Update on Infectious Enterocolitides and the Diseases That They Mimic

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Piranha

Green = Legal/ Red = illegal
Blue = Permit or captive bred (NM)
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
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
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
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>
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<tr>
<td>Norovirus</td>
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<td>Campylobacter</td>
<td><em>Listeria</em></td>
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<td><em>Toxoplasma</em></td>
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## Foods Commonly Associated with GI Infection

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<tr>
<th>Raw Dairy</th>
<th>Shellfish</th>
<th>Meat</th>
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<tr>
<td><em>Salmonella</em></td>
<td><em>Vibrio</em></td>
<td><em>Salmonella</em></td>
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<td><em>Campylobacter</em></td>
<td><em>Hepatitis A</em></td>
<td><em>Campylobacter</em></td>
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<tr>
<td><em>Brucella</em></td>
<td><em>Norwalk virus</em></td>
<td><em>Yersinia</em></td>
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<tr>
<td><em>E. coli</em></td>
<td><em>Rotavirus</em></td>
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<tr>
<td><em>Listeria</em></td>
<td></td>
<td><em>Salmonella</em></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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<tr>
<td>Aeromonas</td>
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<td>X</td>
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<tr>
<td>Yersinia</td>
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<tr>
<td>Cryptosporidium</td>
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<td>X</td>
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<tr>
<td>Giardia</td>
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<td>Strongyloides</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
Challenges for Pathologists When Evaluating a Specimen for an Infectious Process

• The training that most of us get in ID pathology is at odds with the worldwide frequency of infectious diseases
  – Most pathology training in infectious diseases is in microbiology and divorced from examination of tissue sections

• Ideal diagnostic environment involves morphology, microbiology, and often molecular tests
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
HIV Enterocolopathy
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
Resolving Infection
## Infections Producing More Specific Diagnostic Features

<table>
<thead>
<tr>
<th>Pseudomembranes</th>
<th>Granuloma Formation</th>
<th>Diffuse histiocytic</th>
<th>Architectural Distortion</th>
<th>Inclusions/Organisms Visible 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>Actinomycosis</td>
<td></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><em>Salmonella</em></td>
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<td>EHEC</td>
<td>Coccidians</td>
</tr>
<tr>
<td><em>Shigella</em></td>
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<td>Aspergillus</td>
<td>Histoplasmosis</td>
</tr>
<tr>
<td><em>Yersinia</em></td>
<td><em>E. histolytica</em></td>
<td>Mucor</td>
<td>EAEC</td>
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<td><em>Campylobacter</em></td>
<td>LGV</td>
<td>CMV</td>
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<td><em>Aeromonas</em></td>
<td>Syphilis</td>
<td>C. perfringens</td>
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<td><em>CMV</em></td>
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<td><em>M. tuberculosis</em></td>
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IBD vs. Infection
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
<table>
<thead>
<tr>
<th></th>
<th>Fever</th>
<th>Diarrhea</th>
<th>Infective Dose</th>
<th>Prognosis</th>
<th>Pattern</th>
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<td>Usually</td>
<td>Yes, +blood, WBC</td>
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<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
## Common Enteric Infections
### Clinical Features

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

*Courtesy Dr. Brian West*
Architectural distortion, crypt abscesses
Histiocytes and mononuclear cells are most prominent, with fewer neutrophils
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
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
## Common Enteric Infections
### Clinical Features

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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
Shigellosis with marked architectural distortion

from Riddell, Lewin, and Weinstein: *Gastrointestinal Pathology and Its Clinical Implications*
Pseudomembranous Shigellosis

Courtesy Dr. John Hart
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
  - Fistulae
  - Histologic changes of chronicity

Lamps, Madhusudhan, Greenson et al. AJSP 25: 2001
Lamps Madhusudhan, Havens et al. AJSP 27: 2003
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
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
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-ileocecal ulceration
Aeromonas
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
• 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
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
Big unexplained ulcer

? Elderly Pt

Yes

CMV

Get history, tailor workup to that

No

Immunocompromised Pt

Yes

CMV

?HSV

GMS

?AFB
Essentially Normal Bx in Immunocompromised Patient

- Increased apoptotic epithelial cells
  - CMV
  - Adenovirus

- Don’t overlook spirochetosis, coccidians, or Giardia!

- Are they severely immunocompromised?
  - No
    - Done!
  - Yes
    - 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.