CLOSTRIDIUM DIFFICILE UPDATE: A JOINT VENTURE

AMERICAN COLLEGE OF OSTEOPATHIC INTERNISTS
CLINICAL CHALLENGES IN INPATIENT CARE

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UNIVERSITY OF MISSOURI – COLUMBIA

MARCH 25, 2017

DISCLOSURE

AMERICAN COLLEGE OF OSTEOPATHIC INTERNISTS NATIONAL MEETING

Nestle Nutrition Institute Speaker & Consultant

I will not discuss off label use or investigational use in my presentation

ACOI 75

75 YEARS OF DEDICATION TO OUR MEMBERS

Matthew Bechtold MD
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QUESTIONS

What is the burden of *C. difficile*?

What are the *C. difficile* treatment recommendations?

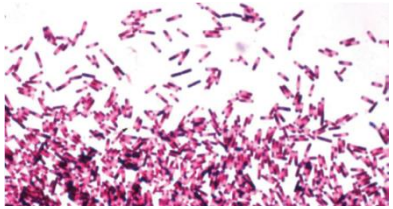
How do we treat severe *C. difficile*?

This is a crappy topic

It's a dirty job but someone has to do it

This should be stimulating

C. DIFFICILE BACKGROUND



ANAEROBIC GRAM + BACILLUS

SPORE-FORMING

TOXIN-PRODUCING

FIRST DESCRIBED IN 1935

PATHOGENIC ROLE DESCRIBED IN 1970's

SPORE FORM

OUTSIDE COLON
RESISTENT TO HEAT, ACID, ANTIBIOTICS

VEGETATIVE FORM

INSIDE COLON
TOXIN-PRODUCING
SUSCEPTIBLE TO ANTIBIOTICS

Hall IC, et al. Am J Dis Child 1935
Bartlett JG. Ann Intern Med 2006
Bartlett JG, et al. Gastroenterology 1978

C. DIFFICILE BACKGROUND

ANTIBIOTIC THERAPY

↓

DISRUPTION OF COLONIC MICROFLORA

↓

***C. DIFFICILE* EXPOSURE AND COLONIZATION**

↓

RELEASE OF

TOXIN A (ENTEROTOXIN) & TOXIN B (CYTOTOXIN)

↓

MUCOSAL INJURY & INFLAMMATION

LaMont JT, et al. UptoDate 2014

C. DIFFICILE BACKGROUND

J-STRAIN

1989-1992

RESISTENT TO CLINDAMYCIN

NAP1/BI/027 STRAIN

2003-2006

MORE SEVERE, REFRACTORY, RELAPSE

INCREASED TOXIN PRODUCTION

MAY BE DUE TO FLUOROQUINOLONES

NORTH AMERICAN PULSED-FIELD TYPE 1
RESTRICTION ENZYME ANALYSIS TYPE BI
PCR RIBOTYPE 027

078 STRAIN

SINCE 2005

SIMILAR TO 027

YOUNGER

COMMUNITY-ASSOCIATED

Miller M, et al. Clin Infect Dis 2010
Pepcin J, et al. Clin Infect Dis 2005
He M, et al. Nat Genet 2013
Goorhuis A, et al. Clin Infect Dis 2008

CLOSTRIDIUM DIFFICILE BURDEN

EPIDEMIOLOGY

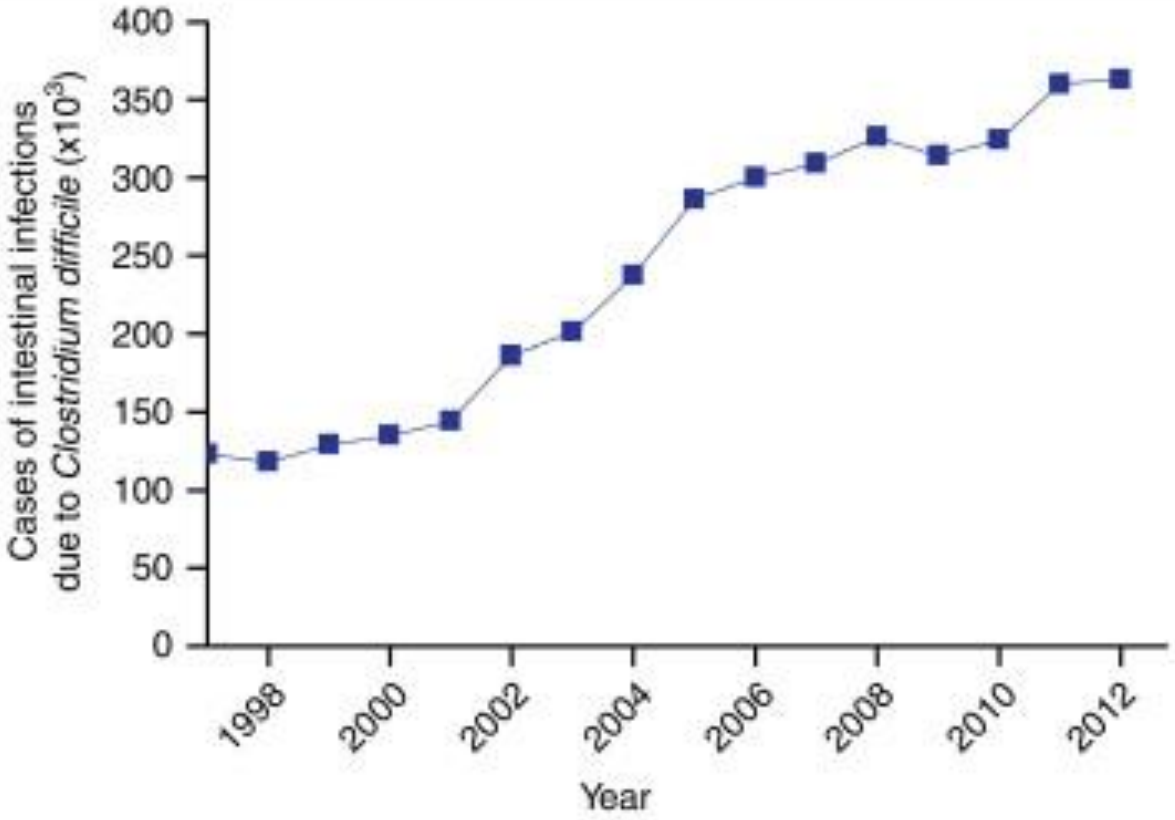
GASTROENTERITIS-ASSOCIATED DEATHS IN UNITED STATES 1999 – 2007

Cause	ICD-10 Code(s)	Total No. of Deaths (%)	Mean Annual No. of Deaths	Rate per 1 000 000[a]
Cause unspecified[b]		44 444 (49.4)	5556	19.1
Presumed infectious	A09	1163 (1.3)	145	0.5
Presumed noninfective	K52.9	39 310 (43.7)	4914	16.9
Other or unspecified viral	A08.3-A08.5	1325 (1.5)	166	0.6
Acute or unspecified vascular[c]	K55.0, K55.9	2815 (3.1)	352	1.2
Cause specified[b]		45 596 (50.6)	5700	19.6
Viral	A08.0-A08.2	85 (0.1)	11	0.04
Clostridium difficile	A04.7	43 517 (48.3)	5440	18.7
Other bacterial	A00.0-A04.6, A04.8-A05.9	1665 (1.8)	208	0.7
Parasitic	A06.0-A07.9	348 (0.4)	44	0.1
Total		90 040 (100)	11 255	38.8

Hall AJ, et al. Clin Infect Dis 2012

EPIDEMIOLOGY

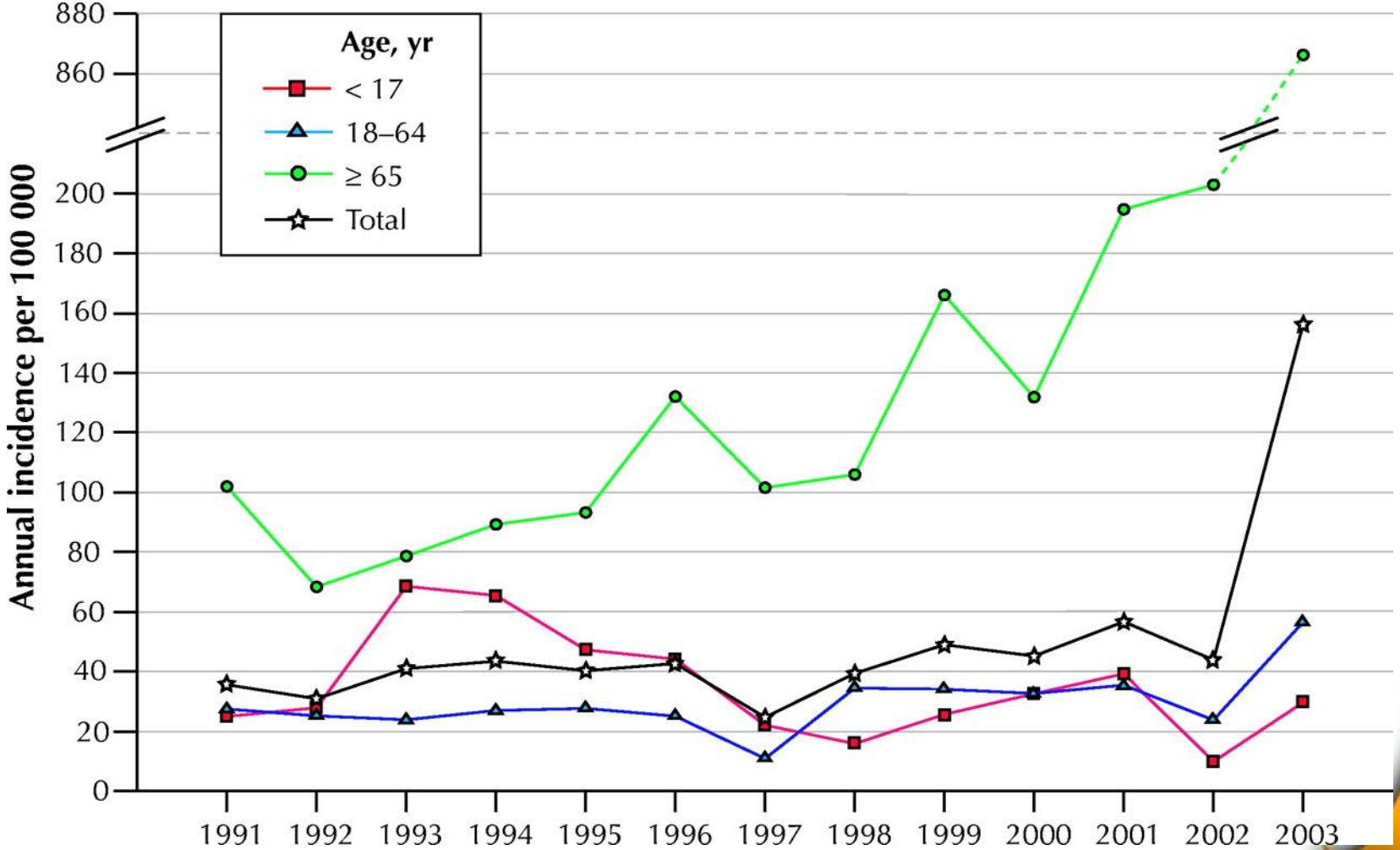
UNITED STATES
1997 - 2012



Ivarsson ME, et al. Drug Discov Today - Epub 2014

EPIDEMIOLOGY

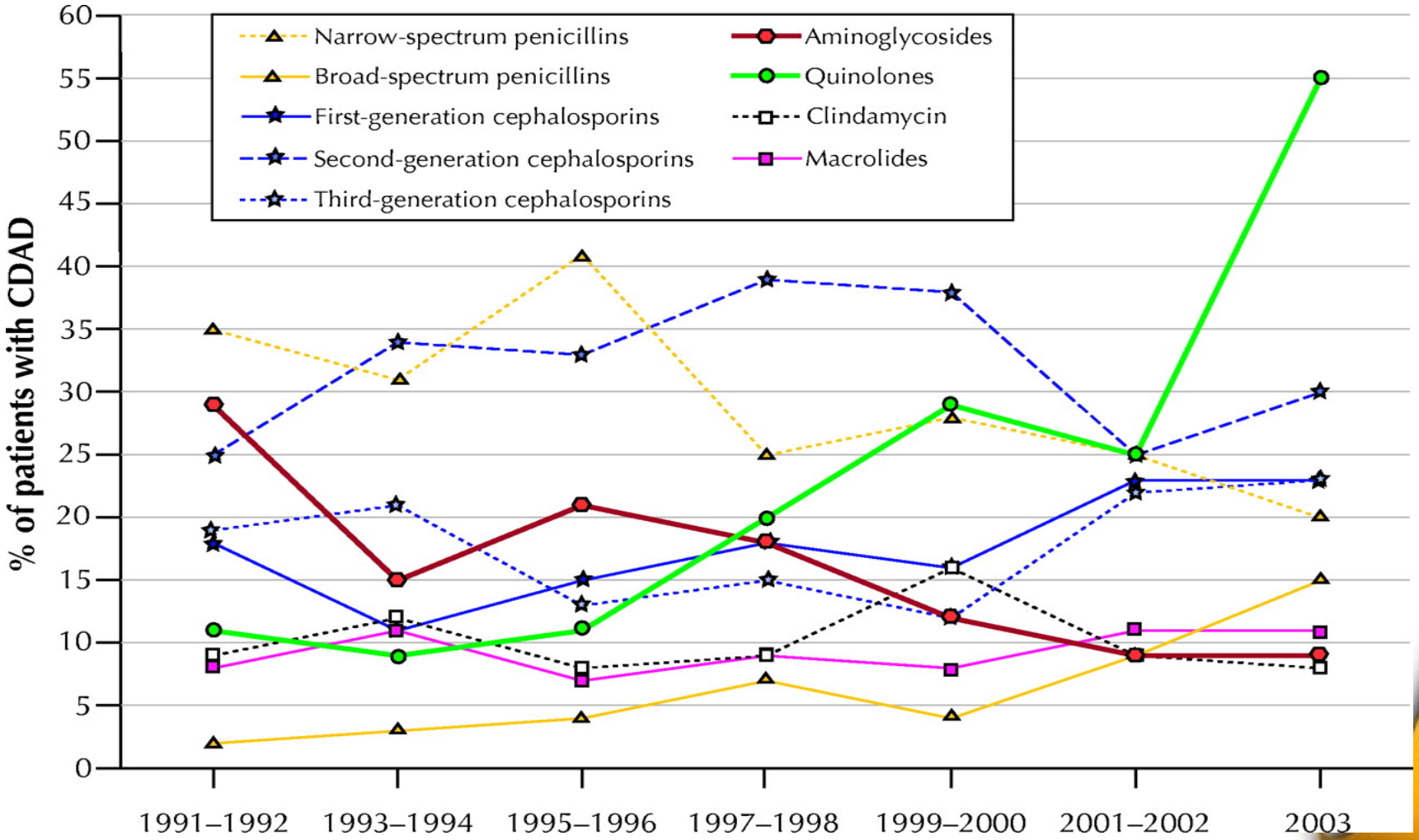
INCIDENCE (PER 100,000 POPULATION) OF CDAD SHERBROOKE, QUEBEC 1991-2003



Pepin J, et al. CMAJ 2004

EPIDEMIOLOGY

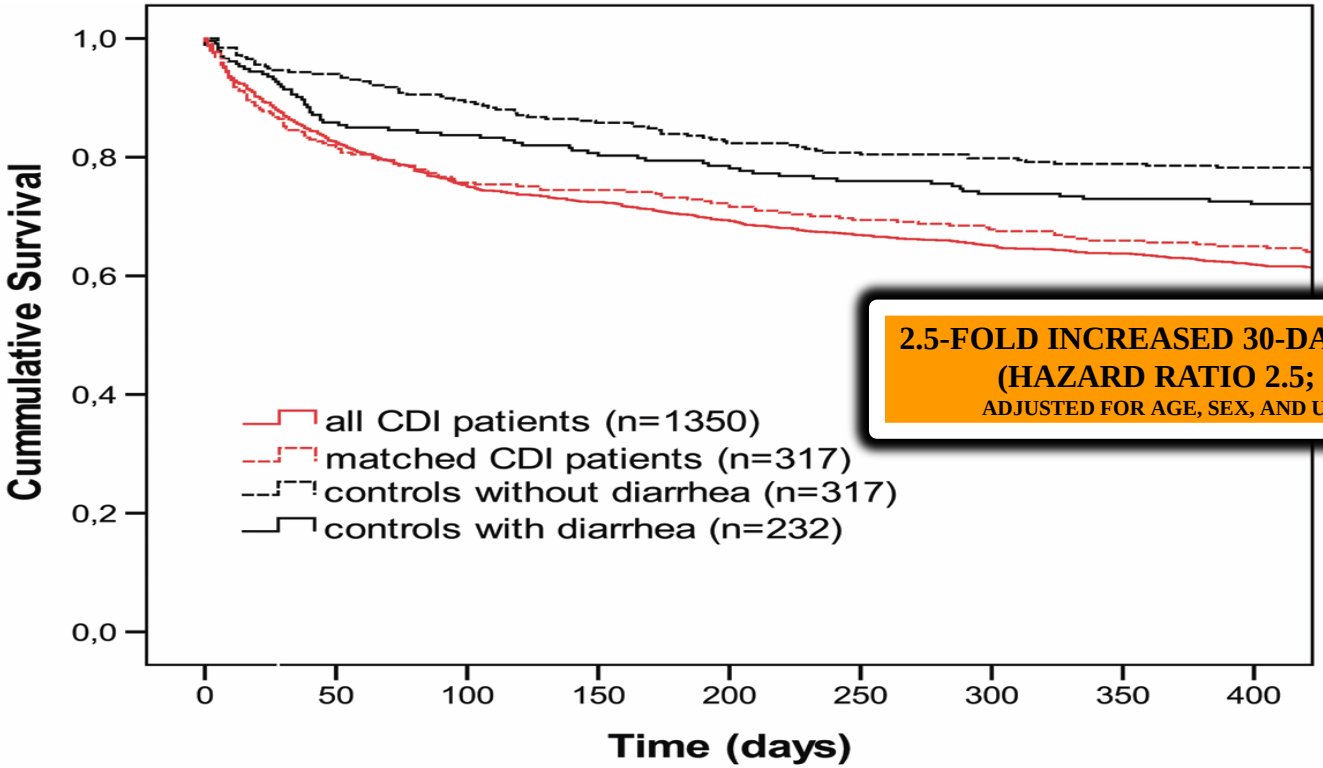
ANTIBIOTIC RECEIVED ≤ 2 MONTHS BEFORE CDAD
SHERBROOKE, QUEBEC
1991–2003



Pepin J, et al. CMAJ 2004

EPIDEMIOLOGY

PROSPECTIVE COHORT IN NETHERLANDS
13 HOSPITALS (n=1,366)
2006-2009



2.5-FOLD INCREASED 30-DAY MORTALITY RATE
(HAZARD RATIO 2.5; 95% CI: 1.4-4.3)
ADJUSTED FOR AGE, SEX, AND UNDERLYING DISEASES

	< 30 days		< 3 months		< 6 months		< 1 year	
Death, no. (%)								
all CDI patients	177 / 1350	13.1%	319 / 1350	23.6%	401 / 1350	29.7%	497 / 1350	36.8%
matched CDI patients	47 / 317	14.8%	74 / 317	23.3%	85 / 317	26.8%	109 / 317	34.4%
controls without diarrhoea	17 / 317	5.4%	31 / 317	9.8%	51 / 317	16.1%	68 / 317	21.5%
controls with diarrhoea	20 / 232	8.6%	38 / 232	16.4%	48 / 232	20.7%	63 / 232	27.2%

Hensgens MP, et al. Clin Infect Dis 2013

EPIDEMIOLOGY

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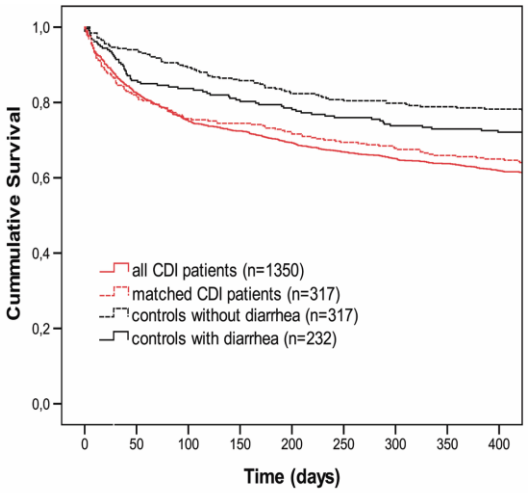

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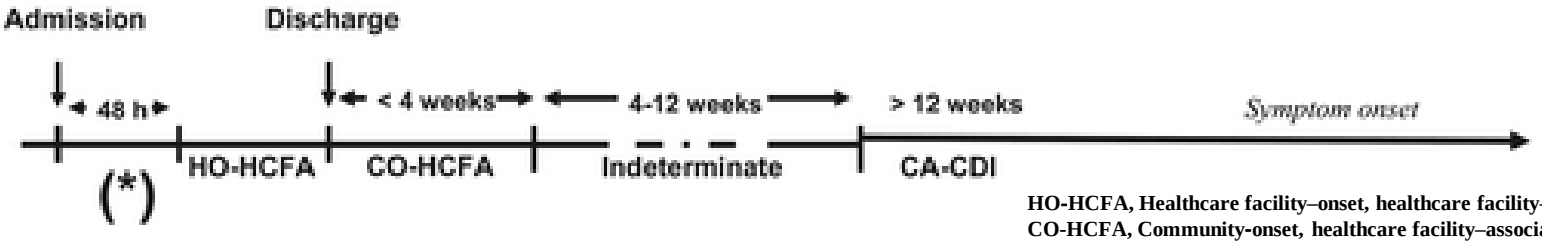
		Deaths		
Stratification	Total N = 1350	<30 d % (n = 177)	<3 mo % (n = 319)	<1 y % (n = 497)
Age group, y				
≤9	58	0.0	1.7	6.9
10–19	40	2.5	7.5	15.0
20–29	33	6.1	9.1	12.1
30–39	52	1.9	3.8	15.4
40–49	90	10.0	14.4	28.9
50–59	191	12.0	18.8	28.3
60–69	252	11.9	23.0	34..5
70–79	351	14.5	29.9	45.6
80–89	244	21.3	34.8	51.2
≥90	39	20.5	33.3	59.0
PCR ribotype				
014	111	10.8	20.7	32.4
078	76	14.5	23.7	38.2
001	57	15.8	22.8	33.3
027	55	21.8	32.7	40.0
Other	387	10.1	20.2	34.9
No type result	664	14.2	25.5	38.6

Hensgens MP, et al. Clin Infect Dis 2013

EPIDEMIOLOGY

NOSOCOMIAL



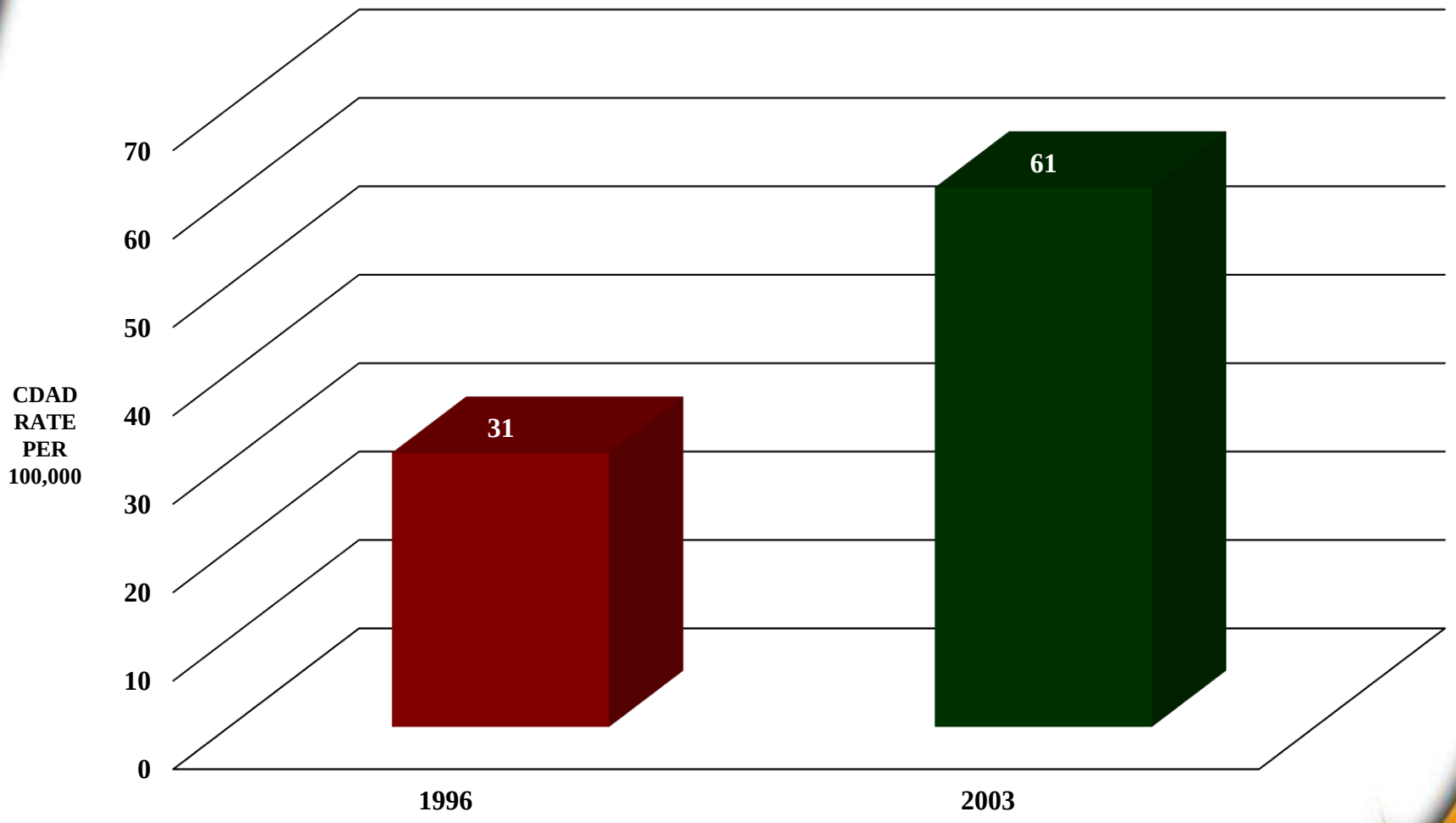
HO-HCFA, Healthcare facility–onset, healthcare facility–associated CDI
CO-HCFA, Community-onset, healthcare facility–associated disease
CA-CDI, Community-associated CDI

COMMUNITY-ASSOCIATED

Cohen SH, et al. Infect Control Hosp Epidemiol 2010

NOSOCOMIAL CDAD

RETROSPECTIVE STUDY IN UNITED STATES NATIONAL HOSPITAL DISCHARGE SURVEY BY CDC 1996-2003



McDonald LC, et al. Emerg Infect Dis 2006

NOSOCOMIAL CDAD

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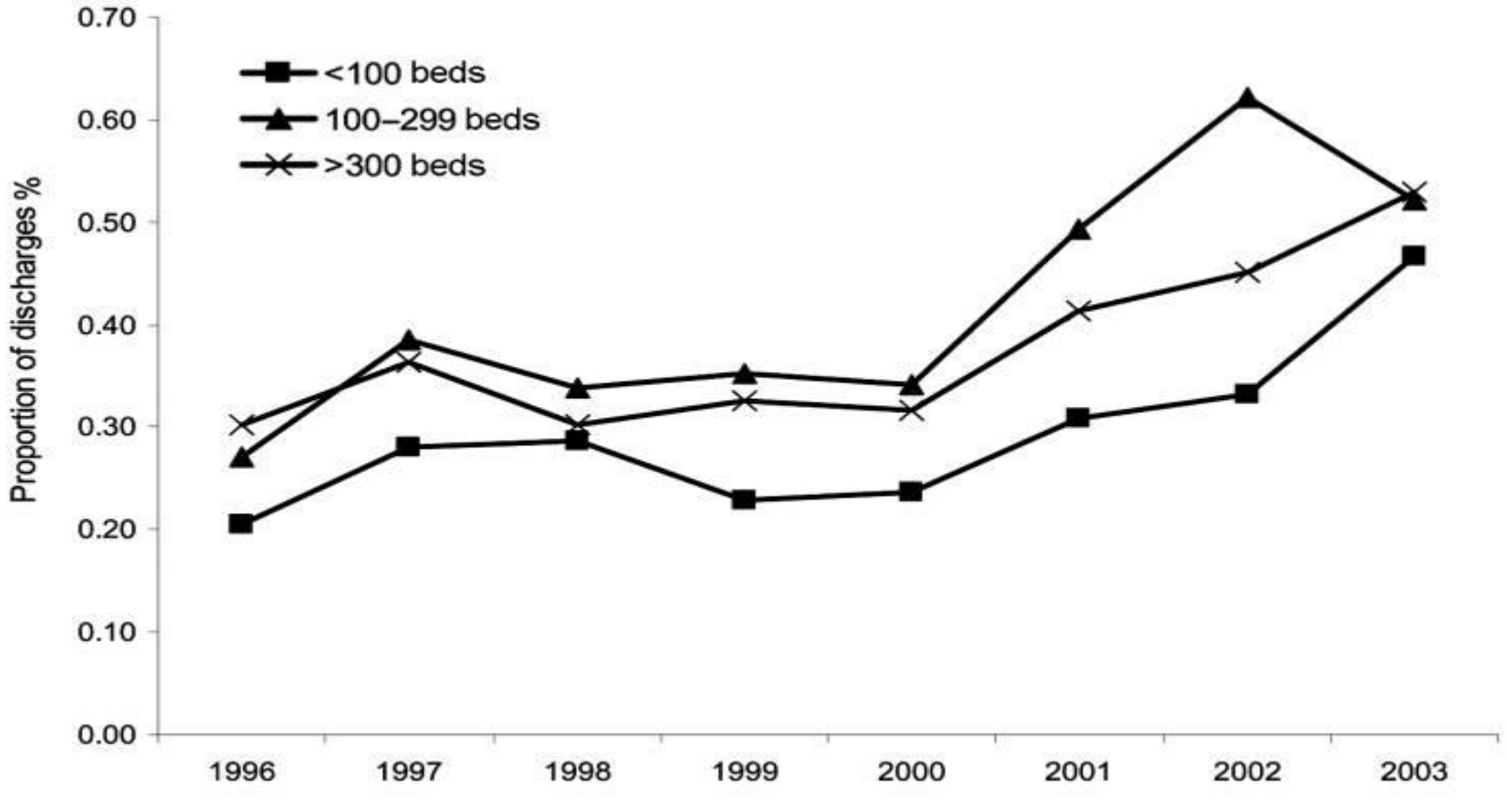
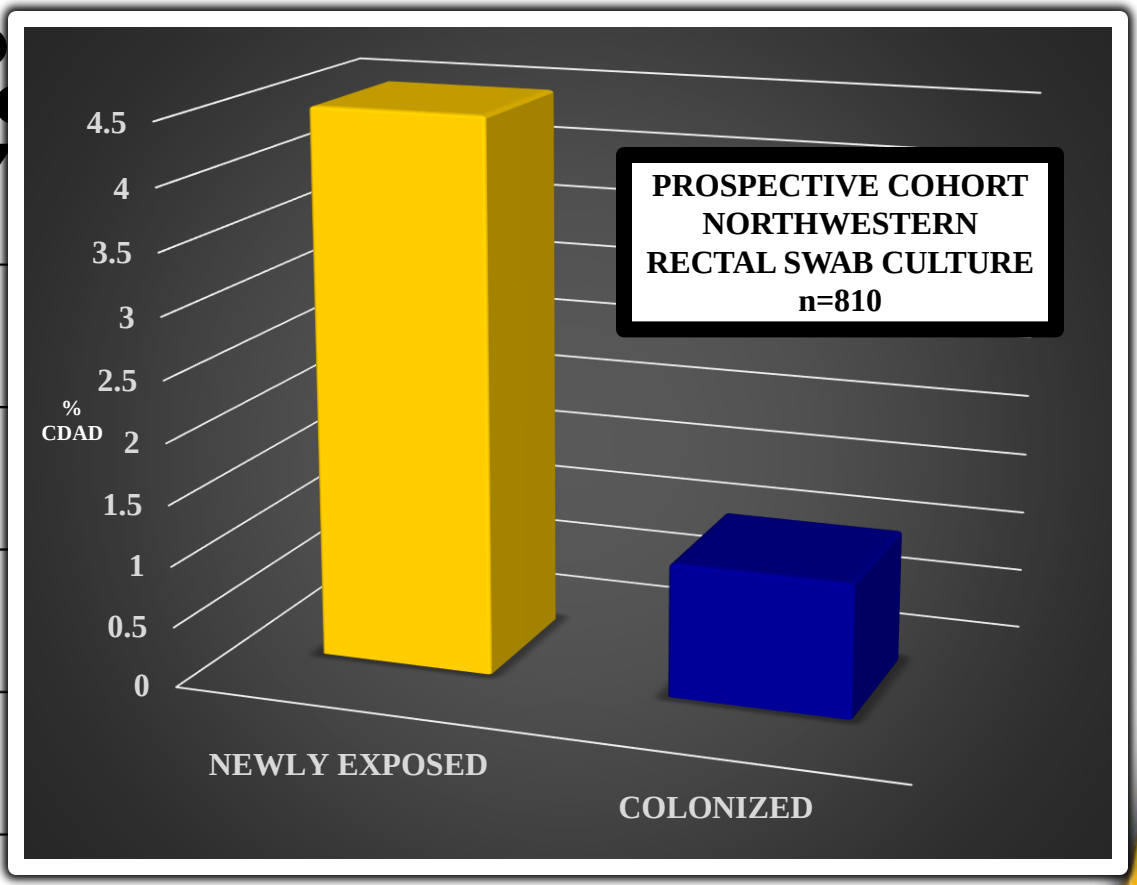
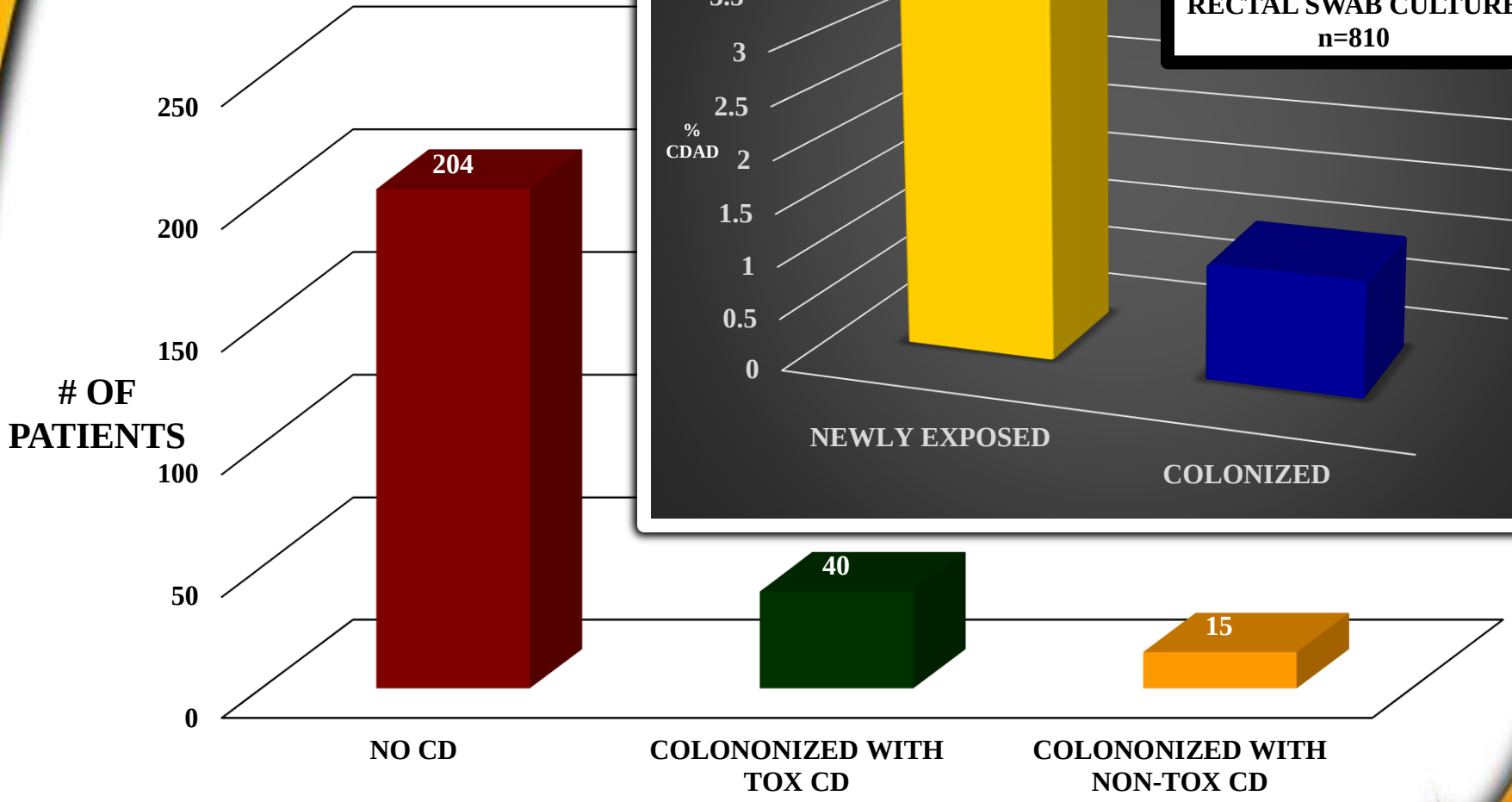


McDonald LC, et al. Emerg Infect Dis 2006

NOSOCOMIAL CDAD

PROSPECTIVE COHO
JUNE 2(
259 ASY
STOOL

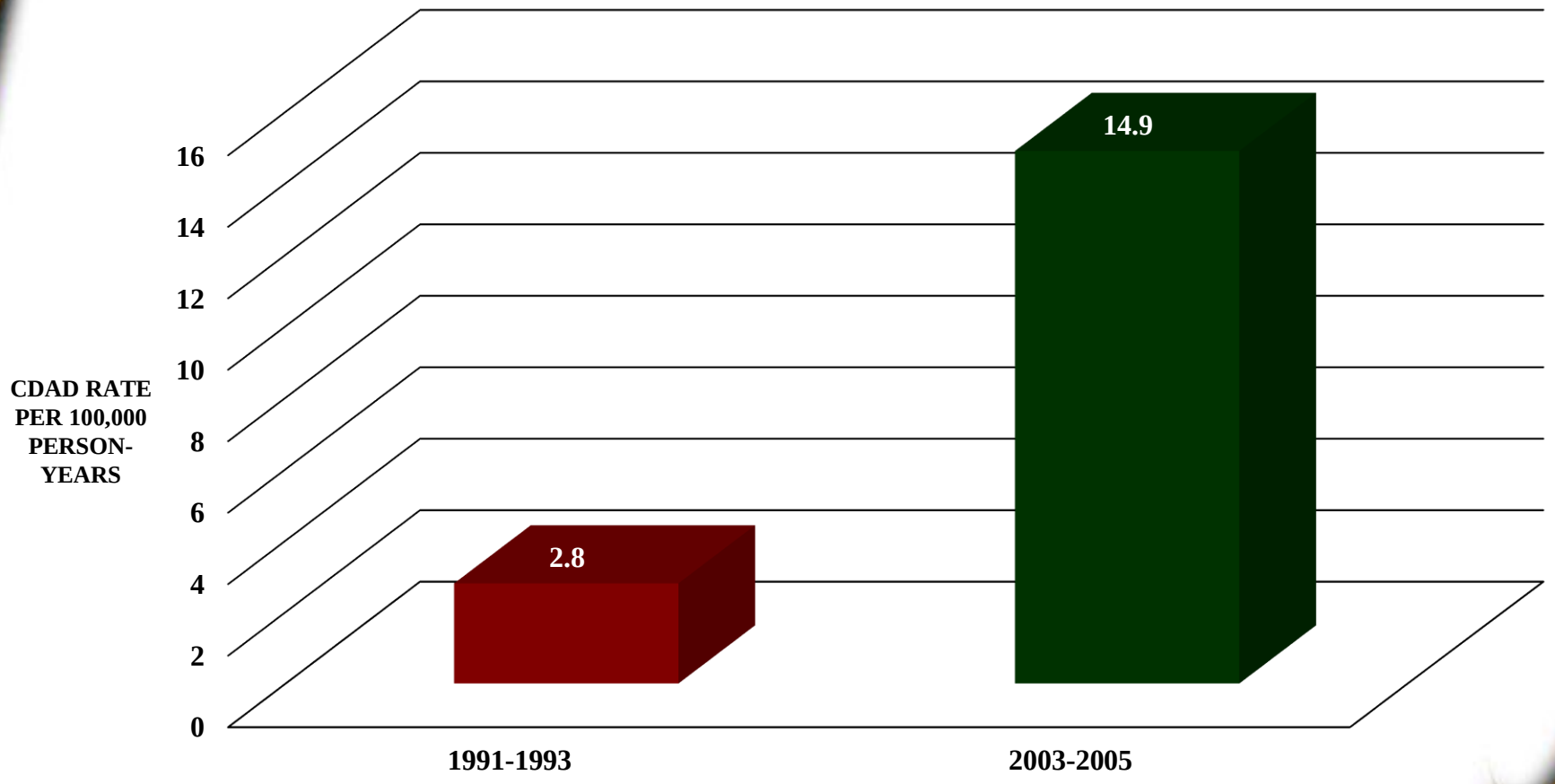




Alasmari F, et al. Clin Infect Dis 2014
Shim JK, et al. Lancet 1998

COMMUNITY CDAD

POPULATION-BASED STUDY IN OLMSTED COUNTY MINNESOTA
ROCHESTER EPIDEMIOLOGY PROJECT
n=385
1991-2005



Khanna S. et al. Am J Gastroenterol 2012

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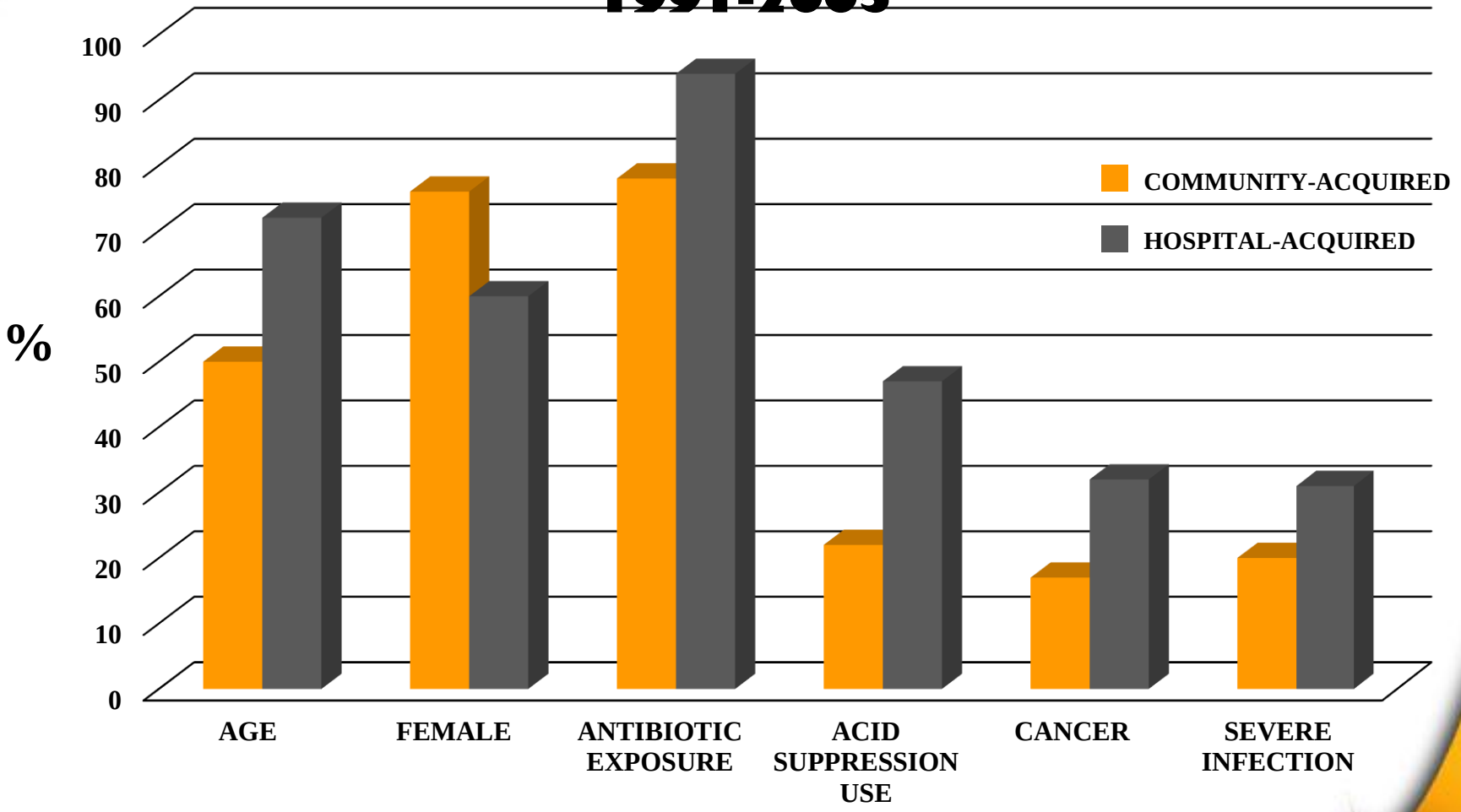


Khanna S. et al. Am J Gastroenterol 2012

WHY?

SICKER PATIENTS

(IMMUNOSUPPRESSION, COMORBIDITIES, ELDERLY)

CHANGING ANTIBIOTIC PRESCRIBING

CHANGING INFECTION CONTROL PRACTICES

NOVEL RISK FACTORS (PPIs)

NEW STRAINS

(ANTIBIOTIC RESISTANCE, NOVEL TOXIN PROFILE)

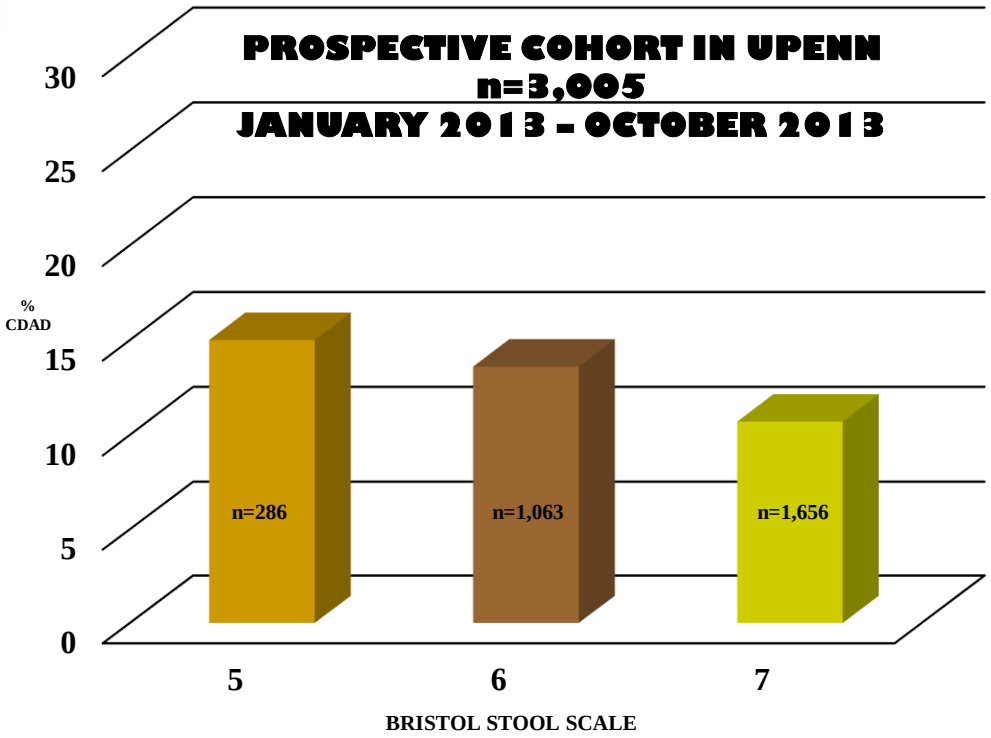
LaMont JT, et al. UptoDate 2014

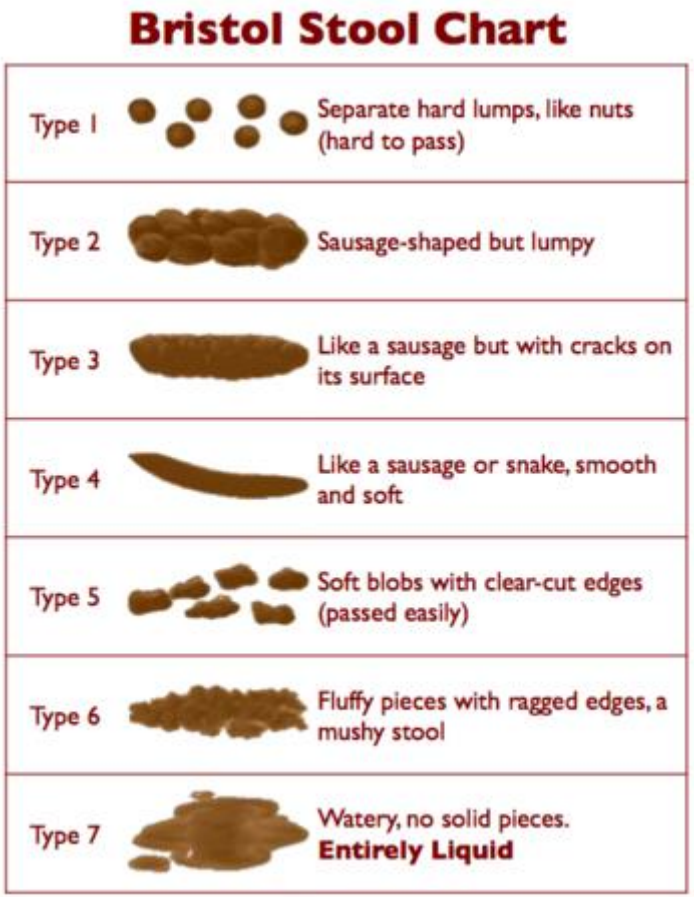
CLOSTRIDIUM DIFFICILE
CLINICAL ASPECTS

CLINICAL SYMPTOMS

DIARRHEA

UP TO 10-15/DAY
LOWER ABDOMINAL PAIN
LEUKOCYTOSIS





Wanahita A, et al. Clin Infect Dis 2002
Heaton KW, et al. Gut 1992
Caroff DA, et al. J Clin Microbiol 2014

RISK FACTORS

ANTIBIOTIC USE
HOSPITALIZATION
ADVANCED AGE
SEVERE ILLNESS
ACID SUPPRESSION
ENTERAL FEEDING
GASTROINTESINAL SURGERY
OBESITY
CHEMOTHERAPY

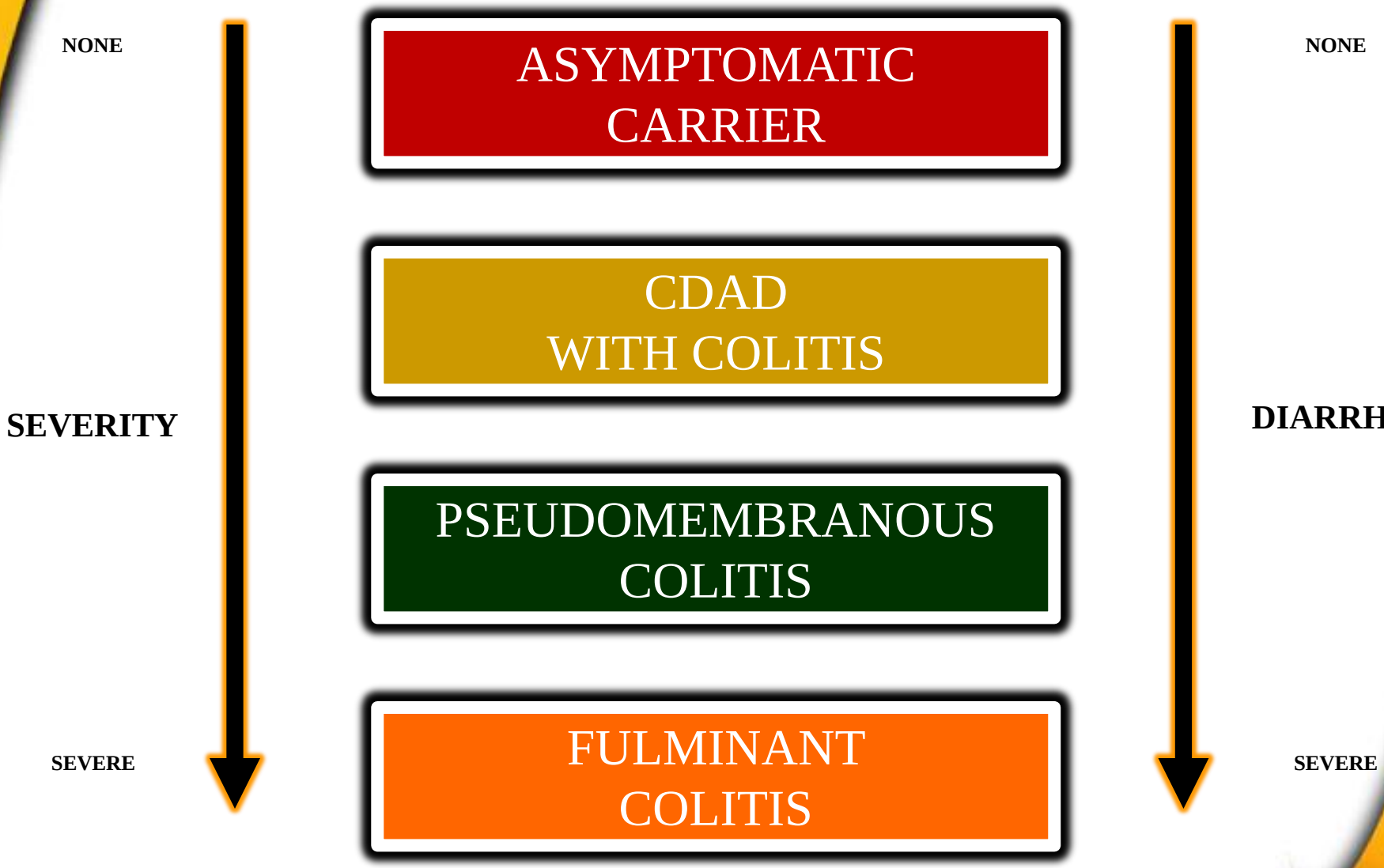
Loo VG, et al. NEJM 2011

ANTIBIOTICS & CDAD

FREQUENT
FLUOROQUINOLONES
CLINDAMYCIN
PENICILLINS (BROAD-SPECTRUM)
CEPHALOSPORINS (BROAD-SPECTRUM)
OCCASIONAL
MACROLIDES
TRIMETHOPRIM
SULFONAMIDES
RARE
AMINOGLYCOSIDES
TETRACYCLINE
CHLORAMPHENICOL
METRONIDAZOLE
VANCOMYCIN

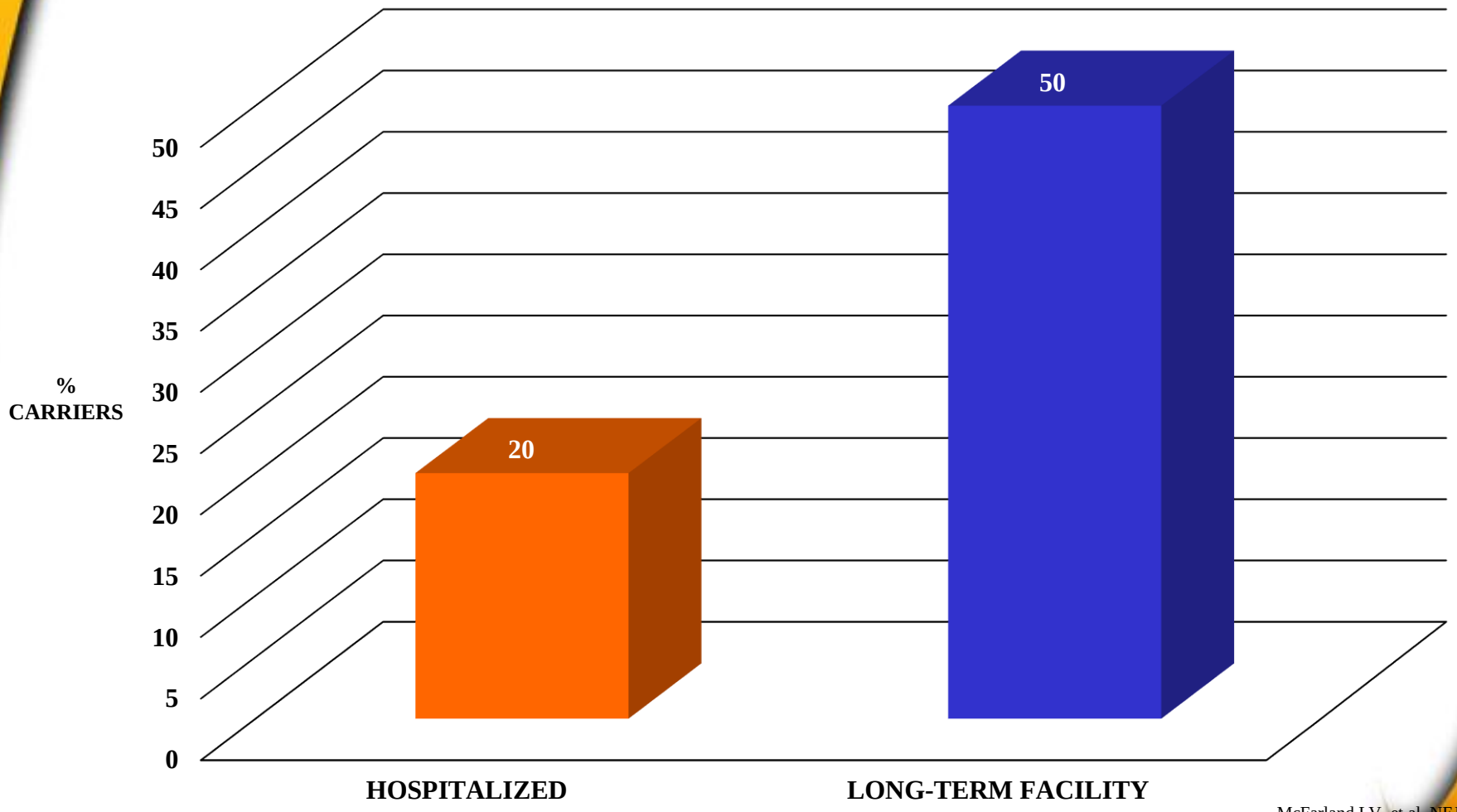
Loo VG, et al. NEJM 2011
LaMont JT, et al. UptoDate 2014

CLINICAL SPECTRUM



Wanahita A, et al. Clin Infect Dis 2002

ASYMPTOMATIC CARRIER

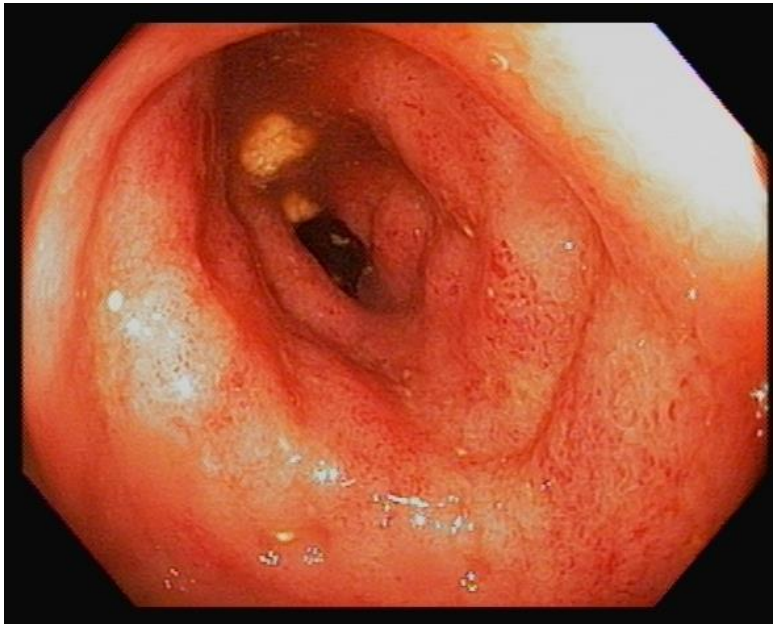


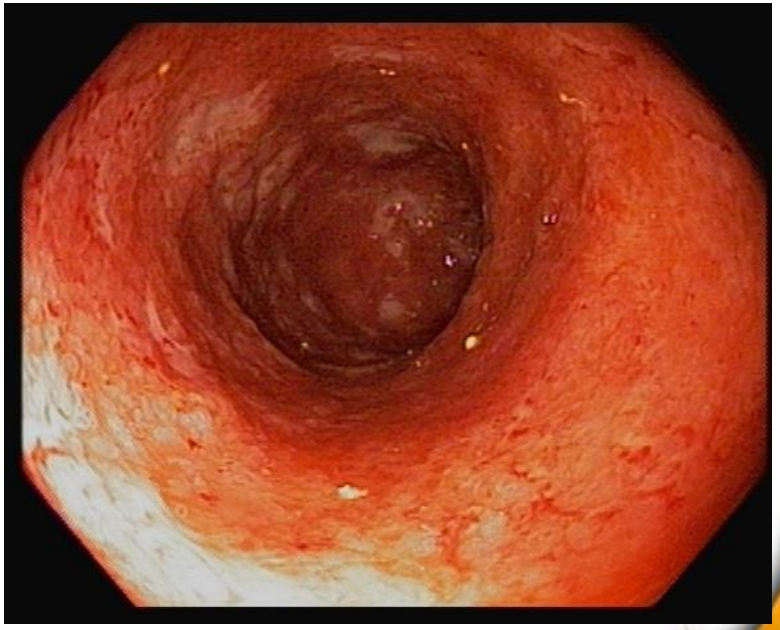
McFarland LV, et al. NEJM 1989
Riggs MM, et al. Clin Infect Dis 2007

CDAD WITH COLITIS

DIARRHEA

UP TO 10-15/DAY
LOWER ABDOMINAL PAIN
LEUKOCYTOSIS
(mean ~15,000)

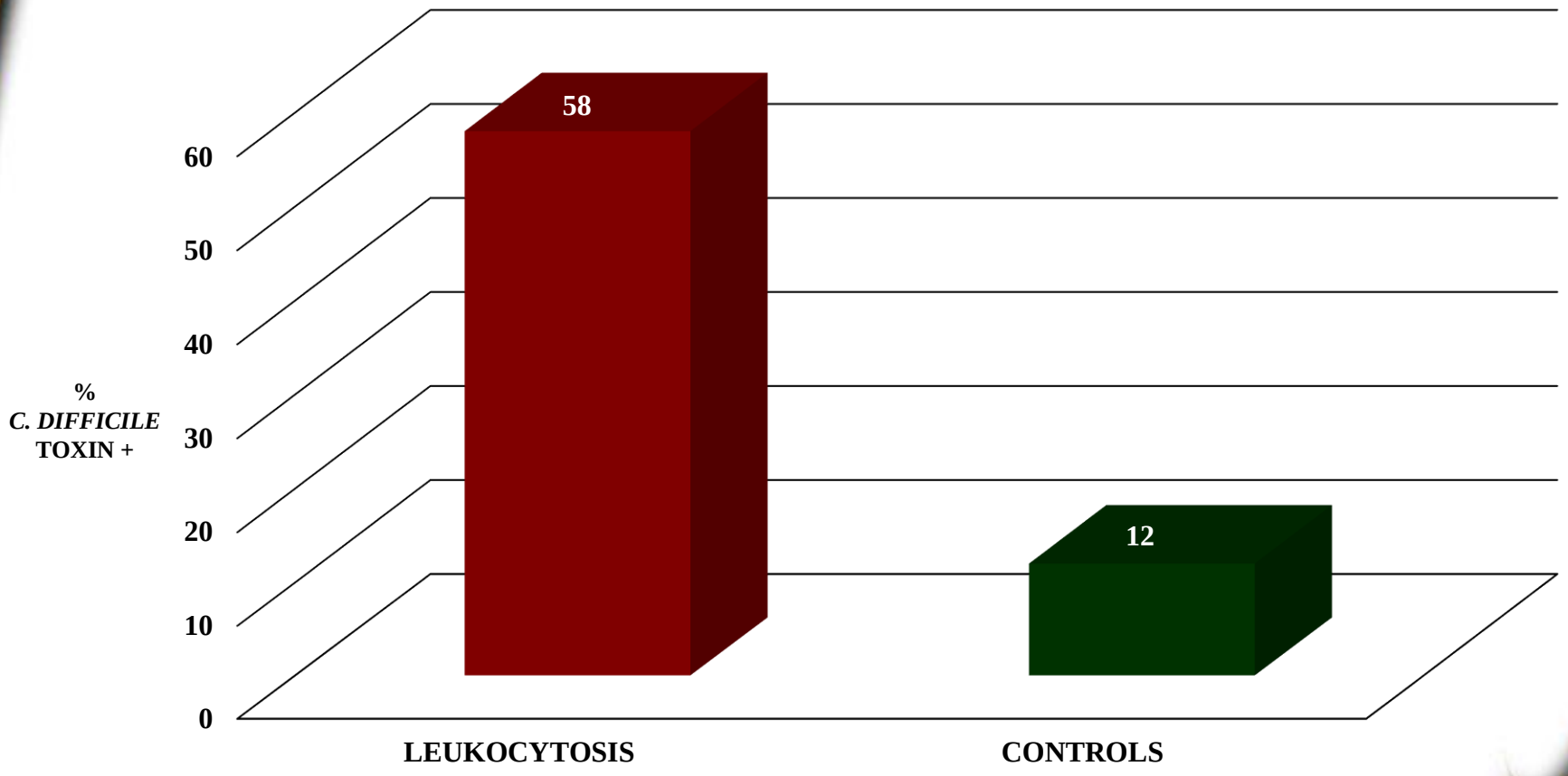




LaMont JT, et al. UptoDate 2014

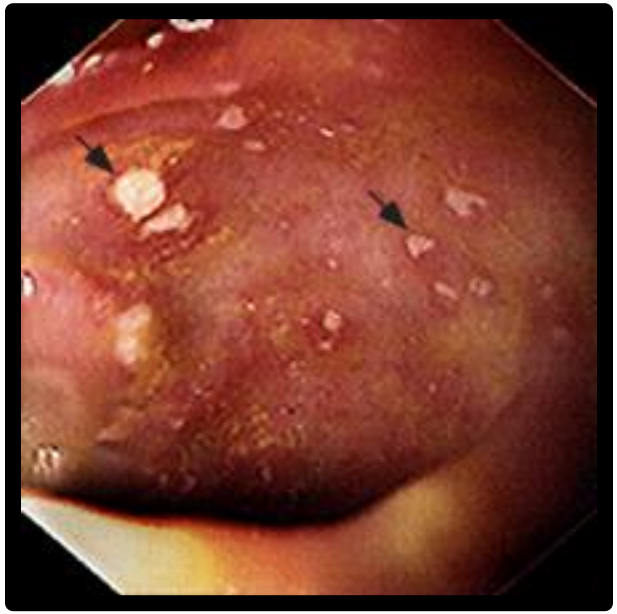
CDAD WITH COLITIS

PROSPECTIVE COHORT IN HOUSTON TEXAS UNEXPLAINED LEUKOCYTOSIS (WBC ≥ 15,000/mm³) VS HOSPITALIZED PATIENTS WITHOUT LEUKOCYTOSIS STOOL BY EIA FOR *C. DIFFICILE* TOXIN n=60 VS 26



Wanahita A, et al. Am J Med 2003

PSEUDOMEMBRANOUS COLITIS



Courtesy of James B McGee MD

Courtesy of James B McGee MD

TOXIN-INDUCED CYSTOSKELETON DISRUPTION → **SHALLOW ULCERATIONS** → **RELEASE OF SERUM PROTEINS, MUCUS, INFLAMMATORY CELLS**

Riegler M, et al. J Clin Invest 1995
LaMont JT, et al. UptoDate 2014

PSEUDOMEMBRANOUS COLITIS

3 TYPES

TYPE 1

MILDER
INFLAMMATION IN SUPERFICIAL EPITHELIUM
CRYPT ABSCESSES OCCASIONAL

TYPE 2

SEVERE DISRUPTION OF GLANDS
MUCIN SECRETION
INFLAMMATION IN BASAL LAMINA

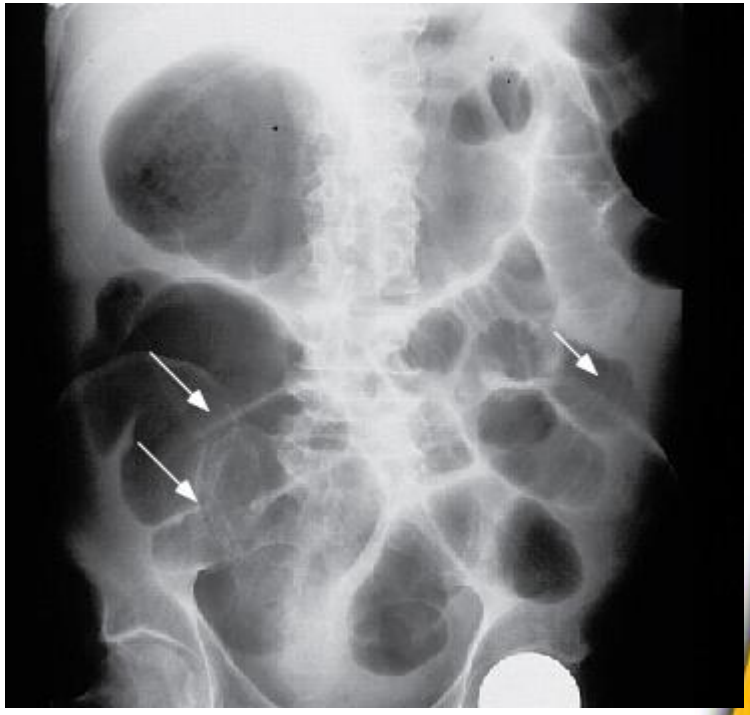
TYPE 3

INTENSE NECROSIS
FULL THICKNESS INFLAMMATION
CONFLUENT PSEUDOMEMBRANES

Price AB, et al. J Clin Pathol 1977

FULMINANT COLITIS

SEVERE PAIN
+/- DIARRHEA
FEVER
HYPOVOLUMEMIA
SEVERE LEUKOCYTOSIS (40,000)



Courtesy of J Thomas LaMont MD

TOXIC MEGACOLON

COLONIC DILATION (>7 cm) + SYSTEMIC TOXICITY

LaMont JT, et al. UptoDate 2014

CLINICAL SPECTRUM

SEVERITY	CRITERIA
MILD-TO-MODERATE DISEASE	DIARRHEA + ANY ADDITIONAL SIGNS OR SYMPTOMS NOT MEETING SEVERE OR COMPLICATED CRITERIA
SEVERE DISEASE	SERUM ALBUMIN < 3 g/dl + ONE OF FOLLOWING: - WBC ≥ 15,000 cells/mm^3 - ABDOMINAL TENDERNESS
SEVERE & COMPLICATED DISEASE	ANY OF THE FOLLOWING ATTRIBUTABLE TO CDAD: - ADMISSION TO ICU FOR CDAD - HYPOTENSION ± VASOPRESSORS - FEVER ≥ 38.5^{o}C - ILEUS OR SIGNIFICANT ABDOMINAL DISTENTION - MENTAL STATUS CHANGES - WBC ≥ 35,000 cells/mm^3 OR < 2,000 cells/mm^3 - SERUM LACTATE > 2.2 mmol/l - END ORGAN FAILURE (VENTILATOR, RENAL FAILURE, ETC)
RECURRENT DISEASE	RECURRENT CDAD ≤ 8 WEEKS OF COMPLETION OF THERAPY

Surawicz CM, et al. Am J Gastroenterol 2013

DIAGNOSIS

DIARRHEA

AND

STOOL TEST + FOR *C. DIFFICILE* TOXINS OR TOXIGENIC *C. DIFFICILE*

OR

ENDOSCOPIC/HISTOLOGIC PSEUDOMEMBRANOUS COLITIS

Kelly CP, et al. NEJM 1994
Crobach MJ, et al. Clin Microbiol Infect 2009

STOOL STUDIES

POLYMERASE CHAIN REACTION

ENZYME IMMUNOASSAY FOR *C. DIFFICILE* GLUTAMATE DEHYDROGENASE

ENZYME IMMUNOASSAY FOR *C. DIFFICILE* TOXINS A & B

CELL CULTURE CYTOTOXICITY ASSAY

SELECTIVE ANAEROBIC CULTURE

Cohen SH, et al. Infect Control Hosp Epidemiol 2010
Kufelnicka AM, et al. Clin Infect Dis 2011

STOOL STUDIES

STOOL STUDY	SENSITIVITY/SPECIFITY	EXTRAS
PCR	87% / 97%	~ 1 HOUR EXPENSIVE
EIA FOR GDH	75-90% / >90%	GDH IS AN ESSENTIAL ENZYME CANNOT DIFFENTIATE TOXIC FROM NON-TOXIC STRAINS HIGH FALSE +
EIA FOR TOXINS	60-85% / 95-100%	HIGH FALSE – NEED 100-1000 pg OF TOXIN
CELL CULTURE CYTOTOXICITY ASSAY	95-100% / 99%	STOOL ON CULTURED CELLS → TOXIN AFFECTS FIBROBLASTS NOT WIDELY AVAILABLE SLOW, ~ 2 DAYS EXPENSIVE NOT STANDARDIZED
SELECTIVE ANAEROBIC CULTURE	96% / 100%	VERY SLOW LABOR INTENSIVE

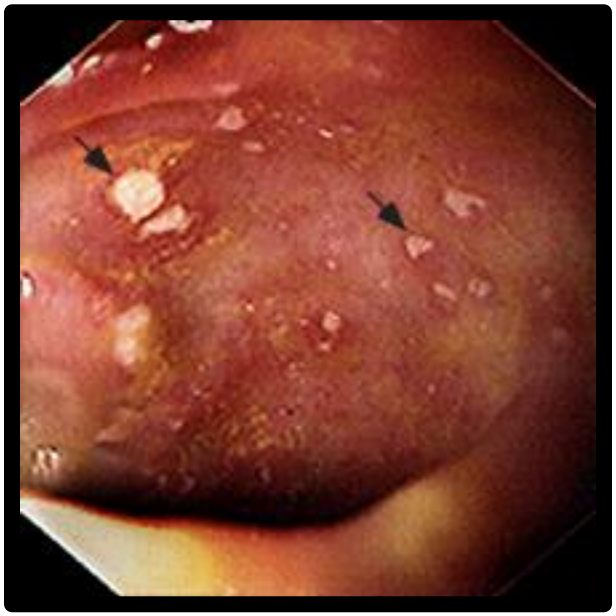
Luo RF, et al. J Clin Microbiol 2010
Brecher SM, et al. Clin Infect Dis 2013
Planche T, et al. Lancet Infect Dis 2008
Shetty N, et al. J Hosp Infect 2011
Shannon-Lowe J, et al. BMJ 2010
Peterson LR, et al. Clin Infect Dis 2007

COLONOSCOPY

PSEUDOMEMBRANES

ABSENT IN 10-20%

RARELY SEEN WITH IBD AND SUPERIMPOSED *C. DIFFICILE*



Courtesy of James B McGee MD

IF LABS NEGATIVE BUT SUSPECT
PROMPT DIAGNOSIS
FAILURE TO ANTIBIOTICS
ATYPICAL PRESENTATION
(ILEUS, LITTLE DIARRHEA)

Courtesy of James B McGee MD

Goodhand JR, et al. Aliment Pharmacol Ther 2011
Ananthakrishnan AN, et al. Expert Rev Gastroenterol Hepatol 2010

DIAGNOSTIC SUMMARY

EIA AND PCR REASONABLY SPECIFIC

REPEAT EIA, GDH, PCR NOT INDICATED

+ TEST + DIARRHEA = TREATMENT

COLONOSCOPY NOT NECESSARY

CLOSTRIDIUM DIFFICILE TREATMENT

INITIAL TREATMENT

DISCONTINUE OTHER ANTIBIOTIC
(IF POSSIBLE)

SUPPORTIVE CARE
IVFs AND ELECTROLYTES

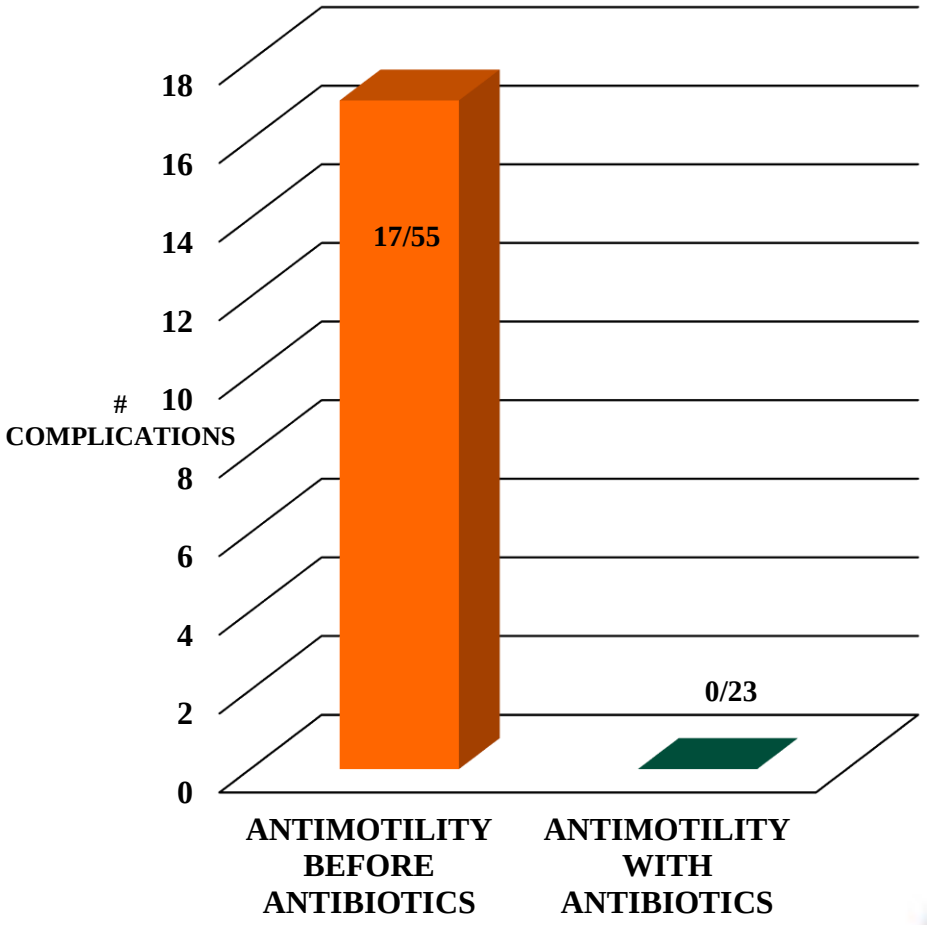
INFECTION CONTROL

AVOID LOPERAMIDE & OPIATES?

ANTIMOTILITY AGENTS

REVIEW OF LITERATURE
1 RETROSPECTIVE STUDY, 19 CASE REPORTS/SERIES
n=55

ANTIMOTILITY AGENT
DIPHENOXYLATE/ATROPINE
LOPERAMIDE
OPIATES TINCTURE OF OPIUM CODEINE MORPHINE



Koo HL et al. Clin Infect Dis 2009
Wilcox MH, et al. J Antimicrob Chemother 1995

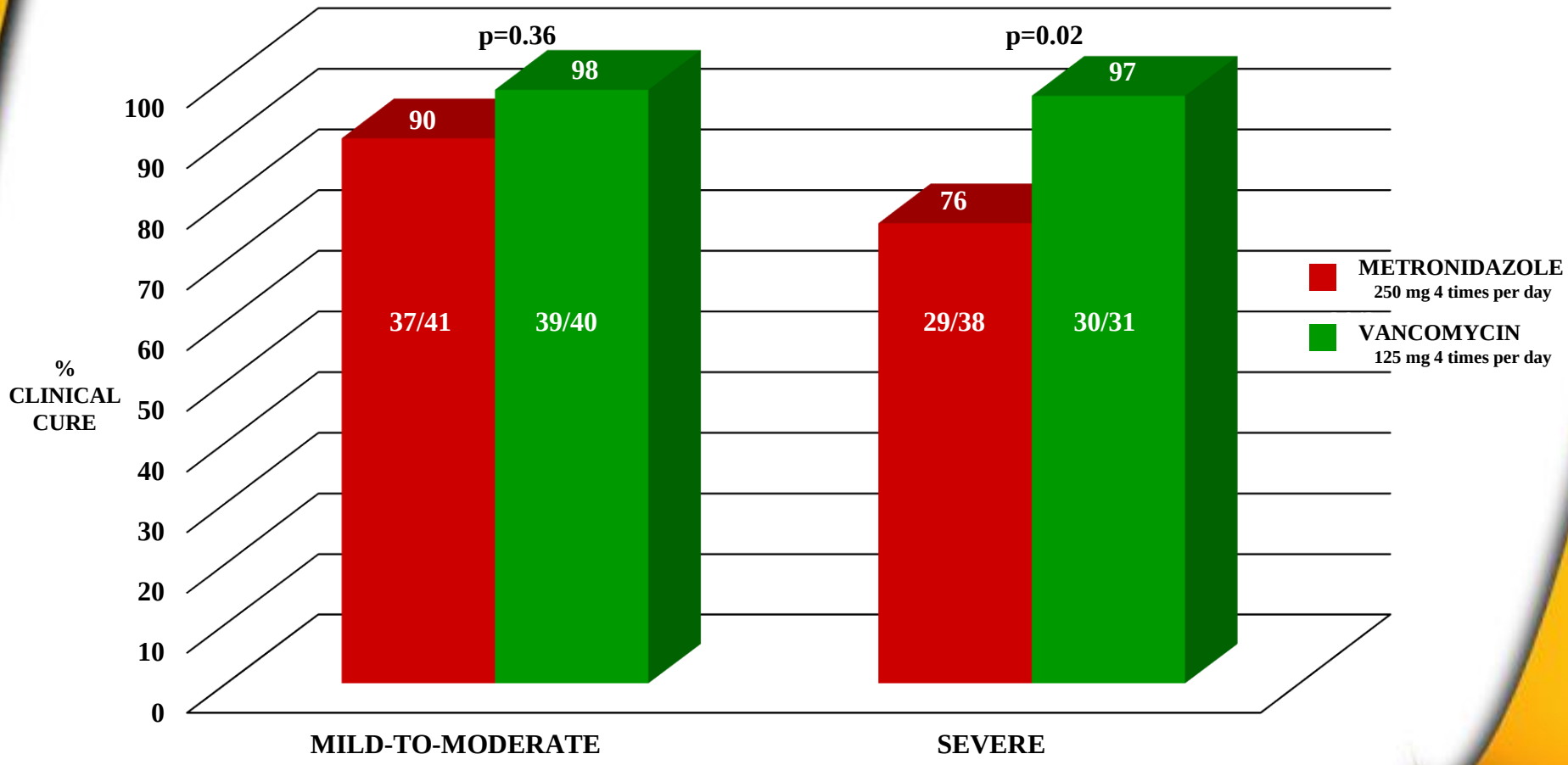
TREATMENT

- METRONIDAZOLE
- VANCOMYCIN
- FIDAXOMICIN
- FECAL MICROBIOTA TRANSPLANTATION
- COLECTOMY

CLOSTRIDIUM DIFFICILE
INITIAL TREATMENT

INITIAL TREATMENT

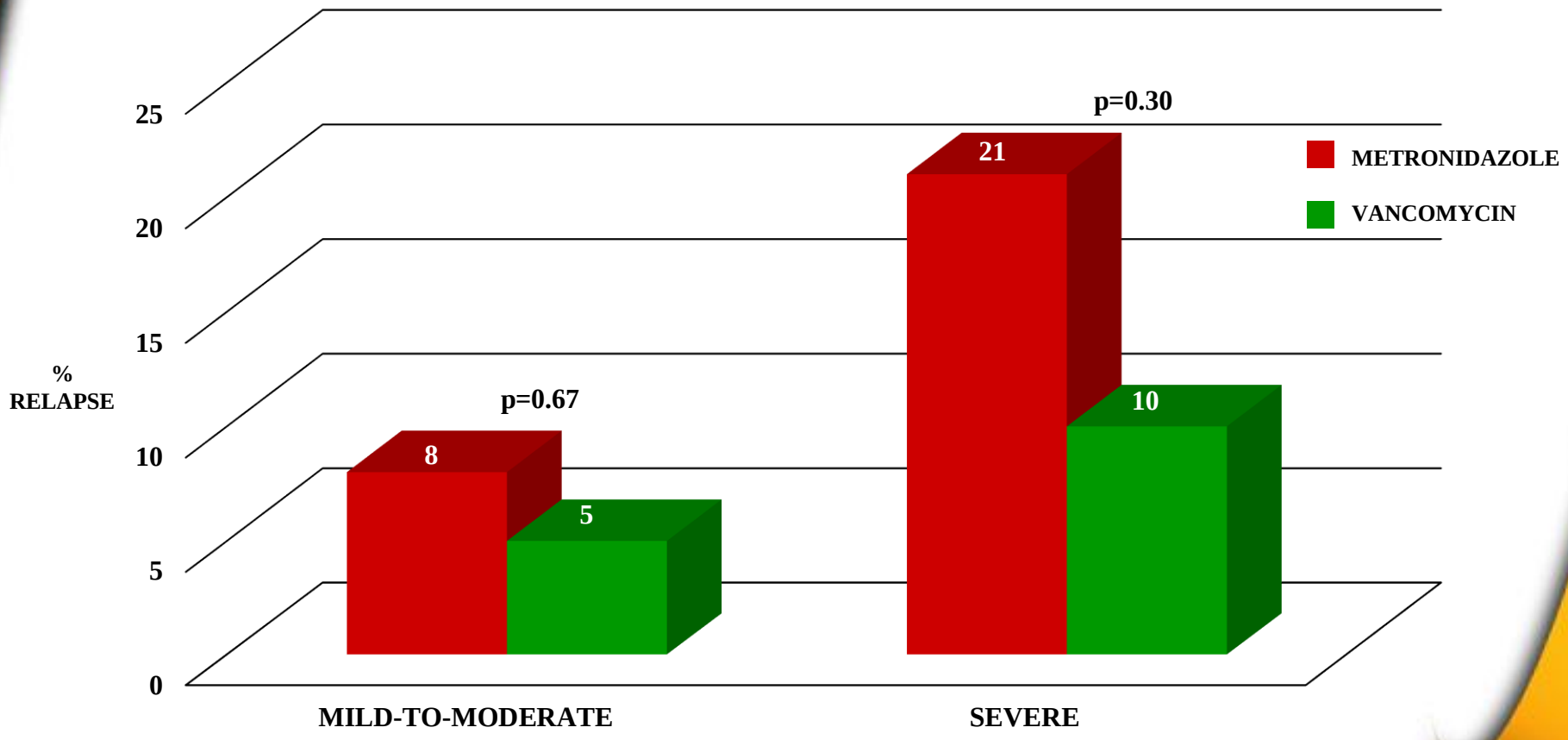
RCT IN CHICAGO ILLINOIS
MILD-TO-MODERATE AND SEVERE CDAD
1994-2002
N=150



Zar FA, et al. Clin Infect Dis 2007

INITIAL TREATMENT

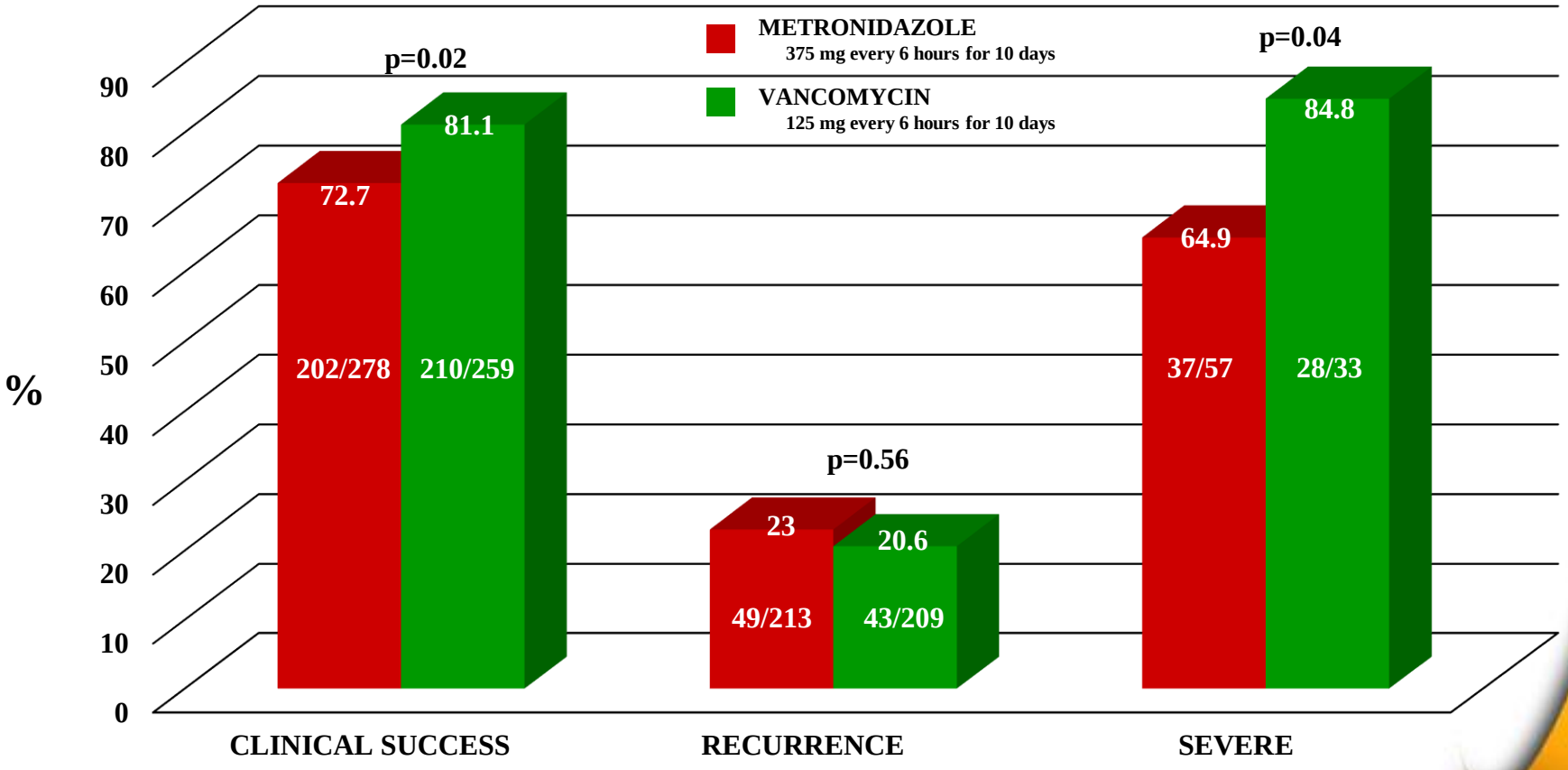
RCT IN CHICAGO ILLINOIS
MILD-TO-MODERATE AND SEVERE CDAD
1994-2002
N=150



Zar FA, et al. Clin Infect Dis 2007

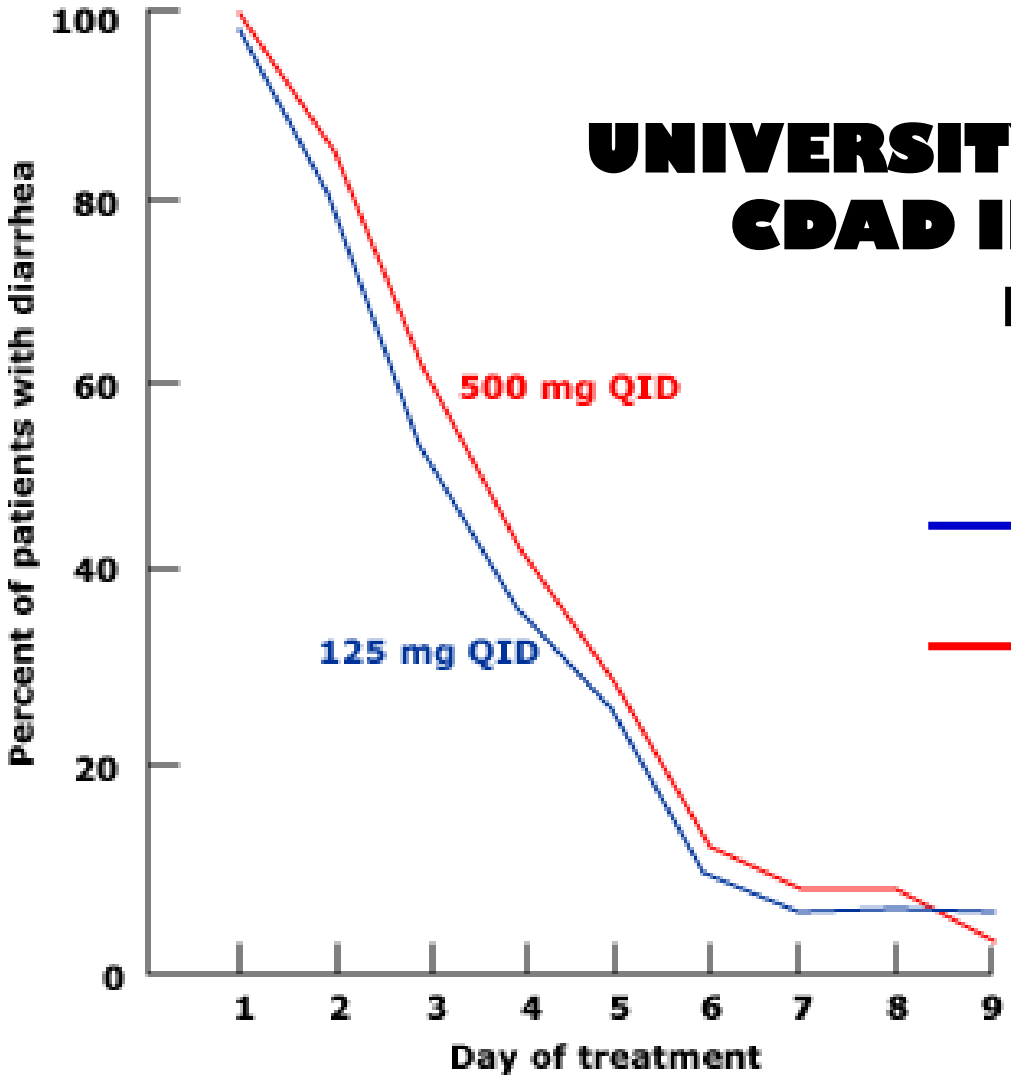
INITIAL TREATMENT

RCT
91 CENTERS IN U.S., CANADA, EUROPE, AUSTRALIA
CDAD
2005-2007
n=537



Johnson S, et al. Clin Infect Dis 2014

INITIAL TREATMENT



RCT
UNIVERSITY OF MICHIGAN
CDAD IN HOSPITAL
n=46

VANCOMYCIN
125 mg QID for 10 days

VANCOMYCIN
500 mg QID for 10 days

Fekety R, et al. Am J Med 1989

CLOSTRIDIUM DIFFICILE RECURRENCES

RECURRENCE TREATMENT

CDAD INFECTION → RESOLUTION OF SYMPTOMS → REAPPEARANCE OF SYMPTOMS

ANTIBIOTIC TREATMENT

REINFECTIONS SIMILAR TO RELAPSES
MOST ≤ 1-3 WEEKS
CAN BE 2-3 MONTHS
1 RECURRENCE = 45-65% OF ANOTHER

RISK FACTORS

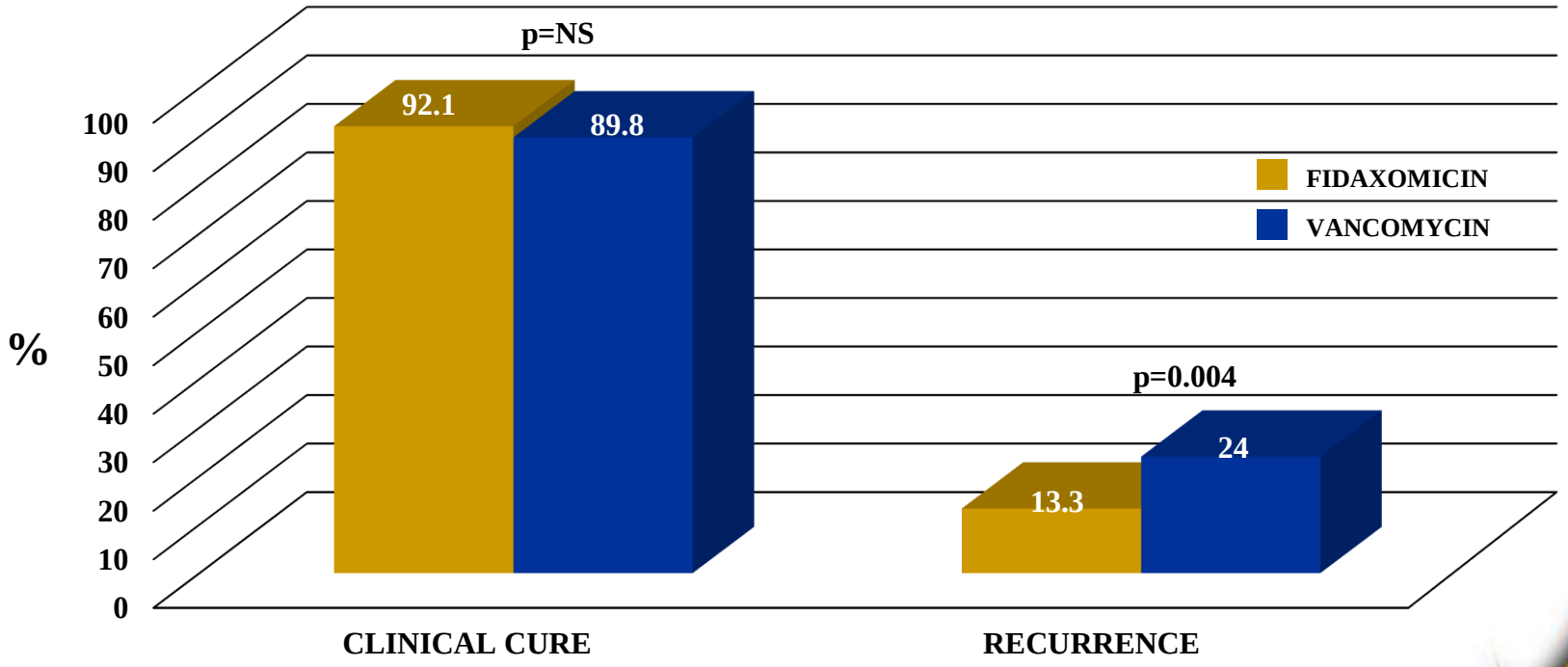
AGE ≥ 65 YEARS
SEVERE UNDERLYING MEDICAL DISORDERS
NEED FOR ONGOING CONCOMITANT ANTIBIOTICS

Barbut F, et al. J Clin Microbiol 2000
McFarland LV. J Med Microbiol 2005
Pepcin J, et al. Clin Infect Dis 2006

RECURRENCE TREATMENT

RCT
67 CENTERS IN U.S. AND CANADA
2006-2008
n=548

FIDAXOMICIN 200 mg PO BID vs VANCOMYCIN 125 mg PO QID X10 DAYS
PER PROTOCOL ANALYSIS

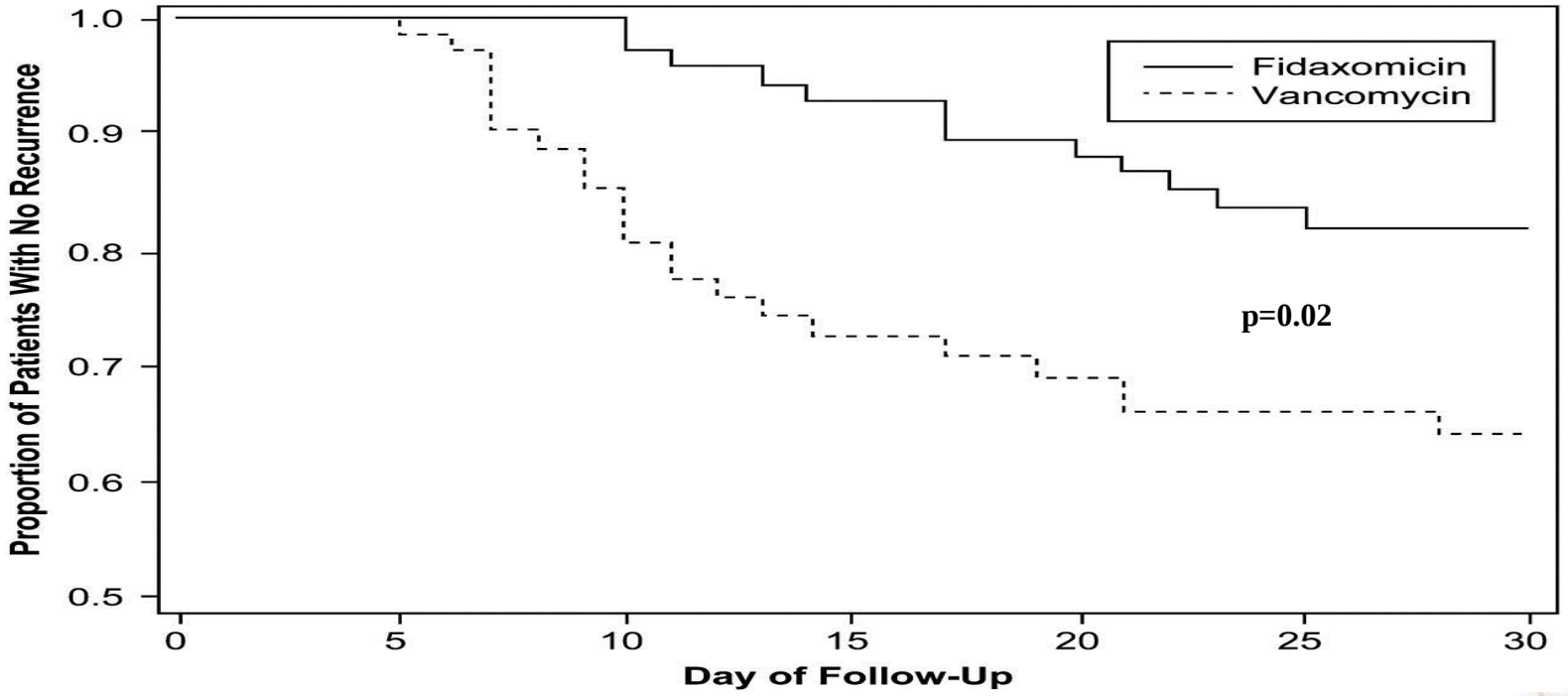


Louie TJ, et al. NEJM 2011

RECURRENCE TREATMENT

RCT – PHASE 3
154 CENTERS IN U.S., CANADA, EUROPE
n=162

FIDAXOMICIN 200 mg PO BID vs VANCOMYCIN 125 mg PO QID X10 DAYS
RECURRENCE ≤ 28 DAYS



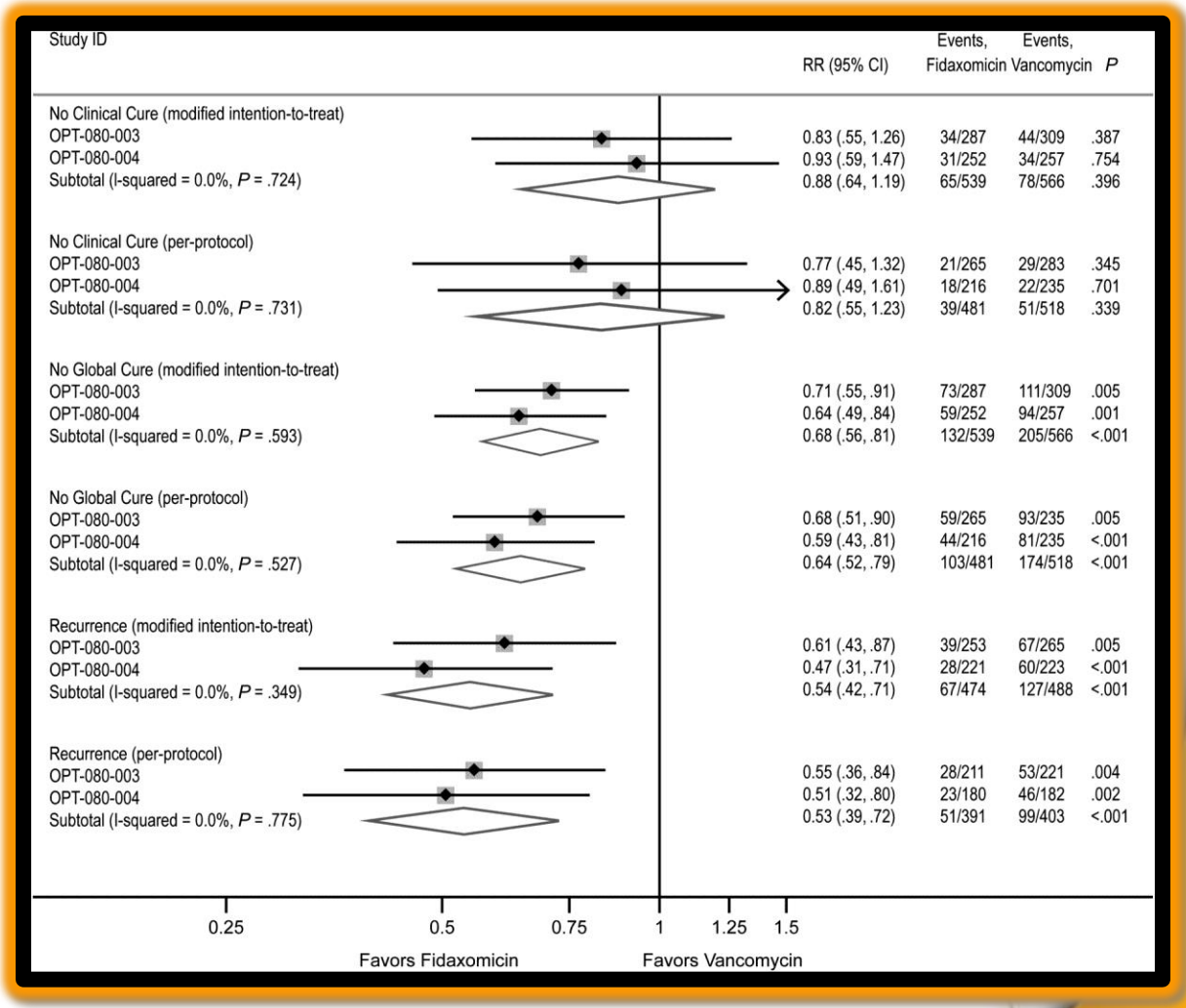
Cornely OA, et al. Clin Infect Dis 2012

RECURRENCE TREATMENT

META-ANALYSIS
n=1,164

FIDAXOMICIN 200 mg PO BID
vs
VANCOMYCIN 125 mg PO QID

X10 DAYS



Crook DW, et al. Clin Infect Dis 2012

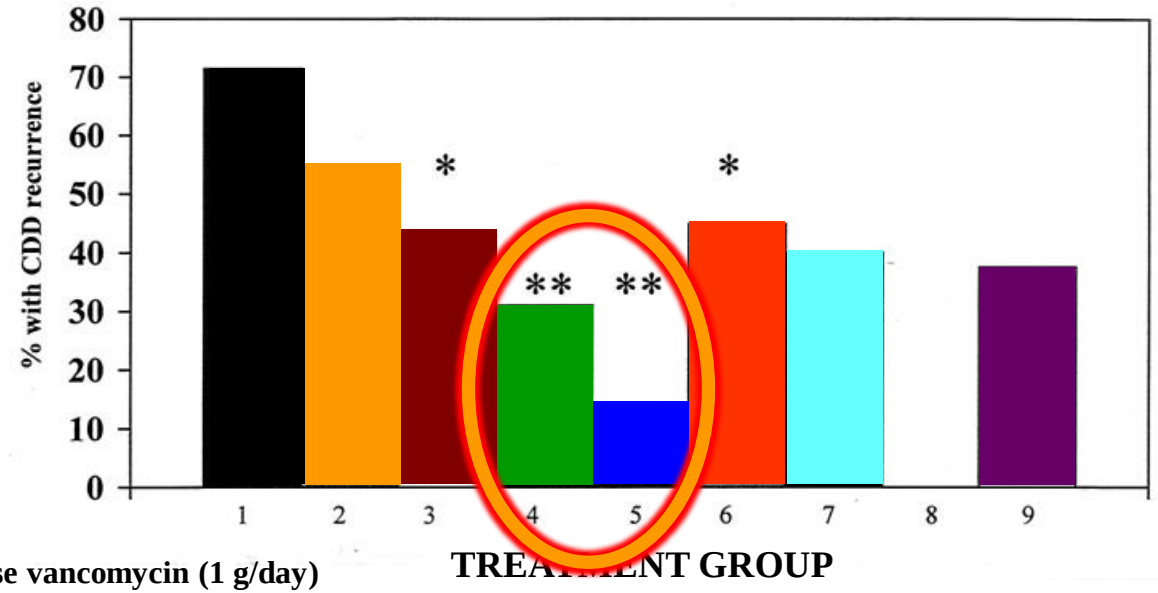
MULTIPLE RECURRENCES TREATMENT

REVIEW OF 2 RCTs
n=163
TAPER REGIMEN

(VANCOMYCIN OR METRONIDAZOLE STARTED AT ONE DOSE OF 500mg - 3g/DAY & THEN DECREASED STEPWISE OVER A PERIOD OF TIME TO DOSES RANGING FROM 125 TO 750mg/DAY)

PULSED REGIMEN

VANCOMYCIN (125-500mg) EVERY 2-3 DAYS OVER A PERIOD OF TIME (USUALLY 3 WK)



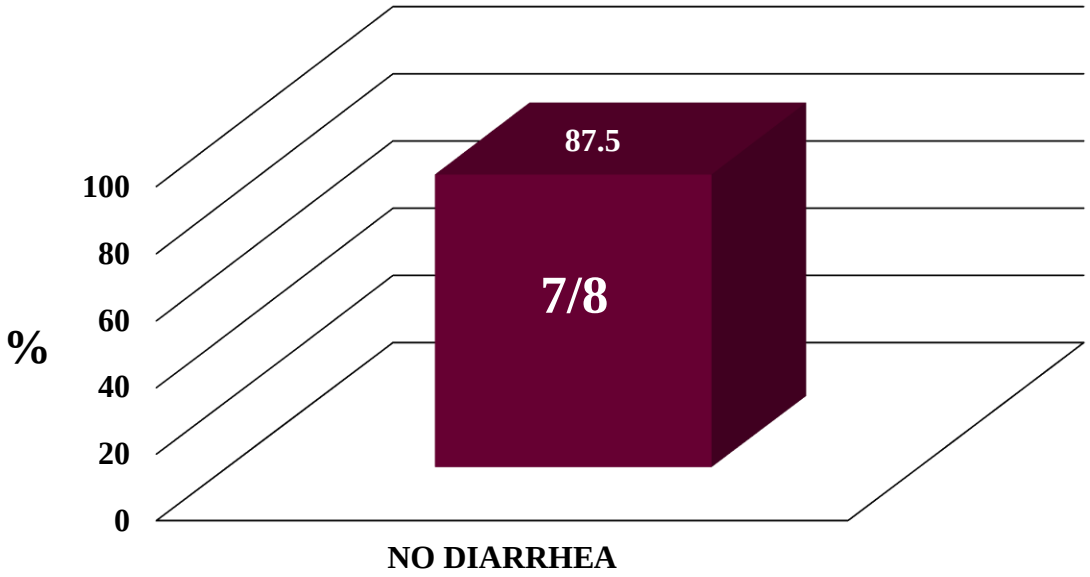
Treatment response in 163 patients with RCDD
1 = medium dose vancomycin
2 = low dose vancomycin
3 = high dose vancomycin
4 = tapered vancomycin
5 = pulsed vancomycin
6 = low dose metronidazole
7 = medium dose metronidazole
8 = high dose metronidazole
9 = miscellaneous

*0.05 < *p* < 0.1, compared to medium dose vancomycin (1 g/day)
***p* < 0.05, compared to medium dose vancomycin (1 g/day).

McFarland LV, et al. Am J Gastroenterol 2002

MULTIPLE RECURRENCES TREATMENT

CASE SERIES AT HINES VA ILLINOIS
n=8 FEMALES
4-8 EPISODES OF RECURRENT CDAD
VANCOMYCIN → ASYMPTOMATIC →
RIFAXIMIN CHASER 400-800mg DAILY TOTAL (BID OR TID) X 2 WEEKS
RIFAXIMIN 400mg PO BID (n=6)
RIFAXIMIN 200mg PO TID (n=1)
RIFAXIMIN 200mg PO BID (n=1)



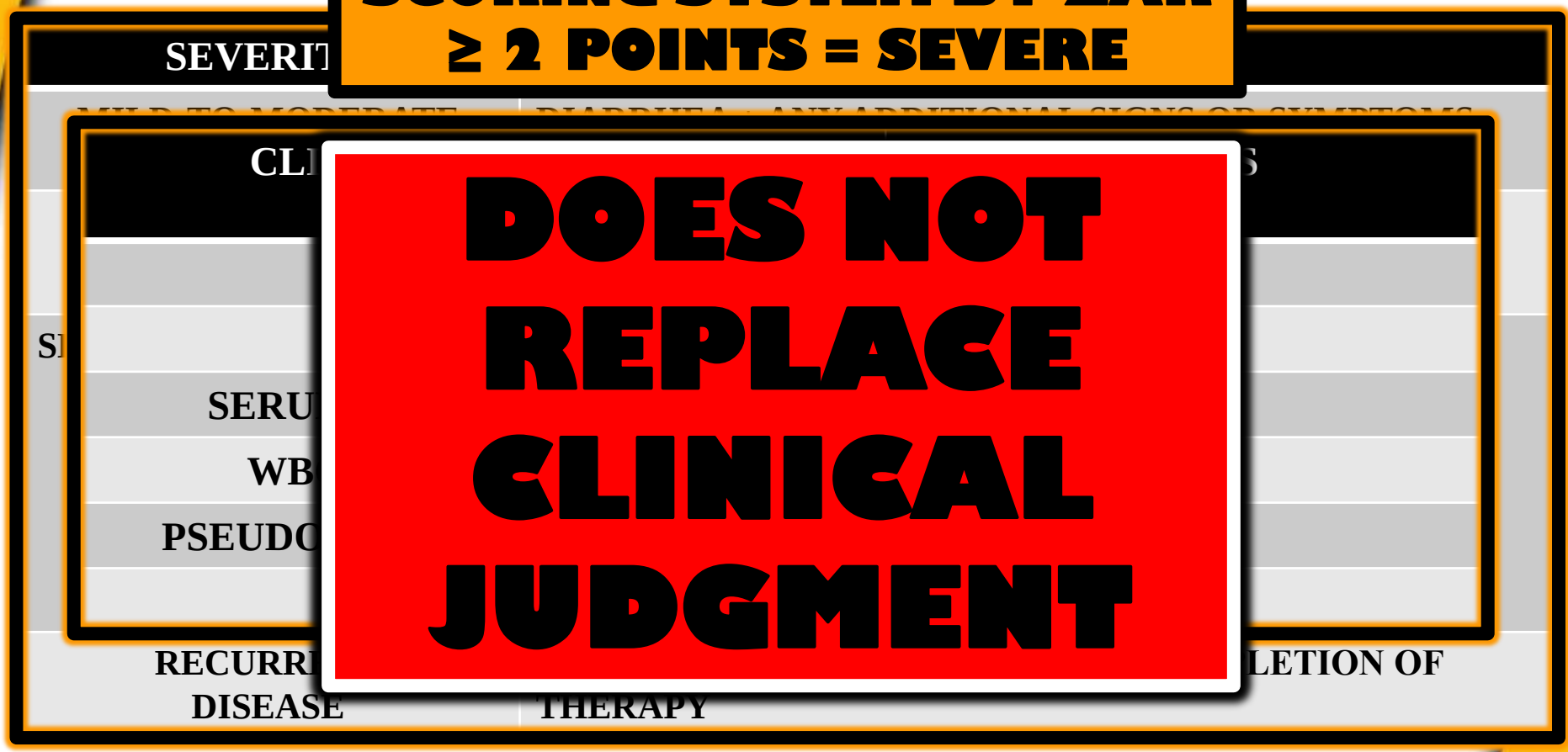
Johnson S, et al. Clin Infect Dis 2007

CLOSTRIDIUM DIFFICILE
SEVERE DISEASE

SEVERE TREATMENT

SCORING SYSTEM BY ZAR
≥ 2 POINTS = SEVERE

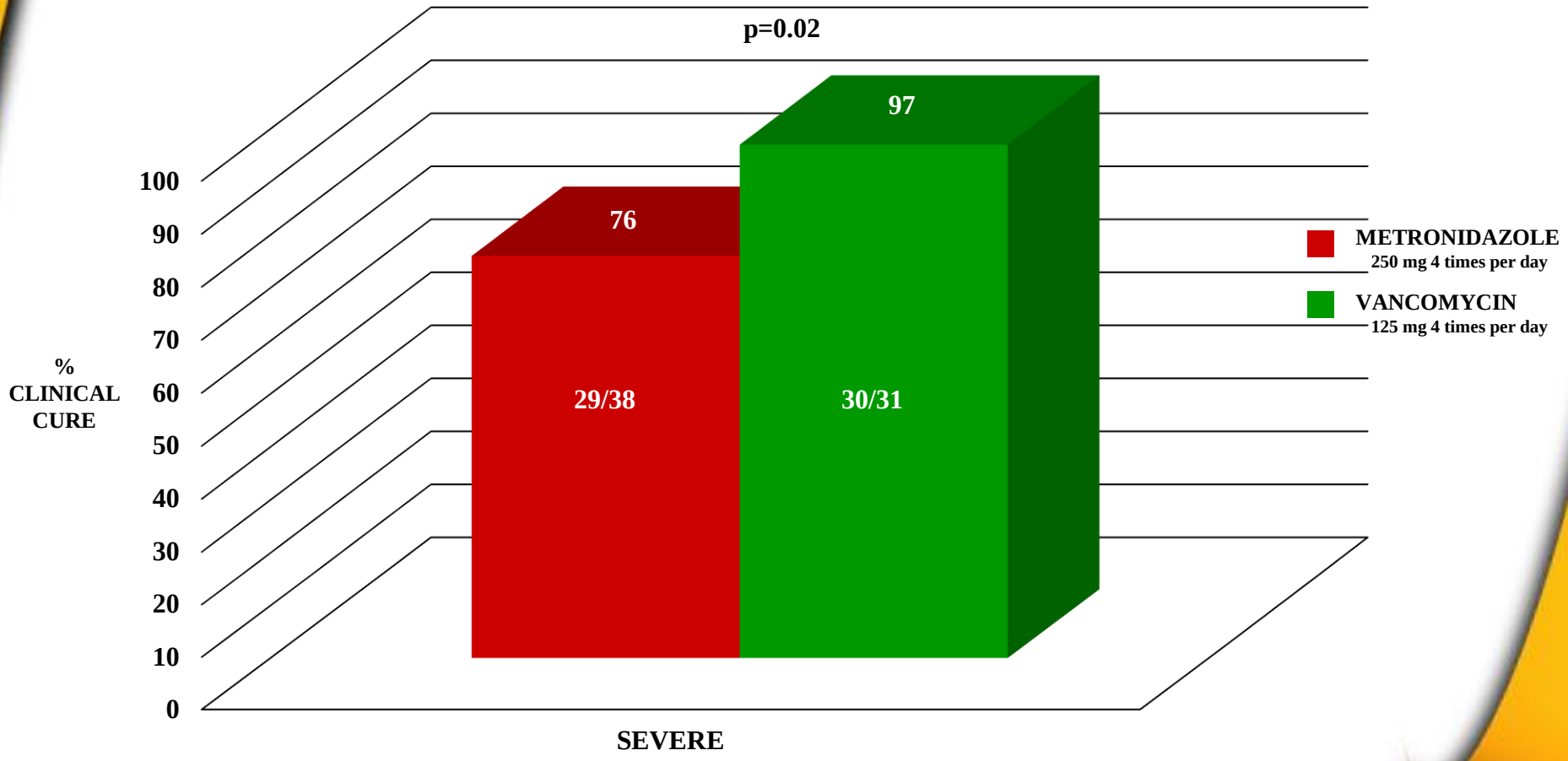
DOES NOT REPLACE CLINICAL JUDGMENT



Surawicz CM, et al. Am J Gastroenterol 2013
Zar FA, et al. Clin Infect Dis 2007

SEVERE TREATMENT

RCT IN CHICAGO ILLINOIS
SEVERE CDAD
1994-2002
N=69



Zar FA, et al. Clin Infect Dis 2007

SEVERE TREATMENT

ORAL ANTIBIOTICS

VANCOMYCIN 125mg QID
VANCOMYCIN 500mg QID
FIDAXOMICIN 200mg BID
METRONIDAZOLE 500mg TID OR 250mg QID

IV ANTIBIOTICS

METRONIDAZOLE 500mg q 8 HOURS
(HIGH BILIARY SECRETION)
TIGECYCLINE IV
VANCOMYCIN IV

DOES NOT WORK

LACKING EVIDENCE

COLONIC ANTIBIOTICS

VANCOMYCIN ENEMAS

Cohen SH, et al. Infect Control Hosp Epidemiol 2010
Zar FA, et al. Clin Infect Dis 2007
Herpers BL, et al. Clin Infect Dis 2009

SEVERE TREATMENT

CASE SERIES AT WASHINGTON UNIVERSITY
SEVERE CDAD WITH ADJUNCTIVE INTRACOLONIC VANCOMYCIN ENEMAS
1998-2001
N=9

VANCOMYCIN IV SOLUTION (0.5-1g DISSOLVED IN 1-2L OF NORMAL SALINE) → GIVEN AS RETENTION ENEMA VIA 18-FR FOLEY CATHETER WITH 30cc BALLOON IN RECTUM X 60 MINUTES q 4-12 HOURS UNTIL CLINICAL IMPROVEMENT

Patient [reference]	Radiography finding[a]	Sigmoidoscopy finding	ICV dosage (duration, days)	Concurrent anti–*C. difficile* medication	Surgery consultation (surgery)	Clinical resolution (outcome)	Eradication of cytotoxin production after ICV therapy	Bacteremia or fungemia (etiologic agent)[b]
1	Diffuse colitis	PMC	1 g q12h (7)	Mtz (iv), Mtz (po), Vm (po)	Yes (No)	Complete (recovered)	Yes	No
2	Diffuse colitis	ND	1 g q12h (10)	Mtz (iv), Mtz (po), Vm (po)	Yes (No)	No (died)	ND	No
3	Right-side colitis	ND	0.5 g q4h (5)	Mtz (iv), Mtz (po)	Yes (No)	Complete (recovered)	Yes	Yes (VRE)
4	Diffuse colitis	ND	0.5 g q4h (4)	Mtz (iv), Mtz (po), Vm (po)	No	Complete (recovered)	ND	No
5	Left-side colitis	PMC	1 g q12h (4)	Mtz (iv), Mtz (po)	No	Complete (recovered)	ND	No
6	Left-side colitis	PMC	0.5 g q8h (14)	Mtz (iv), Mtz (po), Vm (po), Lact, Bct	Yes (No)	Complete (recovered)	Yes	Yes (VRE)
7	Diffuse colitis	ND	1 g q8h (2)	Mtz (iv), Mtz (po), Vm (po)	No	Complete (recovered)	ND	No
8	Diffuse colitis	ND	0.5 g q6h (9)	Mtz (iv), Mtz (po), Vm (po), Lact, Bct	No	Complete (recovered)	No	Yes *(Citrobacter freundii)*
9 [42]	Diffuse colitis	Diffuse edema	0.5 g q6h (6)	Mtz (iv), Mtz (po), Vm (po)	Yes (No)	Complete (recovered)	ND	Yes (*Candida glabrata*, CNS)

NOTE. All patients had confirmed *C. difficile* toxin by cytotoxicity assay (Bartels' Cytotoxicity Assay; Bartels). Bct, bacitracin; CNS, coagulase-negative staphylococci; Lact, lactobacillus; Mtz, metronidazole; ND, not done; PMC, pseudomembranous colitis; Vm, vancomycin; VRE, vancomycin-resistant enterococci.

[a] Abdominal CT scan, plain abdominal film at the onset of symptoms, or both.

[b] Bacteremia or fungemia after the initiation of ICV therapy.

Apisarnthanarak A, et al. Clin Infect Dis 2002

SEVERE TREATMENT

WHEN TO CALL SURGERY

TOXIC MEGACOLON-ASSOCIATED ILEUS, PERITONITIS, IMPENDING PERFORATION

HYPOTENSION

SEPSIS

MULTI-ORGAN FAILURE

WBC ≥ 50,000 cells/mm^3

SERUM LACTATE ≥ 5 mmol/L

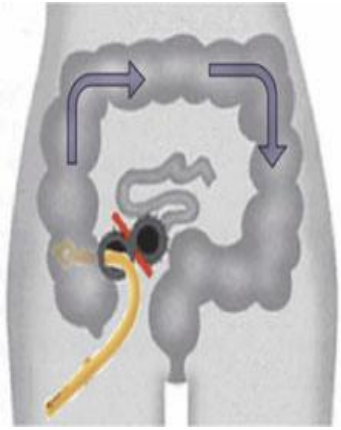
SUBTOTAL COLECTOMY

DIVERTING LOOP ILEOSTOMY

Steele SR, et al. Dis Colon Rectum 2015
Sailhamer EA, et al. Arch Surg 2009

SEVERE TREATMENT

CASE SERIES AT UNIVERSITY OF PITTSBURGH
SEVERE CDAD
DIVERTING LOOP ILEOSTOMY + COLONIC VANCOMYCIN LAVAGE
vs
HISTORICAL COLECTOMY CONTROLS
2009-2011
N=42

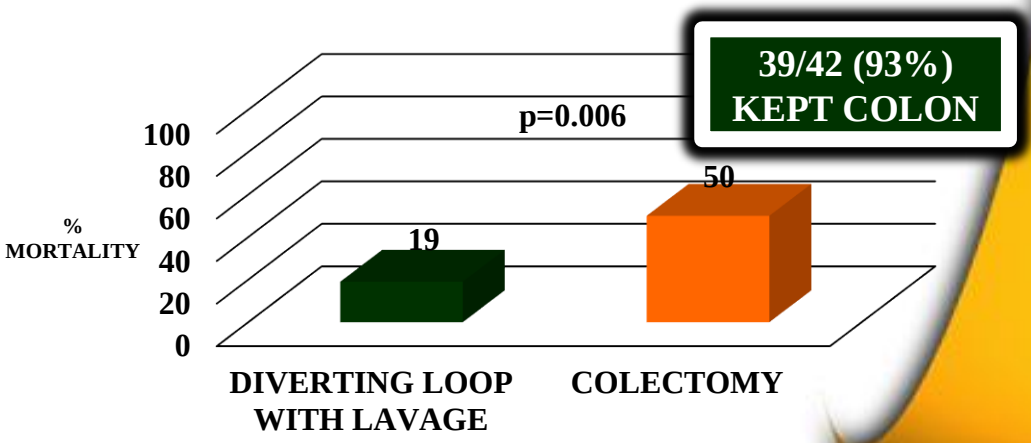


1. Creation of diverting loop ileostomy.
2. Intraoperative antegrade colonic lavage with 8 liters of warmed PEG3350/electrolyte solution via ileostomy.
3. Postoperative antegrade colonic enemas with vancomycin (500 mg in 500 mL X 10 days) via ileostomy.

	Ileostomy/Lavage	Colectomy	*P*
Age, y	65.3 ± 13	62.1 ± 14	0.28
Sex	45% women	45% women	1.0
APACHE-II (mean ± SD)	29.7 ± 5.5	28.5 ± 7.1	0.39
While blood cell count (mean ± SD)	25.4 ± 12.1	27.1 ± 13.2	0.54
Band count (mean ± SD)	21.4 ± 12.2	21.3 ± 12.9	0.97
Albumin (mean ± SD)	2.0 ± 0.8	2.2 ± 0.8	0.26
Intensive care unit	38/42 (90%)	38/42 (90%)	0.64
Intubated	27/42 (64%)	26/42 (62%)	0.82
Vasopressors	31/42 (74%)	32/42 (76%)	0.81
Immunosuppression	19/42 (45%)	17/42 (40%)	0.66
Postoperative death	8/42 (19%)	21/42 (50%)	0.006*

*Odds ratio = 0.24 (0.09–0.63).

Morbidity	Ileostomy/Colonic lavage No. (%)	Colectomy No. (%)
Deep venous thrombosis/pulmonary embolism	1 (2.4%)	3 (7.1%)
Surgical site infection	3 (7.1%)	9 (21%)
Urinary tract infection	3 (7.1%)	4 (9.5%)
Pneumonia	4 (9.5%)	5 (12%)
Inadvertent enterotomy	1 (2.4%)	1 (2.4%)
Reoperation related to ileostomy	2 (4.8%)	4 (9.5%)
"Ileostomy tube" migration	1 (2.4%)	NA



Neal MD, et al. Ann Surg 2011

TREATMENT

SEVERITY	CRITERIA	ACG TREATMENT 2013	SHEA/IDSA TREATMENT 2010
MILD-TO-MODERATE DISEASE	DIARRHEA + ANY ADDITIONAL SIGNS OR SYMPTOMS NOT MEETING SEVERE OR COMPLICATED CRITERIA	METRONIDAZOLE 500mg PO TID X 10 DAYS IF UNABLE TO TAKE, VANCOMYCIN 125mg PO QID X 10 DAYS IF NO IMPROVEMENT IN 5-7 DAYS, CONSIDER CHANGE TO VANCOMYCIN 125mg PO QID X 10 DAYS	METRONIDAZOLE 500mg PO TID X 10-14 DAYS
SEVERE DISEASE	SERUM ALBUMIN < 3 g/dl + ONE OF FOLLOWING: - WBC ≥ 15,000 cells/mm^3 - ABDOMINAL TENDERNESS	VANCOMYCIN 125mg PO QID X 10 DAYS	VANCOMYCIN 125mg PO QID X 10-14 DAYS
SEVERE & COMPLICATED DISEASE	ANY OF THE FOLLOWING ATTRIBUTABLE TO CDAD: - ADMISSION TO ICU FOR CDAD - HYPOTENSION ± VASOPRESSORS - FEVER ≥ 38.5°C - ILEUS OR SIGNIFICANT ABDOMINAL DISTENTION - MENTAL STATUS CHANGES - WBC ≥ 35,000 cells/mm^3 OR < 2,000 cells/mm^3 - SERUM LACTATE > 2.2 mmol/l - END ORGAN FAILURE (VENTILATOR, RENAL FAILURE, ETC)	VANCOMYCIN 125mg PO QID + METRONIDAZOLE 500mg IV q 8 HRS + VANCOMYCIN 500mg in 500cc PR QID SURGICAL CONSULTATION SUGGESTED	VANCOMYCIN 500mg PO QID ± METRONIDAZOLE 500mg IV q 8 HRS ± VANCOMYCIN 500mg in 500cc PR QID (if ileus)
RECURRENT DISEASE	RECURRENT CDAD ≤ 8 WEEKS OF COMPLETION OF THERAPY	REPEAT METRONIDAZOLE OR VANCOMYCIN PULSE REGIMEN CONSIDER FMT AFTER 3 RECURRENCES	VANCOMYCIN TAPER OR PULSE REGIMEN

Surawicz CM, et al. Am J Gastroenterol 2013
Cohen SH, et al. Infect Control Hosp Epidemiol 2010

TREATMENT

DISEASE STAGE	ESCMID TREATMENT 2014
INITIAL DISEASE	METRONIDAZOLE 500mg PO TID X 10 DAYS (A-I) VANCOMYCIN 125mg PO QID X 10 DAYS (B-I) FIDAXOMICIN 200mg PO BID X 10 DAYS (B-I)
SEVERE DISEASE	VANCOMYCIN 125mg PO QID X 10 DAYS (A-I) FIDAXOMICIN 200mg PO BID X 10 DAYS (B-I)
FIRST RECURRENCE OF DISEASE	FIDAXOMICIN 200mg PO BID X 10 DAYS (B-I) VANCOMYCIN 125mg PO QID X 10 DAYS (B-I) METRONIDAZOLE 500mg PO TID X 10 DAYS (C-I)
MULTIPLE RECURRENCES OF DISEASE	FIDAXOMICIN 200mg PO BID X 10 DAYS (B-II) VANCOMYCIN 125mg PO QID X 10 DAYS + PULSE STRATEGY (B-II) VANCOMYCIN 125mg PO QID X 10 DAYS + TAPER STRATEGY (B-II)

ESCMID: European Society of Clinical Microbiology and Infectious Diseases

Debast SB, et al. Clin Microbiol Infect 2014

CLOSTRIDIUM DIFFICILE
ALTERNATIVE THERAPIES

TREATMENT

- ALTERNATIVE ANTIBIOTICS
- PROBIOTICS
- ANION-BINDING RESINS
- IV IMMUNOGLOBULIN
- FECAL TRANSPLANTATION

ALTERNATIVE ANTIBIOTICS

META-ANALYSIS
12 STUDIES
n=1,157

VANCOMYCIN
METRONIDAZOLE
FUSIDIC ACID
NITAZOXANIDE
TEICOPLANIN
RIFAMPIN
RIFAXIMIN
BACITRACIN

NO SINGLE ANTIBIOTIC CLEARLY SUPERIOR

Nelson R, et al. Cochrane Database Syst Rev 2007

ALTERNATIVE PROBIOTICS

META-ANALYSIS
4 RCTs
n=336
TREATMENT OF INITIAL OR RECURRENT CDAD
ADULTS ON VANCOMYCIN/METRONIDAZOLE + PROBIOTIC vs PLACEBO/NO PROBIOTIC

Comparison 1. S.boula

Outcome or subgroup title				Effect size
1 Cessation of diarrhea				Subtotals only
1.1 Patients with initial or recurrent disease				1.33 [1.02, 1.74]
1.2 Patients with recurrent disease				1.67 [0.95, 2.93]
2 Recurrence of diarrhea				Subtotals only
2.1 Patients with initial or recurrent disease				0.59 [0.35, 0.98]
2.2 Patients with recurrent disease				0.33 [0.10, 1.06]

Comparison 2. L. plant

Outcome or subgroup title				Effect size
1 Cessation of diarrhea	1	21	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.73, 1.19]
2 Recurrence of diarrhea	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.22, 1.35]
3 Bacteriological cure				0.75 [0.41, 1.36]

Comparison 3. Lactob

Outcome or subgroup title				Effect size
1 Recurrent CDAD				2.63 [0.35, 19.85]

INSUFFICIENT EVIDENCE TO RECOMMEND PROBIOTIC THERAPY AS AN ADJUNCT TO ANTIBIOTIC THERAPY FOR *C. DIFFICILE* COLITIS

HARMFUL?

BACTEREMIA
FUNGEMIA

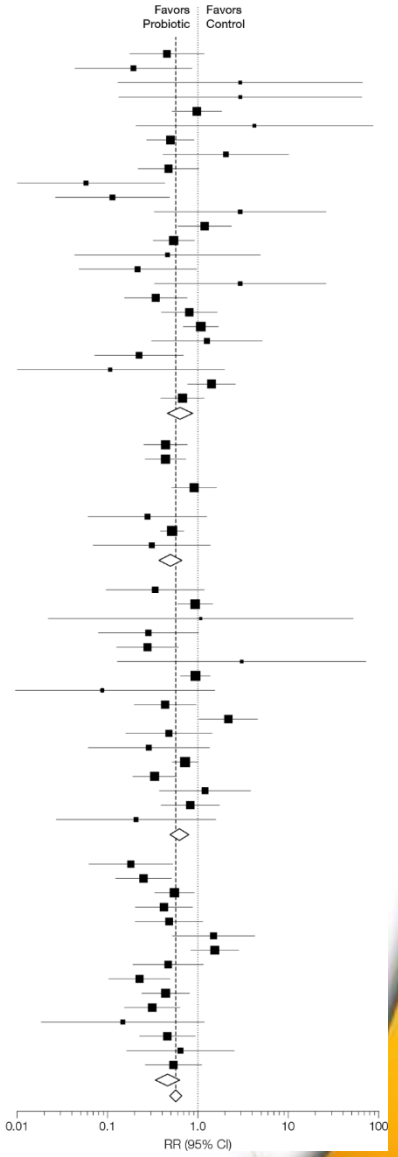
Pillai A, Nelson R. Cochrane Database Syst Rev 2009
Boyle RJ, et al. Am J Clin Nutr 2006

ALTERNATIVE PROBIOTICS

META-ANALYSIS
63 RCTs
n=11,811
INCIDENCE OF ANTIBIOTIC-ASSOCIATED DIARRHEA
ADULTS & CHILDREN ON ANTIBIOTIC(S) + PROBIOTIC vs PLACEBO/NO PROBIOTIC

PREVENTION AND TREATMENT TOGETHER

Study	No. With Antibiotic-Associated Diarrhea/No. in Group (%)		RR (95% CI)
	Intervention	Control	
Genus, Blend			
Jirapinyo,[20] 2002	3/8 (38)	8/10 (80)	0.47 (0.18-1.21)
Sheu,[57] 2002	2/80 (2)	10/80 (12)	0.20 (0.05-0.88)
Sullivan,[57] 2003	1/12 (8)	0/12 (0)	3.00 (0.13-66.80)
Lighthouse,[60] 2004	1/10 (10)	0/10 (0)	3.00 (0.14-65.55)
Plummer,[22] 2004	15/69 (22)	15/69 (22)	1.00 (0.53-1.88)
Schrezenmeir,[61] 2004	2/50 (4)	0/43 (0)	4.31 (0.21-87.30)
Corrêa,[18] 2005	13/87 (15)	24/82 (29)	0.51 (0.28-0.93)
Myllyluoma,[21] 2005	4/23 (17)	2/24 (8)	2.09 (0.42-10.32)
Conway,[64] 2007	9/149 (6)	17/137 (12)	0.49 (0.22-1.06)
de Bortoli,[65] 2007	1/105 (1)	16/101 (16)	0.06 (0.01-0.44)
Park,[66] 2007	2/176 (1)	17/176 (10)	0.12 (0.03-0.50)
Stein,[24] 2007	3/21 (14)	1/21 (5)	3.00 (0.34-26.56)
Kim,[67] 2008	16/168 (10)	14/179 (8)	1.22 (0.61-2.42)
Koning,[68] 2008	9/20 (45)	17/21 (81)	0.56 (0.33-0.94)
Szymański,[25] 2008	1/40 (2)	2/38 (5)	0.48 (0.04-5.03)
Wenus,[69] 2008	2/46 (4)	8/41 (20)	0.22 (0.05-0.99)
Engelbrektson,[70] 2009	3/20 (15)	1/20 (5)	3.00 (0.34-26.45)
Hickson,[19] 2007	7/69 (10)	19/66 (29)	0.35 (0.16-0.78)
Merenstein,[71] 2009	11/61 (18)	14/64 (22)	0.82 (0.41-1.67)
Koning,[72] 2010	13/17 (76)	9/13 (69)	1.10 (0.71-1.73)
de Vrese,[76] 2011	4/30 (13)	3/29 (10)	1.29 (0.32-5.26)
Saneeyan,[77] 2011	3/25 (12)	13/25 (52)	0.23 (0.07-0.71)
Selinger,[23] 2011	0/62 (0)	4/62 (6)	0.11 (0.01-2.02)
Yoon,[78] 2011	20/151 (13)	17/186 (9)	1.45 (0.79-2.67)
Bhalla,[38] 2011	19/176 (11)	26/167 (16)	0.69 (0.40-1.20)
Random effects model			**0.66 (0.49-0.88)**
Genus, *Bacillus*			
Li 2010,[73]	15/122 (12)	34/125 (27)	0.45 (0.26-0.79)
La Rosa,[43] 2003	14/60 (23)	31/60 (52)	0.45 (0.27-0.76)
Genus, *Bifidobacterium*			
Yasar,[75] 2010	14/38 (37)	15/38 (39)	0.93 (0.53-1.66)
Genus, *Enterococcus*			
Borgia,[5,3] 1982	2/40 (5)	7/40 (18)	0.29 (0.06-1.29)
Frigerio,[35] 1986	57/661 (9)	107/662 (16)	0.53 (0.39-0.72)
Wunderlich,[36] 1989	2/23 (9)	6/22 (27)	0.32 (0.07-1.41)
Random effects model			**0.51 (0.38-0.68)**
Genus, *Lactobacillus*			
Gotz,[33] 1979	3/48 (6)	9/50 (18)	0.35 (0.10-1.21)
Tankanow,[49] 1990	10/15 (67)	16/23 (70)	0.96 (0.61-1.50)
Reid,[54] 1992	0/19 (0)	0/21 (0)	1.10 (0.02-52.95)
Arvola,[37] 1999	3/89 (3)	9/78 (12)	0.29 (0.08-1.04)
Vanderhoof,[57] 1999	7/93 (8)	25/95 (26)	0.29 (0.13-0.63)
Felley,[56] 2001	1/26 (4)	0/27 (0)	3.11 (0.13-73.07)
Thomas,[50] 2001	39/152 (26)	40/150 (27)	0.96 (0.66-1.41)
Tursi,[62] 2004	0/35 (0)	5/35 (14)	0.09 (0.01-1.58)
Beausoleil,[17] 2007	7/44 (16)	16/45 (36)	0.45 (0.20-0.98)
Ruszczynski,[45] 2008	20/120 (17)	9/120 (8)	2.22 (1.06-4.68)
Safdar,[46] 2008	4/23 (17)	6/17 (35)	0.49 (0.16-1.48)
Szajewska,[48] 2009	2/44 (5)	6/39 (15)	0.30 (0.06-1.38)
Sampalis,[40] 2010	47/233 (20)	65/239 (27)	0.74 (0.53-1.03)
Gao,[41] 2010	13/86 (15)	37/84 (44)	0.34 (0.20-0.60)
Lönnermark,[44] 2010	6/118 (5)	5/121 (4)	1.23 (0.39-3.92)
Song,[47] 2010	11/103 (11)	14/111 (13)	0.85 (0.40-1.78)
Cimperman,[39] 2011	1/15 (7)	5/16 (3%)	0.21 (0.03-1.62)
Random effects model			**0.64 (0.47-0.86)**
Genus, *Saccharomyces*			
Ligny,[52] 1976	3/20 (15)	16/20 (80)	0.19 (0.06-0.54)
Adam,[26] 1977	9/199 (5)	33/189 (17)	0.26 (0.13-0.53)
Monteiro,[33] 1981	19/121 (16)	33/119 (28)	0.57 (0.34-0.94)
Surawicz,[34] 1989	11/116 (9)	14/64 (22)	0.43 (0.21-0.90)
McFarland,[32] 1995	7/97 (7)	14/96 (15)	0.49 (0.21-1.17)
Lewis,[31] 1998	7/33 (21)	5/36 (14)	1.53 (0.54-4.35)
Benhamou,[55] 1999	25/388 (6)	16/391 (4)	1.57 (0.85-2.90)
Erdeve,[59] 2004	7/127 (6)	12/105 (11)	0.48 (0.20-1.18)
Erdeve,[59] 2004	7/117 (6)	30/117 (26)	0.23 (0.11-0.51)
Duman,[63] 2005	14/204 (7)	28/185 (15)	0.45 (0.25-0.83)
Kotowska,[30] 2005	9/132 (7)	29/137 (21)	0.32 (0.16-0.65)
Can,[28] 2006	1/73 (1)	7/78 (9)	0.15 (0.02-1.21)
Cindoruk,[29] 2007	9/62 (15)	19/62 (31)	0.47 (0.23-0.96)
Bravo,[27] 2008	3/41 (7)	5/45 (11)	0.66 (0.17-2.58)
Song,[74] 2010	11/330 (3)	20/331 (6)	0.55 (0.27-1.13)
Random effects model			**0.48 (0.35-0.65)**
Overall random effects model			**0.58 (0.50-0.68)**



Hempel S, et al. JAMA 2012

ALTERNATIVE PROBIOTICS

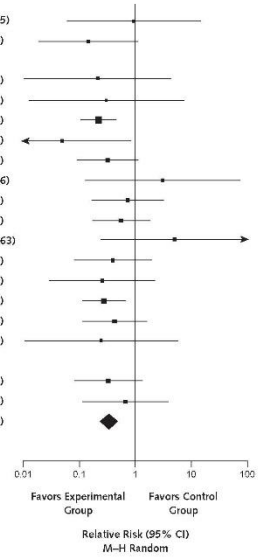
META-ANALYSIS
20 RCTs
n=3,818
INCIDENCE OF CDAD
ADULTS & CHILDREN ON ANTIBIOTIC(S) + PROBIOTIC
vs
PLACEBO/NO PROBIOTIC

Figure 2. Probiotics for the prevention of *Clostridium difficile*–associated diarrhea.

Study, Year (Reference)	Experimental Group, *n* Events	Experimental Group, *n* Total	Control Group, *n* Events	Control Group, *n* Total	Weight, %	Relative Risk (95% CI) M–H Random
Arvola et al, 1999 (32)	1	61	1	58	1.7	0.95 (0.06–14.85)
Beausoleil et al, 2007 (33)	1	44	7	45	3.0	0.15 (0.02–1.14)
Bravo et al, 2008 (34)	0	41	0	45	–	Not estimable
Can et al, 2006 (35)	0	73	2	78	1.4	0.21 (0.01–4.37)
Duman et al, 2005 (36)	0	196	1	180	1.2	0.31 (0.01–7.47)
Gao et al, 2010 (37)	9	171	20	84	23.0	0.22 (0.11–0.46)
Hickson et al, 2007 (38)	0	56	9	53	1.6	0.05 (0.00–0.84)
Kotowska et al, 2005 (39)	3	119	10	127	7.9	0.32 (0.09–1.14)
Lönnermark et al, 2010 (40)	1	80	0	83	1.3	3.11 (0.13–75.26)
McFarland et al, 1995 (41)	3	97	4	96	5.9	0.74 (0.17–3.23)
Miller et al, 2008 (47)	4	95	7	94	8.9	0.57 (0.17–1.87)
Miller et al, 2008 (47)*	2	157	0	159	1.4	5.06 (0.25–104.63)
Plummer et al, 2004 (42)	2	69	5	69	4.9	0.40 (0.08–1.99)
Psaradellis et al, 2010 (48)	1	216	4	221	2.7	0.26 (0.03–2.27)
Rafiq et al, 2007 (49)	5	45	22	55	16.1	0.28 (0.11–0.67)
Ruszczyński et al, 2008 (43)	3	120	7	120	7.2	0.43 (0.11–1.62)
Safdar et al, 2008 (44)	0	23	1	17	1.3	0.25 (0.01–5.79)
Selinger et al, 2011 (50)	0	62	0	62	–	Not estimable
Surawicz et al, 1989 (45)	3	116	5	64	6.5	0.33 (0.08–1.34)
Thomas et al, 2001 (46)	2	133	3	134	4.0	0.67 (0.11–3.96)
Total (95% CI)		1974		1844	100.0	0.34 (0.24–0.49)
Total events, *n*	40		108			

Heterogeneity: $\tau^2 = 0.00$; chi-square = 12.09; $P = 0.79$; $I^2 = 0\%$

Test for overall effect: $Z = 5.87$; $P < 0.001$



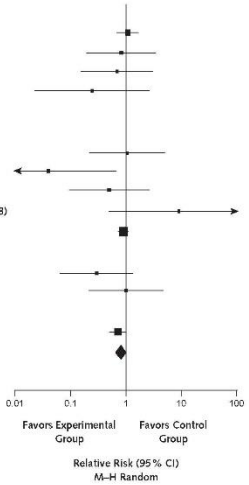
M–H = Mantel–Haenszel.
* Miller and colleagues reported on 2 studies; the dosage of probiotic used was 3 times greater than in the study above.

Figure 3. Risk for adverse effects with probiotics.

Study, Year (Reference)	Experimental Group, *n* Events	Experimental Group, *n* Total	Control Group, *n* Events	Control Group, *n* Total	Weight, %	Relative Risk (95% CI) M–H Random
Arvola et al, 1999 (32)	0	61	0	58	–	Not estimable
Beausoleil et al, 2007 (33)	21	44	20	45	18.9	1.07 (0.68–1.68)
Bravo et al, 2008 (34)	3	41	4	45	2.6	0.82 (0.20–3.46)
Duman et al, 2005 (36)	3	196	4	180	2.5	0.69 (0.16–3.04)
Gao et al, 2010 (37)	1	171	2	84	1.0	0.25 (0.02–2.67)
Hickson et al, 2007 (38)	0	56	0	53	–	Not estimable
Kotowska et al, 2005 (39)	0	119	0	127	–	Not estimable
Lönnermark et al, 2010 (40)	3	80	3	83	2.2	1.04 (0.22–4.99)
McFarland et al, 1995 (41)	0	93	12	92	0.7	0.04 (0.00–0.66)
Miller et al, 2008 (47)	2	95	4	94	2.0	0.49 (0.09–2.64)
Miller et al, 2008 (47)*	4	157	0	159	0.7	9.11 (0.49–167.88)
Psaradellis et al, 2010 (48)	87	216	99	221	38.8	0.90 (0.72–1.12)
Ruszczyński et al, 2008 (43)	0	120	0	120	–	Not estimable
Safdar et al, 2008 (44)	2	23	5	17	2.4	0.30 (0.06–1.35)
Selinger et al, 2011 (50)	3	62	3	62	2.2	1.00 (0.21–4.76)
Surawicz et al, 1989 (45)	0	116	0	64	–	Not estimable
Thomas et al, 2001 (46)	37	133	52	134	26.0	0.72 (0.51–1.01)
Total (95% CI)		1783		1638	100.0	0.82 (0.65–1.05)
Total events, *n*	166		208			

Heterogeneity: $\tau^2 = 0.03$; chi-square = 13.27; $P = 0.28$; $I^2 = 17\%$

Test for overall effect: $Z = 1.58$; $P = 0.11$



M–H = Mantel–Haenszel.
* Miller and colleagues reported on 2 studies; the dosage of probiotic used was 3 times greater than in the study above.

Johnston BC, et al. Ann Intern Med 2012

ALTERNATIVE ANION-BINDING RESINS

CHOLESTIPOL
5g q 12 HOURS
CHOLE
TOL
3

CHOLESY

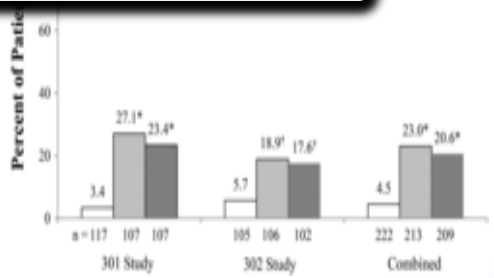
VANCOMYCIN

ALL ANION-BINDING RESINS MUST BE TAKEN 2-3 HOURS APART FROM VANCOMYCIN

1982
RELAPSE OF CDAD
VANCOMYCIN TAPERED + CHOLESTIPOL
11/11 PATIENTS ASYMPTOMATIC AT 6 WEEKS

RCT AT HINES VA ILLINOIS n=563

TOLEVAMER 9g LOAD + 3g q 8 HOURS x 14 DAYS
URS x 10 DAYS
IOURS x 10 DAYS



Mogg GA, et al. Scand J Infect Dis 1980
Kreutzer EW, et al. Johns Hopkins Med J 1978
Tedesco FJ. Am J Gastroenterol 1982
Johnson S, et al. Clin Infect Dis 2014

ALTERNATIVE IV IMMUNOGLOBULINS

RETROSPECTIVE COHORT
UNIVERSITY OF PITTSBURGH
2001-2003
n=36
TREATMENT OF SEVERE CDAD

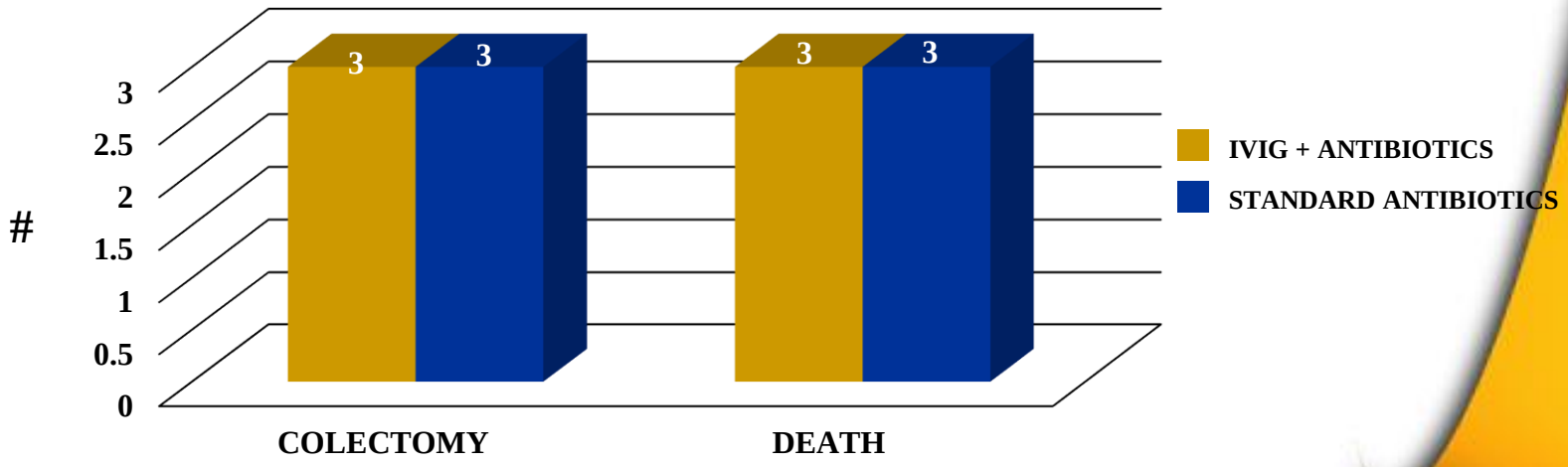
VANCOMYCIN PO/METRONIDAZOLE IV/VANCOMYCIN PR (n=18)

vs

VANCOMYCIN PO/METRONIDAZOLE IV/VANCOMYCIN PR

+

IVIG 200-300mg/kg (n=18)



Juang P, et al. Am J Infect Control 2007

ALTERNATIVE FMT

ORAL

UP TO 30 FROZEN FMT CAPSULES OF HEALTHY UNRELATED DONORS WITH MEAN FECAL MATTER PER CAPSULE 1.6g (1.0-2.05g)

ENEMA

RETENTION ENEMA OF 150g FRESH STOOL/300cc STERILE WATER

COLONOSCOPY

BOWEL PREP

200-300g DONOR STOOL (≤ 6 HOURS) IN 200-300cc STERILE SALINE

NASOENTERIC TUBE

25-30g DONOR STOOL IN 50cc STERILE SALINE (2 TO 3 MINUTES PER 50cc)

Youngster I, et al. JAMA 2014
Kassam Z, et al. Arch Intern Med 2012
Mattila E, et al. Gastroenterology 2012
van Nood E, et al. NEJM 2013

ALTERNATIVE FMT

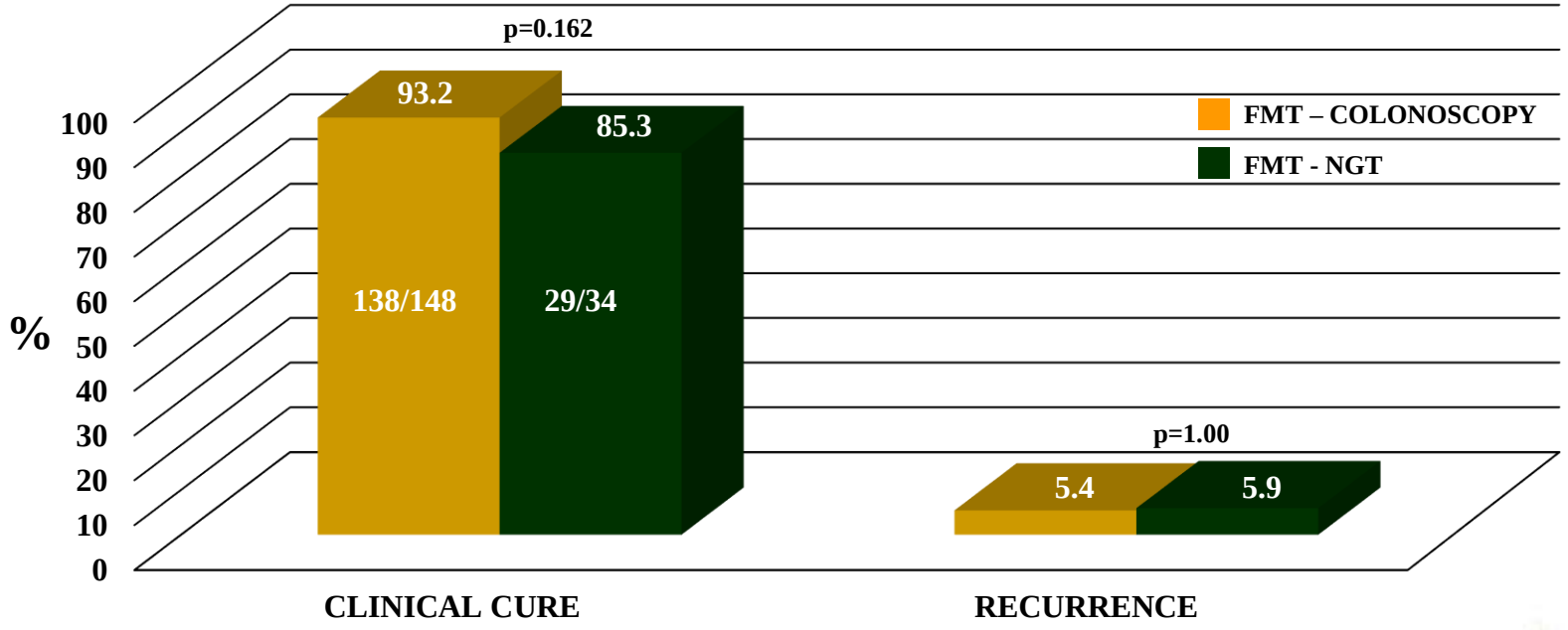
DONOR SCREENING

SAMPLE	INFECTIOUS AGENTS TO BE TESTED	LABORATORY TESTS
Stool	*C difficile*	Culture and toxin A/B test
	Enteric bacterial pathogens	Selective media culture
	Ova and parasites	Light microscopy
Serum	HBV	HBV surface antigen
	HCV	Anti-HCV antibodies by EIA
	HIV 1 and HIV 2	Anti-HIV antibodies by EIA
	Treponema pallidum	Plasma reagin test

Mattila E, et al. Gastroenterology 2012

ALTERNATIVE FMT

REVIEW WITH POOLED ANALYSIS
12 STUDIES
n=182
TREATMENT OF SEVERE CDAD
FMT VIA COLONOSCOPY
VS
FMT VIA NASOGASTRIC TUBE



Postigo R, Kim JH. Infection 2012

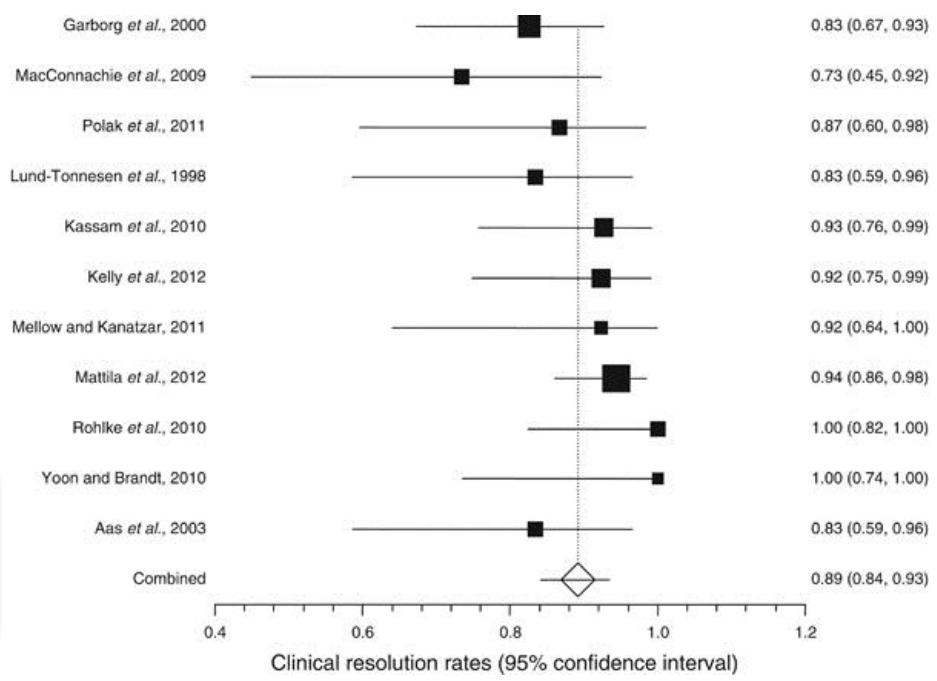
ALTERNATIVE FMT

META-ANALYSIS
11 OBSERVATIONAL STUDIES
n=273
TREATMENT OF RECURRENT OR REFRACTORY CDAD
ANTIBIOTICS + FMT

FMT ROUTE

COLONOSCOPY
ENEMA
NASOGASTRIC TUBE
NASOJEJUNAL TUBE
GASTROSTOMY

CLINICAL RESOLUTION
245/273 (89.7%)



Kassam Z, et al. Am J Gastroenterol 2013

ALTERNATIVE FMT

ADVERSE EVENTS
DIARRHEA
CRAMPING
BELCHING
ALL RESOLVED ≤ 3 HOURS

RCT IN AMSTERDAM 2008-2010 n=43

TREATMENT OF RELAPSE CDAD

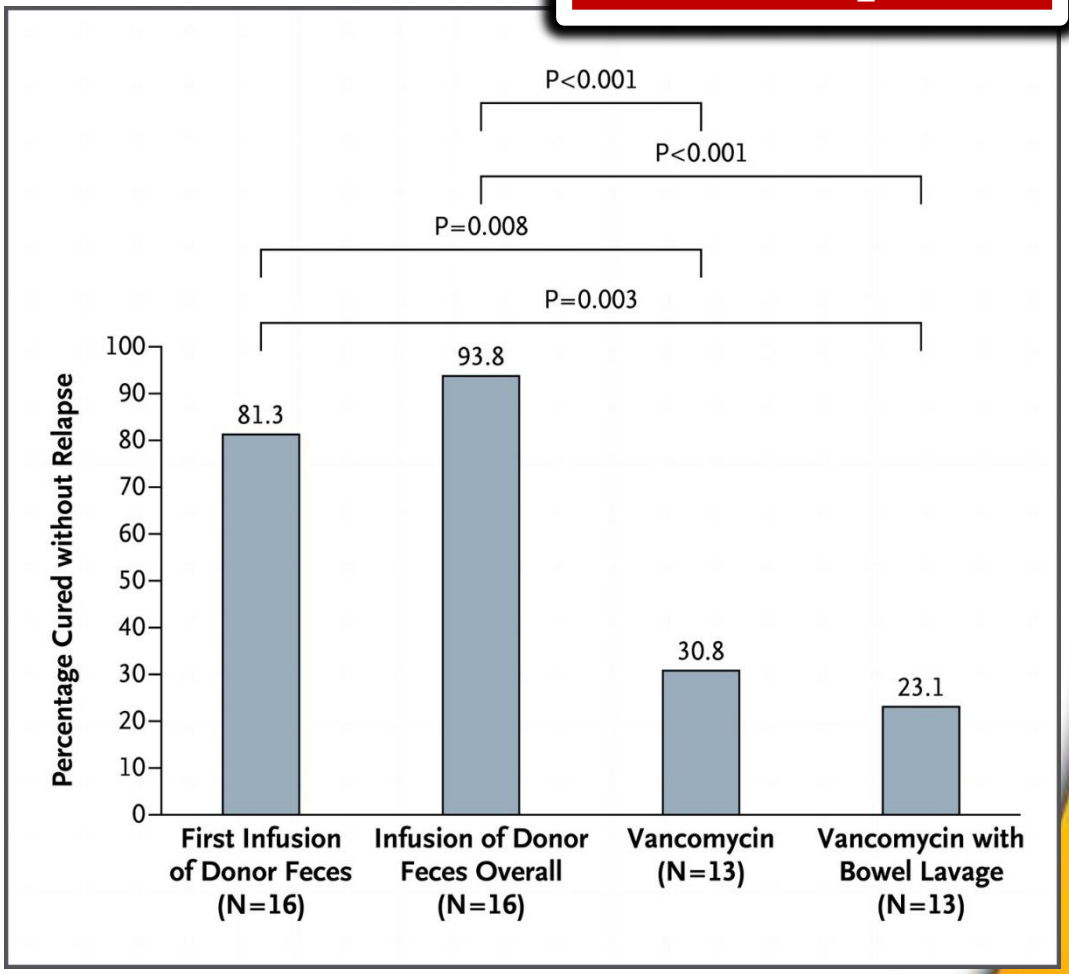
DONOR-FECES INFUSION + VANCOMYCIN (n=17)
500mg PO QID X 4-5 DAYS + BOWEL LAVAGE WITH 4L OF MACROGOL SOLUTION (KLEAN-PREP) ON THE LAST DAY OF ANTIBIOTIC TREATMENT + INFUSION OF A SUSPENSION OF DONOR FECES THROUGH A NASODUODENAL TUBE THE NEXT DAY

VS

VANCOMYCIN (n=13)
500mg PO QID X 14 DAYS

VS

VANCOMYCIN + BOWEL LAVAGE (n=13)
500mg PO QID X 14 DAYS + BOWEL LAVAGE WITH 4L OF MACROGOL SOLUTION (KLEAN-PREP) ON DAY 4 OR 5



van Nood E, et al. NEJM 2013

CLOSTRIDIUM DIFFICILE PREVENTION

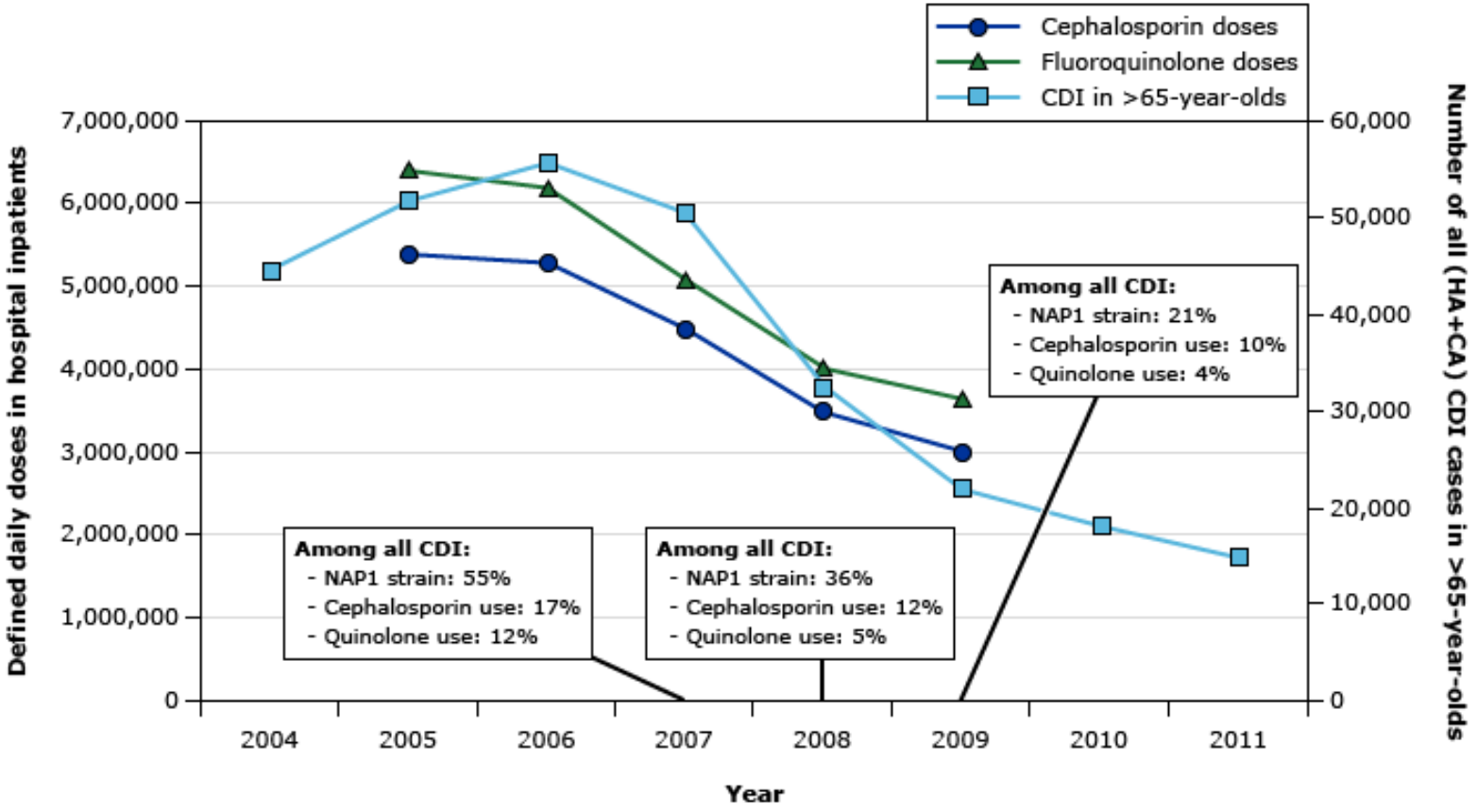
PREVENTION

RECOMMENDATIONS
JUDICIOUS ANTIBIOTIC USE
WASHING HANDS WITH SOAP & WATER
BARRIER PROTECTION
RAPID DETECTION & NOTIFICATION
CONTACT PRECAUTIONS UP TO 48 HOURS AFTER RESOLUTION
DISPOSABLE EQUIPMENT
EARLY ISOLATION
CLOSING LID IN TOILET BEFORE FLUSHING
DISINFECT SURFACES & INSTRUMENTS

CDC. www.cdc.gov/hai/organisms/cdiff/cdiff_infect.html

PREVENTION

ENGLAND



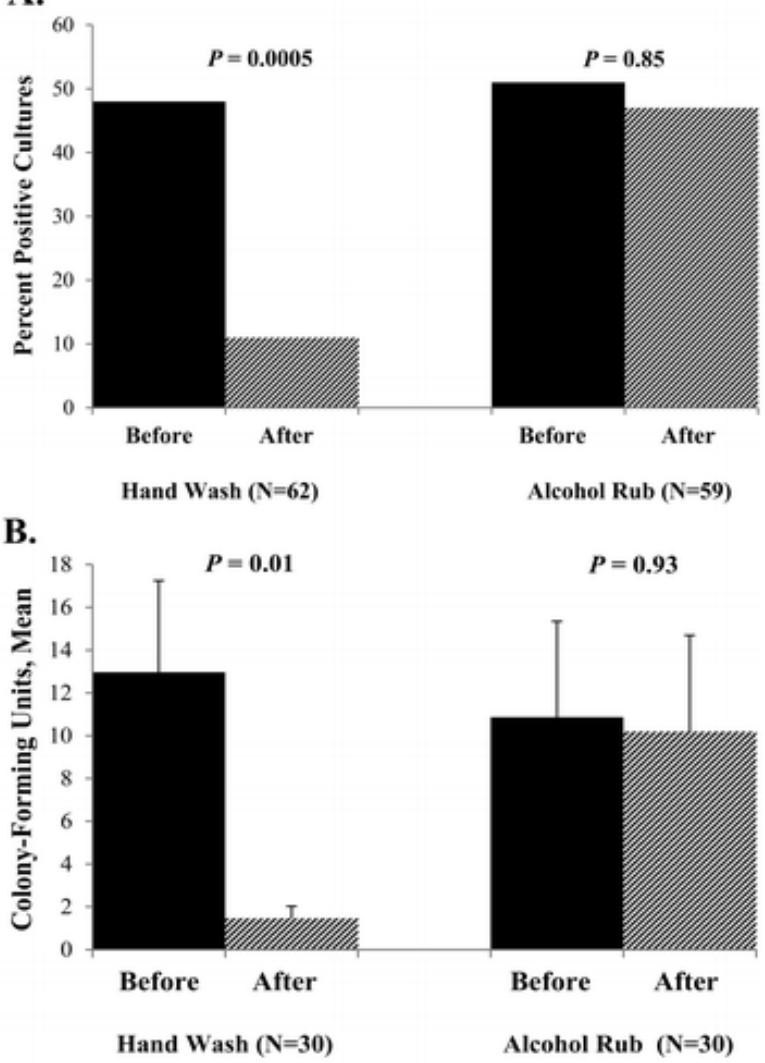
Ashiru-Oredope D, et al. J Antimicrob Chemother 2012
Wilcox MH, et al. Clin Infect Dis 2012
Public Health England: Epidemiological Data Clostridium difficile 2014
Gould C, McDonald LC. UptoDate 2014

PREVENTION

RCT AT CASE WESTERN OHIO

C. DIFFICILE CONTAMINATION AND SPORES ON HANDS

SOAP + WATER
VS
ALCOHOL RUBS



RANDOMIZED CROSSOVER COMPARISON 10 VOLUNTEERS WITH HANDS EXPERIMENTALLY CONTAMINATED BY NONTOXIGENIC *C. DIFFICILE*

TABLE 1. Mean *Clostridium difficile* Colony Counts after Different Hand Hygiene Interventions According to the Whole-Hand Protocol

Intervention	Mean count (95% CI), $\log_{10}$ CFU/mL
Warm water and plain soap	1.99 (1.80–2.09)
Cold water and plain soap	1.90 (1.58–2.22)
Warm water and antibacterial soap	2.31 (2.04–2.58)
Antiseptic hand wipe	3.25 (3.04–3.45)
Alcohol-based handrub	3.74 (3.40–4.07)
No intervention	3.82 (3.54–4.10)

NOTE. CI, confidence interval; CFU, colony-forming unit.

Kundrapu S, et al. Infect Control Hosp Epidemiol 2014
Oughton MT, et al. Infect Control Hosp Epidemiol 2009

CLOSTRIDIUM DIFFICILE FUTURE

FUTURE

TREATMENT OR PROPHYLACTIC TYPE	PRODUCT	SPONSOR	CLINICAL PHASE
ANTIBIOTICS	Cadazolid	Actelion	III (NCT01987895)
	Surotomycin	Cubist	III (NCT01597505)
	SMT19969	Summit Corporation	II (NCT02092935)
	CRS3123	Crestone	I (NCT02106338)
MICROBIOTA SUPPLEMENTS	FMT	Rebiotix	II (NCT01925417)
	SER109	Seres Health	II (not registered)
	VP20621	Shire	II (NCT01259726)
PASSIVE IMMUNIZATION	MK3415A	Merck (MSD)	III (NCT01513239)
VACCINES	CDiffense	Sanofi Pasteur	III (NCT01887912)
	Adjuvanted vaccine	Pfizer	II (not registered)
	IC84	Valneva	I (NCT01296386)
ANTIBIOTIC INACTIVATION	SYN004	Synthetic Biologics	I (not registered)
	DAV132	Da Volterra	I (NCT02176005)

Ivarsson ME, et al. Drug Discov Today - Epub 2014

C. DIFFICILE SUMMARY

CDAD INCREASING IN UNITED STATES

CDAD VARIES IN CLINICAL PRESENTATION AND SEVERITY

CDAD DIAGNOSIS MOSTLY WITH PCR OR EIA

CDAD TREATMENT VARIES AMONG GUIDELINES AND MAY REQUIRE EXPERTS

CDAD PREVENTION IS KEY

THANK YOU FOR YOUR TIME

ANY QUESTIONS?