NASPGHAN Physiology Lecture Series

GI Physiology Module: Absorption of Water and Ions

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Objectives:

1. Understand the mechanisms of intestinal transport of ions
2. Know the location of transport and secretion of ions
3. Understand the absorption of vitamins and minerals
4. Understand the phenomenon of changes in nutrient absorption with luminal nutrient concentration
5. Mechanisms of diarrhea
6. Identify signs and symptoms of excess vitamin and mineral absorption and signs and symptoms of deficiency

I. Background: Fluid and Electrolyte Balance in the GI Tract
   a. Regulation of fluid transport in gut is critical for normal intestinal function
   b. Water follows the osmotic gradient set by electrolyte transit
   c. The regulation of electrolyte balance is therefore a key principal to understanding intestinal fluid balance in health and disease
      i. In healthy state, only 100mL of fluid exits the gut (via stool) per day

II. Intestinal Epithelial cells function as gatekeepers for fluid and ion transit
   b. Paracellular transport of water and electrolytes across tight junctions can occur but most follow electrochemical gradient
   c. Transcellular transport proteins: allow transport of molecules and waters across epithelial barrier, often via active transport against electrochemical gradient
      i. Subject to transcriptional and posttranscriptional regulation
      ii. Mechanistic examples:
         1. Primary Active Transport: Na-ATPase
         2. Secondary Active Transport: Na-GLUC cotransporter
         3. Facilitated Diffusion: Glut-5 (fructose transporter)
III. Anatomic Considerations

a. Based on villi (absorptive) and crypts (secretory), simultaneous absorption and secretions occurs at all levels of the intestine
   i. Absorption primarily depends on molecular cotransport with sodium
   ii. Secretion primarily follows chloride and bicarbonate

b. Locational specialization occurs within the gut
IV. Key examples of Cellular Transport Proteins

a. Na, K ATPase

b. Na-coupled Transport (eg: Sodium-Glucose cotransporter)
c. NaCl Co-transport

![Diagram of NaCl co-transport](image)

Na/H (cation) exchanger works in conjunction with HCO3/Cl (anion) exchanger, allowing NaCl absorption

Adapted from: Guandalini "Acute Diarrhea" Pediatric Gastrointestinal Disease. 4th Ed 2004

d. Chloride secretion

![Diagram of chloride secretion](image)

Na-K ATPase drives Na gradient, further allowing Cl secretion through apical CFTR channel
e. Ultimately, water follows the NaCl gradient

V. Absorption and Secretion in Health versus Diarrheal States
a. In healthy state, absorption (villus) > secretion (crypts)
b. In diarrheal state, chloride secretion (crypt) may be higher than villous NaCl absorption
   i. The pathophysiology of individual diarrheal disease is dependent on how the process affects ion absorption or secretion
c. Basic clinical mechanisms:
   i. Osmotic diarrhea: Malabsorption of solute (eg, carbohydrate / lactose) from small intestine drives fluid losses in colon
   ii. Secretory Diarrhea: Electrolyte secretion (eg, chloride secretion from crypts) drives small intestinal fluid losses
d. Repetitive molecular pathways exist in various infectious diarrheal states
i. Example: Cholera

<table>
<thead>
<tr>
<th>Signal/pathway</th>
<th>Examples</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td>cAMP</td>
<td>Cholera toxin</td>
<td>Blocks NaCl absorption</td>
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<tr>
<td></td>
<td>Heat labile E Coli (ETEC)</td>
<td>Stimulates anion secretion</td>
</tr>
<tr>
<td>cGMP</td>
<td>Heat stable E Coli (EAEC)</td>
<td>Blocks NaCl absorption</td>
</tr>
<tr>
<td></td>
<td>Klebsiella</td>
<td>Stimulate anion secretion</td>
</tr>
<tr>
<td>Ca++ / protein kinase C</td>
<td>C Difficile enterotoxin</td>
<td></td>
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<tr>
<td>Pore forming toxin</td>
<td>Staph Aureus α-toxin</td>
<td>Pore formation along brush border membrane</td>
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<td></td>
<td>C. perfringes</td>
<td></td>
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<tr>
<td>Toxin blocking protein synthesis</td>
<td>EHEC Shiga toxin</td>
<td>A1 subunit of toxin binds ribosome and interrupts protein synthesis</td>
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<tr>
<td></td>
<td>Shigella Shiga toxin</td>
<td></td>
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<tr>
<td>Toxin inducing protein synthesis</td>
<td>Staph toxin A</td>
<td>Upregulate proinflammatory cytokines</td>
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<tr>
<td></td>
<td>EAggEC toxin</td>
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<tr>
<td>Toxin affecting cytoskeleton</td>
<td>Clostridium species</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from: Fasano. “Bacterial Infections” Pediatric Gastrointestinal Disease. 4th Ed 2004
VI. Mineral and Vitamin Absorption

a. Iron
   i. Ferrous iron is absorbed in proximal small intestine
   ii. Ferrous iron is converted to ferric iron, which is coupled with transferrin for transport
   iii. The liver plays a major role in regulation of iron transport

![Diagram of iron absorption](image)

b. Calcium
   i. Absorbed in duodenum
   ii. Regulated by 1,25 hydroxy vitamin D, which regulates the apical, intracellular, and basolateral transport mechanisms

c. Magnesium
   i. Absorbed throughout GI tract, and regulation of absorption is dependent on dietary intake

d. Water Soluble Vitamins
   i. B vitamins and vitamin C are easily taken up by cells, and are generally not stored in tissue
   ii. Vitamin B12:
      1. Requires intrinsic factor for absorption
      2. Partially stored in liver

e. Fat Soluble Vitamins
   i. Digestion, absorption, and transport follows dietary fat
   ii. Stored in hepatocytes and adipocytes

f. Vitamin and mineral excess and deficiency states
<table>
<thead>
<tr>
<th>Micronutrient</th>
<th>Pathophysiology</th>
<th>Syndrome</th>
<th>Syndrome</th>
<th>Laboratory evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minerals and trace elements</td>
<td>Fat malabsorption</td>
<td>Paresthesias, tachy, bone denervation, Weakness, cardiac, CNS</td>
<td>*GI, GU, bone complaints</td>
<td>Serum Ca, PTH, DEXA scan</td>
</tr>
<tr>
<td>Calcium</td>
<td>Fat malabsorption and high GI fluid losses</td>
<td>Poor growth, skin, hair, diarrhea *Hemolytic anemia, neutropenia</td>
<td>*Vomiting, headache, diarrhea, Cu deficiency</td>
<td>Serum Mg</td>
</tr>
<tr>
<td>Zinc</td>
<td>Overload more common in cholestasis</td>
<td>*Hemolytic anemia, neutropenia</td>
<td>Hepatic overload, neurotoxicity</td>
<td>Serum Zn, low alkaline phosphatase</td>
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<tr>
<td>Copper</td>
<td>Overload more common in cholestasis</td>
<td>*Hemolytic anemia, neutropenia</td>
<td>Neurotoxicity</td>
<td>Serum Cu</td>
</tr>
<tr>
<td>Manganese</td>
<td>Absorbed proximally: not routinely in TPN</td>
<td>Microcytic anemia, irritability</td>
<td></td>
<td>Serum Mn</td>
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<tr>
<td>Iron</td>
<td>Absorbed throughout small bowel</td>
<td>Myopathy, cardiomyopathy</td>
<td>*Thyroid enlargement</td>
<td>Ferritin, TIBC, Iron Binding Cap, Hgb, HCT, peripheral smear, Serum selenium</td>
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<tr>
<td>Selenium</td>
<td>Fat-soluble vitamins</td>
<td>Xerophthalmia, blindness Hypovitamnosis, hypophosphatemia, rickets Myopathy, neuropathy, ataxia, hemolytic anemia Bleeding</td>
<td>*Increased ICP, hepatits, vomiting</td>
<td>Vitamin A: retinol binding protein ratio 25-OH vitamin D</td>
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<td>Increased ICP, hepatitis, vomiting</td>
<td>Vitamin E: total serum lipid ratio Prothrombin time, PIVKA assay</td>
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<td>Increased ICP, hepatitis, vomiting</td>
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<td>Myopathy, neuropathy, ataxia, hemolytic anemia Bleeding</td>
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<td>Bleeding</td>
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<tr>
<td>Water-soluble vitamins</td>
<td>Gastric or ileal resection</td>
<td>Megaloblastic anemia, CNS including ataxia</td>
<td>None known</td>
<td>Serum B12, methylmalonic acid, homocysteine</td>
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<tr>
<td>B12</td>
<td>Absorbed proximally</td>
<td>Anemia, thrombocytopenia, stomatitis, glossitis</td>
<td>None known</td>
<td>Serum Folate</td>
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