The Clinical Algorithm for Acute Diarrhea

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Points for discussion

• Review pathophysiology of diarrhea
  – Electrolyte transport
  – Movement of fluid
  – Difference between small and large intestine diarrhea
• Review 4 pathophysiologic types of acute diarrhea and give examples of each type.
• Discuss algorithm for evaluation for normal host

• Will not discuss functional diarrhea as this usually falls into the category of chronic.
• Will not discuss immunocompromised host
Daily Intestinal Fluid Balance

- Oral Intake: 2 Liters
- Saliva: 1 Liter
- Gastric Juice: 2 Liters
- Bile: 1 Liter
- Pancreatic Juice: 2 Liters
- Other: 1 Liter

Total: 9 Liters / Day

Normal Intestinal Fluid Absorption

Normal Fluid Delivery to Upper Small Intestine:
9 Liters/day

- Jejunal absorption: 3-5 Liters/day
- Ileal Absorption: 2-4 Liters/day
- Colon Absorption: 1-2 Liters/day

RESULT: Stool water content < 200 ml
Impaired Small Bowel Absorption

- 9 Liters or more can be delivered to the colon
- Maximally, the colon can absorb 5-6 liters of fluid
- Therefore, Large volume of fluid can overwhelm the colon and result as diarrhea

Small intestinal diarrhea = Large volume of fluid
Alteration of Permeability of luminal membrane to chloride by cAMP and intracellular calcium

Small Bowel Diarrhea
- Large in Volume
- Infrequent
- (3-4 bowel movements per day)
- No Tenesmus
Colonic Diarrhea

- Small in Volume
- Frequent
- (8-10 bowel movements/day)
- Tenesmus

4 Main Pathophysiological Categories of Diarrhea

- Secretory
- Osmotic
- Malabsorptive
- Inflammatory
Secretory, Osmotic, Malabsorptive, Inflammatory

• No one category is independent. The classification of diarrhea is based on the main underlying pathophysiology
• Infectious diarrhea is not a separate category as it may cause any or all of the 4 types of diarrhea. Each type of infection may be different.

1 Secretory Diarrhea

• The intestine has overall net secretion
• Fasting has no effect on the diarrhea
• Absence of fecal osmotic gap
290 - 2(Na + K) < 40

• 290 represents average fecal osmolality
• Na and K represent the main osmotically active cations sodium and potassium
• 2 times the (Na + K) represents the osmolality of the two main cations (sodium and potassium) and their corresponding anions (chloride)
• 40 is a “fudge factor” to account for some other osmotically active components of the fecal material

Secretory Diarrhea: Causes

• Hormones:
  - VIP, Serotonin (Carcinoid), Calcitonin, Gastrin, Thyroid hormone
• Infectious agents:
  - Vibrio cholerae, E. Coli
  - ? Ebola
• Villous adenoma
• Bile salt malabsorption
• Intestinal Resection
• Inflammatory bowel disease
• Collagen vascular diseases
Secretory Diarrhea: Cholera Toxin

- Produced by Vibrio cholera
- Can cause death within 3 hours
- Cholera toxin is composed of 5 “B” subunits that encircle a single “A” Subunit:
  - B binds toxin to a receptor
  - A activates adenylate cyclase
  - Toxin alters intestinal permeability by acting on the tight junctions and causes active chloride secretion

Secretory Diarrhea: Cholera Toxin

- Seen primarily in India and Asia
- Humans are the only host
- Need large inoculum and low gastric acid
- No cell toxicity - Small bowel looks normal on histology
- Stool is described as rice water since it has lost all pigment and has flecks of mucus
- Can be as much as 1 liter per hour
Secretory Diarrhea: Cholera Treatment

- Treatment: **ORAL REHYDRATION** with solution consisting of salt and glucose (Glucose will significantly enhance the absorption of sodium)
- Antibiotics (eg. Tetracycline) will decrease the length of the clinical illness
Osmotic Diarrhea

- Occurs when a poorly absorbed substance acts as an osmotically active solute
- This draws water into the GI lumen and causes diarrhea
- IMPROVES WITH FASTING
- A fecal osmotic gap is present

290 - 2(Na + K) > 40

- Fecal osmolality is made up of charged molecules other than sodium and potassium (and their associated anions)
- When 2(Na + K) is subtracted from the average fecal osmolality of 290, the unmeasured osmotically active molecules are not accounted for
- Therefore the equation is larger than the usual “fudge factor” of 40
Causes of Osmotic Diarrhea

- Carbohydrate malabsorption
- Excessive ingestion of poorly absorbed carbohydrate
- Magnesium - induced diarrhea
- Laxatives containing poorly absorbable anions

**Treatment:** Remove the causative agent.

Carbohydrate Malabsorption

- Disaccharidase deficiencies
- Congenital glucose-galactose malabsorption
- Congenital fuctose malabsorption
Ingestion of poorly absorbed carbohydrate

- Lactulose (not naturally occurring)
  - Fructose and galactose
- Sorbitol - mixed in elixirs, sugar-free gum and mints, naturally occurring in pears, prunes, peaches and orange juice
- Fructose - found in soft drinks, apples, pears, honey, cherries, dates, figs, grapes, prunes
- Mannitol - found in sugar-free products, mints
- Bran / Fiber

Magnesium induced diarrhea

- Food supplements
- Antacids
- Laxatives (eg. Milk of Magnesia)
Laxatives containing poorly absorbed anions

- Sodium sulfate
- Sodium phosphate (Phosphosoda)
- Sodium Citrate

Osmotic Diarrhea: Lactase deficiency

- Lactase
  - Brush-border intestinal enzyme
  - Breaks down the milk sugar, lactose
  - Glucose and Galactose
- If lactase is not present, lactose reaches the colon and undergoes bacterial hydrolysis and fermentation
- Result: Osmotic diarrhea with bloating, cramps and flatulence
- Treatment: Avoid milk and milk products, use lactase supplements, use lactose-free milk, substitute fermented milk products such as yogurt
Lactase Deficiency: Very Common

- 10-20% North American Caucasians
- 80% African Americans
- 95% Asian
- 75% Middle Eastern

Malabsorptive Diarrhea: 3 Common causes

- Impaired delivery of biliary and pancreatic products to the bowel lumen
- Surgical resection of the small bowel and terminal ileum
- Impaired small bowel absorptive surface
**Malabsorptive Diarrhea:**

**bile/pancreatic issues**

- Pancreatic insufficiency results in severe fat malabsorption and steatorrhea (fat in the stool)
- Impaired bile salt delivery to the small bowel lumen results in decreased emulsification and micell formation

**Malabsorptive Diarrhea:**

**Resection of ileum**

- The terminal ileum (TI) is necessary to reabsorb bile salts (Enterohepatic circulation)
- The key number is 100 cm
- If less than 100 cm of TI is resected, hepatic synthesis of bile can increase enough to compensate for the loss of bile salts
- If more than 100 cm of TI is resected, hepatic synthesis of bile cannot compensate for the loss of bile acids and fat malabsorption and steatorrhea occurs
- *Note: Bile acids also cause a primary secretory diarrhea in the colon*
Malabsorptive:
Small Bowel Diarrhea
Celiac Sprue

- Affects the small bowel mucosa and results in a blunting of the normal villous pattern
- Caused by an immune response to Gluten
- If entire small bowel is involved: Diarrhea, weight loss and steatorrhea can occur
- If only proximal small bowel is involved, can see isolated iron or folate deficiency
Inflammatory Diarrhea

- Caused by exudation of serum proteins, mucus, and inflammatory cells from areas of active inflammation and ulceration
- Overlap with osmotic diarrhea and malabsorptive diarrhea
- Main causes:
  - Invasive infectious agents
  - Radiation enteritis/colitis
  - Inflammatory bowel disease

Invasive Infectious Agents

- Campylobacter Jejuni
- Salmonella
- Shigella
- Enteroinvasive E. Coli & Enterohemorrhagic E. Coli 0157:H7
- Clostridium difficile
- Ameba: Entamoeba histolytica
- Vibrio parahaemolyticus
  - Vibrio vulnificus typically causes infection (Cirrhotics)
Work Up: Distinguishing Categories

• Mild vs. Severe
• Secretory vs. Osmotic
• Infectious vs. Inflammatory
• Identify new changes:
  – Surgery
  – Medications
  – Diet

History is Key: Important Questions

• Sudden onset?
• Time period?
• Stool consistency?
• Blood present?
• How urgent?
• How many BMs?
• Large or small volume?
• Tenesmus?
• Weight loss?
• First episode?
• Constant or episodic?
• Resolve with fasting?
• Something new in the diet?
• Related to meals?
• Related to dairy intake?
• Associated symptoms such as fever, joint pain and rash?
How serious?

- Patients most prone to complications:
  - Infants, children and elderly
- Good news – Most etiologies for acute diarrhea resolve spontaneously.
- Antibiotics not usually necessary
  - Can decrease travelers diarrhea by about 1 day
  - Can exacerbate Hemolytic Uremic Syndrome (HUS)
- Oral hydration is most important:
  - Water
  - Sugar
  - Salt

Secretory Vs. Osmotic

**Secretory**
- Not related to food intake
- Occurs day and night
- Continues while fasting
- Identify secretory trigger

**Osmotic**
- Worse after meals
- Occurs during the day
- Stops while fasting
- Identify osmotic trigger
**Infectious Vs. Inflammatory**

**Infectious**
- Acute onset
- Trace back to a “high risk” meal:
  - Raw/undercooked beef or chicken
  - Raw eggs (Tiramisu or Caesar salad)
  - Simmering rice (B. Cereus)
- May know others who also have acute diarrhea after a meal
- Usually resolves within 1 week

**Inflammatory Bowel Disease**
- Subacute onset
- Family history of IBD
- Associated extra-intestinal symptoms (Skin, Eyes, Joints, Mouth)
- Persists longer than 2 weeks
- Ileitis (Crohn’s) – Be careful, could confuse with Yersinia
- Tenesmus (UC) – Be careful, can confuse with infectious colitis

**Infection Vs. Inflammation:**

**Similarities**
- Invasive organisms can cause colitis indistinguishable from ulcerative colitis
  - Inflammatory exudate from the rectum
  - WBCs in stool
  - Possible tenesmus
  - RLQ abdominal pain
  - Mucosa can appear erythematous, edematous, exudative and hemorrhagic
  - Biopsies show acute inflammation
New Changes

• Surgery
  – Cholecystectomy
  – Ileal resection

• Medications
  – Antibiotics
  – Olmesartan (Benicar)
  – Colchicine

• Diet
  – Diet Gum, Deserts or Candy
  – Watch out for Sorbitol

So Cute, but ...
BEWARE: Attack of the sugar-free gummy bears
“Just don’t. Unless it’s a gift for someone you hate.”
“Gastrointestinal Armageddon”

From an Amazon review titled:
“Fully Weaponized Gummy Bears”

“The cramping started about an hour later, and soon enough I was as bloated as a balloon in Macy’s Thanksgiving Day Parade. When the rumbling started I sprinted down the hallway and made it to the bathroom just in time for the Four Horsemen of the Apocalypse to stampede from my backside, laying waste to my home’s septic system AND my will to live. After three hours of a pelvis-shaking Gummy Bear assault, I was spongy and weak, surprised that I had any bones left.”
Work-up

• Travel:
  – Make sure the patient is not from Endemic Ebola area.
• Time:
  – Infectious diarrhea usually resolves within 1 week.
  – Patient is at risk to develop post-infectious IBS
• History is key – Most patients need reassurance and fluids
• Immediate evaluation if patient appears ill
  – Blood: CBC, Electrolytes, magnesium BUN, Creat
  – Stool: Fecal leukocytes, Culture, O&P, C diff, Occult blood
• If diarrhea is persistent or the patient is severely ill
  – Flex Sig with biopsy and stool aspirate
  – Giardia antigen, E. Histolytica Antigen

Summary

• Where sodium goes, water goes
• Small Intestinal Diarrhea = Large & Infrequent
• Large Intestinal Diarrhea = Small & Frequent
• 4 types of diarrhea:
  – Secretory, Osmotic, Malabsorptive and Inflammatory
• History is crucial in determining etiology
• Consider: Severe Vs. Mild, Secretory Vs. Osmotic, Infectious Vs. Inflammatory
• Determine recent surgery, medication and dietary changes
• Beware of weaponized gummy bears
• Antibiotics are not necessary
• If persistent or severe, evaluate with stool studies and flexible sigmoidoscopy.
Thank You
The Diarrhea Persists:
What to do next

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Digestive Health Associates of Texas
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WCOG 2013 WORKING PARTY REPORT
Chronic diarrhea: Definition, classification, diagnosis

Lawrence R Schiller, Darrell S Pardi, Robin Spiller, Carol E Semrad, Christina M Surawicz, Ralph A Giannella, Guenter J Krejs, Michael J G Farthing and Joseph H Sellin

Journal of Gastroenterology and Hepatology 2014;29:6–25
Definition of Chronic Diarrhea

• **Patients** define diarrhea as passage of loose stools, increased stool frequency or urgency of defecation

• **Physicians** should note precisely what the patient means by “diarrhea”
  – Differentiate from fecal incontinence

• **Chronic diarrhea** when symptoms are present >4 weeks

Creating a Differential Diagnosis

• Consider comorbid symptoms and epidemiologic clues

• Use Rome Criteria to make a diagnosis of IBS
  – Pain **must** be present; painless diarrhea is **not** IBS
  – Pain increases before BM and decreases after BM
  – Onset of pain associated with change in stool consistency or frequency

• Take a good dietary intake history
**Think about Iatrogenic Diarrhea**

- Drugs
- Surgery
- Therapeutic radiation

**Drugs Causing Diarrhea**

<table>
<thead>
<tr>
<th>Common causes</th>
<th>Rarer causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antacids, Proton pump inhibitors</td>
<td>Angiotensin converting enzyme inhibitor</td>
</tr>
<tr>
<td>Antineoplastic drugs</td>
<td>Angiotensin receptor blocking agents</td>
</tr>
<tr>
<td>Broad spectrum antibiotics (especially cephalosporins)</td>
<td>Beta-adrenergic receptor antagonists, other antiarrhythmics</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Metformin</td>
<td>Lipase inhibitors</td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory drugs, 5-aminosalicylates</td>
<td>Lithium</td>
</tr>
<tr>
<td>Cholesterol-lowering agents</td>
<td>Prostaglandins</td>
</tr>
<tr>
<td></td>
<td>Vitamin and mineral supplements</td>
</tr>
</tbody>
</table>
Surgeries Causing Diarrhea

- Esophageal, gastric, intestinal, biliary, pancreatic procedures may lead to diarrhea
- Specific syndromes
  - Dumping syndrome
  - Intestinal hurry
  - Bacterial overgrowth
  - Bile acid malabsorption
  - Pancreatic exocrine insufficiency
  - Short bowel syndrome

Stool Characteristics

- Watery stools
  - Osmotic
  - Secretory
- Inflammatory stools
  - Blood or pus
- Fatty stools
  - Maldigestion
  - Malabsorption

DEFINED BY SIMPLE TESTS: Stool Na, K, WBC (or calprotectin), fat content
Diagnostic Testing

- Only when it will impact management
  - Alarm features that mandate further evaluation (e.g., positive fecal occult blood test)
  - When differential diagnosis comes down to two or three entities that can be effectively distinguished by diagnostic tests
  - When differential diagnosis is broad, initial tests to better characterize diarrhea may be helpful
- Therapeutic trials sometimes best approach

Comprehensive Stool Analysis

- Stool weight
- Stool fat content
- Stool electrolytes
  - Na, K
  - Cl, HCO₃
  - pH
- Stool minerals
  - Mg
  - P
- Stool lactoferrin (or calprotectin)
- Reducing substances
- Stool osmolality
- Laxative screening
  - Mg, P
  - Senna
  - Bisacodyl
Fecal Osmotic Gap

- FOG = nonelectrolyte contribution to intraluminal osmolality
- Intraluminal osmolality = plasma osmolality (stool osmolality rises rapidly in vitro)
- Electrolyte contribution = 2 X sum of [Na] + [K] to account for cations + anions
- FOG = 290 – 2 X sum of [Na] + [K]
Interpretation of FOG

• Osmotic diarrhea
  – Low electrolyte concentrations
  – High FOG (>50 mosm/kg)

• Secretory diarrhea
  – High electrolyte concentrations
  – Low FOG (<50 mosm/kg)

Stool Analysis

• Steatorrhea
  – Stool fat excretion >7 g/24h
  – ULN depends in part on stool weight
  – Qualitative analysis (Sudan stain) fairly accurate

• Carbohydrate malabsorption
  – Low stool pH (<6)
  – Increased reducing substances
**Post-analysis Taxonomy of Diarrhea**

- Secretory diarrhea
- Osmotic diarrhea
- Steatorrhea
- Carbohydrate malabsorption
- Low weight diarrhea

**NOT MUTUALLY EXCLUSIVE CATEGORIES**

### Patterns of stool composition\(^1\)

**STOOL WEIGHT >200 g/24h**

<table>
<thead>
<tr>
<th>GROUP</th>
<th>IMPLICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secretory diarrhea without steatorrhea</td>
<td>Microscopic colitis or other secretory diarrheas</td>
</tr>
<tr>
<td>CHO malabsorption without steatorrhea</td>
<td>Ingestion of poorly absorbed carbohydrate</td>
</tr>
<tr>
<td>Steatorrhea with or without CHO malabsorption</td>
<td>Small bowel mucosal disease, SIBO, pancreatic exocrine insufficiency</td>
</tr>
<tr>
<td>Osmotic diarrhea</td>
<td>Ingestion of poorly absorbed ions, PEG</td>
</tr>
</tbody>
</table>

## Patterns of stool composition

**STOOL WEIGHT <200 g/24h**

<table>
<thead>
<tr>
<th>GROUP</th>
<th>IMPLICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>No evidence of diarrhea</td>
<td>Change in frequency, fecal incontinence</td>
</tr>
<tr>
<td>Hyperdefecation (increased frequency)</td>
<td>IBS, proctitis, abnormal reservoir function</td>
</tr>
<tr>
<td>Abnormal consistency</td>
<td>IBS</td>
</tr>
<tr>
<td>Elevated fecal osmotic gap</td>
<td>Mild CHO malabsorption, Mg ingestion</td>
</tr>
<tr>
<td>Steatorrhea</td>
<td>Malabsorption or maldigestion</td>
</tr>
</tbody>
</table>


## General Paradigm

- When diagnosis is difficult, stratifying chronic diarrhea by stool characteristics can facilitate evaluation and focus management.
- The key is to consider all the possibilities.
Most of the time this will result in a diagnosis...

- When it doesn’t, need to consider “difficult-to-diagnose” diarrhea
  - Common problems that are overlooked because they are not considered
  - Rare syndromes

Diarrhea of Obscure Origin (DOO)

**DEFINITION**

- Chronic diarrhea with negative microbiological studies; no evidence of structural gastrointestinal disease or endocrine disease and no history of gastrointestinal surgery or radiation therapy
DOO: Diagnoses

- Fecal incontinence
- Drug-induced diarrhea
- Surreptitious laxative ingestion
- Microscopic colitis syndrome
- Small bowel bacterial overgrowth
- Carbohydrate malabsorption
- Pancreatic exocrine insufficiency
- Bile acid diarrhea
- Endocrine tumor
- Neuropathy
- Idiopathic secretory diarrhea

Idiopathic Secretory Diarrhea

- Diagnostic criteria
  - Chronic diarrhea (>4 weeks)
  - Persistent loose stools
  - No gastrointestinal surgery
  - No systemic disease
  - Negative diagnostic evaluation
  - Stools with characteristics of secretory diarrhea

Idiopathic Secretory Diarrhea

• Clinical picture
  – Previous good health
  – Abrupt onset
  – Frequent, watery stools (mean 10/day, range 5-25/day)
  – Moderate weight loss soon after onset

• Epidemiology
  – Recent travel
  – Rare household contacts
  – No response to antibiotics

• Course
  – Spontaneous complete resolution in all
  – Gradual offset
  – Mean duration: 15 months (range 7—31)
  – No recurrence
Idiopathic Secretory Diarrhea

- Epidemic form (Brainerd diarrhea)
  - Similar history as episodic cases
  - Occurs in outbreaks
  - Associated with common water/milk/food exposure
  - Little secondary transmission
  - Similar time course as episodic cases
  - Infectious agent sought, but not found;
    ?novel agent

Chronic Diarrhea

- Extensive differential diagnosis
- Comprehensive history most useful diagnostic tool
- Stool analysis can provide clues to diagnosis in difficult cases
- Diagnosis is possible in most cases
Did Your Patient Take Antibiotics: Think About *Clostridium difficile* Infection

ACG PG Course, Philadelphia, October 19, 2014

Christina M. Surawicz, MD MACG
Professor of Medicine
Division of Gastroenterology
Department of Medicine
University of Washington

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Today

1. Best Diagnostic Tests
2. Appropriate Therapy
3. Surgery Consult
4. Recurrent CDI
5. Prevention
CDI Mortality and Age

- 65 year older age population projected to increase by 17.3% in next 5 years
- Rates in this age group with CDI are much higher than in younger than age 40
- Mortality in this age group is also much higher
- Prevention, early diagnosis and treatment are imperative

Treatment: Practice Guidelines

Guidelines for Diagnosis, Treatment, and Prevention of *Clostridium difficile* Infections

1. What are the Best Diagnostic Tests for CDI?

**Diagnostic Testing**

- Polymerase Chain Reaction (PCR)
  - New gold standard
- GDH (glutamate dehydrogenase antigen)
  - Very sensitive but not specific
- Enzyme Immune Assays (EIA)
  - Not good stand alone tests
  - Poor sensitivity and specificity
C. difficile Tests

• Test only patients with diarrhea since 80% of infants and 5-15% of adults are carriers
• Do not routinely test 3 stools—low yield
• Don’t test for cure (usually)
• Culture and toxin can stay positive for a month

Surawicz et al, Clin Infect Dis 2000; 31:1012-7

Final Take Home Points

• Diagnostic tests are imperfect
• Even PCR can be negative with pseudomembranous colitis
• If you think your patient has C. difficile and is sick, start empiric therapy with vancomycin
The Future?—Cliff and *C. diff*

A Beagle that can detect *C. difficile*

Cliff

- Cliff—2 year old Beagle
- Trained at Vrije U. in Amsterdam
- Hospital—he sits next to bed when positive
- Detected 25 of 30 cases
  - 265 of 270 negatives
- Almost as good as PCR!
  - YouTube video interesting
2. Appropriate Therapy

3 Effective Oral Antibiotics for CDI

• Metronidazole
  – 500 mg tid x 10 days
• Vancomycin—(FDA approved)
  – 125 mg qid x 10 days
• Fidaxomicin—(FDA approved)
  – 200 mg bid x 10 days
CDI Treatment Depends on Severity

Mild to Moderate

Severe

Severe and Complicated

Cohen et al, IDSA/SHEA guidelines, Infection Control Hosp Epi, 2010; 31:431

Mild to Moderate CDI

• Diarrhea with no criteria for severe CDI
• Diarrhea ≥ 3 loose-stools/24 hours
Treatment of Mild to Moderate CDI

- Stop intercurrent antibiotics is possible
- Metronidazole
  - 500 mg tid x 10 days p.o.
- No antiperistaltics
  - Data poor but medico-legally risky
  - Lose a parameter to follow

Mild to Moderate CDI

- No metronidazole in 1st trimester of pregnancy
  - Placental transmission; facial anomalies reported
- If no better in 3-5 days, switch to vancomycin
- Fidaxomicin an option
  - Expensive
CDI Treatment Depends on Severity

Mild to Moderate

Severe

Severe and Complicated

Simple Clinical Diagnosis for Severe CDI

• Hypoalbuminemia (< 3)
  AND
• Abdominal distension/tenderness
  AND/OR
• Elevated WBC (>15,000)
Treatment of Severe CDI

- Vancomycin 125 mg qid x 10 days
- If not better, can increase Vancomycin to 1-2 gm/day
- It is empiric but may work

CDI Treatment Depends on Severity

- Mild to Moderate
- Severe
- Severe and Complicated
Severe and Complicated CDI

- Admission to ICU
- Hypotension
- Fever > 38.5 °C
- Ileus
- WBC > 35,000 or >2,000
- Serum lactate > 2.2 mmol/L
- Evidence of end organ failure (renal or pulmonary)

Treatment of Severe and Complicated CDI

Vancomycin 500 mg qid p.o.
AND
Metronidazole 500 mg tid IV
AND
Consider vancomycin enemas 500 mg IV
vancomycin in 500 ml NS via rectal tube, clamp 60 min. Repeat qid
Medical Treatment Summary

<table>
<thead>
<tr>
<th>Mild to Moderate</th>
<th>Metronidazole orally (500 mg tid)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>Vancomycin orally (125 mg qid)</td>
</tr>
<tr>
<td>Severe + Complicated</td>
<td>Vancomycin orally (500 mg qid) and Metronidazole IV (500 mg tid) Consider vancomycin enemas if ileus, toxic colon</td>
</tr>
</tbody>
</table>

3. Role of Surgery
Impact of Emergency Colectomy for Fulminant \textit{C. difficile} Colitis

- January 2003 – June 2005, retrospective series of 161 patients
  - Surgery—38; mortality 34%
  - Medical Rx—123; mortality 58%

- Outcome 30-day mortality


Predictors of 30-day Mortality

- ↑ Lactate > 5
- ↑ WBC > 20
- Shock/pressors
- Age > 75
- Colectomy survival benefit in this group
When to Get a Surgery Consult

• No response to maximal medical therapy in 3-5 days in severe/complicated
• Hypotension/shock/sepsis
• Renal or pulmonary decline
• Rising WBC and creatinine/dropping albumin
• Progressive abdominal distension

Diverting Loop Ileostomy—Another Option

• Loop ileostomy with PEG + vancomycin colon lavage
• Laparoscopic in most
• Colon preserved in most
• 80% hooked back-up

Case

A 52-year-old woman with stage IV cervical cancer is undergoing chemotherapy with cisplatin. She develops acute diarrhea and abdominal pain. On exam, she is tender in the left lower quadrant with abdominal distension and has a low grade fever. Hct 38, WBC 17,000, electrolytes are normal except the potassium is a little low. Albumin is 3.5; Stool test for C. difficile Toxin B by PCR is positive.

What is the Most Appropriate Initial Therapy?

A. Metronidazole 500 mg q 6 hrs orally
B. Metronidazole 500 mg q 8 hrs intravenously
C. Vancomycin 125 mg q 6 hrs orally
D. Vancomycin 500 mg in 500 ml saline per rectum
This is Severe CDI

- Distension
- ↑ WBC
- Slightly low albumin
- THUS Vancomycin 125 mg QID

Case Cont’d

Over the next 2 days, she continues to have diarrhea and abdominal pain and develops a fever. The WBC has risen to 35,000 and the albumin is now 2.7. A CT scan shows colon wall thickening in the left colon; you are asked to do a sigmoidoscopy, shown on next slide.
This is Severe + Complicated CDI

- Fever
- No better with therapy
- ↑ WBC
- ↓ Albumin
- THUS ↑ VANCO → 2g/d
  AND
- ADD IV METRONIDAZOLE
Case Cont’d

Over the next 24 hours, she continues to decline with respiratory compromise and increasing abdominal distension. You ask for a surgery consult; the surgeon does not think she can tolerate a colectomy

What is the Next Best Step?

A. Add immune globulin and a probiotic
B. Consider loop ileostomy done laparoscopically
C. Consider fecal microbiota transplant
This is Severe + Complicated CDI and Multiorgan Failure

- Surgery consult
- Consider Loop ileostomy
- I cannot recommend FMT (I wish I could)
  Need more studies

Recurrent CDI—RCDI

- Recurrence of CDI within 8 weeks of successful therapy
- 1 recurrence (10-20%)
- After one, 40-60%
- Due to altered colonic microbiome
Decreased Microbial Diversity in *C. difficile*


**Recommendation:**
Treatment of First CDI Recurrence

- The first recurrence of CDI can be treated with the same regimen that was used for the initial episode
- However, if severe, vancomycin should be used
Treatment of Second Recurrence

- The second recurrence should be treated with a pulsed vancomycin regimen
- Vancomycin Pulse Regimen
  - Vancomycin 125 mg qid x 10 days, then Vancomycin 125 mg a day every 3 days x 10 more doses
  - Simple and not too expensive

Other Therapies?

- Rifaximin “chaser”—2 week vanco, then 2 week rifax; small trial, small neg RCT—(Not FDA approved)
- Fidaxomicin—not studied in RCDI
- Cholestyramine doesn’t bind toxin
- IVIG—case reports
- Monoclonal antibody to Toxins A+B in phase 3 trials
- Vaccines in development
Recommendation: Other Investigational Treatment

- There is limited evidence for the use of adjunct probiotics to decrease recurrences in patients with RCID

Probiotics

- *Saccharomyces boulardii*—2 RCT
  - Decreased recurrences by 50% with adjunct antibiotics
  - Recurrences with high-dose vancomycin
    * (15.7% vs. 50%) but not with low-dose vancomycin or metronidazole

McFarland et al, JAMA 1994; 271:1913,
Surawicz et al, Clin Infect Dis 2000; 31:1012
**Recommendation: Treatment of 3 or more CDI Recurrences**

- If there is a third recurrence after a pulsed vancomycin regimen, fecal microbiota transplant (FMT) should be considered.

**Fecal Microbiota Transplant**

- Stool transplant
- Healthy donor stool to colon via enema, colonoscopy or upper-tract
- Rationale: restore normal microbiome
FMT Works!

- 90% efficacy in meta-analyses
- RCT from Netherlands showed efficacy in RCDI pts via nasoduodenal route
  - 81% resolution
  - 94% w/second infusion

Guo et al, APT 2012; van Nood et al NEJM 2013

Oral Capsules of Frozen FMT

- 20 pts with RCDI
- Standard unrelated donors
- Success: one treatment 14; second treatment 4,
- Overall success rate 90%
- Aesthetically appealing

Youngster et al JAMA Oct 11, 2014
FMT—Cost Effectiveness

- Decision analysis of 4 strategies (M, V, F, FMT)
- 65 yo, modeled 2 recurrences after Rx
- Initial Rx of RCDI
  - FMT—the winner
    - Cure rates 88%
    - Recurrence rate 15%

Konijeti et al Clin Infect Dis 2014; 58:1507-14

What Do I Do?

- Make sure it is RCDI—post-infectious IBS common after CDI
- Make sure it is recurrent, not refractory
  - Refractory disease needs more aggressive therapy
  - Vancomycin pills vs. IV form orally if not responding
- Vancomycin pulse—works sometimes
What Do I Do?

- Sometimes I offer rifaximin or fidaxomicin
- Usually I do FMT

- BUT only if there are no other options since we have limited long term data and it is still considered investigational by the FDA

Case

- A 75-year-old woman is referred to you for recurrent *Clostridium difficile* infection. She has had 4 recurrences. She has had 2 courses of metronidazole, one of fidaxomicin and one with vancomycin and a pulsed regimen. She is very frustrated. She is fine while on treatment, but develops symptoms within 1-2 weeks of ending the treatment regimen. She has had a recent colonoscopy which was normal. She lives independently.
Which is the Next Best Choice for Therapy?

A. Cholestyramine daily
B. Fidaxomicin taper
C. Fecal microbiota transplant
D. *Saccharomyces boulardii*

Answer: C—FMT

With so many recurrences, FMT is the next best step with 90% response rate. Cholestyramine is a binder but there is no evidence that it actually binds *C. difficile* toxin. Fidaxomicin has already failed, so no benefit for a repeat course with a taper. *S. boulardii* decreases recurrences as an adjunct to vancomycin, but is not useful as monotherapy.

Summary: RCDI Treatment

• 1\textsuperscript{st} recurrence
  – Repeat initial regimen
• 2\textsuperscript{nd} recurrence
  – Vancomycin pulse regimen
• 3\textsuperscript{rd} recurrence
  – Consider FMT

What if They Need Antibiotics Again?

• Reassure: recurrence unlikely especially post-FMT
• Suggest most narrow spectrum antibiotics that is appropriate
• I do not give prophylactic metro or vanco but recent retrospective study suggests vanco helpful
• Consider probiotics but what which ones?
  – Single agents or mixtures?
  – Kefir?
Prevention of CDI

What About Cleaning the Home?

- In hospitals, need EPA approved sporicidal cleaners (5000 ppm chlorine containing)
- At home: spray bottle mixture of 1 cup bleach to 9 cups water
  1. Spray surfaces
  2. Sit 10 minutes
  3. Rinse off
How Do We Prevent CDI?

• Wise antibiotic policies
  – Clindamycin, cephalosporins, quinolones
• Hand hygiene (soap and water), barrier and isolation
• Screen patients at admission to hospital?
  – Montreal Heart Institute does this
• Probiotics not ready for prime time in my opinion

Summary

• PCR for Toxin B likely new gold standard stool test
• Stratify disease severity and treat appropriately with metronidazole or vancomycin
• For severe and complicated disease
  – Vancomycin and IV Metronidazole
  – Surgery consult
• Recurrent CDI—consider FMT for worst cases
• Prevention, especially in the hospital setting, is very important