Approach to Inborn Errors of Metabolism

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Goals for this lecture:

- Discuss acute/emergency management of IEMs.
- Review broad categories of IEMs.
- Focus on Board favorite zebras.
- Complete the Board prep. Objectives in most recent 2006 edition.
- Integrate the “Laughing your way through Boards” tips.
- Have fun with this usually stressful topic.

What we WON'T DO:

- Memorize metabolic pathways.
- Mention, think of, or utter the enzyme α-ketoglutarate dehydrogenase complex.
- Laugh at, throw bagels or coffee at, or otherwise mock Drew.
- Discuss the adverse sequelae of the Eagle's previous decision to recruit T.O.

IEM Board/Prep Goals:

- Recognize
  - Urea Cycle defects
  - Organic acidemias
  - S+S of CHO disorders
  - S+S of Galactosemia
  - S+S of hyperinsulinism
  - Glycogen Storage Dz
  - Lipoprotein Disorders
  - Gaucher + Lipid Storage Dz
  - S+S of Tay-Sachs
  - S+S of Fatty Acid and Carnitine metabolism
- Inheritance patterns
- Indication for genetics
- Eval of hypoglycemia
- Eval of acidosis
- Vitamin Rx for enzyme disorders
- Treat Hypoglycemia
- Natural Hx of PKU
- Plan/diet for PKU
- Manage Glycogen storage diseases- Type 1

IEM- Index of Suspicion:

- Rapid deterioration in an otherwise well infant.
- Septic appearing infant or abnl sepsis such as E.coli.
- Failure to thrive.
- Regression in milestones.
- Recurrent emesis or feeding difficulty, alterations in respirations, abnl urine/body smell, changing MS/lethargy, jaundice, sz, intractable hiccups.
- Can masquerade like pyloric stenosis.
- Dietary aversion- proteins, carbs.

Basic Principles:

- Although individually rare, altogether they are 1:800-5000 incidence.
- Broadly Defined: An inherent deficiency in a key metabolic pathway resulting in
  - Cellular Intoxication
  - Energy deprivation
  - Mixture of the two

History and Antecedent Events:

- Catabolic state induction (sepsis,fasting,dehydration)
- Protein intake
- Change or addition of PO proteins, carbs, etc… in formula
- **Gotta ask- Consanguinity
- FHx of SIDS

Assessment:

- Detailed H+P
  - Describe sz
  - Fevers

  -Milestones

  -FHx

  -Mom's GsPs

  -NAT questions

- **Dysmorphology does not r/o IEMs**
- Physical Exam:
  - **Vitals**
  - **Level of alertness**
  - **Abnl activity/mvmts**
  - **CV- perfusion**
  - **Dysmorphology, hair, smell, eyes-cornea**
  - **Abdo- HS megaly**
  - **Neuro- DTRs, tone, etc**
  - **Skin- bruise, pigment, color**

Emergency Management:

- Can be life threatening event requiring rapid assessment and management.
- ABC's

- ABG-acidosis
- BMP, Ca and LFTs
- NH4
- Lactate, Pyruvate
- CBC, Blood Cx if uncertain
- Coags- PT/PTT
- UA-ketones, urine reducing substances, hold for OA/AAs
- Newborn scrn results
- LP- r/o Meningitis, but send lactate STAT, AAs, hold tubes for future
- Drug tox screen if indicated.
- **Hold spun blood or urine sample in fridge for later if possbile.
  - **ABG, Lactate are iced STAT samples
  - ** NH4 should be free flowing, arterial sample

Emergency Management:

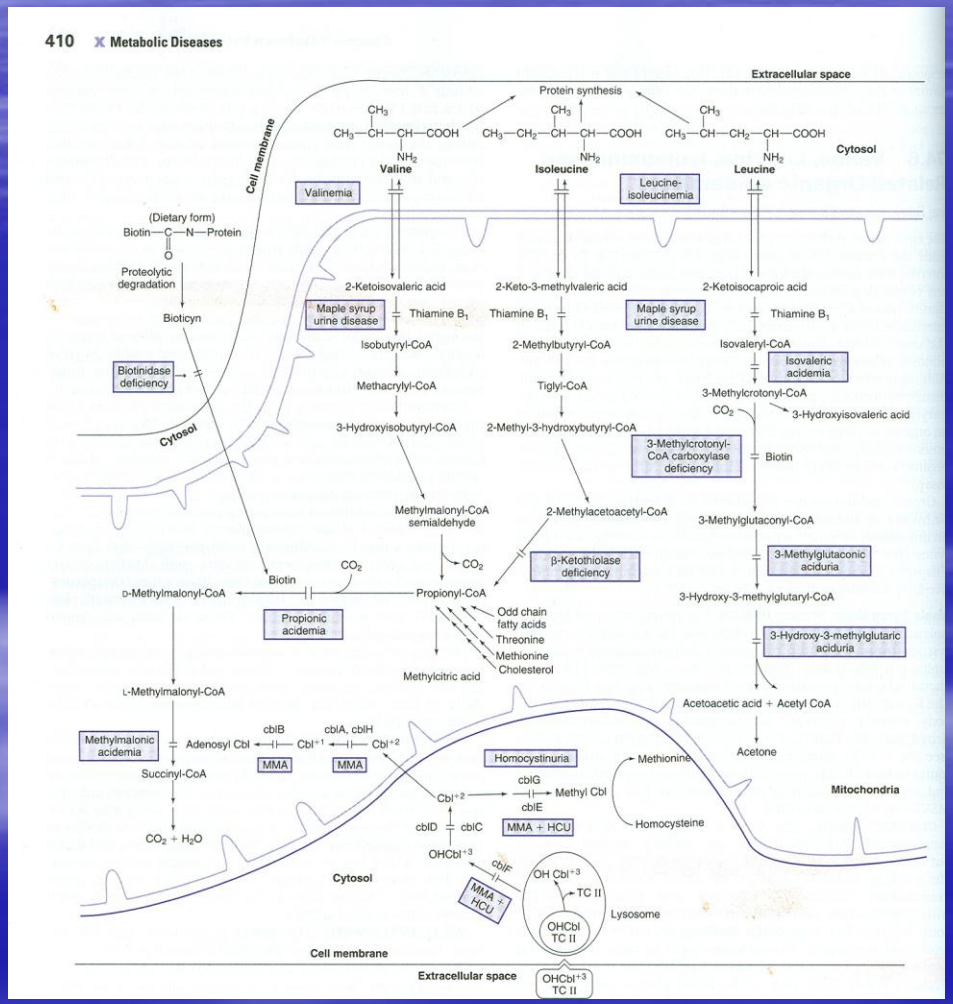
- Correct hypotension.
- NPO, reverse catabolism with D5-D10 1-1.5 x maint.
- Correct hypoglycemia.
- Correct metabolic acidosis.
- Dialysis, lactulose if High/toxic NH4
  - **(nl is <35µmol/L)**
- Search for and treat precipitants; ie: Infection, dehydration.
- Low threshold for Sepsis w/u + ABx if uncertain.
- Pyridoxine for neonatal sz. if AED no-response
- Ativan, Versed, AEDs for status epilepticus.

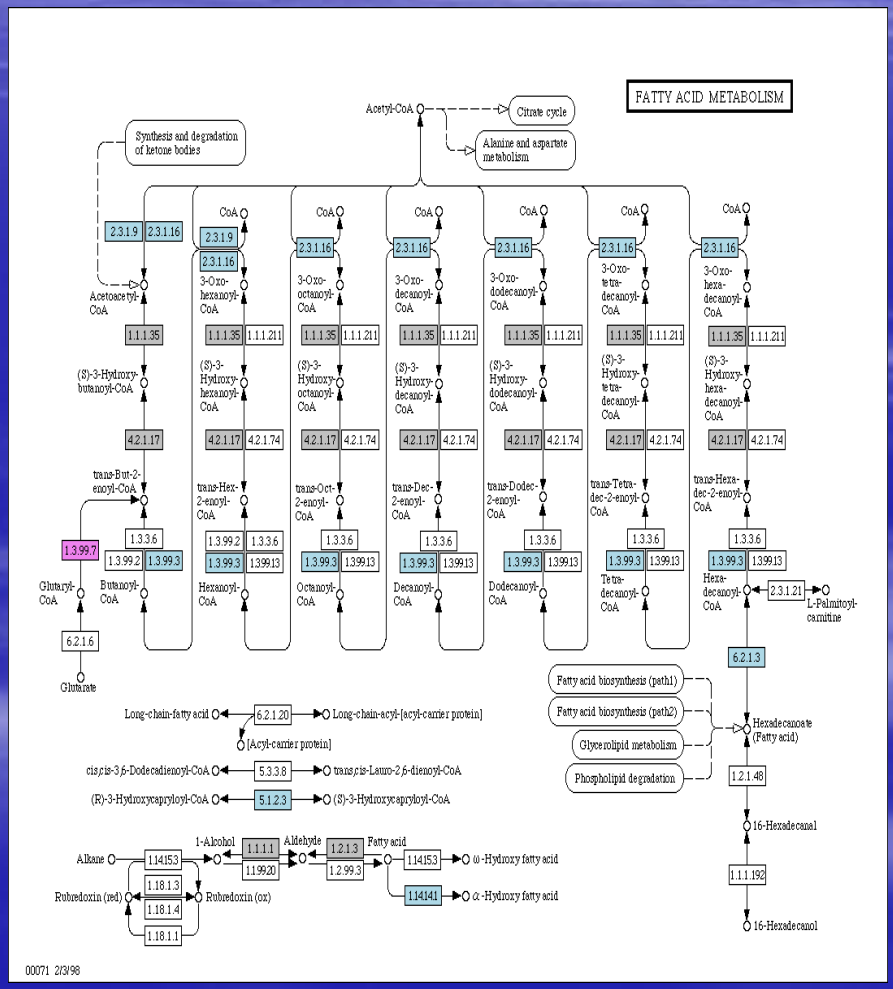
Some quick supplements:

- **Carnitine** for elimination of Organic Acid through creation of carnitine esters.
- **Sodium Benzoate**, **Phenylacetate** for Hyperammonemia elimination.

Stable Patient, Now what?

You could memorize some of these:





The Daunting Differential List:

- Transient Hyperammonemia of Newborn
- Inborn Errors of Metab:
  - Organic Acidemias
  - Fatty Acid Oxidation def
  - Urea Cycle Defects
  - Amino Acidurias
  - Non-ketotic Hyperglycinemia
- Molybdenum Cofactor Deficiency
  - Sulfite Oxidase Deficiency
- Metal Storage Disorders:
- Cholesterol Disorders:
- Leukodystrophies, other…
  - Krabbe disease
- Mitochondrial Disorders
- Glycogen Storage Disorders
- Hyperinsulinism
- Carbohydrate Disorders
- Lysosomal Disorders
  - Mucopolysaccharidoses (X-linked Hunter's, Hurler's)
  - Gaucher disease
  - Tay-Sachs Disease
- Peroxisomal Disorders
  - Zellwegger's (Cerebro-Hepato-renal)
  - X-linked Adrenoleukodystrophy

Patient is stabilized. Now what:

- Broad DDx for IEMs scares people.
- You can group into KEY features.
- Can focus on initial labs = Hyperammonia, hypoglycemia, metabolic acidosis.
- Can focus on Prominent neurologic features.
- Can focus on Dysmorphic features.
- If these don't exactly fit, resort back to categories of IEMs and Neurodegenerative Disorders.

Quick References:

MA: *metabolic acidosis							
NH4:							
Glu:							
Dz:	*Non-ketotic Hyperglycine	*Urea Cycle defects	*Fatty Acid Oxs *OAemia	*OAemia	*OAemia	*OAemia	*Glycogen Strg dfc *Amino Aciduris *Carb Metabolism dfc

Transient Hyperammonemia of Newborn:

- Markedly **high NH4** in an infant **less than 24 HOL, or first 1-2 DOL before protein intake occurs.**
- Often in context of large, premature infant with symptomatic pulmonary disease.
- Very sick infant.
- Unknown precipitant, unknown etiology (possible slow delayed urea cycle initiation), with potential for severe sequelae (20-30% death, 30-40% abnl devo) if not treated.
- Does not recur after being treated.

Organic Acidemias:

- *Acidotic with high Gap
- *Urine Ketones high
- *High to nl Ammonia
- Often present first 2-7 days of life after dietary protein introduced.
- Drunk appearance in infant.
- *May have low WBC and Plts.
- Check serum AAs/OAs, Urine AAs/OAs, CSF OAs/AAs.

Organic Acidemias cont:

- **Multiple Carboxylase Deficiency**

  or

  Defect in Biotin Utilization

- Biotin is vital cofactor in many pathways, defect results in:
- Severe deterioration, dermatitis, alopecia, immune deficiency- candidal skin infections.
- High NH4, acidemic, ketotic like the others.
- Dx by enzyme assay.
- Rx with Biotin 10mg/kg/d PO

**Rocky will get this if he consumes too much Avidin, aka, raw eggs.

Amino Acidurias:

- Maple Syrup Urine Disease
  - **Sweet smell of body fluid esp Urine.**
  - Classically develops in **1st week of Life**.
  - Poor feeding, emesis, lethargy and coma.
  - Periods of **Hypertonicity**.
  - Secondary Hypoglycemia.
  - Possible Metabolic Acidosis, hyperammonemia
  - **Obtain serum/urine AAs/OAs**
  - Treatment requires rapid removal of Branched chain AAs, often through dialysis.

Amino Acidurias:

- Fresh Urine Uric acid and Sulfite Dipstick if neurologic abnormalities are present, low uric acid is suggestive for **molybdenum cofactor deficiency and Sulfite Oxidase Deficiency**.
- Don't forget PKU. Basic on newborn scrn, but only does good if results followed up.

For the Boards:

- *Sweaty feet smell*
  - Isovaleric Acidemia, think *ISOTONER* shoes smell
- What defect may present with Pulmonary Embolus?
- Homocystinuria- and thereafter may ask which supplement to initiate?
- Pyridoxine- due to residual enzyme activity.
- Other names to know:
  - Methylmalonic Acidemia- Rx with large dose vitamin B12
  - Propionic Acidemia- RX with Biotin.

Urea Cycle Defects:

- All but one of the disorders is autosomal recessive.
- Symptom free period and then emesis->lethargy-->>COMA
- Key features:
  - High Ammonia, low BUN
  - Possible Lactic acidosis
  - *Absence of ketonuria*
  - Nl to mild low Glucose
- **Treat high ammonia, infuse glucose, send plasma AAs/OAs, urine orotic acid, and plasma citrulline.
- Infusion of 6ml/kg 10% Arginine HCl over 90 min may help.
- Milder forms may show episodic emesis, confusion, ataxia, and combativeness after high protein meals.

For the Boards:

- Most common Urea cycle defect and also only X-linked:
- Ornithine Transcarbamylase Deficiency

Fatty Acid Oxidation Defects:

- **Autosomal recessive inheritance**
- Examples are MCAD, LCAD, VLCAD
- Defect in acyl-CoA Dehydrogenase, a mitochondrial duty, and important in fasting state.
- KEY features:
- Acute attack of life-threatening coma with Hypoglycemia
- Absence of urine ketones, and reducing substances, nl serum AAs.
- +/- mild acidosis, or hyperammonemia, elevated LFTs, abnl coags. +/-Hepatomegaly-/+
- Dx with serum Acylcarnitine Profile or fibroblast enzyme assay

For the Boards:

- Fetal Defect in LCHAD may result in Prenatal course complicated by :
- Maternal HELLP syndrome

Non-ketotic Hyperglycinemia:

- Unique entity in that Glucose, NH4, pH are all normal.
- 4 types with varying ages of onset, however, classic form is Neonatal with onset in 1st week of life.
- Will present just like the other devastating IEMs. Lethargy, emesis, hypotonia, seizures, etc…
- Uncontrolled hiccups.
- Dx with no urine ketones, and Elevated Glycine.
- No effective Rx. Will require diet restriction.
- Long term is a devastating disease.

Carbohydrate related Disorders:

Galactosemia:

- First 1-2 wks of Life: Presents with hypoglycemia, jaundice, emesis.
- Secondary to intolerance of Galactose. Will be in baby's first meals of breast milk or lactose containing formulas.
- Also index of suspicion for GramNeg or E.coli sepsis.
- Dx assisted by Non-glucose reducing substances in urine.
- Confirmation by Galactose-1-PO uridyl transferase activity in RBCs.
- Adverse sequelae include Cataracts, MR, persistent liver disease.

For the Boards:

- Which is worse?
  - Essential Fructosuria
  - Inherited Fructose Intolerance
- Inherited Fructose Intolerance
  - Occurs after ingestion of Fructose (sucrose= glucose + fructose)
  - Severe and life threatening intoxication of F-1-PO4.
  - Presents with emesis, seizures and profound illness after ingestion of fructose.
  - May also present similar to Galactosemia.
  - Life long avoidance of fructose.

Glycogen Storage Disorders:

- Type 1= Von Gierke's:
  - Shortly after birth: Severe lifethreatening Hypoglycemia
  - Lactic acidosis –due to isolated glycolysis of G6Po
  - Hyper-uricemia, hyper lipidemia
  - Increased association with epistaxis
  - *Hepatomegaly
  - **Adverse response to Glucagon with worsening Lactic acidosis
- Management requires IV glucose, and then as outpt, close NG corn-starch or glucose solution administration to achieve close to nl glucose homeostasis.
- Frequent snacks and meals. Continuous nighttime glucose infusions up to the age of 2.

Glycogen Storage Disorders:

- Type 2- Pompe's disease:
- Normal Glucose
- Do to an accumulation of glycogen in lysosomes.
- **Ancient city of Pompeii was destroyed by Mt. Vesuvius- 79 AD**
- Manifested by massive Cardiomegaly, Hepatomegaly, Macroglossia.
- Fatal If results in CHF.
- Limited therapies in Neonatal Variant.
  - Attempts at enzyme replacement ongoing.

Mitochondrial Disorders:

- Emerging spectrum of diseases with life-time variation of presentation.
- Infantile/Neonatal: may present with encephalopathic picture, regressed milestones, cerebral cortical atrophy.
- Generally lab findings of:
  - Lactic Acidosis
  - NI to low serum pyruvate, incomparison to Lactate
  - NI organic acids.
  - *** Important to check CSF values of the above***

Leigh's Disease

- AKA- Subacute necrosing encephalopathy
- Due to defects in the mitochondrial electron transport chain.
- May have devastating presentation with significant developmental regression.
- Unfavorable natural history.
- May respond to host of supplements.
- **Other Mitochondrial disorders for completion sake**
  - MELAS, MERRF, Leber's HON

Leukodystrophies:

- **Krabbe disease:**
  - Type 1- "Infantile"= irritability, hypertonia, hyperesthesia, and psychomotor arrest, followed by rapid deterioration, optic atrophy, and early death
  - Type 2- Late infantile
  - Type 3- Juvenile
  - Type 4- Adult
- A demyelination disorder due to CNS accumulation of galactosylceramide.
- Diagnosis: supported by cortical atrophy on CT/MRI, High CSF protein and definite evidence of deficient GALC assay in WBCs or skin fibroblasts.

Lysosomal Disorders
Focus on key differences:

- Gaucher Disease:
  - Infantile vs chronic juvenile
  - Organomegaly
  - Bone pain
  - Easy bruisability
  - **low Plts, osteosclerosis, and lytic bone lesions
  - MNEUNOMIC= “Clumsy Gaucho cowboy”
- Tay-Sachs Disease:
  - Progressive neurologic degeneration in first YOL and death by age 4-5 yo
  - AR inheritance with classic Jewish Ashkenazi relationship.
  - Increased startle reflex
  - Cherry red macula
  - Macrocephaly

Peroxisomal Disorders

- Zellweger Syndrome
- aka: Cerebro-hepato-renal syndrome
- Typical and easily recognized dysmorphic facies.
- Progressive degeneration of Brain/Liver/Kidney, with death ~6 mo after onset.
- When screening for PDs. obtain serum Very Long Chain Fatty Acids- VLCFAs

Further Evaluation in IEMs:

- ** Head CT, MRI, Ophtho, Audio, EKG, EEG**
- Genetics consultation.
- Peds Neuro consultation.

Random Questions for the Boards:

- Amino Acids responsible for MSUD?
- Valine, Leucine, Isoleucine
- Name 1 of the 3 classic Metal Storage disorders?
- Menke's Kinky Hair Syndrome (X-link recessive)
- Wilson's Disease
- Neonatal Hemachromatosis
- Lysosomal storage disease associated with Adrenal Gland calcifications?
- Wolman Disease
  - Fatty acid deposits, nl lipid panel
  - **Mneumo= Wool Man Disease → white wool deposits.

Recognize that Smell:

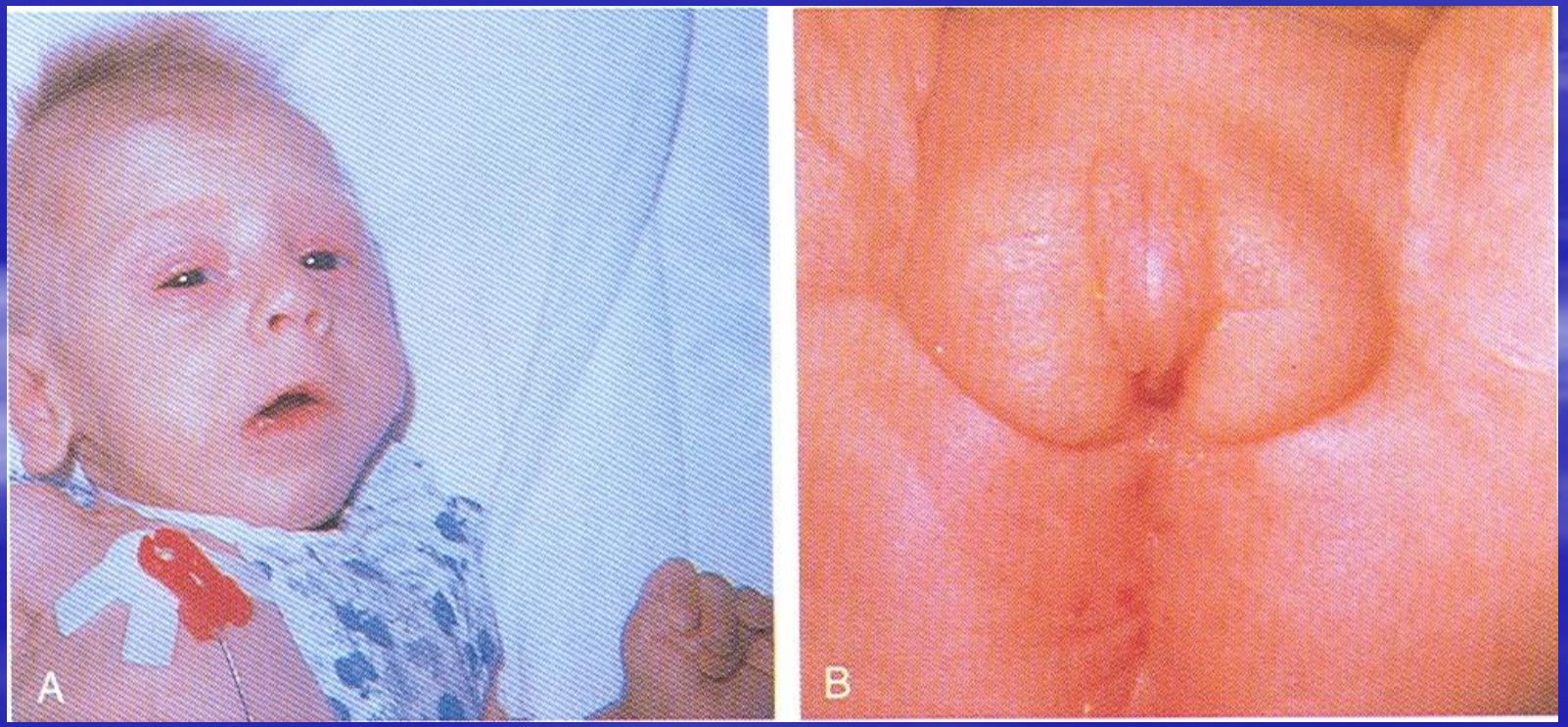
- **Musty or Mousy:**
- PKU
- **Boiled Cabbage**
- Tyrosinemia or hypermethioninemia
- **Maple Syrup**
- maple syrup urine disease
- **Sweaty feet:**
- isovaleric acidemia or glutaric acidemia type II
- **Cat urine**
- multiple carboxylase deficiencies (Biotin deficiency)

Follow up Questions ?

- Name some classic Mucopolysaccharidosis?
- Hunter's (X-linked, no corneal clouding)
- Hurler's (presence of Corneal clouding)
- Morquio Syndrome (nl IQ, short, cloudy cornea) *tattoo on FI
- -How are mucopolysaccharidoses Diagnosed?
- Urine MPSs, definite with Skin Fibroblast Bx
- How to treat **Neonatal Hyperinsulinism**?
- Diazoxide- inhibits pancreatic B-cell insulin secretion.
- Child Dx with PKU, now diet restricted, but with progressive neuro deterioration. What else might be deficient?
- Tetrahydrobiopterin (BH4)

Finally and to wet your appetite for Sat:

- Name this syndrome and the associated metabolic defect.
- Smith-Lemli-Opitz Syndrome: due to defect in **cholesterol synthesis**.



For Reference:

- AAP Guidelines to IEMs. DOI: 10.1542/peds.102.6.e69 *Pediatrics* 1998;102;69- Barbara K. Burton

Quick Algorithms: