Clostridium difficile-Associated Disease (CDAD): Clinical Aspects

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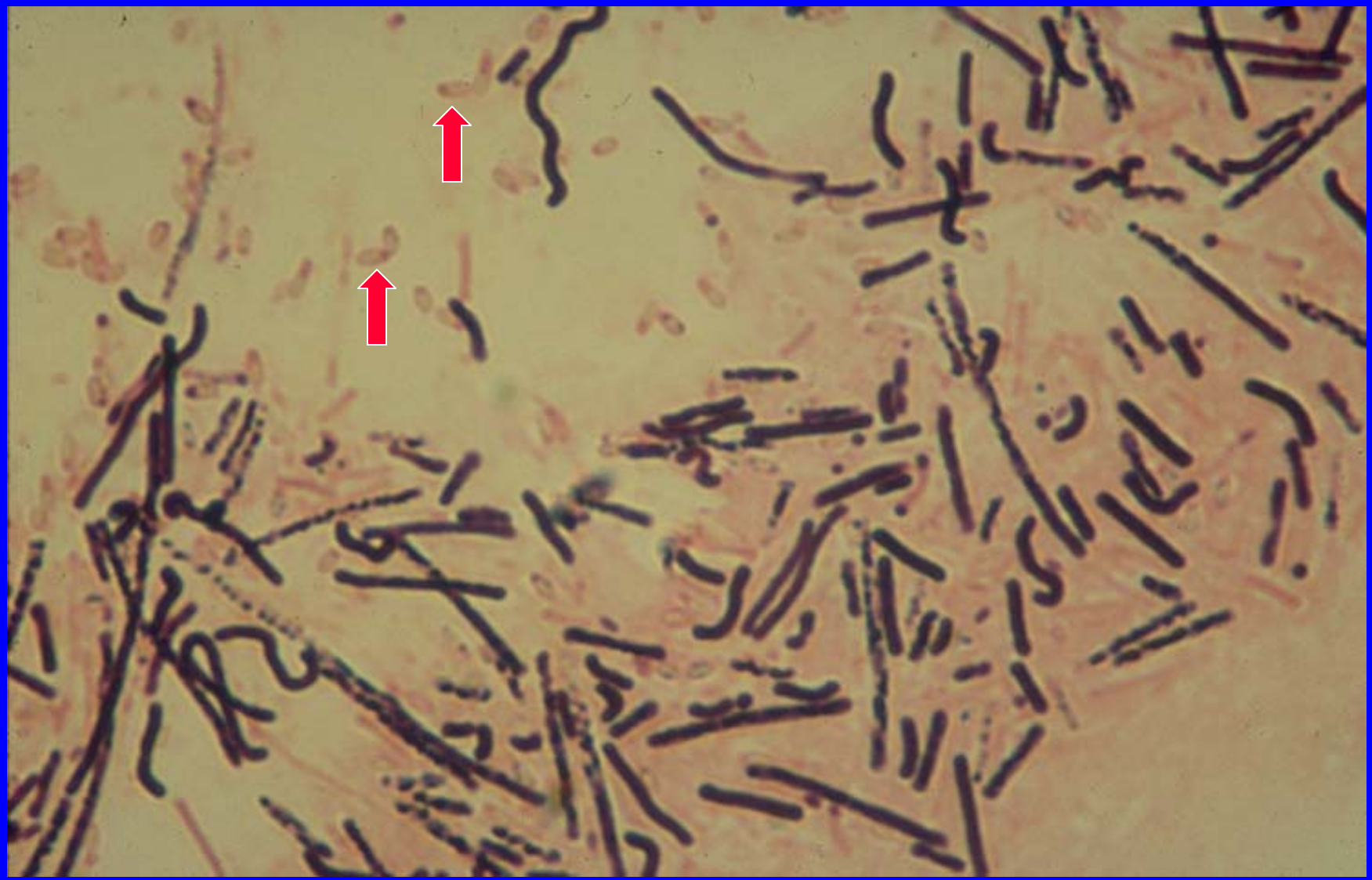
Disclosures: DNG holds patents for the treatment and prevention of CDAD licensed to ViroPharma, and is a consultant for and/or holds research grants from Genzyme, Massachusetts Biological Laboratories, Romark, Optimer, Oscient, Salix, and ViroPharma.

Views expressed are those of the presenter and do not necessarily reflect the views of the U.S. Department of Veterans Affairs, the major funding source for this research.

Unapproved Use: Metronidazole, rifaximin, and nitazoxanide for treatment of CDAD.

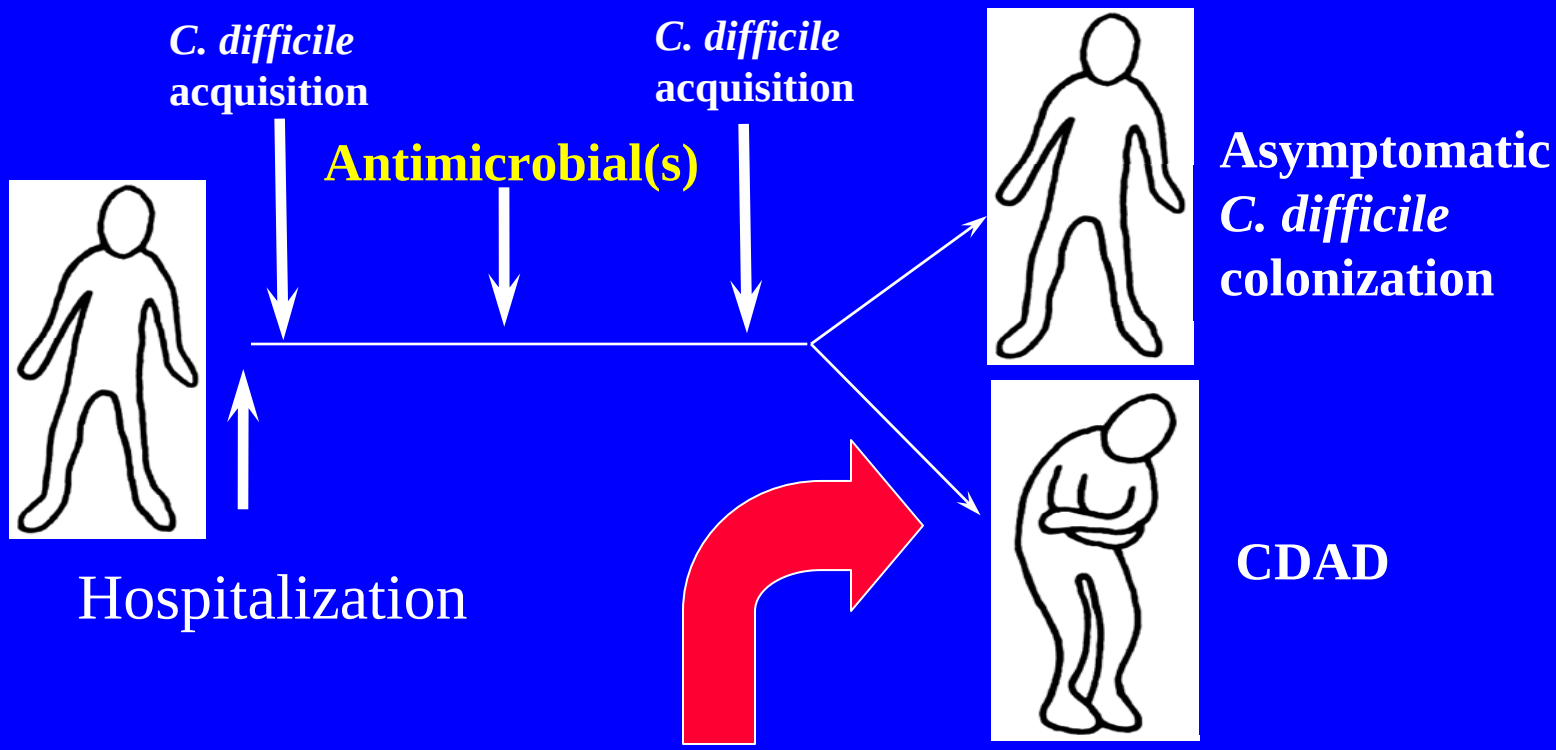
C. Difficile Vegetative Cells and Spores



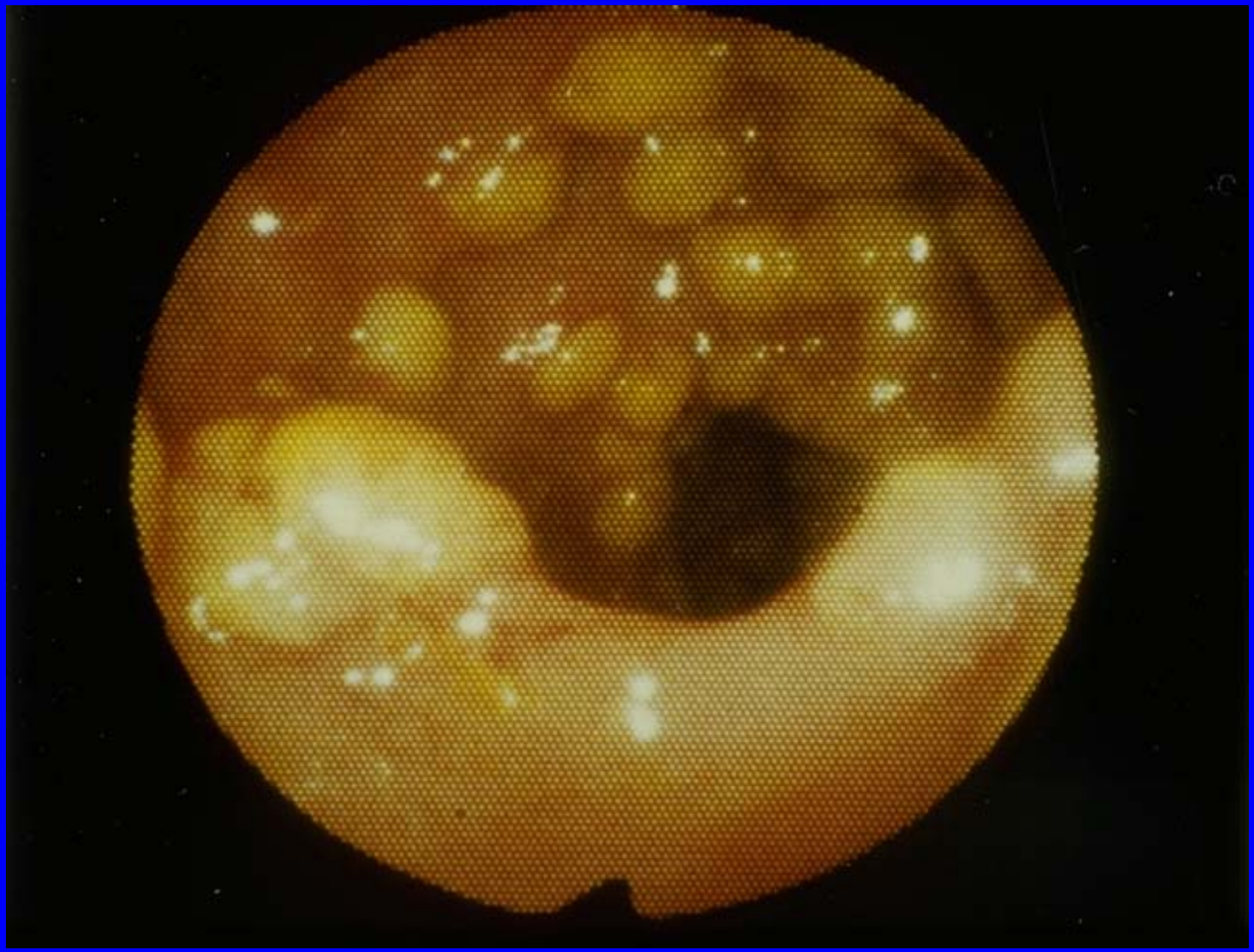
Disease Caused by *Clostridium difficile*

- **Prior antibiotic exposure** places patients at risk of *C. difficile* disease.
- The infection is **acquired** by ingestion of spores of *C. difficile*.
- Following administration of an antibiotic there is a variable-length window during which a patient is susceptible.
- The most common symptom of *C. difficile* infection is diarrhea which is mediated by toxins.
- Severe colitis, sepsis and death may result.

Current Hypothesis for *C. difficile*-Associated Disease (CDAD)



Acquisition of a toxigenic strain of *C. difficile* and failure to mount an anamnestic IgG antibody response to Toxin A results in CDAD.



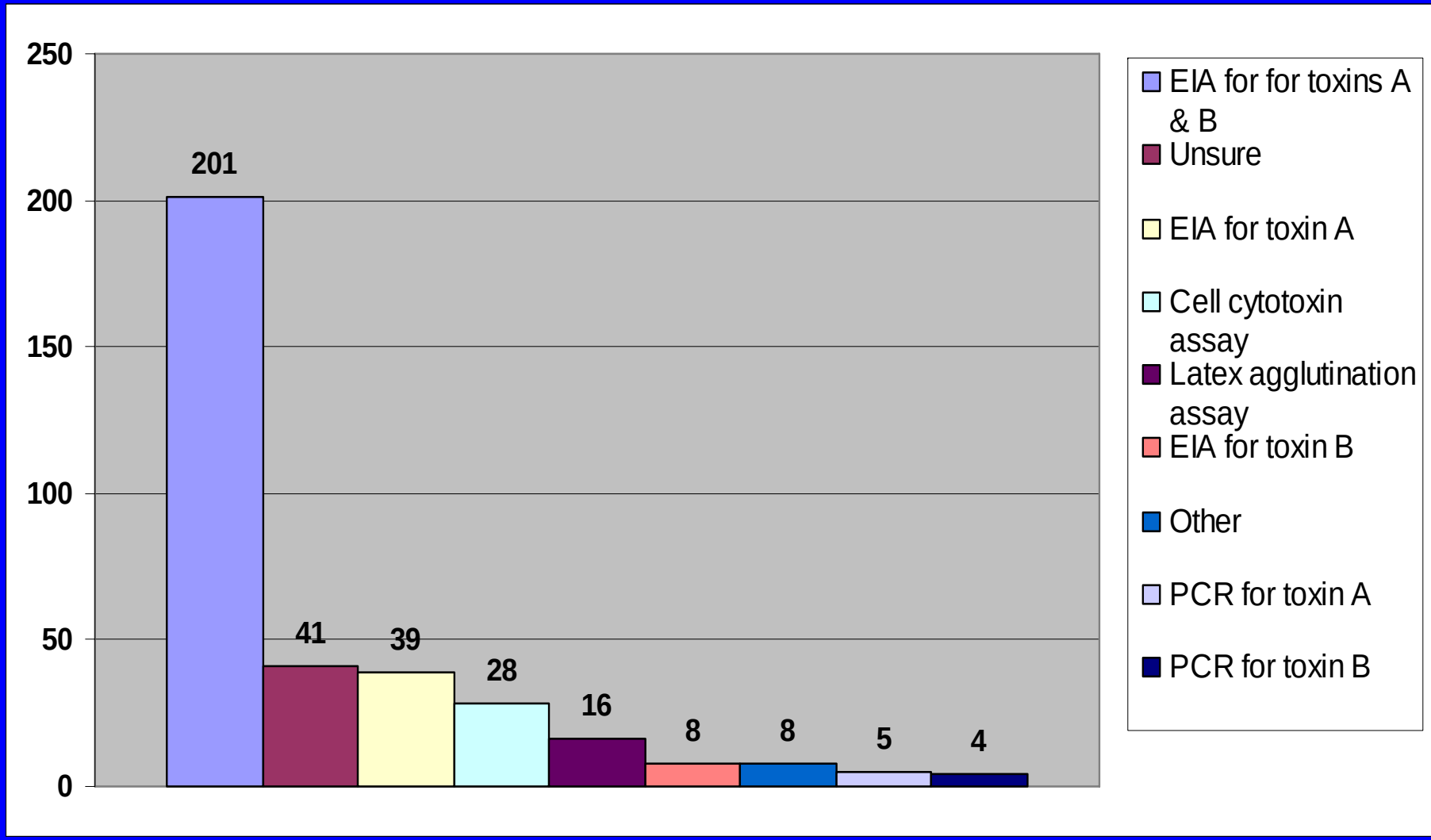
The Four Major *C. difficile*-Associated Disease (CDAD) Clinical Problems

1. Inability to prevent CDAD in high-risk settings such as the hospital.
2. **Lack of a sensitive and rapid diagnostic test for CDAD.**
3. **Absence of a treatment that will prevent recurrence of CDAD.**
4. **Inability to effectively treat fulminant CDAD.**

General Principles of Diagnosis of *C. difficile*-Associated Disease (CDAD)

- Stool culture is the most **sensitive** test for CDAD, but the cell cytotoxin test is the most **specific,** but the most frequent test used is an enzyme immunoassay (EIA) for toxins A and B.
- Flexible sigmoidoscopy is rapid, but is only 50% sensitive in detecting pseudomembranes.
- A rapidly rising White Blood Cell count is a clue to fulminant CDAD.

Method of CDAD Laboratory Diagnosis



Gelone et al Late Breaker Abstract SHEA Ann Mtg Chicago 2006

Relative Sensitivity of *C. difficile* Tests

Culture >

Cell Cytotoxin >

Toxin A & B EIA >

Toxin A EIA >

Latex test >

Endoscopy

Treatment of CDAD: What are the current and future options?

- Current treatments, metronidazole or vancomycin, are antimicrobials that disrupt the normal flora leaving ~20% of patients susceptible to recurrence: relapse (same organism) or reinfection (new organism).
- Newer treatment possibilities:
  - Very narrow spectrum antimicrobials
  - Toxin binding agents
  - Biological agents that prevent recolonization
  - Active and passive vaccines

Treatment of First Recurrence of CDAD

- Recurrence rate correlates with age and hospital length of stay
- **Metronidazole was not inferior to vancomycin for treatment of first recurrence of CDAD**
- **Treatment of first recurrence with the same or a different agent made no difference in outcome**
- **Complications** (shock, colectomy, perforation, megacolon, death) developed in 11% with first recurrence, a higher rate than previously observed

Pepin et al CID 2006;42:758-64, Louie CID 2006;42:765-7

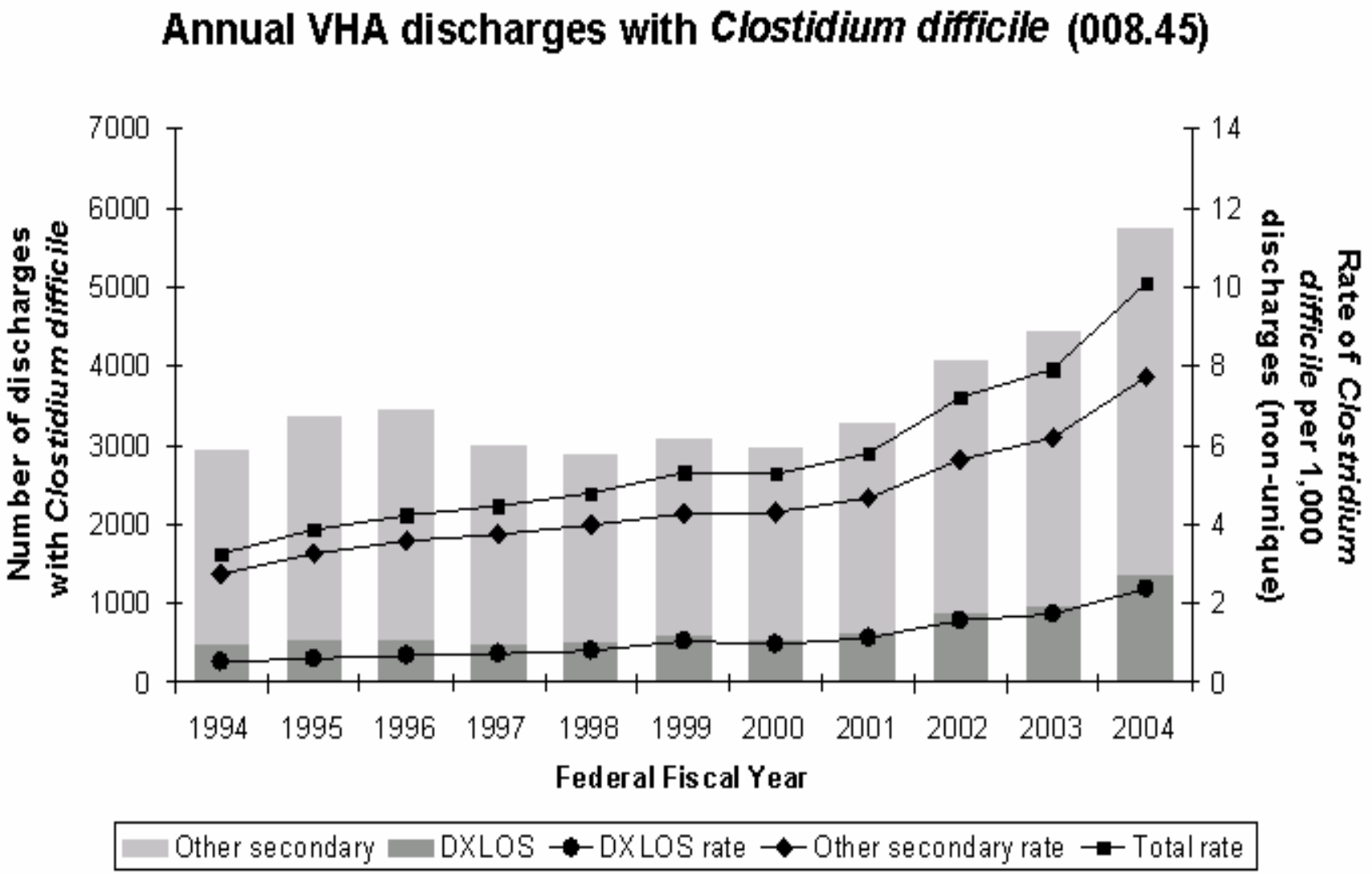
Multiple Recurrences of CDAD

- Risk of subsequent episode in patients who already have had a recurrence: 45%*
- Half of recurrences are caused by new *C. diff* organisms
- Can be FRUSTRATING; Many empiric treatments advocated:
  - Vancomycin regimens : tapering, pulsed dosing, combination treatment with rifampin
  - Biotherapeutic approaches (probiotics) using *S. boulardii* or *Lactobacillus* sp.
  - Passive treatment with Immunoglobulin (IVIG)
  - Toxin binding agents (newer experimental polymer more effective than cholestyramine or cholestipol)
  - Fecal reconstitution using spousal donors

*McFarland LV, et al. Am J Gastro 2002:97:1769

C. difficile: New Clinical Issues

- **CDAD rates are increasing and a common epidemic *C. difficile* strain (BI/NAP1) has been found in the US, Canada, and Europe.**
- **More severe (fulminant) CDAD with higher mortality and higher rates of colectomy**
- **Metronidazole treatment efficacy is questioned.**
- **Disease in the community may be increased.**
- **Peripartum cases may be increased/fulminant.**
- **Proton Pump Inhibitor use may be a risk for CDAD.**


Annual VHA discharges with Clostidium difficile (008.45)
Number of discharges with Clostidium difficile
Rate of Clostridium difficile per 1,000 discharges (non-unique)
7000
6000
5000
4000
3000
2000
1000
0
14
12
10
8
6
4
2
0
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
Federal Fiscal Year
Other secondary
DXLOS
DXLOS rate
Other secondary rate
Total rate

Possible Virulence Factors in Outbreak Strains in U.S. and Quebec

(Toxinotype III, REA type BI, PFGE type NAP1, PCR Ribotype 027)

1. **Binary toxin**
   - **Actin-specific ADP-ribosyltransferase**
   - **Related binary toxins found in *C. perfringens* type E and in *C. spiriforme***

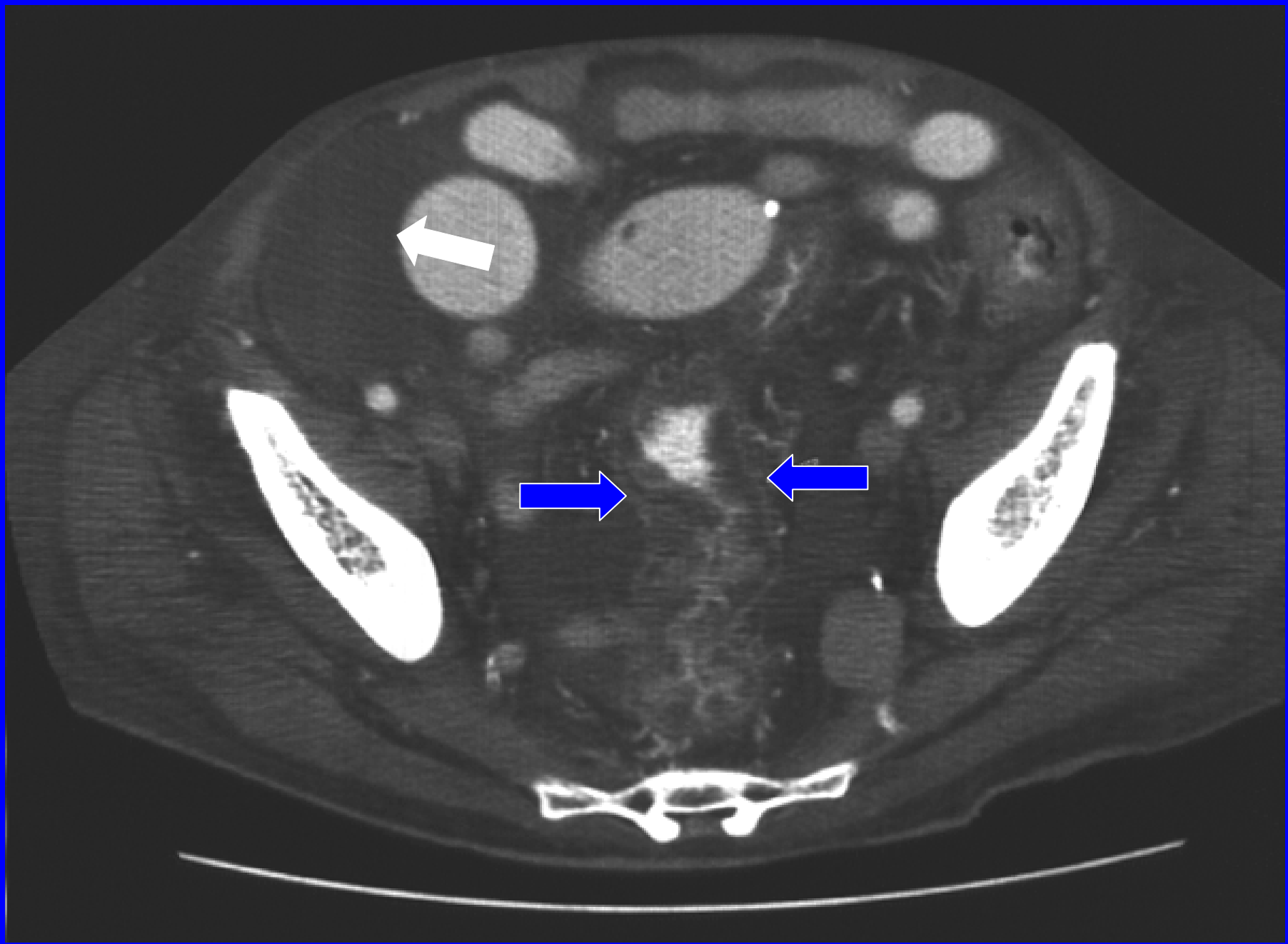
   Stubbs S et al. *FEMS Microbiol Lett.* 2000;186:307-12

2. **Variations in *tcdC* Gene**
   - ***tcdC* variants could result in increased toxin production**
   - **16-20 times higher toxin A and B levels documented**

   Spigaglia P and Mastrantonio P. *J Clin Microbiol.* 2002;40:3470-5

3. **Fluoroquinolone high-level resistance**
   - **gatifloxacin & moxifloxacin**

   McDonald et al NEJM, 2005;353:2433-41



Fulminant CDAD

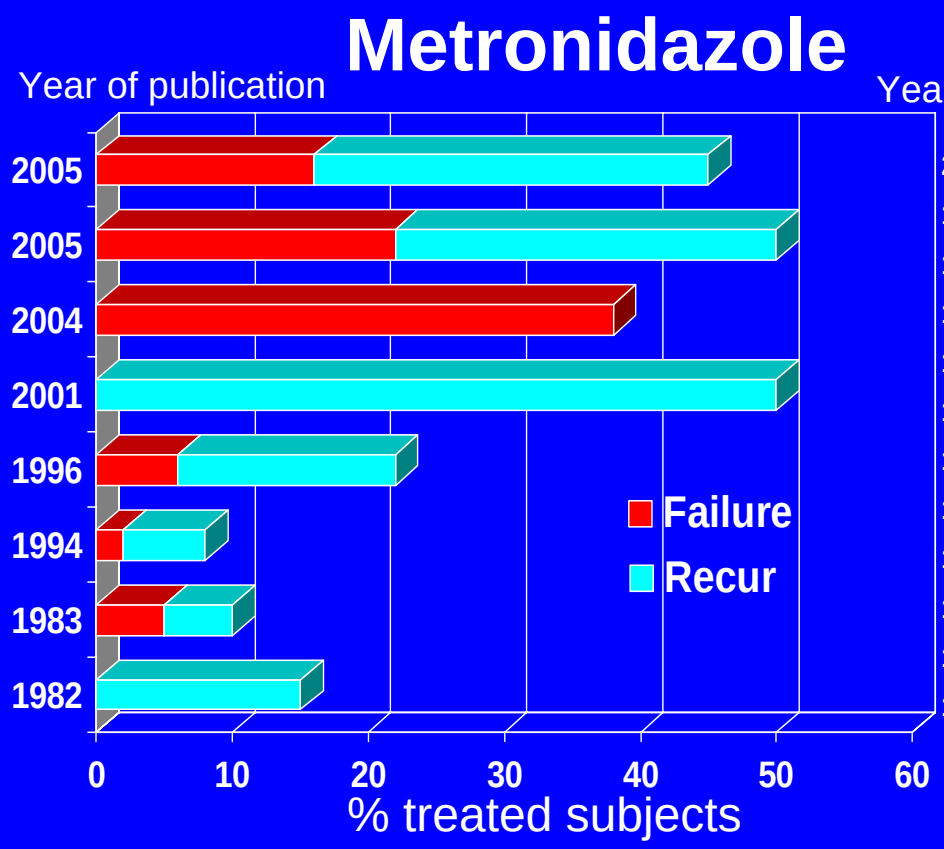
Patients with **fulminant disease** may exhibit toxic megacolon, hypotension, sepsis, ileus, or perforation. It may be difficult to deliver antibiotics to the site of infection. Surgical removal of the colon may be life-saving.

1. Fulminant CDAD seems to be increasing.
2. Rapidly rising WBC may be a clinical clue.
3. There is need for controlled trials of how to best manage such patients including a better clinical algorithm of when to take patients to surgery.

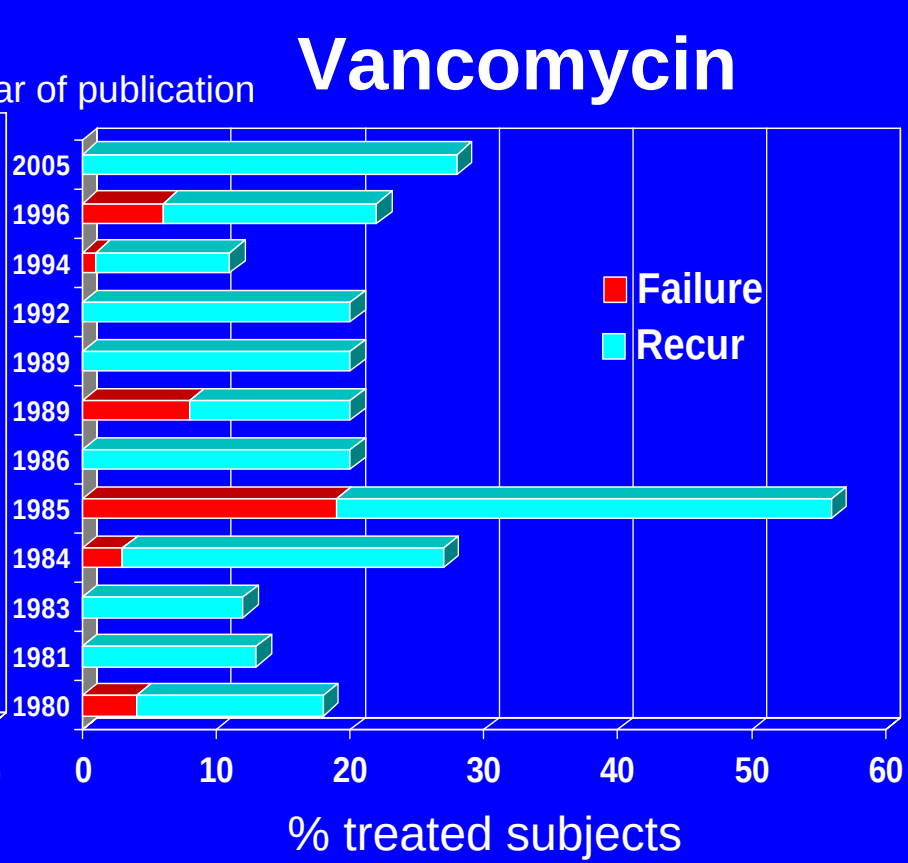
Treatment Controversies

- Is metronidazole still effective therapy for CDAD?

Response to Treatment of *Clostridium difficile*-Associated Disease



20% Recurrence
13% Failure



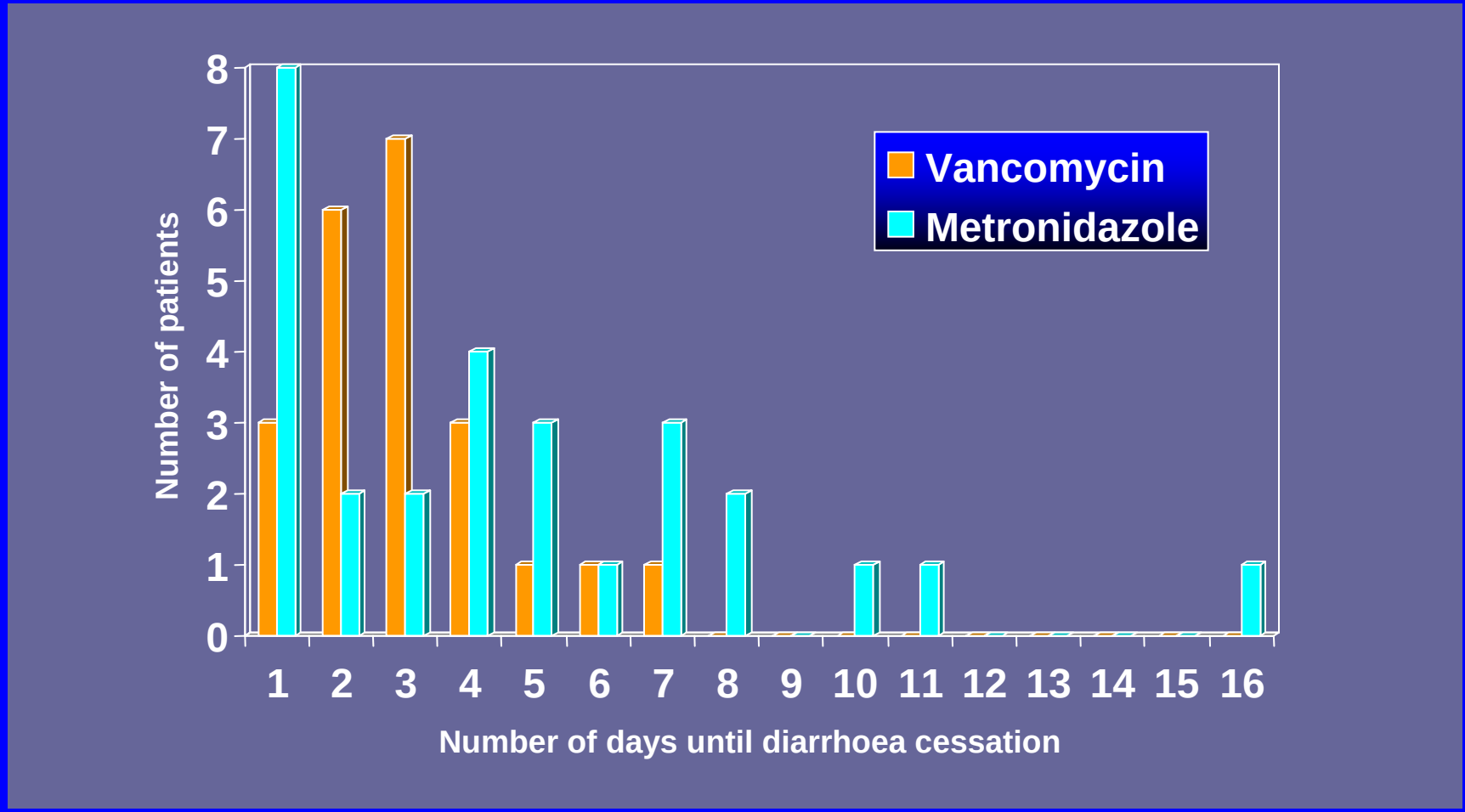
19% Recurrence
4% Failure

Aslam et al. Lancet Infect Dis, 2005;5:549-57

Changing Response to Metronidazole?

Study	Drug	Response Rate	Relapse Rate
Musher-2005 **Observational**	Metro	161/207 **(78%)**	13/161 **(8%) d21** 47/161 **(29%) d90**
Teasley-1983 **Randomized**	Metro	40/42 **(95%)**	2/39 **(5%) d21**
Wenisch-1996 **Randomized**	Metro	29/31 **(94%)**	5/29 **(17%) ≥d30**
Pepin-2005 **Observational**	Metro	323/438 **(74%)**	96/622 **(15%) d60** 109/323 **(34%)d60**
Ref: CID 2005;40:1591-7		Ref: CID 2005;40:1586-90	Ref: CID 2005;40:1599-1600

Response Time for Treatment of CDAD with Metronidazole or Vancomycin



Wilcox MH, Howe R. J Antimicrob Chemother 1995;36:673-9

Community Associated CDAD (CA-CDAD) and Peripartum CDAD

- Voluntary reporting yielded 23 CA-CDAD and 10 peripartum CDAD cases from 4 states over 28 months.
- CA-CDAD rate in Philadelphia was calculated to be a minimum of 7.6 per 100,000 population (no higher than a previous community report).
- 24% of the patients reported no antibiotic use in the previous 3 months (highly unusual, but not verified).
- Only 2 isolates were recovered: each had the binary toxin gene and one had the *tcdC* gene deletion, but neither was toxinotype III (the new “epidemic strain”).

MMWR 2005;54:1201-1205 (Dec 2, 2005)

Severe Peripartum CDAD

- 20 yo F 22 weeks pregnant with preterm labor, 2 wks watery diarrhea up to 10 BM/day. No recent antibiotics or hospitalization. Temp 103.1, WBC 15,800, C diff toxin +, spontaneous abortion day 4, colectomy day 6, survived.
- 31 yo F 14 weeks pregnant with twins, 3 wks watery diarrhea, black stools, 4-5 BM/day. TMP/SMX 3 mo earlier. Admitted to ICU 5 d later, C diff toxin A/B +, dilated colon, poor response to metronidazole and vancomycin. Readmitted in shock 3 d later and spontaneously aborted twins day 2, then patient died day 4.
- 22 yo F delivered M infant by C-section due to eclampsia, day 4 developed fever, gram- bacteremia, renal failure, Rx clindamycin and other abx, day 6 ileus, distended colon, shock, died day 7. Toxic megacolon and enteritis at autopsy. No C. diff test result.
- 21 yo F delivered F infant by C-section, Rx ampicillin, disch day 3 and readmitted next day with abd pain, C. diff toxin +, colectomy day 2 for severe PMC, mother died day 14.

Histories provided by B. Coffman, N. Rouphael, and F. Lewis

CA-CDAD and Gastric Acid Suppression

- Community UK general practice data base (1994-2004) was searched for patients with CA-CDAD and use of gastric acid suppressives (10 controls per case).
- **CA-CDAD rate increased from 1/100K to 22/100K.**
- **PPIs were used in 23% CA-CDAD cases and 8% controls Adj Rate Ratio 2.9 (95% CI 2.4-3.4).**
- H_2 antagonists used in 8% CA-CDAD cases and 4% controls Adj RR 2.0 (95% CI 1.6-2.7).
- **NSAIDS used in 38% CA-CDAD cases and 24% controls Adj RR 1.3 (95% CI 1.2-1.5).**
- **Antibiotics used in 37% CA-CDAD cases and 13% controls Adj RR 3.9 (95% CI 2.7-3.6).**

JAMA 2005;294:2989-2995