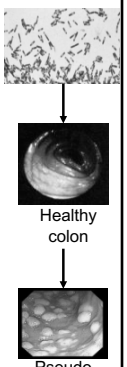
DILEMMAS IN *C. DIFFICILE* MANAGEMENT

Clostridium difficile Associated Diarrhea

- ***Clostridium difficile*-associated disease (CDAD)**
  - **First described in 1978 by Bartlett**
  - **Most common cause of health care-associated infectious diarrhea in adults**
  - **Most common cause of antibiotic-associated diarrhea (15-25%)**



Settle CD, et al. *Aliment Pharmacol Ther*. 1998;12:1217-1223.
Kelly CP, et al. *Annu Rev Med*. 1998;49:375-390.
Anand A, et al. *Am J Gastroenterol*. 1994;89:519-523.

CDI EPIDEMIOLOGY

- **United States:**
  - **>400,000 cases per year**
  - **29,000 deaths per year**
  - **>$1 billion dollars in medical costs**
  - **Projected to become most common HAI in the United States, Europe, and worldwide**
- **Severity increased with emergence of PCR ribotype 027 epidemic strain in the 2000s**
  - **AKA the North American pulsed field type 1 [NAP1] or restriction endonuclease analysis pattern "BI")**

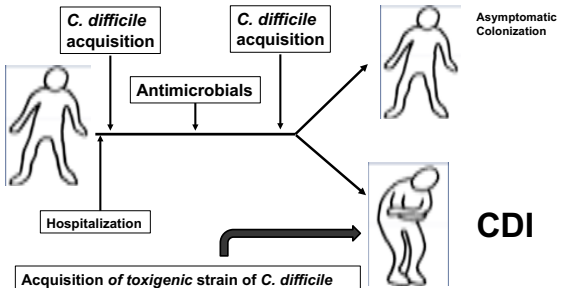
CDI EPIDEMIOLOGY

- Other healthcare-associated infections declined in recent years, but *C. difficile* climbed to historic highs and remains at these unacceptable levels
- Linked to 14,000 deaths –
  - Deaths related to *C. difficile* increased 400% between 2000 and 2007
- >335,000 hospitalizations per year
- Hospital stays caused by C. difficile tripled in the 2000s

CDI EPIDEMIOLOGY

- People most at risk are those who *take antibiotics* and also receive *medical care in any setting*. This could include a nursing home, hospital, doctor's office, outpatient surgery etc.
- Risk generally increases with age; children are at lower risk and older adults are at higher risk
- 50% of infections occur in people <65, but >90% of deaths occur in people 65 and older

PATHOGENESIS MODEL FOR CDI



Clostridium difficile Associated Disease

- Spectrum of infection
  - Asymptomatic carrier
  - Mild disease
  - Severe disease
  - Fulminant infection
    - Toxic megacolon and perforation
    - Diarrhea may be absent with dysmotility

Antimicrobial Use as a Risk Factor for CDI

- Most important modifiable risk factor
  - Suppresses normal flora providing a "niche" for *C.difficile* to flourish
- Virtually every antimicrobial has been associated with CDI
- Longer and multiple antimicrobial exposures increases risk

Infect Control Hosp Epidemiol 2010

Adjusted hazard ratios for CDI by antibiotic received

Antibiotic Class	AHR
Fluoroquinolones	3.44*
1st generation cephalosporins	1.78*
2nd generation cephalosporins	1.89*
3rd generation cephalosporins	1.56*
Clindamycin	1.77*
β-lactam/β-lactamase inhibitors	1.88*
Macrolides	1.65*
Narrow spectrum penicillins	1.37
Aminoglycosides	1.34

Pepin et al, *CID*, 2005

*p<0.05

OTHER RISK FACTORS

- Advanced age
- Cancer chemotherapy
- HIV
- GI surgery or manipulation of the gastrointestinal tract, including tube feeding
- PPIs and histamine-2 blockers

DIAGNOSIS OF C. DIFF DISEASE

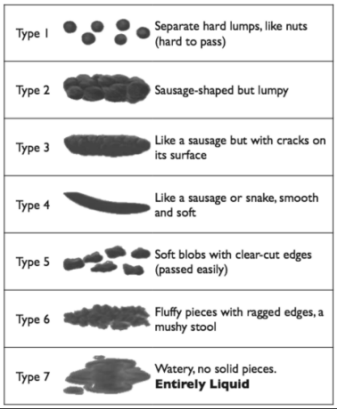
WHO SHOULD BE TESTED FOR CDI?

- Patients with unexplained and new-onset ≥3 unformed stools in 24 hours
  - not clearly attributable to underlying conditions (IBD; therapies such as enteral tube feeding, intensive cancer chemotherapy, or laxatives)

SPECIMEN

- Send only unformed stool

Bristol Stool Chart



WHAT IS THE OPTIMAL TEST?

- Available tests:
  - NAAT (PCR)
  - Glutamate dehydrogenase
  - Cell culture cytotoxicity neutralization assay
  - Toxin A and B enzyme immunoassays
  - Toxigenic culture (“Gold Standard”)

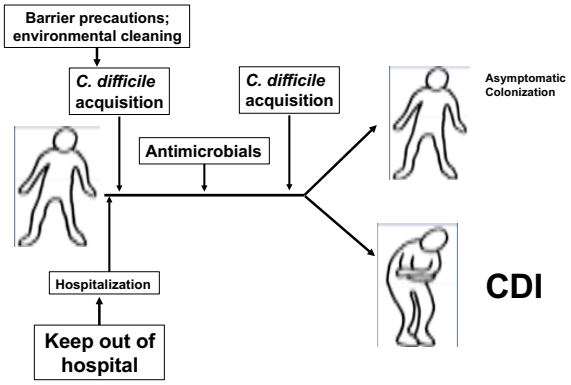
Summary: Diagnostic Tools

Test	Advantage	Disadvantage
Toxin testing (EIA)	Rapid/cheap/easy to use Detects toxin A &/or B	Sensitivity:63-94% Specificity: 75-100%
Toxigenic culture *gold standard	High sensitivity High specificity	Labor intensive/Slow TAT
GDH	Sens:85-95%; Specificity: 89-99% Rapid; Inexpensive	Not a stand alone test
Cell cytotoxicity assay	Sensitivity:67%	Labor intensive/Slow TAT
NAAT	Rapid; stand alone test Sens: 94.4%; Specific: 96.3%	Expensive

WHAT IS THE OPTIMAL TEST?

- **NAAT alone if:**
  - **Clinicians and lab personnel agree**
    - not to submit stool specimens on patients receiving laxatives
    - To submit only from patients with unexplained and new onset >3 unformed stools in 24 hour period
- **Multistep algorithm**
  - **GDH plus toxin**
  - **GDH plus toxin, arbitrated by NAAT**
  - **NAAT plus toxin**

PREVENTION AND MANAGEMENT



Hand Hygiene

Infection Prevention

- Hand hygiene
- Use of gloves and gown on entry to room of patient with CDI (Contact Precautions)

HOW LONG SHOULD CONTACT PRECAUTIONS BE MAINTAINED?

- Continue contact precautions for at least 48 hours after diarrhea has resolved
- Prolong contact precautions until discharge if CDI rates remain high despite implementation of standard infection control measures against CDI

SHOULD ASYMPTOMATIC CARRIERS BE IDENTIFIED AND ISOLATED?

- There are insufficient data to recommend screening for asymptomatic carriage and placing asymptomatic carriers on contact precautions

DAILY ROOM DISINFECTION

- Orenstein et al (2011) instituted daily bleach disinfection of patient rooms and high-touch surfaces
- Reduced rate of CDI from 24.2 to 3.6 per 10,000 patient-days

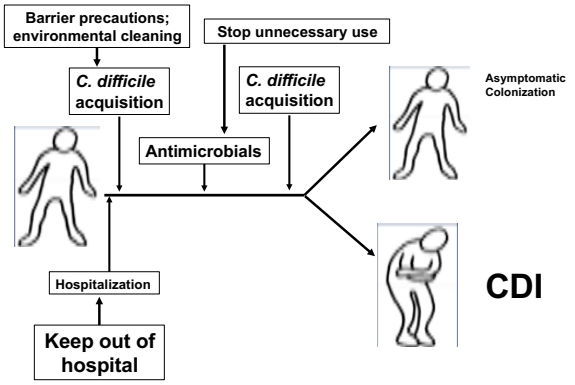
TERMINAL BLEACH DISINFECTION

- Hacek et al. (2010) instituted terminal bleach disinfection, including disinfection of the walls
- Reduced rate of CDI from 8.5 to 4.6 per 10,000 patient-days

TERMINAL CLEANING WITH UV LIGHT

- Uncertain efficacy
- Levin et al.(2013) used pulsed UV treatment in addition to terminal bleach cleaning
  - With treatment of 96% of the patient rooms, decrease in CDI rate from 9.46 to 4.45 per 10,000 patient-days
  - Haas et al.(2014) instituted pulsed UV treatment in addition to terminal bleach disinfection in a large urban hospital, with minimal incremental reduction in CDI rates

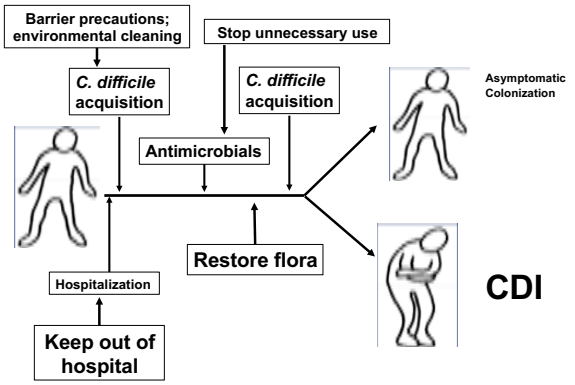
PREVENTION AND MANAGEMENT



ANTIMICROBIAL STEWARDSHIP

- Yam et al.(2012) demonstrated decrease in CDI rates from 8.2 to 3.1 per 10,000 patient-days with audit and feedback system for 6 high-risk antimicrobials,
- Dancer et al.(2013) implemented stewardship lectures and restricted use of ceftriaxone and ciprofloxacin, resulting in CDI reduction from 24 to 5.5 per 10,000 patient-days

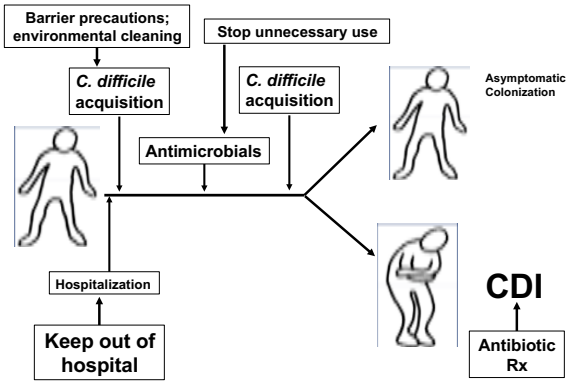
PREVENTION AND MANAGEMENT



PROBIOTICS FOR PREVENTION

- Maziade et al.(2015): quasiexperimental study investigating 10 years of use of high-dose preparation of *Lactobacillus* species
  - reported CDI rate of 2.3 compared with 7.5 per 10,000 patient-days in similar hospitals in the region.
- Another 2015 observational study reported no difference in CDI (9.9 vs 10.4 per 10,000 patient-days) after cessation of bid dosing of *Saccharomyces boulardii* with antibiotics

PREVENTION AND MANAGEMENT



TREATMENT FOR CDI

STANDARD THERAPY

- Withdrawal of inducing agent
  - Any antimicrobials (if possible)
- Avoid drugs with antiperistaltic activity

Bartlett, *Ann Int Med 2006;145:758-764*

WHAT IS THE BEST TREATMENT?

- Either vancomycin or fidaxomicin is recommended over metronidazole for an initial episode of CDI
- Dosage is vancomycin 125 mg orally 4 times per day or fidaxomicin 200 mg twice daily for 10 days

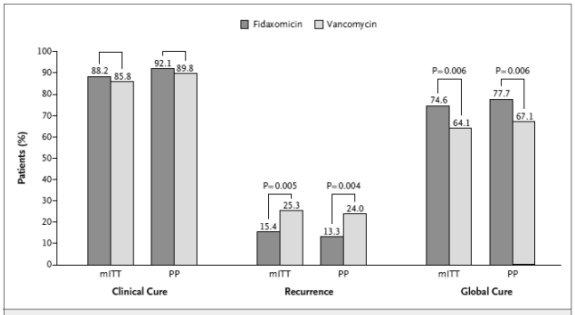


Figure 2. **Rates of Primary and Secondary End Points.**

For the primary outcome of clinical cure, the lower boundary of the 97.5% confidence interval for the difference in cure rates between fidaxomicin and vancomycin was −3.1 percentage points in the modified intention-to-treat (mITT) analysis and −2.6 percentage points in the per-protocol (PP) analysis.

N Engl J Med, 2011

WHAT IS THE BEST TREATMENT FOR FULMINANT CDI?

- **Vancomycin orally**
  - **Per rectum if ileus is present**
  - **Dosage: 500 mg orally 4 times per day or 500 mg in approximately 100 mL normal saline per rectum every 6 hours as retention enema.**
- **IV metronidazole should be administered together with oral or rectal vancomycin, particularly if ileus is present**

Recurrent *C. diff* diarrhea

- **Either relapse of infection of the original strain or re-infection after exposure to new strain**
- **Historically 6-25% have at least one recurrence**
- **Recent reports show an increase in frequency of recurrences after metronidazole therapy, especially in patients aged 65 years or more**

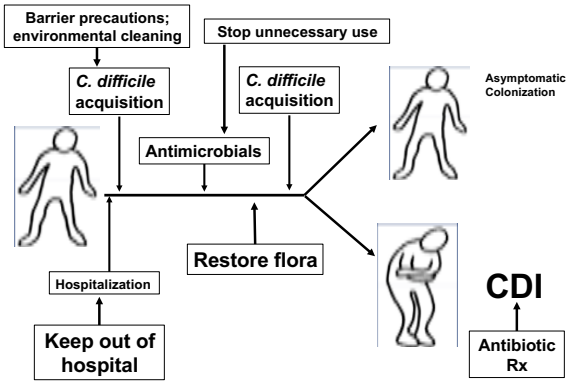
WHAT IS THE BEST TREATMENT FOR RECURRENT CDI?

- Treat first recurrence with
  - oral vancomycin as a tapered and pulsed regimen rather than a second standard 10-day course of vancomycin
    Or
  - 10-day course of fidaxomicin

WHAT IS THE BEST TREATMENT FOR RECURRENT CDI?

- Options for patients with >1 recurrence include
  - Oral vancomycin therapy using a tapered and pulsed regimen
  - Standard course of oral vancomycin followed by rifaximin
  - Fidaxomicin

PREVENTION AND MANAGEMENT



WHAT IS THE BEST TREATMENT FOR RECURRENT CDI?

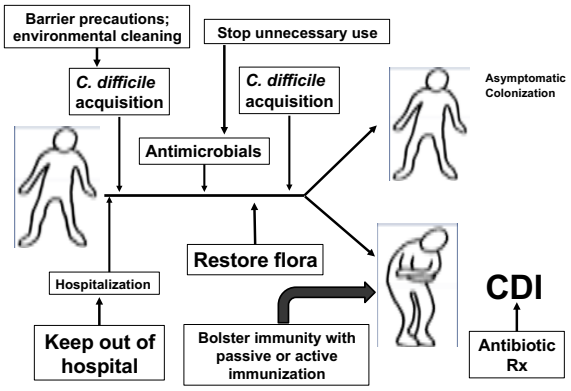
- **Fecal microbiota transplantation is recommended for patients with multiple recurrences of CDI who have failed appropriate antibiotic treatments**

What else is available?

PROBIOTICS

- **Organisms**
  - ***Lactobacillus***
  - ***Saccharomyces boulardii***
  - **Yogurt (*Streptococcus thermophilus*)**
- **Insufficient evidence to recommend**
- **May be useful for prevention**
- **Concern over safety**
  - **Bacteremia/fungemia in immunocompromised patients**

PREVENTION AND MANAGEMENT



BEZLOTOXUMAB

- Monoclonal antibody against *C. difficile* toxin B as a form of passive immunity
- Single IV dose of 10 mg/kg in patients on standard-of-care therapy for CDI had no substantial effect on clinical cure rates but significantly reduced the incidence of recurrent CDI

BEZLOTOXUMAB

- FDA approval in October 2016: "indicated to reduce the recurrence of Clostridium difficile infection (CDI) in patients 18 years of age or older who are receiving antibiotics for CDI and are at high risk for recurrence."

VACCINE

- Antibodies to TcdA and TcdB mediate protection against primary CDI and recurrences
- 3 candidate vaccines in clinical trials
  - IM toxoid vaccine uses formalin-inactivated full-length TcdA and TcdB
  - recombinant full-length TcdA and TcdB vaccine
  - VLA84, a genetic fusion of the truncated cell-binding domains of TcdA and TcdB

THANK YOU

OBJECTIVES

- Upon completion of this program, the participant should be able to:
  - Describe risk factors for and methods to prevent *C. difficile* infection
  - Apply the latest guidelines pertaining to the diagnosis and treatment of *C. difficile* infections
  - Discuss options for the treatment of recurrent *C. difficile* infections

QUESTION #1

- A 56 year old presents with *C. difficile* diarrhea after a course of antibiotics for cellulitis. What would you give?
  1. Oral metronidazole
  2. Oral vancomycin
  3. Intravenous vancomycin
  4. Oral fidaxomycin (Dificid)
  5. Probiotics

QUESTION #1: ANSWER

- A 56 year old presents with *C. difficile* diarrhea after a course of antibiotics for cellulitis. What would you give?
  2. Oral vancomycin

QUESTION #2

- **A 56 year old presents with recurrent *C. difficile* diarrhea. What would you do now?**
  1. **Oral metronidazole 10 day course**
  2. **Oral vancomycin tapered and pulsed for 10 days**
  3. **Oral fidaxomycin (Dificid) 10 day course**
  4. **Probiotics for 30 days**
  5. **Fecal transplant**

QUESTION #2: ANSWER

- **A 56 year old presents with recurrent *C. difficile* diarrhea. What would you give now?**

  2. Oral vancomycin tapered and pulsed for 10 days