Update on Infectious Enterocolitides and the Diseases That They Mimic

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GI Infectious Diseases are Common Throughout the World

- Transplant patients
- Immunocompromised patients
- Immigration/international travel
- Food/water supply issues

Enteric infectious diseases are second leading cause of death worldwide, after cardiovascular disease
Naturally Occurring Foodborne Diseases
CDC Estimates for USA, 2010-11

- 47.8 million illnesses/year
- 128,000 hospitalizations/year
- 3000 deaths/year
- Many food-borne outbreaks and sporadic cases unrecognized

Common Etiologic Agents of Infectious Gastroenteritis in USA

- Food-associated
  - *Salmonella*
  - *S. aureus*
  - *Shigella*
  - *Campylobacter*
  - *C. perfringens*
  - *B. cereus*
  - *EHEC*

- Water-associated
  - *Giardia*
  - *Shigella*
  - Norwalk Virus (norovirus)
  - *Salmonella*
  - *Campylobacter*
  - *C. parvum*
  - *EHEC*

Naturally Occurring Foodborne Diseases
CDC Estimates for USA, 2010-11

Cases with Identified Pathogens

- 47.8 million illnesses/year
  - 9.4 million illnesses/year
- 128,000 hospitalizations/year
  - 55,961 hospitalizations/year
- 5000 deaths/year
  - 1351 deaths/year

Top Domestically-Acquired Pathogens Contributing to Foodborne Illness, Hospitalization, and/or Death

<table>
<thead>
<tr>
<th>Foodborne Illness</th>
<th>Foodborne Illness-associated hospitalization</th>
<th>Foodborne Illness-associated death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norovirus</td>
<td>Norovirus</td>
<td>Norovirus</td>
</tr>
<tr>
<td><em>Salmonella</em> (nontyphoid)</td>
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<td><em>Salmonella</em> (nontyphoid)</td>
</tr>
<tr>
<td><em>C. perfringens</em></td>
<td>Campylobacter</td>
<td>Listeria</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>Toxoplasma</td>
<td>Campylobacter</td>
</tr>
</tbody>
</table>
Foods Commonly Associated with GI Infection

<table>
<thead>
<tr>
<th>Raw Dairy</th>
<th>Shellfish</th>
<th>Meat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmonella</td>
<td>Vibrio</td>
<td>Salmonella</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>Hepatitis A</td>
<td>Campylobacter</td>
</tr>
<tr>
<td>Brucella</td>
<td>Norwalk virus</td>
<td>Yersinia</td>
</tr>
<tr>
<td>E. coli</td>
<td>Rotavirus</td>
<td></td>
</tr>
<tr>
<td>Listeria</td>
<td>Salmonella</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Fang et al Inf Dis Clin N Amer 5:681-701, 1991

Naturally-Occurring Food-Borne Outbreaks

- (2010) *Salmonella* + salami: 184 infections; 1.2 million lbs. recalled
- (2009) *E. coli* + ground beef: 26 infections in 8 states; 545,699 lbs. recalled
- (1998) *Listeria* + hotdogs: 17 deaths; 30 million pounds recalled
- (1990s) Raspberries + *Cyclospora*: 2500 infections in 21 states

Enteric Infections Acquired from Animals (rare!)

<table>
<thead>
<tr>
<th></th>
<th>Birds</th>
<th>Cats</th>
<th>Dogs</th>
<th>Goats</th>
<th>Hamsters</th>
<th>Monkeys</th>
<th>Sheep</th>
<th>Snake</th>
<th>Turtle</th>
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</thead>
<tbody>
<tr>
<td><em>Aeromonas</em></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td><em>Campylobacter</em></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><em>Salmonella</em></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tr>
<tr>
<td><em>Yersinia</em></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Cryptosporidium</em></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
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<td></td>
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<tr>
<td><em>Giardia</em></td>
<td>X</td>
<td>X</td>
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<tr>
<td><em>Strongyloides</em></td>
<td></td>
<td>X</td>
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</table>
Challenges for Pathologists When Evaluating a Specimen for an Infectious Process

- Everything is in formalin
  - No cultures
  - Possibly no molecular
- Available resources/techniques that aid in diagnosis may be limited/unavailable, expensive, or unknown to pathologist
- Lack of pertinent history
- Patient given abx before biopsy procedure

Anatomic Pathologist’s Goals When Evaluating a Specimen for Infectious Processes

- Distinguish infectious processes from other processes (ischemia, chronic idiopathic inflammatory bowel disease)
- Try (enthusiastically!) to identify infectious organism or pattern of infection
  - Biopsy often out long before culture result
  - Tissue often not preserved for other studies
- Be aware of resources/techniques that aid in diagnosis

Why should surgical pathologists care about bugs?

- Many can’t be cultured-must recognize patterns of disease in tissue
  - HIV
  - HCV
  - Hantavirus
  - SARS
  - Pneumocystis jiroveci (carinii)
  - Coccidians
Aids to Diagnosis

- **Immunostains**
  - Availability
- **Special histochemical stains**
  - Gram: hard to tell enteric pathogens from normal commensals
  - Silver impregnation: high background
- **Culture**
  - Organism may be fastidious
  - Can’t tell virulent from nonvirulent strains
  - Patient may have gotten abx

Aids to Diagnosis

- **Serologic studies**
  - Many cross-reactive organisms
  - Need acute and convalescent titers
  - False negatives in immunocompromised, very old, or very young patients
- **Molecular testing**
  - Formalin fixation limits yield
  - Block may be exhausted

ID Molecular Testing and FFPE Tissue

- Can be done
- Targets must be SMALL (<500 base pairs)
- Primers should target genes exclusively present in pathogenic strains
- Molecular testing must be correlated with histologic findings

Responsibilities of the Anatomic Pathologist

- Optimize opportunities to intervene and guide the workup:
  - Get material for culture, molecular studies
  - Rapid evaluation techniques
    - Frozen section
    - Touch preps
    - Air dried smears
    - Smears, touch preps, and frozens can be used for same-day special stains
Responsibilities of the Anatomic Pathologist

- Formulate final anatomic diagnoses that correlate clinical history with
  - Histology
  - Special stains
  - Immunologic studies
  - Molecular studies
  - Cultures (if possible)

Helpful History

- Travel
- Food intake
- Work/environmental exposure
- Animal exposure/zoonoses
- Tick, other vector exposure
- Sexual practices
- Immune status

General Classification of Histologic Patterns in Infectious Enterocolitides

- Minimal or no inflammation
- Acute infectious-type enterocolitis/ASLC
- More specific or suggestive patterns:
  - Pseudomembranes
  - Granulomas
  - Diffuse histiocytic infiltrate
  - Architectural distortion
  - Viral inclusions or other visible organisms

Histologic pattern directs diagnostic algorithm

Infections Producing Minimal or No Inflammation

- *Vibrio* and non-*Vibrio cholerae*
- Enteropathogenic and Enteroadherent *E. coli*
- Spirochetosis
- *Neisseria* species
- Many enteric viruses
Infections Producing ASLC/AITC Pattern

- *Campylobacter* species
- *Shigella*
- *Aeromonas*
- Syphilis (+/- plasma cells)
- Occasionally:
  - *Yersinia*
  - *C. difficile*
  - Non-typhoid *Salmonella*
PMN infiltrate
• Intact architecture
• +/- crypt abscesses
• No basal plasma cells
• Surface damage

Most common histologic pattern in enteric infections

Infections Producing More Specific Diagnostic Features

<table>
<thead>
<tr>
<th>Pseudo-membranes</th>
<th>Granuloma Formation</th>
<th>Diffuse histiocytic</th>
<th>Architectural Distortion</th>
<th>Inclusions/ Organisms Viable on H&amp;E</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. difficile</td>
<td>Yersinia</td>
<td>R. equi</td>
<td>Salmonella</td>
<td>CMV/HSV</td>
</tr>
<tr>
<td>EHEC</td>
<td>M. Tb</td>
<td>MAI</td>
<td>Shigella</td>
<td>EAEC</td>
</tr>
<tr>
<td>Rarely Shigella</td>
<td>Fungi</td>
<td>Whipple’s Disease</td>
<td>Amoeba</td>
<td>Spirochetosis</td>
</tr>
<tr>
<td></td>
<td>Actinomycosis</td>
<td>Sometimes Aeromonas</td>
<td>Fungi</td>
<td>Amoeba</td>
</tr>
</tbody>
</table>
GI Infectious Diseases That Mimic Other Processes

<table>
<thead>
<tr>
<th>Mimics of Crohn’s</th>
<th>Mimics of UC</th>
<th>Mimics of Ischemia</th>
<th>Mimics of Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmonella</td>
<td>Salmonella</td>
<td>EHEC</td>
<td>Coccidians</td>
</tr>
<tr>
<td>Shigella</td>
<td>Shigella</td>
<td>Aspergilus</td>
<td>Histoplasmosis</td>
</tr>
<tr>
<td>Yersinia</td>
<td>E. histolytica</td>
<td>Mucor</td>
<td>EAEC</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>LGV</td>
<td>CMV</td>
<td></td>
</tr>
<tr>
<td>Aeromonas</td>
<td>Syphilis</td>
<td>C. perfringens</td>
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</tr>
<tr>
<td>E. histolytica</td>
<td></td>
<td>C. difficile</td>
<td></td>
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<tr>
<td>CMV</td>
<td></td>
<td></td>
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<tr>
<td>M. tuberculosis</td>
<td></td>
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Specific GI Infectious Disease Examples

- Commonly encountered
  - Responsible for majority of food-related illnesses worldwide
- Mimic other inflammatory conditions

*Campylobacter* species

- Most common stool isolate in USA
- Contaminates meat, poultry, water, milk
  - Fecal-oral transmission also possible
- Common pathogen associated with focal active colitis pattern

*Schneider, Havens, Goldblum, et al. AJSP 30: 2006*
### Common Enteric Infections

**Clinical Features**

<table>
<thead>
<tr>
<th></th>
<th>Fever</th>
<th>Diarrhea</th>
<th>Infective Dose</th>
<th>Prognosis</th>
<th>Pattern</th>
<th>Other</th>
</tr>
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<tbody>
<tr>
<td>Campylobacter</td>
<td>Usually</td>
<td>Yes, +blood, WBC</td>
<td>500 bugs</td>
<td>Usually self-limited; relapse common</td>
<td>AITC</td>
<td>Arthropathy, abs</td>
</tr>
<tr>
<td>Salmonella (Typhoid)</td>
<td>Yes, high</td>
<td>Yes, at 2-3 weeks</td>
<td>1000</td>
<td>Need abx; may cause sepsis</td>
<td>IBD mimic</td>
<td>Rash, leukopenia, HSM</td>
</tr>
<tr>
<td>Salmonella (non-Typhoid)</td>
<td>Yes</td>
<td>Yes</td>
<td>1000</td>
<td>Good with abx</td>
<td>AITC; rarely mimics IBD</td>
<td>Milder illness</td>
</tr>
<tr>
<td>Shigella</td>
<td>Yes</td>
<td>Yes, +blood, mucus, pus</td>
<td>10-100</td>
<td>Need abx; may cause sepsis, perforation</td>
<td>AITC or IBD mimic</td>
<td>Constitutional sx, HUS</td>
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- Lamina propria neutrophils
  - More prominent superficially
- +/- Cryptitis and crypt abscesses
- Preservation of crypt architecture

**Campylobacter**

- **Diagnosis:**
  - Culture is mainstay
    - Patients often on empiric abx therapy prior to biopsy
  - Darkfield examination of stool smears
  - Campy antigens on immunoassay
  - Molecular testing
**Salmonella species**

**Clinical**
- **Typhoid (S. Typhi or Paratyphi)**
  - Rising fever
  - Abdominal pain
  - Rash
  - Leukopenia
  - Hepatosplenomegaly
  - Diarrhea @ 2-3 weeks
- **Non-typhoid serotypes (Enteritidis, Muenchen, Typhimurium)**
  - Milder illness
  - Nausea
  - Vomiting
  - Milder fever
  - Watery diarrhea

**Salmonella species**

**Gross Pathology**
- Favors ileum, appendix, right colon
- Thickened wall, raised nodules over Peyer patches
- Ulceration and necrosis
- Mesenteric adenopathy
- Milder findings in non-typhoid species, but considerable overlap

**Common Enteric Infections Clinical Features**

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Ulcers typically occur over Peyer’s patches, with necrosis of mucosa

Courtesy Dr. Brian West
**Salmonella**

- Features that mimic CIIBD:
  - Apthous, linear, and/or deep ulcers
  - Crypt distortion
  - Right side distribution with ileal involvement may mimic Crohn’s in particular

**Architectural distortion, crypt abscesses**

**Histiocytes and mononuclear cells are most prominent, with fewer neutrophils**

**Non-typhoid *Salmonella***
Salmonella species
Differential Diagnosis

- Stool cultures help resolve!
- Other enteric pathogens
  - Longer incubation period (10-15 days)
  - Neutrophils less prominent
  - Granulomas unusual
- Idiopathic IBD
  - Can see significant crypt distortion

Shigella species

- Invasive, virulent bacteria
- Typically from contaminated water
- Fecal-oral transmission also possible

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<td>Yes</td>
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</table>
**Shigella species**
Pathologic Findings

- Favors left colon
- +/- pseudomembranes
- Early shigellosis has AITC pattern
- Later in the disease there is often significant mucosal damage, architectural distortion

**Shigella**

- Features that mimic CIIBD
  - Mucosal destruction with significant architectural distortion
  - Left side distribution can mimic ulcerative colitis in particular
**Yersinia (enterocolitica and pseudotuberculosis)**

- One of the most common causes of bacterial enteritis in N. America and Europe
- Wide variety of acute and chronic GI manifestations
- Contaminates meat, shellfish, poultry, milk and dairy, water

**Chitterlings**

*also Chitlins or Chitlings*

- “The small intestines of pigs, especially when cooked and eaten as food.”
  - Probable diminutive of Old English *cieter*, intestines
The Chitterling Data
Tauxe et al

- CDC studied a group of children in Atlanta in 1990 with gastroenteritis secondary to YE (by stool isolate)
- Outbreaks clustered around holidays
- More than 50% exposed to raw pork intestines during household chitterling preparation
- Similar data acquired in Belgium where eating raw and undercooked pork is common

Yersinia
Gross Pathology

- Involves ileum, right colon, and appendix preferentially
- Thickened wall with apthous and linear ulcers
- Associated lymphadenopathy
Granulomatous Appendicitis

Yersinia enterocolitica
**Yersinia**
Mimic of Crohn’s Disease

- Yersiniosis
  - Isolated appendiceal involvement
  - More acute clinical onset
- Crohn’s
  - Disease in multiple sites
  - Creeping fat
  - Fistulæ
  - Histologic changes of chronicity

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**Aeromonas species**

- Originally recognized as pathogen in turtles and other water dwelling creatures, but only recently in humans
  - *A. hydrophila, A. veronii,* and *A. sobria* now recognized as important to human GI disease
- Associated with water sources, fish, seafood, veggies, raw milk, ice cream, meat

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**Aeromonas sp.**

- Particularly a problem in young children (< one year of age), the elderly, and immunocompromised patients, but can affect anyone
- Summer peak
- *Pleisiomonas* species probably emerging as similar pathogen

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**Clinical Findings**

- Bloody diarrhea, often mucoid
- Nausea, vomiting, crampy abdominal pain
- May have fever and fecal WBCs
- Duration of symptoms may range from days to much longer
Pathologic Findings

- Often segmental distribution
- Edema, friability, erosions, exudate, loss of vascular pattern
  - DDx: Ischemia, Crohn’s disease
- Usually shows AITC pattern
  - Ulceration, focal architectural distortion may be seen, mimicking IBD
Aeromonas species

- *Aeromonas* is now an accepted cause of infectious enterocolitis in humans
- Cultures are key to diagnosis
  - Some recommend culturing all new onset IBD patients, especially kids
  - Molecular testing also available
- May mimic Crohn’s both grossly and histologically


E. histolytica

- Infects 10% of world population
- Clinical: ranges from asymptomatic to fulminant colitis
- In USA, associated with homosexual population and unsanitized water

E. histolytica

- Typical
  - Flask shaped ulcers
  - Right sided involvement
- Atypical
  - Pseudomembranes
  - Toxic megacolon
  - Crohn’s-like
    - Skip lesions
    - Linear or geographic ulcers
    - Architectural distortion
    - Organisms may be mistaken for macrophages
E. histolytica: architectural distortion and skip lesions mimic Crohn’s disease

Courtesy Dr. David Green
• Foamy cytoplasm
• Pale, round, eccentric nuclei
• Ingested red cells are pathognomonic of *E. histolytica*

**Enterohemorrhagic *E. coli***

- Usually serotype 0157:H7
- Causes “ischemic-pattern” colitis
  - Shiga-like toxins cause thrombosis
- Contaminates meat, produce, water
- Children and elderly at increased risk
  - TTP, HUS
Enterohemorrhagic *E. coli*

Clinical Features

- Crampy pain, watery and/or bloody diarrhea
- Right sided colitis
- Mild or no fever
- Rare fecal leukocytes

- Hemorrhagic necrosis
- Ulceration with fibrinopurulent exudate
- Variably present pseudomembranes, microthrombi
Enteric Viruses

- Rarely biopsied
- Adenovirus, rotavirus, coronavirus, enterovirus
- Diagnosis usually made by stool culture/immunoassay

Courtesy Dr. Joel Greenson
Diagnosis of GI Infectious Diseases

- Many infectious entities are underdiagnosed
  - HIGH INDEX OF SUSPICION!
- Cultures may not be useful/available
  - Patient already got antibiotics
  - Everything is in formalin
- Serologies
  - False negatives
  - Cross-reactivity
- **Molecular testing**

Utility of Special Stains in Evaluation of Biopsies for GI Infections

- Monkemuller et al, AJCP 2000
  - HIV patients
  - 28 months
  - Sensitivity and specificity for CMV diagnosis on H&E were 97% and 100%
  - AFB/GMS stains did not identify previously diagnoses infection in any patient
  - Long-term follow-up revealed no missed infections on H&E
  - Stains doubled cost
Essentially Normal Bx in Immunocompromised Patient

Increased apoptotic epithelial cells

Don’t overlook spirochetosis, coccidians, or Giardia!

Are they severely immunocompromised?

No

CMV Adenovirus

Yes

Done!

Get history, consider GMS, CMV

Summary

- Infectious (including food-borne) gastrointestinal disease is common, and probably underdiagnosed
- Microbiological and molecular techniques are invaluable partners to biopsy
- Infectious processes may mimic other types of IBD
- Pathologists and lab workers are essential to evaluating food-borne outbreaks

It's a great party until someone ends up outside wearing a lampshade on their head.