Disclosures

- None
Objectives

- Milk Protein Allergy
- Colic vs Reflux vs Milk Protein Allergy
- Common Etiologies for GI Bleeding
- Allergic Colitis vs IBD
- Very Early Onset IBD
Cow Milk Protein Allergy (CMPA)

- Allergic to cow’s milk protein, with high cross-reactivity to soy
- Major Flag: poor weight gain, diarrhea with mucousy/bloody stools
- Minor Flag: vomiting, fussiness, frequent reflux
  - Milk Protein Allergy vs Colic vs Reflux
  - Growing well with normal stools? Colic/Reflux
- Calprotectin may not be helpful
- Diagnosis clinically
### Calprotectin in Healthy Infants

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>N</th>
<th>Boys Median FC (5th−95th), µg/g</th>
<th>N</th>
<th>Girls Median FC (5th−95th), µg/g</th>
<th>N (%)</th>
<th>Median FC (5th−95th), µg/g</th>
<th>Median FC (5th−95th), log10µg/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>1−3</td>
<td>45</td>
<td>323.2 (78−867)</td>
<td>29</td>
<td>378.1 (70−1065)</td>
<td>75(26.0)</td>
<td>375.2 (77−962)</td>
<td>2.574 (1.885−2.983)</td>
</tr>
<tr>
<td>3−6</td>
<td>35</td>
<td>217.9 (50−635)</td>
<td>26</td>
<td>219.7 (54−800)</td>
<td>61(21.2)</td>
<td>217.9 (53−621)</td>
<td>2.338 (1.726−2.793)</td>
</tr>
<tr>
<td>6−9</td>
<td>31</td>
<td>127.7 (10−453)</td>
<td>20</td>
<td>123.5 (35−338)</td>
<td>51(17.7)</td>
<td>127.7 (10−362)</td>
<td>2.106 (1.000−2.558)</td>
</tr>
<tr>
<td>9−12</td>
<td>29</td>
<td>94.8 (10−482)</td>
<td>22</td>
<td>109.5 (14−382)</td>
<td>51(17.7)</td>
<td>96.1 (10−398)</td>
<td>1.983 (1.000−2.600)</td>
</tr>
<tr>
<td>12−18</td>
<td>32</td>
<td>89.8 (17−386)</td>
<td>18</td>
<td>177.9 (20−532)</td>
<td>50(17.4)</td>
<td>104.2 (10−501)</td>
<td>2.016 (0.998−2.670)</td>
</tr>
<tr>
<td>All</td>
<td>173</td>
<td>154.3 (18−623)</td>
<td>115</td>
<td>212.4 (34−904)</td>
<td>288</td>
<td>174.3 (24−764)</td>
<td>2.241 (1.370−2.883)</td>
</tr>
</tbody>
</table>

Colic

- Baby is clinically well, but fussy and crying
- Reassuring parents can be hard, especially when they are desperate to try things
- Trialing different formulas
  - Soy-based formula
  - Partially-Hydrolyzed Formula (Not hypoallergenic)
    - Similac Total Comfort, Enfamil Gentlease, Gerber Gentle/Smooth
  - ?Extensively-Hydrolyzed Formula
Gastroesophageal Reflux

- Frequent transit relaxation of lower esophageal sphincter
Gastroesophageal Reflux

- **GER vs GERD**
  - GER is a normal physiologic process with passage of gastric contents into the esophagus
  - GERD is GER when it causes issues, like symptoms, esophageal injury, poor weight gain, etc

- **GER in infants is normal baby spit up**
  - Formula changes and medications may not help
  - Reflux precautions, small frequent feeds, keep upright/inclined after eating, thickened feeds
Gastroesophageal Reflux

- Thickening milk for Reflux
  - Oatmeal cereal over rice cereal
  - Enfamil A.R is thickened with Rice starch
  - Gel-Mix (carob bean gum)

- Reflux medications don’t stop reflux from occurring

- Medications only decreases the acidity, so helpful with GERD
Reflux Medications

- H2-Blocker
  - Ranitidine (Zantac), Famotidine (Pepcid), Cimetidine

- Proton Pump Inhibitors
  - Omeprazole (Prilosec), Pantoprazole (Protonix), Lansoprazole (Prevacid), Esomeprazole (Nexium)

- Try to avoid long term usage
  - Decreases absorption of Calcium, Iron, B12, Mag
  - Increased risk of pneumonia, Cdiff, dementia, acute kidney drug injury
Colic vs Reflux vs CMPA

- Poor weight gain or mucousy/bloody stools -> Tx for CMPA
- Growing well with normal stools, but baby fussy/vomiting
  - Reassure/Treat for Colic and/or Reflux
- Trial of extensively hydrolyzed formula helped fussiness/vomiting
  - Continue treating as CMPA, but consider earlier re-introduction or trial back to regular formula
CMPA – Change Formula

- No Soy-based formula due to high cross-reactivity
- Jump straight to extensively-hydrolyzed formula
  - Alimentum, Nutramigen, Pregestimil
- 10% require amino-acid based
  - Elecare, Neocate, Alfamino
- Hypoallergenic formulas taste and smell BAD
- They are expensive ($20 vs $30 vs $45), can last ~2-3 days
Breastfeeding Mom/Child must avoid all foods containing milk and Soy

Must read labels
- Milk, Dairy, Whey, Casein
- Soybean, Soybean oil, Soy lecithin

Milk and Soy in MANY foods
- Soy in many shelf-stable foods (esp baked goods)

French Fries
Ingredients: Potatoes, Vegetable Oil (canola Oil, Corn Oil, Soybean Oil, Hydrogenated Soybean Oil, Natural Beef Flavor [wheat And Milk Derivatives]*), Dextrose, Sodium Acid Pyrophosphate (maintain Color), Salt. *natural Beef Flavor Contains Hydrolyzed Wheat And Hydrolyzed Milk As Starting Ingredients.

Contains: Wheat, Milk.
Common Misconception

- Milk Protein Allergy is NOT the same as lactose intolerance
- Babies DO NOT get lactose intolerance
- Lactose is the carbohydrate/sugar in all mammalian milk, including human breastmilk
- Lactose-intolerance starts earliest at age 2, but many develop it later
- Dairy-free diet is VERY different from lactose-free diet
Chronic FPIES

- Other possible allergens
  - Beef, Eggs, Peanuts, Tree Nuts, Wheat
- No testing available, so is “trial and error”
- The more eliminations, the more restrictive the diet becomes
- Ensure diet has enough calories, proteins and is complete
  - Iron? Vitamin D? Calcium?
- Consider supplementing or temporary holding breastfeed
- Can freeze breastmilk, label it and save for re-introduction
What is left to eat?

- Vegans goods will be dairy and egg free, but most use soy or nuts as substitutes. Daiya is coconut based.
- Pea, Hemp, Oat milk. Vegan protein shake
- Most Fruits and Vegetables, Rice, Potatoe
- Chicken, Pork, Beans, Seafood
- Sunflower Butter, Avocado
- Hypoallergenic Food Companies
  - Red Plate Foods, Enjoy Life, MadeGood
At 9-10 months, Soy Lecithin/Oil then Protein

Goal of vegan birthday cake (using soy)

At 12 months, start “Milk Ladder”
- Baked Dairy (cookie, muffin, pancake)
- Cheese
- Yogurt
- Whole Milk
Milk Alternatives

- At 12 months, switch infant formula to cow milk alternatives
- Give either Soy, Hemp, Oat or Pea (SHOP) Milk
- Rice and coconut milk has almost no protein
- Almond milk is low in both calorie and protein
Not Improving?

- Still failure to thrive?
- Is nutrition significant?
  - May need more than the average caloric needs for age
- Malabsorption stool studies
  - Fat: Fecal fat and elastase
  - Protein: Alpha-1-antitrypsin (not serum)
  - Carbohydrates: Reducing substance
- Most common cause of fat malabsorption is cystic fibrosis
Not Improving?

- Still having bloody stools despite AA formula?
- Consider Flexible Sigmoidoscopy
- Ddx for bloody stools in children
Blood or Not blood?

• Can appear as red blood if vomited or in stool
  • Foods containing red food coloring (Jelly, Kool Aid), tomatoes, strawberries, and beets

• Can appear as melena
  • Blueberries, spinach, licorice, grape juice, and certain medications such as Pepto-Bismol (due to bismuth) and Iron

• Question is best answered with a guaiac
Guaiac is a colorless compound that turns blue when placed in contact with substances that have peroxidase activity (such as heme portion of hemoglobin) and hydrogen peroxide.
“False-positives” with foods containing peroxidase activity
- Red meat, melons, grapes, radishes, turnips, cauliflower, broccoli

“False-negative” with anti-oxidant properties
- Vitamin C
Melena may be seen in patients who have swallowed blood:
- Maternal blood, post tonsillectomy, or epistaxis
- Females on their periods may appear to have hematochezia
- Hematuria may be mistaken for hematochezia
- Can be difficult to distinguish hemoptysis and hematemesis
Where in GI Tract? Upper or Lower?

- **Upper GI bleeding** - proximal to the ligament of Treitz
  - Esophagus, stomach, duodenum
  - Melena – Black and tarry

- **Lower GI bleeding** - distal to the ligament of Treitz
  - Small bowel and colon
  - Hematochezia – Red blood

- Melena can be seen with bleeding from proximal small bowel

- Hematochezia can be seen with massive UGI bleeding

- In infants, hematochezia may be due to an upper GI source owing to shorter intestinal transit time
## Etiologies of UGI Bleeding: In relative order of frequency

<table>
<thead>
<tr>
<th>Newborn</th>
<th>Infant</th>
<th>Child-Adolescent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swallowed maternal blood</td>
<td>Stress gastritis or ulcer</td>
<td>Mallory-Weiss tear</td>
</tr>
<tr>
<td>Vitamin K deficiency</td>
<td>Acid-peptic disease</td>
<td>Acid-peptic disease</td>
</tr>
<tr>
<td>Stress gastritis or ulcer</td>
<td>Mallory-Weiss tear</td>
<td>Varices</td>
</tr>
<tr>
<td>Acid-peptic disease</td>
<td>Vascular anomaly</td>
<td>Caustic ingestion</td>
</tr>
<tr>
<td>Vascular anomaly</td>
<td>Gastrointestinal duplication</td>
<td>Vasculitis (Henoch-Schonlein purpura)</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>Duodenal/gastric webs</td>
<td>Bowel obstruction</td>
</tr>
<tr>
<td>Milk-protein sensitivity</td>
<td>Bowel obstruction</td>
<td>Dieulafoy lesion, hemobilia</td>
</tr>
</tbody>
</table>
# Common Etiologies of Lower GI Bleed based on Age

<table>
<thead>
<tr>
<th>Newborn (Birth – 1 mth)</th>
<th>Infant (1 mth – 2 yr)</th>
<th>Preschool Age (2-5 yr)</th>
<th>School Age (&gt;5 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necrotizing enterocolitis</td>
<td></td>
<td>Anal fissure</td>
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<td></td>
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<td>Malrotation with volvulus</td>
<td>Henoch-Schönlein purpura</td>
<td>Polyp</td>
<td></td>
</tr>
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<td>Hirschsprung disease enterocolitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic proctocolitis</td>
<td>Meckel diverticulum</td>
<td>Inflammatory bowel disease</td>
<td></td>
</tr>
<tr>
<td>Lymphonodular hyperplasia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intussusception</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

From Walker – Lower Gastrointestinal Bleed
## Potential Etiologies of Lower GI Bleed based on History

<table>
<thead>
<tr>
<th>Amount of blood loss</th>
<th>Appearance of bleeding</th>
<th>Characteristics of stools</th>
<th>Pain</th>
<th>Underlying disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small</td>
<td>Red</td>
<td>Hard</td>
<td>Yes</td>
<td>Anal fissure</td>
</tr>
<tr>
<td>Small to moderate</td>
<td>Red</td>
<td>Loose</td>
<td>Variable (abdominal)</td>
<td>Allergic proctocolitis, infectious colitis, hemolytic uremic syndrome, IBD</td>
</tr>
<tr>
<td>Small to moderate</td>
<td>Red</td>
<td>Normal, coated with blood</td>
<td>No</td>
<td>Polyp</td>
</tr>
<tr>
<td>Moderate</td>
<td>Red to tarry</td>
<td>Normal</td>
<td>Yes (abdominal)</td>
<td>Henoch-Schönlein purpura</td>
</tr>
<tr>
<td>Moderate</td>
<td>Red to tarry, currant jelly</td>
<td>Normal</td>
<td>Yes (abdominal)</td>
<td>Intussusception</td>
</tr>
<tr>
<td>Moderate</td>
<td>Red to tarry</td>
<td>Loose</td>
<td>Yes (abdominal)</td>
<td>Hirschsprung disease enterocolitis</td>
</tr>
<tr>
<td>Moderate</td>
<td>Red to tarry</td>
<td>Normal</td>
<td>Yes (abdominal)</td>
<td>Meckel diverticulum, angiodysplasia</td>
</tr>
</tbody>
</table>

From Walker – Lower Gastrointestinal Bleed
## Infectious Colitis

<table>
<thead>
<tr>
<th>Bacterial pathogens</th>
<th>Parasitic pathogens</th>
<th>Viral pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmonella</td>
<td>Entamoeba histolytica</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Shigella</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Campylobacter jejuni</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yersinia enterocolitica</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escherichia coli (esp O157:17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klebsiella oxytoca</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Allergic Proctocolitis

- Food protein (milk/soy) causes an inflammatory enteropathy
- Diagnosis clinically, doesn’t need endoscopy
- On colonic biopsies
  - Focal increase in the number of eosinophils
  - Mucosa architecture is preserved
Inflammatory Bowel Disease

- Chronic architectural changes (atrophy, irregularity and shortening of crypts, thickening of the muscularis mucosae, metaplasia), small intestinal villous blunting, granulomas, increased eosinophils

- The peak incidence of IBD occurs the ages of 15 and 25 years

- ~25 -30% CD and ~20% of UC present before the age of 20
Inflammatory Bowel Disease

- Colitis phenotype is very common in pediatrics
- 90-95% of Ulcerative Colitis and 25% Crohn’s Disease present with rectal bleeding and/or bloody diarrhea
- UC-like disease in younger children labelled with caution because of high probability of subsequent evolution to Chron’s disease

Very Early Onset IBD (VEO-IBD)

- IBD in children <6 years of age
- Infantile IBD in children <2 years
- Very Rare
  - VEO-IBD representing 3% of pediatric IBD
  - 1/3 of these VEOIBD patients are infantile
- Disease severity often is higher
- Likely associated with a gene defects that alter immune function or disturb epithelial barrier function

Very Early Onset IBD DDx/Assc

- Chronic granulomatous disease
- Interleukin-10 (IL-10) signaling defects
- Atypical severe combined immunodeficiency
- Common variable immunodeficiency
- Wiskott-Aldrich syndrome
- Agammaglobulinemia
- Hyperimmunoglobulin M syndrome
- Familial hemophagocytic lymphohistiocytosis
- IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked)
- Autoimmune enteropathy
I: Initial evaluation

- Patient history
- Family history
- Establish IBD-like pathology by upper- and lower-GI endoscopy and histology, small bowel imaging, biochemistry (CBC, CRP, ESR, albumin, consider fecal calprotectin):
  1. Histology
  2. Extent of disease
  3. Disease activity
- Consider/exclude infections such as *Giardia*, CMV, *C. difficile*, TB, HIV, etc
- Consider/exclude other causes of intestinal inflammation such as celiac disease, allergic colitis (CMPA)

II: Functional screening, followed by genetic confirmation strategy

<p>| Children with IBD onset &lt;6 years of age in whom immune deficiency is suspected: |</p>
<table>
<thead>
<tr>
<th>Test</th>
<th>Disease group/syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC</td>
<td>Neutropenia</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Lymphopenia</td>
</tr>
<tr>
<td>Neutrophil oxidative burst assay</td>
<td>CGD</td>
</tr>
<tr>
<td>Immunoglobulins (IgA, IgG, IgM, IgE)</td>
<td>CVID</td>
</tr>
<tr>
<td></td>
<td>Agammaglobulinemia</td>
</tr>
<tr>
<td></td>
<td>Hyper-IgM</td>
</tr>
<tr>
<td></td>
<td>Hyper-IgE</td>
</tr>
<tr>
<td>Lymphocyte subsets (CD3, CD4, CD8, CD19/20, NK cells)</td>
<td>SCID</td>
</tr>
<tr>
<td></td>
<td>Agammaglobulinemia</td>
</tr>
</tbody>
</table>

Selected patients: *

<table>
<thead>
<tr>
<th>Test</th>
<th>Disease group/syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOXP3+ CD25+ CD4+ T cells</td>
<td>IPEX</td>
</tr>
<tr>
<td>XIAP</td>
<td>XLP2</td>
</tr>
<tr>
<td>IL-10 suppression of LPS-induced PBMC activation</td>
<td>IL-10 receptor defect</td>
</tr>
</tbody>
</table>

III: Genetic screening, followed by functional confirmation strategy

Genetic screening:
- Multiple candidate sequencing
- Whole-exome sequencing
- Whole-genome sequencing
Primary Immunodeficiencies

- GI manifestations include intractable diarrhea, malabsorption, failure to thrive, or IBD
- Recurrent, severe or atypical infectious diarrhea
  - Defects in both B and T cells are susceptible to infections by bacterial, viral, and fungal organisms.
  - Bacterial infections are commonly observed in B cell defects.
  - Viral and fungal infections are characteristic of less severe T cell defects.
  - Impaired phagocytosis results in both bacterial and fungal infections.
Primary Immunodeficiencies

- Increased risk for GI autoimmune and inflammatory diseases
  - IBD or IBD-like colitis, PSC, Celiac, Autoimmune hepatitis, pernicious anemia

- Local dysregulation of the GI immune system may result in inappropriate immune responses that lead to autoimmunity or uncontrolled inflammation.

- Ineffective immune responses that do not fully clear invading pathogens, can further provoke further inflammation

- Selective IgA deficiency increased risk of celiac disease
Chronic Granulomatous Disease (CGD)

- Defects in the phagocyte’s nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex, which generate reactive species of oxygen for its respiratory burst
- Inability of phagocytes (neutrophils, monocytes, and macrophages) to destroy certain microbes
- Recurrent bacterial and fungal infections caused by catalase-positive microorganisms
  - Aspergillus species
  - S. aureus
  - Burkholderia (Pseudomonas) cepacian complex
  - Serratia marcescens
  - Nocardia species
Chronic Granulomatous Disease (CGD)

- Common infections: Pneumonia, Abscesses (skin, perianal, liver), Suppurative adenitis, Osteomyelitis, Bacteremia/fungemia, Cellulitis/impetigo

- Inflammatory granuloma formations, especially in hollow organs like lungs, GI and GU tracts
  - 30-40% of patients have colitis

- Neutrophil Oxidative Burst Assay
  - Needs a control sample from a healthy un-related adult

- Treatment with prophylactic antibiotics and antifungals
I: Initial evaluation

- Patient history
- Family history
- Establish IBD-like pathology by upper- and lower-GI endoscopy and histology, small bowel imaging, biochemistry (CBC, CRP, ESR, albumin, consider fecal calprotectin):
  1. Histology
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II: Functional screening, followed by genetic confirmation strategy

| Children with IBD onset <6 years of age in whom immune deficiency is suspected: |
| Test | Disease group/syndrome |
| CBC | Neutropenia, Thrombocytopenia, Lymphopenia |
| Neutrophil oxidative burst assay | CGD |
| Immunoglobulins (IgA, IgG, IgM, IgE) | CVID, Agammaglobulinemia, Hyper-IgM, Hyper-IgE |
| Lymphocyte subsets (CD3, CD4, CD8, CD19/20, NK cells) | SCID, Agammaglobulinemia |

Selected patients:

| Test | Disease group/syndrome |
| FOXP3+ CD25+ CD4+ T cells | IPEX |
| XIAP | XLP2 |
| IL-10 suppression of LPS-induced PBMC activation | IL-10 receptor defect |

III: Genetic screening, followed by functional confirmation strategy

- Genetic screening:
  - Multiple candidate sequencing
  - Whole-exome sequencing
  - Whole-genome sequencing
Monogenic IBD

- Rare genetic disorders that produce IBD-like intestinal inflammation and typically present in infancy - VEO-IBD
- Over 60 unique monogenic IBD disorders have been described, including:
  - Epithelial barrier and response defects (eg, IKBKG, TTC7, ADAM17)
  - Dysfunction of neutrophil granulocytes (eg, NCF2, NCF4, SLC37A4)
  - Hyper- and autoinflammatory disorders (eg, XIAP)
  - Complex defects in T- and B-cell function (eg, LRBA, CD40LG; WAS)
  - Regulatory T cells and IL-10 signaling (eg, IL10R, IL10, FOXP3)

- Some gene defects affect predominantly hematopoietic cells (IL-10R, IL-10, XIAP, FOXP3), so respond to stem cell transplant
IL-10 and IL-10 Receptor Defects

- Interleukin (IL)-10 plays downregulates the inflammatory processes
  - Inhibits production of proinflammatory cytokines like IL-12 and tumor necrosis factor (TNF)
  - Controls the growth and differentiation of a variety of cells in the immune system, including T and B cells, natural killer cells, granulocytes, and endothelial cells

- VEO-IBD with severe and progressive colitis, perianal involvement, extraintestinal manifestations including folliculitis and arthritis

- IBD treatments often need to be very aggressive, and still not be sufficient

- Hematopoietic stem cell transplantation has been successful
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Nodular Lymphoid Hyperplasia (NLD)

- Benign condition found in many healthy individuals, especially children. Many consider it a normal finding if there’s no other abnormality.
- But also found in allergic enterocolitis and immunodeficiencies.
- Lesions usually located in the small intestine, but sometimes in colon or stomach.
- Lesions can thin the mucosa and predispose it to ulceration and irritation, causing hematochezia.
- Blood loss is usually minimal and painless, but is present in multiple stools.
- Resolves spontaneously over time/age.
Nodular Lymphoid Hyperplasia (NLD)

Isolated NLD

Allergic Colitis

Nodular Lymphoid Hyperplasia (NLD)

In patient with CVID and Refractory Giardiasis

Growing well with normal stools -> Colic / Reflux
Responded to hypoallergenic formula -> CMPA / FPIES
Poor weight gain or mucousy / bloody stools -> CMPA / FPIES
Bloody diarrhea despite AA formula -> VEO-IBD
Diagnosed with VEO-IBD -> Immunodeficiency and Genetic w/u
Thank You!

Doernbecher Children's Hospital