

# International Guidelines for the Diagnosis and Management of Hyperinsulinism

Diva D. De Leon<sup>a</sup> Jean Baptiste Arnoux<sup>b</sup> Indraneel Banerjee<sup>c</sup>  
Ignacio Bergada<sup>d</sup> Tricia Bhatti<sup>e</sup> Louise S. Conwell<sup>f</sup> Junfen Fu<sup>g</sup>  
Sarah E. Flanagan<sup>h</sup> David Gillis<sup>i</sup> Thomas Meissner<sup>j</sup> Klaus Mohnike<sup>k</sup>  
Tai L.S. Pasquini<sup>l</sup> Pratik Shah<sup>m</sup> Charles A. Stanley<sup>a</sup> Adrian Vella<sup>n</sup>  
Tohru Yorifuji<sup>o</sup> Paul S. Thornton<sup>p</sup>

<sup>a</sup>Congenital Hyperinsulinism Center and Division of Endocrinology and Diabetes, Department of Pediatrics, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; <sup>b</sup>Reference Center for Inherited Metabolic Diseases, Necker-Enfants Malades Hospital, AP-HP, University of Paris-Cité, Paris, France; <sup>c</sup>Paediatric Endocrinology, Royal Manchester Children's Hospital, University of Manchester, Manchester, UK; <sup>d</sup>Centro de Investigaciones Endocrinológicas "Dr. César Bergadá" (CONICET – FEI), Division de Endocrinología, Hospital de Niños Ricardo Gutiérrez, Buenos Aires, Argentina; <sup>e</sup>Department of Clinical Pathology and Laboratory Medicine, Children's Hospital of Philadelphia and Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; <sup>f</sup>Australia and Children's Health Queensland Clinical Unit, Department of Endocrinology and Diabetes, Queensland Children's Hospital, Children's Health Queensland, Greater Brisbane Clinical School, Medical School, Faculty of Medicine, University of Queensland, Brisbane, QLD, Australia; <sup>g</sup>National Clinical Research Center for Child Health, Department of Endocrinology, The Children's Hospital of Zhejiang University School of Medicine, Hangzhou, China; <sup>h</sup>Institute of Biomedical and Clinical Science, University of Exeter Medical School, Exeter, UK; <sup>i</sup>Hadassah Medical Center, Department of Pediatrics, Ein-Kerem, Jerusalem and Faculty of Medicine, Hebrew-University, Jerusalem, Israel; <sup>j</sup>Department of General Pediatrics, Neonatology and Pediatric Cardiology, University Children's Hospital, Medical Faculty, Heinrich Heine University, Duesseldorf, Germany; <sup>k</sup>Department of General Pediatrics, Otto-von-Guericke University Magdeburg, Magdeburg, Germany; <sup>l</sup>Research and Policy Director, Congenital Hyperinsulinism International, Glen Ridge, NJ, USA; <sup>m</sup>Pediatric Endocrinology, The Royal London Children's Hospital, Queen Mary University of London, London, UK; <sup>n</sup>Division of Diabetes, Endocrinology and Metabolism, Mayo Clinic, Rochester, MN, USA; <sup>o</sup>Pediatric Endocrinology and Metabolism, Children's Medical Center, Osaka City General Hospital, Osaka, Japan; <sup>p</sup>Congenital Hyperinsulinism Center, Cook Children's Medical Center and Texas Christian University Burnett School of Medicine, Fort Worth, TX, USA

## Keywords

Hyperinsulinism · Guidelines · Hypoglycemia · Insulin

## Abstract

**Background:** Hyperinsulinism (HI) due to dysregulation of pancreatic beta-cell insulin secretion is the most common and most severe cause of persistent hypoglycemia in infants

and children. In the 65 years since HI in children was first described, there has been a dramatic advancement in the diagnostic tools available, including new genetic techniques and novel radiologic imaging for focal HI; however, there have been almost no new therapeutic modalities since the development of diazoxide. **Summary:** Recent advances in neonatal research and genetics have improved our understanding of the pathophysiology of both transient and persistent forms of neonatal hyperinsulinism. Rapid turnaround of genetic test results combined with advanced radiologic imaging can permit identification and localization of surgically-curable focal lesions in a large proportion of children with congenital forms of HI, but are only available in certain centers in “developed” countries. Diazoxide, the only drug currently approved for treating HI, was recently designated as an “essential medicine” by the World Health Organization but has been approved in only 16% of Latin American countries and remains unavailable in many underdeveloped areas of the world. Novel treatments for HI are emerging, but they await completion of safety and efficacy trials before being considered for clinical use. **Key Messages:** This international consensus statement on diagnosis and management of HI was developed in order to assist specialists, general pediatricians, and neonatologists in early recognition and treatment of HI with the ultimate aim of reducing the prevalence of brain injury caused by hypoglycemia. A previous statement on diagnosis and management of HI in Japan was published in 2017. The current document provides an updated guideline for management of infants and children with HI and includes potential accommodations for less-developed regions of the world where resources may be limited.

© 2023 The Author(s).  
Published by S. Karger AG, Basel

## Method of Development of Evidence-Based Clinical Practice Guidelines

The guideline-writing committee comprised a group of 17 members including 13 pediatric endocrinologists, an adult endocrinologist, a pathologist, a genetic scientist, and a representative of an international patient advocacy organization for HI. Following a preparatory meeting (September 2019), working groups were assigned, and each undertook a literature review. The combined work was collated into a single document which was revised by all members of the writing committee over a 3-year period. Participating pediatric endocrine societies of the International Consortium of Pediatric Endocrinology (ICPE) were invited to review the document with feedback incorporated into the final version. The evidence was graded

using the framework of Grading of Recommendations, Assessment, Development, and Evaluation (GRADE), describing both the strength of recommendations and the quality of the evidence [1]. A detailed description of the grading scheme has been previously published [2].

In terms of strength of recommendations, strong recommendations used the phrase “we recommend” and the number 1, and conditional recommendations used the phrase “we suggest” and the number 2. Cross-filled circles indicate the quality of the evidence such that ⊕○○○ denotes very low-quality evidence; ⊕⊕○○, low-quality; ⊕⊕⊕○, moderate-quality, and ⊕⊕⊕⊕, high-quality. In the absence of sufficient evidence, conclusions were based on expert opinion.

High-quality evidence is defined as “well-performed Randomized Controlled Trials (RCTs) or very strong evidence from unbiased observational studies”; moderate-quality is defined as “RCTs with some limitations or strong evidence from unbiased observational studies”; low-quality is defined as “RCTs with serious flaws or some evidence from observational studies”; and very low-quality is defined as “unsystematic clinical observations or very indirect evidence observational studies” [2].

## 1. The Diagnosis of Hyperinsulinism

### 1.1 We Recommend Making a Specific Diagnosis of Hyperinsulinism Based on Measurements, at a Time of Hypoglycemia, of Plasma Levels of Metabolic Fuels (Beta-Hydroxybutyrate [BOHB] and Free Fatty Acids [FFA]) and Hormones (Insulin, Growth Hormone, Cortisol) and Determination of the Glycemic Response to a Pharmacologic Dose of Glucagon [Grade 1 ⊕⊕⊕○]

The diagnosis of HI is made on the basis of increased insulin action and/or inadequate suppression of plasma insulin during either spontaneous or fasting-induced hypoglycemia. Insulin should be measured using a high-sensitivity assay [3]. Increased insulin action can be demonstrated by increased glucose requirement (e.g., >8 mg/kg/min in a neonate normal 4–6 mg/kg/min [4]), inappropriately suppressed plasma concentrations of FFA and BOHB during hypoglycemia, and an inappropriate glycemic response to glucagon at a time of hypoglycemia (Table 1) [5–7]. Suppression of BOHB and preservation of a large glycemic response to glucagon are particularly sensitive markers of inappropriate insulin action. In the absence of multiple pituitary hormone deficiencies in neonates, an inappropriately large glycemic response to glucagon stimulation may be considered diagnostic, particularly when plasma insulin concentration is

low (Table 1). Newborn infants, tested before 72 h of life during the time of transitional hypoglycemia, should be re-tested after 72 h if hypoglycemia is still present to confirm the diagnosis [8]. Provocative stimulation tests with glucose, leucine, or protein are not useful for establishing the diagnosis of HI but may be helpful in defining the subtype of HI [9–11]. Occasionally, there will be a discrepancy between markers of insulin action and insulin levels with elevated insulin levels in the presence of high ketones and absent glucagon response. In these cases, it is possible the insulin assay is not as sensitive as it could be, and the focus should be on the markers of insulin action, not the insulin level itself.

*1.2 We Recommend Genetic Testing for all Children except for Those Likely to Have an Acquired Form of Hyperinsulinism [GRADE 1⊕⊕⊕○]*

*1.3 We Recommend Evaluation of Infants with Hyperinsulinism for Multi-System Syndromes Associated with Hyperinsulinism [GRADE 1⊕⊕○○]*

*1.4 We Recommend Screening all Children Whose Hyperinsulinism Occurs after the Age of 2 years of Life for Insulinoma [Grade 1⊕⊕○○]*

It is important to determine the precise etiology of HI because the diagnosis may direct choice of therapy and need for long-term follow-up [12]. HI presenting in the immediate neonatal period may be caused by either genetic or acquired conditions (Table 2). Acquired HI may be secondary to perinatal factors such as maternal diabetes, perinatal stress, birth asphyxia, intrauterine growth restriction, exposure to maternal drugs, or high rates of maternal glucose infusions during delivery. Cases of Perinatal Stress-Induced Hyperinsulinism (PSHI) typically present in the first 24 h of life and affect approximately 1 in 1,200–1,700 newborns [13, 14]; they often resolve within the first 10–14 days of life. PSHI is an exaggerated form of transitional hypoglycemia triggered by hypoxia-mediated reduction of the beta-cell glucose threshold for suppression of insulin secretion [8, 15, 16]. In approximately 1 in 12,000–13,600 newborns, a more severe form of PSHI occurs which persists beyond the first 2 weeks of life and may require treatment with diazoxide [17, 18]. Genetic testing is not usually recommended for infants with PSHI because there is no current evidence of a genetic etiology.

When there is a family history suggestive of maturity-onset diabetes of the young (MODY), genetic testing for *HNF1A* and *HNF4A* should be considered

because these conditions can cause transient hyperinsulinism in the newborn period [19–21]. In children older than 2 years of age with acquired HI, the possibility of an insulinoma should be considered [22, 23]. Insulinomas are usually solitary and benign, but they can be multiple and are rarely malignant. Insulinomas can be a component of multiple endocrine neoplasia type 1, and genetic investigations should be directed accordingly [24].

Genetically inherited forms of HI cause isolated pancreatic dysfunction but also may be associated with syndromes affecting multiple organs (Syndromic HI) (Table 3). Genetic forms of HI may present in the newborn period, but may not be detected until later in life. Non-syndromic genetic HI is estimated to occur in approximately 1:25,000–1:45,000 newborns [70–73]. Loss-of-function variants in the *ABCC8* and *KCNJ11* genes, which encode the beta-cell ATP-sensitive potassium ( $K_{ATP}$ ) channel (shown in Fig. 1), are the most frequent cause [74]. Most recently, heterozygous non-coding variants which prevent silencing of Hexokinase 1 within the pancreatic beta-cell have also been shown to be an important cause of isolated HI [75]. Certain genetic types of HI have characteristic phenotypes that can assist in their diagnosis; glutamate dehydrogenase (GDH) HI is associated with moderately elevated plasma ammonia concentrations [76] and short-chain hydroxyacyl-CoA dehydrogenase (SCHAD) HI may be associated with elevated plasma C4-OH acyl carnitine and urine 3-OH-glutarate levels [77]. Protein-induced hypoglycemia is part of the phenotype in GDH-HI, SCHAD-HI, and  $K_{ATP}$ -HI [11, 60, 78]. Anaerobic exercise can induce hypoglycemia in some patients with activating variants in the promoter region of *SLC16A1*, the gene encoding the monocarboxylate transporter 1 (MCT1) pyruvate transporter reported in a small number of cases [79]. Patients with glucokinase (GCK) HI may develop ketotic hypoglycemia with prolonged fasting, in contrast to the hypoketotic hypoglycemia usually found in HI, especially in the setting of glucose levels dropping below the altered threshold for insulin secretion [27]. Patients with somatic mutations associated with localized islet nuclear enlargement (LINE) pathology usually present at a later age [80].

#### Alternate Classification of HI

HI may usefully be classified according to the response to diazoxide, the first-line drug for controlling hypoglycemia in children with HI. In the diazoxide-unresponsive group up to 90% of cases have pathogenic

**Table 1.** Diagnostic features of HI at the time of hypoglycemia (plasma glucose <50 mg/dL [2.8 mmol/L])

Evidence of excessive insulin action at the time of hypoglycemia
1. Suppressed plasma $\beta$ -hydroxybutyrate (<1.8 mmol/L)
2. Suppressed plasma free fatty acids (<1.7 mmol/L)
3. Inappropriately large glycaemic response to glucagon ( $\geq 30$ mg/dL [ $\geq 1.7$ mmol/L])
4. Increased glucose infusion rate required to maintain euglycemia above normal for age
>8 mg/kg/min for neonates
>3 mg/kg/min for adults
Evidence of excessive insulin secretion/inadequate suppression of insulin secretion at the time of hypoglycemia (these are less definitive than evidence of excessive insulin action)
1. Plasma insulin >1.25 $\mu$ U/mL (8.7 pmol/L)
2. C-peptide >0.5 ng/mL (>0.17 nmol/L)

variant(s) in *ABCC8* or *KCNJ11* [74] with diffuse or focal pancreatic histopathology. Recessive bi-allelic variants or dominant mono-allelic *ABCC8* or *KCNJ11* pathogenic variants cause diffuse HI. In contrast, focal HI results from the combination of a paternally inherited recessive *ABCC8* or *KCNJ11* pathogenic variant and paternal isodisomy of the 11p15 chromosomal region confined to the pancreatic lesion [81]. In some cases, paternal isodisomy of chromosome 11p15 occurs in multiple tissues, causing Beckwith-Wiedemann Syndrome spectrum (BWSp); severe diazoxide-unresponsive HI can occur in BWSp due to 11pUPD when there is a concurrent paternally inherited *ABCC8* or *KCNJ11* disease-causing variant [82]. Therefore, diazoxide unresponsiveness indicates a higher likelihood of finding a genetic etiology. The classification of HI into diazoxide responsive or not presumes access to and treatment with diazoxide. However, in some circumstances, diazoxide may not be available, or the person with HI may be intolerant or experience unacceptable side effects. In such cases, the decision to undertake genetic testing should be made on the merits of the individual case.

Some “atypical” histological forms of HI with localized islet pancreatic involvement (named Localized Islet Nuclear Enlargement [LINE] HI or “mosaic” HI) are caused by somatic dominant variants of the *ABCC8* and *GCK* genes [80, 83–86]. Increased Hexokinase 1 (*HK1*) protein expression has also been identified in pancreatic tissue, suggesting a role for pancreatic *HK1* in HI pathogenesis [85].

Genetic testing is recommended whenever acquired HI is unlikely. This should include children with diazoxide-unresponsive HI as well as those with diazoxide-responsive HI which persists beyond the first 3 months of

life. Rapid testing of the *ABCC8* and *KCNJ11* genes is crucial for the management of children with diazoxide-unresponsive HI because the presence of a paternally inherited pathogenic variant predicts a focal lesion with a sensitivity of 97% [74]. Pancreatic imaging (see Recommendation 1.5 below) can then be performed to localize the lesion prior to surgery which is curative in the majority of cases. For centers unable to perform such imaging, rapid genetic testing of *ABCC8* and *KCNJ11* will provide information on cases likely to benefit from transfer to a center with appropriate imaging and surgical capacities [87]. If access to rapid testing of these genes is limited, effort should be made to contact one of several international laboratories able to screen the *ABCC8* and *KCNJ11* genes, sometimes at reduced cost on compassionate grounds.

When no pathogenic variant in *ABCC8* or *KCNJ11* is found on rapid testing or when HI has persisted beyond 3 months, genetic testing of all known HI genes should be performed. The current method of choice is next-generation sequencing by either targeted panel analysis or whole exome/genome sequencing since these provide rapid and cost-effective screening of multiple genes in parallel. It is important to emphasize that no single test is able to detect all forms of genetic variation reported in HI [88]. For example, Sanger sequencing is unable to detect large copy number variants that may occur in some HI genes; in addition, non-coding variants deep within intronic regions will not be detected by exome sequencing or gene panels that do not target these regions (e.g., deep intronic variants in *ABCC8*, *HADH*, and *HK1*) [89]. Also important to note is that separate methylation testing for imprinting defects in the 11p BWS region will be required for children with clinical suspicion of BWSp [90].

**Table 2.** Classification of hyperinsulinism disorders in infants and children

	Risk factors	Clinical features
(a) Acquired neonatal HI	Maternal diabetes, including gestational diabetes	Large for gestational age (LGA)
	Perinatal stress-induced HI	Small for gestational age (SGA) Maternal hypertension, pre-eclampsia, eclampsia
	Maternal drugs	Ritodrine, sulfonylurea, high GIR during labor, etc.
(b) Acquired non-neonatal HI	Paraneoplastic HI	Insulinoma ( <i>sporadic or MEN1</i> )
	Surgically-induced HI	Post-gastric bypass, post-fundoplication for gastro-esophageal reflux ( <i>NIPHS: non insulinoma pancreatogenous hypoglycemia syndrome</i> )
	Drug-induced HI	Antidiabetic medications ( <i>Insulin, sulfonylureas</i> )
	Autoimmune HI (anti-insulin or insulin receptor-activating antibodies)	Spontaneous or associated with drugs or viral infections) Hirata's disease ( <i>insulin autoimmune syndrome: anti-insulin antibodies post sulphydryl medications: methimazole, carbimazole, alpha-lipoic acid and post measles virus, mumps virus, rubella virus, varicella zoster virus, coxsackie B virus and hepatitis C virus</i> )
	Histology	Genes
(c) Genetic HI: isolated HI	Diffuse form	<i>ABCC8, KCNJ11, GLUD1, GCK, HNF4A, HNF1A, HADH, SLC16A1, INSR</i>
	Focal form	Paternally inherited AR variants of <i>ABCC8</i> or <i>KCNJ11</i>
	LINE- HI (mosaic HI, atypical HI)	Sporadic mosaic AD variants of <i>ABCC8, GCK, and inappropriate expression of HK1</i>
	Syndrome	Gene
(d) Genetic HI: syndromic HI	Beckwith-Wiedemann syndrome	Genetic or epigenetic changes of imprinted region 11p15.5. (especially paternal UPD11p; also mutations of imprinting control genes). Pat UPD11p combined with paternal recessive <i>ABCC8</i> or <i>KCNJ11</i> mutation
	Kabuki syndrome	<i>KMT2D, KDM6A (usually mosaic)</i>
	Turner syndrome	Mosaic partial or complete X chromosome monosomy
	See complete list of syndromal HI in table 2	
(e) HI mimickers: hypoinsulinemic hypoketotic hypoglycemia	Autoimmune mimicker	Insulin resistance syndrome type B ( <i>anti-insulin receptor antibodies post viral infection (HIV, HTLV1, hepatitis C) or lymphoproliferative disease, or autoimmune disease (lupus)</i> )
	Paraneoplastic secretion of pro-IGF2	Non-islets cells tumor hypoglycemia (NICTH, Doege-Potter syndrome)
	Genetic disorders of insulin signaling	Mutations in <i>AKT2, AKT3, PIK3CA, PIK3R2, CCND2, INSR.</i>
	Fatty acid oxidation disorders	Abnormalities in the carnitine cycle, beta-oxidation, electron transfer, and ketone synthesis

**Table 3.** The genetic etiology of hyperinsulinism

Gene/genetic loci	Phenotype MIM number	Phenotype	Mode of inheritance	Histology	Ref
<i>ABCC8</i>	# 256450	Isolated	AR AD/mosaic AR LOH*	Diffuse Diffuse Atypical Focal	[25] [26] [27, 28] [29]
	# 606528	Hyperinsulinism with enteropathy and deafness	AR (contiguous deletion including <i>USH1C</i> )	Diffuse	[30]
<i>ADK</i>	# 614300	ADK deficiency syndrome	AR	Diffuse	[31]
<i>ALG3</i>	# 601110	Congenital disorder of glycosylation type 1d	AR	Diffuse	[32]
<i>ALG6</i>	# 603147	Congenital disorder of glycosylation type 1c	AR	Diffuse	[33]
<i>CACNA1C</i>	# 601005	Timothy syndrome	AD	Diffuse	[34]
<i>CACNA1D</i>	# 615474	PASNA syndrome	AD	Diffuse	[35]
<i>CDKN1C</i>	# 130650	Beckwith-Wiedemann Spectrum	AD	Diffuse	[36]
<i>CREBBP</i>	# 180849	Rubinstein Taybi syndrome 1	AD	Diffuse	[37]
<i>DIS3L2</i>	# 267000	Perlman syndrome	AR	Diffuse	[38]
<i>EIF2S3</i>	# 300148	MEHMO syndrome	XLR	Diffuse	[39]
<i>EP300</i>	# 613684	Rubinstein Taybi syndrome 2	AD	Diffuse	[37]
<i>FAH</i>	# 276700	Tyrosinaemia type I	AR	Diffuse	[40]
<i>FOXA2</i>	–	Syndromic	AD	Diffuse	[41]
<i>GCK</i>	# 602485	Isolated	AD/mosaic	Diffuse/ atypical	[42]
<i>GLUD1</i>	# 606762	Hyperinsulinism-hyperammonaemia syndrome	AD	Diffuse	[43]
<i>GPC3</i>	# 312870	Simpson-Golabi-Behmel syndrome	XLR	Diffuse	[44]
<i>HADH</i>	# 609975	Isolated	AR	Diffuse	[45]
<i>HK1</i>	–	Isolated	AD	Diffuse	[46]
<i>HNF1A</i>	# 600496	Isolated	AD	Diffuse	[21]
<i>HNF4A</i>	# 125850	Isolated	AD	Diffuse	[19]
	# 616026	Fanconi renotubular syndrome	AD (p.Arg76Trp)	Diffuse	[21]
<i>HRAS</i>	# 218040	Costello syndrome	AD	Diffuse	[47]
<i>INSR</i>	# 609968	Isolated	AD	Diffuse	[48]
<i>KCNJ11</i>	# 601820	Isolated	AR AD AR LOH*	Diffuse Diffuse Focal	[49] [50] [29]
	# 192500	Long QT syndrome	AD	Diffuse	[51]
	# 147920	Kabuki syndrome	AD	Diffuse	[52]
<i>KDM6A</i>	# 300867	Kabuki syndrome	XLD	Diffuse	[53]
<i>MPI</i>	# 602579	Congenital disorder of glycosylation type 1b	AR	Diffuse	[54]
<i>PGM1</i>	# 614921	Congenital disorder of glycosylation type 1 t	AR	Diffuse	[55]

**Table 3** (continued)

Gene/genetic loci	Phenotype MIM number	Phenotype	Mode of inheritance	Histology	Ref
<i>PMM2</i>	# 212065	Congenital disorder of glycosylation type 1a	AR	Diffuse	[56]
	–	HI and polycystic kidney disease	AR (c.-167G>T)	Diffuse	[57]
<i>PHOX2B</i>	# 209880	Central hypoventilation syndrome	AD	Diffuse	[58]
<i>NSD1</i>	# 117550	Sotos syndrome	AD	Diffuse	[59]
<i>SLC16A1</i>	# 610021	Isolated (exercise-induced HI)	AD	Diffuse	[60]
<i>TRMT10A</i>	# 616033	Syndromic	AR	Diffuse	[61]
<i>YARS1</i>	# 619418	Yars-related disease	AR	Diffuse	[62]
Chr5q35 deletion	# 117550	Sotos syndrome	AD	Diffuse	[63]
Chr9p24 deletion	# 151870	9p deletion syndrome	AD	Diffuse	[64]
Chr11p15 imprinting abnormality	# 130650	Beckwith-Wiedemann Spectrum	Sporadic	Diffuse	[65]
Chr13 trisomy	–	Patau syndrome	Sporadic	Diffuse	[66]
ChrX monosomy	–	Turner syndrome	Sporadic	Diffuse	[67]

\*Loss of the maternal 11p15 allele within pancreas in combination with a paternally inherited recessive *ABCC8* or *KCNJ11* mutation.

*1.5 We Recommend that Pancreatic Imaging Studies (e.g., <sup>18</sup>F-DOPA PET Scan) to Localize a Potentially Resectable Focal Lesion Be Performed in Infants with Diazoxide-Unresponsive Hyperinsulinism, except in Those with Genetic Evidence of Diffuse Disease [GRADE 1 ⊕⊕⊕○]*

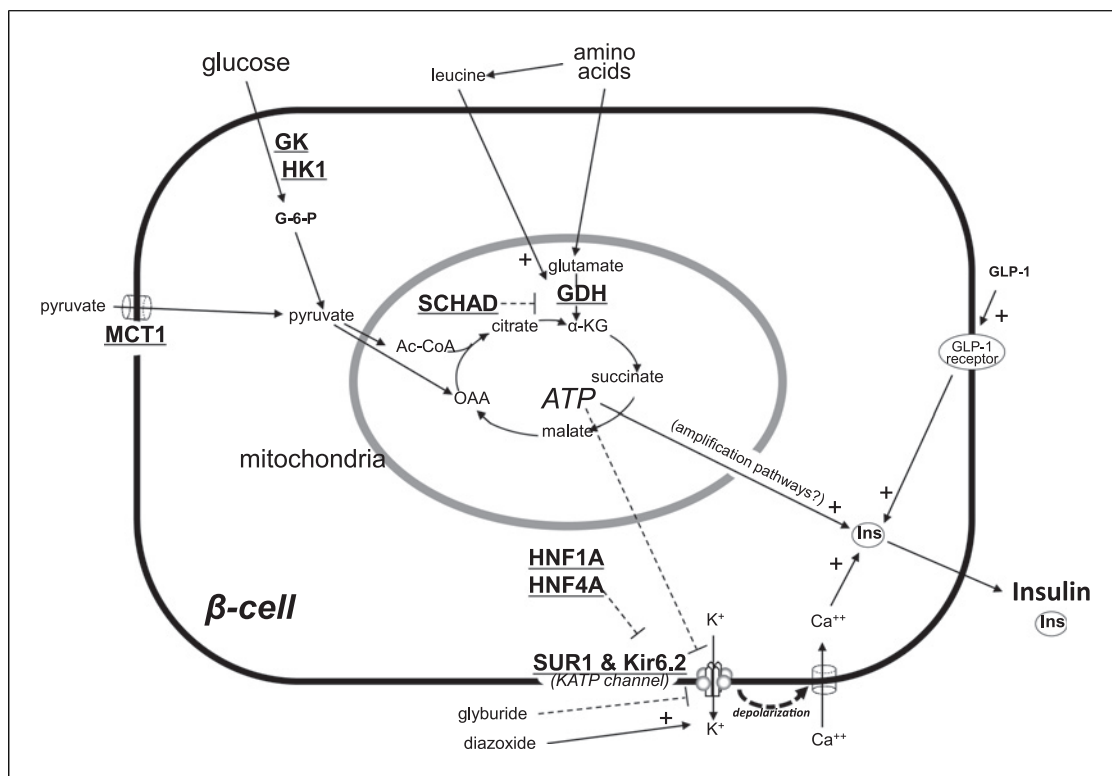
The finding of a single paternally-inherited recessive *ABCC8* or *KCNJ11* pathogenic variant offers a positive predictive value up to 94% for focal HI [74, 91]. For these infants and for diazoxide-unresponsive infants with negative or inconclusive genetic testing, we recommend imaging of the pancreas using 6-fluoro-(<sup>18</sup>F)-L-3,4-dihydroxyphenylalanine positron emission tomography (<sup>18</sup>F-DOPA PET scan) in combination with CT or MRI to help localize the focal lesion [92, 93]. Published studies of 286 histologically assessed cases have reported a sensitivity ranging from 75% to 100% and specificity ranging from 88% to 100% for focal HI [93]. When a focal lesion is detected, the accuracy of localization with <sup>18</sup>F-DOPA PET scan is greater than 90% [93], but it is highly dependent on the experience of the reader. Very small lesions may not be detected by <sup>18</sup>F-DOPA PET scan; thus, a negative study does not rule out focal HI. For infants with genetic evidence of diffuse disease (e.g., dominant variants, bi-allelic *K<sub>ATP</sub>* channel variants, or glucokinase variants), there is no

need for pancreatic imaging with an <sup>18</sup>F-DOPA PET scan. Recently, <sup>68</sup>Gallium-NOGADA-exendin-4-PET/CT has been reported as a beta-cell-specific tracer but has to be further evaluated before being recommended as an additional option [94]. Imaging of the pancreas using conventional techniques such as ultrasound, computerized tomography (CT), and magnetic resonance imaging (MRI) is not helpful in detecting focal lesions in children with congenital HI and should be restricted to older children in whom an acquired insulinoma is suspected.

## 2. Medical Management

*2.1 We Recommend that the Goal of Treatment for Hyperinsulinism Is to Maintain Plasma Glucose Concentrations within the Normal Range of 70–100 mg/dL (3.9–5.6 mmol/L) [Grade 1 ⊕⊕⊕○]*

The immediate goal of therapy is to promptly restore plasma glucose to the normal range of 70–100 mg/dL (3.9–5.6 mmol/L) [95]. Following stabilization of glucose, efforts should be directed at identifying the optimal treatment regimen according to the type of HI. The Pediatric Endocrine Society (PES) guidelines established a treatment goal of >70 mg/dL (3.9 mmol/L) for the management of children with



**Fig. 1.** Schematic beta-cell with pathways involved in insulin secretion. Pathways of glucose and amino acid stimulation of beta-cell insulin secretion showing sites of the more common genetic forms of hyperinsulinism, such as the ATP-sensitive ( $K_{ATP}$ ) potassium channel, comprised of SUR1 and Kir6.2 subunits encoded by the *ABCC8* and *KCNJ11* genes. Most genetic forms of hyperinsulinism affect steps by which increased ATP generation closes  $K_{ATP}$  channels to depolarize the plasma membrane and activate an influx of calcium to “trigger” release of insulin from storage granules into the circulation. Additional factors, such as stimulation by the gut incretin, GLP1, can act downstream of the

triggering pathway to “amplify” insulin release. Drugs such as diazoxide and glyburide bind to the  $K_{ATP}$  channel to inhibit or activate insulin release, respectively. GK, glucokinase; HK1, hexokinase 1; GDH, glutamate dehydrogenase; SCHAD, short-chain acyl-CoA dehydrogenase; MCT1, mono-carboxylate transporter 1; ATP, adenosine triphosphate; HNF1A & HNF4A, hepatic nuclear factors 1 alpha and 4 alpha; SUR1, sulfonylurea receptor 1; Kir6.2, potassium channel subunit;  $K_{ATP}$  channel, ATP-sensitive potassium channel;  $K^+$ , potassium ion;  $Ca^{++}$ , calcium ion; Ins, insulin; GLP1, glucagon-like peptide 1. Dotted line with dash indicates inhibit, Solid line with + indicates stimulates.

hypoglycemia disorders in order to prevent hypoglycemia unawareness [95] and to have a safe margin above the threshold of hypoglycemia that causes brain damage.

Despite attempts to meet the PES glycemic targets, studies have shown that glucose levels may be found below this range (70–100 mg/dL, 3.9–5.6 mmol/L) in children with severe forms of hyperinsulinism in up to 15–20% measurements [96]. In circumstances such as these, a lower hypoglycemia threshold of 63 mg/dL (3.5 mmol/L) may need to be accepted in individual patients, depending on the severity and frequency of hypoglycemia and the availability of alternative treatment.

The frequency of monitoring for the presence of hypoglycemia by glucometer testing should be tailored to the individuals’ needs with typical monitoring before

meals and bedtime supplemented by additional testing when needed. There is not enough current evidence to make a suggestion regarding the use of continuous glucose monitoring by subcutaneous sensors.

### 2.2 We Recommend that Intravenous Glucose (Dextrose) Infusion Be Used as the Initial Treatment to Promptly Restore Euglycaemia for Neonates with Hyperinsulinism [Grade 1 ⊕⊕⊕○]

Intravenous glucose (dextrose) should be used for initial treatment of hypoglycemia to restore plasma glucose levels to the normal range without delay. The usual dose is 200 mg/kg (2 mL/kg of 10% dextrose solution), followed by continuous infusion of dextrose at a rate sufficient to maintain plasma glucose above 70 mg/

dL (typically 8 mg/kg/min or greater) [97]. In cases where the child is known to have hypoglycemia caused by hyperinsulinism and IV therapy is not immediately available, pharmacologic doses of glucagon (0.5–1 mg or 20–30 µg/kg) can be used as an alternative acute therapy, given either intramuscularly or subcutaneously, with an effect lasting up to 40–60 min allowing time for IV insertion [95]. Since the rates of glucose consumption can be as high as 20–30 mg/kg/min in infants with HI, rapid increases in the glucose infusion rate (GIR) may be required. In such children, with clear evidence of increased glucose utilization, we suggest rapidly increasing glucose infusion rates by increments of 4 mg/kg/min or greater, taking care not to induce fluid overload [98]. Following a 200 mg/kg dextrose bolus and an infusion of 8 mg/kg/min dextrose steady state levels in glucose are reached in 10 min, allowing repeat testing to be accurate and avoid over treatment [99]. To avoid fluid overload, central venous catheters may be required in order to provide dextrose solutions in high concentration.

### *2.3 We Recommend Continuous Intravenous Infusion of Glucagon for Infants at Risk of Fluid Overload because of a High Glucose Requirement [Grade 1⊕⊕⊕]*

When high-dose intravenous glucose is required, continuous intravenous infusion of glucagon as an additional therapy can help control hypoglycemia and prevent complications from fluid overload by reducing the rate of intravenous dextrose infusions required to prevent hypoglycemia [100]. An intravenous infusion of glucagon (dose range 2.5–20 µg/kg/h) can aid in maintaining euglycemia in HI by stimulation of hepatic glucose production from glycogenolysis and inhibition of hepatic glucose uptake [101, 102]. Adverse side effects of glucagon infusion may include vomiting (13%), rash (2%), and respiratory distress (19%) [100]. A rare but important side effect associated with glucagon is a necrolytic migratory erythema skin rash (NME) [103, 104]. Long-term continuous infusion of glucagon by subcutaneous pumps has been reported but is currently unreliable because of the formation of fibrils and crystals that block infusion lines [105].

### *2.4 We Recommend Diazoxide as the First-Line Treatment for Patients with an Established Diagnosis of Hyperinsulinism [Grade 1⊕⊕⊕⊕]*

Diazoxide is a benzothiadiazide related to thiazide diuretics that was initially developed for treatment of hypertension but later found to be useful to treat HI due

to its suppressive effect on insulin secretion [106]. In 1976, diazoxide was approved in the USA by the Food and Drug Administration (FDA) for HI in children. Diazoxide suppresses insulin secretion by opening the beta-cell  $K_{ATP}$  channels [107]. The therapeutic dose range of diazoxide in infants and children is 5–15 mg/kg/day po with higher doses offering no additional benefits but greater side effects. In adults, a dose range of 3–8 mg/kg/day is recommended (diazoxide prescribing information, [accessdata.fda.gov](https://www.accessdata.fda.gov)). The half-life of diazoxide in children was recently estimated to be  $15 \pm 5.3$  h [108]; thus, diazoxide may be administered two or three times daily. To avoid diazoxide-associated fluid retention, particularly in newborn infants [109, 110], a diuretic should be started concomitantly with the initiation of diazoxide. Doses of chlorothiazide of 10 mg/kg/day or hydrochlorothiazide of 1–2 mg/kg/day may be used, particularly when giving higher (>10 mg/kg/day) doses of diazoxide [111].

Responsiveness to diazoxide can be demonstrated by showing that the cardinal feature of HI, hypoketotic hypoglycemia, has been reversed. In practice, this means demonstrating that the infant or child can fast and generate hyperketonemia (BOHB levels >1.8 mmol/L) prior to developing hypoglycemia (plasma glucose levels below 50–60 mg/dL [ $<2.8$ – $3.3$  mmol/L]) [112]. In patients in whom the rate of dextrose infusion cannot be reduced after 5 days of treatment with diazoxide at a dose of 15 mg/kg/day or in whom unresponsiveness has been confirmed by a fasting test, diazoxide should be discontinued. Unresponsiveness to diazoxide suggests a  $K_{ATP}$  channel defect [74], although other genetic forms of HI may also be diazoxide-unresponsive, such as glucokinase HI and hexokinase HI.

The acute side effects of diazoxide include salt and water retention which may lead to fluid overload, edema, hyponatremia, tachypnea, and respiratory failure [109]. Pulmonary hypertension has also been described with diazoxide [113–115]; in a large cohort of infants [109] the frequency of diazoxide-related pulmonary hypertension was 2.4%. The most common long-term side effect of diazoxide is hypertrichosis recently reported to occur in 84.1% of children [116]. Coarsening of facial features has been reported in 24% [111, 117]. Other rarer adverse events include neutropenia (15.6%), thrombocytopenia (4.7%), and hyperuricemia (5.0%). The clinical significance of the neutropenia is not known, and the level of neutropenia that deserves discontinuation of diazoxide is also not known. A CBC may be drawn prior to starting diazoxide to ensure there is no evidence of pre-existing neutropenia or thrombocytopenia. The overall frequency of serious adverse events requiring

diazoxide discontinuation is estimated at 9.7% [110]. The rate of side effects appears to be higher in infants treated for perinatal stress-induced HI or premature babies [110]. For these reasons, screening for side effects during diazoxide therapy is recommended, including an echocardiogram 1 week after initiation of therapy with diazoxide and for symptoms of pulmonary hypertension. In addition, a complete blood count with differential and serum uric acid levels should be done every 6 months [111]. While there are no published data to evaluate the clinical significance of elevated uric acid levels associated with the use of diazoxide, studies in other populations have shown that chronic hyperuricemia in children can lead to monosodium urate deposits that may progress to gout, just as in adults [118]. Thus, we consider it important to screen for hyperuricemia in children treated with diazoxide given the reported 5% frequency of hyperuricemia in this population [109].

*2.5 We Suggest the Use of Somatostatin Analogues as Second-Line Treatment for Infants with Hyperinsulinism Who Are Diazoxide-Unresponsive or Have Unacceptable Diazoxide Side Effects or Are Unable to Obtain Diazoxide [Grade 2⊕⊕○○]*

Short- or long-acting somatostatin analogs (SSA) used in patients with HI include octreotide [119, 120], long-acting octreotide (octreotide LAR) [121, 122], and lanreotide [122–126]. Octreotide has been used since the late 1980s as a long-term therapy for HI to avoid the need for pancreatectomy or in cases that could not be controlled following subtotal pancreatectomy [119, 120, 127, 128, 129]. However, the use of octreotide therapy is limited by loss of efficacy due to tachyphylaxis [120, 130] and the occurrence of important side effects [131–134], including necrotizing enterocolitis (NEC), particularly in premature and high-risk infants with hemodynamic instability or sepsis [132, 135–137]. While somatostatin analogs are commonly used as second-line treatment of HI, this indication has not been approved by the United States FDA.

Octreotide can be administered in 2–4 subcutaneous doses/day or by continuous subcutaneous infusion using commercial pumps intended for insulin administration [127, 129]. The starting dose of octreotide is 5–10 µg/kg/day, and it can be titrated up to a maximum of 20 µg/kg/day [138, 139]. In an effort to prevent the development of tachyphylaxis, some centers use two doses of octreotide during the daytime in combination with continuous overnight dextrose administered through a gastrostomy tube [35].

A single monthly injection of a long-acting SSA can have a therapeutic advantage over multiple daily octreotide injections or continuous subcutaneous octreotide by a pump with attendant risk of pump disconnection and failure. The

dose of long-acting SSA preparations required to control hypoglycemia is variable, and there are insufficient data available to make a recommendation, but expert consensus suggests calculating the total monthly dose of octreotide and administering it as a single dose of Octreotide LAR once per month. For lanreotide, the calculation is not equivalent; thus, 30–60 mg once per month is a typical starting dose. Screening for side effects while on SSA therapy is recommended, including growth monitoring, obtaining a gall bladder ultrasound to evaluate for cholelithiasis, and laboratory evaluation for liver enzymes, growth factors, and thyroid function at least every 6 months.

*2.6 We Suggest that Medications Which Lack Adequate Proof of Efficacy (i.e., Nifedipine, Sirolimus, etc.) Not Be Used to Treat Hyperinsulinism unless Part of an Approved Investigational Protocol [Grade 2⊕⊕○○]*

Despite *in vitro* studies showing inhibition of insulin secretion by calcium-channel blockers and early reports suggesting beneficial effects of nifedipine in infants with HI, most major centers have not found it useful and do not recommend its use [140]. However, in patients with HI due to genetic defects of the *CACNA1D* calcium channel, it has been suggested that nifedipine may improve not only hypoglycemia but also neuromuscular manifestations [141, 142].

Sirolimus, an inhibitor of mammalian target of rapamycin (mTOR), has been used in some children with HI resistant to conventional medical therapies, based on reports of beneficial responses in adults with insulinoma [143]. However, due to serious concerns over the risk of life-threatening infections, such as hepatitis, diabetes mellitus, and pancreatic insufficiency [144–148], and the absence of robust clinical effectiveness data, the Guideline Committee cannot recommend sirolimus for routine clinical use in HI. Exceptions should only be made for studies of the drug carried out under approved investigational protocols. Glucocorticoids have been used in the past in an effort to increase glucose levels by inducing insulin resistance; however, we suggest that they are not effective in treatment of HI and should be avoided since the risks of this therapy strongly outweigh any benefits.

*2.7 We Suggest Carbohydrate Supplementation to Maintain Euglycaemia in Infants and Children with Hyperinsulinism Who Are Not Adequately Controlled on Pharmacologic Therapy Alone [Grade 2⊕⊕○○]*

Many children with HI continue to have unstable hypoglycemia requiring continuous intravenous treatment with glucose despite maximal medical and/or

surgical treatment. For these children, continuous intragastric infusion of glucose may be used, either via nasogastric tube or, preferably, via gastrostomy using portable pumps [149]. Solutions containing glucose (dextrose or maltodextrin polymer powder) at concentrations up to 20% may be tolerated. In some cases, glucose supplementation of formula feedings to increase the total carbohydrate content to 15% may be helpful [150]; however, care should be taken when using glucose supplementation to avoid interfering with appetite and normal feeding behavior or inducing obesity due to the excess calories [151].

Some reports have suggested that drinks containing uncooked cornstarch may increase fasting tolerance in older children and adults with HI who have unstable control of hypoglycemia, similar to the use of uncooked cornstarch in children with glycogen storage disorders. Doses of 1–2 gm/kg may be used, but only in children over 9 months old since cornstarch is poorly digested in younger infants. In the absence of controlled studies demonstrating its effectiveness in HI, the Guideline Committee was unable to provide a consensus recommendation on use of cornstarch in children with HI.

### 3. Surgical Management

#### 3.1 We Recommend that Surgery Be Considered for Children Suspected to Have a Resectable Focal Lesion [GRADE 1⊕⊕⊕○]

#### 3.2 We Suggest that Infants with Hyperinsulinism due to Diffuse Pancreatic Disease Should Undergo Surgery if Hypoglycemia Is Not Adequately Controlled despite Maximal Medical Therapy [GRADE 2⊕⊕○○]

When genetic tests and radiologic imaging studies suggest the likelihood of a focal lesion, surgical resection is the approach of choice since infants can be cured and avoid either ongoing hypoglycemia or the development of diabetes mellitus. This is especially true if the location of the lesion allows complete resection and if the surgical team has the necessary expertise, including a protocol for intraoperative examination of frozen biopsies to guide the operative strategy [152–154]. For example, in some cases, removal of lesions in the pancreatic head may require a Roux-en-Y pancreatojejunostomy that preserves pancreatic duct connections from the body and tail of the pancreas [87].

At surgery for suspected focal HI, biopsies should be taken from the pancreatic head, body, and tail to clearly establish whether there is diffuse disease versus an

underlying focal lesion. Diffuse HI can be recognized by increased numbers of islet cells with large nuclei (nucleomegaly) throughout the pancreas; ascertainment of islet nucleomegaly is ideally undertaken by a pathologist experienced in the recognition of HI. Focal lesions are typically small, 0.5–1 cm in diameter, and contain increased masses of endocrine cells often interspersed with acinar cells and duct structures; biopsies from the remaining pancreas are histologically unremarkable. Focal HI lesions are often unencapsulated and frequently extend into the adjacent normal parenchyma, creating a challenge for assessing involvement of resection margins. In BWSp, there is a similar expansion of islet cell tissue, extending over large areas of the pancreas, making complete resection more difficult. In some cases of HI, histologic changes typical of diffuse HI occur only in localized regions of the pancreas; this has been termed LINE-HI, mosaic, or “atypical” hyperinsulinism and may be associated with somatic variants of HI genes, such as *ABCC8*, *GCK*, and inappropriate expression of *HK1* [80, 85]. Due to the variety of histologic forms of congenital HI, the choice and plan for pancreatic resection should be in close collaboration with a pathologist experienced in HI and with access to a high-quality laboratory and suitable protocols for rapid and accurate review of pancreatic biopsies.

In cases of diffuse HI that have been diagnosed by genetic testing, medical treatment is the first choice; however, if hypoglycemia cannot be adequately controlled, pancreatectomy may be required. For diffuse HI, a 90–98% pancreatectomy is recommended to strike a balance between control of hypoglycemia and the delayed development of diabetes, while preserving bile duct drainage [155, 156].

Following surgery, immunohistochemical staining of permanent sections should be performed using neuroendocrine markers (chromogranin and synaptophysin) to highlight endocrine tissue and for assessment of margin involvement. In focal lesions and in regions of endocrine cell overgrowth in BWSp, loss of maternal heterozygosity at 11p15 can be demonstrated by loss of nuclear p57 staining in lesion cells [157].

The immediate postsurgical management of children with HI may be complicated and, thus, should be in an appropriate intensive care setting. Intraoperative and postoperative plasma glucose fluctuations are common and do not reflect the ultimate glycemic outcome of surgery. However, prevention of postoperative hypoglycemia during this period is important to minimize neuroglycopenia. Plasma glucose levels should be monitored closely, with a goal of preventing hypo or hyperglycemia [158]. Insulin therapy by either subcutaneous injection or intravenous

**Table 4.** Diagnostic fasting test

---

Perform test only on a unit with trained medical/nursing staff who are experienced in the performance of fasting studies

1. Have IV access and D10% (2–5 mL/kg) for emergency resuscitation
2. Measure glucose by POC meter every 2–3 h until glucose <70 mg/dL (<3.9 mmol/L); then every 2 h until <60 mg/dL (<3.3 mmol/L); then hourly until ≤50 mg/dL (<2.8 mmol/L)
  - a. When glucose <60 mg/dL (<3.3 mmol/L) send specimen for laboratory confirmation of plasma glucose
3. Measure beta-hydroxybutyrate every 2–3 h and when glucose <50 mg/dL (<2.8 mmol/L)
  - a. When plasma glucose ≤50 mg/dL (<2.8 mmol/L) draw blood for the CRITICAL sample
    - i. Glucose, insulin, beta-hydroxybutyrate, free fatty acids
    - ii. Ammonia, cortisol, growth hormone, lactate, acyl carnitine profile, urine organic acids
    - iii. Special circumstances: C-peptide, proinsulin, sulphonylurea screen, toxicology screen, serum amino-acids
4. Perform Glucagon Stimulation Test once CRITICAL samples are obtained
  1. Measure glucose using POC meter and then give glucagon 30 µg/kg or 0.5–1 mg by IM or IV push as long as glucose is < 50 mg/dL (<2.8 mmol/L)
  2. Monitor glucose using POC meter every 10 min for 40 min
  3. Terminate test if glucose is still below 50 mg/dL (<2.8 mmol/L) after 30 min
  4. After 40 min, may feed and resume treatment to maintain plasma glucose >70 mg/dL (3.9 mmol/L)

---

**Table 5.** Safety/cure fasting test

---

1. Have blood drawing IV line in place
2. Check glucose (POC meter) and beta-hydroxybutyrate every 2–3 h until glucose <70 mg/dL; then every 2 h until <60 mg/dL; then hourly until <50 mg/dL When glucose <60 mg/dL (by POC meter), send specimen for laboratory confirmation of plasma glucose
  - a. Terminate fast when
    1. Plasma BOHB >2 mmol/L on two separate samples 1 h apart
    2. Plasma glucose <50 mg/dL
    3. Duration of fasting >18 h in <1 year old or >36 h in children 1–10 years old or 72 h in >10 years old

---

insulin infusion should be started if there is persistent hyperglycemia postoperatively (>250 mg/dL [>14 mmol/L]) [158] that does not respond to fluid therapy or if there is hyperglycemia with hyperketonemia (beta-hydroxybutyrate levels >2 mmol/L). If there is a persisting insulin requirement at the time of conversion to enteral feeding, insulin administration can be transitioned to the subcutaneous route. Conversely, children who cannot be weaned from intravenous glucose-containing infusions without hypoglycemia may require further medical management for persisting hyperinsulinism.

Following pancreatectomy, regardless of underlying diagnosis, all children should be evaluated to determine whether they are euglycemic, have persistent hypoglycemia, or have hyperglycemia requiring insulin treatment.

Children who are weaned from IV glucose without hypoglycemia should have a fasting study performed to demonstrate whether they are cured or need further medical management. Details on how to perform either diagnostic or safety/cure fasts are summarized in Tables 4 and 5 [159]. Cure of HI can be demonstrated by the development of hyperketonemia (beta-hydroxybutyrate >1.8 mmol/L) prior to development of hypoglycemia (glucose <50 mg/dL [2.8 mmol/L]). Further resection of pancreatic tissue may be required in medically unmanageable cases [160].

The cure rate of surgery for focal HI is high and is reported to be >95% in some studies [87]. This can be achieved without the risk of subsequent diabetes when just the focal lesion is removed. Following 95–98% pancreatectomy for diffuse disease, hypoglycemia may

recur in up to 50–60% of patients: in such cases, additional medical therapies are usually sufficient to achieve euglycemia, although some may require second surgery. Approximately 25% of the patients in the post-operative period have permanent diabetes, and this number can rise to 91% by 14 years of age [86, 87, 161–164].

Children who have undergone greater than 50% pancreatectomy or a pancreateojejunostomy are at risk for exocrine pancreatic insufficiency requiring pancreatic enzyme replacement [73]. A fecal elastase assay is commonly used for screening [165]. Other recommended monitoring includes plasma levels of fat-soluble vitamins (vitamins A, D, and E) and coagulation tests for vitamin K deficiency [166].

#### 4. Discharge Planning

##### 4.1 We Suggest that Discharge Planning for Children with Hyperinsulinism Include an Assessment of Fasting Tolerance [GRADE 2⊕⊕○]

Prior to discharge from the hospital, a fasting study to determine the control of HI is suggested for all children, regardless of whether they are on medical therapy or have undergone pancreatic resection. The fasting duration should be predetermined for each patient to ensure that they will be safe in their home environment and to guide the child's sleeping, feeding, and glucose monitoring regimen. For those with ongoing hypoglycemia, we suggest gastrostomy tube placement prior to discharge home for use in emergency situations or for continuous overnight feeds/dextrose when fasting tolerance is too short for safe overnight glucose control. Contingency plans should be considered for accidental disconnection of overnight continuous intragastric infusions; these may include the use of a continuous glucose monitoring system and nocturnal enuresis alarm pad (to identify fluid leaks). Individuals with ongoing hypoglycemia should also have access to glucagon therapy for emergency rescue.

An individualized approach should be taken for decision-making regarding child and family readiness for safe discharge home. Upon discharge, any required medications, supplies for glucose monitoring, discharge summary letter/emergency management plans for hypoglycemia/hyperglycemia, and follow-up plans should be provided to the family both in their language and the primary language of the country in which they reside. Other medical and psychological co-morbidities should also be addressed before discharge. In a recent study, caregivers have reported that the ongoing worry associated with managing the complexity of their child's HI can impact their physical and mental health. Therefore,

we suggest providing psychological resources to families and offering them connections to hyperinsulinism patient organizations for support [167]. Referral for genetic consultation and counseling may also be indicated [168].

#### 5. Long-Term Management of Patients with Hyperinsulinism

##### 5.1 We Suggest Regular Follow-Up and Monitoring to Assess Glycemic Control, Medication Side Effects, and the Development of Diabetes or Pancreatic Insufficiency [Grade 2⊕⊕○]

All children with HI need regular monitoring of their plasma glucose levels at home to guide treatment adjustments. In a patient driven report, more than 65.2% of patients required adjustments to the regimen in the first 3 months following discharge and despite careful follow-up, intermittent hypoglycemia is common [116]. The side effects of the HI medications [111, 128, 169] should be monitored, and support should be provided from the multidisciplinary feeding team in the hospital as well as in the community. In some children with certain forms of HI (e.g., defects in *ABCC8*, *KCNJ11*, *HNF-1A*, and *HNF-4A*), severity may decrease over time [170–172], allowing dose adjustments to medications.

For patients who have undergone a pancreatectomy and are no longer on treatment for hypoglycemia, screening for diabetes should include hemoglobin A1c every 6–12 months and monitoring for symptoms of hyperglycemia. Transition to diabetes may be slow, and some patients may have both fasting hypoglycemia and postprandial hyperglycemia. The need for diabetes medications should be evaluated on an individual basis, taking into account the current HbA1c, ability to fast without hypoglycemia, and presence or absence of symptoms of diabetes.

In patients with postsurgical diabetes mellitus, insulin treatment by conventional or pump therapy similar to children with type 1 diabetes mellitus is necessary to achieve optimal glycemic control [173]. Pancreatic enzyme replacement therapy should be initiated when there is evidence of pancreatic insufficiency [166].

##### 5.2 We Recommend that, due to the Increased Risk of Neurocognitive Deficits and Feeding Difficulties, All Children with Hyperinsulinism Should Undergo a Referral for Developmental Surveillance, Feeding Assessment, and Early Intervention [GRADE 1⊕⊕○]

Neurodevelopment delays and neurological disorders, including epilepsy and microcephaly, due to hypoglycemic brain injury occur frequently in patients with HI [163, 164,

172]. Infantile spasms [174]; an increase in motor and speech delay during early childhood [175]; or deficits in attention, memory, visual, and sensorimotor functions have also been reported. Children with transient HI are also at risk of developing neurodevelopmental deficits with reported incidence rates ranging between 26 and 44% [170, 176, 177, 178]. Abnormal neurodevelopment and seizures are particularly high in HI associated with *GLUD1* pathogenic variants [25].

Children with HI should have regular neurodevelopmental follow-up and monitoring that should include formal neurodevelopmental testing during early childhood for appropriate educational and rehabilitative placement. The care of children with HI may need to involve neurodevelopmental pediatricians, physiotherapists, occupational therapists, and speech and language therapists [26].

Feeding problems that may be associated with HI are complex, multifactorial, and often iatrogenic [151]. Feeding issues have been reported in 68.6% of all patients [116]. Vomiting, sucking and swallowing difficulties, and food aversion can occur either in isolation or combination. The use of medications that cause nausea and anorexia and have unpleasant taste, and the use of intravenous glucose support and tube feedings with high carbohydrate content that impair appetite, can interrupt the development of normal feeding milestones and put infants with HI at risk of feeding problems. Although the goal of preventing hypoglycemia is the primary goal in the newborn period, we suggest encouraging oral feeding over tube feeding especially when intravenous glucose support is being used to control hypoglycemia [28]. Prompt management of medical problems, such as vomiting and gastroesophageal reflux, may help prevent long-term feeding problems. In addition, in children with ongoing hypoglycemia, insertion of a gastrostomy tube should be considered for prompt correction of hypoglycemia, and parents should be advised of the possibility of tube dependency and how to avoid this complication.

### *5.3 We Suggest that Programs Be Established for the Transition to Adult Care for Children and Adolescents with Hyperinsulinism and Ongoing Medical Needs, and for the Development of Adult Programs for Adults with Hyperinsulinism [Grade 2⊕⊕⊕]*

Adults with HI who continue to have complex needs require transition of care to appropriately trained adult specialists to address all ongoing issues, including HI treatment, neurodevelopmental delays and memory issues, hypoglycemia unawareness, risk of developing diabetes, and implications of genetic diagnosis.

## **Conclusions**

Scientific and clinical advances over the last three decades have improved our understanding of the pathophysiology of HI in children and have led to treatment approaches that take into account the many differences in their genotype and phenotype. Despite these advances, treatment options are still limited for most children with HI. Affected children continue to experience high rates of neurological sequelae due to hypoglycemia-induced brain damage. To improve neurological outcomes, prompt recognition of hypoglycemia and its etiology leading to rapid and effective treatment are essential.

Currently, pancreatectomy may be required for the surgical treatment of diffuse HI. New medical therapies are urgently needed to prevent the need for pancreatectomy and the resultant hypoglycemia and diabetes in the postoperative period. In addition, alternative medical therapy choices are needed to replace those current medications that may cause significant side effects.

Centers caring for infants and children with HI should consider developing multidisciplinary teams to provide all aspects of care, including social and psychological support not only for the children but also the families. An individualized approach to each child would be preferred to ensure optimal patient experience and outcomes. It is also important to offer long-term peer support to patients and families. There are a host of national and international family support organizations that can be found online (<https://congenitalhi.org/links/>).

These guidelines provide a systematic approach to the diagnosis and management of children with persistent hypoglycemia due to hyperinsulinism while at the same time recognizing that access to diagnostic tools, medications, and medical and surgical expertise is limited in many areas of the world and that good-quality evidence is often lacking. This further illustrates the urgent need for collaborative research efforts to generate this evidence and revise our recommendations in the future.

## **Acknowledgments**

The authors would like to acknowledge the great contributions to science in the field of hyperinsulinism by Prof. Mark Dunne. His premature death during the preparation of this manuscript left us all saddened, and we dedicate this manuscript to his memory in honor of his leadership in the field of Hyperinsulinism. The authors would like to thank the patient and caregiver representatives of the Congenital Hyperinsulinism Collaborative Research Network for providing the patient perspective. The authors thank the members of the societies of the ICPE for reviewing this manuscript and for their thoughtful feedback. This paper has been endorsed by the

societies of the International Consortium of Pediatric Endocrinology: Australasian Paediatric Endocrine Group (APEG), Asia Pacific Paediatric Endocrine Society (APPEs), Pediatric Endocrine Society (PES), European Society for Paediatric Endocrinology (ESPE), Latin American Society for Pediatric Endocrinology (SLEP), Japanese Society for Pediatric Endocrinology (JSPE), International Society for Pediatric and Adolescent Diabetes (ISPAD), African Society for Pediatric and Adolescent Endocrinology (ASPAE), Arab Society for Pediatric Endocrinology and Diabetes (ASPED), Indian Society for Pediatric and Adolescent Endocrinology (ISPAE), Global Pediatric Endocrinology and Diabetes (GPED), and the Chinese Society for Pediatric Endocrinology and Metabolism.

### Conflict of Interest Statement

D.D.L. has received research funding from Zealand Pharma, Tiburio Therapeutics, Twist Bioscience, and Crinetics Pharmaceuticals and consulting fees from Zealand Pharma, Crinetics Pharmaceuticals, Hanmi Pharmaceutical, and Eiger Biopharmaceuticals and is named inventor in patents # USA Patent Number 9,616,108, 2017, USA Patent Number 9,821,031, 2017, Europe Patent Number EP 2120994, 2018, Europe Patent Number EP2818181, 2019. J.B.A. has received consulting fees from Alexion, Immedica, Zealand Pharma, Sobi, Pierre Fabre, and BioMari and speaker honorarium from Sanofi, Genzyme, Recordati, Pierre Fabre, and Vitaflor. I.B. has received funding support from Merck, Crinetics, Zealand, and Diurnal. He is also the Chair of the ESPE Communications Committee and BSPED-NIHR Clinical Studies Group. He is a co-opted member of NICE guidelines. L.S.C. is an advisory Board member and consultant to Zealand Pharma. T.M. received research payments from Zealand Pharma. T.L.S.P. is an employee of Congenital

Hyperinsulinism International. A.V. received an investigator-initiated grant from Novo Nordisk and has consulted for vTv Therapeutics, Zealand Pharmaceuticals, Crinetics, and Rezolute. P.S.T. has received research payments from Ascendis, Novo Nordisk, OPKO, Rezolute, and Zealand and was a member of the Board of the PES at the time of writing. The following report to have no COI: I.B., T.B., J.F.F., S.E.F., D.G., K.M., P.S., C.A.S., and T.Y.

### Funding Sources

D.D.L. is funded by grants from the NIH-NIDDK: R01-DK056268, R01-DK098517. T.B. is supported by NIH/NIDDK DK056268-22. S.E.F. is a Wellcome Trust Senior Research Fellow (Grant No. 223187/Z/21/Z). T.M. is funded by Ilse-Bagel Foundation, Düsseldorf, Germany. K.M. received funding from MetabERN. A.V. is supported by NIH/NIDDK DK78646, DK116231, and DK126206. P.S.T. is partially funded by the Cook Children's Health Care System Endowed Chair for Hyperinsulinism.

### Author Contributions

D.D.L. and P.S.T. jointly formulated the plan to write the manuscript, selected the co-authors, coordinated the societies, wrote sections of the first draft, edited the subsequent drafts, reviewed the references for accuracy, and approved the final draft. J.B.A., I.B., I.Ber., T.B., L.S.C., J.F.F., S.E.F., D.G., T.M., K.M., T.L.S.P., P.S., C.A.S., A.V., and T.Y. each wrote first drafts of their sections, edited subsequent drafts, reviewed the manuscript, and approved the manuscript.

### References

- Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. *BMJ*. 2004 Jun 19;328(7454):1490.
- Swiglo BA, Murad MH, Schunemann HJ, Kunz R, Vigersky RA, Guyatt GH, et al. A case for clarity, consistency, and helpfulness: state-of-the-art clinical practice guidelines in endocrinology using the grading of recommendations, assessment, development, and evaluation system. *J Clin Endocrinol Metab*. 2008 Mar;93(3):666–73.
- Siersbaek J, Larsen AR, Nybo M, Christesen HT. A sensitive plasma insulin immunoassay to establish the diagnosis of congenital hyperinsulinism. *Front Endocrinol*. 2020;11:614993.
- Bier DM, Leake RD, Haymond MW, Arnold KJ, Gruenke LD, Sperling MA, et al. Measurement of “true” glucose production rates in infancy and childhood with 6,6-dideuteroglucose. *Diabetes*. 1977 Nov;26(11):1016–23.
- Palladino AA, Bennett MJ, Stanley CA. Hyperinsulinism in infancy and childhood: when an insulin level is not always enough. *Clin Chem*. 2008 Feb;54(2):256–63.
- 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 Jan;168:212–9.
- Sakakibara A, Hashimoto Y, Kawakita R, Hosokawa Y, Nagahara K, Hasegawa Y, et al. Diagnosis of congenital hyperinsulinism: biochemical profiles during hypoglycemia. *Pediatr Diabetes*. 2018 Mar;19(2):259–64.
- Stanley CA, Rozance PJ, Thornton PS, De Leon DD, Harris D, Haymond MW, et al. Re-evaluating “transitional neonatal hypoglycemia”: mechanism and implications for management. *J Pediatr*. 2015 Jun;166(6):1520–5.e1.
- Grimberg A, Ferry RJ Jr, Kelly A, Koo-McCoy S, Polonsky K, Glaser B, et al. Dysregulation of insulin secretion in children with congenital hyperinsulinism due to sulfonylurea receptor mutations. *Diabetes*. 2001 Feb;50(2):322–8.
- Kelly A, Ng D, Ferry RJ Jr, Grimberg A, Koo-McCoy S, Thornton PS, et al. Acute insulin responses to leucine in children with the hyperinsulinism/hyperammonemia syndrome. *J Clin Endocrinol Metab*. 2001 Aug;86(8):3724–8.
- Fournier SH, Stanley CA, Kelly A. Protein-sensitive hypoglycemia without leucine sensitivity in hyperinsulinism caused by K(ATP) channel mutations. *J Pediatr*. 2006 Jul;149(1):47–52.
- Arnoux JB, de Lonlay P. Hyperinsulinism. In: Hollak CEM, Lacmann R, editors. *Inherited metabolic disease in adults: a clinical guide*. Oxford University Press; 2016. p. 29–33.
- Gray KD, Dudash K, Escobar C, Freeland C, Harrison T, McMillan C, et al. Prevalence and safety of diazoxide in the neonatal intensive care unit. *J Perinatol*. 2018 Nov;38(11):1496–502.
- Bailey MJ, Rout A, Harding JE, Alswelker JM, Cutfield WS, McKinlay CJD. Prolonged transitional neonatal hypoglycemia: characterisation of a clinical syndrome. *J Perinatol*. 2021 May;41(5):1149–57.
- Lord K, De Leon DD. Meeting report: updates in diagnosis and management of hyperinsulinism and neonatal hypoglycemia: highlights from the fourth international hyperinsulinism symposium. *Pediatr Endocrinol Rev*. 2020 Jun;17(3):268–77.

- 16 Yang J, Hammoud B, Li C, Ridler A, Yau D, Kim J, et al. Decreased KATP channel activity contributes to the low glucose threshold for insulin secretion of rat neonatal islets. *Endocrinology*. 2021 Sep 1; 162(9):162.
- 17 Hoe FM, Thornton PS, Wanner LA, Steinkrauss L, Simmons RA, Stanley CA. Clinical features and insulin regulation in infants with a syndrome of prolonged neonatal hyperinsulinism. *J Pediatr*. 2006 Feb;148(2):207–12.
- 18 Yamada Y, Kitayama K, Oyachi M, Higuchi S, Kawakita R, Kanamori Y, et al. Nationwide survey of endogenous hyperinsulinemic hypoglycemia in Japan (2017–2018): congenital hyperinsulinism, insulinoma, non-insulinoma pancreatogenous hypoglycemia syndrome and insulin autoimmune syndrome (Hirata's disease). *J Diabetes Investig*. 2020 May;11(3):554–63.
- 19 Pearson ER, Boj SF, Steele AM, Barrett T, Stals K, Shield JP, et al. Macrosumia and hyperinsulinaemic hypoglycaemia in patients with heterozygous mutations in the HNF4A gene. *PLoS Med*. 2007 Apr;4(4):e118.
- 20 Stancescu DE, Hughes N, Kaplan B, Stanley CA, De Leon DD. Novel presentations of congenital hyperinsulinism due to mutations in the MODY genes: HNF1A and HNF4A. *J Clin Endocrinol Metab*. 2012 Oct; 97(10):E2026–30.
- 21 Tung JY, Boodhansingh K, Stanley CA, De Leon DD. Clinical heterogeneity of hyperinsulinism due to HNF1A and HNF4A mutations. *Pediatr Diabetes*. 2018 Aug; 19(5):910–6.
- 22 Padidela R, Fiest M, Arya V, Smith VV, Ashworth M, Rampling D, et al. Insulinoma in childhood: clinical, radiological, molecular and histological aspects of nine patients. *Eur J Endocrinol*. 2014 May;170(5):741–7.
- 23 Bhatti TR, Ganapathy K, Huppman AR, Conlin L, Boodhansingh KE, MacMullen C, et al. Histologic and molecular profile of pediatric insulinomas: evidence of a paternal parent-of-origin effect. *J Clin Endocrinol Metab*. 2016 Mar;101(3):914–22.
- 24 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 Apr;94(4):1069–73.
- 25 Palladino AA, Stanley CA. The hyperinsulinism/hyperammonemia syndrome. *Rev Endocr Metab Disord*. 2010 Sep;11(3):171–8.
- 26 Güemes M, Rahman SA, Kapoor RR, Flanagan S, Houghton JAL, Misra S, et al. Hyperinsulinemic hypoglycemia in children and adolescents: recent advances in understanding of pathophysiology and management. *Rev Endocr Metab Disord*. 2020 Dec;21(4):577–97.
- 27 Sayed S, Langdon DR, Odili S, Chen P, Buettger C, Schiffman AB, et al. Extremes of clinical and enzymatic phenotypes in children with hyperinsulinism caused by glucokinase activating mutations. *Diabetes*. 2009 Jun;58(6):1419–27.
- 28 Lau C. Development of infant oral feeding skills: what do we know? *Am J Clin Nutr*. 2016 Feb;103(2):616S–21S.
- 29 Thomas PM, Cote GJ, Wohllk N, Haddad B, Mathew PM, Rabl W, et al. Mutations in the sulfonylurea receptor gene in familial persistent hyperinsulinemic hypoglycemia of infancy. *Science*. 1995 Apr 21;268(5209):426–9.
- 30 Huopio H, Reimann F, Ashfield R, Komulainen J, Lenko HL, Rahier J, et al. Dominantly inherited hyperinsulinism caused by a mutation in the sulfonylurea receptor type 1. *J Clin Invest*. 2000 Oct;106(7):897–906.
- 31 Houghton JA, Banerjee I, Shaikh G, Jabbar S, Laver TW, Cheesman E, et al. Unravelling the genetic causes of mosaic islet morphology in congenital hyperinsulinism. *J Pathol Clin Res*. 2020 Jan;6(1):12–6.
- 32 de Lonlay P, Fournet JC, Rahier J, Gross-Morand MS, Poggi-Travert F, Foussier V, et al. Somatic deletion of the imprinted 11p15 region in sporadic persistent hyperinsulinemic hypoglycemia of infancy is specific of focal adenomatous hyperplasia and endorses partial pancreatectomy. *J Clin Invest*. 1997 Aug 15;100(4):802–7.
- 33 Bitner-Glindzicz M, Lindley KJ, Rutland P, Blyndon D, Smith VV, Milla PJ, et al. A recessive contiguous gene deletion causing infantile hyperinsulinism, enteropathy and deafness identifies the Usher type 1C gene. *Nat Genet*. 2000 Sep;26(1):56–60.
- 34 Stauffer C, Lindner M, Dionisi-Vici C, Freisinger P, Dobbelaere D, Douillard C, et al. Adenosine kinase deficiency: expanding the clinical spectrum and evaluating therapeutic options. *J Inherit Metab Dis*. 2016 Mar;39(2):273–83.
- 35 Palladino AA, Stanley CA. A specialized team approach to diagnosis and medical versus surgical treatment of infants with congenital hyperinsulinism. *Semin Pediatr Surg*. 2011 Feb;20(1):32–7.
- 36 Sun L, Eklund EA, Chung WK, Wang C, Cohen J, Freeze HH. Congenital disorder of glycosylation id presenting with hyperinsulinemic hypoglycemia and islet cell hyperplasia. *J Clin Endocrinol Metab*. 2005 Jul;90(7):4371–5.
- 37 Morava E, Tiemes V, Thiel C, Seta N, de Lonlay P, de Klerk H, et al. ALG6-CDG: a recognizable phenotype with epilepsy, proximal muscle weakness, ataxia and behavioral and limb anomalies. *J Inherit Metab Dis*. 2016 Sep;39(5):713–23.
- 38 Kummer S, Rinne S, Seemann G, Bachmann N, Timothy K, Thornton PS, et al. Hyperinsulinemic hypoglycemia associated with a Ca(V)1.2 variant with mixed gain- and loss-of-function effects. *Int J Mol Sci*. 2022 Jul 22; 23(15):8097.
- 39 Hatada I, Ohashi H, Fukushima Y, Kaneko Y, Inoue M, Komoto Y, et al. An imprinted gene p57KIP2 is mutated in Beckwith-Wiedemann syndrome. *Nat Genet*. 1996 Oct;14(2):171–3.
- 40 Welters A, El-Khairi R, Dastamani A, Bachmann N, Bergmann C, Gilbert C, et al. Persistent hyperinsulinaemic hypoglycaemia in children with Rubinstein-Taybi syndrome. *Eur J Endocrinol*. 2019 Aug;181(2):121–8.
- 41 Henneveld HT, van Lingen RA, Hamel BC, Stolte-Dijkstra I, van Essen AJ, Perlman syndrome: four additional cases and review. *Am J Med Genet*. 1999 Oct 29;86(5):439–46.
- 42 Gregory LC, Ferreira CB, Young-Baird SK, Williams HJ, Harakalova M, van Haften G, et al. Impaired EIF2S3 function associated with a novel phenotype of X-linked hypopituitarism with glucose dysregulation. *EBioMedicine*. 2019 Apr;42:470–80.
- 43 Baumann U, Preece MA, Green A, Kelly DA, McKiernan PJ. Hyperinsulinism in tyrosinaemia type I. *J Inherit Metab Dis*. 2005;28(2):131–5.
- 44 Giri D, Vignola ML, Gualtieri A, Scagliotti V, McNamara P, Peak M, et al. Novel FOXA2 mutation causes hyperinsulinism, hypopituitarism with craniofacial and endoderm-derived organ abnormalities. *Hum Mol Genet*. 2017 Nov 15;26(22):4315–26.
- 45 Glaser B, Kesavan P, Heyman M, Davis E, Cuesta A, Buchs A, et al. Familial hyperinsulinism caused by an activating glucokinase mutation. *N Engl J Med*. 1998 Jan 22; 338(4):226–30.
- 46 Stanley CA, Lieu YK, Hsu BY, Burlina AB, Greenberg CR, Hopwood NJ, et al. Hyperinsulinism and hyperammonemia in infants with regulatory mutations of the glutamate dehydrogenase gene. *N Engl J Med*. 1998 May 7;338(19):1352–7.
- 47 Terespolsky D, Farrell SA, Siegel-Bartelt J, Weksberg R. Infantile lethal variant of Simpson-Golabi-Behmel syndrome associated with hydrops fetalis. *Am J Med Genet*. 1995 Nov 20;59(3):329–33.
- 48 Clayton PT, Eaton S, Aynsley-Green A, Edginton M, Hussain K, Krywawych S, et al. Hyperinsulinism in short-chain L-3-hydroxyacyl-CoA dehydrogenase deficiency reveals the importance of beta-oxidation in insulin secretion. *J Clin Invest*. 2001 Aug; 108(3):457–65.
- 49 Alexander S, Ramadan D, Alkhaty H, Al-Sharkawi I, Backer KC, El-Sabban F, et al. Costello syndrome and hyperinsulinemic hypoglycemia. *Am J Med Genet*. 2005 Dec 15;139(3):227–30.
- 50 Hojlund K, Hansen T, Lajer M, Henriksen JE, Levin K, Lindholm J, et al. A novel syndrome of autosomal-dominant hyperinsulinemic hypoglycemia linked to a mutation in the human insulin receptor gene. *Diabetes*. 2004 Jun;53(6):1592–8.

- 51 Thomas P, Ye Y, Lightner E. Mutation of the pancreatic islet inward rectifier Kir6.2 also leads to familial persistent hyperinsulinemic hypoglycemia of infancy. *Hum Mol Genet*. 1996 Nov;5(11):1809–12.
- 52 Lin YW, MacMullen C, Ganguly A, Stanley CA, Shyng SL. A novel KCNJ11 mutation associated with congenital hyperinsulinism reduces the intrinsic open probability of beta-cell ATP-sensitive potassium channels. *J Biol Chem*. 2006 Feb 3;281(5):3006–12.
- 53 Torekov SS, Iepsen E, Christiansen M, Linneberg A, Pedersen O, Holst JJ, et al. KCNQ1 long QT syndrome patients have hyperinsulinemia and symptomatic hypoglycemia. *Diabetes*. 2014 Apr;63(4):1315–25.
- 54 Ng SB, Bigham AW, Buckingham KJ, Hannibal MC, McMillin MJ, Gildersleeve HI, et al. Exome sequencing identifies MLL2 mutations as a cause of Kabuki syndrome. *Nat Genet*. 2010 Sep;42(9):790–3.
- 55 Gole H, Chuk R, Coman D. Persistent hyperinsulinism in kabuki syndrome 2: case report and literature review. *Clin Pract*. 2016 Aug 8;6(3):848.
- 56 Deeb A, Al Amoodi A. A novel homozygous mutation in the mannose phosphate isomerase gene causing congenital disorder of glycation and hyperinsulinemic hypoglycemia in an infant. *Clin Case Rep*. 2018 Mar; 6(3):479–83.
- 57 Tegtmeier LC, Rust S, van Scherpenzeel M, Ng BG, Losfeld ME, Timal S, et al. Multiple phenotypes in phosphoglucomutase 1 deficiency. *N Engl J Med*. 2014 Feb 6;370(6):533–42.
- 58 Bohles H, Sewell AA, Gebhardt B, Reinecke-Luthge A, Kloppel G, Marquardt T. Hyperinsulinaemic hypoglycaemia—leading symptom in a patient with congenital disorder of glycosylation Ia (phosphomannomutase deficiency). *J Inherit Metab Dis*. 2001 Dec;24(8):858–62.
- 59 Cabezas OR, Flanagan SE, Stanescu H, Garcia-Martinez E, Caswell R, Lango-Allen H, et al. Polycystic kidney disease with hyperinsulinemic hypoglycemia caused by a promoter mutation in phosphomannomutase 2. *J Am Soc Nephrol*. 2017 Aug;28(8):2529–39.
- 60 Kapoor RR, James C, Flanagan SE, Ellard S, Eaton S, Hussain K. 3-Hydroxyacyl-coenzyme A dehydrogenase deficiency and hyperinsulinemic hypoglycemia: characterization of a novel mutation and severe dietary protein sensitivity. *J Clin Endocrinol Metab*. 2009 Jul;94(7):2221–5.
- 61 Hennewig U, Hadzik B, Vogel M, Meissner T, Goecke T, Peters H, et al. Congenital central hypoventilation syndrome with hyperinsulinism in a preterm infant. *J Hum Genet*. 2008;53(6):573–7.
- 62 Carrasco Salas P, Palma Milla C, Lezana Rosales JM, Benito C, Franco Freire S, Lopez Siles J. Hyperinsulinemic hypoglycemia in a patient with an intragenic NSD1 mutation. *Am J Med Genet*. 2016 Feb;170A(2):544–6.
- 63 Gillis D, Krishnamohan A, Yaacov B, Shaag A, Jackman JE, Elpeleg O. TRMT10A dysfunction is associated with abnormalities in glucose homeostasis, short stature and microcephaly. *J Med Genet*. 2014 Sep;51(9):581–6.
- 64 Zeiad R, Ferren EC, Young DD, De Lancy SJ, Dedousis D, Schillaci LA, et al. A novel homozygous missense mutation in the YARS gene: expanding the phenotype of YARS multisystem disease. *J Endocr Soc*. 2021 Feb 1;5(2):bvaa196.
- 65 Douglas J, Tatton-Brown K, Coleman K, Guerrero S, Berg J, Cole TR, et al. Partial NSD1 deletions cause 5% of Sotos syndrome and are readily identifiable by multiplex ligation dependent probe amplification. *J Med Genet*. 2005 Sep;42(9):e56.
- 66 Banerjee I, Senniappan S, Laver TW, Caswell R, Zenker M, Mohnike K, et al. Refinement of the critical genomic region for congenital hyperinsulinism in the Chromosome 9p deletion syndrome. *Wellcome Open Res*. 2019;4:149.
- 67 Munns CF, Batch JA. Hyperinsulinism and Beckwith-Wiedemann syndrome. *Arch Dis Child Fetal Neonatal Ed*. 2001 Jan;84(1):F67–9.
- 68 Tamame T, Hori N, Homma H, Yoshida R, Inokuchi M, Kosaki K, et al. Hyperinsulinemic hypoglycemia in a newborn infant with trisomy 13. *Am J Med Genet*. 2004 Sep 1;129A(3):321–2.
- 69 Alkhayyat H, Christesen HB, Steer J, Stewart H, Brusgaard K, Hussain K. Mosaic Turner syndrome and hyperinsulinaemic hypoglycaemia. *J Pediatr Endocrinol Metab*. 2006 Dec;19(12):1451–7.
- 70 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. *Nihon Shonika Gakkai Zasshi*. 2011;115:563–9.
- 71 Rozenkova K, Malikova J, Nessa A, Dusatkova L, Bjorkhaug L, Obermannova B, et al. High incidence of heterozygous ABCC8 and HNF1A mutations in Czech patients with congenital hyperinsulinism. *J Clin Endocrinol Metab*. 2015 Dec;100(12):E1540–9.
- 72 Yau D, Laver TW, Dastamani A, Senniappan S, Houghton JAL, Shaikh G, et al. Using referral rates for genetic testing to determine the incidence of a rare disease: the minimal incidence of congenital hyperinsulinism in the UK is 1 in 28,389. *PLoS One*. 2020;15(2):e0228417.
- 73 Mannisto JME, Jaaskelainen J, Otonkoski T, Huopio H. Long-term outcome and treatment in persistent and transient congenital hyperinsulinism: a Finnish population-based study. *J Clin Endocrinol Metab*. 2021 Mar 25;106(4):e1542–51.
- 74 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 Feb;98(2):E355–63.
- 75 Wakeling MN, Owens ND, Hopkinson JR, Johnson MB, Houghton JAL, Dastamani A, et al. Non-coding variants disrupting a tissue-specific regulatory element in HK1 cause congenital hyperinsulinism. *Nat Genet*. 2022 Nov;54(11):1615–20.
- 76 Weinzimer SA, Stanley CA, Berry GT, Yudkoff M, Tuchman M, Thornton PS. A syndrome of congenital hyperinsulinism and hyperammonemia. *J Pediatr*. 1997 Apr;130(4):661–4.
- 77 Molven A, Matre GE, Duran M, Wanders RJ, Rishaug U, Njolstad PR, et al. Familial hyperinsulinemic hypoglycemia caused by a defect in the SCHAD enzyme of mitochondrial fatty acid oxidation. *Diabetes*. 2004 Jan;53(1):221–7.
- 78 Hsu BY, Kelly A, Thornton PS, Greenberg CR, Dilling LA, Stanley CA. Protein-sensitive and fasting hypoglycemia in children with the hyperinsulinism/hyperammonemia syndrome. *J Pediatr*. 2001 Mar;138(3):383–9.
- 79 Otonkoski T, Jiao H, Kaminen-Ahola N, Tapia-Paez I, Ullah MS, Parton LE, et al. Physical exercise-induced hypoglycemia caused by failed silencing of monocarboxylate transporter 1 in pancreatic beta cells. *Am J Hum Genet*. 2007 Sep;81(3):467–74.
- 80 Boodhansingh KE, Yang Z, Li C, Chen P, Lord K, Becker SA, et al. Localized islet nuclear enlargement hyperinsulinism (LINE-HI) due to ABCC8 and GCK mosaic mutations. *Eur J Endocrinol*. 2022 Aug 1;187(2):301–13.
- 81 Damaj L, le Lorch M, Verkarre V, Werl C, Hubert L, Nihoul-Fekete C, et al. Chromosome 11p15 paternal isodisomy in focal forms of neonatal hyperinsulinism. *J Clin Endocrinol Metab*. 2008 Dec;93(12):4941–7.
- 82 Kalish JM, Boodhansingh KE, Bhatti TR, Ganguly A, Conlin LK, Becker SA, et al. Congenital hyperinsulinism in children with paternal 11p uniparental isodisomy and Beckwith-Wiedemann syndrome. *J Med Genet*. 2016 Jan;53(1):53–61.
- 83 Giurgea I, Sanlaville D, Fournet JC, Sempoux C, Bellanne-Chantelot C, Touati G, et al. Congenital hyperinsulinism and mosaic abnormalities of the ploidy. *J Med Genet*. 2006 Mar;43(3):248–54.
- 84 Sempoux C, Capito C, Bellanne-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 Dec;96(12):3785–93.
- 85 Henquin JC, Sempoux C, Marchandise J, Godecharles S, Guiot Y, Nenquin M, et al. Congenital hyperinsulinism caused by hexokinase I expression or glucokinase-activating mutation in a subset of beta-cells. *Diabetes*. 2013 May;62(5):1689–96.

- 86 Lord K, Dzata E, Snider KE, Gallagher PR, De Leon DD. Clinical presentation and management of children with diffuse and focal hyperinsulinism: a review of 223 cases. *J Clin Endocrinol Metab*. 2013 Nov;98(11):E1786–9.
- 87 Adzick NS, De Leon DD, States LJ, Lord K, Bhatti TR, Becker SA, et al. Surgical treatment of congenital hyperinsulinism: results from 500 pancreatectomies in neonates and children. *J Pediatr Surg*. 2019 Jan;54(1):27–32.
- 88 Hewat TI, Johnson MB, Flanagan SE. Congenital hyperinsulinism: current laboratory-based approaches to the genetic diagnosis of a heterogeneous disease. *Front Endocrinol*. 2022;13:873254.
- 89 Flanagan SE, Xie W, Caswell R, Damhuis A, Vianey-Saban C, Akcay T, et al. Next-generation sequencing reveals deep intronic cryptic ABCC8 and HADH splicing founder mutations causing hyperinsulinism by pseudoxon activation. *Am J Hum Genet*. 2013 Jan 10;92(1):131–6.
- 90 Brioude F, Kalish JM, Mussa A, Foster AC, Blik J, Ferrero GB, et al. Expert consensus document: clinical and molecular diagnosis, screening and management of Beckwith-Wiedemann syndrome: an international consensus statement. *Nat Rev Endocrinol*. 2018 Apr;14(4):229–49.
- 91 Mohnike K, Wieland I, Barthlen W, Vogelgesang S, Empting S, Mohnike W, et al. Clinical and genetic evaluation of patients with KATP channel mutations from the German registry for congenital hyperinsulinism. *Horm Res Paediatr*. 2014;81(3):156–68.
- 92 Garg PK, Putegnat B, Truong L, Reynolds C, Sanchez I, Nedrelov JK, et al. Visual interpretation, not SUV ratios, is the ideal method to interpret 18F-DOPA PET scans to aid in the cure of patients with focal congenital hyperinsulinism. *PLoS One*. 2020;15(10):e0241243.
- 93 States LJ, Saade-Lemus S, De Leon DD. 18-F-1,3,4-dihydroxyphenylalanine PET/computed tomography in the management of congenital hyperinsulinism. *Pet Clin*. 2020 Jul;15(3):349–59.
- 94 Boss M, Rottenburger C, Brenner W, Blankenstein O, Prasad V, Prasad S, et al. <sup>68</sup>Ga-NODAGA-Exendin-4 PET/CT improves the detection of focal congenital hyperinsulinism. *J Nucl Med*. 2022;63:310–5.
- 95 Thornton PS, Stanley CA, De Leon DD, Harris D, Haymond MW, Hussain K, et al. Recommendations from the pediatric endocrine society for evaluation and management of persistent hypoglycemia in neonates, infants, and children. *J Pediatr*. 2015 Aug;167(2):238–45.
- 96 De Leon DD, Thornton PS, Kendall DM, Birch S, Boge E, Ivkovic J, et al. Self-monitoring plasma glucose and continuous glucose monitoring in children with congenital hyperinsulinism during standard of care treatment. *Pediatric Endocrine Society Annual Meeting*. *Horm Res Paediatr*. 2022.
- 97 Narvey MR, Marks SD. The screening and management of newborns at risk for low blood glucose. *Paediatr Child Health*. 2019 Dec;24(8):536–54.
- 98 Wackernagel D, Gustafsson A, Edstedt Bonamy AK, Reims A, Ahlsson F, Elfving M, et al. Swedish national guideline for prevention and treatment of neonatal hypoglycaemia in newborn infants with gestational age  $\geq 35$  weeks. *Acta Paediatr*. 2020 Jan;109(1):31–44.
- 99 Lilien LD, Pildes RS, Srinivasan G, Voora S, Yeh TF. Treatment of neonatal hypoglycemia with minibolus and intravenous glucose infusion. *J Pediatr*. 1980 Aug;97(2):295–8.
- 100 Hawkes CP, Lado JJ, Givler S, De Leon DD. The effect of continuous intravenous glucagon on glucose requirements in infants with congenital hyperinsulinism. *JIMD Rep*. 2019;45:45–50.
- 101 Muller TD, Finan B, Clemmensen C, DiMarchi RD, Tschoep MH. The new biology and pharmacology of glucagon. *Physiol Rev*. 2017 Apr;97(2):721–66.
- 102 Salomon-Estebanez M, Yau D, Dunne MJ, Worth C, Birch S, Walewski JL, et al. Efficacy of dose-titrated glucagon infusions in the management of congenital hyperinsulinism: a case series. *Front Endocrinol*. 2020;11:441.
- 103 Wald M, Lawrenz K, Luckner D, Seimann R, Mohnike K, Schober E. Glucagon therapy as a possible cause of erythema necrolyticum migrans in two neonates with persistent hyperinsulinaemic hypoglycaemia. *Eur J Pediatr*. 2002 Nov;161(11):600–3.
- 104 Coughlin CC, Roy SM, Arkin LM, Adzick NS, Yan AC, De Leon DD, et al. Iatrogenic necrolytic migratory erythema in an infant with congenital hyperinsulinism. *Pediatr Dermatol*. 2016 Mar-Apr;33(2):e43–7.
- 105 Mohnike K, Blankenstein O, Pfuetzner A, Potzsch S, Schober E, Steiner S, et al. Long-term non-surgical therapy of severe persistent congenital hyperinsulinism with glucagon. *Horm Res*. 2008;70(1):59–64.
- 106 Drash A, Wolff F. Drug therapy in leucine-sensitive hypoglycemia. *Metabolism*. 1964 Jun;13:487–92.
- 107 Ashcroft FM. ATP-sensitive potassium channelopathies: focus on insulin secretion. *J Clin Invest*. 2005 Aug;115(8):2047–58.
- 108 Kizu R, Nishimura K, Sato R, Kosaki K, Tanaka T, Tanigawara Y, et al. Population pharmacokinetics of diazoxide in children with hyperinsulinemic hypoglycemia. *Horm Res Paediatr*. 2017;88(5):316–23.
- 109 Herrera A, Vajravelu ME, Givler S, Mitteer L, Avitabile CM, Lord K, et al. Prevalence of adverse events in children with congenital hyperinsulinism treated with diazoxide. *J Clin Endocrinol Metab*. 2018 Dec 1;103(12):4365–72.
- 110 Thornton P, Truong L, Reynolds C, Hamby T, Nedrelov J. Rate of serious adverse events associated with diazoxide treatment of patients with hyperinsulinism. *Horm Res Paediatr*. 2019;91(1):25–32.
- 111 Brar PC, Heksch R, Cossen K, De Leon DD, Kamboj MK, Marks SD, et al. Management and appropriate use of diazoxide in infants and children with hyperinsulinism. *J Clin Endocrinol Metab*. 2020 Dec 1;105(12):3750–61.
- 112 Yau D, Stanley CA. Diazoxide-responsive forms of congenital hyperinsulinism. In: De Leon-Crutchlow DD, Stanley CA, editors. *Congenital Hyperinsulinism: a practical guide to diagnosis and management*. Switzerland: Springer; 2019. p. 15–32.
- 113 Silvani P, Camporesi A, Mandelli A, Wolfler A, Salvo I. A case of severe diazoxide toxicity. *Paediatr Anaesth*. 2004 Jul;14(7):607–9.
- 114 Nebesio TD, Hoover WC, Caldwell RL, Nitu ME, Eugster EA. Development of pulmonary hypertension in an infant treated with diazoxide. *J Pediatr Endocrinol Metab*. 2007 Aug;20(8):939–44.
- 115 Timlin MR, Black AB, Delaney HM, Matos RI, Percival CS. Development of pulmonary hypertension during treatment with diazoxide: a case series and literature review. *Pediatr Cardiol*. 2017 Aug;38(6):1247–50.
- 116 Pasquini TLS, Mesfin M, Schmitt J, Raskin J. Global registries in congenital hyperinsulinism. *Front Endocrinol*. 2022;13:876903.
- 117 de Lonlay P, Cormier-Daire V, Amiel J, Touati G, Goldenberg A, Fournet JC, et al. Facial appearance in persistent hyperinsulinemic hypoglycemia. *Am J Med Genet*. 2002 Aug 1;111(2):130–3.
- 118 Sun N, Zhong S, Li Y, Wu L, Di Y. Urate crystals deposition in the feet of overweight juveniles and those with symptomatic hyperuricemia: a dual-energy CT study. *J Pediatr Endocrinol Metab*. 2016 May 1;29(5):579–83.
- 119 Glaser B, Landau H, Smilovici A, Neshor R. Persistent hyperinsulinaemic hypoglycaemia of infancy: long-term treatment with the somatostatin analogue Sandostatin. *Clin Endocrinol*. 1989 Jul;31(1):71–80.
- 120 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 Oct;123(4):637–43.
- 121 Le Quan Sang KH, Arnoux JB, Mamoune A, Saint-Martin C, Bellanne-Chantelot C, Valayannopoulos V, et al. Successful treatment of congenital hyperinsulinism with long-acting release octreotide. *Eur J Endocrinol*. 2012 Feb;166(2):333–9.
- 122 van der Steen I, van Albada ME, Mohnike K, Christesen HT, Empting S, Salomon-Estebanez M, et al. A multicenter experience with long-acting somatostatin analogues in patients with congenital hyperinsulinism. *Horm Res Paediatr*. 2018;89(2):82–9.

- 123 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 Aug; 96(8):2312–7.
- 124 Kuhnen 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(2):106–12.
- 125 Shah P, Rahman SA, McElroy S, Gilbert C, Morgan K, Hinchey L, et al. Use of long-acting somatostatin analogues (lanreotide) in an adolescent with diazoxide-responsive congenital hyperinsulinism and its psychological impact. *Horm Res Paediatr*. 2015; 84(5):355–60.
- 126 Cuff H, Lord K, Ballester L, Scully T, Stewart N, De Leon DD. The use of lanreotide in the treatment of congenital hyperinsulinism. *J Clin Endocrinol Metab*. 2022 Jul 14;107(8): e3115–20.
- 127 Glaser B, Hirsch HJ, Landau H. Persistent hyperinsulinemic hypoglycemia of infancy: long-term octreotide treatment without pancreatectomy. *J Pediatr*. 1993 Oct;123(4): 644–50.
- 128 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 Oct;99(10):3660–7.
- 129 Hosokawa Y, Kawakita R, Yokoya S, Ogata T, Ozono K, Arisaka O, et al. Efficacy and safety of octreotide for the treatment of congenital hyperinsulinism: a prospective, open-label clinical trial and an observational study in Japan using a nationwide registry. *Endocr J*. 2017 Sep 30;64(9):867–80.
- 130 Hipkin RW, Friedman J, Clark RB, Eppler CM, Schonbrunn A. Agonist-induced desensitization, internalization, and phosphorylation of the sst2A somatostatin receptor. *J Biol Chem*. 1997 May 23;272(21): 13869–76.
- 131 McKnight JA, McCance DR, Crothers JG, Atkinson AB. Changes in glucose tolerance and development of gall stones during high dose treatment with octreotide for acromegaly. *BMJ*. 1989 Sep 2;299(6699):604–5.
- 132 Laje P, Halaby L, Adzick NS, Stanley CA. Necrotizing enterocolitis in neonates receiving octreotide for the management of congenital hyperinsulinism. *Pediatr Diabetes*. 2010 Mar;11(2):142–7.
- 133 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 Nov 25; 10(1):150.
- 134 Ros-Perez P, Golmayo L, Cilleruelo ML, Gutierrez C, Celaya P, Lacamara N, et al. Octreotide-related exocrine pancreatic insufficiency (EPI) in congenital hyperinsulinism. *J Pediatr Endocrinol Metab*. 2020 Jul 28;33(7):947–50.
- 135 Hawkes CP, Adzick NS, Palladino AA, De Leon DD. Late presentation of fulminant necrotizing enterocolitis in a child with hyperinsulinism on octreotide therapy. *Horm Res Paediatr*. 2016;86(2):131–6.
- 136 Martini S, Aceti A, Lima M, Maffi M, Faldella G, Corvaglia L. Octreotide in a critically ill extremely preterm infant with perforated necrotizing enterocolitis. *Pediatrics*. 2016 Aug;138(2):e20160467.
- 137 McMahon AW, Wharton GT, Thornton P, De Leon DD. Octreotide use and safety in infants with hyperinsulinism. *Pharmacopidemiol Drug Saf*. 2017 Jan;26(1):26–31.
- 138 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 Jul 30;2012:bcr2012006271.
- 139 Haris B, Saraswathi S, Hussain K. Somatostatin analogues for the treatment of hyperinsulinaemic hypoglycaemia. *Ther Adv Endocrinol Metab*. 2020;11: 2042018820965068.
- 140 Guemes M, Shah P, Silvera S, Morgan K, Gilbert C, Hinchey L, et al. Assessment of nifedipine therapy in hyperinsulinemic hypoglycemia due to mutations in the ABCC8 gene. *J Clin Endocrinol Metab*. 2017 Mar 1;102(3):822–30.
- 141 Flanagan SE, Vairo F, Johnson MB, Caswell R, Laver TW, Lango Allen H, et al. A CACNA1D mutation in a patient with persistent hyperinsulinaemic hypoglycaemia, heart defects, and severe hypotonia. *Pediatr Diabetes*. 2017 Jun;18(4):320–3.
- 142 De Mingo Alemany MC, Mifsud Grau L, Moreno Macian F, Ferrer Lorente B, Leon Carinena S. A de novo CACNA1D missense mutation in a patient with congenital hyperinsulinism, primary hyperaldosteronism and hypotonia. *Channels*. 2020 Dec;14(1):175–80.
- 143 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 Mar 20;370(12):1131–7.
- 144 Szymanowski M, Estebanez MS, Padidela R, Han B, Mosinska K, Stevens A, et al. mTOR inhibitors for the treatment of severe congenital hyperinsulinism: perspectives on limited therapeutic success. *J Clin Endocrinol Metab*. 2016 Dec; 101(12):4719–29.
- 145 Banerjee I, De Leon D, Dunne MJ. Extreme caution on the use of sirolimus for the congenital hyperinsulinism in infancy patient. *Orphanet J Rare Dis*. 2017 Apr 14;12(1):70.
- 146 Dastamani A, Guemes M, Walker J, Shah P, Hussain K. Sirolimus precipitating diabetes mellitus in a patient with congenital hyperinsulinaemic hypoglycaemia due to autosomal dominant ABCC8 mutation. *J Pediatr Endocrinol Metab*. 2017 Oct 26;30(11): 1219–22.
- 147 Haliloğlu B, Tuzun H, Flanagan SE, Celik M, Kaya A, Ellard S, et al. Sirolimus-induced hepatitis in two patients with hyperinsulinemic hypoglycemia. *J Clin Res Pediatr Endocrinol*. 2018 Jul 31;10(3):279–83.
- 148 Maria G, Antonia D, Michael A, Kate M, Sian E, Sarah FE, et al. Sirolimus: efficacy and complications in children with hyperinsulinemic hypoglycemia: a 5-year follow-up study. *J Endocr Soc*. 2019 Apr 1;3(4): 699–713.
- 149 Vajravelu ME, Congdon M, Mitteer L, Koh J, Givler S, Shults J, et al. Continuous intragastric dextrose: a therapeutic option for refractory hypoglycemia in congenital hyperinsulinism. *Horm Res Paediatr*. 2019; 91(1):62–8.
- 150 Truong L, Reynolds C, O'Bryan K, Walkley E, Pyke L, Thornton P. Powdered maltodextrin is more cost effective than IV D20% solutions in the treatment of congenital hyperinsulinism. Pediatric Endocrine Society Annual Meeting. Forth Worth, TX; 2020.
- 151 Banerjee I, Forsythe L, Skae M, Avatapalle HB, Rigby L, Bowden LE, et al. Feeding problems are persistent in children with severe congenital hyperinsulinism. *Front Endocrinol*. 2016;7:8.
- 152 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 Mar;39(3):270–5.
- 153 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 Oct;28(10):1326–35.
- 154 Kanamori Y, Watanabe T, Yorifuji T, Masue M, Sasaki H, Nio M. Congenital hyperinsulinism treated by surgical resection of the hyperplastic lesion which had been preoperatively diagnosed by 18F-DOPA PET examination in Japan: a nationwide survey. *Pediatr Surg Int*. 2018 Oct;34(10):1093–8.
- 155 Yorifuji T, Horikawa R, Hasegawa T, Adachi M, Soneda S, Minagawa M, et al. Clinical practice guidelines for congenital hyperinsulinism. *Clin Pediatr Endocrinol*. 2017; 26(3):127–52.
- 156 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 Jan; 47(1):130–5.
- 157 Bhatti TR, Ruchelli ED. Histopathology of the pancreas in congenital hyperinsulinism. In: De Leon-Crutchlow DD, Stanley CA, editors. *Congenital Hyperinsulinism: a practical guide to diagnosis and management*. Switzerland: Springer; 2019. p. 95–104.

- 158 Lord K, Duran M, Rintoul N. Perioperative management of hyperinsulinism. In: De Leon-Crutchlow DD, Stanley CA, editors. [Congenital Hyperinsulinism: a practical guide to diagnosis and management](#). Switzerland: Springer; 2019. p. 113–8.
- 159 Thornton PS, Stanley CA. Approach to the diagnosis of neonates and infants with persistent hypoglycemia. In: De Leon-Crutchlow, Stanley E, editors. [Congenital hyperinsulinism: a practical guide to diagnosis and management](#). Contemporary Endocrinology. Switzerland: Springer Nature Switzerland AG; 2019. p. 1–13.
- 160 Ackermann AM, De Leon-Crutchlow DD. Management of the child with persistent hypoglycemia after surgery. In: De Leon-Crutchlow DD, Stanley CA, editors. [Congenital Hyperinsulinism: a practical guide to the diagnosis and management](#). Switzerland: Springer; 2019. p. 119–30.
- 161 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 Feb;35(2): 198–203.
- 162 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(5):e98054.
- 163 Lord K, Radcliffe J, Gallagher PR, Adzick NS, Stanley CA, De Leon DD. High risk of diabetes and neurobehavioral deficits in individuals with surgically treated hyperinsulinism. *J Clin Endocrinol Metab*. 2015 Nov;100(11):4133–9.
- 164 Ludwig A, Enke S, Heindorf J, Empting S, Meissner T, Mohnike K. Formal neurocognitive testing in 60 patients with congenital hyperinsulinism. *Horm Res Paediatr*. 2018;89(1):1–6.
- 165 Perbtani Y, Forsmark CE. Update on the diagnosis and management of exocrine pancreatic insufficiency. *Res*. 2019 Nov 26;8:F1000.
- 166 Brownwell JN, McKnight-Menci H, Maqbool A, Thornton PS. Management of diabetes and pancreatic insufficiency after pancreatectomy. In: De Leon-Crutchlow DD, Stanley CA, editors. [Congenital Hyperinsulinism: a practical guide to the diagnosis and management](#). Switzerland: Springer; 2019. p. 131–41.
- 167 Raskin J, Pasquini TLS, Bose S, Tallis D, Schmitt J. Congenital hyperinsulinism international: a community focused on improving the lives of people living with congenital hyperinsulinism. *Front Endocrinol*. 2022;13:886552.
- 168 Flanagan SE, Boodhansingh KE, Lalonde E, Ganguly A. Molecular diagnosis of congenital hyperinsulinism. In: De Leon-Crutchlow DD, Stanley CA, editors. [Congenital Hyperinsulinism: a practical guide to the diagnosis and management](#). Switzerland: Springer; 2019. p. 61–9.
- 169 Sun L, Coy DH. Somatostatin and its analogs. *Curr Drug Targets*. 2016;17(5):529–37.
- 170 Meissner T, Wendel U, Burgard P, Schaetzle S, Mayatepek E. Long-term follow-up of 114 patients with congenital hyperinsulinism. *Eur J Endocrinol*. 2003 Jul;149(1):43–51.
- 171 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 Apr;168(4):557–64.
- 172 Salomon-Estebanez M, Flanagan SE, Ellard S, Rigby L, Bowden L, Mohamed Z, et al. Conservatively treated Congenital Hyperinsulinism (CHI) due to K-ATP channel gene mutations: reducing severity over time. *Orphanet J Rare Dis*. 2016 Dec 1;11(1):163.
- 173 Welters A, Meissner T, Grulich-Henn J, Frohlich-Reiterer E, Warncke K, Mohnike K, et al. Characterization of diabetes following pancreatic surgery in patients with congenital hyperinsulinism. *Orphanet J Rare Dis*. 2018 Dec 22;13(1):230.
- 174 Kumaran A, Kar S, Kapoor RR, Hussain K. The clinical problem of hyperinsulinemic hypoglycemia and resultant infantile spasms. *Pediatrics*. 2010 Nov;126(5):e1231–6.
- 175 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 Oct 3;6:63.
- 176 Menni F, de Lonlay P, Sevin C, Touati G, Peigne C, Barbier V, et al. Neurologic outcomes of 90 neonates and infants with persistent hyperinsulinemic hypoglycemia. *Pediatrics*. 2001 Mar;107(3):476–9.
- 177 Avatapalle HB, Banerjee I, Shah S, Pryce M, Nicholson J, Rigby L, et al. Abnormal neurodevelopmental outcomes are common in children with transient congenital hyperinsulinism. *Front Endocrinol*. 2013;4:60.
- 178 Muukkonen L, Mannisto J, Jaaskelainen J, Hannonen R, Huopio H. The effect of hypoglycaemia on neurocognitive outcome in children and adolescents with transient or persistent congenital hyperinsulinism. *Dev Med Child Neurol*. 2019 Apr;61(4):451–7.