Values are general rules of thumb, there can be exceptions/imperfect adherence to rules.....

Hypoglycemia in infants, children, teens

Created by Dr. Lane

"Critical labs" (in order of priority)
1.) Stat chem-8
2.) Cortisol
3.) serum ketones
4.) insulin
5.) Free Fatty acids
6.) lactate
7.) C-peptide

acidemia (bicarb < 15 - 17 mEq/L)

Hi Lactate

*** Glycogen Storage Dz 1a & b**
- *Glucose-6 phosphatase deficiency*
- *hypoglycemia in infants & young child can be as short as 1-2 hrs after meal, mimicking POST-prandial hypoglycemia*
- *hepatomegaly*
- *Unlike other GSDs, hypoglycemia in GSD I is characterized by hypoketosis due to inhibition of FAO by malonic acid [UpToDate]*
- *uric acid high (uric nrl. In GSD 0,3,6,9)*
- *short stature*
- *genetics preferred as confirmatory test for all GSDs*
- *G6P shunts down glycolytic pathway --> lactic acid. Untreated may be between 5 to 10 mmol/L*

*** Gluconeogenesis disorder**

Fruct 1,6 Bisphosphatase def
- *mild hypogly, severe lactic acidosis*
- *moderate hepatomegaly*

Pyruvate carboxylase def(PC gene)
- *FTT, devel delay, recurrent sz*
- *Hi lactate:pyruvate ratio (>25)*
- *low B-OHB: acetoacetate ratio (<0.8)*
- *fasting and/or POSTprandial hypogly*

PEPCK def
- *super rare*

*** Mitochondrial disorder**
- *CPK & ammonia may be high*
- *Ketones AND lactate could be high*

*** Pyruvate dehydrogenase def**
- *mild hypogly, severe lactic acidosis*

*** HMG CoA lyase def**
- *hepatomegaly*

*** EtOH**

Hi Ketones/β-OHB

*** Glycogen Storage Disease 0**
- *low pre-alb*
- *POSTprand hyperglyc & hyperlactate*
- *may present as asympt glucosuria*

*** Glycogen Storage Disease 3**
- *hepatomegaly*
- *transaminitis can mimic viral hepatitis*
- *incr. CK but usu not weak as children*
- *hypogly mild but ketosis prominent*
- *can have HOCM*

*** Glycogen Storage Disease 6**
- *hepatomegaly*
- *low prealb*
- *short stature*

*** Glycogen Storage Disease 9**
- *most common of all GSDs*
- *hepatomegaly*
- *ketotic hypogly or ketotic NORMOgly*
- *short stature*
- *rarely motor, speech, cognitive delays*

*** Ketone Utilization defect**

SCOT

B-Ketothiolase

*** Cortisol deficiency**

*** GH deficiency**

*** Organic acidemias**

*** "Ketotic Hypoglycemia"**

no acidemia (bicarb > 16 to 18)

Lo Ketones/β-OHB High FFA

*** Fatty Acid Oxidation**
- *Abnrl U organic acid pattern*

Lo Ketones/β-OHB Lo FFA

Hyperinsulinism
- Newbrn transitional hyperins
- SGA
- IDM
- Stress hyperinsulinism
- Congenital hyperinsulinism
  (ammonia may help for GLUD1)
- Insulinoma
- "Noninsulinoma pancreatogenous"
- Insulin autoimmune hypoglycemia (Ab to insulin or insulin-R), T1DM?
- Sulfonylurea/meglit. ins release
- Munchausen insulin injections
- **exercise induced** (GOF SLC16A1/MCT1) shuttles pyruvate
- **LOF KCNE1/Kv7.1** long QT, POSTprand hypogly
- **?LOF KCNQ1** (heterotetramer w/Kv7.1)

…opituitarism (rarely)

Insulin uU/mL	C-Peptide nmol/L	Ins/C-pep ratio (on molar basis)	Proinsulin pmol/L	
>> 3	<0.2	>1	< 5	= Exogenous
≥ 3	≥ 0.2		≥ 5	= Endogenous

Hypoglycemic disorders of Amino Acid metabolism/ Organic acidemias

all have poor growth, hepatomegaly, delayed devel, vomiting

Methylmalonic acidemia
- *incr. ammonia, incr. glycine on plasma AAs*
- *abnr. Urine amino acids*

3-Hydroxy 3-Methyl Glutaric Acidemia
- *HYPOketotic hypoglycemia*

Hereditray tyrosinemia
- *diarrhea*
- *cabbage smell*

Ethylmalonic Adipicaciduria
- nnn

Glutaric aciduria type 2
- sweaty feet smell

Maple syrup urine disease
- *rapid neurological deterioration if untreated*

Other:

Herditary fructose intol (LOF aldolase B)
- POSTprandial hypoglycemia
- hepatomegaly, recessive
- urinary reducing substances positive

Galactosemia
- urinary reducing substances positive

Ethanol

Drugs (hi dose methadone, etc)

Post-Gastric Bypass & Dumping syndrome

Diagram adapted by Andrew Lane MD from original published by Charles Stanley, MD

Hyperinsulinism in Infants

Box 1
Causes of hyperinsulinism

Congenital
- K_{ATP}-HI (*ABCC8, KCNJ11*) ← may present as LGA
- GDH-HI (*GLUD1*)
- GCK-HI (*GCK*)
- HNF4α-HI (*HNF4A*)
- HNF1α-HI (*HNF1A*)
- SCHAD-HI (*HADH*)
- UCP2-HI (*UCP2*)
- Exercise-induced HI (*SLC16A1*)
- Phosphoglucomutase 1 deficiency (*PGM1*)

Perinatal stress
- Intrauterine growth rest
- Birth asphyxia
- Maternal preeclampsia/e
- Congenital heart disease
- Meconium aspiration syr
- Prematurity

Syndromic
- Beckwith-Wiedemann
- Turner
- Soto
- Kabuki

* Resolves within first 3-6 mo of life
* Some are unresponsive to diazoxide, especially if HIE with liver dysfunction
* "Based on the information regarding the risks of diazoxide and the fact that the majority of PSHI cases settle spontaneously, we suggest waiting to start diazoxide for 7 to 10 days in infants suspected to have PSHI, provided their glucose levels can safely be maintained > 70mg/dL with intravenous fluids in addition to feeds and as long as the glucose infusion rate required to do so is falling (GRADE 2+) (3)."

Thorton et al: "A plasma glucose concentration of 50 mg/dL is sufficiently low to elicit the metabolic and neuroendocrine responses required for diagnosis "
Lord & De Leon: "To minimize false positive results, the plasma glucose threshold for obtaining a critical sample is less than 50 mg/dL."

Box 3
Diagnostic criteria

When plasma glucose less than 50 mg/dL
- Low β-hydroxybutyrate (<1.8 mmol/L)
- Low free fatty acids (<1.7 mmol)
- Plus/minus detectable insulin/C-peptide
- Positive glycemic response to glucagon (30-point rise in glucose)

Exclude neonatal panhypopituitarism:
- Cortisol greater than 10 μg/dL Lord & De Leon, no reference cited for using cutoff of 10 mg/dL
- Growth hormone greater than 7 ng/mL

Immed after plasma glucose/ insulin/ B-OHB/ FFA drawn, give glucagon 1 mg IV then get glucometer glucose every 10 min x 40 min

HI established

* Start Diazoxide (5-15 mg/kg/day)
* Keep fluids <150 cc/kg/day
* PLUS hydrochlorothiazide 1-2 mg/kg/day divide q12 hr
* Baseline cardiol consult, ECHO in 1 wk even in infant w/ no pulmonary hypertension
* Baseline CBC, uric acid, Monitor for neutropenia (15%),thrombopenia, hyperuricemia at 5-7 days and q 3-6 months thereafter

HI not established

* Hormone replacement if hypopit?
* Comprehensive hypoglycemia gene panel?

Diazoxide unresponsive
(= After 5 days on max dosing still requires dextrose, or BG <70 during 12 hr safety fast)

Stop diazoxide and send expedited tests for ABCC8 and KCNJ11, including parent-of-origin testing

Diazoxide responsive

* Likely diagnoses: GDH, GCK, SCHAD, HNF4A, dom KATP
* Consider test for Kabuki, Turner, Glycosyl, BWS, etc.
* Continue diazoxide
* To determine if can stop: reduce dose q 2-4 wks if BG >70, when off monitor for hypoglycemia for 5 days and perform 15-18 hr safety fast to prove resolution of HI

Positive

if Paternally inherited ABCC8/KCNJ11 mutation

Focal HI

* Usually unresponsive to diazoxide
* Needs 18F-DOPA PET
* Surgery curative
* paternal monoallelic recessive mutations plus a somatic loss of maternal 11p15 region causative

If:

* GCK mutation
* Biallelic recessive in ABCC8 or Biallelic recessive in KCNJ11
* Syndromic ex. Beckwith-Weidman, Kabuki, Soto, etc

Diffuse HI

* Does not benefit from imaging
* Most responsive to diazoxide but some remain unresponsive
* continuous feeds, may require partial pancreotectomy if fails medical therapy
* Octreotide (assoc. w/ fatal NEC) may consider AFTER first 6-8 wks of neonatal period

Negative

Needs 18F-DOPA PET bc still could be focal HI.

Paternally inherited monoallelic recessive mutations in combination with a somatic loss of maternal 11p15 region cause focal HI, which can be cured by surgery

Algorithm by Andrew Lane, from: Hyperinsulinism in the Neonate. Lord and De León, Clinics in Perinatology, 2018-03-01, Vol 45, Issue 1, pp 61-74, and Sperling 4th edition Chapter 6, and Management and Appropriate Use of Diazoxide in Infants with Hyperinsulinism. Cheema Brar P, et. al, JCEM, 2020, Vol. 105, No. 12, 1–12, and Thornton PS et al, Recommendations from Ped Endo Society for eval and manage of persistent hypoglycemia in neonates, infants, and children. J. Pediatrics 2015

Hyperinsulinism in Infants

Transient Hyperinsulinism

(IDM, IUGR, Maternal toxemia, Birth asphyxia, perinatal stress)

"Based on the information regarding the risks of diazoxide and the fact that the majority of PSHI cases settle spontaneously, we suggest waiting to start diazoxide for 7 to 10 days in infants suspected to have PSHI, provided their glucose levels can safely be maintained > 70mg/dL with intravenous fluids in addition to feeds and as long as the glucose infusion rate required to do so is falling (GRADE 2+) (3)."

Persistent Hyperinsulinism

Diffuse

(usually responsive to diazoxide except activating mutations in glucokinase)

Often monogenic ex. SUR, Kir6.2, etc. or syndromic ex. Beckwith-Weidman, Kabuki, Soto, etc.

Focal

(usually unresponsive to diazoxide)

paternally inherited monoallelic recessive mutations in combination with a somatic loss of maternal 11p15 region cause focal HI, which can be cured by surgery.

Imaging and surgery

<u>Prior to starting diazoxide:</u>

* get cardiology consult and baseline ECHO
* Get baseline CBC/diff (neutropenia in 15%, thrombocytopenia)
* Get baselinr uric acid (hyperuricemia)

<u>Starting diazoxide:</u>

* Dosing is 5-15 mg/kg/day divided q 8 hours, available as 50mg/mL oral solution
* If transient HI start with lower doses, esp if cardiopulmonary risk factors
* When diazoxide started also start hydrochlorothiazide (to reduce risk of pulmonary hypertension) 1-2 mg/kg/day divide q12 hr
* Keep fluids <150 cc/kg/day

<u>After starting:</u>

* consider ECHO in 1 week even in infant with no pulmonary hypertension
* Monitor for neutropenia, hyperuricemia at 5-7 days and q 3-6 months thereafter

<u>If BGs improve:</u>

* Reduce dose every 2-4 weeks if BG >70
* Once off monitor for hypoglycemia for at least 5 days and perform safety fast of 15-18 hours to prove resolution of HI

Adapted from: Management and Appropriate Use of Diazoxide in Infants with Hyperinsulinism. Cheema Brar P, et. al, The Journal of Clinical Endocrinology & Metabolism, 2020, Vol. 105, No. 12, 1–12

Uncommon causes of hypoglycemia in adults (and kids)

Fasting

Sulfonylurea ingestion ***(see Klein-Schwartz W. et. al. Br. J. Clin Pharm. 2015)***

- a single tablet in young kids can cause significant hypoglycemia
- kids: onset usually within 8 hrs, rarely delayed 11-45 hrs. Recurrence up to 30-70 hrs reported. Adults: onset usually rapid
- hypoglycemia may be recurrent and persist for up to 8 days

FAO defects

- myopathy, neuropathy, blindness

Fructose-1,6-bisphosphatase deficiency

-lactic acidosis and elevated LFTs

"Big IGF2"

-paraneoplastic

-IGF2/IGF1 ratio >10 (nrl<3)

Anti-insulin receptor antibodies

- often acanthosis and elevated insulin

Post-prandial

GOF in glucokinase

- 7% of congenital hyperinsulinism
- can be fasting or more commonly post-prandial
- consider when in pt seemingly insulinoma but imaging is negative
- aut dom, so often hx in relatives
- hypoglycemia BG usually in 35-55 mg/dL range even on fasting tests

Insulin receptor mutations

- can be diagnosed in adulthood in a heterozygous state
- often late postprandial hypoglycemia, 3 hr post OGTT
- homozygous infant w/ Rabson–Mendenhall --> pauci-symptomatic heterozygosity in parents

Hereditary glucose intolerance

- late post-prandial hypoglycemia
- LFTs elevated

Anti-insulin antibodies

- if in non-diabetic called Hirata syndrome, and is often associated with Graves
- predominantly post-prandial hypoglycemia

[Glycogen Storage Dz 1a & b] hypoglycemia in infants & young children can be as short as 1-2 hours after meal, so can mimic post-prandial hypoglycemia

Defects in Ketone Utilization

Beta-ketothiolase deficiency

* Autosomal recessive
* As of 2020, extremely rare, only 50 to 60 reported individuals worldwide
* LOF mutation in *ACAT1*, which processes isoleucine and processes ketones
* Typical onset age 6 – 24 months
* Fasting or illness or stress --> ketone buildup in CNS --> emesis, fatigue, sz, depressed breathing

Succinyl-CoA:3-oxoacid CoA transferase(SCOT) deficiency

* LOF in *OXCT1* gene that catalyzes transfer of coenzymeA from succinyl-coA to acetoacetate
* 30 people described worldwide
* Mild SCOT deficiency may not have have persistent ketonemia and ketonuria

Monocarboxylate Transporter 1 deficiency

* LOF in *SLC16A1*
* GOF/overexpression: exercise-induced hyperinsulinemia