PEDIATRIC INFLAMMATORY BOWEL DISEASE: FUNDAMENTALS AND FUTURE INSIGHTS
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Disclosure

- Jay N. Shah, DO, MPH, has no relationships with commercial companies to disclose.

Learning Objectives

- At the end of this presentation the participant will be able to:
  1. Identify the history/epidemiology of pediatric IBD
  2. Demonstrate understanding of the basic management of IBD
  3. Understand areas of health supervision
  4. Characterize future areas of research in the field

UC historical origins

- Dr. Matthew Baillie, Scottish physician (1761-1823)
- Samuel Wilks (London, 1875): case report of young woman with severe bloody diarrhea; ulceration and inflammation of entire colon

Crohn’s historical origins

- In 1612 Gullelmus Fabricius Hildenus noted at autopsy in a boy who had died after persistent “abdominal pain” and diarrhea that “the ulcerated cecum [was] contracted and invaginated into the ileum.”
- G.B. Morgagni in his 1769 “De Sedibus et Causis Morborum” described ulceration and perforation of an inflamed distal ileum and enlarged mesenteric lymph nodes in a young man of 20 with a history of diarrhea and fever culminating in death after 14 days.
- Abraham Colles of Dublin in 1830 described Crohn’s disease among children and the complicating perianal, rectovaginal and rectovesical fistulas.
- In 1889 Samuel Fenwick, in a 27 year old woman with a history of diarrhea and weight loss, at autopsy observed “adherent loops of intestine with a communication between the cecum and adherent small intestine…”

Crohn’s historical origins

- Etiologic speculation included bacteria, viruses, abdominal trauma and impaired vascular and lymphatic circulation
- First described in 1932 by Burrill Crohn, Leon Ginzburg, and Gordon D. Oppenheimer in JAMA
  - “Regional ileitis: A Pathologic and Clinical Entity”
  - 14 patients with diarrhea, weight loss, abdominal pain
  - Showed that symptoms were not from tuberculosis
- Epidemiological approach to IBD began in the 1950s
  - 1st population study for UC (1961-1966), for Crohn’s (1956-1967)
  - Baltimore, U.S. in 1960s (Mendeloff, et al)
IBD statistics

- Incidence (new cases)
  - Crohn’s: 10.7 per 100,000 people; 33,000 per year
  - UC: 12.2 per 100,000 people; 38,000 per year
- ~1.7 million people with IBD in U.S.
  - Crohn’s: ~780,000; UC: ~910,000
- UC with male predominance; Crohn’s equal
- Limited data on racial impact; race appears to have impact on extra-intestinal manifestations
  - AA – uveitis
  - Hispanics – erythema nodosum

Pediatric IBD Incidence

- 5-25% of IBD diagnosed in pediatric age
- Overall incidence of IBD: 9.5 per 100,000
- Stable over past 8 years

Etiology

- Genetic Predisposition
- Immune System Disturbance
- Environmental Triggers

Ulcerative colitis

- Clinical
  - Continuous inflammation from rectum with related symptoms
  - Atypical (↑ in pediatrics)
    - Macrosopic rectal sparing/skip lesions
    - Periappendiceal inflammation
    - Backwash ileitis
    - Upper GI inflammation (50%)
- Incidence: 2.8 per 100,000 person years in children
  - ¼ the rate of Crohns in children
  - 12% of UC patients present before 20 years old
Mucosal integrity
- Goblet cells (form mucous layer)
  - UC patients have thinner, more variable mucosal layer
- Genetic (Family history in 20% of patients)
  - CDH1: encodes E-cadherin (mediates intercellular adhesion)
  - HNF4A: regulates expression of adherens junction, tight junction, and desmosome
  - IL1, IL7, IL8, IL12
  - DAP kinase (a negative regulator of autophagy)
- Immune
  - pANCA, ASCA, anti-CBir may be positive
- Dysbiosis
  - E. coli induces colitis in IL-2 knockout mice

Etiology

- Mild: PUCAI 10-34
  - oral 5-ASA (mesalamine/sulfasalazine), 50-100 mg/kg/day
    - sulfasalazine: inexpensive, but ↑ allergic reactions, photosensitivity, and needs folic acid supplementation
    - Balsalazide: split by colonic bacteria → release mesalamine

Treatment

- Moderate: PUCAI 35-64
  - Induction
    - Prednisone
    - Budesonide
  - Maintenance
    - 5-ASA
    - 6MP/Azathioprine
    - Side effects: hepatotoxicity, pancreatitis, bone marrow suppression, lymphoma, melanoma
    - At one year, 50-75% are steroid free
  - Anti-TNF-α agents
    - Remicade
    - Humira
Ileal Pouch-Anal Anastomosis

- Required in 25-30% of UC patients
- Excellent post-operative quality of life (similar to general population)
- 6-7 Bowel Movements per day
  - 1-2 in the evening
- Daytime continence
- Rare night time incontinence

Pouchitis

- Incidence:
  - Adults
    - Acute pouchitis 25-40%
    - Chronic pouchitis 10-15%
  - Children
    - Acute pouchitis 35-49%
    - Chronic or recurrent pouchitis 10%

- Treatment:
  - Acute: ciprofloxacin > metronidazole
  - VSL #3 more effective than placebo for prevention and chronic pouchitis

Crohn's disease

- Can affect any part of GI tract
- Most common site: ileum
- Presenting signs: diarrhea, abdominal pain/cramping, fatigue, weight loss, loss of appetite, fever, joint pain, skin lesions

PCDAI

<table>
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<tr>
<th>Parameter</th>
<th>Score</th>
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<tbody>
<tr>
<td>Emorbidities</td>
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<td>Weight</td>
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<td>Height</td>
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<td>Age</td>
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<tr>
<td>Steroid use</td>
<td>0</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>0</td>
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</tbody>
</table>

**Example Calculation**

- Weight: (100 - 5) = 95
- Height: (100 - 3) = 97
- Age: 2
- Steroid use: 1
- Hospitalization: 0

**Total Score:** 95 + 97 + 2 + 1 + 0 = 195

**Normal:** 200-550

**Severe:** > 550
Crohn's disease

- Localization
  - UGI (proximal to ligament of Treitz)
  - ileal
  - ileocolonic
  - colonic
  - perianal
- Behavior
  - stricturing
  - penetrating
  - perianal

Crohn's disease vs UC

- Patchy distribution
- Transmural inflammation
- Granulomas on tissue histology
- Association with smoking
- Extra-intestinal manifestations
- Association with weight loss/growth delays
- Intestinal stenosis, fistula, abscess, perianal skin tags, oral aphthous ulcers

IBD serologic markers

- Antibodies against variety of antigens (neutrophil, yeast, bacteria, fungi); many still under investigation
- May be helpful differentiating IBD from non-IBD, UC from CD
- May also help predict disease course, medication responsiveness, prognosis
- Not clearly linked to pathogenesis, probably reflect loss of immune tolerance

Disease location/behavior

- ASCA (specific for CD) — marker of small bowel disease, magnitude may predict stricturing phenotype, early complications
- pANCA — marker of colonic disease and UC-like phenotype, negative predictor for surgery, pouchitis
- Anti-CBlr1, anti-OmpC, anti-I2 — associated with penetrating/stricturing, more likely to require small bowel surgery
- Multiple positive \(\rightarrow\) more aggressive disease
pANCA or CBir1 positivity increases risk for acute pouchitis

Fleshner P. Clin Gastro Hep. 2008

TPMT activity

- Determines risk for myelosuppression
- 10% with low activity
- 0.3% with negligible activity
- Increasingly the standard of care to obtain an activity level prior to starting therapy

What are the main side-effects of 6MP/Azathioprine? (Adult Data)

<table>
<thead>
<tr>
<th>Event</th>
<th>Estimated Frequency (annual)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop therapy due to adverse event</td>
<td>11% (11/100)</td>
</tr>
<tr>
<td>Allergic reactions</td>
<td>2% (2/100)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2% (2/100)</td>
</tr>
<tr>
<td>Hepatitis/abnormal liver tests</td>
<td>2% (2/100)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>3% (3/100)</td>
</tr>
<tr>
<td>Serious infections</td>
<td>5% (5/100)</td>
</tr>
<tr>
<td>Non-Hodgkin's lymphoma</td>
<td>0.04% (4/10,000)</td>
</tr>
</tbody>
</table>

Siegel, CA. Practical Gastroenterology 2007; 30(11): 14-24. With courtesy of Corey A. Siegel, MD, MS

Infliximab/Adalimumab

- Recombinant chimeric mouse/human monoclonal antibody (IgG1)
  - anti TNF-α
- Remission
  - induced in 50% of patients with moderate-severe UC/CD
Adalimumab for Induction and Maintenance in Pediatric CD

Clinical Response (PCDAI decrease ≥ 15 points)

Clinical Remission (PCDAI decrease < 10 points)

SONIC Clinical Remission Without Corticosteroids: Week 26

What are the main side-effects associated with anti-TNF therapy? (Adult Data)

Infection

- Thiopurines most linked to viral infections; anti-TNF agents more linked to bacterial, fungal infections
- Crohn’s Therapy, Resource, Evaluation and Assessment Tool registry: increased risk of serious infection with anti-TNF therapy (OR = 1.43, 95% CI 1.11-1.84)
- Other studies have shown a less pronounced risk, or no increased risk at all

Viral infection

- Most common: URIs (same as general population)
- Continue medication, unless high fever or concerns for dehydration (temporarily stop immunosuppression, restart as viral symptoms resolve)
- Viruses more common with thiopurines than anti-TNF
- EBV particularly concerning (lymphoma, mononucleosis, hepatitis, bone marrow suppression, HLH)
- Recommend stopping (and not restarting) thiopurines in male patients with new-onset EBV mononucleosis; recommend stopping and restarting thiopurines after recovery from acute infection in female patients
Viral infection

- HPV: cutaneous and anogenital lesions in IBD patients on immunosuppression (warts)
- Prospective study of 230 patients, significant increase in viral warts in those receiving AZA/6-MP compared to those off immunosuppression (17.2% vs 3.3%, P=0.004)
- Increase in abnormal pap smears compared to controls (42% vs 7%, P<0.001)
- Recommend regular gynecologic exams for female IBD patients; HPV vaccine to all patients before starting immunosuppression

Viral infection – CMV

- Corticosteroids and cyclosporine have been linked with CMV activation in IBD patients
  - Anti-TNFs not associated; conflicting data regarding association between thiopurines and CMV activation
- CMV reactivation:
  - 1) Localized to colon, no systemic disease
  - 2) CMV infection with viremia, without intestinal involvement
  - 3) CMV systemic disease, including the colon

A Systematic Review of Factors That Contribute to Hepatosplenic T-Cell Lymphoma in Patients With Inflammatory Bowel Disease

- 100-200 cases of HSTCL reported at time of publication
  - 36 cases involving IBD patients receiving thiopurines
  - 20 of 36 cases received anti-TNF therapy (all 20 received infliximab, 4 also received adalimumab after infliximab)

Absolute risk on thiopurines
- 1:45,000 for all patients
- 1:7404 for men younger than 35
- Absolute risk on thiopurine + anti-TNF
  - 1:22,000 for all patients
  - 1:3534 for men younger than 35
  - “Caution in prescribing combination therapy to male IBD patients age 35 years and younger is recommended and in this specific population should be considered only in cases in which a clear benefit is expected.”

Stopping, Continuing or Restarting Immunomodulators and Biologics When an Infection or Malignancy Develops

- Ejay M. Sweger, MD, MPh and Miguel Riquelme, MD

Note 5: Summary of Demographic Characteristics and Outcomes of Patients With IBD and HSTCL

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Malignancies

- No increased risk in developing solid tumors from thiopurines or anti-TNFs, nor with recurrence
- Lymphoma — most associated with thiopurines; biologics marginally increased risk when used in combination
  - Exception: 1) HSTL – higher risk in combination
  - 2) Acute EBV-related lymphoma rare (0.1/1000 patient-years, much higher if male – 3/1000 patient-years)
  - 3) ~PTLD – usually older than 30 years
    - Unlike acute EBV mononucleosis lymphoma, patient has been exposed to EBV in past and have Ig’s to EBV

Pediatric Prevalence of EIM

<table>
<thead>
<tr>
<th>Total</th>
<th>CIP</th>
<th>UC</th>
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<tbody>
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</tbody>
</table>

Pediatric Prevalence of EIM

- Total: 200
- CIP: 198
- UC: 86

Peripheral arthropathies in IBD

- Inflammatory arthritis – pain, swelling of joint, warmth of joint, increased fluid with decreased joint mobility
- Ankles, knees, elbows and hips most common
- Peripheral joints > axial
- Can occur before, during or after IBD diagnosis
- Affect 26% of pediatric IBD patients
- Type 1 correlates with active bowel disease

Eye abnormalities

- Uveitis
- Episcleritis
- Scleritis

Hepatobiliary Manifestations of IBD

| Table 2. HPS Manifestations Associated with IBD
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>IBD Manifestation</td>
<td>Literature/Clinic</td>
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<tr>
<td>-------------------</td>
<td>-------------------</td>
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<tr>
<td>Primary sclerosing cholangitis (PSC)</td>
<td>+/– (+/– Cryptic or Blandstein)</td>
</tr>
<tr>
<td>Small duct PSC</td>
<td>+/– (+/– Cryptic or Blandstein)</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>+/– (+/– Cryptic or Blandstein)</td>
</tr>
<tr>
<td>Extrahepatic cholangitis</td>
<td>+/– (+/– Cryptic or Blandstein)</td>
</tr>
<tr>
<td>Pancreatitis (type 1)</td>
<td>+/– (+/– Cryptic or Blandstein)</td>
</tr>
<tr>
<td>Gallstones</td>
<td>+/– (+/– Cryptic or Blandstein)</td>
</tr>
<tr>
<td>Portal vein thrombosis and hepatic failure</td>
<td>+/– (+/– Cryptic or Blandstein)</td>
</tr>
<tr>
<td>Drug-induced hepatitis (autoimmune, cryptogenic)</td>
<td>+/– (+/– Cryptic or Blandstein)</td>
</tr>
<tr>
<td>Rejection of transplant B (cryptogenic)</td>
<td>+/– (+/– Cryptic or Blandstein)</td>
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<tr>
<td>Drug-induced pancreatitis (cryptogenic)</td>
<td>+/– (+/– Cryptic or Blandstein)</td>
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<td>Benign eventualities</td>
<td>+/– (+/– Cryptic or Blandstein)</td>
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<tr>
<td>Adenomatous polyps</td>
<td>+/– (+/– Cryptic or Blandstein)</td>
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<tr>
<td>Hepatitis C</td>
<td>+/– (+/– Cryptic or Blandstein)</td>
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<tr>
<td>Gallbladder polyps</td>
<td>+/– (+/– Cryptic or Blandstein)</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>+/– (+/– Cryptic or Blandstein)</td>
</tr>
</tbody>
</table>

Bourikas et al, 2009
Bourikas et al, 2009
Dotson et al, 2010
D weiter et al, 2011
Navaneethan et al, 2010
**Erythema nodosum**
- Rapid onset
- Bilateral, multiple, symmetric, warm, red, and painful nodules
- Most common site is the anterior lower extremity
- Fever, malaise, and joint pain may occur
- Typical course lasts for 3–6 weeks without ulceration and scarring of the skin.
- Biopsy specimens show immune complex depositions in subcutaneous fat
- Affects women more than men
- Associated with colonic IBD
- CD>UC
- Associated with arthritis

Yuksel et al, 2008

**Pyoderma gangrenosum**
- Initially a painful, erythematous skin lesion, followed by pustule formation and rapid ulceration
- Later evolves into an erythematous border surrounds a sterile, necrotic center
- Occurs with uveitis and arthritis
- Can occur anywhere on the body

Yuksel et al, 2008

**Aphthous stomatitis**
- Most common lesion in IBD (4-20%)
- Responds to IBD therapy
- Does not have a vesicular stage (unlike HSV and coxsackie virus)
- Topical lidocaine can give symptom relief

Larsen et al, 2010

**Perianal fistula – Pathophysiology**
- Two general theories
  - Pressure from fecal passage extends existing fissures or ulcers.
  - begin with the development of a microabscess in an infected rectal gland that subsequently extends.
- Genetics
  - IBD5 locus on chromosome 5q31
  - IRGM gene that is involved in autophagy.
Health Supervision

- Frequency of office visits: q 4-12 months
- Height, weight, BMI
- Thorough history/physical exam
  - Skin lesions (EN, NMSC)
  - Skin color, pruritus (PSC, AIH)
  - Visual changes (uveitis); ophtho exam q 1-2 years
  - Perianal region (tags, fissures, fistulae)
  - Oral aphthous ulcers
  - Documentation of Tanner staging (growth delay)
Health Supervision

- **Labs**
  - CBC, ESR/CRP, LFTs
  - UA (interstitial nephritis on ASA therapy)
  - Fecal calprotectin/lactoferrin (correlates with clinical and endoscopic indices of disease activity)

- **Nutritional assessment**
  - CD patient at risk for macro/micro nutrient deficiencies
  - Iron deficiency
  - B12 and folate with TI involvement
  - Significant bowel disease: zinc deficiency

- **Bone health**
  - Affected by nutritional deficiencies, physical inactivity, inflammatory cytokines, glucocorticoids
  - DXA to determine bone mineral density; further eval with bone age, serum Ca, iCa, Phos, Mg, PTH, vitamin D; possible referral to pediatric endocrinologist for bone-active agents
  - Likely role of vitamin D with modulation of immune system (north-south geographic distribution)

- **Mental health**
  - Depression has been correlated with pain, diarrhea, weight loss, and elevated ESR
  - Screening studies suggest 25% of pediatric IBD patients display depressive symptoms
  - Children’s Depression Inventory as screening tool (5 mins, score ≥10 should prompt referral to mental health professional)
  - Cognitive behavioral therapy has been shown to be effective
  - 504 plan

- **Immunizations**
  - Recommend immunization with all inactivated vaccines (diphtheria, pertussis, acellular tetanus, HBV, H. flu, inactivated polio, influenza, pneumococcus, MCV; followed by HPV and meningococcal)
  - If on immunosuppressants, NO live vaccines (rotavirus, MMR, intransal flu, Varicella)
  - If no history of Varicella or immunization, vaccinate prior to initiation of immunosuppressive therapy (conversely, at least one month after stopping steroids)
  - HbsAb negative prior to anti-TNF therapy

- **Genetic counseling**
  - CD with higher risk with first-degree relative than UC
  - Overall risk of developing IBD in offspring of affected parents: 5-10x general population
  - Phrasing: ~0.5% risk in gen pop = ~5% risk
  - Overall likelihood of colon cancer (6%) and breast cancer in women (12%)

- **Exclusive enteral nutrition**
  - Can be used as primary therapy in children with mild to moderate CD for induction of remission; comparable efficacy compared with children treated with corticosteroids
  - Ensure, Pediasure, or Boost at 120% RDA; typically 1.5kcal/mL
  - Induction in response typically takes 6 weeks
  - Alternative options: 80% nutritional therapy; overnight NG feeds

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Gut microbiota

- Bacterial numbers: ~1 trillion/g luminal contents in colon
- Absence of colitis in germ-free mice; subsequent immune-mediated colitis in presence of microbiota
- Alteration of intestinal microbiota with probiotics (Lactobacillus GG, VSL#3)

PRO-KIIDS

- Pediatric Resource Organization for Kids with Inflammatory Intestinal Digestive Diseases
- Large scale, multi-center
- Two current studies
  - RISK
  - PROTECT

PROTECT

- 5 year study, enrolling 430 children newly diagnosed with UC
- Monitoring response to mesalamine and prednisone
- Blood, stool, biopsy specimens
- Understand the effects of genetics, mechanisms of inflammation, vitamin D and microbiome on clinical outcomes

RISK study

- 47 pediatric IBD centers throughout US and Canada
- Cohort of 1300 children with initial diagnosis of CD, followed for at least 3 years
- Idea: About 15% of children with new CD progress to complicated disease (stricturing/perforating) within 3 years – which ones will do this? (i.e., can we develop a risk stratification model?)
- Immunochip with over 200,000 SNPs
- Serum immune markers (ASCA, ompC, CbIr, etc)
- Banking of DNA/plasma, stool, mucosal biopsies

Microbiome Initiative

- Identifying the components, genes and metabolic products of intestinal bacteria and viruses in normal healthy people,
- Comparing the bacterial and viral species, genes, and metabolic products in IBD patients with those of people without IBD to identify unique differences in IBD patients,
- Developing bioinformatic techniques to analyze these data sets so that all IBD investigators can effectively utilize the results, which will be in public databases accessible to all investigators
- Developing a gene chip that can easily be used by IBD investigators to determine if a functional gene is present in a clinical or experimental sample.

NEOPICS

- The interNational Early Onset Pediatric IBD Cohort Study
- International consortium to identify and investigate the causes and develop new treatments for very young children and infants with IBD
- 51 centers on 5 continents
Clinical Features of VEO-IBD

- **VEO-IBD**
  - Colon involved:
    - 80% < 10 yrs of age
    - Decreases with age
  - Ileum involved:
    - Rare at <10 yrs of age
  - Positive FH – 40-50%
  - Strictures – 20-46%
  - Surgery – up to 71%
  - Extension of disease – up to 40%
- **Adult IBD**
  - Solitary colonic involvement:
    - <20%
  - Ileal involvement:
    - up to 80%
  - Positive FH – 14-20%
  - Strictures – 29-40%
  - Surgery – up to 55%
  - Extension – up to 16%

VEO-IBD

- **Cause**
  - Environmental, gut bacteria, abnormal immune response, genetics
  - IL10R pathway, NAPDH oxidase genes, rare SNPs (CYBB, NCF1)
- **Treatment**
  - No treatment guidelines
  - Cautious about surgery – extensive colonic disease → small bowel
  - Whole exome sequencing may ultimately provide clue

Questions?