Management of Complications of Chronic Liver Disease: “When to Refer to Transplant?”

Philip Rosenthal, M.D.
Professor of Pediatrics & Surgery
University of California, San Francisco
THE LIVER

- Largest organ in body
- RUQ of abdomen
- Sheltered by rib cage
- In adult, weighs 3 lbs.
LIVER: GROSS ANATOMY

- Separated into 2 lobes: Right and Left
- Right lobe is ~6X larger than the left
- Porta hepatis is entry site for blood vessels and exit site for bile ducts
Liver Transplantation

- Anatomical segments
- Living-related
- Split
- Reduced-sized

Split liver
HEPATIC CIRCULATION

- A dual blood supply
- Portal vein drains intestines and spleen—provides 75% of liver’s blood supply
- Hepatic artery supplies oxygenated blood from aorta—provides 25% of blood supply
CELLULAR ARCHITECTURE

- Portal vein and hepatic artery branch within the lobes to form **sinusoids** that run parallel to rows of **hepatocytes** (liver cells)
- Sinusoids allow exchange of substances to liver cells
CELLULAR ARCHITECTURE

- Hepatocytes are most abundant and metabolically active
- **Kupffer cells** in the sinusoids are scavenger cells for foreign matter, worn-out blood cells and bacteria
CELLULAR ARCHITECTURE

• The liver is organized into polyhedral units - lobules
• On cut section, a lobule is hexagonal with 6 portal triads at the periphery
• Portal triad - branch of hepatic artery, portal vein, bile duct
REGENERATIVE ABILITY

- Hepatocytes rarely divide but have the capacity to reproduce in response to appropriate stimuli.
- This process can restore the liver to within 5-10% of its original weight.
- Liver regeneration plays an important role after surgical resection or after injury that destroys portions of the liver.
LIVER FUNCTIONS

• Purification, transformation and clearance of:
  – ammonia
  – bilirubin
  – hormones
  – drugs
  – toxins
LIVER FUNCTIONS

• Regulation of:
  – glucose
  – cholesterol

• Storage of:
  – glucose
  – fat-soluble vitamins
  – folate
  – vitamin B12
  – copper
  – iron
LIVER FUNCTIONS

• Synthesis and secretion of:
  – albumin
  – clotting factors
  – transporter proteins
  – cholesterol
  – bile
  – glucose
  – complement
Hepatic Disorders

- Metabolic disorders
  - Glycogen storage
  - Urea cycle OTC, CPS
  - Alpha 1 antitrypsin
  - Wilson's
- Cholestatic
  - Biliary atresia
  - Alagille syndrome
  - PFIC (Byler's)
- Hepatitis
  - A,B,C
  - Neonatal autoimmune
- Hepatoblastoma/HCC
- FHF
- Cystic (combined KLTx)
- other
Metabolic Diseases

- Tyrosinemia
  - NTBC therapy effective in most
  - Transplant indicated for adenoma/carcinoma formation
- Crigler-Najjar
- Urea cycle defects
- Fatty acid oxidation defects
- Glycogen storage disease
PROGNOSIS
Recognizing High Risk Patients

• Acute Liver Failure
• Age less than 3 months
• Advanced malnutrition
• Recurrent infections
• Multi-organ system disease
MEDICAL MANAGEMENT OF LIVER TRANSPLANT CANDIDATES

• Management of complicated portal hypertension
• Nutritional support
• Aggressive management of infection
• Appropriate immunizations
Treatment Options

- Supportive
- Nutrition
- Vitamins
- Antipruritics
- Ursodeoxycholic Acid
- Transplantation
General Principles

- With cholestasis, fat-soluble vitamins and medium chain triglycerides are usually required to optimize growth.
- Children who are anicteric but who have cirrhosis present a different challenge since hypermetabolism, enteropathy, and increased protein oxidation may occur.
General Principles

• Various inborn errors of metabolism that cause liver disease (i.e. galactosemia, tyrosinemia, hereditary fructose intolerance, Wilson disease) have specific nutritional requirements and dietary restrictions

• The success of pediatric liver transplantation has made the recognition of the importance of nutritional support in the pretransplant period imperative to optimize the success of the transplant
Nutritional Assessment of the Child with Liver Disease

• A nutritional assessment is needed to determine the degree of malnutrition if present and to tailor the nutritional intervention

• The severity of malnutrition may not correlate with the degree of vitamin or trace mineral deficiency or the degree of hepatic dysfunction
Nutritional Assessment of the Child with Liver Disease

• A number of obstacles complicate the ability to accurately assess the nutritional status of a child with liver disease
  – Body weight may be deceptive because organomegaly from an enlarged liver or spleen, edema or ascites can mask weight loss and actually increase or falsely inflate the weight
  – Height is a better indicator of malnutrition in these children and can be a reliable tool to determine chronic malnutrition
  – A decrease in height for age percentile may be indicative of the duration of malnutrition
Nutritional Assessment of the Child with Liver Disease

- Triceps skinfold and arm circumference measurements provide a sensitive indicator of nutritional status in children with chronic liver disease
- Lower extremities are more prone to peripheral edema and fluid retention than upper extremities
- Upper extremity measurements may be a better indicator of body fat stores and muscle mass
Nutritional Assessment of the Child with Liver Disease

- Reduced fat fold thickness and mid upper arm circumference have been observed in children prior to weight or height reductions.
- In children, early reduction in fat and muscle stores reflects the preferential utilization of fat stores to conserve protein stores for energy in the malnourished state.
- To optimize the accuracy of anthropometric measurements, it is best to utilize a single observer using a standard technique with serial measurements.
Nutritional Assessment of the Child with Liver Disease

- Measurement of plasma proteins including albumin, transferrin, prealbumin, and retinol-binding protein that are synthesized by the liver has been used to determine visceral protein nutriture.
- Diminished serum levels of these proteins may not accurately reflect the body’s visceral protein status.
- The serum concentrations of these proteins more closely relate with the severity of liver injury as opposed to the degree of malnutrition as assessed by anthropometric measurements.
Nutritional Assessment of the Child with Liver Disease

• Hypoalbuminemia in chronic liver disease patients often results due to third spacing of fluid and protein in ascites or the extravascular compartment

• There is often increased catabolism of albumin without a compensatory increase in albumin synthesis, due to inadequate reserves and malabsorption of amino acids and peptides
Nutritional Assessment of the Child with Liver Disease

• Nitrogen balance studies are difficult to evaluate in children with chronic liver disease
• Impairment of hepatic urea synthesis leads to underestimation of urinary nitrogen losses
• Ammonia accumulates in the intra- and extracellular compartments instead of being excreted by the kidneys
Nutritional Assessment of the Child with Liver Disease

• The creatinine-height index is a good indicator of lean body mass if renal function is unimpaired

• When utilizing the creatinine-height index, dietary protein intake, trauma, and infection must be considered since they all can alter creatinine excretion
Nutritional Assessment of the Child with Liver Disease

• Immune status is sometimes utilized as an indirect measure of nutritional status.

• However, liver disease and, in particular, hypersplenism can result in lymphopenia, abnormal skin tests for delayed hypersensitivity, or decreased concentrations of complement irrespective of nutritional status.

• Immunologic markers are of limited usefulness in children with liver disease.
Malabsorption in chronic liver disease

- Fat
- Steatorrhea is frequently observed in patients with cirrhosis and/or chronic cholestasis
- There is a poor correlation between the degree of biliary obstruction and the amount of fat excreted in the stools
- Intraluminal bile salt concentrations are below the critical micellar concentration such that intraluminal products of lipolysis cannot form micellar solutions
- Often a prolonged prothrombin time is observed
- A trial of parenteral vitamin K administration daily will often correct the prothrombin time and points to poor fat-soluble vitamin absorption
Malabsorption in chronic liver disease

• Fat

• Treatment with a low fat diet supplemented with medium chain triglyceride (MCT) (C8-C12 fatty acids) containing formulas [Pregestimil (Mead Johnson, approx. 60% MCT), Alimentum (Ross, approx. 50% MCT) or Portagen (Mead Johnson, approx. 87% MCT)] or MCT oil helps to decrease the degree of steatorrhea and may help to improve the nutritional status of the child

• MCT-enhanced diets can also improve energy intake in older children with cholestasis

• MCT does not require intraluminal bile salts for micellar formation in order to be absorbed in the intestinal lumen.

• MCTs are relatively water soluble and directly absorbed into the portal circulation.
Malabsorption in chronic liver disease

- **Essential Fatty Acids**
- The malabsorption of fat, especially long chain triglyceride (LCT), and inadequate intake can lead to essential fatty acid (EFA) deficiency
- EFAs are fatty acids that cannot be synthesized by desaturation or elongation of shorter fatty acids
- Linoleic acid and linolenic acid are the two main EFAs
- Arachadonic acid, derived from linoleic acid, is also considered an EFA
- Deficiency of EFAs may result in growth impairment, a dry scaly rash, thrombocytopenia and impaired immune function
- LCTs are poorly absorbed if cholestasis is present
- Infants have a small linoleic acid store
- Cholestasis in infants places them at an increased EFA deficiency risk
Malabsorption in chronic liver disease

- **Essential Fatty Acids**
- Pregestimil and Alimentum provide only 7-14% of calories as linoleic acid
- To prevent EFA deficiency, at least 3-4% of calories should be linoleic acid
- If cholestasis is severe enough to allow 30-40% of dietary fat to be malabsorbed, then EFA deficiency may ensue
- Portagen, containing 87% MCT and <3% EFA is not recommended for long-term use in children with cholestatic liver disease because essential fatty acid deficiency may occur if supplementation is not provided
- Corn oil or safflower oil containing linoleic acid can be added to foods or a lipid emulsion (Microlipid, Novartis) can be added to formula to provide additional linoleic acid
Malabsorption in chronic liver disease

- **Fat Soluble Vitamins**
- Bile acids in the intestinal lumen are not only important for fat absorption from the lumen but also for fat-soluble vitamin absorption
- Vitamins A, D, E and K are all dependent upon intraluminal bile acid concentration
- When the intraluminal bile acid concentration falls below a critical micellar concentration (1.5-2.0 mM), malabsorption of fat-soluble vitamins ensues
- Cholestyramine and colestipol, bile acid binding resins, may deplete enteral bile acids and interfere with fat-soluble vitamin absorption from the intestines
- Vitamin A and vitamin E require hydrolysis by an intestinal esterase that is bile acid dependent prior to intestinal absorption
Malabsorption in chronic liver disease

- **Fat Soluble Vitamins**
- In infants, cholestasis leads to rapid depletion of body stores of fat-soluble vitamins with both biochemical and clinical features of deficiency evident unless adequate supplementation is utilized.
- Evaluation for fat-soluble vitamin deficiency, supplementation and monitoring are all necessary for infants and children with cholestasis.
- In order to alleviate the malabsorption of fat-soluble vitamins in chronic liver disease, a doubling of the daily dose of an aqueous preparation of vitamins A, D, E and K may be utilized as a starting dose.
Malabsorption in chronic liver disease

• Fat Soluble Vitamins
  • Periodic determination of serum vitamin A, 25 OH-D, and vitamin E levels may be necessary to optimize nutritional support and may result in supplementation of individual fat soluble vitamins
  • As a surrogate for vitamin K, prothrombin time and/or INR (international normalized ratio) may be serially followed
  • Hypocalcemia, due to dietary calcium deficiency or malabsorption, with can lead to resultant rickets and osteopenia on bone radiographs may be observed
  • Large doses of vitamin D supplements (5-20,000 IU/day) may be required to correct this condition
## Vitamin supplementation in children with cholestasis

<table>
<thead>
<tr>
<th><strong>Vitamin</strong></th>
<th><strong>Recommended dose</strong></th>
<th><strong>Preparation</strong></th>
<th><strong>Dose provided</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vitamin A</strong></td>
<td>Oral supplementation of vitamin A ranges from 5,000 to 25,000 IU/day of water-miscible vitamin A</td>
<td>Vitamin A capsules ADEK drops (Axcan Pharma) ADEK tablets Vitamin A parenteral (Aquasol A Parenteral, Mayne Pharma)</td>
<td>10,000 U/capsule or 25,000 U/capsule, generic 3170 IU/ml of vitamin A as palmitate and 50% as beta carotene 9,000 IU of vitamin A as palmitate and 60% as beta-carotene 50,000 U/ml-15 mg retinol</td>
</tr>
<tr>
<td><strong>Vitamin D</strong></td>
<td>600-2000 IU/day 0.02 μg/kg</td>
<td>Oral vitamin D supplementation (Drisdol, Sanofi-Synthelabo) 1,25-OH vitamin D (Calcijex-AAbbott, calcitriol injection)</td>
<td>ergocalciferol 50,000 IU/capsule, 8,000 U/ml 1 μg/ml</td>
</tr>
<tr>
<td><strong>Vitamin E</strong></td>
<td>In infants, 50-100 IU/day In older children with vitamin E deficiency, 15-25 IU/kg/day</td>
<td>α-tocopherol, Aqua-E (Yasoo Health) Liqui-E (TPGS-d-alpha tocopheryl poly-ethylene glycol 1000 succinate, Twinlabs)</td>
<td>20 IU/ml 400 IU/15 ml</td>
</tr>
<tr>
<td><strong>Vitamin K</strong></td>
<td>Daily or twice weekly dose of 2.5-10 mg, dependent upon response to therapy Subcutaneous or intravenous vitamin K administration (1-5 mg dependent on size)</td>
<td>[Mephyton, Merck and Co., (vitamin K1 AquaMephyton, [Merck and Co., (vitamin K1)].]</td>
<td>5 mg. Tablets 2 mg/ml or 10 mg/ml</td>
</tr>
</tbody>
</table>
Portal Hypertension: Definition

- Elevation of the portal pressure >10-12 mm Hg
- Most commonly the result of obstruction of portal venous flow by presinusoidal, sinusoidal or postsinusoidal blockage
- Rare increased splanchnic blood flow
Portal Hypertension

- Postsinusoidal obstruction characterized by hepatic synthetic compromise, coagulopathy and progressive liver failure
- Treatment for postsinusoidal obstruction may require liver transplantation for definitive correction
Portal Hypertension: Diagnosis

• Clinical history concentrate on family history of inherited metabolic diseases or exposure to virus or toxins causing cirrhosis

• Physical exam
  – Ascites
  – Liver size and contour
  – Nutritional status
  – Hypersplenism (spleen size or bruising)
  – Hepatopulmonary syndrome (spider angiomas, clubbing, cyanosis)
Portal Hypertension: Evaluation

- Historical events (umbilical catheters)
- Hypercoagulopathy
  - Protein S, C, Factor V Leiden
- Ultrasonography
  - Doppler- direction and velocity of portal flow
- MRA
  - Definition of portal anatomy
Portal Hypertension: Surveillance

- Spleen size on PE
- WBC and platelet counts
- Ultrasonography
- Endoscopy
- Upright oxygen saturation (Hepatopulmonary syndrome)
Portal Hypertension: Surveillance

- Endoscopy
- Varices
  - Site of acute GI bleeding
- Portal hypertensive gastropathy
- Large varices
- Red spots
- Therapy
  - Sclerotherapy
  - Banding
Portal Hypertension: Interventions

- Pharmacologic, Endoscopic, Surgical
- Based upon natural history of the disease and life threatening complications
- GI Bleeding most common complication
  - Fluid resuscitation (be careful not to overload)
  - Blood replacement
  - NG tube
  - H₂ blocker or PPI
  - Vitamin K, FFP, cryoprecipitate, platelets
Portal Hypertension: Pharmacologic

- Vasopressin
- Increases splanchnic vascular tone, decreases splanchnic arterial inflow and thus decreases portal venous pressure
- Initial bolus 0.3 units/kg over 20 minutes followed by continuous infusion 0.002-0.005 U/kg/minute
- Controls variceal bleed in 53-85% of children (Karrer & Narkewicz Sem Ped Surg 1999;8;193)
- Systemic vasoconstriction to heart, bowel and kidneys impairs cardiac function and exacerbates fluid retention
Portal Hypertension: Pharmacologic

- Somatostatin and Octreotide
- Somatostatin, 14-amino acid peptide
  - Reduces splanchnic blood flow by selective mesenteric vascular smooth muscle constriction
  - Short half-life complicates its use
- Octreotide
  - Can be given sq but best given IV drip (25-50 μg/m²/hour or 1.0 μg/kg/hour)
- Both drugs achieve excellent results in controlling bleeding in adult trials - no trials in children
Portal Hypertension: Pharmacologic

- Beta-Blockers
- No role in acute bleeding, useful for prophylaxis
- Decrease heart rate by 25%- decreases cardiac output, portal inflow
- In adults, efficacy assessed in patients:
  - with documented varices to prevent 1st bleed (primary)
  - Following 1st bleed to prevent further bleeds (secondary)
- In primary prophylaxis, 3.9% vs. 21.6% control
- In secondary prophylaxis, controversy:
  - In Child A 3%, but in Child B or C 46-72%
Beta–Blockers in Children

- Decrease heart rate by 25% - decreases cardiac output, portal inflow
- Shashidhar et al. JPGN 1999;29:12
  7/21 (33%) bled on propranalol Rx, 2/21 (10%) noncompliant, 4/21 (19%) inadequately dosed
  Propranalol efficient for preventing 1st bleed, but only useful in Child-Pugh A children to prevent recurrent bleeding
Portal Hypertension

- Mechanism: increased resistance to blood flow from the visceral or splanchnic portal circulation to the right atrium
- Presinusoidal obstruction does not cause impairment in hepatic synthetic function
- Treatment for presinusoidal obstruction should be directed toward prevention of hemorrhage while spontaneous collaterals develop
Portosystemic Shunting

- Intrinsic liver disease minimal - relatively intact function
- Refractory variceal hemorrhage
- Pre-emptive for renal transplant in severe portal hypertension
- Careful consideration for future renal or liver transplant
Portal Hypertension: Interventions

- Primary vs. secondary prophylaxis
- Activity restrictions (weight lifting)
- β-blockade: propranolol
- Band ligation
- Surgical shunt
- Immunization issues
  - Pneumococcal, meningococcal
Portal Hypertension: Sclerotherapy

- 5% ethanolamine, 1-5% tetradecyl sulfate, 5% sodium morrhuate
- 3-6 sessions over 2-4 weeks
- Complications: retrosternal pain, fever, dysphagia
- Esophageal ulcers at injection site 70-80%
- Esophageal strictures, perforation or mediastinitis in 10-20%
Portal Hypertension: Sclerotherapy

• In children with extrahepatic portal hypertension, recurrent variceal bleeding developed in 31% over 8.7 years (Stringer et al Gut 1994;35:257)

• In children with intrahepatic disease, recurrent variceal bleeding developed in 75% (Fox et al. JPGN 1995;20: 202)
Portal Hypertension: Band Ligation

- In children, variceal obliteration in 73-100%
- Recurrence in 75% with intrahepatic disease
- Small size of child’s esophagus limits number of O-rings that can be placed in 1 session
- Below 1 y.o. the thinness of esophageal wall makes full-thickness ligation a risk-contraindicated <1 year

Price et al J Ped Surg 1996;31:1056
Fox et al. JPGN 1995;20:202
Portal Hypertension: Primary Prophylaxis

• In children, EST and EBL utilized
• Goncalves et al J Ped Surg 2000;35:401 prophylactic EST decreased bleeding 42% to 6% in randomized controlled trial
• But 16% developed congestive hypertensive gastropathy
• No effect on patient survival
Portal Hypertension: Primary Prophylaxis

- In children, EBL utilized
- For intrahepatic disease, 72% varices eradicated or improved
- 66% required EST in addition to achieve control
- 27% no control or recurrence
- Congestive hypertensive gastropathy noted
Biliary Disease: Interventions

- High index of suspicion
- ? Prophylactic antibiotics
- ? Ursodeoxycholic acid
Liver Transplant
Timing: When to Transplant?
Referral for Transplant Evaluation

• EARLY!!!!
• When you are uncertain
• Complications of Liver Disease
  – Portal hypertension, ascites and bleeding
  – FTT
  – Recurrent cholangitis
  – Intractable itching