C. difficile Infection:

How it all comes out

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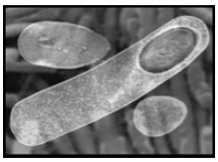
The speaker has no conflicts to disclose.



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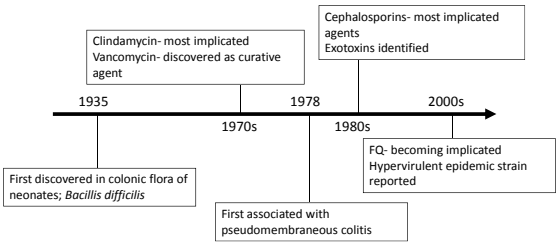
Objectives

- Describe the changes in epidemiology that have occurred over the last decade with *C. difficile* associate diarrhea (CDAD)
- Identify the characteristics of patients with CDAD
- Discuss the treatment options available to treat CDAD
- Describe a plan to manage patients with CDAD

2

C. Difficile History



Bartlett JG. *N Eng J Med* 2002;346:334-339.

Background

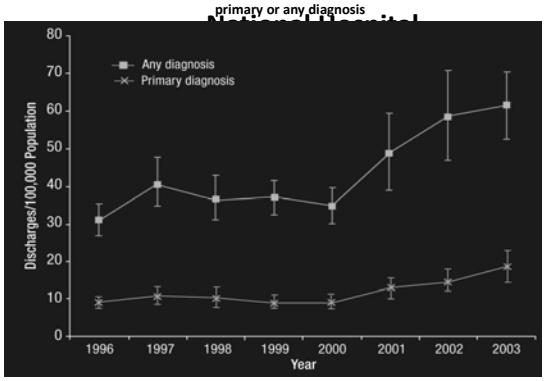
- Spore-forming, gram-positive bacteria that causes diarrhea and colitis
- Identified in the late 1930s but not as pathogen until late 1970s
- Accounts for 15% to 25% of all episodes of antibiotic-associated diarrhea
- Suspect *Clostridium difficile* infection in any patient with diarrhea who has been hospitalized and has recently received antibiotics

Background

- *C. difficile* infection remains a disease mostly associated with healthcare (at least 80%)
- More disease reported in traditionally 'low risk' persons such as healthy persons in the community, and peripartum women.
- May lead to significant complications
- Rate and severity of CDAD are increasing

McDonald LC, et al. *N Engl J Med.* 2005;353.2433-2441.

Estimates of short-stay hospital discharges with *C. difficile* listed as primary or any diagnosis



From McDonald LC, et al. *Emerg Infect Dis.* 2006;12:409-415; with permission.

"Three-hit" Disease

Exposure to antimicrobials

⇩

Toxigenic *C.difficile*

⇩

Additional factor

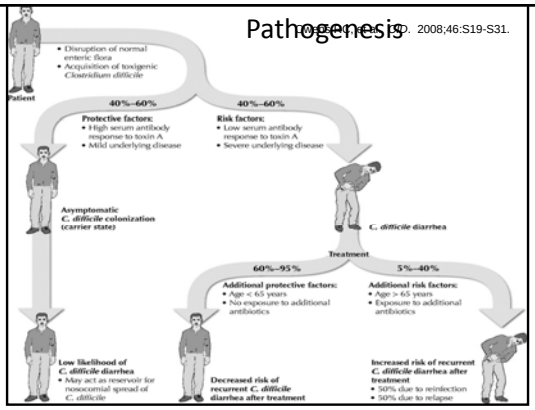
host immunity

virulence of strain

antimicrobials

Clin Infect Dis 1998;26:1027-1036.

Pathogenesis



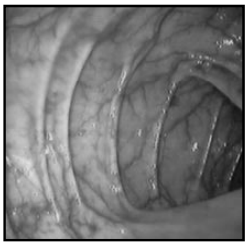
Clin Infect Dis. 2008;46:S19-S31.

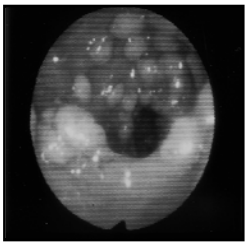
Complications of CDAD

- Treatment failures
- Intensive care unit admission
- Pseudomembranous colitis
- Perforation of colon
- Colectomy
- Toxic megacolon
- Sepsis / Shock
- Death (rare, but increasing)

Mandell, *et al.* Principles and Practice of Infectious Diseases, 6th ed. 2005.

Pseudomembraneous Colitis





Schroeder MS. *Am Fam Physician* 2005;71:921-928.

Toxic Megacolon

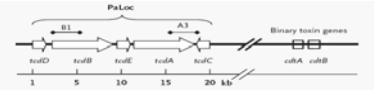
States with BI/NAP1/027 strain of *C. difficile* (N = 40)

November 2008

Centers for Disease Control: http://www.cdc.gov/ncidod/dhqp/id_Cdiff_data.

Virulence

- Wild-type, pathogenic strains
  - Primary virulence factors – toxins A & B
- Epidemic strains (BI/NAP1)
  - Deletion of negative regulatory gene
  - Binary toxin
  - Fluoroquinolone resistance
  - Hypersporulation capacity



McDonald LC, et al. *N Engl J Med.* 2005;353.2433-2441.

Explanations for the Changing Epidemiology

Explanations for the Changing Epidemiology

- Possibly caused by changes in
  - Antimicrobial use
  - Other drug prescribing practices
  - Infection control practices
- Emergence of a new strain of *C. difficile*
  - Increased virulence
  - Antimicrobial resistance
- Aging of the overall population and, specifically, of the hospital inpatient population

Diagnosis

- Recognition of cases
  - Profuse diarrhea
  - Loss of appetite
  - Nausea
  - Fever
  - Leukocytosis
  - Abdominal pain
  - Hypoalbuminemia

McDonald LC, *et al. CCJM.* 2006;73:187-197.
Bartlett JG, *et al. CID.* 2008;46:S12-S18.

Risk Factors

- Antimicrobial exposure (< 2 months)
- Age greater than 65 years
- Prolonged hospitalization
- Severe underlying illness
- Immunocompromised patients
- GI surgery/manipulations

Owens RC, et al. *CID*. 2008;46:S19-S31.

GI Drugs as Risk Factors

- Proton pump inhibitors
- H_2 receptor antagonists
  - Disrupt normal GI flora
  - Increase gastrointestinal pH
  - Allow for pathogen colonization
  - Is this possible explanation of community-acquired disease
- In one study use of PPI's increased risk of *C. difficile* colitis by a factor of 2

Antibiotic agents that predispose to *Clostridium difficile* infection

Frequently	Infrequently	Rarely
Ampicillin ⟸	Quinolones?	IV Aminoglycosides
Amoxicillin	Tetracyclines	Bacitracin
Cephalosporins	Sulfonamides	Metronidazole
Clindamycin	Macrolides	Vancomycin

Hurley BW. Arch Intern Med. 2002; 162:2177-2184

Tests For Diagnosis

- **Stool tests.** Toxins produced by C. difficile bacteria usually detected in stool. There are several types of lab tests (enzyme immunoassay, polymerase chain reaction [PCR], and tissue culture assay).
- **Colon examination.** Flexible to look for areas of inflammation and pseudomembranes.
- **Imaging tests.** Computerized tomography (CT) scan, can show a thickening of the wall of your colon, which is common in pseudomembranous colitis.

Owens RC, et al. *CID*. 2008;46:S19-S31.

Laboratory Test	Detects	Advantages	Disadvantages
Cytotoxin assay	Toxin B	Highly sensitive and specific	Requires tissue culture; takes 24-48h
EIA toxin test	Toxin A and/or B	Fast, easy to perform, high specificity	Not as sensitive as the cytotoxin assay
Latex agglutination test	Bacterial enzyme	Fast, inexpensive, easy to perform	Poor sensitivity and specificity
Stool culture	Toxigenic and nontoxigenic C diff	Sensitive, allows strain typing	Not specific to toxin producing bacteria. Labor intensive
Glutamate dehydrogenase (GDH) EIA	Glutamate dehydrogenase (*C. difficile* antigen)	Sensitive and specific, high negative predictive value	Limited experience, Not specific for toxin producing bacteria
PCR assay	Toxin A and B gene	Fast, high specificity and sensitivity	Expensive; limited experience

Poutanen SM. CMAJ. 2004; 171(1):51-8
Hurley BW. Arch Intern Med. 2002; 162:2177-2184
Bayandelle P. Can J Infect Dis Med Microbiol 2007;18:371

Management

- Cessation of the causative antibiotic <u>if possible</u>
- Non-antibiotic management
  - Correction of fluid loss and electrolyte imbalance
  - Avoidance of antiperistalsis agents
  - Infection control policies
  - Surgical therapy
- Antibiotic management
  - May be initiated empirically if suspected

Hurley BW. Arch Intern Med. 2002; 162:2177-2184
Fekety R. Am J Gastroenterology 1997; 92:739-750

Present Treatment Options

- **Metronidazole***
  - **250mg PO four times daily or 500mg PO TID**
  - **500mg Q6-8h IV- if patient is NPO**
- **Oral Vancomycin***
  - **125mg-500mg PO Q6h**
- **Fidaxomicin**
  - **200mg PO Q12h**
- **Rarely Bacitracin**
  - **25,000 Units PO Q6h**

Hurley BW. Arch Intern Med. 2002; 162:2177-2184
Fetsky R. Am J Gastroenterology 1997; 92:739-750
Cohen SH et al. Infect Control Hosp Epidemiol 2010;31:00-000
Fidaxomicin PI, 2011

*Treatment duration 10-14 days

Vancomycin Retention Enemas

- Alternative when oral route is compromised
- 500mg diluted in 1000ml of 0.9% NaCl
  - Administer via 18-french foley catheter with a 30ml balloon inserted into the rectum, instill solution, clamp catheter for 60 minutes
  - After 60 minutes, deflate balloon and remove catheter
  - Repeat Q8h

Expected Response

Agent	Cure Rate*	Relapse Rate	Time to Resolution
Metronidazole	94 - 95%	5 - 16%	2.4 - 3.2 days
Vancomycin	94 - 100%	15 - 16%	2.6 - 3.1 days

***Successful treatment of the initial episode of *C. difficile*-associated disease.**

Johnson SJ, Gerding DN. *Clostridium difficile*. In: *Antimicrobial Therapy & Vaccines.* 2nd edition. Yu V, et al., eds. New York: Apple Trees Productions; 2002.

Response of *C. difficile*-Associated Infection to Metronidazole Therapy

Reference	Response Rate	Relapse Rate
Fernandez A, et al. *J Clin Gastroenterol.* 2004;38:414-418	**61/99 (62%)**	
Musher DM, et al. *Clin Infect Dis.* 2005;40:1586-1590	**161/207 (78%)**	**13/161 (8%) d21 47/161 (29%) d90**
Pépin J, et al. *Clin Infect Dis.* 2005;40:1591-1597	**323/435 (74%)**	**96/622 (15%) d60 109/323 (34%)**

1. Fernandez A, et al. Factors associated with failure of metronidazole in *Clostridium difficile*-associated disease. *J Clin Gastroenterol.* 2004;38:414-418.
2. Musher DM, et al. Relatively poor outcome after treatment of *Clostridium difficile* colitis with metronidazole. *Clin Infect Dis.* 2005;40:1586-1590.
3. Pépin J, et al. Increasing risk of relapse after treatment of *Clostridium difficile* colitis in Québec, Canada. *Clin Infect Dis.* 2005;40:1591-1597.

Fidaxomicin (OPT-80, PAR-101)

- 18-membered macrocyclic antibiotics
- Activity only against gram positive bacteria
- Pharmacokinetics
  - High concentrations in the stool
  - Relatively little absorption
- Clinical data
  - Effectiveness
  - Lower recurrence rates
    - Only compared to vancomycin
  - Well tolerated (so far…)

Sullivan KM et al. Ann Pharmacother 2010;44:352

Summary of Guidelines

IDSA[1]	SHEA[2]	ACG[3]	ASHP[4]
• Rehydration (mild disease) • Withdrawal of offending agent, if possible • Metronidazole 250 mg QID or 500 mg TID × 10 days **Note:** IDSA guidelines are for infectious diarrhea and not specifically for *C. difficile*-associated disease (CDAD)	• No treatment in 20% • Discontinue offending antibiotic if possible • 10-day treatment with metronidazole or vancomycin • Same treatment for first recurrence	• Discontinue antibiotics, if possible • Provide supportive therapy • Oral treatment with metronidazole preferred • Empirical treatment with metronidazole before diagnosis if confirmed in seriously ill patient • Oral vancomycin for certain conditions	• Oral metronidazole for most patients with CDAD • Oral vancomycin reserved for severe life-threatening CDAD, failure of metronidazole, when oral metronidazole cannot be used • Duration of either therapy is 10 days • Treat first relapse with same agent

1. **Guerrant RL, et al. *Clin Infect Dis.* 2001;32:331-351.**
2. **Gerding DN, et al. *Infect Control Hosp Epidemiol.* 1995;16:459-477.**
3. **Fekety R. *Am J Gastroenterol.* 1997;92:739-750.**
4. **ASHP. *Am J Health-Syst Pharm.* 1998;55:1407-1411.**

SHEA/IDSA 2010

TABLE 3. Recommendations for the Treatment of *Clostridium difficile* Infection (CDI)

Clinical definition	*Supportive clinical data*	Recommended treatment	Strength of recommendation
Initial episode, mild or moderate	Leukocytosis with a white blood cell count of 15,000 cells/μL or lower and a serum creatinine level less than 1.5 times the premorbid level	Metronidazole, 500 mg 3 times per day by mouth for 10–14 days	A-I
Initial episode, severe[a]	Leukocytosis with a white blood cell count of 15,000 cells/μL or higher or serum creatinine level greater than or equal to 1.5 times the premorbid level	Vancomycin, 125 mg 4 times per day by mouth for 10–14 days	B-I
Initial episode, severe, complicated	Hypotension or shock, ileus, megacolon	Vancomycin, 500 mg 4 times per day by mouth or by nasogastric tube, plus metronidazole, 500 mg every 8 hours intravenously. If complete ileus, consider adding rectal instillation of vancomycin	C-III
First recurrence	…	Same as for initial episode	A-II
Second recurrence	…	Vancomycin in a tapered and/or pulsed regimen	B-III

[a] The criteria proposed for defining severe or complicated CDI are based on expert opinion. These may need to be reviewed in the future upon publication of prospectively validated severity scores for patients with CDI.

Cohen SH et al. Infect Control Hosp Epidemiol 2010;31:00-000

Recurrence Treatment

- Retreat with initial regimen or alternative
  - (Consider vancomycin if ≥2 recurrence)
- Switching agents
- Tapering antibiotics
- Adding rifampin to vancomycin
- Immune studies
- Anion exhange resins
- Exogenous flora

Hurley BW et al. Arch Intern Med. 2002; 162:2177-2184
Fetsky R et al. Am J Gastroenterology 1997; 92:739-750
Cohen SH et al. Infect Control Hosp Epidemiol 2010;31
Gerding DN et al. Clin Infect Dis 2008;46:S32-42

Vancomycin Taper and Pulse Dosing

- Week 1: 125 mg qid
- Week 2: 125 mg bid
- Week 3: 125 mg daily
- Week 4: 125 mg every other day
- Weeks 5-6: 125 mg every 3 days

Probiotics

- Preserve or re-establish protective role of endogenous flora
- Oral or rectal administration
- Bacteria (bacteriotherapy)
- +Yeasts (biotherapy)

J Infect 1996;32:1-10

Probiotics

- Data supporting use is lacking for primary prevention or recurrence
  - Limited by study design, product variability, etc.
    - Notable references supporting use:
      - Hickson M et al. BMJ 2007;355:80
      - McFarland LV et al. JAMA 1994;271:1913
- Currently not recommended*
  - Risks: Invasive disease (i.e. bacteremia/fungemia)
- Perhaps use in prevention of AAD?

*- Large, well designed clinical trials required: Risk vs. benefit

Cohen SH et al. Infect Control Hosp Epidemiol 2010;31:00-000
Gerding DN et al. Clin Infect Dis 2008;46:S32-42

Nitazoxanide

- New thiazolide agent (Alinia^{R})
- MOA: Inhibits pyruvate-ferredoxin oxidoreductase (PFOR)
- Approved as orphan drug for treatment of protozal and helminthic GI infections
- *In vitro* and *in vivo* activity against *C. difficile*
- One clinical trial showed drug to be effective in 75% of metronidazole failures

Musher DM et al. Clin Infect Dis 2006;43:411-420
Fox LM et al. Clin Infect Dis 2005;40:1173-80
McVay CS et al. Antimicob Agents Chemother 2000;44:2254-8

Rifaximin

- Semisynthetic analog of rifampin
  - Poor oral bioavailability
- *In vitro* activity against *C. difficile*
- Limited clinical experience
  - Role in preventing relapse
    - Case series
  - Results of a randomized, open-label trial (n=20)
    - Vancomycin vs. Rifaximin (200mg TID x 10 days)
- Concerns: Rifamycin resistance

Gerard L et al. Epert Rev. Anti Infect Ther 2005;3(2):201-211
Boano M et al. Microbiol. Medica 1990;5:74-77
Johnson S et al. Anaerobe 2009;311-290-1
Johnson S. Clin Infect Dis 2007;44:846-8

Immunotherapy

- Passive immunity
  - IVIG (contains IgG antitoxin A)
    - Case reports/case series
  - Other (monoclonal antibodies)
- Active immunity (Vaccine)
  - Efficacy demonstrated in several animal studies
  - Clinical experience
    - Aboudola et al. (n=30)
    - Result: 50 fold increase in concentrations of anti-toxin A IgG
  - Phase II- Study of a Clostridium Difficile Toxoid Vaccine (ACAM-CDIFF™) in Subjects With Clostridium Difficile Infection (Sanofi-Aventis)
    - http://clinicaltrials.gov/ct2/show/NCT00772343

Wilcox MH. Journal of Antimicrobial Chemotherapy 2004. 53:882-884
Leung DY et al. J. Pediatr 1991; 118:633-7
Aboudola S. et al. 2003;71,3:1608-1610
Lowey I et al. NEJM 2010;362:197

Recurrent CDAD: Fecal Transplantation

Recurrent CDAD: Fecal Transplantation

Recurrent *Clostridium difficile* Colitis: Case Series Involving 18 Patients Treated with Donor Stool Administered via a Nasogastric Tube

Johannes Aas,[1] Charles E. Gessert,[2] and Johan S. Bakken[3]
[1]Department of Gastroenterology, [2]Division of Education and Research, and [3]Department of Infectious Diseases, St. Mary's/Duluth Clinic Health System, Duluth, Minnesota

Clostridium difficile–associated diarrhea and colitis have emerged as major complications associated with use of systemic antimicrobials. In this study, the medical records for 18 subjects who received donor stool by nasogastric tube for recurrent *C. difficile* infection during a 9-year period at a single institution were retrospectively reviewed. During the period between the initial diagnosis of *C. difficile* colitis and the stool treatments, the 18 subjects received a total of 64 courses of antimicrobials (range, 2–7 courses; median, 3 courses). During the 90 days after receipt of treatment with stool, 2 patients died of unrelated illnesses. One of the 16 survivors experienced a single recurrence of *C. difficile* colitis during 90-day follow-up. No adverse effects associated with stool treatment were observed. Patients with recurrent *C. difficile* colitis may benefit from the introduction of stool from healthy donors via a nasogastric tube.

Recurrent CDAD: Fecal Transplantation

- Preparation of donor specimen
  - Fresh (<6 hours)
  - ~30 g or ~2 cm^3 volume
  - Add 50 mL 0.9 normal saline, and homogenize with blender
  - Filter suspension with paper coffee filter
  - Refilter

Aas J, et al. *Clin Infect Dis.* 2003;36:580-585.

Tolevamer (GT160-246)

- Novel, non-antibiotic, high molecular weight polymer introduced by Genzyme Corp. for treatment of CDI
  - MOA: Binds toxins A & B
- Phase 2 trial results (GTC-80-203)
  - 289 patients
  - 3g/day vs. 6g/day vs. Vancomycin
- Phase 3 studies- Disappointing

http://genzyme.com/corp/licensing/genz_pdf_tolevamer_nonconfidential.pdf
Braunlin W et.al. Biophysical Journal. July 2004:534-539

Ramoplanin

- Lipoglycodepsipeptide antibiotic
  - » Disrupts bacterial cell wall synthesis
- Activity against gram positive bacteria
- Poor oral bioavailability
  - High fecal concentrations
- Clinical data
  - Phase II
    - – Overview: 200-400mg BID x 10 days vs. vancomycin
      - » Similar end of therapy response rate
  - Phase III
- Safety
  - – Minimal adverse effects and drug interactions

Farver DK et al. Ann Pharmacother 2005;39:883
http://www.ramotherapeutics.com/products_pipeline_ramoplanin.php

Last but not least: Infection Control

- Judicious use of antimicrobials
  - – *Antimicrobial Stewardship Programs*
- Hand washing
- Use contact isolation precautions
  - – Wear gloves & gowns
- Environmental cleaning
- Facilities
- Educate staff

Summary

- Incidence is increasing
- Epidemic strain has been identified
- Optimal method of treating complicated *C. difficile*-associated disease is unknown
- Standard regimens may not be useful for severe or multiple recurrent disease
- Control measures prevent transmission
- We need new therapeutic options

Health Care Burden

$1.1 billion in health care costs

Prolonged hospital stay (3.6 days)

Additional cost of $3,669 to $7,234/stay

ICHP 2011 Annual Meeting
C. Difficile – How It All Comes Out
Larry Danziger, PharmD

Post Test:

1. All of the following laboratory factors were predictive of an increased risk for CDAD in the current study, except:

A. White blood cell count >20,000 cells/mL

B. Serum albumin <2.5 g/dL

C. Creatinine >2 mg/dL

D. Alanine aminotransferase >40 U/L

2. Which of the following patient factors is not associated with an increased risk for severe CDAD?

A. Age >70 years

B. gender

C. Antimicrobial use

D. Previous hospital stay

3. What percent of patients will have a recurrence of CDAD after their first episode of disease?

A. 0-10%

B. 20 -30%

C. 30-40%

D. 40-50%

4. Which of the following is not a main symptom of CDAD?

A. watery diarrhea

B. fever

C. Weight gain

D. abdominal pain/tenderness

5. Which of the following antibiotics is approved by the FDA for use in the treatment of CDAD

A. Fidaxomicin

B. Vancomycin

C. Metronidazole

D. Both A and B