My child was diagnosed IBD, Now What?

Judy Fuentevilla, MD
The good and the bad

• Good
  – Diagnosis is made
  – We have treatment
  – Disease is manageable
  – Lots of new therapies

• Bad
  – There is no cure
  – You have to take drugs
  – Disease might manage you
  – Therapies may have side effects

Tough Questions

• Why ????
• Diagnosis
  – UC vs Crohn’s vs something else
• Treatment ?
  – ASA drugs?
  – Steroids? Type ? Duration?
  – Immunomodulation
  – Remicade etc
• Surgery?
• Diet?
More Tough Questions

• How do I tell my child about his or her IBD?
• How is IBD going to affect my child’s daily life?
• What are the challenges children may face at school and in their social lives, especially as they grow older?

EDUCATIONAL GOALS

• Brief overview
• Differences between kids and adult
  – Diagnosis
  – Treatment
  – Response
  – Growth!
  – Development
  – Transitions

Additional information on IBD medications, complementary treatments, and other resources
INCREASING INCIDENCE OF IBD

Incidence per $10^5$
(Ölmsted County, MN)

Crohn's disease
Ulcerative colitis

Loftus EVJ et al. Gastroenterology 1998; 114:1181

Crohn's Incidence has Doubled in Children over the Past Decade

Incidence has doubled in the pediatric age group over the past decade.
80,000 affected in the U.S.

Loftus, Gastroenterology 2003
How common is IBD in the United States?

25% of IBD occurs in childhood
USA Prevalence
An estimated 1.4 million people in US.
Around 5000 children per year.
Overall approximately 50,000-100,000 children have IBD in the United States.
What is IBD?

• Chronic relapsing and remitting condition involving the gastrointestinal tract as well as extra intestinal manifestations.
• Includes the disease spectrum of
  – Crohn’s Disease
  – Ulcerative Colitis
  – IBD Unclassified (formerly indeterminate colitis)

Inflammatory Bowel Disease

**Ulcerative Colitis (UC)**
- Mucosal / submucosal only
- Colon only

**Crohn’s Disease (CD)**
- All layers of wall at risk
- All regions GI tract

Indeterminate
Ulcerative Colitis and Crohn's Disease

- Diffuse mucosal inflammation limited to colon
- Affects rectum
- May involve all or part of rest of colon

- Patchy transmural inflammation
- May affect any part of GI tract
Ulcerative Colitis – Disease distribution

Mild → Severe

Etiologic Hypotheses

**Persistent infection**
- Mycobacteria
- *Helicobacter* sp.
- Measles-mumps
- Listeria
- Toxigenic *E. coli*

**Defective mucosal integrity**
- Altered mucus
- Increased permeability
- Cellular starvation
- Impaired restitution

**Dysbiosis**
- ↓ protective bacteria
- ↑ aggressive commensals

**Dysregulated immune response**
- Loss of tolerance
- Aggressive cellular activation
- Defective apoptosis
Multi-factorial Pathogenesis of IBD

Genes
Mucosal Immune System
Environment

IBD - Environmental Risk Factors

- Smoking: ↓↓↓↓
- Appendectomy: ↓↓
- High sanitation level in childhood: 0
- High intake refined carbohydrates: 0
- Perinatal infection: ?
- Breast feeding: ?
- Oral contraceptives: ↑↑?
Genetic Susceptibility

Concordance in twins:

Monozygotic 44-50% 5-14%
Dizygotic 8% 0%

Associated with:
- Early onset
- Strictures
- Surgery

Tysh et al. Gut 1988; 29:950
Ornholm M et al. Scand J. Gastroenterology 2006; 35:1076

NOD2/CARD15

Figure 1: Structure of NOD2/CARD15 and localization within the region LRR of the 3 principal mutations associated with Crohn's disease.
Diagnosis in Kids

Variable symptoms
  growth failure
  poorly localized discomfort
Different diagnostic possibilities
  CGD and other immunodeficiencies
  Henoch Schoenlein

IBD PRESENTATION

Rectal bleeding – More in UC
Abdominal pain
Diarrhea
Weight loss- More in CD
Growth Failure
Perianal disease- CD
Mouth ulcers- More in CD
Rash: erythema nodosum
Fever
Anemia
Joint pain
Extraintestinal Manifestations

Transplant what?

- Bowel transplant in Crohn’s patients with severe short bowel syndrome—rapid recurrence of Crohn’s in the new bowel despite rigorous immune suppression
- Bone marrow transplant induces long lasting remission in Crohn’s disease.
Crohn’s vs UC vs Something Else

IBD Screening

- 98% of children with IBD have one of the following screening abnormalities at presentation:
  - Anemia
  - Thrombocytosis
  - Leukocytosis
  - Hypoalbumenia
  - Elevated ESR
  - Hematochezia
- CBC, albumin, ESR and hemoccult will pick up almost all cases!
  - Data from over 500 cases, unpublished
Approximately 1/3 of positive serologies were false + Serology 4X more expensive

### Diagnosis of IBD

- Negative infectious stool studies
  - Culture, O&P, C. difficile
- Stool calprotectin
- CBC, ESR/CRP, LFT’ s, albumin
- Upper and lower endoscopy with biopsies
- Capsule endoscopy?
- Radiology
  - UGI/SBFT, CT, MRI, US
- PPD, CXR if indicated
Ulcerative Colitis

Non-caseating granulomas
Increased # of histiocytes

Crohn’s Disease
IBD Mimics

• Bacteria
  – Brucellosis
  – Tb
  – Salmonella etc
  – Yersinia
  – C diff

• Parasites
  – Amoebiasis
  – Anikasiasis
  – Canine hookworm
  – Trichuris
  – giardiasis

• Viruses
  – HIV
  – CMV
  – EBV

• Non-infectious
  – Henoch-Schoenlein
  – lymphoma
  – Behcet’s
  – Connective tissue disease
  – Celiac disease
  – immunodeficiency
  – Appendicitis
  – Eating disorders
  – Functional (IBS)

Special Kid Problems

• Harder to tell Crohns from UC in younger patients
• Makes surgical decisions difficult

• Very Young Pts (<3yrs)
  – Often severe, difficult to treat
  – Emerging data that many have specific immunodef.
  – Bone marrow transplants being done in selected severe case
Worse Prognosis

- Crohn's
  - Youth
  - Perianal disease
  - Stricture/fistulae
  - Wt loss/growth failure
  - Ileo-colonic
  - NOD2 +

- UC
  - Pancolitis
  - Fail to respond to steroids
  - High titer p-anca
  - Fulminant presentation

Complications
GROWTH RETARDATION
RISK OF COLORECTAL CANCER

IBD - Pediatric Complications

UC - Complications

Risk of Colorectal Cancer

Cumulative probability %

Time from diagnosis (years)

Gut 2001, 48:526
Other complications

- Myositis/periostitis
- Arthritis
  - Peripheral
  - Central (ankylosing spondylitis)
- Sclerosing cholangitis/autoimmune hepatitis
- Strictures/fistulae (Crohn’s)
- Pulmonary infiltrates/nodules
- Skin lesions
  - Erythema nodosum
  - Pyoderma gangrenosum
  - “metastatic” crohn’s

Bone Disease

- Decreased bone mineral density is common in children and adolescents with Crohn’s disease

MULTI-FACTORIAL

- Poor calcium absorption/intake
- vitamin D deficiency
- Decreased physical activity
- Inflammation
- Steroid use increases short- and long-term risk.

Dresner-Pollak et al; Am J Gastroenterol 2000;95;699-704
Goals of therapy

• Induce remission (rapidly) to allow normal life
• Maintain remission
• Avoid toxicity
• Mucosal restoration
• Avoid hassles!
• Does not necessarily include the “perfect stool”

Therapeutic Approach

• Bottom Up
  – Start with 5 ASA
  – If not better, begin steroid
  – If not better, unable to wean, add immunomodulator
  – If not better, start biologic

• Top Down
  – Start with biologic
  – Transition to immunomodulator, if tolerated
  – Transition to 5 ASA, if tolerated in UC
"Bottom Up" Strategy

- Standard, Sequential
- Cost-effective
- Minimal side effects

- Surgery and Biologics
- Immune Suppressants
  - ESR/CRP, LFT’s, albumin
  - Azathioprine/6-MP
  - Corticosteroids

- Anti-inflammatory Drugs
  - Aminosalicylates
  - Antibiotics

"Top-down" Strategy

- Biologics
- Early aggressive use of biologics.
  - Induces rapid clinical response.
- Surgery
- May improve QOL
Top down versus Bottom up

- Bottom up
  - Slower (longer to reach remission in sick patient)
  - Cheaper?
  - Safer?

- Top Down
  - Quicker
  - Expensive (?over log run)
  - May prevent permanent damage to bowel
  - More effective in
    - Growth failure
    - Fistulizing disease

Therapies for IBD

- 5-ASA drugs
- Antibiotics
- Steroids
- Immunomodulators
- Biologics
- Nutrition
- Surgery
IBD - Oral Aminosalicylate Delivery

**pH-dependent**
- Acrylate-coated mesalamine
  - Asacol®, Claversal®, Salofalk®, Rafferal®

**Time release**
- Ethylcellulose-encapsulated mesalamine
  - Pentasa®

**Bacterial cleavage**
- Azobond - linked 5-ASA
  - Sulfasalazine - Azulfidine®
  - Olsalazine - Dipentum®
  - Balsalazide - Colazal®

### ASA Cost (US$)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost/day</th>
<th>Cost/year</th>
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<tbody>
<tr>
<td>SASP</td>
<td>0.68</td>
<td>248.20</td>
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<tr>
<td>Asacol</td>
<td>8.73</td>
<td>3149.95</td>
</tr>
<tr>
<td>Lialda</td>
<td>18.90</td>
<td>6898.50</td>
</tr>
<tr>
<td>Colazal</td>
<td>8.06</td>
<td>2941.90</td>
</tr>
<tr>
<td>Pentasa</td>
<td>6.86</td>
<td>2503.90</td>
</tr>
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</table>
Mesalazine for Maintenance of Medically Induced Remission in Crohn’s Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Date</th>
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<tbody>
<tr>
<td>Thomson</td>
<td>1990</td>
</tr>
<tr>
<td>Prantera</td>
<td>1992</td>
</tr>
<tr>
<td>Brignola</td>
<td>1992</td>
</tr>
<tr>
<td>Gendre</td>
<td>1993</td>
</tr>
<tr>
<td>Bresci</td>
<td>1994</td>
</tr>
<tr>
<td>Thomson</td>
<td>1995</td>
</tr>
<tr>
<td>Arber</td>
<td>1995</td>
</tr>
<tr>
<td>Modigliani</td>
<td>1996</td>
</tr>
<tr>
<td>Sutherland</td>
<td>1997</td>
</tr>
<tr>
<td>De Franchis</td>
<td>1997</td>
</tr>
</tbody>
</table>

RESULTS OF CORTICOSTEROID THERAPY FOR CROHN’S DISEASE

IBD - CD

Results of Corticosteroid Therapy

Active Disease 109 patients

Treat with Prednisolone

30 days:

- Complete Response 52 patients (48%)
- Partial Response 35 patients (32%)
- No Response 22 patients (20%)

Attempt to wean Prednisolone

One year:

- Prolonged Response Off Steroids 48 patients (55%)
- Steroid Dependent 39 patients (45%)

Munkholm P. Gut 1984; 35:360
Corticosteroid complications

- "Major" = bad
  - Growth inhibition
  - Loss of bone density
  - Hypertension
  - Cataracts
  - High blood sugar

- "Minor" = ugly
  - Weight gain
  - Acne
  - Hirsutism
  - Mood swings
  - Insomnia

Side effects are dose and duration dependent

Budesonide (Entecort)

Timed release for ileum/R colon
1st pass hepatic clearance
  - Reduced steroid side effects
  - Children have more systemic effect than adults

Induction of remission for moderate R sided Crohns

Role in maintenance ??
Immunomodulators

- Mercaptopurine
- Azathioprine
- Methotrexate
Safety and 6MP/AZA

- TPMT deficiency-severe neutropenia (30%)
  - Pretest enzyme level
- Random neutropenia (70%)
  - Routine cbc’s, awareness
- Pancreatitis (idiosyncratic)
- Small absolute increase risk lymphoma
- Hepatitis
  - Usually mild, transient

Biologic Therapy for Crohn’s Disease

Anti-TNF agents

- Infliximab- Chimeric monoclonal antibody (1998)

- Adalimumab-huminized mab (2007)

- Certolizumab pegol- pegylated Fab Fragment of human mab (2008)
Antibodies to TNF

Chimerized Infliximab

Humanized CDP 571

Mouse
Human

Infliximab in Children with Crohn’s Disease:
The REACH Trial (n=112)

Clinical Response at 10 weeks

Remission at 54 weeks

ACCENT I (Adults) REACH (Peds)

q8 weeks q12 weeks
Adverse Effects of Infliximab

- Immediate infusion reactions
  - Headache, flushing, rash, fever, abdominal pain, chest pain, wheezing, anaphylaxis
- Serum sickness-like syndrome
  - High human anti-chimeric antibody titers
- “Lupus-like” syndrome
- Infection
  - URI, peri-rectal abscess, reactivation TB
- ? Worsening of strictures
- ? Risk of cancer

Adverse Event Associated with Biologics Agents

<table>
<thead>
<tr>
<th>Common Complications</th>
<th>Infusion reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td>Fever/chills</td>
</tr>
<tr>
<td></td>
<td>Hives</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
</tr>
<tr>
<td>Rare, but Important Complications</td>
<td>HSTCL</td>
</tr>
<tr>
<td></td>
<td>Other lymphomas (Epstein-Barr virus positive &amp; negative)</td>
</tr>
<tr>
<td></td>
<td>Non melanoma skin cancer</td>
</tr>
<tr>
<td></td>
<td>TB and increased risk of infections</td>
</tr>
<tr>
<td></td>
<td>(Histoplasma)</td>
</tr>
<tr>
<td></td>
<td>Cytopenia, increased liver chemistries</td>
</tr>
<tr>
<td></td>
<td>Psoriatic rash</td>
</tr>
<tr>
<td></td>
<td>Demyelination syndromes</td>
</tr>
<tr>
<td></td>
<td>Lupus-like reactions</td>
</tr>
<tr>
<td>Recommended Monitoring</td>
<td>PPD</td>
</tr>
<tr>
<td></td>
<td>Chest x-ray, if symptomatic</td>
</tr>
<tr>
<td></td>
<td>Routine skin examinations</td>
</tr>
<tr>
<td></td>
<td>Also: CBC, liver chemistries</td>
</tr>
<tr>
<td></td>
<td>Hepatitis B Surface antigen</td>
</tr>
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</table>
Common Drugs for IBD

<table>
<thead>
<tr>
<th>Drug</th>
<th>UC</th>
<th>Crohn’s</th>
<th>Toxicity</th>
<th>Healing</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-ASA</td>
<td>+++</td>
<td>+/-</td>
<td>min</td>
<td>+</td>
</tr>
<tr>
<td>steroid</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>6MP/AZA</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Remicade</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>

Novel Therapies for IBD

- GCSF
- Growth Hormone
- Fish oil
- Probiotics
  - VSL#3 helpful for pouchitis
  - E coli Nissle similar to 5-ASA for UC
- Natalizumab-anti integrin antibody-blocks leukocyte-endothelial interaction
- Autologous stem cell transplant for Crohn’s
Surgery?  
Good?  
Bad?  
Ugly?

**Indications for Surgery**

**Absolute**
- Exsanguinating hemorrhage
- Perforation
- Cancer or dysplasia
- Unresponsive acute disease

**Relative**
- Chronic intractability
- Steroid dependency
- Growth retardation
- Systemic complications
Indications for Surgery in Crohn’s Disease

- Failure of medical therapy
- Recurrent obstruction
- Perforation
- Fistula or abscess
- Hemorrhage
- Growth retardation (children)
- Carcinoma.

Munkholm et al. Gastroenterology 1993;105:1716

Factors to weigh for elective surgery in IBD

- Expected benefit
  - Cure and end of cancer risk in UC,
  - Remission in Crohn’s
- Risk-long and short term
  - Incontinence
  - fertility issues for women post colectomy
- Toxicity of medical options
- Timing
- Individual/family preferences
Nutritional Therapy in IBD

- Nutrition support as proven therapy
  - TPN may suppress symptoms, but relapse occurs upon refeeding
  - EN is less effective than glucocorticosteroids

- Treat with EN or TPN if
  - ‘Malnourished’ and cannot maintain oral intake
  - Short bowel syndrome unable to maintain fluid / energy balance
  - Growth failure

Nutritional Therapy in IBD

- Difficult to distinguish severe illness from malnutrition

- Use table foods when possible

- “Bowel rest” not proven therapy
Specific Carbohydrate Diet

- Foods to avoid: Canned vegetables, canned fruits, unless they are packed in their own juices; All cereal grains, including flour, potatoes, yams, parsnips, chickpeas, bean sprouts, soybeans, mung beans, fava beans, and seaweed; Processed meats, breaded or canned fish, processed cheeses, smoked or canned meat; Milk or dried milk solids; Buttermilk or scidophilus milk, commercially prepared yogurt and sour cream, soymilk, instant tea or coffee, coffee substitutes, beer; Cornstarch, arrowroot or other starches, chocolate or carob, bouillon cubes or instant soup bases, all products made with refined sugar, agar agar, carrageenan or pectin, ketchup, ice cream, molasses, corn or maple syrup, flours made from legumes, baking powder, medication containing sugar, all seeds.
The Bass IBD Diet

- “Avoid all broken glass and metal objects”

Quality of Life
Living with IBD: Family Life

• Parental concerns
  • Will my child be able to participate in sports or social activities?
  • What happens when they go to college?
  • What about dating?
  • What about having children of their own?
  • Will IBD affect career opportunities?
• Sibling concerns
  “This is tough but we can handle it”

Some Families Seem to take IBD in Stride, How Do They Do It?

• Balance demands of illness with other family needs
• Get support
• Ask for help. With everything. From everyone.
• All family members are involved
• When do I seek help?
Lowered grades, withdrawal, lack of pleasure in social or recreational activities, significant family stress, more arguments
Symptoms of Depression or Anxiety are Common in Children with IBD

• 25-30 % of children with IBD have symptoms of depression and anxiety
• 10-30% meet criteria for clinical depression or an anxiety disorder.
• Predictors of depression:
  Family History, Stressful life events; steroid treatment; older age.

Effective therapy can be implemented if the diagnosis of anxiety and depression is made.

What about the parent?
From one parent to another…

• Road can sometimes be depressing, frightening and isolating, Don’t try to do it alone. People all around you are dying to help you, all you need to do is ask.
• Ask for help. With everything. From everyone.
• Share you story widely to raise awareness
• Join Team Challenge or Take Steps to connect with other IBD families and to fundraise for better treatments and cure
• Care of yourself. Fill your parental well with all things good: good food, exercise, friends, entertainment and joy. This will help you in so many ways.

• Ask questions. Talk to your GI doc, your pediatrician, your support group. The more information you collect, the better. IBD does not necessarily have a predictable course so it’s good to get a broad understanding of the disease.
Other Resources

• CCFA
• NASPGHAN
  – GiKids.org
  – IBDU [www.ibdu.org]

Team Work, Information to:

● understand and improve digestive health
● work with health care providers
● live a more independent life
● understand what works in plain language instead of medical jargon
Summary

- IBD is a disease of immune dysregulation
- Colonoscopy/endoscopy with biopsy is the cornerstone of diagnosis
- Newer therapies allow mucosal healing to occur
- All children with inflammatory bowel disease are entitled to normal growth and activity
Thanks for Special People

- Patients and families
- Colleagues in GI
- Hospital and clinic staff
Thank you