Epidemiology of Inflammatory Bowel Disease

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Loftus Disclosures (last 12 months)

• Consultant
  – AbbVie
  – UCB
  – Janssen
  – Takeda
  – Immune Pharmaceuticals
  – MedImmune
  – Celgene

• Research support
  – AbbVie
  – UCB
  – Bristol-Myers Squibb
  – Shire
  – Genentech
  – Janssen
  – Amgen
  – Pfizer
  – Takeda
  – Takeda
  – GlaxoSmithKline
  – Robarts Clinical Trials
Overview

- Incidence and Prevalence
- New Regions
- Racial/Ethnic Differences
- Risk Factors
  - “Old”: smoking, appendectomy, etc.
  - “New”: hygiene, antibiotics, diet, etc.
Temporal Trends in Crohn’s Incidence

Molodecky NA et al, Gastroenterology 2012;142:46-54.e-42.
Temporal Trends in UC Incidence

Molodecky NA et al, Gastroenterology 2012;142:46-54.e-42.
Changing Geographic Distribution of IBD
“North-South Gradient”
Not just IBD...

...but also in other immune-mediated diseases.

North-South Gradient in US?

• Nurses’ Health Studies
• Geographic residence at birth, and ages 15 years and 30 years recorded
• Stratified incidence by northern, middle, and southern latitudes

• Effect was strongest for residence at age 30
• Incidence of UC was 36% lower in southern latitudes relative to northern
• Incidence of Crohn’s was 53% lower in southern relative to northern

Rise of IBD in Asia

Thia KT et al, Am J Gastroenterol 2008
Incidence of IBD Among South Asians and Native Britons in Leicestershire, 1981-89

Probert et al, Gut 1992;33:687
Jayanthi et al, QJMed 1992;82:125
Genetics Can’t Explain It All

- Prevalence of NOD2 mutations varies widely in populations
  - Low in Scandinavia, Finland, Australia
  - High in Belgium, Canada
  - Doesn’t correlate with Crohn’s incidence rates
- Don’t forget the twin studies!!!
  - 20-50% concordance in identical twins

Relationship Between Environmental Factors and Development of CD and UC

Risk elevated

- OC use
- GI infections
- High carbs/fats
- Urban/pollution
- Antibiotics
- Smoking
- Stress
- Linoleic acid

Lowered risk

- Vitamin D
- High fiber
- H. pylori
- Helminth
- Smoking

Crohn’s disease
Ulcerative colitis
Both CD and UC

OC = oral contraceptive; GI = gastrointestinal; carbs = carbohydrates.

Cigarette Smoking and IBD: Updated Meta-Analysis

<table>
<thead>
<tr>
<th>Crohn’s Disease</th>
<th>Ulcerative Colitis</th>
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<tbody>
<tr>
<td>• 9 studies, &gt;10,000 patients</td>
<td>• 13 studies, &gt;11,000 patients</td>
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<tr>
<td>for Crohn’s</td>
<td>for UC</td>
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<tr>
<td>• Current smoking is</td>
<td>• Current smoking is protective of</td>
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<td>associated with Crohn’s:</td>
<td>development of UC: RR, 0.58 (95% CI,</td>
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<td>RR, 1.76 (1.40 – 2.22)</td>
<td>0.45 - 0.75)</td>
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<tr>
<td>• Former smoking is weakly</td>
<td>• Quitting smoking is associated with</td>
</tr>
<tr>
<td>associated with Crohn’s:</td>
<td>UC: RR, 1.79 (1.37 - 2.34)</td>
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<tr>
<td>RR, 1.30 (0.97 – 1.76)</td>
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Appendectomy Is Protective Against the Risk of Ulcerative Colitis

• Multiple studies show that risk of UC is decreased by almost 70% among those who underwent appendectomy
• But only among those undergoing appendectomy for appendicitis under the age of 20 years
• Slight increased risk of Crohn’s?
  - But may be confounded by fact that some patients with Crohn’s present with RLQ abdominal pain and are mistakenly diagnosed with appendicitis

Kotroubakis et al, Inflamm Bowel Dis 2002;8:277
Andersson et al, N Engl J Med 2001;344:808
Oral Contraceptive Meta-Analysis

Crohn’s Disease

Adjusted RR, 1.46 (1.26-1.70)

• Former OCP use not associated with increased RR

Ulcerative Colitis

Adjusted RR, 1.28 (1.06-1.54)

Nurses’ Health Studies

• Advantage:
  – Allows for high-quality risk factor analysis since data are collected prospectively

• Disadvantage:
  – Does it only apply to women who are diagnosed with IBD in their 30’s or later?

• Nearly 250,000 women enrolled
• Millions of person-years of follow-up
• Prospectively collected data
• Incident cases of IBD identified over time – approximately 400 each
Summary of Nurses’ Health Study Findings

- **Protective Factor**
  - Long-chain n-3 polyunsaturated fatty acids, UC
  - Dietary fiber intake, CD
    - Fruits > vegetables > cereal/grains/legume

- **Risk Factor**
  - Ex-smoking, UC
  - Smoking, CD
  - Hormone replacement, UC
  - Oral contraceptives, CD
  - NSAID use >15 days/month for both
  - Vitamin D deficiency, CD > UC
  - Depressive symptoms, CD
  - Trans-unsaturated fats, UC

Higuchi L et al, Am J Gastroenterol 2012;107:1399-1406
Khalili H et al, Gastroenterology 2012;143:1199-1206
Incidence of Infection and Autoimmunity: Inverse Relationship?

If infections do protect against autoimmune diseases …

“…There is a certain irony in the fact that we must now search for new ways to reproduce the infectious diseases against which we have been fighting with great success over the past three decades.”

TB = tuberculosis; MS = multiple sclerosis.
‘Hygiene Hypothesis’

• Incidence of immune-mediated diseases rising in developed countries
  – Related to modern hygiene, lack of exposure to bacteria?
• Conflicting data in IBD
  – Manitoba case-control: early childhood exposure to pets, being from larger families protective
  – Montreal case-control: owning a pet was risk factor; less crowding, owning personal towel were protective

Bernstein CN et al, Am J Gastroenterol 2006;101:993-1002
H. Pylori Infection and IBD Risk: Meta-Analysis

- 23 articles
- Pooled risk of IBD in H. pylori infected individuals: 0.64 (0.54-0.75)
  - 0.60 in Crohn’s, 0.75 in UC
  - Significant heterogeneity
  - Subgroups analyses by methods of diagnosis, region, age couldn’t explain

Luther J et al, Inflamm Bowel Dis 2010;16:1077-84.
Is Helminth Exposure Protective?

• Can have profound effects on mucosal immune system

• South African case-control study: childhood exposure to helminths, OR of Crohn’s, 0.2 (0.1-0.4) and OR of UC, 0.2 (0.1-0.6)

• Small trials of *Trichuris suis* ova (pig whipworm eggs) in IBD showed beneficial effect, larger studies underway

Antibiotic Use and Risk of IBD

• Case-control study of pediatric onset IBD in Manitoba
  - 58% of cases had antibiotics prescribed in 1st yr of life, vs. 39% of controls (OR, 2.9; 1.2-7.0)

• Case-control study of adult onset IBD in Manitoba
  - 12% of cases had at least 3 antibiotic courses 2-5 yrs before dx vs 7% of controls
  - OR, 1.5 (1.3-1.8)

Gastroenteritis and Risk of IBD

- U.S. military database: infectious gastroenteritis increased risk of IBD by 40%
  - Previous IBS diagnosis along with gastroenteritis increased risk of IBD 5-fold
- Large GPRD study in U.K. showed 2- to 3-fold increased risk of IBD among those with gastroenteritis

Garcia-Rodriguez LA et al, Gastroenterology 2006;130:1588-94.
Diet and Microbiome and IBD?

- Large differences in microbiome between regions and between rural/urban
- High fat diets increase Proteobacteria and Firmicutes and decrease Bacteroidetes

Kashyap PC et al, J Allergy Clin Immunol 2013;152:250-250.e5
Wu GD et al, Anaerobe 2013 (online early)
The Return of Diet as a Risk Factor?

- Difficult to study
- May exert effect indirectly via microflora
- Increased sugar intake
- Increased fat intake
- Increased protein intake
- Future studies may need to focus on dietary patterns rather than individual foods

Chapman-Kiddell CA et al, Inflamm Bowel Dis 2010
Psychological Stress and IBD

- Recent systematic review of 18 prospective studies examining stress as a risk factor for disease exacerbations
- 13 studies showed significant association
- Coping behaviors appear to modulate effect of stress

Camara RJA et al, Digestion 2009
How Modern Lifestyle Might Alter Enteric Microflora

- Improved sanitation
- Decline in endemic parasitism
- Decreased exposure to soil microbes
- Decline in *Helicobacter*
- Increased antibiotic usage
- Less crowded living conditions
- Refrigeration
- Sedentary lifestyle / obesity
- Increased consumption refined sugars, saturated fats

“Life on concrete”

Adapted from Bernstein C & Shanahan F. Gut 2008; 57: 1185-91.
Conclusions

• Incidence and prevalence of IBD still rising in many areas
• Studies of migrant populations suggest environmental factors
• Hygiene hypothesis is promising
  - H. pylori infection and helminth exposure protective
• Changes in fecal microbiome?
• Vitamin D deficiency may explain north-south gradient
• In summary, IBD epidemiology rapidly evolving!