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**Evolution of IBD: Research Lessons Learned**

I have the following financial relationships to disclose:  
Janssen  
UCB

**IBD: The Pediatric Burden & the impact of Pediatric IBD research**

- 1.2 million people with IBD in the US, estimated 80-100,000 children with IBD
- About 20-25% of all IBD is diagnosed during the pediatric age
- Identification of BIOTYPE = Genotype + Phenotype + Immunotype + Bacteriotype + ???  
  clearest in pediatric IBD leading to Risk stratification and personalized therapy in IBD.

**Major Issues in IBD Diagnosis and Therapy Plagued us over the last few decades!**

- The cause of IBD!
- Differential diagnosis between CD and UC (colonic disease)
- Limited endoscopic approaches & lack of good small bowel imaging
- Surgery: the only answer to failure of medical therapy (sulfasalazine and steroid)
- Complete lack of studies in the pediatric age group while knowing pediatric disease is different from adult disease?
- Inability to induce long lasting remission (& mucosal healing)

**Evolution of IBD:**

**What have we learned in the last 50 years?**

**Agenda for the talk**

- IBD epidemiology & natural history
- Pediatric disease activity index: PCDAI & PUCAI
- TNF in stool leading to discovery of anti-TNF as groundbreaking therapy in IBD
- Gene discoveries and therapeutic targets
- Microbiome, diet and intestinal inflammation
- Risk Prognostication in IBD
- Evolution of collaborative research in pediatrics compared to single center/investigator effort

**Evolution of IBD epidemiology and natural History**
Rising Incidence-global trends

Crohn’s disease  Ulcerative Colitis

Molodecky, Gastroenterology, 2012

Worldwide Incidence

Crohn’s disease  Ulcerative colitis

Benchimol, Inflamm Bowel Dis, 2011

Rising Incidence, becoming stable in Omstead county, MN

Crohn’s disease  Ulcerative Colitis

Loftus, Inflamm Bowel Dis, 2007

Incidence: Pediatric IBD

Overall incidence of IBD: 9.5 per 100,000
Incidence stable over last 8 years

Adamiak, Inflamm Bowel Disease, in press 2012

Rising incidence of UC in Korea

* Incidence in Korea increased 3-4 decades after North America and Western Europe
* Might this be due to “Westernization”?

Yang S-K et al, J Gastroenterol Hepatol, 2000

Incidence in Indian Migrants to UK

<table>
<thead>
<tr>
<th>Location (area)</th>
<th>Year</th>
<th>Ulcerative colitis</th>
<th>Crohn’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lecrossen, England (2)</td>
<td>1981-1989</td>
<td>15.9</td>
<td>3.1</td>
</tr>
<tr>
<td>North Asians</td>
<td>1981-1989</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>Europeans</td>
<td>1981-1989</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td>Europeans</td>
<td>1991-1994</td>
<td>7.0</td>
<td></td>
</tr>
</tbody>
</table>

IBD incidence in South Asian migrants ≥ Western-born population

Regional Variation: Crohn's disease prevalence

- 213 (206-220) *
- 211 (204-217) *
- 180 (174-186)

Evolution of IBD epidemiology and natural History

Research Lessons learned
- World-wide increase in IBD
  - Globally, IBD is still rising
  - Incidence stabilized in western countries!
  - Increasing in developing countries & new populations – where the research should be targeted!!

The PCDAI
- Abdominal pain (0-10)
- Stools/bleeding (0-10)
- Functioning/well being (0-10)
- Laboratory:
  - Hct (0-5)
  - ESR (0-5)
  - Albumin (0-10)
  - Weight (0-10)
  - Height velocity (z score) (0-10)
  - Abdominal exam (0-10)
  - Perirectal disease (0-10)
  - EIM (0-10)

Studies evaluating the PCDAI & PUCAI in different scenarios
- Gastroenterology 2007;132:863-73
  - Pediatr Infliximab trial
- Gastroenterology 2012;143:365-74
  - Pediatr Adalimumab trial
  - Pediatr Gastroenterol Nutr 2007;44:185-91
  - Pediatr Natalizumab trial
  - Infanum Inst J 2011;17(8):1726-30
  - J Clin Epulsem 2008;57:331-338
  - Gastroenterology 2007;133:423-432

The PUCAI

Development of Pediatric Disease Activity Indices: PCDAI & PUCAI

Correlation of the PUCAI with colonoscopy
TNF in stool leading to discovery of anti-TNF as groundbreaking therapy in IBD

Different anti-TNF: comparable results (Years 2000 to 2006)

REACH: Pediatric CD infliximab trial
Anti-TNF therapy is highly efficacious in inducing remission

Early aggressive biologic therapy induced more mucosal healing than conventional management of Crohn’s disease

Anti-TNF: fewer surgeries and post-surgical recurrence
**Anti-TNF: ‘Top down’**

**Evolution in the initial approach in pediatric IBD**

- 10 year-old presented with rectal bleeding, perianal pain
- Growth failure and iron deficiency anemia
- Exam under anesthesia & MRI: recto-labial fistula and perianal fistulae
- Endoscopy: severe left sided Crohn’s colitis & inflammation
- Induction with ‘top down’ biologic therapy rather than ‘step up’ therapy

**Before**

**After**

**Steroids vs 6-MP for maintenance of remission in pediatric Crohn’s**

<table>
<thead>
<tr>
<th>Days Since Remission Induction</th>
<th>% of Patients in Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>50</td>
<td>91%</td>
</tr>
<tr>
<td>100</td>
<td>90%</td>
</tr>
<tr>
<td>150</td>
<td>89%</td>
</tr>
<tr>
<td>200</td>
<td>88%</td>
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<tr>
<td>250</td>
<td>87%</td>
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<td>450</td>
<td>83%</td>
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<td>500</td>
<td>82%</td>
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<tr>
<td>550</td>
<td>81%</td>
</tr>
<tr>
<td>600</td>
<td>80%</td>
</tr>
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**Crohn’s disease: therapeutic evolution**

1980: Antibiotics
1979: Sulfasalazine, Steroids
1998: Infliximab
1994: Methotrexate, Budesonide
1993: 5-ASA
2005: Second-generation Biologicals

**Pediatric CD Registry and Wisconsin population-based cohort study**

<table>
<thead>
<tr>
<th>Time point</th>
<th>N</th>
<th>% on AZA/6-MP/MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>At Diagnosis</td>
<td>578</td>
<td>21%</td>
</tr>
<tr>
<td>30 days</td>
<td>525</td>
<td>41%</td>
</tr>
<tr>
<td>3 months</td>
<td>515</td>
<td>56%</td>
</tr>
<tr>
<td>1 year</td>
<td>410</td>
<td>69%</td>
</tr>
<tr>
<td>2 years</td>
<td>276</td>
<td>76%</td>
</tr>
</tbody>
</table>

**Infliximab: Cumulative Commercial Patient exposure by Indication**

**Hepatosplenic T-cell Lymphoma in Infliximab-treated Patients: Cumulative Review**

- 27 reported/possible cases
- All were reported between 2002 and February 2011
- All patients had reported exposure to azathioprine or 6-mercaptopurine
- 5 cases with another anti-TNF-α antagonist
- 26 confirmed cases reported to be HSTCL, all in IBD (22 CD, 4 UC)
- 23 cases have been fatal
The therapeutic “pendulum”

2004 – everyone on combination therapy
2008 – everyone on biologic or immunomodulator monotherapy
2012 – more use of combination therapy

Pediatric IBD; impact of HSTCL is HUGE

What we have:
- Fatal form of lymphoma
- Large, population-based FDA mandated registry (DEVELOP - short and long-term) is ongoing.

What we need:
- More follow up
- Risk stratification and translational studies

Genetics of IBD and therapeutic targets

Timeline of genetic discoveries in IBD

Many loci are shared, few are specific
Loci segregates specific disease mechanism

Less organ-specific, More mechanism/pathway oriented
Clinical and therapeutic value of genetic discoveries in IBD

Mucosal gene signatures to predict response to infliximab in patients with ulcerative colitis

Children carrying 14 or more of the common CD-risk alleles have a ~15-fold increased risk of developing CD, and children carrying 8 or more of the common UC-risk alleles have a ~7-fold increased risk of developing UC.

Imielinski M et al. Nat Genetics 2009;41:1335

Children carrying 34 or more of the common CD-risk alleles have a ~13-fold increased risk of developing CD, and children carrying 20 or more of the common UC-risk alleles have a ~7-fold increased risk of developing UC.

These initial findings need replication in large, well phenotyped and prospective cohorts.

Gene discovery can help in diagnosis and therapy

Drug-mediated modulation of autophagy

Evolution of IBD Genetics and therapeutic targets

Research Lessons learned

CD and UC are very closely related.

Genetics of IBD is shared with many other complex disorders. The genetic research has become less organ-specific, but focuses on molecular level and common pathways.

Identification of clusters of 'Bio-types' can be used to target specific biological pathways.

Firm genomic diagnosis can be used for definitive therapies to reverse the IBD.
Microbiome, diet and intestinal inflammation

Our environment determines the composition of the gut microbiota

Antibiotics and Pediatric IBD

Experimental evidence supporting the hygiene hypothesis
Summary of gut microbiota main composition in IBD

<table>
<thead>
<tr>
<th>Phylotype</th>
<th>Healthy</th>
<th>Disease (IBD)</th>
<th>'Clean' Pigs</th>
<th>'Dirty' pigs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Firmicutes</td>
<td>![↑]</td>
<td>![↓]</td>
<td>![↓]</td>
<td>![↑]</td>
</tr>
<tr>
<td>Bacteroidetes</td>
<td>![↑]</td>
<td>![↓]</td>
<td>![↑]</td>
<td>![↑]</td>
</tr>
<tr>
<td>Proteobacteria</td>
<td>![↓]</td>
<td>![↑]</td>
<td>![↑]</td>
<td>![↑]</td>
</tr>
</tbody>
</table>

Diet shapes the gut microbiota

- **Rural Africa (Burkina Faso)**: High carbohydrate, fiber and low animal protein diet. Children breast-fed up to the age of 3.
- **Urban Europe (Florence, Italy)**: Typical western diet high in animal protein. Children breast-fed for up to age 1.

Dietary patterns are associated with specific gut microbial patterns

- **Protein & animal fat**: Included in the Western diet but not the normal diet.
- **Carbohydrates**: Included in the normal diet but not the Western diet.

Modulation of bacterial function by food additives

- **Normal diet**: Low in malto +
- **Western diet**: High in malto +

Different bacterial species induce different phenotypes of colitis in IL-10-deficient mice

- **Germ-free**: No colitis
- **Commensal bacteria**: Pancolitis (Right sided) Onset 1 wk
- **E. faecalis**: Left sided 10-12 wks
- **E. coli**: Right sided 3 weeks
- **E. coli + E. faecalis**: Pancolitis 1 week

Recurrence of ileal Crohn’s disease before and after infusion of intestinal contents

- **Ileocolic resection, 1st anastomosis, recurrence 85%**
- **Resection, 1st anastomosis, proximal diversion, no recurrence**
- **Takedown of proximal ostomy, recurrence <1 month**
- **Reinfusion of luminal contents, inflammation within 1 week**
Evolution of collaborative research in pediatrics compared to single center/investigator effort

Risk Stratification (Prognostication) in IBD

More antibody types, more disease risk

Preliminary microbial analysis from the RISK cohort
- MiSeq 16S rRNA gene sequencing (V4)
- ~10k filtered seqs/sample
- 61 CD, 31 control
- CD: 51 no complications, 10 w/ complications

Study:
- Genetic makeup
- Bacteria in bowel
- Serology (reactive to bacteria, food, infections, etc)
- Environmental exposures

1,200 children w/ Crohn's disease at diagnosis
160 – 200 patients w/ complication / surgery

3 year follow up

Research:
- PRO-KIDS Research Database

1200 children w/ Crohn's disease at diagnosis

Study:
- Genetic makeup
- Bacteria in bowel
- Serology (reactive to bacteria, food, infections, etc)
- Environmental exposures

1,200 children w/ Crohn's disease at diagnosis
160 – 200 patients w/ complication / surgery

3 year follow up

Research:
- PRO-KIDS Research Database
In patients with ileal CD, Ruminococcaceae, and Faecalibacterium were dramatically decreased compared to control subjects.

In patients with ileal CD, Fusobacteria were dramatically increased compared to control subjects.

Preliminary microbial analysis show both decreased and increased taxa in risk cohort.

Fecal microbiota transplant for IBD

Systematic review: faecal microbiota transplantation in the management of inflammatory bowel disease

17 case series: 41 patients with IBD (27 UC)

- reduction of symptoms: 76%
- cessation of IBD medications: 76%
- disease remission: 63%
- resolution of concurrent C. difficile: 100%

Perhaps, we can do selective FMT based on individual’s flora and genetics.

Can the host’s mucosal gene expression at the time of diagnosis predict complications?

Evolution of IBD
Risk Stratification
Research Lessons learned

- Small proportion (20%) of CD accounts for 80% of complicated disease (and healthcare needs)
- These high risk patients are identifiable at the time of diagnosis with relatively low cost
- Individualized care based on RISK
  - Best approach for risk/benefit ratio
  - Reduce overall cost in long term

Remember the Key note speech delivered by Dr Clark.

IBD: The Pediatric Burden & the impact of Pediatric IBD research

- 1.2 million people with IBD in the US, estimated 80-100,000 children with IBD
- About 20-25% of all IBD is diagnosed during the pediatric age
- Identification of BIOTYPE = Genotype + Phenotype + Immunotype + Bacteriotype + ?? Future of IBD management.

Hypothesis: IBD biotypes drive the IBD phenotype and outcome
ACKNOWLEDGEMENT

Topics and contents I have chosen for the talk were suggested by the following IBD'ologists and scientists:

Francisco Sylvester
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Jeff Hyams
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Marla Dubinsky
Ted Denson
Alex Muise
Tim Boyle
Claudio Fiocchi
Timing as a critical factor in IBD: early life stress, "sensitive period", and IBD evolution

Life with IBD

Early disease Late disease

Less plasticity, "insensitive" period

Life before IBD

Clinical symptoms, diagnosis

Exposed, EGG, GEG, epigenetics, etc.

Life after IBD

Remission, recurrences, hospitalizations, operations, cancer, etc.

Response / no response to therapy

Unknown ultimate outcome

Sensitive period

Early life events: fetal development, exposures, contact, immune priming, GEG and GEG, interactions, epigenetics, etc.

Conception Birth

Early life stress, "sensitive period", and IBD evolution