Malabsorption in Children

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Objectives
- Define malabsorption. Discuss its clinical presentations and etiologies in children
- Describe the diagnostic work up.
- Current treatment and management strategies
  - Focus on enteral nutrition
  - Course and prognosis

Disclosures
- Ryan Carvalho MD, discloses the following relationships with commercial companies:
  - Grant/Research Support from CCFA (sub-investigator)
  - Consultant for Nestle nutrition and Nestle Health Sciences
  - Advisory board for Nestle Nutrition, North America
  - Future employee to Nestle Nutrition

Malabsorption (Criteria outside infancy)
- Patients considered to have malabsorption in the enteral nutrition (EN) literature include patients who
  - Have moderately impaired gastrointestinal tract function
  - Critically ill in the intensive care unit
  - Undergone abdominal surgery or bowel resection
  - Variations of the above who develop diarrhea after the start of EN.

Nomenclature
- Malabsorption refers to defective mucosal absorption of nutrients. It may occur for many nutrients or specific carbohydrates, fats, or micronutrients.
  - Malabsorption (anecdotal) reaches clinical significance when 90% of organ function is impaired
- Mal-digestion denotes impaired nutrient hydrolysis.
- However, the two entities are so closely linked that in clinical practice malabsorption serves as a global term for all aspects of their impairment.

Physiology

<table>
<thead>
<tr>
<th>Material/Volume</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterile water</td>
<td>7.33</td>
</tr>
<tr>
<td>Calcium gluconate</td>
<td>7.30</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>7.40</td>
</tr>
<tr>
<td>Tris buffer</td>
<td>7.4</td>
</tr>
<tr>
<td>0.9% NaCl</td>
<td>7.4</td>
</tr>
<tr>
<td>0.45% NaCl</td>
<td>7.4</td>
</tr>
</tbody>
</table>


Normal absorption

<table>
<thead>
<tr>
<th>Food Item</th>
<th>Mode of absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteins</td>
<td>Digestion and Ionic</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>Digestion and Ionic</td>
</tr>
<tr>
<td>Lipids</td>
<td>Digestion and Ionic</td>
</tr>
<tr>
<td>Vitamins</td>
<td>Absorption</td>
</tr>
<tr>
<td>Minerals</td>
<td>Absorption</td>
</tr>
<tr>
<td>Water</td>
<td>Absorption</td>
</tr>
</tbody>
</table>

Luminal phase

- Enterokinase deficiency
- Trypsinogen deficiency
- Impaired micelle formation
- Bacterial overgrowth

Mucosal phase

- Impaired brush border activity
  - Lactase & sucrase-isomaltase deficiency
- Inherited or acquired mucosal defects
  - Glucose-galactose malabsorption
  - A-betalipoproteinemia, Hartnup disease
- Acquired defects of absorptive surface area
  - Crohn's disease, Celiac disease, Intestinal resection, Lymphoma
- Infections
  - Giardiasis, Tropical sprue

Transport phase

- Carbohydrate
  - Subsequent entry of the final monosaccharide's (glucose, galactose, fructose) into the enterocytes through the brush border occurs via carrier molecules.
  - Glucose and galactose share SGLT-1
  - Fructose uses a carrier down a concentration gradient

- Protein
  - Free amino acids are taken up by enterocytes through specific Na-linked carrier systems, whereas the small peptides are translocated into the absorptive epithelial cells by a system with a broad specificity.
  - In the first few months of life, the latter system is much more active than those that transport amino acids and is thought to play a bigger physiological role

- Lipids
  - Chylomicrons are transported into lymphatics
  - Triglyceride transport into lacteal
Carbohydrate

- Carbohydrates in the diet (starches, sucrose, lactose).
- Amylase digestion include maltose, maltotriose, and higher residues of glucose polymers.
- The final hydrolysis of disaccharides and oligosaccharides occurs at the brush border of the enterocytes,
  - sucrase-isomaltase breaks down maltose, isomaltose (to glucose), and sucrose (to glucose and fructose)
  - glucoamylase releases glucose from glucose polymers
  - lactase splits lactose into glucose and galactose

<table>
<thead>
<tr>
<th>Starch</th>
<th>Salivary and pancreatic amylase</th>
<th>Brush border glucoamylase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large starch molecules</td>
<td>Pancreatic enzymes</td>
<td>Pancreatic Insufficiency</td>
</tr>
<tr>
<td>Lactose, maltose, sucrose</td>
<td>Brush border disaccharidases</td>
<td>Transient loss after infections</td>
</tr>
<tr>
<td>Lactose</td>
<td>Congenital lactase deficiency</td>
<td>Extremely rare</td>
</tr>
<tr>
<td>Sucrose, isomaltose</td>
<td>Congenital enzyme deficiency (CED)</td>
<td>Most common CED</td>
</tr>
<tr>
<td>Glucose, galactose</td>
<td>SGLT-1 deficiency</td>
<td>AR inheritance</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>Small Bowel bacterial overgrowth</td>
<td>Dysmotility, medications, surgery</td>
</tr>
</tbody>
</table>

History: Genetic influences

- Congenital sucrase-isomaltase deficiency is most common in Canadian Eskimos and natives of Greenland.
- Congenital lactase deficiency is more common in infants of Finnish descent (Chr 2q21)
- Deficiency of trehalose, a sugar found almost exclusively in mushrooms, is rare, except in natives of Greenland.
- Adult-onset lactase deficiency is most common in persons of Asian, African, and Mediterranean descent.

Protein

- Stomach:
  - Pepsinogens are activated to pepsins by a pH < 4
  - Proteins are hydrolyzed to LMW peptides.
- Duodenum
  - Pancreatic proteases (activated by trypsin) further split them into LMW peptides and free amino acid
  - The final products of intra-luminal digestion are composed of LMW peptides (2-6 amino acid residues) for 70% and free amino acids for 30%.
  - Brush border bound peptidases further hydrolyze peptides to release a mixture of free amino acids and small peptides (2-3 amino acid residues).

Protein digestion

Protein malabsorption

<table>
<thead>
<tr>
<th>Malabsorption</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>Pancreatic exocrine insufficiency</td>
</tr>
<tr>
<td>Protein</td>
<td>Congenital enterokinase deficiency</td>
</tr>
<tr>
<td>Protein loosing enteropathy</td>
<td>Mucosal injury: Protein sensitive syndromes, inflammatory bowel disease, Autoimmune disorders</td>
</tr>
<tr>
<td>Protein loosing enteropathy</td>
<td>Congenital lymphangiectasia Milroy disease (associated limb edema)</td>
</tr>
</tbody>
</table>
Fat Absorption

- **GASTRIC PHASE**
  - lingual lipase
- **INTESTINAL**
  - luminal
  - mucosal
  - lymphatic (delivery)

Lipids

- A lingual lipase is responsible for the first partial hydrolysis of triglycerides:
  - this enzyme becomes active in persons with low gastric pH levels and is active even in premature infants.
- Majority of triglyceride digestion occurs in the duodeno-jejunal lumen because of pancreatic enzymes
  - Primarily the lipase-colipase complex.
  - Low capacity in babies, “physiologic steatorrhea newborn”
- Adequate concentrations of intraluminal conjugated bile salts are needed to form micelles
  - secretion of bile acids may also be partially inadequate in very young patients.

Fat malabsorption

<table>
<thead>
<tr>
<th>Fat Malabsorption</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe fat malabsorption</td>
<td>Exocrine pancreatic insufficiency, Cystic fibrosis, Schwachman-Diamond, Johanssen-Blizzard, Pearson syndrome</td>
</tr>
<tr>
<td>Biliary &amp; Cholestatic liver disease. Impaired bile production</td>
<td></td>
</tr>
<tr>
<td>Steal inflammation, resection.</td>
<td></td>
</tr>
<tr>
<td>Moderate fat malabsorption</td>
<td>Small bowel bacterial overgrowth</td>
</tr>
<tr>
<td></td>
<td>Abetalipoproteinemia</td>
</tr>
<tr>
<td></td>
<td>Lymphangiectasia</td>
</tr>
</tbody>
</table>

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

INTESTINAL DYSFUNCTION in Acute Care

The spectrum of GI Dysfunction in the ICU

- Ischemia
- Obstruction
- Peritonitis
- Hypo-perfusion, Electrolyte imbalance
- Drugs, Malnutrition, NPO, Infection & Multiple other Insults & Causes

<table>
<thead>
<tr>
<th>Severe Dysfunction</th>
<th>GI Dysfunction</th>
<th>Normally functional GI tract</th>
</tr>
</thead>
</table>
INTESTINAL DYSFUNCTION: MALABSORPTION

<table>
<thead>
<tr>
<th>Cause</th>
<th>Dysfunction</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid &amp; electrolyte imbalance</td>
<td>• Loss of biliary/ pancreatic/ enteral digestive capacity</td>
<td>• Diarrhea</td>
</tr>
<tr>
<td>Poor nutritional status</td>
<td>• Loss of villous trophism</td>
<td>• Luminal loss of nutrient</td>
</tr>
<tr>
<td>No luminal nutrient</td>
<td>• Gut wall edema</td>
<td>• Increased Protein Energy deficit</td>
</tr>
</tbody>
</table>

MALDIGESTION MALABSORPTION

<table>
<thead>
<tr>
<th>Classification of Causes</th>
<th>Biology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>Giardia, Cryptosporidum, tropical diseases</td>
</tr>
<tr>
<td>Inflammatory conditions</td>
<td>Crohn’s disease, Ulcerative Colitis</td>
</tr>
<tr>
<td>Allergies</td>
<td>Food: Milk, Soy, Eggs, Nuts, seafood</td>
</tr>
<tr>
<td>Enzyme deficiencies</td>
<td>Lactose intolerance, Sucrase-Isomaltase deficiency, Trihalose deficiency</td>
</tr>
<tr>
<td>Pancreatic disorders</td>
<td>Cystic Fibrosis, Shwachman Diamond syndrome, Pearson Syndrome, Johanssen Blizzard syndrome</td>
</tr>
<tr>
<td>Autoimmune conditions</td>
<td>Celiac disease</td>
</tr>
<tr>
<td>Congenital enteropathies</td>
<td>Autoimmune enteropathy, Microvillus inclusion disease, tufting enteropathy, IPEX syndrome</td>
</tr>
<tr>
<td>Toddlers diarrhea</td>
<td>Dietary intake of high sugar, low fat</td>
</tr>
<tr>
<td>Systemic Conditions</td>
<td>Hyperthyroidism, Antibiotic associated diarrhea, medications, graft versus host disease, malignancy</td>
</tr>
<tr>
<td>Short gut syndrome</td>
<td>Post NEC, surgical resection, Gastroschisis, SBSO</td>
</tr>
</tbody>
</table>

Symptoms and signs of malabsorption

<table>
<thead>
<tr>
<th>System</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEENT</td>
<td>Alopecia, hair thinning, Pale conjunctiva, Aphthous ulcers, Cheilitis, glossitis</td>
</tr>
<tr>
<td>Extremities</td>
<td>Koilonychia, Edema</td>
</tr>
<tr>
<td>Neurology</td>
<td>Motor weakness, peripheral neuropathy, Sjogren’s, Chestek’s, Trouseau sign (Hypo Ca, Hypo Mg)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Micro/Polyarthropathy, Myalgia, weakness</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Steatorrhea, diarrhea, Fatulence, abdominal distention, Hepatomegaly, Splenomegaly</td>
</tr>
<tr>
<td>CHILDREN</td>
<td>Poor growth, Weight loss or poor weight gain, Pubertal disturbance</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Anemia, bleeding disorders</td>
</tr>
<tr>
<td>Bone</td>
<td>Osteopenia, Osteoporosis, Fractures</td>
</tr>
</tbody>
</table>

Evaluation of a suspected malabsorption

• Good History
• Complete physical exam
• Anthropometrics and growth chart are critical
• Labs
  – Blood count, Total protein/Albumin, metabolic panel
  – Celiac screen (Quant IgA, TTG IgA, EMA IgA), CRP/ESR, Iron studies, Vitamin D, Zn, B12, folate
• Stool studies
  – Infections — Giardia, Crypto etc,
  – fecal elastase
  – Reducing substances, Alpha 1 Antitrypsin (serum – stool), fecal fat (72 hour)

Investigations

<table>
<thead>
<tr>
<th>Test</th>
<th>Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schilling test</td>
<td>To evaluate cause of vitamin B12 deficiency</td>
</tr>
<tr>
<td>Ferritin level</td>
<td>Chronic anaemia, fetal intervillous mthaemia</td>
</tr>
<tr>
<td>RBC tolerance test</td>
<td>Small intestinal disease</td>
</tr>
<tr>
<td>Small intestinal biopsies</td>
<td>Small intestinal disease</td>
</tr>
<tr>
<td>Leukocytes with small intestinal biopsy</td>
<td>Small intestinal disease</td>
</tr>
<tr>
<td>US abdomen, CT abdomen</td>
<td>Chronic mesenteric, Torsion, volvulus</td>
</tr>
<tr>
<td>CRP</td>
<td>Chronic peritonitis</td>
</tr>
<tr>
<td>Stool culture</td>
<td>Chronic anaemia, fetal intervillous mthaemia</td>
</tr>
<tr>
<td>Bone biopsy</td>
<td>Bacterial overgrowth syndrome, Lactate defail</td>
</tr>
</tbody>
</table>

Author: Lee Goldman, MD and Dennis Ausiello, MD. Chapter: Approach to the Patient with Diarrhea and Malabsorption Page: 558
The proof is in the poop

<table>
<thead>
<tr>
<th>Endoscopy</th>
<th>Intestinal Malabsorption</th>
<th>Diarrhea due to Fermentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Stool</td>
<td>Liquid, pale, nonbloody, greasy, constant fecal stream</td>
<td>Liquid, pale, nonbloody, greasy, constant fecal stream</td>
</tr>
<tr>
<td>Rarely seen class of nutrient</td>
<td>Never affected only fat malabsorption does occur</td>
<td>Never affected only fat malabsorption does occur</td>
</tr>
</tbody>
</table>

Test
- Fecal Fat:
- Stool test
- 
- Glucose, Fructose, Gastrin, Diamond, iatrogenic enteropathy
- 
- Positive symptoms

Celiac Disease
- Celiac disease is an autoimmune disorder that can occur in genetically predisposed people where the ingestion of gluten leads to damage in the small intestine.
- Presents with both intestinal and extraintestinal symptoms

Shwachman-Diamond Syndrome
- First described in 1964
- Affecting the exocrine pancreas and bone marrow
- General features
  - Most present in infancy or early childhood with failure to thrive
- Recurrent infections
  - Chronic neutropenia–At least 3x over a period of 3 months or more
  - Persistent thrombocytopenia
  - Persistent pancytopenia
  - Myelodysplasia with or without clonal abnormalities

Autoimmune enteropathy
- Immunologically mediated disorder of the small and possibly large intestine usually resulting in loss of surface area severe enough to mandate parenteral nutrition if left untreated.
- Profound Diarrhea
- Nutrient malabsorption is universally present
- Anti-Enterocyte antibody

Endoscopic evaluation
- Endoscopy with Small bowel biopsy
  - Celiac disease, Autoimmune enteropathy, Microvillus inclusion disease, Tufting enteropathy, Giardiasis disease, Intestinal infestations
- Endoscopy with disaccharidase levels
  - Lactase, Sucrase-isomaltase deficiency
- Endoscopy with duodenal aspirate
  - Small bowel bacterial overgrowth
- Endoscopy with Secretin challenge
  - Pancreatic insufficiency
- Endoscopy with Colonoscopy
  - Inflammatory Bowel disease

What your poop is telling you

<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/dL</td>
<td>Intestinal permeability</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>&lt;2.5% (mean age 7)</td>
<td>Fat malabsorption</td>
</tr>
<tr>
<td>Lactase</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>
Infantile Enteropathies

IPEX
- Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome
- Watery Diarrhea, Endocrinopathy (usually diabetes), Dermatitis
- Mutations (in most cases) are in FOXP3 gene

Microvillus Inclusion disease
- Congenital AR condition
- Patchy or contiguous
- Watery diarrhea, significant malabsorption
- TPN dependant

Short Bowel Syndrome

- Short bowel syndrome in children is a malabsorptive state with insufficient functional intestine to support adequate digestion and absorption either due to surgical resection or congenital disease.

Adaptation

- The capacity of the intestine to undergo successful structural and physiological alterations, to allow the patient to grow while receiving only enteral or oral nutrition.
  - Patient age
  - Underlying diagnosis
  - Portion of small or large bowel resected
  - Ileocecal valve
  - Intrinsic adaptive potential of remaining bowel
  - Health of other organs assisting in digestion/absorption
  - Bacterial overgrowth
  - Type and timing of enteral feeding

Small bowel bacterial overgrowth causing malabsorption

- Small bowel bacterial overgrowth of normal flora alters the intraluminal metabolism of carbohydrates and results in their malabsorption.
- Organic acids stimulate motility and may directly injure the intestinal mucosa.
- D-lactic acidosis

Small bowel bacterial overgrowth causing malabsorption

- Altered intraluminal metabolism of bile acids.
  - Anaerobes and Staphylococcus aureus deconjugate bile acids and impedes their active reabsorption by the terminal ileum.
- Congenital deficiency in the sodium–bile acid cotransporter
- Deconjugated bile acids directly inhibit the carbohydrate transporters, reduce intraluminal pH levels, and damage the enterocyte.
### Treatment of Carbohydrate malabsorption

- Initiate treatment in severe acquired carbohydrate intolerance by eliminating all dietary carbohydrates until the diarrhea is resolved.
- In patients with the most severe carbohydrate intolerance, use MJ3232A,
  - a casein-based formula that contains essential amino acids and medium-chain triglyceride (MCT) oil and no carbohydrates. Parenteral dextrose must be supplied.
- Once the diarrhea has resolved, slowly reintroduce fructose into the diet as the only enteral carbohydrate source.

### Treatment of Protein malabsorption

- A gluten-free diet helps treat celiac.
- Protease and lipase supplements are the therapy for pancreatic insufficiency.
- Antibiotics are the therapy for bacterial overgrowth.
- Corticosteroids, anti-inflammatory agents, such as mesalamine, and other therapies are used to treat regional enteritis
- Immunomodulator therapy for autoimmune enteropathy

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### Peptide vs. free amino acids.

- Peptide-based feedings have been shown to:
  - improve nitrogen retention/balance;
  - improve visceral protein synthesis;
  - improve absorption /reduce diarrhea;
  - maintain/restore gut integrity;
  - reduce bacterial translocation;
  - and improve outcomes.

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### Peptide vs. free amino acids.

- The GI tract has specific and discrete uptake systems and it appears that small peptides consisting of 4–12 amino acids are absorbed more easily and uniformly than corresponding mixtures of free amino acids.

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### Di-peptide & Tri-peptide absorption

- The di- and tripeptides of semi-elemental formulas have specific uptake transport mechanisms and are thought to be absorbed more efficiently than individual amino acids or whole proteins, the nitrogen sources in elemental and polymeric formulas respectively.
- Certain semi-elemental formulas also stimulated jejunal absorption.

---

### Peptide absorption

- The di- and tripeptides of semi-elemental formulas have specific uptake transport mechanisms and are thought to be absorbed more efficiently than individual amino acids or whole proteins, the nitrogen sources in elemental and polymeric formulas respectively.
- Certain semi-elemental formulas also stimulated jejunal absorption.
Treatment of Fat Malabsorption

- MCT oil is more easily absorbed directly into the enterocyte and is transported through the portal vein to the liver.
- Fat-soluble vitamin supplements.
- Supplements in patients with fat malabsorption should also include linoleic and linolenic fatty acids.

<table>
<thead>
<tr>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug Class</strong></td>
</tr>
<tr>
<td>Pancreatic enzyme</td>
</tr>
<tr>
<td>Bile salt binding agents</td>
</tr>
<tr>
<td>Antibiotics</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>Anti-Diarrhea</td>
</tr>
<tr>
<td>Immunomodulators</td>
</tr>
</tbody>
</table>

Prognosis

- Mucosal atrophy caused by infectious gastroenteritis, food-sensitivity enteropathies, or malnutrition can result in an 80% reduction of intestinal surface area.
- Repair of the small bowel is usually rapid (4-6 days).
- In some patients, repair may be slow, and after 2 months, the villi surface area is 63% normal and the microvillus surface area is only 38% normal.

Conclusion

- It takes a team to treat malabsorption
  - Physician, Dietician, Pharmacist, Social worker, Surgeon
- The growth chart and anthropometrics are critical to the diagnosis and treatment follow up
- After the initial work up, if abnormal: consider a referral to a pediatric gastroenterologist
- Remember to examine the Poop!