Update in Pediatric IBD: 2018

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Objectives

• Explain our current understanding of factors that likely play a role in causing IBD
• Discuss our changing philosophy on treatment
• Predicting the future: How we will know what therapies to use
Start with the basics

• **Inflammation** is the body's response to injury. To protect itself from foreign invaders such as viruses and bacteria, to repair damaged tissue. When there is a danger the immune system activates to keep us safe. That is a good thing. We could not survive without inflammation.

• BUT, when the inflammation is not controlled or directed against the wrong targets it can cause us harm. That is a bad thing.
Inflammatory Bowel Disease(s) 101a

- Crohn’s disease
- Ulcerative colitis
- IBD-unspecified (indeterminate colitis)
Inflammatory Bowel Disease

- Ulcerative colitis
- Crohn’s disease

Normal colon

Ulcerative colitis

Crohn’s disease
Chronic Intestinal Inflammation Leads to:

- Abdominal pain
- Diarrhea
- Rectal bleeding
- Weight loss
- Fatigue
- Arthritis
- Rash
- Growth failure
- Cancer
- And more
Exact cause(s) currently unknown
No curative treatment
Major increase in new cases
Current Theories of What Causes IBD

• Genetic predisposition: **Your DNA** (genetic abnormality in how intestine interacts with bacteria)
• Epithelial cell abnormality: **The Wall** (defective barrier at lining of intestine, called the mucosal barrier)
• Intestinal microbiome: **The Bugs**
  – Unidentified bacteria
  – Altered ratios of pro (bad)- vs. anti (good)-inflammatory bacteria
  – Dysbiosis, abnormal concentrations of certain bacteria, but overall less bacterial diversity than normal. A bad mix of fewer than the usual number of bugs
Genetic Contribution to IBD

• Greatest risk factor- first degree relative with IBD, 5% likelihood
• Identical twin: 40% likelihood
• 85% of patients have no family history
• >200 susceptibility genes identified
• Likely overall contribution of genes to developing IBD, no more than 10-15%
Background: Shared genes immune-mediated diseases
Immigrants from low→high incidence region have rates comparable to high incidence natives. Trend not explained by genetics, but environmental changes (Westernized diet, gut microbiota?)


Loftus EV. Gastroenterology 2004; Thia KT. Am J Gastroenterol 2008
Incidence of IBD Throughout the World

Incidence group
- Low
- Low with increase
- Medium
- High
- No data
Who?

• Peak incidence 20-30 years (CD), 30-40 years (UC); 15-20% with pediatric onset

• Males = females

• Group with greatest increase over the past 20 years, young children
Over the past 20 years we have seen an explosion of new cases of IBD. But genes don’t change quickly

Environments change:
- Diet
- Antibiotic exposure

Intestinal Microbiome
Crohn's and the Hygiene Hypothesis

By Eugene L. Heyden, RN

www.impactofvitamind.com
Low hygiene, high pathogen burden: immunoregulation
High hygiene, low pathogen burden: autoimmunity, allergy
Inflammatory bowel disease in immigrants to Canada and their children: a population-based cohort study*

- Health administration database, Ontario, CA, 1994-2010

*Every decade of older immigration at arrival = 9.9% lower risk of IBD

*Benchimol et al. Am J Gastroenterol 2015;110:553
Earlier exposure to Canadian environment results in increased risk

- Canadian-born children of immigrants from some regions assumed the high Canadian incidence of IBD, indicating that the underlying risk is activated with earlier life exposure to the Canadian environment in certain groups.

Benchimol et al., Am J Gastroenterol 2015, PMID 25756238
The Human Microbiome

- Comprised of Bacteria, Viruses, others (Archaea, Eukaryotes)

- Distinctive microbiomes at each body site (gut, lung, skin, mucosa etc.)

The Gut Microbiome
- Human gut is home to ~ 100 trillion bacterial cells
- Density of $10^{11}$ to $10^{12}$ per gram in the colon
- Genome size of microbiota at least 100-fold greater than human
- Large numbers species present, most unidentified

Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa

Carlotta De Filippo, Duccio Cavalieri, Monica Di Paola, Matteo Ramazzotti, Jean Baptiste Poullet, Sebastien Massart, Silvia Collini, Giuseppe Pieraccini, and Paolo Lionetti.

PNAS. 2010.

African Diet: High fiber and carbohydrate, low animal fat and protein.

European Diet: High animal fat and protein, low fiber.
Western Diet: Promotes a Pro-inflammatory Intestinal Microbiome

- Greater amounts of meat and fats, particularly polyunsaturated fatty acids (PUFAs) and omega-6 (n-6) fatty acids. Linoleic acid (an n-6 PUFA) present in high concentrations in red meat, cooking oils, and margarine.
- Milk fat
- High sugar

- Lower risk among people with diets high in fiber, fruits, and vegetables. Believed to occur via increased production of SCFAs, which might increase barrier function by serving as a source of energy for colonocytes. SCFAs also promote immune tolerance by increasing development of T-regulatory
- The anti-colitic effects of plant-based compounds have also been studied, including curcurmin, green tea, polyphenols, and fermented grains.

Lee et al. Gastroenterology 2015;148:1087
But let me be very clear....

\[ \neq \quad \text{IBD} \]
What Protects Us From the Harmful Effects of the Microbiome
The Mucus Layer

• Multilayered mucus structures covers the intestinal surface thus allowing the vast majority of gut bacteria to be kept at a safe distance from cells that line the intestine.

• Agents that disrupt mucus-bacterial interactions might have the potential to promote diseases associated with gut inflammation.

• Emulsifiers, detergent-like molecules that are a common components of processed foods, can increase the passage of bacteria into and through the lining cells.

• Polysorbate 60, Polysorbate 80, carboxymethylcellulose
Dietary Emulsifiers

- Polysorbate 80
- Carboxymethylcellulose
Emulsifiers Affect Mucous Layer and Bacterial Proximity to Epithelium
Chaissing et al. Nature 2014
From: Hypothesis: Increased consumption of emulsifiers as an explanation for the rising incidence of Crohn's disease
J Crohns Colitis | © 2013 European Crohn's and Colitis Organisation
Early life antibiotic exposure


  In multivariate analyses, compared with cases and controls without an otitis media diagnosis, individuals with an otitis media diagnosis by age 5 years were 2.8-fold more likely to be an IBD case (95% CI, 1.5-5.2; P = 0.001).


  Exposure before 1 year of age had an adjusted hazard ratio of 5.51 (95% confidence interval [CI]: 1.66–18.28) but decreased to 2.62 (95% CI: 1.61–4.25) and 1.57 (95% CI: 1.35–1.84) by 5 and 15 years, respectively. Each antibiotic course increased the IBD hazard by 6% (4%–8%). A dose-response effect existed, with receipt of >2 antibiotic courses more highly associated with IBD development than receipt of 1 to 2 courses, with adjusted hazard ratios of 4.77 (95% CI: 2.13–10.68) versus 3.33 (95% CI: 1.69–6.58).
Hazard of developing IBD if ever previously exposed to antianaerobic antibiotics, according to age.

Matthew P. Kronman et al. Pediatrics 2012;130:e794-e803

©2012 by American Academy of Pediatrics
A, Proportion of subjects developing IBD according to age and antianaerobic antibiotic exposure status.

Matthew P. Kronman et al. Pediatrics 2012;130:e794-e803
So What Does All This Mean

• In some people a combination of their DNA, early life exposures to certain diet, antibiotics, and likely other environmental factors increases the likelihood of developing IBD
• BUT, some people get IBD with none of this
• AND, most people do not get IBD despite all of this
• These are clues to us as we search for the cause(s)
We have made progress since the 1980s

- Azulfidine
- Prednisone
- Antibiotics
- Intravenous nutrition
- Tube feeding
- Surgery
This is what we saw in the 1980’s, but not any more

Delayed Growth and Development

Medication toxicity
Revolutionary Change in Treatment: 1998, the Age of monoclonal antibody therapy: proteins that neutralize chemicals in the intestine that promote inflammation

Remicade (infliximab)
Humira (adalimumab)
Simponi (golimumab)
Cimzia (certolizumab)
Tysabri (natalizumab)
Entyvio (vedolizumab)
Stelara (ustekinumab)
We can do better!

How much better?
CURE?

GENE EXPRESSION NORMALIZATION

ULTRASTRUCTURAL HEALING/MRE

HISTOLOGIC HEALING: Biopsy

ENDOSCOPIC MUCOSAL HEALING

LABORATORY IMPROVEMENT: CRP, ESR, CALPROTECTIN

SYMPTOM IMPROVEMENT

PYRAMID OF SUCCESSFUL THERAPY
Progressive Bowel Damage in CD

What you see on the outside does not always indicate Symptom assessment is not enough

Pariente et al. Inflamm Bowel Dis 2011
Colombel Gastroenterology 2017
Mucosal Healing Has Become The Holy Grail

“I have finally found it. Mucosal healing.”
Mucosal healing means the absence of visible Inflammation. Healing is used as a noun. Healing can also be used as a verb and then it means improving, ↓ activity score.
Treat to Target

It means looking on the inside periodically.

It means you have to check the levels of the medications we are using to make sure we are giving an adequate amount.
Benefits of Improving Achieving Mucosal Healing in Adults

• Sustained clinical remission
• Reduction in steroid and immunosuppressive use
• Decreased hospitalization rates
• Reduction in colectomy and surgical resection
• Reduction in colorectal cancer risk
• Benefit may even be greater in children who have the longest horizon for disease duration

Dulai et al. Gastrointestinal Endoscopy 2015;82:246
What Does This Mean Practically

• Optimizing care early, not late, for children with more severe disease
• Taking medications as instructed
• Regular follow-up and close monitoring
Increased Effectiveness of Early Therapy With Anti–Tumor Necrosis Factor-α vs an Immunomodulator in Children With Crohn’s Disease


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Predict the Future and Match Our Therapy to Anticipated Course: Risk Stratification

Where we have been

Over treatment

Where we need to be

Under treatment
One Approach Does Not Fit All Patients

Risk Stratification: Using BIG data to predict outcome and tailor therapy
UNDERSTANDING DIFFERENT
Two Key Initiatives

• RISK study (CCFA): 2008 to present, 1100 newly diagnosed children with Crohn’s disease, careful clinical follow-up and biospecimens (DNA, plasma, stool, biopsy tissue)

• PROTECT: Predicting Response to Standardized Colitis Therapy (NIDDK): 2012 to present, 430 newly diagnosed children with ulcerative colitis careful clinical follow-up and biospecimens (DNA, plasma, stool, biopsy tissue) treated with standardized therapy

• These studies are already changing the way we think about pediatric IBD
Much heavy lifting still to be done. Importance of research
This Ain’t Easy

Take home lessons:
1. It is important to understand the natural history of pediatric IBD
2. Early use of our best medications is needed in children with more severe disease
3. Current research is not only allowing us to better understand these diseases, but to choose the best therapy for each child
4. We are all in this together
ACKNOWLEDGEMENT

It is a partnership
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- Clinical Trials Unit
- Attending Physicians
- Research Services
- IBD Nurses
- Radiology
- Endoscopy
- Surgery
- Nutritionists
- Pathology
- Research Support
- Psychology & Social Work

[Images of medical professionals]