Current Medical Treatment Options

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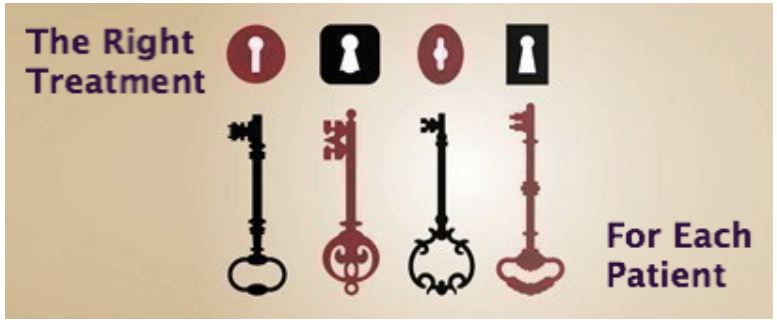
Goals of therapy in hyperinsulinism

- **Immediate:**
  - To promptly restore plasma glucose to normal range (>70 mg/dL)
- **Mid-term:**
  - To identify optimal treatment regimens according to type of hyperinsulinism
  - To maintain normal plasma glucose concentrations while encouraging normal feeding/diet
- **Long-term:**
  - To prevent brain damage
  - To promote normal life and development

Precision Medicine

- **Individualized treatment plan:**
  - According to genotype (genetic testing results)
  - According to the phenotype (clinical manifestations)
- **Requires:**
  - Comprehensive investigations to understand all aspects of the condition
  - Different treatment options – one treatment modality may “not fit all”
- **Is it possible for HI?**
  - Yes – for focal HI
  - Sort of – for non-focal HI



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Diazoxide

- First-line of therapy for hyperinsulinism
- Dose:
  - 5-15 mg/kg/day by mouth divided bid
  - Only suspension available in US – capsules in other countries
- Types of HI:
  - Perinatal stress-induced HI, HIHA, HNF1A, HNF4A, dominant K_{ATP}, genetic negative, some GCK HI
- Side effects:
  - Edema (18%)
  - Pulmonary hypertension (2.1%-4.8%)
  - Hypertrichosis (52%)
  - Neutropenia (15.6%)
  - Thrombocytopenia (4.7%)
  - Hyperuricemia (5%)

Herrerra, et al. *J Clin Endocrinol Metab*, 2018
Thornton, et al. Horm Res Paediatr, 2019
Welters A, et al. *Orphanet J Rare Dis*, 2015; 10:150

Diazoxide

- Screening for side effects:
  - Echocardiogram:
    - ~ 1 week after initiation
  - Laboratory studies:
    - Blood counts, chemistry, uric acid

Herrerra, et al. *J Clin Endocrinol Metab*, 2018

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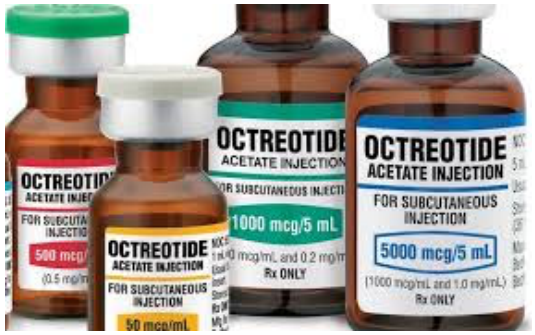
Octreotide



- Dosing: 10-20 mcg/kg/day by subcutaneous injection
  - ✓ Every 6 hrs
  - ✓ Given 2 times a day in combination with continuous intragastric dextrose or continuous enteral feedings
  - ✓ Continuous subcutaneous administration through an insulin pump
- Effectiveness:
  - ✓ Tachyphylaxis common
- Side effects:
  - ✓ Suppression of growth and thyroid function
  - ✓ GI side effects
  - ✓ Gall bladder pathology (32%*)
  - ✓ Transient elevation of LFTs (46.4%*)
  - ✓ Thrombosis (2%***)
  - ✓ Necrotizing enterocolitis (1%***)

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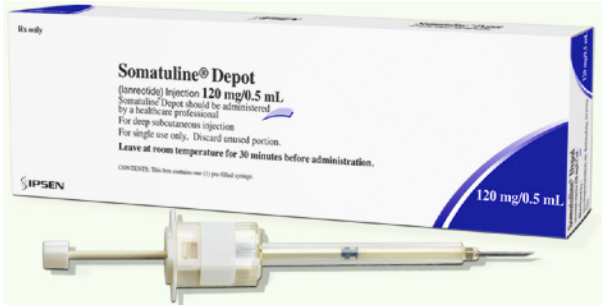
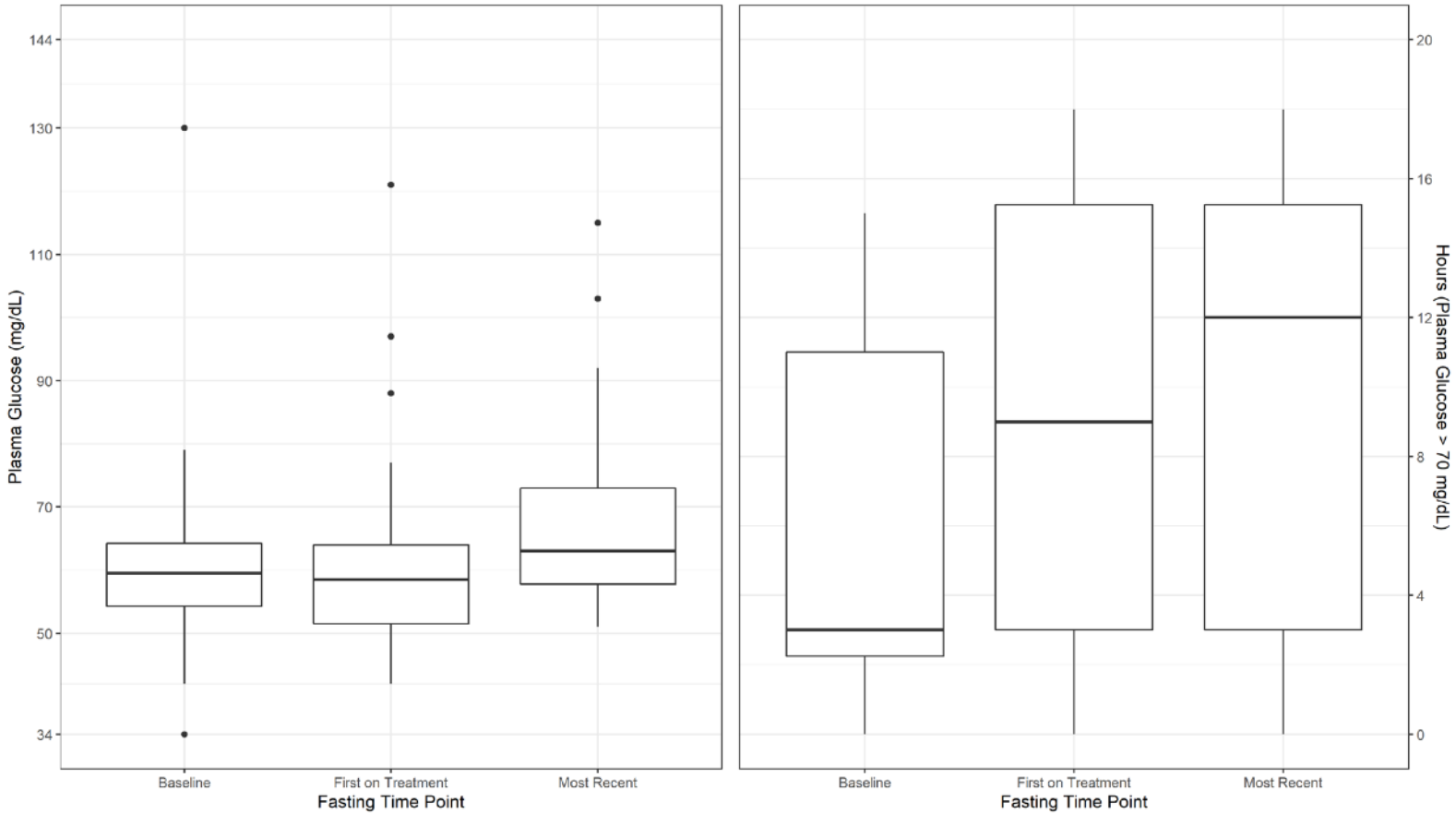
*Welters A, et al. *Orphanet J Rare Dis*, 2015; 10:150 (n=111); **Demirbilek, et al. *J Clin Endocrinol Metab*, 2014 (n=28); ***McMahon, et al. *Pharmacoepidemiol Drug Saf*, 2017 (n=103)

Use of *lanreotide* in the treatment of HI



- Lanreotide
  - Somatostatin analogue
  - Deep subcutaneous injection every 28 days
  - Dose: 30-90 mg
- Our experience:
  - 54 children and adults with HI
  - Median age: 4.6 years (1.5-28.5)
  - Genetics: 63% K_{ATP}HI
  - Response: 42% able to discontinue other treatments and managed on lanreotide alone
  - Side effects: subcutaneous nodules (26%), gallstones (11%)



Cuff, Lord, Stewart, De Leon. *J Clin Endocrinol Metab*, 2022

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Somatostatin Analogues

- Screening for side effects:
  - Growth and weight gain
    - Every 6 months
  - Gallbladder ultrasound:
    - Every 6 months
  - Laboratory studies:
    - Every 6 months
    - Liver function tests, growth factors, thyroid function tests, fat-soluble vitamin levels

Herrerra, et al. *J Clin Endocrinol Metab*, 2018
Welters A, et al. *Orphanet J Rare Dis*, 2015; 10:150
Demirbilek, et al. J Clin Endocrinol Metab, 2014
McMahon, et al. *Pharmacoepidemiol Drug Saf,* 2017
Adzick, *J Ped Surg*, 2019

Continuous Intragastric Dextrose

- Dosing:
  - ✓D10-20%
  - ✓Not more than 10 mg/kg/min
  - ✓Continuously by gastrostomy
- Side effects:
  - ✓Vomiting 33%
  - ✓Diarrhea 4.8%
  - ✓Tube/pump malfunction 57%

Table 3. Cohort characteristics by month of dextrose exposure

	Approximate month of follow-up		
	0	6	12
Growth evaluation			
Subjects, *n*	29	26	23
Mean weight Z-score (SD)	+0.48 (1.71)	+0.78 (1.43)	+0.96 (1.53)
Mean length Z-score (SD)	−0.36 (1.62)	−0.10 (1.23)	−0.08 (1.28)
Mean WFL-Z (SD)	+1.14 (1.53)	+1.13 (1.50)	+1.30 (1.40)
Mean BMI-Z (SD)	+0.96 (1.66)	+1.12 (1.50)	+1.35 (1.31)
Overweight by WFL-Z > +1.04 (95% CI)	48% (30–67%)	65% (44–82%)	52% (31–73%)
Overweight by BMI-Z > +1.04 (95% CI)	48% (30–67%)	65% (44–82%)	52% (31–73%)
Secondary outcomes			
Subjects, *n*	32	28	25
Enteral nutrition (95% CI)	72% (53–85%)	58% (39–75%)	39% (22–59%)
Feeding difficulties (95% CI)	31% (17–50%)	36% (20–55%)	36% (20–56%)

WFL-Z, weight-for-length Z-score; BMI-Z, body mass index Z-score.

Vajravelu, et al. *Horm Res Paediatr*, 2018

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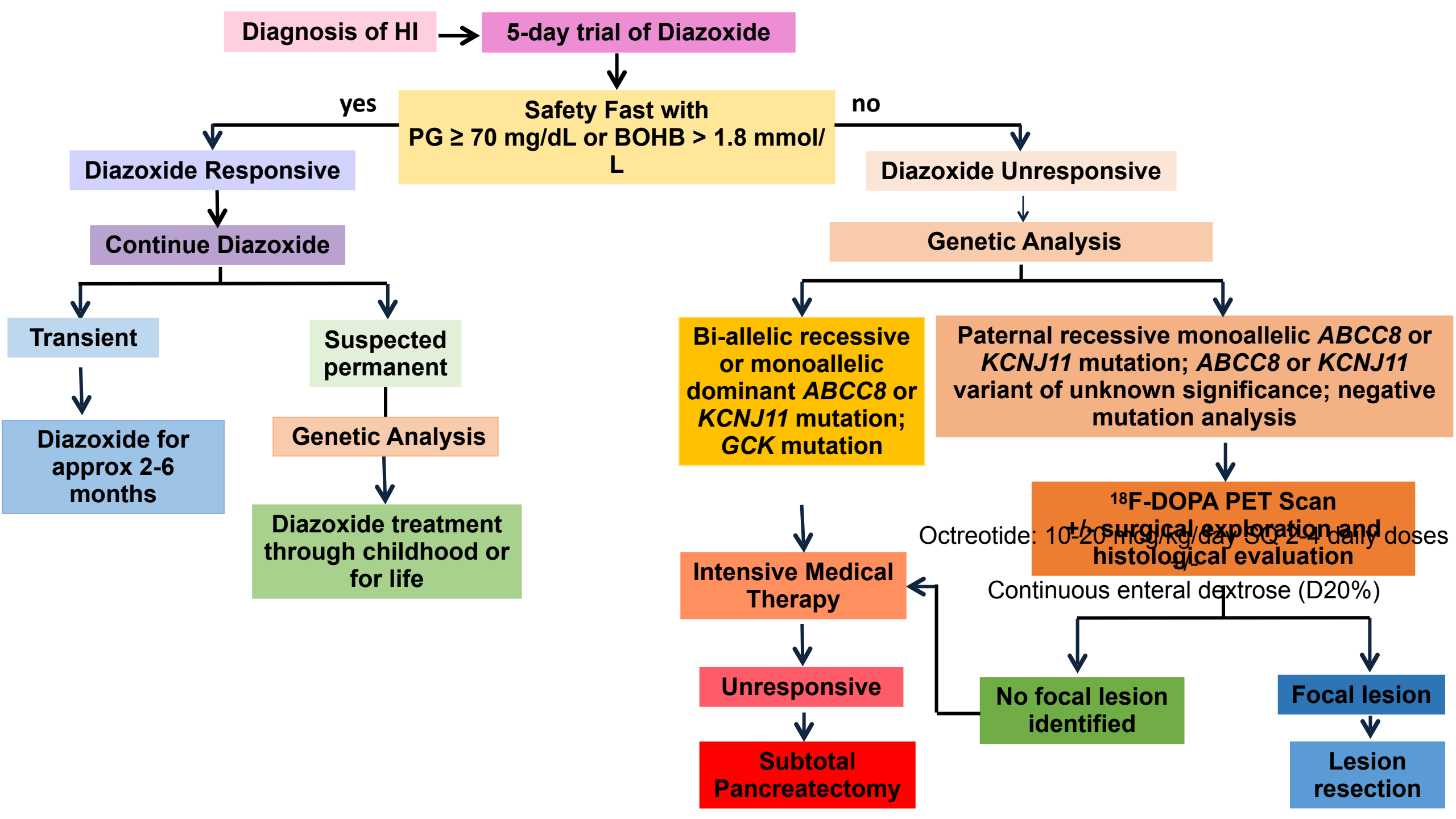
How do we determine treatment responsiveness?

- Fasting test:
  - Duration depending on the age of the child:
    - 12-18 hrs
  - Monitor:
    - Glucose and ketone levels
  - Effectiveness:
    - Able to fast with plasma glucoses > 70 mg/dL
    - Ketones increase as glucose decreases 50-60 mg/dL

Importance of determining treatment *responsiveness*

- For phenotypic characterization:
  - Identification of infants that need additional evaluation for the possibility of focal disease

- For adequate glycemic control:
  - Goal is to maintain euglycemia while receiving an age-appropriate feeding regimen, allowing for periods of fasting at night


Diagnosis of HI
5-day trial of Diazoxide
Safety Fast with
PG ≥ 70 mg/dL or BOHB > 1.8 mmol/L
yes
no
Diazoxide Responsive
Continue Diazoxide
Transient
Diazoxide for approx 2-6 months
Suspected permanent
Genetic Analysis
Diazoxide treatment through childhood or for life
Diazoxide Unresponsive
Genetic Analysis
Bi-allelic recessive or monoallelic dominant ABCC8 or KCNJ11 mutation; GCK mutation
Paternal recessive monoallelic ABCC8 or KCNJ11 mutation; ABCC8 or KCNJ11 variant of unknown significance; negative mutation analysis
18F-DOPA PET Scan
+/- surgical exploration and histological evaluation
Octreotide: 10-20 mcg/kg/day SQ 2-4 daily doses
Continuous enteral dextrose (D20%)
Intensive Medical Therapy
Unresponsive
Subtotal Pancreatectomy
No focal lesion identified
Focal lesion
Lesion resection

Follow-up

- Ongoing monitoring
  - For side effects of therapy
  - Glycemic control:
    - ✓ Glucose meter vs. CGMS
    - ✓ Inpatient evaluations: safety fast
  - Growth and development
- Discontinuation of treatment
  - Depends on type of hyperinsulinism
  - Normal plasma glucoses on minimal treatment support
  - When resolution is suspected
    - ✓ Transient hyperinsulinism
    - ✓ Focal cases
  - Importance of demonstrating resolution
    - ✓ Fasting test

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Take home *points*

- The management of infants and children with hyperinsulinism requires a stepwise, comprehensive and multidisciplinary approach
  - Define genotype and phenotype (including diazoxide-responsiveness)
  - Determine best treatment path
  - Assessment of effectiveness of treatment
  - Close monitoring for side effects, complications, glycemic control




Thank you

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