Managing Congenital Hyperinsulinism in the Neonatal Period

Vall d'Hebron Hospital's Approach and Experience

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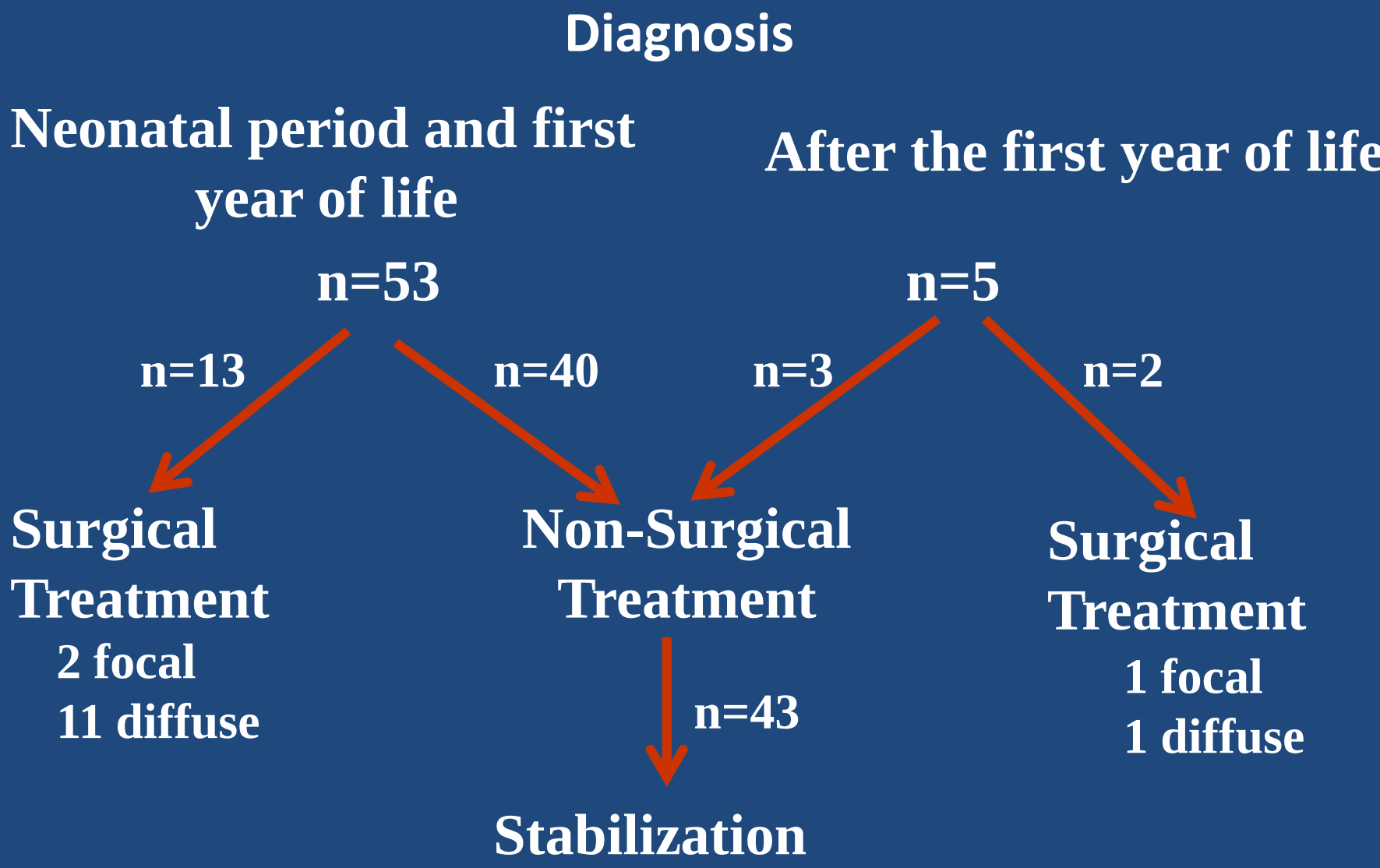
Vall d'Hebron Hospital's Approach and Experience

- The first approach to a neonate with hyperinsulinism is critical and challenging, it must be aimed towards the avoidance of neurological sequelae as much as possible.
- Heterogeneous condition
- Congenital Hyperinsulinism is the most severe cause of hypoglycemia

58 Patients with Persistent CHI



TREATMENT OBJECTIVES

- Maintaining a glycemia >60mg/dL as much as possible

- If Hypoglycemia develops, detecting and treating it as soon as possible.

- Avoid neurological damage.

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-GENERAL SUPPORT

- **Specialized Neonatal Unit**

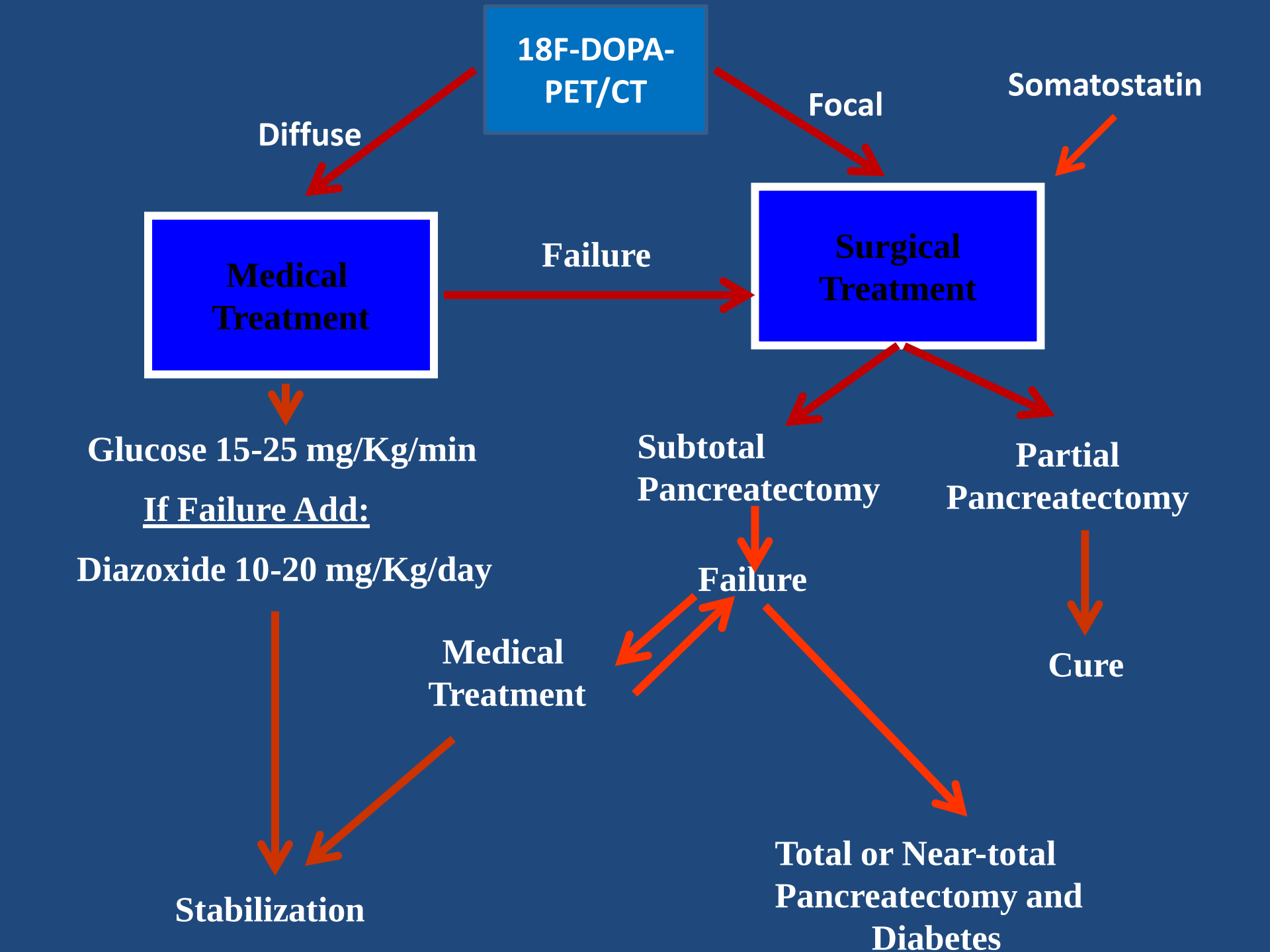
  Catheter care

  Treatment of comorbidities

  Continuous glucose monitoring

SPECIFIC TREATMENT

- **Carbohydrate supply**
- **Pharmacological treatment**
- **Surgery**


18F-DOPA-PET/CT
Diffuse
Focal
Somatostatin
Medical Treatment
Failure
Surgical Treatment
Glucose 15-25 mg/Kg/min
If Failure Add:
Diazoxide 10-20 mg/Kg/day
Subtotal Pancreatectomy
Partial Pancreatectomy
Failure
Medical Treatment
Cure
Stabilization
Total or Near-total Pancreatectomy and Diabetes

Carbohydrates, First Line of Treatment

- **Carbohydrate supply can go up to 25 mg/kg/min. It will rarely be below 15 mg/kg/min.**

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- **Intravenous at the beginning, but enteral as soon as possible.**

- **Low osmolarity soy based formula (135mOsm/L) allows to give up to 20% maltodextrin.**

- **Continuous enteral infusion which very slowly is divided into several feedings a day.**

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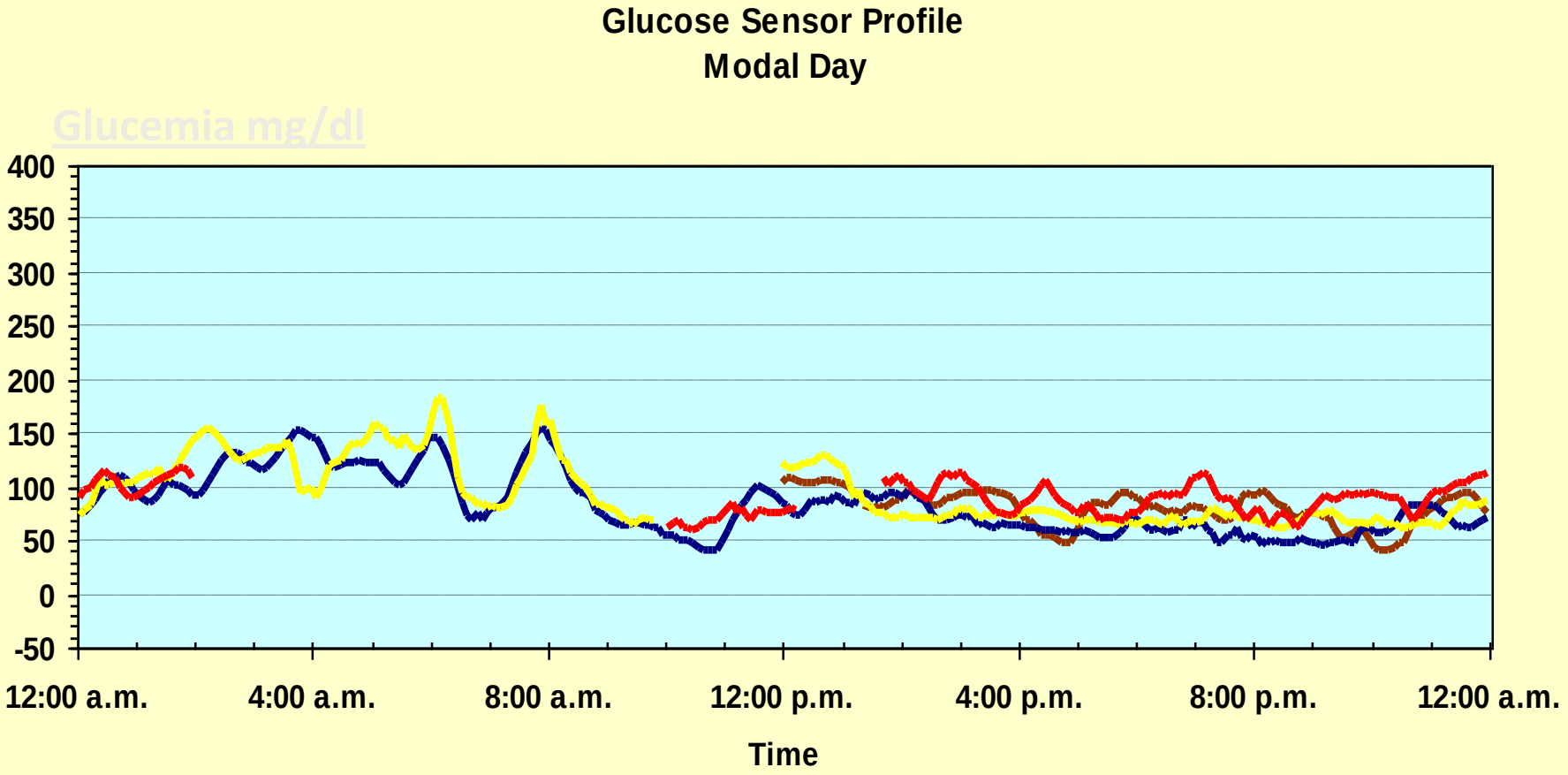
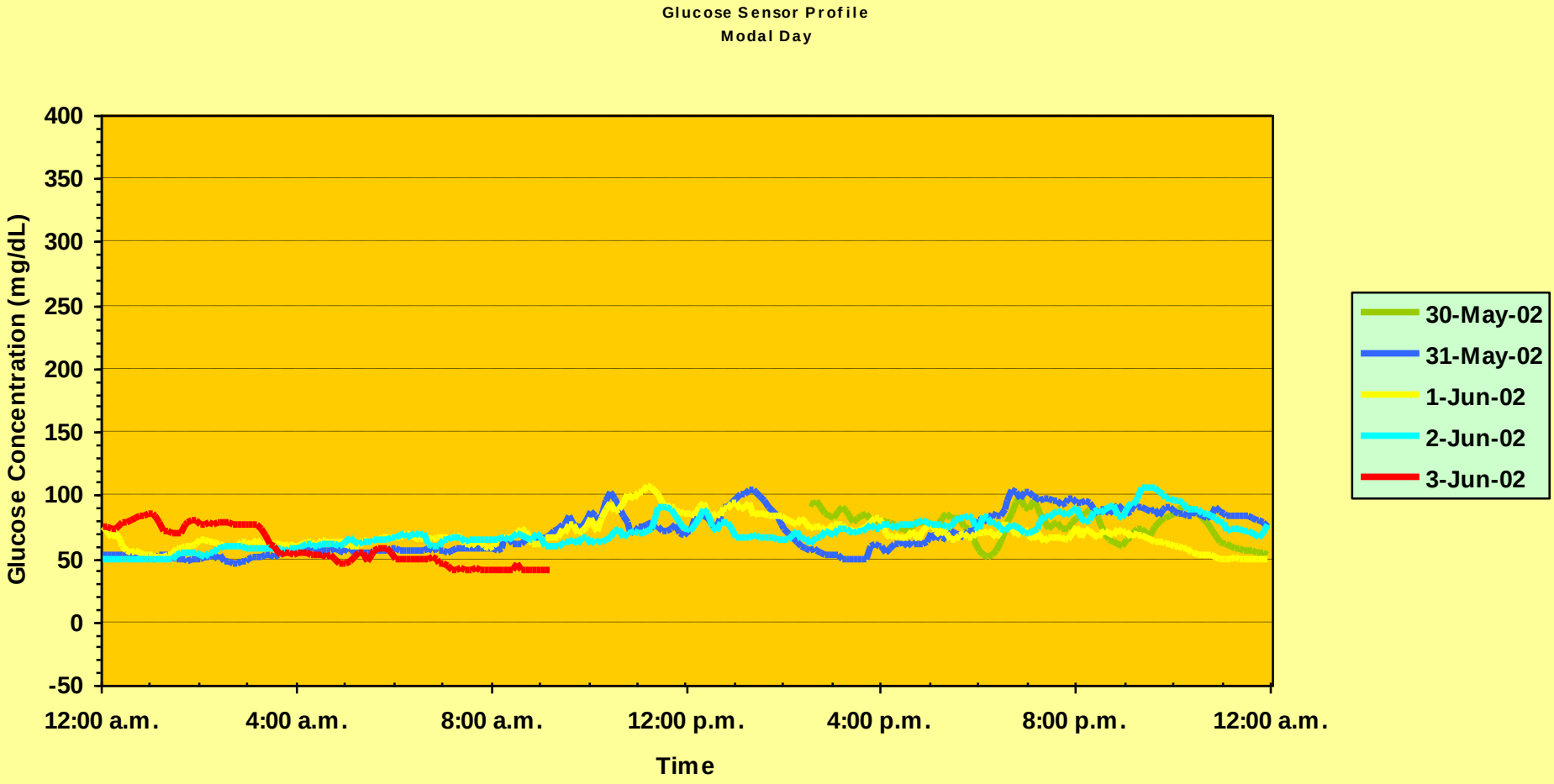
- **Continuous enteral infusion may be needed up to three months after birth.**

- **Continuous nighttime enteral feeding may be necessary for up to 6 years of age.**

INFANT WITH HYPERINSULINISM UNDER CONTINUOUS ENTERAL FEEDING



INSUFFICIENT CONTINUOUS ENTERAL FEEDING



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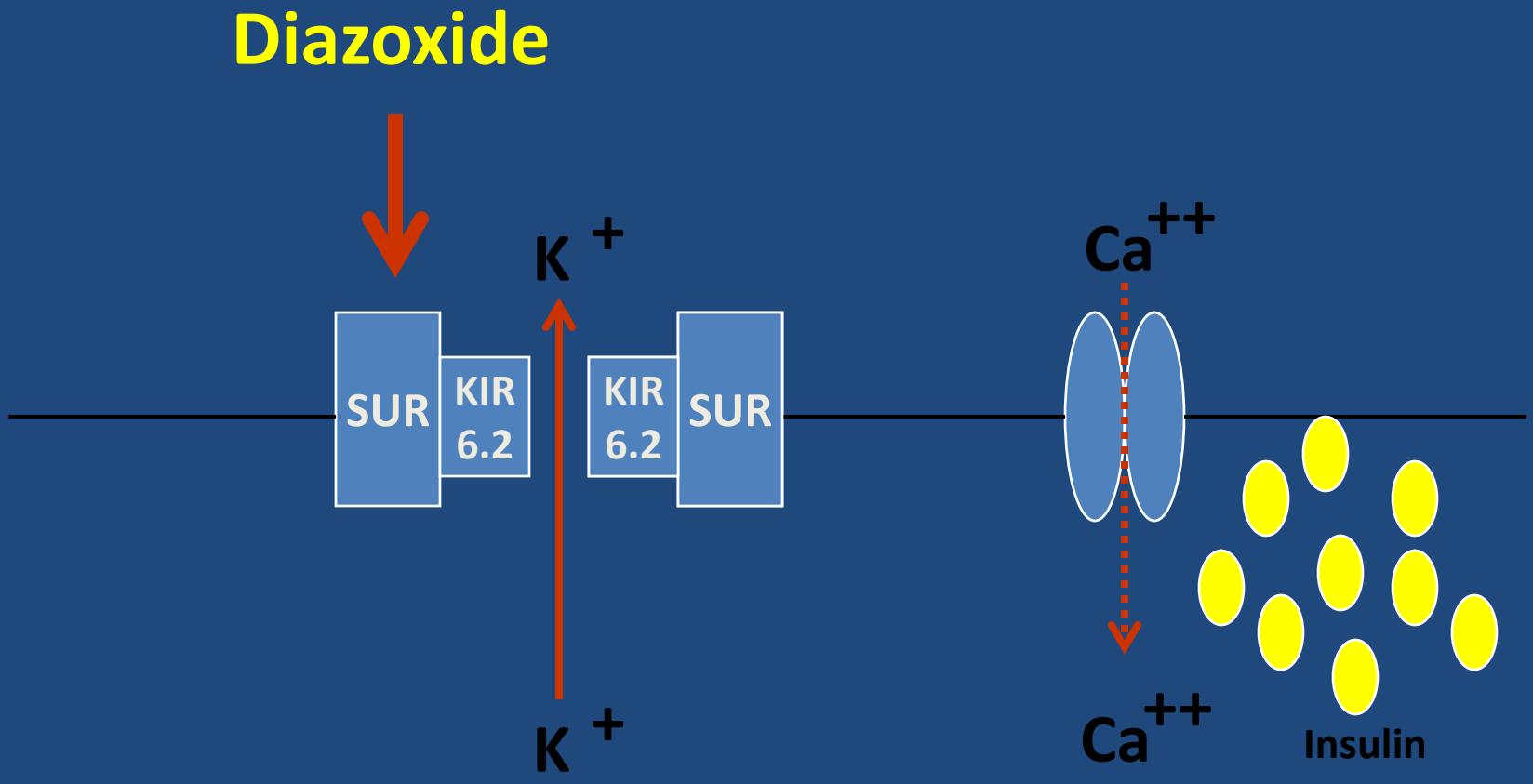
Pharmacological treatment

Diazoxide

Dose: 5 –15 mg/kg/day

If higher doses are needed → non-responder


Diazoxide
K +
SUR
KIR 6.2
KIR 6.2
SUR
K +
Ca++
Ca++
Insulin

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Diazoxide

- Usually ineffective for the most severe, neonatal onset forms (recessive diffuse and the focal forms affecting The KATP channel)

- Dominant KATP channel CHI quite often responds to diazoxide though some unresponsive cases have been published.

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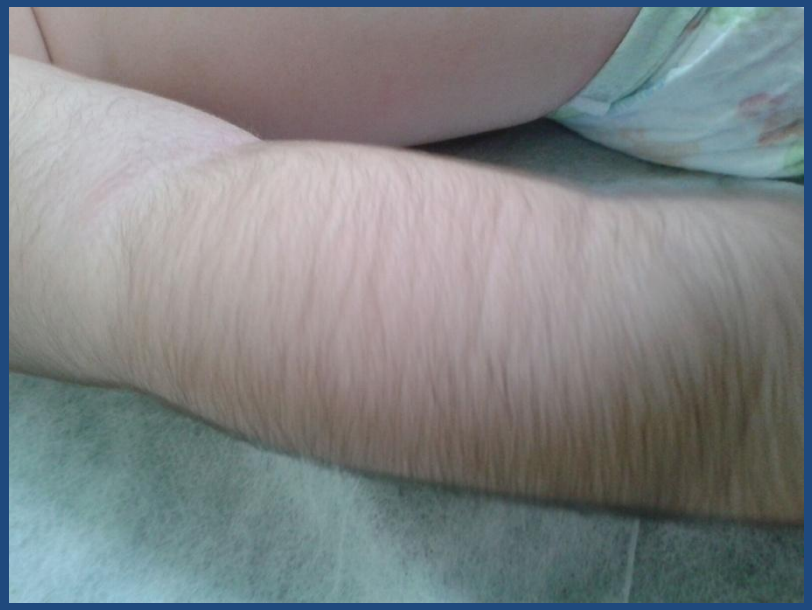
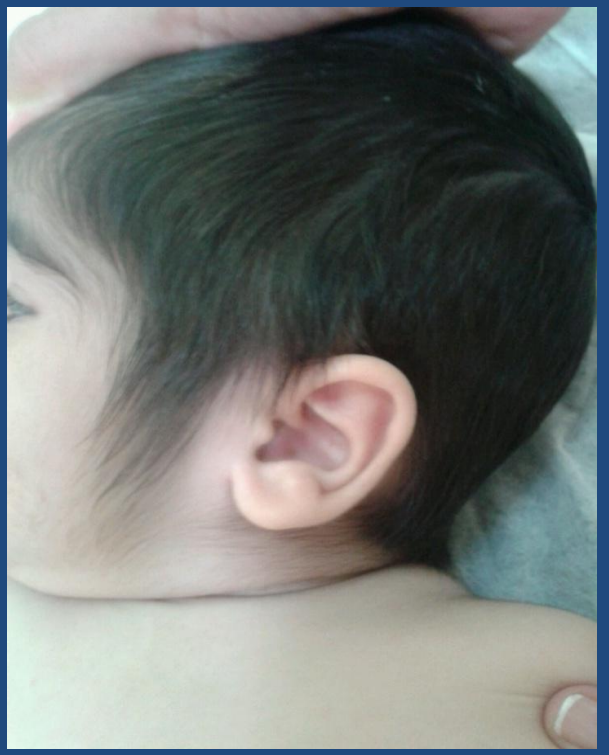
Diazoxide

- ADVERSE EVENTS:
  - Hypertrichosis : Completely reversible when the drug is stopped.





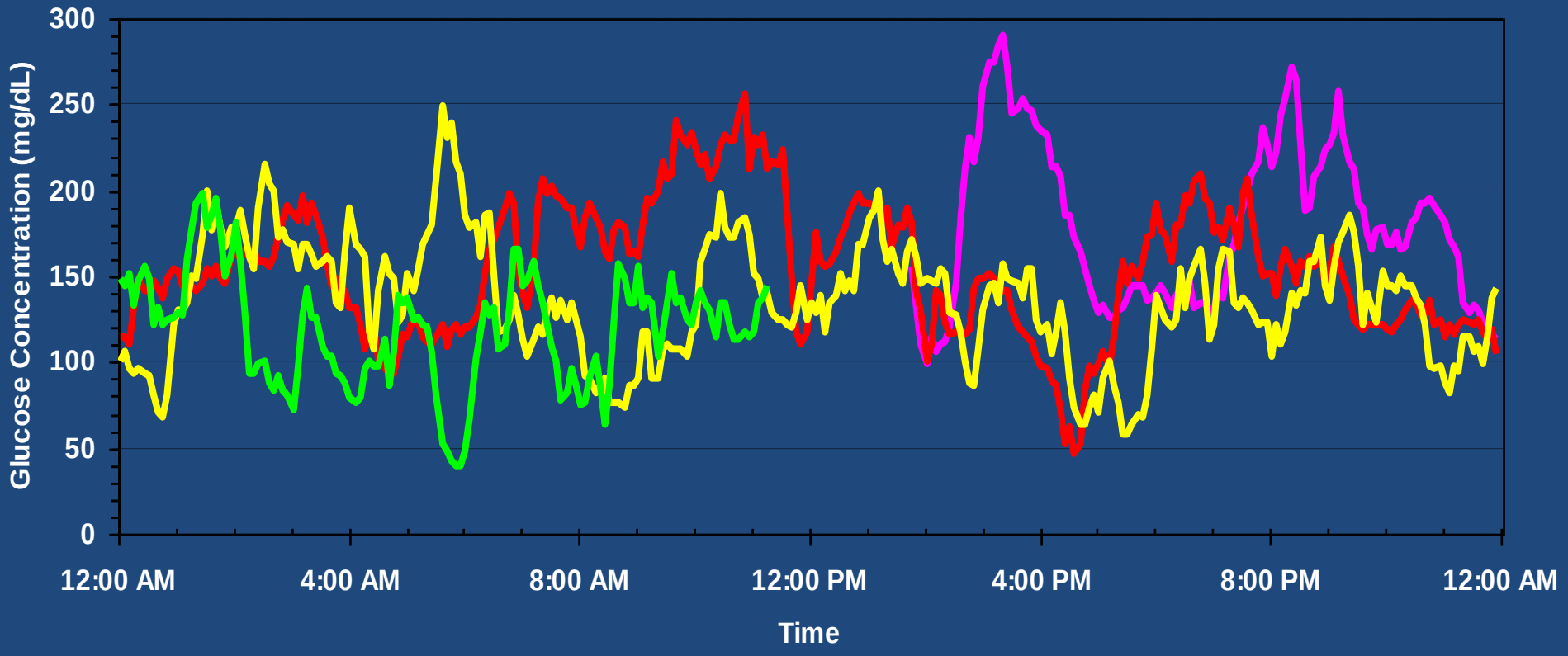
Diazoxide

- ADVERSE EFFECTS
  - Water and sodium retention : Poses risk of congestive heart failure or reopening of the ductus arteriosus.

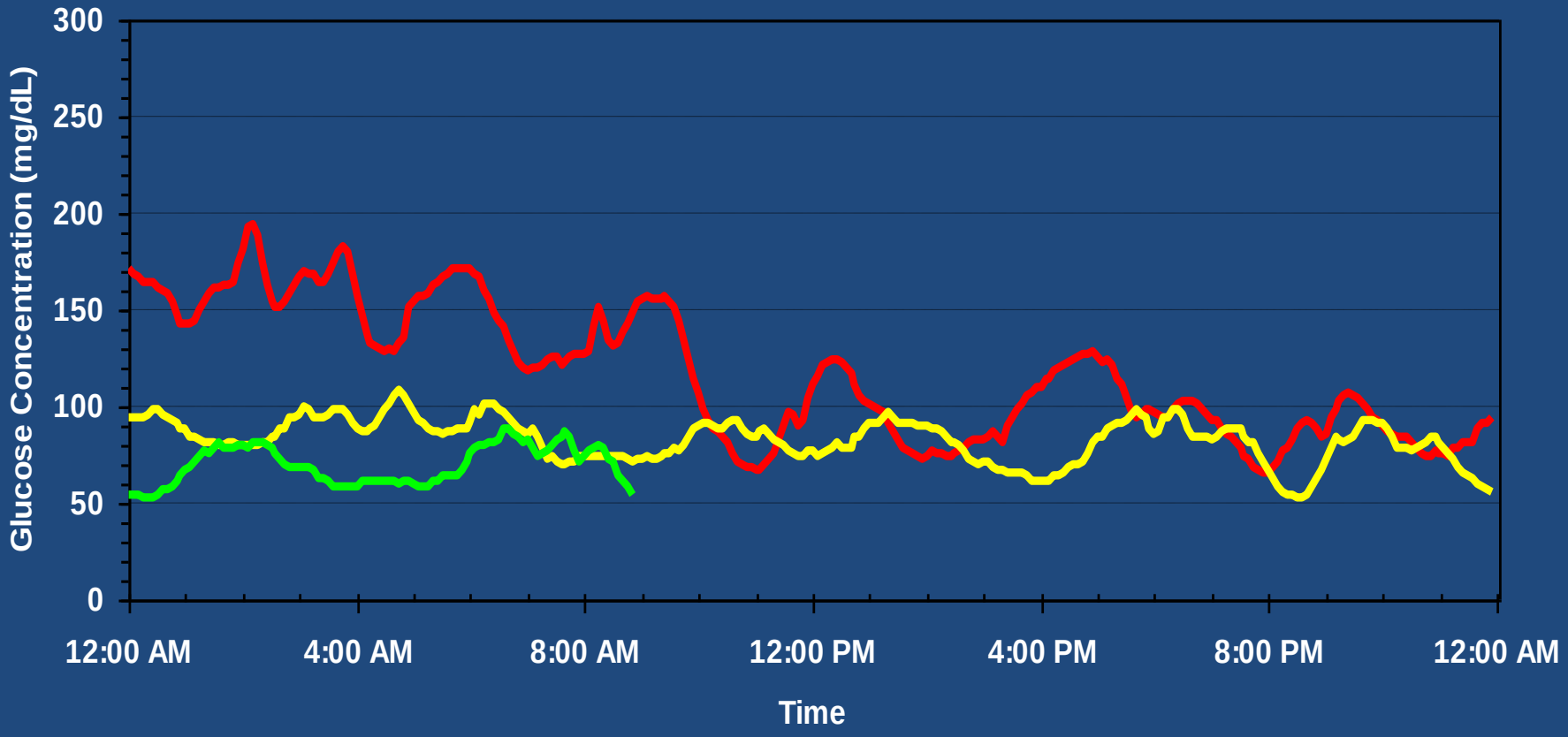
    It is advised to coadministrate diuretics , usually thiazides

  - Others: Hyperuricemia and Neutropenia. (Very rare)

Diazoxide Treatment 10 mg/Kg/day



Same Patient Receiving 7.5 mg/Kg/day



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Pharmacological treatment

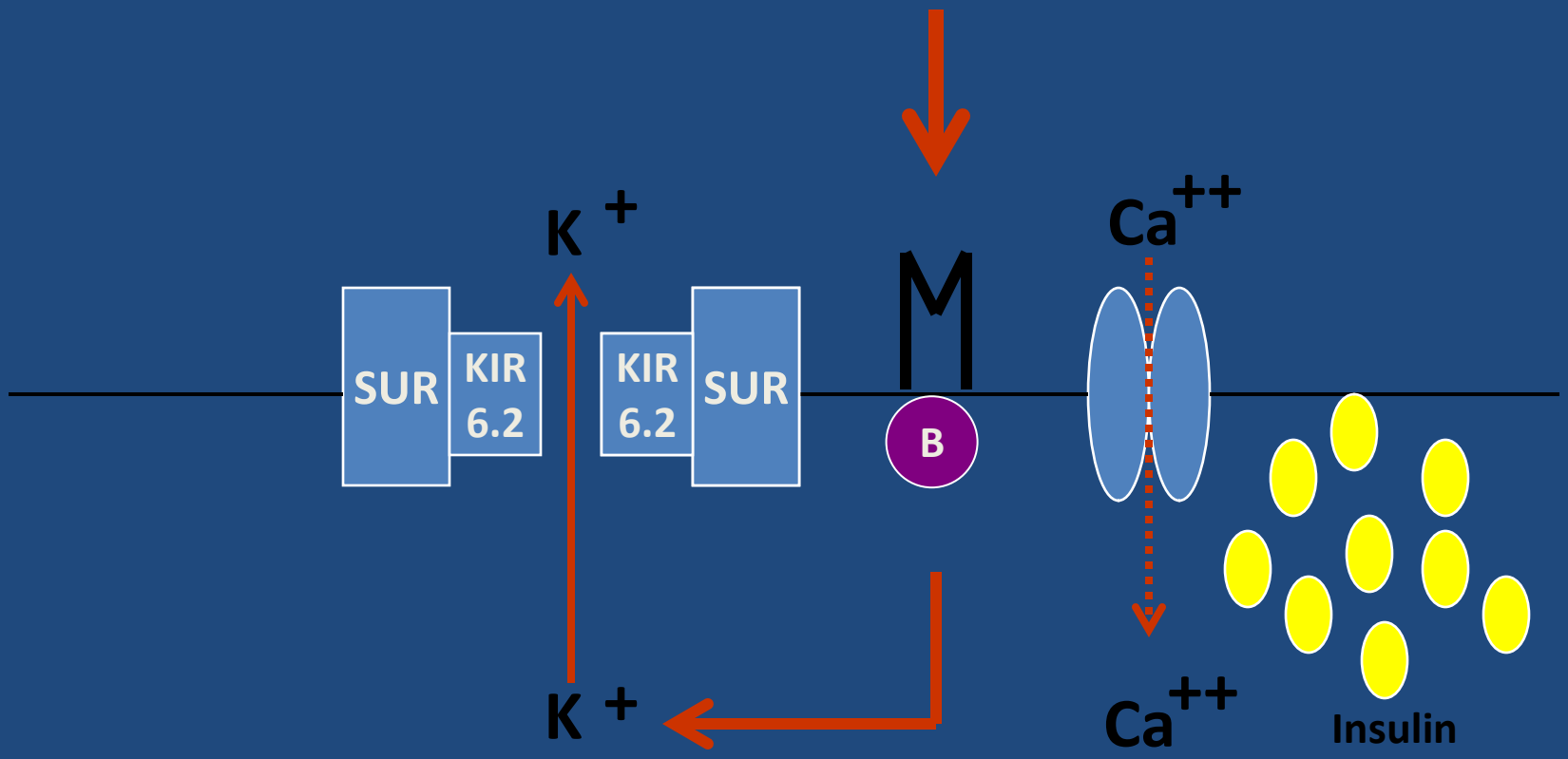
Somatostatin and Somatostatin Analogs

Somatostatin Dose: 6 mcg/kg/hour given as an infusion

Octreotide (Analog) Dose: 2.5 -10 mcg/kg/6hours SC

Lanreotide (Analog) Dose: 40 mg/14- 21 days SC

Somatostatin



Somatostatin and Somatostatin Analogs

- In the Pancreas it inhibits: glucagon, insulin and exocrine function.

- It also inhibits: Growth hormone, TSH, gastrin, cholecystokinin , VIP, among others.

Somatostatin and Somatostatin Analogs

- ADVERSE EFFECTS:
  - Tachyphylaxis
  - Malabsortion
  - Growth deceleration
  - Rarer are: Hepatitis, necrotizing enterocolitis, long QT syndrome and cholelithiasis

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Somatostatin

In our hospital it is only used when the medical treatment fails, in preparation for pancreatectomy. It is only used as an IV infusion with the patient on TPN.

Dose: 6 mcg/Kg/hour

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Pharmacological treatment

Glucagon

- Glucagon stimulates glycogenolysis increasing hepatic glucose output.
- It is administered by intravenous, subcutaneous, or intramuscular routes.
- First line treatment during hypoglycemic crisis.
- It can be used as a last resource for the short term control of diazoxide unresponsive patients.

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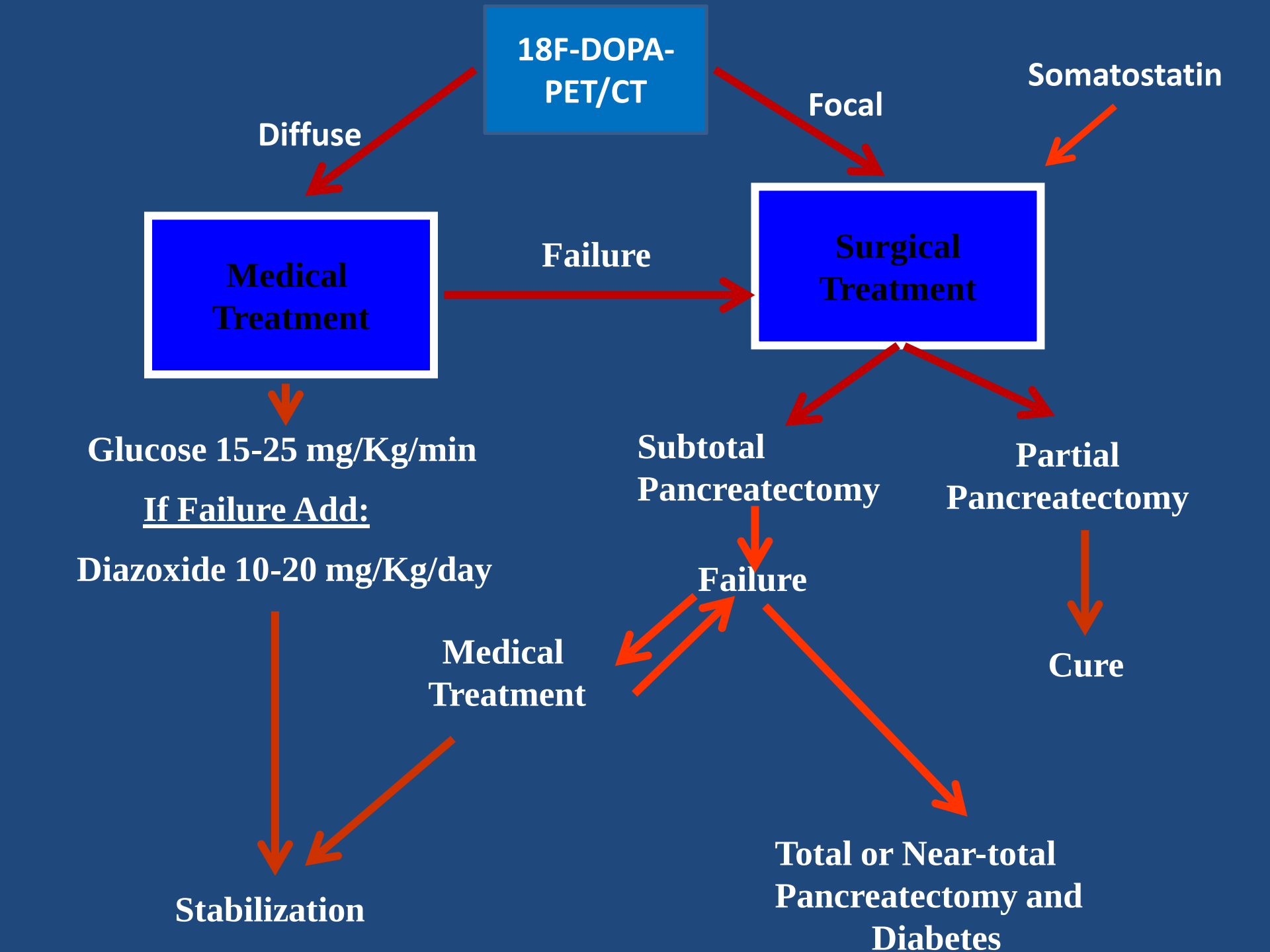
Novel medications for diazoxide-unresponsive CHI

SIROLIMUS

EXENDIN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Diffuse
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Medical Treatment
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Subtotal Pancreatectomy
Partial Pancreatectomy
Failure
Medical Treatment
Cure
Stabilization
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- Since 1974 there have been 58 cases of PCHI diagnosed and treated at our centre.
  - 41 of these have had genetic study (pending in 2).
    - **21 of them have presented ABCC8 mutations.**
      - **18 were non-responders to diazoxide.**
    - 1 GLUD
    - HNF4A
    - KABUKI

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- Only 6 of 18 patients non-responders to diazoxide with ABCC8 mutations, have been pancreatectomized.

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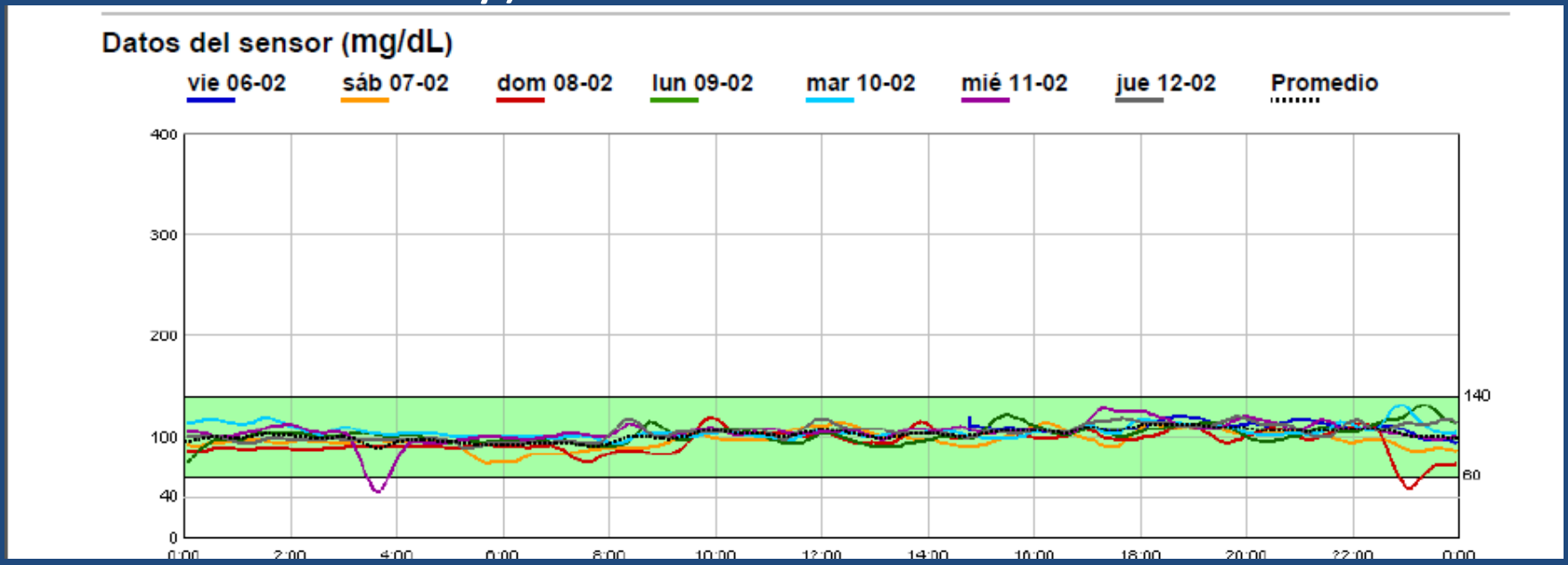
- In most cases it was possible to control the hypoglycemic events with intensive enteral support.

- The hyperinsulinemia eventually improved during evolution.

6 Euglucemic Patients

- Diagnosed in the newborn period except one diagnosed at 8 months.
- Currently they are 8, 10, 11, 13, 14 and 14 years old.
- Only one has neurological sequelae (seizures and a visual deficiency).



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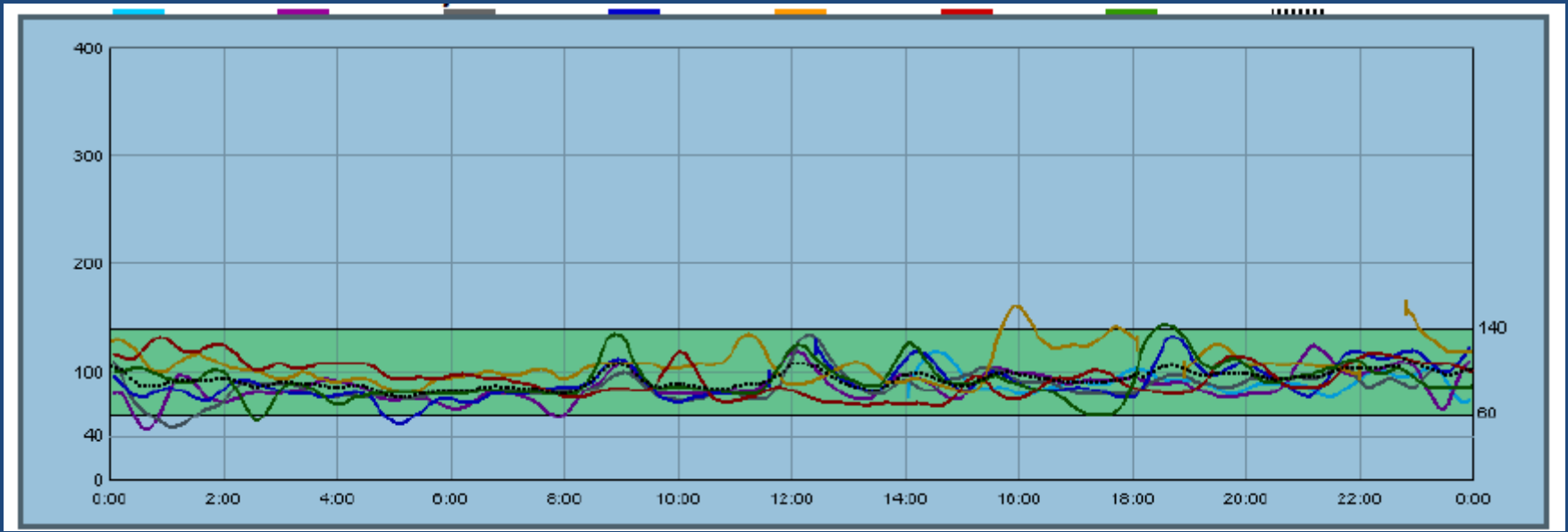
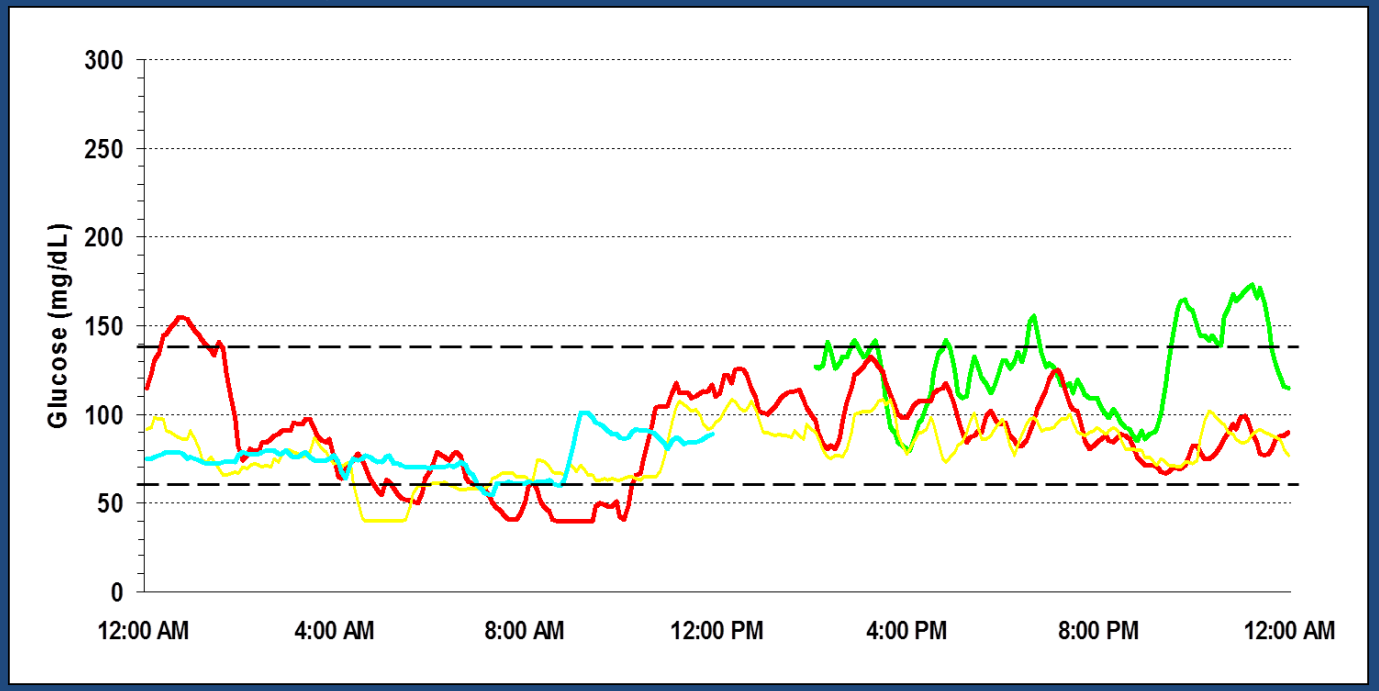


2 Patients with Glucose Intolerance

- Diagnosed during the newborn period and at 7 months of age.
- Currently 14 and 18 years old.

The one diagnosed in the newborn period has severe neurodevelopmental delay.

Glucose intolerance at 6 years old.



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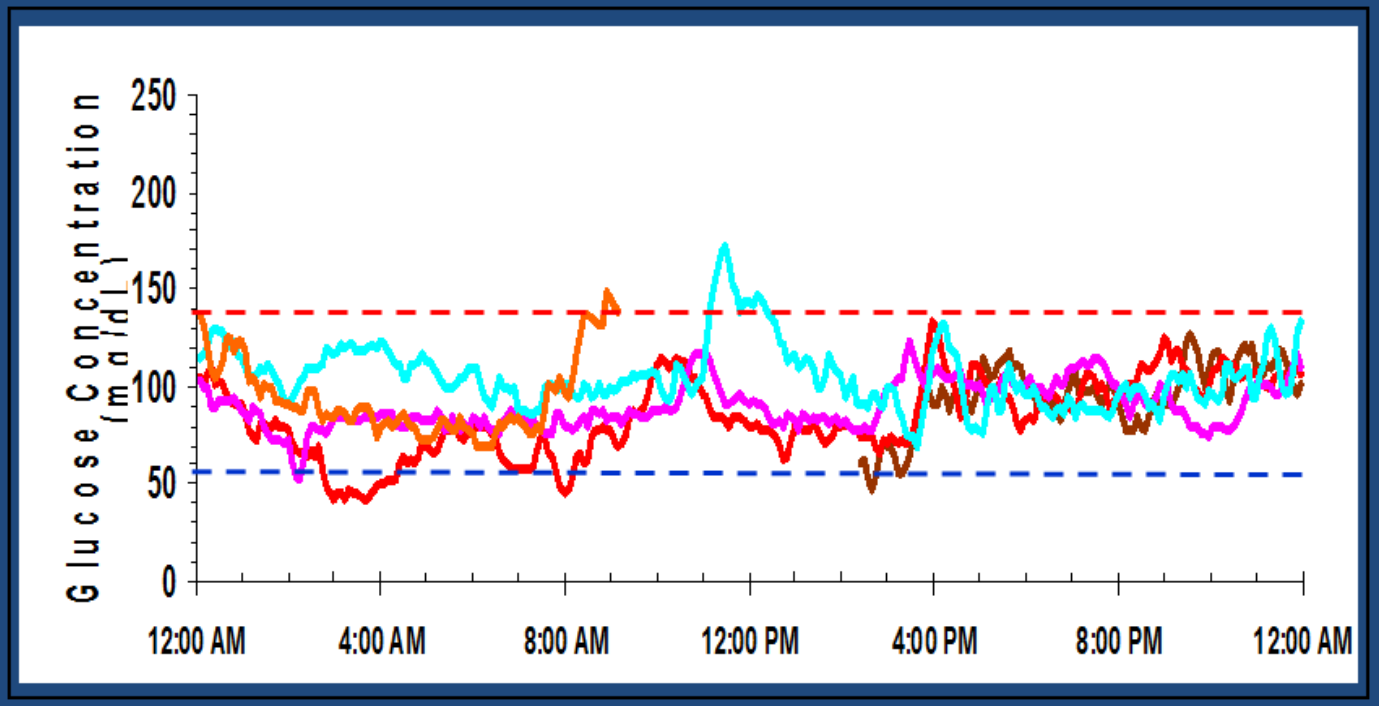

Glucose intolerance at 10 months of age.

4 Diabetic Patients

- Three were diagnosed with CHI during the neonatal period, and one at 5 months of age.
- Currently 14, 32, 25, 39 years old.
- Diagnosed with diabetes from early adolescence to early adulthood.
- Two have no neurological sequelae, one has moderate neurodevelopmental delay, and one controlled seizures.

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- Natural history evolving to diabetes
  - New type of monogenic diabetes?

Thank you very much!

Muchas Gracias!