Medical and Nutritional Management of Inflammatory Bowel Disease

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Overview:

I. Advances in IBD 2013: Pathogenesis and treatment

II. Medical treatment goals in IBD
   - Personalizing therapy
   - Healing inflammation

II. Nutritional management of IBD
   - Vitamin B12
   - Vitamin D

IV. Summary
I. Advances in IBD 2013: Pathogenesis and Treatment
Normal colon

Crohn’s disease

Ulcerative colitis
IBD Incidence: Environmental Factors
Your Intestinal Bacteria

Lots of bacteria
  50% of fecal solids
  >400 species
  Most non-culturable
  1-2 kg of body weight

Other life forms undefined
  Archaea
  Fungi
  Protists
  Viruses

Total human cells in the body

You are only 10% Human

\(10^{12} - 10^{13}\)

\(10^{13} - 10^{14}\)

Your Intestinal Bacteria

Kindly provided by Dr. Jon Braun
Microbial makeup of the human colon

16S: only 10 of 70 divisions of Bacteria

High-fat diet determines the composition of the microbiome independently of obesity

- Decrease in **Bacteroidetes**
- Increase in **Firmicutes** and **Proteobacteria**
- Microbiome displays increase in genes associated with nutrient transport, bacterial chemotaxis and flagellar assembly
IBD incidence in Japan
Evolution of Enteric Flora

- Mummy coprolites—paleofeces
- PCR of colonic DNA
- Electron microscopy
- Less *Bifidobacteria*, more *Bacteroides* in English flora vs. rural African flora


Tomkins, *J Hygiene*, 1981
‘Heritability’ of the intestinal microbiome

- Microbiota ‘inherited’ from mothers
- Modified by genetic and environmental factors

Turnbaugh et al, Nature 2009
Altered bacterial phyla identified in the human gut microbiota of IBD

- Decreased abundance and diversity of Bacteroidetes in IBD
- Altered composition of Firmicutes and Maintenance of Proteobacteria in IBD
- Some Proteobacteria (E. coli) are adherent to the epithelium via binding to CEACAM6

Frank DN et al, PNAS 2007
Peterson DA et al, Cell Host & Microbe 2008
Barnich N et al, J Clin Invest 2007
Injurious and Protective bacteria at the Intestinal Surface Associated With Crohn’s Disease

Bad bacteria candidates
Elevated in patients and in flares
Products damage intestine
Adherent/invasive *E. coli*
Segmented filamentous bacteria
*Lachnospiraceae (CBir)*

Good bacteria candidates
Reduced in patients and in flares
Products protect intestine
*Faecalibacterium prausnitzii*
*Lactobacillus ssp.*
*Bacteroides fragilis*
Dominant Gastrointestinal Bacteria in Normal Humans

**Stomach** $0-10^2$
- Lactobacillus
- Candida
- Streptococcus
- Helicobacter pylori
- Peptostreptococcus

**Duodenum** $10^2$
- Streptococcus
- Lactobacillus

**Distal Ileum** $10^7-10^8$
- Clostridium
- Bacteroides sp
- Coliforms

**Jejunum** $10^2$
- Streptococcus
- Lactobacillus

**Colon** $10^{11}$
- Bacteroides
- Bifidobacterium
- Clostridium coccoides
- Clostridium leptum/fusobacterium

**Proximal Ileum** $10^3$
- Streptococcus
- Lactobacillus
Normal GI mucosa
- Surface area with external environment
- Largest immune organ in body
- Physiologic inflammation
- Oral tolerance
  - “You are only 10% human”

Crohn’s disease
- Destructive chronic inflammation
- No “autoimmune target” identified in body
- Impaired tolerance to enteric flora?
Normal enteric flora and gut inflammation

Immune reactivity to dietary and enteric flora antigens in Crohn’s disease & control patients

II. Medical Treatment Goals in IBD
## Drug therapy for IBD 2013

### First line therapy
- 5-ASA
- Balsalazide
- Antibiotics (metronidazole, Ciprofloxacin, rifaximin, Amoxicillin, Ceftin, Minocycline, Tetracycline)
- Budesonide
- Budesonide enema

### Second line therapy
- Steroids
- Azathioprine/6-MP
- Methotrexate
- Immunomodulators
- Biologic Therapy
  - infliximab
  - adalimumab
  - certolizumab pegol
  - natalizumab

### Immunomodulators
- Mycophenolate mofetil
- Leflunomide
- FK 506
- Thioguanine
- Thalidomide
- Cyclophosphamide

### Investigational Immunomodulators
- Vedolizumab
- Golimumab
- Ustekinumab
- Tofacitinib
- Stem cell transplant
- GM-CSF
- Trichuris suis
- FMT

### In development
- Polymeric diet
- TPN
- Omega 3 fatty acids
- Curcumin

### Nutritional therapy
- Elemental diet
- Polymeric diet
- TPN
- Omega 3 fatty acids
- Curcumin
Natural History of Crohn’s disease

- Heterogeneity of Crohn’s disease.
- Mild, Moderate and Severe CD phenotypes.
<table>
<thead>
<tr>
<th>Patient -1</th>
<th>Patient -2</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 year old boy with weight loss and diarrhea</td>
<td>13 year old boy with weight loss and diarrhea</td>
</tr>
<tr>
<td>Diagnosis – Crohn’s disease of ileum and colon</td>
<td>Diagnosis – Crohn’s disease of ileum and colon</td>
</tr>
<tr>
<td>Treated with steroids + immune modifiers</td>
<td>Treated with steroids + immune modifiers</td>
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</tbody>
</table>

With permission, S Kugathasan MD
2003 - Tale of 2 boys

Patient -1
- He had been in clinical remission for first 2 years
- Relapse required a short course of steroids
- Normal growth and timely puberty
- He has been in remission since then
- Repeat colonoscopy – all lesions were healed.

Patient -2
- Became steroid dependent; no response to most meds. Allergic to biologic therapy. Retreatment following episodic dosing.
- 1st surgery in 6 months
- Recurrence of Crohn’s
- Delayed puberty
- Stunted growth
- More steroids, tube feeding
- Bowel perforation needed 2nd surgery
- Further hospitalization and TPN
- 3rd surgery for ‘ostomy’
- Doing OK, hoping to get his bowel reconnected in future

With permission, S Kugathasan MD
What we need for IBD diagnosis, prognostication and clinical management
Crohn’s Disease: 1960’s historical perspective

Treatment: Prednisone and sulfasalazine.

Goals of Surgery:
- Relieve obstruction (and penetrating complications)
- Discontinue medical therapy (chronic steroids)

No post-op maintenance therapy.
Wide excision, wide anastomosis to maintain lumenal patency.
### Probability of Surgery for Crohn’s Disease

<table>
<thead>
<tr>
<th>Years After Diagnosis</th>
<th>Patients (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>1 Surgery</td>
</tr>
<tr>
<td>5</td>
<td>37</td>
</tr>
<tr>
<td>10</td>
<td>39</td>
</tr>
<tr>
<td>15</td>
<td>34</td>
</tr>
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</table>

Efficacy of Azathioprine as Maintenance Therapy in Patients with Active Crohn’s Disease

* Remission induced by prednisolone tapered over 12 wk

Azathioprine Intolerance in CD: Rates of Early Adverse Reactions

P = .008

5% Autoimmune Hepatitis
29% Crohn’s Disease

10%: Severe adverse reactions to azathioprine/6MP, including fevers, headache, pancreatitis, respiratory failure, blistering skin lesions within 4 weeks of initiation

Biologic era in IBD management:
Healing of refractory ulceration/fistula with Infliximab

Construct of Anti-TNF-α Biologic Agents

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

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

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

**Legend**
- Red: Mouse
- Yellow: Human
- PEG, polyethylene glycol.
PRECiSE 2: Week 26 Clinical Response or Remission by Duration of Crohn’s Disease

*P < 0.01; †P < 0.05; ‡P < 0.001 vs placebo.

Corticosteroid-Free Clinical Remission at Week 26 in the SONIC Study

Primary Endpoint

AZA + placebo: 52/170 (30.6%)  
IFX + placebo: 75/169 (44.4%)  
IFX+ AZA: 96/169 (56.8%)

P < 0.001 (AZA + placebo vs. IFX+ AZA)  
P = 0.009 (AZA + placebo vs. IFX + placebo)  
P = 0.022 (IFX + placebo vs. IFX+ AZA)

43% do not achieve remission

Durability of Infliximab for CD

- 50% of CD patients have discontinued infliximab by 6 years of maintenance therapy (n=153)
- 82% of these patients were on combination immunosuppression

Effect of Prior Episodic Dosing on Long-term Performance of Infliximab Maintenance: Hospitalizations and Surgeries at 3 years

- 40 patients with prior irregular dosing
- 61 patients with scheduled maintenance
- Total excess cost in the PI exposure cohort of $11,464 during the third year of infliximab maintenance therapy per patient

Crohn's disease - medical management algorithm:

No partial obstruction or abscess detected

Mild

- 5-ASA, Budesonide, or antibiotics

Moderate

- Corticosteroid taper
- AZA/6MP/MTX to induce/maintain remission

- Yes
  - breakthrough
  - AZA/6MP/MTX maintenance

Severe

- Unable to taper Corticosteroids
- Inadequate response to AZA/6MP/MTX
  - infliximab, adalimumab, certolizumab, natalizumab maintenance

Surgical patients
Can we predict which UC patients are at risk of colectomy?
Risk of colectomy and history of medical hospitalization for UC (n=246; 103 hospitalized)

How do we assess IBD patient status in the clinic?

- Question: “How have you been doing?”
- Patient answer: “Pretty good.”
Symptom based therapy in Crohn’s disease

- Assumption – patients are symptomatic when their disease is active, and patients with no symptoms are “fine.” This is the basis for all Phase II-III trial recruitment and clinical care in Crohn’s disease.
C-reactive protein
- Produced in liver
- Binds pneumococcal C protein
- Half-life of 19 hours
- Genetically determined

Erythrocyte Sedimentation Rate (ESR)
- Non-specific

Platelet count
- Response to IL-6 acute phase

Solem CA et al. Inflamm Bowel Dis 2005: 11; 707-12.
Inflammatory markers in hospitalized UC patients

Rate of marker positivity in hospitalized patients

- CRP: 78.3%
- ESR: 69.5%
- Platelets: 63%

Surgical outcome: 16/46 encounters (34.7%) required colectomy for refractory disease.

# Harvey-Bradshaw Index of Crohn’s disease activity

## Simplified clinical index of Harvey and Bradshaw

<table>
<thead>
<tr>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>General wellbeing (0 = very well, 1 = slightly below par, 2 = poor, 3 = very poor, 4 = terrible)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain (0 = none, 1 = mild, 2 = moderate, 3 = severe)</td>
<td></td>
</tr>
<tr>
<td>Number of liquid stools daily</td>
<td></td>
</tr>
<tr>
<td>Abdominal mass (0 = none, 1 = dubious, 2 = definite, 3 = definite and tender)</td>
<td></td>
</tr>
<tr>
<td>Complications: arthralgia, uveitis, erythema nodosum, pyoderma gangrenosum, aphthous ulcers, anal fissure, new fistula, abscess (score 1 per item)</td>
<td></td>
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Health-related Quality of Life: SIBDQ

- Important in chronic diseases which can build up a cumulative impact over time.
- Incorporates patients’ view point; understand impact of disease on individual patients’ lives.
- Influenced by:
  - Demographic characteristics
  - Disease and treatment
  - Coping skills and social support
  - Co-morbid illness
- Short Inflammatory Bowel Disease Questionnaire (SIBDQ)
  - 10 item questionnaire, items derived by stepwise regression.
  - 4 domains – bowel, systemic, social, emotional
  - All items score on a 7-point scale (1=bad, 7=optimal)

The SIBDQ

1. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks?
2. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problems?
3. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done over the past 2 weeks?
4. **How often during the last 2 weeks have you been troubled by pain in the abdomen?**
5. How often during the last 2 weeks have you felt depressed or discouraged?
6. Overall, in the last 2 weeks, how much of a problem have you had passing large amounts of gas?
7. Overall, in the last 2 weeks, how much of a problem have you had maintaining or getting to the weight you would like to be?
8. How often during the last 2 weeks have you felt relaxed and free of tension?
9. How much of the time during the last 2 weeks have you been troubled by a feelings of having to go to the toilet even though your bowels were empty?
10. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problems?

Health-related Quality of Life: SIBDQ in >5000 clinic visits

Work disability in Crohn’s disease

SIBDQ and Harvey Bradshaw in routine Crohn’s disease clinical care UPMC IBD Center

Higher SIBDQ, better QOL. Higher HB, worse disease activity.

Feels well, doing well
Feels poorly, doing poorly

SIBDQ

HB score
Crohn’s disease: Disconnect between CRP and SIBDQ

$y = -0.0027x + 1.0968$

$R^2 = 0.0004$

Patients who feel well
CRP > 0.5 mg/dL

SIBDQ > 55
The correlation of disease symptoms and activity in Crohn’s disease

- 68% of CD patients
- 14% of patients: All symptoms – no inflammation “IBS in IBD”
- 18% of patients – First symptom is surgical complication
UPMC IBD Center algorithm for Medical and Surgical management of IBD

- Rapid progression to immunomodulators
- Limitation of steroid use
- Maintenance of remission therapy – guided by symptoms, labs and endoscopy
- Identification of infections/adverse drug reactions/functional symptoms
- Infliximab, adalimumab, certolizumab for AZA/6MP/MTX breakthrough/failure
- Identification and surgical treatment of obstruction/abscess
- Post-operative maintenance of remission therapy
III. Nutritional Management of IBD
Malnutrition in IBD

Red flags

Weight loss:
- results from anorexia, malabsorption and intestinal losses rather than hypermetabolism
- at time of dx: 85% of pediatric CD and 65% of pediatric UC lose wt
- 20-75% of adults experience it with exacerbation

Anemia:
- occurs in 54-80%.
- Vitamin B12 and folic acid deficiency, bone marrow suppression secondary to drug therapy and anemia of chronic disease.
Causes of Malnutrition

- Decreased nutrient intake
  - Iatrogenic dietary restrictions
  - Intake–associated pain and Sitophobia.
  - Altered taste: Zinc/copper/nickel deficiency, Metronidazole.
  - Anorexia

- Iatrogenic
  - Surgical complications: resections and bypass
  - Medications (Corticosteroids/ca, Sulfasalazine/folate, Cholestyramine/fat + fat soluble vit and ca deficiency)

- Increased requirements
  - Hyper catabolic state (fever, sepsis)
  - Growth in children
<table>
<thead>
<tr>
<th>Nutritional Deficiency</th>
<th>Frequency %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoalbuminemia</td>
<td>25-80</td>
</tr>
<tr>
<td>Anemia</td>
<td>60-80</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>39-81</td>
</tr>
<tr>
<td>Vitamin B12 deficiency</td>
<td>20-60</td>
</tr>
<tr>
<td>Folic acid deficiency</td>
<td>36-54</td>
</tr>
<tr>
<td>Calcium deficiency</td>
<td>13</td>
</tr>
<tr>
<td>Magnesium deficiency</td>
<td>14-33</td>
</tr>
<tr>
<td>Potassium deficiency</td>
<td>6-20</td>
</tr>
<tr>
<td>Vitamin A deficiency</td>
<td>11</td>
</tr>
<tr>
<td>Vitamin C deficiency</td>
<td>*</td>
</tr>
<tr>
<td>Vitamin D deficiency</td>
<td>75</td>
</tr>
<tr>
<td>Vitamin K deficiency</td>
<td>*</td>
</tr>
<tr>
<td>Zinc deficiency</td>
<td>40-50</td>
</tr>
<tr>
<td>Copper deficiency</td>
<td>*</td>
</tr>
</tbody>
</table>

Frequency % of Nutritional deficiencies in IBD patients

Nutrition deficiencies

**Vitamins**

- **Vit A:**
  - night blindness
  - supplements 5,000-10,000 IU/day
  - watch for toxicity: liver, skin changes and risk for bone fractures

- **Vit B12**
  - due to TI involvement or resection
  - manifests as anemia, glossitis, neurologic changes: paresthesias, confusion, poor memory
  - IM injection and nasal spray supplements available at 100-1000 mcg/month

- **Folic Acid:**
  - in 40% of CD pts and 60% in UC pts
  - low intake. drugs
  - protective effect against dysplasia and colorectal cancer in UC.
Nutrition deficiencies

- **Vitamin C**
  - causes bleeding, impaired wound healing
  - oral supplement 500-1000mg/day

- **Vitamin D**
  - occur in 75% of CD and 35% in UC
  - causes osteoporosis, bone pain.
  - oral supplement 400-800 unit/day
  - new data supports higher replacement – 4000 IU orally per day

- **Vitamin K**
  - result from fat malabsorption, antibiotics
  - oral supplement 5mg/day
General nutrition consideration in IBD

- No single uniformly effective dietary protocol for pts with IBD

- Dietary restrictions are questionable

- Controlled studies did not support low residue neither high fiber low refined sugar diet in maintaining remission in CD pts

- Exclusion of specific foods on the basis of individual clinical intolerance improves the clinical course of IBD *especially cereals, dairy products and yeast.

Every patient with IBD should consider daily multivitamin (children's chewable is well tolerated).

IBD patients with history of CD resection or colectomy with J pouch reconstruction should have vitamin B12 monitored / replaced with subcutaneous injections.

IBD pts should receive low dose folic acid and Vit B12 to protect against the thromboembolic complications of raised homocysteinaemia.

All IBD patients should have vitamin D monitored and replaced with oral supplementation (especially if on frequent steroids)

Avoid oral Magnesium, potassium or iron supplements – may cause diarrhea, mucosal injury
IV. Summary – How to achieve optimal medical and nutritional management of IBD
Take charge!

Be an active participant in your care

Understand the goals of treatment

Ask questions – including what to do if it isn’t working
Treatment of Inflammatory Bowel Disease

- Surgery
- Medications
- Emotional Support
- Nutrition
IBD: Management Goals

Establish Diagnosis

- Address psychosocial issues
- Identify dysplasia and detect cancer
- Improve daily functioning
- Replenish nutritional deficits
- Maintain remission
- Relieve symptoms
- Treat inflammation
- Treat complications
- Minimize treatment toxicity
Goals of treatment – I
Inducing remission

1. If you are sick, you have to get better
   - Medications
   - Surgery
   - Identifying complicating factors – infections, drug side effects, symptoms unrelated to inflammation
Goals of treatment – II
Maintaining remission

2. Once you are better, emphasis should be on keeping you well
   - Medications
   - Smoking (avoid)
   - Avoid drug side effects - NSAIDs
Environmental Triggers

- Infections
- NSAIDs
- Stress
- Smoking
- Antibiotics
- Diet

IBD
IBD and *Clostridium difficile*

Anaerobic bacillus associated with pseudomembranous colitis

Increasing incidence and severity in North America. Doubling of cases in past 10 years. Cost $1.1 billion annually

Increased *C. difficile* susceptibility and severity in IBD patients

Associated with disturbance in flora – antibiotics, NPO, diverted bowel segments

Food is “prebiotic” for normal enteric flora when treating *C. difficile*

Fig. 1: Annual incidence (per 100 000 population) of Clostridium difficile-associated diarrhea (CDAD) in Sherbrooke, Que., 1991–2003.

Pépin J et al. CMAJ 2004;171:466-472
3. What to watch out for in the longterm
   - Drug side effects
   - Bone health
   - Pregnancy issues
   - Cancer prevention
What you can do to help

- Ask questions from your health care providers
- Keep a copy of your medical records at your home
  - Americans frequently move
  - Encounter different health care providers/systems
- Get information
  - Reliable sources
  - Crohn’s and Colitis Foundation of America (www.ccfa.org)
  - National Institutes of Health (www.nih.gov)
- Use common sense
  - Take good care of yourself – healthy diet, good quality sleep and exercise
Acknowledgements

UPMC IBD Center
University of Pittsburgh School of Medicine

Miguel Regueiro, MD
Richard Duerr, MD
Leonard Baidoo, MD
Janet Harrison, MD
Jason Swoger, MD, MPH
Marc Schwartz, MD
Arthur Barrie, MD, PhD
Sandra El Hachem, MD
Katie Weyant, CRNP
Beth Rothert, RN, BSN
Jennifer Rosenberry, RN
Kristy Rosenberry, RN
Amy Kulas, RN
Kim Baker, RN
Claudia Ramos-Rivers, MD

William Rivers
Annette Wilson, PhD
Joann Fultz
Bettina Buchholz, MD
Andrew Watson, MD, MLitt
Wolf Schraut, MD
David Medich, MD
Jennifer Holder-Murray, MD
Eva Szigethy, MD, PhD
Wendy Elliott, PhD
David Benhayon, MD, PhD
Alka Goyal MD
David Keljo, MD
Douglas Hartman, MD
Anwar Dudekula, MD
Mahesh Gajendran, MD
Mike Dunn, MD
Anthony J. Bauer, PhD
David G. Binion, MD