

# **Guidelines for Treatment and Prevention of *Clostridium difficile* Infection**

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# **Disclosure of Financial Relationships**

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**Has no relationships with any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.**

# Today

1. What are the best diagnostic tests for CDI?
2. How do I choose appropriate therapy for my patients with CDI?
3. When should I get a surgery consult for my patient with CDI?
4. How do I treat patients with recurrent CDI?
5. How do we prevent CDI?

**1. What are the best diagnostic tests for CDI?**

# Diagnostic Testing

Detection of toxin in stools

Tests are imperfect and evolving

Test only patients with diarrhea since 80% of infants and 5-15% of adults are carriers

# Diagnostic Testing

- Tissue culture toxin B  
    Old gold standard
- Toxigenic Culture
- GDH (glutamate dehydrogenase antigen)
- Enzyme Immune Assays (EIA)
- Polymerase Chain Reaction (PCR)

# GDH Tests

GDH is common antigen, glutamate dehydrogenase, Clostridial but not specific for toxin producing *C. difficile*

Very sensitive but not specific

Used as screen

If negative – no further testing

If positive – second step is confirmatory testing like PCR

# EIA Tests

Toxin A only – will miss 1-3% of Toxin B positive, A negative strains

Toxins A + B - better

Specific but not sensitive

Should not be stand alone tests



# PCR

Nucleic acid amplification test – PCR for Toxin B gene

Very sensitive and specific

PCR real time

Expensive but quick and accurate

Rapid diagnosis can reduce hospital costs

Can now use rectal swabs for PCR

Useful if patient has ileus

PCR is probably the new gold standard

# ***C. difficile* Tests**

Do not routinely test 3 stools

Low yield

Don't test for cure (usually)

Culture and toxin can stay positive for a month

Khanna et al, J Clin Gastro 2012; 46:846; Wenischet al, Clin Infect Dis 1996;22:813; Surawicz et al, Clin Infect Dis 2000; 31:1012-7

# A Final Take Home Point

BUT diagnostic tests are imperfect

If you think your patient has *C. difficile* and is sick, start empiric therapy

# The Future? – Cliff and C. diff



A Beagle that can detect *C. difficile*

# Cliff

Cliff – 2 year old Beagle

Trained at Vrije U. in Amsterdam

Hospital

Detected 25 of 30 cases

265 of 270 negatives

Sits next to bed

**2. How do I choose  
appropriate therapy for my  
patients with CDI?**

# 3 Effective Oral Antibiotics for CDI

Metronidazole

500 mg tid x 10 days

Vancomycin – (FDA approved)

125 mg qid x 10 days

Fidaxomicin – (FDA approved)

200 mg bid x 10 days

# What is Fidaxomicin?

Macrocyclic antibiotic – Poorly absorbed

Equivalent to vancomycin – mild to moderate CDI

Fewer recurrences with fidaxomicin:

15% (F) vs 24% (V)

Thus the cost is twice that of vanco

Not tested in severe cases or recurrent cases



# Cost of Treatment

Treatment	10 day cost
Metronidazole pills (500mg)	\$15-30
Vancomycin pills (125 mg)	\$1,800
Vancomycin generic	\$106
IV vancomycin given orally	\$400
Fidaxomicin (200mg)	\$2,700

# CDI Treatment Depends on Severity

**Mild to Moderate**

Severe

Severe and Complicated

Cohen et al, IDSA/SHEA guidelines, Infection Control Hosp Epi, 2010; 31:431

Surawicz et al, ACG guidelines, Am J Gastroenterol, 2013; 108:478-498

# Mild to Moderate CDI

Diarrhea with no criteria for severe CDI

Diarrhea  $\geq 3$  loose-stools/24-hours

# Treatment of Mild to Moderate CDI

Stop intercurrent antibiotics if possible

Metronidazole

500 mg tid x 10 days p.o.

No antiperistaltics

Data poor but medico-legally risky

Lose a parameter to follow

# CDI Treatment Depends on Severity

Mild to Moderate

**Severe**

Severe and Complicated

# Simple Clinical Diagnosis for Severe CDI

Hypoalbuminemia ( $< 3$ ) AND

Abdominal distension/tenderness  
and/or

Elevated WBC ( $> 15,000$ )

# How did we come up with these criteria?

Criteria have not been validated

Good negative predictive values but,

Poor at predicting poor outcomes

Multiple scoring systems for CDI severity

Clinical, lab, x-ray criteria

IDSA definition:

WBC > 15,000 or

Creatinine  $\uparrow$  1.5 x baseline

# Comparison of Clinical Severity Score Indices for CDI

Tested all 8 scoring systems

Prospective evaluation – 184 pts

non severe- 165

severe- 19

Severe defined as

ICU

Surgery

Death



# Result

None of the scoring systems was very good

Four criteria correlated with poor outcome

Abdominal distension

Fever

WBC > 20,000

Albumin < 3

# Simple Clinical Diagnosis for Severe CDI

Hypoalbuminemia ( $< 3$ ) AND

Abdominal distension/tenderness  
and/or

Elevated WBC ( $> 15,000$ )

# Treatment of Severe CDI

Vancomycin 125 mg qid x 10 days

If not better, can increase Vancomycin  
to 1-2 gm/day  
empiric but may work

# CDI Treatment Depends on Severity

Mild to Moderate

Severe

**Severe and Complicated**

# Severe and Complicated CDI

Admission to ICU

Hypotension

Fever  $> 38.5$  °C

Ileus

WBC  $> 35,000$  or  $< 2000$

Serum lactate  $> 2.2$  mmol/L

Evidence of end organ failure (renal or pulmonary)

# Treatment of Severe and Complicated CDI

Vancomycin 500 mg qid p.o.

and

Metronidazole 500 mg tid IV

# Treatment of Severe and Complicated CDI

Continue enteral feeding if possible

Nutrition for microbiome

Consider vancomycin enemas

500 mg IV vancomycin in 100 ml NS via rectal tube, clamp 60 min. Repeat qid

# Unproven Therapies

Tigecycline IV

Nitazoxanide p.o.

IVIG (immune globulin)

Fecal bacteriotherapy



# CDI and IBD

Higher morbidity and mortality (4 -6x)

↑ colectomy rates

Risks: Colon disease

Severe disease

Immune suppression

Especially steroids

Ananthakrishnan et al, IBD 2011; 17:976-83

# CDI - IBD

Test all flares

Inpatient

Outpatient

Test pouchitis

Test unexplained increase ileostomy output

# Treatment – CDI and IBD

Treat CDI first

If severe, treat both CDI and IBD

Keep immune suppression going

Don't escalate for 3 days?

# Medical Treatment Summary

<b>Mild to moderate</b>	Metronidazole orally (500 mg tid)
<b>Severe</b>	Vancomycin orally (125 mg qid)
<b>Severe + complicated</b>	Vancomycin orally (500 mg qid) and metronidazole IV(500 mg tid)  Consider vancomycin enemas if Ileus, toxic colon

**3. When should I get a surgery consult for my patient with CDI?**

# Case

56 y o man S/P liver transplant, with adenocarcinoma at the splenic flexure, detected on screening colonoscopy

Preop: WBC 8100, Alb 3.5, Cr 1.5

Left hemicolectomy

Next 3 days

Incisional pain

Ambulating

No flatus

# Hospital Course

Day 5

↑ abdominal distension and pain  
WBC 18,000

Day 6

Dilated colon, transverse colon 13-14 cm diameter

Pain, fever, diarrhea

WBC 24,600

Albumin 2.2.

Cr 2.3

*C. difficile* Toxin A +

# Treatment

Vancomycin p.o.  
+ metronidazole IV

But:

- ↑ Diarrhea
- ↑ Colon distension





# Course

↑ Creatinine

↑ WBC

↓ Albumin

No response to maximal medical therapy

Back to OR at day 10 for Colectomy /  
Ileostomy

# Post-op Course

Rocky post-op course but eventually did well  
WBC 10,300; Creatinine 1.2

**Does the literature help us  
define criteria for surgical  
intervention?**

# Impact of Emergency Colectomy for Fulminant *C. difficile* Colitis

January 2003 – June 2005, retrospective series  
of 161 patients

Surgery – 38

Medical Rx– 123

In ICU due to CDI or ICU with CDI severe  
enough to warrant ICU

Outcome 30 Day mortality

# Indications for Colectomy

Colectomy	38 Patients
Persistent shock	15
NR to med Rx	10
Megacolon	11
Perforation	2

# Mortality – Overall

Therapy	Mortality
Medical Rx	58%
Surgery	34%

# Predictors of 30 d Mortality

↑ Lactate > 5

↑ WBC > 20

Shock/pressors

Age > 75

Colectomy survival benefit in this group

# When to Get a Surgery Consult

Hypotension / shock

Sepsis

Renal or pulmonary failure

WBC > 50,000

Lactate > 5

Progressive abdominal tenderness or  
distension

Severe and complicated and not better after 5  
days of maximal medical therapy



# Diverting Loop Ileostomy – Another Option

Loop ileostomy with PEG + vancomycin  
colon lavage

Laparoscopic in most

Colon preserved in most

80% hooked back up

# Loop Ileostomy – Results

Years	Number of pts	Mortality
2009-2011	42	8/42 (19%)
Prior to 2009	42	21/42 (50%)

**4. How do I treat patients with recurrent CDI?**

# Pathophysiology – RCDI

Impaired immune response

Patients with RCDI had ↓ IgG to Toxin A

In a vaccine study, lower levels of anti-toxin B Ab were associated with recurrence

Altered colonic microbiota

Kyne, Lancet 2001  
Leav et al, Vaccine 2009

# RCDI – Evidence of the Altered Microbiome

Evaluated microbiome in 7 pts with CDI and 3 controls

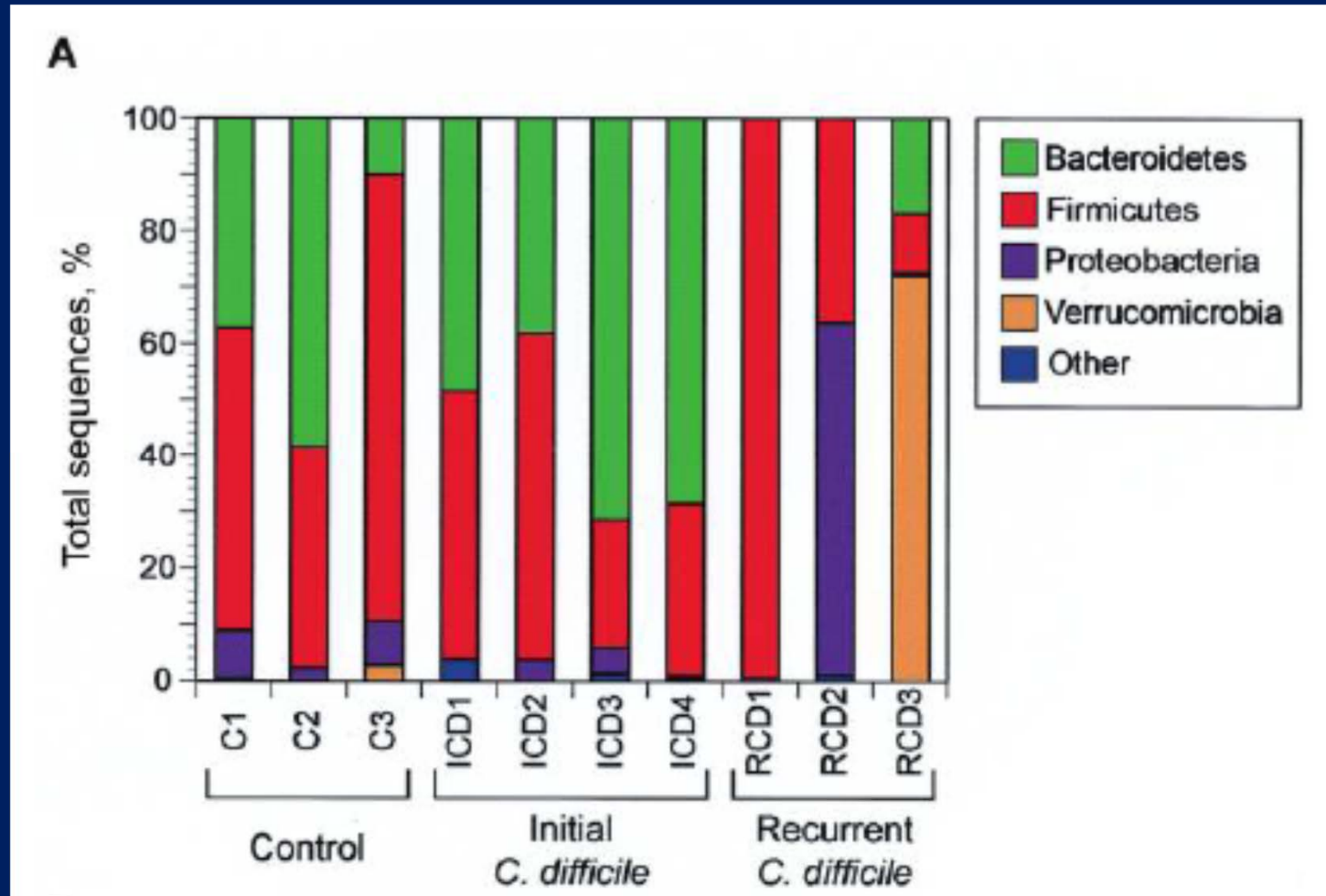
Bacteroidetes and Firmicutes = majority

3 developed RCDI

Microbiota was less diverse

More other bacteria

# Colon Microbiota



Chang JY, et al, J Infect Dis. 2008;197:435-8.

# Treatment of RCDI

Repeat antibiotics are needed - with  
Metronidazole or Vancomycin

Pulse and taper decreases recurrences

I think pulse more important than taper

Do not use Metronidazole long term

# RCDI – Vancomycin Regimen

Vancomycin 125 mg qid x 10 days,  
then Vancomycin 125 mg a day every  
3 days x 10

Simple and not too expensive

Courtesy of Dr. Scott Curry, U. of Pittsburgh



# Other Antibiotics?

Rifaximin “chaser” (2 wks vanco + 2 wk Rifaximin)

Two small series

Fidaxomicin

No trials in RCDI

Neither drug FDA approved for RCDI

# Immune Approaches

IVIg – case reports

Vaccines – 5 yrs away

Monoclonal antibody to toxin A and B as adjunct to antibiotics promising but still in trials – phase 3 trials

# Probiotics

## *Saccharomyces boulardii*

Decreased recurrences by 50% with adjunct antibiotics

Recurrences with high dose Vancomycin (15.7% vs 50%) but not with low dose Vancomycin or Metronidazole

## Risks:

Fungemia in immunosuppressed and in ICU patients with central lines

McFarland et al, JAMA 1994; 271:1913  
Surawicz et al, Clin Infect Dis 2000; 31:1012

**“Human stool is the ultimate  
probiotic”**

Lawrence Brandt, MD  
Albert Einstein College of Medicine  
Bronx, NY, 2013

# When was Stool Transplant First Documented?

- A. 1700 years ago in China?
- B. 1958 in post op patients in Denver?
- C. On Grey's Anatomy in 2008?

# Answer = A

1700 years ago in China, 4<sup>th</sup> Century used human feces to treat severe diarrhea; 16<sup>th</sup> century used infant feces, called “yellow soup”

Grey’s Anatomy – 2008 “In the Midnight Hour”, done in emergency room

# Fecal Enemas

Fecal enema as adjunct in the treatment of pseudomembranous enterocolitis – 4 patients

Fecal enemas to treat 16 patients with severe *Clostridium difficile* disease

Eiseman et al, Surgery 1958; 47:178-83  
Bowden, Amer Surgeon, 1981; 47:178-83

# Successful Treatment of RCDI

Fecal enemas

1 case RCDI

Rectal instillates of microbes mixture of 10 aerobic and anaerobic species in 6 pts with RCDI

Schwan, Lancet, 1983; 2: 845

Tvede, Rask-Madsen, Lancet, 1989; 1: 1156-60



# Terminology – Restoring the Normal Microbiota

Fecal bacteriotherapy

Fecal enemas

Fecal flora reconstitution

Stool transplant

Fecal microbiota transplant (FMT) = now the new accepted terminology

# FMT – Methods

Colonoscopic route – healthy spouse donor stool to right colon via colonoscopy

Stool Per NG tube

Per enema, done at home

Persky and Brandt, Am J Gastroenterol 2000; 95:3283

Aas et al, Clin Inf Dis 2003; 36:580

Silverman et al, Clin Gastro Hep 2010; 8:471

# Results of FMT for RCDI - Systematic Review

317 patients, 27 papers, stool delivered by  
all routes

92% success

89% after one treatment

5% after retreatment

Lowest response rate with NGT-76%

Gough et al, Clin Inf Dis, 2011; 53:994-1002

# FMT - Unanswered Questions

Does it work?

Why does it work?

Is it safe?

What's the best method?

# Does it Work?

Duodenal Infusion of Donor Feces for  
Recurrent *C. difficile*

Van Nood E, et al

N Engl J Med 2013; 368:407-15

# Duodenal Infusion of Donor Feces for RCDI

Regimen	Number of patients
Vancomycin 2 gm/day for 14 days	13
Vancomycin 2 gm/day for 4 days with gut lavage but no donor feces infusion	13
Vancomycin 2 gm/day for 4 days with gut lavage and donor feces via nasoduodenal tube	16

# Results Vancomycin Resolution of RCDI

Regimen	Response	Notes
Vancomycin alone	4/13 (31%)	
Vancomycin and gut lavage	3/13 (23%)	
Vancomycin and gut lavage and donor stool	13/16 (81%)	2/3 responded to second infusion

# Why Does It Work?

Microbiota pre and post FMT- 1 case

Pre

Deficient in Bacteroidetes

Had more atypical populations

Post (2 wks)

Resembled donor stool

Bacteroidetes dominated

Post (33 days)

Bacteroidetes dominated



# Is it Safe?

## Long Term Follow Up Study- FMT via Colonoscopy

Lawrence Brandt	Bronx, NY
Colleen Kelly	Providence, RI
Mark Mellow	Oklahoma City, OK
Neil Stollman	Oakland, CA
Christina Surawicz	Seattle, WA

(Brandt et al, Am J Gastro 2012; 107:1079)

# Results

77 patients – 56 women

Duration – 11 months average

Age 22 – 88 (65 mean)

Ave 5 recurrences

Follow-up 3-68 months

Resolution – within 6 days commonly

91% immediate cure

Of 7 failures

2 retransplanted

4 retreated

# Long Term Safety

- 4 had a new medical condition
  - Peripheral neuropathy
  - Sjögren syndrome
  - ITP
  - Rheumatoid arthritis
- No infections or deaths related
  - 1 sepsis – 6 months later in Crohn's pt.
  - 1 pneumonia

**In US,  
FDA no longer requires  
Investigational New Drug Application  
(IND) for FMT**

**Trials ongoing in Canada**

# What's the Best Method - Is Colonoscopy Better?

- NIH funded RCT - Drs. Colleen Kelly (Brown University) and Lawrence Brandt (A Einstein University)
- Control – colonoscopy with the patients own stool

# RCDI – Recent Meeting Updates

- Donor stool in gel capsules – 27 patients  
Louie et al, ID Week, October 2013
- FMT cost effective
  - By colonoscopy
  - By decision analysis  
Konijetti et al, ACG, October 2013
- FMT appears safe in immune suppressed patients – 83 patients  
Ilhunnah, ACG, October 2013

# My Opinion

If we are still doing stool transplant in 5 years, scientists have failed us

We should be able to identify and culture the essential “good” bacteria

# Stool Substitute for RCDI – “RePOOPulating” the Gut

Isolated 33 strains of bacteria from a healthy  
41 y.o. female donor

Synthetic stool given via colonoscopy

Successful treatment of 2 RCDI patients

6 month follow up

Petrof, Allen-Vercoe et al, Microbiome 2013;

1:3



# RCDI Treatment

1<sup>st</sup> recurrence

Repeat initial regimen

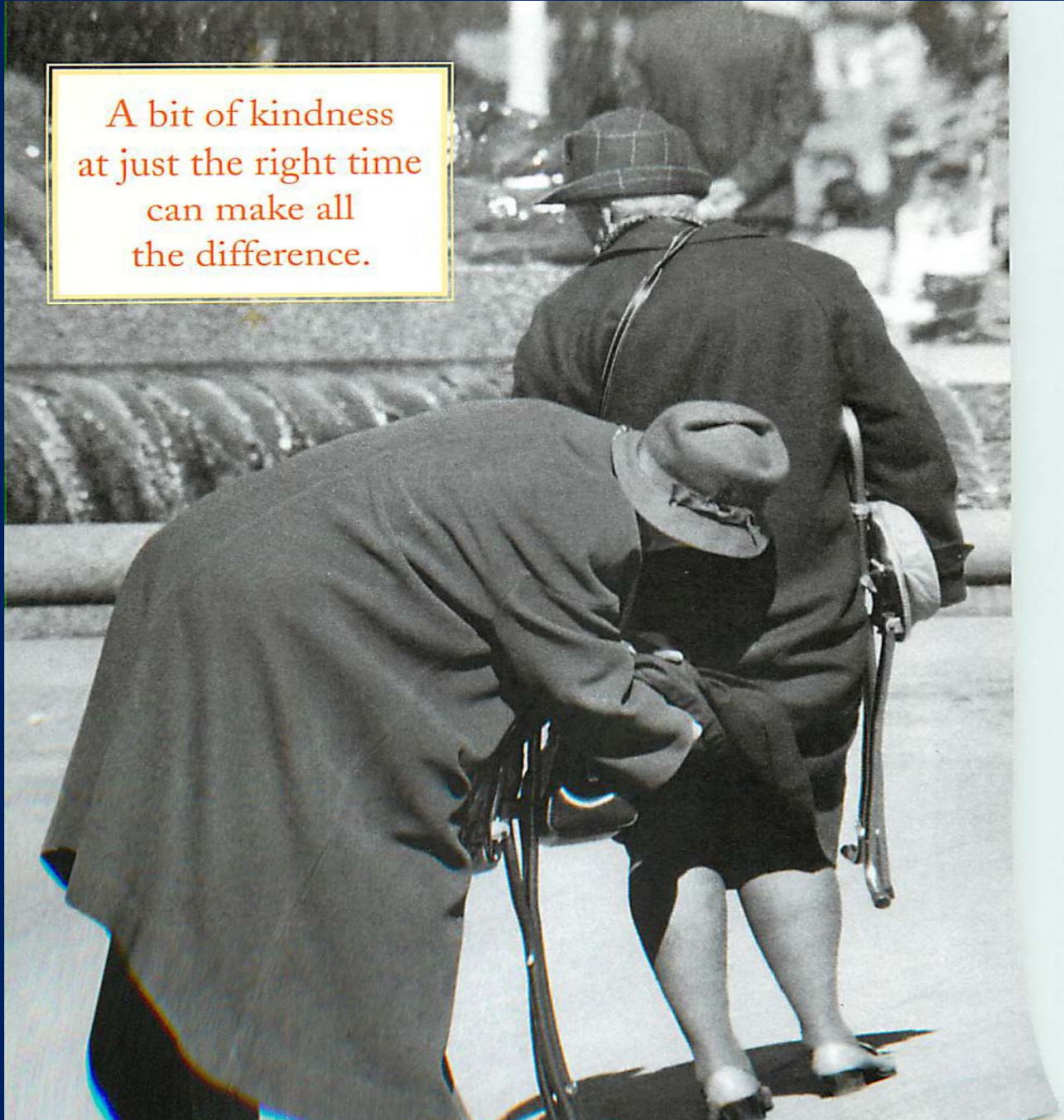
2<sup>nd</sup> recurrence

Vancomycin pulse regimen

3<sup>rd</sup> recurrence

Consider FMT

A bit of kindness  
at just the right time  
can make all  
the difference.



# Prevention

- Wise antibiotic policies
- Hand hygiene + barrier
- Screen patients at admission to hospital  
(Montreal Heart Institute)
- Bleach cleaning at home
- Probiotics?

# Diverse Sources of CDI

Whole genome sequencing

Symptomatic CDI

Oxford community, UK

(Eyre et al NEJM 2013; 369:1195-1205)

# Results

- 1223 cases (2007-2011)
- Hospital based transmission or related to another case – only 35%
- Most was not patient-to-patient transmission
- Other sources:
  - Asymptomatic people
  - Environment
  - Meat
  - Pets

# Disinfection

- Bleach – 1 cup in 9 cups water
- Spray over kitchen, bathroom, cell phone
- Leave wet – spray x 10 minutes then rinse off
- Toss soiled underwear or launder repeatedly

# Probiotics - Prevention

AAD • Good data

*Lactobacillus GG*

*Saccharomyces boulardii*

CDI • Recent meta-analysis favored use

Multiple agents

(Johnston et al, Ann Intern Med 2012; 157:878-885)

• Health Canada – approved Bio-K<sup>+</sup> (L. acidophilus, CL1285, L. casei, LBC80R) in 2013

(Gao et al, Am J Gastroenterol 2010)

# Prevention

Wise antibiotic policies

Hand hygiene

Barrier

Bleach cleaning at home



# Summary

- PCR for Toxin B likely new gold standard stool test
- Mild to moderate disease
  - Metronidazole
- Severe Disease
  - Vancomycin
- Severe and complicated disease
  - Vancomycin and IV Metronidazole
  - Surgery consult
- Recurrent CDI – a treatment challenge