What's new in *C. difficile* infection management?

A review of the updated North American guidelines and evaluation of the evidence behind their recommendations

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Disclosure

- Relationships with commercial interests:
  - Grants/Research Support: Canadian Society of Hospital Pharmacists, Canadian Institutes of Health Research
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  - Other:
    - Nova Scotia Health Authority and Dalhousie University employee

Outline: *C. difficile* Infection (CDI)

- Etiology
- Pathophysiology
- Risk factors
- Diagnosis
- Severity stratification
- Therapeutic alternatives
  - First episode and recurrent
- Treatment recommendation evidence

Objectives

By the end of this presentation, pharmacists should be able to:

- Describe the **etiologic organism** causing CDI
- Outline the **pathophysiology** for CDI
- Be familiar with the characteristic **signs, symptoms, and tests used to diagnose** CDI
- **Stratify CDIs by severity**
- Identify **therapeutic alternatives** for first episode and recurrent CDI
- Discuss the **evidence** pertaining to the **treatment of CDI** in the updated IDSA and SHEA guidelines

Case: HW

ID	HW 64 yo female, 68 kg, 5”3
CC	“Diarrhea”
HPI	• 1 week ago: 1 day ED visit for pyelonephritis, sent home with PO antibiotics • Presents to hospital this morning with 7 unformed BM/day X 2 days
PMHX	• Two UTIs in the last year • Occasional heartburn with the consumption of spicy food
MPTA	• Rabeprazole 20 mg po daily X 1 year • Ciprofloxacin 400 mg IV X 1 dose in hospital 1 week ago, discharged on ciprofloxacin 500 mg po BID to complete 10 days of therapy Vaccinations: UTD
Allergies	NKDA
SHx	Retired school teacher. Denies: sick contacts at home, recent dietary changes, exotic travel, and ETOH/tobacco/illicit drug use.
FHx	N/A

Case: HW

ROS	(Physical exam and labs collected today)
Vitals	Afebrile, BP 118/70 mm Hg, HR 72 bpm, RR 17/minute
General	A/O X 3, denies: chills, sweats, malaise
GI	Abdomen soft, tender to palpate, mildly distended
GU	Denies previous signs and symptoms of UTI
Labs	WBC= 14 (3.1-9.7) Neuts= 9.1 (1.2- 6.0) SCr= 98 (73 on last admission)
Micro	Stool: Positive for *C. difficile* (+ GDH EIA and Toxin B PCR)
Current Meds	Rabeprazole 20 mg po daily (restarted on medication reconciliation orders) Dimenhydrinate 50 mg po/IV q6h prn nausea/vomiting Loperamide 4 mg po STAT, then 2 mg po prn after each loose bowel movement

Case: HW

- **What is the name of the pathogen causing HW's infection?**

  Clostridium difficile X

- **What is HW's current DTP (include severity category)?**

  HW has mild-moderate CDAD, an indication for antimicrobial therapy X

- **What are your recommendations for HW?**

  Metronidazole 500 mg po q8h x 10 days X

Why are *C. difficile* Infections Important?

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C. difficile strikes Cape Breton again

Nine hospital patients are now ill

CBC News Posted: Jan 03, 2012 9:42 AM AT | Last Updated: Jan 03, 2012 9:39 AM AT

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There has been another outbreak of C. difficile at the Cape Breton Regional Hospital in Sydney.

Three patients in the medical unit have been infected, bringing the total to nine people with the hospital-acquired infection, Clostridium difficile.

There are now nine cases of C. difficile at the Cape Breton Regional Hospital. (CBC)

Why are *C. difficile* Infections Important?

- Most common
  - Cause of healthcare-acquired infections in hospitals
  - Healthcare associated diarrhea
- Incidence is increasing in the community
- Responsible for 20-30% of antibiotic associated diarrhea

Why are *Clostridium difficile* Infections Important?

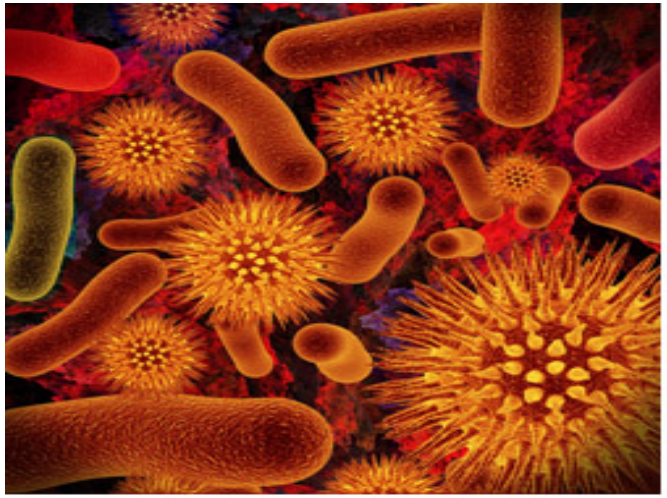
- 10-20% of patients relapse
- Complications include:
  - Volume depletion
  - Electrolyte disturbance
  - Hypotension
  - Toxic megacolon
  - Bowel perforation
  - SIRS/Sepsis
  - Death (2-7%)

Case: HW

- **What is the name of the pathogen causing HW's infection?**
  - *Clostridium difficile* **X**
  - *Clostridioides difficile*

Clostridioides difficile

- Formerly known as *Clostridium difficile*
- Gram positive bacilli, anaerobic, spore-forming
- Found in:
  - Environment (soil)
  - Animal/human GI tract
- Transmissible nosocomial pathogen
- Pathogenic strains produce:
  - Enterotoxin A (Toxin A)
  - Cytotoxin B (Toxin B)

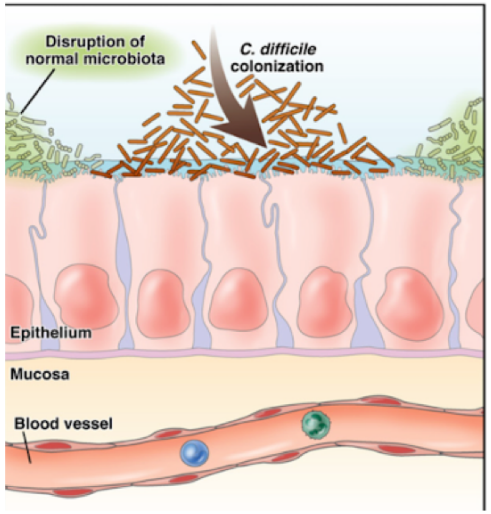


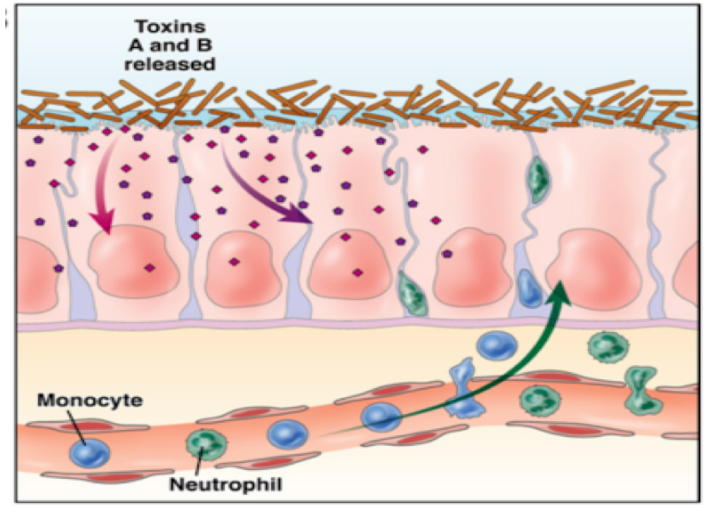
Clostridioides difficile

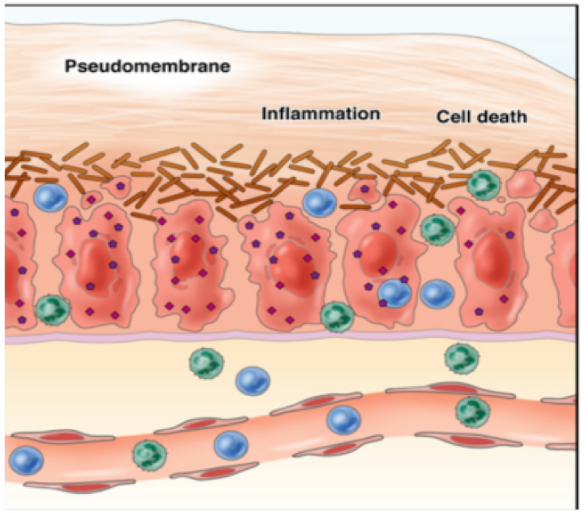
- NAP1/BI/027:
  - Virulent strain associated with ↑ severity, mortality, and recurrence
    - Severity= ICU stay, colectomy
  - Genes to produce an additional binary toxin
  - Mutation causing deletion of toxin A and B negative regulator

Pathophysiology

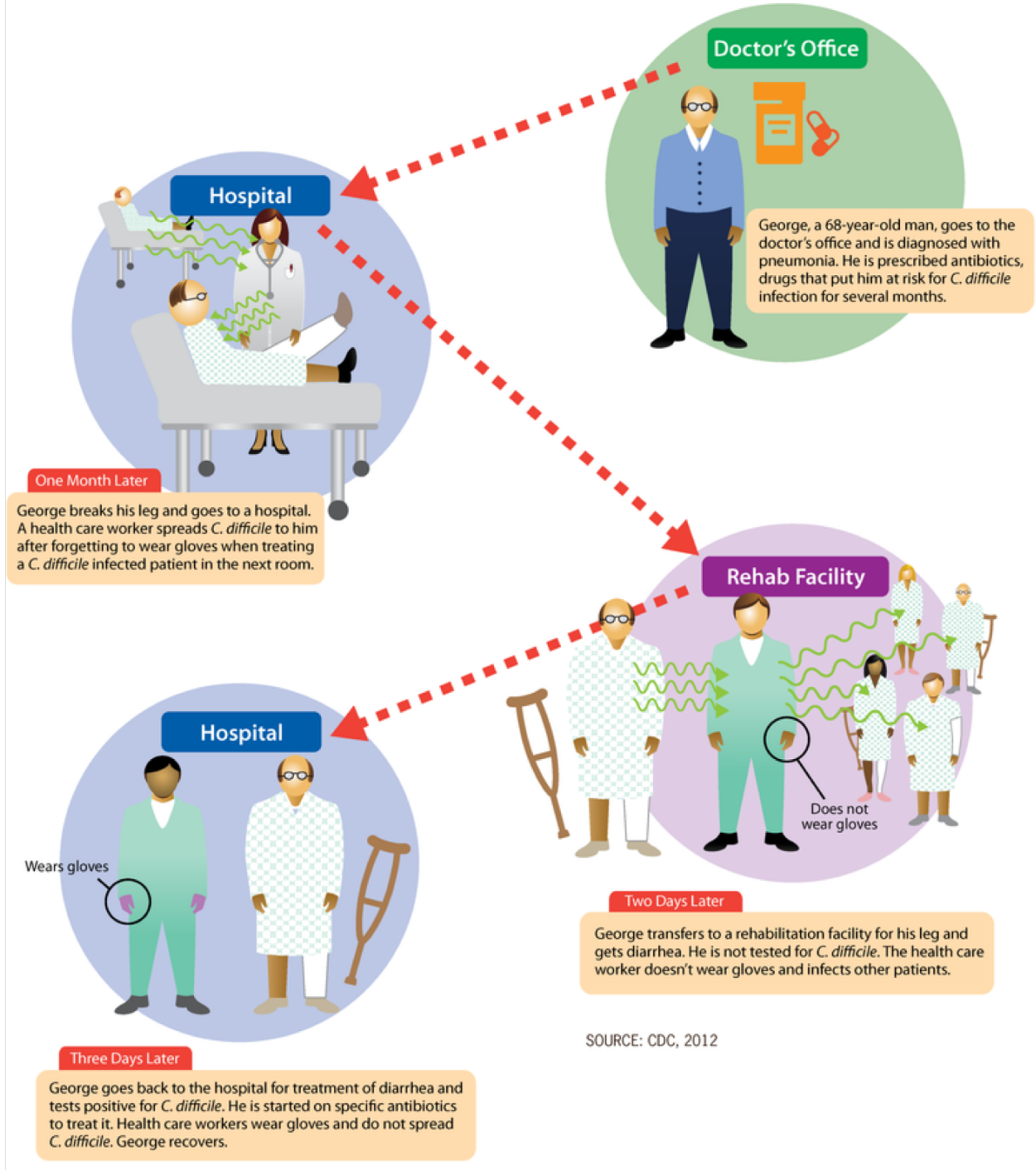
- Prerequisites:
  - Disruption of normal GI flora
  - *C. difficile* acquisition from an exogenous source (fecal-oral route)
- Other factors:
  - Host susceptibility
  - Virulence of the *C. difficile* strain
  - Nature and extent of antimicrobial exposure







Clin Gastroenterol Hepatol. 2012 Jun;10(6):581-92.


Doctor's Office
George, a 68-year-old man, goes to the doctor's office and is diagnosed with pneumonia. He is prescribed antibiotics, drugs that put him at risk for C. difficile infection for several months.
Hospital
One Month Later
George breaks his leg and goes to a hospital. A health care worker spreads C. difficile to him after forgetting to wear gloves when treating a C. difficile infected patient in the next room.
Rehab Facility
Does not wear gloves
Two Days Later
George transfers to a rehabilitation facility for his leg and gets diarrhea. He is not tested for C. difficile. The health care worker doesn't wear gloves and infects other patients.
Hospital
Wears gloves
Three Days Later
George goes back to the hospital for treatment of diarrhea and tests positive for C. difficile. He is started on specific antibiotics to treat it. Health care workers wear gloves and do not spread C. difficile. George recovers.
SOURCE: CDC, 2012

Risk Factors

- Antibiotic exposure in past 8-12 weeks
- Antineopastics in past 8 weeks
- Older age (>64 years)
- Prolonged hospitalization
- Long term care residence
- Comorbidities
- GI tract manipulation
- Acid suppression (?)

Risk Factors

Antibiotic exposure

- CDI can result from 1 dose
- Can occur up to 12 weeks after completion of antibiotic
  - Highest risk during and 4 weeks after completion of antibiotic
  - 96% of patients with symptomatic CDI receive antibiotics within 14 days before onset of diarrhea
- Increased risk with prolonged duration or multiple antibiotics
- CDI associated with all antibiotic classes
- High risk:
  - Third/fourth generation cephalosporins, clindamycin, carbapenems, fluoroquinolones
- Low risk:
  - Tetracyclines

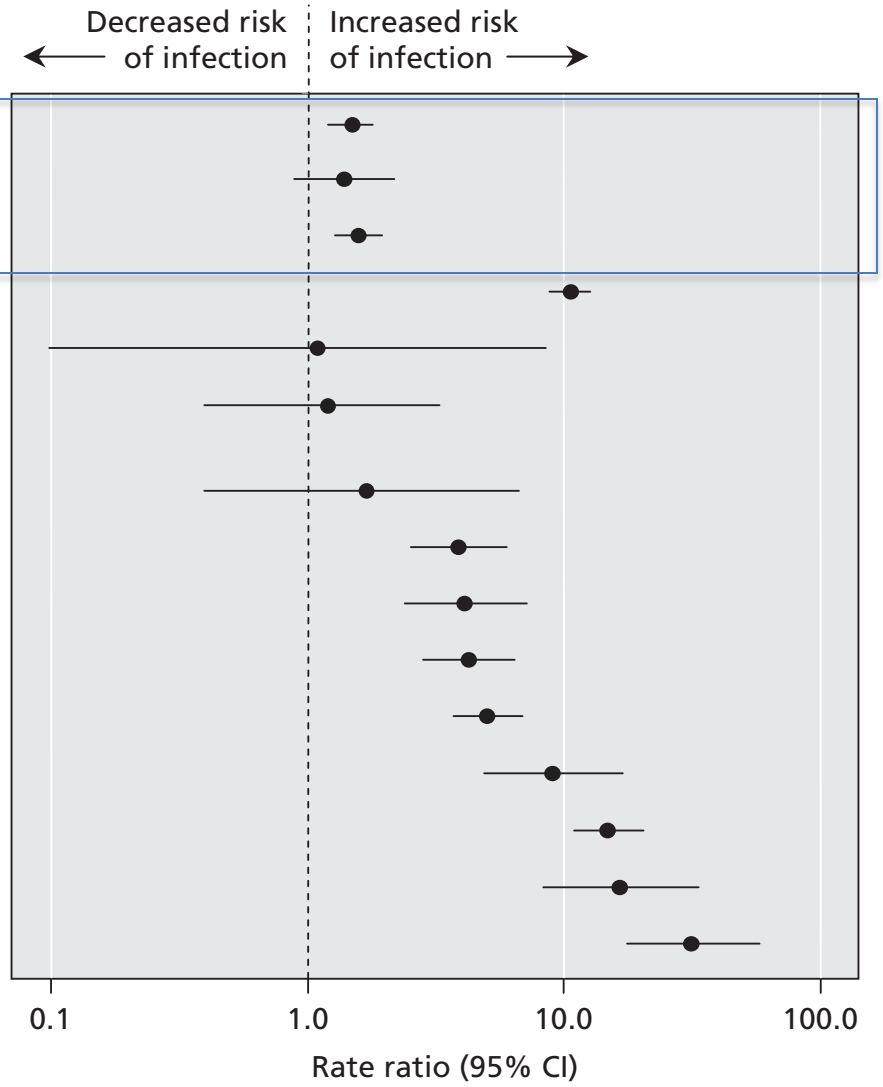
Proton pump inhibitors (antacids): possible risk of *Clostridium difficile*-associated diarrhea

Starting date:	February 16, 2012
Posting date:	February 16, 2012
Type of communication:	Advisory
Subcategory:	Drugs
Source of recall:	Health Canada
Identification number:	RA-110005424

Report a Concern

Risk Factors

Drug therapy	Adjusted RR (95% CI)
Any antacid	1.5 (1.2–1.8)
Histamine$_2$-receptor antagonist	1.4 (0.9–2.2)
Proton pump inhibitors	1.6 (1.3–2.0)
Any antibiotic	10.6 (8.9–12.8)
Tetracyclines	1.1 (0.1–8.6)
Trimethoprim–sulfamethoxazole	1.2 (0.4–3.3)
Other antibiotics	1.7 (0.4–6.8)
Macrolides	3.9 (2.5–5.9)
Levofloxacin	4.1 (2.4–7.1)
Penicillins	4.3 (2.8–6.4)
Ciprofloxacin	5.0 (3.7–6.9)
Moxifloxacin	9.1 (4.9–17.0)
Cephalosporins	14.9 (10.9–20.3)
Gatifloxacin	16.7 (8.3–33.6)
Clindamycin	31.8 (17.6–57.6)



CMAJ 2008; 79:767-72

Risk Factors: H2RAs/PPIs

- Many studies show an epidemiologic association between acid–suppressing medications (primarily PPIs) and CDI
- Other well-controlled studies suggest association is the result of confounding
  - underlying severity of illness
  - non-CDI diarrhea (PPIs cause diarrhea on their own)
  - duration of hospital stay
- There is insufficient evidence for discontinuation of PPIs as a measure for preventing CDI

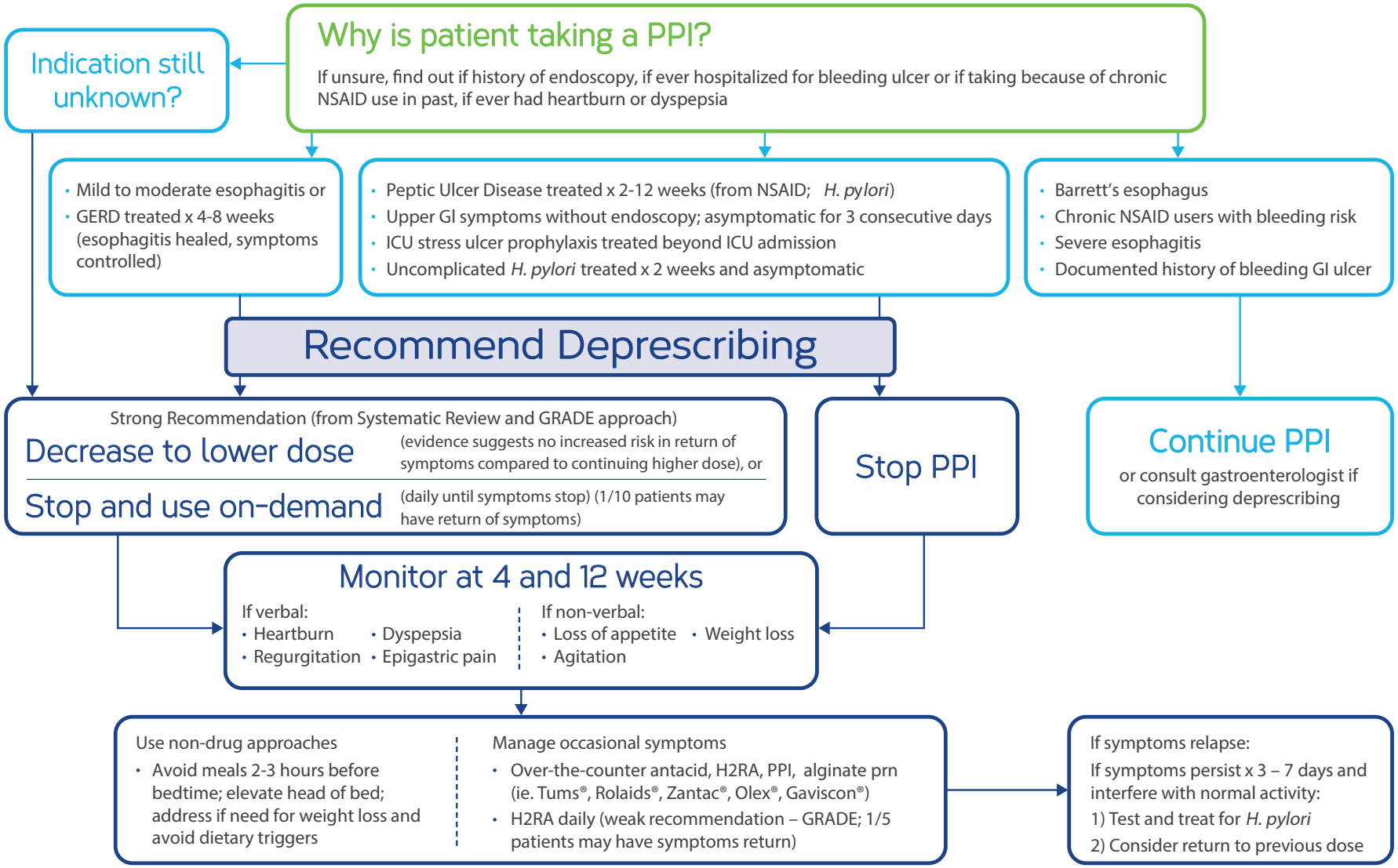
PPI Risk – Bottom Line

- Don't maintain long term PPI therapy for GI symptoms without an attempt to stop/reduce at least once per year in most patients
  - Patients with Barrett's esophagus, Los Angeles Grade D esophagitis, and gastrointestinal bleeding would be exempt from this

- PPIs are effective drugs for the treatment of GERD. Patients should always be prescribed the lowest dose of drug that manages their symptoms

- Even though GERD is often chronic, over time may not require acid suppression

deprescribing.org | Proton Pump Inhibitor (PPI) Deprescribing Algorithm



PPI Availability

PPI	Standard dose (healing) (once daily)*	Low dose (maintenance) (once daily)
Omeprazole (Losec®) - Capsule	20 mg+	10 mg+
Esomeprazole (Nexium®) - Tablet	20[a] or 40[b] mg	20 mg
Lansoprazole (Prevacid®) - Capsule	30 mg+	15 mg+
Dexlansoprazole (Dexilant®) - Tablet	30[c] or 60[d] mg	30 mg
Pantoprazole (Tecta®, Pantoloc®) - Tablet	40 mg	20 mg
Rabeprazole (Pariet®) - Tablet	20 mg	10 mg

Legend

a Non-erosive reflux disease

b Reflux esophagitis

c Symptomatic non-erosive gastroesophageal reflux disease

d Healing of erosive esophagitis

+ Can be sprinkled on food

* Standard dose PPI taken BID only indicated in treatment of peptic ulcer caused by *H. pylori*; PPI should generally be stopped once eradication therapy is complete unless risk factors warrant continuing PPI (see guideline for details)

Key

GERD = gastroesophageal reflux disease

NSAID = nonsteroidal anti-inflammatory drugs

H2RA = H2 receptor antagonist

SR = systematic review

GRADE = Grading of Recommendations Assessment, Development and Evaluation

Engaging patients and caregivers

Patients and/or caregivers may be more likely to engage if they understand the rationale for deprescribing (risks of continued PPI use; long-term therapy may not be necessary), and the deprescribing process

PPI side effects

- When an ongoing indication is unclear, the risk of side effects may outweigh the chance of benefit
- PPIs are associated with higher risk of fractures, *C. difficile* infections and diarrhea, community-acquired pneumonia, vitamin B12 deficiency and hypomagnesemia
- Common side effects include headache, nausea, diarrhea and rash

Tapering doses

- No evidence that one tapering approach is better than another
- Lowering the PPI dose (for example, from twice daily to once daily, or halving the dose, or taking every second day) OR stopping the PPI and using it on-demand are equally recommended strong options
- Choose what is most convenient and acceptable to the patient

On-demand definition

Daily intake of a PPI for a period sufficient to achieve resolution of the individual's reflux-related symptoms; following symptom resolution, the medication is discontinued until the individual's symptoms recur, at which point, medication is again taken daily until the symptoms resolve

Diagnosis

- *C. difficile* infection diagnosis requires:
  - Symptoms: diarrhea (>/= 3 unformed stools/24 hours) or ileus AND
    - Stool positive *C. difficile* toxins or detection of toxigenic *C. difficile*

    OR
    - Colonoscopic/histopathologic findings of pseudomembranous colitis

Clinical Manifestations

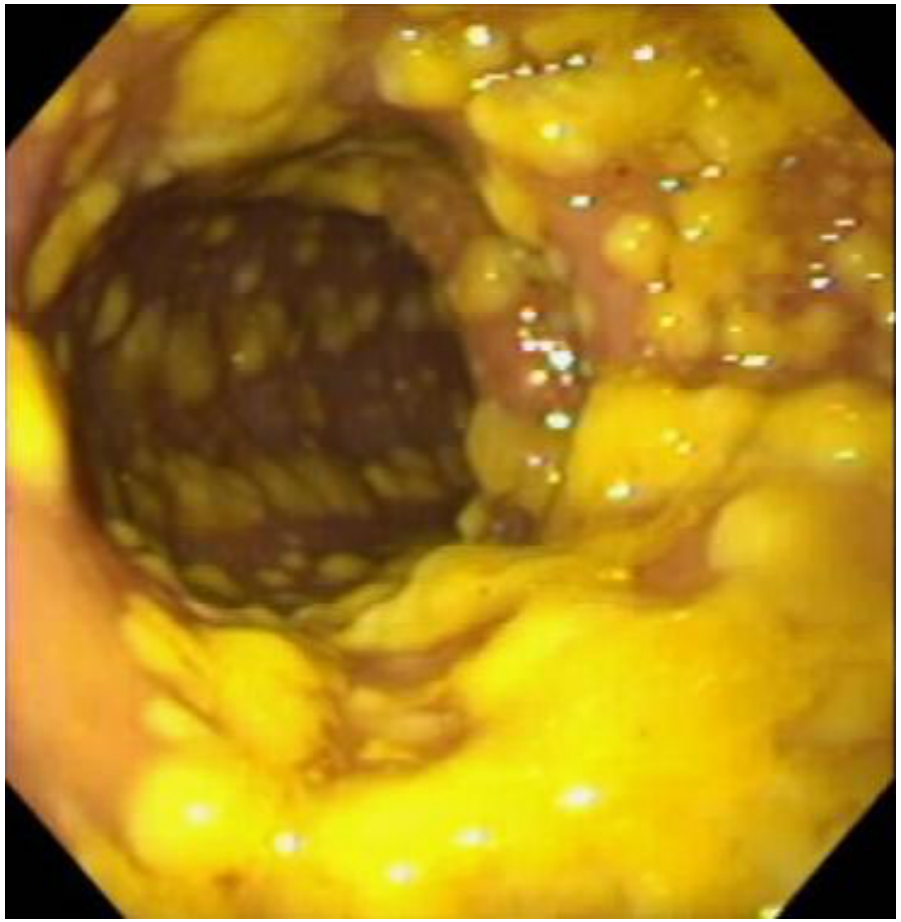
Symptomless carriage

↓

Mild or moderate diarrhea

↓

Fulminant pseudomembranous colitis



http://img.medscapestatic.com/pi/meds/ckb/20/35820tn.jpg

Clinical Presentation

Vitals	Fever, ↑ HR, ↑ RR
General	Rigors, chills, malaise
CVD	↓ BP
GI	Diarrhea (+/- mucous, occult blood), abdo pain, cramping, pseudomembranous colitis, colonic ileus, toxic dilatation
GU	↑ SCR
MSK/Derm	Arthritis (rare)
Labs	↑↑WBC, ↑ Neuts, hypovolemia, electrolyte imbalances, ↑ lactate

Diagnosis

Test	Target	Sensitivity	Specificity	Comments
Cell culture cytotoxicity assay	Toxin B	86%	99%	Cytotoxin assay: Detects toxins in the supernatants of patient feces. Results in 24-48 hrs. Cytotoxigenic culture: Detects toxins directly from fecal sample. Results in > 72 hrs.
PCR	Toxin B gene	89%	95%	Fast turn-around time (~1 hr). May remain positive for 3-4 weeks after resolution of clinical symptoms. Expensive.
EIA	Toxin A or A&B	60-86%	91-97%	Rapid, but less sensitive than cell cytotoxin assay.
EIA	Bacterial surface enzyme glutamate dehydrogenase (GDH)	88%	94%	Cannot distinguish between toxigenic and nontoxigenic strains. Highly sensitive and rapid results (~1 hr). Good initial screening step in a multistep approach.

In Central Zone: Currently using EIA (GDH) followed by Toxin B PCR for all patients

- **Fact or Fiction? The microbiology lab will only test unformed bowel movements for CDI.**
- FICTON
  - Requesting unformed stool samples is a method used to reduce inappropriate samples
  - In cases of ileus or non-diarrheal stool specimen, it is important to communicate with the microbiology laboratory and explain the necessity to test for *C. difficile*

Case: HW

- **What are the goals of therapy for HW?**
  - Reduce mortality
  - Cure infection
  - Prevent complications/morbidity: Volume depletion, electrolyte disturbance, hypotension, toxic megacolon, bowel perforation, sepsis
  - Resolve signs and symptoms: </=3 BM/day (in 3-5 days), normalize: WBC, abdominal tenderness, distension, nausea
  - Prevent recurrent infection: 10-25% of patients relapse
  - Prevent adverse events
  - Reduce/eliminate modifiable risk factors
  - Patient education

Preventative Strategies

- Antimicrobial stewardship
- Hand hygiene
- Contact precautions (glove, gown)
- Private rooms or cohort
- Environmental cleaning/disinfection/use of disposables

Therapeutic Alternatives

Therapeutic Alternatives

- General tips:
  - Discontinue unnecessary/inciting antibiotics ASAP
  - **Avoid antidiarrheal agents**
  - Initiate empiric therapy immediately when a substantial delay in laboratory confirmation is expected, or for fulminant CDI

Therapeutic Alternatives

- Metronidazole
- Vancomycin
- Fidaxomicin

Consider:

1) Efficacy
2) Toxicity
3) Patient specific factors
4) Ease of administration
5) Cost

Therapeutic Alternatives

	Metronidazole	Vancomycin	Fidaxomicin
Administration	PO/IV	PO/PR	PO
Convenience	TID	QID	BID
AE	Peripheral neuropathy, GI intolerance (nausea), headache, dizziness, metallic taste, urine discoloration	VRE, well tolerated. N/V/D. If use IV orally, bad taste.	Well tolerated. GI intolerance, hypersensitivity.
DI	Warfarin, disulfiram-like reaction with ETOH	Cholestyramine	Cholestyramine, Lactobacillus
Cost	$	$$$	$$$$
Resistance in Clinical Isolates	Increased MIC reported in some studies	Not reported	One clinical isolate with increased MIC
Notes	Fecal levels decrease with colitis resolution	Preferred in pregnancy/nursing	

Treatment by Severity

Case: HW

- **What is HW's current DTP (include severity category)?**
  - HW has mild-moderate CDAD, an indication for antimicrobial therapy **X**
  - HW has non-severe CDAD, an indication for antimicrobial therapy

Initial Episode CDI

Severity	Non-severe (previously known as mild to moderate)	Severe	Fulminant (previously known as severe complicated)
Criteria	WBC</=15 AND SCr </=132.6 µmol/L (1.5 mg/dL)	WBC> 15 OR SCr >132.6 µmol/L (1.5 mg/dL)	Hypotension, shock, ileus, megacolon
Options	1. Vancomycin 125 mg po QID x 10 days OR 2. Fidaxomicin 200 mg po BID x 10 days OR 3. 1 + 2 unavailable or ≤18 years of age: Metronidazole 500 mg po q8h x 10 days	1. Vancomycin 125 mg po QID x 10 days OR 2. Fidaxomicin 200 mg po BID x 10 days	1. Vancomcyin 500 mg PO/NG QID if Ileus present ADD - Vancomycin 500 mg (in 100 mL NS) PR q6h PLUS - Metronidazole 500 mg IV q8h

Metro vs. Vanco…

Vanco for all (non-severe and severe)?

- 5 RCTs (4 publications) compare metronidazole to vancomycin
  - Teasley 1983
  - Wenisch 1996
  - Zar 2007
  - Johnson 2014

Lancet 1983; 2:1043–6
Clin Infect Dis 1996; 22:813–8
Clin Infect Dis 2007; 45:302–7
Clin Infect Dis 2014; 59:345–54

Zar et al.

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 (%)			
	Mtz group	Vm group	Total	*P*[a]
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.

Subgroup PP analysis of severe patients

Limitations:

- ***Arbitrary severe CDI definition, differs from guidelines***
- ***Comparison= metronidazole 250 mg po QID***
- ***ITT analysis is NSS***

Clin Infect Dis 2007; 45: 302–307.

Johnson et al.

Overall cure rates:

- 72.7% (202/278) with metronidazole and 81.1% (210/259) with vancomycin (*P* = 0.02)
  - Mild CDI: 78.7% (59/75) metronidazole vs. 82.7% (62/75) vancomycin (*P* = 0.54)
  - Severe CDI: 66.3% (61/92) metronidazole vs. 78.5% (51/65) vancomycin (*P* = 0.059)

Table 6. Evidence for Resolution of Symptoms and Sustained Resolution ~1 Month (21–30 Days) After Treatment for Specific *Clostridium difficile* Treatment Agents

Outcomes	No. of Participants (No. of Studies)	Percentage Resolution	Relative Effect[a] (95% CI)	*P* Value	Quality of Evidence (GRADE)[b]	Reference, First Author
Direct comparisons of metronidazole and vancomycin						
Resolution of diarrhea at end of (10 days) treatment	RCTs prior to 2000: 156 (2)	95 (MTR) 98 (VAN)	RR, 0.97 (.91–1.03)	.4		Teasley [168] Wenisch [310]
? Per protocol →	RCTs since 2000: 687[c] (3)	75 (MTR) 85 (VAN)	RR, 0.89 (.82–.96)	.002		Zar [188] Johnson [170]
	All RCTs: 843 (5)	78 (MTR) 87 (VAN)	RR, 0.89 (.85–.96)	.0008	⊕⊕⊕⊕ High	
Resolution of diarrhea at end of treatment without CDI recurrence ~1 month after treatment	RCTs prior to 2000: 156 (2)	85 (MTR) 84 (VAN)	RR, 1.0 (.90–1.2)	1.0		Teasley [168] Wenisch [310]
	RCTs since 2000: 687[c] (3)	59 (MTR) 70 (VAN)	RR, 0.84 (.74–.94)	.002		Zar [188] Johnson [170]
	All RCTs: 843 (5)	63 (MTR) 73 (VAN)	RR, 0.87 (.79–.96)	.003	⊕⊕⊕⊕ High	
Direct comparisons of fidaxomicin and vancomycin						
Resolution of diarrhea at end of (10 days) treatment	1105[d] (2)	88 (FDX) 86 (VAN)	RR, 1.0 (.98–1.1)	.36	⊕⊕⊕⊕ High	Louie [321] Cornely [324]
Resolution of diarrhea at end of treatment without CDI recurrence ~1 month after treatment	1105[d] (2)	71 (FDX) 57 (VAN)	RR, 1.2 (1.1–1.4)	<.0001	⊕⊕⊕⊕ High	Louie [321] Cornely [324]
Direct comparisons of FMT and vancomycin						
Resolution of diarrhea at end of treatment without CDI recurrence 56 days after treatment	29 (1)	81 (FMT) 31 (VAN[e])	RR, 2.6 (1.1, 6.2)	.01	⊕⊕⊕⊖ Moderate	van Nood [367]

Abbreviations: CDI, *Clostridium difficile* infection; CI, confidence interval; FDX, fidaxomicin; FMT, fecal microbiota transplantation; GRADE, *Grading* of Recommendations, Assessment, Development and Evaluation; MTR, metronidazole; RCT, randomized controlled trial; RR, relative risk; VAN, vancomycin.

[a]All relative risks calculated using vancomycin as the comparator agent. An RR <1.0 represents results favoring the use of vancomycin; an RR >1.0 represents results favoring the comparator.

[b]For GRADE interpretation, see Figure 1.

[c]Full analysis set. Population in the 2 phase 3 tolevamer trials published in the same journal article [170].

[d]Modified intention-to-treat population (combined analysis of both phase 3 fidaxomicin trials [390]).

[e]A second control group of 13 patients who received a bowel lavage in addition to vancomycin was included in this study. The RR for this comparison (FMT vs VAN + lavage) was 3.5 (95% CI, 1.1–9.8).

Analysis 1.1. Comparison 1 Metronidazole vs Vancomycin, Outcome 1 Sustained Symptomatic Cure with all exclusions treated as failures.

Review: Antibiotic treatment for *Clostridium difficile*-associated diarrhoea in adults

Comparison: 1 Metronidazole vs Vancomycin

Outcome: 1 Sustained Symptomatic Cure with all exclusions treated as failures

Sustained symptomatic cure defined as initial symptomatic response and no recurrence of CDI

Study or subgroup	Metronidazole n/N	Vancomycin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Johnson 2014	202/278	212/259		63.6 %	0.89 [0.81, 0.97]
Teasley 1983	35/45	39/56		10.1 %	1.12 [0.88, 1.41]
Wenisch 1996	24/31	24/31		7.0 %	1.00 [0.76, 1.31]
Zar 2007	57/90	64/82		19.4 %	0.81 [0.67, 0.99]
Total (95% CI)	**444**	**428**		**100.0 %**	**0.90 [0.84, 0.97]**

Total events: 318 (Metronidazole), 339 (Vancomycin)

Heterogeneity: $Chi^2 = 5.04$, $df = 3$ ($P = 0.17$); $I^2 = 40\%$

Test for overall effect: $Z = 2.62$ ($P = 0.0087$)

Test for subgroup differences: Not applicable

0.2 0.5 1 2 5

Favours vancomycin Favours metronidazole

Metro vs. Vanco…

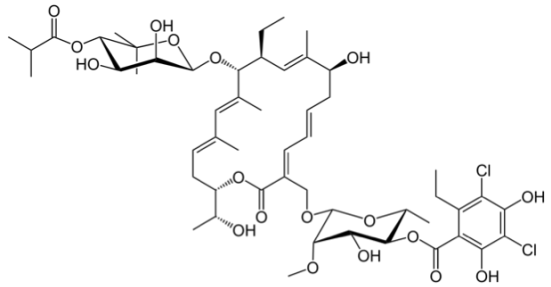
Comparison 1. Metronidazole vs Vancomycin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Sustained Symptomatic Cure with all exclusions treated as failures	4	872	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.84, 0.97]
2 Bacteriologic Cure	2	163	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.62, 1.17]
3 Sustained Cure (Combined symptomatic and bacteriologic cure)	1	172	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.68, 0.99]
3.1 Mild disease	1	90	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.71, 1.09]
3.2 Severe disease	1	82	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.52, 1.04]

Metro vs. Vanco…

- Retrospective, propensity-matched cohort study evaluated 47 471 CDI patients in the US Department of Veterans Affairs health care system from Jan 1, 2005- Dec 31, 2012
- All-cause 30-day mortality:
  - Any severity: Vancomycin (vs. metro) less likely to die
    - adjusted relative risk, 0.86; 95% CI, 0.74 to 0.98
    - adjusted risk difference, –0.02; 95% CI, –0.03 to –0.01
  - Severe CDI: Vancomycin (vs. metro) reduced the risk
    - adjusted relative risk, 0.79; 95% CI, 0.65 to 0.97
    - adjusted risk difference, –0.04; 95% CI, –0.07 to –0.01

Fidaxomicin



- MOA: Macrocyclic antibiotic. Narrow spectrum of activity, minimal systemic absorption.
- Outcomes: 2 DB RCTs have shown fidaxomicin to be non-inferior to vancomycin for CDI end of treatment clinical cure
  - Fidaxomicin had less CDI recurrence than vancomycin 28 days post treatment for non-NAP1/027 (less virulent) strains when studied in 1st or 2nd case
- Dose: 200 mg PO BID x 10 days (~$2000 CAD)
- AE: hypersensitivity, constipation (1.2%), nausea (2.7%), rash (2.8%), vomiting (1.2%)

N Engl J Med 2011;364:422-31
Lancet Infect Dis 2012;12281-9

Fidaxomicin

- Post hoc subgroup analyses of 2 phase 3 trials compared fidaxomicin to vancomycin in groups at high risk for CDI recurrence
  - Taking concomitant antibiotics while being treated for CDI (27.5% on concomitant antibiotic)
    - Cure rate with fidaxomicin was 90% compared to 79.4% with vancomycin (p=0.04)
  - Patients with cancer (10.6% had cancer)
    - Cure was more likely with fidaxomicin (OR 2, p=0.065) and recurrence was less likely (OR 0.37, p=0.018)
- High quality randomized controlled trials are required to assess the efficacy for these indications

Clin Infect Dis 2011;53(5):440-7.
J Clin Oncol 2013;31(19):2493-9.

Fidaxomicin

Current central zone restrictions…

- On the recommendation of the Division of Infectious Diseases for:
  - *C. difficile* infections that have failed therapy with metronidazole and vancomycin
  - Patients with a documented allergy to vancomycin
  - Patients with a documented severe adverse drug reaction to vancomycin

- **Fact or Fiction? Fidaxomicin is superior to vancomycin for clinical cure in the treatment of fulminant CDI.**
- Fiction
- Not studied in this population as they were excluded from fidaxomicin trials
- Case report of fistula topical use post colectomy

Int J Surg Case Rep. 2018;42:79-81.

Case: HW

- **What are your recommendations for HW?**
  - Metronidazole 500 mg po q8h x 10 days **X**
  - Vancomycin 125 mg po QID x 10 days
- **What are ALL of your recommendations for HW?**
  - Reassess need for continued ciprofloxacin
  - Reassess PPI (no indication)
  - Replacement of fluid and electrolytes prn
  - Avoidance of anti-motility medications
  - Vancomycin 125 mg po QID x 10 days
- **Outline your monitoring plan for HW.**

Duration

- Majority of RCT data for CDI use **10-day** regimens
  - Some have delayed response to treatment, particularly those treated with metronidazole
  - If improved, but have not had symptom resolution by 10 days, extension to 14 days should be considered

Monitoring

Efficacy	Desired change	Who	When	Comments
Vital signs: T, HR, BP, RR	Normal	RN	Daily	
Diarrhea episodes	Unformed stool < 3 /day	RN, RX, MD	Daily (more often if severe complicated)	Clinical response expected in 3-5 days (closer to 5 if on metronidazole) Should decrease to <3 per day for at least 2 days by the end of therapy.
Abdo pain	Resolved	RN, RX, MD	Daily	
Fever	T < 38	RN, RX, MD	Daily	
WBC/Neut	< 11	RX, MD	2X/week (more often if severe complicated)	Measure if in hospital. May take 7-10 days to normalize.
Lytes, SCR			2X/ week	Measure if in hospital
Note: Test of cure has limited value				

Monitoring

Toxicity (Vancomycin PO)	Undesired change	Who	When
Chills, drug fever	Presence	RN, RX, MD	Daily
Bitter taste, stomatitis	Presence	RN, RX, MD	Daily
Nausea/vomiting/diarrhea	Presence	RN, RX, MD	Daily
Rash	Presence	RN, RX, MD	Daily
Eosinophilia/neutropenia/ thrombocytopenia	Presence	RN, RX, MD	1-2X/ week if in hospital

Case: HW

- HW's diarrhea resolves and she is discharged without complications.
- However, 4 weeks after completing your suggested treatment, she presents to the ED with abdominal pain, weakness, and nausea.
- HW reports 5 BM/day for the last 4 days. On admission her WBC is 40.4 and SCR is 140 .

Case: HW

- **What is HW's current DTP (include CDI severity category)?**
- HW has **severe, first recurrence of,** CDI and requires antimicrobial therapy.
- **What do you recommend for HW?**
- Vancomycin 125 mg po QID X 10 days **X**

Recurrent CDI

- First recurrence:
  - If metronidazole was used for initial episode:
    - Vancomycin 125 mg po QID x 10 days
  - If vancomycin was used for initial episode:
    - Vancomycin PO tapered and pulsed regimen (125 mg QID X 10–14 days, BID X 1 week, daily X 1 week, then every 2 or 3 days for 2–8 weeks) OR
    - Fidaxomicin 200 mg po BID x 10 days
- Second or subsequent recurrence:
  - Vancomycin PO tapered and pulsed regimen OR
  - Vancomycin 125 mg po QID x 10 days followed by rifaximin 400 mg po TID X 20 days OR
  - Fidaxomicin 200 mg po BID x 10 days OR
  - Fecal microbiota transplantation

Recurrent CDI

Table 1. Recommendations for the Treatment of *Clostridium difficile* Infection in Adults

Clinical Definition	Supportive Clinical Data	Recommended Treatment[a]	Strength of Recommendation/ Quality of Evidence
First recurrence	…	• VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR	Weak/Low
		• Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (eg, 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks), OR	Weak/Low
		• FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode	Weak/Moderate
Second or subsequent recurrence	…	• VAN in a tapered and pulsed regimen, OR	Weak/Low
		• VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR	Weak/Low
		• FDX 200 mg given twice daily for 10 days, OR	Weak/Low
		• Fecal microbiota transplantation[c]	Strong/Moderate

- **Fact or Fiction? Fidaxomicin is superior to vancomycin for clinical cure in the treatment of those with multiple recurrences (>1) of CDI**.
- Fiction:
- Frist recurrence:
  - Vancomycin and fidaxomicin are equally effective in resolving CDI symptoms
  - But fidaxomicin has been shown to be associated with a lower likelihood of CDI recurrence after a first recurrence
- Multiple recurrences:
  - Uncontrolled, post-approval experience suggests less efficacious for cure and subsequent recurrence, particularly ≥2 recurrences

Clin Infect Dis 2012; 55 (suppl 2): S132–S142
Clin Infect Dis 2012; 55 (suppl 2): S154–S161
J Clin Gastroenterol 2016. doi:10.1097

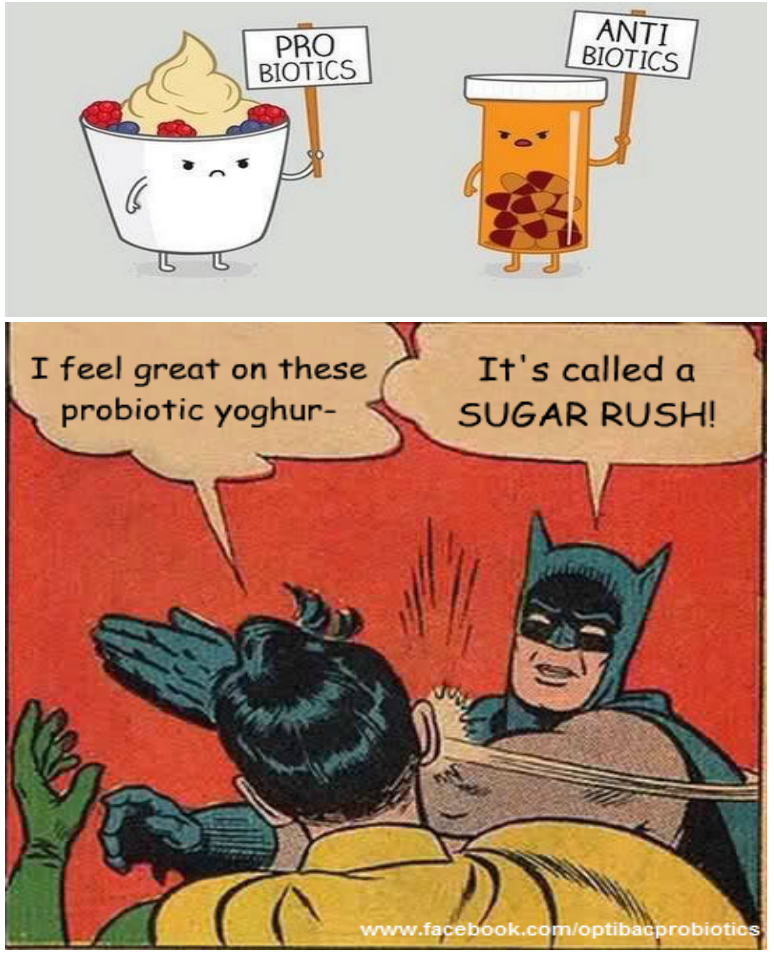
Fecal Microbiota Transplantation

- Recommended for those with multiple recurrences who fail antibiotic treatments
- Donor: screen for transmissible agents
- RCT stopped after interim analysis
  - 81% had resolution of CDAD vs. 31% receiving vancomycin vs. 23% receiving vancomycin with bowel lavage (p<0.001-for both comparisons)
- Systematic review of RCTs, case series and case reports
  - Across all studies for recurrent CDI, symptom resolution in ~ 85% of cases
  - FMT may have a substantial effect with few short-term adverse events for recurrent CDI

Ann Intern Med. 2015 May 5;162(9):630-8
N Engl J Med 2013;368:407-15
2017 IDSA CDI Guidelines

Probiotics

- Guidelines do <u>not</u> recommend for prophylaxis or treatment
- Meta analysis limitations:
  - Variability of probiotic regimens
  - Missing data
- PLACIDE:
  - Recent large RCT (2941 inpatients) in those > 65 found no evidence that mulitstrain probiotic (*Lactobacilli* and *Bifidobacteria)* prevented AAD or CDAD



Case

- **What is HW's current DTP (include CDI severity category)?**
- HW has **severe, first recurrence of,** CDI and requires antimicrobial therapy.
- **What do you recommend for HW?**
- Vancomycin 125 mg po QID X 10 days **X**
- Vancomycin PO tapered and pulsed regimen
  - 125 mg QID X 10–14 days, BID X 1 week, daily X 1 week, then every 2 or 3 days for 2–8 weeks

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Questions