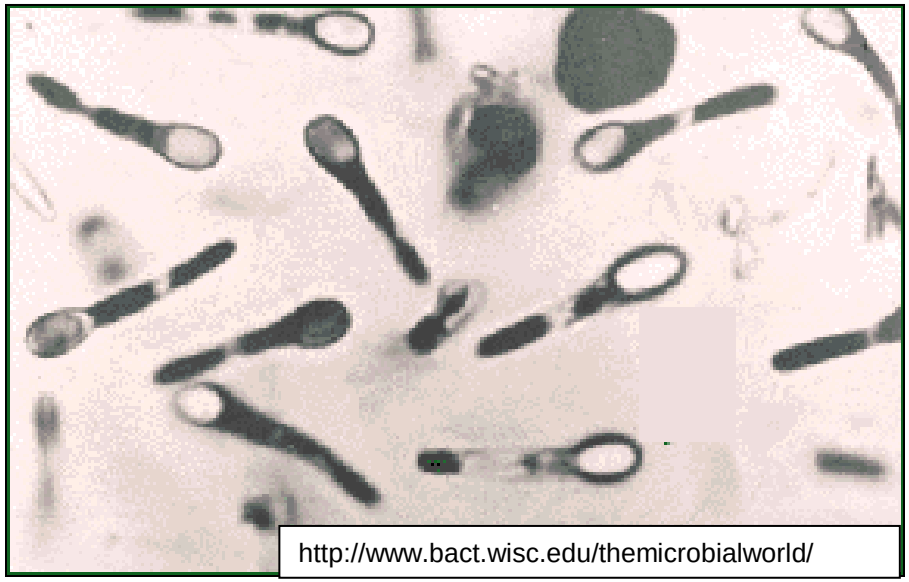

Update on Diagnostic Testing for *C. difficile* and Nosocomial Diarrhea: Where are we now?

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Disclosures

I have received research materials from:

- Cepheid
- TechLab
- Meridian
- Alere

Objectives

After this talk, the participant should be able to:

- Explain the strengths and limitations of tests for *C. difficile* DNA or antigens vs. toxins
- Explain the role of inflammation in *C. difficile* infection and criteria for mild-moderate vs. severe disease
- List 5 common causes of non-*C. difficile* nosocomial diarrhea

Definitions

- Nosocomial diarrhea
  - Onset ≥3rd hospital day
  - ≥3 diarrheal stools x ≥1 day
  - New diarrhea in hospital due to hospital exposure
  - 10-25% = CDI
  - ≥75% due to some other cause
- *C. difficile* infection (CDI) vs. carrier

Incidence & significance

Nosocomial diarrhea

- ~10% of hospitalized pts.
- ≥3.7 million pts./year
- Morbidity & mortality:
  - ↑UTI, wound infections
  - fluid & electrolyte loss
  - ?nutritional impact
- Healthcare costs
  - ↑ hospital days/costs?

***C. difficile* infection (CDI)**

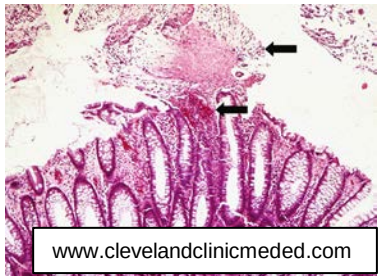
- ~1% of hospitalized pts.
- ~300,000 pts./year
- Morbidity & mortality:
  - ~15% complications
  - ~20% recur
  - 3-5% attributable death
- Healthcare costs
  - 2-3 hospital days/case
  - 1.1-3.2 billion USD/yr

The spectrum of *C. difficile* disease

Rupnik et al.
Nat Rev Microbiol 2012

www.gastrolab.net

www.sharinginhealth.ca



www.clevelandclinicmeded.com

www2.cfpc.ca

60% | **40%**

Asymptomatic	Mild-mod disease Diarrhea but nl WBC	Severe disease Colitis & ↑WBC/Cr	Complicated CDI Megacolon, shock
	50%	33%	~15%

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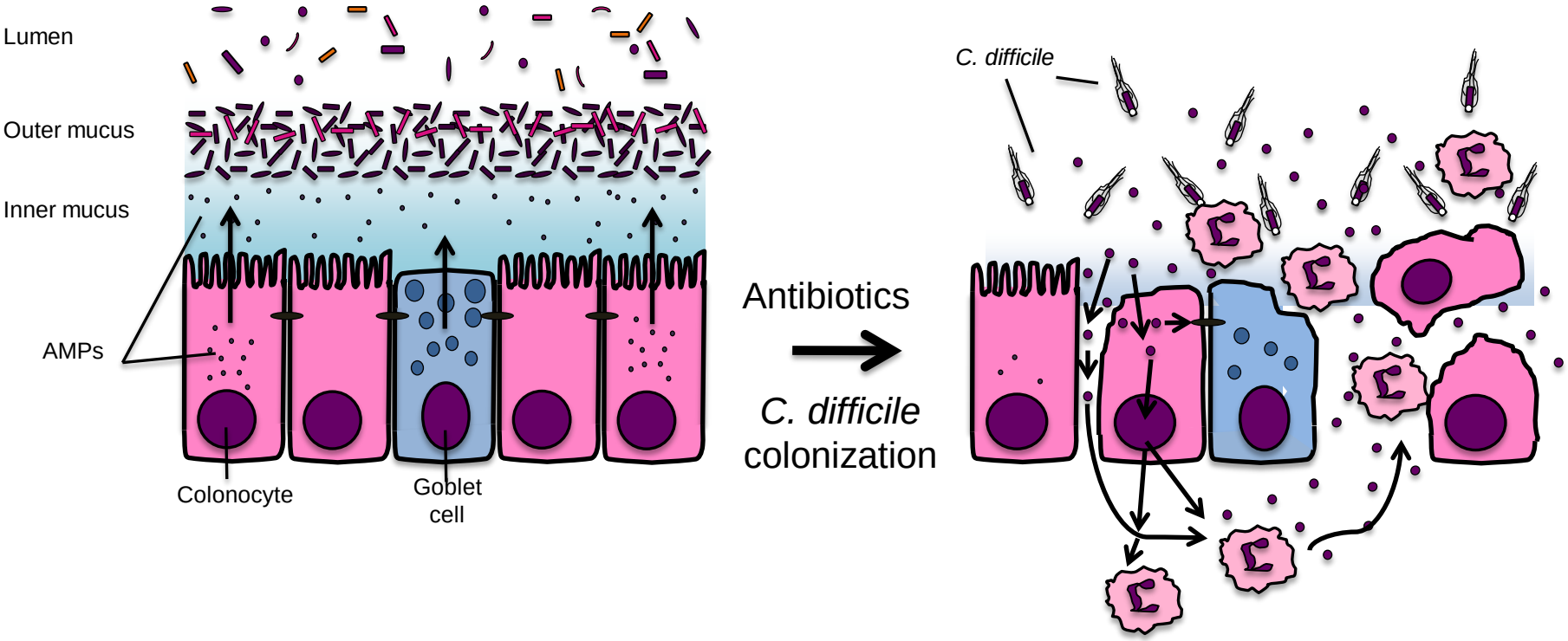
C. difficile disease is mediated by toxins & inflammation

Healthy host
and microbiota

Disrupted biota, *C. difficile*
overgrowth, toxin injury & inflammation



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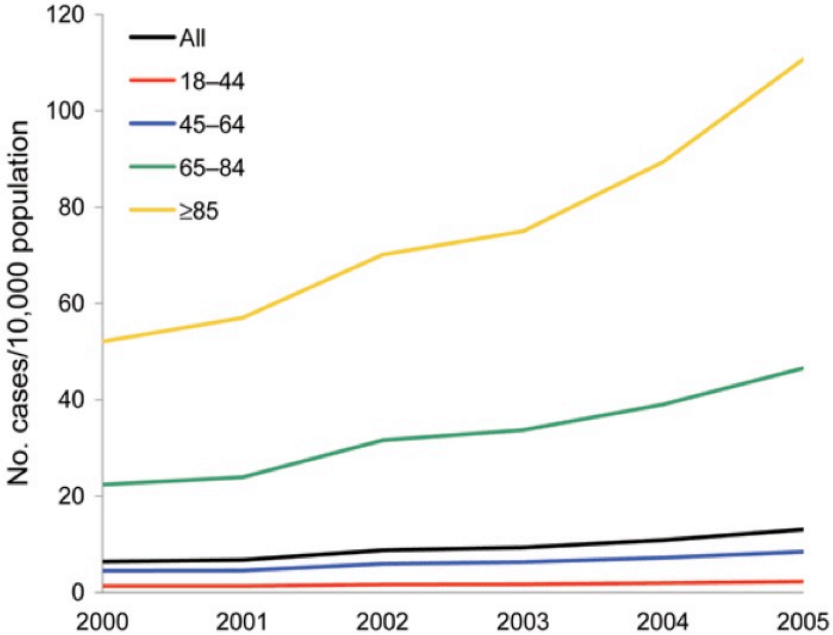
The frequency & severity of *C. difficile* infection has increased…..

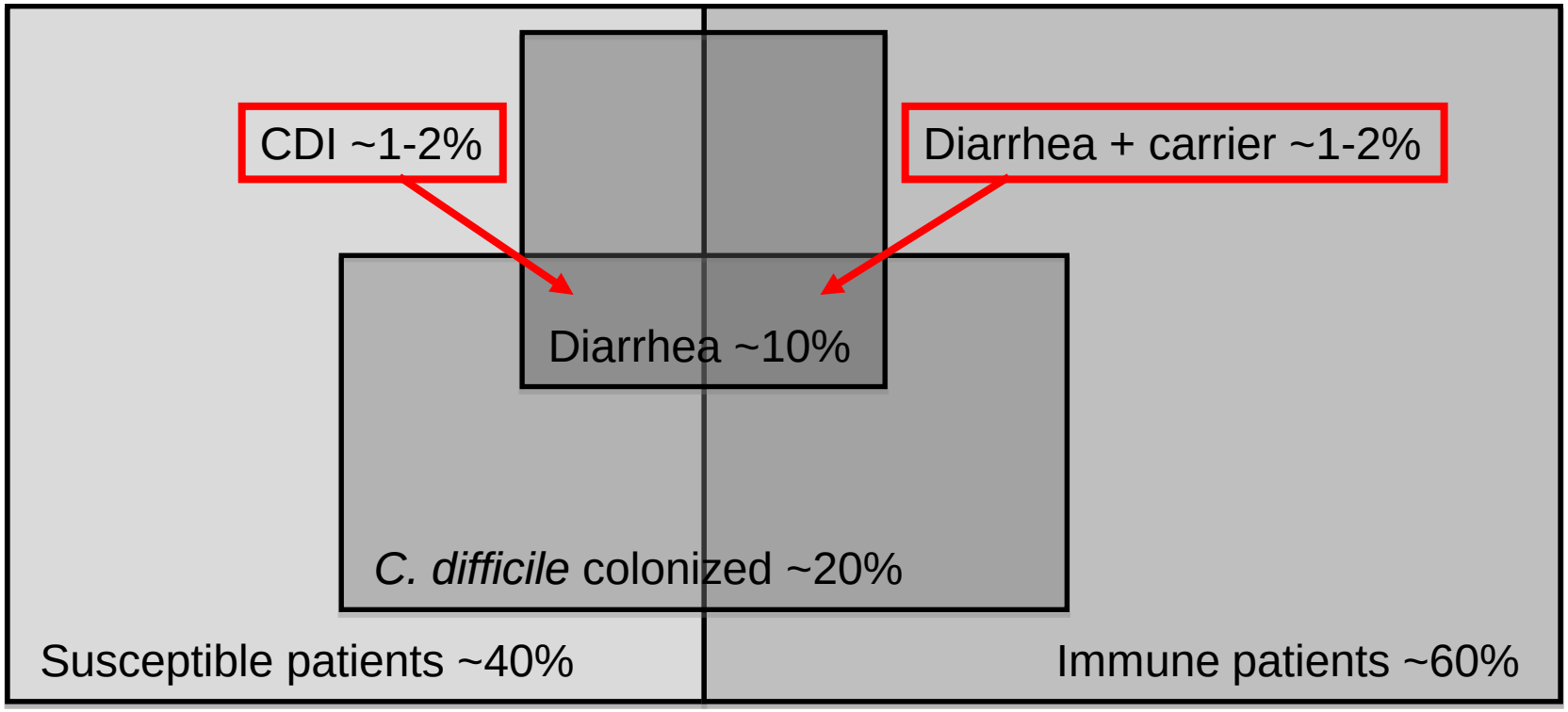
- From 2000-2009
  - >200% ↑ CDI cases
  - >400% ↑ CDI mortality
- Associated with:
  - Epidemic BI/NAP1/027 strain
  - Antibiotic use
  - More sensitive tests?

Increasing age-specific incidence of CDI in the U.S., 2000-2005.



Zilberberg, et al. *Emerg Infect Dis* 2008

….but colonization and immunity are also common in healthcare settings



Hospitalized patients

Available tests for *C. difficile*

Analytical sensitivity vs. clinical specificity (Dubberke et al. JCM 2011)

Test method	Target	Sensitivity for *C. difficile* vs. toxigenic culture	Specificity for *C. difficile* + clinical symptoms
Toxin immunoassay	Toxins A&B	40-92%	93-96%
Cell culture cytotoxicity	Toxin B>>A	67-86%	93-95%
DNA amplification	*tcd*B or *tcd*A	87-100%	84-86%
Glutamate dehydrogenase immunoassay	GDH enzyme (log phase)	80-95%	80-85%
Toxigenic culture	Bacteria + in vitro toxin production	----	90-92%

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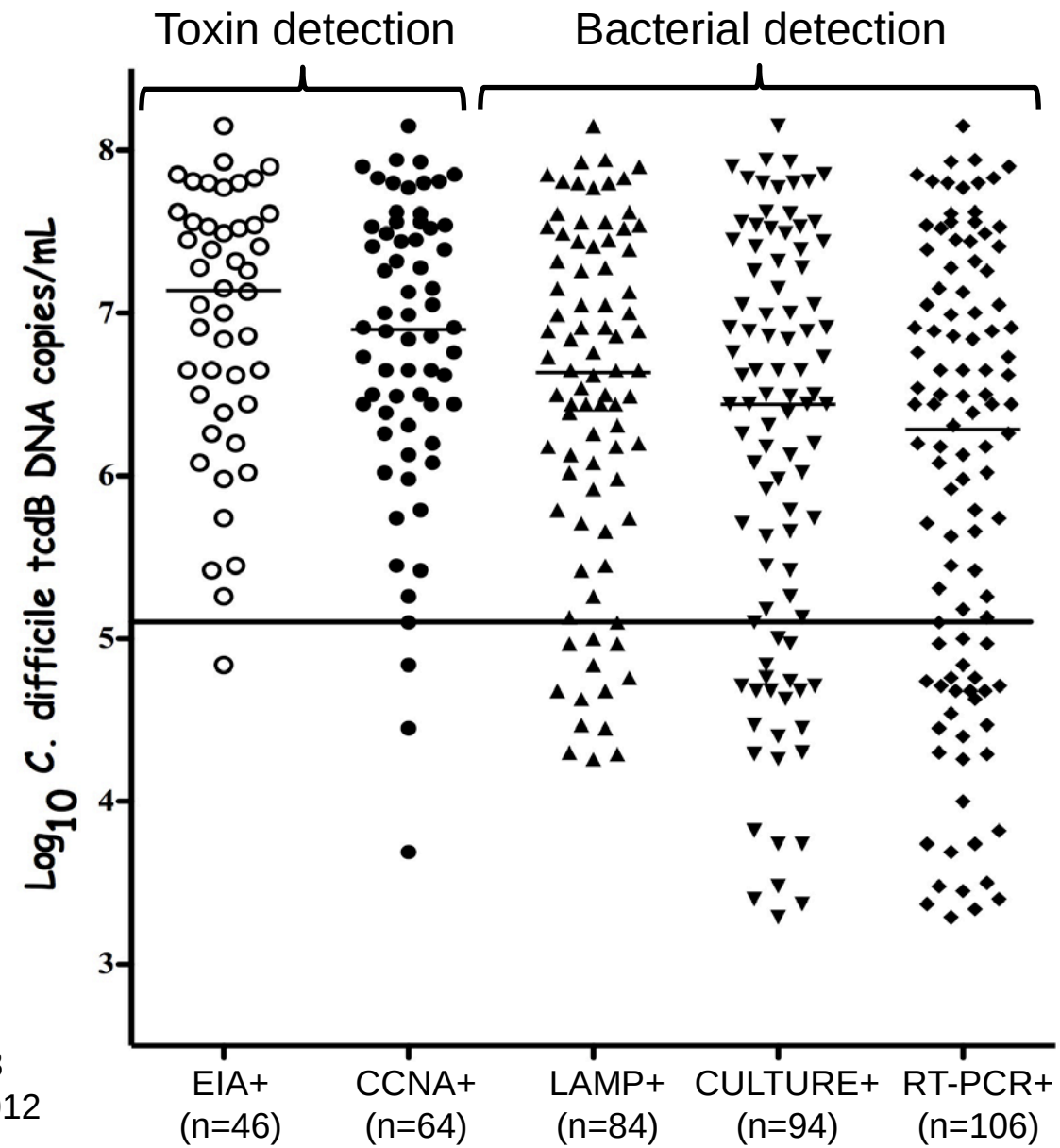

Adapted from:
Gyorke et al. JCM 2013
Leslie et al. EJCMID 2012

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So, what's the best diagnostic test…?

Sensitive but specific for active disease

- Historically (1979-2005) - toxin tests favored
  - Gold standard = cell cytotoxin assay
  - Toxin-/*C. difficile*+ patients = colonized
- Recently (2005-2013) – shift ➡ PCR/NAAT/Ag
  - Gold standard: toxigenic culture
  - Toxin assays only ~40-70% sensitive

So, what's the best diagnostic test…?

No test is perfect:

- Toxin tests may miss occasional cases
- Culture & PCR probably overdiagnose

Both under & overdiagnosis have significant implications

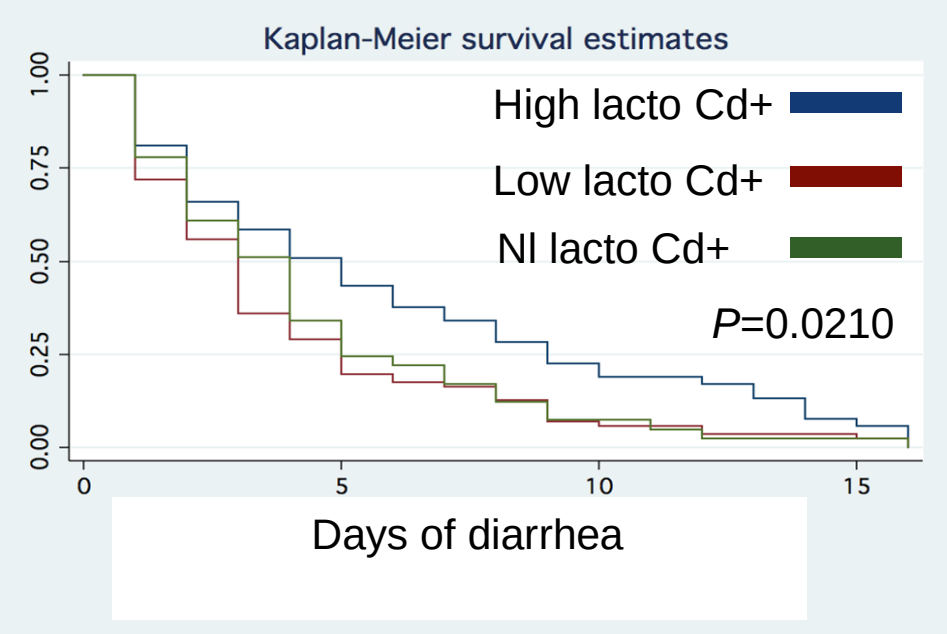
Is there a role for inflammatory markers as adjunctive tests?

TABLE 1 Lactoferrin values by *C. difficile* test result status[a]

	C. difficile result				Lactoferrin value (μg/ml)		Proportion (%) of samples with lactoferrin values above:	
Group	GDH	Toxin	PCR	No. of samples	Median	Range	80 μg/ml	100 μg/ml
1	Neg	NA	NA	43	13	3–143	18.6	9.3
2	Pos	Neg	Neg	14	18	4–78	0	0
3	Pos	Pos	NA	25	80*	3–124	52.0**	40.0***
4	Pos	Neg	Pos	30	24	4–160	13.3	6.7

[a] Neg, negative; Pos, positive, NA, not applicable; *, median lactoferrin value significantly higher than other individual groups (Mann-Whitney U test); **, no. of samples in group 3 above cutoff versus group 1 ($P = 0.004$), versus group 2 ($P < 0.001$), versus group 4 ($P = 0.007$); ***, no. of samples in group 3 above cutoff versus group 1 ($P = 0.004$), versus group 2 ($P = 0.007$), versus group 4 ($P = 0.007$).

LaSala et al. JCM 2012



CR Polage, unpublished data

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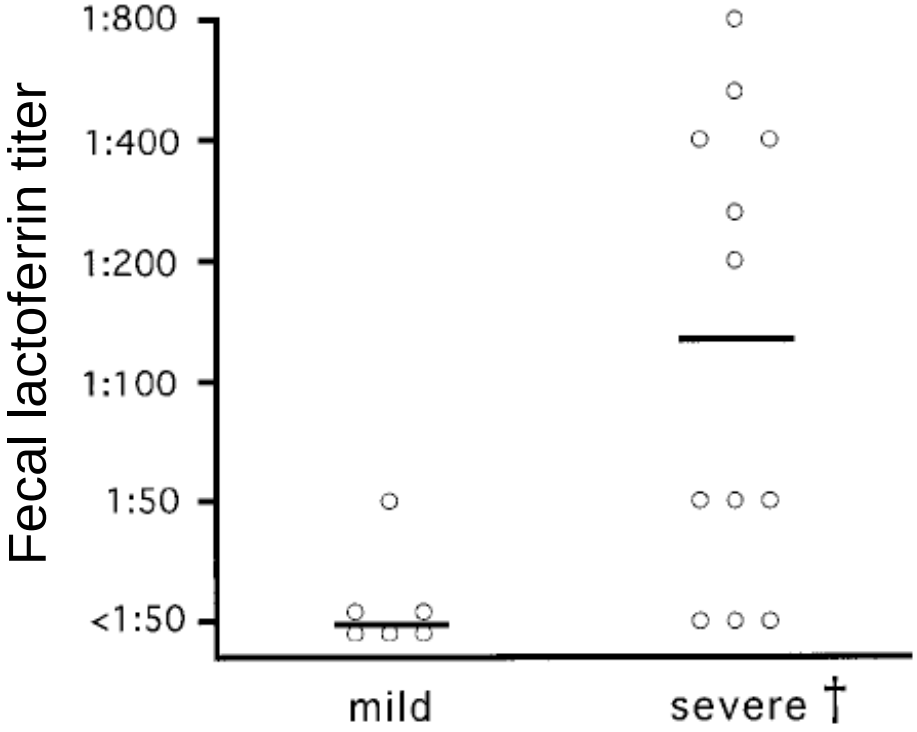
Definition of severe CDI and risk factors for complications

- Severe CDI as a predictor of complications
  - WBC≥15/mm^3 *or*
  - Cr≥1.5 x baseline
- Other predictors
  - Age≥ 65 yrs
  - Albumin<2.5 mg/dL
  - ↑comorbidities, & underlying illness
  - BI/NAP1/027 strain?



Steiner et al. CDLI 2006

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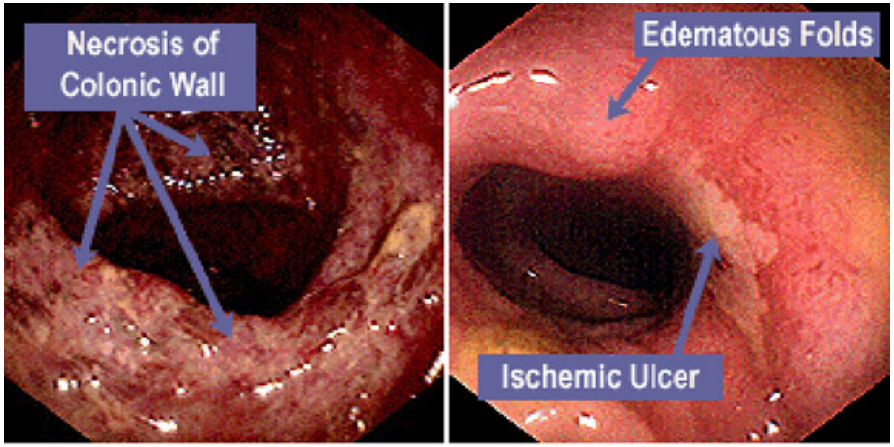
Other causes of nosocomial diarrhea
Medications

	Diarrhea Frequency	Non-inflammatory diarrhea	Inflammatory diarrhea
Antiarrhythmics	8-30%	X	
Antibiotics	5-35%	X	X
Anti-inflammatory	≥20%	X	X
Anti-retrovirals	≥20%	X	
Colchicine	80%	X	
Cytotoxic chemo	30-80%	X	X
Immunosuppressants	30-60%		X
Laxatives (Mg^{++}, stimulant, osmotic)	≥20%	X	X
Osmotic carbs (sorbitol etc)		X	
Tyrosine kinase inhibitors	20-60%	X	X

Other causes of noscomial diarrhea
Underlying illness

- Fecal impaction
- Ischemic colitis
- Opiate withdrawal
- Hypoalbuminemia
- Graft versus host disease
- IBD, IBS, etc.?

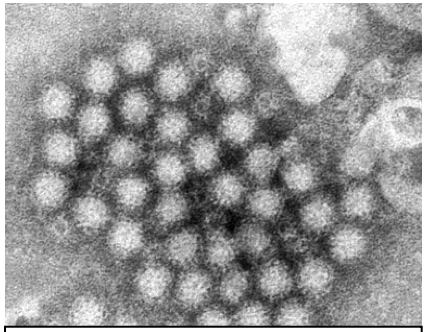


Ischemic colitis Endoscopy of ischemic colitis may reveal continuous necrosis and mucosal friability that resembles ulcerative colitis (left panel); discrete ulcers with surrounding edema may also be seen (right panel). Courtesy of James B McGee, MD.

pleiad.umdnj.edu/pathology_course/

Other causes of noscomial diarrhea
Norovirus

- #1 foodborne gastroenteritis
- Winter vomiting illness
  - Abrupt onset vomiting +/- diarrhea
  - Short duration
- Epi still uncertain in hospitals
  - Outbreaks!
  - Sporadic?
  - Only 50% have vomiting
  - Prolonged in immunocompromised
- RT-PCR is test of choice



www.medicinenet.com

Other causes of noscomial diarrhea

toxigenic *Klebsiella oxytoca*

- ~50% strains toxin+
- 1-5% healthy population carry toxin+ strain
- ⬆ with antibiotics
- Bloody diarrhea & hemorrhagic colitis
  - ~15% bloody AAD
  - 60-80% AAHC

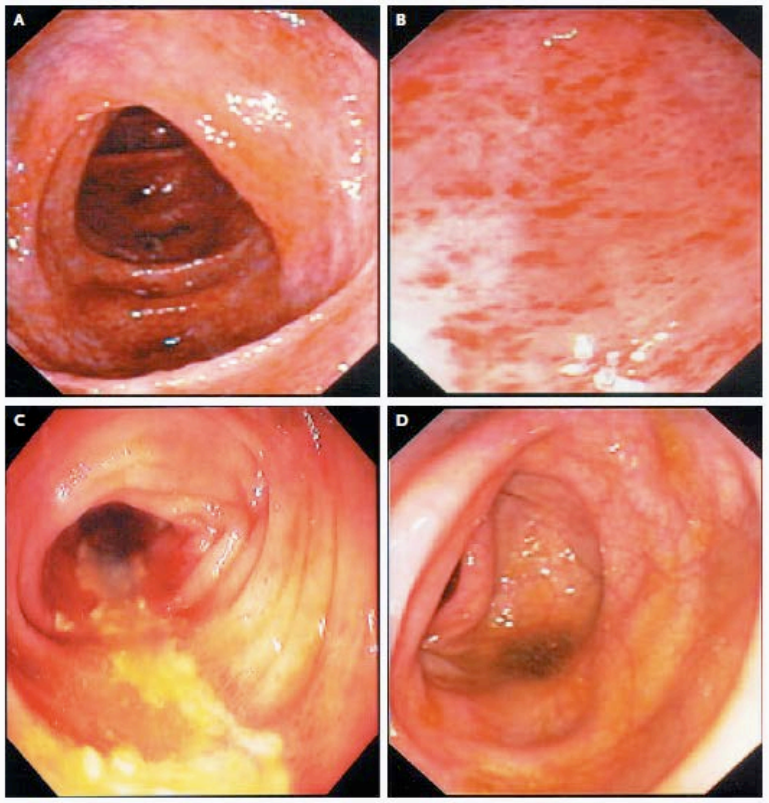


Figure 1. Colonoscopic Images in Two Patients with Antibiotic-Associated Hemorrhagic Colitis.
Panel A shows mucosal edema and hemorrhage in the transverse colon in Patient 4; Panel B shows a close-up of mucosal hemorrhage in the same patient. Panel C shows longitudinal ulceration in the sigmoid colon in Patient 2; Panel D shows rectal sparing in the same patient.

Hogenauer NEJM 2006

Other causes of noscomial diarrhea

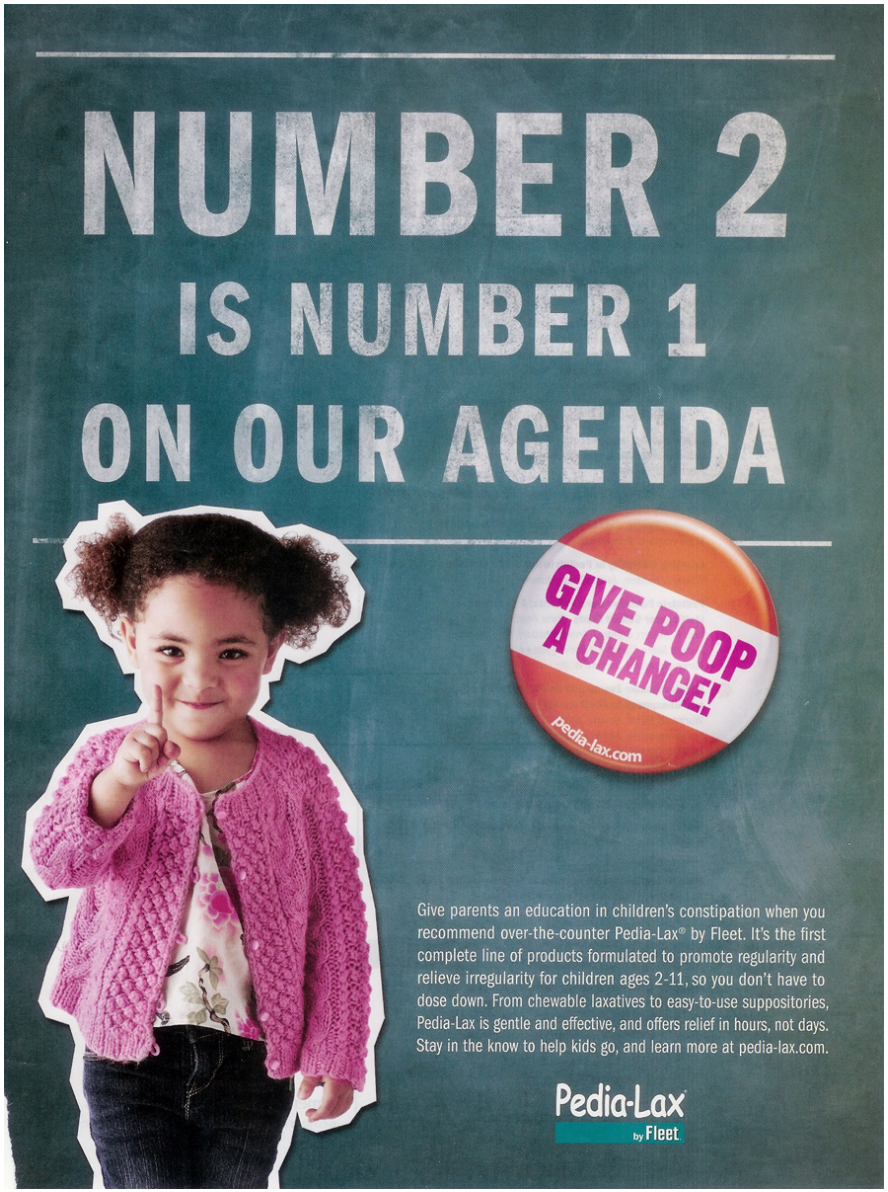
Occasional bacterial causes

Organism	Frequency	Testing?
toxigenic *C. perfringens*	≤3%	N/A special request
toxigenic *S. aureus*	<1%	N/A special request
toxigenic *Bacteroides fragilis*	? (<5%)	N/A

Take home messages….

- *C. difficile* testing is evolving
  - Toxin tests are insensitive
  - DNA / bacterial tests are sensitive but non-specific
  - Expect role for adjunctive tests in future
- Severe CDI defined by ↑WBC or Creatinine
  - ↑risk of complications; treat aggressively
- Many other causes of nosocomial diarrhea
  - Most are non-infectious due to meds & underlying illness

Questions?


NUMBER 2
IS NUMBER 1
ON OUR AGENDA
GIVE POOP A CHANCE!
pedia-lax.com
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