PEDIATRIC - IBD

SHIMON REIF, MD
DEPARTMENT OF PEDIATRICS
HADASSAH MEDICAL CENTER
DISCLAIMER

• IBD IN 30 MINUTES – NO WAY!!!

• Highlights in Pediatric IBD – yes, we can do

• IBD in the "קהילה" – Impossible

IBD is the same disease in the community or in the hospital
IBD

Genetic susceptibility (NOD2, ...)

Immunological factors

Environment (Smoking, Stress, Diet... *)

* Reif S, Gilat T; Gastroenterology, Gut
Gene-Environment Interaction

IBD - Pathogenesis

- Luminal antigens
- Food
- Bacteria

 Genetic susceptibility

 Environmental triggers

C/S
No breast feeding
Early antibiotic exposure
The Increasing Incidence of Immunoregulatory Disorders
IBD: A Disease of the Rich?
Pathogenesis
imbalance between innate and immunologic system

• The normal gut’s immune system is normally in a state of “physiologic” inflammation reacting to the antigenic load presented to it by microbes and food

• In IBD there is impairment of this natural immunologic response (innate)

• Instead there is unchecked over response of the immunologic response

• Tissue damage, increased permeability
CD - Distinguishing Features

- Granuloma
- Strictures
- Asymmetric involvement
- Focal lesions
- Skip lesions
- Small bowel involvement
- Fistulization
- 20-30% without gross bleeding
- Rectal sparing
- Perineal disease

Endoscopic features
Crohn’s Disease: Anatomic Distribution

- Small bowel alone (33%) – L2
- Ileocolic (45%) – L3
- Colon alone (20%) – L1
- Upper GI – L4

Frequency of involvement:
- Most
- Least
Extraintestinal Manifestations of IBD

- **Skin**
  - Erythema nodosum
  - Pyoderma gangrenosum

- **Joints**
  - Peripheral arthritis
  - Sacroileitis
  - Ankylosing spondylitis

- **Eye**
  - Uveitis
  - Episcleritis
  - Iritis

- **Hepatobiliary complications**
  - Gallstones
  - PSC

- **Renal complications**
  - Nephrolithiasis
  - Recurrent UTIs
Inflammatory Arthritis

Used by permission of The American College of Rheumatology
Aphthous Stomatitis
Erythema Nodosum

Courtesy of J-F Colombel, MD.
Pyoderma Gangrenosum
Sacroiliitis in IBD

Courtesy of J-F Colombet, MD
Uveitis
Sclerosing Cholangitis in IBD

Courtesy of J-F Colombel, MD.
endoscopic appearance
The Capsule (WCE)
Natural history of Crohn’s disease: 90% of patients develop stricturing or penetrating complications

- Retrospective study of 2,002 CD patients with regular follow-up in a single University
- More than 70% develop complications within 10 years

Cosnes J, et al. Inflamm Bowel Dis 2002;8:244–250
Early disease – Inflammation

Late disease – Tissue remodeling

Time
Changes in Crohn’s disease behavior and location

- Retrospective study of 297 CD patients with regular follow-up in a single University Hospital

Indolent course Crohn’s disease

Aggressive course Crohn’s disease

Goals of Therapy for IBD

• Inducing remission
• Maintaining remission
• Restoring and maintaining nutrition
• Maintaining patient’s quality of life
• Prevention of complications
• Surgical intervention (selection of optimal time for surgery)
**Signs:**
- Fever
- Mass
- Growth

**Symptoms:**
- Pain
- Stool frequency
- Well-being

**Function:**
- Appetite
- Sleep
- Job Performance
- Social relationships
Levels of Improvement

• Clinical response
  – Patient feels better, but is not well – just less sick
• Clinical remission
  – Patient feels well
• Laboratory remission
  – Hematocrit, CRP, ESR, albumin normal
  – Fecal markers – calprotectin
• Remission on imaging
• Endoscopic remission - “mucosal healing”
### Therapy for Crohn’s disease

<table>
<thead>
<tr>
<th>First line therapy</th>
<th>Immunomodulators/Second line therapy</th>
<th>Biologic Therapy</th>
<th>Biologics - in development</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-ASA budesonide</td>
<td>corticosteroids budesonide azathioprine/6-MP methotrexate</td>
<td>infliximab adalimumab certolizumab pegol natalizumab</td>
<td>mesenchymal stem cells abatacept thalidomide anti IL-12 (ABT-874) <em>Trichuris suis</em> probiotic therapy visilizumab (anti-CD3) Adacolumn (leukocytophagesis) golimumab fontalizumab</td>
</tr>
<tr>
<td>antibiotics (metronidazole, Cipro, rifaximin,</td>
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<tr>
<td>Nutritional therapy</td>
<td>Investigational Immunomodulators</td>
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<tr>
<td>elemental diet TPN</td>
<td>mycophenolate mofetil leflunamide FK 506 thioguanine stem cell transplant</td>
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</table>
Current Therapy for IBD is Sequential and Based on Disease Activity

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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<tbody>
<tr>
<td>Aminosalicylates</td>
<td>Oral/Parenteral Glucocorticoids</td>
<td>Parental Glucocorticoids</td>
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<tr>
<td></td>
<td></td>
<td>Anti-TNFα</td>
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<tr>
<td></td>
<td></td>
<td>Cyclosporine-A</td>
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<tr>
<td>Antibiotics nutrition</td>
<td>nutrition</td>
<td>Bowel Rest</td>
</tr>
<tr>
<td>Oral Glucocorticoids</td>
<td>Thiopurines Methotrexate</td>
<td>Surgery</td>
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<tr>
<td>Thiopurines Methotrexate</td>
<td></td>
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<tr>
<td>Anti-TNFα</td>
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</table>
Inductive Therapies

- **UC**
  - Aminosalicylates
  - Corticosteroids
  - Cyclosporin
  - Anti-TNF

- **CD**
  - Aminosalicylates
  - Corticosteroids
  - Antibiotics
  - Anti-TNF
Maintenance Therapies

- **Immunosuppressors**
  - Thiopurines
  - Methotrexate

- **Aminosalicylates/Salazopyrin** – mainly for UC

- Anti-TNF

**NOT corticosteroids**
Step-up vs Top-down Approach

- 5-Aminosalicylates and Antibiotics
- Corticosteroids
- Immunosuppressives
- Biologics (TNF Antagonists)
5-Aminosalicylates

Mesalamine (Rafasal, Pentasa, Asacol) – oral / topical

Salazopyrine (Sulfasalazine)- oral
(sensitivity to Sulfa, G6PD-def)

Effective in mild Crohn’s colitis
Not proven effective in Crohn’s disease of small bowel

Effective in ulcerative colitis
Long-term prevention of CRC

SE: Anorexia/ Dyspepsia/ Nausea
Hemolysis / Agranulocytosis
Nephropathy / Pneumonitis: Rare (<0.3%)
Thiopurines and Natural Purines

6-Mercaptopurine

Hypoxanthine

6-Thioguanine

Guanine
Thiopurines

**Type A - toxic metabolites**
- General malaise and nausea (11%)
- Infectious complications (7.4%) - CMV, opportunistic
- Hepatitis (0.3–1.3%)
- **Myelosuppression** (1.4–5%)

**Type B - Immune-mediated (2%)**
often occur within 2–4 weeks after start of treatment
Fever, Rash and Arthralgia

**Pancreatitis (1.4–3.3%)** - idiosyncratic reaction
Thiopurine metabolism

11% of population – Intermediate TPMT levels (homozygous)
Higher 6-TG levels- require lower doses, high response rate
Methotrexate

In Crohn’s disease – induction therapy
   Maintenance of remission

In UC – not proven to be effective

**Adverse events:**
Teratogenic (and toxic to sperm)
Folate antagonist:
add folate Rx to prevent nausea, stomatitis
Diarrhea, hair loss, mild leukopenia
Hepatic Fibrosis
Severe Intestinal pneumonitis
Construct of Anti-TNF-α Biologic Agents

- **Infliximab**
  - Chimeric monoclonal antibody (75% human IgG₁ isotype)
  - Mouse and Human

- **Adalimumab**
  - Human recombinant antibody (100% human IgG₁ isotype)

- **Certolizumab Pegol**
  - Humanized Fab’ fragment (95% human IgG₁ isotype)

- **Mouse**
- **Human**
- **PEG, polyethylene glycol**
Mucosal and histologic healing after infliximab in Early CD
Biologic era in IBD management: Healing of refractory ulceration/fistula with Infliximab

Pretreatment 4 Weeks posttreatment

pretreatment 2 weeks 10 weeks 18 weeks
Endoscopic Healing and Reduced Hospitalizations and Surgeries: Infliximab maintenance for Crohn’s disease

Infections associated with infliximab

Tuberculosis

Other infections

– Bacterial [Pneumococcal] infection
– Opportunistic infections:
  • *Pneumocystis jiroveci (carinii)*
  • Histoplasmosis, Cryptococcosis, Coccidioidomycosis
  • Listeriosis
– Reactivation of viral infections
  • HBV, HCV
  • EBV, CMV
  • HSV

Keane J, N Engl J Med
Malignancies

- In clinical trials of all TNF inhibitors, more cases of lymphoma were observed compared with controls and the expected rate in the general population\(^1\)
  - Patients with RA\(^2\) and CD\(^3,4\) may be at higher risk for developing lymphoma

- Occurrence of other malignancies is consistent with expected rate\(^5,6\)

Hepato-splenic Lymphoma

Pediatric case reports ~10
All combined therapy Infliximab and AZA

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\(^7\)http://www.emea.europa.eu/humandocs/Humans/EPAR/remicade/remicade.htm - Scientific discussion
Vaccinations for IBD patients
When first seen

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<tr>
<th>Item</th>
<th>Comment</th>
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</table>
| **General** | As for general population  
                      Check immune status as appropriate (table 2) |
| **At diagnosis of IBD†** | Varicella vaccine (if no history of chickenpox and  
                              negative VZV serology)  
                              Hepatitis B (if HBV serology is negative)  
                              Pneumococcal polysaccharide vaccine  
                              Influenza (trivalent inactivated)  
                              Human papilloma virus (in young women, if not already  
                              given as part of national vaccination strategy) |
| **Annually** | Influenza (trivalent, inactivated) |
| **Booster** | Pneumococcal polysaccharide vaccine (3–5 years) |
| **Discretionary** | Travel vaccines: take advice from appropriate specialist;  
                               live vaccines (eg, yellow fever, oral poliomyelitis) should  
                               be avoided if on immunomodulators*  
                               Chest x ray, tuberculin skin test, or interferon γ release  
                               assay prior to anti-TNF therapy‡ |
בדידותيومמקליעתובאCarthy/לפי התהליכים הבאים:

1. HB-Surface-Ag, HB-Surface-Ab, HB-Core Ab: בדיקה לחלקת כבד נגיפת מסון B
2. HAV IgG: בדיקה לחלקת כבד נגיפת מסון A
3. HCV Ab: בדיקה לחלקת כבד נגיפת מסון C
4. VZV-IgG: בדיקה ל הדבר מסתכלת
5. -HIV: בדיקות V2, הו-EBV
6. SRVV ו-EBV: *בדידותيومאנאף עדין מתtımמה שתאן
7. סופרetAddress, תפקודיibrated
8. עלוםروم
9. תבניות עורות לעסקאות (PPD)
הטיסונים הממליציים:

1. שפעת עונתית + H1N1 - מיידי שינה.

2. Pneumovax - מייד 5 שניות לקראה/лепני התחלתי אימונומודולטורים/ביוליונים.

3. לחולות על חיסון: חיסון לעותב נגיף מדוג B.

4. לחולות על חיסון: חיסון לעותב נגיף מדוג A.

5. לחולות על חיסון: חיסון לע VZV* (ימונים לעמידה ממושכת ובחרלת שכבת מטיפלת באימונומודולטורים/ביוליונים).


יש לה⁽י POSSIBLE錯誤⁾ክנט מילים מדויקות באימונומודולטורים/ביוליונים.
Surgery for IBD
General Concepts

- Majority will need surgery: 78% over twenty years
- Surgery generally indicated for complications of disease
- Surgery must be directed at area of bowel responsible for complication
Pouchitis: disease phenotype

Acute
- Increase in bowel movements
- Urgency
- Cramps
- Rectal bleeding
- Fever

Recurrent acute
- <4 episodes/year

Chronic
- > 4 weeks of symptoms/treatment

Crohn’s like 3-13%
- Fistulizing
- Fibrostenotic
- Inflammatory

Antibiotic responsive

Antibiotic dependent

Antibiotic refractory

Shen B Clin Col Rectal Surg 2010
IBD Management
Summary

• There is no “one size fits all” to IBD therapy
  – Therapy and decision making are tailored to the individual

• Algorithms are based upon available evidence
  – Evidence is in constant flux

• Success of algorithms depends upon optimization of each step of therapy and considerable judgment about each outcome
  – Skillful application of medical therapy makes all the difference in outcomes
Pitfalls for Pediatric IBD

• 25% of all IBD are children
  – CD > UC  4:1

• Growth failure is unique to pediatric IBD
  – 30-50% of CD ped. Pts
  – 10% of UC ped. Pts

• Malnutrition/micronutrient deficiencies
  more likely due to increased metabolic needs for growth
Nutrition

• Growth/Nutrition is a problem before we meet the pt.
  – Possible direct effects of inflam. mediators
  – Anorexic effects of inflam. mediators
• Patients don’t feel well
  – Post-prandial pain --> dec. intake
  – anorexia (intake 55-80% of RDA of cal. Needs)
Steroids – The Bad Guy

- alter linear growth
- proteolytic/ osteolytic
- inhibit bone growth
Increased needs  
Malabsorption

Malnutrition

Suboptimal intake  
Increased GI losses

Corticosteroids

Growth Failure  
Cytokines
Nutritional Treatment

- Reduce antigenic load
- Increase caloric consumption
- Correct micronutrient deficiency
- Primary therapy
- Adjuvant therapy
- Preventive
- Complications
Nutritional Treatment

- TPN – complications
- Elemental diet – Its value not proved
- Polymeric diet – Same benefit as elemental
- Special diet: Glutamine, Butyrate, TGF β
- N-3 fatty acid
- Probiotics
- Prebiotics
Enteral Nutrition

- Possible Mechanisms:
  - Decrease antigen load to the GI tract
  - Alter intestinal microbial flora
  - Decrease intestinal synthesis of inflammatory mediators via reduction of dietary fat
  - Provision of micronutrients to diseased bowel
    - Mostly small bowel
    - Motivated patient/family
Elemental Formulas

– Common practice for remission is elemental or semi-elemental formula

– **However!!!!**
– Bad taste
– May need for NGT/G-tube
– Formula composition for protein and/or fat source have not proven to make a difference in studies

– Thus no proven beneficial effect over non elemental formula
Risk of Colorectal Cancer

Cumulative probability %

Time from diagnosis (years)

UC - Complications

Gut 2001, 48:526
Increased risk

- Long duration
- Anatomical extent
- PSC
- Family history of CRC

Possible protection

- 5-ASA
- Folate
- Tight medical control
PROTECTION

• Surveillance colonoscopy

  Multiple biopsies

• Procto-colectomy (for UC)
The definition of Crohn’s Disease is the same in children and adults:

- Same locations of bowel affected
- Appears to be the same disorder
- Same gastrointestinal symptoms
- Same endoscopic appearance
- Same biopsy appearance

However!!!
Pediatric Vs Adult IBD

- Pediatric phenotype may be more severe, and aggressive (penetrating)
- Relatively stable in adults in contrast to children where disease extension is common
- Lower incidence of positive serologic tests (ASCA, p-ANCA)
- Response to current therapies appears similar
- Growth remains a unique pediatric problem
- Dosing and safety cannot be extrapolated from adult studies and require independent study
Pediatric Vs Adult IBD

• Age can affect clinical expression
• distribution varies by age <10 years, higher colonic only, for CD
  >10 years, more similar to adults
• Upper GI involvement is common in children
In young children it may be difficult to distinguish CD from UC because of the primary colonic phenotype for young children with CD.
Initial diagnosis may change in up to 10-15%
Doctor, will my IBD have an effect on my child?”

Aims: To investigate short- and long-term morbidity and/or developmental defects in offspring of mothers who have IBD during pregnancy

Dotan I, Reif S, JCC 2013
MAIN FINDINGS – short term

• Newborns to IBD mothers-significantly lower birth weights vs. controls: 3.13 ±0.6 vs. 3.27 kg ±0.45, p=0.005

• Mothers with IBD had more spontaneous abortions

• No difference in preterm birth

• Slight increase in congenital anomalies
**IBD in pregnancy has a long-term effect on offspring's morbidity**

<table>
<thead>
<tr>
<th></th>
<th>IBD (%)</th>
<th>Control (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3 Intercurrent infections, 1\textsuperscript{st}, 2\textsuperscript{nd}, 3\textsuperscript{rd} year</td>
<td>23, 20, 17</td>
<td>42, 46, 53</td>
<td>0.001</td>
</tr>
<tr>
<td>Wheezing bronchitis</td>
<td>9</td>
<td>18</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>5.5</td>
<td>11.1</td>
<td>0.028</td>
</tr>
<tr>
<td>IBD</td>
<td>2.8</td>
<td>0</td>
<td>0.045</td>
</tr>
<tr>
<td>ADHD</td>
<td>5</td>
<td>0.8</td>
<td>0.03</td>
</tr>
<tr>
<td>More methylphenidate (ritalin) use in CD (5.4%) vs. UC (0%) offspring (p=0.02)</td>
<td></td>
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</tr>
<tr>
<td>When adjusted for smoking 0.05</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Gross motor abnormalities</td>
<td>4.4</td>
<td>0.7</td>
<td>0.04</td>
</tr>
</tbody>
</table>
“You don’t need a colonoscopy, but I’m sending you for one because, quite frankly, I don’t like you.”
THANK YOU