Clostridium difficile: the Misunderstood Pathogen

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Issues to Consider

- Historical overview
- The myriad causes of hospital acquired diarrhea
- Microbiology and ecology of *Clostridium difficile*
- Epidemiology
- Transmission of disease
- Pathogenesis
- Clinical manifestations of disease
- Diagnosis and differential diagnosis
- Principles of therapy
- Antibiotic Stewardship
- The role of alternative therapies
- Infection control issues
For unclear but probably several reasons, the incidence of disease is increasing dramatically.

Asymptomatic carriage of the organism is extremely common in hospitalized patients receiving antibiotics, and these patients usually do not become ill.

The vast majority of antibiotic associated diarrhea is not caused by *Clostridium difficile*.

*Clostridium difficile* forms spores that can survive for a long time in the environment.

No product that kills spores is safe to use on your hands.
While mechanical dislodging with soap is the only way to deal with spores on your hands, we use antibacterial soap in order to kill the vegetative forms of the organism.

Diagnosis is no longer made by culture, rather an EIA of stool with sensitivity of only about 75%.

Once a positive test is obtained there is no reason to retest that patient, specifically there is no rationale for doing a “test of persistence” or “test of cure”.

Antimicrobial therapy frequently does not eradicate the organism from the stool, rather it reduces the amount and allows the normal flora to return.

Isolation continues until diarrhea resolves.
The First Case

- 22 year old female, patient of Dr. William Osler
- “A miserable, emaciated creature in a wretched physical condition.”
- Underwent surgical resection of a gastric tumor on August 26, 1892
- Postoperatively developed diarrhea that became progressively more severe
- Died on post op day 15

“Diphtheritic membrane”

Figure 1. Photomicrograph of histologic specimen from a patient with antibiotic-associated PMC. Specimen was stored in the Pathology Department of Johns Hopkins Hospital (Baltimore) 10 September 1892 and then recently resectioned (courtesy of John H. Yardley, Department of Pathology, Johns Hopkins University School of Medicine).
A fatal case of pseudo membranous colitis in 1948 was linked to streptomycin use, led to reexamination of the 1893 case.

“Myriads of gram positive cocci” found—Staphylococcus aureus postulated as cause.

Studies in 1950’s and 60’s document an association but did not prove causation.

When C. difficile identified S. aureus research dries up.

S. aureus may still play a role in some cases of antibiotic associated diarrhea with or without pseudo membranes.
Introduction of the lincosamide class of antimicrobials resulted in a significant increase in cases of pseudo membranous colitis, which was also called “clindamycin colitis”

Seminal study by Tedesco in St. Louis
- 200 consecutive patients treated with clindamycin
- 42 developed diarrhea
- 20 had pseudo membranous colitis—alarming number
- \textit{S. aureus} not found in these patients

Extensive studies using the hamster model

Generous support from Eli Lilly, the maker of clindamycin
What Causes Antibiotic Associated Diarrhea?

- *Clostridium difficile* is the major recognized cause but only accounts for about 15–20% of all cases.

- Most causes unknown. Several candidates studied:
  - *Candida* species
  - *Clostridium perfringens*
  - *Staphylococcus aureus*
  - Serendipitous infection by viruses, *Salmonella*, etc.
  - Non–infectious changes in colonic fatty acid and carbohydrate metabolism induced by antibiotics.
Clostridium difficile: the Organism
An anaerobic, spore forming gram positive rod first described as a member of the normal flora of healthy infants in 1935. Due to the difficulty in cultivating the organism it was originally called Bacillus difficilis. Given its current name 3 years later. Closely related to C. sordellii but not to other toxigenic clostridia like C. perfringens, C. botulinum or C. tetani. Can be grown on selective media (CCFA).
Environmental Sources of C. difficile
Dual Modes of Existence

Vegetative form
- Found in the gut, survives in the environment for 4–6 hours
- Susceptible to gastric acid, antibacterial soaps, alcohol based hand foams
- Neutralization of stomach acid with pantoprazole may allow the vegetative form to become pathogenic

Spore form
- Found in the gut and in the environment
- Spore formation induced by stressing the organism: exposure to the environment, exposure to antimicrobials, sub lethal concentrations of microbicidal cleaning products
- Resistant to stomach acid, antibacterial soaps and alcohol based hand gels
- Can survive for a long time on surfaces
Vegetative vs. spore forms
Toxin Production

- 5–25% of strains do not produce toxins and don’t cause disease
- **Toxin A**
  - 308 kd enter toxin and cytotoxin
  - Chemo attractant for neutrophils
  - Activator for macrophages and mast cells
- **Toxin B**
  - 269 kd potent cytotoxin
  - Disrupts the actin cytoskeleton
  - Found to be a potent necrotizing enterotoxin
  - Probably acts synergistically with toxin A
Normal Bowel Flora is Protective

- The indigenous microbiota of the gut constitutes a complex and poorly understood host defense system. Typically contains $10^{11} - 10^{12}$ bacteria per gram of feces. Four major groupings
  - *Bacteroides* sp
  - *Bifidobacterium* sp
  - *Clostridium coccoides* group
  - *Clostridium leptum* group
- En masse they confer colonization resistance against *C. difficile*
- Depletion of monosaccharide components of mucin that serve as carbon sources for growth of *C. difficile*
Epidemiology

- The most common recognized cause of nosocomial diarrhea
- Incidence and severity increasing:
  - A new strain has been identified that carries an additional toxin (iota toxin)
  - *C. difficile* acquiring resistance to more antimicrobials
  - Probably other as yet unrecognized reasons
- Frequency varies by institution
- Results in 3.6 excess hospital days, cost of $3,700/pt
- Readmissions for CDAD cost $128,000 per hospital per year
- Conservative estimate of US cost per year $1.1 billion
Acquisition of the Organism

- In healthy adults intestinal carriage rates of toxigenic *C. difficile* are 5% or less
- Carriage in healthy adults thought to be transient
- High prevalence in newborns—up to 60–70%—all asymptomatic
- In hospitalized patients colonization begins upon admission in patients given antimicrobials
  - 13–20% within the first week
  - 50% in patients hospitalized for more than 4 weeks
- Even relatively minute amounts of antimicrobials can predispose to colonization
Healthcare facilities–acquired infections in most cases, are the results of environmental contamination, and poor patient hygiene during hospitalization, and not how sick the patient were at the time of admission.

“A pessimist see the difficulty in every opportunity; an optimist see the opportunity in every difficulty”….. W. Churchill
The importance of cleaning

The Inanimate Environment Can Facilitate Transmission

X represents VRE culture positive sites

~ Contaminated surfaces increase cross-transmission ~

Magnitude of Antibiotic Use in The U.S.

- Antibiotics are the 2\textsuperscript{nd} most commonly used class of drug in the U.S.
- 8 billion dollars/year
- 200–300 million antibiotic prescriptions written/year, 25,000 tons of drug dispensed
Magnitude of Antibiotic Use

- 45% for out-patient use
- 25–40% of all hospitalized patients receive antibiotics
- Patients use half of the antibiotics; agriculture and aquaculture account for the remaining half
- Antibiotics are societal drugs: Increase use of levofloxacin
Pathogens Most Often Associated With Inappropriate Antimicrobial Treatment

- **P. aeruginosa**
- **MRSA**
- **Candida spp**
- **Enterobacter spp**
- **Klebsiella pneumoniae**
- **Xanthomonas maltophilia**
- **Enterococcus spp**
- **MSSA**
- **VRE**

The chart illustrates the frequency of inadequate treatment (%).
Three critical events necessary for CDAD

- Disruption of the normal colonic micro flora by antimicrobials or other means
- Ingestion by the patient of a toxigenic strain of *C. difficile* and its arrival intact in the lower GI tract
- One or more additional requirements for developing invasive disease
  - Advancing age
  - Severe underlying disease of any kind
  - Prolonged hospital stays
  - Manipulation of the GI tract (NG tubes, enemas, surgery, motility altering drugs)
  - Acid neutralizing drugs
Medications Associated with CDAD

- Most common antimicrobials
  - Clindamycin
  - Ampicillin/amoxicillin
  - Cephalosporins
  - Fluoroquinolones
- Infrequent– Tetracyclines, macrolides, TMP/SMX
- Rare or never– IV aminoglycosides, metronidazole, vancomycin, bacitracin
- Chemotherapeutics with antibacterial activities
  - Ifosfamide, carboplatin etoposide 8% incidence
  - Others Mtx, 5FU, doxorubicin, cyclophosphamide
- Bowel preparation regimens
Clinical Disease Spectrum

- Asymptomatic colonization 2–5 or more X more common than clinical illness of any type
- Mild diarrhea, minimal discomfort
- Typical CDAD:
  - Crampy abdominal pain
  - Profuse diarrhea with mucoid, greenish watery stool with a characteristic odor
  - Low grade fever and leukocytosis
- More severe disease with high fever, marked leukocytosis
Colitis can be throughout colon, but usually most severe in distal colon and rectum.

Localized right sided disease can present a diagnostic challenge.

Fulminant disease with ileus, toxic megacolon.

Uncommonly extraintestinal disease.

Reactive arthritis.
Pseudomembranous colitis  Gross appearance of the colon from a patient with pseudomembranous colitis. The pseudomembranes are yellow or off-white raised plaques 0.2 to 2.0 cm in diameter which are scattered over fairly normal appearing intervening mucosa. Courtesy of J Thomas LaMont, MD.
Diagnosis

- Endoscopy looking for pseudo membranes
  - Quick, and specific
  - Pseudo membrane formation usually starts on the right side
  - Pseudo membrane formation a late manifestation

- Culture
  - Takes several days
  - Need cytotoxic assay of organism after culture

- Immunoassays
Sensitivity: manufacturer states 95% compared to cytotoxic assay
Treatment of CDAD

General principles

- Whenever possible withdraw the offending antibiotic
- Use oral antimicrobials whenever possible
- Be patient—some improvement seen in first 2 days but mean time until resolution of diarrhea is 2–4 days. Don’t call them nonresponders until 6 days of therapy
- Treat for 10 days
- Avoid antiperistaltic agents
- No role for test of cure assays
Metronidazole

- MIC$_{90}$ of 0.4 ug/ml vs. *C. difficile*
- 98% cure rate documented
- Well absorbed in the upper GI tract: in healthy volunteers fecal concentration of drug low to undetectable
- Bactericidal fecal concentrations achieved in the stool of patients with CDAD: fecal concentrations decrease as diarrhea improves
  - Drug secreted directly across inflamed mucosa
  - Decreased intestinal transit time with diarrhea decreases absorption
Vancomycin

- MIC$_{90}$ of 1.6 ug/ml
- Fecal concentrations of 2,000 to 5,000 ug/ml with po drug
- Cure rates 98–100%
- Second line therapy due to concerns of selecting for vancomycin resistant *Enterococcus* (VRE)
- No drug in GI tract when given IV
- Can be given by enema
Relapsed Disease

- Due to spores that germinate in gut after withdrawal of the antibiotic
- Happens in 20+ % of patients who initially respond. Increased risk in
  - Age > 65
  - Increased severity of underlying disease
  - Exposure to additional antibiotics after treatment
  - Low serum IgG response to toxin A
- Half of relapses are actually re-infections
- Antibiotic resistance unlikely
- Most patients will respond to a second course of the same antimicrobial
Treatment of Multiple Relapses

- No controlled studies, lots of anecdotes and “personal favorite” regimens
- Tapering courses of vancomycin or metronidazole
- Vancomycin plus rifampin
- Yogurt or other *Lactobacillus* preparations
- *Saccharomyces boulardii* plus antibiotics
- Intravenous immune globulin
- Cholestyramine with or without antimicrobials
Infection Control Issues

- Two main approaches
  - Efforts directed at preventing horizontal spread including barrier methods, environmental cleaning
  - Efforts to minimize the possibility that organism exposure will result in a clinical infection, using antimicrobial restriction and limiting overall use of antimicrobials
PHLB-Hospital Acquired VRE and C. Difficile 2005-2011

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**Number of HAI's**

- VRE
- C. Difficile

Steiros Algorithm Implementation
Antibiotic Stewardship Implementation

PHLB has not had a case of hospital acquired C. Difficile in over 2.5 YEARS!

Contact Precautions including private room for all patients with diarrhea until *C. difficile* has been ruled out.

When should they come out of isolation? Since many healthy persons and persons without diarrhea who are in hospitals carry *C. difficile* in their intestinal tract there is no rationale for continuing isolation for patients who no longer have diarrhea, or to test them for carriage once the diarrhea has ceased.
Hand washing

- Hand washing between all patient encounters
- Switch to alcohol based foams: is it contributing to *C. difficile* transmission?

Environmental Cleaning

Many common cleaners actually promote conversion of the vegetative form to the spore.
Bleach is the single most effective agent for spore killing.
Clean Care is Safe Care........