



## The Scoop on Poop: Therapeutic Considerations for *C. difficile*-associated Disease (CDAD).

Aaron M Tejani, BSc(Pharm), PharmD, ACPR  
Fraser Health Pharmacy Services

## Declaration

- Have not accepted honorariums/gifts directly or indirectly from the pharmaceutical industry in 4 years
- No direct or indirect financial associations with the pharmaceutical industry in the last 4 years

## The Plan

- Background on *C. difficile*-associated disease (CDAD)
  - Epidemiology
  - Pathophysiology
  - Diagnostics
- Risk factors and prevention for/of CDAD
- Treatment options with supporting evidence
- Role of the pharmacist
- Questions/Comments

## Epidemiology

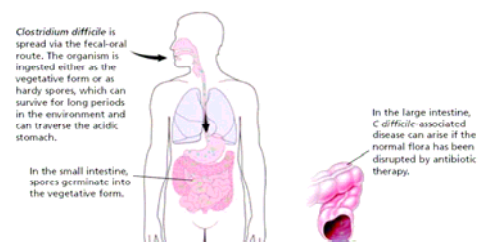
- 1997 study of 19 Canadian hospitals and nosocomial CDAD (269 cases)
  - 15% mortality rate (1-2% due to CDAD)
  - Morbidity
    - Dehydration (3%)
    - Hypokalemia (2%)
    - GI bleed (1%)
    - Bowel perforation (0.4%)
    - Sepsis (0.4%)
  - Annual cost of readmission per facility/year
    - \$128,000

Infect Control Hosp Epidemiol 2002;23:137-140.

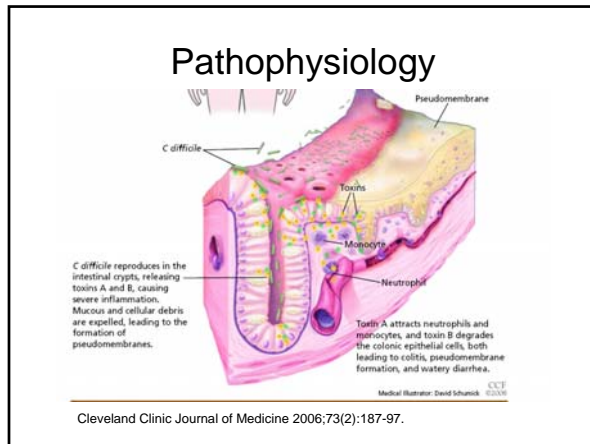
## Epidemiology

- Incidence from 1997 (*Can J Infect Dis* 2001;12:81-8.)
  - In hospital: 38-95 cases per 100 000 patient days
    - 3.4-8.4 cases per 1000 admissions
  - Community: 7.7-12 cases per 100 000 patient days
- Risk of colonization increases with duration of stay (*Lancet* 1990;336:97-100.)
  - 1% with <1 week stay
  - ~50% with >4 weeks stay

## Pathophysiology



Cleveland Clinic Journal of Medicine 2006;73(2):187-97.



- ### Pathophysiology
- Anaerobic **spore forming** bacillus
    - Spores allow survival in patients and in the environment
  - Spores are easily picked up by people
    - Hence fecal-oral transmission
  - One-percent of spores survive acid in stomach
  - Bile acids in small intestine lead to germination

- ### Colonization
- Common
    - Do not use empiric treatment in most cases
      - More details later
  - Colonization may increase immunity
    - Observational data suggests higher immune response in those that are colonized
      - Lancet 1998; 351:633–636.
      - NEJM 2000; 342:390–397.

- ### Toxin Production
- No toxin production = No disease!
    - i.e. Colonization may be asymptomatic
      - This will be re-visited in the “treatment” section
    - Toxin A
    - Toxin B
    - Binary toxin
      - Produced by NAP 1 Strain (implicated in Europe and NA outbreaks)
        - 16 X more Toxin A production
        - 23 X more Toxin B production
        - Relevance of Binary toxin is unknown

- ### Toxin Production
- CDAD not always associated with Toxin production
    - i.e. Patients need to be symptomatic to warrant pharmacotherapy
  - When should you look for CDAD?
    - i.e. Incubation period
      - Immediately (from risk factor presence)
      - Several weeks after risk factors are gone

- ### Disruption of Normal Colonic Flora
- Necessary for clinical disease
  - Usually secondary to antibiotic exposure

## Disease Continuum

- Mild CDAD
  - Mild diarrhea (>2 loose stools per day)
  - Tenesmus
  - Low grade or absent leukocytosis
  - Mild abdominal discomfort

## Disease Continuum

- Moderate
  - Fever
  - Dehydration
  - Nausea and vomiting
  - Abdominal tenderness
  - Leukocytosis
  - Severe watery/loose diarrhea

## Disease Continuum

- Severe
  - Pseudomembranous colitis (with bloody stools)
  - Sepsis or shock
  - Colonic perforation
    - Usually requires surgery
  - Toxic megacolon (Mortality 34-48%)
    - Usually requires surgery
  - Ascites
  - Paralytic ileus
  - Hypoalbuminemia
  - Improvement in diarrhea

## Diagnosis

- Only test loose/watery stools
  - Solid stool that is *C. difficile* +ve is likely as colonization is common
- Most labs will not test solid stool
  - Rarely intestinal ileus may be suspected
    - If so, contact lab to do the test of solid stool

## Diagnosis

**TABLE 1**  
Advantages and disadvantages of diagnostic testing methods for *C. difficile*

Diagnostic test	Time to report time	Sensitivity	Advantages	Disadvantages
Endoscopy	2 hours	51%	Diagnostic of pseudomembranous colitis	Low sensitivity
Anaerobic culture	72 hours	89%–100%	Results useful for molecular typing	Does not distinguish toxin-producing strains
Toxin cytotoxic assay	48 hours	94%–100%	Detects A-B+ strains Gold standard	False positives Results vary with experience of laboratory staff
Common antigen	15–45 minutes	58%–92%	Detects A-B+ strains Easy to use	Does not distinguish toxin-producing strains Cross-reacts with other enterobiers
Enzyme-linked immunosorbent assay (ELISA)—toxin A	2 hours	80%–95%	Easy to use	Does not detect A-B+ strains
ELISA—toxin A + B	2 hours		Detects A-B+ strains	Increased sensitivity for low-level toxin production
Immunochromatographic—toxin A	< 1 hour	60%–85%	Simple to use Rapid	Does not detect A-B+ strains

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## Monitoring Progress

- Fever resolution in 1-2 days
- Diarrhea resolution in 2-5 days
- If symptoms do not progress do not consider treatment failure until 7 days
- Surgical consult if signs of severe disease

## Risk Factors

- Antibiotic Exposure
  - Source of >90% of cases of CDAD
  - 2<sup>nd</sup> and 3<sup>rd</sup> generation Cephalosporins and Penicillins
  - Clindamycin
  - Sulfonamides
  - Quinolones
  - Metronidazole

## Antibiotics and Risk of CDAD: General Statement

- All antibiotics are potentially problematic
  - Cephalosporins, Clindamycin, Quinolones, Ampicillin
- Bacteroides elimination is a big problem
  - Anaerobes provide most protection against *C. difficile* out of all intestinal flora
  - In patients with CDAD relapse Bacteroides was the most common missing agent
  - MESSAGE: Avoid overuse of metronidazole

CMAJ • JULY 6, 2004; 171 (1):45-46

## Other Risk Factors

- Chemotherapy
- Advanced age
- Severe underlying illness
- Acid-suppressing drugs
  - PPI
  - H2RA
- Long hospital stay

## Specific Drug-Risk Issues

- Clindamycin
  - Not deserving of **all** the attention!
  - *Thomas et al* Systematic review on causation.  
Journal of Antimicrobial Chemotherapy (2003) 51, 1339–1350
    - Not much **good** data to determine causal relation
    - Similar rates of CDAD with a several of classes
      - OR ranged from 2.42 to 42 with Clindamycin
      - OR ranged from 3.84 to 26 with 3<sup>rd</sup> Gen Cephalosporins

## Specific Drug-Risk Issues

- Quinolones
  - Several case control and cohort studies demonstrated this class as the major risk factor
    - Ongoing debate based on quality of evidence to date
  - Quebec Study Clin Infect Dis 2005;41:1254-60.
    - Tried to identify risk factors linked with CDAD cases
    - Quinolones were the worst
    - Hyper virulent strain with high resistance to Quinolones
  - Dhalla et al Antimicrobial Agents and Chemotherapy 2006, p. 3216–3219
    - No difference between Moxifloxacin and Levofloxacin
  - Other weaker studies have conflicting findings

## Specific Drug-Risk Issues

- Proton pump inhibitors and H2RAs
  - A number of observational studies suggest an increased risk with these agents
    - with PPI
      - RR 2.9 (95% CI 2.4 to 3.4) JAMA 2005;294:2989-95
      - OR 2.5 (95% CI 1.5 to 4.2) JAMA 2004;292:1955-60
      - OR 2.1 (95% CI 1.2 to 3.5) CMAJ 2004;171:33-8
      - **Bottom line: potentially 2-3 times more likely if you have received or are on a PPI**
    - RR 2.0 (95% CI 1.6 to 2.7) with H2RA
      - JAMA 2005;294:2989-95
      - **Similar risk with H2RA and PPI**

## Drugs, Risk of CDAD, and Main Themes

- Avoid unnecessary anaerobic coverage
  - E.g. metronidazole
- Avoid broad spectrum antibiotics
  - Antibiotic stewardship!
- Avoid unnecessary use of acid suppressing agents

## Prevention

- Hand washing
  - Soap and water is the most effective measure
  - Alcohol-based products may be used but are generally less effective
    - Alcohol has no effect on spores but mechanical action of hand-washing may help get rid of them
      - [www.cdc.gov/ncidod/dhqp/id\\_CdiffFAQ\\_HCP.html#10](http://www.cdc.gov/ncidod/dhqp/id_CdiffFAQ_HCP.html#10)
- Eliminating or reducing risk factors

## Empiric Treatment

- In general, empiric therapy **not** warranted
  - 30% of diarrhea in hospitalized patients is due to *C. difficile*
- Consider empiric treatment **ONLY** if:
  - If patient rapidly worsening or severely ill

Cleveland Clinic Journal of Medicine 2006;73(2):187-97.

## Treatment

- Probiotics
- Binding Resins
- Metronidazole
- Vancomycin
- Adding Rifampin
- What to do for refractory/relapsing CDAD
- Emerging therapies

## Levels of Evidence

- Focus on:
  - Systematic reviews
  - Randomized controlled trials

## Probiotics

- Examples:
  - *Saccharomyces boulardii*
  - *Lactobacillus* (various forms)
  - Several others
- Mechanism of action
  - Restore the GI flora balance
  - Flora restoration prevents pathogens from proliferating
    - Immune stimulation, reduce pathogen adherence, toxin receptor modification, etc
- Recommended effective dose
  - 5 billion CFU per day for 5 days
    - Canadian natural health products directorate

## Probiotics

- Risks
  - Fungemia and bacteremia-rare
- Only work if they are resistant to antibiotics being used
  - Theoretical concern:
    - Resistance genes can be transferred to organisms for which antibiotics are being used
    - Could promote resistance?

## Probiotic Evidence

- One systematic review specifically for CDAD (Dendukuri et al. 2005 available at [www.mcgill.ca/tau/](http://www.mcgill.ca/tau/))
- For prevention of CDAD:
  - 1 RCT, n=138, Lactobacillus and bifidobacterium
    - No benefit seen with Probiotics but study poorly done
  - 5 RCTS of antibiotic-associated diarrhea (AAD) that looked at C. diff +ve patients
    - No statistically significant benefit of Probiotics

## Probiotic Evidence

- One systematic review specifically for CDAD (Dendukuri et al. 2005 available at [www.mcgill.ca/tau/](http://www.mcgill.ca/tau/))
- For treatment of CDAD:
  - 3 RCTS
    - McFarland 1994 (S. boulardii)
      - Recurrent CDAD: ARR 18.4% (95% CI 0.3 to 34.9%)
        - » Imprecise finding, needs more research
      - Benefit seen for patients with recurrent CDAD all treated with high dose Vancomycin
    - Surawicz 2000 (S. boulardii)
      - No overall benefit
      - Questionable benefit seen in High-dose Vancomycin subgroup
    - Wullt 2003 (L. plantarum)
      - Sample size too small to draw conclusions
      - No suggestion of benefit

## Probiotic Summary

- **No** evidence of benefit to date for:
  - Prevention of CDAD
  - Treatment of CDAD
- Note:
  - There is evidence of benefit in AAD
    - Scheike I et al. West Midlands Health Technology Assessment Collaboration 2005 Report

## Binding Resins

- E.g. Cholestyramine, Colestipol
- Mechanism of action:
  - Bind toxins
- Risks
  - Also bind Metronidazole and Vancomycin
- Evidence
  - No suggestion of benefit
  - No good RCTS

## Cochrane Review 2004 Antibiotic treatment for CDAD in Adults Bricker et al.

- All RCTS evaluating antibiotics for the treatment of CDAD
- Diarrhea definitions:
  - 2 loose/watery stools to 6 loose stools in 36 hours
- 9 RCTS
- Agents with RCTS:
  - Metronidazole, Vancomycin, Bacitracin, Fusidic acid, Teicoplanin

Cochrane Review 2004  
Antibiotic treatment for CDAD in Adults  
Bricker et al.

Comparison 01. Metronidazole versus Vancomycin

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Symptomatic Initial Response	2	163	Relative Risk (Fixed) 95% CI	0.97 [0.88, 1.07]
02 Symptomatic Cure	2	163	Relative Risk (Fixed) 95% CI	1.01 [0.87, 1.18]
03 Bacteriologic Initial Cure	1	62	Relative Risk (Fixed) 95% CI	0.96 [0.70, 1.30]
04 Bacteriologic Cure	2	174	Relative Risk (Fixed) 95% CI	0.74 [0.53, 1.03]
05 Symptomatic Recurrence	2	148	Relative Risk (Fixed) 95% CI	0.71 [0.29, 1.75]
06 Bacteriologic Recurrence	1	45	Relative Risk (Fixed) 95% CI	1.05 [0.51, 2.14]

**Bottom Line: Metronidazole versus Vancomycin**

- No difference with respect to any of the outcomes reported in trials
- No Metronidazole versus placebo trials?????
- Why do we use Metronidazole first line?
  - Cheaper
  - Reduce pressure to induce Vancomycin-resistant Enterococcus

What Are the Absolute Numbers?  
(Metronidazole versus Vancomycin)

Outcome	M %	V %	P-value
Symptom cure	80.3	79.3	0.9
Initial symptom response	89.5	92.0	0.6
Initial bacter. Cure	71.0	74.2	0.8
Bacter. Cure	39.1	52.9	0.7
Symptom recurr.	10.3	13.8	0.5
Bacter. Recurr.	41.0	39.1	0.9

Cochrane Review 2004  
Antibiotic treatment for CDAD in Adults  
Bricker et al.

Comparison 02. Bacitracin versus Vancomycin

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Symptomatic Initial Response	2	82	Relative Risk (Fixed) 95% CI	0.94 [0.72, 1.22]
02 Symptomatic Cure	2	82	Relative Risk (Fixed) 95% CI	0.68 [0.41, 1.11]
03 Bacteriologic Initial Response	2	72	Relative Risk (Fixed) 95% CI	0.52 [0.32, 0.84]
04 Symptomatic Recurrence	2	60	Relative Risk (Fixed) 95% CI	1.36 [0.64, 2.86]

**Bottom line: Bacitracin versus Vancomycin**

- Bacitracin is **worse** with respect to initial bacterial response but no different for all other outcomes

Cochrane Review 2004  
Antibiotic treatment for CDAD in Adults  
Bricker et al.

Comparison 03. Teicoplanin versus Vancomycin

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Symptomatic Initial Response	2	110	Relative Risk (Fixed) 95% CI	1.07 [0.95, 1.19]
02 Symptomatic Cure	2	110	Relative Risk (Fixed) 95% CI	1.21 [1.00, 1.46]
03 Bacteriologic Initial Response	2	110	Relative Risk (Fixed) 95% CI	1.43 [1.14, 1.81]
04 Bacteriologic Cure	1	59	Relative Risk (Fixed) 95% CI	1.82 [1.19, 2.78]
05 Symptomatic Recurrence	2	101	Relative Risk (Fixed) 95% CI	0.42 [0.14, 1.26]
06 Bacteriologic Recurrence	1	49	Relative Risk (Fixed) 95% CI	0.29 [0.09, 0.96]

**Bottom line: Teicoplanin versus Vancomycin**

- Teicoplanin **better** than Vancomycin for:
  - Symptom cure (Borderline statistical significance)
  - Bacteriological cure/initial response
- Teicoplanin is worse than Vancomycin for:
  - Bacteriologic recurrence

Cochrane Review 2004  
Antibiotic treatment for CDAD in Adults  
Bricker et al.

Comparison 04. Fusidic Acid versus Vancomycin

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Symptomatic Initial Response	1	60	Relative Risk (Fixed) 95% CI	1.00 [0.87, 1.14]
02 Symptomatic Cure	1	60	Relative Risk (Fixed) 95% CI	0.85 [0.61, 1.17]
03 Bacteriologic Initial Response	1	60	Relative Risk (Fixed) 95% CI	0.74 [0.50, 1.10]
04 Bacteriologic Cure	1	60	Relative Risk (Fixed) 95% CI	0.08 [0.01, 0.54]
05 Symptomatic Recurrence	1	56	Relative Risk (Fixed) 95% CI	1.72 [0.64, 4.61]
06 Bacteriologic Recurrence	1	39	Relative Risk (Fixed) 95% CI	2.40 [1.42, 4.05]

**Bottom line: Fusidic acid versus Vancomycin**

- Fusidic acid **better** than Vancomycin for: Bacteriologic recurrence
- Fusidic acid is worse than Vancomycin for: Bacteriologic cure

Cochrane Review 2004  
Antibiotic treatment for CDAD in Adults  
Bricker et al.

Comparison 05. Vancomycin versus Placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Symptomatic Initial Response			Relative Risk (Fixed) 95% CI	Subtotals only
02 Bacteriologic Initial Response			Relative Risk (Fixed) 95% CI	Subtotals only

**Bottom line: Vancomycin versus Placebo**

- Hard to draw conclusions for symptom outcomes (small sample size)
- Vancomycin is better for bacteriologic resolution

Cochrane Review 2004  
Antibiotic treatment for CDAD in Adults  
Bricker et al.

Comparison 07. High Dose versus Low Dose Antibiotics

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Symptomatic Initial Response	2	103	Relative Risk (Fixed) 95% CI	0.82 [0.68, 0.99]
02 Symptomatic Recurrence	2	85	Relative Risk (Fixed) 95% CI	1.20 [0.64, 2.26]
03 Symptomatic Cure	2	103	Relative Risk (Fixed) 95% CI	0.78 [0.56, 1.08]
04 Bacteriologic Cure	2	103	Relative Risk (Fixed) 95% CI	0.87 [0.53, 1.42]

**Bottom line:** High dose versus low dose antibiotics

- No clinically relevant differences between high doses and low doses

Cochrane Review 2004  
Antibiotic treatment for CDAD in Adults  
Bricker et al.

- Review authors' conclusions:
  - **Surgery, sepsis, death occurred too infrequently in studies to draw conclusions**
  - **For symptom cure, all agents studied were more or less equal**
  - Teicoplanin maybe slightly more effective than Vancomycin
  - Placebo-controlled studies are needed
  - **Mild disease may not need antibiotic treatment**
  - **Very little data to be certain of anything**

Recurrence/Relapse Treatment Options

- 18%-35% of patients will have recurrence
  - Due to new strain
  - Due to residual spores causing infection
- If >2 relapses
  - 50-60% chance of another infection
- Metronidazole failure predictors
  - Concurrent antibiotic therapy and failure
    - J Clin Gastroenterol 2006;40:49-54
    - RR 2.0 (95% CI 1.29 to 3.10)
  - Albumin <2.5 (indicator of severe mucosal damage?) and ICU Stay
    - J Clin Gastroenterol 2004;38:414-418
    - Low albumin OR 11.7 (95% CI 4.0 to 31.6)
    - ICU Stay OR 4.1 (95% CI 1.3 to 12.2)

Recurrence/Relapse Treatment Options

- Retreat with Metronidazole or Vancomycin?
  - Not based on RCTs
  - Observational studies suggest some success
  - Optimal regimen unknown
- Vancomycin taper to eliminate residual spores?
  - Case series and post-hoc analysis of an RCT placebo arm (Am J Gastroenterol 2002;97(7):1769-75.)
  - Dose: 125mg qid 1 week, 125mg bid 1 week, 125mg od 1 week, 125mg eod 1 week, then 125 mg q3days for 2 weeks

Cannot Take Oral Medications?

- Vancomycin retention enemas?
  - 0.5–1 g of Vancomycin dissolved in 1–2 L of NaCl 0.9% q4-12 hours retained for 60 minutes
  - No RCT evidence
  - Suggestion of benefit from observational data
- IV Metronidazole 500 mg q6-8 hours
  - No RCT evidence
  - Suggestion of benefit from observational data

Addition of Rifampin?

- For first episode infection
  - 1 RCT in addition to Metronidazole
  - No additional benefit
  - Clin Infect Dis. 2006 Sep 1;43(5):547-52
- For refractory infection
  - No RCT data
  - Case series data suggests benefit in combination with Vancomycin

## Other Treatment Options

- Fecal (healthy stool) enemas?
  - No RCT data
  - Case reports
- Refer to Jodlowski et al. *Ann Pharmacother* 2006;40:2164-9.
  - Vaccine, Rifamixin, IVIg
  - No RCT data for any of these

## Treatment Summary

<u>Treatment</u>	<u>Indication</u>	<u>Benefit</u>
Vancomycin po	Recurrence	Unknown
Metronidazole po	Recurrence	Unknown
Vancomycin po <i>taper</i>	Recurrence	Maybe
IV Metronidazole	No oral route	Unknown
Rifampin add-on	1 <sup>st</sup> episode	-No benefit
	Refractory	-Unknown
Metronidazole	1 <sup>st</sup> episode	Beneficial*
Vancomycin	1 <sup>st</sup> episode	Beneficial
Bacitracin	1 <sup>st</sup> episode	Beneficial*
Fusidic acid	1 <sup>st</sup> episode	Beneficial*

\*No placebo RCT data to support benefit, but comparative data suggests benefit, and all essentially produce similar benefit

## Role of the Pharmacist

- Key themes
  - Promote hand-washing with soap/water
  - Antibiotic stewardship
    - DC them if possible in patients with CDAD
    - Promote appropriate use in general
  - Careful use of Acid-suppressing agents
    - PPIs and H2RAs
  - DC antiperistaltic agents in patient with CDAD
    - This is based on theory but is reasonable

## Role of the Pharmacist

- Additional themes
  - Know the evidence
    - What we know
    - What we DON'T know
  - Promote appropriate research
    - E.g. Usefulness of treating mild disease??

## Questions

“Seize the moment of excited curiosity on any subject to solve your doubts; for if you let it pass, the desire may never return, and you may remain in ignorance.”

William Wirt (1772 - 1834)