Update on *C. difficile* and Select Other Causes of Infectious Diarrhea

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Outline

• Overview of diarrhea/gastroenteritis
• *C. difficile* diarrhea
• Viral diarrhea incl norovirus
• Traveler’s diarrhea

Diarrhea: a global cause of disease

• 2nd leading cause of morbidity/mortality worldwide
• In the US
  – 200-375 million episodes/year
  – 73 million physician visits
  – 1.8 million hospitalizations
  – 5000 deaths
  – Each person has 1-2 diarrheal illnesses/yr

Case

• ID is a 64 yo male who underwent a CABG procedure that was complicated by a prolonged intubation, fevers, and a possible nosocomial pneumonia. The pt was extubated recently and just completed a 10 d course of Zosyn. He now has low grade temps and watery diarrhea. His abdominal exam is unremarkable. His WBC is 10.2 with a slight left shift. His Cr is stable at 1.3. His stool for *C. diff* toxin is positive.

What is the appropriate treatment

1. Stop all antibiotics and see if patient improves
2. PO flagyl 500 mg TID x 10-14 d
3. PO vancomycin 125 mg PO QID x 10-14 d

Diarrhea in hospitalized pts

• Rarely caused by enteric bacteria, parasites, candida
• Abx-associated diarrhea
  – ~20% caused by *C. difficile*
  – Cytotoxin-producing *Klebsiella oxytoca* is newly recognized cause of hemorrhagic colitis in pts w/suspected *C. diff* (Hogenauer et al, NEJM, 2006)
• Drugs
• Iatrogenic
**Clostridium difficile**

*Kelly, JAMA, 2009; IDSA guidelines May 2010*

- Gram positive spore-forming rod
  - Persists in environment; resistant to alcohol and acid
  - Under appropriate conditions, germinates to vegetative (replicative) form which can produce Toxins
- Responsible for ~20% AAD diarrhea
  - Link to CDI established in 1978
  - 300,000 cases/yr in US
  - Increasing incidence (doubled between 2001-2005) and severity
- Emergence of epidemic/hypervirulent strain (NAPB1/027)

**Incidence/Prevalence**

- 3-5% healthy adults are colonized
- Higher in other populations
  - 8% nursing home residents
  - 7-14% of elderly hospitalized adults
  - 13% of pts admitted to ID ward (most HIV+)
  - 14% of HSCT recipients
- Majority of disease-causing organisms are hospital acquired

**Hospital Acquisition of C. diff**

*N Engl J Med 1989;320:204-210*

- Prospective study of 428 pts admitted to medical ward over 11 months
  - 7% positive on admission
  - 21% acquired C. diff
  - 63% asymptomatic
  - 37% developed diarrhea
  - Median time to acquisition: 12 days (range 3-98 days)

**Pathophysiology: Toxin-mediated disease**

- Disease is caused by Toxins A & B
  - No tissue invasion, no bacteremia, only causes disease in the colon (very rarely terminal ileum in pts w/inflammatory bowel disease)
  - Toxin A: potent enterotoxin (causes fluid loss) and WBC attractant (causes inflammation)
  - Toxin B: kills cells
  - Disease producing strains produce Toxin A&B or B
    - More likely to be asymptomatic if culture +/Toxin –

**Pathogenesis**

Normal flora prevents C. difficile germination/replication
Abx alter microflora:
Elimination of Bacteroides Facilitates spore germination

**Hypervirulent C. diff (B1/NAP1/027)**

- Encodes new toxin
  - Role unclear
- Overproduces Toxins A & B
- Ciprofloxacin resistant
- Reduced susceptibility to metronidazole
- Predominant strains in some settings
- Increased mortality (2x)
Clinical Signs/Sx

- Sx range from asymptomatic to severe
  - Mild-mod disease: <10 stools/day, no fever, WBC<15K, Cr<1.5x nl, minimal abd pain
  - Severe disease: fever, severe abd pain, WBC>15-20K, Cr>1.5x nl, hypoalbumenemia, septic shock, hypotension, toxic megacolon, or colonic perforation
- 90-95% have watery diarrhea; 5-10% bloody diarrhea
- 80% have abd pain, leukocytosis, fever
- May progress to toxic megacolon/perforation

Lab diagnosis

- Only test symptomatic pts
- Cytotoxin assay
  - Add stool filtrate to cultured cells
  - Sensitive, specific, but labor intensive
  - 48-72 hrs to complete
- EIA for toxins
  - Rapid (test for toxins A & B)
  - 1000X less sensitive (20-25% false neg rate)
- PCR for toxin B gene

Summary of tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytotoxin assay</td>
<td>90-100%</td>
<td>99%</td>
<td>Sensitive, specific</td>
<td>Labor-intensive, 48-72 hrs to complete</td>
</tr>
<tr>
<td>EIA</td>
<td>95%</td>
<td>99%</td>
<td>Rapid (test for toxins A &amp; B)</td>
<td>1000X less sensitive</td>
</tr>
<tr>
<td>PCR for toxin B gene</td>
<td>95%</td>
<td>99%</td>
<td>Rapid, same day results</td>
<td>Doesn’t distinguish Toxin+ from Toxin-</td>
</tr>
</tbody>
</table>

2-stage testing

- Screen (EIA) for bacterial glutamate dehydrogenase (GDH), metabolic enzyme specific to C. diff
  - >95% sensitive, negative predictive value 99%
  - Rapid, same day results
  - Doesn’t distinguish Toxin+ from Toxin-
- PCR for toxin B gene
  - 95% sensitivity
  - Rapid, same day results
- If negative and sx persist, repeat in 72 hrs

Risk factors

- Antibiotics
  - Usually develops after 5-10 d of abx, can occur after 1 dose or as late as 4-6 wks after discontinuation of abx
  - 96% of pts have h/o abx exposure in prior 2 wks
  - 100% have h/o exposure to abx in prior 3 mos
- Chemotherapy
  - Some agents have anti-bacterial activity
- PPI
- Health care facility
- New exposure to C.diff
  - Colonization and development of antibodies to toxins may be protective
- Community acquired cases without abx exposure reported

Antibiotics Associated With C. difficile

<table>
<thead>
<tr>
<th>Frequent</th>
<th>Infrequent</th>
<th>Rare</th>
</tr>
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<tbody>
<tr>
<td>Cephalosporins (especially 2nd &amp; 3rd gen agents)</td>
<td>Tetracyclines</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>Ampicillin &amp; amoxicillin</td>
<td>Trimethoprim-sulfamethoxazole</td>
<td>Metronidazole</td>
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<tr>
<td>Clindamycin</td>
<td>Macrolides</td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Vancomycin</td>
<td>Rifampin</td>
</tr>
</tbody>
</table>
Transmission

NEJM 1989

• Pt-pt transmission
  – Time-space clustering of cases
  – Identical immunoblot types
  – More frequent and earlier acquisition if roommates positive
• Hand carriage amongst hospital personnel common

Infection Control

1. Patient isolation in a single room, preferably with a bathroom
2. Strict contact precautions
3. Terminal room cleansing with 1:10 bleach
4. Avoidance of rectal thermometers
5. Soap and water for hand washing
6. Antibiotic control (clindamycin, 3rd generation cephalosporins)

Treatment

• Three first line drugs
  – Metronidazole (Flagyl®)
    • Not FDA approved but used since 1978
  – Oral vancomycin (Vancocin®)
    • FDA approved in 1978
  – Fidaxomicin (Dificid®)
    • FDA approved in 2011

Flagyl vs Vanco
Zar et al, CID 2007 45:302

• 172 CDAD patients enrolled, 150 completed study
• Metronidazole 250 mg PO QID X 10 days
• Vancomycin 125 mg PO QID X 10 days
• Disease severity:
  – Age > 60
  – Temp > 38.3°C
  – WBC > 15,000 cells/mm³
  – Albumin < 2.5 mg/dL
  – Endoscopic evidence of pseudomembranes

Flagyl vs Vanco
Zar et al, CID 2007 45:302

• 69 severe cases
  – 97% of pts treated with vanco cured; 10% relapse
  – 76% treated with Flagyl cured: 21% relapse
• 81 mild cases
  – No difference in vanco vs flagyl rx

Treatment of C. diff

• Discontinue all unnecessary antibiotics. If possible, switch to more “low risk” antibiotics
• Avoid narcotics and other agents known to reduce peristalsis
• Infection control measures
• Oral antibiotic treatment
  – Non-severe cases: PO flagyl (500 mg TID x 10-14 d)
  – Severe cases: PO vanco (125 mg PO QID x 10-14 d)
  – NPO pt: IV flagyl, if severe, consider vanco PR
• Probiotics?
### Suggested approach

**NEJM Kelly & LaMont 359:1932, 2008**

**Infect Cont Hosp Epidemiol 2010**

<table>
<thead>
<tr>
<th>Clinical definition</th>
<th>Suggested clinical data</th>
<th>Recommended treatment</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial episode, mild or moderate</td>
<td>Leukocytosis with a white blood cell count of 10,000 cells/μl or lower and a serum creatinine level less than 1.5 times the prehistoric level</td>
<td>Metronidazole, 600 mg 3 times per day by mouth for 10-14 days</td>
<td>A-I</td>
</tr>
<tr>
<td>Initial episode, severe</td>
<td>Leukocytosis with a white blood cell count of 10,000 cells/μl or higher or a serum creatinine level greater than or equal to 1.5 times the prehistoric level</td>
<td>Vancomycin, 125 mg 4 times per day by mouth for 10-14 days</td>
<td>B-I</td>
</tr>
<tr>
<td>Initial episode, severe, complicated</td>
<td>Hypoxia or shock, lines, sepsis</td>
<td>Vancomycin, 500 mg 4 times per day by mouth or by nasogastric tube, plus metronidazole, 500 mg every 8 hours intravenously. If complete failure, consider adding oral instillation of vancomycin</td>
<td>C-III</td>
</tr>
</tbody>
</table>

### Treatment in NPO Patient With Severe Disease

- IV or PO metronidazole re-enters small bowel via hepatic re-circulation, delivers active agent intraluminally.
- IV metronidazole never compared with PO vancomycin or PO metronidazole, but recommended in the patient with ileus or toxic megacolon
- Vancomycin 500 mg QID by retention enema or NG tube
- Intravenous immune globulin (IVIG)
- Monoclonal ab
- Tigecycline
- Colectomy

### Recurrent C. difficile

- Incidence: 20%
  - Higher risk in pts w/ h/o relapse
- 50% have same organism, 50% have new strain
- Not related to severity of initial C. diff disease, inciting abx, Vancomycin vs Metronidazole rx, or persistence of C. diff within 72 hrs post initial rx
  - No role to reculture or retest at end of Rx
  - Carriage 3-4 wks after initial rx was assoc with recurrent disease
- Usually occurred within 2 wks of discontinuation of Metronidazole or Vancomycin
- Usually not drug failure

### Relapse and Recurrence

- Single recurrence: Rx w/ standard course PO metronidazole or PO vancomycin
- Recurrent disease: PO vancomycin in tapering dose over 4 weeks or 125 mg PO QOD for 6 weeks
- Immune globulin 400 mg/Kg and consider repeat in 3 weeks
- Monoclonal Ab in conjunction w/flagyl or vanco (7% recurrence vs 25% in controls) (Lowry et al, NEJM, 2010).
- Rifamicin: 2 wks after completing PO Vanco course
  - Resistance does develop (Johnson et al, CID, 2007)
- Fecal transplant

### Fidaxomicin vs Vancomycin

- Prospective, randomized, double-blind, controlled study
- Compare fidaxomicin 200 mg orally twice daily (287 patients) and vancomycin 125 mg orally four times daily (309 patients)
- Exclusions
  - Severe disease (megacolon)
  - IBD
  - More than one recurrence

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**Fidaxomicin versus Vancomycin for *Clostridium difficile* Infection**

Thomas J. Louie, M.D., Mark A. Miller, M.D., Kathleen M. Mullane, D.O., Karl Weiss, M.D., Arnold Lennette, M.D., Yoav Golan, M.D., Sherwood Gorbach, M.D., Pamela Sears, Ph.D., and Youe-Kong Shue, Ph.D., for the OPT-80-003 Clinical Study Group.

Role of Fidaxomicin in Therapy

- Use in recurrences?
- COST IS AN ISSUE
  - Fidaxomicin is $1200 for 10 days
  - Metronidazole and vancomycin are a fraction of the cost

Other (Second-Line) Therapies for C. difficile

- Nitazoxanide (Alinia®)—500 mg BID X 7-10 days (Clin Infect Dis 2006;43:421)
- Rifaximin 400 mg QID X 10-14 days
  - Used as a “chaser” for therapy of recurrent disease (Clin Infect Dis 2007;44:846)
- Toxin binding agents—cholestyramine/Tolevamer 2 gm TID X 14 days (Clin Infect Dis 2006;43:411)
- Probiotics—no good data to support the use for prevention of C. difficile disease

Probiotics for C. difficile

- Evolving area of study
- Difficult to generalize because of different products/doses/durations used in studies
- Best data is for PROPHYLAXIS
  - May decrease risk of C. diff in high-risk patients taking antibiotics (elderly/IBD/PPI)
- Little data to support adjunctive administration of probiotics for routine use in treatment of C. difficile
- May be efficacious in recurrent disease—data not robust

Case

- MQ is a 44 year old woman that seen Sept 2006
- In MVA in Jan 2003 requiring spinal surgery
- Subsequently developed fecal incontinence unresponsive to conservative therapy
- June 2003 underwent sphincteroplasty with perioperative antibiotics
- 2 weeks later developed diarrhea with positive C. difficile toxin assay
- Treated with metronidazole for 2 weeks; relapse treated with vancomycin

Case

- In the subsequent 3 years treated with:
  - Several courses of metronidazole, including one of six months resulting in peripheral neuropathy
  - Multiple courses of oral vancomycin
  - Saccharomyces boulardii
  - Nitazoxanide (Alinia®)
  - Cholestyramine
  - IVIG
- Every attempt at stopping medication resulted in a relapse
- Underwent successful fecal transplant
Fecal Microbiota Transplantation (FMT): the beginning of a new era?

Not exactly new...

• Eiseman B, Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis, Surgery 1958:44:854 to
• “re-establish the balance of nature”…“3/4 pts had immediate and dramatic responses”…“this simple yet rational therapeutic method should be given more extensive clinical evaluation”

Fast forward >50 yrs later

• Rationale: repopulate the colonic microbiota, inhibit C. diff colonization/germination
• Various non-controlled trials demonstrate efficacy > 90% (~300 cases reported)
  – Reports of successful therapy by retention enemas, duodenal tube, rectal tube, colonoscopy, home enemas
  – Gough et al, CID, 2011
  – 88% success with single treatment

Why hasn’t it been widely adopted?

• Esthetically unappealing
  – treating S with S
• Logistically challenging
• Lack of randomized controlled trials
• Only patients with recalcitrant C. diff likely to undergo FMT

Two major advances

• We now have qualitative & quantitative methods to examine changes in microbiota
• Randomized controlled trial for duodenal FMT

The human microbiome

• The normal gut flora is your friend
  – Necessary for gut development, metabolism, nutrient acquisition, immune system function
• Changes in the gut microbiota associated with disease
  – Obesity, IBD, AAD
• Abx disrupt your nl flora!
• Most intestinal microbiota are not culturable
• New technologies to quantify & classify flora
  – Clone and sequence highly conserved gene (16s rRNA) to quantify and categorize (phylogenetic comparisons)
  – “deep” sequencing directly of stool samples
  – Bioinformatics
Original Article

Duodenal Infusion of Donor Feces for Recurrent Clostridium difficile

Els van Nood, M.D., Anne Vrieze, M.D., Max Neuteloor, M.D., Ph.D., Susana Fuentes, Ph.D., Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Vlaar, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D., Joop F. W. M. Bartelsman, M.D., Jan G. P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D., Marcel G. W. Dijkgraaf, Ph.D., and Josbert J. Kuijper, M.D., Ph.D.

N Engl J Med
Volume 368(5):407-415
January 31, 2013

Results

• Three groups (unblinded)
  – duodenal infusion of donor feces after 4 days vancomycin Rx and bowel lavage (16)
  – Vancomycin Rx x 14 D (13)
  – Vancomycin Rx 14 D + lavage (12)
• Endpoint: resolution of diarrhea without relapse after 10 wks
• Study stopped after interim analysis
  – 13/16 cures after 1st infusion (Rec 1/16)
  – 2/3 cures with 2nd infusion
  – 4/13 cures Vanco alone (Rec 8/13)
  – 3/13 cures Vanco + lavage (Rec 7/13)
  – 6/18 relapses cured w/FMT
• Adverse effects: Infusion related Cramping (30%) & diarrhea (90%)

Microbial Diversity

Indications for FMT

• Recurrent or relapsing CDI
  – >= 3 episodes mild-mod CDI and failure of 6-8 wk Vanco taper
  – >= 2 episodes severe CDI req hospitalization assoc w/significant morbidity
• Moderate CDI not responding to >= 7 d vancomycin
• Severe CDI & no response to Rx after 48 hrs

A more holistic view of CDI

• NI flora prevents C. diff colonization and/or germination
• Abx disrupt normal flora (defense against colonization & germination
• Toxin production-inflamm response, diarrhea
• Abx tx directly kills C. diff but also suppresses nl flora
• Host develops antibodies to neutralize toxin
• Pulsed abx may balance direct inhibition of C. diff w/repopulation of nl flora
• FMT may be much more effective!
Back to the future

- Defined microbiota replacement
  - Frozen
  - Defined (synthetic)
  - Available in oral form
- Primary treatment?
- Critically ill pts?
- Immunocompromised pts?

Case

- 32 yo female calls your office c/o diarrhea x 2 days. She notes 8 loose stools in the past 24 hrs. She has a low grade temp, mild nausea, and has vomited x 2. She denies bloody stools, recent travel, ingestion of unusual foods. No sick contacts.

Differential Dx

- Infectious
- Ischemic
- IBD
- Iatrogenic/Osmotic
- Malabsorption

Etiology of severe acute gastroenteritis in adults in ER

- Prospective multicenter ER-based study (JID 205:1374)
- Serum, rectal swabs, loose stool
- Pathogens found in 25%
- Whole stool more sensitive than rectal swab

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Whole Stool, % (No. Positive/No. Tested)</th>
<th>Rectal Swab, % (No. Positive/No. Tested)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norovirus</td>
<td>28 (9/127)</td>
<td>6.6 (9/135)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>18 (10/106)</td>
<td>2.9 (10/34)</td>
<td>0.4</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>5 (2/13)</td>
<td>Not tested</td>
<td></td>
</tr>
<tr>
<td>Astrovirus</td>
<td>17 (2/12)</td>
<td>3.8 (2/61)</td>
<td>0.07*</td>
</tr>
<tr>
<td>Calicivirus</td>
<td>5.2 (1/93)</td>
<td>2.2 (4/185)</td>
<td>0.21</td>
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<tr>
<td>Shiga toxin</td>
<td>5.3 (1/95)</td>
<td>Not tested</td>
<td></td>
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<tr>
<td>E. histolytica</td>
<td>3 (4/120)</td>
<td>0 (0/113)</td>
<td>0.03</td>
</tr>
<tr>
<td>CMV</td>
<td>3 (4/120)</td>
<td>1.6 (1/61)</td>
<td>0.46</td>
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<tr>
<td>Salmonella spp.</td>
<td>3.8 (1/93)</td>
<td>0.0 (0/113)</td>
<td>0.07*</td>
</tr>
<tr>
<td>Bacillus</td>
<td>3.8 (1/93)</td>
<td>0.0 (0/113)</td>
<td>0.07*</td>
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<tr>
<td>Shigella</td>
<td>5.3 (1/95)</td>
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<td></td>
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<tr>
<td>Stool characteristics</td>
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<tr>
<td>Frequency &amp; quantity</td>
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<tr>
<td>Presence of dysenteric symptoms</td>
<td></td>
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<tr>
<td>Symptoms of volume depletion</td>
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<tr>
<td>Associated symptoms</td>
<td></td>
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<tr>
<td>Epidemiologic clues</td>
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</tbody>
</table>
Be a Sherlock Holmes

- Travel to developing area
- Day-care center attendance or employment
- Consumption of raw meats, eggs, unpasteurized milk/cheese, swimming in or drinking from untreated fresh water
- Farm or zoo animals, reptiles
- Exposure to other ill persons
- Medications, esp. antibiotics
- Underlying medical conditions
- Receptive anal intercourse or oral/anal contact
- Food-handler or caregiver

Viral diarrhea

- Usually resolves ≤ 3 days

Norwalk Rotavirus
Norovirus

Glass et al, NEJM, 2009

- Single stranded, noneveloped RNA virus
- Caliciviridae family
- Genogroups->genotypes->strains
- Replicates only in GI tract
- Percists in environment
- Humans are the only reservoir

Just a little stomach flu...

- Inc 24-48 hrs
- Sudden onset diarrhea, vomiting, abd pain, malaise, low grade fever
  - Profuse and projectile
- Usually self-limited, resolves ≤ 3 d
  - Prolonged and severe sx in elderly, very young
  - Prolonged asymptomatic shedding
    - Up to 8 wks in healthy pts
    - Up to 1 yr in severely ill pts

Larry the vomiting robot

Dx

- Not culturable
- Older techniques: EM, stool ELISA
- Gold standard: RT-PCR (since early 1990’s)
  - 68% sensitive
  - 99% specific
  - Avail at public health depts, state, national labs, sendouts
**Evolving epidemiology**
- Most common cause of gastroenteritis
- Leading cause of diarrhea
- Leading cause of foodborne-associated illnesses
- Responsible for 50% of gastroenteritis outbreaks worldwide
- Greatly under-reported
  - Only 1/1562 cases identified
  - 21 million cases/yr US
  - ~71,000 norovirus-associated hospitalizations costing $493 million/yr (CID 2011: 52, 466)
  - ~800 deaths/yr US
  - 200,000 deaths annually children <5 developing nations

**Evolving epidemiology**
- Increased outbreaks in nursing homes and long-term care facilities
- Associated with poor outcome in older pts
  - Longer illness
  - Acute renal failure, arrhythmias, hypokalemia, chronic diarrhea

**Norovirus is a moving target**
- Antigenic shift and drift (like influenza)
  - Change in viral capsid affects binding to GI tract oligosaccharides
  - New variant->new epidemic wave
  - New pandemic strain every 2-4 yrs
- GI, GII, GIV cause most human infxns
  - GII.4 strains predominant since 1990’s
  - New GII.4 Sydney strain reported which has rapidly spread across world (CDC)

**Why is norovirus so difficult to contain?**
- Highly transmissible: a little goes a long way...
  - ID_{50}: 10-100 virions
  - Facile 2˚ spread
    - Viral shedding precedes clinical illness in >30% of pts
    - Prolonged shedding
      - Up to 8 wks in healthy hosts
      - Up to 1 yr in IC hosts
    - Asymptomatic shedders
  - Withstands wide range of temps and persists in environment
  - Immunity is short-lived and not cross-protective against antigenic variants

**Why is norovirus so difficult to contain?**
- Multiple modes of transmission
  - Food
    - Globalization of food distribution
    - Increased # of people who handle the food we eat
    - Increased consumption of food at risk of contamination (fresh vegetables and fruit)
  - Water
  - Airborne via vomitus
    - Susceptibility correlates w/distance from vomiting event
  - Contact w/contaminated surfaces
  - Fomites
  - Person-person contact
  - Resistant to many disinfectants

**Interrupting transmission**
- Disinfection
  - Wipe surface w/detergent to remove particle debris followed by hypochlorite bleach (5000 ppm) as disinfectant
  - Other disinfectants less efficient: (quanternary ammonium compounds, alcohols)
  - Alcohol-based disinfectants are insufficient
- Wash hands for 1 min w/soap & water, rinse for 20 sec, dry w/disposable towels
Interrupting transmission

- Institutional settings
  - Cohort pts and staff
  - Minimize transport, visitors
  - Isolation, contact precautions for sick pts (48 hrs after sx resolve)
  - Sick staff stay home until 48 hrs after sx resolve
  - Alcohol in, soap & water out

Is the GII.4 variant more virulent?

Desai et al, CID 2012

- Meta-analysis 1993-2011
- GII.4 strains
  - higher hospitalization (RR 9.4)
  - Higher mortality (RR 3.1)
  - Deaths mostly associated with healthcare facility outbreaks

Vaccine?

- Challenging due to rapid evolution of antigenic variants and short-lived immunity
- Ligocyte

Norovirus: The perfect pathogen?

- Highly contagious
- Rapidly & prolifically shed
- Constantly evolving
- Evoke limited immunity
- Only moderately virulent—doesn’t kill host

Patient education

Planning your next cruise....

Cdc vessel sanitation site
Holy sh**

Case IIB

- 32 yo female calls your office c/o diarrhea x 3 days. She notes 8 loose stools in the past 24 hrs. She has a low grade temp, mild nausea, and has vomited x 2. She denies bloody stools. She returned 2 days ago from a 2 week trip to India.

What would you do

1. Tell her to drink plenty of fluids, take lomotil as needed, and that her sx will likely resolve on their own
2. Treat her empirically with a 3 day course of levofloxacin
3. Treat her empirically with a single dose of azithromycin
4. Have her come into your office with plans to send stool for culture including Cholera, O&P, with plans to start her on azithromycin

Traveler’s diarrhea

- Most common illness in travelers
- Onset usually 5-15 days after arrival
- Usually resolves spontaneously 3-5 d
- 40-60% incidence during 2-3 wk vacation in persons from industrialized countries->developing regions

Traveler’s diarrhea:critters

- Occurs in naïve/non-immune hosts
  - ETEC most common
  - Also enteropathogenic E. coli
  - Campylobacter>Shigella, Salmonella
    - Incr FQ resistance in Campylobacter
  - Aeromonas, Pleisiomonas, V. cholera, V. parahaemolyticus
  - Rotavirus
  - Parasites (prolonged diarrhea: E. histolytica, Giardia, Cryptosporidium)
  - Blastocystis hominis unlikely to be a pathogen
  - 20-30% have no identifiable cause

Most likely microorganisms depend on location

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Late American (late)</th>
<th>Caribbean (late)</th>
<th>South Asia (%)</th>
<th>Southeast Asia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteropathogenic E.coli</td>
<td>50.5</td>
<td>51.1</td>
<td>60.6</td>
<td>50.0</td>
</tr>
<tr>
<td>Enteropathogenic, enteropathogenic, and diarrheogenic E.coli</td>
<td>0.3</td>
<td>1.1</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Shigella spp.</td>
<td>0.6</td>
<td>0.8</td>
<td>0.9</td>
<td>0.7</td>
</tr>
<tr>
<td>Salmonella spp.</td>
<td>0.1</td>
<td>0.3</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Aeromonas spp.</td>
<td>0.8</td>
<td>1.2</td>
<td>2.4</td>
<td>3.2</td>
</tr>
<tr>
<td>Campylobacter spp.</td>
<td>0.05</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Enteropathogenic Aeromonas</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4rd component</td>
<td>1.2</td>
<td>2.3</td>
<td>5.4</td>
<td>4.8</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>0.1</td>
<td>0.3</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Cryptosporidium</td>
<td>0.2</td>
<td>0.3</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Vibrio cholera</td>
<td>0.1</td>
<td>0.2</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>EHEC</td>
<td>1.0</td>
<td>1.2</td>
<td>2.4</td>
<td>3.6</td>
</tr>
<tr>
<td>Vibrio parahemolyticus</td>
<td>0.1</td>
<td>0.2</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Bacillus cereus</td>
<td>0.1</td>
<td>0.2</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Enterotoxigenic E. coli</td>
<td>0.1</td>
<td>0.3</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Enteropathogenic Campylobacter</td>
<td>0.05</td>
<td>0.1</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>No pathogens identified</td>
<td>88.8</td>
<td>43.7</td>
<td>80.8</td>
<td>43.7</td>
</tr>
</tbody>
</table>

Traveler’s diarrhea:critters

- Occurs in naïve/non-immune hosts
  - ETEC most common
  - Also enteropathogenic E. coli
  - Campylobacter>Shigella, Salmonella
    - Incr FQ resistance in Campylobacter
  - Aeromonas, Pleisiomonas, V. cholera, V. parahaemolyticus
  - Rotavirus
  - Parasites (prolonged diarrhea: E. histolytica, Giardia, Cryptosporidium)
  - Blastocystis hominis unlikely to be a pathogen
  - 20-30% have no identifiable cause
Traveler’s diarrhea: Px

• Boil it, cook it, peel it
  – Avoid tap water, ice, bottled noncarbonated beverages
  – Avoid raw veggies, unpeeled fruits, raw meat, and seafood
• Ab prophylaxis rarely required

Traveler’s diarrhea: Rx

• Oral rehydration usually sufficient
• Antimotility agents
  – Loperamide 4 mg followed by 2 mg q loose stool (<16 mg/day)
  – Not recommended if sx of dysentery (high fever, bloody stool)
• Dysentery:
  – Levofloxacin 500 mg qd until sx resolve or 3 days
  – Azithro (1000 mg) or 500 mg qd x 3d (preferable in SE & India)
  2/2 high rate of Cipro-R Campylobacter
    • Tribble et al CID 2007:
      • 96% cure single dose azithro
      • 95% cure 3D azithro
      • 71% cure levo
      • Cure rate related to levo resistant Campy
  – Reduce duration of sx ~1 d

Prophylaxis options

• If traveler cannot tolerate few days of illness
  • Achlorhydria, IC, underlying chronic GI disease, CRF, DM, ostomies
  • Politicians, athletes
• Rifamixin-effective against ETEC & other non-invasive bacteria
• Peptobismol 2 tabs QID effective in preventing ETEC (bacteriostatic)
  – ~60% effective
  – Side effects: black tongue & stool, mild tinnitus
  – Avoid if allergic to salicylates or on salicylates or anti-coagulants
  – Not to exceed 3 weeks

Common regimens

<table>
<thead>
<tr>
<th>Table 2 Common treatments for TD</th>
<th>Infect Dis Clin N Am 26 (2012) 691–706</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
<td><strong>Dosage</strong></td>
</tr>
<tr>
<td>Symptomatic Treatment</td>
<td></td>
</tr>
<tr>
<td>Bismuth subsalicylate 1 dose of 525 mg (2 tablets of Pyzium Bismol Chewable Tablets) po every 10 min, no more than 8 doses per day</td>
<td></td>
</tr>
<tr>
<td>Loperamide 4 mg po, then 2 mg after each loose stool, not to exceed 16 mg per day (for 48 h)</td>
<td></td>
</tr>
<tr>
<td>Antibiotic Treatment Fluoroquinolones</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin 500 mg po, bid</td>
<td></td>
</tr>
<tr>
<td>Ofloxacin 200 mg po, bid</td>
<td></td>
</tr>
<tr>
<td>Azithromycin 1000 mg po, once</td>
<td></td>
</tr>
<tr>
<td>Rifampin 200 mg po, bid</td>
<td></td>
</tr>
</tbody>
</table>

Practical approach:

• Have pt fill prescription for quinolone or azithro prior to travel
  – take if pt gets mod-severe diarrheal illness
• Have pt bring loperamide
  – take if pt has mild diarrheal illness or more severe illness if NO bloody diarrhea
Initial management
(prior to culture results)

- Mild sx: Non-inflammatory diarrhea
  - Developed country: hydrate & observe, ± antimotility agent
  - Traveler’s diarrhea: hydration, anti-motility agent, single
dose of levofloxicin or azithromycin
- Mod Sx: Inflammatory diarrhea
  - Levofloxicin or Azithromycin 1-3 d unless C. diff suspected
  - Loperamide if no bloody diarrhea
  - Flagyl if C. difficile or E. histolytica suspected
  - If no improvement in 48 hrs, seek medical evaluation
- To culture or not to culture...that is the question

What about EHEC?

- 95% of pts have bloody stools at least some
time during their illness
- Abx shown to exac illness (Wong et al NEJM 2000)
  - Likely by decreasing nl flora and/or enhancing toxin
  production
- How to distinguish dysentry from EHEC
  - Rely on case epidemiology-if returning travel to 3rd
  world countries, more likely shigella
  - If domestically acquired, concern for EHEC
  - Send stool cultures if in first 6 d of illness and await results
  before prescribing abx

What would you do

✔ 1. Tell her to drink plenty of fluids, take lomotil as
needed, and that her sx will likely resolve on their
own
2. Treat her empirically with a 3 day course of
levofloxicin (not good for travel to India or SE asia 2˚
to increasing resistance in Campylobacter)
✔ 3. Treat her empirically with a single dose of
azithromycin
✔ 4. Have her come into your office with plans to send
stool for culture, O&P, with plans to start her on
azithromycin

Probiotics

- Beneficial microorganisms (lactobacillus or S.
boulardii)
- Possible mechanisms
  - Lactose digestion
  - Production of anti-microbial agents
  - Competition for space or nutrients
  - Immune modulation
- Possible uses-no clear indications
  - Pediatric viral gastroenteritis
  - C. difficile & antibiotic associated diarrhea
  - Traveler’s diarrhea???

Main refs

- Said et al, CID 2008:47:1202-1208
- Glass et al, NEJM 361:18, 2009

http://www.cdc.gov/ncidod/dvrd/revb/gastro/norovirus.htm