Why is inflammatory bowel disease increasing in Asia?

Claudio Fiocchi
The Cleveland Clinic Foundation
Lerner Research Institute
Departments of Pathobiology, Gastroenterology & Hepatology
Cleveland, Ohio, USA
Distribution of IBD: 1970-1990
Is this the future distribution of IBD?
Key questions on IBD pathogenesis

1. Why has IBD appeared in Northern Europe and North America first?

2. Why has only later IBD appeared in the rest of Europe, Japan and South America?

3. Why is it only now that Asian countries begin to see IBD?

4. Does the progressive rise in IBD in time and space hold any clues to its pathogenesis?

5. Can the emergence of IBD in Asia help to answer questions about IBD anywhere else?
Cumulative Number of IBD Patients Registered in Japan

Ulcerative colitis

Crohn’s disease

Courtesy of Dr. H. Ogata
Increasing incidence of IBD in Korea

Ulcerative colitis

Crohn’s disease

Courtesy of Dr. Won Ho Kim
Numbers of Chinese UC patients hospitalized and screened by endoscopy from 1990-2003

Courtesy of Dr. Qin Ouyang
Increasing incidence of IBD in Malaysia

Kitahora et al., 1995
Progressive Increase of IBD Incidence in Puerto Rico

**FIGURE 6.** The incidence of inflammatory bowel disease in southwest Puerto Rico, 1996–2000, separated by primary diagnosis (*nonspecifed IBD*).
Distribution of new onset pediatric IBD cases in Wisconsin from 2000 to 2001

- Crohn's disease: 129
- Ulcerative colitis: 60
- Indeterminate colitis: 10

New IBD diagnosis
- Caucasian: 87%
- Asian: 6%
- African-American: 4%
- Hispanic: 2%
- Other: 0.5%

General population
- Caucasian: 86%
- Asian: 6%
- African-American: 4%
- Hispanic: 2%
- Other: 2%

IBD families
- No family history: 89%
- 1st degree: 8%
- 2nd degree: 3%

Changes in frequency and age of pediatric IBD

% Entire CD population

1970’ 1980’

Age at diagnosis

1970’ 1980’
Familial and Genetic Predisposition to IBD
Key features of IBD in Asia

1. The rise of IBD in Asia is real and is generally comparable among different Asian countries.

2. The pattern of IBD emergence in Asia is similar to that of other countries where IBD is also recently appearing.

3. IBD in Asia displays features characteristics of “new IBD”, with generally less severe clinical manifestations, lack of familial incidence, and few pediatric cases.
The incidence of *infectious* diseases has decreased and of *immune-mediated* disorders has increased over the last four decades.

![Graph showing the decrease in infectious diseases and the increase in immune disorders from 1955 to 1995.](image-url)
Components of IBD pathogenesis

1. The genetic make up
2. The environment
3. The enteric flora
4. The immune system
Components of IBD pathogenesis

1. The genetic make up
2. The environment
3. The enteric flora
4. The immune system
Genetic Associations in IBD

**Genetic Associations in IBD**

1. **IBD7**
   - TNF-R family
   - HSPG2
   - UBE1L
   - TGF-β2
   - TGF-β4
   - E2G

2. **IBD9**
   - CCR5
   - CCR9
   - hMLH1
   - IL12A

3. **IBD5**
   - IL-2 gene
   - CD4
   - OCTN

4. **IBD10**
   - HLA Class I-III
   - TNF

5. **IBD3**
   - MUC3
   - EGFR
   - HGF

6. **IBD12**
   - VDR
   - NRAMP2
   - STAT6
   - MMP 18
   - AVIL
   - Interferon-γ
   - B2-integrin

7. **IBD4**
   - TCR α and δ
   - Proteasome cluster
   - Leukotriene B4 receptor

8. **IBD8**
   - ICAM1
   - C3
   - TBXA2
   - LTB4H

9. **X**

**Linkage significance**

- **Confirmed & replicated**
- **Other**

*Significance levels defined by Lander and Kruglyak*
Genetic Mutations Associated with IBD

Crohn’s disease
Chromosome 16 (IBD1): NOD2/CARD15 gene
Protein is involved in bacterial recognition and apoptosis

Chromosome 5 (IBD5): OCTN gene
Protein is an organic cation transporter

Inflammatory bowel disease
Chromosome 10: GLD5 gene
Protein is involved in epithelial integrity
Ethnicity and IBD genetics

**HLA**
- DRB1*1502 associated with UC in Jewish and Japanese populations
- DRB1*0103 associated with UC and CD in non-Jewish population

**NOD2/CARD15 (IBD1)**
- No association with CD in Japanese or Chinese populations
- Different mutation frequencies in Jews

**OCTN (IBD5), DLG5**
- No association with CD in the Japanese population

**NRAMP1, IL-18**
- Association with CD and UC, respectively, in Japanese patients

Courtesy of Dr. M. Silverberg
1. IBD in Asia is apparently not associated with the same genetic mutations detected in Western countries.

2. Different genetic associations may be underlying IBD in Asian populations.

3. The lack of common genetic mutations in Asian IBD patients and the rapid rise in incidence suggest a major role of environmental factors in the development of IBD in Asia.
Psoriasis
Major depression
Schizophrenia
IQ
Neurotic/extrovert
Diabetes
Asthma
Cardiac disease
Cancer
Multiple sclerosis

Adapted from Chakravarti and Little, Nature 2003
Components of IBD pathogenesis

1. The genetic make up
2. The environment
3. The enteric flora
4. The immune system
The ten leading causes of death in the United States during the last century

Increase in autoimmune diseases
Increase in host susceptibility
Restricted immune system stimulation
Selective nutrition
Clean food & water
Hygiene & sanitation
Lack of parasites

Decrease in infectious diseases
Decrease in host susceptibility
Decrease in disease transmission
New antigen exposure
Immunizations
Safer food & water
Antibiotics

Better nutrition
Better housing

Environmental factors

Genes

Immune system

Inflammatory bowel disease

Geography and social status

Stress

Microbes and enteric flora

Permeability

Appendectomy

Drugs

Diet

Smoking

Genes

Immune system
Potential contribution of stress to IBD pathogenesis

Stress!!!

Neuroendocrine response

Dietary antigens

Enteric flora

Bowel inflammation

Mucosal immune system activation

Mucus

Permeability

Key features of IBD in Asia

1. Multiple environmental factors are probably associated with the appearance of IBD in Asia.

2. The environmental factors predisposing to IBD in Asia are likely to be similar to those of Western countries.

3. Due to their large number, it is doubtful that specific environmental factors responsible for Asian IBD can be easily identified.
Components of IBD pathogenesis

1. The genetic make up
2. The environment
3. The enteric flora
4. The immune system
Types and concentration of bacteria in the human gastrointestinal tract

**UPPER BOWEL**
(Stomach and Duodenum)
(10^1-10^3 CFU/ml)
Lactobacilli, Streptococci, Yeasts

**SMALL BOWEL**
(Jejunum and ileum)
(10^4-10^8 CFU/ml)
Lactobacilli, Streptococci, Enterobacteriaceae, Bacteroides, Fusobacteria, Bifidobacteria

**LARGE BOWEL (Colon)**
(10^{10}-10^{12} CFU/ml)
Bacteroides, Clostridia, Pseudomonas, Bifidobacteria, Streptococci, Lactobacilli, Veillonella, Protozoa, Yeasts, Fusobacteria, Proteus, Enterobacteriaceae, Staphylococci

C. De Simone
**Temporal succession of bacterial composition in infant stools**

<table>
<thead>
<tr>
<th>Month</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>11</td>
<td>14</td>
<td>17</td>
<td>19</td>
<td>21</td>
<td>24</td>
<td>30</td>
<td>32</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>51</td>
<td>66</td>
<td>82</td>
<td>108</td>
<td>122</td>
<td>159</td>
<td>181</td>
<td>207</td>
<td>238</td>
</tr>
<tr>
<td></td>
<td>272</td>
<td>294</td>
<td>323</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Breast-milk**

**Weaning**

**Withdrawal of breast-milk**

<table>
<thead>
<tr>
<th>N</th>
<th>Species</th>
<th>%</th>
<th>N</th>
<th>Species</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><em>E. coli</em></td>
<td>97</td>
<td>9</td>
<td><em>Veillonella atypica</em></td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td><em>Veillonella dispar</em></td>
<td>97</td>
<td>10</td>
<td><em>Enterobacter aerogenes</em></td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td><em>Streptococcus thermophilus</em></td>
<td>99</td>
<td>11</td>
<td><em>Clostridium neonatale</em></td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td><em>Enterococcus raffinosus</em></td>
<td>96</td>
<td>12</td>
<td><em>Clostridium neonatale</em></td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td><em>Ruminococcus gnavus</em></td>
<td>96</td>
<td>13</td>
<td><em>Clostridium neonatale</em></td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td><em>Enterococcus avium</em></td>
<td>99</td>
<td>14</td>
<td><em>Bifidobacterium breve</em></td>
<td>98</td>
</tr>
<tr>
<td>7</td>
<td><em>Streptococcus salivarius</em></td>
<td>96</td>
<td>15</td>
<td><em>Veillonella dispar</em></td>
<td>96</td>
</tr>
<tr>
<td>8</td>
<td><em>Clostridium paraputrificum</em></td>
<td>91</td>
<td>16</td>
<td><em>Streptococcus salivarius</em></td>
<td>98</td>
</tr>
</tbody>
</table>

Favier et al. 2002
Influence of the intestinal flora on immunity in early life

Differences in the composition of the gut flora between infants who *will* and infants that *will not* develop allergies are demonstrable before the development of clinical manifestations of atopy.

*(B. Bjorksten et al. J Allergy Clin Immunol 2001)*

In young mice, signals provided by the intestinal flora inhibit the development of allergic responses. Changes in flora composition induced by antibiotics render the mice susceptible to allergy.

Evidence implicating the gut flora in the pathogenesis of IBD

- Occurrence of IBD lesions in gut segments with the highest concentrations of bacteria
- Increased numbers of bacteria in the mucosa of IBD patients
- Beneficial effect of fecal stream diversion in preventing CD and recurrence upon restoration of fecal flow
- Attenuation of IBD by antibiotics and probiotics
- Immunological reactivity against bacterial antigens in IBD patients
Main features of the enteric flora in IBD

- The study of the flora is as challenging, but potentially as rewarding as genetics.
- The flora plays a key role in most animal model of IBD, as well as humans.
- The flora of IBD patients differs from that of control subjects, is unstable and shows reduced diversity.
- Some *E. coli* and *B. vulgatus* may have a special detrimental role in IBD.

Key features of IBD in Asia

1. The commensal enteric flora is likely to be involved in the pathogenesis of Asian IBD as it is in Western IBD

2. Alterations in flora composition may be underlying the development of IBD in Asia

3. It is unknown whether changes in flora composition in Asian IBD patients are similar or different from those of Western patients

4. The common occurrence of enteric infections may complicate studies on the role of the gut flora in the pathogenesis of IBD in Asia
Components of IBD pathogenesis

1. The genetic make up
2. The environment
3. The enteric flora
4. The immune system
Plasticity of the Immune Response in Early life

Environmental allergens
- Th2
- Th1
- No response

Microorganisms
- CTL
- Th2
- Th1

Vaccines
- Th1
- CTL
- Th2
- Th1
- No response

Infections
- Th2
- Th1

Standard immunizations
- Th1
- CTL
- Th2
- Th1
- No response

B. Adkins, 2003
Immune responses “imprinted” in early life are maintained into adulthood
**Hygiene hypothesis:**

**postulated mechanisms**

**“Clean” lifestyle**

- Th1
- Hay fever
- Asthma
- Atopic eczema
- Food allergy
- Low microbial exposure
- Weak immune stimulation

**“Dirty” lifestyle**

- Th2
- Low allergy
- Strong immune stimulation
- High microbial exposure

*Matricardi & Bonini*
*Clin Exp Allergy 2000*
Hygiene hypothesis: postulated mechanisms

Low allergy

Strong immune stimulation

High microbial exposure

“Dirty” lifestyle

Matricardi & Bonini
Clin Exp Allergy 2000

Th1

Hay fever

Asthma

Atopic eczema

Food allergy

Crohn’s disease

High allergy

Weak immune stimulation

Low microbial exposure

“Clean” lifestyle
Hygiene hypothesis: postulated mechanisms

"Dirty" lifestyle

Low allergy

Strong immune stimulation

High microbial exposure

"Clean" lifestyle

High allergy

Weak immune stimulation

Low microbial exposure

Th1

Hay fever

Asthma

Atopic eczema

Food allergy

Th2

Crohn's disease

"Clean" lifestyle

Matricardi & Bonini
Clin Exp Allergy 2000
Hygiene hypothesis: postulated mechanisms

Low allergy

High allergy

"Dirty" lifestyle

"Clean" lifestyle

High microbial exposure

Weak immune stimulation

Low microbial exposure

Strong immune stimulation

Th1

Th2

Hay fever

Asthma

Atopic eczema

Food allergy

Crohn’s disease

Asia: Another defect?

Matricardi & Bonini
Clin Exp Allergy 2000
Hygiene hypothesis: postulated mechanisms

"Clean" lifestyle

- High allergy
- Weak immune stimulation
- Low microbial exposure

Th1
- Strong immune stimulation
- High microbial exposure
- Hay fever
- Ulcerative colitis

Th2
- Weak immune stimulation
- Atopic eczema
- Food allergy
- Asthma

"Dirty" lifestyle

- Low allergy
- Strong immune stimulation
- Ulcerative colitis

Matricardi & Bonini
Clin Exp Allergy 2000

“Clean” lifestyle

“Dirty” lifestyle
The hygiene hypothesis: contradictions, limitations, and complementary theories

- Th2-skewed helminthic diseases are not associated with an increase in allergic manifestations

- Th1-mediated autoimmune or chronic inflammatory diseases are also increasing, such as Crohn’s disease

- The effect of infections on immunity depends on multiple factors: the type and time of infection, target organ and tissue, dose, duration, other infections, host characteristics, and the stage of immune development

- Defective immune education (by DC) or immunoregulation (by Treg) may be necessary to better explain the hygiene hypothesis concept
The modified hygiene hypothesis: altered immune regulatory networks

Vaccines, hygiene and antibiotics: little Th1 stimulation, increase in T\textsubscript{H2}.

Skin prick tested children

Weak regulatory network

Low exposure to pathogens: Low IL-10 & TGF-β

Allergic responses:
- Asthma,
- Rhinoconjunctivitis

Inflammatory molecules

Seropositive for allergens: but little allergic disease

Strong regulatory network

High exposure to pathogens: High IL-10 & TGF-β

Helminth infections:
- strong stimulation of Th2 responses.

Low IL-4, IL-5, IL-13

IgE

T\textsubscript{H2}

Mucus production

Smooth muscle cell contraction

The hygiene hypothesis: a unifying theory

“The Th1/Th2 and the counter-regulatory (Treg) paradigms may both be relevant in explaining the hygiene hypothesis, but their relative importance is likely to differ between developed and developing countries due to differences in exposure to microbial agents”
Integration of immune and environmental factors in IBD pathogenesis

Dietary antigens

Enteric flora

Physiological stimulation ("inflammation")
of the mucosal immune system
Integration of immune and environmental factors in IBD pathogenesis

Dietary antigens  Enteric flora  Pathogens

Self-limited pathological inflammation and new priming of the mucosal immune system
Integration of immune and environmental factors in IBD pathogenesis

- Dietary antigens
- Enteric flora
- Pathogens
- Xenobiotics

Pathological stimulation and additional priming of the mucosal immune system

*FODMAPs*

- Fermentable
- Oligo-
- Di-
- Mono-saccharides
- And
- Polyols
Integration of immune and environmental factors in IBD pathogenesis

- Dietary antigens
- Enteric flora
- Pathogens
- Xenobiotics

Increased cytokine release by mucosal immune cells
Integration of immune and environmental factors in IBD pathogenesis

- Dietary antigens
- Enteric flora
- Pathogens
- Xenobiotics

Cytokine-induced increase in intestinal permeability
Integration of immune and environmental factors in IBD pathogenesis

Dietary antigens  Enteric flora  Pathogens  Xenobiotics

Increased antigen absorption
Integration of immune and environmental factors in IBD pathogenesis

Secondary immune activation and further cytokine release

- Dietary antigens
- Enteric flora
- Pathogens
- Xenobiotics

Cytokines

Secondary immune activation and further cytokine release

FODMAPs
Persistent activation of the mucosal immune system

Chronic intestinal inflammation

Integration of immune and environmental factors in IBD pathogenesis

Dietary antigens
Enteric flora
Pathogens
Xenobiotics

FODMAPs

Chronic intestinal inflammation
Integration of immune and environmental factors in IBD pathogenesis

- Altered dietary antigens
- Abnormal enteric flora
- New pathogens
- Xenobiotics
- FODMAPs*

Hygiene hypothesis: lack of adequate immunoregulation

Integration of immune and environmental factors in IBD pathogenesis leads to

- Impairment of DCreg, Treg, and effector T cells

Chronic intestinal inflammation
Key features of IBD in Asia

1. Based on macroscopic and histologic evidence, the immune inflammatory response appears to be the same in Asian and Western IBD.

2. The hygiene hypothesis-based immune response is a reasonable effector mechanism to explain IBD in Asia.

3. The dietary, flora modulation, immunosuppressive, and biological approaches used in Western IBD patients should be just as effective in controlling the IBD-associated immune response of Asian patients.
Can Asia offer new therapeutic options for IBD?
Initial appearance: 2000 BC - 220 AD
Continental spreading: 7th - 8th centuries
European spreading: 16\textsuperscript{th} century
American spreading: 1825
Acupuncture: is this the future therapy of IBD?