Disclosures

• Member of the UCDC – an NIH-sponsored Rare Disease Consortium

• Investigator for clinical trials with Hyperion Therapeutics for novel ammonia-scavenging medications

• Investigator in clinical trial with Cytonet to monitor subjects treated with hepatocyte infusions for urea cycle disorders
What are inborn errors of metabolism?

- Genetic conditions – a person is born with the disorder
- Often autosomal recessive
  - Parents are “carriers”
  - Child is first person in family to have condition
- Genetic error is usually in an enzyme controlling a metabolic pathway
- Blockage in metabolic pathway results in accumulation of toxic material in the system
How do we find the affected person?

- Newborn screening
- Family history
- Baby gets very sick
Current treatments not involving transplantation

• Restrict the material for which there is a blockage in the metabolic pathway
  – Example: protein in disorders where ammonia accumulates

• Remove the abnormal material that accumulates
  – Example: dialysis or scavenger medications in disorders where ammonia accumulates
Kinds of metabolic conditions that affect the liver

• Liver is central to many metabolic pathways
• Needed for recycling and processing of most proteins in foods
• Needed for storing part of our body’s starch supply as hepatic glycogen
• Blocks in metabolic pathways can either
  – Not affect liver function but affect the overall accumulation of abnormal metabolic products
  OR
  – Damage the liver resulting in abnormal liver function tests and eventual scarring and loss of function
Why liver transplantation in treatment of inborn errors of metabolism?

• In conditions without underlying liver damage, transplant replaces abnormal enzyme with a normal liver.

• In conditions with liver-damaging byproducts, transplant replaces damaged liver.
  – Replaces abnormal enzyme function.
  – May prevent liver cancer that can occur due to constant liver damage caused by the disorders.
Why make this distinction?

• The only way to fix a badly damaged liver is to replace it – not amenable to partial corrections

• If the liver is ITSELF ok, with just a metabolic block, may only need partial correction for substantial metabolic improvement or stabilization.
Spectrum of conditions: considerations for treatments

• Medical complexity
  – Volatility – how often do episodes occur
  – Degree to which decompensation is life-threatening

• Availability of less-invasive treatments

• Does the condition cause damage outside of the liver?

*RISK vs. BENEFIT!*
What makes us consider early liver transplant for an IBEM?

• Is the condition so severe that it is difficult to maintain stability?
• Are treatments that are available complicated and expensive?
• Would a liver transplant stabilize or prevent further extra-hepatic consequences (BRAIN DAMAGE)
Options in liver transplant

(Disclaimer! I am not a transplant surgeon or transplant expert!)

• Orthotopic liver transplant
• Partial or “split” liver
• Living related donor segment
• Hepatocytes
  – Gene therapy
  – Donated
Orthotopic liver transplant

“The gold standard”

• Advantage:
  – Complete metabolic correction

• Disadvantages:
  – Requires a similar sized donor – very scarce resource
  – Immunosuppression required after
  – Some size limitations: tiny connections for tiny person

Consequence: scarce so requires triage to the most severe cases with the best neurologic outcomes with treatment
Partial or split liver

- Much more available
- Size matching still an issue, so may not be available for very small patients
- Still requires immunosuppression
- Yields metabolic correction or replacement of damaged organ
Living related donor

• Less chance for rejection
• Donor is readily available so can do as a planned procedure
• Size limitations – size of donor lobe and recipient liver site prevents its use in infants
Gene therapy

- Auto-transplantation with patient’s own treated hepatocytes
- Advantage: no immunosuppression
- Disadvantages:
  - Invasive to patient to obtain hepatocytes
  - Vector safety
Donor Hepatocytes

• Advantages:
  – Readily available
  – No gene therapy vector required, cells have normal metabolism

• Disadvantages:
  – May need immunosuppression
  – Partial correction
Why even consider partial correction?

• Examples:
  – PKU and hyperphenylalaninemia
  – Forms of maple syrup urine disease
  – Urea cycle disorders spectrum of disease
Current trial with Cytonet

- Limited to infants with severe, neonatal onset urea cycle disorders
- Hepatocyte infusion as a bridge to transplant
- Requests examination of explanted liver at the time of transplant
- Goal is to stabilize or moderate severity of the disorders
Conclusions

- Liver transplantations may be lifesaving and is the therapy of choice for selected severe inborn errors of metabolism
- Livers are scarce
- Other options may provide stabilization or support pending transplant
Babies and their families!!!! Who is this all for??