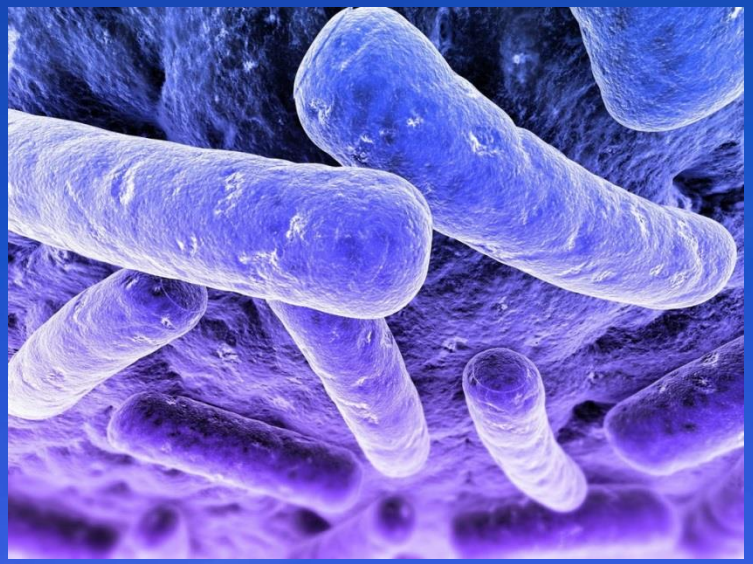
Clostridium difficile Infection 2017

26th Annual Southwestern Conference on Medicine April 30, 2017

Robert Orenstein, DO
Chair, Infectious Diseases
Mayo Clinic in Arizona
orenstein.robert@mayo.edu



Disclosures

- Mayo Clinic has received funding from my role as an investigator on several clinical trials of new products for CDI
  - Rebiotix
  - Crestovo
  - Merck
- I have been an advisor for ReBiotix
- I will discuss off label uses of several drugs and discuss several investigational agents including FMT

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Goals

At the end of this talk participants will

- Know the current epidemiology of *C. difficile* and how it impacts hospital practice
- Know the limitations of diagnostic testing for *C. difficile* infection
- Know the pathogenesis of CDI
- Name the new and upcoming therapeutics for CDI
- Know the role of Biotherapeutic approaches to prevent CDI

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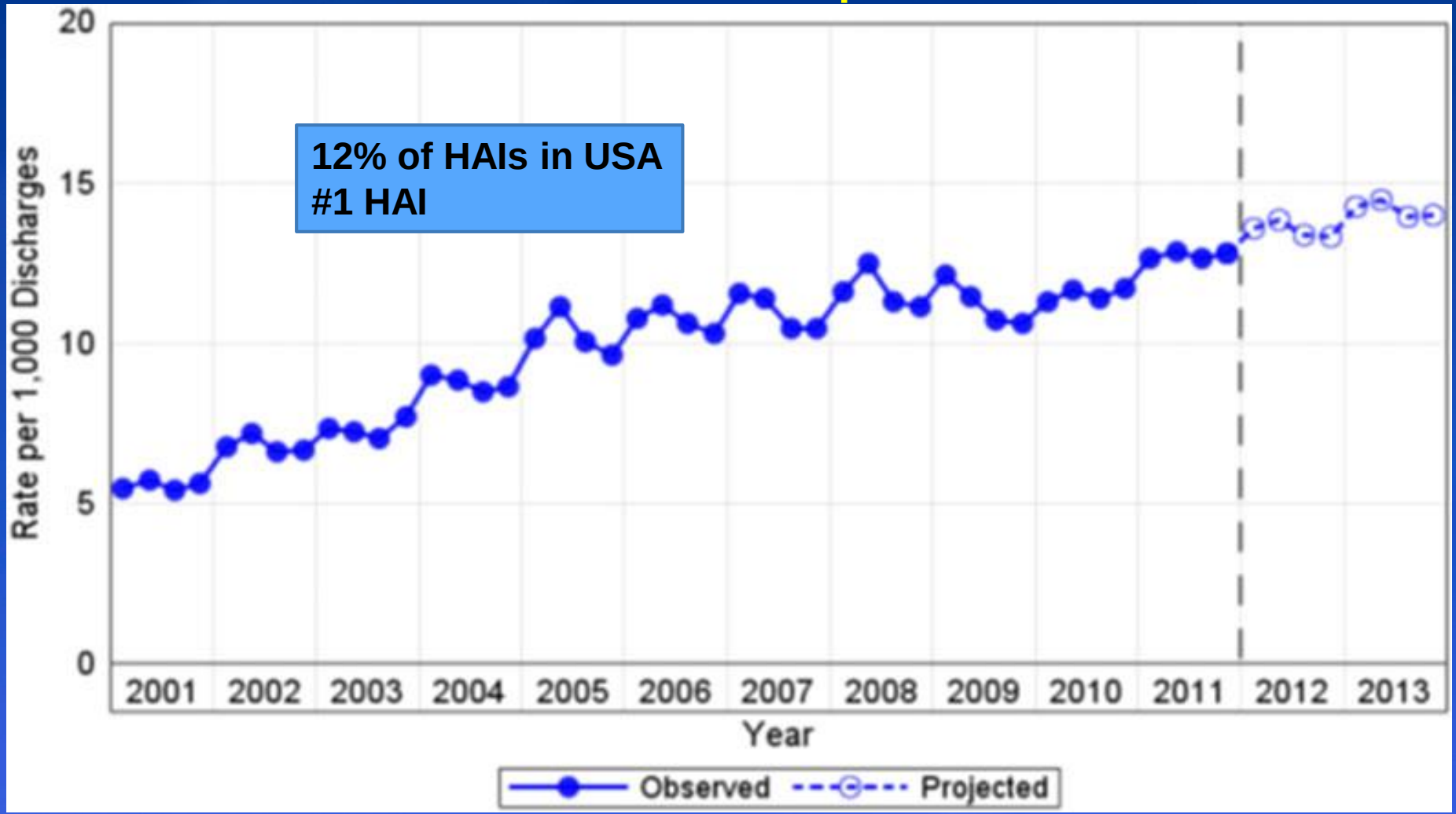
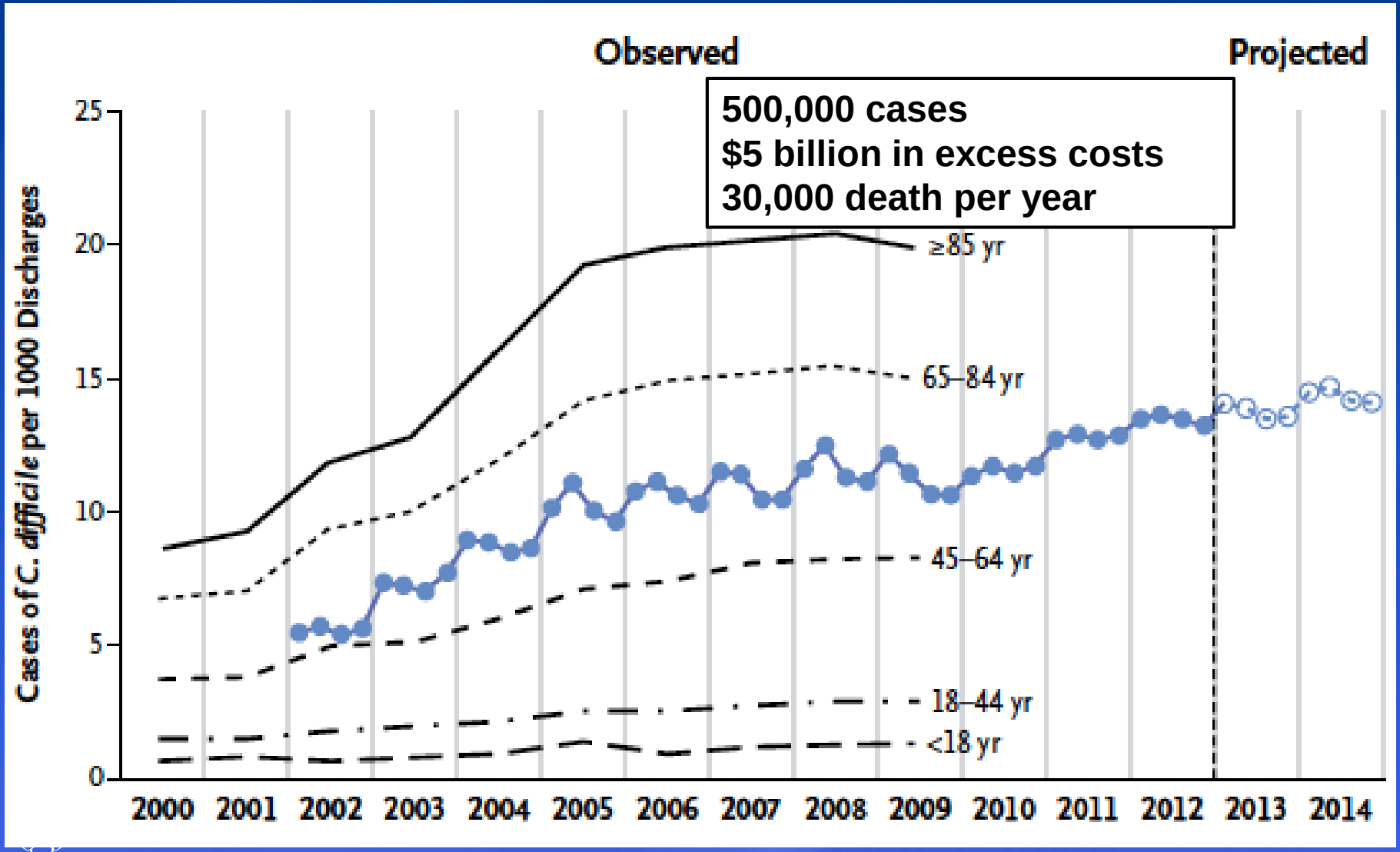
Rates of CDI related hospitalization in USA



Evans et al CID 2015;60S2

Incidence of CDI

Leffler NEJM 2015:372;1539



How Common is C. difficile?

- It depends
  - Colonization vs infection
  - Outpatients vs inpatients
  - SNF vs free living

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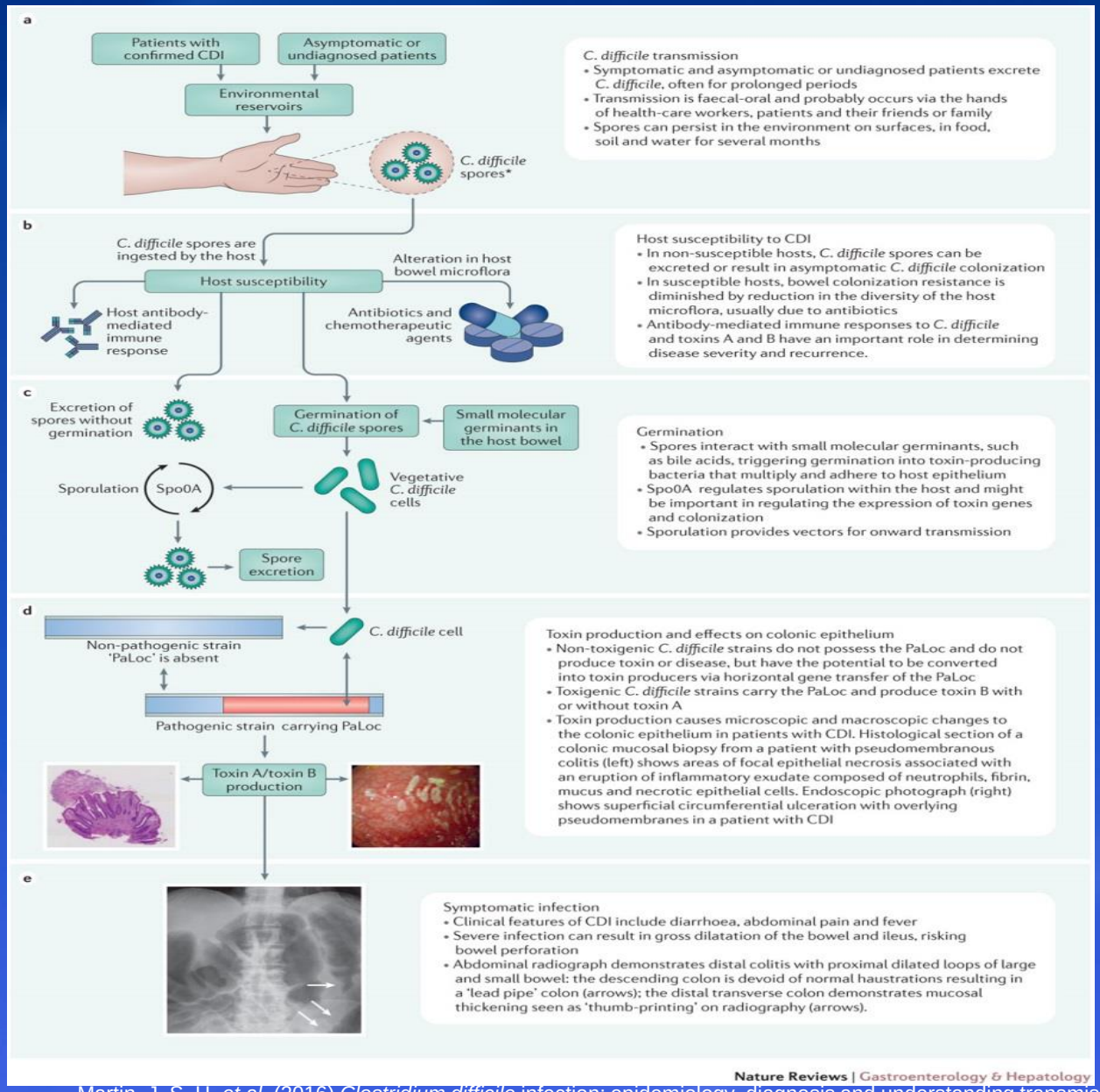
Clostridium difficile acquisition, germination and infection



Martin, J. S. H. *et al.* (2016) *Clostridium difficile* infection: epidemiology, diagnosis and understanding transmission
Nat. Rev. Gastroenterol. Hepatol. doi:10.1038/nrgastro.2016.25

What are the risk factors?

- Older age (>65)
- Low levels of Ab to CD toxin B
- **Alteration of the gut microbiota** - diet
  - Role of excess Zinc - calprotectin
- Antimicrobials (more and longer)
  - Clinda, FQ, Amino-PCNS, Cephs
  - Rare w/Dapto, Tige, TCN, MTN, AG
- Hospitalization/Institutionalization
- Critical Care

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Epidemiology of CDI Olmsted County

15 years 1991-2005

	Community-acquired (n=157)	Healthcare facility acquired (n=192)	*P*
Age, median	50	72	<0.001
Female gender	76%	60%	0.002
Antibiotic exposure	78%	94%	<0.001
H2B/PPI	22%	47%	<0.001
Cancer	17%	32%	<0.0001
Recurrent CDI	28%	30%	0.66

Khanna S et al *Am J Gastroenterol* 2012;107:89.

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Mechanisms of Colonization w/CDiff

- Ingestion of spores from the environment
- Interaction with gastric acid
- Interaction with bile acids – uncoating of spores
- Vegetative Cdiff cells penetrate mucus layer in the colon and adhere to epithelial cells
- Disruption of the normal flora- breakdown of colonization resistance
- Colonization may be long standing – months
- Spores can be shed for 6 weeks in sxtic CDI after resolution

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Where is *C. difficile* coming from?

- 40-60% neonates carry this
  - by age 1 only 2-3% of normal people carry this bug in their colon
- Widespread in environment, cats and dogs, farm animals
- 20-30% of hospitalized patients carry *C. difficile* and increases with duration of stay
- 4-20% of long-term care residents
- Conn/MD study – 3.9% with sx CDI EID Oct 2011

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Asymptomatic Colonization

- 320 participants screened at hospital entry
- 9.7% were positive by PCR for Cdiff
- Independent Risk Factors were:
  - ***Recent hospitalization***
  - ***Chronic dialysis***
  - ***Corticosteroid use***
- Screening these 3 risks - identifies 74% of CD carriers at admission

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Leekha S ***Am J Infect Control*** **2013;41:390-3**

Prevalence of C. diff **Colonization**

- Healthy neonates/infants 18-90%
- Healthy adults 0-15%
- Elderly LTC 0-51%
- Hospital
  - Elderly 0.6-15%
  - Inpts 4-29%
  - Rehab units 11-50%
  - Surgical pts on px 17%
  - ICU 2-7%
  - IBD 11%
  - Heme CA 8%

Furuya-Kanamori L et al BMC Infect Disease 2015;15:1516

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C difficile and the Hospital

- Where is C. diff coming from? Colonization
  - Prevalence of toxigenic CD 8-10%
  - 6-fold risk of infection vs non-colonized
    - 20-50% of adults in LTC are colonized
    - 20-30% of HSCT at admission
      - 12% toxigenic 17% non
      - 61% w/toxigenic dev CDI – median 12d
- Hospital pts transmit at rate 15X asxtic
- LTC transmit at 27% of hospital pt
- Community at 0.1% of hospital pts

Durham DP Emerg Infect Dis 2016;22:608

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What about Carriers?

- **2/3 of patients with fecal CD colonization become asymptomatic carriers**
- Over a 3-month period - 73 long-term care residents.
  - Five (7%) patients were found to have CDAD.
  - Of the remaining 68 patients, 35 (**51%**) were asymptomatic carriers, and 13 (37%) of these 35 patients carried epidemic NAP1 strain
  - Nine of the 35 carriers had a history of CDAD.

Asymptomatic carriers were associated with significantly higher rates of skin and environmental contamination than were noncarriers

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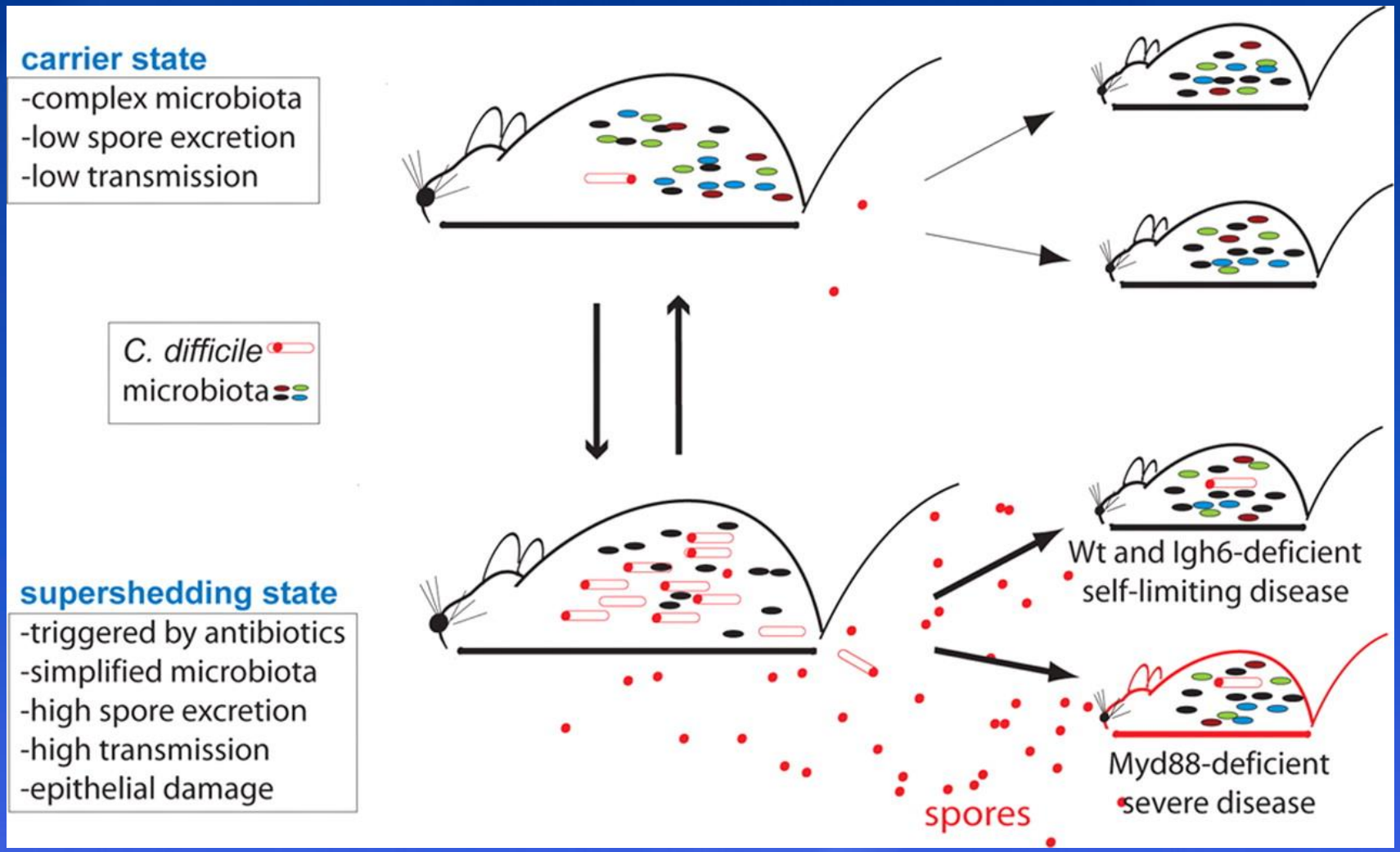
Relationship of *C Diff* Carrier State to Antibiotics and Shedding



Dawley TD et al Antibiotic Treatment of *Clostridium difficile* Carrier Mice Triggers a Supershedder State, Spore-Mediated Transmission, and Severe Disease in Immunocompromised Hosts Infect and Immunity 2009;77:9:3661-669.

Diagnosis of Clostridium difficile infection

Test	Sensitivity	Specificity	Advantage	Disadvant
Cytotoxin assay	80-90%	99-100%	Gold standard	Requires Cx, 48h; toxin B only
EIA toxin A/B	65-85%	95-100%	Rapid 2-6h	Less sens
GDH by LA	58-68%	80-96%	Rapid, easy	Requires confirmn
PCR toxin gene	92-97%	100%	Rapid, sensitive	Detects colonized, not toxin effect
Stool Culture	90-100%	98-100%	Strain type	2-5 days

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Selected test performances - MCA

Test	Sens, %	Spec, %	NPV	PPV	Comments
GDH	93 (56/60)	93	99	64	Missed 4 Positives
Xpert	100 (60/60)	98	100	88	4 Pos unconfirmed
GDH → Xpert	93 (56/60)	99	99	93	
Focus	93 (56/60)	99	99	95	Missed 4 Positives
GDH → Focus	93 (56/60)	99	98	100	

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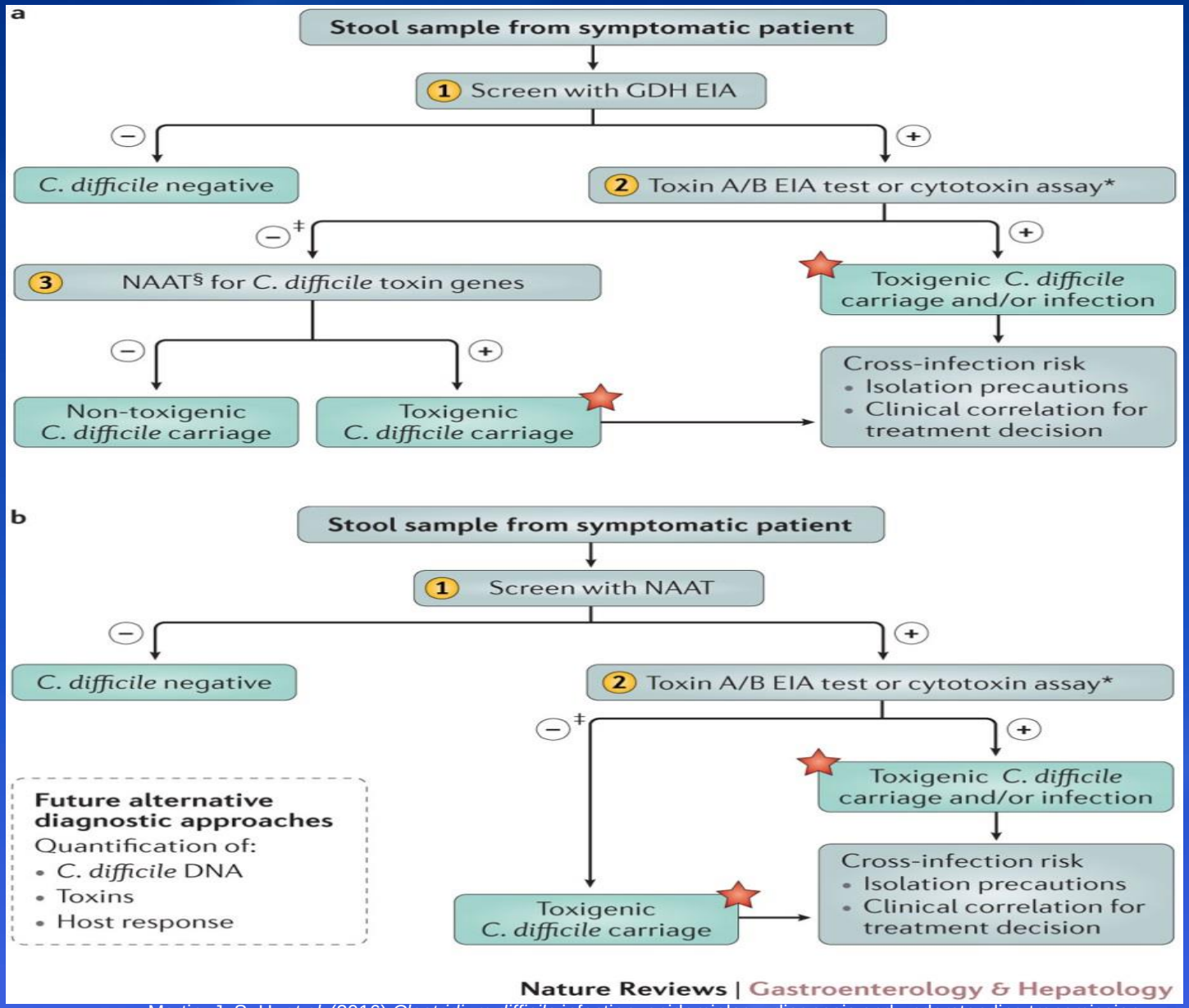
Testing for the diagnosis of CDI



Martin, J. S. H. *et al*. (2016) *Clostridium difficile* infection: epidemiology, diagnosis and understanding transmission *Nat. Rev. Gastroenterol. Hepatol.* doi:10.1038/nrgastro.2016.25

Over diagnosis of C. difficile

- Treated pts may shed for 6 weeks
- After treatment tests can remain + for months
- Repeat testing is discouraged
- **Up to 1/3 pts have post CDI IBS** (mixed or d)
  - Longer CDI duration, current anxiety and higher BMI
- Review all meds, laxatives etc

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Wadgwa A et al Aliment Pharmacol Ther 2016;44:576-82

PCR and Overdiagnosis

- PCR+/Toxin - vs Toxin +/PCR+
  - Less diarrhea at time of test
  - More rapid resolution of diarrhea
  - Fewer CDI complications or death
- PCR Sensitivity near 100% but Specificity in 80% range; PPV 44-47%
- Negative predictive value of toxin EIAs is at least 95%
- CDC – increase in CDI by 43-67% in PCR era
- 20% to 44% of patients tested on a laxative regimen.

Polage CR JAMA Intern Med 2015;1751792

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Burden of recurrent CDI

- Median risk for 1 recurrence is 22%-25%
  - Second episode – 38%
  - Third 29%
  - Fourth of more - 27%
  - 34% with rCDI required hospitalization
  - 28% developed severe CDI, 4% complication

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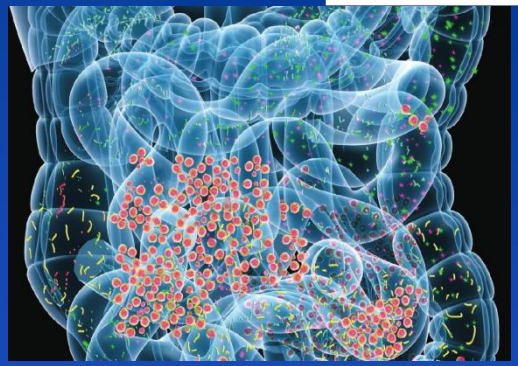
Development of Disease is a 2 Hit Event

Antibiotics alone do not cause C. difficile disease



- Disruption of the protective microbiota
- Consumption of *C. difficile*

These can be independent and separated in time

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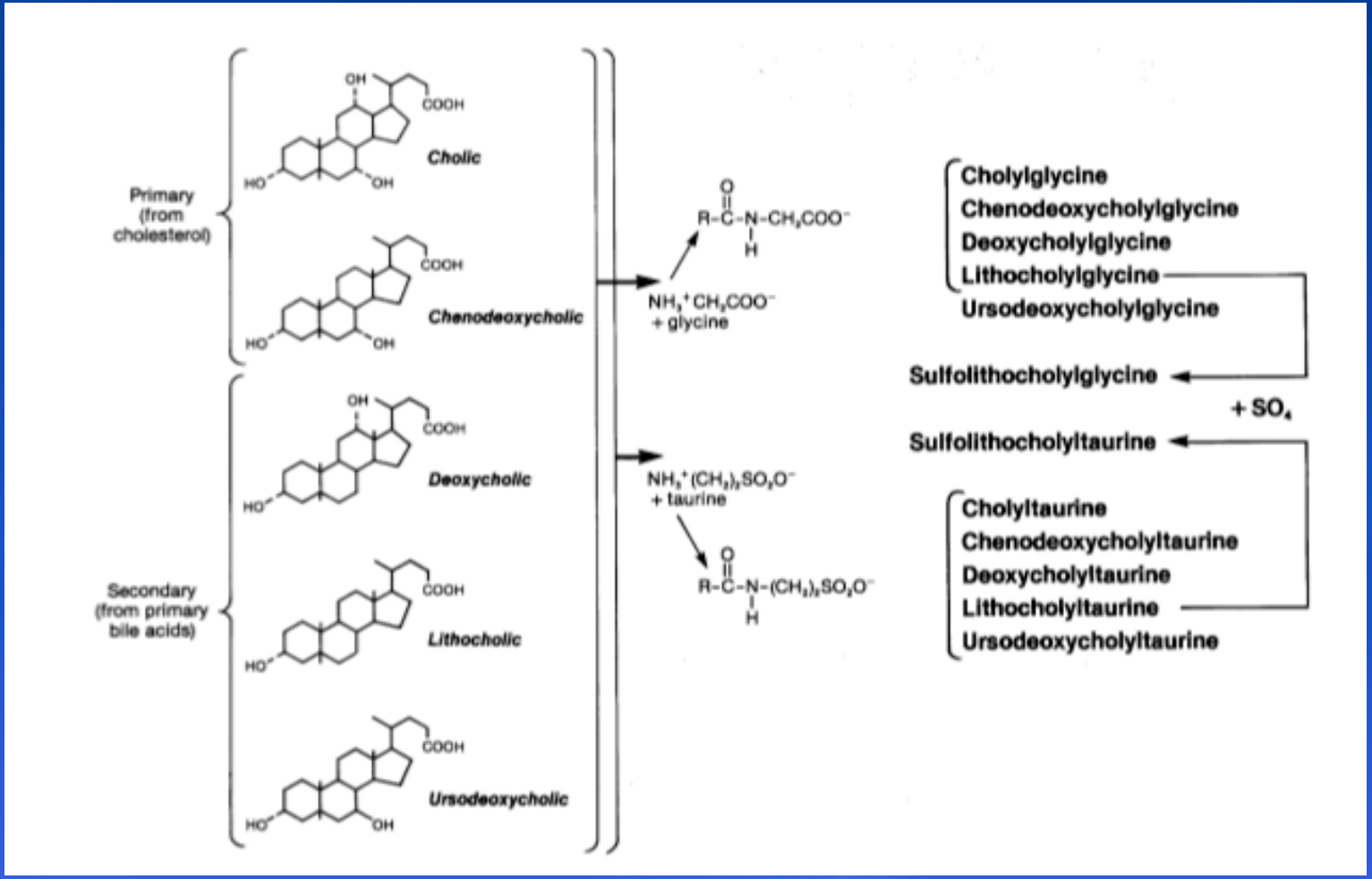
Secondary Bile Acids made by colonic bacteria



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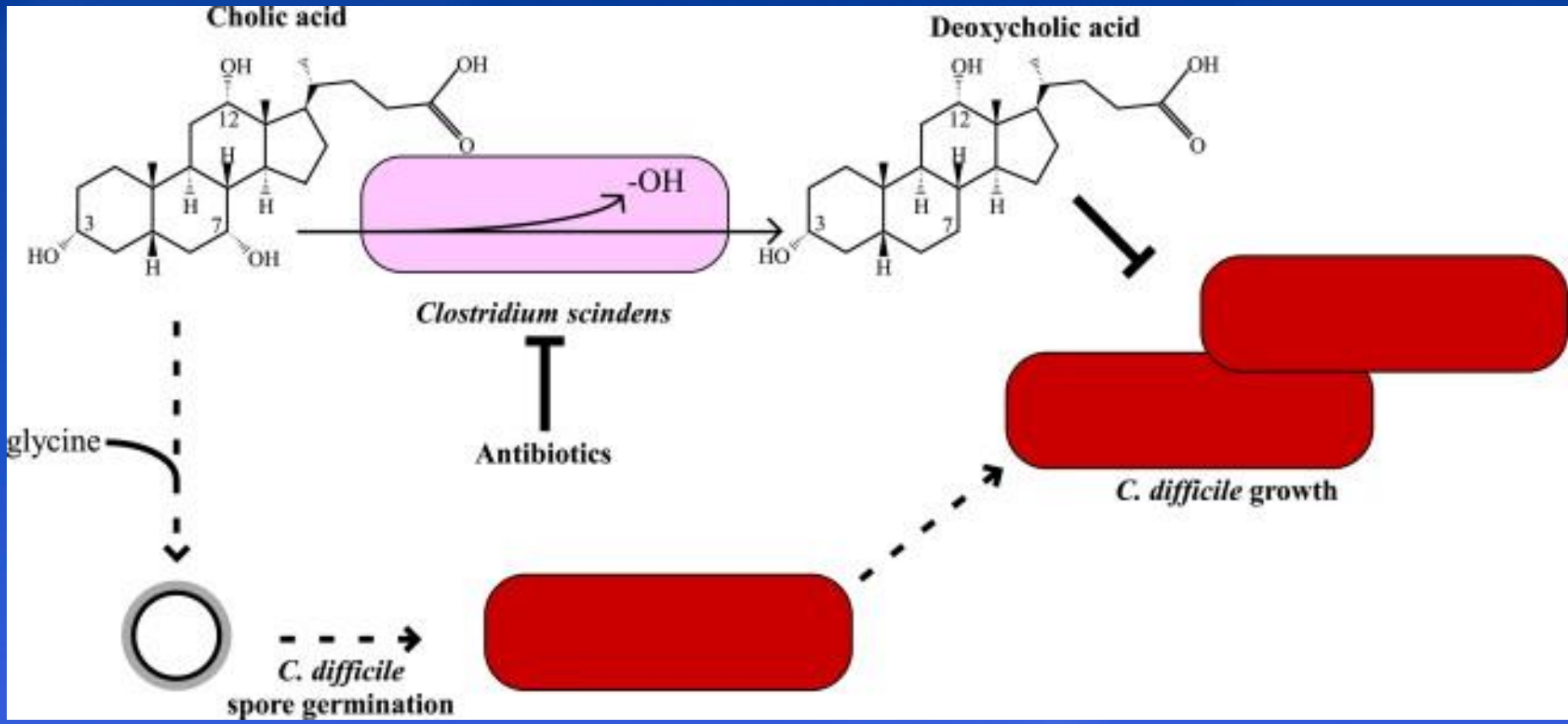
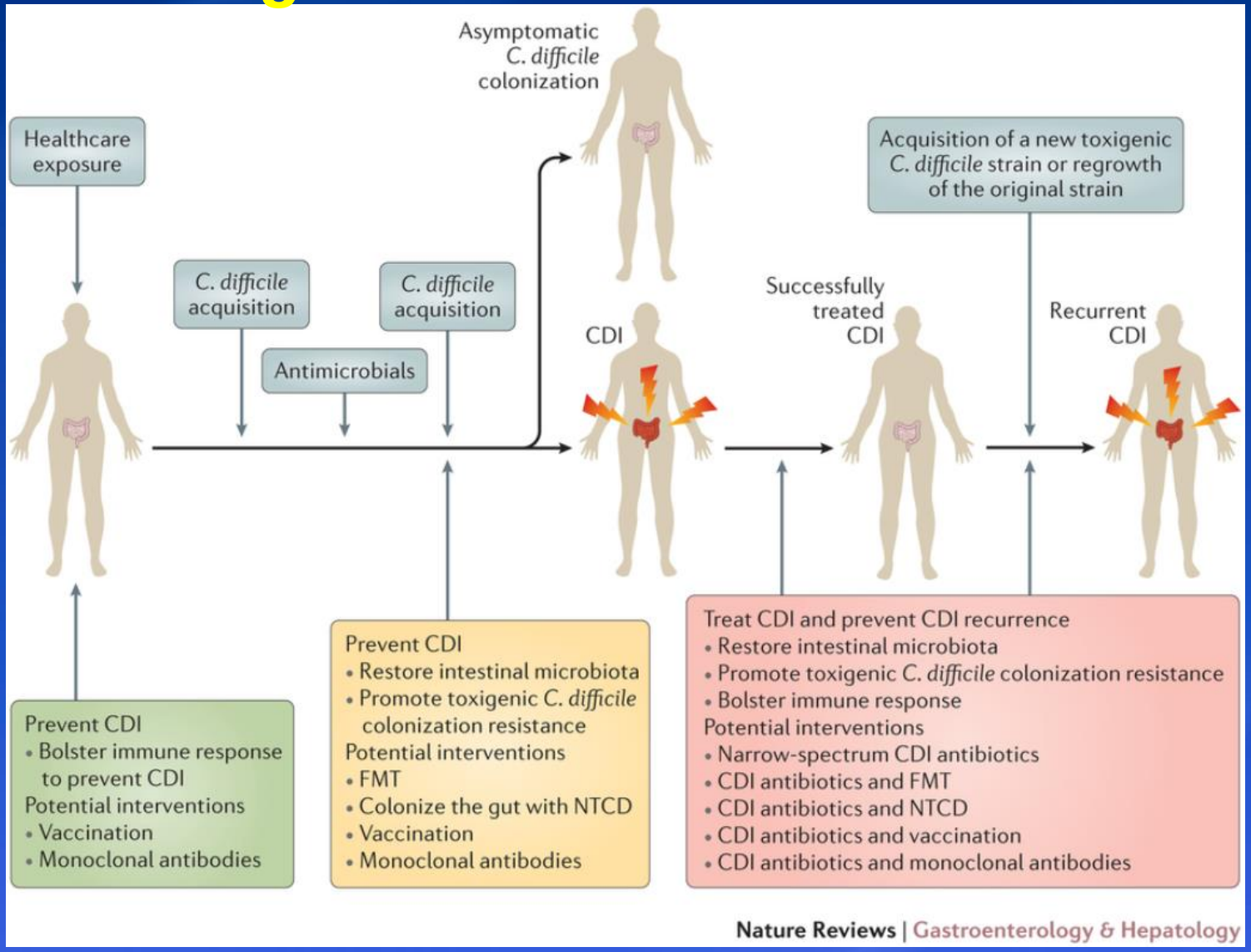
C scindens 7a-dehydroylation prevents C. difficile growth



Strategies to Prevent and Treat CDI



Kociolek, L. K. & Gerding, D. N. (2016) Breakthroughs in the treatment and prevention of *Clostridium difficile* infection *Nat. Rev. Gastroenterol. Hepatol.* doi:10.1038/nrgastro.2015.220

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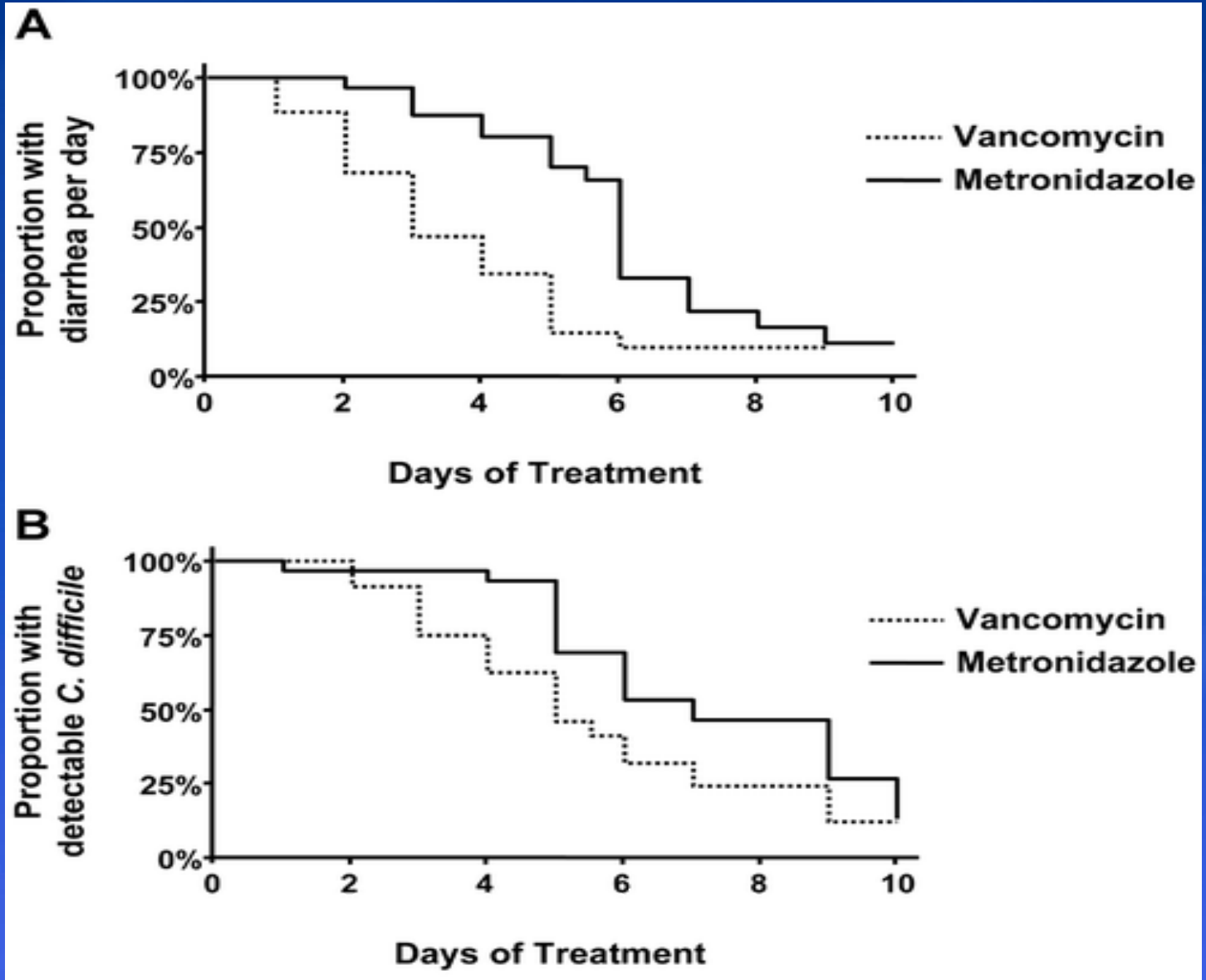
Time to Improvement
Vancomycin versus Metronidazole

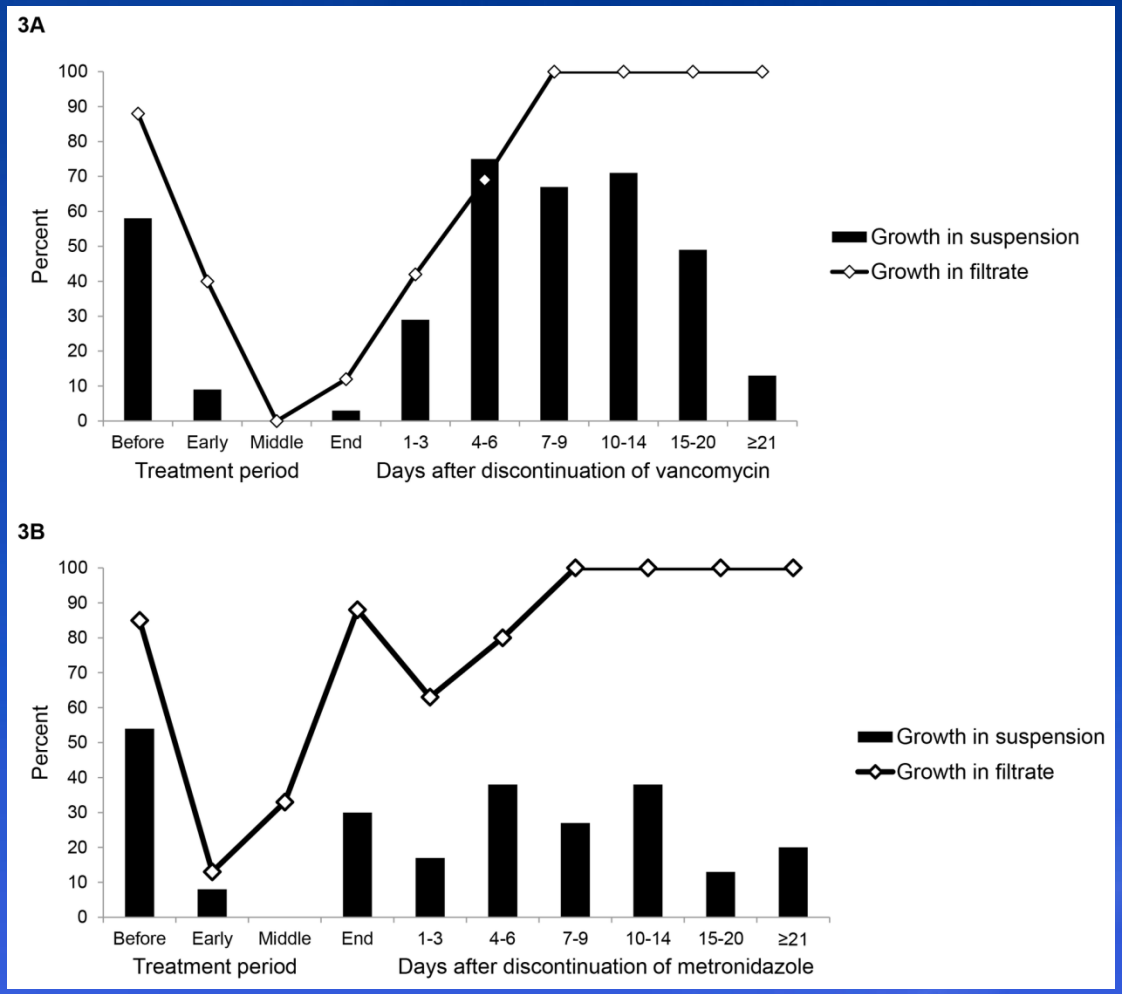


The Vulnerability Zone

- Vancomycin maintains inhibitory activity 4-5 days after completed
- Metronidazole – no late activity
- 14-21 days after treatment stools support CD growth
- 21-28 days after – most inhibit
- 3 phyla are associated with intact colonization resistance
  - Actinobacteria
  - Firmicutes
  - Tenericutes

Abujamel T *Plos One* Oct 2013;8

What happens to C. diff when you stop Metronidazole or Vancomycin treatment



Vancomycin, Metronidazole or Fidaxomicin

- Studies now indicate Metronidazole less effective than Vancomycin
- Increased short term mortality in MTN treated
- MTN - Not recommended in mod-severe disease nor in IBD
- Fidaxomicin – less recurrence, more expensive
- Vancomycin DOC for most

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Fidaxomicin in the real world

- Used after first recurrence rather than primary
- High rate of recurrence CDI (40%) in patients who received fidaxomicin (Stony Brook study)

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Is there Benefit to Combination Therapies or High Dose Antimicrobials?

- Combination therapy – Vanco + Metro
  - No difference in cure rates (57.1 v 65%)
  - No difference in time to cure (7 vs 8 d)
  - No difference in recurrence
  - More complications in combination

  Bass SN *J Hosp Infect* 2013;85:22-27
- High dose Vancomycin vs Standard
  - No difference in cure rates, time to response
  - Trend toward more recurrence with low dose

  Lam SW International *J Antimicrob Agents* 2013

  I use combination when concerned about oral administration reaching colon

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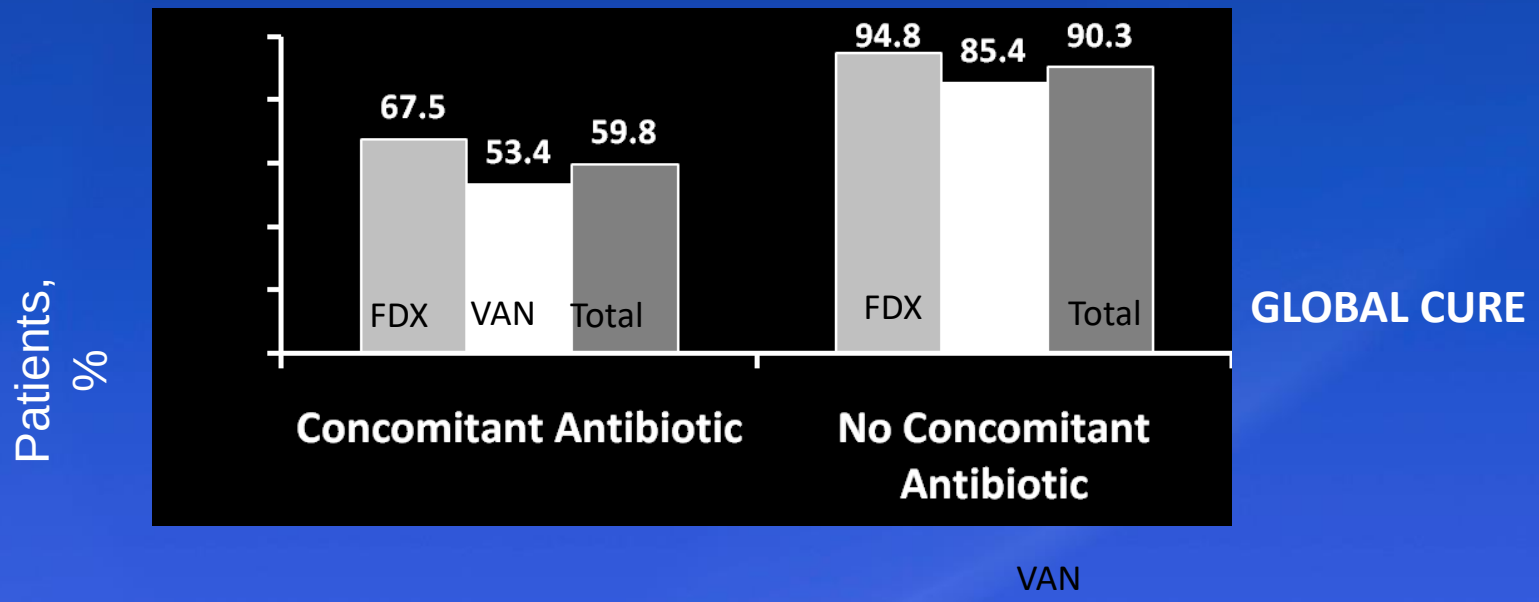
Administration of Antibiotics After Initial CDI Therapy

Continued Use of Antibiotics is Associated with Recurrence

- Continued use of non-*C.diff* antibiotic after diagnosis of CDI carries a with **4.23 (*P*<0.001) risk** for recurrent disease
- Phase 3 study of fidaxomicin vs vancomycin linked concomitant antibiotics with lower rates of cure without recurrence at 30d



Garey KW, et al. *J Hosp Infect*. 2008;70:298-304. 2. Johnson S, et al. DDW 2010; Abstract 711c.

Options for Antibiotics to treat infections in those with prior C difficile Infection

- Limited data
- Doxycycline – most data
  - Use for URTI, LRTI, SSTI
- UTI
  - Fosfomycin, Nitrofurantoin
- Shortest possible course

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AntiBx Prophylaxis to prevent rCDI

MTN 1-3 days prior – retrospective cohort

- The rate of *C. difficile* infection was 1.4% in the patients who received metronidazole and 6.5% in those who did not (*P*<0.001). In a multivariable analysis accounting for age, sex, and comorbidities, patients receiving metronidazole had an 80% reduced risk for developing *C. difficile* infection.

Rodriguez S et al *Clin Gastroenterol Hepatol* 2014

Oral Vancomycin prophylaxis vs SOC

- 4.2% vs 26.6%
- 125 or 250 mg BID
- Recur defined by PCR+, diarrhea <4 weeks

Van Hise *Clin Infect Dis* 2016

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Abx Prophylaxis and CDI

- *Wong ICAAC 2015* secondary prophylaxis of CDI in high-risk patients. This study included patients who were treated with antibiotics for a non-CDI indication 14 to 90 days following an initial CDI diagnosis. Patients receiving prophylaxis relapsed less often than the control group (**6.25% vs. 19.3%;** *P* = .003) — a 67.6% risk reduction
- *King ICAAC 2015*, a retrospective cohort study that compared either oral vancomycin, or metronidazole (IV or oral) with no prophylaxis. Patients were included if they had a positive PCR for *C. difficile* toxin between 2011 and 2013 and subsequently received a minimum 5 days of broad-spectrum antibiotics at least 2 weeks after completion of CDI therapy. The study included 339 eligible patients. The patients who received prophylaxis had a CDI relapse rate of **1.8% vs. 5.7%** for the control group. There was no difference in relapse rates between vancomycin- and metronidazole-treated patients.

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What about C. difficile in patients with IBD?

- Test pts with a flare for CDI
- Test for rCDI if sxs recur
- Treat with Vancomycin not Metronidazole
- Hospitalize those with severe symptoms
- Postpone steroid escalation during acute CDI
- Refer for FMT if recurrent disease

Management of Clostridium difficile Infection in Inflammatory Bowel Disease: Expert Review from the Clinical Practice Updates Committee of the AGA Institute
Khanna S et al *Clin Gastro and Hepatol* 2017;15:166-174

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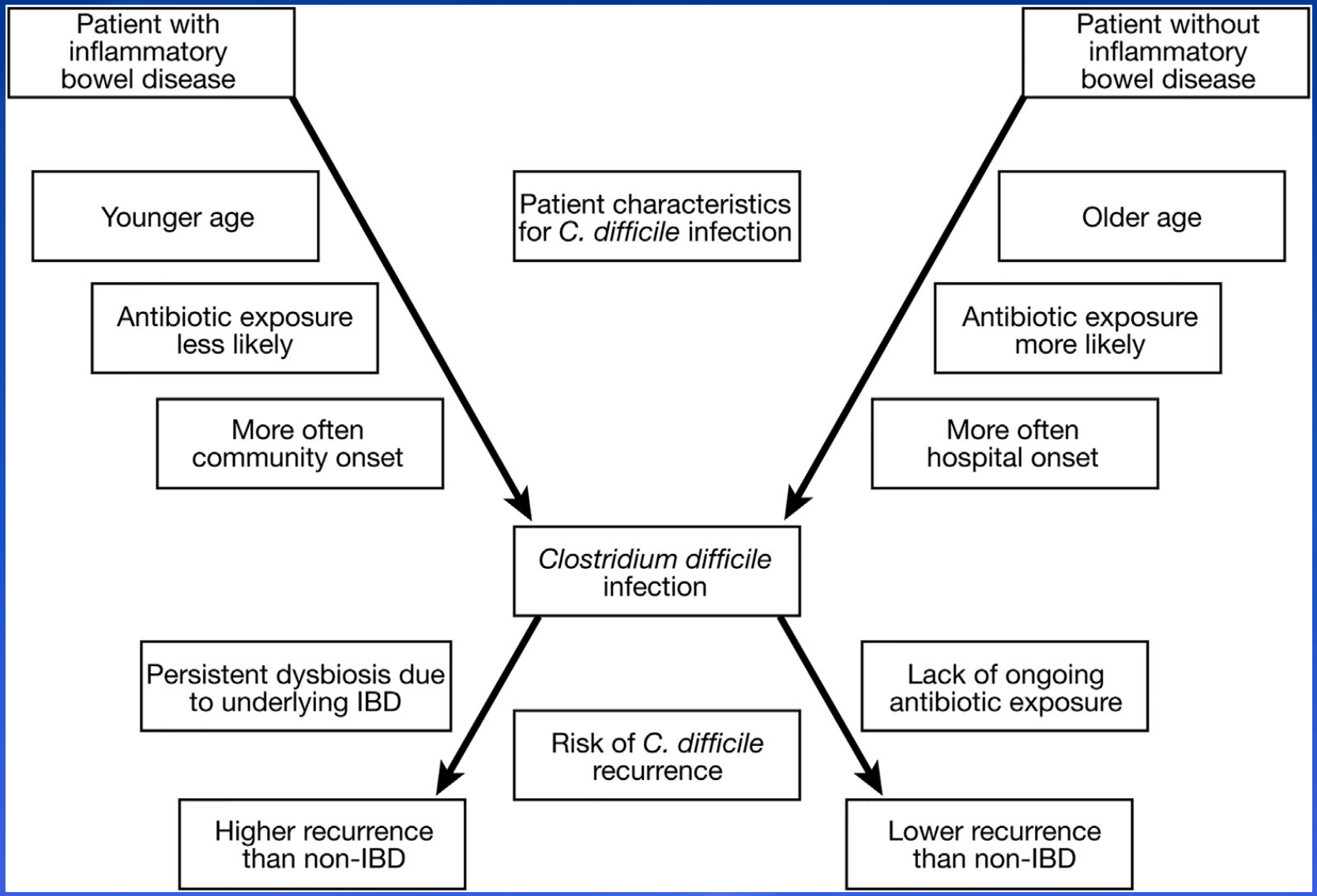
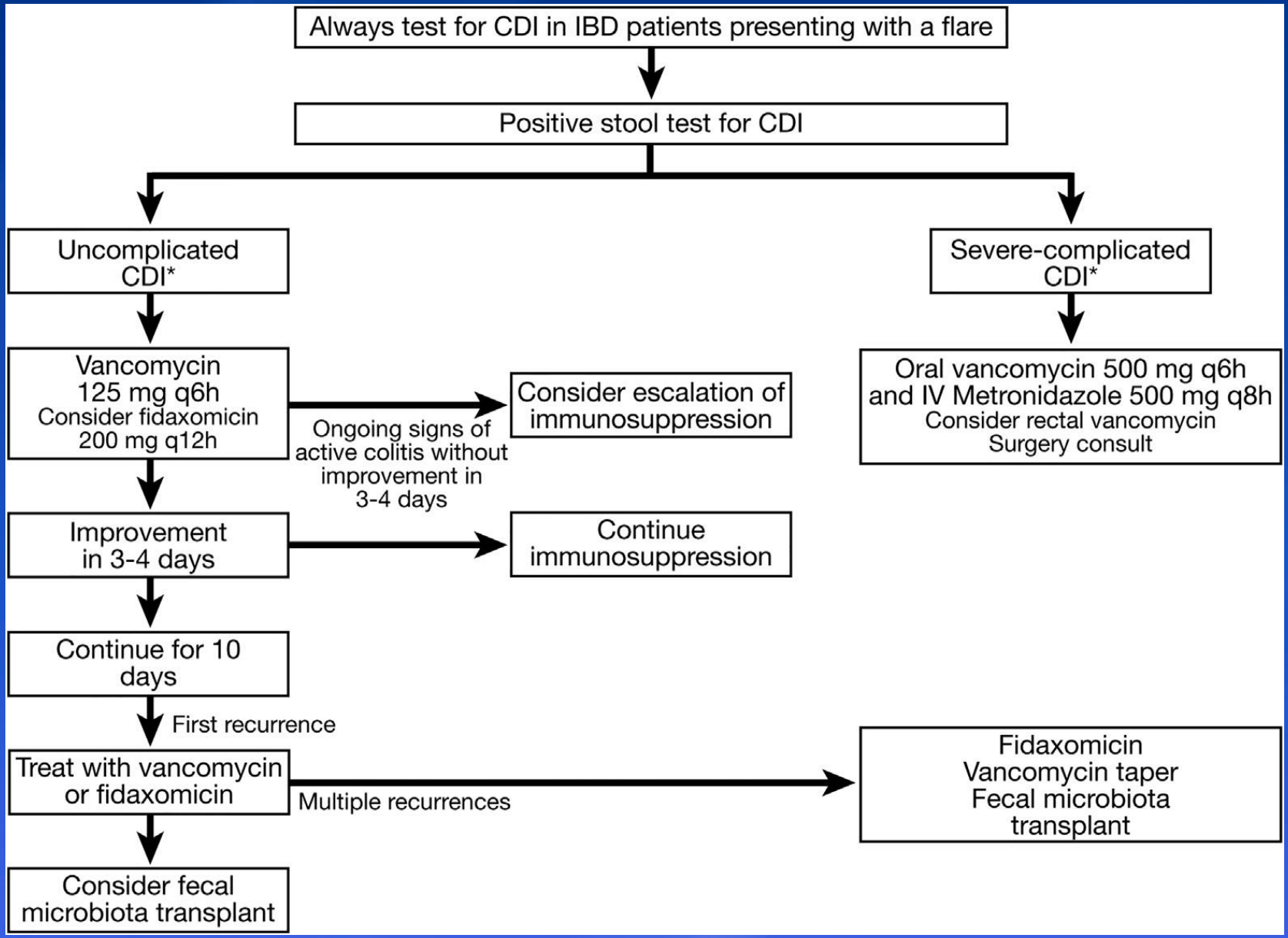
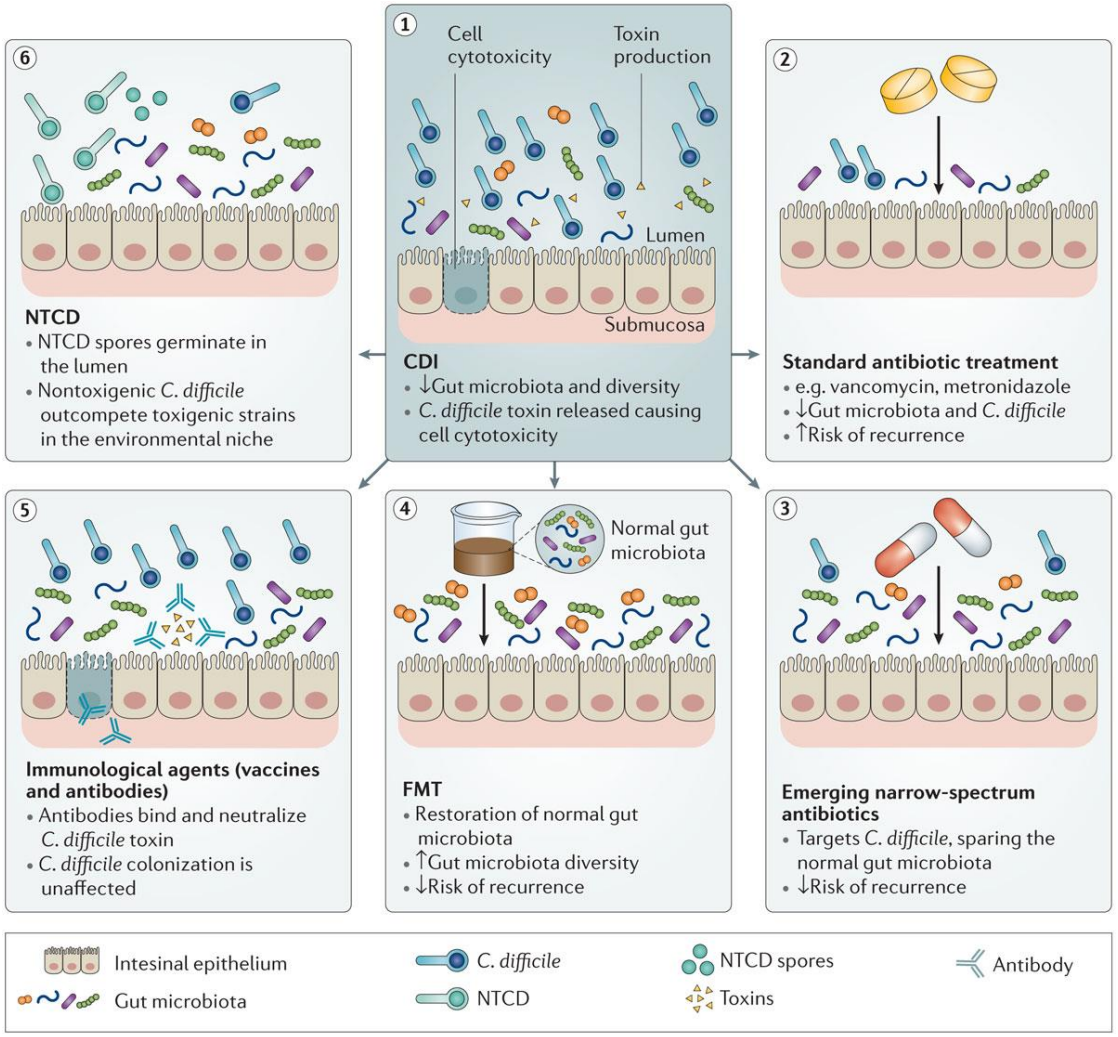
CDI and IBD



Managing CDI in IBD



Emerging Treatment Options for CDI



Nature Reviews | Gastroenterology & Hepatology

Kociolek, L. K. & Gerding, D. N. (2016) Breakthroughs in the treatment and prevention of *Clostridium difficile* infection *Nat. Rev. Gastroenterol. Hepatol.* doi:10.1038/nrgastro.2015.220

Antibiotics in development for CDI treatment

Table 1 | **Antibiotic therapies currently in clinical development for CDI**

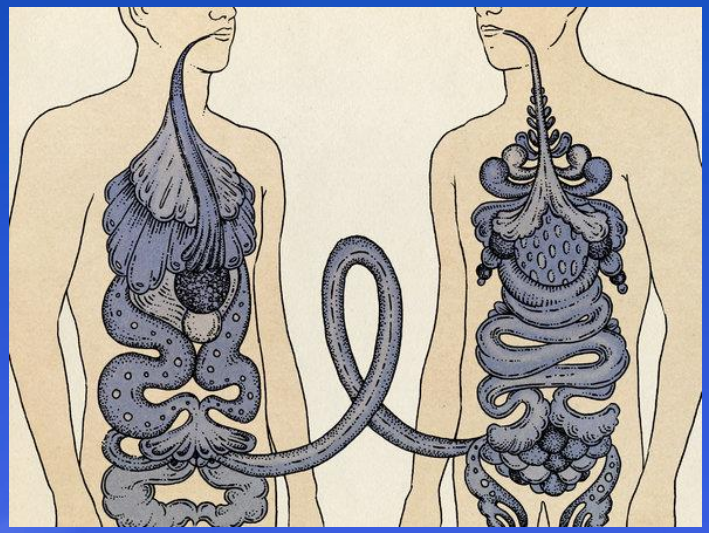
Antibiotic	Mechanism of action	Clinical status (ClinicalTrials.gov identifier)	Published clinical data
Surotomycin (CB-183315)	Disrupts bacterial cell membrane	Phase III NCT01597505 and NCT01598311	Phase II trial results: rates of CDI recurrence among 210 adults with CDI were 36%, 28% and 17% within 28 days post-treatment with vancomycin 125 mg four times daily, surotomycin 125 mg twice daily and surotomycin 250 mg twice daily, respectively[37]
Cadazolid	Protein synthesis inhibitor primarily Fluoroquinolone moiety also confers weak inhibition of DNA synthesis	Phase III NCT01983683 and NCT01987895	• Phase II trial results: clinical CDI cure rates among 84 adults receiving vancomycin or one of three different doses of cadazolid were similar • All three doses of cadazolid resulted in lower recurrence rates than vancomycin (18–25% versus 50%)[43]
Ridinilazole (SMT19969)	DNA synthesis inhibitor	Phase II NCT02092935	Phase I trial results: among healthy adults, SMT19969 resulted in high faecal drug levels, low plasma drug levels, and no reported serious adverse events[33]

CDI, *Clostridium difficile* infection.

Kociolek, L. K. & Gerding, D. N. (2016) Breakthroughs in the treatment and prevention of *Clostridium difficile* infection *Nat. Rev. Gastroenterol. Hepatol.* doi:10.1038/nrgastro.2015.220

Fecal Microbiota Transplantation

- Instillation of stool from a healthy person into an ill person in order to cure a certain disease
- Instillation of stool from a healthy person into another person at risk for a disease in order to prevent that disease



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Current Indication for FMT

- Recurrent infections that have failed >2 courses of therapy (ie 3rd episode)
  - responded to Vancomycin
  - Presence of >3 unformed stools/d for at least 2 days
- Recent positive C. difficile test
  - Presence of diarrhea off antibiotic therapy
- 2nd episode of Severe CDI
- Refractory CDI

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The Forest Analogy

FMT =

Donor testing for FMT – Open Biome

Figure 1: Stool and Serology Investigations

Stool testing	Serological testing
Clostridium difficile Toxin B, PCR	HIV 1/2, antigen and antibody
Salmonella, Culture	Hepatitis A, IgM antibody
Shigella, Culture	Hepatitis B, (IgM anti-HBc, anti-HBsAg)
Campylobacter, Culture	Hepatitis C, antibody
Shiga Toxin, EIA (with reflex to *E. coli* O157, Culture)	Treponema pallidum, antibody
Vibrio, Culture	HTLV-I/II, antibody
Cryptosporidium, EIA	Complete Blood Count (CBC)
Helicobacter pylori, EIA	Hepatic Function Panel
Norovirus, EIA	
Rotavirus, EIA	
Adenovirus, EIA	
Vancomycin-resistant Enterococcus (VRE), Culture	
Giardia, EIA	
Microsporidia Exam	
Cyclospora and Isospora Examination	
Ova and Parasites Exam	

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Mayo – GI pathogen panel

Success of FMT at Mayo Clinic in Arizona

MCA ARIZONA: **94.7 %** Success (Dec 2016)

Success by procedure 88.6%

231 – single FMT – 221 cured, 9 failures, 1 LTFU

- 264 procedures on 247 patients
- 231 single; 15 – 2; 1 3 FMT repeat pts.
- Avg. Age: 62.6 years (19-93)
- Females 163 (66%) Males 84 (34%)
- Colonoscopy 232 EGD 17 NJ 4 Stoma 6 Combo 5

National Average: 90-100%

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Fecal Microbiota Transplant **Prevents Recurrence**

- Overall for 4 RCT one time 72%
  - Dutch Nasogastric trial – 43 pt – 81% vs Vanco 31%
  - Italy – *Cammarota* 39 pts Colonoscopy FMT vs oral Vanco taper – 65% vs 26%
  - US – Youngster – frozen NG vs Colon (20 pts)
    - 70% overall (8/10 colon, 6/10 in ng)
  - US – *Kelly* Colonoscopic (pt) – RCT
    - 91% cure vs placebo 63% (p 0.024)
  - US – *Orenstein* ReBiotix Phase 2b Trial - *86%

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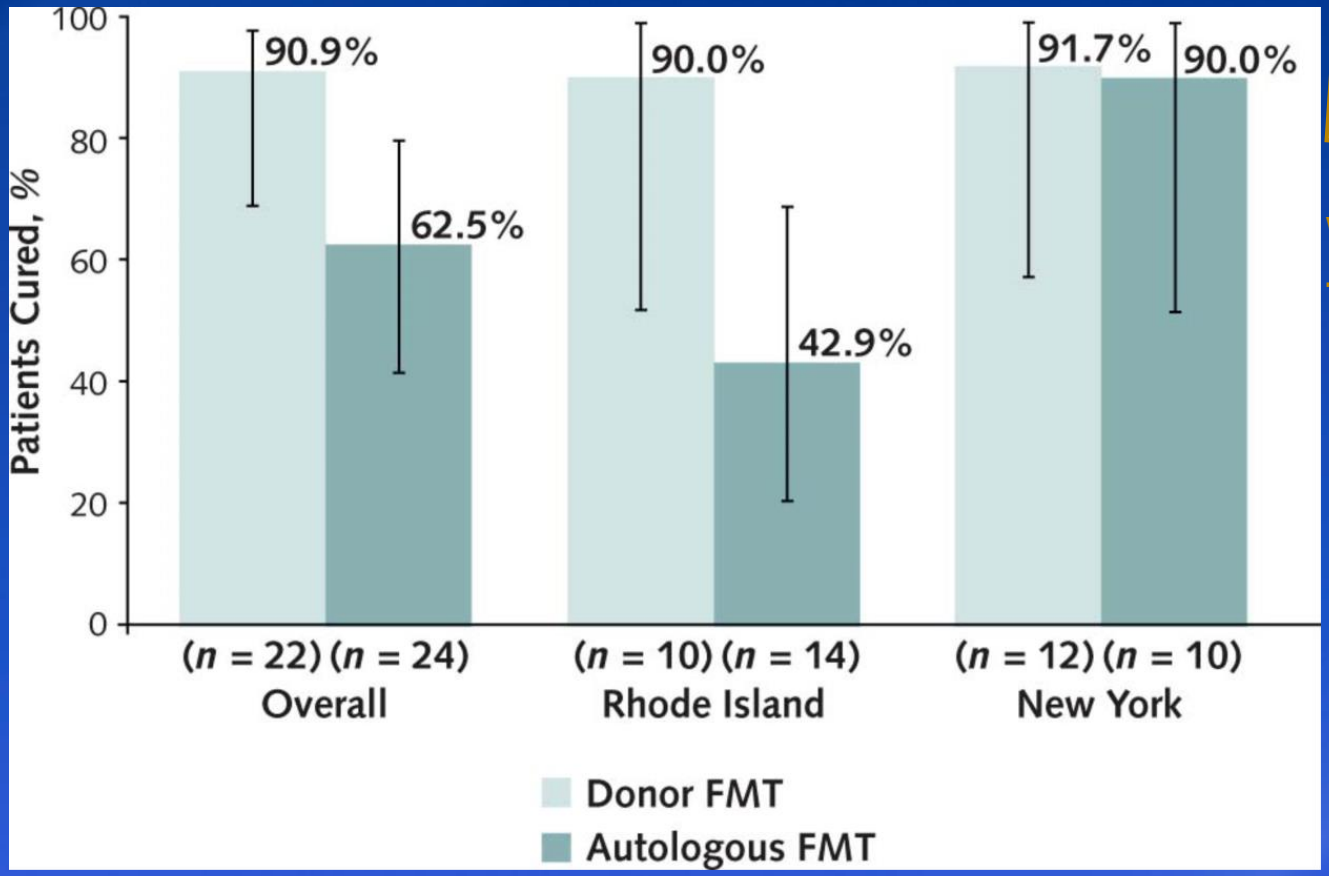
Role of FMT to Prevent Multiply Recurrent CDI



What is up with the placebo?

Rates of clinical cure in the intention-to-treat population, overall and by site. Error bars represent 95% CIs. FMT = fecal microbiota transplantation.

Kelly C et al Ann Intern Med. Published online August 23, 2016. doi:10.7326/M16-0271

Safety and Efficacy of FMT from Stool Bank

2050 treated subjects – **overall efficacy 84%**

Figure 1: Efficacy of FMT by *Clostridium difficile* infection classification and fecal microbiota preparation type

Clostridium. difficile Infection Classification	Total			250 mL			30mL		
	N	Efficacy (%)	P-value	N	Efficacy (%)	P-value	N	Efficacy (%)	P-value
Recurrent	1542	85.9	<0.001	1322	87.0	<0.001	220	79.5	0.278
Mixed (e.g. recurrent and severe)	259	79.2	0.021	229	80.0	0.047	30	66.7	0.118
Refractory	159	74.2	<0.001	126	75.4	<0.01	33	69.7	0.228
Severe	90	83.3	0.85	65	81.5	<0.01	25	88	0.205

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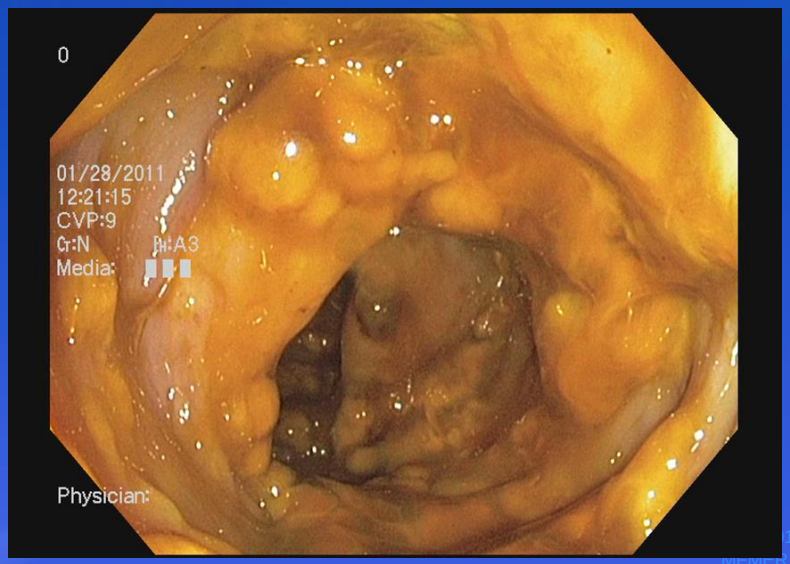
Colectomy for Severe CDI

- Used in severe disease
- Rates of 1-3%
- Systematic review 31 studies – 1433 pts
- 1.1% CDI cases required colectomy
- 30% were severe disease
- 30 day mortality – 41%



Bhangu A et al *Br J Surg* 2012;29:1525

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Diverting Loop Ileostomy & Colon Lavage

- Alternate to total colectomy
- 8 liters of warmed PEG and Vancomycin
- Post-op Vanco 500mg/500 ml q8H x 10d
  - Deliver via Malecot cath in efferent limb
  - Also receive IV Metronidazole

Neal et al *Am Surg* 2011;254:423

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Can FMT Help in Severe *C. difficile* Disease?

- CDI refractory to po +/- rectal Vanco and IV MTN
  - Prospective series 29 pts – 27/29 (93%) resolved
  - 100% cure for severe
  - 89% for severe complicated
  - 2 died – sepsis
  - 76% survival at 3 months

Challenge is the logistics – access to therapeutic microbiota

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Fischer M et al Aliment Pharmacol Ther 2015;42:470-6

The pipeline of products for CDI

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ReBiotix
RBX 2660 - enema and 7455 –oral cap

- In Phase 3 – Commercialized Microbiota
- Phase 2 – 52% 1st enema 78.6% 2nd
- Overall success 27/31 – 87.1%
- Phase 2b data being reported
  - Placebo 45.5% (20/24) vs 67% 1 enema
  - 87.5% all comers – inc open label
- Phase 3 Upcoming summer 2017
  - 1 enema, no prep
- Phase 1 RBX 7455 – capsule – 10^9 cfu
- 8 caps/day = 1 enema – 4 d BID vs 2d BID

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CP101 - Crestovo

- Oral full spectrum *lyophilized* capsules
  - 1st trial non-frozen oral
- Phase 2 trial starting in May 2017
  - 6×10^{11} vs 3×10^{11}
  - 10 caps one time vs placebo

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SERES Products –spores

- **SERES 109**
  - Phase 2 multiply recurrent CDI – 1 x10^8 spores
  - 59 S109 vs 30 placebo – 44% vs 53% recur
  - Not statistically significant
  - Re- entering Phase 2- ECOSPOR III
  - 4 caps daily x 3 days oral (3 x 10^7 scfu)

- SERES 262 – Phase 1b
  - Synthetic oral capsule 12 bacterial strains in spore form

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Viropharma
Non-toxigenic C difficile Spores
CDI Recurrence w/in 6 Weeks

Table 4. CDI Recurrence Within 6 Weeks as Defined by Diarrhea Criteria and by Investigator Decision to Re-treat for Recurrent CDI

Events in Intention-to-Treat Safety Population	Placebo (n = 43)	NTCD-M3 Dosage 10^4 Spores/d for 7 d (n = 41)	10^7 Spores/d for 7 d (n = 43)	10^7 Spores/d for 14 d (n = 41)	All (n = 125)
CDI recurrence, No. (%)	13 (30)	6 (15)	2 (5)	6 (15)	14 (11)
Unadjusted comparison with placebo, *P* value[a]		.09	.002	.09	.003
Adjusted comparison with placebo[b]					
Odds ratio (95% CI)		0.4 (0.1-1.2)	0.1 (0.0-0.6)	0.4 (0.1-1.2)	0.28 (0.11-0.69)
P value		.11	.01	.10	.006
Use of antibacterial treatment for CDI, No. (%)	14 (33)	6 (15)	4 (9)	7 (17)	17 (14)
Unadjusted comparison with placebo, *P* value[a]		.05	.008	.10	.006
Adjusted comparison with placebo[b]					
Odds ratio (95% CI)		0.3 (0.1-1.1)	0.2 (0.1-0.8)	0.4 (0.1-1.3)	0.32 (0.14-0.75)
P value		.07	.02	.14	.009
CDI recurrence based on NTCD colonization, No./total (%)[c]					
Colonized with NTCD	0/4 (0)	1/26 (4)	1/31 (3)	0/29 (0)	2/86 (2)[d]
Not colonized with NTCD	13/39 (33)	5/15 (33)	1/12 (8)	6/12 (50)	12/39 (31)[d]
CDI recurrence based on presence of toxin-positive *C difficile* on day 1, No./total (%)					
Day 1 toxin-positive *C difficile*	1/6 (17)	3/12 (25)	2/9 (22)	3/9 (33)	8/30 (27)
No day 1 toxin-positive *C difficile*	12/37 (32)	3/29 (10)	0/34 (0)	3/32 (9)	6/95 (6)

Abbreviations: CDI, *Clostridium difficile* infection; NTCD, nontoxigenic *C difficile*; NTCD-M3, nontoxigenic *C difficile* strain M3.

[a] Treatment comparison with placebo using 2-sided χ^2 test at a significance level of $P = .05$.

[b] Logistic regression model analysis adjusting for relevant covariates: use of metronidazole, use of vancomycin, and primary episode vs first recurrence for odds ratios, 95% CIs, and the corresponding *P* values for model-adjusted treatment comparison with placebo. Odds ratios of less than 1 indicate a lower risk in NTCD-M3 dosage groups compared with placebo.

[c] Colonization was defined as NTCD in stool culture at any time after the end of study drug therapy to week 6.

[d] Recurrence rate of 2% vs 31% is significantly different (odds ratio, 0.01; 95% CI, 0.00-0.05; $P < .001$) for colonized vs not colonized with NTCD.

JAMA. 2015;313(17):1719-1727. doi:10.1001/jama.2015.3725

Stool Bank
OpenBiome (501c3)

$385/bottle

$385/dose

$535/dose – 30 caps

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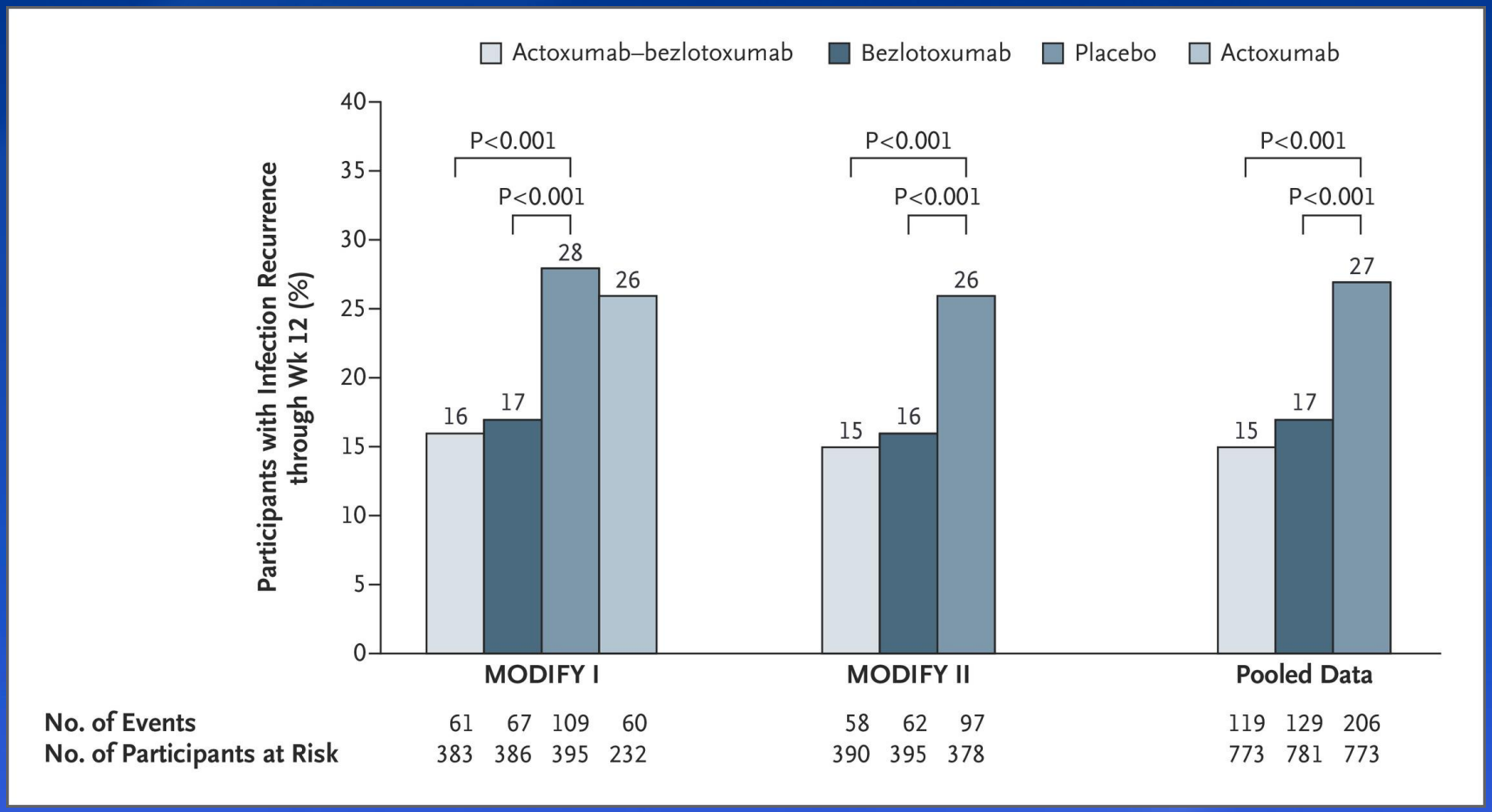
Monoclonal Antibody vs Toxin B

- Bezlotoxumab (Zinplava)
  - Humanized monoclonal IgG1/kappa Ab vs CD tB
  - Single IV dose 10mg/kg over 60 min
  - In both MODIFY I and MODIFY II, the rate of C. difficile infection recurrence through week 12 was significantly lower in the bezlotoxumab arms (17.4%, p=0.0003) compared to the placebo arms (27.6%) and (25.7%), respectively.
  - Half life 19 days
  - most common adverse reactions through four weeks after infusion (nausea, diarrhea and pyrexia)
  - FDA Concern regarding endpoints – delay review
  - Cost – 3500$

Participants with Recurrent *Clostridium difficile* Infection during the 12-Week Follow-up Period.



Wilcox MH et al. N Engl J Med 2017;376:305-317

MODIFY 1 and 2 Studies

Future Preventive Strategies for CDI

Table 3 | **Characteristics of potential interventions for prevention of CDI**

Intervention	Effectiveness in humans	Time to prevention onset	Duration of prevention	Use for primary CDI prevention	Use for recurrent CDI prevention	Projected cost
FMT or derivatives	Excellent for prevention of multiply recurrent CDI	Rapid (1–2 days)	Likely to be effective until further antibiotics are given	Untested	Yes	Low
Nontoxigenic *C. difficile*	Excellent for first and second CDI recurrence prevention	Rapid (1–2 days)	Effective for duration of colonization and thereafter until further antibiotics	Untested, but effective in animal models	Yes	Low
Monoclonal antibodies	Excellent for first and second CDI recurrence prevention	Very rapid (immediate)	Unknown, but not expected to persist beyond several half-lives	Untested	Yes	High
Injectable vaccine	Unknown, only 3 patients tested	Slow (weeks to months)	Unknown, but expected to be long	Yes	Unknown, depends upon time required for antibody response	Low
Oral vaccine	Unknown, no patients tested	Slow (weeks to months)	Unknown, but expected to be long	Yes	Unknown, depends upon time required for antibody response	Low

CDI, *Clostridium difficile* infection; FMT, faecal microbiota transplantation.

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Kociolek, L. K. & Gerding, D. N. (2016) Breakthroughs in the treatment and prevention of *Clostridium difficile* infection *Nat. Rev. Gastroenterol. Hepatol.* doi:10.1038/nrgastro.2015.220


CLOROX
HEALTHCARE
Bleach Germicidal Wipes
MEDICAL EQUIPMENT SURFACES

The Bottom line

C diff is bad...you can get it at home; if you take acid suppression, use chemo, or were hospitalized in the past 60 days -you may be asymptomatically colonized; if you are old - 2% per year after age 18; take antibiotics or acid suppression you are at risk for healthcare acquired CDI. The longer you stay hospitalized the greater the risk of infection.

- if you are old; get infected with the NAP 1 strain and take PPIs and are hospitalized >1 week - you're in deep poo - literally.
-

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What's in YOUR Wallet?

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7 extra hospital days for c-dif from the neighbor $7,000

200 Chux pads $600

Hand washing..... Priceless

Coming Attractions