Malabsorption

Samuel Kocoshis, M.D.
Professor of Pediatrics, University of Cincinnati College of Medicine
Director, Nutrition and Intestinal Transplantation, Cincinnati Children’s Hospital Medical Center.

Outline

• The digestive/absorptive process
• Distinction between maldigestion and malabsorption
• Clinical features of malabsorption/maldigestion
• Laboratory evaluation of malabsorption/maldigestion
• Examples of malabsorption/maldigestion
  – Shwachman syndrome
  – Autoimmune enteropathy
  – Short bowel syndrome

Small Bowel

• Internal surface 3m²
• Presence of Kerckring valves, villi and microvilli multiplies the absorptive surface to 250 m²
• Explains the clinical dissociation between malabsorption and enteropathy.

Exocrine pancreas

• Contains lobules formed by acini (80% of parenchyma) and ducts (5%)
• Acinus
  – 6-8 pyramidal acinar cells with apical poles facing the lumen that leads to a duct.
  – Large number of secretory vesicles (zymogen granules)

Digestive Secretion

• 3 phases
  – Cephalic
    • Mediated by vagal nerves
    • Stimulates ACINAR cell secretions without affecting DUCTAL cell secretions
  – Gastric
    • Begins when food distends the stomach
    • Low volume enzyme rich secretion
  – Intestinal
    • Begins when gastric juice and food enter the duodenum
    • Regulated by hormones and vagovagal reflexes
    • Both DUCTAL and ACINAR secretions increase

CCK, vagovagal reflex
Secretin, CCK, cholinergic input
Carbohydrates

- Starch and simple sugars
  - (40-50% of the calories in the western diet)
- Only starch molecules require preliminary intraluminal digestion

α-amylase

- Produced in salivary glands and the pancreatic acini
- 5-6% of total protein in pancreatic secretions
- Cleaves α-1,4-glucose linkage
- Pancreatic amylase insufficiency occurs normally in newborns
  - salivary and brush border glucoamylase; allow amounts of starch to be given
  - similarly for exocrine pancreas deficiency to occur levels need to be below 10% of normal.

Proteins

- Most adults consume 70 – 100g of protein daily
- Begins in stomach with gastric acid denatures protein and activates pepsinogens I and II.
- Trypsin, chymotrypsin and elastase cleave internal peptide bonds
- Carbopeptidases A & B cleave amino acids from the carboxy-terminus of peptides.

Lipids

- Triglycerides account for > 95% of the 100 to 150g of fat consumed daily.
- 15% of fatty acids are released in the stomach, digestion continues in small intestine with different pancreas
- Need to be digested into long chain C14-22, medium chain C6-12, and short chain < C6 monoacylglycerol.
**FAT**

- Digestion starts in stomach
  - Gastric lipase (produced in fundus)
    - Acidic optimum pH, hydrolyzes MCT and LCT, not dependent on bile salts (inhibited), resistant to pepsin.
  - Starter of pancreatic lipolysis (favoring emulsification of lipid droplets)
  - More important in neonates whose pancreatic lipase is low.

**Pancreatic Lipase**

- Acts at the oil/water interface
- Releases FFA and MG from TG
- Pancreatic triglyceride lipase cleaves the majority of fatty acids from diet
  - Congenital deficiency malabsorb 50-60% of TAG
- Bile salts increase the interface by emulsifying ingested lipid droplets (favoring lipase activity) and inhibiting action by forming a film between oil and lipase, colipase restores lipase activity

**Role of Conjugated Bile Acids**

- Cholic and chenodeoxycholic acids are conjugated with glycine and taurine and excreted into the bile
- Conjugated bile acids allow much better micellar solubilization
- Colonic bacteria transform them into deoxycholic and lithocholic acids
- Under conditions of health, 97% are reabsorbed in the distal ileum

**Malabsorption Syndrome**

- Alteration of digestive processes
Malabsorption Syndrome

- Alteration of digestive processes
- Alteration of uptake and transport
  - Alterations of Intestinal Wall
  - Alterations of Circulation
- Alterations caused by microbial agents
  - To mucosa
  - To bile
  - To nutrients themselves

Malabsorption

- Symptoms are due to:
  - Persistence of nutrients in the lumen
    - Diarrhea, steatorrhea, meteorism, abdominal discomfort
  - Decreased tissue utilization of nutrients
    - weight loss, anemia, etc.

Differential Diagnosis for Steatorrhea

- Causes for fat malabsorption and steatorrhea are much more numerous than those of carbohydrate and protein malabsorption.
  - Lipase or colipase deficiency(ies)
  - Exocrine pancreatic insufficiency
  - Abnormal bile salt synthesis, excretion, deconjugation, reabsorption
  - Impaired TG resynthesis
  - Chylomicron formation/excretion
  - Abnormal intestinal lymphatics
  - Bacterial overgrowth
  - Mucosal disease

Careful History Is the Most Important Step

What About Mucosal Disease?

- Fat in stool is mainly FFA partly hydroxylated by the colonic flora, which have a secretory effect.
- Moderate Steatorrhea observed in subtotal villous atrophy usually not sufficient to make the stools grossly greasy
  - Tend to be watery from associated carbohydrate fermentation and secretory effect of hydroxylated fatty acids

<table>
<thead>
<tr>
<th>Exocrine Pancreatic Insufficiency</th>
<th>Intestinal Malabsorption</th>
<th>Diarrhea due to Fermentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool</td>
<td>Loose, pasty, homogenous, grossly greasy, constant volume</td>
<td>Loose, liquid, acidic smell, rarely greasy, abdominal distention</td>
</tr>
<tr>
<td>Rarely one class of nutrient</td>
<td>Never affect only fat malabsorption</td>
<td>Less severe steatorrhea</td>
</tr>
<tr>
<td>Test</td>
<td>Fecal Elastase, Sweat test</td>
<td>Breath H2 test, Fecal reducing substances, Disaccharidases</td>
</tr>
<tr>
<td>Causes</td>
<td>Cystic Fibrosis, Shwachman Diamond, Johanson Blizzard, Pearson Syndrome</td>
<td>Celiac Disease, Giardia Lamblia, Bacterial Overgrowth, Immune Deficiency</td>
</tr>
</tbody>
</table>
### Test Normal Values Implication

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal Values</th>
<th>Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>α1-antitrypsin concentration</td>
<td>&lt;0.9mg/g</td>
<td>† intestinal permeability</td>
</tr>
<tr>
<td>Steatocrit</td>
<td>&lt;2.5% (over age 2)</td>
<td>Fat malabsorption</td>
</tr>
<tr>
<td>Fecal reducing substances</td>
<td>Absent</td>
<td>Carbohydrate malabsorption</td>
</tr>
<tr>
<td>Elastase Concentration</td>
<td>&gt;200 µg/g</td>
<td>Pancreatic function</td>
</tr>
<tr>
<td>Calprotectin Concentration</td>
<td>&lt;50 µg/g</td>
<td>Intestinal inflammation</td>
</tr>
</tbody>
</table>

### Fecal Elastase 1

- Sterol-binding protein
  - Human & pancreas specific
  - Porcine supplements do not alter measurement
- Elastase 1 is assessed via ELISA
- False positives
  - High volume Diarrhea
  - Bacterial overgrowth

### Shwachman-Diamond Syndrome

- First described in 1964- syndrome affecting the exocrine pancreas and bone marrow
- Prevalence 20x lower than CF
- 7q11-SBDS gene
  - 3 common mutations account for 74% of alleles associated with SDS.
- SBDS protein
  - Associated with RNA metabolism or ribosomal function

### SDS: Clinical Manifestations

- General features
  - Lower than average weight and height at birth
  - Failure to thrive
  - Most present in infancy or early childhood with
    - Malabsorption
    - Malnutrition
    - Growth Failure
    - Recurrent Infections

### Bone marrow dysfunction

1. Chronic neutropenia
   - At least 3x over a period of 3 months or more
2. Persistent thrombocytopenia
3. Persistent pancytopenia
4. Myelodysplasia with or without clonal abnormalities

### Metaphyseal Dysostosis
Exocrine Pancreas

- Varying severity
- Universal Manifestation
- Unlike CF (pancreatic ductal obstruction), there is failure of pancreatic acini to develop
  - Reduced enzyme output
  - Preserved ductal function (fluid, Na,K,Cl and HCO3)
- Enlargement of pancreas due to liposis

Lipotic Pancreas

- Stimulated pancreatic secretions fall more than 98% below the mean reference value.
- Clinical evidence of steatorrhea
- Subset of patients show moderate improvement in pancreatic acinar capacity with advancing age.
- Pts with pancreatic insufficiency have serum trypsinogen of <6 µg/ml, those with normal fat absorption have serum trypsinogen values >6
  - (20% of this patients values are within reference range 16.6-45.5)

Natural History of SDS

- 50% of affected patients will show sufficient improvement in pancreatic acinar capacity to no longer require enzyme supplements.
  - All these patients continue to have evidence of pancreatic dysfunction based upon quantitative intubation techniques.
- Liver disease also improves over time

Enzyme Replacement

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Daily fat intake (g)</th>
<th>Daily lipase units</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.5</td>
<td>25</td>
<td>12,500-25,000</td>
</tr>
<tr>
<td>0.5 - 1</td>
<td>30</td>
<td>15,000-30,000</td>
</tr>
<tr>
<td>1 - 3</td>
<td>35</td>
<td>17,500-140,000</td>
</tr>
<tr>
<td>4 - 6</td>
<td>50</td>
<td>25,000-200,000</td>
</tr>
<tr>
<td>7 - 10</td>
<td>60</td>
<td>30,000-240,000</td>
</tr>
<tr>
<td>11 - 14</td>
<td>90</td>
<td>45,000-360,000</td>
</tr>
<tr>
<td>15 - 18</td>
<td>110</td>
<td>55,000-440,000</td>
</tr>
</tbody>
</table>

Autoimmune Enteropathy

- No true consensus as to the definition
- An operational definition used by many is the following:
  - Immunologically mediated disorder of the small and possibly aor large intestine usually resulting in loss of surface area severe enough to mandate parenteral nutrition if left untreated.
- Some insist that circulating anti enterocyte antibodies be present to establish the diagnosis
  - What about anti-goblet cell antibodies? Are they specific?
Antieterocyte Antibodies

- These are performed on the patient’s serum
- They are humeral antibodies, but are probably an epiphenomenon.
- They were originally measured by indirect immunofluorescence
  - Mirakian et al. BMJ 1986;293:1132–1136
- An ELISA is now available
- Patients can have IgG, IgA, or IgM antibodies
- Tend to be quite specific, but tend to wax and wane.

Gastrointestinal Manifestations

- Profound Diarrhea
  - Diarrhea has both a secretory and an osmotic component
  - Macro- and micro- nutrient malabsorption is universally present
- Gastrointestinal bleeding may (if colon is involved) or may not be present
- Dysphagia may be present if there is esophageal involvement with stricturing

Autimmune Enteropathy

- Autoimmune enteropathy is a common manifestation of the following disorders
  - Common variable immunodeficiency
  - Polysaccharide immunodeficiency
  - Severe combined immunodeficiency
- APECED
- IPEX
**APECED**

- Autoimmune
- Poly
- Endocrinopathy
- Candidiasis
- Ectodermal
- Dystrophy

**APECED--Diagnosis**

- Two of the following 3 disorders must be present
  - Hypoparathyroidism
  - Candidiasis
  - Adrenal insufficiency

**Organ-specificity of APECED**

- Enteritis
- Colitis
- Atrophic Gastritis
- Hepatitis
- Hypogonadism
- Adrenal Insufficiency
- Hypoparathyroidism
- Alopecia
- Vitiligo
- Keratopathy
- Diabetes
- Thyroiditis
- Tooth Dysplasia
- Membranoproliferative nephritis

**Nails in Candidiasis**

- Enamel Hypoplasia and Peg Teeth

**Genetic Basis for APECED**

- Mutation on chromosome 21q22.3
  - This region encodes the AIRE gene
- AIRE encodes a transcription factor that forms nuclear bodies and interacts with a transcriptional regulator
- The mutation results in impaired cellular immunity against candida and the development of multiple autoantibodies
Treatment of APECED

• Treat organ hypofunction
• Immunosuppressant Therapy
  – Corticosteroids
  – Azathioprine
  – Cyclophosphamide
  – Methotrexate
  – Calcineurin Inhibitors
• Bone Marrow Transplantation

IPEX

• Immunodysregulation
• Polyendocrinopathy
• Enteropathy
• X Linked

Initial Manifestations

• Development of systemic autoimmunity in the first year of life
• Usually with a triad of symptoms:
  – Watery Diarrhea
  – Endocrinopathy (usually neonatal diabetes)
  – Dermatitis

Protean Clinical Findings

• DM 1
• Enteropathy
• Eczema
• Anemia (Coombs Positive)
• Autoimmune thrombocytopenia / neutropenia
• Hypothyroidism
• Tubular Nephropathy

Genetics of IPEX

• X-linked recessive
• Mutations (in most cases) are in FOXP3 gene
• Relevant role of FOXP3 is in the generation and function of Tregs
• Initially identified in mouse model
  – Scurfy mouse (sf): Natural mutant resembling IPEX
Laboratory Findings in IPEX

• There are no specific laboratory findings: Only those associated with the noted manifestations
• Things that can be seen
  – Elevated serum concentration of immunoglobulin E (IgE)
  – Autoantibodies to pancreatic islet antigens, thyroid antigens, small bowel mucosa
  – Autoimmune anemia, thrombocytopenia, and/or neutropenia
  – Intermittent eosinophilia
• Normal immunologic surveillance

Perspectives on Treatment

• Two front approach
  – Treatment of phenotypic manifestations
    • Diabetes
    • Eczema
  – Treatment of disease
    • Immunosuppression
      – Regimens including steroids with CSA or Tacrolimus
      – Sirolimus which permits differentiation of precursors into Tregs
    • BMT
      – May be only truly curative therapy, but clearly much more dangerous in APECED
      – Nonablative conditioning is the preferred approach

Intestinal Failure

Operational Definition

• Reduction of intestinal absorption severe enough to require nutrient, fluid, or electrolyte supplementation
  – TPN necessary=severe
  – TEN necessary=mild

Magnitude of the Problem

• In 1992, 40,000 North Americans were on TPN
• The average per capita expenditure per TPN patient per day was $1000.
• The total expenditure was $40,000,000/day or $14,600,000,000/year.
• Even in Mexico with a much smaller gross national product than the US, the annual cost of short gut is $50,000/patient
• Intestinal transplantation costs $300,000-$400,000/patient

Mosi-oa-tunya (Victoria Falls)
How Long Would Annual Diarrheal Water Flow over Victoria Falls?

- Flow is 3-8 million liters/minute
- Acute diarrhea—4 hours
  - Assuming 1 billion people pass 2 billion liters/year
- Chronic diarrhea—38 hours
  - Assuming that 100 million people pass ½ liter/day x 1 year

*Modified from reasoning espoused by Dr. Mary Estes*

Typical Physiologic Changes of Short Bowel Syndrome

- Rapid Transit (Stage I—several weeks)
- Slow Transit (Stage II weeks to months)
- Gastric Hypersecretion
- Macromolecular Penetration
- Hormonal Imbalance
- Salt Loss (especially after colon resected)
- Bacterial Overgrowth
- Bile Acid and Fatty Acid Malabsorption

Gastric Hypersecretion

- Occurs in 50% early in post-op course
  - improves with time
- ↑peptic ulcer disease
- ↑diarrhea, ↓absorption (effect on pancreas)
- Etiology
  - ↓gastrin catabolism by SB
  - ↓inhibitors of gastrin secretion
    - (secretin, CCK, GIP, VIP, glucagon)

Mechanisms and Consequences

- Loss of duodenum
  - Fe, Ca, Mg are maximally absorbed in duodenum but quantitatively more absorption occurs in distal small bowel
  - ↓duodenal resection may not necessarily result in deficiencies
- Loss of duodenum and proximal jejunum
  - loss of CCK and secretin result in sluggish bile flow

Mechanisms and Consequences

- Loss of jejunum
  - Disaccharide intolerance due to loss of length
  - Water soluble vitamin deficiencies
  - Folate can be malabsorbed, but folate synthesized by luminal bacteria as well as ileal adaptation usually result in elevated folate levels.

Mechanisms and Consequences

- Loss of distal ileum
  - Malabsorption of IF-bound B₁₂
  - Malabsorption of conjugated bile salts
    - ↓bile salt pool, fat malabsorption, fat soluble vitamins
  - Malabsorption of Ca, Mg, Zn → insoluble soaps with unabsorbed fat
  - Malabsorption of oxalate → stones usually occur with intact colon
  - Contamination of SB with colonic bacteria → deconjugate bile salts fatty acids → OH-fatty acids
Basic Principals of TPNology

- Early phase
  - Fluid and electrolyte balance
  - TPN providing all nutrients in moderation
- Gradual introduction of enteral feeds as a continuous drip
- Monitor adequacy of Na intake by monitoring urinary Na (applies to late phase too!!)
- Monitor glucose infusion rate and keep below 12.5 mg/kg/min. (Lloyd D, Nutr. 1998:14:101.)
- Keep non-nitrogen calorie to nitrogen ratio >150<250

Cholestatic Liver Disease: A Life-Threatening Complication of Intestinal Failure

Are These the Culprits?

Stigmasterol and FXR Target Genes

Consequences of Stopping Lipid

- Essential fatty acid deficiency—do we really believe that rubbing the child with vegetable oil will correct this?
- Elevated glucose infusion rate resulting in:
  - An increased respiratory quotient—generally when GIR is >12-13 mg/kg/minute
  - Hyperinsulinemia leading to:
    - Hepatic steatosis
    - Hypertriglyceridemia—what a paradox (less lipid results in more triglycerides!)
  - An increased rate of sepsis!

Direct bilirubin trajectories over time (weeks from baseline) for the fish-oil (A) and soybean (B) cohorts

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Pitfalls in Giving Omega 3 Lipid

• EFA Deficiency?
  – Not especially likely insofar as arachidonic acid is 2.1% of its lipid
• Thrombocytopenia/Thrombasthenia?
• Progression of Fibrosis Despite Resolution of Cholestasis?
• ...And What Happens to Biliary Phospholipids?
• Is SMOF* the Lipid of the Future?

*SMOF stands for soy, medium chain fat, olive oil, fish oil

What Governs the Outcome?

Whether or not full adaptation occurs before the complications of TPN (end stage liver disease, fatal infection, loss of access, metabolic/mechanical complication) occur.

Ancillary Management

• Acid blockade (early vs. late)
  – Pro: Treat hypersecretion, GER common
  – Con: Possibly predisposes to overgrowth
• Give B12 every 3 months (after TPN outgrown)
• Antiperistaltics
  – Loperamide improves water absorption AND motility
• Pancreatic enzymes
  – Measure fecal elastase!!!
• Treat contaminated bowel syndrome

Typical Nutrition Regimen

• Provide balanced TPN
  – ~2g/kg/d of protein
  – ~2g/kg/d of lipid
  – Glucose infusion rate of <13 mg/kg/min
• Give continuous gastrostomy or jejunostomy feedings at a low rate (1-2 ml/kg and vent stomach if necessary)
• Provide sham feedings (initially), then small volume oral feeds
• Increase feedings by 1-3 ml/hr/week
• Maintain + fluid balance
• Do not reduce feedings unless there is weight loss despite positive fluid balance
• A rough rule of thumb: ~50 ml/kg/day of fecal output

Typical Enteral Nutrition Regimen

• Give continuous gastrostomy or jejunostomy feedings at a low rate (1-2 ml/kg and vent stomach if necessary)
• Provide sham feedings (initially), then small volume oral feeds
• Increase feedings by 1-3 ml/hr/week
• Maintain + fluid balance
• Do not reduce feedings unless there is weight loss despite positive fluid balance

Bowel Lengthening

• Non-transplant bowel rehabilitative surgery has been characterized by a great deal of nonsense.
• Two procedures have emerged as the most promising.
  – The Bianchi procedure
  – The S.T.E.P. procedure
Diagrammatic Representation of Bianchi Procedure


Diagrammatic Representation of S.T.E.P. Procedure


Bowel Transplantation: When All Else Fails