedure of choice for treatment of persistent hyperinsulinemic hypoglycemia of the neonate? *J Pediatr Surg* 1997;32: 342–6 (LOW). [[Medline](#)] [[CrossRef](#)]
  106. Cherian MP, Abduljabbar MA. Persistent hyperinsulinemic hypoglycemia of infancy (PHHI): Long-term outcome following 95% pancreatectomy. *J Pediatr Endocrinol Metab* 2005;18: 1441–8 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
  107. Barthlen W, Mohnike W, Mohnike K. Techniques in pediatric surgery: congenital hyperinsulinism. *Horm Res Paediatr* 2010;74: 438–43 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
  108. Palladino AA, Stanley CA. A specialized team approach to diagnosis and medical versus surgical treatment of infants with congenital hyperinsulinism. *Semin Pediatr Surg* 2011;20: 32–7 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
  109. McAndrew HF, Smith V, Spitz L. Surgical complications of pancreatectomy for persistent hyperinsulinaemic hypoglycaemia of infancy. *J Pediatr Surg* 2003;38: 13–6, discussion 13–6 (LOW). [[Medline](#)] [[CrossRef](#)]
  110. Fékété CN, de Lonlay P, Jaubert F, Rahier J, Brunelle F, Saudubray JM. The surgical management of congenital hyperinsulinemic hypoglycemia in infancy. *J Pediatr Surg* 2004;39: 267–9 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
  111. Adzick NS, Thornton PS, Stanley CA, Kaye RD, Ruchelli E. A multidisciplinary approach to the focal form of congenital hyperinsulinism leads to successful treatment by partial pancreatectomy. *J Pediatr Surg* 2004;39: 270–5 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
  112. Pierro A, Nah SA. Surgical management of congenital hyperinsulinism of infancy. *Semin Pediatr Surg* 2011;20: 50–3 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
  113. Ferry RJ Jr, Kelly A, Grimberg A, Koo-McCoy S, Shapiro MJ, Fellows KE, *et al.* Calcium-stimulated insulin secretion in diffuse and focal forms of congenital hyperinsulinism. *J Pediatr* 2000;137: 239–46 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
  114. Barthlen W. Surgery in congenital hyperinsulinism-tips and tricks not only for surgeons. A practical guide. *Semin Pediatr Surg* 2011;20: 56–9 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
  115. Zani A, Nah SA, Ron O, Totonelli G, Ismail D, Smith VV, *et al.* The predictive value of preoperative fluorine-18-L-3,4-dihydroxyphenylalanine positron emission tomography-computed tomography scans in children with congenital hyperinsulinism of infancy. *J Pediatr Surg* 2011;46: 204–8 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
  116. von Rohden L, Mohnike K, Mau H, Eberhard T, Mohnike W, Blankenstein O, *et al.* Visualization of the focus in congenital hyperinsulinism by intraoperative sonography. *Semin Pediatr Surg* 2011;20: 28–31 (LOW). [[Medline](#)] [[CrossRef](#)]
  117. Arya VB, Flanagan SE, Kumaran A, Shield JP, Ellard S, Hussain K, *et al.* Clinical and molecular characterisation of hyperinsulinaemic hypoglycaemia in infants born small-for-gestational age. *Arch Dis Child Fetal Neonatal Ed* 2013;98: F356–8 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
  118. Touati G, Poggi-Travert F, Ogier de Baulny H, Rahier J, Brunelle F, Nihoul-Fekete C, *et al.* Long-term treatment of persistent hyperinsulinaemic hypoglycaemia of infancy with diazoxide: a retrospective review of 77 cases and analysis of efficacy-predicting criteria. *Eur J Pediatr* 1998;157: 628–33 (MEDIUM). [[Medline](#)] [[CrossRef](#)]

119. Le Quan Sang KH, Arnoux JB, Mamoune A, Saint-Martin C, Bellanné-Chantelot C, Valayannopoulos V, *et al.* Successful treatment of congenital hyperinsulinism with long-acting release octreotide. *Eur J Endocrinol* 2012;166: 333–9 (LOW). [[Medline](#)] [[CrossRef](#)]
120. Calabria AC, Li C, Gallagher PR, Stanley CA, De León DD. GLP-1 receptor antagonist exendin-(939) elevates fasting blood glucose levels in congenital hyperinsulinism owing to inactivating mutations in the ATP-sensitive K<sup>+</sup> channel. *Diabetes* 2012;61: 2585–91 (MEDIUM). [[Medline](#)] [[CrossRef](#)]
121. Modan-Moses D, Koren I, Mazor-Aronovitch K, Pinhas-Hamiel O, Landau H. Treatment of congenital hyperinsulinism with lanreotide acetate (Somatuline Autogel). *J Clin Endocrinol Metab* 2011;96: 2312–7 (LOW). [[Medline](#)] [[CrossRef](#)]
122. Kühnen P, Marquard J, Ernert A, Meissner T, Raile K, Wannemacher G, *et al.* Long-term lanreotide treatment in six patients with congenital hyperinsulinism. *Horm Res Paediatr* 2012;78: 106–12 (LOW). [[Medline](#)] [[CrossRef](#)]
123. Corbin JA, Bhaskar V, Goldfine ID, Issafras H, Bedinger DH, Lau A, *et al.* Inhibition of insulin receptor function by a human, allosteric monoclonal antibody: a potential new approach for the treatment of hyperinsulinemic hypoglycemia. *MAbs* 2014;6: 262–72 (LOW). [[Medline](#)] [[CrossRef](#)]
124. de Heide LJ, Laskewitz AJ, Apers JA. Treatment of severe postRYGB hyperinsulinemic hypoglycemia with pasireotide: a comparison with octreotide on insulin, glucagon, and GLP-1. *Surg Obes Relat Dis* 2014;10: e31–3 (LOW). [[Medline](#)] [[CrossRef](#)]
125. Skae M, Avatapalle HB, Banerjee I, Rigby L, Vail A, Foster P, *et al.* Reduced glycemic variability in diazoxide-responsive children with congenital hyperinsulinism using supplemental omega-3-polyunsaturated fatty acids; a pilot trial with MaxEPA(R.). *Front Endocrinol (Lausanne)* 2014;5: 31 (MEDIUM). [[Medline](#)]
126. Senniappan S, Alexandrescu S, Tatevian N, Shah P, Arya V, Flanagan S, *et al.* Sirolimus therapy in infants with severe hyperinsulinemic hypoglycemia. *N Engl J Med* 2014;370: 1131–7 (MEDIUM). [[Medline](#)] [[CrossRef](#)]