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PEDIATRIC GASTROENTEROLOGY, HEPATOLOGY & NUTRITION
GRAND ROUNDS 2016

DISCLOSURES

I have no actual or potential conflict of interest in relation to this presentation and no relationships with commercial companies to disclose.

I will be discussing “off-label” uses of the following medications:
• Vedolizumab or Entyvio

EDUCATIONAL OBJECTIVES

• Discuss epidemiology & pathogenesis of pediatric IBD
• Discuss initial and follow-up management
• Learn the effects of IBD on growth & development
• Review the role of C. difficile in pediatric IBD
• Review therapeutic agents & evolving practice guidelines
• Introduce newer agents in the pipeline
• Discuss the role of diet & enteral nutrition
• Review NASPGHAN guidelines for primary health supervision of children & adolescents with IBD

LEARNING OBJECTIVES

At the end of this presentation the participant will be able to:
1. IDENTIFY THE CHALLENGES IN PEDIATRIC IBD
2. RECOGNIZE DIAGNOSTIC AND THERAPEUTIC ADVANCES IN IBD MANAGEMENT
3. REFER TO EVOLVING PRACTICE GUIDELINES IN PEDIATRIC IBD

EPIDEMIOLOGY OF PEDIATRIC IBD

• Incidence & Prevalence:
  • ~71 per 100,000
  • ~5–7% annual increase in incidence

• Initially Caucasian >> Asian/African American but environmental factors ⇒ “equalizing” role

• Overcrowding, ↑ # siblings, personal hygiene, dietary patterns

• “Hygiene hypothesis” ⇒ exposure to childhood infection confers protection (~AI d/s)

“HYGIENE HYPOTHESIS” IN IBD

Use of antibiotics ⇒ infections early in life
↓
Intestinal dysbiosis
↓
↑ risk for IBD

ANTIBIOTICS AFFECTING INTESTINAL MICROBIOTA

Amin et al. Am J Gastroenterol 2008;103:1039–1041
FAMILY HISTORY IN IBD

Presentation at a younger age (p<0.001); more aggressive clinical course

↑ Probability of anti-TNF use: (50.0 vs 43.4%; p = 0.007)
↑ Probability of intestinal resection: (55.0 vs 32.2%; p = 0.007)

MULTIFACTORIAL ETIOLOGY OF IBD

GUT IMMUNOPATHOGENESIS

- Foxp3+ Treg cells → IL-10 & TGF-β1 – dependent immune regulatory mechanisms

IBD – TYPES AND LOCATION

- Ulcerative Colitis
- Crohn's Disease
- Indeterminate Colitis
**IBD – CLINICAL PRESENTATION**

<table>
<thead>
<tr>
<th>Symptom/Sign</th>
<th>Crohn's Disease</th>
<th>Ulcerative Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Pain</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>++++</td>
<td>+++</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td>Weight loss</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>Growth failure</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Perianal disease</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Mouth ulcers</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Fever</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Anemia</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Arthritis</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

**CROHN’S DISEASE vs ULCERATIVE COLITIS**

<table>
<thead>
<tr>
<th></th>
<th>Crohn’s Disease</th>
<th>Ulcerative Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any portion of GI</td>
<td>Colon only</td>
<td></td>
</tr>
<tr>
<td>Skip areas</td>
<td>Continuous</td>
<td></td>
</tr>
<tr>
<td>Rectal Sparing</td>
<td>No rectal sparing</td>
<td></td>
</tr>
<tr>
<td>Non-caseating granulomas</td>
<td>No granulomas</td>
<td></td>
</tr>
<tr>
<td>Trans-mural inflammation</td>
<td>Mucosal inflammation</td>
<td></td>
</tr>
<tr>
<td>Fistulae and abscesses</td>
<td>Abscesses rare</td>
<td></td>
</tr>
<tr>
<td>Strictures common</td>
<td>Strictures rare</td>
<td></td>
</tr>
<tr>
<td>Ileum and ceum commonly involved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perianal disease</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**IBD - EXTRAINTESTINAL MANIFESTATIONS**

- **HEPATOBILIARY DISEASE**
- **MOUTH SORES**
- **ERYTHEMA NODOSUM**
- **PYODERMA GANGRENOsum**

**IBD - EXTRAINTESTINAL MANIFESTATIONS: EYE**

- **UVEITIS**
- **EPISCLERITIS**

**IBD – PERIANAL DISEASE**

- Perianal abscesses, fistulae and fissures
- Perianal disease is noted in about 30% of children with newly diagnosed Crohn’s disease

Superficial fistulas → Fistulotomy

A noncutting seton → soft rubber tube threaded into the perianal fistula & loosely tied; maintains drainage of the fistula → ↓ risk of perianal abscess

AGA Practice Committee. Gastroenterology 2003;125:1508–1530

NASPGHAN GUIDELINES for the management algorithm of perianal fistula

GROWTH FAILURE IN PEDIATRIC IBD

Increased energy needs
Malabsorption of nutrients
Increased GI losses
Corticosteroids

Growth Failure

Inflammation

Increased GI losses → Malnutrition

Initiation of infliximab therapy:
- ↓ PCDAI scores
- ↑ Trabecular BMD & cortical area z scores

Role of TNFα on bone mineral density

TNFα: negative effects on bone growth
- inhibition of osteoblasts
- activation of osteoclasts

Steroid therapy adds to the injury!

Classification of CD
CLASSIFICATION OF UC

Fecal Calprotectin in IBD

- Uses:
  - diagnosis of IBD
  - monitor disease activity
  - evaluate response to therapy
  - predict relapse
  - post-operative recurrence
  - differentiate IBD from IBS

- Not used in isolation; in combination with other diagnostic modalities
- Sensitivity: 92% & Specificity: 76%
**ROC curve analysis** → detecting endoscopic recurrence

Best cut-off value for FC as a marker of endoscopic recurrence => Optimum sensitivity, specificity & NPV → \(100 \, \mu g/g\)

**Best cut-off value for FC as a marker of endoscopic recurrence**

- Optimum sensitivity, specificity & NPV
- \(100 \, \mu g/g\)

**ALGORITHM FOR MONITORING OF IBD**

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMAGING STUDIES</td>
<td></td>
</tr>
<tr>
<td>• Upper GI series w/ SBFT</td>
<td>→ Provides limited information about the presence or extent of extramural or mesenteric disease</td>
</tr>
<tr>
<td>• Abdominal and pelvic CT scan</td>
<td>→ Direct visualization of the extent of bowel wall inflammation and peri-intestinal involvement</td>
</tr>
<tr>
<td></td>
<td>→ Uses radiation</td>
</tr>
<tr>
<td>• Abdominal US</td>
<td>→ Identification of wall thickening or abdominal/pelvic abscesses</td>
</tr>
<tr>
<td></td>
<td>→ Less expensive, avoids radiation</td>
</tr>
<tr>
<td></td>
<td>→ Requires technical expertise in IBD</td>
</tr>
<tr>
<td>• Magnetic Resonance Imaging (MRE &amp; pelvic MRI)</td>
<td>→ Diagnostic modality of choice without radiation (cumulative wiped IBD)</td>
</tr>
<tr>
<td></td>
<td>→ Direct delineation of transmural inflammation</td>
</tr>
<tr>
<td></td>
<td>→ Best for evaluation of perianal disease (fistulae/abscesses)</td>
</tr>
</tbody>
</table>

**MR Enterography**

**Abdominal CT Scan**
**ENDOSCOPIC APPEARANCE OF NORMAL TERMINAL ILEUM AND COLON**

- Smooth and shiny villi seen
- Lymphoid follicles (Peyer’s patches)
- Normal vascular pattern
- No mucosal friability/erosions

**ENDOSCOPIC APPEARANCE OF CROHN’S DISEASE**

- Deep fissures
- Cobble-stoning
- Segmental distribution
- Relative rectal sparing
- Terminal ileum involvement
- Granulomas on biopsy

**ENDOSCOPIC APPEARANCE OF ULCERATIVE COLITIS**

- Loss of vascular pattern
- Granularity with erosions
- Exudates
- Diffuse continuous disease
- No ileal involvement

**CLASSIFICATION OF SMALL BOWEL DISEASE**
IBD HISTOPATHOLOGY

Crohn's disease
Ulcerative colitis

Granuloma
Crypt abscess

THE C. DIFFICILE – IBD CONUNDRUM...

SOLVING THE MYSTERY

THE STATS:

- Multivariate logistic regression analysis for risk of C. diff:
  - Previous hospitalization
  - Antibiotic exposure
  - PPI exposure
  - Type of therapy for IBD

- Having IBD was the only factor that contributed significantly (P = 0.004) to the risk of CDI

CHALLENGES WITH C. DIFFICILE IN IBD

- Symptomatic: ? IBD flare or ? CDI
- C. diff PCR: ↑ sensitivity
- ↓ pseudo-membranes
- High treatment failure rate (57%) regardless of IBD type & Rx of C. diff
- FMT: microbial diversity non-sustainable → ↑ return to pre-FMT baseline in 6 months in IBD pts

CMV COLITIS IN IBD

- ↑ TNF-α in IBD + immunosuppression → reactivation of latent CMV infection → colonic injury and necrosis
- Prevalence: ↑ 25% – colectomy; 45% – steroid refractory
- 70-85% remission rates w/ anti-viral therapy

- CMV IgM Abs → active CMV colitis
- ECCO recommendations:
  - Qn PCR: CMV DNA in colonic tissue

IBD or IBS?

Crohn’s vs. IBS

IBS is more common than Crohn’s. As many as 1 in 5 American adults has signs and symptoms of IBS.
MEDICAL MANAGEMENT OF INFLAMMATORY BOWEL DISEASE

IMMUNOMODULATORS:
*AZATHIOPRINE (AZA) / 6 MERCAPTOPURINE (6 MP)
*METHOTREXATE (MTX)

ADVERSE EFFECTS
- Gastrointestinal (e.g., nausea, vomiting, abdominal pain)
- Nephrotoxicity
- Lymphopenia
- Anemia
- Hyperuricemia
- Rash
- Maculopapular afety

RATIONALE FOR TESTING OF TPMT & THIOPURINE METABOLITES

- A priori dose reduction in TPMT variants reduces hematologic adverse events
- Thiopurine Metabolite testing:
  - to guide dose increases or modifications in active disease
  - to determine therapy compliance
MERCAPTOPURINE IN MAINTAINING REMISSION IN PEDIATRIC CD


AZATHIOPRINE-RELATED LYMPHOPROLIFERATIVE DISORDERS

Magro F et al. J Crohns Colitis 2014;8:31

BIOLOGICS: THE TURNING POINT?

BIOLOGIC AGENTS – ADVERSE EVENTS

• Infusion reactions
• Lupus – like reaction
• Rare complications

IBD – 37% RISK OF MELANOMA INDEPENDENT OF THERAPY

Monitor:

Labs: CBC, LFT's
Skin exams
Pediatric Grand Rounds - University of TX Health Science Center at San Antonio

08/19/2016

THERAPEUTIC DRUG MONITORING (TDM)

DRUG LEVELS BASED DOSING vs CLINICALLY BASED DOSING (TAXIT TRIAL)

30-35% secondary loss of response to anti-TNFα therapy mainly due to immunogenicity, ADA & enhanced drug clearance

ACCELERATED IFX INDUCTION REGIMEN IN ASUC

CRP LEVELS

Accelerated dosing → Greater daily suppression of CRP

MONOTHERAPY? COMBOTHERAPY?

• 6-TGN → ↓ IFX Immunogenicity & ↓ ADA levels

TABLE 2. Studies on the Impact of Therapeutic Modulation on Anti-TNF Efficiency and Pharmacokinetics in Patients with BD on Combiotherapy

TABLE 5. Clinical Utility of Week 14 IFX Level Cut Points

<table>
<thead>
<tr>
<th>IFX14 Cut</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>80</td>
<td>80</td>
<td>45</td>
<td>66</td>
</tr>
<tr>
<td>&lt;2</td>
<td>70</td>
<td>50</td>
<td>45</td>
<td>66</td>
</tr>
<tr>
<td>&lt;3</td>
<td>53</td>
<td>70</td>
<td>64</td>
<td>46</td>
</tr>
<tr>
<td>&lt;4</td>
<td>50</td>
<td>85</td>
<td>83</td>
<td>53</td>
</tr>
<tr>
<td>&lt;5</td>
<td>47</td>
<td>90</td>
<td>88</td>
<td>53</td>
</tr>
<tr>
<td>&lt;5.5</td>
<td>37</td>
<td>95</td>
<td>92</td>
<td>50</td>
</tr>
<tr>
<td>&lt;6</td>
<td>33</td>
<td>100</td>
<td>100</td>
<td>50</td>
</tr>
</tbody>
</table>
**VEDOLIZUMAB**

- VDZ → humanized anti-α4β7 integrin mAb that binds to the α4β7 molecule
- Effects gut-selective blockade of lymphocyte trafficking
- US FDA approved in adults for moderate-to-severe UC & CD (May 20, 2014)
- Patient’s who have failed/intolerant to steroids +/- immunomodulators & anti-TNFα, or naïve to anti-TNFα agents
- Week 52 clinical remission ~ 40-45% (p < 0.001)
- Time to remission is more gradual (3-6 weeks)

**Minimal AE similar to placebo:**
- nasopharyngitis
- URI
- influenza
- fatigue, H/A, arthralgia

**DIET IN IBD**

- Dietary factors contribute to the pathogenesis of IBD:
  - induce dysbiosis of gut microbiome
  - luminal Ags

  "Westernized" diet:
  - ↑ animal fats: δ-6 PUFA in red meat (beef & pork)
  - CHO: sugars/sweeteners & "confectionaries"
  - Food additives & fast food

  Food preservatives & additives
  - sulfur
  - maltodextrin
  - Microparticles: titanium dioxide, aluminum silicates, and talc

**DIET IN IBD**

- Fiber: protective against CD
  - positively modulates the internal microbiome
  - fermented by bacteria into SCFA
  - anti-inflammatory effects

**SPECIFIC CARBOHYDRATE DIET (SCD)**

- Diet containing primarily monosaccharides
  - readily absorbed & provide optimal nutrition
  - lower amounts of disaccharide sugars enter the colon
  - reversal to the normal gut microbiome

- Contains:
  - almond, nut & coconut flours
  - Only sugar allowed is fructose (honey)
  - Excludes dairy products except fermented yogurt
  - Excludes grains (wheat, rice, corn)

**LACTOSE - FREE DIET?**

- Lactose intolerance: malabsorption from lactase deficiency
- Reduce lactose intake; no restriction required

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*Shah et al. Nutrition in Clinical Practice 30 Number 4 August 2015 462–473*
**ENTERAL NUTRITION IN IBD**

**NASPGHAN ENTERAL NUTRITION WORKING GROUP**

**Hypotheses:**
- Elimination of dietary Ags → ↓ inflammatory mediators
- Optimal nutrition (+ micronutrients) → improve mucosal healing

**EEN** (Exclusive Enteral Nutrition)
- sole dietary source
- primary medical therapy to induce remission

**PEN** (Partial Enteral Nutrition)
- in addition to a normal diet
- improve nutritional status or maintain remission

**Pediatric vs Adult Healthcare**

**Pediatric Care**
- Family centered; Parent primary caregiver
- Ignore growing independence of patient

**Adult Care**
- Patient centered
- Acknowledges patient autonomy and independence

**Adolescents with IBD:**
- Fewer clinic visits
- More documented non-compliance
- More active IBD on endoscopic evaluation
- Higher Crohn's disease activity

**Resources for Successful Transition**

**Educational Resources for Providers**
- Transition in IBD www.ibdtransition.org.uk/

**Transition Readiness Assessment and Tools**
- www.naspghan.org

**Resources and Tools for Adolescents and Parents**
- Crohns and Colitis Foundation of America (CCFA)
- Society for Adolescent Health and Medicine

**Transition Advocacy and Support for Patients, Parents and Providers**

**Resources for Pediatricians and Providers**

**Affiliates**
- Society for Adolescent Health and Medicine (SAHM)
- American Gastroenterological Association (AGA)
- American Society for Gastrointestinal Endoscopy (ASGE)
- Crohn’s and Colitis Foundation of America (CCFA)
- American Society for Gastrointestinal Endoscopy (ASGE)
- American Gastroenterological Association (AGA)

**Transition Process**

- Age 12 - Transition begins
- Age 18 - Pre-transfer Visit
- Transfer conference – pediatric and adult providers, social work
- First adult visit in pediatric location
- Adult follow-up determined

**Pediatric Grand Rounds - University of TX Health Science Center at San Antonio**

**08/19/2016**
REFERENCES

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15. Impact of Inflammatory Bowel Disease on the Quality of Life in Adolescents. Pediatr Gastroenterol Nutr 2013:2:44