Diagnostic Challenges in Asia
Defining Ulcerative vs Infectious Colitis

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Major Etiologic Theories on Inflammatory Bowel Diseases

*Role of Microbial Factors*

- Reaction to persistent pathogenic infection in the intestine
- Subtle alterations in bacterial function and composition (*dysbiosis*)
- Defective mucosal barrier to resident normal luminal bacterial products
- Aberrant host immune response, *including* loss of immune tolerance to normal ubiquitous luminal antigens
### Infectious Pathogens Suggested to Cause Inflammatory Disease

<table>
<thead>
<tr>
<th>Crohn’s disease</th>
<th>Ulcerative colitis</th>
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</thead>
<tbody>
<tr>
<td><em>Mycobacterium paratuberculosis</em></td>
<td>Pathogenic <em>Escherichia coli</em></td>
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<tr>
<td><em>Mycobacterium kansasii</em></td>
<td>Diplostreptococcus</td>
</tr>
<tr>
<td>Paramyxovirus (measles)</td>
<td><em>Fusobacterium necrophorum</em></td>
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<tr>
<td><em>Listeria monocytogenes</em></td>
<td><em>Shigella</em></td>
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<tr>
<td>Chlamydia</td>
<td><em>Helicobacter hepaticus</em></td>
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<td>RNA reovirus</td>
<td>RNA virus</td>
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<tr>
<td>L forms of <em>Pseudomonas maltophilia</em></td>
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<tr>
<td>Viruses</td>
<td>Bacteria</td>
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<tr>
<td>Cytomegalovirus</td>
<td><em>Clostridium difficile</em></td>
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<tr>
<td>Rotavirus</td>
<td><em>Salmonella</em></td>
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<tr>
<td>Norwalk agent</td>
<td><em>Shigella</em></td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
<td><em>Campylobacter jejuni</em></td>
</tr>
<tr>
<td>Influenza A and B</td>
<td><em>Yersinia</em></td>
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<tr>
<td>Parainfluenza</td>
<td>Enteropathogenic <em>Escherchia coli</em></td>
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<tr>
<td>Rubella</td>
<td><em>Aeromonas</em></td>
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<tr>
<td>Epstein-Barr virus</td>
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<tr>
<td>Herpes simplex virus</td>
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<tr>
<td>Adenovirus</td>
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</table>
Role of Pathogens in the Induction and Relapse of IBD

- common pathogens precede IBD, exacerbate symptoms and reactivate quiescent disease (Sartor, 2000)
- *Shigella, Salmonella, Yersinia* have been implicated (Powell, 1966)
- seasonal variations in the onset of UC, but not CD (Moum, 1996)
- more than 50% of IBD relapses may be associated with respiratory infections (Mee, 1978)
- history of foreign travel and transient enteric infection (Farell, 2002)
Infectious Colitis vs. Ulcerative Colitis
Realities in the Asia Pacific Region

• diarrhea is a major cause of morbidity and mortality in Asia, especially in children
• *E. histolytica*, *E. coli*, *Shigella*, and *viruses* are the most common etiology
• there is a low threshold for physicians to commit to a diagnosis of an infectious etiology without proper examination
• misuse/abuse of anti-infective agents is rampant
• reports of IBD in the region is on the rise
Inflammatory Bowel Disease in the Philippines

<table>
<thead>
<tr>
<th>Ulcerative Colitis</th>
<th>n = 41</th>
</tr>
</thead>
</table>

Male:Female 24:17

Age
- Mean (yrs) 43.98
- Range (yrs) 16 – 88

Presenting Symptoms
- Chronic diarrhea 53.6%
- Bloody diarrhea 46.3%
- Abdominal pain 17.1%

IBD Club of the Philippines, 2004
### Distribution of Lesions in Ulcerative Colitis

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>Rectum</td>
<td>2.4%</td>
</tr>
<tr>
<td>Rectosigmoid</td>
<td>19.5%</td>
</tr>
<tr>
<td>Transverse/Descending/Rectum</td>
<td>14.6%</td>
</tr>
<tr>
<td>Pancolitis</td>
<td>63.5%</td>
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</tbody>
</table>

**Failed anti-Amoebic Therapy**: 46.0%

IBD Club of the Philippines, 2004
The most difficult decision is to establish whether the diagnosis is ulcerative colitis or Crohn's disease.

IBD: How Confident Is Our Diagnosis in Asia?

Differential Diagnosis

Vasculitis
Ischaemia
Infections

<table>
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<tr>
<th>Ulcerative Colitis</th>
<th>Crohn’s Disease</th>
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<tbody>
<tr>
<td>- E. histolytica</td>
<td>- Tuberculosis</td>
</tr>
<tr>
<td>- Shigella, Salmonella</td>
<td>- Chlamydia</td>
</tr>
<tr>
<td>- E. coli 0157:H7</td>
<td>- Yersinia</td>
</tr>
<tr>
<td>- Campylobacter</td>
<td>- Listeria</td>
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<tr>
<td>- Clostridium difficile</td>
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<tr>
<td>- Cytomegalovirus</td>
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Diagnostic Work-Up in the Asia

Infectious Colitis

- stool cultures for bacterial pathogens
- careful examination of stools and biopsy material for viral, parasitic, and protozoal infection
- endoscopic examination of colonic lesions
- high endemicity and serologic shortcomings

Pseudomembranous Colitis

- history of antibiotic exposure
- toxin assay for Clostridium difficile
Amoebiasis

- 40,000 -100,000 die yearly
- second leading cause of death from parasitic disease

- in endemic areas, 38% of acute diarrheal disease in the OPD
- 17% of amoebiasis in the US in 1993 were from Asia and the Pacific Islands
The species of *Entamoeba*

*Entamoeba dispar*  
- a non-pathogenic commensal

*Entamoeba dysenteriae*  
- a tissue-invasive pathogen  
  
  Brumpt ME et al, 1925

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*Entamoeba dispar*  
- a non-pathogenic commensal

*Entamoeba histolytica*  
- a tissue-invasive pathogen  
  
  Sargeaunt PG et al, 1978
Dysenteries, when they set in with fever, [alvine] intestinal discharges of a mixed character, or with inflammation of the liver ........ are bad!

Hippocrates
Amoebiasis

Two Clinical Presentations

Amoebic Colitis
Amoebic Liver Abscess
Amoebic Colitis

Pathology

- mucosal thickening
- multiple discreet ulcers
- normal intervening mucosa or diffusedly inflammed/edematous
- necrosis and perforation
Amoebic Colitis

Pathophysiology

Cytolysis
: *amoebapores*

Apoptosis
: *caspase*

Alteration of Cellular Permeability
: *cysteine proteininases*
1. Amoebic adherence to intestinal epithelial cell
   - Gal/N-acetyllectin
   - Intestinal epithelial cells

2. Activation of amoebic virulence programme
   - Amoebic cysteine proteinase
   - Amebapore

3. Cell damage with release of pIL-1β
   - Extracellular amoebic cysteine proteinase cleaving pIL-1β

4. IL-1β activates NF-κB in distal cells—cytokines and inflammatory mediators produced
   - IL-1β
   - IL-1β
   - IL-8
   - COX-2

5. Neutrophils influx in response to IL-8 and other chemoattractants
   - Neutrophil migration damages epithelial barrier
   - Macrophages arrive in response to chemokines; release TNF α

6. Mediators released by neutrophils damage epithelial cells
   - Amoeba uses cysteine proteinase to cleave extracellular matrix proteins and invade

Colonoscopic Findings in Amoebic Colitis
Colonoscopic Findings in Severe Amoebic Colitis
Amoebic Colitis

Pathology

: lateral extension through submucosal layers (i.e., flask-shaped ulcers)

: important role of cysteine proteininases
The Amoebic Ulcer
The *E. histolytica* Trophozoite
Ulcerative Colitis vs Amoebic Colitis

- Bloody diarrhea has a short history and an acute onset with tenesmus and more motions per day
- Endoscopic lesions are patchy with normal intervening mucosae
- Microscopy and histology may be helpful in identifying enteroinvasive E. histolytica
Clinical Features of Infectious Colitis

Hemorrhagic Colitis

- EHEC 0157:H7
- Shigella
- Vibrio parahaemolyticus
- Salmonella
- Campylobacter
## Clinical Features of Infectious Colitis

<table>
<thead>
<tr>
<th>Strains</th>
<th>Mechanisms</th>
<th>Types of Patients</th>
<th>Clinical Features</th>
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<tbody>
<tr>
<td>Enteropathogenic (EPEC)</td>
<td>Localized adherence O serogroups</td>
<td>Children</td>
<td>Watery Diarrhea</td>
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<tr>
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<td>Newborn Nursery Outbreaks</td>
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<tr>
<td>Enteroinvasive (EIEC)</td>
<td>Shiga-like Toxin Epithelial Cell Adherence O serogroups</td>
<td>Children and Adults</td>
<td>Dysentery WBC &amp; RBC in stools</td>
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<tr>
<td>Enterohemorrhagic (EHEC)</td>
<td>Shiga-like Toxin (plenty) O serogroups; 015:H7</td>
<td>Children and Adults</td>
<td>Bloody diarrhea Hemolytic-Uremic Syndrome</td>
</tr>
</tbody>
</table>
Clinical Features of Infectious Colitis

Enterohemorrhagic E. coli (EHEC)

- 0.6% - 2.4% of all cases of diarrhea
- 15% - 36% of hemorrhagic colitis in the US, UK, Canada
- incubation period: 1-14 days
- bloody diarrhea, severe abdominal cramping, fever, chills
- patchy erythema, edema, superficial ulcers, friable mucosa
- “thumbprinting” in ascending and transverse colon
- median duration of diarrhea: 3-8 days
- hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura have been reported
“The disease descended to the bowels, producing violent ulceration and uncontrollable diarrhea.”

Peloponnesian War
Clinical Features of Infectious Colitis

Shigella  (Bacillary Dysentery)

• 10% - 20% of all cases of diarrhea
• disease of children between 6 months to 5 years
• Phase I: fever, abdominal pain, nonbloody diarrhea
• Phase II: tenesmus, bloody diarrhea
• median duration of diarrhea: children 3 days, adults 1-4 weeks
• diagnosis: bacterial culture, sigmoidoscopy, biopsy
• treatment: ampicillin, trimethoprim-sulfamethoxazole, ciprofloxacin
Clinical Features of Infectious Colitis

Shigella (Bacillary Dysentery)

- **Group A**: *S. dysenteriae* – 10 serotypes
  - the *Shiga bacillus*, produces the worst disease
- **Group B**: *S. flexneri* – 14 serotypes
  - the most common organism in tropical countries
- **Group C**: *S. boydii* – 18 serotypes
- **Group D**: *S. sonnei* – 1 serotype
  - 60%-80% of dysenteries in US
  - produces the mildest disease
Clinical Features of Infectious Colitis

Shigella (Bacillary Dysentery)

- elaborates enterotoxin and invades lower gut mucosa
- severe local inflammatory response, edema, microabscess formation, loss of goblet cells, destruction of cellular architecture
- patchy erythema, superficial ulcers, friable mucosa
- perforation, severe protein loss may occur
- extraintestinal manifestations include meningismus, hemolytic-uremic syndrome, thrombocytopenia, asymmetric, large joint arthritis (2-3wks after onset)
Clinical Features of Infectious Colitis

**Shigella (Bacillary Dysentery)**

*Subacute Form*

- bloody diarrhea, with cramping, for 2-4 weeks
- rectal pain is a prominent presentation
- untreated bacillary dysentery may present similarly
- sigmoidoscopic, histologic and radiographic features may be difficult to differentiate from UC
- Two major characteristics:
  - positive culture for Shigella
  - improvement with appropriate antibiotic therapy
Shigellosis

A, The view of the rectum on sigmoidoscopy shows narrowing and mucosal inflammation similar to that seen in ulcerative colitis. B, Histologic features include a severe inflammatory infiltrate of polymorphonuclear leukocytes and macrophages of the mucosa and submucosa, loss of surface epithelial cells, numerous crypt abscesses.
Campylobacter colitis

The colitis is patchy, with areas of erythema and erosion (left). The rectal mucosa on the right is hyperemic, without loss of the mucosal vascular pattern. *Campylobacter jejuni* was identified on stool culture.
Cytomegalovirus colitis

Endoscopic findings may include diffuse colitis as well as solitary ulcers of the colon.

The ulcer may be large with raised edges but the surrounding mucosa is normal.
Two classic cytomegalovirus inclusions can be seen (arrows) in this focus of granulation tissue.
Parallels in the Clinical Features of *H. pylori* Infection and IB

- Widespread exposure of human beings to the bacterium
- Persistence of carriage over decades with only a fraction developing disease
- Induction of chronic inflammation
- Waxing and waning clinical course
- Progression over decades to adenocarcinoma
Clinical Features of *Helicobacter hepaticus* Infection

- potential pathogen for IBD *(Blaser, 1997)*
- proliferative typhlitis and hepatitis in immunosuppressed mice *(Ward, 1996)*
- induces severe colitis in CD45RB$^{\text{high}}$ reconstituted SCID mice *(Cahill, 1997)*
- widespread contaminant of murine colonies *(Shames, 1995)*
- implicated in human biliary disease *(Fox, 1998)*
- can cause colitis in TCR$\alpha\beta$ mutant mice *(Chin, 2000)*
Non-Specific Therapy of Infectious Diarrhea

EFFECTIVE

• Fluids: intravenous, oral rehydration
• Food: continue nutrition intake
  : avoid lactose, caffeine, methylxanthines
• Anti Motility Drugs
  : Loperamide, Diphenoxylate
  : codeine, paregoric, tincture of opium
• Bismuth subsalisylate
• Lactobacillus GG (children with rotavirus)
• Antisecretory drugs, e.g., zaldaride maleate
Infectious Colitis vs. Ulcerative Colitis
Realities in the Asia Pacific Region

SUMMARY

• Infectious diarrhea is a major cause of morbidity and mortality in Asia, especially in children

• Colonic lesions may mimic UC, their onset is acute, the clinical course is short, and an identifiable pathogen can be isolated

• Physicians should be reminded to perform the proper diagnostic examinations on all patients before initiating therapy

• The diagnosis of IBD should be considered even on the first presentation
APDW
The Asian Pacific Digestive Week 2006
PHILIPPINES
2006

November 26-29, 2006
Waterfront Hotel,
Lahug Cebu City, Philippines

WEBSITE: apdw2006.org