Disclosures

• I have nothing to disclose
Objectives

• What is unique about pediatric IBD
• What does a primary care provider need to know when treating children with IBD
• How pediatric IBD researchers are advancing our understanding of IBD
Inflammatory Bowel Diseases
Pediatric IBD is Common

- Wisconsin Children¹
  - 9.9 in 100,000
  - Approximately 1500 children in WI
- USA
  - 1 – 1.5 million
  - 100,000 children
- Type 1 Diabetes
  - 150,000 children

¹. Adamiak, T et al. Inflammatory Bowel Disease 2013
Pediatric versus Adult IBD

- More Severe Phenotype
  - Pancolitis is more common in children with UC
    - 80-90 % vs. 60 %
  - More aggressive
    - More difficulty in achieving steroid independence
- Colon only involvement more common with CD
  - 2/3’s of children with CD vs 30% of adults
- Male to Female ratio in CD
  - 1.6 : 1 vs. 1 : 1 in adults
Very Early Onset IBD (VEOIBD)

- Paris Classification (< 10 years)
- Earlier
- Unique phenotype
- Is it really something else
VEOIBD

• Many primary immunodeficiencies look like IBD
  • Advances in genomics has greatly expanded our ability to understand *these diseases*
  • WES
  • WGS
  • Custom sequencing panels
• NEOPICS
• Mayo Clinic Center for Individualized Medicine
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<th>Syndrome/disorder</th>
<th>Gene</th>
<th>Inheritance</th>
<th>CD-like</th>
<th>UC-like</th>
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<th>Disease location (1-5)</th>
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Gastroenterology 2014; 147:990-1007
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NOTE: Genetic defects are grouped according to functional subgroups. Gene names refer to HUGO gene nomenclature. CD-like and UC-like were marked only when patient characteristics in the original reports were described as typical CD or UC pathologies. Unclassified or indeterminate colitis is the not specified default option. Disease location is classified as follows: 1, mouth; 2, enteroptathy; 3, enterocolitis; 4, isolated ileitis; 5, colitis; 6, perianal disease. Epithelial defects refer in particular to finding of epithelial lining nonadherent at the basal membrane or increased epithelial apoptosis and epithelial tufting. Key laboratory findings are provided in Supplementary Table 1, and examples of additional defects of possible or unclear relevance are listed in the Supplementary Information for Table 1.

HLH, hemophagocytic lymphohistiocytosis; AR, autosomal recessive; eb, epidermolysis bullosa; X, X-linked; A, arthritis; vas, vasculitis; n, nail; h, hair; AD, autosomal dominant; e, eczema; f, folliculitis/pseudofolliculitis; SJ, Spiegel syndrome; p, pannis; AIAH, autoimmune hemolytic anemia; AN, autoimmune neutropenia; PBC, primary sclerosing cholangitis; HT, Hashimoto thyroiditis; AIAH, autoimmune hepatitis; TID, type 1 diabetes mellitus; MAS, macrophage activation syndrome; NSIP, non-specific interstitial pneumonitis; S, serositis.

*Personal information and communication.
Back to Practical Matters

- The care of children with IBD requires collaboration between
  - Patient and family
  - Primary care providers
  - Gastroenterologist
  - School
  - Other specialists
    - Endocrinology
    - Surgeon
    - Psychology
    - Social Worker
    - Dermatology

- Urgent and primary care issues often are related to medications
5-Aminosalicylates

- “Safest”
- Least effective
  - Mild to moderate UC
- Sulfasalazine, mesalamine, olsalazine, balsalazide
- What could possibly go wrong?
5-ASA’s

• Common
  • Headache, GI
  • Allergic
    • Sulfa
    • Mimic IBD flare
    • Interstitial nephritis
  • Pancreatitis

• Rare but important
  • Stevens-Johnson syndrome
  • Pneumonitis
  • Hemolysis
5-ASA’s: What might I see in my office?

- Reaction can mimic IBD flare
- Renal toxicity
  - We *should* be monitoring for this
- Pancreatitis
Case number 1

- 16 y/o Febrile male
- Sick for 2 days, Fatigue, sore throat
- Mono exposure
- Temp 102, Non-toxic
- Pharyngitis, hepatosplenomegaly
- PMH: Crohn’s in remission on 6-mercaptopurine
- What to do?
Thiopurines

- 6-mercaptopurine, Azathioprine
- Spectacular pediatric data
- Slow onset of action

Thiopurines

- Monitoring
  - Myelosuppression
  - TPMT
  - CBC, ALT/AST
- Early (first 6 weeks)
  - Rash, fever, flu-like symptoms
  - Pancreatitis
- Hair loss (very rare), telogen effluvium common in CD
- Over half a century of pediatric experience
Thiopurines: *The Ugly*

- Lymphoma
  - Hepatospleno-T-cell Lymphoma
- Lymphoproliferative disorders
  - HLH associated with infections (EBV)
- Non-melanoma skin CA’s
- HPV
Thiopurines

• Can I immunize?
  • Myth: “Immunosuppressed so won’t respond”
  • Truth: No live vaccines

• How immunosuppressed is my patient?
  • Mixed reports on infection risk (small)
Case number 1

- 16 y/o Febrile male
- Sick for 2 days, Fatigue, sore throat
- Mono exposure
- Temp 102, Non-toxic
- Pharyngitis, hepatosplenomegalgy
- PMH: Crohn’s in remission on 6-mercaptopurine

- What to do?
Mono-like illness on 6-MP

- CBC
- Liver enzymes
- Ferritin
- Leukopenia, transaminitis
- Supportive care, held 6-MP
- Better, restart
Methotrexate

- Folate analog
- Crohn’s > UC
- SQ or PO
- Increased usage following association of HSTCL with thiopurines
Methotrexate

• GI symptoms esp. around time of dose
  • Folate supplement
  • Oral ulcerations: vs herpes vs IBD
• Myelosuppression
• Hepatotoxicity
• Dosing misadventures: WEEKLY dosing not daily
• Risk of infection probably similar to thiopurines
Methotrexate: The ugly

- Fibrosing pneumonitis
  - Insidious onset
  - Chronic cough
- TERATOGENICITY
- Inadequate IBD data RE: malignancy risk
Anti-TNF biologics

- **Infliximab (IFX)**
- **Adalimumab (ADA)**
- **Golimumab**
- **Certolizumab pegol (CZP)**

**Legend:**
- Green = murine
- Orange = human

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Anti-TNF biologics

- Particularly effective for fistulizing disease
- Improves growth rapidly
- Used to induce and maintain remission
- Who should receive this up front?
Anti-TNF biologics

- Infusion reactions (infliximab)
- Localized skin reactions (injectables)
- Psoriatic eruptions
- Anti-bodies to agent
  - Avoid episodic use
Anti-TNF biologics: The Ugly

- Auto anti-body formation
  - Lupus-like reactions
- Delayed hypersensitivity reactions
- Serum sickness-like reactions
- Leukemias and lymphomas
  - HSTCL black box warning
- Skin cancers
Case number 2

- 16 y/o male
- Crohn’s disease, surgery 18 mo ago
- On infliximab
- Fever since last night
- “Worst I’ve ever felt”
- T = 104
- No focus of infection
Anti-TNF biologics: The uglier

- Infections
  - TB
  - Hepatitis B
  - Histo
  - Other unusual organisms
Calcineurin inhibitors

• Tacrolimus, cyclosporine
• Rescue therapy for UC
• Small amount of data for CD
• Often requires high levels to get satisfaction
  • Higher risk of toxicity
Calcineurin inhibitors: The ugly

- Hypertension
- Elevated LFT’s
- Gingival hyperplasia, hirsutism, coarsening facial features
- Metabolic
  - Hypomagnesemia
  - Hypocholesterolemia
  - Hyperglycemia
- Nephrotoxicity
Calcineurin inhibitors: The ugly

• Opportunistic infections
• PCP prophylaxis
• Monitoring for metabolic disturbances, renal toxicity
• Monitoring drug levels
• Bridge to something else
CCFA Sponsored Clinical Research Network: PRO-KIIDS

1200 children with Crohn’s at diagnosis: RISK Study

Study:
Genetics
Bacteria in bowel
Immune reactivity to bacteria, food, infections etc
Environmental Exposures

3 years
160 – 200 patients with complication / surgery

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The Next Step

- Ulcerative Colitis
- Bio specimens
  - Sera
  - DNA
  - Tissue
  - Stool
- Protocoled therapy
- Mesalamine
Quality Improvement--ImproveCareNow

66 centers, 34 states and England
535 pediatric gastroenterologists
18,700 children with IBD
Conclusion

• Pediatric IBD is common
• Patients with IBD may require individualized management of common medical problems
• Pediatricians are leading the advancement of our understanding of the pathogenesis and treatment of IBD