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How do we handle *Clostridium difficile* infections in IBD?

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- Honoraria/consulting – Abbott, UCB Pharma
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- Investigator initiated studies – UCB Pharma, Abbott

Overview

I. Background – *C. difficile*

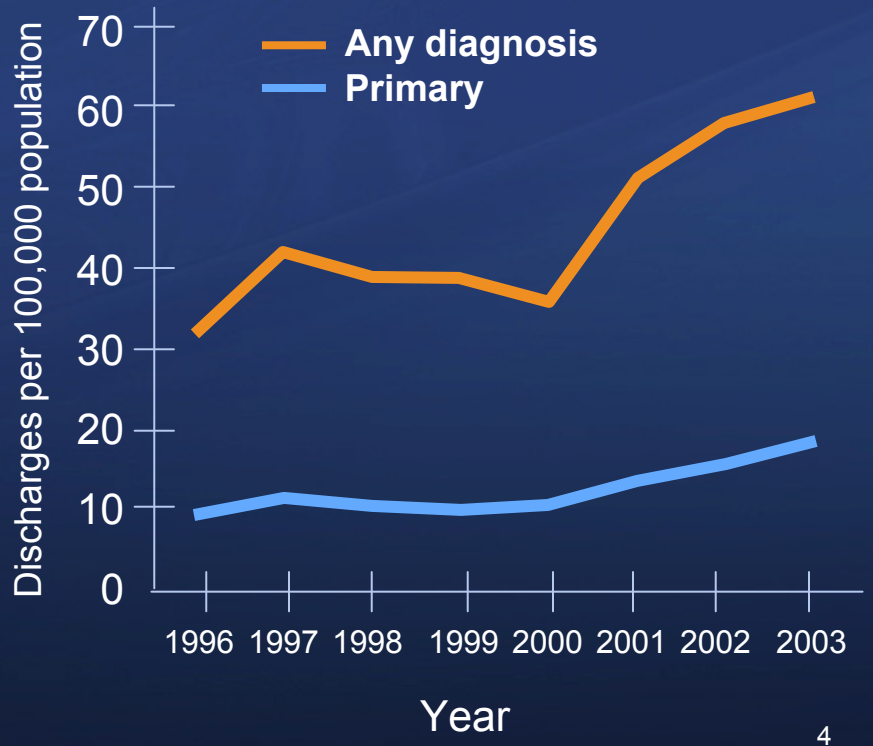
II. Impact of *C. difficile* on IBD

III. Diagnostic considerations *C. difficile*

IV. Treatment considerations

C. difficile: Changing Spectrum of Clinical Disease

- In the past: *C. difficile* linked to antibiotic use. Most cases treated successfully with metronidazole
- Doubling of *C. difficile* associated disease between 1996 - 2003
- >500,000 cases in US annually
- >15,000 deaths in US annually
- Diminished therapeutic response to metronidazole (50% failure rate with initial course of treatment)
- Increasing impact on IBD patients reported



1. McDonald LC et al. *Emerg Infect Dis*. 2006;12:409-415.
2. Musher DM et al. *Clin Infect Dis*. 2005;40:1586-1590.
3. Loo VG et al. *N Engl J Med*. 2005;353:2442.

Clostridium difficile and IBD

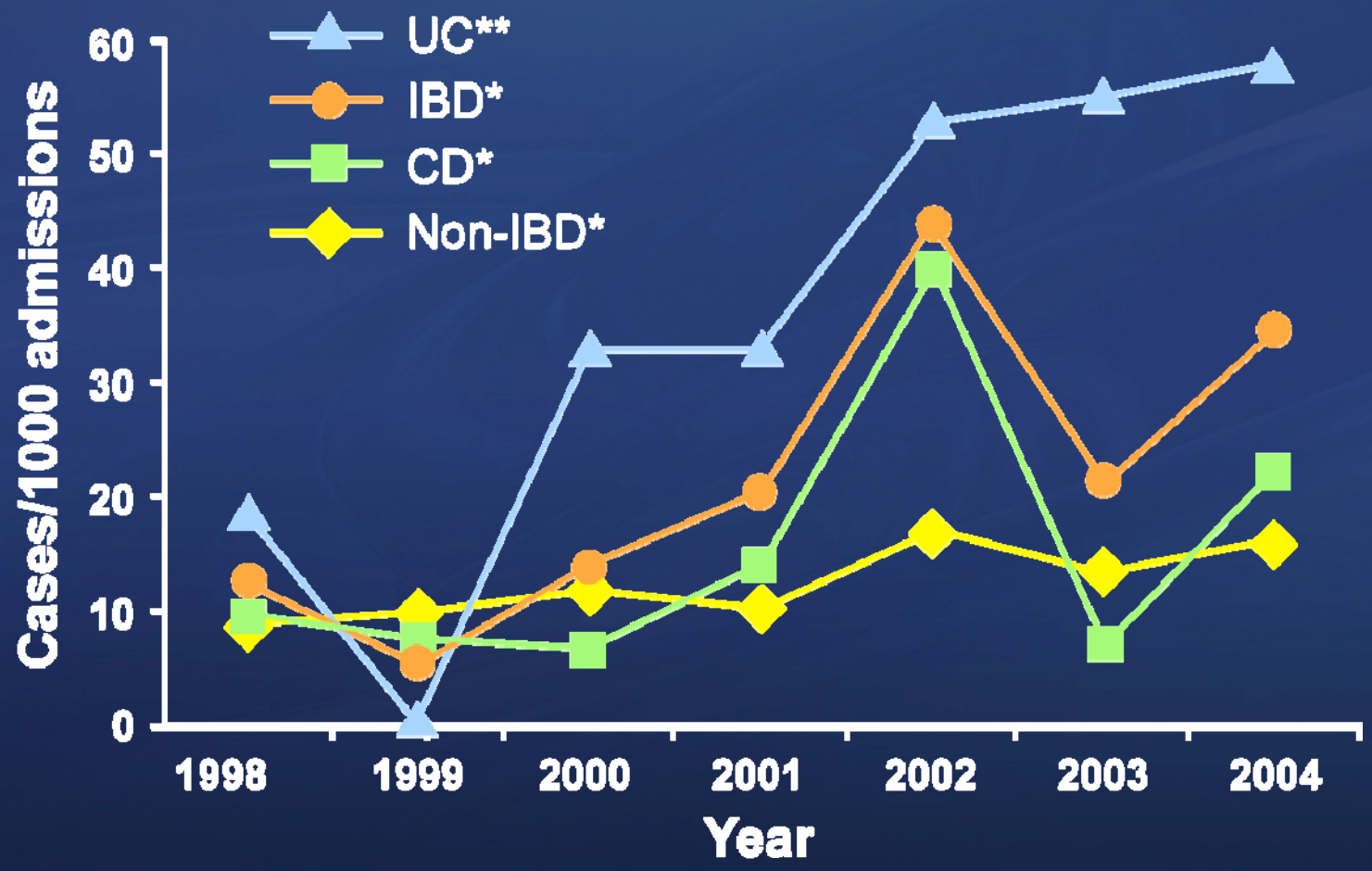
- *C. difficile* and IBD present in identical fashion ranging from mild diarrhea to fulminant colitis.
- Early studies performed 2 decades ago indicated little overlap between *C. difficile* and IBD. it concluded “No need for routine screening for *C. difficile* in IBD population”.
- Recent studies: Increasing incidence and severity of *C. difficile* in IBD population
- *C. difficile* recently identified to have a significant negative impact on IBD morbidity

1. Kochlar R et al. *J Clin Gastroenterol*. 1993;16:26-30.
2. Bolton RP et al. *Lancet.* 1980;1:383-384.
3. Trnka Y et al. *Gastroenterology*. 1981;80:693-696.
4. Issa M et al. *Clin Gastroenterol Hepatol*. 2007;5345-351.
5. Rodemann JF et al. *Clin Gastroenterol Hepatol*. 2007; 5:339-344.
6. Ananthakrishnan A et al. *Gut*. 2008;57:205-210.

Increasing Impact of *Clostridium difficile* on IBD

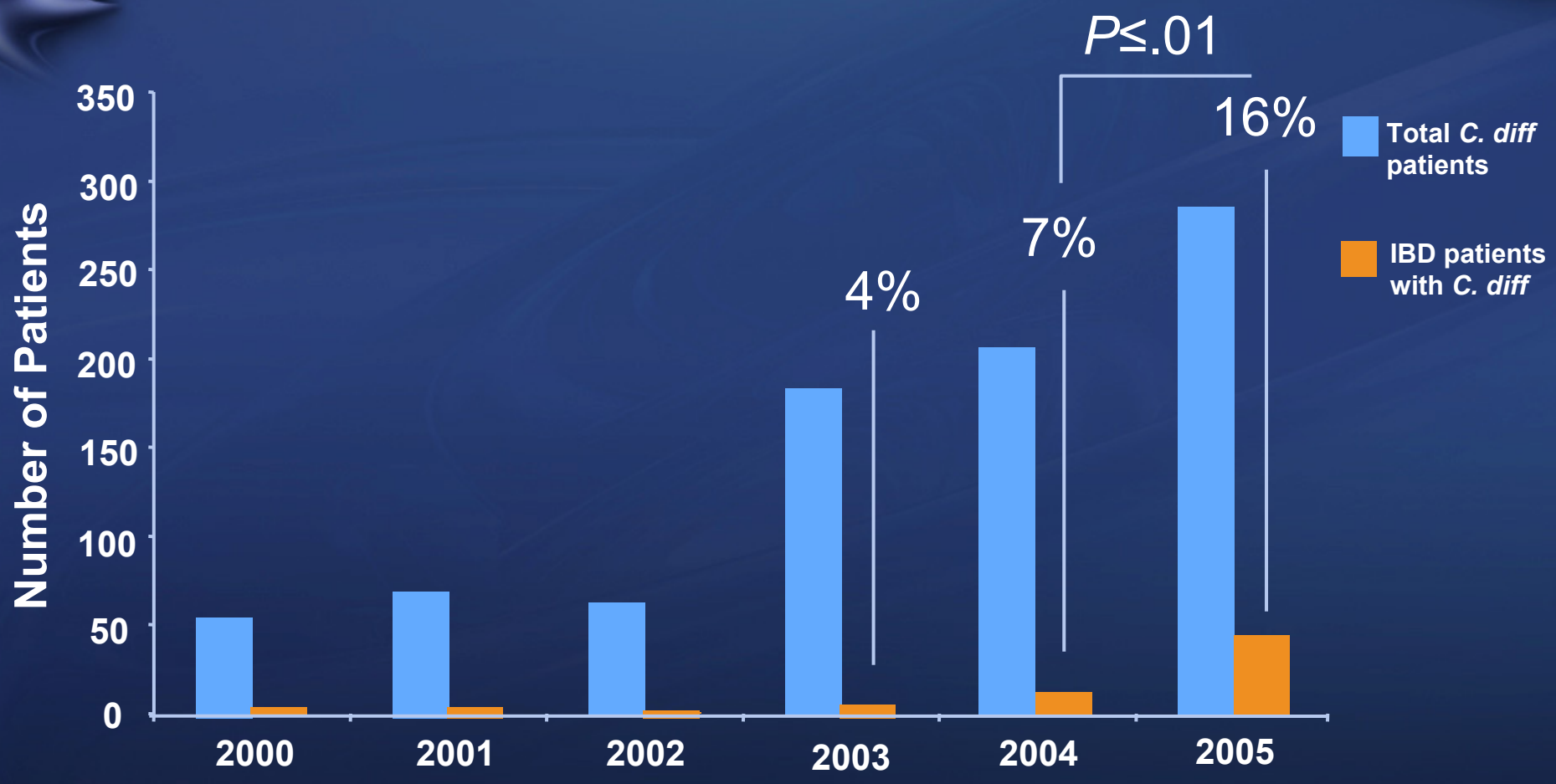
Issa M et al. *Clin Gastroenterol Hepatol*. 2007;5:345-351.

Increasing Impact of *Clostridium difficile* on IBD



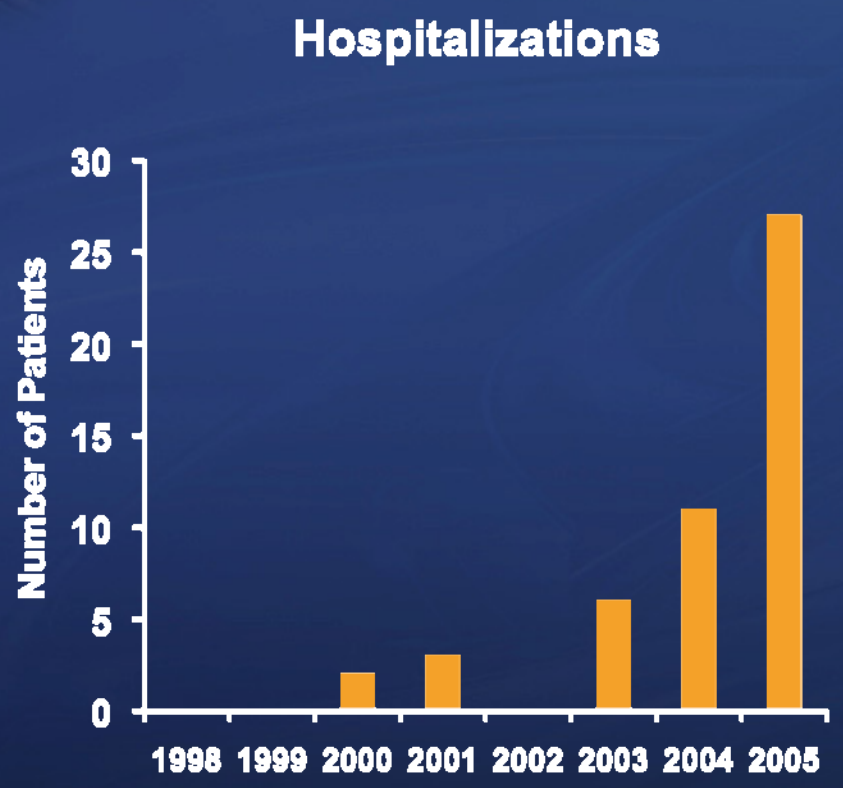
Rodemann JF et al. *Clin Gastroenterol Hepatol*. 2007;5: 339-44.
Meyer AM et al. *J Clin Gastroenterol*. 2004;38(9): 772-5

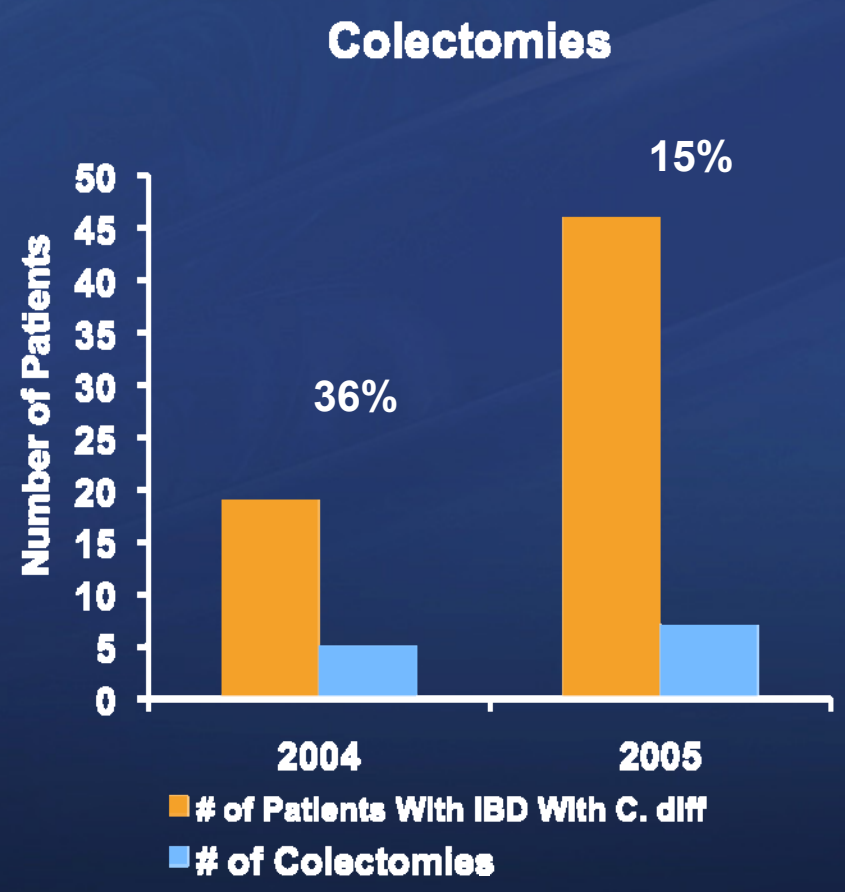
Increasing Proportion of *Clostridium difficile* Patients With IBD



Issa M et al. *Clin Gastroenterol Hepatol*. 2007;5:345-351.

Complications: *C. difficile*-Infected Patients With IBD*

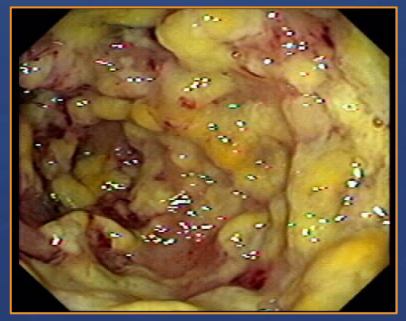
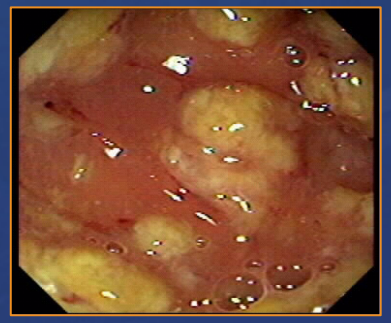




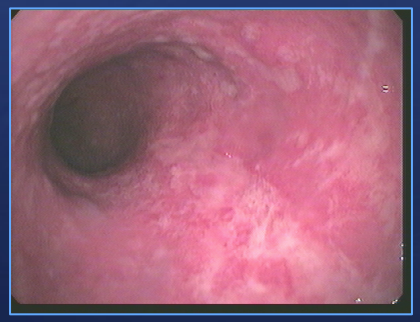
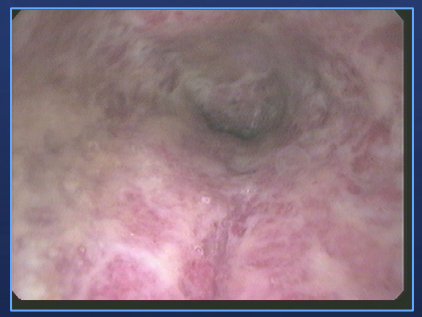
*Preliminary data.
Issa M et al. *Clin Gastroenterol Hepatol*. 2007;5:345-351.

Endoscopic Appearance of *Clostridium difficile*

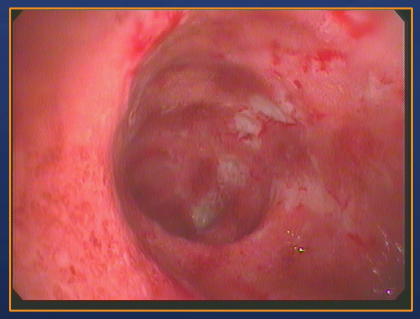
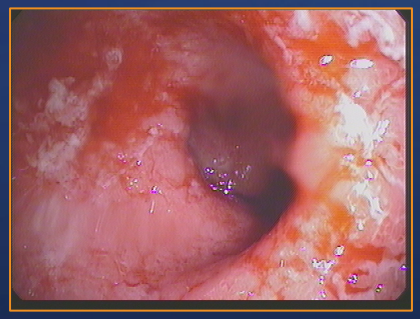
Endoscopic appearance of *C. diff* in control patients

Endoscopic appearance of *C. diff* in patients with IBD

Ulcerative Colitis

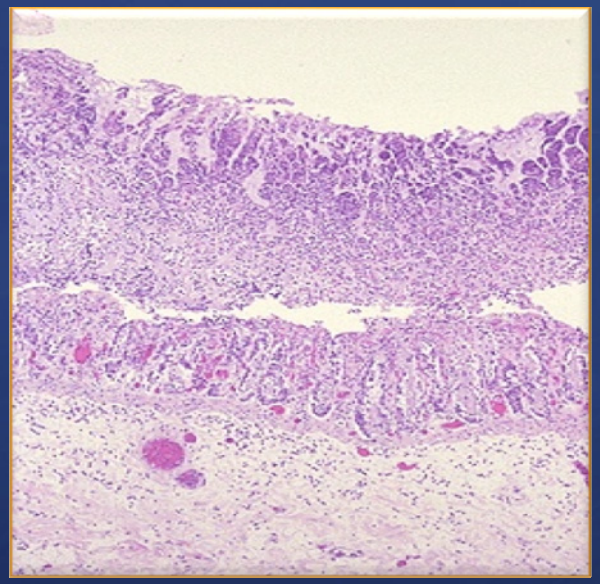



Crohn's Disease

Issa M et al. *Clin Gastroenterol Hepatol*. 2007;5:345-351.

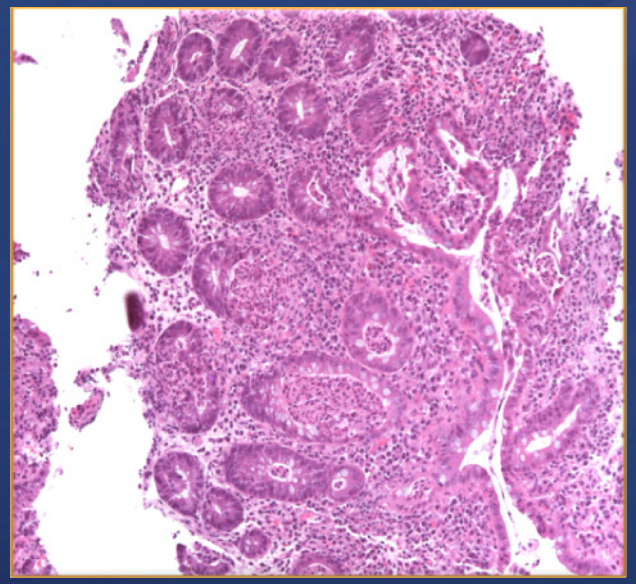
Histologic Appearance *C. difficile*

Control patient



Classic pseudomembrane on histology—mucin, fibrin, necrotic debris

Crohn's disease patient



Extensive cryptitis crypt abscesses in Crohn's colitis patient with active *C. difficile*. No inflammatory pseudomembranes are identified.

Issa M et al. *Clin Gastroenterol Hepatol*. 2007;5:345-351.

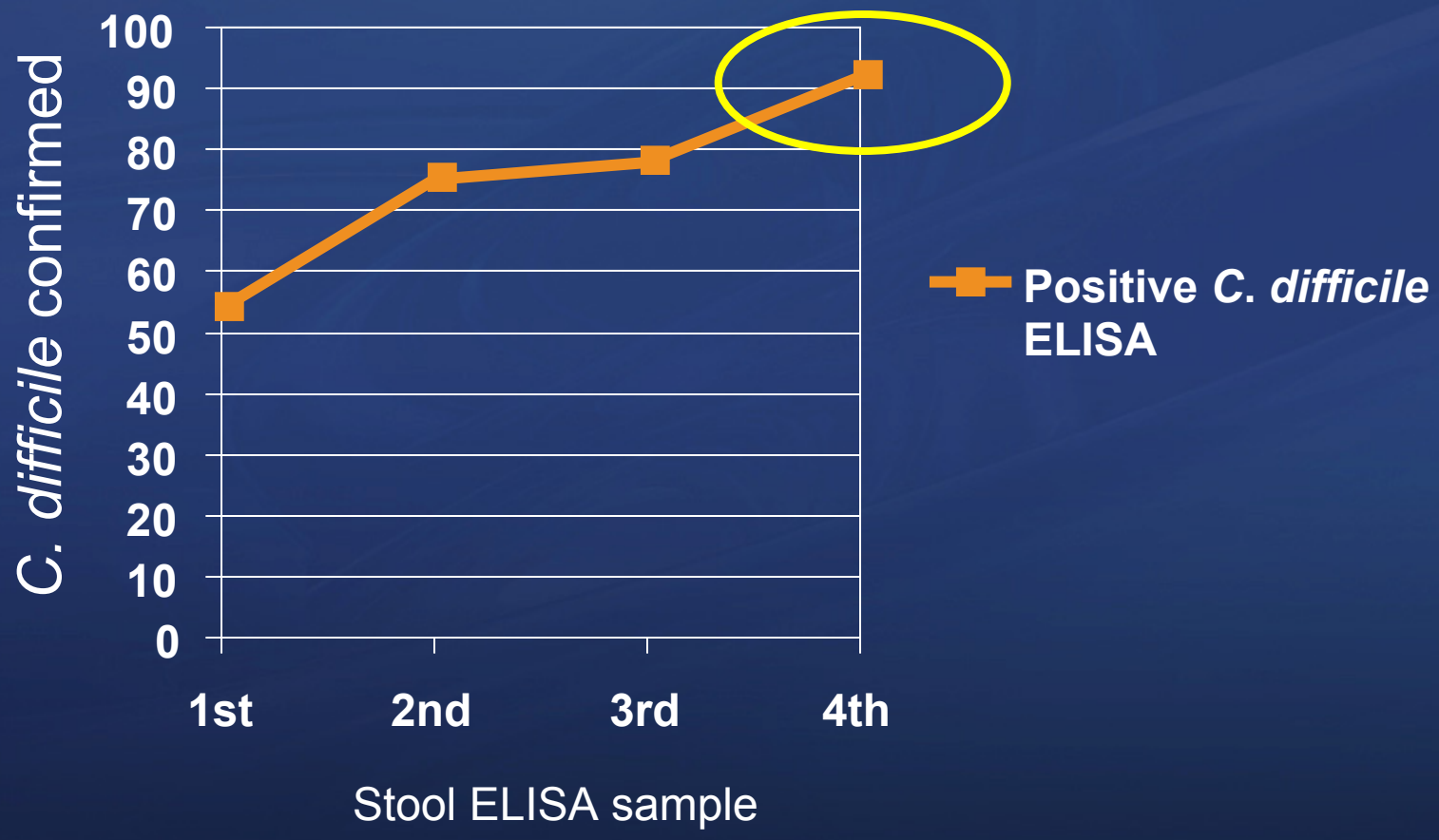
Demographic Data: IBD Patients With *C. difficile*

91%
Colonic IBD

61% recent
antibiotic exposure

Issa M et al. *Clin Gastroenterol Hepatol*. 2007;5:345-351.

Stool ELISA Testing in IBD Patients for *C. Difficile* Toxins A and B



Issa M et al. *Clin Gastroenterol Hepatol*. 2007;5:345-351.

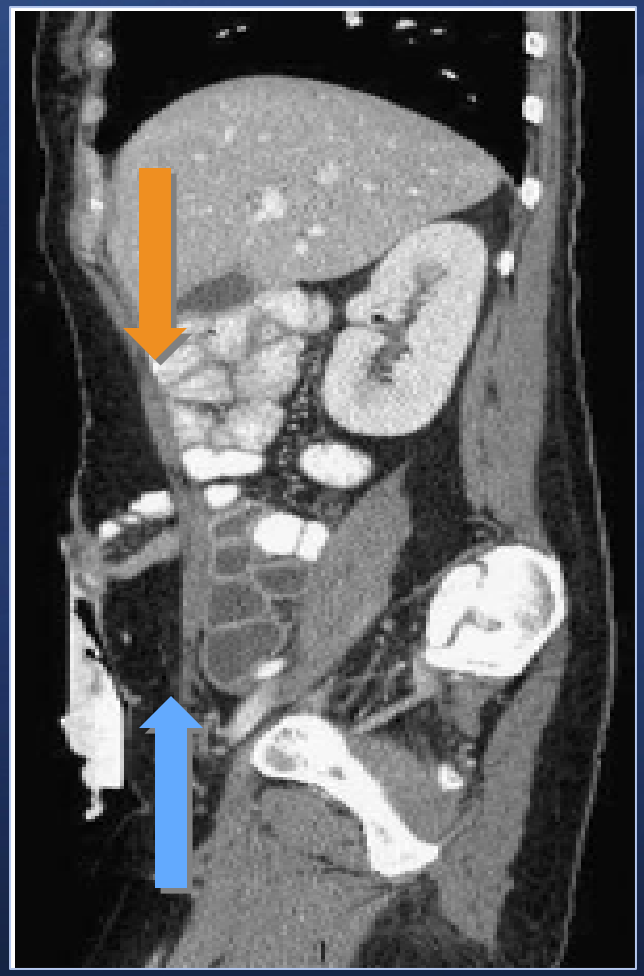
Special IBD Scenarios with C. difficile

- *C. difficile* in ileo-anal pouchitis
  - Two case reports
  - Chronic refractory pouchitis
  - Unresponsive to broad spectrum antibiotics
  - In both cases *C. difficile* developed while patients were on metronidazole therapy
- *C. difficile* in segments of diverted bowel
  - One case report of *C. difficile* in UC pt following subtotal colectomy with end-ileostomy
  - Treated successfully with 10 day course of metronidazole suppositories

1. Mann SD et al. *Dis Colon Rectum*. 2003;46: 267-270.
2. Shen B et al. *Dig Dis Sci*. 2006;51: 2361-2364.
3. Tsironi E et al. *Dis Colon Rectum*. 2006;49:1074-1077.

C. difficile Enteritis: An Early Postoperative Complication in IBD Patients Following Colectomy

- Rare but associated with significant morbidity with mortality rates ranging from 60%-83%
- MCW institutional series of six patients (2004-2006)
  - *C. difficile* manifested in high volume watery ileostomy output, ileus and fever with leukocytosis
  - No mortality with prompt diagnosis and therapy



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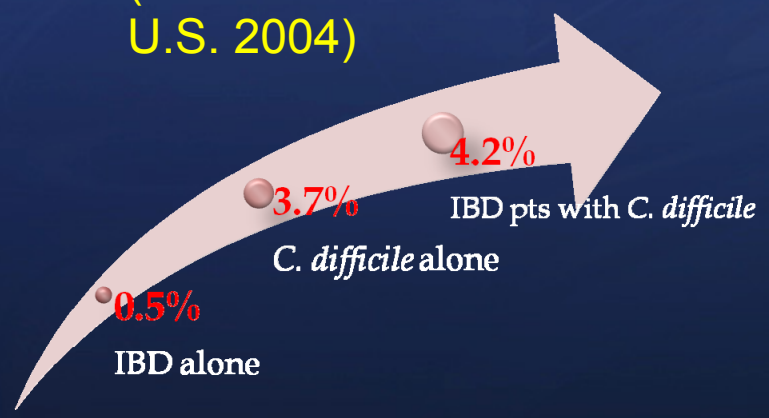
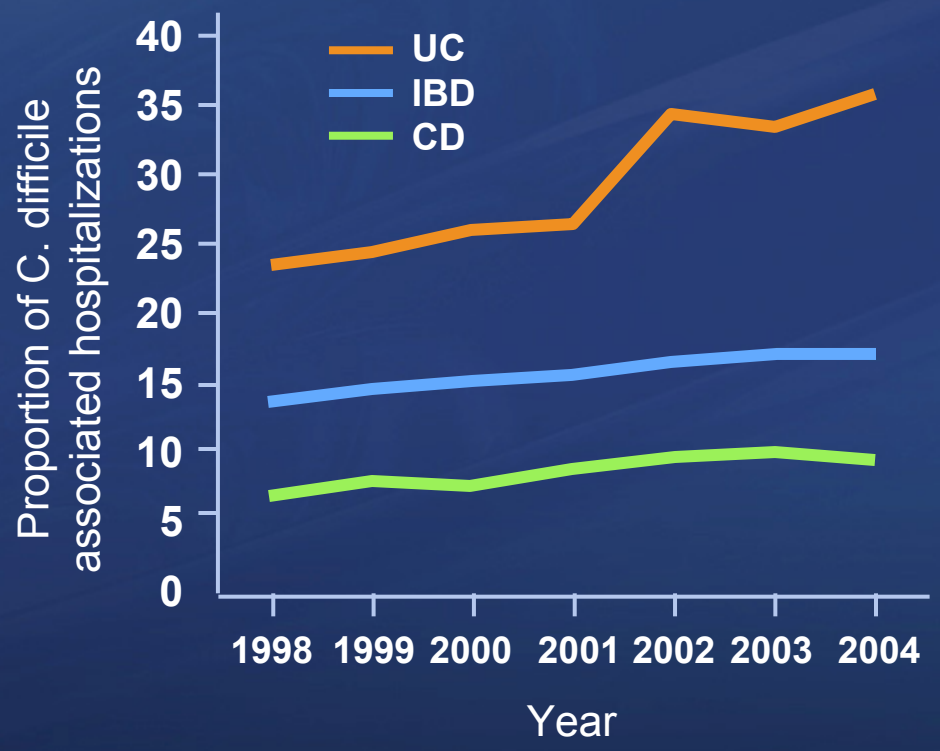
Clostridium difficile in IBD: Morbidity and Mortality

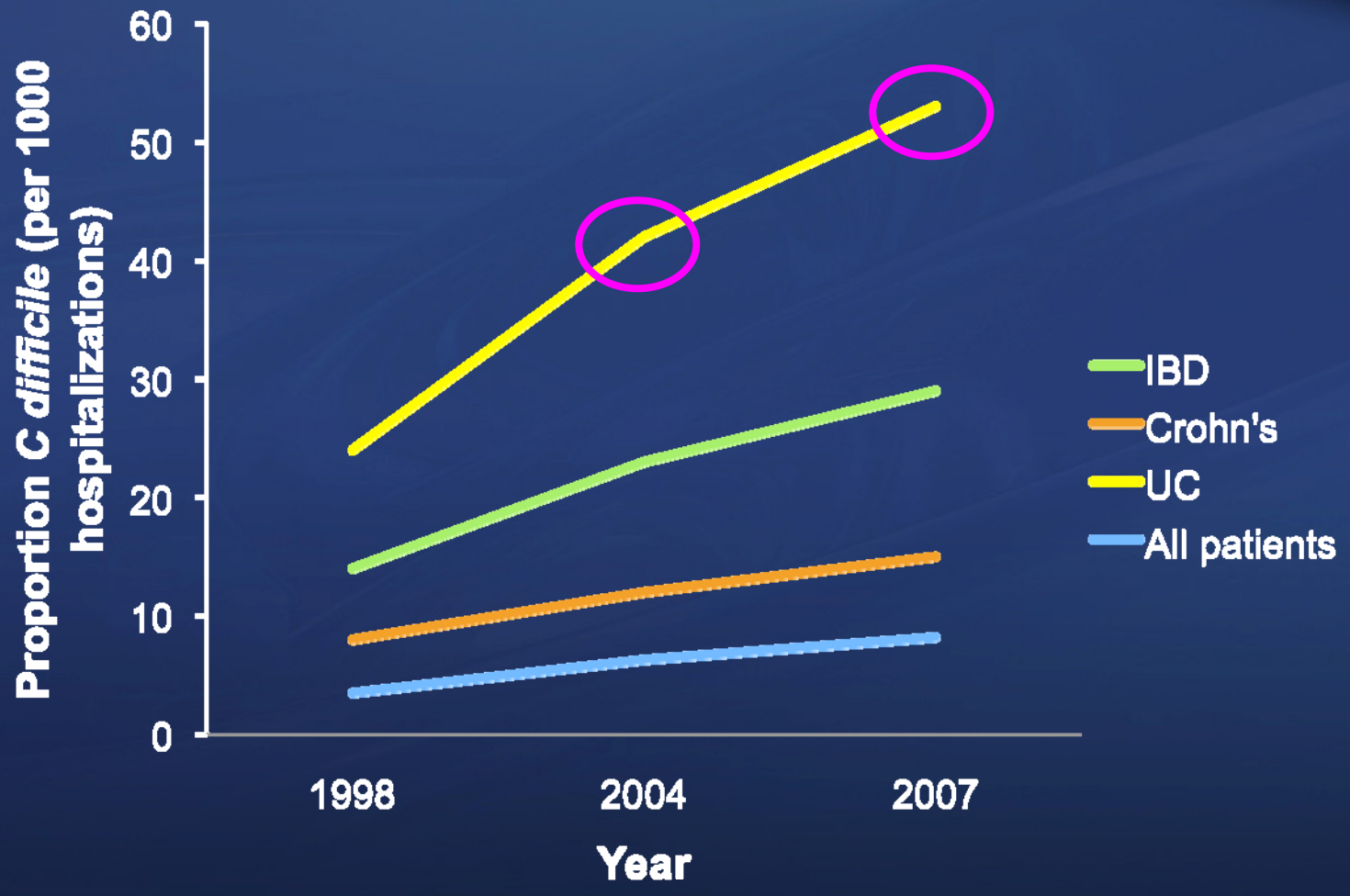
- IBD patients with *C. difficile* compared with IBD alone:
  - Longer hospital stay
  - Increased hospitalization costs
  - Higher colectomy rates
  - Increased mortality rate –
  - 118 IBD *C. diff* deaths in NIS 2004
  - (>500 IBD *C. diff* deaths in U.S. 2004)





Ananthakrishnan A, et al. *Gut*. 2008;57:205-210.

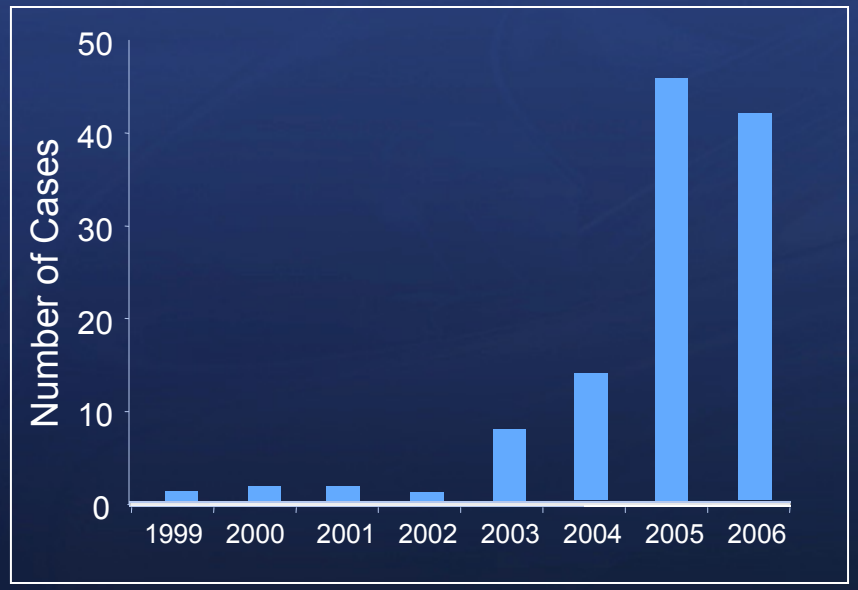
Clostridium difficile in IBD: Increasing U.S. hospitalizations 2004 - 2007

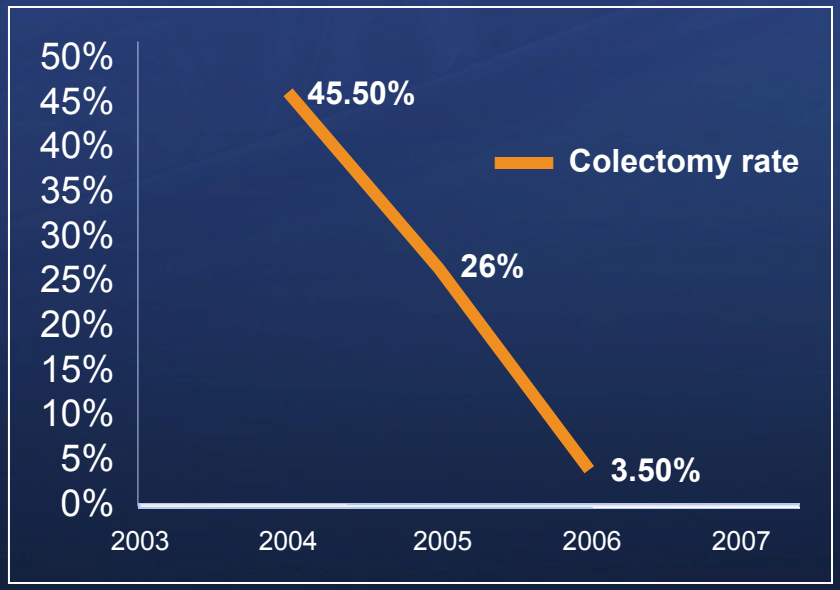


Ananthakrishnan AN et al. Med Clin N Am. 2009.

Decreasing colectomy rate among hospitalized IBD patients with C. difficile

- Number of infections and rate of hospitalization remained constant, but significant decrease in colectomy rate
  - High index of suspicion
  - Use of oral vancomycin – superiority over metronidazole
  - Decreased corticosteroid dosing





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C. difficile and IBD: Summary I

- *C. difficile* has doubled in North American Medical Centers in the past decade.
- IBD colitis patients are affected at highest rate.
- *C. difficile* in IBD is associated with high rates of hospitalization, colectomy and increased mortality.
- Antibiotic use may not be required to precipitate infection.
- Endoscopic and Histologic appearance is not classical – pseudomembranes are rare in IBD.
- Multiple stool ELISA samples for toxin analysis are required to make a diagnosis.

C. difficile and IBD: Summary II

- Metronidazole failure rate is 50%; Oral vancomycin may be superior in hospitalized patients.
- *C. difficile* enteritis may occur in post-colectomy patients and patients with ileoanal pouch reconstruction.
- *C. difficile* recurrence rates are high.
- Early surgical consultation for patients developing severe disease (>10 BM/day, WBC>20K, severe abdominal pain, ileus).
- Hand washing with soap and water is essential to prevent nosocomial transmission.