Introduction

This first *Pediatric Gastroenterology, Hepatology and Nutrition Handbook* a compendium from the NASPGHAN Fellows Committee, was conceived as a handy, problem-based, reference tool for the fellows in-training; but it grew from there into the handbook you now hold in your hands. It was designed to provide the most useful clinical information in a concise and convenient format. There are two versions of the handbook on the CD-ROM enclosed in this packet. One is organized in a problem-based outline format to be downloaded and used within a PDA platform. The second is designed for use on desktop or laptop computers (Windows or Mac-OS). It contains the entire “text” content, with tables and flow-charts in textbook quality print, for use as handouts or as teaching aids for rounds, talks, consults, etc.

The authors were recruited from among the fellows training in North American programs and the information contained within the handbook was compiled from a variety of sources. Every effort has been made to verify the accuracy of the information here presented. This reference, however, is intended to be used as a handbook and therefore does not include a comprehensive review of these topics. Specific terms, such as medications, are cross-linked within the chapters as indicated and flowcharts and tables are arranged to be user-friendly and maximize viewable screen space. The chapters represent, what we felt, were the most common clinical concerns presented to the practicing pediatric gastroenterologist, but are by no means comprehensive. With each passing year it is our hope that the Handbook will be expanded and refined to enhance its value to the entire NASPGHAN membership.

We would like to thank all the people who gave us their time and effort in crafting these fine chapters and without whom, this first handbook would not have been possible. Thank you for your faith in this enterprise. We would also like to thank the NASPGHAN leadership, specifically Dr. Richard Colletti and Dr. Harland Winter for their support and sage advice. To Margaret Stallings and the staff at NASPGHAN we give our thanks for their invaluable help. The efforts of Dr. William Berquist and the members of the Professional Education Committee in revising the final chapters are also greatly appreciated. Finally, this project would not have been possible without the generous support of SHS North America and we would like to thank them as well. We sincerely hope you find the material here covered to be truly helpful and easy to use. As always, we will welcome your comments and will keep on working to make each subsequent edition better.

Sincerely,

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Index

I. Vomiting.................................................................................................................... 4
II. Dysphagia.................................................................................................................. 6
III. Functional Constipation & Encopresis ................................................................. 8
IV. Dyspepsia................................................................................................................. 11
V. Acute Diarrhea ....................................................................................................... 13
VI. Chronic Diarrhea.................................................................................................... 17
VII. Obesity.................................................................................................................. 20
VIII. Upper GI Bleeding .............................................................................................. 23
IX. Lower Gastrointestinal Bleeding .......................................................................... 26
X. Ascites .................................................................................................................... 28
XI. Neonatal Cholestasis ............................................................................................ 32
XII. Cholestasis in Children and Adolescents ............................................................ 37
XIII. Biochemical Tests of the Liver .......................................................................... 42
XIV. Parental Nutrition Guidelines ........................................................................... 44
XV. Drug Formulary .................................................................................................... 49
I. Vomiting

A. Definition
Vomiting is a physical act that results in the gastric contents forcefully brought up to and out of the mouth, aided by a sustained contraction of the abdominal muscles and the diaphragm at a time when the cardia of the stomach is raised and the pylorus is contracted.

B. Pathophysiology
1. Vomiting Center (VC): is located in the dorsal portion of the medulla and that vomiting can be induced with electrical stimulation of this area. Afferent neural inputs to the VC are transmitted via the vagus and the sympathetic nerves.
2. Chemoreceptor trigger zone (CTZ): located in the area postrema of the medulla in the fourth ventricle.
3. Emetic stimuli can induce vomiting by two ways: Stimulating VC directly or indirectly by stimulating CTZ, which in turn activates the VC. VC can be stimulated directly by afferent stimuli from GI tract (chemical), pharynx, vestibular system, heart, peritoneum, thalamus, hypothalamus and cerebral cortex. CTZ can be stimulated by drugs (opiates, digitalis, ergot derivatives, chemotherapy agents, ipecac, dopamine agonists), uremia, hypoxia, DKA, radiation and motion sickness.
4. Effector pathways: events leading to vomiting are the same. The emetic reflex begins with transient nausea and autonomic excitation, followed by nonperistaltic small bowel contractions and gallbladder contractions, then by intensive retrograde peristaltic wave that forces small bowel contents into the stomach suppressing gastric activity. The inspiratory muscles contract against a closed glottis (retching) resulting in esophageal dilation, then the abdominal muscles contract pushing gastric contents into the esophagus.

C. Associated Phenomena
1. Hypersalivation
2. Cardiac Rhythm disturbances
3. Pupillary dilatation
4. Defecation

D. Differential Diagnosis
1. Nonbilious
   a) Infectious: Most common cause of vomiting in children.
      (1) Viral: Most common viral agent is rotavirus
      (2) Bacterial: Salmonella, Shigella, Campylobacter, E. Coli, H. pylori
      (3) UTI, pyelonephritis, chronic sinusitis, otitis media, pharyngitis, pneumonia, peritonitis, hepatitis and meningitis
      (4) Parasites: Giardia
   b) Inflammatory: IBD, pancreatitis, appendicitis, cholecystitis, esophagitis,
   c) Gastritis, food allergy, cow’s milk protein allergy, celiac disease
   d) Metabolic
      (1) Inborn errors of metabolism: like MCAD deficiency, OTC deficiency,
      (2) Usually present in early infancy, associated with neurological symptoms, and metabolic acidosis, hyperammonemia, hypoglycemia and/or ketosis
      (3) Acute intermittent porphyrias
      (4) Uremia
   e) Endocrine
      (1) Diabetes mellitus (DKA), adrenal insufficiency (Addison’s),
      (2) Carcinoid syndrome, ZE syndrome
   f) Neurologic:
      (1) Increased ICP: hydrocephalus, intracranial tumors, intracranial hemorrhage
      (2) Cyclic Vomiting Syndrome: recurring attacks of severe vomiting,
      (3) sporadic and unpredictable in some and cyclic and predictable in others, usually in AM, with strong family history of migraine, diagnosed by clinical presentation and exclusion of other organic disorders
      (2) Abdominal migraine and migraine headaches
   h) Motion sickness
   i) Psychogenic: self-induced to seek attention, rumination, bulimia, anorexia nervosa, depression
2. Mechanical
   a) Newborn: Esophageal atresia, pyloric stenosis, gastric atresia, duodenal atresia, esophageal stenosis, duodenal web, intestinal duplication, annular pancreas, strictures due to NEC, Hirschsprung’s, midgut volvulus with malrotation, meconium ileus
   b) Children and adolescents: intussusception, malrotation, strictures due to inflammation, gastric volvulus, gastric outlet obstruction, inguinal hernia, SMA syndrome, UPJ obstruction, foreign body, bezoar, duodenal hematoma, surgical adhesions
   c) Functional: achalasia, GERD, gastroparesis, scleroderma, pseudo-obstruction, Ileus, familial dysautonomia
   d) Toxic: Drugs, poisonings (lead, staph toxin)
   e) Other: Overfeeding, Reye Syndrome, pregnancy
   f) Bilious
      (1) Mainly anatomic conditions causing obstruction distal to the lig of Treitz.
3. Consequences of Vomiting
   a) Metabolic:
      (1) Potassium deficiency
      (2) Alkalosis
      (3) Sodium depletion
   b) Nutritional
   c) Mechanical injuries to esophagus and stomach:
      (1) Mallory-Weiss
      (2) Boerhaave’s syndrome
      (3) Tears of the short gastric arteries resulting in shock and hemopitoneum
d) Dental: erosions and caries  
e) Purpura

E. Treatment

<table>
<thead>
<tr>
<th>Name</th>
<th>Indication</th>
<th>Mechanism</th>
</tr>
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<tbody>
<tr>
<td><strong>Mild Antiemetic Activity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihistamines: diphenhydramine, hydroxyzine, promethazine, meclizine</td>
<td>Motion sickness and mild chemotherapy induced vomiting</td>
<td>Probable Labyrinthine suppression and H1 block in CNS</td>
</tr>
<tr>
<td>Anticholinergics: Hyoscyamine</td>
<td>Prophylaxis of motion sickness</td>
<td>Antimuscarinic effect in labyrinth or CNS</td>
</tr>
<tr>
<td>Benzodiazepines: Lorazepam, midazolam, diazepam</td>
<td>Chemotherapy induced vomiting</td>
<td>GABA inhibition</td>
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<tr>
<td><strong>Moderate Antiemetic Activity</strong></td>
<td></td>
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</tr>
<tr>
<td>Phenothiazines: Prochlorperazine, perphenazine chlorpromazine, promethazine</td>
<td>Chemotherapy and Cyclic Vomiting Syndrome</td>
<td>D2 receptor antagonist at CTZ</td>
</tr>
<tr>
<td>Buthyropheneone: Droperidol, haloperidole, domperidone</td>
<td>Cyclic vomiting syndrome, postoperative, chemotherapy, Domperidone for motility disorders.</td>
<td>D2 receptor antagonist at CTZ D2 receptor block at enteric nervous system</td>
</tr>
<tr>
<td>Corticosteroids: Dexamethasone</td>
<td>Mild chemotherapy vomiting, emesis from increased ICP</td>
<td>Unknown</td>
</tr>
<tr>
<td>Cannabinoids: Dronabinol, nabilone</td>
<td>Chemotherapy</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Potent Antiemetic Activity</strong></td>
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</tbody>
</table>
| Metoclopramide            | Chemotherapy, motility disorders, GERD | Normal dose: D2 receptor blockade at CTZ and enteric nervous system  
High dose: 5-HT3 activity enterically |
| Trimethobenzamide         | Often for acute gastroenteritis and to abort CVS | D2 receptor blockade                                        |
| Cisapride                 | Motility disorders, GERD. Discontinued because of cardiac effects | Enteric acetylcholine release                                |
| 5-HT3 Receptor Antagonists: Ondansetron, granisetron | Chemotherapy and postoperative vomiting | 5-HT3 receptor blockade mainly in enteric nervous system |

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G. References
II. **Dysphagia**

A. **Definition:**
   From the Greek "difficult to swallow." In the pediatric patients, swallowing disorders are rarely isolated. In contrast to adults, growth and development of the swallowing apparatus, oromotor reflexes and maturation of feeding behavior should be considered in the pediatric population.

B. **Clinical manifestations and complications of impaired deglutition:**
   1. Cough
   2. Pain on swallowing
   3. Food impaction
   4. Halitosis
   5. Respiratory: apnea and bradycardia, choking episodes, chronic noisy breathing, reactive airway disease, chronic or recurrent pneumonia, bronchitis, otitis media and atelectasis.
   6. Malnutrition
   7. Sialorrhea
   8. Chest Pain
   9. Regurgitation
   10. Weight loss
   11. Globus pallidus-sensation of lump or tightness in throat

C. **Differential diagnosis:**
   1. Oral Phase:
      a) Nasopharyngeal: choanal atresia and stenosis, infections, tumors, trauma
      b) Oral cavity and oropharynx: cleft lip/palate, hypopharyngeal web/stenosis, craniofacial syndromes, trauma, adenoid/tonsil hypertrophy, pharyngitis
      c) Larynx: stenosis, webs, paralysis, laryngomalacia, laryngotraechoesophageal cleft, trauma, post-intubation
   2. Pharyngeal Phase:
      a) Anatomical defects: stenosis, webs, intubation, endoscopy, trauma
      b) Oropharyngeal incoordination and motility disorders: cricopharyngeal dysfunction-cricopharyngeal hypertension, hypotension, incoordination
      c) Neurologic defects
         (1) CNS: Head trauma, hypoxic brain damage, cortical atrophy, microcephy, craniofacial syndromes, trauma
         (2) Peripheral nervous system: trauma, congenital
         (3) Neuromuscular: myotonic muscular dystrophy, myasthenia gravis, guilian-barre syndrome, poliomyelitis
   3. Esophageal Phase:
      (1) Anatomic defects: strictures, stenosis, webs, diverticulae, tracheoesophageal fistula, trauma, aberrant cervical thymus
      (2) Vascular abnormalities: aberrant right subclavian artery, double aortic arch, right aortic arch with left ligamentum
      (3) Mucosal lesion: esophagitis (caused by GERD, infections like candida, CMV, HSV, TB and HIV, caustic ingestion, burns, radiation and also eosinophilic esophagitis, cow's milk protein and food allergy, arthritis, esophagus, malignancy and food impaction, drugs that cause direct esophageal mucosal damage like tetracycline, potassium chloride, quinidine, aspirin and NSAID's
      (4) Esophageal motility disorder:
         (a) Primary esophageal motility disorders: Idiopathic achalasia, diffuse esophageal spasm, nutcracker esophagus, non-specific esophageal motility disorder, esophageal paralysis (atonic).
         (b) Secondary esophageal motility disorders: GERD, eosinophilic esophagitis, chronic intestinal pseudo-obstruction, dermatomyositis, systemic lupus erythematosus, scleroderma, diabetes, thyroid disorders, chagas’ disease, medications, depression, bulimia, anorexia, Graft-versus-host disease, mitochondrial disorders, neurologic, paraneoplastic syndrome.
      (5) Drug Effect: associated with reduced LES tone and reflux like theophylline, calcium channel blockers, nitrates, alcohol, fat and chocolate)
D. Algorithm for evaluation and management of Dysphagia in Children

Algorithm for Evaluation and Management of Dysphagia in Children

E. Management of Cricopharyngeal/Esophageal Motility Disorders

1. CP Hypertension: consider CP Myotomy
2. CP Hypotension Incoordination: Aspiration control/Nutrition
3. Diffuse esophageal spasm, nutcracker esophagus, non-specific esophageal motility disorder-aggressive PPI treatment and prokinetics (GERD/esophagitis is the most common reason). Reports of TCA alleviating symptoms of globus pallidus, and chest pain.
4. Idiopathic Achalasia: Heller myotomy±partial fundoplication (Thai) vs. Botox of LES

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III. Functional Constipation & Encopresis

A. Definitions:
1. Constipation: delay or difficulty with defecation, present for two or more weeks. Note: To achieve a normal defecation a child should have a normal rectum and puborectalis muscle, normal internal and external anal sphincters, and normal innervation of these structures through both the autonomic and somatic nervous systems.
2. Encopresis: involuntary fecal soiling or incontinence secondary to chronic constipation. Physiologic encopresis is most common and is manifested as overflow incontinence that occurs as a result of severe constipation, fecal impaction and a dilated rectum. Related behavioral components including active stool withholding, fear, and embarrassment that may resolve with adequate treatment.
3. Normal defecation: frequency of defecation and the consistency of stool are related to age and diet. Some infants have a bowel movement after each feed due to an active gastrocolic reflex and others, particularly breast fed infants, can have normal stools every 2-3 days. Frequency declines to a mean average of 1.7 stools per day at 2 years of age and 1.2 stools per day at 4 years of age. After 4 years, the frequency remains unchanged.
4. Idiopathic constipation: (functional constipation or fecal retention) is commonly due to a painful defecation event such as an anal fissure, bad toilet-training experience, changes in routine or diet, stressful events, intercurrent illness, unavailability of toilets, or postponing defecation because the child is “too busy”. On the urge to defecate, he/she contracts his external anal sphincter to avoid pain or discomfort resulting in stool withholding. Chronic retention results in abdominal cramps, abdominal distension, irritability, and decreased oral intake. Chronic rectal dilatation results in decreased sensory capability, and weakened propulsive peristaltic activity. Eventually, the constipation becomes self-perpetuating.

B. Physiology of Defecation:
Stool movement into the rectum stimulates the rectal wall, sends signals via the intrinsic nervous system resulting in the relaxation of the internal anal sphincter developing the sense of urgency associated with defecation. If defecation is convenient, the external sphincter will relax and stool is propelled by colonic peristalsis and a secondary reflex, via the somatic nervous system, is activated resulting in contraction of the abdominal musculature emptying the distal colon. If defecation is inconvenient, contraction of the external sphincter is initiated, first by reflex and then intentionally. Stool retention is assisted by contraction of the puborectalis muscle, which constrict and angulates the anal canal. If sustained, the reflex to the internal sphincter wanes and the urge to defecate disappears.

C. Background:
Chronic constipation is common, 3% of primary care physician office visits and 20-25% of the referrals to a pediatric gastroenterologist. It is important to distinguish functional constipation (i.e. without evidence of a pathological cause) from constipation with an organic cause. Beyond the neonatal period, the most common cause of constipation is functional or idiopathic constipation.

D. History
1. Delay in passing first meconium?
2. Hx of any period of normal stooling?
3. Duration of constipation?
4. Caliber (small in Hirschsprung’s, large in functional)
5. Frequency and consistency of stools?
6. How long does it take to pass stool?
7. Blood with stool?
8. Fecal soiling? (Sometimes may be mistaken for diarrhea by some parents)
9. Stool withholding behavior?
10. Change in formula, diet, and travel?
11. Problems with toilet training?
12. Associated symptoms such as fever, vomiting, and bloody diarrhea? (Consider Hirschsprung’s enterocolitis)
13. What studies and/or medications have been used?
14. What other things have the parents been doing to manage the problem?
15. Are there other physical conditions/diagnoses e.g. UTIs, genetic syndromes, surgeries?
16. Does the child take any other medications regularly?
17. Is there any family history of constipation, colon problems?

E. Red Flags
1. Fever, Vomiting, Bloody Diarrhea
2. Failure to thrive
3. Tight, empty rectum with presence of palpable abdominal fecal mass
4. Abnormal neurological exam

F. Physical exam:
1. In addition to a thorough physical exam including vital signs and growth parameters, make sure you check the following:
   a) Abdomen: Distention, fecal masses, tenderness, and bowel sounds
   b) Back: signs of spinal abnormalities e.g. spinal dimpling, tuft of hair
   c) Rectal exam: during the first visit
      (1) Position of anus?
      (2) Anal wink?
      (3) Anal fissures, skin tags?
      (4) Soiling in the underwear or around the anus?
      (5) Anal stenosis?
      (6) Anal sphincter tone (nut-cracker sphincter)?
      (7) Rectal vault dilatation?
      (8) Stool in rectum: consistency, fecal impaction→ explosive stool upon withdrawal of finger?
      (9) Hemoccult test
   d) Neurological exam: is essential
      (1) Lower extremity tone and strength
      (2) Cremasteric reflex
      (3) Deep tendon reflexes
G. **Laboratory Studies:**
   1. These tests would be advisable for children who remain constipated in spite of medical therapy:
   2. T4/TSH
   3. Celiac Panel
   4. Serum Calcium
   5. Serum Lead level
   6. Sweat test (if clinically indicated)

H. **Radiologic studies:**
   1. Abdominal X-ray (KUB):
      a) Helpful in the child who is obese with incomplete abdominal exam, refuses a rectal exam, or in whom there are other psychological factors (sexual abuse).
      b) Might be helpful if no stool in rectum to evaluate for obstruction.
   2. Unprepared barium enema
      a) To evaluate for possible Hirschsprung’s disease.
      b) Unprepared means no clean out (no enemas, no suppositories) and no rectal exam 48-72 hours prior to the study.

I. **Management:**
   1. **Goals:**
      a) Pass 1-2 soft stools daily (painless stools help to overcome fear and withholding
      b) Allow the rectal vault to approach a normal size (on average this may take 6-12 months or longer
      c) Establish an adequate diet and fluid intake, a regular toilet routine and eliminate fear of defecation.
         (1) Diet: It is important to encourage balanced diet that includes whole grains, fruits and vegetables as part of the treatment for constipation in children, elimination of certain foods e.g. milk, and cheese is not necessary and therefore not recommended.
      Fiber supplements are not recommended in children with dilated rectum since they are bulking agents.
   (2) **Fecal Impaction**
     If the impaction is significant, suppositories are not likely to be an effective way to evacuate the stool. Both oral and rectal therapy (enemas) might be needed.
     **Mineral oil** (rectal) may be used to soften hard stool in preparation for a stimulating enema or oral laxative.

J. **Treatment**
   1. **Stool Softeners:** act to soften stool but do not create the urge to defecate. Not a good choice for long-term use.
      a) **Mineral oil:** oral or rectal, not recommended in a child less than one year of age because of the risk of aspiration and lipid pneumonia. May be mixed with orange juice or try a Popsicle/freezer pop crushed and pour oil over top and feed with spoon.
      b) **Docusate sodium** (Colace®) not effective for long-term management but may be helpful for the child that continues to have hard stools after laxative therapy completed.
   2. **Stimulants:** Act by stimulating the colon to contract.
      a) **Bisacodyl:** Oral or suppository
      b) **Glycerine:** suppositories are often prescribed but rarely helpful for removing hard impactions
      c) **Senna (Senokot®):** Available in pills or liquid (chocolate flavored) and in Ex-Lax® chocolate squares and granules. Needs to be used with a stool softener.
   3. **Osmotic:** The first three laxatives listed below are fermented in the colon to create the osmotic effect.
      a) **Malt extract (Maltsupex®)** Safe and can be added to infant formula.
      b) **Dark corn syrup:** The glycoproteins that give the dark corn syrup its brown color are unabsorbed and pass into the colon. Works best in infants. Light corn syrup is ineffective.
      c) **Lactulose** (liquid or powder, Kristalose™): Safe. Side effects: increased gas as a byproduct of its fermentation, and tolerance to lactulose may develop as a result of change in the fermentation capacity of the colon.
      d) **Magnesium hydroxide** (Milk of Magnesia) (also has some stimulant action). Given once a day, better at night. May be flavored with syrups e.g. chocolate, strawberry. Starts working in 6-10 hours. Comes in concentrated formulation that permits the child to take ½ the volume of the regular dose.
      e) **Polyethylene Glycol Electrolyte Solution & Powder:** (Miralax®)
         (1) A non-absorbable electrolyte solution that can be taken orally or by nasogastric tube if used for disimpaction or cleaning before colonoscopy
         (2) Powdered form that dissolves in 4-8 oz water or flavored beverage is also available. Also given once a day
         (3) Side effects include nausea, vomiting, bloating, and abdominal cramps. Aspiration pneumonia is a potential risk with nasogastric tube administration. Safety of long-term maintenance is not well established.
   4. **Enemas**
      a) In cases of impaction it may be helpful to soften the stool in the rectal vault with **mineral oil** (oral or enema) or liquid glycerin (Baby Lax®) before starting oral laxatives.
      b) Generally, no more than two enemas should be given in a single day.
      c) A large-volume enema (e.g. saline or soapsuds) usually is more effective than a small-volume enema (e.g. sodium phosphate) in significant constipation.
      d) There is a risk of mechanical trauma to rectal wall, abdominal distention, vomiting.
      e) **Phosphate enemas:** (Fleet Enema®) it is an osmotic laxative, avoided in children less than 1 year of age because of renal immaturity
      f) Frequent use or large volume may cause severe and lethal episodes of hyperphosphatemia, hypocalcemia, with tetany.
      Use with caution in patients with renal impairment.
         (1) **Soap suds enema:** is prepared by adding 1 tsp of dish washing detergent (for hand use) to 1000 mls of water. Normal dose is 20 ml/kg (max 1 L). Soap suds enemas are not intended to be used for routine management of constipation. They are useful primarily for removing impacted stool. The routine use of soapsuds enemas can result in a detergent proctitis.
         (2) **Saline enema:** may be helpful if the child is not severely impacted. They can be prepared at home by mixing 1 tsp of table salt in 1000 mls of water; normal dose is 20 ml/kg (max 1 L). Saline enemas can be used in enema programs for children with anorectal malformations and spina bifida.
(3) Tween 80/Gastrografin: This enema consists of a detergent (Tween 80) and water-soluble contrast (Gastrografin) given under fluoroscopic control to assure filling of the colon and promote evacuation. Given in radiology department allowing imaging of colon.

(4) Pulsated Intermittent Evacuation Enema (PIEE)
(a) Is a newly developed device that works by mechanically destroying hard stool using pulsated water in varying volumes. It is generally given without sedation. The patient must weigh a minimum of 15 kg.

5. Stopping the Laxative:
   a) When the goals of treatment are met (the average treatment time is 6-12 months) → taper the laxative slowly, usually by ½ tsp increments with 2 weeks between decreases. The next decrease is not made unless the child has been doing well on the previous lowered dose.
   b) Keep a daily record of the stools passed during the taper and for a minimum of 3 months after stopping laxative treatment.

6. Behavioral therapy:
   a) Remember children withhold to avoid pain. Stool withholding behaviors are often eliminated or at least decreased when the pain is eliminated by the laxative program that produces painless bowel movements.
   b) Be supportive and encourage children to relax with bowel movements.
   c) DO NOT PUNISH!
   d) Simple rewards like using a calendar or chart with stickers provide positive support to reinforce the child’s progress. (e.g. “Smiley Faces”)
   e) Most children do not want to soil but frequently have developed tolerance to soiling and are not concerned about soiled clothing. It therefore may require more effort to get them to use the bathroom. Children with attention deficit and hyperactivity, tend to have more problems because they may be easily distracted.
   f) For some children, it may be helpful to enlist the help of a behavioral psychologist to support the medical treatment plan.

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L. References:
Altemeier WA, Hemme, C. A pediatrician’s view: the importance of successful Passage. Pediatric Annals. 28 (5) 276-278, May 1999.
Buttross S. Encopresis in the child a behavioral disorder: when the initial Treatment does not work. Pediatric Annals. 28 (5) 317-321, May 1999.
North American Society for Pediatric Gastroenterology and Nutrition medical position statement Constipation in Infants and Children: Evaluation and Treatment.
Parker PH. To do or not to do? that is the question. Pediatric Annals. 28 (5) 283-290, May 1999.
**IV. Dyspepsia**

A. **Definition**: Elegant but inadequate term derived from the Greek "bad to digest". "chronic or recurrent pain or discomfort centered in the upper abdomen (epigastrium)" most widely accepted definition1

B. **Prevalence**: 20% of adolescents in the community report upper abdominal pain, with 5-10% experiencing nausea2, 3.

C. **Clinical Manifestations1, 4:**
   1. Retching
   2. Vomiting
   3. Fullness
   4. Belching
   5. Queasiness
   6. Nausea
   7. Bloating
   8. Early Satiety
   9. Upper Abdominal Pain

D. **Differential Diagnosis:**
   1. Functional Disorders
      a) Functional Dyspepsia-Pediatric Rome II criteria-In children mature enough to provide an accurate pain history, at least 12 weeks, which need not be consecutive, within the preceding 12 months of:
         (1) Persistent or recurrent pain or discomfort centered in the upper abdomen; and
         (2) No evidence (including at upper endoscopy) that organic disease is likely to explain the symptoms; and
         (3) No evidence that dyspepsia is exclusively relieved by defecation or associated with the onset of a change in stool frequency or stool form.
      b) GERD1-Predominant symptom is "heartburn"-see chapter on GERD
      c) Rumination Syndrome-6 weeks in the previous 12 months of recurrent regurgitation of recently ingested food which:
         (1) Begins within 30 minutes of meal ingestion
         (2) Is associated with either re-swallowing or expulsion of food
         (3) Is not associated with mechanical obstruction
         (4) Does not respond to treatment for GERD
         (5) Is not associated with nocturnal symptoms
      d) Post-viral Gastroparesis6- Symptoms following a viral illness
      e) Abdominal migraine: In 12 months time, 3 or more paroxysmal episodes of mid-line abdominal pain associated with headache, photophobia or an aura-warning period and a family history of migraines. In the absence of a documented metabolic, GI, CNS or biochemical abnormality
   2. Inflammatory/ Mucosal Disease
      a) H. pylori infection
      b) NSAID use
      c) Inflammatory Bowel Disease
      d) Eosinophilic-Allergic Gastroenteritis
      e) Peptic disease
      f) Menetrier’s disease
      g) Parasites
      h) Varioloform gastritis
      i) Celiac Disease
      j) Schoenlein-Henoch Purpura
      k) Lactose/Carbohydrate mal-absorption or intolerance
   3. Anatomic Disorder
      a) Malrotation
      b) Duodenal web
   4. Other:
      a) Chronic Pancreatitis
      b) Chronic cholecystitis
      c) Uretero-pelvic Obstruction Abdominal Epilepsy:
      d) Psychogenic vomiting
      e) Anorexia Nervosa

E. **Diagnostic Evaluation:**
   1. General
      a) Physical Exam
      b) Basic laboratory tests: CBC, ESR, Albumin, Urinalysis, Liver tests, Amylase/Lipase, Stool for Occult blood, Giardia Ag (O+P).
   2. Radiology
      a) Ultrasound-useful to screen biliary-hepatic-pancreatic system, diagnosis of UPJ obstruction
      b) UGI-useful to evaluate anatomic obstruction/malrotation of the upper gastrointestinal tract
      c) Scintigraphy-useful to evaluate rate of gastric emptying, and may guide prokinetic therapy.
   3. Endoscopic Evaluation
      a) Indications:
         (1) Suspicion of reflux esophagitis
         (2) Removal of foreign object
         (3) Unexplained abdominal or chest pain
         (4) Unexplained vomiting
         (5) Stricture dilatation
4. Esophageal pH monitoring
   a) Indications—useful to detect extra-esophageal manifestations of GERD, and unrecognized GERD.
5. Esophageal Manometry
   a) Indications—symptoms of dysphagia- with or without evidence of achalasia on UGI

F. Therapy

1. General Principles
   a) Anti-reflux measures
   b) Trigger avoidance

2. Diet
   a) Timing of meals
   b) Small-frequent feedings
   c) Liquid diet—may facilitate delayed gastric emptying

3. Alternative
   a) Hypnotherapy

4. Pharmacotherapy
   a) Anti-acid medication:
      (1) H2 Blockers:
         (a) Cimetidine
         (b) Famotidine
         (c) Ranitidine
      (2) Proton Pump Inhibitors:
         (a) Omeprazole
         (b) Esomeprazole
         (c) Lansoprazole
         (d) Pantoprazole
   b) Pro-kinetic medications
      (1) Metoclopramide
      (2) Domperidone
      (3) Cisapride
      (4) Tegaserod
   c) Visceral Sensitivity
      (1) Tri-cyclic antidepressant
   d) Impaired Gastric Accomodation
      (1) Sumatriptin

5. Surgical Therapy
   a) Nutritional supplementation-Gastrostomy or Jejunostomy
   b) GERD—consider fundoplication—may exacerbate symptoms

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H. References
V. Acute Diarrhea

A. Definition
1. Abrupt onset of increased fluid content of the stools, usually with an augmentation in the frequency of the number of stools
2. Duration < 2 weeks
3. Excess water content of the stools from an alteration in the function of the small and large intestinal processes involved in the absorption of organic substrates and water

B. Epidemiology
1. In developing countries, acute diarrhea is still one of the major causes of death in the children under 5 years of age.
   a) Children in these regions may have between 3 and 8 episodes of diarrhea per year.
   b) The World Health Organization (WHO) estimates that 3 million of children die per year due to diarrhea.
2. In developed countries it is still an extremely common problem.
   a) In the United States estimated that 1-2 episodes per child per year occur in children below 5 years of age
   b) Accounts for 10% of hospital admissions for children in this age range and about 400 deaths/year
   c) In England the hospitalization rate is approximately 7% below 5 years of age.

C. Etiology
1. Infectious: most common cause of acute diarrhea in children
   a) Pathogens and relative frequencies (developed countries)
      (1) Viruses
         (a) Rotavirus: 25-40%
         (b) Calicivirus: 1-20%
         (c) Astrovirus: 4-9%
         (d) Enteric-type adenovirus: 2-4%
         (e) Norwalk-like virus:?
      (2) Bacteria
         (a) Campylobacter jejuni: 4-8%
         (b) Salmonella: 3-7%
         (c) Escherichia coli: 2-5%
         (d) Shigella: 1-3%
         (e) Yersinia enterocolitica: 1-2%
         (f) Aeromonas hydrophilia: 0-2%
         (g) Clostridium difficile: 0-2%
      (3) Parasites
         (a) Giardia Lamblia: 1-3%
         (b) Cryptosporidium: 1-3%

2. Allergic/ Adverse Food Reaction
   a) Allergy
   b) Toxin Mediated
      (1) Staph aureus
      (2) Scombroid
   c) Adverse Reaction
      (1) Fruits/juices

3. Drug Induced
   a) Antibiotics
   b) Laxatives
   c) Motility agents
      (1) Metoclopramide
      (2) Erythromycin
      (3) Cisapride
      (4) Tegaserod
   d) Miscellaneous
      (1) Caffeine
      (2) Alcohol
      (3) Histamine

4. Traveler’s diarrhea
   a) At least 80% of diarrhea in travelers from developed countries to developing countries is caused by bacterial pathogens
   b) Most common illness acquired by visitors to developing countries, affecting 20-50% of the 35 million people who travel from industrialized countries each year.
   c) No pathogen is identified in half of the cases
      (1) Most common pathogens found in the adult population are Escherichia coli, Shigella, Salmonella, Campylobacter, Vibrio parahaemolyticus (in Asia), rotavirus (in Latin America), and Giardia lamblia
      (2) If a bacterial infection suspected, empirical antibiotics are suggested, with nalidixic acid, TMP-SMX, furazolidone and erythromycin (if campylobacter infection is a possibility)
5. Others
   a) Systemic infection
   b) Urinary Tract Infection
   c) Acute appendicitis

D. Pathogenesis:
   1. Normal Physiology
      a) Normal small intestine absorbs large amounts of sodium, chloride and bicarbonate, and secretes H+ ions, bicarbonate and chloride.
      b) Water passively follows the transport of solutes.
      c) Absorption takes place in the mature epithelial cells lining the middle and upper part of the small intestinal villi.
      d) Secretion occurs predominantly in the crypts (undifferentiated cells).
      e) Absorptive capacity normally exceeds the secretory activity, resulting in net absorption of water and electrolytes.

   2. Sodium: Most important ion in this process has three main mechanisms of absorption
      a) Sodium absorption coupled to nutrients
         (1) Remains intact during most of the acute diarrheal disorders
         (a) Is considered the pathophysiological basis for the utilization of orally administered hydration solutions in children with diarrhea
         (b) Specific carrier ("SGLT-1") which is involved in coupling the entry of glucose across the brush border to that of Na.
         (c) Some carriers for different categories of amino acids also couple their entry into the enterocyte with the downhill transport of Na.
      b) Electrogenic, amiloride-sensitive sodium absorption
         (1) Sodium can enter the cell down its electrochemical gradient, through selective channels uncoupled to other substrates in the ileum and throughout the colon.
      c) Neutral NaCl absorption
         (1) Predominates in the ileum
         (2) Mediated by two coupled antiports; one exchanges Na+/H+ (cation exchanger) and the other exchanges Cl-/HCO3- (anion exchanger).
         (3) Transport process most responsible for intestinal Na and water absorption in the absence of intraluminal nutrients.

   3. Chloride and bicarbonate
      a) The major anions being actively secreted into the crypts of the gut lumen.
      b) Electrogenic, as a result, passive diffusion of Na (cation) and water follows.
      c) Regulatory agents responsible for the homeostasis of the absorption and secretion of water and electrolytes are hormone peptides, active amines, arachidonic acid metabolites, and nitric oxide.

4. Diarrhea: When the system is altered, diarrhea ensues and can be a result of an osmotic force in the lumen (ex: lactose in lactose malabsorbers) or an increased secretory state (enterotoxin-induced diarrhea).
   a) Osmotic diarrhea
      (1) Moderately increased stool output
      (2) Stops with fasting
      (3) Stool osmolality normal to increased
      (4) Stool sodium usually < 50 mEq/L
      (5) Large stool osmolality gap (Osmolality - (2[Na + K] ) > 100 mOsm
         (a) Large gap due to increased amount of organic acids produced by fermentation of malabsorbed carbohydrates, less from secreted ions
      (6) Secretory diarrhea
         (a) Very large stool output
         (b) No change with fasting
         (c) Normal stool osmolality
         (d) Stool Na usually > 70 mEq/L
         (e) Low stool osmolality gap (Osmolality - (2[Na + K] ) < 50 mOsm
         (f) The majority of the measured stool osmolality is accounted for by secreted ions, little or none due to organic acids
   b) Mixed Diarrhea
      (1) Combination of osmotic and secretory diarrhea
      (2) Stool osmolality gap (Osmolality - (2[Na + K] ) = 50-100 mOsm
   c) Viruses causing enteritis invade mature intestinal epithelial cells, multiply, cause cell lysis, and then re-invade cells further down the small intestine.
   d) Consequence is a malabsorptive or osmotic diarrhea.

5. Diarrhea caused by bacterial infection is most frequently secretory
   a) Due to changes in epithelial cell ion transport
   b) May adhere to or invade the epithelium, producing either enterotoxin or cytotoxins.

E. Clinical Presentation
   1. Benign self-limited condition, resolving in a few days in developed countries.
      a) Clinical presentation and course of illness are dependent on the host and on the infecting organism.
      (1) Usually, the younger the child, the higher is the risk of acute dehydration as a result of high body water turnover and limited renal compensatory capacity of very young children.
      b) Depending on the infecting organism, the clinical pattern of the acute episode of diarrhea differs:
   2. Direct cytotoxic effect
      a) Location: proximal small intestine
      b) Etiologies
         (1) Virus
            (a) Enteropathogenic Escherichia coli (EPEC)
         (2) Giardia
c) Presentation: copious watery diarrhea, vomiting, dehydration (frequent); often with lactose intolerance; no blood in the stools.

3. Enterotoxin
   a) Location: small intestine
   b) Etiologies
      (1) Enterotoxigenic E. coli
      (2) Vibrio cholerae
   c) Presentation: watery diarrhea, can be copious, no blood in the stools.

4. Invasion
   a) Location: distal ileum and colon
   b) Etiologies
      (1) Salmonella
      (2) Shigella
      (3) Yersinia
      (4) Campylobacter
      (5) Enteroinvasive E. coli
   c) Presentation: dysentery, cramps, fever.

5. Cytotoxicity
   a) Location: colon
   b) Etiologies
      (1) Clostridium difficile
      (2) Enterohemorrhagic E. coli (EHEC)
      (3) Shigella
   c) Presentation: Dysentery, cramps, fever
      (1) EHEC (O157: H7) or Shigella may be followed by hemolytic-uremic syndrome.
      (a) If EHEC (O157: H7) is detected in a stool sample, child is often hospitalized for surveillance of the renal function
      (2) C. difficile infection may range in severity from mild antibiotic associated diarrhea to pseudomembranous colitis with toxic megacolon

6. Post-enteritis diarrhea (PED)
   a) Complicates 10% of the cases of acute diarrhea
   b) Defined by the WHO as an episode of acute diarrhea which lasts for at least 14 days
      (1) In developing countries, PED is inversely correlated with age.
   c) Risk factors are malnutrition and immunodeficiency.
   d) PED causes 30-40% of all diarrheal deaths in underdeveloped countries.
      (1) Can develop due to persistent bacterial colonization, lactose intolerance and protein sensitization
      (2) Protein sensitization is the most common among children from developed countries, in whom PED is very unusual

F. Management

1. Rehydration
   a) Main goal of the initial therapy of acute diarrhea.
   b) Oral rehydration therapy (ORT) by the WHO
      (1) Developed 30 years ago.
      (2) Based on maintenance of glucose/Na absorption during acute diarrheal episodes, permitting the PO route for rehydration instead of IV
      (3) Effective even when the damage to the epithelium is diffuse and severe, with infections such as Rotavirus
   c) Debate about the ideal concentration of the components of the oral solution indicated for children from developed countries.
      (1) WHO solution, indicated mainly for the children from underdeveloped countries in whom diarrheal losses are higher, contains more sodium, glucose and is more osmolar (osmolarity= 90 mMol/L) than the solution indicated for developed countries (45-60 mMol/L).
      (a) Recent systematic review of the literature concerning lower osmolarity ORS showed reduced need for unscheduled intravenous infusions, lower stool volume, and less vomiting, compared with standard WHO rehydration solution.
      (2) In developing countries, some rice based preparations were shown to be effective, possibly reducing the number of days with diarrhea.
   d) The volume of ORS to be prescribed is between 50-100 ml/kg to be administered during 3-4 hours, per os
   e) Glucose-based ORS most safe, effective, physiologic and effective way to rehydrate, and maintain hydration in children with acute diarrhea worldwide, as recommended by WHO, American Academy of Pediatrics and ESPGHAN.

2. Refeeding
   a) Breast-fed infants should continue to take breast milk during an episode of acute diarrhea, even if the infant is dehydrated
      (1) Must receive the breast-milk and the ORS
      (2) Formula-fed infants more controversial
      (3) ESPGHAN & WHO, recommend ORS for mild or moderately dehydrated children over 3-4 hours and then with a rapid re-introduction of normal feeding.
      (4) Not necessary to change the quality of food after a period of acute diarrhea, although often still prescribed, with no benefit for the child.

3. Antibiotics
   a) Occasionally bacterial infections may be treated with antibiotics, but they are not useful in the majority of cases of acute diarrhea
   b) Consensus statement recommended antibiotic treatment for V. cholerae, Shigella, Giardia lamblia and Entamoeba histolytica
      (1) Cholera: tetracycline is indicated in children over 8 years of age and trimethoprim/ sulfamethoxazole (TMP-SMX) in younger children.
      (2) Shigella: ampicillin is used in sensitive strains and TMP-SMX in resistant strains.
      (3) Giardiasis and amebiasis: metronidazole.
      (4) Special situations
(a) Enteropathogenic E. coli when the course is prolonged
(b) Enteroinvasive E. coli & Yersinia in patients with sickle cell disease or other immun-suppressed states
(c) Salmonella in very young infants, if febrile or with positive blood culture

4. Clostridium difficile
   a) Stop all other antibiotics if possible
   b) If serious infection the treat with Metronidazole PO or Vancomycin PO, ? if efficacy equal with IV Tx

5. Micronutrients
   a) Zinc deficiency is common in malnourished children with diarrhea
      (1) Trial in Bangladesh showed that zinc supplementation (20mg/day) during the acute episode of diarrhea reduced the duration of diarrhea, diminished stool output and resulted in better weight gain, and normalized serum zinc concentrations.

6. Probiotics
   a) Bacteria, derived from healthy, live microflora
      (1) Yeasts and even helminths have also been used
   b) Long been used to treat human diseases
   c) Lactobacillus GG is the most investigated and was proven effective for the prevention and/or treatment of acute diarrhea in children and adults, particularly in rotaviral gastroenteritis.

7. Antidiarrheal: There is no place for antidiarrheal agents (e.g., loperamide) in the treatment of acute diarrhea.

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H. References
VI. Chronic Diarrhea

A. **Definition** – An increase in frequency, fluidity, or volume (>10 g/kg/day in children) of stool persisting for one month or longer, relative to the usual stool habits of an individual.

B. **Pathophysiology**

1. **Secretory**
   - Fluid secretion accompanies active ion secretion by the intestine
   - The gap between the measured stool osmolality and two times the sum of the stool sodium and potassium is typically < 40, and stool sodium concentration is frequently greater than 90 meq/L
   - Diarrhea persists despite fasting by the individual
   - Causes
     - Enterotoxin-producing bacterial pathogens (Vibrio cholera or enterotoxigenic E. Coli)
     - Enterotropin-hormone-secreting tumors (carcinoid, VIPoma, gastrinoma, neural crest tumors, medullary carcinoma of thyroid)
     - Ingestion of laxatives (cascara, senna, phenolphthalein)
     - Congenital ultrastructural and metabolic abnormalities of enterocytes

2. **Osmotic (Malabsorptive)**
   - Accumulation of nonabsorbable solutes in intestinal lumen results in an increase in intraluminal osmotic pressure, retarding water and electrolyte absorption
   - The gap between the measured stool osmolality and two times the sum of the stool sodium and potassium concentrations is typically > 80
   - Diarrhea resolves with fasting
   - Causes
     - Excessive ingestion of nonabsorbable solutes (i.e. sorbitol)
     - Consumption of laxatives containing poorly absorbed ions (magnesium)
     - Carbohydrate malabsorption (disaccharidase deficiency, celiac disease)
     - Pancreatic insufficiency (cystic fibrosis)
     - Overfeeding.

3. **Abnormal intestinal motility**
   - Increased intestinal motility results in decreased mucosal contact time
     - Causes of increased motility
       - Extensive bowel resection (short gut syndrome)
       - Inflammation (inflammatory bowel disease)
       - Hyperthyroidism
       - Hypocalcemia
       - Toddler’s Diarrhea
         - May represent a variant of irritable bowel syndrome, characterized by rapid transit through the colon
         - May be associated with excess carbohydrate (i.e. fruit juice) consumption
         - Growth usually normal unless diet overly restrictive
     - Decreased intestinal motility may result in stasis and bacterial overgrowth
       - Bacterial deconjugation of bile salts to dihydroxy bile acids, and the resultant metabolism of unabsorbed fatty acids to hydroxy fatty acids, may lead to colonic secretory diarrhea
     - Causes of decreased motility
       - Malnutrition
       - Intestinal pseudo-obstruction
       - Scleroderma
       - Endocrinopathies
         - Hypothyroidism
         - Hypercalcemia
         - Diabetes mellitus

4. **Mucosal damage**
   - Reduction of mucosal surface area and/or damage to the mucosal surface impairs water and electrolyte uptake
   - Causes
     - Inflammatory bowel disease
     - Infectious enteritis
     - Allergic gastroenteropathy
     - Celiac disease
     - Radiation enteritis

5. **Protracted Diarrhea of Infancy**
   - Defined as chronic diarrhea of more than two weeks duration beginning before 6 months of age and associated with malabsorption and malnutrition
   - Causes
     - Cow’s milk/soy protein intolerance
       - Most common cause
       - May present with vomiting, irritability, bloody stools, poor feeding and/or diarrhea
       - Stool pH may be low and test + for reducing substances, but with WBC’s consistent with colitis
       - High rate of cross-reactivity between cow’s milk and soy protein allergy (up to 50%)
     - Protracted infectious enteritis
       - Enterocyte injury may induce or unmask milk or soy protein sensitivity by altering permeability of mucosal membrane
       - Villous injury may result in secondary lactase/disaccharidase deficiency
     - Microvillus inclusion disease
       - Rare congenital abnormality in microvillus membrane resulting in characteristic inclusions of microvilli on electron microscopy of small bowel
       - Presents shortly after birth and usually fatal without small bowel transplant
     - Tufting Enteropathy
(a) Similar to microvillus inclusion disease but with abnormal attachment of microvilli to mucosal surface, resulting in alteration of normal enterocyte architecture (tufting)

(5) Autoimmune enteropathy
   (a) Presence of antibodies directed at small bowel epithelium (Anti-enterocyte antibodies) causing upper tract inflammation and malabsorption

(6) Congenital Chloridorrhea
   (a) Congenital transport defect in which chloride-bicarbonate exchange transporter in ileum and colon is reversed, resulting in chloride and water secretion
   (b) Stool chloride > sodium and potassium combined

(7) Hirschsprung’s Disease
   (a) May present with chronic diarrhea and enterocolitis in small but significant minority of patients

(8) Congenital sucrose-isomaltase deficiency
   (a) Does not present until sucrose introduced into diet
   (b) Stools may be negative for reducing substances since sucrose non-reducing sugar, but pH low

C. Evaluation

1. History
   a) Stool history should include frequency, consistency, appearance, presence of fecal incontinence, and the presence of mucus or blood
   b) Presence of nocturnal symptoms and the duration of symptoms should also be elucidated
   c) Accurate diet history, including ingestion of fruit juices and dairy products
   d) Age of onset, ethnicity, medications, and travel and family histories

2. Physical examination
   a) Growth parameters, including height, weight, OFC, and weight-height ratio (or BMI), should be plotted
   b) Vital signs may confirm a suspicion of dehydration or endocrinopathy
   c) Look for evidence of weight loss or muscle wasting
   d) Abdominal examination may reveal distention, organomegaly, thickened bowel loops, bowel sounds, bruits, or masses
   e) Anorectal examination is essential, allowing for instant inspection of stool, occult blood status, presence of impaction, and active perianal disease
   f) Extraabdominal examination may reveal skin, joint, lymph, eye or thyroid gland abnormalities.

3. Stool
   a) Qualitative or quantitative fecal fat analysis, fecal alpha-1 antitrypsin, and fecal pH and reducing substances are used to define fat, protein, and carbohydrate malabsorption, respectively
   b) Fecal gram stain may demonstrate leukocytes, suggesting inflammatory or infectious diarrhea
   c) Stool culture for enteric pathogens and Clostridium difficile, and stool analysis for ova and parasites and Giardia antigen are less likely to be positive in chronic diarrhea
   d) Fecal elastase measurement is a screening tool for pancreatic insufficiency
   e) Simultaneous stool osmolality and stool electrolytes allows for calculation of stool osmotic gap and differentiation between secretory and osmotic diarrhea
   f) An elevated stool magnesium level suggests laxative abuse.

4. Blood
   a) Complete blood count screens for anemia, and white blood cell count is often elevated in inflammatory bowel disease
   b) Inflammatory markers, such as sedimentation rate, C-reactive protein, and platelet count, are often elevated in inflammatory bowel disease
   c) Fat-soluble vitamin deficiency can be assessed by serum carotene, prothrombin time, and vitamin A, D, and E levels
   d) Decreased total protein and albumin levels in combination with elevated fecal alpha-1 antitrypsin suggest protein-losing enteropathy
   e) Measurement of gastrointestinal hormones, including gastrin and VIP, is used to screen for neuroendocrine tumors
   f) Consider screening for Celiac disease with anti-endomysial antibody and/or tissue transglutaminase IgA, coupled with quantitative IgA to rule out false negatives from IgA deficiency

5. Endoscopy
   a) Individuals with prolonged bloody diarrhea should undergo endoscopic examination with biopsies
      (1) Profuse diarrhea following antibiotic use dictates laboratory and/or endoscopic evaluation for Clostridium difficile
      (2) Melanosis coli (dark staining of colonic mucosa) may be present with laxative abuse
   b) Upper gastrointestinal endoscopy allows for the collection of duodenal fluid for culture in cases of suspected bacterial overgrowth, and for the collection of small intestinal biopsies for histologic and electron microscopic analyses.

6. Other
   a) Contrast radiographic studies allow for evaluation of inflammatory bowel disease and intestinal obstruction, blind loops, Hirschsprung’s and fistulas
   b) Abdominal/endoscopic ultrasound or CT is used for suspicion of neurogenic tumors or gastrinoma
   c) Lactose-hydrogen breath test for suspected lactose intolerance

D. Therapy: appropriate therapy rests on identifying and treating the underlying cause

1. Diet
   a) The resumption of a regular diet for age is necessary, especially when physical examination is normal
   b) Limitation of fruit juice or lactose-containing products may be indicated, depending on history
   c) High fat, low carbohydrate diet may be helpful in toddler’s diarrhea
   d) Gluten-free diet indicated for Celiac disease
   e) Avoidance of suspected food allergens may be indicated by presentation, family history and results of medical evaluation
      (1) Protein hydrolysate formula for infants with suspected milk/soy protein allergy (i.e. Alimentum, Nutramigen, Pregestimil) however a small percentage may require elemental formula (i.e. Neocate, Elecare, Vivonex)
2. Empiric therapy with anticholinergics, pancreatic enzymes, antibiotics, or bile salt sequestering agents is not recommended.
3. Therapy follows proper diagnosis
   a) Octreotide may be used in chronic secretory diarrhea due to neuroendocrine tumors
   b) Antibiotics indicated for enteric infections, bacterial overgrowth
   c) Appropriate immunomodulator treatment for Inflammatory Bowel Disease and Autoimmune enteropathy
   d) Surgical evaluation for Hirschsprung’s, transplant in microvillus inclusion disease and other congenital disorders

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F. References
VII.  **Obesity**

A.  **Definition:** Obesity is defined as excess body fat.

1.  Since BMI is an excellent estimate of excess adiposity, the body mass index (weight/height2) is widely used in adult populations as the sole criterion for classifying patients as either overweight (BMI, 25-29.9 kg/m2) or obese (BMI, > 30 kg/m2).
   a)  Adult BMI >35 with identified comorbidity considered morbidly obese
   b)  Adult BMI > 40 (even without identified comorbidity) considered morbidly obese

2.  Body mass index in childhood changes substantially with age
   a)  In the United States, the 85th and 95th centiles of body mass index for age and sex based on nationally representative survey data have been recommended as cut off points to identify overweight and obesity
      (1)  Generally BMI > 85%ile but < 95%ile for age considered overweight
      (2)  BMI > 95%ile for age considered obese
      (3)  BMI > 97%ile for age considered morbidly obese
      (4)  Cutoffs may overestimate adiposity in athletic youths with large muscle mass

B.  **Epidemiology**

1.  Adults
   a)  Overweight: In 1999 34% of Americans met the criteria for overweight, the highest percentage ever observed.
   b)  Obese: In 1999, almost 27% of the American population had BMIs of greater than 30 kg/m2.

2.  Children: The prevalence of child and adolescent obesity has increased dramatically over the last 30 years.
   a)  For all race and ethnic groups combined, the prevalence of overweight and obesity was 22% and 10.9%, respectively
   b)  The highest prevalence of overweight is found among 6 to 11 years old African-American girls (31%) and Mexican-American boys of similar age (33%).

3.  Risk Factors
   a)  The two most important risk factors are parental obesity and ethnic background
      (1)  Investigators noted that if both parents were obese, 80% of the children developed obesity
      (2)  If one parent was obese, about 50% of the children developed obesity
      (3)  If neither parent was obese, only 10% of the children became obese.
   b)  Obese children are at risk for becoming obese adults. The risk of remaining obese increases with age and the degree of obesity.
   c)  Children in the USA spend 75% of their waking hours being inactive, compared with remarkably little time in vigorous physical activity; estimated at only 12 min per day.
   d)  The epidemic increase in childhood overweight is the most common health problem facing US children

C.  **Causes**

1.  Obesity is a direct consequence of the first law of thermodynamics. Energy that is not consumed must be stored. Obese persons become obese because of cumulative excess in energy intake that exceeds their energy requirements.
2.  Although the combination of increased energy intake and decreased physical activity is responsible for most child and adolescent obesity, a strong body of evidence suggests that genetic factors contribute greatly to the severity of symptoms resulting from this “obesigenic” environment.
3.  Obese children tend to consume diets higher in fat which have higher caloric density.
4.  Decreased resting metabolic rate may also be another factor involved in the development of obesity.

D.  **Differential Diagnosis**

1.  Primary Obesity
   a)  For most obese children, the cause is primary obesity and is not associated with a specific clinical, metabolic or genetic syndrome.
      (1)  Primary obesity is associated with increased height, advanced bone age, and early puberty.
   b)  Fewer than 5% of all cases are due to an underlying medical disorder.

2.  Endocrine Disorders
   a)  Cushing syndrome
   b)  Hypothyroidism
   c)  Pseudohypothyroidism type I
   d)  Hyperinsulinemia
   e)  Growth hormone deficiency
   f)  Panhypopituitarism
   g)  Stein-Leventhal syndrome (polycystic ovary syndrome)

3.  Congenital Disorders
   a)  Muscular dystrophy
   b)  Myelodysplasia

4.  Chromosomal Disorders
   a)  Prader-Willi syndrome
   b)  Down syndrome
   c)  Turner syndrome
   d)  Klinefelter syndrome
   e)  Laurence-Moon-Biedl synd
   f)  Alstrom-Hallgren syndrome
   g)  Carpenter’s syndrome
   h)  Cohen’s syndrome

5.  Medications: certain drugs associated with increased weight gain
   a)  Diabetes drugs: insulin, sulfonylurea, thiazolidinediones
   b)  Psychiatric/ Neurologic drugs: tricyclic antidepressants, SSRI’s, MAOI’s, lithium, clozapine, olanzapine, risperidone, valproic acid, carbamazepine, gabapentin
   c)  Hormones: corticosteroids, hormonal contraceptives, postgestational steroids
   d)  Miscellaneous agents: antihistamines, α-blockers, β-blockers
E. Medical Complications
1. Cardiovascular: Hypertension, hypertriglyceridemia, increased VLDL, hypercholesterolemia, increased LDL, decreased HDL, myocardial hypertrophy
3. Endocrine: Early puberty, diabetes mellitus type II (adolescents)/ insulin resistance, sodium retention, polycystic ovary syndrome
4. Dermatologic: Acanthosis nigricans, varicose veins, striae/stretch marks, skin irritation, maceration, hidradenitis suppurativa
5. Neurologic: Pseudotumor cerebri
6. Pulmonary: Obstructive sleep apnea, Pickwickian syndrome
7. Musculoskeletal: Blount’s disease (tibia vara), slipped capital femoral epiphysis, osteoarthritis, forearm fracture, flat feet
8. Immunologic: Impaired cell-mediated immunity, reversed CD4-CD8 ratio
9. Gastrointestinal Complications:
   a) Reflux Esophagitis - Hiatal hernia, increased intra-abdominal pressure
   b) Esophageal Carcinoma
   c) Gallstones- Gallbladder cancer: More prevalent in women (increased cholesterol saturation index)
   d) Liver Disease Nonalcoholic steatohepatitis (NASH) or nonalcoholic fatty liver disease (NAFLD) which may progress to cirrhosis (15% to 20% patients after approximately one decade) or liver failure and increase risk for hepatocellular carcinoma
   e) Pancreatitis: Obese persons are at higher risk for pancreatitis due to gallstones, hypertriglyceridemia, and hypertryglyceridemia associated with diabetes.
   f) Colonic Polyps and Cancer of the colon

F. Physical Examination
1. Anthropometric measurements: height, weight, BMI, skinfold thickness (triceps), mid-arm circumference and waist circumference.
2. Fat distribution pattern (central or gynecoid).
3. Tonsillar hypertrophy
4. Thyromegally, thyroid nodules
5. Hepatomegally (fatty liver).
6. Hyperpigmented skin in the axilla, neck and groin (acanthosis nigricans).
7. Skin lesions in inguinal area and perineum (hydradenitis suppurativa)
8. Tanner staging
9. Blood pressure

G. Laboratory and Imaging
1. Thyroid status: TSH, T4 (especially if height is less than 50th percentile)
2. Lipoprotein profile, fasting (total cholesterol, HDL, LDL, triglycerides)
3. Fasting glucose and insulin levels (for those with acanthosis nigricans)
4. ALT, AST, GGT (NAFLD, cholelithiasis)
5. Bone age
6. CRP- may reflect cardiovascular risk status

H. Prognosis
1. Poor for long-term maintenance of weight loss (with current regimens)
2. Obesity cannot be cured but can be modified by consistent changes in eating behaviors and physical activity.

I. Treatment
1. Conventional
   a) Most efforts to reduce obesity in children have used either family-based or school-based approaches.
   b) Although a few family-based studies produced significant long-term weight loss in motivated individuals, the overall success has been disappointing, leading some specialists to conclude that treatment of obese children is unrealistically optimistic.
   c) Treatment in childhood, however, has the advantage of having fewer years of obesigenic behavior to overcome and continued vertical growth. It therefore may offer the best window of opportunity for treatment of this chronic condition.
   d) The major components of all obesity programs are education, calorie restriction, increased physical activity, and behavioral changes (limitation of television watching).
   e) A common sense approach to prevention and treatment of childhood obesity should include family participation in the care plan, long-term follow-up as a chronic condition and a realistic weight goal for weight loss and maintenance.
2. Diets
   a) Although numerous "fad diets" are continuously proposed, there are few that are supported by rigorous clinical trials in adults, much less children
   b) Ketogenic diets, such as Atkins and Protein sparing modified fast diets are being studied (in both adults and adolescents) and have been shown in short term studies to result in greater weight loss and improvement in lipid profiles, compared to traditional low fat, low calorie diets
      (1) Most subjects seem to regain the weight after coming off the diet and long-term maintenance of ketosis is not usually recommended
      (2) Most successful studies were performed under strict dietary supervision, and would be quite difficult to maintain off protocol, especially for adolescents
      (3) Inadequate adherence to ketogenic diets may result in significant weight gain from increased caloric density of diet
      (4) Gallstones, arrhythmias, constipation, electrolyte disturbances have all been described on ketogenic diets
   c) Conventional low fat, low calorie diets
      (1) In adults it decreases body weight by 5-10% and weight is generally regained with discontinuation of the drug
      (2) Side effects of steatorrhea and flatulence with dietary fat intake may limit compliance
   d) Sibutramine is a mixed serotonin, dopamine and norepinephrine reuptake inhibitor which acts in the CNS to decrease appetite
      (1) In adults it may reduce body-weight by 5-10%, and this is generally regained with discontinuation of the drug
      (2) Generally well-tolerated
   e) Orlistat is a pancreatic lipase inhibitor which decreases dietary fat absorption to about 30%
      (1) In adults it decreases body weight by 5-10% and weight is generally regained with discontinuation of the drug
      (2) Side effects of steatorrhea and flatulence with dietary fat intake may limit compliance

3. Medications: There are currently no weight-loss medications approved for use in children, although multicenter trials using sibutramine and orlistat have been performed in adolescents with short-term success
   a) Orlistat is a pancreatic lipase inhibitor which decreases dietary fat absorption to about 30%
      (1) In adults it decreases body weight by 5-10% and weight is generally regained with discontinuation of the drug
      (2) Side effects of steatorrhea and flatulence with dietary fat intake may limit compliance
   b) Sibutramine is a mixed serotonin, dopamine and norepinephrine reuptake inhibitor which acts in the CNS to decrease appetite
      (1) In adults it may reduce body-weight by 5-10%, and this is generally regained with discontinuation of the drug
      (2) Generally well-tolerated

4. Dermatologic: There are currently no weight-loss medications approved for use in children, although multicenter trials using sibutramine and orlistat have been performed in adolescents with short-term success
   a) Orlistat is a pancreatic lipase inhibitor which decreases dietary fat absorption to about 30%
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      (2) Side effects of steatorrhea and flatulence with dietary fat intake may limit compliance
   b) Sibutramine is a mixed serotonin, dopamine and norepinephrine reuptake inhibitor which acts in the CNS to decrease appetite
      (1) In adults it may reduce body-weight by 5-10%, and this is generally regained with discontinuation of the drug
      (2) Generally well-tolerated
c) Metformin is a well-established medication for treatment of type 2 diabetes and polycystic ovary syndrome. It may be useful for treatment of insulin resistance in obese children and result in weight-loss as well. 
d) Bupropion is an antidepressant medication that has been found in placebo-controlled studies to result in improved weight-loss in both depressed and non-depressed adults participating in weight-loss programs.
e) Other: More than 75 weight-loss drugs are in various stages of the FDA approval process before being approved for use in adults.

4. Surgery: Bariatric surgery creates an anatomic barrier preventing over-consumption and accumulation of excess calories either by restricting the gastric reservoir or by inducing malabsorption.
   a) Types
      (1) Gastric bypass (the most common performed today)
      (2) Gastric restriction
      (3) Jejunooileal bypass
      (4) Biliopancreatic bypass
   b) Although surgical treatment remains, by far, the most effective form of obesity therapy, there is a very high rate of morbidity (70% of patients who undergo gastric bypass experience dumping) and mortality in obese adults.
   c) The limited experience in children and adolescents seems to confirm a similar rate of complications.
   d) The use of bariatric surgery is only indicated in morbidly obese patients who have been properly screened and who have failed maximal medical management. Use in morbidly obese adolescents remains controversial.

J. Prevention
1. Prevention and treatment of obesity ultimately involves eating less and being more physically active.
2. Appropriate screening measures should be in place to identify children at-risk for development of obesity and intervene as early as possible with simple dietary and behavioral changes
   a) Limit excess intake of high-calorie beverages such as whole milk, fruit juices and soft drinks.
   b) Educate families on the risks of fast food intake and teach children to make healthier choices when eating out.

K. Conclusion
1. Given the profound consequences of childhood inactivity, poor nutrition, and obesity throughout the lifespan, urgency is warranted in responding to this epidemic.
2. Childhood obesity remains a very serious problem, with 25% to 50% of obese children ultimately becoming obese adults.
3. Fifty-year follow-up studies of obese adolescents have demonstrated increased morbidity and mortality, even independent of ultimate adult body weight status.

L. Authors
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M. References
VIII. Upper GI Bleeding

A. Etiology

1. Birth to 1 month
   a) Gastritis (peptic or allergic)
   b) Gastric or duodenal ulcer
   c) Esophagitis
   d) Coagulopathy (DIC, hemorrhagic disease)
   e) Vascular anomaly
   f) Necrotizing enterocolitis
   g) Factitious (swallowed maternal blood, epistaxis, hemoptysis)

2. Childhood (1 month - 18 years)
   a) Gastric or duodenal ulcer 25-75 %
   b) Gastritis 15-25 %
      i) Peptic
      ii) Allergic
      iii) H. pylori
      iv) Medication related
      v) Mechanical trauma (foreign body, NG or G-tube)
      vi) Zollinger Ellison syndrome
   c) Esophagitis 10-25 %
      i) Peptic
      ii) Allergic
      iii) Infectious etiologies (CMV, HSV, Fungal) in immunocompromised
   d) Varices secondary to liver disease or portal vein obstruction (0-15 %)
   e) Mallory-Weiss tear
   f) Gastrointestinal duplication
   g) Vascular anomaly
   h) Dieulafoy lesion
      i) Rupture of small mucosal artery into gastric lumen, presenting with massive UGI bleeding
      ii) Usually in proximal third of stomach, associated with the lesser curve
      iii) Rare in children
   i) Coagulopathy
   j) Hemobilia
   k) G-tube or NG-tube trauma
   l) Factitious (epistaxis, hemoptysis, red food or drinks, red meat, iron supplementation. If "melena", may be secondary to bismuth subsalicylate)

B. Presentation

1. Hematemesis (or bloody NG output) (69%)
2. Melena (53%)
3. Hematochezia (if rapid transport through GI tract, h/o of bowel resection) (16%)
4. Anemia
5. Abdominal pain
6. Shock
7. Syncope

C. Evaluation

1. History: Recent vomiting, feeding refusal, pain, stress, h/o liver disease, cystic fibrosis, coagulopathy, vitamin K given after delivery, possibility of foreign body, caustic ingestion or H. pylori infection, breast feeding, h/o recent dental work, oral surgery or GI procedures
2. Exam: HR, BP, orthostatics, pallor, jaundice, cutaneous evidence of chronic liver disease or cutaneous vascular malformations, evidence of nasal or oropharyngeal source, abdominal distention or rigidity, hepatosplenomegaly, capillary refill, perfusion
3. Laboratory:
   a) TYPE AND CROSS,
   b) HCT/Hg, Platelets
   c) PT/PTT
   d) Liver enzymes, Albumin
4. NG lavage
   a) Assists with location and determination of degree of active bleeding.
   b) Use room temperature normal saline, NOT ice cold water (risk of hypothermia, does not help with hemostasis)
   c) Can have false negative if bleeding site is distal to pylorus, or if volume of saline used is too small
   d) Tube poses small risk of exacerbating bleeding
5. Gastroccult emesis or NG aspirate, Hemoccult stool
6. Apt-Downey test to differentiate swallowed maternal blood
   a) Mix 1:5 bloody stool or emesis:water (should have at least 1-2 cc of sample)
   b) Centrifuge at 2000 rpm for 2 minutes
   c) Discard supernatant and use for remainder of evaluation, may discard cellular debris
   d) Mix 1 cc of 0.25N NaOH to 5 cc supernatant
   e) Observe for color change after 2 minutes
      i) Fetal hemoglobin remains pink
      ii) Adult hemoglobin turns yellow-brown as it is denatured
7. Imaging (often low yield, but interventional radiology can be helpful in diagnosis and establishment of hemostasis)
   a) Abdominal plain film and upright for FB, perforation, NEC
   b) Ultrasound with doppler if liver disease suspected
   c) Tagged red cell scan (need 0.1 cc/ minute rate of bleeding)
      i) Tc-99m labeled RBC’s re-injected into peripheral bloodstream to look for active bleeding
      ii) Can obtain delayed view at 24 hours if initially negative, and this may detect intraluminal pools of blood as small as 5 cc (Location of pool may not accurately correlate with site of bleeding).
d) Angiography (need > .5 cc/ minute rate of active bleeding)
   (1) Indicated for actively bleeding lesions or chronic bleeding not identified by other tests
   (2) Femoral artery approach, catheter guided through mesenteric arteries and contrast medium injected
   (3) Interventional techniques can be therapeutic

e) Barium studies are insensitive and may delay therapy
   a) If endoscopic therapy likely to be necessary, consider general endotracheal anesthesia

D. Therapy

1. General/ Supportive
   a) Oxygen as needed
   b) Ensure good IV access at all times
   c) Volume resuscitation as needed
   d) Monitor vital signs frequently, follow serial Hgb/HCT as needed to assess persistence and severity of bleeding
   e) Type and screen for PRBC's, transfuse as indicated for rapidly decreasing HCT, vital sign instability
   f) Optimize coagulation (Vitamin K, FFP) as needed

2. Medical
   a) IV/PO H2 blocker (acid reduction)
      (1) Ranitidine
      (2) Famotidine
      (3) Nizatidine
      (4) Cimetidine
   b) IV/PO PPI (acid reduction)
      (1) Omeprazole
      (2) Lansoprazole
      (3) Rabeprazole
      (4) Pantoprazole
   c) IV Octreotide (vasoconstriction) for ongoing upper GI bleeding
      (1) Limited pediatric data
      (2) May decrease transfusion requirements by slowing variceal and non-variceal upper GI bleeding
   d) PO/PG Sucralfate (cytoprotective)
   e) PO/PG Misoprostol (cytoprotective)
   f) Therapy for H. pylori infection (antimicrobial) if indicated

3. Endoscopic (After medical therapy fails to control continued bleeding)
   a) Variceal bleeding
      (1) Band ligation
         (a) Advantages
            (i) Has been shown to be at least as effective as sclerotherapy in eradicating varices in adults and children
            (ii) Lower rate of all forms of complications
         (b) Disadvantages
            (i) Decreased visualization when variceal band ligator attached
            (ii) Requires at least two esophageal intubations
            (iii) May be more difficult than sclerotherapy in treatment of actively bleeding lesions
            (iv) Use limited in smaller children due to size of apparatus (currently minimum 9mm endoscope, adapter has outer diameter range of 12-13 mm)
         (c) Complications
            (i) Rebleeding
            (ii) Esophageal ulcers
            (iii) Esophageal perforation
            (iv) Food impaction at banded site
            (v) Predisposition to bacteremia
         (d) Technique
            (i) Identify varices using standard upper endoscopy
            (ii) Attach variceal band ligator to tip of endoscope (use of multi-band attachments decreases need for repetitive esophageal intubation)
            (iii) Advance endoscope until most distal target varix identified and deflect tip toward varix
            (iv) Apply suction until varix causes "red-out", then trigger band placement
            (v) Repeat as needed, moving proximally
      (2) Sclerotherapy
         (a) Advantages
            (i) Only one esophageal intubation
            (ii) Smaller equipment may be used, thus smaller children may be treated
            (iii) Better visualization
            (iv) May be easier in treatment of actively bleeding lesions
         (b) Disadvantages: More frequent and severe complications than band ligation
         (c) Complications
            (i) Chest pain, acute dysphagia, fever are common
            (ii) Tissue necrosis and ulceration, possibly leading to fistulization into adjacent organs
            (iii) Strictureing
            (iv) Rebleeding
            (v) Esophageal perforation
            (vi) Predisposition to bacteremia
         (d) Technique
            (i) Identify varices using standard upper endoscopy
            (ii) Via endoscope channel, using 23 or 25 gauge, 4 or 6 mm needle, inject sclerosing agent into varix
            (iii) Recommended to only sclerose varices in the distal 5-6 cm of the esophagus to avoid complications
(iv) Sclerosing agents include Sodium Morrhuate, ethanolamine oleate, polidocanol, sodium tetradecyl sulfate alone or mixed with ethanol. All have been used with comparable success.

(3) Non-variceal Upper GI bleeding (most published pediatric experience limited to case reports)
   a) Sclerotherapy for gastroduodenal ulcers as in adults
   b) Laser therapy has been used to treat diffuse bleeding in adults, but rarely in children. Can be performed using 1.5 mm catheter via pediatric endoscope
   c) Hemostatic clips may be applied endoscopically to halt focal arterial or venous bleeding, but can be cumbersome

b) Sengstaken-Blakemore tube
   1) Indicated in acute, uncontrollable esophageal hemorrhage, or for use as a temporizing measure until an appropriate therapeutic center can be reached.
   2) Esophageal balloon is used to tamponade bleeding sites. Should be decompressed after 12-24 hours (incidence of mucosal damage increases with duration of use)
   3) Serious complications in up to 20% of patients (upper airway obstruction due to balloon migration, esophageal ulceration or perforation due to excessive pressure

c) TIPS (Transjugular Intrahepatic Portosystemic Shunt)
   1) Indicated in recurrent variceal bleeding and refractory ascites, and provides effective therapy for the complications of portal hypertension
   2) A temporizing measure to serve as bridge to transplantation
   3) Technique
      a) Via right internal jugular vein, needle advanced through liver parenchyma, bridging the hepatic vein and portal system
      b) Tract is dilated and expandable stent placed

d) Surgery: Important to involve surgical team early in case adverse or unexpected events occur

E. Authors
   Brad Barth, MD, MPH

F. Reference
   Fox V. Pediatric endoscopy. Gastroenterological endoscopy, C Lightdale, ed, Thieme, New York, 2002; 720-752
IX. Lower Gastrointestinal Bleeding

A. Definitions
1. Hematemesis is the passage of vomited blood that has a coffee ground or bright red color. This usually implies hemorrhage proximal to the ligament of Treitz.
2. Hematochezia is the passage of bright or dark red blood per rectum, usually indicating a lower GI source, although this may also be due to a fast intestinal transit time or a massive upper GI bleed.
3. Melena is the passage of black, tarry stools associated with bleeding proximal to the ileocecal valve or, less commonly, in the ascending colon if the colonic transit is sufficiently slow to allow bacteria to denature the hemoglobin.
4. Occult bleeding is the presence of blood in stool that is not grossly detectable.

B. Physician Assessment
1. History taking should include the source, magnitude, duration of the bleeding, as well as any associated gastrointestinal and systemic symptoms.
2. Review of systems and family history should include GI disorders, liver disease, bleeding diatheses and medication use.
3. Physician should establish that blood is indeed present in the stool as food and medication can change the color of the stool. Table 1
4. Physical exam should initially be aimed at recognizing the signs and symptoms of shock.
   a) Later on, a careful examination of the skin, abdomen, perineum and rectum should be done looking for rashes, vascular malformations, stigmata of liver disease, presence of abdominal masses, tenderness, peritoneal irritation, skin tags, fistulas, anal fissures and hemorrhoids. A stool guaiac test is essential to confirm the presence of blood, however some substances can interfere with guaiac tests. Table 2

C. Differential Diagnosis

<table>
<thead>
<tr>
<th>Table 1. Substances that Commonly Color Stools</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Red</td>
<td>Black</td>
</tr>
<tr>
<td>Commercial Dyes #2 &amp; #3</td>
<td>Bismuth</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Activated charcoal</td>
</tr>
<tr>
<td>Beets</td>
<td>Iron</td>
</tr>
<tr>
<td>Laxatives</td>
<td>Spinach</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Blueberries</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Licorice, Lead, Dirt, Dark chocolate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2- Substances that interfere with Guaiac Tests for Fecal Occult Blood</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>False-positive Results</td>
<td>False-negative Results</td>
</tr>
<tr>
<td>Meat</td>
<td>Vitamin C</td>
</tr>
<tr>
<td>Ferrous Sulfate (stool pH &lt;6.0)</td>
<td>Storage of specimen &gt;4days</td>
</tr>
</tbody>
</table>
| Tomatoes, bean sprouts, cauliflower, broccoli, horseradish, turnips, fresh red cherries, cantaloupes, grapes | (Hemoglobin degradation)   
|                                                | Outdated reagent or card    |

C. Lower GI Bleeding Chart
Table 3—Causes of Lower Intestinal Bleeding

<table>
<thead>
<tr>
<th>Infants</th>
<th>Common</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>Anal Fissure</td>
<td>Vascular lesions</td>
</tr>
<tr>
<td></td>
<td>Cow’s milk protein allergy</td>
<td>Hirschsprung’s enterocolitis</td>
</tr>
<tr>
<td></td>
<td>NEC</td>
<td>Meckel diverticulum</td>
</tr>
<tr>
<td></td>
<td>Swallowed maternal blood</td>
<td>Intestinal duplication</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intussusception</td>
</tr>
<tr>
<td>Children</td>
<td>Anal fissure</td>
<td>Inflammatory Bowel Disease</td>
</tr>
<tr>
<td></td>
<td>Intussusception</td>
<td>(&lt;4 years old)</td>
</tr>
<tr>
<td></td>
<td>Infectious enterocolitis</td>
<td>Vascular malformations</td>
</tr>
<tr>
<td></td>
<td>(Salmonella, Shigella, Campylobacter, E. Coli 0157, Yersinia, C. Diff)</td>
<td>Hemolytic-Uremic Syndrome</td>
</tr>
<tr>
<td></td>
<td>Infectious Bowel Disease</td>
<td>Cectis</td>
</tr>
<tr>
<td></td>
<td>(&gt;4 years old)</td>
<td>Infectious Diarrhea (CMV, amebiasis)</td>
</tr>
<tr>
<td></td>
<td>Meckel’s diverticulum</td>
<td>Hemorrhoids</td>
</tr>
<tr>
<td></td>
<td>Perianal streptococcal cellulites</td>
<td>Colonic or rectal varices</td>
</tr>
<tr>
<td></td>
<td>Juvenile/inflammatory polyp</td>
<td>Ulcer at surgical anastomosis</td>
</tr>
</tbody>
</table>

Table 4—Conditions Associated with Intestinal Bleeding

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intestinal Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turner Syndrome</td>
<td>Venous ectasia, Inflammatory Bowel Disease</td>
</tr>
<tr>
<td>Epidermolysis Bullosa</td>
<td>Esophageal lesion, Anal fissure, colonic stricture</td>
</tr>
<tr>
<td>Down Syndrome</td>
<td>Hirschsprung’s Disease, Meckel’s diverticulum, Pyloric Stenosis</td>
</tr>
<tr>
<td>Ehlers-Danlos Syndrome</td>
<td>Fragile vascular walls</td>
</tr>
<tr>
<td>Hermansky-Pudlak Syndrome</td>
<td>Hermansky-Pudlak Syndrome</td>
</tr>
<tr>
<td>Blue rubber bleb nevus Syndrome</td>
<td>Vascular malformations</td>
</tr>
<tr>
<td>Osler-Weber-Rendu Syndrome</td>
<td>Vascular malformations, epistaxis</td>
</tr>
<tr>
<td>Klippel-Trenaunay Syndrome</td>
<td>Vascular malformations</td>
</tr>
<tr>
<td>Pseudoxanthoma Elasticum</td>
<td>Fragile vascular walls</td>
</tr>
<tr>
<td>Glycogen storage disease type 1b</td>
<td>Inflammatory Bowel disease</td>
</tr>
</tbody>
</table>

D. Authors
Rima Fawaz M.D.

E. References
X. **Ascites**

**A. Background**

1. Term ascites is derived from the Greek word "askos" meaning bag or sack
2. Defined as the pathological accumulation of fluid in the peritoneal cavity
3. May be congenital or acquired
4. Typically results from hepatic or urinary tract disease in children
5. Management depends on the causative factors

**B. Etiology:** Most common etiologies vary by age of patient

1. **Hepatobiliary**
   a) Cirrhosis: ascites results from portal hypertension
   b) Portal dysplasia
   c) Congenital Hepatic Fibrosis
   d) Hepatitis: viral and alcoholic
   e) Budd-Chiari syndrome
   f) Liver metastasis
   g) Biliary atresia with cirrhosis
   h) Common bile duct perforation
   i) Gallbladder rupture
   j) Portal vein thrombosis
2. **Cardiovascular**
   a) Congestive heart failure/ arrhythmia
   b) Hydrops
3. **Genitourinary**
   a) Hydronephrosis
   b) Multi-cystic kidney
   c) Nephrotic syndrome
   d) Peritoneal dialysis
   e) Obstructive uropathy
   f) Bladder rupture/injury
   g) Kidney rupture
   h) Ovarian cyst
4. **Gastrointestinal**
   a) Malrotation with bowel compromise/ perforation
   b) Perforation
   c) Acute appendicitis
   d) Jejunal atresia
   e) Meconium peritonitis
   f) Pyloric duplication
   g) Protein-losing enteropathy/ intestinal lymphangiectasia
5. **Infectious**
   a) Cytomegalovirus
   b) Tularemia
   c) Spontaneous bacterial peritonitis
   d) Tuberculous peritonitis
   e) Parvovirus with hydrops
   f) Syphilis
   g) Chronic granulomatous disease
6. **Metabolic with associated cirrhosis**
   a) Niemann-Pick type C
   b) Neonatal hemochromatosis
   c) Lysosomal storage disease
   d) Wolman’s disease
   e) Cystic Fibrosis
   f) Galactosemia
   g) α-1 anti-trypsin disease
7. **Other**
   a) Pancreatic
   b) Chylous
   c) Trisomy
   d) Turner’s syndrome
   e) Ventriculo-peritoneal shunt
   f) Neoplasm
   g) Serositis
   h) Post-liver transplantation
   i) Peritoneal carcinomatosis
   j) Idiopathic
   k) Pseudo-ascites
      (1) Celiac disease
      (2) Cystic mesothelioma
      (3) Omental cyst
I) Hemolytic anemia
m) IVC Hyperalimentation
n) Protein-calorie malnutrition
o) Letterer-Siwe Disease

C. Pathophysiology
1. Cirrhotic ascites
   a) Distortion and obstruction of the sinusoidal vessels from hepatic venous outflow blockage caused by regenerative nodules and fibrosis
   b) Widespread changes in circulation also important
   c) Hypoalbuminemia in decompensated cirrhosis exacerbates the ascites by decreasing oncotic pressure
   d) Hypotheses
      (1) Underfill theory: contracted blood volume with secondary sodium and water retention
      (2) Overflow theory: unknown hepatorenal mechanism causes sodium and water retention
      (3) Vasodilation of the periphery

2. Non-cirrhotic ascites: a wide variety of mechanisms result in peritoneal fluid accumulation
   a) In low and high output heart failure as well as in nephrotic syndrome, decreased arterial blood volume leads to sodium and water retention
   b) Infectious and malignant peritoneal disorders cause peritoneal inflammation and exudation
   c) Chylous ascites results from congenital or acquired lymphatic obstruction or damage
   d) Leakage from a viscus in biliary, pancreatic and urinary ascites
   e) Underlying portal hypertension as well as another cause for ascites may coexist- "mixed" ascites accounts for about 5%
   f) Hepatic venous outflow obstruction in Budd Chiari leads to massive ascites

D. Clinical Presentation
1. Increasingly diagnosed in the fetus by prenatal ultrasound
   a) Anatomic, metabolic, hemolytic and chylous etiologies must be evaluated in newborns with ascites of unclear etiology
2. May develop acutely or insidiously
3. Older children may present with weight gain, edema, increasing abdominal girth, and bulging flanks
4. Hernias (femoral, inguinal and umbilical) and an inverted umbilicus are seen in advanced ascites
5. Quantification of ascites maybe done on this simple scale
   a) Grade 1: detectable by careful exam
   b) Grade 2: small volume and easily detected
   c) Grade 3: obvious but not tense
   d) Grade 4: tense ascites
6. Physical Exam findings
   a) In those with cirrhotic ascites evidence of chronic liver disease like jaundice, spider angiomas, umbilical, abdominal wall or gastrostomy collateral veins, prominent clubbing, and palmar erythema may be present
b) Splenomegaly and prominent abdominal wall veins often denotes portal hypertension
c) Evaluation should also attempt to identify:
   (1) Cardiac disease (murmur, jugular vein distention, pericardial friction rub)
   (2) Renal disorder
   (3) Peritonitis (diffuse abdominal pain, rebound tenderness)
   (4) Pancreatitis (abdominal pain radiating to the back)
   (5) Lymphatic obstruction (lymphedema)
   (6) Hypoalbuminemia (edema)
   (7) Hemolysis
   (8) Nutritional disorders

E. Diagnosis
1. Physical Exam
   a) Shifting dullness
      (1) The most sensitive clinical sign of ascites
   b) Sensitivity of 60-88% and a specificity of 56-97%
2. Fluid wave
3. Bulging flanks
4. Percussion: distinguishes ascites from obesity or an abdominal mass
   a) Abdominal radiographs
      (1) Centralization of bowel gas pattern
      (2) Flank strip sign
      (3) Diffuse haziness
      (4) Medial displacement of the liver edge
   b) Ultrasound
      (1) Most sensitive technique and can detect as little as 100 cc of free abdominal fluid in the adult
      (2) May detect intra-peritoneal fluid and debris in infants with abdominal distention
      (3) May identify potential intra-abdominal masses, vascular anomalies, and provide information about the size and echotexture of the liver and spleen.
   c) CT scan/ MRI
3. Paracentesis
   a) Procedure of choice for the evaluation of ascites with unclear etiology
   b) Also recommended to detect infectious peritonitis, when patients are hospitalized, and when there is clinical deterioration
   c) Few Contraindications and can be usually be performed despite prolonged prothrombin time, except in the setting of DIC or active fibrinolysis
   d) Complications
      (1) Bleeding
      (2) Abdominal wall hematoma
      (3) Infection
      (4) Bowel perforation
(5) Sudden labial or scrotal edema
(6) Persistent leak at the puncture site
(7) These can be limited by using a Z track, sterile technique, and avoiding scars

e) Technique
   (1) Site
      (a) Traditional approach is a midline site caudad to the umbilicus
      (b) An alternative location is the flank, 2 cm superior and medial to the anterior superior iliac spine
   (2) Positioning: most procedures can be done with the patient supine, slight elevation of the head of bed to pull ascites to lower abdomen.
   (3) Ultrasound guidance maybe used in selected situations (obesity, multiple scars)
   (4) Percussion is used to pick the best flank if a midline approach is not utilized
   (5) Catheter:
      (a) A narrow bore catheter or metal needle (16 or 18 gauge angiocath or spinal needle) is sufficient to withdraw the necessary 10 to 20 cc of fluid needed for a diagnostic procedure
      (b) For larger volumes consider catheters specifically designed for paracentesis (ie 15 gauge Caldwell needle)

f) Fluid Analysis
   (1) The fluid is inspected grossly and sent for analysis
      (a) Routine: cell count, gram stain, albumin, total protein and culture (in blood Cx bottle)
        (i) Bedside inoculation of culture bottles with adequate volume of fluid (10 cc) increases the yield of these cultures.
      (b) Optional: glucose, triglycerides, amylase, LDH, bilirubin
      (c) Unusual: TB culture/AFB stain, cytology/Cytospin, pH, lactate, peritoneal biopsy
   (2) Additional tests can be ordered based on clinical findings and gross appearance of the ascitic fluid
      (a) Turbid and cloudy: infectious
      (b) Hemorrhagic: pancreatic, malignant, or tuberculosis
      (c) Milky: chylous
      (d) Straw colored; cirrhosis, renal, cardiac, or nutritional.
   (3) Serum-ascites albumin gradient (SAAG) = serum albumin – ascites albumin
      (a) High gradient ascites (SAAG > 1.1 gm/dl)
         (i) -Cirrhosis
            (a) Ascitic fluid from patients with liver disease and no secondary complications is generally straw colored, protein count is < 2.5 gm/dl, SAAG > 1.1 gm/dl, cell count is < 250 cells/mm3 with mostly lymphocytes, and the glucose and LDH are similar to serum values.
            (ii) Alcoholhepatitis
            (iii) Cardiac ascites
            (iv) Liver metastases
            (v) Fulminant hepatic failure
            (vi) Budd-Chiari syndrome
            (vii) Portal Vein thrombosis
            (viii) Veno-occlusive disease
            (ix) Acute fatty liver of pregnancy
            (x) Mixed ascites
      (b) Low gradient ascites (SAAG < 1.1 gm/dl)
         (i) Peritoneal carcinomatosis
         (ii) Tuberculosis
         (iii) Pancreatic ascites
         (iv) Biliary ascites
         (v) Nephrotic syndrome
         (vi) Connective tissue disease
         (vii) Bowel obstruction
         (viii) Bowel infarction
   (c) If portal hypertension is present, the SAAG is greater than 1.1 gm/dl with 97% accuracy

F. Management: Successful treatment of ascites depends on addressing the primary underlying cause

1. Cirrhosis
   a) Treatment has not been shown to improve survival or liver function
   b) Can improve quality of life and prevent complications of ascites
   c) Medical therapy for cirrhotic ascites includes dietary sodium restriction, fluid restriction, and diuretics
   d) Therapeutic large volume (LV) paracentesis with or without albumin infusion is effective for diuretic-refractory tense ascites
   e) Additional measures for those who remain refractory may involve transjugular intrahepatic portosystemic shunt (TIPS), peritoneovenous shunt (PN shunt), or orthotopic liver transplantation (OLTx)

2. Cardiac ascites: uncommon, but occurs in both high and low output failure
   a) Similar ascitic fluid analysis to cirrhosis
   b) Treatment with sodium restriction, diuretics
   c) Medical therapy to improve cardiac output and to reverse underlying etiology (arrhythmia, anemia, congestive heart failure)

3. Biliary ascites: uncommon, seen with common bile duct perforation in infants, trauma and gallbladder rupture
   a) Ascitic fluid is bilious and total bilirubin value is > serum value (this may also be seen in bowel perforation)
   b) Treatment is surgical

4. Pancreatic ascites: Rare, complication of acute pancreatitis, pancreatic duct leakage or rupture from a pseudocyst
   a) May have underlying infection
   b) Ascitic fluid may be hemorrhagic with elevated amylase

5. Chylous ascites: Uncommon, seen in congenital abnormalities and acquired obstruction of lymphatics, post-surgical, trauma (child abuse), and abdominal processes (Tb, malignancy, mesenteric adenitis)
   a) Ascitic fluid is milky and triglycerides are > serum value (usually >1000 mg/dl)
   b) Treatment involves long chain fatty acid restriction, MCT added to diet, TPN, and recently octreotide

6. Uroascites: Uncommon, occurs in newborns from urinary tract obstruction/disruption, anomalies, trauma or iatrogenic
a) Ascitic fluid is similar to that seen with cirrhosis although is the result of urine accumulation.  
b) Treatment is surgical

7. Spontaneous bacterial peritonitis (SBP): Infection of ascitic fluid without evidence of abdominal source
   a) Occurs mainly in pre-existing cirrhotic ascites and presents with abdominal distention, pain, fever, diffuse tenderness and worsening jaundice. Although, maybe asymptomatic
   b) Ascitic fluid has predominance of polymorphonuclear cells and leukocyte > 250 cells/mm3
   c) Treatment is with a broad spectrum antibiotic with gram-negative coverage (cefotaxime) as well as adequate coverage for S. pneumoniae

8. Bacterial peritonitis: Must be differentiated from SBP. Occurs in setting of intestinal perforation, intra-abdominal abscess.
   a) Ascitic fluid shows >10,000 PMN's/mm3, low glucose (< 50mg/dl), elevated LDH (225 mU/ml), elevated total protein (> 1 gm/dl) and multiple organisms are cultured
   b) Treatment is surgical and antibiotics

9. Tuberculous peritonitis: Rare in children and if seen usually in setting of immunodeficiency or alcoholic cirrhosis
   a) Tubercles stud the peritoneum causing exudation of fluid
   b) Mononuclear cells predominate in the ascitic fluid
   c) AFB smears lack sensitivity and culture requires large volume to be positive, so peritonoscopy is critical if suspected
   d) Treatment is with anti-tuberculous drugs

10. General Treatment Modalities
   a) Sodium restriction
       (1) Technique: achieve negative Na balance
       (2) RESTRICTION: 2 meq/kg or 1-2 gm/day for adults
       (3) Disadvantages: works poorly alone, negative impact on appetite and nutrition
   b) Fluid restriction
       (1) Technique: Not until Na <125
       (2) Disadvantage: Most pts are not hyponatremic
   c) Spironolactone
       (1) Dose: 2-3 mg/kg, ↑ up to 4-6 mg/kg, 400 mg maximum
       (2) Disadvantages: Hyperkalemic metabolic acidosis
   d) Furosemide
       (1) Dose: 1 mg/kg, ↑ up to 2-4 mg/kg, 160 mg maximum
       (2) Disadvantages: Hypokalemic alkalosis
   e) LV paracentesis
       (1) Technique: Up to 100 ml/kg, max of 5 liters
       (2) Specifics: Safe, rapid, symptomatic relief. Most give albumin. Use needle designed for paracentesis if possible (15 g Caldwell) or 16/18 g IV catheter
       (3) Disadvantages: Reaccumulation
   f) TIPS
       (1) Technique: Non-surgical, hepatic-portal fistula
       (2) Specifics: Lowers portal pressure, prevents rebleeding, alleviates cirrhotic ascites
       (3) Disadvantages: encephalopathy, high rate of shunt occlusion, long term efficacy?
   g) Peritoneovenous shunt
       (1) Technique: Surgical
       (2) Specifics: LeVeen, Denver shunts
       (3) Disadvantages: High morbidity/mortality

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H. References
Machin GA. Diseases causing fetal and neonatal ascites. Pediatric Pathology 4:195-211;1985
XI. Neonatal Cholestasis

A. Definitions

1. Cholestasis is defined physiologically as a reduction in bile flow
   a) Impaired bile flow is characterized by an accumulation in the liver and serum of substances that normally are secreted in the bile, such as bilirubin, bile acids and cholesterol.
2. Conjugated hyperbilirubinemia is the most recognizable laboratory manifestation of cholestasis, and its finding is always pathologic.
3. Clinical features of cholestasis include:
   a) Jaundice
   b) Pruritus
   c) Acholic stools
   d) Dark urine
4. These features result from:
   a) Functional defect in bile formation, mainly related to intrahepatic disorders (Hepatocellular cholestasis)
   b) Impairment in bile secretion and flow in relation to extrahepatic disorders (Ductular/Ductal cholestasis)
5. Lab findings include:
   a) Conjugated bilirubin ≥ 2 mg% or 20% of total bilirubin
   b) Increased ALP (more than 3-fold normal values)
   c) Increased GGT more than 5 fold
   d) AST/ALT increased no more than 5-8 fold.
   e) Increased bile acids (>50 umol/l) and cholesterol
   f) ALT:ALP ratio <2

B. Significance of cholestatic jaundice

1. Neonatal cholestasis is present in 1/2500-5000 infants
2. Many of the underlying pathologies related to it can be life-threatening at some point
   a) Must identify specific entities that are treatable medically or surgically
   b) Early appropriate therapy may minimize further liver damage and optimize the infant’s growth and development.

C. Diagnosis

1. Clinical presentations of many of the disorders capable of producing cholestasis in infancy are similar (jaundice, dark urine, acholic stools, and varying degrees of hepatomegaly)
   a) Degree of impairment of hepatocellular synthetic function and hepatocellular necrosis among these conditions is quite variable
   b) In 70-80% of infants who have cholestasis, extensive evaluation leads to a diagnosis of either idiopathic neonatal hepatitis or extrahepatic biliary atresia
2. Careful history and physical examination are mandatory and examination of the stools is essential.
3. In the history consider:
   a) Timing and type of onset of clinical picture
   b) Consanguinity
   c) Ethnicity
   d) Family history of cystic fibrosis
   e) Infectious contacts including investigation on TORCHES
   f) Medications that may be hepatotoxic
   g) Prematurity
4. Physical exam
   a) General appearance (i.e. toxic appearance may suggest sepsis, galactosemia; well appearance may suggest biliary atresia)
   b) Facies (trisomies, Alagille’s)
   c) Heart murmur (hypoperfusion, Alagille’s)
   d) Cataracts (galactosemia)
   e) Rash/purpura (TORCH, sepsis)
   f) Hepato/splenomegaly
5. Labs
   a) Serum bilirubin, which should always be fractionated
   b) AST, ALT, GGT, ALP
      (1) Increased ALT/AST=Implies some hepatocellular damage
      (2) Increased ALK P/5’ nucleotidase=Suggests hepatobiliary disease
   c) Positive bilirubin/urobilinogen in urine
   d) Hematologic
      (1) CBC, smear
      (2) Coombs’ (for unconjugated hyperbilirubinemia, or for rare cases of Coombs associated autoimmune hepatitis in infants)
         (a) Reticulocyte count
         (b) PT/PTT (Prolonged PT=May be due to impaired hepatic synthesis or fat malabsorption as well as malabsorption of vit. K)
e) Elevated serum bile acids, cholesterol and triglycerides

f) Positive reducing substances in urine (Related to galactosemia)

g) TORCH titers (Toxoplasma IgG, IgM/ Rubella IgG, IgM / Cytomegalovirus IgM / Herpes Simplex Virus culture, PCR, titer)

h) Bacterial cultures (urine and blood, especially if toxic-appearing)

i) Hepatitis screen (IgM in mother and neonate)

j) Thyroid studies

k) Galactose-1-PUT

l) α-fetoprotein (may be elevated in newborns, but is extremely elevated in tyrosinemia)

m) Sweat test

n) Serum AA screen and urine organic acids

o) α-1-antitrypsin levels; protease inhibitor phenotype (MM, ZZ)

p) Urine succinylacetone (for tyrosinemia)

6. Imaging

a) Ultrasound of liver, gallbladder and spleen
   - Provides useful information
   - No radiation exposure
   - May detect choledochal cysts, an abdominal mass that compresses the biliary tract, biliary stones, absent gallbladder (found in 90% of biliary atresia patients), “triangular cord” sign (sensitivity 83-100%) or ascites
   - Provides information regarding portal flow, if Doppler ultrasound is requested.

b) Hepatobiliary scintigraphy (HIDA, DISIDA)
   - May differentiate extrahepatic from intrahepatic causes of obstruction
   - Helpful in excluding EHBA
   - Not very specific and patients with paucity of bile ducts may have false (+) results
   - Priming with \textit{phenobarbital} (3-5 mg/kg/day for 48-72 hrs) may enhance biliary excretion and increases the specificity
     - Result is considered positive when there is good uptake of the radionuclide by the liver and but no excretion to the gut within 24 hrs.

    a) Skull, long bones, spine X rays looking for bony abnormalities (that could be related to syndromes).

    d) Intraoperative cholangiogram may need to be performed since none of the above are 100% sensitive or specific.

7. Liver Biopsy

a) The most reliable means for determining the diagnosis in a neonate who has cholestasis
   - Early in the course of some disorders, such as biliary atresia and α-1-antitrypsin deficiency, characteristic histologic changes may not be evident

b) Important histologic features to examine include:
   - Hepatocytes (giant cells, inclusions, PAS+/diastase material, necrosis)
   - Portal areas (degree of inflammation, number and character of bile ducts)
   - Central veins (presence of congestion)
   - Degree of fibrosis, presence of cirrhosis
   - Intralobular bilirubinostasis

D. Factors predisposing neonates to cholestasis

1. The neonate experiences a period of relative cholestasis (physiologic cholestasis) in relation to the following:
   - Decreased bile acid secretory rate which is affected by caloric and fluid intake
   - Elevated basal serum bile acid levels which are qualitatively abnormal
   - Decreased ileal reabsorption
   - Inefficient hepatocyte uptake and transport of bile acids
   - Decreased conjugation, sulfation and glucoronidation

2. Non-specific insults in this age group result in cholestatic effects including hepatocyte giant cell transformation, cholestasis, inflammation, hepatocellular necrosis, extramedullary erythropoiesis and fibrosis.

E. Differential Diagnosis

1. Intrahepatic Disorders
   a) Idiopathic neonatal hepatitis(Also known as Giant Cell Hepatitis)
      - The extrahepatic biliary tracts are patent
      - Histologic findings include portal inflammation, giant cell transformation, increased extramedullary erythropoiesis, and bile stasis.
      - Alicholic stools are infrequent
        - Jaundice develops during the 1st week of life in >50% of patients
        - Hepatoplenomegaly is a regular finding
        - These findings usually resolve, but approximately 20% of these patients could have a fulminant course or develop progressive fibrosis.

   b) Infectious (TORCHES and miscellaneous)
      - Infectious agents may damage the liver directly by invasion of hepatocytes or indirectly by production of hepatotoxins.
      - Sepsis
        - Can cause cholestasis through liver injury related to endotoxins and/or effector substances – inflammatory cytokines- acting directly on the liver
          - There is evidence showing that pro-inflammatory cytokines are potent inhibitors of hepatobiliary transporter gene expression, explaining impaired transport function that leads to hyperbilirubinemia and cholestasis
        - Sepsis can also be related to cholestasis through the effects of ischemia/hypoperfusion –septic shock-, medications/antibiotic side effects and parenteral nutrition.
      - TORCHES Infections
        - Often have low birth weight, and have associated hepatosplenomegaly, rashes, thrombocytopenia and ocular abnormalities
        - The appropriate use of viral cultures, serologic titers, imaging and ophthalmologic examinations lead to the diagnosis in the majority of these babies
        - These infections include:
          - Toxoplasmosis
          - Other
c) Genetic/Metabolic: Disorders of carbohydrates, amino acid and lipid metabolism may result in cholestasis and frequently present with vomiting, lethargy, poor feeding, irritability and jaundice.

1. Disorders of carbohydrate metabolism
   a) Galactosemia
      i) An autosomal recessive disorder results from a deficiency of galactose-1-P-uridyltransferase
      ii) Accumulation of galactose-1-P results in jaundice, hepatomegaly, vomiting, failure to thrive, cataracts, hypoglycemia and aminoaciduria
      iii) Non-glucose reducing substances may be found in the urine, but the definitive diagnosis relies on the finding of a decrease in the concentration of galactose-1-P-uridyltransferase within red blood cells.
   b) Fructosuria: Clinical syndrome similar to galactosemia.
   c) Glycogen storage disease type IV (rarely presents as neonatal cholestasis): Glycogen filled hepatocytes, enzyme analysis of liver tissue

2. Disorders of amino acid metabolism
   a) Tyrosinemia: Elevated urine succinylacetone, increased AFP and coagulopathy disproportionate to other biochemical findings

3. Disorders of lipid metabolism
   a) Niemann-Pick disease
   b) Cholesterol ester storage disease
   c) Wolman's disease
   d) Gaucher's disease (rarely presents with cholestasis)

4. Disorders of bile acid metabolism
   a) 3β-Hydroxy-C27-steroid dehydrogenase/isomerase deficiency
      i) Second step in primary bile acid synthesis
      ii) Identified in Saudi Arabian lineage
      iii) Characterized by normal GGT and serum bile acid levels, despite level of cholestasis and elevated aminotransferases
      iv) Diagnosis made by FAB-MS analysis of urine with absence of normal glyco and tauro conjugates of primary bile acids
   b) ∆4-3-Oxosteroid 5β-reductase deficiency
      i) Fourth step in bile acid synthesis
      ii) GGT generally elevated
      iii) Diagnosis made by FAB-MS

5. Chromosomal disorders
   a) Trisomies 17, 18, 21
   b) Donahue's syndrome

6. Miscellaneous
   a) α1-antitrypsin deficiency
      i) Transmitted in an autosomal recessive fashion
      ii) Variants of α1-Antitrypsin deficiency are classified according to protease inhibitory (Pi) phenotype system
      iii) More than 80 variants have been reported
      iv) The Z allele is the deficient variant most commonly associated with clinical disease
      v) Children who have clinical liver disease often display the phenotype ZZ
      vi) Affected infants typically develop jaundice in the first 2-4 mo of life
      vii) In most cases, the jaundice resolves by 7 months, although fulminant hepatic failure and death occasionally occur. Cirrhosis may present later in life. Most individuals with ZZ manifest no liver disease.
      viii) Dx is made by determining serum α1-antitrypsin concentration and Pi phenotyping
      ix) Hepatic transplantation is currently the only effective management for end stage liver disease.
   b) Cystic fibrosis
   c) Neonatal iron storage disease
   d) Zellweger's syndrome: Cerebrohepatorenal syndrome
      i) Cholestatic jaundice, severe mental retardation, hypotonia, renal cortical cysts
      ii) Abnormal facies characterized by epicanthal folds, hypertelorism and a prominent forehead.

7. Endocrine
   a) Hypothyroidism
   b) Neonatal hypopituitarism (often with septo-optic dysplasia)
   c) Congenital adrenal hypoplasia

8. Cardiac
   a) Any pathology that causes hypoperfusion could cause direct liver injury
      i) Congestive heart failure
      ii) Hypoplastic left heart syndrome. This type of presentation is associated with striking increase in transaminases (2000's-3000's) and creatine phosphokinase levels followed in 1-2 days by jaundice that may persist for one month or more

9. Other
   a) Persistent intrahepatic cholestasis comprised a heterogeneous group of poorly delineated syndromes
   b) Common features include constant/episodic cholestasis, manifest by pruritus, jaundice, malabsorption, hypercholesterolemia and FTT
   c) In some of these conditions (paucity of bile ducts) pruritus often becomes the primary clinical feature in the first year of life, with subsequent development of widespread xanthomas
   d) Conditions presenting with these features include:
(a) Alagille’s syndrome: The liver disease in Alagille syndrome progresses quite slowly; survival into adulthood is common.
   (i) Hypoplasia of intrahepatic ducts
   (ii) Characteristic facies (small pointed chin, broad forehead, straight nose, and hypertelorism)
   (iii) Vertebral defects (hemi vertebrae, butterfly vertebrae)
   (iv) CV anomalies (peripheral pulmonary stenosis, coarctation of the aorta, tetralogy of Fallot)
   (v) Ocular abnormalities (posterior embryotoxon, exotropia, band keratopathy, and chloidal folds)
   (vi) Growth retardation
(b) Progressive Familial Intrahepatic Cholestasis (PFIC) Syndromes
   (i) PFIC type 1 (Byler’s syndrome)
      (a) Severe form of familial intrahepatic cholestasis that leads to the development of cirrhosis.
      (b) Notable for absence of hypercholesterolemia and low to normal GGT; transmitted in autosomal recessive fashion
      (c) Due to mutation in FIC1 transporter gene, speculated to play a role in enterohepatic circulation of bile salts
      (d) Treatment: biliary diversion, liver transplantation
   (ii) Benign recurrent intrahepatic cholestasis (BRIC)
      (a) Also due to mutation in FIC1 gene, but less severe than PFIC type 1, due to some residual FIC1 activity
      (b) Syndrome consisting of recurrent attacks of jaundice, pruritus, anorexia, and weight loss
      (c) Asymptomatic between attacks
   (iii) PFIC type 2
      (a) Phenotypically similar to PFIC type 1 but more severe
      (b) Due to mutation in BSEP gene, thought to be the main bile salt transporter in the canalicular membrane
      (c) Also characterized by low GGT
      (d) Liver transplantation is the only therapy
   (iv) PFIC type 3
      (a) The only form of PFIC with elevated GGT
      (b) Later onset and more severe course than PFIC 1 or 2
      (c) Due to defect in MDR3 gene, responsible for translocation of phosphatidylcholine into bile, therefore more susceptible to bile duct epithelial injury from bile salt detergent effects
(c) North American Indian cirrhosis
(d) TPN related cholestasis
   (i) Has become the most the most common cause of conjugated hyperbilirubinemia in the NICU, with a variable range of severity.
   (ii) 30-50% of infants who receive TPN for more than 2 weeks develop cholestasis and the percentage increases to 80% in premature babies that have received it for more than 30 days
   (iii) The etiology is likely multifactorial, involving functional immaturity of neonatal bile secretion, lack of enteral feedings, sepsis, infection, glucose and lipid overload, quantity and quality of AA, lack of specific AA (such as Taurine) and toxic components of TPN infusates.
   (iv) Most of the patients liver function abnormalities resolve within 4-6 months after discontinuing TPN
   (v) TPN associated cholestasis is a diagnosis based on clinical findings and the absence of other known cholestatic disorders
   (vi) The main preventive measure is to start enteral feeds promptly, but cycling TPN may decrease cholestasis in these babies by decreasing the risk for fatty infiltration of the liver.
(e) Drug toxicities
   (i) Drug-induced cholestasis has become an increasingly important problem caused by metabolic or immunological idiosyncrasy to a drug, making this effect unpredictable
   (ii) Some medications may be primarily cholestatic and others may result in hepatocellular necrosis
(f) Histiocytosis X
(g) Shock (associated with hypoperfusion)
(h) Perinatal asphyxia (associated with hypoperfusion)
(i) Insipidated bile syndrome
(j) Intestinal obstruction (due to decreased ileal reabsorption)
(k) NEC
(l) Lupus
(m) Neoplasms (Hepatoblastoma, etc)

2. Extrahepatic Disorders
   a) Biliary atresia
      (1) Incidence ranges from 1/10000 to 1/20000 live births, more frequent in females
      (2) Most appear to be postnatal obliteration of the extrahepatic biliary tree, but up to 20% may be true congenital anomalies (these usually associated with other anomalies such as duodenal atresia, malrotation, vascular abnormalities and polysplenia)
      (3) In 80% of the patients the obstruction is present at the porta hepatitis
      (4) Appear normal at birth, and remain healthy until 3-6 wks of age, when jaundice is more evident, and they have acholic stools and firm hepatomegaly
      (5) Typically, AST and ALT may be 2-5 times the upper limit, and conjugated bilirubin greater than 3 mg/dl; with GGT and cholesterol higher than in other causes of cholestasis
      (6) With progression biliary cirrhosis develops as well as failure to thrive
      (7) Liver Bx with variable degrees of bile stasis, prominent bile duct proliferation and periportal inflammation and fibrosis
(8) Definitive diagnosis is made with exploratory laparotomy with intraoperative cholangiography
(9) If untreated, the life expectancy is 2 yrs, with death resulting from liver failure and/or portal hypertension
b) Choledochal cysts
   (1) Dilatations of the biliary tree, most common is fusiform dilatation of the extrahepatic biliary tree
   (2) More frequent in females
   (3) Diagnosis is made by US and treatment is complete excision
c) Choledolithiasis/ Choledocholithiasis
d) Bile duct stenosis
e) Choledocho-pancreatico-ductal junction anomaly
f) Bile plug syndrome
   (1) Complication of neonatal hemolysis, TPN, diuretic therapy and bowel dysfunction
   (2) Treatment is supportive and prompt starting of enteral feedings
g) Extrinsic bile duct compression

F. Therapy

1. No specific therapy is available to reverse cholestasis and its complications; therefore, these patients require medical management in an effort to maximize growth, prevent specific nutrient deficiencies and improve the overall quality of life.

2. Medical treatment of cause
   a) Sepsis/ UTI
   b) NEC
   c) Dietary regimens for galactosemia, fructosemia and tyrosinemia (improves renal function).
   d) NTBC (Nitro-trifluoromethylbenzoyl-cyclohexanedione) treatment for tyrosinemia, diet therapy not usually effective in progression of liver disease.
   e) Early introduction of enteral feedings and prompt discontinuation of TPN
      (1) Removing Manganese and cutting copper in half in TPN (no good trials but theoretically reduces oxidant injury).
      (2) Cycling TPN
   f) Removal of hepatotoxic medications
   g) Hormonal replacement

3. Nutritional Support
   a) A, D, E, and K vitamin supplementation and MCT predominant formula
   b) Calcium supplementation
   c) Other micronutrients that may be deficient include zinc and iron, sometimes requiring supplementation

4. Medical Support
   a) Pruritus/Xanthomas
      (1) Cholestyramine and cholestipol
      (2) Ursodeoxycholic acid
      (3) Rifampin, naloxone, hydroxyzine or diphenhydramine
   b) PORTAL HTN: Management of ascites includes salt restriction and diuretics

5. Surgical Options
   a) Kasai procedure for extrahepatic biliary atresia
   b) Partial external bile diversion for pruritus
   c) Porto-venous shunt for portal HTN/ascites
   d) Surgical resection of choledochal cyst or stone
   e) Correction of intestinal obstruction

6. Liver Transplantation
   a) Indicated for patients who develop end-stage liver disease
   b) Good survival rates
   c) A long-term, good quality of life is the rule rather than the exception.
   d) Life-long immune suppression may cause post-surgical complications (infection, nephrotoxicity and malignancy)

G. Authors

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H. Reference:

Liver Disease in Children (2nd edition) by Suchy, Sokol and Ballisteri.
Cholestasis in Children and Adolescents

A. Definition:
1. The clinical, biochemical and histological manifestations of defective bile acid transport from the liver to the intestine.
2. Most result from inflammatory and destructive processes affecting the intrahepatic or extrahepatic biliary tree or developmental defects.
3. Can progress towards cirrhosis and hepatocellular insufficiency requiring liver transplantation.

B. Etiology:
1. Cholangiopathies of the extrahepatic bile ducts:
   a) Biliary atresia
      (1) Necroinflammatory destructive cholangitis resulting in progressive destruction and obliterating fibrosis of the bile duct.
      (2) Intrahepatic bile ducts are also subjected to this dynamic, progressive, inflammatory, destructive process.
      (3) Atresia is defined as absence of the lumen in part or the entire extrahepatic biliary tract, causing complete obstruction of bile flow.
      (4) 15% have major abnormalities outside biliary system, such as polysplenia, malrotation, situs inversus and congenital heart disease.
      (5) Characterized by pale stools, jaundice, hepatosplenomegaly and FTT.
      (6) HIDA scan may be helpful in diagnosis, showing no excretion of bile into the small intestine.
      (7) Kasai portoenterostomy +/- OLT are treatment options.

   b) Anatomic anomalies of extrahepatic bile ducts
      (1) Agenesis of extrahepatic bile ducts
      (2) Aberrant and Accessory bile ducts
      (3) Bile duct duplication
      (4) Congenital bronchobiliary fistula
      (5) Spontaneous perforation of the CBD
      (6) Bile duct hypoplasia

   c) Congenital Bile duct cysts:
      (1) Choledochal cyst
         (a) Congenital anomaly of the biliary tract, characterized by varying degrees of cystic dilatation at varying segments of the biliary tract (extra or intrahepatic).
         (b) Five subtypes based on nature and location of the cystic dilatation.
         (c) The classic triad of intermittent abdominal pain, jaundice and right epigastric mass varies in incidence, uncommon in children and occurs in 20%.
         (d) Conjugated hyperbilirubinemia, hyperamylasemia or signs of mild chronic liver disease with obstructive symptoms are seen.
         (e) Children older than two years of age, present more commonly with pain.
         (f) Diagnosis is by ultrasound, CT or cholangiography.
         (g) Complete surgical excision of the cyst mucosa with jejunal Roux-en-Y loop is the treatment.
         (h) Cholangitis and pancreatitis secondary to stone formation are complications.
         (i) Adenocarcinoma of residual cyst tissue or gall bladder develops in 4-8% beyond age 20 yrs.

      (2) Congenital dilatation of the CBD

2. Cholangiopathies of intrahepatic bile ducts:
   a) Atretic cholangiopathies
      (1) Intrahepatic bile duct atresia: Atresia is not complete, but involves a reduced ratio of the number of interlobular ducts to the number of portal tracts.

   b) Paucity of Interlobular bile ducts:
      (1) Defined as ratio of the number of interlobular ducts to the number of portal tracts of less than 0.5 (Normal being 0.9-1.8).
      (2) The portal tracts devoid of bile ducts appear hypoplastic and the total number of portal tracts per unit of tissue section is reduced compared with normal control subjects.
      (3) Syndromic (Alagille’s syndrome)
         (a) Associated with other extrahepatic anomalies
            (i) Triangular facies
            (ii) Butterfly vertebra
            (iii) Peripheral pulmonic stenosis
            (iv) Posterior embryotoxon on ophthalmologic exam
         (b) Progressive intrahepatic bile duct destruction and hypoplastic extrahepatic bile ducts
         (c) Caused by the alteration of a single gene, JAG1 (involved in cell signaling) at chromosomal location 20p12.
         (d) Transmitted as an autosomal dominant gene with 94% penetrance and variable expressivity.
         (e) Prognosis is variable, with some requiring OLT and others characterized by resolution of jaundice, xanthomas and improvement in pruritis.
         (f) Hepatocellular carcinoma is a complication.

      (4) Non-Syndromic
         (a) May be an isolated defect.
         (b) Most frequent diagnosis in patients with conjugated hyperbilirubinemia in the first month of life
         (c) Heterogeneous group associated with
            (i) Infections (CMV, rubella, syphilis, and Hepatitis B)
            (ii) Alpha1 antitrypsin deficiency
            (iii) Endocrine disorders (hypopituitarism)
            (iv) Chromosomal anomalies (trisomy 21, Turner’s syndrome)
            (v) Altered bile acid metabolism
            (vi) Byler’s disease
            (vii) Norwegian cholestasis
            (viii) Idiopathic causes
         (d) Progressive cholangiopathy with apparently faster bile duct destruction
         (e) Prognosis is variable because it is not a homogeneous group.
c) Combined extrahepatic bile duct atresia and paucity of interlobular bile ducts

3. Fibrocystic Cholangiopathies: Dilatation of segments of the intrahepatic bile ducts associated with variable fibrosis. Most often associated with cystic diseases of the kidney.
   a) Autosomal recessive polycystic kidney disease (ARPKD)
   b) Congenital Hepatic Fibrosis (CHF)
      (1) AR disease characterized by hepatic fibrosis, portal hypertension and is usually associated with renal abnormalities of ARPKD4.
      (2) Histopathologic picture is variable
         (a) Characterized in some by fibrous enlargement of the portal tracts, which contains variable numbers of abnormally shaped bile ducts
         (b) Others show bands of connective tissue of variable width linking adjacent portal tracts
      (3) Typically seen in older children and adolescents with minimal renal involvement
      (4) Spectrum and severity of clinical features vary
      (5) Subtypes of CHF are recognized based on clinical symptoms
         (a) Portal hypertensive (most common, often presenting with esophageal variceal hemorrhage)
         (b) Cholangitic (characterized by cholestasis and recurrent cholangitis)
         (c) Mixed and latent forms (manifests later in life or is discovered incidentally)
      (6) Symptoms may appear early or late
      (7) Lab values in the absence of cholangitis and portal HTN are normal (AST, ALT, Bilirubin) although mild cholestasis may be seen
      (8) Liver is normal in size and firm in consistency
      (9) Diagnosis is by Ultrasound and CT of abdomen, with liver biopsy
      (10) Therapy depends on type of CHF
         (a) Antibiotics for cholangitis
         (b) Sclerotherapy, band ligation and portosystemic shunts for variceal bleeding
         (c) Transplantation is curative and indications for this would include recurrent cholangitis or progressive hepatic dysfunction.
   c) Caroli’s disease (Pure form)
      (1) Congenital ectasia or dilatation of the larger segmental intrahepatic bile ducts
      (2) Dilated portions are in continuity with the rest of the biliary system and hence contain bile (communicating type of cystic disease)
      (3) The saccular dilatations of the ducts lead to stagnation of bile, predisposing to biliary sludge formation and intraductal lithiasis, often complicated by superinfection
      (4) Not hereditary
      (5) May be associated with choledochal cysts
      (6) Presenting symptoms: abdominal pain and hepatomegaly with steatorrhea
      (7) Antibiotics +/- lobectomy of the affected lobe are treatment options.
   d) Caroli’s syndrome (Combined form)
      (1) Inherited as an AR trait
      (2) Same as Caroli’s disease but is associated with periportal fibrosis and the kidney lesions of ARPKD (corresponding to congenital hepatic fibrosis)
      (3) Variations in anatomic location and in the clinical presentation have been reported
      (4) Associated with periportal fibrosis (corresponds to CHF)
      (5) Presentation may be a combination of the classic symptoms of Caroli’s disease (cholangitis, septicemia) and CHF (cholangitis and portal hypertension)
      (6) Complications include amyloidosis and cholangiocarcinoma (Biliary Ca increased incidence of 100 times)
      (7) Lithiasis and bile stagnation with risk of infection exists
      (8) Diagnosis by Ultrasound, CT, isotope scans and cholangiograms.
   e) Autosomal dominant polycystic kidney disease (ADPKD)
   f) Isolated polycystic liver disease
   g) Mesenchymal Hamartoma
   h) Solitary (non-parasitic) cyst

4. Progressive familial intrahepatic cholestasis:
   a) Presents in infancy or anytime during first year of life
   b) It is an AR inherited disorder of childhood
   c) Leads to death from liver failure at ages ranging from infancy to adolescence
   d) Disorders of bile acid transporter proteins leads to PFIC
   e) Differs from BA synthesis defects in that bile acid levels in serum are elevated and pruritis is a prominent clinical manifestation
   f) Normal cholangiograms of intra and extra hepatic bile ducts
   g) Three types with three different mutations in the hepatocellular transport system genes involved in bile formation
      (1) PFIC 1 (Byler’s Disease)
         (a) Labs: normal GGT, normal cholesterol, high concentrations of serum primary bile acids
         (b) Pruritus a prominent feature
         (c) Histology shows canaliculare cholestasis, minimal giant cell transformation, and slight lobular and portal fibrosis with absence of a true ductular proliferation.
      (2) PFIC 2 (BSEP deficiency)
         (a) Also associated with severe pruritus
         (b) Labs: normal GGT and high serum primary bice acid concentration, low primary bile acid concentration
         (c) Defect is in the canalicular membrane with ATP dependant bile acid transport into bile being defective
         (d) More severe than PFIC1, jaundice is permanent and rapid appearance of liver failure.
      (3) PFIC 3(MDR3 deficiency)
         (a) Associated with mild to moderate pruritus
         (b) Labs: high GGT, moderate increase in serum primary bile acid concentration, low phospholipid concentration
         (c) Histology: ductular proliferation and inflammation and portal fibrosis, appearing like biliary cirrhosis
         (d) Defect is in the canalicular membrane with ATP dependent translocation of phosphatidylcholine into bile being defective
(e) Usually present later in life, increased risk of portal hypertension and GI bleeding and end up with liver failure later age.

h) Treatment
(1) UDCA: increases hepatocyte excretion of endogenous bile acids and limits their return to the liver by inhibiting their intestinal reabsorption
(2) Partial external biliary diversion provides effective relief from pruritis and reversal of liver disease in PFIC 1 & 2
(3) OLT is an option if cirrhosis is present.

5. Progressive obliteratorive:
a) Primary Sclerosing cholangitis – fibrosis of the biliary tree
   (1) Chronic hepatobiliary disorder that may affect patients of all ages
   (2) Characterized by inflammation of the intra and extra hepatic ducts
   (3) Leads to focal dilatation, narrowing or obliteration accompanied by local periductular fibrosis
   (4) Progression to biliary cirrhosis and portal hypertension may occur
   (5) Diagnosis
      (a) Cholangiography best defines the structural abnormalities of the larger bile ducts
      (b) Liver biopsy also helpful
   (6) Three presentations:
      (a) Neonatal onset
      (b) Postneonatal onset with an associated disease (IBD, AIH, histiocytosis, immunodeficiency, etc)
      (c) Postneonatal onset without any associated disease
   (7) Subtypes:
      (a) Isolated PSC
      (b) PSC – IBD complex:
         (i) Liver disease may precede, coincide with or follow the diagnosis of IBD
         (ii) Severity/ activity of IBD may not correlate with activity of PSC
      (c) PSC - autoimmune hepatitis (AIH) complex/ overlap syndrome
   (8) Symptoms: prolonged jaundice, progressive fatigue, malaise, anorexia, hepatosplenomegaly, weight loss and pruritus. RUQ pain, fever and hyperbilirubinemia is often noted. May be completely asymptomatic.
   (a) Children may present with poor growth and delayed puberty
   (9) Labs: No specific lab findings for PSC. Mildly elevated ALT, bilirubin, PT, GGT and ALP, elevated ESR, IgG, ANA or ASMA, ANCA and decreased albumin
   (10) Complications: Cholangiocarcinoma, needs monitoring
   (11) Management: supportive. Symptomatic relief with Ursodeoxycholic acid and fat-soluble vitamin supplements in addition to monitoring for malnutrition and prevention of complications is indicated. Immunosuppressives such as Prednisone +/- azathioprine have been used.
   b) North American Indian cirrhosis

6. Bile acid synthesis defects (BASD)
a) Pathogenesis
   (1) Results from an insufficient production of normal primary bile acids, chenodeoxycholic acid and cholic acid combined with accumulation of potentially toxic intermediary metabolites as a result of a block in the synthesis
   (2) Cholestasis is exacerbated by a lack of primary bile acids that are essential for promoting bile flow
   (3) Two categories depending on whether the enzyme catalyzes reaction in the steroid nucleus or in the side chain
   (4) Deficiency of bile acids in bile, leads to defective absorption of lipids, which leads to deficiency of fat-soluble vitamins and poor growth
   (5) Bile acid transport elements may be secondarily affected in BASD.
   b) Diagnosis: specific BASD diagnosis based on mass spectrometry, which detects atypical bile acids in urine and serum on the basis of molecular weight
   c) Presentation: May present in neonatal period, early childhood or adolescence with jaundice, persistent cholestasis
   d) Labs: conjugated hyperbilirubinemia, elevated ALT, normal GGT, low or normal serum bile acid levels and the presence of atypical bile acids in serum and urine.
   e) Histology: progressive hepatocyte injury accompanied by perportal inflammation with progressive fibrosis, intralobular cholestasis and regressive canalicular changes
   f) Treatment: primary bile acids may be beneficial in supportive therapy

7. Metabolic:
a) α1- antitrypsin deficiency
   (1) Presentation
      (a) May present in infancy with persistent jaundice, late childhood or early adolescence with unexplained prolonged obstructive jaundice with or without pruritus
      (b) Resembles biliary atresia but shows paucity of intrahepatic bile ducts
      (c) May include hepatosplenomegaly, abdominal distension, ascites or hemorrhage from esophageal varices. May also present as chronic hepatitis, cirrhosis, portal hypertension or hepatocellular carcinoma of unknown origin
   (2) Labs: elevated conjugated bilirubin, ALT, ALP, GGT, PT and cholesterol
   (3) Diagnosis:
      (a) Established by a serum α1-AT phenotype determination by isoelectric focusing or by agarose gel electrophoresis at acid pH.
      (b) Serum concentration of α1-AT may be helpful if used with phenotype to distinguish individuals who are homozygous for the Z allele from the S2 compound heterozygotes, both of whom may develop liver disease. Also important for genetic counseling
   (4) Histology: PAS positive, diastase resistant globules in the endoplasmic reticulum of hepatocytes
   (5) Treatment: avoidance of smoking and supportive treatment with prevention of complications, shunt surgery and OLT.
   (6) Prognosis: highly variable with some requiring liver transplantation and others being asymptomatic for years
   b) Cystic fibrosis
   (1) Approximately 25% will have hepatobiliary complications
   (2) 5-10% of patients developing multilobular biliary cirrhosis by late childhood
   (3) Cholestatic and retention of hepatotoxic bile salts occurs as a result of obstruction of bile ducts by inpsissated secretions and viscid mucus.
   (4) Ursodeoxycholic acid is used to promote bile flow.
c) Galactosemia
8. Endocrine:
   a) Hypopituitarism
   b) Adrenal disorders
9. Obstructive:
   a) Cholelithiasis
      (1) Negligible incidence of cholelithiasis in males, but in adolescent females there is a remarkable increase in incidence between 11-13 yrs of age
      (2) In pediatric patients 72% are pigmented stones, 17% are cholesterol and 11% have stones whose composition is unknown
         (a) Up to 5 yrs of age, pigment stones are more common and from 6 yrs onwards, cholesterol stones are more common
      (3) Causes: Hemolytic disease (30%), TPN, lack of ileocecal valve, short bowel syndrome, Wilson’s disease, Byler’s syndrome, defects in bile acid synthesis, CF, pregnancy, BCP use
      (4) Presentation: May be asymptomatic or may present with abdominal pain, mild increase in serum bilirubin, aminotransferase and alkaline phosphatase
      (5) Diagnosis: ultrasound is the most sensitive and specific diagnostic tool, ERCP for evaluation/ removal of CBD stones
      (6) Treatment: Cholecystectomy is the treatment of choice, lithotripsy is an alternative
   b) Malignant neoplasms
   c) GVHD
   d) Lymphohistiocytic disorders
10. Other syndromes:
    a) Dubin Johnson syndrome
       (1) Epidemiology: Autosomal recessive, more common than rotor’s syndrome, especially in males
       (2) Presentation:
          (a) Although hepatic anion storage is normal, there is a decrease in bile secretion into canaliculi
          (b) Increase in conjugated and unconjugated bilirubin with normal LFT’s and normal bile acids
          (c) Intercurrent illness, pregnancy, BCP may precipitate presentation, results in increase of direct bili to 20 mg/dL
          (d) May present with non-specific abdominal pain and hepatomegaly anytime from birth to adulthood
       (3) Histology: may show a distinctive brown-black pigmentation that is grossly visible (secondary to melanin or metabolism of epinephrine) in lysosomes
       (4) Diagnosis:
          (a) Oral cholecystography fails to visualize the gall bladder in Dubin Johnson syndrome
          (b) There is normal or slightly increased excretion of urinary coproporphyrins.
    b) Rotor’s syndrome
       (1) Epidemiology
          (a) Autosomal recessive, less common than DJS
          (b) Seen in early childhood (no sex difference)
       (2) Pathogenesis:
          (a) Due to deficient glutathione transferase activity and decreased storage
          (b) Therefore both direct and indirect bilirubin refluxes back into circulation.
       (3) Diagnosis:
          (a) Hyperbilirubinemia (direct and indirect) with normal LFT’s and bile acids
          (b) Liver histology and oral cholecystography are normal
          (c) Urinary coproporphyrin III and I is 2.5-5 times higher than normal
       (4) Prognosis: Asymptomatic except for jaundice. No treatment required.
    c) Chromosomal disorders: (Trisomy 18, 21)
11. Drugs / Toxins:
    a) TPN cholestasis
    b) Other drugs – Estrogens/OCP, cyclosporine, haloperidol, erythromycin, azathioprine

C. Clinical Presentation
1. Jaundice
2. Pruritus
3. Malnutrition
4. Hepatosplenomegaly
5. +/- Ascites
6. +/- Abdominal pain/ distension.

D. Pathogenesis
1. Altered bile duct morphogenesis
2. Infections, ischemia, or toxins in combination with genetic or immunologic susceptibility likely plays a role.
3. Bile acid is toxic to the biliary epithelium and results in the symptom complex at presentation

E. Diagnosis
1. Serum
   a) Bilirubin (conjugated, unconjugated and delta)
   b) ALT, AST, GGT, ALP, Alb
   c) INR, PTT
   d) TSH, Free T4
   e) A1-AT phenotype
   f) Cholesterol
g) Serum bile acid levels
h) Serum amino acids
i) α1-antitrypsin level and phenotype

2. Urine
   a) Urine reducing substances, Glucose
   b) Succinyl acetone
   c) Organic acids
   d) Bile acids

3. Radiology
   a) Vertebral X ray for butterfly vertebrae
   b) Abdominal ultrasound vs CT scan
   c) Isotope scans/ HIDA
   d) Cholangiography

4. Miscellaneous
   a) Sweat chloride or DNA testing for CF
   b) Ophthalmology exam
   c) Echocardiogram
   d) Liver biopsy

F. Management
   1. Supportive
      a) Supportive treatment mostly for syndromic or non-syndromic causes until OLT is an option.
      b) Fat soluble vitamin supplements
      c) For TPN/drugs, discontinue agents or minimize effect
      d) For α1-AT deficiency, avoidance of smoking and supportive treatment with prevention of complications

   2. Medical
      a) Treat the cause of cholestasis if possible
      b) For bile acid synthetic defects, replace cholic acid
      c) Ursodeoxycholic acid
      d) Phenobarb, Rifampin or Cholestyramine for pruritus
      e) Manage/ prevent upper GI bleeds and portal hypertension – sclerotherapy, band ligation, β-blockers, octreotide

   3. Surgical
      a) Kasai procedure for biliary atresia
      b) In case of obstruction, relieve the obstruction (ERCP, lithotripsy, surgery, etc)
      c) For severe pruritus partial external biliary diversion
      d) Portosystemic shunt for intractable ascites/ portal HTN
      e) Liver transplant as indicated

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H. References:
**XIII. Biochemical Tests of the Liver**

A. **Introduction**: No one test can sufficiently evaluate liver disease. The tests that are commonly used have limited sensitivity and specificity and should be combined with a careful history and physical exam to evaluate for potential liver abnormality.

B. **Tests of Hepatic Cell Injury**:

1. Aspartate Aminotransferase: (AST, formerly serum glutamic oxaloacetic transaminase, SGOT).
   a) Catalyzes the transfer of a α amino group from aspartate to α-ketoglutarate with the release of oxaloacetate and glutamate.
   b) Present as both cytosolic and mitochondrial isoenzymes.
   c) Present in liver, cardiac muscle, skeletal muscle, pancreas, kidney, and red cells.

   a) Catalyzes the transfer of a α amino group from alanine to α-ketoglutarate with the release of pyruvate and glutamate.
   b) It is present only in the cytosol.
   c) It is present in high concentrations in the liver, and lower concentrations in muscle.
   d) More specific for hepatocyte damage than AST.
   e) Can be markedly elevated in muscle disease.

3. The AST/ALT Ratio:
   a) Serum AST and ALT levels are elevated in cases of liver inflammation and hepatocyte injury.
   b) Modest elevations in levels (<500U/L) are found in many types of liver disease.
   c) Marked elevations are found in acute hepatocellular injury such as viral hepatitis, drug-induced hepatitis, and hepatic ischemia.
   d) The degree of enzyme elevation is not predictive of outcome in acute hepatitis.
   e) The AST: ALT ratio is >2 in adults with alcoholic liver disease. This ratio rises in adults and children with chronic liver disease and cirrhosis.
   f) The AST: ALT ratio is < or = 1 in acute and chronic (nonalcoholic) liver disease.
   g) AST and ALT levels are useful in monitoring the progression of liver disease but are not specific for a particular diagnosis.

4. Lactic Dehydrogenase: (LDH)
   a) Enzyme is found in a wide variety of tissues including liver, red cells, cardiac muscle and kidney.
   b) There are 5 isoenzymes.
   c) Elevation is seen with skeletal and cardiac muscle injury, hemolysis, stroke, and renal infarction. Therefore, it is less sensitive and specific for the detection of liver disease than AST and ALT.
   d) Massive, but transient elevations are seen with ischemic hepatitis.

C. **Tests of Cholestasis**:

1. Alkaline Phosphatase: (AP)
   a) Group of enzymes that catalyze the hydrolysis of phosphate esters at an alkaline pH.
   b) Found in liver (canalicular membrane), bone (osteoblasts), small intestine, kidney, placenta and tumors (Regan isoenzyme).
   c) Liver and bone are the major sources of AP in the serum (bone isoenzyme).
   d) Elevated hepatic isoenzyme results from increased enzyme synthesis and release rather than impaired biliary secretion.
   e) Does not distinguish intrahepatic from extrahepatic biliary obstruction.
   f) Serum activity of AP is decreased in Wilson Disease and in zinc deficiency, zinc is a cofactor for this enzyme.

2. Gamma Glutamyl Transpeptidase: (GGT)
   a) Microsomal enzyme found in the epithelium of small bile ductules and hepatocytes.
   b) Catalyzes the transfer of γ-glutamyl groups between peptides or to an amino acid residue.
   c) Present in the kidney, pancreas, spleen, brain, heart, lung, and placenta.
   d) Not significantly present in bone, thus is useful in confirming the hepatic origin of elevated AP.
   e) Serum levels are highest in the newborn and the premature infant (5-8 times the adult normal level) and decline by 6-9 months of life.
   f) It is elevated in cases of biliary obstruction, as well as paucity of intrahepatic bile ducts in (Alagille’s syndrome).
   g) Useful in differentiating the progressive familial intrahepatic cholestasis (PFIC) syndromes- normal in PFIC-1 (Byler’s) and PFIC-2, and elevated in PFIC-3.

3. 5’-Nucleotidase: (5-NT)
   a) Hydrolyzes the 5’-adenosine monophosphate and similar nucleotides to inorganic phosphate.
   b) Located in sinusoidal and canalicular membranes in the liver.
   c) Elevation is specific for liver disease in the non-pregnant patient, and can be used to confirm the hepatic origin of and elevated AP.

4. Bilirubin:
   a) Bilirubin is a yellow tetrapyrrole pigment derived from the degradation of heme.
   b) Newly formed bilirubin (unconjugated) is bound to albumin and taken to the liver, where it is conjugated to one or two moieties of glucuronic acid (bilirubin monoglucuronide and diglucuronide).
   c) A fourth form occurs in the serum with elevated levels of conjugated bilirubin when it becomes bound to albumin (δ bilirubin or bil-alb).
   d) Elevation of unconjugated bilirubin is indicative of hemolysis or Gilbert’s disease.
   e) Elevation of conjugated bilirubin (> 2.0 mg/dl or 15% of total) is indicative of hepatobiliary disease and is always pathologic (indicates inherited or acquired defects in hepatic excretion).
   f) The presence of bilirubin in the urine is an indication of conjugated hyperbilirubinemia because unconjugated bilirubin is not excreted in the urine.

D. **Tests of Hepatic Synthetic Function**:

1. Prothrombin Time: (PT)
   a) Measures the rate of conversion of prothrombin to thrombin.
   b) Reflects the activity of the extrinsic coagulation pathway (factors I, II, V, VII, and X).
   c) Except factors VIII and Von Willerbrand, all factors are synthesized in hepatocytes.
   d) PT is a good indicator of liver synthetic function if vitamin K deficiency is excluded (factors II, VII, IX, and X are vitamin K dependant).
   e) A prolonged PT, especially > 4 seconds, in chronic liver disease suggests a poor prognosis.

2. Albumin and Other Serum Proteins:
a) Albumin is synthesized in the rER of hepatocytes at the rate of 150mg/kg/day, and has a half-life of 20 days.
b) Decreases in serum albumin can be caused by decrease in synthesis with significant parenchymal liver disease.
c) Serum albumin level is also affected by many other extrahepatic factors including nutritional and volume status, catabolism, loss in urine or stool, vascular integrity and hormonal factors.
d) Because of the long half-life of this protein, a low level is considered secondary to chronic, not acute, liver injury.
e) Serum α1 and α2 globulins are synthesized in the liver, unlike serum γ-globulins which are synthesized in lymphocytes.
f) Unlike albumin, globulin levels are elevated in severe or active liver disease and the cause for this is uncertain.

3. Ammonia:
   a) Ammonia is produced mostly by the large intestine and cleared by the liver.
   b) The liver normally clears about 80% of portal vein ammonia in a single pass.
   c) In chronic liver disease, a disturbed urea cycle function as well as portal systemic shunting allows a large load of ammonia to bypass the liver and reach the central nervous system.
   d) Fasting serum levels should be measured, a protein meal will elevate post-prandial levels in patients with mild liver disease.
   e) Increasing levels of fasting serum ammonia may herald the development of hepatic encephalopathy.

E. Tests of Quantitative Liver Function:
1. These tests of “dynamic liver function” have been developed to reflect liver function accurately at a given point in time.
   a) For these tests a substrate is administered and it’s disappearance from the serum/saliva, and the appearance of its metabolites in plasma or breath is measured.
   b) Compounds with a high extraction ratio (70-80% of drug removed in one pass through the liver) are used to measure hepatic blood flow. These include:
      (1) Sulfobromophthalein
      (2) Indocyanine green (ICG)
      (3) radiolabeled bile acids.
   c) Compounds with a low extraction ratio (20-30%) are used to measure functional hepatic mass or hepatic metabolic capacity. These include:
      (1) Antipyrine clearance
      (2) Aminopyrine breath test (ABT)
      (3) Caffeine clearance
      (4) Galactose elimination capacity
      (5) Monoethylglycinexylidide (MEGX)

F. Tests for Specific Liver Diseases:
1. Serum Ferritin:
   a) Ferritin is a major iron storage protein mostly distributed in human tissues, with a small amount in the serum.
   b) Not specific for liver disease and can be elevated secondary to inflammation or other iron overload conditions.
   c) Useful for the detection of idiopathic hemochromatosis where levels are elevated, higher in patients with liver failure (>1000mcg/L) than those with pre-cirrhotic disease
2. Ceruloplasmin:
   a) Major copper binging protein synthesized by the liver.
   b) Its level is depressed markedly in patients who are homozygotes for Wilson’s disease.
   c) Some patients with Wilson’s disease may have normal to only slightly decreased levels, and in these cases a 24-hour urine collection for copper excretion can be helpful in making a diagnosis.
3. α-Fetoprotein:
   a) This plasma protein is found during fetal life, and continues to be present is newborns, with levels declining to adult normals by one year of age.
   b) Elevation of serum levels of α-fetoprotein are sensitive and specific for hepatocellular carcinoma and hepatoblastoma.
   c) It is a useful test to follow in high-risk groups such as patients with glycogen storage disease, chronic hepatitis B, alcoholic cirrhosis, and hemochromatosis.
4. α1-Antitrypsin:
   a) This protein is the major component of the α1 serum globulins.
   b) A1AT activity is determined genetically, and the different phenotypes can be detected by gel electrophoresis. This is called the protease inhibitor system (Pi), and the phenotype PiZZ is the only one clearly associated with the development of neonatal hepatitis and cirrhosis due to abnormal A1AT hepatocyte storage.

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H. References:
XIV. Parental Nutrition Guidelines

A. Starting parenteral nutrition.
   1. Start PN if you anticipate minimal to no enteral feeds after 5-7 days of illness or due to underlying pathology.
   2. Patient must be hemodynamically and biochemically stable. PN cannot be used for fluid resuscitation.
   3. Ordering forms vary between institutions but traditionally you will need to indicate the % of dextrose and amino acids, and the amount of intralipids. You will also need to specify a total volume to be provided daily, and the amount of electrolytes, trace elements and multivitamins.
   4. A maximum osmolality of 900 mOsm/L (10% Dextrose and 2% Aac with standard electrolytes) is allowed for peripheral PN, to prevent phlebitis and sclerosis. Higher osmolarities may be infused centrally.
   5. Consider checking if your institution has a dietician or nutrition support team. They usually provide helpful suggestions when starting PN.
   6. The minimal infusion rate for the prevention of hypoglycemia is 4 mg/kg/min. You may start at 5 mg/kg/min, and advance by 2 mg/kg/min every day, until levels of about 12 mg/kg/min are tolerated.
   7. In situations of hyperglycemia preventing the administration of sufficient calories, insulin may be added to PN.
   8. Amino acids are the major source of protein in PN. Some centers do not count them in calorie calculations. Use trophamine in neonates and infants, and Rrarasol in older children.
   9. The ratio of protein to non-protein calories is a useful measure of macronutrient balance. Metabolism is generally optimal when the ration of non-protein energy to nitrogen is between 150:1 and 250:1. Burn patients and other children with high protein requirements may be optimally fed with a ratio of 100:1. The ratio is calculated as follows: [Carbohydrate calories + fat calories]: [protein intake (g) / 6.25]
   10. You may start lipids by giving 1 g/kg/d, and advance by 0.5-1 g/kg/d. Do not exceed 3 g/kg/d or 50% of caloric intake. Monitor triglyceride levels when advancing intralipids.

B. PN fluid management:
   1. PN fluid requirements may be calculated using the Holliday-Segar method (table 1).
   2. Adjust fluid requirements according to fluid losses, such as from diarrhea, emesis, NG output losses, ostomy losses, fever, tachypnea.
   3. Do not use PN for resuscitation purposes. Maintain the rate of PN infusion as constant as possible.
   4. If you increase the volume of a PN solution, you must adjust all electrolytes, especially if they are expressed per liter of solution on the PN form.
   5. Concentrated PN solutions are may result in high osmolarities and may exceed the limits of solubility of calcium and phosphorus salts causing precipitation.
   6. Daily parenteral fluid requirements:

<table>
<thead>
<tr>
<th>Table 1: Daily parenteral fluid requirements:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight</td>
</tr>
<tr>
<td>0-10 kg</td>
</tr>
<tr>
<td>10-20 kg</td>
</tr>
<tr>
<td>&gt;20 kg</td>
</tr>
</tbody>
</table>

C. PN electrolytes management:
   1. Adjust electrolyte concentrations based on estimated or measured electrolyte losses, such as in diarrhea, NG tube drainage, or ostomy losses.
   2. Acute changes in serum electrolytes should not be corrected by changing PN rates. Use separate solutions for this, non-acute, less severe electrolyte disturbances can be corrected with changes in PN composition. (Check at what time of the day the previous PN solution was started in relation to the abnormal lab value, to make better judgements).
   3. Calcium phosphate solubility is dependent on calcium and phosphorus salt concentrations, pH, temperature, amino acid concentration, infusion time, and magnesium availability.
   4. For high calcium and phosphorus requirements, increase Aac concentration or PN volume if possible. You may use Trophamine TM or add L-cysteine (1000 mg/liter). Avoid solutions with borderline calcium phosphate compatibility, since variables such as temperature and time may cause delayed precipitation.
   5. Daily parenteral electrolyte requirements:

<table>
<thead>
<tr>
<th>Table 2: Daily parenteral electrolyte requirements:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Element</td>
</tr>
<tr>
<td>Sodium</td>
</tr>
<tr>
<td>Potassium</td>
</tr>
<tr>
<td>Calcium</td>
</tr>
<tr>
<td>Magnesium</td>
</tr>
<tr>
<td>Phosphorus</td>
</tr>
<tr>
<td>Chloride</td>
</tr>
</tbody>
</table>
6. Suggested daily calories and macronutrient requirements:

<table>
<thead>
<tr>
<th>Age</th>
<th>Calories (g/kg/d)</th>
<th>Carbohydrates (g/kg/d)</th>
<th>Protein (g/kg/d)</th>
<th>Fat (g/kg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature</td>
<td>80-120</td>
<td>4-18</td>
<td>2.0-3.0</td>
<td>0.5-3.0</td>
</tr>
<tr>
<td>Term infants</td>
<td>105</td>
<td>8-23</td>
<td>2.5-3.0</td>
<td>0.5-4.0</td>
</tr>
<tr>
<td>1-3 years</td>
<td>75-90</td>
<td>8-23</td>
<td>1.5-2.5</td>
<td>0.5-2.5</td>
</tr>
<tr>
<td>4-6 years</td>
<td>65-75</td>
<td>8-23</td>
<td>1.5-2.5</td>
<td>0.5-2.5</td>
</tr>
<tr>
<td>7-10 years</td>
<td>55-75</td>
<td>8-23</td>
<td>1.5-2.5</td>
<td>0.5-2.5</td>
</tr>
<tr>
<td>11-18 years</td>
<td>40-55</td>
<td>8-23</td>
<td>1.5-2.5</td>
<td>0.5-2.0</td>
</tr>
</tbody>
</table>

D. PN micronutrient supplementation:

1. Suggested daily trace elements:

<table>
<thead>
<tr>
<th>Element</th>
<th>Dose</th>
<th>Max</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc</td>
<td>100 µg/kg/d (300 µg/kg/d in premature infants to 3 month of age)</td>
<td>5000 µg</td>
<td>Increase dose with intestinal losses and catabolic states</td>
</tr>
<tr>
<td>Copper</td>
<td>20 µg/kg/d</td>
<td>300 µg</td>
<td>Decrease dose with cholestasis</td>
</tr>
<tr>
<td>Manganese</td>
<td>2-10 µg/kg/d</td>
<td></td>
<td>Decrease dose with cholestasis</td>
</tr>
<tr>
<td>Chromium</td>
<td>0.2 µg/kg/d</td>
<td>5.0</td>
<td>Increase dose with intestinal losses, decrease dose with renal dysfunction</td>
</tr>
<tr>
<td>Selenium*</td>
<td>1-3 µg/kg/d (max 30-40 µg/d)</td>
<td>30</td>
<td>Decrease dose with renal dysfunction, consider increasing dose with intestinal losses</td>
</tr>
<tr>
<td>Carnitine*</td>
<td>1-2 mg/kg/d</td>
<td></td>
<td>Increase dose in primary carnitine deficiency</td>
</tr>
</tbody>
</table>

a) * May be added after 1 month of NPO status and/or minimal enteral intake.

b) Pediatric multivitamins are essential in PN. Check with your PN pharmacist as to which formulation is available.

c) Trace elements commonly added to PN solutions include zinc, copper, manganese and chromium (check levels periodically).

d) Consider checking 25-OH vitamin D especially when a patient is being weaned from chronic PN.

E. Medications and PN:

1. Medications incompatible with parenteral nutrition solutions:

   a) Acetazolamide
   b) Acyclovir
   c) Amphoterin
   d) Amphoterin B lipid complex
   e) Ampicillin
   f) Ampicillin/sulbactam
   g) Calcium salts
   h) Cefazolin
   i) Ciprofloxacin
   j) Cisplatinum
   k) Cyclosporine
   l) Cytarabine
   m) Diazepam
   n) Doxorubicin
   o) Filaastim
   p) Foscarnet
   q) Furosemide
   r) Gancyclovir
   s) Imipenem
   t) Indomethacin
   u) Mannitol
   v) Methotrexate
   w) Metoclopramide
   x) Metronidazole
   y) Midazolam
   z) Nitoglycerin
   aa) Nitroprusside
   bb) Octreotide
   cc) Phenytin
   dd) Promethazine
   ee) Trimethoprim/sulfamethoxazole
   ff) Tromethamine
2. **Medications incompatible with lipids:**
   a) Acetazolamide
   b) Acyclovir
   c) Amikacin
   d) Aminophylline
   e) Amphotericin
   f) Amphotericin B lipid complex
   g) Ampicillin
   h) Ampicillin/sulbactam
   i) Calcium salts
   j) Ciprofloxacin
   k) Cyclosporine
   l) Diazepam
   m) Doxorubicin
   n) Filgrastim
   o) Foscarnet
   p) Furosemide
   q) Gancyclovir
   r) Heparin
   s) Imipenem
   t) Indomethacin
   u) Iron dextran
   v) Magnesium salts
   w) Metronidazole
   x) Midazolam
   y) Morphine
   z) Nitroglycerin
   aa) Nitroprusside
   bb) Phenytoin
   cc) Trimethoprim/sulfamethoxazole
   dd) Tromethamine

F. **Metabolic complications of PN:**

1. **Hyperglycemia:**
   a) Prevention:
      (1) Limit dextrose infusion to ~10-15%
      (2) Limit dextrose increments to 5% per day
      (3) Monitor serum and urine glucose
   b) Treatment:
      (1) Decrease dextrose intake
      (2) Add insulin to TPN or give IV insulin (if indicated).
2. **Hypoglycemia:**
   a) Prevention:
      (1) Avoid abrupt cessation of PN
   b) Treatment:
      (1) IV dextrose
3. **Hypercapnia:**
   a) Prevention:
      (1) Avoid excessive caloric or dextrose infusion
   b) Treatment:
      (1) Decrease total caloric intake and/or increase calories as fat
4. **Azotemia:**
   a) Prevention:
      (1) Adequate hydration prior to PN initiation
      (2) Avoid excessive amino acid infusion
      (3) Provide adequate nutrition to minimize lean tissue catabolism
      (4) Monitor BUN
   b) Treatment:
      (1) Free water administration in the PN bag or IV dextrose
      (2) Increase free water in subsequent PN bags
      (3) Decrease amino acid infusion
5. **Hypertriglyceridemia:**
   a) Prevention:
      (1) Avoid excessive lipid infusion
      (2) Monitor serum triglycerides weekly
      (3) Infuse lipids over 18-20 hours
   b) Treatment:
      (1) Decrease lipid infusion, may give lipids qod
      (a) If sustained, give only 0.5-1.0 g/kg/d of lipids
6. **Hypokalemia:**
   a) Prevention:
      (1) Adequate potassium in PN
      (2) Monitor serum potassium daily until stable, then biweekly
   b) Treatment:
      (1) If mild, increase potassium in PN
      (2) If severe, IV potassium
7. **Hyperkalemia:**
   a) Prevention:
      (1) Avoid excessive potassium administration
      (2) In patients with renal insufficiency, with appropriate restriction, monitor K daily.
b) Treatment:
   (1) Decrease potassium in PN

8. Hyponatremia:
   a) Prevention:
      (1) Adequate sodium in PN
      (2) Avoid excessive fluid administration
      (3) Monitor serum sodium daily until stable, then biweekly
   b) Treatment:
      (1) Fluid restriction
      (2) If mild, increase sodium in PN
      (3) If severe, slow IV sodium in a crystalloid solution

9. Hypernatremia:
   a) Prevention:
      (1) Provide adequate fluid
      (2) Avoid excessive sodium administration
      (3) Monitor intake/output, urine sodium, osmolarity
   b) Treatment:
      (1) Fluid restriction
      (2) If mild, increase sodium in PN

10. Metabolic acidosis:
    a) Prevention:
        (1) Measure and replace intestinal losses
        (2) Avoid excessive chloride in PN
    b) Treatment:
        (1) Treat underlying cause
        (2) Increase acetate and decrease chloride in PN

11. Metabolic alkalosis:
    a) Prevention:
        (1) Measure and replace NG output
    b) Treatment:
        (1) Treat underlying cause
        (2) Increase chloride and decrease acetate in PN

12. Hypocalcemia:
    a) Prevention:
        (1) Adequate calcium in PN
        (2) Monitor serum calcium biweekly
        (3) Monitor ionized calcium in hypoalbuminemic state
        (4) Monitor PTH and vitamin D levels
    b) Treatment:
        (1) Correct magnesium deficiency
        (2) Increase calcium in PN if ionized calcium is low

13. Hypercalcemia:
    a) Prevention:
        (1) Monitor serum calcium until stable.
        (2) Restrict as appropriate
    b) Treatment:
        (1) Decrease calcium in PN
        (2) IV normal saline
        (3) May need to remove vitamin D from PN

14. Hypomagnesemia:
    a) Prevention:
        (1) Adequate magnesium in PN
        (2) Monitor serum magnesium until stable.
    b) Treatment:
        (1) If mild, increase magnesium in PN
        (2) If severe, IV magnesium

15. Hypermagnesemia:
    a) Prevention:
        (1) In patients with renal insufficiency, restrict as appropriate.
        (2) Avoid excessive magnesium administration
    b) Treatment:
        (1) Decrease magnesium in PN

16. Hypophosphatemia:
    a) Prevention:
        (1) Monitor serum phosphorus daily until stable.
    b) Treatment:
        (1) If mild, increase phosphorus in PN
        (2) If severe, IV phosphorus

17. Hyperphosphatemia:
    a) Prevention:
        (1) Monitor serum phosphorus daily until stable, then biweekly
        (2) Monitor serum phosphorus in patients with renal insufficiency, restrict as appropriate
        (3) Avoid excessive phosphorus administration
    b) Treatment:
        (1) Decrease phosphorus in PN
G. Useful conversion factors needed in PN ordering (table):

   Conversion of grams to moles:
   Na mg x 0.043 = mmol
   K mg x 0.025 = mmol
   Cl mg x 0.028 = mmol
   Fe mg x 0.018 = mmol
   Ca mg x 0.025 = mmol
   Mg mg x 0.041 = mmol
   Mn mg x 0.018 = mmol
   Cu mg x 0.015 = mmol
   Zn mg x 0.019 = mmol
   Cr mg x 0.019 = mmol
   Mo mg x 0.010 = mmol

H. Caloric estimates of different PN solutions (Calories / cc) (table):

| Table 7. Caloric estimates of different PN solutions (Calories / cc): |
|-----------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Dextrose        | 5 %   | 10%   | 12.5% | 15%   | 17.5% | 20%   | 22.5% | 25%   | 27.0% | 30%   |
| %AA's           |       |       |       |       |       |       |       |       |       |       |
| 1               | 0.21  | 0.38  | 0.47  | 0.5   | 0.64  | 0.72  | 0.81  | 0.89  | 0.98  | 1.06  |
| 1.5             | 0.23  | 0.40  | 0.49  | 0.57  | 0.66  | 0.74  | 0.83  | 0.91  | 1.00  | 1.08  |
| 2               | 0.25  | 0.42  | 0.51  | 0.59  | 0.68  | 0.76  | 0.85  | 0.93  | 1.02  | 1.10  |
| 2.5             | 0.27  | 0.44  | 0.53  | 0.61  | 0.70  | 0.78  | 0.87  | 0.95  | 1.04  | 1.12  |
| 3               | 0.29  | 0.46  | 0.55  | 0.63  | 0.72  | 0.80  | 0.89  | 0.97  | 1.06  | 1.14  |
| 3.5             | 0.31  | 0.48  | 0.57  | 0.65  | 0.74  | 0.82  | 0.91  | 0.99  | 1.08  | 1.16  |
| 4               | 0.33  | 0.50  | 0.59  | 0.67  | 0.76  | 0.84  | 0.93  | 1.01  | 1.10  | 1.18  |
| 4.5             | 0.35  | 0.52  | 0.61  | 0.69  | 0.78  | 0.86  | 0.95  | 1.03  | 1.12  | 1.20  |
| 5               | 0.37  | 0.54  | 0.63  | 0.71  | 0.80  | 0.88  | 0.97  | 1.05  | 1.14  | 1.22  |

I. Authors

Mirna Chehade, MD

J. References:

  Grant JP. Handbook of Total Parenteral Nutrition. W.B. Saunders Company, 1992

The author would like to thank Kate Samela, MS, RD for useful comments.
### XV. Drug Formulary

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
<th>Dosage</th>
<th>Forms</th>
<th>Adverse Effects</th>
<th>Drug Interactions</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alendronate</strong>&lt;br&gt; (Fosamax)**</td>
<td></td>
<td>Adults: 10 mg PO QD&lt;br&gt;Take with 8 ounces of plain water 30 minutes before first food, beverage, or other medication. Do not lie down for at least 30 minutes after taking alendronate&lt;br&gt;Adults: 2-3 g/dose q 3-6 hrs or 1 and 3 hrs after meals and at bedtime&lt;br&gt;GI bleeding prophylaxis: Infant: 120-320 mg/dose PO q 1-2 hrs&lt;br&gt;Children: 320-960 mg/dose PO q 1-2 hrs&lt;br&gt;Adults: 2-4 g/dose PO q hr</td>
<td>5 mg, 10 mg, 35 mg, 40 mg, 70 mg tabs</td>
<td>Pill esophagitis&lt;br&gt;Transient Hypocalcemia and hypophosphatemia</td>
<td>1. Bioavailability of alendronate is increased when administered with oral and IV ranitidine&lt;br&gt;2. Increases incidence of GI adverse effects from NSAIDs / salicylates&lt;br&gt;3. Reduced absorption with antacids, calcium, iron, multivitamins and dairy products.</td>
<td>Use: bone demineralization caused by chronic steroid use and symptomatic Paget’s bone disease.&lt;br&gt;Contraindication: esophagitis and hypocalcemia.&lt;br&gt;Overdose: severe GI symptoms, hypocalcemia or hypophosphatemia. Treat with milk or antacids to bind alendronate. Not dialyzable. Ensure adequate calcium and vitamin D intake while receiving alendronate.</td>
</tr>
<tr>
<td><strong>Aluminum Hydroxide</strong>&lt;br&gt;(OTC)**</td>
<td>Alternagel, Amphogel, ALU-Cap, ALU-Tab, Dialume</td>
<td></td>
<td>Constipation&lt;br&gt;Hyperphosphatemia, hypomagnesemia&lt;br&gt;(high doses)&lt;br&gt;Discoloration of feces (white speckles)</td>
<td>May result in decreased bioavailability of medications if administered concurrently. To minimize this interaction, administer the antacid dose 2 hrs before or 1 hour after the medication dose.</td>
<td>Use: hyperacidity; hyperphosphatemia.&lt;br&gt;Precaution: in setting of renal failure or prematurity aluminum toxicity may occur.</td>
<td></td>
</tr>
<tr>
<td><strong>Aluminum / Magnesium Hydroxide</strong>&lt;br&gt;(Maalox, Mylanta)**</td>
<td>Maalox, Mylanta</td>
<td></td>
<td>Diarrhea&lt;br&gt;Constipation&lt;br&gt;Discoloration of feces (white speckles)</td>
<td>May result in decreased bioavailability of medications if administered concurrently. To minimize this interaction, administer the antacid dose 2 hrs before or 1 hour after the medication dose.</td>
<td>Precaution: in setting of renal failure or prematurity, excess aluminum or magnesium absorption may occur. Alternagel&gt;Maalox&gt;Mylanta&gt;Amphogel in neutralizing capacity.</td>
<td></td>
</tr>
<tr>
<td><strong>Amoxicillin</strong>&lt;br&gt;(Amoxil, Trimox)**</td>
<td></td>
<td>Children: 40 mg/kg/day PO divided q6h (80-90 mg/kg/day PO divided q12 for penicillin resistant S. pneumoniae)</td>
<td>Rash&lt;br&gt;Nausea/Vomiting&lt;br&gt;Seizures (high doses)&lt;br&gt;Intestinal nephritis&lt;br&gt;Hypersensitivity reactions</td>
<td>1. Results in increased bisphosphonate levels&lt;br&gt;2. Decreased effectiveness of oral contraceptives</td>
<td>Contraindication: penicillin allergy&lt;br&gt;Tricyclic Antidepressant&lt;br&gt;For chronic pain, use lower doses, 25-75 mg QD.&lt;br&gt;Contraindicated in patients with cardiac rhythm disorders. Consider using this or nortriptyline or paroxetine for IFN-alpha induced depression.</td>
<td></td>
</tr>
<tr>
<td><strong>Amitriptyline</strong>&lt;br&gt;(Elavil)**</td>
<td></td>
<td>Adults: 250 mg, 500 mg caps&lt;br&gt;Suspension: 25 mg/mL&lt;br&gt;50 mg/mL</td>
<td>Anticholinergic (blurred vision, confusion, constipation, urinary retention, hypotension, Parkinsonian syndrome)&lt;br&gt;Drowsiness&lt;br&gt;Headache&lt;br&gt;Nausea / vomiting&lt;br&gt;Increased appetite&lt;br&gt;Sexual dysfunction&lt;br&gt;Increased QT interval&lt;br&gt;More side effects than most other TCAs; consider Nortriptyline instead&lt;br&gt;1. Additive effects with CNS depressants&lt;br&gt;2. Increased risk of arrhythmias in combination with disopyramide&lt;br&gt;3. Increased risk of neurotoxicity, seizures, or serotonin syndrome in combination with MAO inhibitors&lt;br&gt;4. May potentiate the effect of oral anticoagulants</td>
<td>Tricyclic Antidepressant&lt;br&gt;For chronic pain, use lower doses, 25-75 mg QD.&lt;br&gt;Contraindicated in patients with cardiac rhythm disorders. Consider using this or nortriptyline or paroxetine for IFN-alpha induced depression.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ampicillin</strong></td>
<td>Omnipen, Principen</td>
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<tr>
<td>Endocarditis prophylaxis (high risk):</td>
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</tr>
<tr>
<td>Children: 50 mg/kg IV/IM</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Adults: 2 gm IV/IM 30 min before procedure with gentamicin (1.5 mg/kg), repeat ampicillin 6 hrs later with ½ the dose (Max dose=2 g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>250 mg, 500 mg caps 125 mg, 250 mg, 500 mg, 1 g, 2 g inj</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Rash</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Results in increased methotrexate levels</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Decreased effectiveness of oral contraceptives.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Probencid may increase ampicillin levels</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contraindication: penicillin allergy Use Vancomycin with gentamicin if penicillin allergic. Adjust for renal impairment. Sodium content: 3 mEq per gm of ampicillin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Ampicillin/subactam</strong></th>
<th>Unasyn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose expressed as ampicillin</td>
<td></td>
</tr>
<tr>
<td>Children: 100-200 mg amg/kg/day IV divided q6h</td>
<td></td>
</tr>
<tr>
<td>Adults: 1-2 g amp/kg IV q6-8h</td>
<td></td>
</tr>
<tr>
<td>50 mg amp/mL inj</td>
<td></td>
</tr>
<tr>
<td>Nausea/Vomiting Seizures Interstitial nephritis Hypersensitivity reactions Pseudomembranous colitis</td>
<td></td>
</tr>
<tr>
<td>1. Increases methotrexate levels</td>
<td></td>
</tr>
<tr>
<td>2. Decreases effectiveness of oral contraceptives.</td>
<td></td>
</tr>
<tr>
<td>Contraindication: penicillin allergy</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Azathioprine</strong></th>
<th>Imuran</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Children and Adults: 1-2 mg/kg PO/IV QD</td>
<td></td>
</tr>
<tr>
<td>50 mg tabs 5 mg/mL inj</td>
<td></td>
</tr>
<tr>
<td>Nausea Vomiting Diarrhea Bone marrow suppression Hypersensitivity reactions Hepatotoxicity Stomatitis Pancreatitis</td>
<td></td>
</tr>
<tr>
<td>1. Metabolism blocked by allopurinol. Reduce azathioprine dose 25-33%.</td>
<td></td>
</tr>
<tr>
<td>2. Decreases anticoagulant effect of warfarin</td>
<td></td>
</tr>
<tr>
<td>Azathioprine is metabolized to mercaptopurine. Can monitor metabolite levels</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Bethanechol</strong></th>
<th>Urecholine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prokinetic:</td>
<td></td>
</tr>
<tr>
<td>Children: 0.1-0.2 mg/kg/dose PO TID-QID</td>
<td></td>
</tr>
<tr>
<td>Adults: 10-50 mg PO BID-QID</td>
<td></td>
</tr>
<tr>
<td>5 mg, 10 mg, 25 mg, 50 mg tabs</td>
<td></td>
</tr>
<tr>
<td>Nausea Vomiting Diarrhea Abdominal pain Diaphoresis Urinary frequency Bronchial constriction Lacrimation Miosis</td>
<td></td>
</tr>
<tr>
<td>1. Increases effects of cholinergic agents</td>
<td></td>
</tr>
<tr>
<td>2. Cholinergic effects counteracted by atropine</td>
<td></td>
</tr>
<tr>
<td>Administer 30-60 minutes before meals Use with caution in patients with hyperthyroidism, asthma, and peptic ulcer disease</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Biotin (OTC)</strong></th>
<th>coenzyme R, vitamin H</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holocarboxylase synthetase deficiency/HCD or Biotinidase deficiency:</td>
<td></td>
</tr>
<tr>
<td>• Children and adults: 5-10 mg PO QD</td>
<td></td>
</tr>
<tr>
<td>RDA not established; requirement: 100-200 ug/day</td>
<td></td>
</tr>
<tr>
<td>5 mg capsules Tablets: 300 ug, 2.5 mg, 3 mg, 5 mg, 10 mg</td>
<td></td>
</tr>
<tr>
<td>None known</td>
<td></td>
</tr>
<tr>
<td>None known</td>
<td></td>
</tr>
<tr>
<td>Symptoms/signs of HCD: rash, alopecia, organic aciduria, metabolic acidosis, vomiting, seizures.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Bisacodyl (OTC)</strong></th>
<th>Ducolax</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Children: Oral administration:</td>
<td></td>
</tr>
<tr>
<td>3-12 yr: 5-10 mg PO QD or 0.3 mg/kg/day</td>
<td></td>
</tr>
<tr>
<td>2-11 years: 5-10 mg PR QD</td>
<td></td>
</tr>
<tr>
<td>&gt; 12 yr and Adults: 5-15 mg PO/PR QD</td>
<td></td>
</tr>
<tr>
<td>5 mg tabs (enteric coated) 5 mg, 10 mg supp</td>
<td></td>
</tr>
<tr>
<td>Nausea Vomiting Diarrhea Abdominal cramping</td>
<td></td>
</tr>
<tr>
<td>Antacids may prematurely dissolve enteric coating leading to gastric irritation.</td>
<td></td>
</tr>
<tr>
<td>Swallow tablet whole on empty stomach. Do not administer within 1 hour of milk and dairy products (causes gastric irritation) Onset: oral 6-10 hrs; rectal 15-60 min</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Calcium Carbonate Supplements (OTC)</strong></th>
<th>Tums, Tums EX, Tums 500, OsCal, Caltrate, Rolaid, Calcium Carb Susp</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDA: Doses are expressed in terms of elemental calcium</td>
<td></td>
</tr>
<tr>
<td>Children: 0-6 months: 210 mg 6-12 months: 270 mg 1-3 yr: 500 mg 4-8 yr: 800 mg 9-18 yr: 1300 mg Adults: 19-50 yr: 1000 mg &gt; 51 yr: 1200 mg Pregnant and Lactating: &lt; 19 yr: 1300 mg 19-50 yr: 1000 mg</td>
<td></td>
</tr>
<tr>
<td>Elemental calcium is in parentheses</td>
<td></td>
</tr>
<tr>
<td>Tums: 500 mg (200 mg) Tums EX: 750 mg (300 mg) Tums 500: 1250 mg (500 mg) OsCal: 1250 mg (500 mg) Caltrate: 1500 mg (600 mg) Rolaid: 500 mg (200 mg) Rolaid LO: 1000 mg (400 mg) Calcium Carb Susp 1250 mg/5mL (500</td>
<td></td>
</tr>
<tr>
<td>Constipation, hypercalcemia, nephrolithiasis, milk-alkali syndrome</td>
<td></td>
</tr>
<tr>
<td>1. May potentiate digoxin toxicity</td>
<td></td>
</tr>
<tr>
<td>2. May antagonize effects of calcium channel blockers</td>
<td></td>
</tr>
<tr>
<td>3. Decreases bioavailability of iron salts, quinolones, tetracyclines, salicylates, zinc and alendronate</td>
<td></td>
</tr>
<tr>
<td>Absorption inhibited by high phosphate load. Administer with plenty of water to prevent constipation. Administer between meals to maximize calcium absorption and minimize phosphate binding</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Dosage and Administration</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Carnitine</td>
<td><strong>Carnitor, Vitacarn = L-carnitine</strong></td>
</tr>
<tr>
<td></td>
<td>Carnitine Deficiency:</td>
</tr>
<tr>
<td></td>
<td>• Neonates: 50-100 mg/kg/day IV in TPN</td>
</tr>
<tr>
<td></td>
<td>• Children: 50-100 mg/kg/day IV divided BID-QID; max 3 g/day after each dialysis</td>
</tr>
<tr>
<td></td>
<td>(maintenance dose = 5 g/kg/day after 3-4 weeks)</td>
</tr>
<tr>
<td></td>
<td>• Adults (CHF, hemodialysis): 0.5 g PO TID</td>
</tr>
<tr>
<td></td>
<td><strong>330 mg tabs</strong></td>
</tr>
<tr>
<td></td>
<td>250 mg capsule 100 mg/ml solution 200 mg/ml inj</td>
</tr>
<tr>
<td></td>
<td><strong>Body odor (dose related)</strong></td>
</tr>
<tr>
<td></td>
<td>• Diarrhea</td>
</tr>
<tr>
<td></td>
<td>• Nausea/vomiting</td>
</tr>
<tr>
<td></td>
<td>• Cramps</td>
</tr>
<tr>
<td></td>
<td>• Seizures</td>
</tr>
<tr>
<td></td>
<td>• Cramps</td>
</tr>
<tr>
<td></td>
<td>• Dizziness</td>
</tr>
<tr>
<td></td>
<td>• Depression</td>
</tr>
<tr>
<td></td>
<td>• Paresthesia</td>
</tr>
<tr>
<td></td>
<td>• Fever</td>
</tr>
<tr>
<td></td>
<td>• Hypertension</td>
</tr>
<tr>
<td></td>
<td>• Hypercalcemia</td>
</tr>
<tr>
<td></td>
<td>• Muscle weakness</td>
</tr>
<tr>
<td></td>
<td><strong>Valproic acid</strong></td>
</tr>
<tr>
<td></td>
<td>Sodium Benzoate D,L carnitine (sold in health food stores as vitamin BT)</td>
</tr>
<tr>
<td></td>
<td><strong>Inhibits competitively inhibits L-carnitine</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Little data supports the use of carnitine supplementation in malnourished or critically ill patients, although serum levels are often low. Reference range:</strong></td>
</tr>
<tr>
<td></td>
<td>Free carnitine: &gt;20 micromoles/L</td>
</tr>
<tr>
<td></td>
<td>Acylcarnitine: free carnitine ratio: = (total carnitine-free carnitine) /free carnitine</td>
</tr>
<tr>
<td></td>
<td>Normal ratio: &lt;0.4</td>
</tr>
<tr>
<td>Cefazolin</td>
<td><strong>Ancef, Kefzol</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Infection:</strong></td>
</tr>
<tr>
<td></td>
<td>• Neonates: 50-100 mg/kg/day IV/IM</td>
</tr>
<tr>
<td></td>
<td>• Children: 50-100 mg/kg/day IV/IM</td>
</tr>
<tr>
<td></td>
<td>• Adults: 2-4 gm PO TID before or 2-4 hours after procedure</td>
</tr>
<tr>
<td></td>
<td><strong>300 mg, 1000 mg inj</strong></td>
</tr>
<tr>
<td>Cholestyramine</td>
<td><strong>Questran</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Children (dose expressed as anhydrous resin):</strong></td>
</tr>
<tr>
<td></td>
<td>• 240 mg/kg/day PO divided TID</td>
</tr>
<tr>
<td></td>
<td>• Adults: 3-4 gm PO TID-QID (max 32 gm/day)</td>
</tr>
<tr>
<td></td>
<td><strong>4 gm anhydrous resin per scoop or packet</strong> (9 gm total weight per scoop)</td>
</tr>
<tr>
<td></td>
<td><strong>Nausea, vomiting, electrolyte abnormalities, constipation, rash</strong></td>
</tr>
<tr>
<td>Cimetidine</td>
<td><strong>Tagamet, Tagamet-HB</strong></td>
</tr>
<tr>
<td></td>
<td>**Neonates: 5-10 mg/kg/day PO/IV/IM</td>
</tr>
<tr>
<td></td>
<td>• Infants: 10-20 mg/kg/day PO/IV/IM</td>
</tr>
<tr>
<td></td>
<td>• Children: 20-40 mg/kg/day PO/IV/IM</td>
</tr>
<tr>
<td></td>
<td>• Adults: 300 mg PO/IV q 6h</td>
</tr>
<tr>
<td></td>
<td><strong>May increase to 600 mg PO q 6h for adults with hyperscreotory conditions</strong></td>
</tr>
<tr>
<td></td>
<td><strong>200 mg, 300 mg, 400 mg, 600 mg tabs 60 mg/mL elixer 150 mg/mL inj Alcohol content of elixer= 2.8%</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Body odor (dose related)</strong></td>
</tr>
<tr>
<td></td>
<td>• Diarrhea</td>
</tr>
<tr>
<td></td>
<td>• Nausea/vomiting</td>
</tr>
<tr>
<td></td>
<td>• Confusion</td>
</tr>
<tr>
<td></td>
<td>• Dizziness</td>
</tr>
<tr>
<td></td>
<td>• Gynecomastia</td>
</tr>
<tr>
<td></td>
<td>• Neutropenia</td>
</tr>
<tr>
<td></td>
<td>• Myelosuppression</td>
</tr>
<tr>
<td></td>
<td>• Elevated LFTs</td>
</tr>
<tr>
<td></td>
<td>• Hypotension</td>
</tr>
<tr>
<td></td>
<td>• Bradycardia, cardiac arrhythmias with rapid IV infusion</td>
</tr>
<tr>
<td></td>
<td><strong>Inhibits the hepatic metabolism of drugs metabolized by the cytochrome P450 pathway including phenytoin, theophylline, warfarin, tricyclic antidepressants, carbamazepine, cyclosporine, tacrolimus, quinidine, and certain benzodiazepines. Decrease the absorption of iron, tetracycline, ketoconazole and fluconazole.</strong></td>
</tr>
<tr>
<td>Cisapride</td>
<td><strong>Propulsid</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Children: 0.1-0.3 mg/kg/dose PO TID-QID (max 10 mg/dose)</strong></td>
</tr>
<tr>
<td></td>
<td>• Adults: 10-20 mg</td>
</tr>
<tr>
<td></td>
<td><strong>10 mg, 20 mg tabs 1 mg/mL susp Available via limited access protocol only</strong></td>
</tr>
<tr>
<td></td>
<td>** QT prolongation**</td>
</tr>
<tr>
<td></td>
<td>• Tagamet, Tagamet-HB</td>
</tr>
<tr>
<td></td>
<td><strong>Nausea/Vomiting/Abdominal cramping Headache</strong></td>
</tr>
<tr>
<td></td>
<td><strong>QT prolongation has occurred when cisapride is administered with azole antifungals,</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Drug interactions with cisapride have resulted in ventricular tachycardia and torsade de points. Take cisapride 15 minutes before meals.</strong></td>
</tr>
<tr>
<td>Drug</td>
<td>Indication</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Cromolyn sodium</strong></td>
<td>Gastrocrom</td>
</tr>
<tr>
<td><strong>Cyclosporine</strong></td>
<td>Neoral, SangCya, Sandimmune</td>
</tr>
<tr>
<td><strong>Cyproheptadine</strong></td>
<td>Periactin</td>
</tr>
<tr>
<td><strong>Diphenoxylate/atropine</strong></td>
<td>Lomotil</td>
</tr>
<tr>
<td><strong>Docusate (OTC)</strong></td>
<td>Colace</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>( \text{mg/day divided QD-QID})</td>
</tr>
<tr>
<td>----------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>3-6 years: 20-60 mg/day divided QD-QID</td>
<td></td>
</tr>
<tr>
<td>6-12 years: 40-120 mg/day divided QD-QID</td>
<td></td>
</tr>
<tr>
<td>• Adults: 50-400 mg/day divided QD-QID</td>
<td></td>
</tr>
<tr>
<td>Resulting in intestinal, liver, or spleen inflammation.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ferric Gluconate Injectable</th>
<th>Feosol, Ferrin-sol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose expressed as elemental iron</td>
<td></td>
</tr>
<tr>
<td>• Children: Prohydrolaxis: 1-2 mg elem iron/kg/day divided QD-QID Moderate deficiency</td>
<td></td>
</tr>
<tr>
<td>• Adults: 50-400 mg/day divided QD-QID</td>
<td></td>
</tr>
<tr>
<td>Nausea, diarrhea, constipation, dark stools, discoloration of urine, liquid preps may stain teeth</td>
<td></td>
</tr>
<tr>
<td>1. Concurrent administration results in decreased absorption of tetracycline, levofloxacin, and certain quinolones.</td>
<td></td>
</tr>
<tr>
<td>Take with food Hemoglobin values increase in 2-4 weeks.</td>
<td></td>
</tr>
<tr>
<td>Do not crush sustained release products.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ferric Dextran Infed</th>
<th>Dexferrum Infed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency Anemia</td>
<td></td>
</tr>
<tr>
<td>• Children 5 - 15 kg: (IM/IV) Dose (mL) = 0.0476 x Wt x (desired Hb - observed Hb) + (1 mL/5 kg Wt)</td>
<td></td>
</tr>
<tr>
<td>Max daily dose IM &lt; 5 kg child: 25 mg S-10 kg: 50 mg Max TOTAL dose 14 mL</td>
<td></td>
</tr>
<tr>
<td>• Children &gt;15 kg and Adults (IM/IV): Dose (mL) = 0.0476 x LBW x (desired Hb - observed Hb) + (1 mL/5 kg LBW) Max daily dose IM &gt; 10 kg: 100 mg (LBW=Lean Weight in Kg)</td>
<td></td>
</tr>
<tr>
<td>50 mg/ml</td>
<td></td>
</tr>
<tr>
<td>Anaphylaxis (immediate or delayed) Hypotension Skin discoloration if given SC</td>
<td></td>
</tr>
<tr>
<td>Infusion rate should not exceed 12.5 mg/min (test dose no longer required) Do not give SC Contraindications: Hemachromatosis Hemolytic anemia</td>
<td></td>
</tr>
<tr>
<td>Do test dose 1 hr prior to giving dose: Infants: 0.25 ml Children and adults: 0.5 ml Max infusion rate 25 mg/min Do not give SC Contraindications: Hemochromatosis Hemolytic anemia</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Erythromycin</th>
<th>Prokinetic:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Children: 1mg/kg/dose QID</td>
<td></td>
</tr>
<tr>
<td>• Adults: 20-40 mg PO QD</td>
<td></td>
</tr>
<tr>
<td>Pepcid: 10 mg, 20 mg, 40 mg tabs 0.4 mg/mL inj ??</td>
<td></td>
</tr>
<tr>
<td>40 mg/5 ml suspension Pepcid AC: 10 mg chewable tabs</td>
<td></td>
</tr>
<tr>
<td>Headache Diarrhea Nausea Abdominal pain</td>
<td></td>
</tr>
<tr>
<td>1. Bioavailability slightly decreased by antacids 2. Decreases bioavailability of ketoconazole and itraconazole, delavirdine</td>
<td></td>
</tr>
<tr>
<td>Take one hour before eating or drinking when using for prophylaxis.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Famotidine</th>
<th>Pepcid, Pepcid AC</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Children: 1-2 mg/kg/day PO/IV divided Q 8-12 h</td>
<td></td>
</tr>
<tr>
<td>• Adults: 20-40 mg/day PO/IV divided QD-BID Maintenance: 20 mg PO QD</td>
<td></td>
</tr>
<tr>
<td>20 mg, 40 mg capsules</td>
<td></td>
</tr>
<tr>
<td>Headache Diarrhea Nausea</td>
<td></td>
</tr>
<tr>
<td>1. Clarithromycin, amoxicillin: increase esomeprazole levels 2. Markedly increases levels of diazepam 3. Food decreases absorption</td>
<td></td>
</tr>
<tr>
<td>Proton pump inhibitor, optical isomer of omeprazole.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fentanyl</th>
<th>Sublimaze</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation for minor procedure</td>
<td></td>
</tr>
<tr>
<td>• Children: 1-3 ug/kg/dose IV repeated q30-60 min</td>
<td></td>
</tr>
<tr>
<td>• Adults: 0.5-1 ug/kg/dose IV repeated q30-60 min</td>
<td></td>
</tr>
<tr>
<td>0.05 mg/mL inj</td>
<td></td>
</tr>
<tr>
<td>CNS depression Euphoria Drowsiness Nausea/Vomiting Constipation/Diarrhea Elevated LFTs</td>
<td></td>
</tr>
<tr>
<td>1. Bioavailability of warfarin slightly decreased by cimetidine 2. Increases theophylline levels 3. Potentiates anticoagulant effect of warfarin</td>
<td></td>
</tr>
<tr>
<td>Caution: an opioid antagonist, resuscitative and intubation equipment must be available when administering fentanyl.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Eosinophilia</th>
<th>Eosinophilia</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-sol Feosol, Fer-in-sol</td>
<td>Eosinophilia: 1-2 mg elem iron/kg/day divided QD-QID Moderate deficiency</td>
</tr>
<tr>
<td>Feosol: 325 mg (65 mg elem iron) tab 44 mg/mL (8.8 mg elem iron/mL) liq or elixir Fer-in-sol: 125 mg/mL (25 mg/L elem iron)</td>
<td></td>
</tr>
<tr>
<td>Nausea, diarrhea, constipation, dark stools, discoloration of urine, liquid preps may stain teeth</td>
<td></td>
</tr>
<tr>
<td>1. Concurrent administration results in decreased absorption of tetracycline, levofloxacin, and certain quinolones.</td>
<td></td>
</tr>
<tr>
<td>Take with food Hemoglobin values increase in 2-4 weeks. Do not crush sustained release products.</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Administration</td>
</tr>
<tr>
<td>------</td>
<td>----------------</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Remicade</td>
</tr>
<tr>
<td>Interferon alpha 2b</td>
<td>Intron A</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Lasix</td>
</tr>
<tr>
<td>Flumazenil</td>
<td>Romazicon</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Garamycin</td>
</tr>
<tr>
<td>Hydrocortisone enema</td>
<td>Cortenema</td>
</tr>
<tr>
<td>Furoxone</td>
<td>Furazolidone</td>
</tr>
<tr>
<td>Flumazenil</td>
<td>Romazicon</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Garamycin</td>
</tr>
<tr>
<td>Glucagon</td>
<td>Glucagon</td>
</tr>
<tr>
<td>Hydrocortisone enema</td>
<td>Cortenema</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Remicade</td>
</tr>
<tr>
<td>Interferon alpha 2b</td>
<td>Intron A</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Garamycin</td>
</tr>
<tr>
<td>Flumazenil</td>
<td>Romazicon</td>
</tr>
<tr>
<td>Furoxone</td>
<td>Furazolidone</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Garamycin</td>
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<td>Lasix</td>
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<td>Romazicon</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Garamycin</td>
</tr>
<tr>
<td>Glucagon</td>
<td>Glucagon</td>
</tr>
<tr>
<td>Hydrocortisone enema</td>
<td>Cortenema</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Remicade</td>
</tr>
<tr>
<td>Interferon alpha 2b</td>
<td>Intron A</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Garamycin</td>
</tr>
<tr>
<td>Flumazenil</td>
<td>Romazicon</td>
</tr>
<tr>
<td>Furoxone</td>
<td>Furazolidone</td>
</tr>
<tr>
<td>Medication</td>
<td>Dosage &amp; Formulations</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Iodoquinol</strong></td>
<td><strong>Yodoxin</strong></td>
</tr>
<tr>
<td>Lactulose</td>
<td><strong>Dulphalac, Kristalose</strong></td>
</tr>
<tr>
<td>Lamivudine</td>
<td><strong>Epivir-HBV - 3TC</strong></td>
</tr>
<tr>
<td>Lansoprazole</td>
<td><strong>Prevacid</strong></td>
</tr>
<tr>
<td>Loperamide</td>
<td><strong>Imodium, Imodium AD</strong></td>
</tr>
<tr>
<td>Magnesium hydroxide</td>
<td><strong>Milk of magnesia</strong></td>
</tr>
<tr>
<td>Megestrol</td>
<td><strong>Megace</strong></td>
</tr>
<tr>
<td>Meperidine</td>
<td><strong>Demerol</strong></td>
</tr>
<tr>
<td>Drug</td>
<td>Dosage and Administration</td>
</tr>
<tr>
<td>------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>10 mg, 25 mg, 50 mg, 75 mg, 100 mg single dose inj</td>
</tr>
<tr>
<td>Mesalamine</td>
<td>Asacol: 400 mg enteric coated tab  Pentasa: 250 mg controlled release cap  Rowasa: 500 mg suppo 4 g/60 mL enema</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>2.5 mg tab 25 mg/ml, 50 mg/ml inj</td>
</tr>
<tr>
<td>Methylcellulose</td>
<td>2 gm/heaping TBSP</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>2 mg, 4 mg, 8 mg, 16 mg, 24 mg, 32 mg tabs 40 mg, 125 mg, 500 mg, 1000 mg, 2000 mg inj</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>5 mg, 10 mg tab 1 mg/mL syrup (sugar free) 5 mg/mL inj</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>375 mg caps 750 mg extended release 250 mg, 500 mg tabs 5 mg/ml inj 10 mg/mL susp Recipe for preparation: 250 mg tabs x 8</td>
</tr>
</tbody>
</table>

Caution: do not administer with alcohol or alcohol-containing products due to disulfiram reaction.
Food delays and decreases peak concentrations. Take with food only if GI upset occurs.
Dose adjust for renal impairment and severe hepatic impairment.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand</th>
<th>Dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olsalazine</td>
<td>Dipentum</td>
<td>Adults: 0.5-1.5g PO divided BID</td>
<td>Nausea, Diarrhea, Abdominal cramping, Headache</td>
</tr>
<tr>
<td>Octreotide</td>
<td>Sandostatin</td>
<td>Adults: 0.05-0.1mg/kg IV divided BID TID</td>
<td>Bradycardia, Arhythmias, Diarrhea, Hypoglycemia, Gallbladder abnormalities</td>
</tr>
<tr>
<td>Naloxone</td>
<td>Narcan</td>
<td>Adults: 0.4-2 mg/dose IV Q2-3 min up to 10 mg</td>
<td>Hypotension, hypertension, nausea, vomiting</td>
</tr>
<tr>
<td>Misoprostol</td>
<td>Cellcept</td>
<td>Children: 400-800 mcg/m2/dose PO divided Q12hrs</td>
<td>Absorption decreased by antacids and cholesterol</td>
</tr>
<tr>
<td>Mineral oil</td>
<td>Fleet mineral oil</td>
<td>Adults: 0.5-45 mL/day PO</td>
<td>Fluid/Electrolyte imbalance, Nausea/Vomiting, Diarrhea, Lipid pneumonitis (with aspiration)</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Versed</td>
<td>Adults: 5-45 mL/day PO</td>
<td>Respiratory depression, Nausea, Vomiting, Diarrhea, Amnesia</td>
</tr>
<tr>
<td>Mineral oil</td>
<td>Kondremul, Fleet mineral oil</td>
<td>Children: 1-3 mL/kg/day PO</td>
<td>Headache, Abdominal cramping, Diarrhea, Nausea</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>Cellcept</td>
<td>Adults: 500 mg/m2/dose PO or 30 mg/kg/day divided Q12hrs</td>
<td>Absorption decreased by antacids and cholesterol</td>
</tr>
<tr>
<td>Nasal Spray</td>
<td>Dipentum</td>
<td>Adults: 0.5-1.5g PO divided BID</td>
<td>Nausea, Diarrhea, Abdominal cramping, Headache</td>
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</tr>
<tr>
<td>Drug</td>
<td>Children: mg/kg PO divided QD-BID</td>
<td>Adults: mg PO QD-BID</td>
<td>Ondansetron: 1-2 mg/mL suspension</td>
</tr>
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</tr>
<tr>
<td>Prilosec</td>
<td>0.5-1.5 mg/kg PO divided QD-BID</td>
<td>10-20 mg PO QD-BID</td>
<td>Zofran: 4 and 8 mg, 24 mg tabs</td>
</tr>
<tr>
<td>Prilosec</td>
<td>10 mg, 20 mg caps</td>
<td>4 mg PO Q4h x 3 doses, then repeat Q8 h OR: 0.15 mg/kg IV Q4-8 QD</td>
<td>Zofran: 4 mg/5ml soln Zofran QOD (orally disintegrating tablets): 4 mg and 8 mg</td>
</tr>
<tr>
<td>Prilosec</td>
<td>2 mg/mL susp</td>
<td>8 mg PO Q4h x 3 doses then repeat Q8 h OR: 32 mg IV x 1 OR: 0.15 mg/kg IV Q4h x 3</td>
<td>Zofran ODT (orally disintegrating tablets): 4 mg and 8 mg</td>
</tr>
<tr>
<td>Zofran</td>
<td>Recipe for preparation: 20 mg capsule x 1 Open capsule and mix with 10 mL of sodium bicarbonate Inj (1 mg/ML). Stable for 14 days at room temp</td>
<td>Headache Vertigo Insomnia Nausea Diarrhea Rash Constipation Discoloration of feces Agranulocytosis, thrombocytopenia Elevated LFTs</td>
<td>Capsules may be opened and added to applesauce for PO administration. Animal studies raised concern of gastric cancers with long term use. This risk was not supported by several long-term studies in humans. Range of effective doses in the literature 0.7-3.5 mg/kg/day (Hassall, 2000)</td>
</tr>
<tr>
<td>Viokase</td>
<td>2 mg/mL susp</td>
<td>8 mg PO Q4h x 3 doses then repeat Q8 h OR: 32 mg IV x 1 OR: 0.15 mg/kg IV Q4h x 3</td>
<td>Zofran ODT (orally disintegrating tablets): 4 mg and 8 mg</td>
</tr>
<tr>
<td>Creon</td>
<td>2 mg/mL susp</td>
<td>8 mg PO Q4h x 3 doses then repeat Q8 h OR: 0.15 mg/kg IV Q4h x 3</td>
<td>Ultrase: 4 mg and 8 mg disintegrating tablets: 4 mg and 8 mg</td>
</tr>
<tr>
<td>Creon</td>
<td>2 mg/mL susp</td>
<td>8 mg PO Q4h x 3 doses then repeat Q8 h OR: 0.15 mg/kg IV Q4h x 3</td>
<td>Prilosec: 10 mg, 20 mg caps 2 mg/mL suspension</td>
</tr>
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<td>Creon</td>
<td>2 mg/mL susp</td>
<td>8 mg PO Q4h x 3 doses then repeat Q8 h OR: 0.15 mg/kg IV Q4h x 3</td>
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<td>8 mg PO Q4h x 3 doses then repeat Q8 h OR: 0.15 mg/kg IV Q4h x 3</td>
<td>Prilosec: 10 mg, 20 mg caps 2 mg/mL suspension</td>
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<td>2 mg/mL susp</td>
<td>8 mg PO Q4h x 3 doses then repeat Q8 h OR: 0.15 mg/kg IV Q4h x 3</td>
<td>Prilosec: 10 mg, 20 mg caps 2 mg/mL suspension</td>
</tr>
<tr>
<td>NASPGHAN</td>
<td>Pediatric Gastroenterology Hepatology and Nutrition Handbook</td>
<td></td>
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</tr>
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<td>----------------</td>
<td>-------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Rifampin

**Brand names:** Rifadin, Cuprimin, Depen

- **Dosage:**
  - Children: 10-20 mg/kg/day PO/IV divided BID
  - Adults: 150 mg PO/BID

- **Indications:**
  - Cholesterolosis
  - Premature and newborn: 2 mg/kg/day PO divided Q12h; 1.5 mg/kg/day IV divided Q12h

- **Side effects:**
  - Constipation, headache, dizziness, fatigue, irritability, diarrhea, lethargy, thrombocytopenia, elevation of transaminases

- **Additional information:**
  - Doses of up to 10 mg/kg have been used in dose-ranging trials with a concomitant increase in efficacy and no apparent adverse effects.
  - Continuous IV infusion at same daily dose is preferred to IV boluses for active bleeding.
  - Dose adjust for renal impairment.

### Prednisone

**Brand names:** Prelone, Pediapred, Miralax

- **Dosage:**
  - Adults: 17 GM (about 1 heaping teaspoonful) of powder per day in 8 ounces of water.

- **Side effects:**
  - Nausea, Abdominal bloating, Cramping, Flatulence, dehydration and hypokalemia reported in children.

- **Additional information:**
  - Two to 4 days may be required to produce a bowel movement.

### Prednisolone

**Brand names:** Pediapred, Prelone

- **Dosage:**
  - IBID: Children and Adults: 1-2 mg/kg/day PO divided BID

- **Side effects:**
  - Nausea, Vomiting, Abdominal cramps, Abdominal distention

- **Additional information:**
  - Take with food
  - May decrease vaccine effectiveness

### Phenobarbital

**Dosage:**

- **Bowel prep for colonoscopy or constipation:**
  - Children: 75-100 ml/kg PO
  - As prep, infuse 25-50 ml/kg/hr until rectal effluent is clear (<10 kg: 50 ml/kg over 4 hrs then reassess)
  - Adults: 4-6 L PO
  - May use smaller doses for maintenance treatment of constipation

- **Side effects:**
  - Nausea, Abdominal bloating, Cramping, Flatulence, dehydration and hypokalemia reported in children.

- **Additional information:**
  - The addition of flavoring agents is not recommended. If flavoring agent is required, use one without bright color (i.e. use lemonade flavor).

### Polyethylene Glycol

**Brand names:** Golytely, Coylet, Nulystyl, Miralax

- **Dosage:**
  - Liquid Pred: 15 mg/mL elixir
  - Pediatric 3 mg/mL elixir

- **Side effects:**
  - Constipation, headache, dizziness, fatigue, irritability, diarrhea, lethargy, thrombocytopenia, elevation of transaminases

- **Additional information:**
  - Doses of up to 10 mg/kg have been used in dose-ranging trials with a concomitant increase in efficacy and no apparent adverse effects.
  - Continuous IV infusion at same daily dose is preferred to IV boluses for active bleeding.
  - Dose adjust for renal impairment.

### Polyethylene Glycol Electrolyte Solution

**Dosage:**

- **Choleric:** 5 mg/kg/day PO divided BID

- **Side effects:**
  - Nausea, Vomiting, Abdominal cramps, Abdominal distention

- **Additional information:**
  - Take with food
  - May decrease vaccine effectiveness
<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Dosage and Administration</th>
<th>Adverse Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfasalazine</td>
<td>Azulfidine</td>
<td>3-4 g/day PO divided TID</td>
<td>Diarrhea, Nausea, vomiting</td>
<td>Contraindicated in sulfa allergy. Patients should receive folate supplements. Monitoring of CBC and LFTs recommended. May cause orange-yellow discoloration of urine and skin.</td>
</tr>
<tr>
<td><strong>Vitamin K</strong></td>
<td><strong>Pharmacology</strong></td>
<td><strong>Dosing</strong></td>
<td><strong>Adverse Effects</strong></td>
<td><strong>Precautions</strong></td>
</tr>
<tr>
<td>--------------</td>
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</tr>
<tr>
<td>Vitamin K</td>
<td>Deficiency: Deficient if &lt;0.6 mg/gm</td>
<td>should be adjusted based on drug levels.</td>
<td>Thrombocytopenia, leukopenia, elevated AST, ALT and LDH</td>
<td>Increases risk of 2nd lymphomas</td>
</tr>
<tr>
<td>Ursodeoxycholic acid</td>
<td>Actigall, Ursodiol</td>
<td>• Children: 10 -30 mg/kg/day PO divided BID • Adults: 300 mg PO BID</td>
<td>Actigall: 300 mg caps Ursos: 250 mg tabs</td>
<td>Suspenson may be made at 60 mg/mL (see info section)</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Vanocin</td>
<td>C. Difficile: (metronidazol is drug of choice) 20-40 mg/kg/day PO divided QID x 7-10 days Endocarditis Prophylaxis (PCN allergic patients): • Children: 20 mg/kg (Max 1 g) IV over 1 hour (with gentamicin) • Adults: 1 gm 125 mg, 250 mg caps oral soln (powder): 50 mg/ml (1 gm); 83.3 mg/ml (10 gm) 500 mg, 1000 mg inj Dilute injection to 5 mg/mL</td>
<td>Ototoxicity (high peak) Nephrotoxicity (high trough) Red man syndrome (rapid infusion)</td>
<td>Additive nephrotoxicity with aminoglycosides and other nephrotoxic medications</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>Pitressin</td>
<td>GI Bleeding: • Children: 0.2-0.5 Unit/1.76m2/min IV • Adults: 0.2-0.5 Unit/min IV Optional loading dose of 20 units in adults 20 Units/mL inj</td>
<td>Hypertension, hyponatremia, oliguria</td>
<td>Antidiuretic effect decreased by lithium, epinephrine, demeclocycline, heparin, and alcohol</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>Aquasol A</td>
<td>Cholestasis: 5,000-15,000 IU PO QD Cystic Fibrosis: 5,000 IU PO QD RDA: 500-1000 IU PO QD 5,000 IU= 0.1 mL= 3 drops 25,000 IU, 50,000 IU caps 50,000 IU/mL inj</td>
<td>Papilledema Dry skin Sore tongue Hyperostoses</td>
<td>1. Decreases serum conversion of measles vaccine in younger infants 2. Increased incidence of pseudotumor cerebri with Minocycline</td>
</tr>
<tr>
<td>Vitamin ADEK</td>
<td>ADEK</td>
<td>Cystic Fibrosis: 0-1 yr: 1 mL PO QD 1-2 yr: 2 mL PO QD 2-12 yr: 1 tablet PO QD &gt; 12 yr: 2 tablets PO QD Tablets, drops</td>
<td>May increase or decrease anticoagulant effects of warfarin</td>
<td>May antagonize effects of calcium channel blockers</td>
</tr>
<tr>
<td>Vitamin D 1,25-OH (Calcitriol)</td>
<td>Rocaltrol</td>
<td>• Children: 0.015-0.040 ug/kg/day PO QD • Adults: 0.25-2 ug/day PO QD</td>
<td>Hypercalcemia, polyuria, nephrolithiasis, nausea, vomiting, constipation</td>
<td>May antagonize effects of calcium channel blockers</td>
</tr>
<tr>
<td>Vitamin D 25-OH (Calcifediol)</td>
<td>Calderol</td>
<td>3-5 µg/kg PO QD</td>
<td>Hypercalcemia, polyuria, nephrolithiasis, nausea, vomiting, constipation</td>
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</tr>
<tr>
<td>Vitamin D2 (ergocalciferol)</td>
<td>Drisdol</td>
<td>Cholestasis: 5000-8000 IU PO QD Cystic Fibrosis: 400 IU PO QD RDA: 400 IU PO QD (02=ergocalciferol) 8000 IU=1 mL= 40 drops 40 units = 1 mcg</td>
<td>Hypercalcemia, polyuria, nephrolithiasis, nausea, vomiting, constipation</td>
<td>May antagonize effects of calcium channel blockers</td>
</tr>
<tr>
<td>Vitamin E (D-alpha tocophero)</td>
<td>LiquiE, Aquasol E</td>
<td>Cholestasis: LiquiE: 15-25 IU/kg PO QD Aquasol E: 50-400 IU PO QD Cystic Fibrosis: Aquasol E: 25-400 IU QD</td>
<td>Muscle Weakness Nausea Diarrhea</td>
<td>1. Increases anticoagulant effect of Warfarin 2. May antagonize Vitamin K</td>
</tr>
<tr>
<td>Vitamin K1 (phytonadione)</td>
<td>Mephyton</td>
<td>Cholestasis: 2.5-5 mg PO/IV/SC/IV QD or QOD Cystic Fibrosis: 2.5-5 mg/week PO if &lt; 1yr. Increase to BID if on antibiotics. Treat patients &gt; 1yr if on antibiotics or if liver disease present. Vit K deficiency: 1-2 mg IM/SC/IV</td>
<td>5 mg tabs 10 mg/mL inj</td>
<td>Flushing Hypotension GI upset Pain at injection site Precautions: Anaphylactic Reactions- Rare severe hypersensitivity reactions have occurred after IV use. Severe hemolytic anemia and hyperbilirubinemia has been reported rarely in neonates following large doses (10-20 mg) of phytonadione.</td>
</tr>
<tr>
<td>Zinc sulfate (23% zinc)</td>
<td>Liver Failure: 1 mg/year of age up to 10 mg</td>
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<tr>
<td>Zinc sulfate</td>
<td>(Dose expressed as mg of elemental zinc) Supplement in TPN (IV):</td>
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<tr>
<td></td>
<td>• Infants:</td>
<td></td>
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<tr>
<td></td>
<td>Prematures: 400 ug/kg/day</td>
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<tr>
<td></td>
<td>&lt;3 months: 300 ug/kg/day</td>
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</tr>
<tr>
<td></td>
<td>&gt;3 months and children &lt;5 yr: 100 ug/kg/day (max: 5 mg/day)</td>
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</tr>
<tr>
<td></td>
<td>• Children &gt;5 yrs: 2-5 mg/day</td>
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</tr>
<tr>
<td></td>
<td>Deficiency:</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>• Children: 1 mg/kg/day elemental zinc PO divided BID-TID</td>
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<td>• Adults: 25-50 mg elemental zinc/dose PO TID</td>
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<td>110 mg (25 mg elem zinc), 220 mg (50 mg elem zinc) capsule 66 mg (15 mg elem zinc), 110 mg (25 mg elem zinc), 200 mg (45 mg elem zinc) tablet 10 mg/mL solution</td>
<td>Nausea</td>
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<tr>
<td></td>
<td>Vomiting</td>
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<tr>
<td></td>
<td>Neutropenia</td>
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<td>Leukopenia</td>
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<td>Jaundice</td>
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<td>Pulmonary edema</td>
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<td>Blurred vision</td>
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</table>

1. Decreases absorption of tetracycline and quinolones  
2. Absorption decreased by iron.  

Serum reference range: 70-130 ug/dl  
Add to parenteral nutrition solution if long term use (> 3 months)  
Consider zinc level and supplement in patients with chronic diarrhea  
Signs of deficiency: Poor growth, decreased taste, hypogonadism, perioral skin changes.  
Do not administer undiluted by direct injection into a peripheral vein, may cause phlebitis