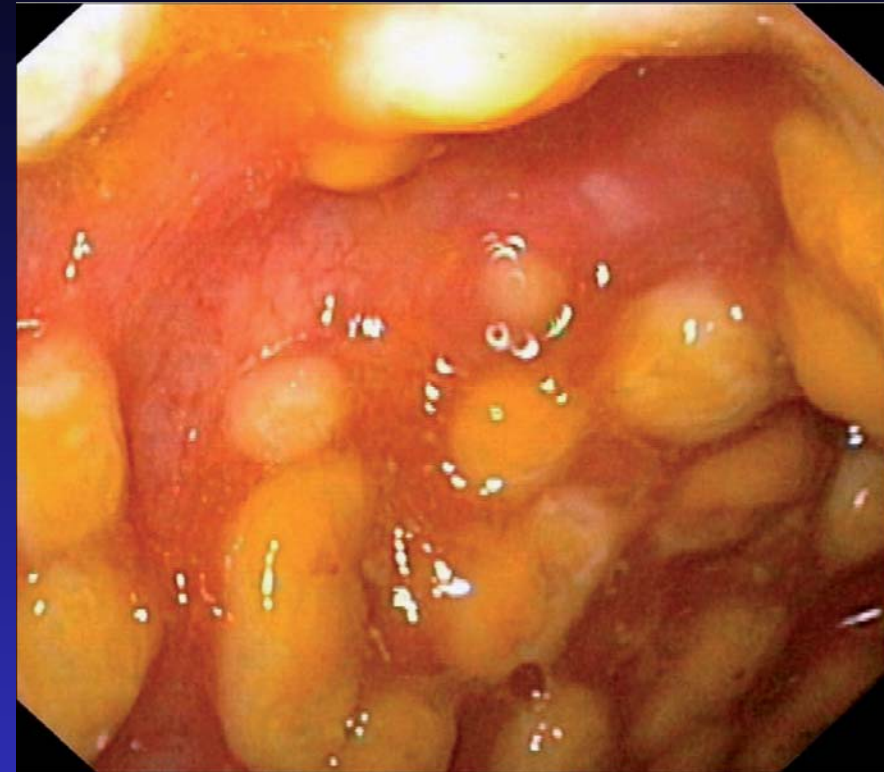


***Clostridium difficile* Colitis: Epidemiology, Diagnosis & Treatment 2009**

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Lancet 371:1486, 2008

**‘A good set of bowels is worth more to a man
than any quantity of brains.’ Josh Billings**

Objective

To present the current status of the epidemiology and treatment of *Clostridium difficile* colitis.

Disclosures: Salix (rifaximin) consultant

Unlabeled/unapproved drug use:

Everything but vancomycin.

Vancomycin is the only FDA-approved drug for *C. difficile* disease.

Antibiotic-associated Diarrhea (AAD)

Occurs in 5-25% of antibiotic treatment courses*.
most common with > 3 days of Abx but one dose is sufficient

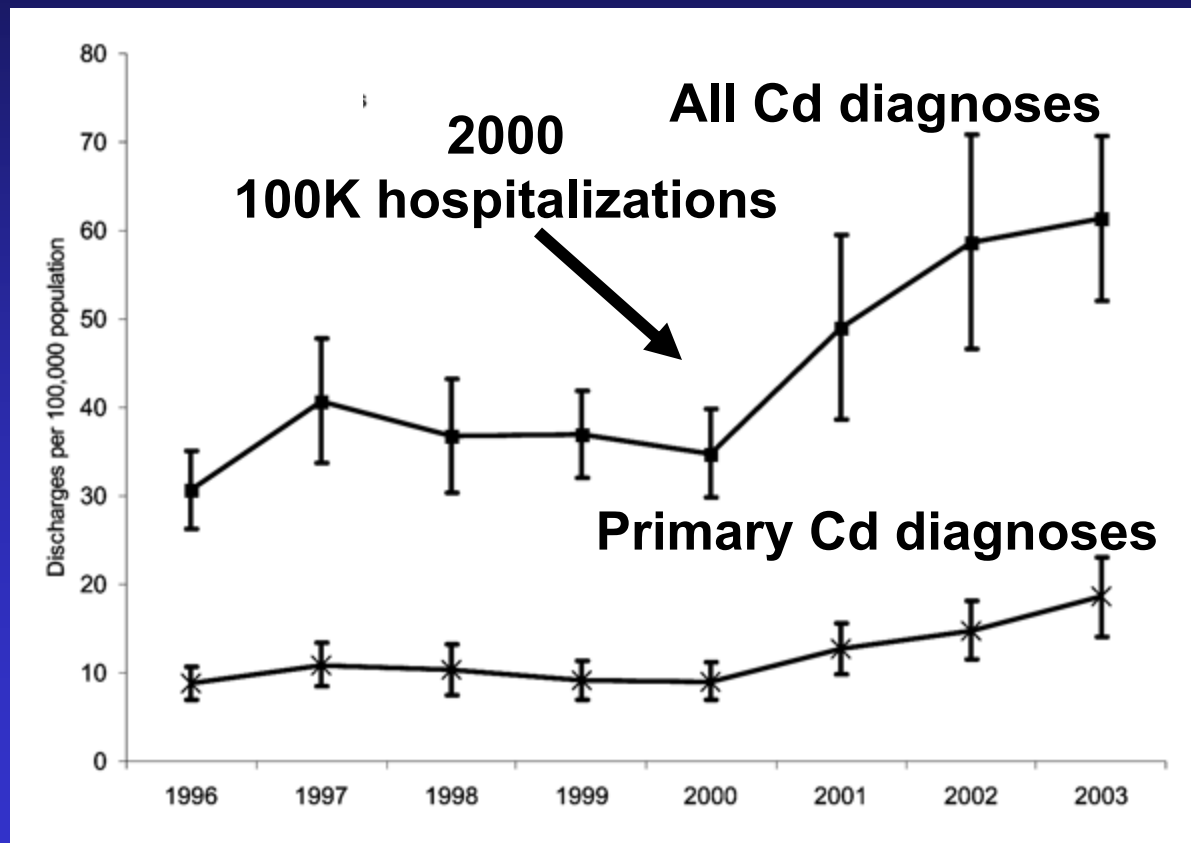
10-40% of AAD is associated with *C. difficile* infection
but nearly all AA colitis is *C. difficile* infection.

Other agents: cytotoxic *Klebsiella oxytoca***
-Abx (PCNs)-associated segmental, right-sided
hemorrhagic colitis

*eg. 5-10% ampicillin, 10-25% amoxicillin-clavulanate

** NEJM 355:2418, 2006; CID 47:e74, 2008.

***C. difficile* Disease is Increasing in Short Stay Hospitals (1996-2003)**



2005
>250K hospitalizations

Cd Disease Rates:
4X greater in 45-64 yo
23X greater in ≥ 65 yo
(compared to <45 yo)

EID 12:410, 2006.
CID 45:1274, 2007

Outbreaks of Enhanced Virulence *C. difficile*

Clinical manifestations: increased disease severity*
poor response to metronidazole
increased relapse rates
increased mortality

Onset 2002; Canada (Quebec), US ► global

NOT new strains of *C. difficile* (date to 1983)

- mostly REA Type BI, PFGE type NAP1,
Toxinotype III strains, PCR ribotype 027 (**NAP1/027**)
- others? (**NEW**: toxinotype V/ribotype 078—pigs, cattle)

* abdominal pain, diarrhea, leukemoid rxn, RF, hypoalbuminemia, toxic megacolon, colectomy, sepsis

NEJM 353:2433, 2442,2503, 2005; Lancet 366:1079, 2005.

CMAJ, October 25, 2005, CMAJ 171:466, 2004; AIM 145:758, 2006, **CID 47:1162, 2008.**

The Complexity of *C. difficile*

Toxin A (*tcdA*), Toxin B (*tcdB*) —→ PaLoc (19.6 kb)

- PaLoc contains *tcdA*, *tcdB*, *tcdC*, *tcdD*, *tcdE*
- PaLoc variants define toxinotypes (I-XX)
- toxinotype 0 is reference strain
- TxA+B+ and TxA-B+ Cd —→ disease

Binary toxin (CDT, *cdtA*, *cdtB*) —→ not in PaLoc

- actin-specific ADP-ribosyltransferase
- secretory in rabbit ileal loops but alone no hamster cecitis

Enhanced virulence *C. difficile*

- Toxin A, B and Binary toxin positive
- tcdC* variants with 20-fold increase in TxA & Tx B production
- quinolone resistant, hypersporulation

J Med Micro 53:887, 2004; CID 40: 265, 2005; Lancet 366:1079, 2005;
CMAJ, Oct 25, 2005; JID 193:1143, 2006; JID 196:1813, 2007.

Epidemiology of *C. difficile* Diarrhea

HA-CDAD (~80-90%)

- any hospital or long-term care admission in last 4 wks
- rivals MRSA as a nosocomial infection

CA-CDAD (~10-20%)

- symptom onset > 12 wks after last healthcare facility adm.

Risk Factors

Antibiotics

Gastric acid suppressants (PPI, H₂RA)

Hospital exposure

- esp to ward with pt with CDAD, 'CDAD pressure'
- length of stay key

Age

Medical or surgical comorbidity

ICHE 28:140, 2007; CID 45:1543, 2007 (N=382 endemic CDAD, 36,086 admissions)

Specific Antibiotics & *C. difficile* risk

Greatest Risk

2nd/3rd generation cephalosporins

Quinolones (Odds ratios similar to cephalosporins)

Clindamycin

Ampicillin/amoxicillin

Lesser Risk

1st generation cephalosporins

Aminoglycosides

Macrolides

Vancomycin/metronidazole

Extended spectrum PCNs

CID 45:1141, 1543, 2007.

Trimethoprim

Tetracyclines

Carbapenems

NEJM 341:1689, 1999.

EID 9:730, 2003.

CID 38:640, 2004 & 41:1254, 2005.

NEJM 253:2442, 2005.

Community-acquired *C. difficile* disease (CA-CDAD)

Role of PPIs in CA-CDAD?

Disease occurring in populations considered at low risk:
usually mild disease, some severe with bloody diarrhea
up to 65% no antibiotics in prior 90 days
young patient age (~50% \leq 18 yo in one report)
peripartum women
colonic conditions (IBD, esp. UC)
not only epidemic strain (O78?)

CA-CDAD at present likely underestimated

JAMA 294:2989, 2005; CMAJ 175:745, 2006; CID 43:1272, 2006;
MMWR 54:1201, 2005 (definition CA-CDAD); CID 45:1141, 2007; JAC 62:388, 2008

Clinical Pearls: *Clostridium difficile* colitis

Fever—not typically prominent
present in 10-15%

Leukocytosis—common in hospitalized patients
with *C. difficile* diarrhea

40-50% WBC >15K (average WBC, 15.5K)

WBC > 30,000, 25% + Cd colitis

Symptoms/signs of colitis subtle or absent
at time increased WBC first recognized.

Amer J Gastroent 95:3137, 2000; CID 34:1585, 2002;
Amer J Medicine 115:543, 2003.

Recurrent *C. difficile* Disease

(~50% relapses, ~50% reinfections; 2/3 occur within 30d)

Chief complication of *C. difficile* infection
occurring in 20-25% (10-50%) of cases.

NOT due to antibiotic resistance to Metro/Vanco

Mechanism: An immune-mediated disease?

- failure to develop serum anti-TxA IgG

(antibodies protect against diarrhea but not colonization)

- IL-8 polymorphisms

(-251 AA (vs. AT, TT) predispose to ↑IL-8 & ↓Ab)

CID 24:324, 1997; CID 26:954, 1998, Gastroenterology 130:1311, 2006;
NEJM 342:390, 2000; Clin GE & Hepatology 5:672, 707, 912, 966, 2007.

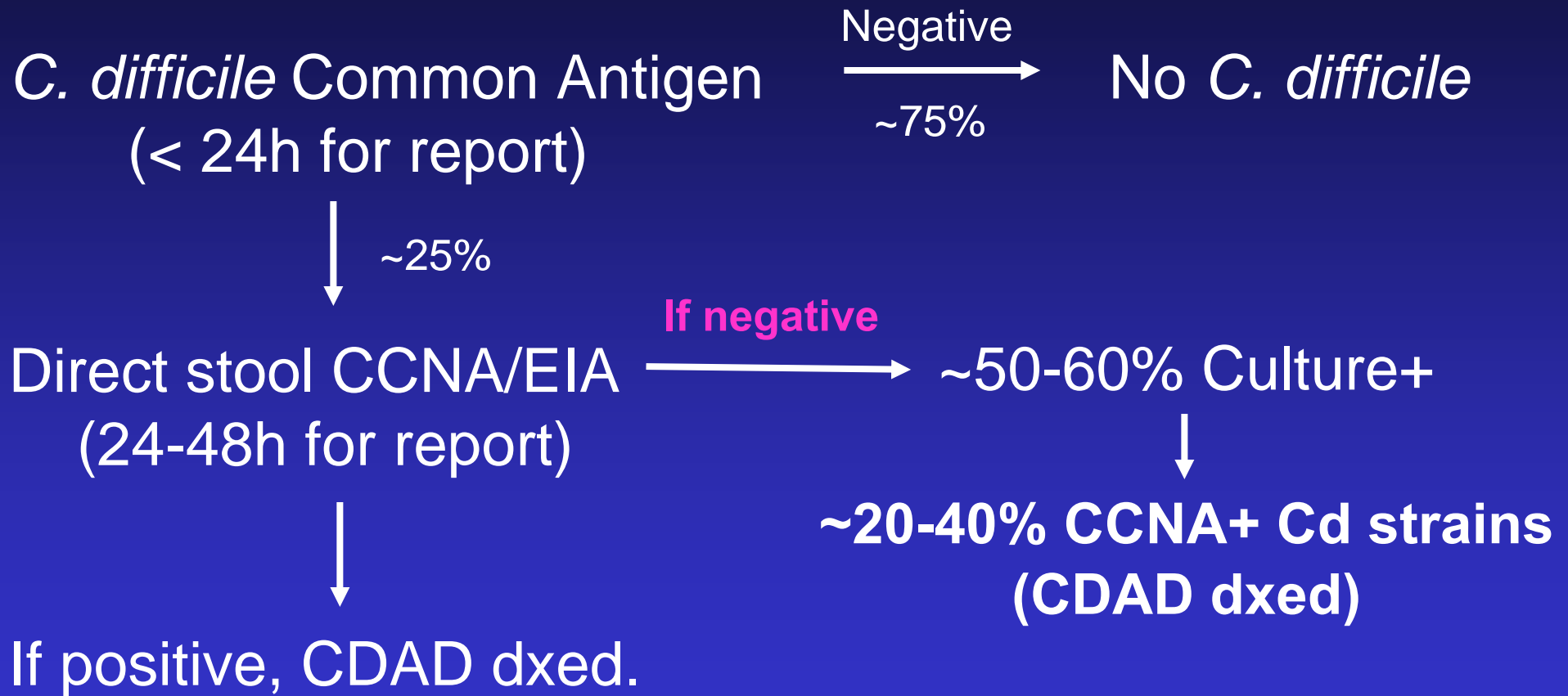
Diagnosis of *C. difficile* Disease

(requires detection of toxin)

Assay	Test Time	Test Characteristics	Toxin Detection
Culture	3 days	Detects all Cd	No
TC Assay	≥ 2 days	Sensitive ($>85\%$) Specific ($>95\%$) Unstandardized	Tx B $>$ Tx A
Common Ag*	< 1 h	Detects all Cd Sensitive (85-100%) Not specific ($\sim 30\%$)	No
Tx A &/ B EIA	< 4 h	Less Sensitive (45-99%) Specific ($\geq 95\%$)	Yes
[Real-time PCR	< 4 h	93% sensitive, 97% specific	Yes (txB)]

* Cd Common Ag = Glutamate dehydrogenase (GDH)

Algorithm for *C. difficile* Diagnosis



One sample sufficient (0/1101 second sample +, 2/247 third +)?.

JCM 43:2994, 2005; JCM 44:1145, 2006; JCM 45:3601, 2007; JCM 46:328, 2008; ICHE 28:113, 2007

Guidelines for *C. difficile* Diagnostic Testing

Test diarrheal (and soft) stools.

No 'Test of Cure' should be performed.

Only test specimens in patient older than one year of age.

Diarrhea developing after 3 days of hospitalization should be tested only for *C. difficile* toxin (the 3 day rule).

Exceptions: > 65 yo with comorbid medical conditions, immunocompromised patients*, nosocomial outbreak, extraintestinal manifestations of enteric pathogens**

NEJM 346:334, 2002; JAMA 285:313, 2001; J Hosp Infec 67:121, 2007.

*HIV, neutropenia

**erythema nodosum, arthritis, mesenteric lymphadenitis

Therapy of *C. difficile* Disease

D/C antibiotics/Change to 'lower risk' Abx
Hydration

No antiperistaltics

Metronidazole (250 mg QID, 500 mg TID)

10-14 days

avoid in pregnancy, lactation

Alternative: Vancomycin (125-250 mg QID)

Only FDA-approved therapy.

NEJM 346:334, 2002; CID 35:690, 2002; CMAJ 171:51, 2004.

Vancomycin is superior for severe CDAD

Zar et al.	Metronidazole	Vancomycin	
Mild	88%	98%	cure, NS
Severe	71%	91%	P<0.04
All	80%	95%	P<0.009
Relapse	14%	7%	NS

Zar et al, prospective, randomized, double-blind, placebo-controlled trial, N=172 (150 completed), CID 45:302, 2007; CID 47:56, 2008.

Scoring CDAD for Severity

Zar et al (CID 45:302, 2007)

Severe CDAD >2 pts

- 1 pt** age >60 yo
temp >38.3°C
Albumin <2.5 mg/dL
WBC >15K
- 2 pts** PME on endoscopy
ICU

Belmares et al (J Infect 55:495, 2007)

Score >2 67% metronidazole failure
≤2 94% metronidazole success

- 1 pt** Fever ($\geq 38^{\circ}\text{C}$)
Ileus
systolic BP <100
WBC 15-30K
- 2 pts** WBC >30K
- 0-2 pts** CT findings
-thickened wall, dilatation, ascites

CDC definition severe CDAD: ICU, surgery, death within 30 days
ICHE 28:140, 2007.

Approach to Aggressive *C. difficile* Disease

CT abdomen*

IV metronidazole (500 mg q6h) PLUS

Vancomycin (NG/enema)**

ICU

Surgical consult

Limit antibiotics to Cd treatment, if possible

IV Ig?

* ileus, perforation, toxic megacolon, thickened bowel wall, ascites

** 500 mg-1 gm, clamp tube 60 min, repeat q6h

Treating Recurrent CDAD*

(without formal studies)

First recurrence: reconfirm dx & repeat rx (V or M, 10-14 days)

Second recurrence: 'Taper & Pulse' vancomycin* (7 weeks)

Third recurrence: Vancomycin with Rifaximin Chaser**

Other: Prolonged vancomycin (125 mg daily or every other day)

(avoid metronidazole, peripheral sensory neuropathy)

Intravenous immunoglobulin therapy

- 400 mg/kg for 1-2 doses (every 3 wks)

Fecal infusion therapy

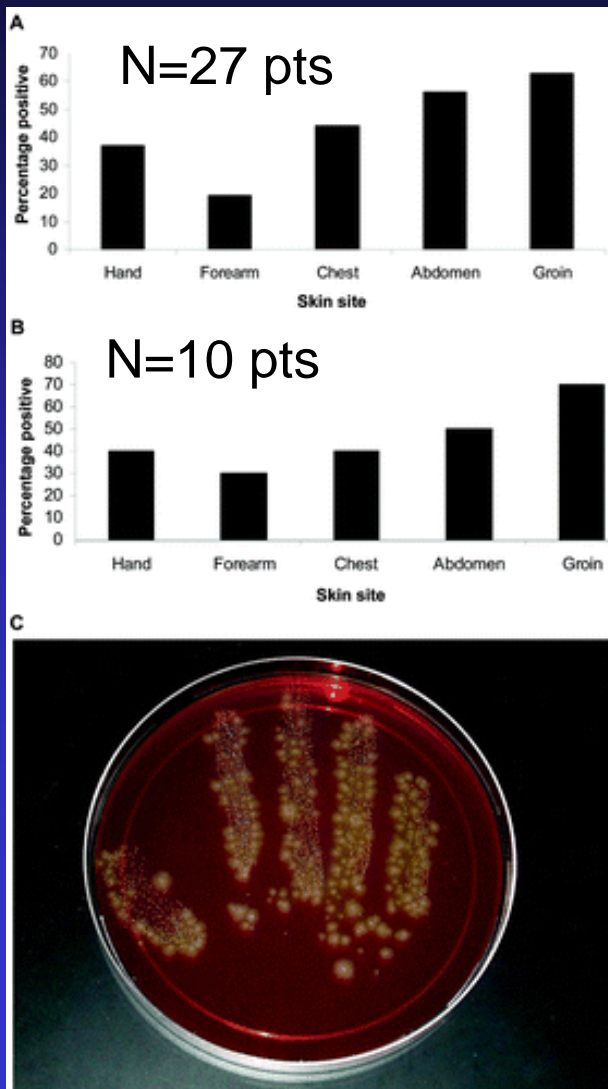
Probiotics

- *Lactobacillus GG*, *Saccharomyces boulardii*

- Kefir

*NEJM 359:1932, 2008; **Rifaximin 400-800 mg/d in 2-3 doses X 14 days (CID 44:846, 2007)
ACP Journal Club Vol 145 (Sept/Oct 2006); Lancet ID 5:549, 2005; Gastroenter 130:1311, 2006.

Clostridium difficile & Infection Control



Hard to kill spores.
Hand-wash and Alcohol gels
Isolate patients
Barrier precautions
Mechanical cleaning*
Ozone gas
Hydrogen peroxide
Antimicrobial management

CID 46:447, 2007

Top, skin sites
Bottom, sterile gloves

* Sporocidal solutions

Investigative Therapies: *C. difficile* Disease

Antibiotic Therapies

Nitazoxanide

Rifaximin

OPT80 (PAR101, Difimicin)

Others- tinidazole, ramoplanin

Immunoglobulin Therapy (gut or systemic delivery)

Toxin Binders (colestipol, cholestyramine, tolevamer) **OUT**

Restoring the Flora (prebiotics, nontoxigenic Cd, synbiotics)

Vaccine (Cd toxoid)

Medarex and Mass. Biologic Lab
Phase 2 Trial of Monoclonal Antibody Combination
for the Treatment of CDAD
Press release: Nov 3, 2008

Multi-center, randomized, double-blind, placebo-controlled

200 patients with CDAD rxed with metro/vanco and
randomized to receive IV placebo or humanized Abs to
Cd toxins A & B.

Recurrence rate: placebo group >20%
antibody group 70% reduction (~6% ?)
($P < 0.0004$, intent-to-treat)

New Wrinkles in CDAD

A food-borne infection?

new overlap calf and human Cd types

~20% ground beef + toxigenic Cd (2/3 NAP1 strain)

CDAD precipitates longer term morbidity & mortality?

N=760 CDAD pts (2003-2007), 34% died by 6 months
after stool turned Cd tx negative

AADD preventable with probiotics?

2 studies, randomized, placebo-controlled, double-blinded

But which probiotic strain or strains?

Only 8% of pts on antibiotics enrolled in studies

EID 13:485, 2007, Clin Micro Infec 13:457, 2007; CID 45:523, 2007; BMJ 335:80, 2007;
Can J GE 21:732, 2007.