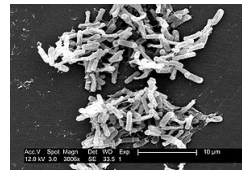


C. difficile: answers to the difficult questions

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Clostridium difficile

- Anaerobic spore-forming gram positive bacilli
 - “difficult” to culture
- Ubiquitous in environment; especially soil
- Pathogenic strains produce toxin A & B



Clostridium difficile infection (CDI)

- ≥ 3 unformed stools in 24 hours + positive *C. difficile* toxin result or colonoscopic/histopathologic findings of pseudomembranous colitis
- Healthcare associated: > 72 hours hospitalization or within 60 days discharge

Epidemiology

- Accounts for 20-30% antibiotic associated diarrhea
- Most common cause of infectious diarrhea in health care setting
- Canadian surveys 1997 & 2005
 - 3.8 to 9.5 cases per 10,000 patient days in acute care hospitals
 - Mortality ~2%

Ann Intern Med 2010; 153:ITC 4-1-14

Infect Control Hosp Epidemiol 2010; 31:431-55

Epidemiology

- Changing epidemiology
 - More severe disease, especially age > 65, since 2001 in US & Canada
 - Quebec: 2002-06 ↑ severe & recurrent CDI
 - Attributable 30d mortality 6.9%; additional 7.5% mortality indirectly
 - Majority of isolates - hypervirulent strain: NAP1/B1/027
 - 15-20x ↑ toxin A & B production; binary toxin production
 - Associated with increased fluoroquinolone usage

Ann Intern Med 2010; 152:ITC 4.1-14 Infect Control Hosp Epidemiol 2010; 31:431-55

Epidemiology

- KGH

1) Infection Rates by Type and Fiscal Period Table

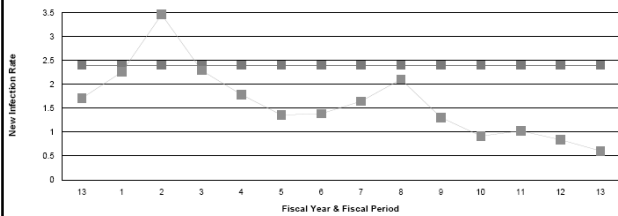
		2008													2009														
		13	1	2	3	4	5	6	7	8	9	10	11	12	13	1	2	3	4	5	6	7	8	9	10	11	12	13	
HealthCare Associated	PatientDays	9949	11684	10408	10489	10101	10311	10104	10336	9988	10716	9802	10727	10728	9899	9949	11684	10408	10489	10101	10311	10104	10336	9988	10716	9802	10727	10728	9899
New Infection	InfectionCount	16	16	38	17	13	10	9	11	19	12	8	10	9	3	16	16	38	17	13	10	9	11	19	12	8	10	9	3
	InfectionRate	1.61	1.44	2.88	1.63	1.29	0.97	0.89	1.09	1.90	1.12	0.82	0.93	0.84	0.30	1.61	1.44	2.88	1.63	1.29	0.97	0.89	1.09	1.90	1.12	0.82	0.93	0.84	0.30
Healthcare Associated	PatientDays	9949	11684	10408	10489	10101	10311	10104	10336	9988	10716	9802	10727	10728	9899	9949	11684	10408	10489	10101	10311	10104	10336	9988	10716	9802	10727	10728	9899
Relapse	InfectionCount	1	9	6	7	5	4	5	6	2	2	1	1	0	3	1	9	6	7	5	4	5	6	2	2	1	1	0	3
	InfectionRate	0.10	0.81	0.58	0.67	0.50	0.39	0.49	0.58	0.20	0.19	0.10	0.09	0.01	0.30	0.10	0.81	0.58	0.67	0.50	0.39	0.49	0.58	0.20	0.19	0.10	0.09	0.01	0.30

- Up to 33% mortality within 30 days of diagnosis

COICC data

Epidemiology

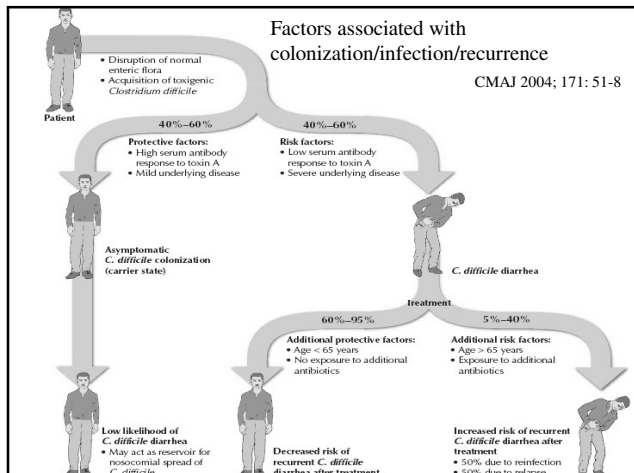
- KGH



COICC data

Factors associated with colonization/infection/recurrence

CMAJ 2004; 171: 51-8



Risk factors

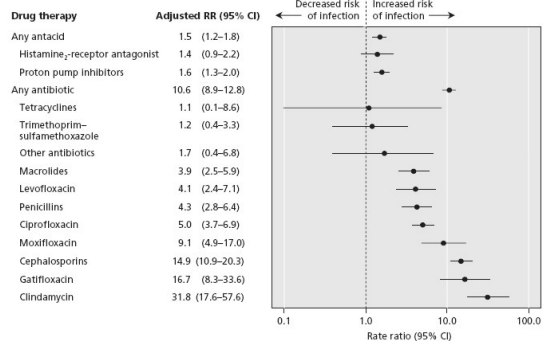
- Antibiotic exposure
- Advanced age
- Hospitalization/ long term care residence
 - ↑ risk with ↑ duration
- Cancer chemotherapy
- Severe/multiple underlying diseases (e.g. immunosuppression, malignancy, renal failure, malnutrition)
- GI manipulation (e.g. surgery, feeding tubes)
- Acid suppression (e.g. PPIs)

Ann Intern Med 2010; 153:ITC 4-1-14
 Infect Control Hosp Epidemiol 2010; 31:421-55

Risk factors - antibiotics

- Reported after single dose, including surgical prophylaxis
- ↑ risk with longer exposure or multiple antibiotics
- Associated with all classes of antibiotics
 - Rarely with vancomycin, metronidazole

Infect Control Hosp Epidemiol 2010; 31:421-55



CMAJ 2008; 179:767-72

Clinical presentation

- Asymptomatic carriage
 - ~50% C diff carriers = asymptomatic colonization
- Symptoms
 - fever, malaise, cramping, diarrhea (watery; may be bloody), nausea, abdominal discomfort, anorexia, leukocytosis
- Fulminant colitis (1-3%)
 - fever, diffuse abdominal pain/distention, may not have diarrhea if toxic megacolon/paralytic ileus
 - Mortality with toxic megacolon – 24-38%

CMAJ 2004; 171: 51-8

Treatment

- Discontinue all unnecessary antibiotics
 - Up to 25% mild cases respond to this alone within 48-72 hours
 - But do not delay metronidazole/vancomycin therapy
 - Increasing incidence of fulminant disease & hypervirulent strain, cannot predict rapid clinical deterioration
- Avoid antimotility agents
- No evidence for combination therapy in most patients
 - Exception: IV metronidazole + PR vancomycin in ileus

Clin Infect Dis 2008; 46; S32-42
Infect Control Hosp Epidemiol 2010; 31:421-55

Treatment

- PO therapy preferred if working gut
 - IV vancomycin does not reach colon
 - PO vancomycin – minimal absorption; eliminated unchanged in feces
 - IV and PO metronidazole achieve similar colonic concentrations; IV not well-studied
- No evidence that cholestyramine/colestipol beneficial
 - May bind metronidazole/vancomycin and decrease efficacy

Infect Control Hosp Epidemiol 2010; 31:421-55

Antimotility agents

- Limited data surrounding use in CDI
- 55 patients (case reports, case series)
 - 19 (35%) clinical resolution
 - 17 (31%) developed toxic megacolon
 - 9 (16%) died
 - All patients with complications/death were given antimotility agents prior to starting metronidazole/vancomycin treatment
- Other concerns: may mask worsening diarrhea or treatment failure

Clin Infect Dis 2009; 48; 598-605
Clin Infect Dis 2009; 48; 606-8

Treatment – 1st or 2nd episode

- Most patients
 - Metronidazole 500 mg po TID x 10-14 days
 - Early studies show no difference in outcomes compared to vancomycin
 - Not recommended after 2 treatment courses or for prolonged duration – cumulative risk neurotoxicity

Infect Control Hosp Epidemiol 2010; 31:421-55

Treatment – 1st or 2nd episode

- Severe episode
 - Vancomycin 125 mg po QID x 10-14 days
 - But what is severe?
 - Expert opinion: Scr 1.5x prembid level, WBC > 15,000 cells/mm³, hypotension, ICU admission, toxic megacolon, ileus
 - One study: severity assessment score based on 6 variables (unclear how score developed)

Clin Infect Dis 2007; 45: 302-7
Infect Control Hosp Epidemiol 2010; 31:431-55

Table 1. Baseline characteristics of patients with *Clostridium difficile*-associated diarrhea (CDAD), by disease severity and treatment.

Characteristic	Mild disease		Severe disease	
	Mtz group	Vm group	Mtz group	Vm group
Total no. of patients (male patients:female patients)	41 (25:16)	40 (19:21)	38 (18:20)	31 (20:11)
Age, mean years ± SD	57.9 ± 16.8	56.8 ± 11.5	57.5 ± 9.5	61.9 ± 16.4
>80 years of age	16 (39)	19 (48)	17 (45)	19 (61)
Received antibiotic therapy prior to onset of CDAD	41 (100)	40 (100)	38 (100)	31 (100)
Received antibiotic therapy within 14 days prior to onset of CDAD	39 (95)	39 (98)	37 (97)	28 (90)
Underlying disease				
Cardiovascular disease and/or hypertension	24 (58)	30 (75)	29 (76)	22 (71)
Malignancy	4 (10)	7 (18)	8 (21)	11 (35)
Chronic respiratory disease	5 (12)	7 (18)	10 (26)	8 (26)
Diabetes mellitus	8 (20)	13 (33)	7 (18)	10 (32)
Renal failure	5 (12)	8 (20)	11 (29)	16 (52)
Mean no. of bowel movements ± SD	5 ± 1	6 ± 1	5 ± 1	6 ± 1
Temperature >38.3° C	9 (22)	12 (30)	23 (61)	18 (58)
Albumin level <2.5 mg/dL	7 (18)	13 (33)	15 (39)	18 (58)
WBC count >15,000 cells/mm ³	10 (24)	6 (15)	15 (39)	12 (39)
Hospitalized in the ICU	0 (0)	0 (0)	3 (8)	2 (6)
Presence of pseudomembranous colitis	0 (0)	0 (0)	6 (16)	5 (16)

NOTE. Data are no. (%) of patients, unless otherwise indicated. All *P* values were >.05 when comparing treatment regimens within disease severity groups as determined using Fisher's exact test for categorical variables and the unpaired Student's *t* test for continuous variables. ICU, intensive care unit; Mtz, metronidazole; Vm, vancomycin.

Clin Infect Dis 2007; 45: 302-7

Table 2. Rate of cure of *Clostridium difficile*-associated diarrhea by disease severity and treatment.

Disease severity	No. of patients cured/ no. of patients treated (%)			<i>P</i> ^a
	Mtz group	Vm group	Total	
Mild	37/41 (90)	39/40 (98)	76/81 (94)	.36
Severe	29/38 (76)	30/31 (97)	59/69 (86)	.02
All	66/79 (84)	69/71 (97)	135/150 (90)	

NOTE. Mtz, metronidazole; Vm, vancomycin.

^a *P* values were calculated using Fisher's exact test.

Clin Infect Dis 2007; 45: 302-7

Dosing

- Is a higher dose of metronidazole better?
 - 250 mg po QID also studied for C diff, but never compared to 500 mg po TID
 - Failures reported with both doses
 - 2007 study vs. vancomycin: 250 mg QID
 - Expert opinion: 500 mg po TID preferred

Clin Infect Dis 2007; 45: 302-7

Infect Control Hosp Epidemiol 2010; 31:431-55

Dosing

- Is a higher dose of vancomycin better?
 - 46 patients: 125 mg po QID vs 500 mg po QID
 - No difference in clinical response
 - “Moderately or severely ill”, but not defined
 - 2007 study vs metronidazole: 125 mg po QID
 - Expert opinion: reserve higher doses for severe, complicated episodes (e.g. ileus, toxic megacolon, septic shock) or multiple recurrences

Am J Med 1989; 86: 15-9
Clin Infect Dis 2007; 45: 302-7

Infect Control Hosp Epidemiol 2010; 31:421-55

Duration

- 10 days minimum based on RCTs
 - Remember: KGH has 7-day autostop if no duration specified
- Expert opinion: extend to 14 days if immunocompromised, severe disease, incomplete clinical response at 7-10 days
- What if offending antibiotics can't be stopped?
 - No studies to guide us; consider lower risk antibiotic, extension CDI treatment
- Test of cure?
 - Not necessary; patients will excrete toxin for weeks after treatment

Infect Control Hosp Epidemiol 2010; 31:421-55

Severe, complicated episode

- Ileus, toxic megacolon
 - Oral therapy may not reach colon
- Case series of 9 patients
 - 0.5-1 g inj vancomycin dissolved in 1-2 L NS; 60 min retention enema q4-12h
 - 500 mg in 1L NS & perfuse 1-3 mL/min to 2g/24 hrs
 - Concomitant IV/PO metronidazole + PO vancomycin
- Expert opinion: metronidazole 500 mg IV q8h + vancomycin 500 mg PO/NG q6h
 - Add PR vancomycin if complete ileus

Clin Infect Dis 2002; 35: 690-6

Infect Control Hosp Epidemiol 2010; 31:421-55

Recurrent CDI

- 1st recurrence – treat as initial episode
- 2nd recurrence
 - Tapering/pulsed vancomycin
 - Varying regimens, most common in literature:
 - 125 mg PO QID x 10-14 days
 - Then 125 mg PO BID x 7 days
 - Then 125 mg po daily x 7 days
 - Then 125 mg po Q2-3days x 2-8 weeks
- Address risk factors (e.g. antibiotics, PPI)

Infect Control Hosp Epidemiol 2010; 31:421-55

Recurrent CDI

- >4 recurrences, failed vancomycin + probiotics
 - Possible stool transplant candidate?
 - 96% success rate in 48 patients over 15 years in Calgary
 - Similar success rates in other case series in literature
 - Issues: donor availability, logistics, infection control

Role of probiotics

- Variety of formulations/doses studied
 - *Lactobacillus spp.*
 - *Saccharomyces boulardii*
- Variable efficacy
- Appear to reduce risk of antibiotic associated diarrhea
- Inconclusive for treatment/prevention CDI
- Recurrent CDI: *S. boulardii* 500 mg po BID x 4 weeks decreased recurrences with concurrent vancomycin
 - Potential for fungemia in immunocompromised, critically ill or patients with central line

Clin Gastroenterol 2008; 42: 628-70 Infect Control Hosp Epidemiol 2010; 31: 421-55

Alternative agents

- Rifamycins
 - Role not established
 - Resistance may develop on therapy
 - No benefit of rifampin combined with metronidazole vs metronidazole alone for 1st episode
 - Rifaximin chaser in recurrent CDI – 7/8 women had no further recurrences
 - 400 mg po BID x 2 weeks post vancomycin therapy
 - Available in US; not available in Canada

Clin Infect Dis 2007; 43: 846-8
Clin Infect Dis 2006; 43: 547-52

Alternative agents

- Nitazoxanide
 - Available in US; Special Access in Canada
 - 500 mg po bid x 10 days
 - Similar outcomes to vancomycin and metronidazole in small studies initial episodes CDI
 - Observational study – 19/35 patients who relapsed on metronidazole responded to nitazoxanide

Expert Opin Pharmacother 2010; 19: 825-36

Alternative agents

- Fidaxomicin
 - New class of macrocyclic antibiotics
 - Currently not available
 - Minimal systemic absorption
 - 200 mg po bid x 10d
 - Similar outcomes to vancomycin at end of treatment
 - Decreased recurrences within 28d (13.3% vs. 24%)

Expert Opin Invest Drugs 2010; 11:1569-78

Alternative agents

- Passive immunization
 - IVIG
 - Up to 400 mg/kg
 - Mostly animal or small, retrospective studies
 - Anti-toxin A and B monoclonal antibodies
 - Phase II RCT – 7% vs 38% recurrence in placebo
- Active immunization
 - Vaccine currently being studied



Clostridium difficile Treatment Kelowna Acute and Residential Care

Allergies - Check one box:
 None known Unable to obtain
 True-Allergy ADR Record (if in use at the facility)
 List: _____

Weight (kg) _____

Unkoned orders are initiated by default. Bosed orders require physician check mark to be initiated.

INFECTION CONTROL PRECAUTIONS:

- Contact precautions for *C. difficile*.
- Post appropriate signage (Form 807914) outside patient's room (acute care).
- Wear gown and gloves for patient care.
- Patient should have separate bathroom or commode.
- Wash hands with soap and water when leaving patient's room.

NOTE: alcohol-based hand hygiene product is not effective against *C. difficile* spores.

DIET

- NPO Diet as tolerated Other (please specify) _____

MONITORING

- Temp, BP, HR, RR, O₂ sats Q _____

LABORATORY

- CBC and differential
- renal panel

DIAGNOSTICS

- Stool for *C. difficile* toxin, if not already done
- Stool for C&S, ova & parasites
- Other (please specify) _____

INTRAVENOUS THERAPY AND HYDRATION

- Normal saline IV at _____ mL/hr
- Other (please specify) _____

MEDICATIONS

- Discontinue antiarrhythmals (atrapulgit, loperamide and/or diphenoxylate-atropine).
- Discontinue antibiotics if possible; order must be written on line below to d/c antibiotics.

Discontinue _____

If first or second episode:

- metronidazole 500 mg PO/NG TID x 10 days

If more than one recurrence, acute renal failure or hypotension secondary to *C. difficile* associated diarrhea, clinical deterioration on metronidazole, metronidazole intolerance/allergy, and/or endoscopically confirmed pseudomembranous colitis:

- vancomycin 125 mg PO/NG QID x 10 days

If NPO and unable to take PO/NG medications:

- metronidazole 500 mg IV Q8H x 10 days

NOTE: The PO/NG route is more effective than IV. Change to PO/NG medication as soon as possible. IV vancomycin is not effective vs. *C. difficile* associated diarrhea

Date (dd/mm/yyyy)	Time	Physician Signature	Printed Name or College ID#
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Fax page to Pharmacy

629174 Jan 28-10

Prevention is key

- Infection control measures
- Antimicrobial stewardship