

Management of Recurrent *C. difficile* Infections

Wayne Ghesquiere MD, FRCP(C)
Infectious Diseases & Internal Medicine
Victoria, BC





ILLITERATE?

WRITE FOR FREE HELP.

ILLITERACY FOUNDATION
806 MAIN STREET

LATTAR



IHA Expectations of Hospitalist Staff



Disclosure Statement

Dr Ghesquiere has received honorarium payments from the following sponsors in the past;

- ▶ **Presentations for CHE and/or research from Abbott, Gilead, GSK, Merck, Pfizer, Roche, Sanofi-Pasteur.**
- 

Disclosure of Commercial Support

- ▶ This program has received financial support from the **Victoria Division of Family Practice** in the form of **operating budget**.
- ▶ This program has received in-kind support from **Island Health and the Island Medical Program** in the form of **meeting support**.
- ▶ **Potential for conflict(s) of interest:**
 - Dr Wayne Ghesquiere has no conflict of interest

Mitigating Potential Bias

- ▶ **Bias has been mitigated by using evidence based medicine**
- 


Objectives

1. Review management of C. diff infection
2. Epidemiology
3. What to do about recurrent infection

Objectives

1. Review management of C. diff infection in the LTC patient
2. Epidemiology
3. What to do about recurrent infection

Common Questions


- 1. How to interpret the lab results?**
 - 2. How to treat the first and recurrent episodes?**
 - 3. What are the signs of severe CDI?**
- 

“Where’s the Beef?”

Summary: Take Home Points

- 1. If the infection is mild to moderate treat the first episode and 1st relapse with Metronidazole 500mg tid X 14 days.**
- 2. Treat the second relapse with Vancomycin 125 mg qid X 14 days**
- 3. Treat the third relapse with tapering regimen of Vancomycin over 6 weeks**
- 4. In older patients i.e. those >65 years or patients with severe C.diff start with Vancomycin 125 mgs qid X 14 days**

Summary: Take Home Points

- 5. Recurrent diarrhea may be due to other causes i.e. Post Infectious IBS or IBD**
 - 6. Do not do a test of cure for C. diff.**
 - 7. Probiotics benefit is questionable.**
 - 8. Wash your hands.**
- 

Guidelines



Infection Control

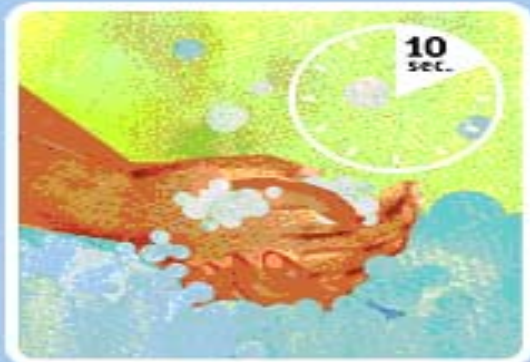
Black

White

C. diff prevention



Healthy Handwashing



1 Wash with soap and water for 10 seconds.



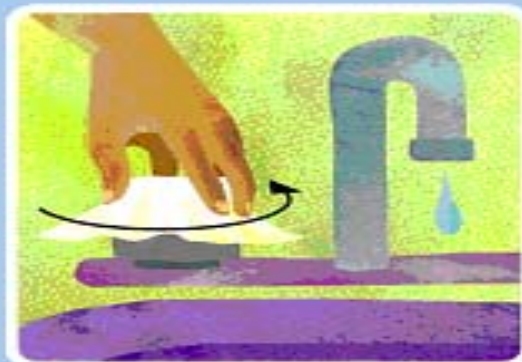
2 Help children wash their hands.



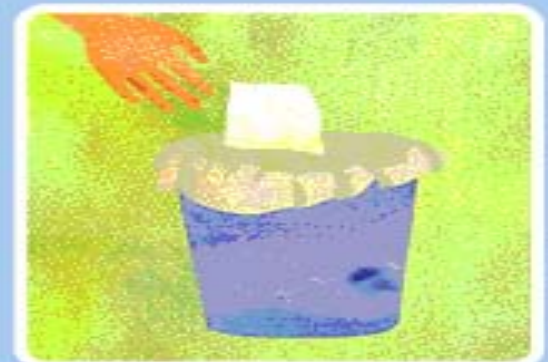
3 Rinse well.



4 Dry hands with a single-use towel.



5 Use towel to turn off water.



6 Place in a container lined with a plastic bag.

Contaminated Environment

Table 3. Environmental Isolation of *C. difficile*.

CULTURE SOURCE	ROOMS WITH CULTURE-NEGATIVE PATIENTS*	ROOMS WITH ASYMPTOMATIC CARRIERS	ROOMS WITH PATIENTS WITH <i>C. DIFFICILE</i> DIARRHEA	TOTAL POSITIVE/ TOTAL TESTED (%)
	<i>no. of positive cultures (%)</i>			
Bedrail	0	2	10	12/31 (39)
Commode	1	3	1	5/13 (38)
Floor	5	3	18	26/72 (36)
Call button	1	2	6	9/30 (30)
Windowsill	0	1	2	3/10 (30)
Toilet	0	0	3	3/17 (18)
Other†	0	0	4	4/43 (9)
Total positive cultures	7 (8)	11 (29)	44 (49)	62 (29)
No. of cultures	88	38	90	216


*Rooms in which no patients with positive cultures for *C. difficile* were in residence for >48 hours.

†Other sources include the dialysis machine (one), the sink (one), nasogastric alimentation preparation (one), and slipper bottoms (one).

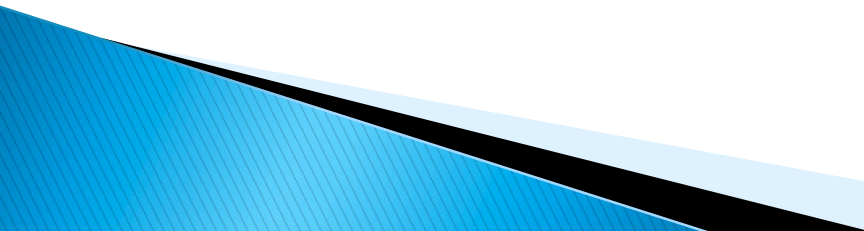
IT'S OKAY...
I'VE GOT DIARRHEA!



Case #1

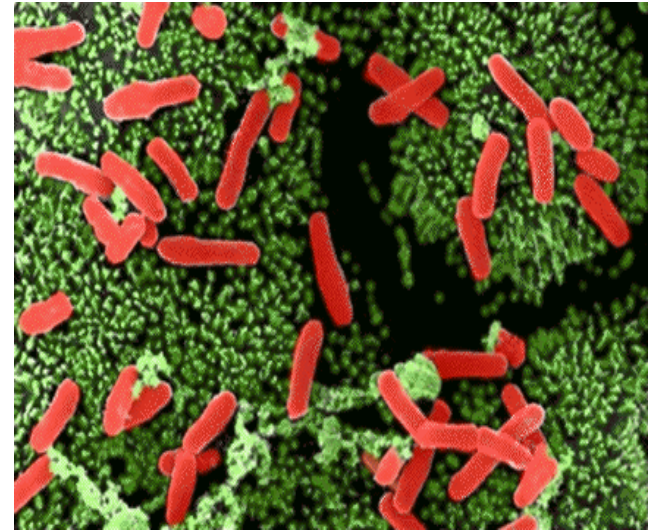
- ▶ 74 year female complains of diarrhea for 7 days after she finished antibiotic prescribed by her dentist for an infected tooth after a root canal
 - ▶ She has 15 watery “greenish” stools a day.
 - ▶ PMH: mild IBS
 - ▶ O/E: afebrile, BP 115/75, HR 85
 - ▶ Abd soft, minimal discomfort
- 

Case #1

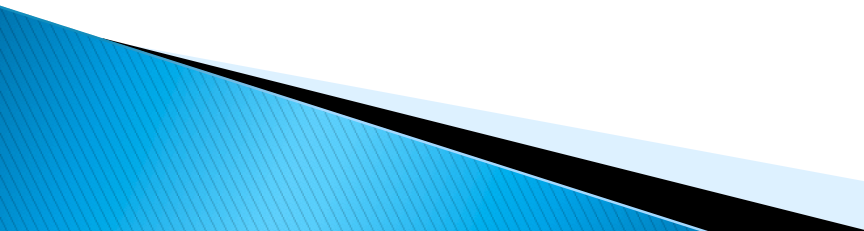
- ▶ Medications: none
 - ▶ No travel, pets, camping
 - ▶ Family members are well
 - ▶ Non-smoker, No illicit drug use
 - ▶ Has eaten out in restaurants with her family 1 week ago yet all other family members are well.
 - ▶ **Where should we go from here?**
- 

CDI Overview

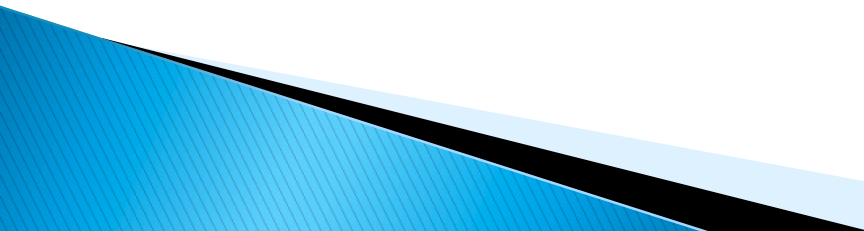
- ▶ Spore-forming, anaerobic, gram-positive bacterium
- ▶ Causes gastrointestinal infections resulting in diarrhea and colitis
 - Severity ranges from mild colitis to toxic megacolon and death
- ▶ Leading cause of healthcare-associated infectious diarrhea in US
- ▶ Rivals methicillin-resistant *Staphylococcus aureus* (MRSA) as the most common organism to cause healthcare-associated infections in US



CLOSTRIDIUM DIFFICILE

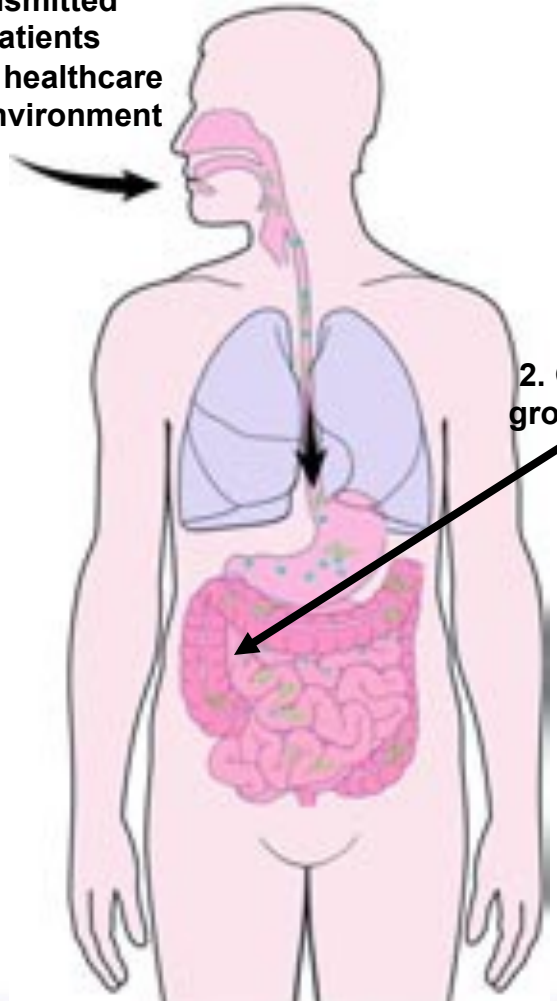
- Gram positive spore-forming anaerobic bacillus
 - spores are resistant to destruction by environmental influences (heat, desiccation) including many chemicals
 - colonizes up to 3-5% adult humans without causing symptoms
 - normal flora in children <1 year of age
- 

COLONIZATION

- asymptomatic colonization
 - 7-26% among adult patients in acute care facilities
 - 5-7% among elderly patients in LTCF
 - 20-50% in facilities where CDI is endemic
 - risk of colonization increases linearly with time
 - as high as 40% after 4 weeks of hospitalization
- 

Background: Pathogenesis of CDI

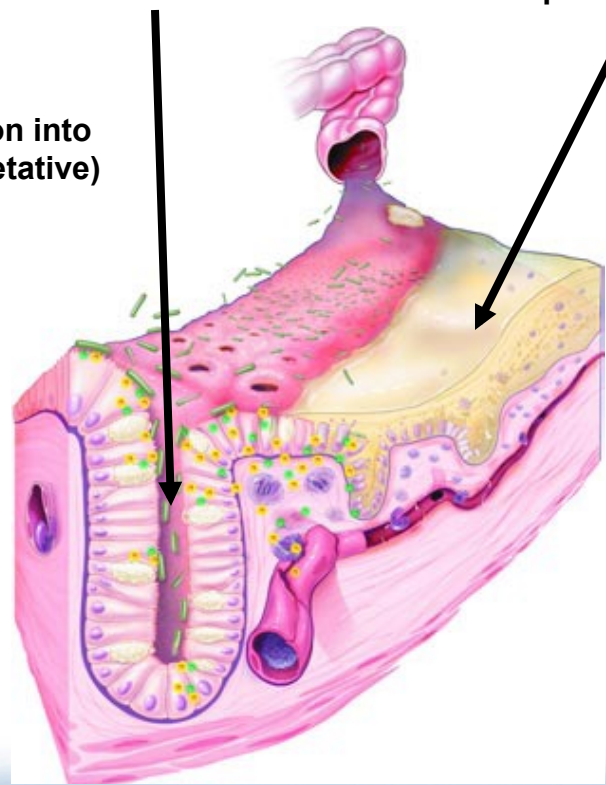
1. Ingestion of spores transmitted from other patients via the hands of healthcare personnel and environment



2. Germination into growing (vegetative) form

3. Altered lower intestine flora (due to antimicrobial use) allows proliferation of *C. difficile* in colon

4. Toxin A & B Production leads to colon damage +/- pseudomembrane



Sunenshine et al. Cleve Clin J Med. 2006;73:187-97.



- Disruption of normal enteric flora
- Acquisition of toxigenic *Clostridium difficile*

Patient

40%–60%

Protective factors:

- High serum antibody response to toxin A
- Mild underlying disease

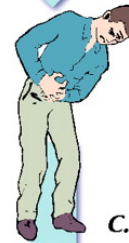
40%–60%

Risk factors:

- Low serum antibody response to toxin A
- Severe underlying disease



Asymptomatic
C. difficile colonization
(carrier state)



C. difficile diarrhea

Treatment

60%–95%

Additional protective factors:

- Age < 65 years
- No exposure to additional antibiotics

5%–40%

Additional risk factors:

- Age > 65 years
- Exposure to additional antibiotics



Low likelihood of
C. difficile diarrhea

- May act as reservoir for nosocomial spread of *C. difficile*



Decreased risk of
recurrent *C. difficile*
diarrhea after treatment

Increased risk of recurrent
C. difficile diarrhea after
treatment

- 50% due to reinfection
- 50% due to relapse



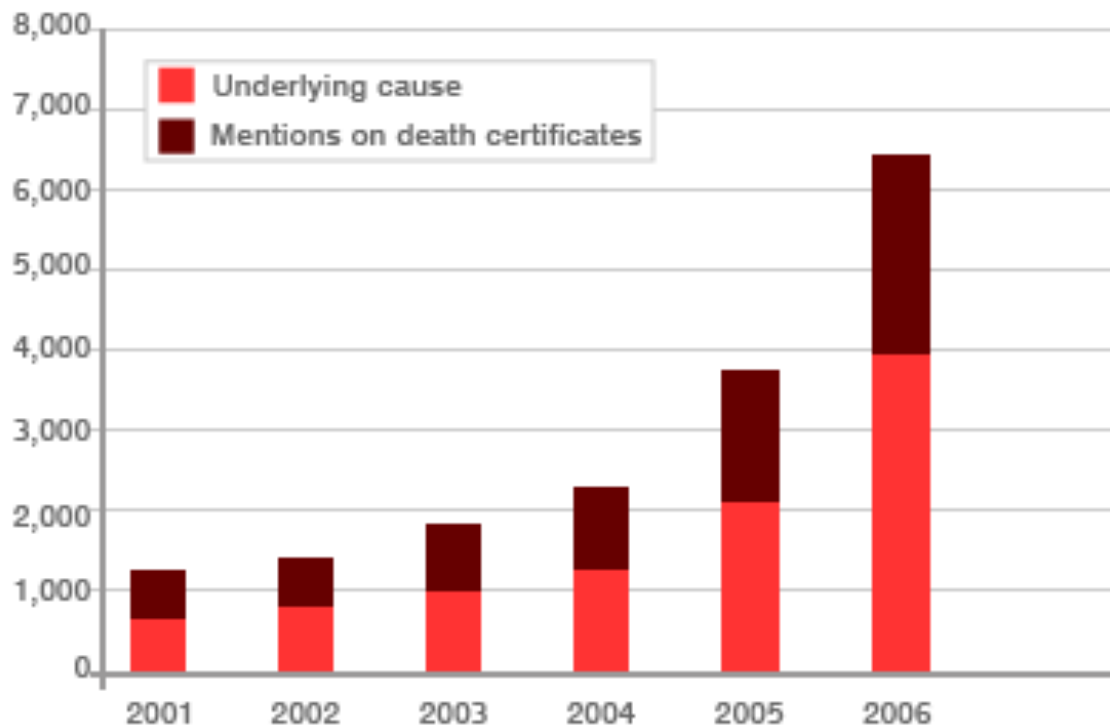
Features of *C. difficile* infection

- ▶ *Cd* frequently colonizes healthy newborns and adults who have been hospitalized
- ▶ Strains which cause disease express toxin A and/or toxin B
- ▶ Infection with toxigenic strain can produce:
 - no symptoms/no disease
 - mild watery diarrhea
 - colitis with or without pseudomembranes

CDAD is it becoming more frequent and severe?

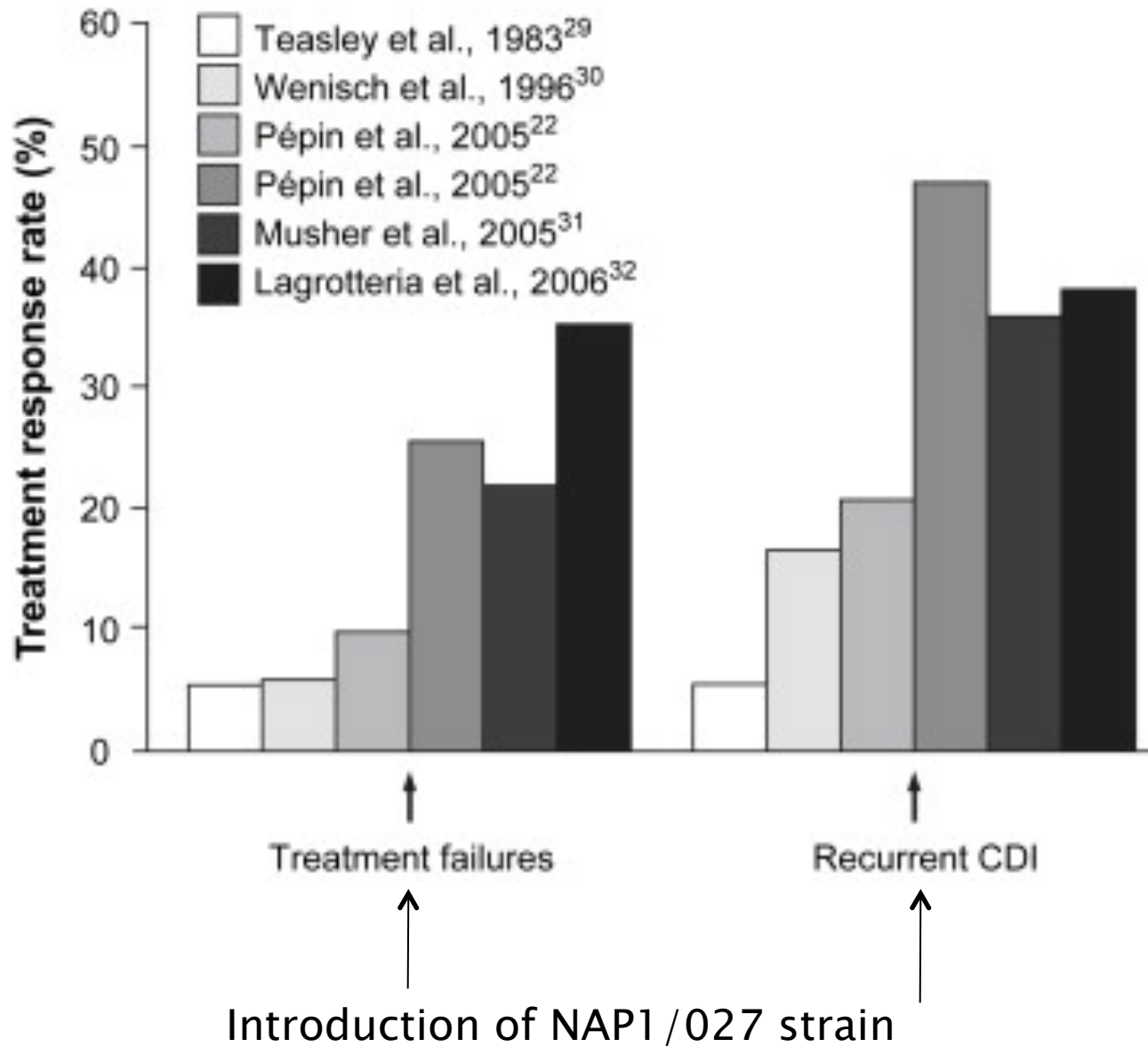
C. DIFFICILE DEATHS IN ENGLAND AND WALES

Number of deaths



SOURCE: ONS

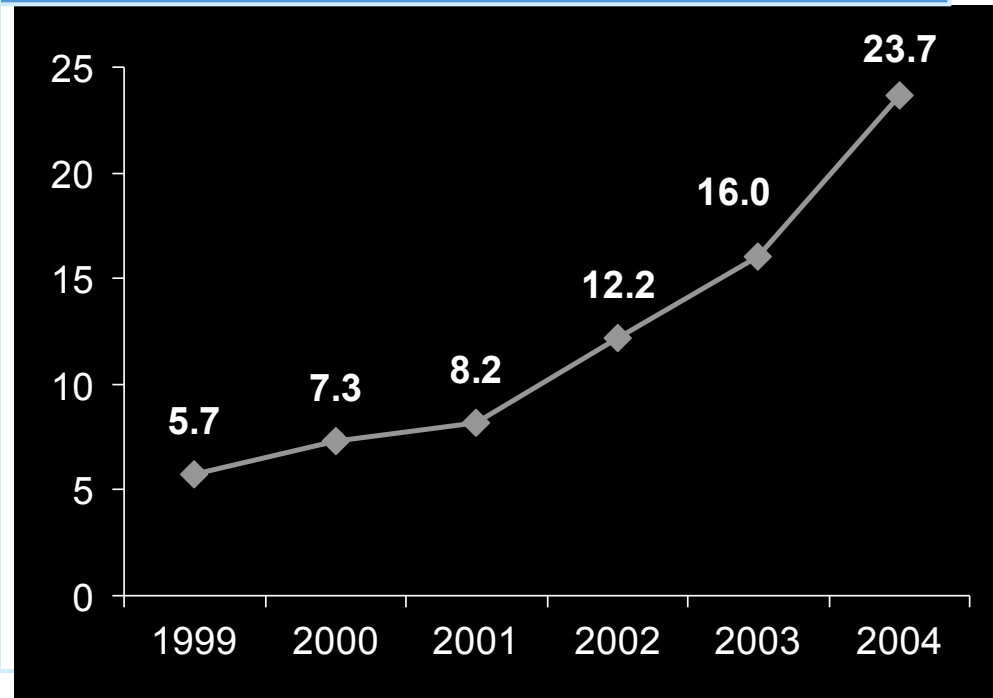
Source: BBC.co.uk Feb. 2008



Marked Increase in CDI Rates and CDI-Related Mortality

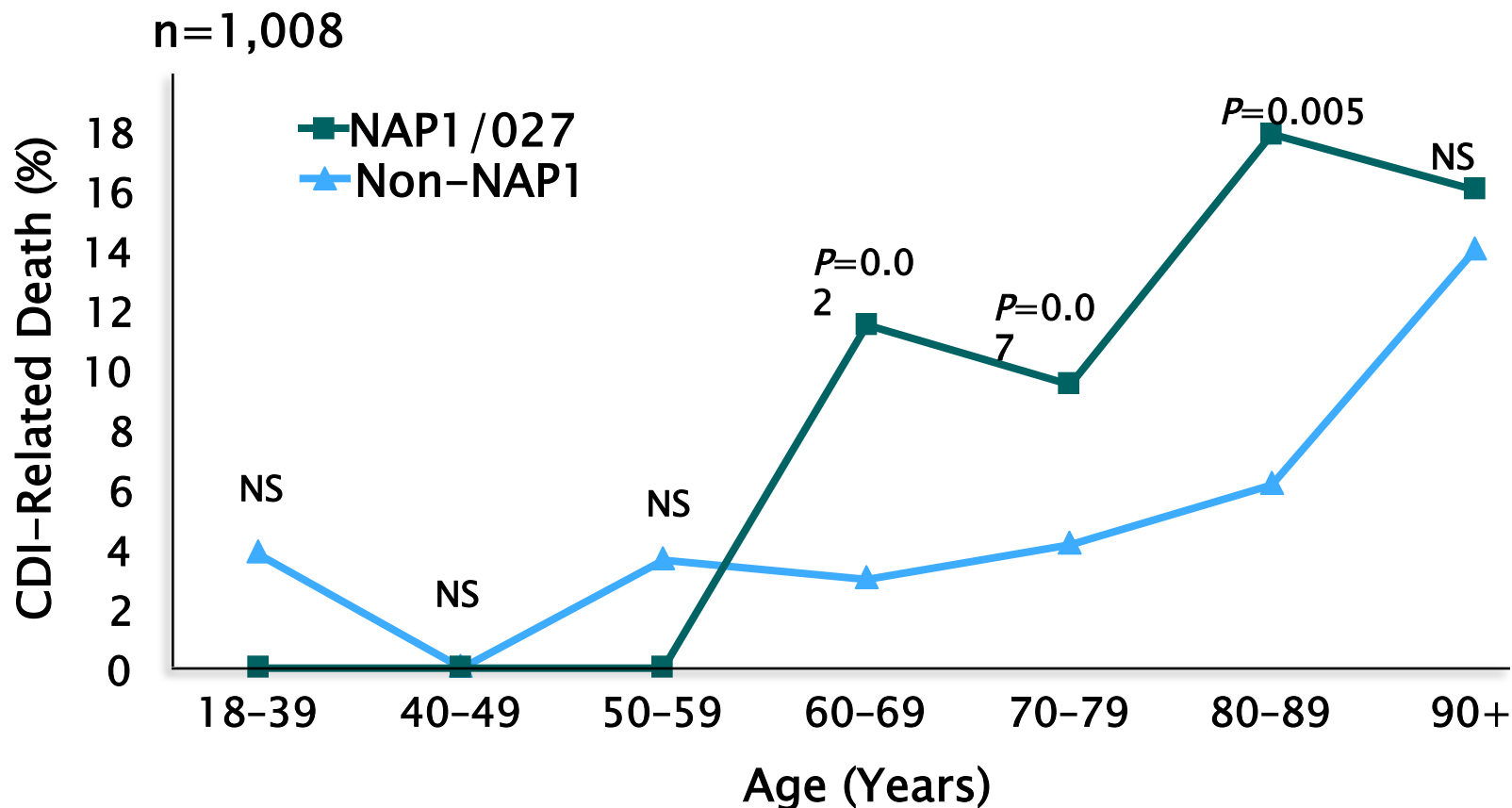
- New “hypervirulent” strain of *C difficile* (“NAP1/027/BI”) associated with higher CDI rates and severity¹
- Since 2003, CDI-related mortality rates as high as 14% have been seen in North America²
- A Canadian study confirmed the bulk of mortality occurred in adults >60 years of age, especially those infected with NAP1 strain⁴

CDI mortality rates per million US population³



1. Kuijper EJ, et al. *Clin Microbiol Infect.* 2006;12(suppl 6):2-18.
2. Pépin J, et al. *CMAJ.* 2004;171(5):466-472.
3. Redelings MD, et al. *Emerg Infect Dis.* 2007;13(9):1417-1419.
4. Miller M, et al. *Clin Infect Dis.* 2010;50(2):194-201.

Effect of Strain Type and Age on CDI-Related Death

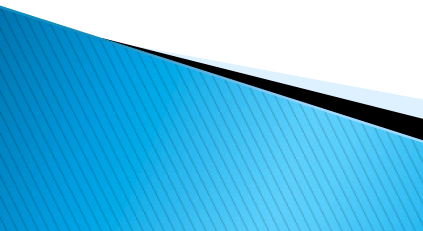


SEPTEMBER 12, 1994 \$3.50

TIME

REVENGE OF THE **Killer Microbes**

Are we losing the
war against
infectious diseases?



NAP1 /ribo027 strains in Fidaxomicin trial

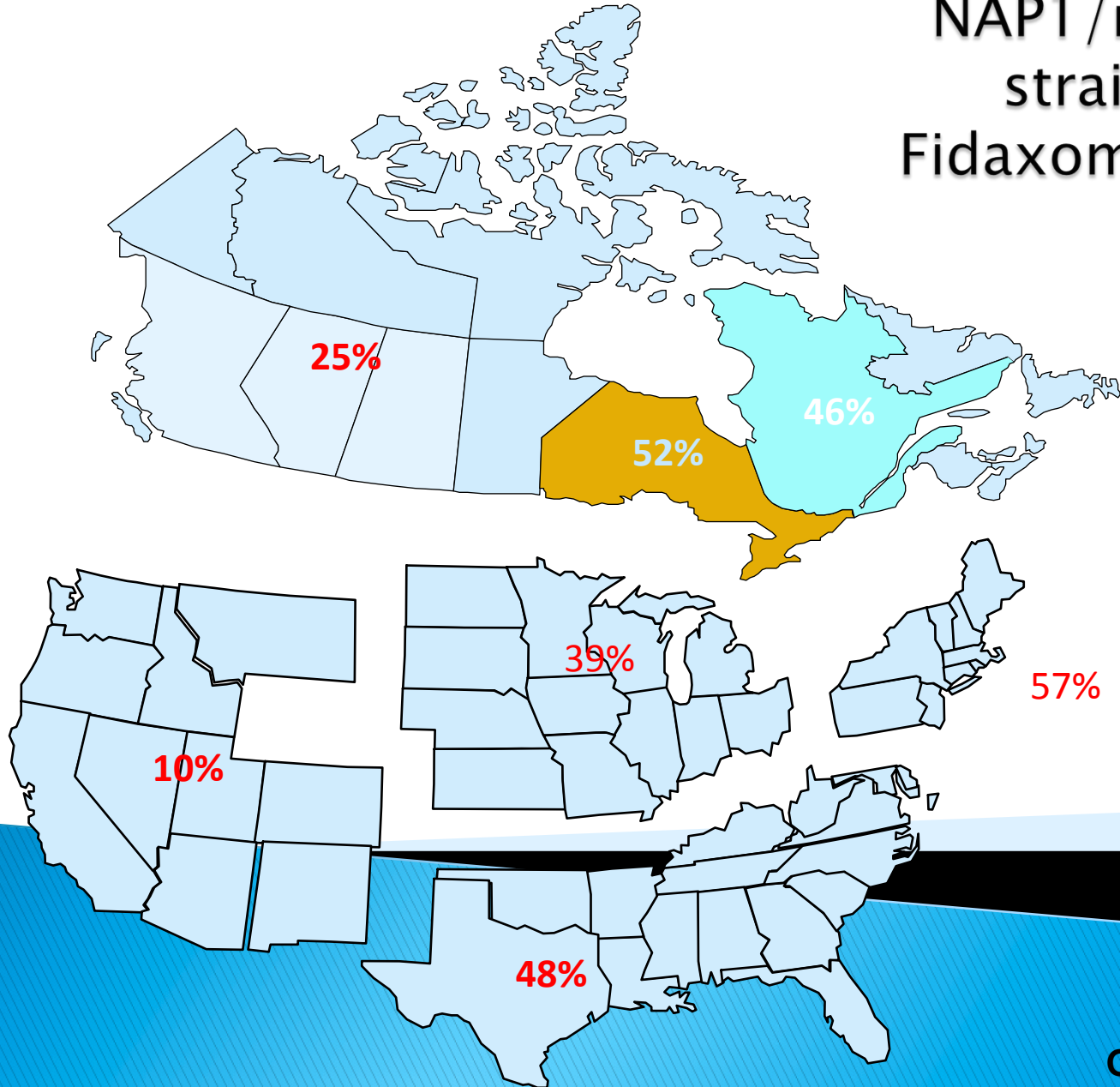
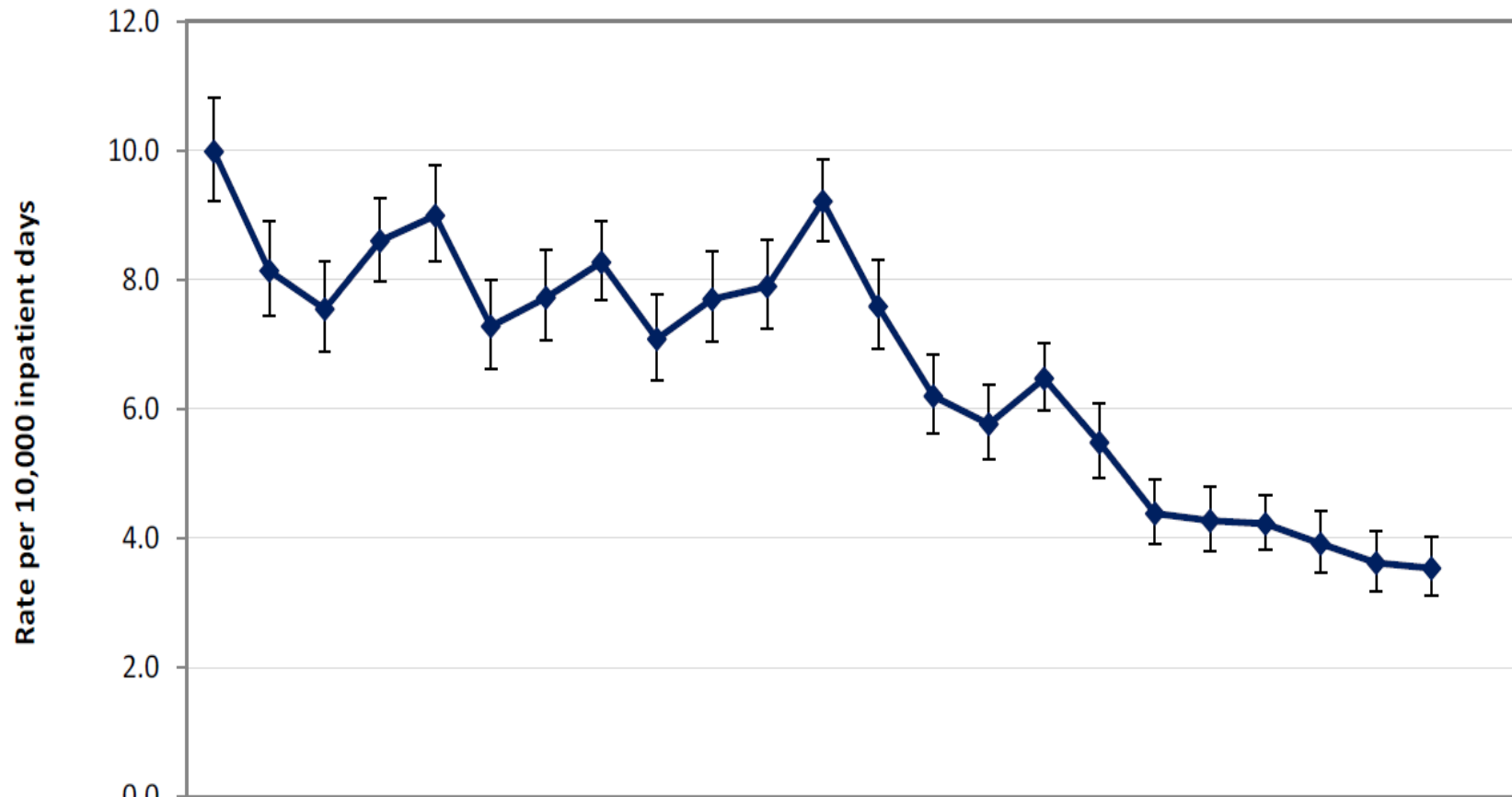


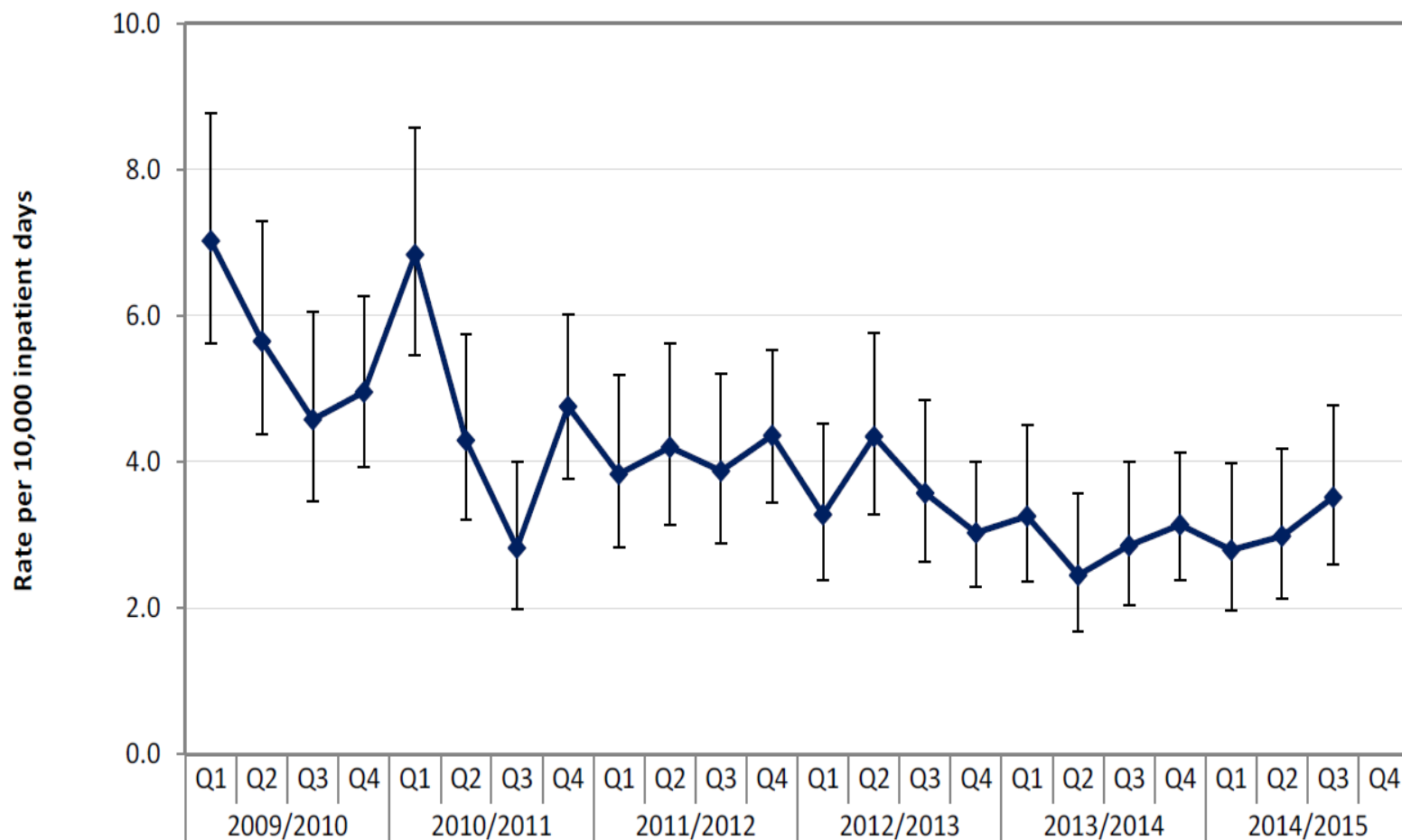
Figure 1. Number of new cases and rate of CDI associated with the reporting facility, by fiscal year and quarter, British Columbia¹



	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
	2009/2010				2010/2011				2011/2012				2012/2013				2013/2014				2014/2015			
◆ Rate per 10,000 inpatient days	10.	8.1	7.5	8.6	9.0	7.3	7.7	8.3	7.1	7.7	7.9	9.2	7.6	6.2	5.8	6.5	5.5	4.4	4.3	4.2	3.9	3.6	3.5	
Number of cases	611	476	450	673	557	438	473	684	431	464	509	808	480	390	377	588	351	285	286	389	254	236	238	

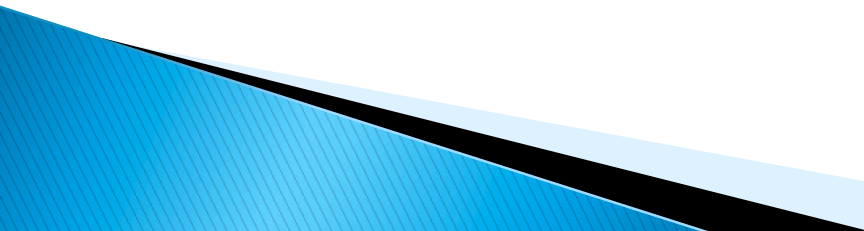
Fiscal year and quarter

Figure 5. Number of new cases and rate of CDI associated with the reporting facility, by fiscal year and quarter for Island Health⁴




Fiscal year and quarter

Risk factors for C. diff acquisition

- ▶ Antibiotic use
 - ▶ Hospitalization
 - ▶ Proximity to a patient with C. diff
 - ▶ Chemotherapy (esp. with doxorubicin, 5-FU, MTX, alkylating agents)
 - ▶ GI manipulation (surgery, enemas)
 - ▶ Severe underlying illness
- 

Diagnosis of CDAD

- ▶ **Toxin assay**
 - ▶ **Antigen detection**
 - ▶ **Culture**
 - ▶ **Endoscopy**
 - ▶ **CT**
- 

Utility of commonly used tests for CDAD

<u>Assay</u>	<u>Sensitivity</u>	<u>Specificity</u>	<u>PPV</u>	<u>NPV</u>
Cytotoxin	98	99	96	99
Immunocard Toxin A	54	99	94	84
Oxoid Toxin A	50	98	91	83
Techlab Toxin A/B	79	98	94	92
Premier Toxin A&B	80	98	94	93
Culture	57*	100*	100	85
Endoscopy [†]	51	100	100	ND

From: O'Conner D et al, J. Clin. Micro. 39(2001):2846

* For presence of organism

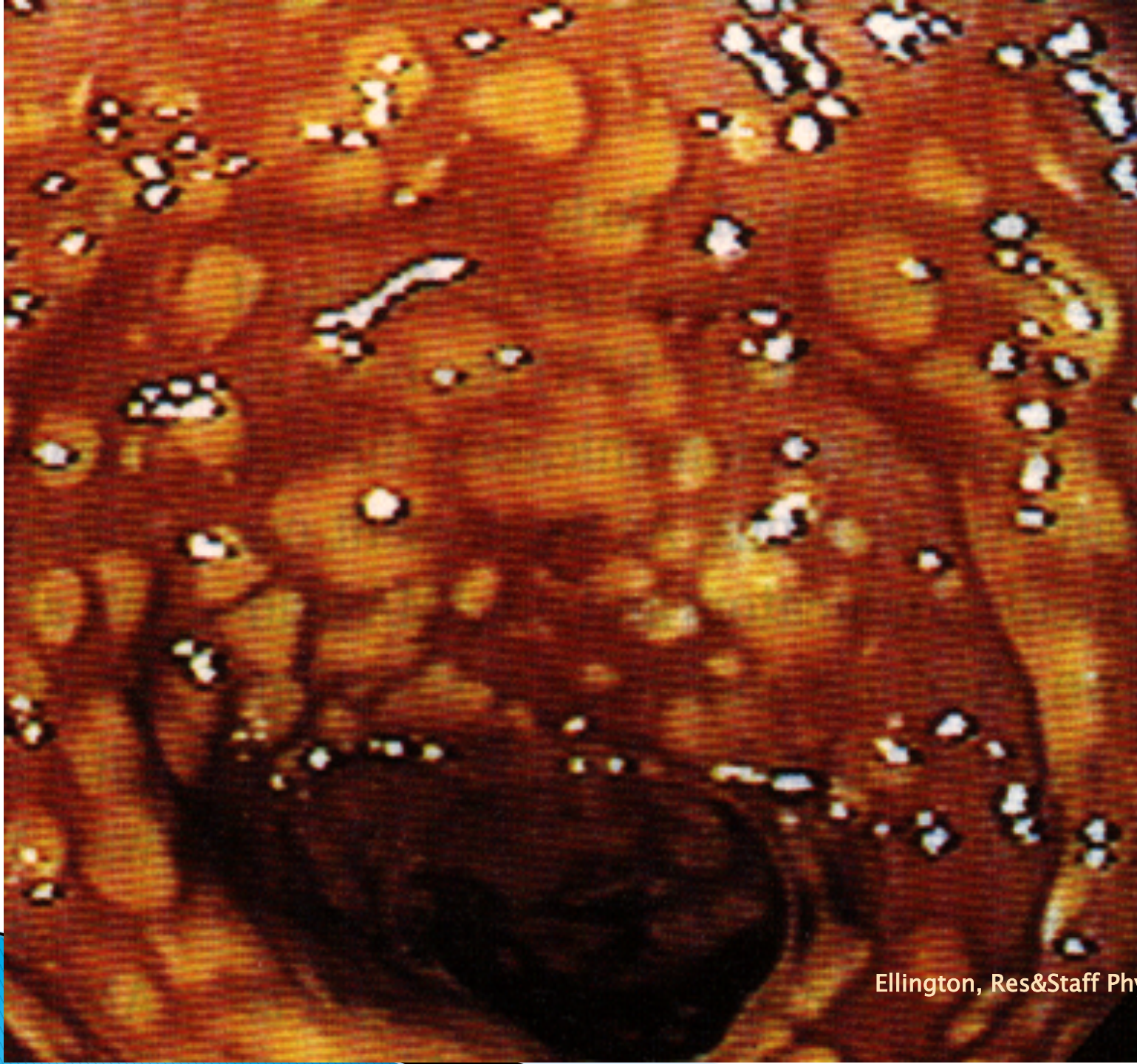
† From Thielman N, PPID, Ch. 84

Diagnostic tests:

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Toxin A/B EIA	73	98	73	98
Cell cytotoxicity assay	77	97	70	98
Real Time PCR*	93	97	73	98
Culture +toxin test*	100	96	68	100

* $p < 0.01$ -0.05 vs EIA

Peterson LR et al, CID 2007; 45:1152



Ellington, Res&Staff Phys, '99.

**Using a dog's superior olfactory sensitivity
to identify Clostridium difficile in stools and
patients: proof of principle study
(BMJ 2012; 345 -13 December 2012)**

- ▶ Conclusion A trained dog was able to detect C difficile with high estimated sensitivity and specificity, both in stool samples and in hospital patients infected with C difficile.



Case 1... continued

Stool results demonstrate

- ▶ **Clostridium diff antigen assay Positive**
- ▶ **Toxin A & B Assay Positive**

Treatment on *Clostridium difficile* Associated Diarrhea (CDAD)

1. Discontinue the inciting antibiotic as soon as possible.
2. Implement contact precautions.

Initial episode

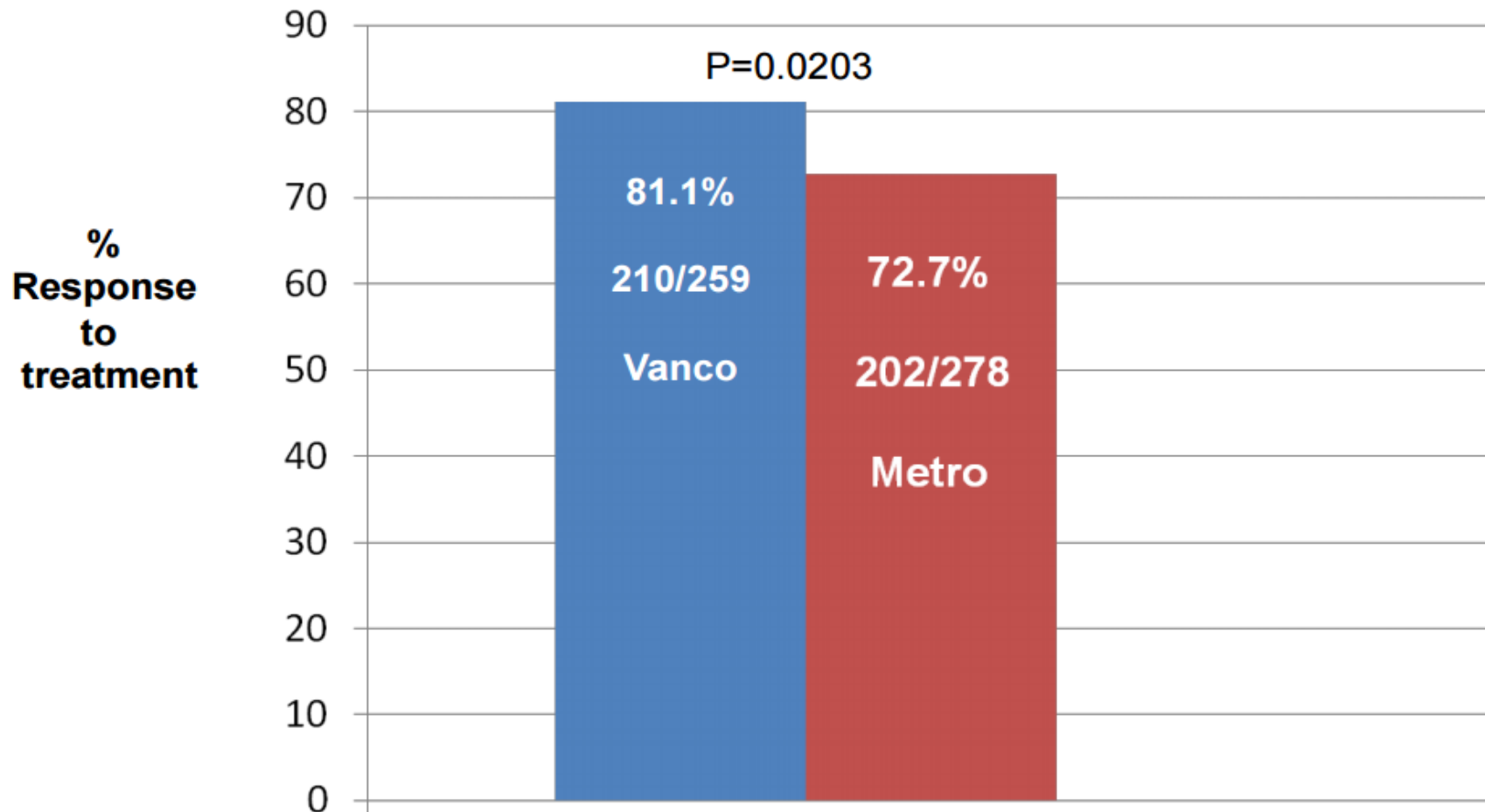
Preferred: metronidazole 500 mg po TID
or 250 mg po QID for 10–14 days.

Alternative if intolerant to metronidazole :
vancomycin 125 mg po QID for 10 – 14 days.



Comparison of metronidazole vs vancomycin in 2 trials

[Genzyme 301 and 302) S.Johnson et al, IDSA, San Diego, Oct 19, 2012



Is CDI primarily a hospital disease?: clearly not.


Zilberberg, Tabak, Sievert et al, K-1906, icaac 2009

Hospital Onset, after 48 hr admission.	50.4%
Community onset, Hospital Associated (within 4 wk of hospital discharge)	17.4%
Community Onset, indeterminate (onset >4–12 wk post discharge)	9.0%
Community onset no hospital association	23.2%

- ▶ 88 hosp database
- ▶ 1, 397,000 patients
- ▶ 10, 170 CDI cases (non-recurrent) = 0.73%
- ▶ Hosp Onset (HO) = 6.3 per 10,000 patient days
- ▶ 1 / 3 of CDI is not

Also : Campbell et al, ICHE 2009; 30:526. [30% recurrent disease burden]

Case #1

- ▶ Patient returns 3 weeks later
 - ▶ She took the metronidazole for 2 weeks.
 - ▶ She improved but symptoms reoccurred with 12 watery stools a day
 - ▶ Now what?
- 

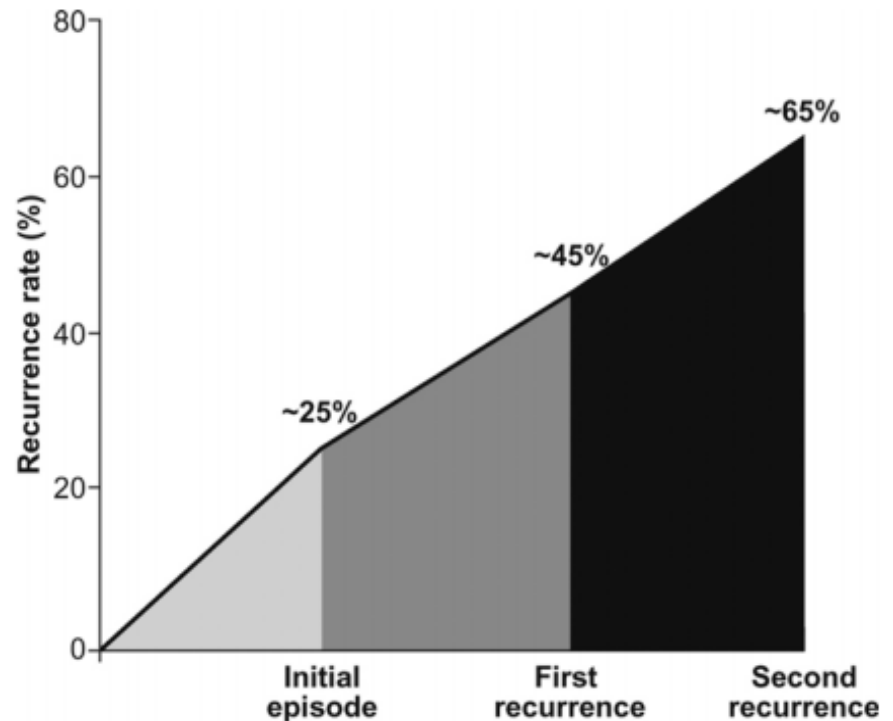
What about recurrent C. diff?



"Diarrhea Hotline... your call is important to us... please hold..."

Frequency of CDI Recurrence

- Up to 25% within 30 days after treatment with metronidazole or vancomycin
- Rate doubles after ≥ 2 or more recurrences

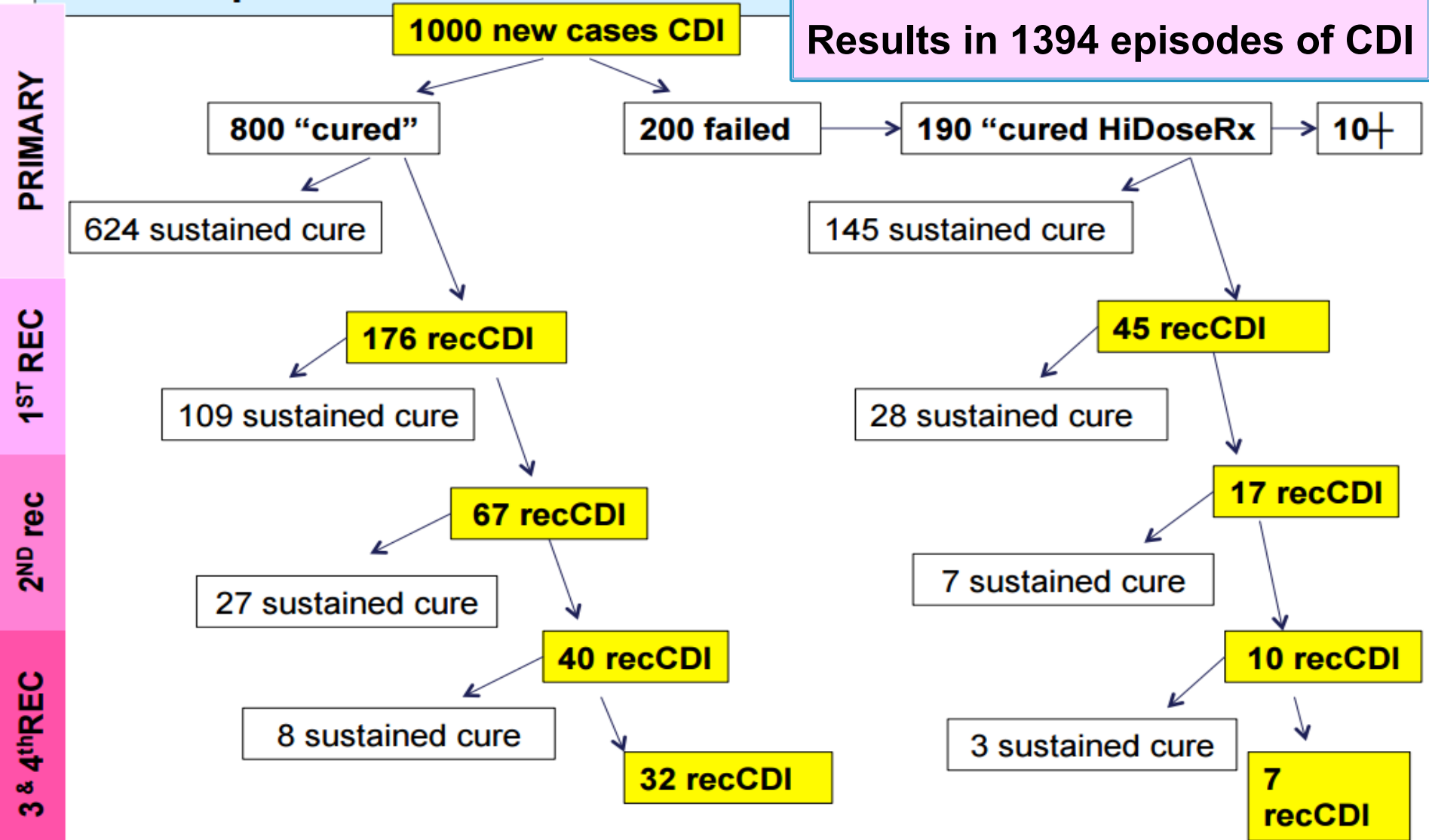


Sources:

Kelly C et al., Clin Micro Infect. 2012; 18 (Suppl 6), 21-27

McFarland LV et al. Am J Gastroenterol. 2002; 97: 1669

Treatment of 1000 cases of Clostridium difficile infection with metronidazole or vancomycin: effect of cumulative response patterns on total episodes of disease



Some current drugs for *C. difficile*

Drug	Dosage	Advantages	Disadvantages
Vancomycin	125 mg p.o QID	No drug is superior; likely best drug for severe disease	Cost
Metronidazole	500 mg p.o. TID	Cost	Higher failure rate than Vancomycin; equally prone to causing VRE
Rifaximin	200 mg p.o. TID	Nonabsorbable; may be beneficial in controlling relapses (“chaser”)	Small studies; evolving resistance in monotherapy
Nitazoxanide	500 mg p.o. BID	Noninferior to MTZ and Vancomycin	Only small data sets so far
Fusidic acid	250 mg p.o TID	Noninferior to MTZ in 1 trial	Minimal data; rapid resistance

Treatment of non-severe *Clostridium difficile* Associated Diarrhea

First relapse

Confirm diagnosis. Often patients will have a post inflammatory irritable bowel which presents as persistent diarrhea despite eradication of the infection.

Repeat treatment as follows:

Preferred: metronidazole 500 mg po TID or 250 mg po QID for 14 days +/- probiotics (see below)

Alternative if intolerant to metronidazole (see below for definition of intolerance): vancomycin 125 mg po QID for 14 days.



Intolerance to metronidazole is defined as follows:

ADVERSE REACTIONS SIGNIFICANT

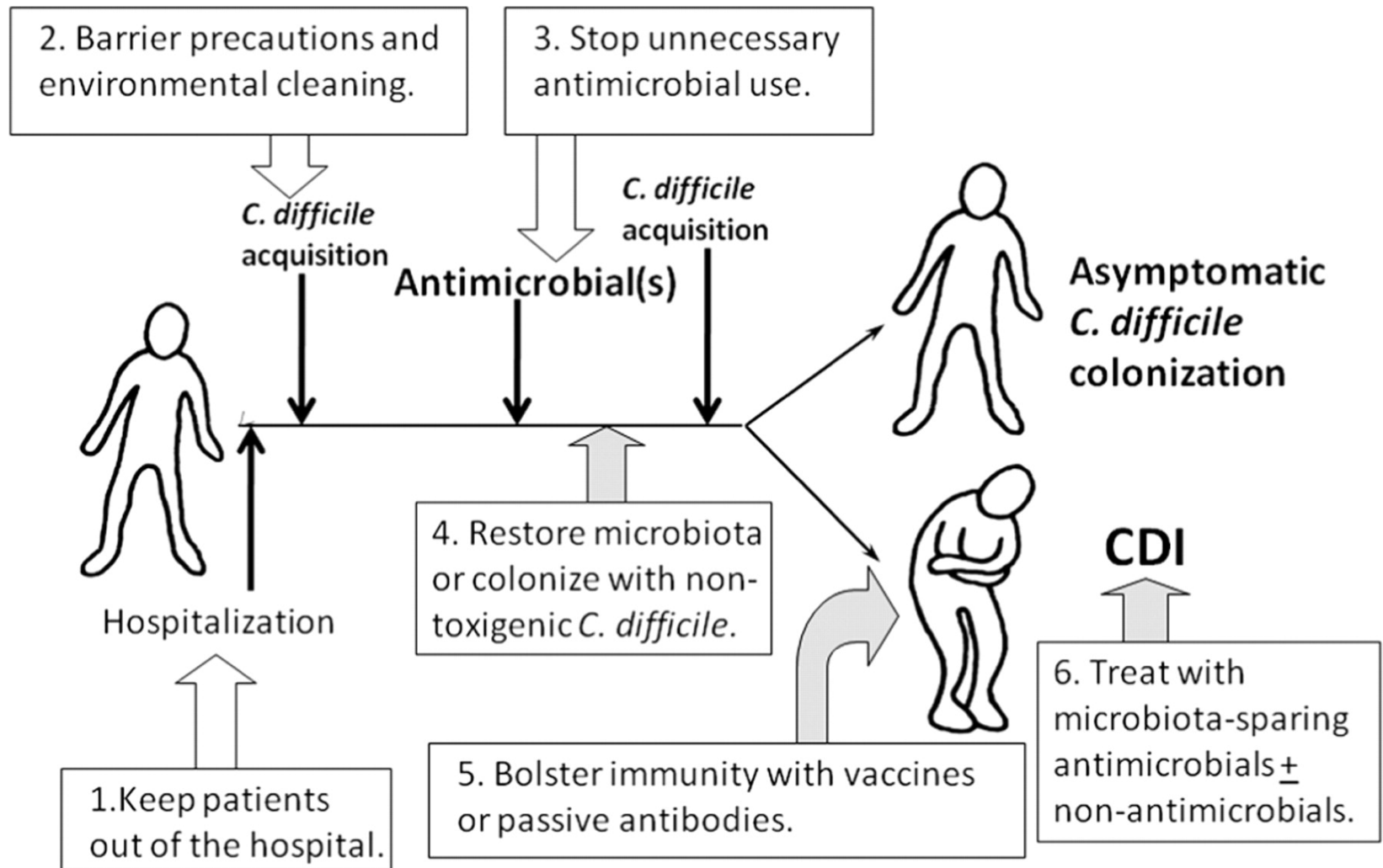
Central nervous system: Ataxia, confusion, coordination impaired, dizziness, fever, headache, insomnia, irritability, seizure, vertigo

Dermatologic: Erythematous rash, urticaria

Endocrine & metabolic: Disulfiram-like reaction

Neuromuscular & skeletal: Peripheral neuropathy, weakness

Schematic of current hospital epidemiology and management strategies to prevent and treat *Clostridium difficile* infection (CDI).



Gerding D N , and Johnson S Clin Infect Dis. 2010;51:1306-1313

Treatment of non-severe *Clostridium difficile* Associated Diarrhea

Second relapse

Confirm diagnosis.

Vancomycin 125 mg po QID for 14 days +/- probiotics (see below)

Third /subsequent relapses

Confirm Diagnosis

Tapering and pulsed oral vancomycin:

- 125 mg po four times daily for 14 days
- 125 mg po twice daily for 7 days
- 125 mg po once daily for 7days
- 125 mg po every other day for 7 days
- 125 mg po every 3 days for 7 days



What about Probiotics Use

A three week course of probiotics (eg, **Saccharomyces boulardii 500 mg orally twice daily**) may be used. The probiotics may be overlapped with the final week of the treatment and continued for two additional weeks in the absence of antibiotics.



Cost: \$11/100 caps (10^9 cfu/pill)
Cost for 30 day treatment: \$99


Probiotics for CDAD

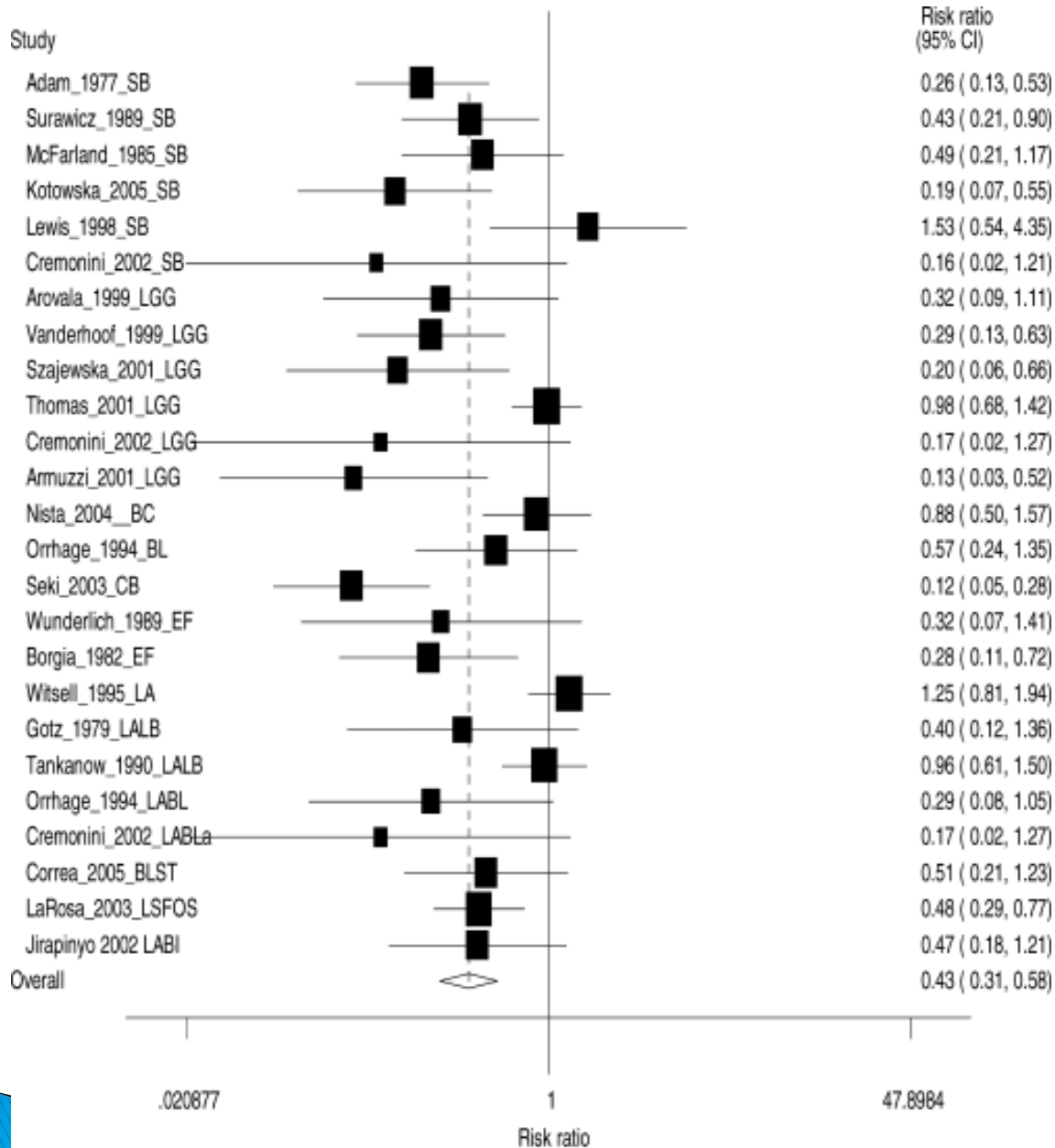
- ▶ Rationale: replete the gut with “good flora” to prevent growth of *C. difficile* spores or to protect the intestinal epithelium
- ▶ Examples:
 - Yeasts
 - lactose-fermenting bacteria

Probiotics

- ▶ Not recommended (C-III)
- ▶ Based on limited data and risk of bloodstream infection.

Saccharomyces boulardii

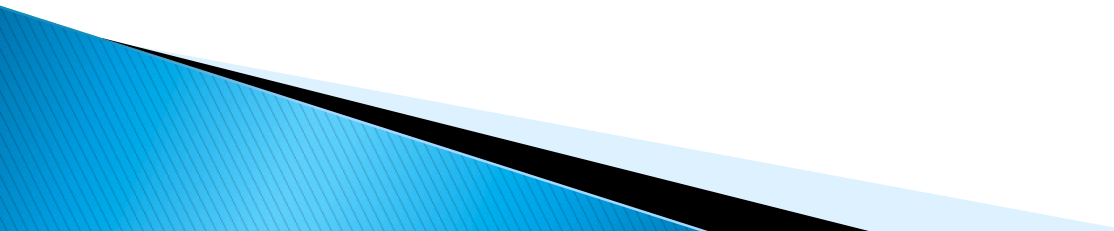
- ▶ A nonpathogenic yeast
 - ▶ First isolated from Lychee fruit in 1920s
 - ▶ Grows at 37 °C
 - ▶ Used as “holistic” antidiarrheal agent
 - ▶ Reduces diarrhea in tube-fed ICU patients
 - ▶ Beneficial in small trials in Crohn’s DZ and traveler’s diarrhea prevention
- 




Meta-analysis of probiotics for prevention of antibiotic-associated diarrhea

McFarland L,
Am. J. Gastro.
2006, 101:812

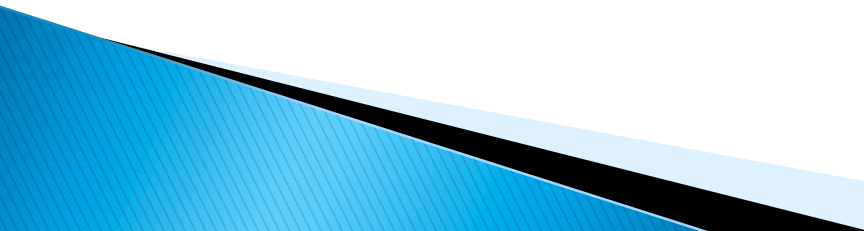
Not all Probiotics are Effective



Additional Clinical Pearls

- ▶ **Do not do a test of cure.**
 - ▶ **Often the organism is still present**
 - ▶ **Avoid dairy and wheat products for 1-2 months to help settle symptoms**
 - ▶ **Avoid “bowel stoppers”**
- 

Case 1... continued

- ▶ Six weeks later you are call that the patient has loose stools 2-3 a day
 - ▶ Stool results now demonstrate
 - ▶ Antigen **Negative**
 - ▶ Toxin assay **Negative**
 - ▶ Culture **Positive** for C diff
- 

**STONED BIDGE
CHURCH OF GOD**

**HONK IF YOU LOVE
JESUS TEXT
WHILE DRIVING IF YOU
WANT TO MEET HIM**

**SUN. SCHOOL
10:00 AM**

**SUN. WORSHIP
11:00 AM & 6:00 PM**

**WED.
7:00 PM**

Pastor Floyd Ingram

Case #2

78 year old woman

- ▶ cc: 3 day history watery diarrhea >10 bm/d, feverish, weak
- ▶ pmh: dental infection 3 weeks prior
- ▶ Exam: HR 110 BP 100/60 T 37.8 O2 93%
volume depletion
- ▶ diffusely tender abdomen (no peritoneal sx)
- ▶ perianal irritation

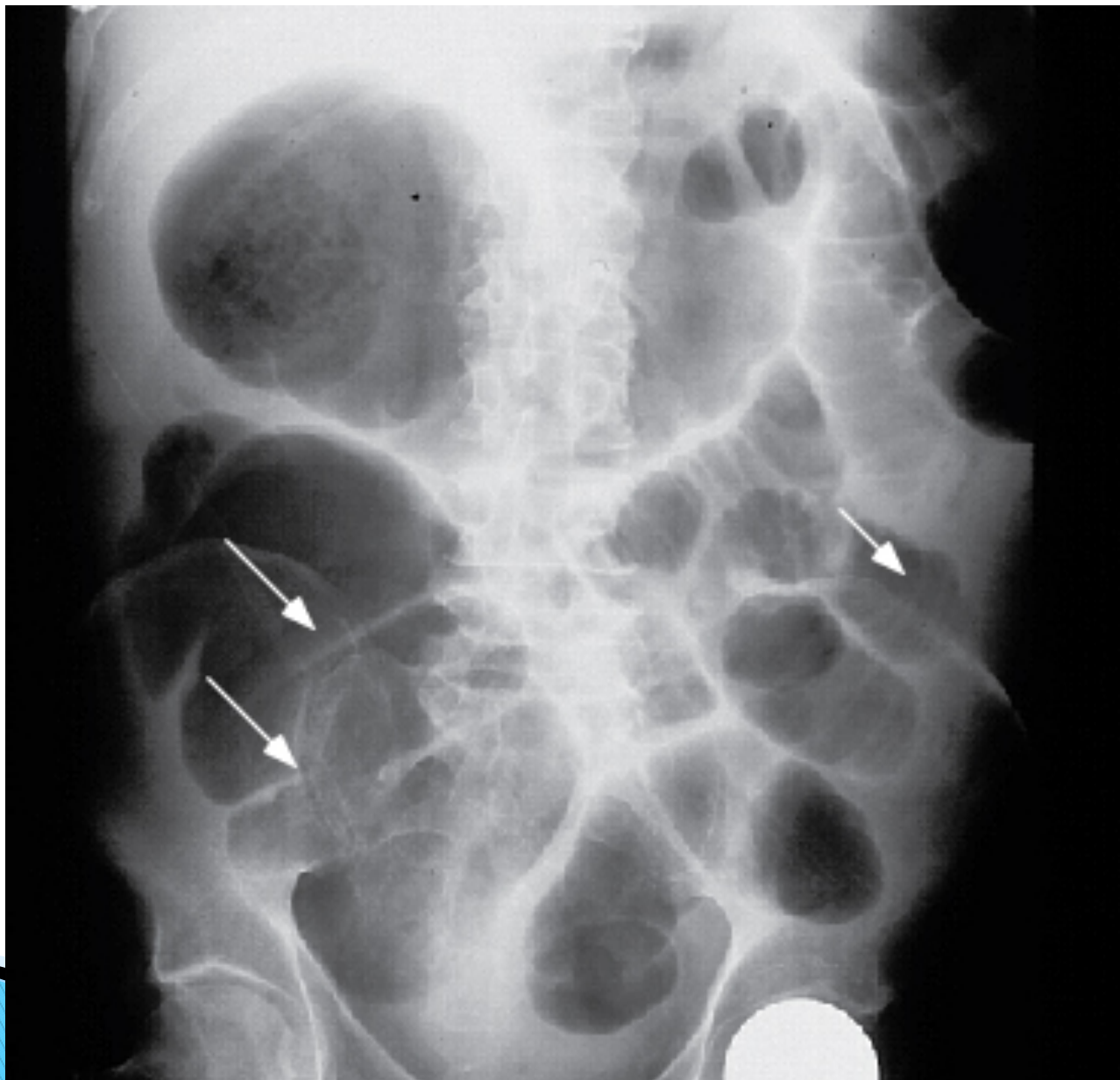
Case #2

- ▶ no medications
- ▶ NKDA
- ▶ non smoker/EtOH/drugs
- ▶ no known immunosuppression
- ▶ no HIV/hepatitis
- ▶ no sick contacts/animal exposure/water-soil exposure/travel/bites/new foods/sexual contacts

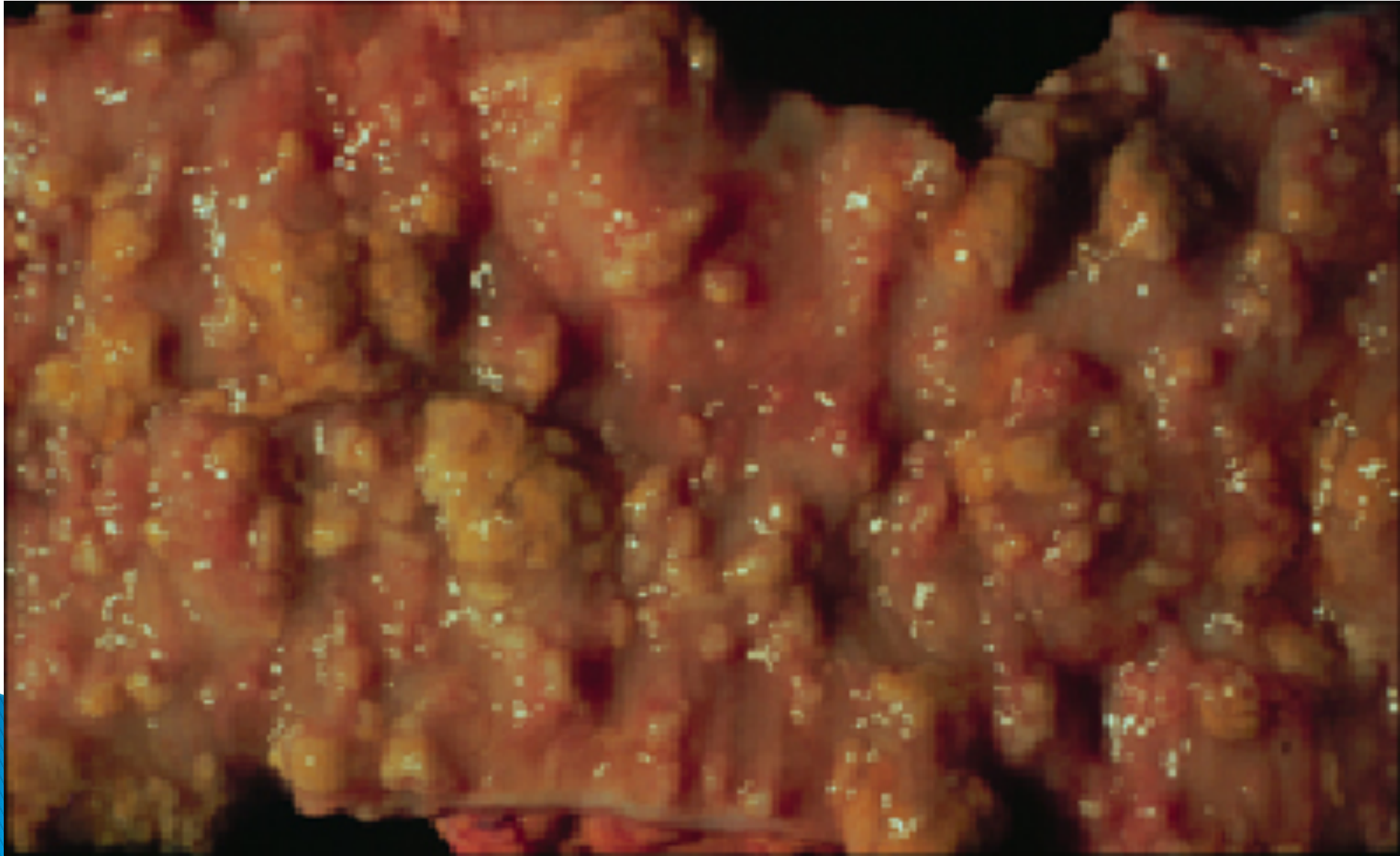
Case #2

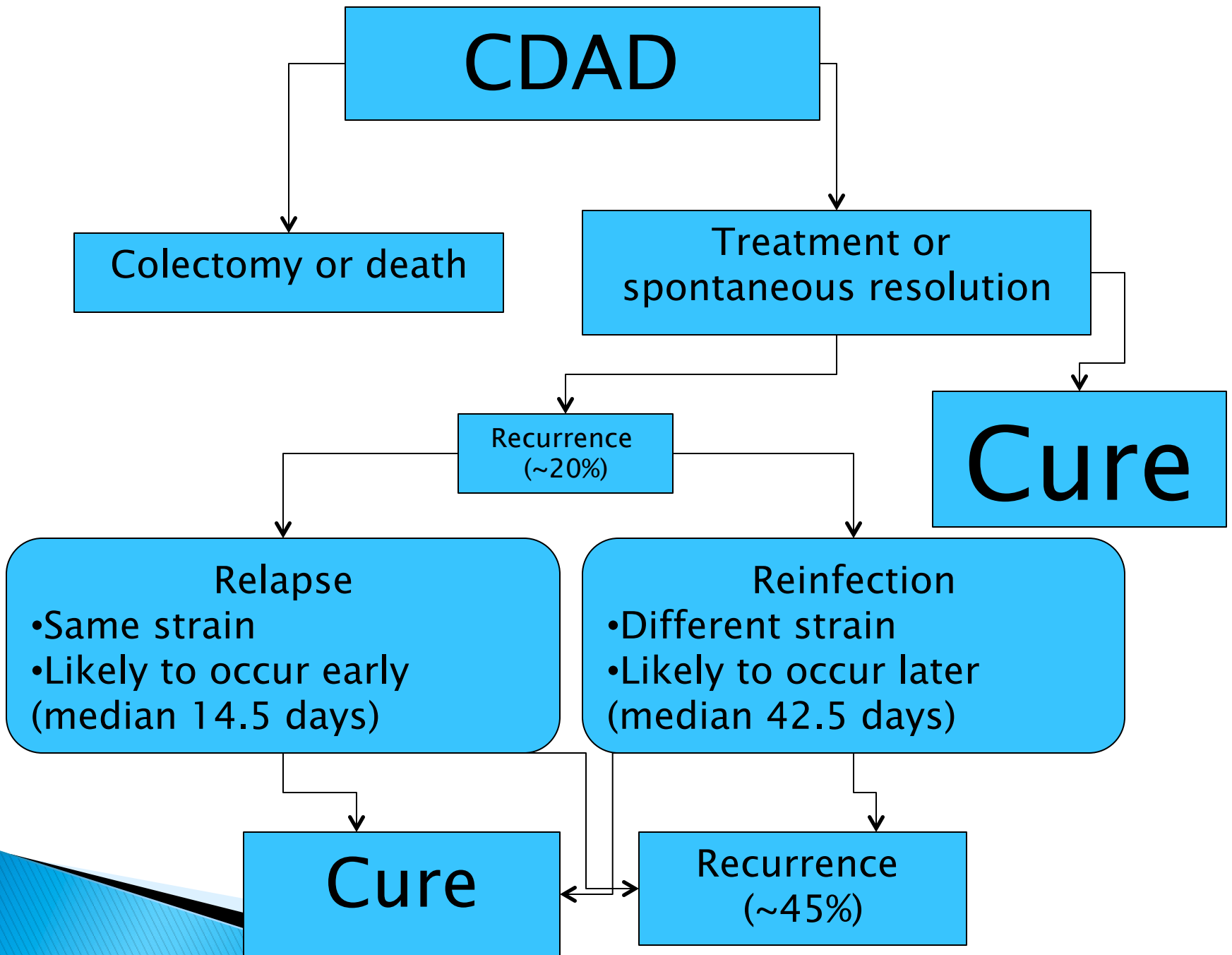
- ▶ Labs:
- ▶ WBC 33 Hbg 110 plt 543
- ▶ creatinine 230
- ▶ lactate 3
- ▶ septic work-up: pending
- ▶ stool studies (stool C&S, O&P, C. diff)
- ▶ Stool Toxin and Antigen assay **Positive**

Abdominal X-ray



Severe Clostridium difficile



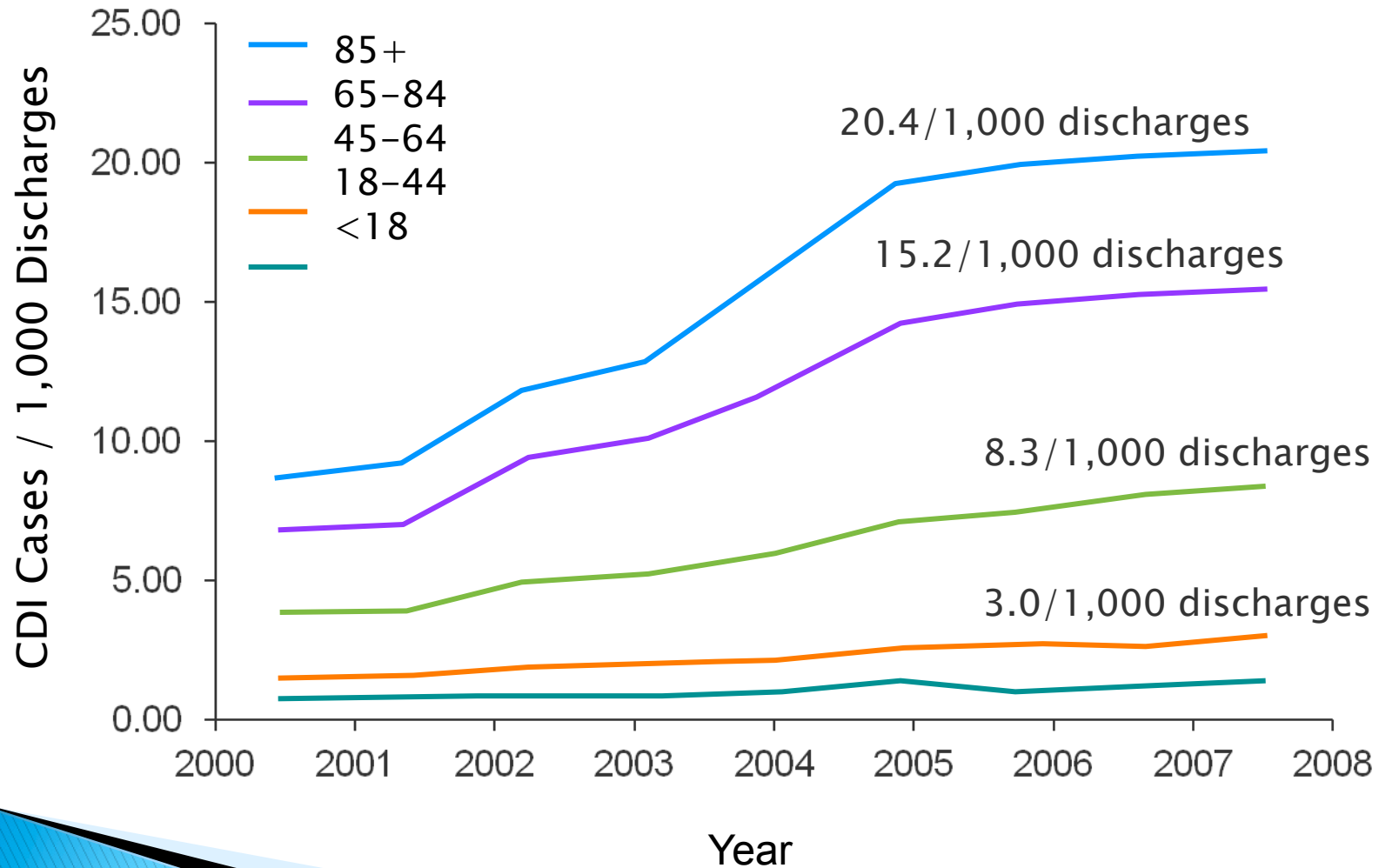


What is severe CDI?

- ▶ **WBC > 15**
- ▶ **Creatinine > 1.5xN**
- ▶ **Other factors:**
 - ▶ **Age > 65,**
 - ▶ **temp > 38.3,**
 - ▶ **albumin < 25**



CDI Incidence by Age



Severe AND Complicated

- ▶ Hypotension/shock
- ▶ Ileus
- ▶ Toxic megacolon

Treatment for severe + complicated C. diff

- ▶ oral vancomycin 125 (500) mg po qid
- ▶ + IV metronidazole 500 mg q8h
- ▶ No IV vancomycin
- ▶ surgical consult
- ▶ If lactate >5 → 75% post-op mortality

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.

From Zar et al, CID 2007.

One point each for age >60 years, temperature >38.3°C, albumin level <2.5 mg/dL, or peripheral WBC count >15,000 cells/mm³ within 48 h of enrollment. 2 points for pseudomembranes or ICU admission.

Severe = ≥2 points

Severe C. diff

- ▶ in acute severe disease:
 - ▶ No role for fecal transplant
 - ▶ No role for monoclonal antibodies
 - ▶ No role for probiotics
- 

Treatment of Severe *Clostridium difficile* Associated Diarrhea

Determination of disease severity is left to clinician judgment and may include any or all of:

- ✓ severe abdominal pain;
- ✓ fever;
- ✓ hypotension; or ileus;
- ✓ toxic megacolon;
- ✓ age > 65 yrs



2. Vancomycin is superior to metronidazole in sicker patients.

Preferred: vancomycin 125 mg po QID for 10–14 days. If patient is unable to take oral medications vancomycin may need to be given by NG and possibly with IV metronidazole.

Conclusions: C. diff

- ▶ If you suspect C. diff, you can treat empirically (don't need to wait for lab results)
- ▶ Severe:
 - WBC > 15, ↑creatinine
 - vancomycin 125 mg po qid
- ▶ Severe and complicated
 - Ileus/shock/megacolon
 - Vancomycin 500mg po/ng qid + IV metronidazole 500 mg tid
 - surgery



New and Nonconventional Treatment for CDI



Wayne Ghesquiere MD, FRCPC
Infectious Diseases VIHA
Clinical Assistant Prof Medicine, UBC
Victoria, BC



ILLITERATE?

WRITE FOR FREE HELP.

ILLITERACY FOUNDATION
806 MAIN STREET

LATTAR



Nonstandard Interventions to Treat CDI or Reduce the Risk of Recurrence

- ***Antibiotics + probiotics***
- ***Probiotics***
- ***Oligofructose prebiotic***
- ***Fecal flora reconstitution***
- ***C. difficile-specific polyclonal antibody-enriched immune whey***
- ***Toxin-neutralizing antibodies***
- ***Toxin absorptive resins***
- ***IV immunoglobulin***



Comparative Effectiveness Results for Treatment of CDI With Antibiotics + Adjunctive Therapy

- ▶ **Overall conclusions:**
 - **Probiotics administered as an adjunct to antibiotic treatment were not more effective than treatment with antibiotics alone. (*Low strength of evidence*)**
 - **Adding probiotics containing *Saccharomyces spp.* to antibiotics for primary treatment may increase the risk for fungemia-related complications in critically ill patients and adds no known benefit. (*Low strength of evidence*)**



Overall Conclusions: Nonstandard Interventions to Treat CDI or Reduce the Risk of Recurrence

- ▶ C. difficile immune whey is well tolerated and may prevent recurrence of CDI at rates similar to metronidazole. (Low Strength of Evidence)
- ▶ Fecal flora reconstitution via fecal transplantation may prevent recurrent infections for up to 1 year. (Low Strength of Evidence)
- ▶ Probiotics, prebiotics, and toxin-neutralizing antibodies alone may not reduce CDI incidence rates. (Low Strength of Evidence)
- ▶ Oligofructose prebiotic (Low Strength of Evidence) and toxin-neutralizing antibodies (Moderate Strength of Evidence) have the potential to help reduce the risk of recurrent infections



Other treatment options

- ▶ **IV metronidazole—inferior to oral therapy**
- ▶ **Tolevamer (toxin binding resin)—inferior in controlled trial—w/d from market**
- ▶ **Teicoplanin—possibly superior to vancomycin, but not available in North America**
- ▶ **Cholestyramine, bacitracin—used rarely**
- ▶ **IVIG—often used in severe or recurrent cases—no good data**



Alternative CDI Therapies: IVIG

- Inconclusive evidence regarding the benefit of intravenous immunoglobulin (IVIG) in CDI

Study	Type	N	Population	Potential Benefit of IVIG?	
				Yes	No
McPherson 2006 ¹	Retrospective Review	14	Severe, refractory, recurrent CDI	X	
Abougergi 2010 ²	Observational study and literature review	21	Severe <i>C. difficile</i> colitis		X
Wilcox 2004 ³	Descriptive study	5	Intractable, severe <i>C. difficile</i> diarrhea		X
O'Horo 2009 ⁴	Systematic review	--	CDI	inconclusive	inconclusive
Hassoun 2007 ⁵	Case review	1	Severe <i>C. difficile</i> colitis	X	

1. McPherson S, et al. *Dis Colon Rectum*. 2006;49:640-645. 2. Abougergi MS, et al. *J Hosp Med*. 2010;5:E1-E9. 3. Wilcox MH. *J Antimicrob Chemother*. 2004;53:882-884. 4. O'Horo J, et al. *N. Int J Infect Dis*. 2009;13:663-667. 5. Hassoun A, Ibrahim F. *Am J Geriatr Pharmacother*. 2007;5:48-51.

Alternative CDI Therapies: Rifaximin

- ▶ Rifaximin “chaser” therapy for multiple recurrent CDI¹
 - Rifaximin 400 mg BID for 14 days immediately following last course of vancomycin
 - Seven of eight patients had no further diarrhea recurrence
 - Single case of rifaximin resistance with recurrent CDI after a second course of rifaximin
 - Follow up experience with 6 patients
 - 2 recurred, rifaximin resistance identified in one
- ▶ Issues with resistance²
 - Rifampin resistance observed in 36.8% of 470 recovered isolates and 81.5% of 205 epidemic clone isolates

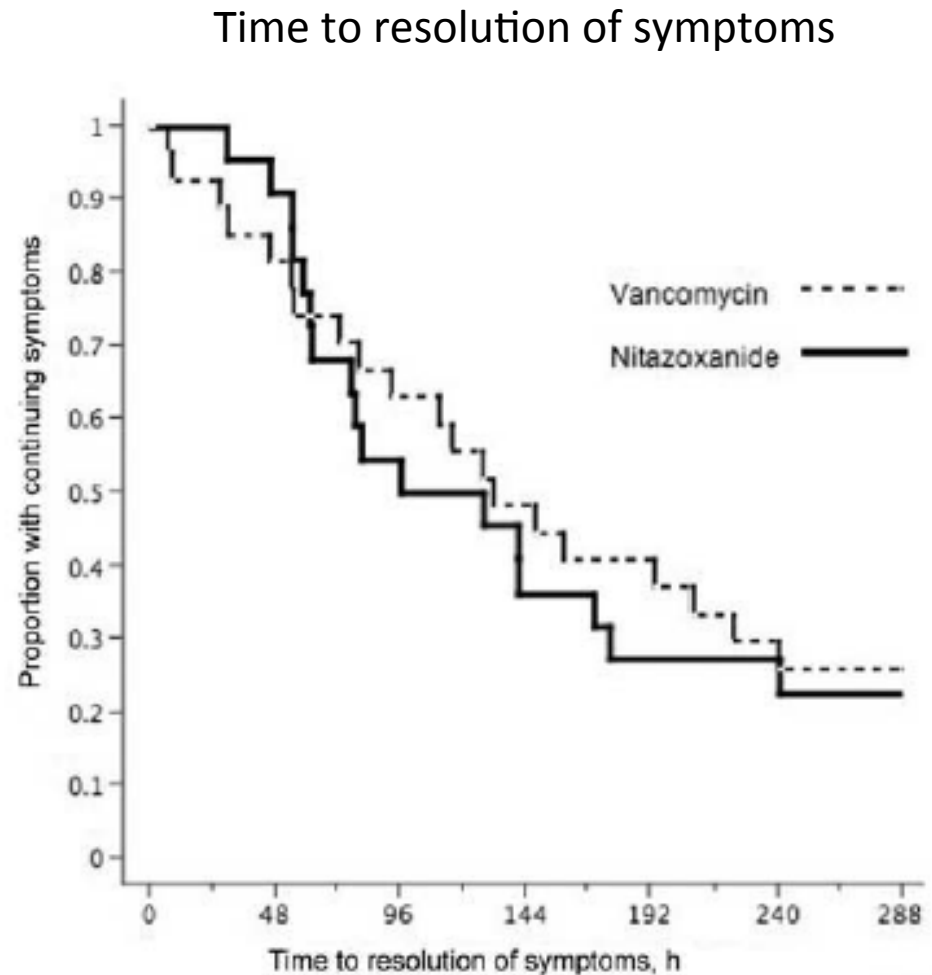
1. Johnson S, et al. *Clin Infect Dis*. 2007;44:846-848.

2. Curry SR, et al. *Clin Infect Dis*. 2009;48:425-429.

3. Johnson S, et al. *Anaerobe*. 2009; 15:290-1

Alternative CDI Therapies: Nitazoxanide

- ▶ May be effective in patients who failed treatment with metronidazole¹
 - 66% cure rate in 35 patients who failed treatment with metronidazole
- ▶ Non-inferior to vancomycin in small study of 50 patients (Figure)²
 - Initial response:
 - Vancomycin: 87%
 - Nitazoxanide: 94%
 - Similar time to complete resolution of symptoms



1. Musher DM, et al. *J Antimicrob Chemother.* 2007;59:705-710.

2. Musher DM, et al. *Clin Infect Dis.* 2009;48:e41-e46; with permission.

What's in the pipeline?



Fidaxomicin

- ▶ **Novel macrocyclic antibiotic with narrow spectrum of activity (active against gram-positive anaerobes but not gram-negative anaerobes)**
- ▶ **Low MIC against *C. difficile***
- ▶ **Administered orally**



Fidaxomicin phase III

- ▶ 548 adults randomized to vancomycin 125 mg po QID or fidaxomicin 200 mg po BID for 10 days
- ▶ Baseline characteristics not significantly different

	Vancomycin	Fidaxomicin	significance
Resolution at day 12	89.8%	92.1%	NS
(modified intention-to-treat)	85.8%	88.2%	NS
Recurrence within 4 weeks	24%	13.3%	p=0.004
(modified intention-to-treat)	25.3%	15.4%	p=0.006
All-cause mortality	6.5%	5.3%	NS

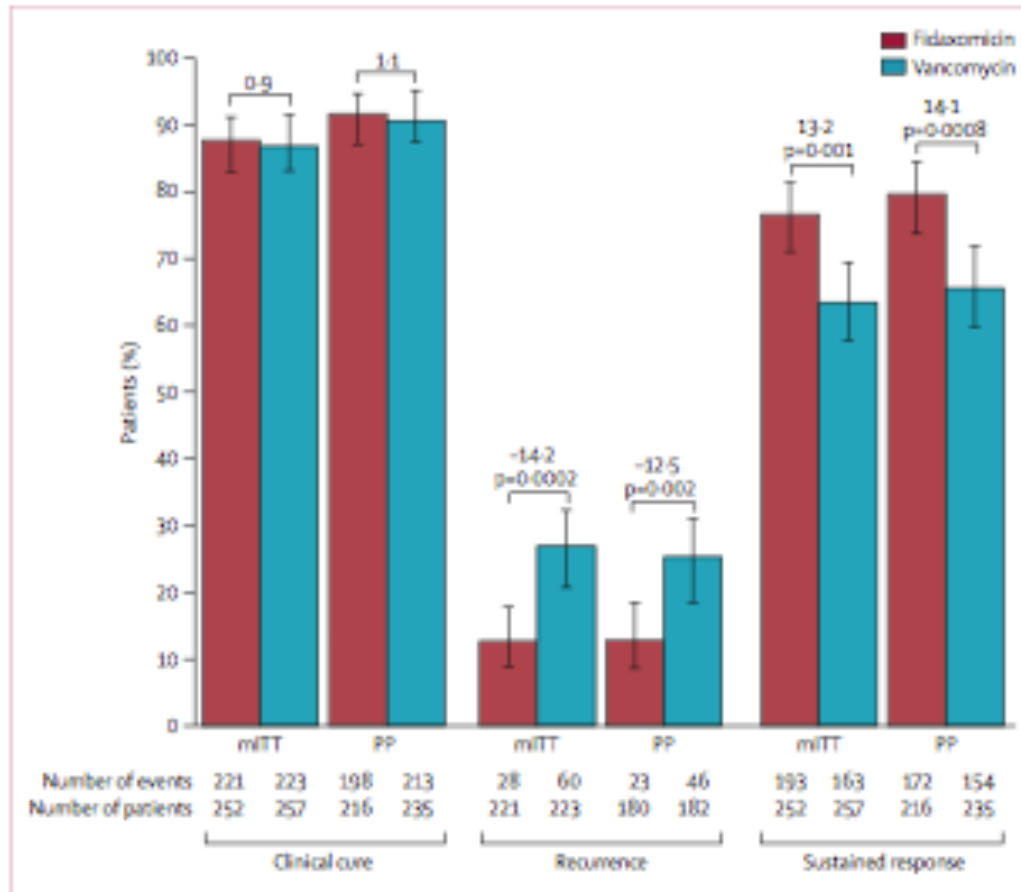
T. Louie et al, 19th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Helsinki, May, 2009

Fidaxomicin

Fidaxomicin versus vancomycin for infection with *Clostridium difficile* in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial

Oliver A Cornely, Derrick W Crook, Roberto Esposito, André Poirier, Michael S Somero, Karl Weiss, Pamela Sears, Sherwood Garbach, for the OPT-80-004 Clinical Study Group

Lancet Inf Dis
Feb, 8, 2012



More good news about fidaxomicin

MAJOR ARTICLE

Clinical Infectious Diseases 2011,53(5):440-447

- ▶ **Concomitant antibiotics delay response to vanc/ fidax and increase risk of relapses**
- ▶ **Fidax superior to vanc in clinical cure (95% v 79%) in presence of concomitant antibiotics**
- ▶ **Lower relapse rate with fidax (17% vs 29%)**

Efficacy of Fidaxomicin Versus Vancomycin as Therapy for *Clostridium difficile* Infection in Individuals Taking Concomitant Antibiotics for Other Concurrent Infections

Kathleen M. Mullane,¹ Mark A. Miller,² Karl Weiss,³ Arnold Lentnek,⁴ Yoav Golan,³ Pamela S. Sears,⁴ Youe-Kong Shue,⁵ Thomas J. Louie,⁷ and Sherwood L. Gorbach^{3,6}



The not-so-good news

- ▶ *More recent paper (Petrelli et al, CID, April 2012)*
- ▶ *Analysis of all subjects combined from the Phase III Fidaxomicin vs. Vancomycin trials*
- ▶ *Benefit of fidaxomicin highest in non-NAP1/BI cases (16.6% vs 27.4%; $p = .007$)*
- ▶ *Recurrence rate not significantly different in NAP1/BI cases (23% vs 31%; $p=0.2$)*
- ▶ *Studies not powered to answer this question*
- ▶ *No significant benefit over vanco in patients with relapsed disease (again, not powered).*



Adverse Effect of Fidaxomicin





Health Canada says fecal transplants should be restricted to trials

WENDY STUECK

VANCOUVER — The Globe and Mail

Published Friday, Mar. 27 2015, 7:00 AM EDT

Last updated Friday, Mar. 27 2015, 7:00 AM EDT



Fecal Microbiota Transplantation for Relapsing *Clostridium difficile* Infection in 26 Patients

Methodology and Results

(*J Clin Gastroenterol* 2012;46:145-149)

Long-Term Follow-Up of Colonoscopic Fecal Microbiota Transplant for Recurrent *Clostridium difficile* Infection

Lawrence J. Brandt, MD, MACG¹, Olga C. Aroniadis, MD¹, Mark Mellow, MD, FACP², Amy Kanatzar, BA², Colleen Kelly, MD³, Tina Park, MD³, Neil Stollman, MD, FACP^{4,5}, Faith Rohilke, BA⁶ and Christina Surawicz, MD, MACG⁷

CONCLUSIONS: FMT is a rational, durable, safe, and acceptable treatment option for patients with recurrent CDI.

Am J Gastroenterol advance online publication, 27 March 2012; doi:10.1038/ajg.2012.60

Standardized Frozen Preparation for Transplantation of Fecal Microbiota for Recurrent *Clostridium difficile* Infection

Matthew J. Hamilton, PhD¹, Alexa R. Weingarden¹, Michael J. Sadowsky, PhD^{1,3} and Alexander Khoruts, MD^{2,3}

Am J Gastroenterol advance online publication, 31 January 2012; doi:10.1038/ajg.2011.482



Donor stool “transplant”

- ▶ **Case series of 18 patients in Duluth, Minn. All patients with at least 2 laboratory-confirmed, symptomatic *C. diff* relapses**
- ▶ **Mean duration of illness 102 days; mean # of prior treatment courses 3.6**
- ▶ **15/16 patients cured; 1 relapse successfully treated with repeat infusion**

Aas J et al, CID 2003;36:580



Fecal Microbiota Transplant

Lab Sample	Infectious agent	Lab test
<u>Blood</u>	HAV	HAV antibody IgM and IgG
	HBV	Antibody to hepatitis B surface antigen, antibody to hepatitis B core antigen
	HCV	HCV antibody (RIBA-II)
	HIV-1 and HIV-2	EIA
	<i>Treponema Pallidum</i>	Rigid plasma reagin test
	<i>H. Pylori</i>	<i>H. Pylori</i> antibody
<u>Stool</u>	<i>C. difficile</i>	Toxin A or Toxin B (cytotoxin)
	Enteric bacterial pathogens	Selective stool culture
	Ova and parasites	Light microscopy

Fecal transplant

Stool collection and administration

Collect stool sample from healthy donor

Add triple the amount of saline to feces in blender

Blend at medium/high speed until all fecal material is emulsified

Allow the emulsion (mixture) to settle for 5-10 minutes

Using a 30 cc syringe, decant supernatant into an enema bottle

Refrigerate until ready to use

Discontinue all prior CDAD treatment 24 hrs prior to transplant

CDI Treatment in Total Days

Fecal Transplant

Patient No.	CDI Treatment in Total Days					Fecal Transplant	
	Metronidazole Monotherapy	Vancomycin Monotherapy	Metronidazole + Vancomycin	Vancomycin Taper Protocol	Probiotics	Clinical Outcome	Days of Resolution
1	18	17	Resolution	663
2	45	63	Resolution	682
3	19	...	42	Resolution	687
4	14	19	Resolution	687
5 ^b	1	12	34	Resolution	692
6	7	...	15	15	...	Resolution ²	167

93% of patients experienced clinical resolution

22/27 resolved within 24 hours of transplant

14	28	14	...	63	...	Resolution	627
15 ^a	14	7	Treatment failure ^a	NA
16	14	19	Resolution	173
17	14	17	Resolution	194
18	42	...	10	Resolution	176
19	14	14	...	58	...	Resolution	51
20	14	7	Resolution	159
21	7	13	Resolution	263
22	14	7	...	31	...	Resolution	600
23	43	...	10	Resolution	268
24	14	15	75	Resolution	243
25	28	48	Resolution	268
26	58	...	48	Resolution	134
27 ^a	9	...	13	Treatment failure ^a	NA

Problems with fecal replacement therapy

1. Need trial data.
2. No consensus on best methods (Donor, route, frequency, drug treatment)
3. Standardization of procedure
4. Liability (no adverse outcomes reported)





<http://www.npr.org/blogs/health/2014/10/11/355126926/frozen-poop-pills-fight-life-threatening-infections>

SHEA/IDSA Treatment Recommendations

Clinical scenario	Supportive clinical data	Recommended treatment
Mild to moderate	Leukocytosis (WBC < 15,000 cells/uL) or SCr level < 1.5 times premorbid level	Metronidazole 500 mg 3 times per day PO for 10–14 days
Severe	Leukocytosis (WBC ≥ 15,000 cells/uL) or SCr level ≥ 1.5 times premorbid level	Vancomycin 125 mg 4 times per day PO for 10–14 days
Severe, complicated	Hypotension or shock, ileus, megacolon	Vancomycin 500 mg 4 times per day PO or by nasogastric tube <i>plus</i> metronidazole 500 mg IV q 8 hrs

Approach to recurrent disease


- ▶ **Get patients stable and asymptomatic on lowest dose of vanco (usually qOD-q3d)**
- ▶ **If symptoms develop or persist, do not assume they are due to CDI**
 - **Post-infectious IBS, microscopic colitis, etc.**
- ▶ **I do not use fidaxomicin or combination Rx in these patients because of lack of studied benefit**
- ▶ **Don't do a test of cure for C. diff.**



Summary: Take Home Points

1. If the infection is mild to moderate treat the first and 1st relapse with Metronidazole 500mg tid X 14 days.
2. Treat the second relapse with Vancomycin 125 mg qid X 14 days
3. Treat the third relapse with tapering regimen of Vancomycin over 6 weeks
4. In older patients i.e. those >65 years or severe C.diff start with Vancomycin 125 mgs qid X 14 days

Summary: Take Home Points

5. Recurrent diarrhea may be due to other causes i.e. Post Infectious IBS or IBD
 6. Do not do a test of cure for C. diff.
 7. Probiotics benefit is questionable.
 8. Wash hands
- 



???

