Clostridioides difficile: When Your #2 Becomes a #3 Review and Guideline Update

Matthew Greene

Vanderbilt University Medical Center, Infectious Diseases

28 September 2018

Table of Colontents

1. Case
   - an aside and some principles
2. History and Pathophysiology
   - “colonization resistance”
3. Epidemiology
   - risk factors
   - emergence of NAP1
   - Antimicrobial Stewardship
4. Diagnosis
   - symptoms and testing
5. Treatment

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- PCN “allergy”
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B. vancomycin PO x 10 days
C. rifaximin PO X 10 days
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Clinical Infectious Diseases

IDSA GUIDELINE

IDSA Infectious Diseases Society of America

hivma hiv medicine association

OXFORD

Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)

L. Clifford McDonald,[1] Dale N. Gerding,[2] Stuart Johnson,[2,3] Johan S. Bakken,[4] Karen C. Carroll,[5] Susan E. Coffin,[6] Erik R. Dubberke,[7] Kevin W. Garey,[8] Carolyn V. Gould,[1] Ciaran Kelly,[9] Vivian Loo,[10] Julia Shaklee Sammons,[6] Thomas J. Sandora,[11] and Mark H. Wilcox[12]

An Aside

American Dental Association and

American Academy of Orthopedic Surgeons 2013

- "unconvincing data" supports prophylaxis

Caution with even 1 dose of antibiotic exposure!

- "The most important modifiable risk factor for …

C. difficile infection is exposure to antibiotic agents"

Watters et al J Am Acad Orthop Surg 2013
Sollecito et al J Am Dent Assoc 2015
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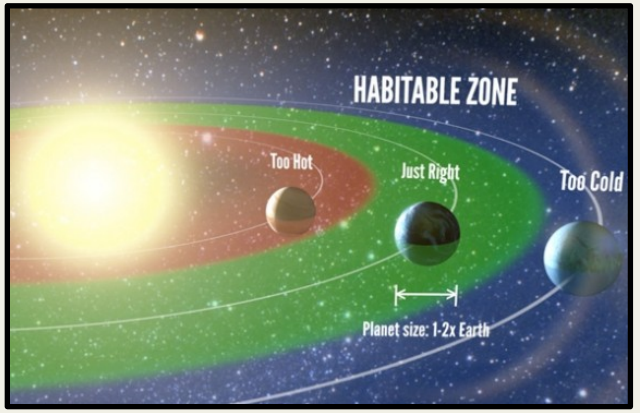
Principles of Antibiotic Use

"Zero days of therapy is a nice, short duration."

Hecker et al Arch Intern Med 2003

- 650 non ICU patients
  - ≈30% days of therapy unnecessary



Fleming-Dutra et al JAMA 2016

- 184,032 outpatient encounters
  - 12.6% resulted in antibiotic prescription ("sinusitis")
  - ≈30-40% of prescriptions inappropriate

Trivedi SHEA 2017
Hecker et al. Arch Intern Med 2003
Fleming Dutra et al JAMA 2016

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Land Before Slime

Pseudomembranous colitis (PMC) described 1893

- clearly not associated with antibiotic exposure
  - rare cases of CDI still “spontaneous”
- linked to clindamycin exposure 1974
  - termed “clindamycin-associated colitis”
- not associated with *C. difficile* until 1978
  - demonstrated in a hamster model

Other pathogens can cause PMC

- *Staphylococcal aureus*
- *Clostridium perfringens*
- *Klebsiella oxytoca*

Gerding and Young PPID 2015

Who's That Swirl?

Clostridiodes (previously *Clostridium*) *difficile*

- obligate Gram positive anaerobe
- survives in the environment as a hardy spore
  - soil, surface water, animals in nature
  - healthcare workers/surfaces, colonized patients
    - resistant to alcohol-based cleaning solutions
- spores ingested by fecal-oral route
  - ≈1% of vegetative cells survive to duodenum
  - spores germinate into the vegetative state
    - triggered by bile acids

Gerding and Young PPID 2015
Gil et al Future Microbiol 2018

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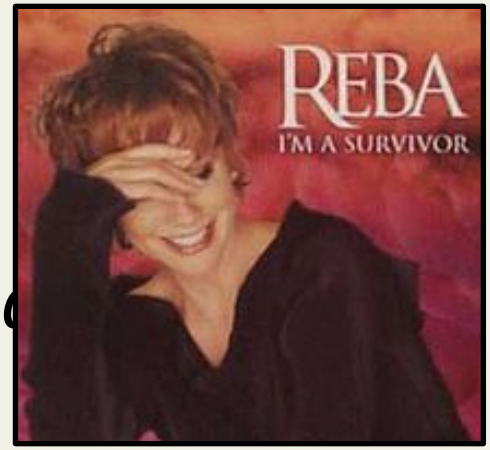

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An Imbalanced Diet

"Colonization resistance"

- normal gut microbiota
  - resists pathogenic microbes
    - nutrient competition
    - physical and ecologic niches
    - antimicrobial and host immune system signals
- altered microbiota (eg, antibiotic exposure)
  - disrupts colonic homeostasis
  - affords pathogen ingrowth and virulence

Gerding and Young PPID 2015
Gil et al Future Microbiol 2018

Toxic Relationship

C. difficile virulence

- *tcdA* and *tcdB* genes produce toxins A and B
  - all pathogenic *C. difficile* produces B
  - alters intracellular junctions/epithelial permeability
    - invites inflammatory cytokines
    - neutrophils, ROS, substance P, mast cell activation, etc.
- binary toxin ("common antigen")
  - "hijacks" microtubule organization
  - increases pathogen adherence
- pseudomembrane = neutrophils, fibrin, mucin, "cellular debris"

Gerding and Young PPID 2015
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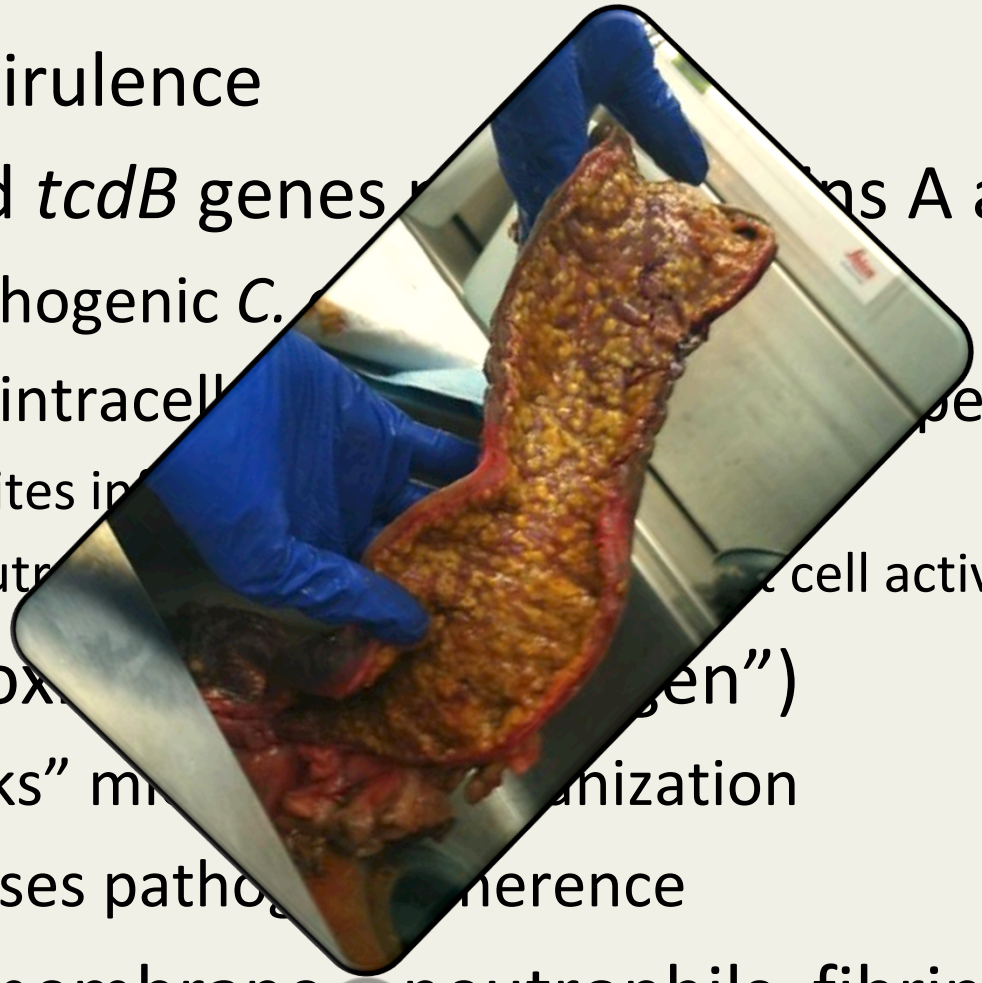

ns A and B

permeability

cell activation, etc.

en”)

nization

herence

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Poop Quiz!

What percentage of healthy, non hospitalized adults will be colonized with *C. difficile?*

1. 0-10%
2. 10-20%
3. 30-40%
4. 40-50%

McDonald et al CID 2018

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What percentage of healthy, non hospitalized adults will be colonized with *C. difficile?*

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3. 30-40%
4. 40-50%

McDonald et al CID 2018

Poopulation Studies

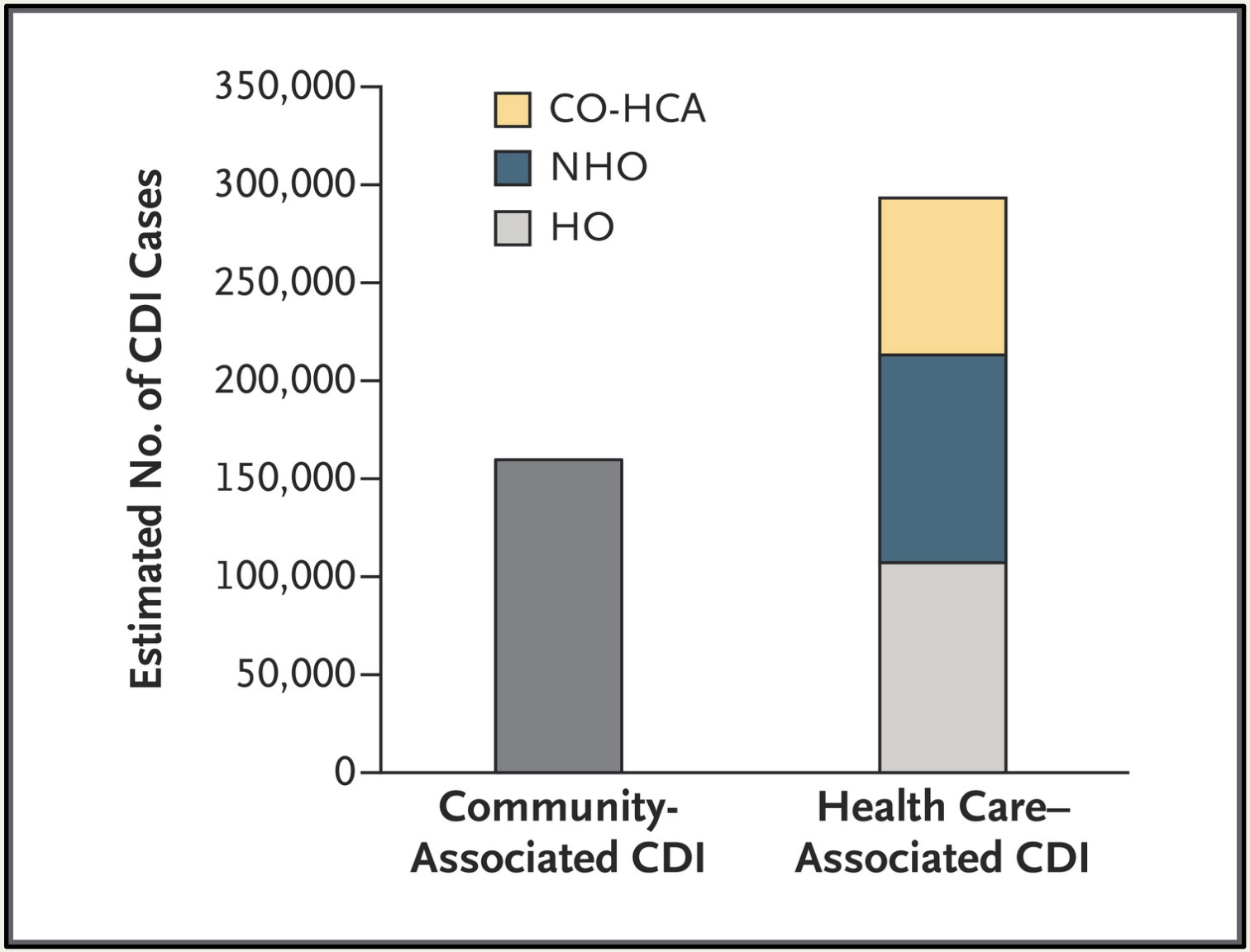
Colonization increases with healthcare exposure

- asymptomatic long-term care residents 5-7%
- asymptomatic inpatient 3-26%

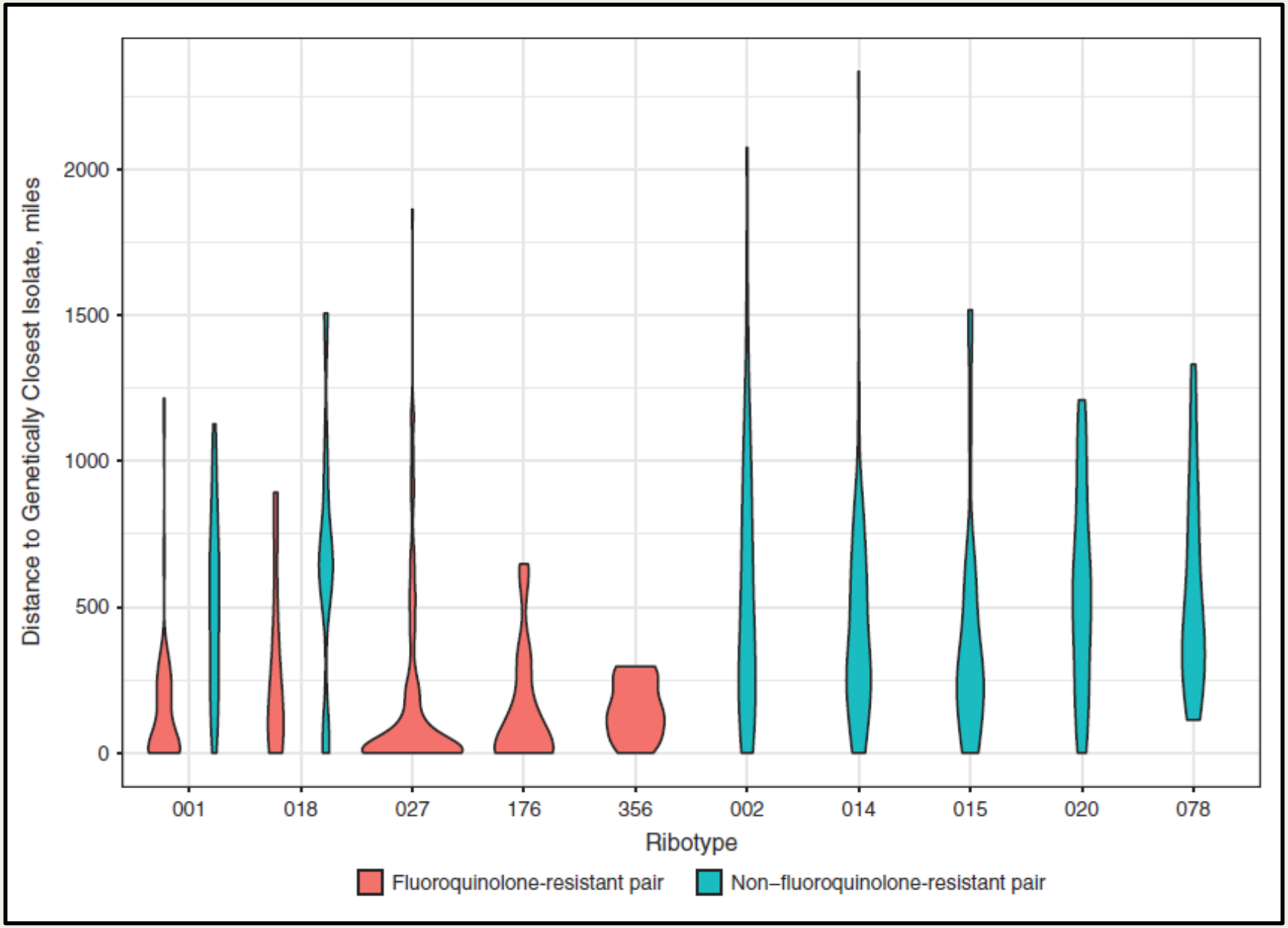
Colonization does not confer risk for disease

- protective non pathogenic strains?
- progressive antibody response to toxins?

Poutanen and Simor Can Med Assoc J 2004
Gil et al Future Microbiol 2018



Lessa NEJM 2015

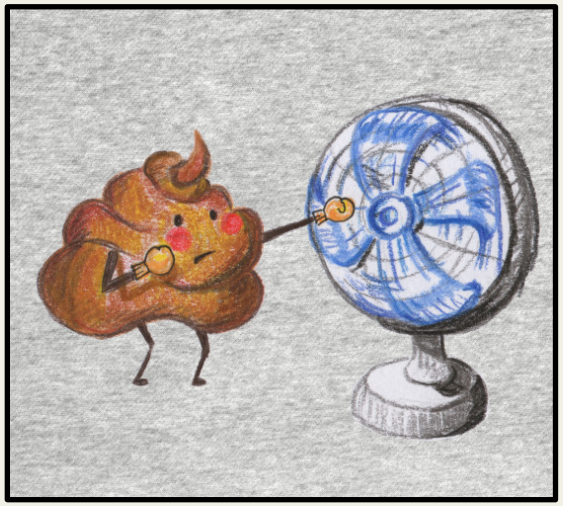


Eyre et al CID 2018

When the *C. diff* Hits the Fan

C. difficile infection (CDI) in USA

- the most common healthcare associated infection
- ≈500,000 yearly infections
- ≈30,000 yearly deaths
- ≈$3500-10000 per episode
- ≈$4.8 billion yearly inpatient costs



Peaked in Canada and Europe ≈2010 then declined

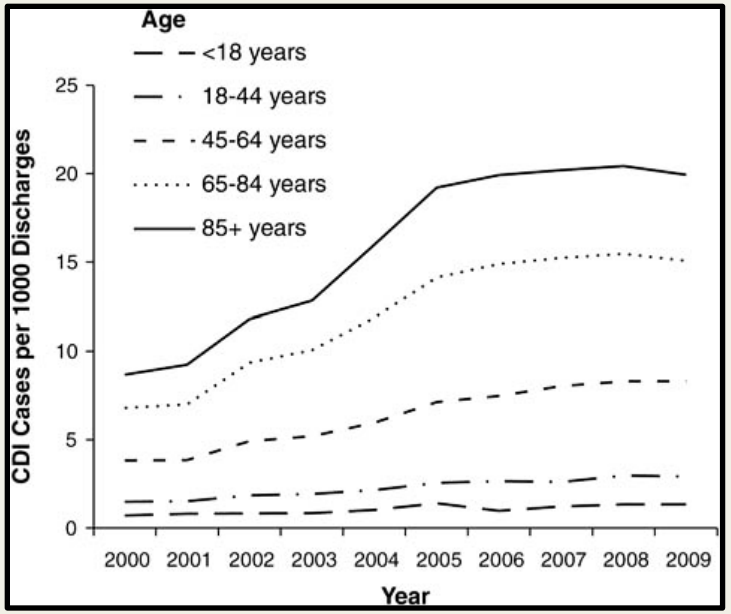
US rates have plateaued since 2010

Gerding and Young PPID 2015
McDonald et al CID 2018
Gil et al Future Microbiol 2018

The Crap Map

How do I get to *C. difficile* infection?

- <u>antibiotic exposure</u>
  - certain classes
    - quinolone, cephalosporins (3rd and 4th gen), clindamycin, etc.
  - number and duration of antibiotics
    - highest risk during course and 1 month afterward
- healthcare exposure
  - duration of exposure
- age
- comorbidities
  - immune suppression
  - inflammatory bowel disease, etc.
- proton pump inhibitors?



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Off Roading

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PLOS one

Higher Rates of *Clostridium difficile* Infection among Smokers

Mary A. M. Rogers[1]*, M. Todd Greene[1], Sanjay Saint[1,2], Carol E. Chenoweth[1], Preeti N. Malani[1,2], Itishree Trivedi[1], David M. Aronoff[1]

1 Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, United States of America, **2** Ann Arbor Veterans Affairs Medical Center, Ann Arbor, Michigan, United States of America

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BMC Medicine

RESEARCH ARTICLE Open Access

Depression, antidepressant medications, and risk of *Clostridium difficile* infection

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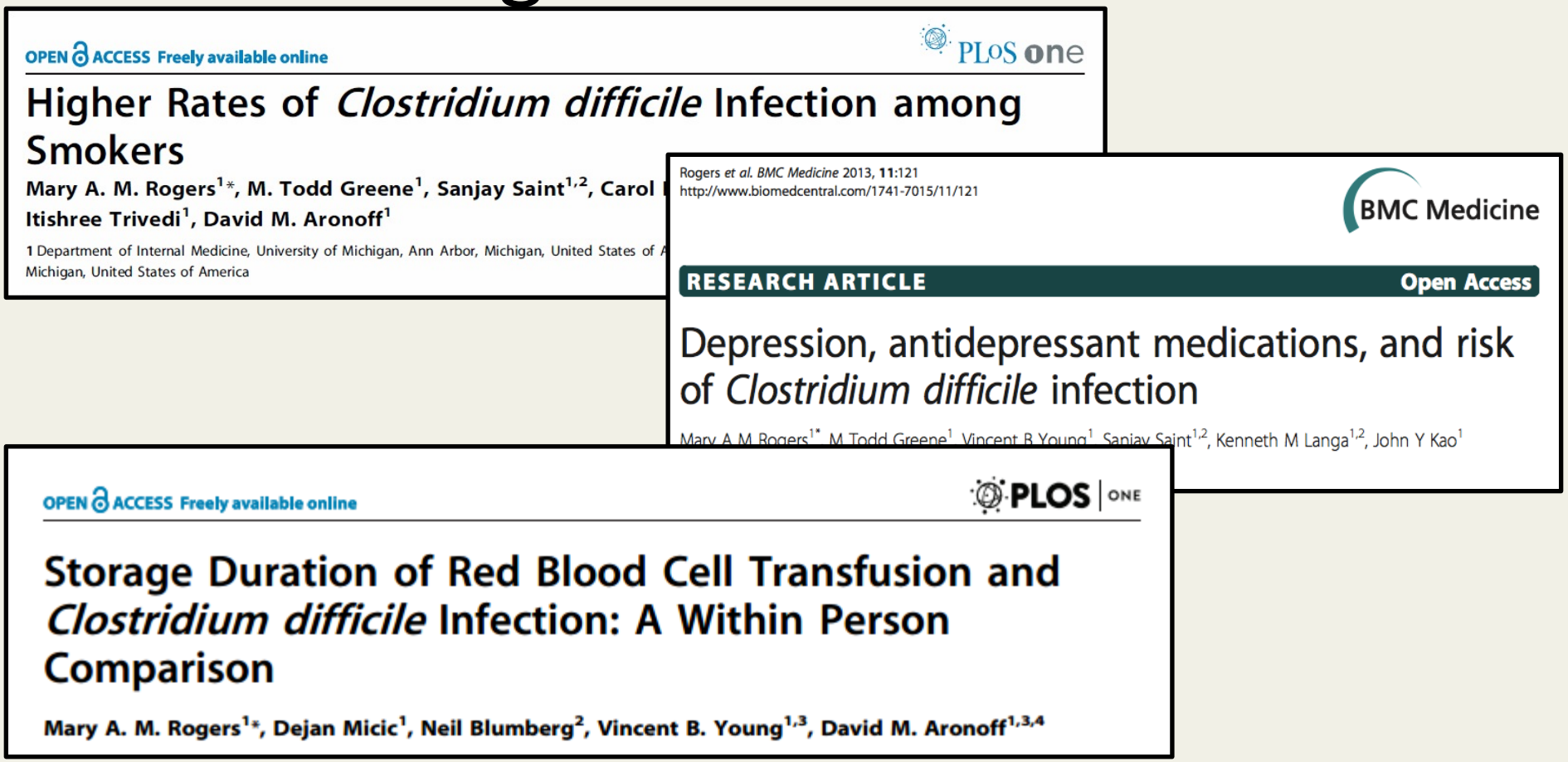

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Storage Duration of Red Blood Cell Transfusion and *Clostridium difficile* Infection: A Within Person Comparison

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ORIGINAL ARTICLE INFECTIOUS DISEASES

The influence of non-steroidal anti-inflammatory drugs on the gut microbiome

M. A. M. Rogers[1] and D. M. Aronoff[2]

1) *Department of Internal Medicine, University of Michigan, Ann Arbor, MI and* 2) *Department of Medicine and Department of Pathology, Microbiology, & Immunology, Vanderbilt University School of Medicine, Nashville, TN, USA*

NAP1 Kid on the Block

North American pulsed-field gel electrophoresis type 1 (aka ribotype 027)

- associated with virulent epidemics
  - colectomy rates 1.8-6.2%
    - baseline 0.3-1.2%
- typically quinolone resistant
- pathogenesis not entirely clear
  - possible *tcdC* mutation yields more toxin production
  - increased ability to sporulate
  - produces binary toxin linked to worse 14d mortality

Gerding and Young PPID 2015
Gil et al Future Microbiol 2018

Le Poop Quiz!

How many provinces are in Canada*?*

1. 6
2. 10
3. 12
4. 15

Wikipedia

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How many provinces are in Canada*?*

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Poutine

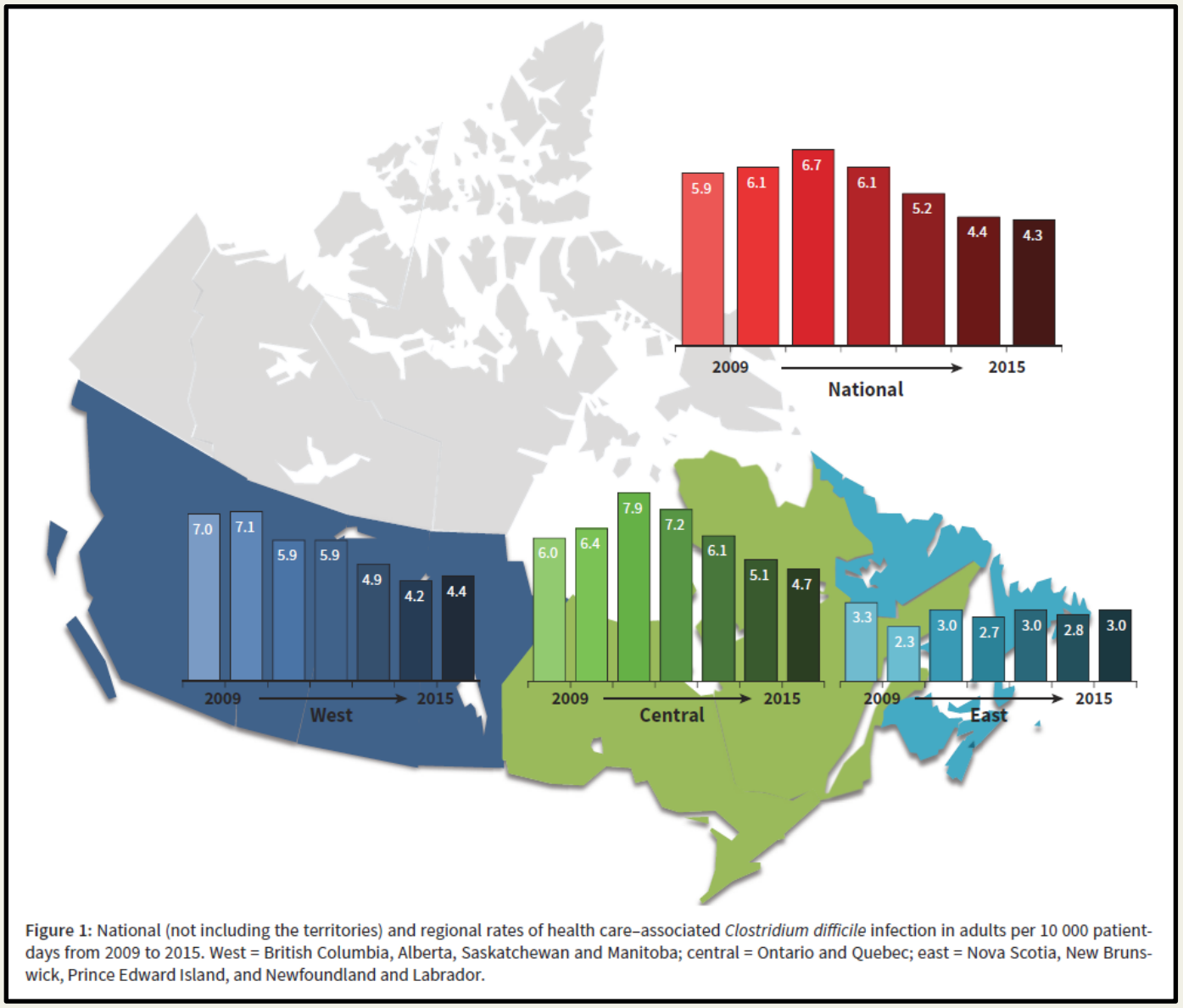

Figure 1: National (not including the territories) and regional rates of health care–associated *Clostridium difficile* infection in adults per 10 000 patient-days from 2009 to 2015. West = British Columbia, Alberta, Saskatchewan and Manitoba; central = Ontario and Quebec; east = Nova Scotia, New Brunswick, Prince Edward Island, and Newfoundland and Labrador.

Katz et al CMAJ2018

Poutine

20,623 Canadian cases 2009-2015

- NAP1 (37.6%)
  - higher percentage in central Canada
  - 94.6% resistant to moxifloxacin
  - higher overall death rate (15.6% vs 10.6%)
    - attributed to *C. difficile* (6.6% vs 2.9%)
    - not different in patients >85 years of age
- remarkable decline in rates, including NAP1
  - diagnostics and reporting
  - environmental cleaning (sporicidal agents)
  - Antimicrobial Stewardship

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  - diagnostics and reporting
  - environmental cleaning (sporicidal agents)
  - **Antimicrobial Stewardship**

Katz et al CMAJ2018

Antimicrobial Stewardshi*

No RCT data but 15 quasi-experimental studies

- interventions to decrease antibiotic exposure
- targeted antibiotics included
  - quinolones (n=7)
  - cephalosporins (n=10)
  - clindamycin (n=5)
  - amoxicillin or amox-clavulanate (n=3)
- all achieved antibiotic reduction 50->90%
  - *C. difficile* rates decreased 33-90%

McDonald et al CID 2018

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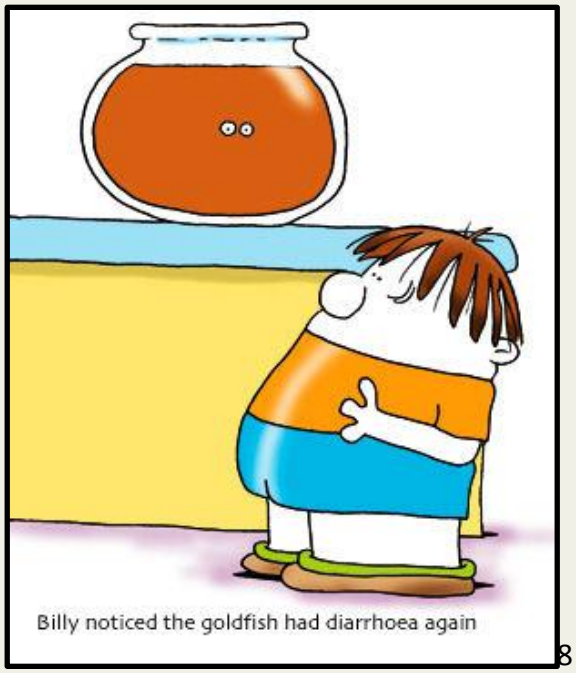
Ooooh That Smell

When to test?

- no laxatives in the last 48hrs
- ≥ 3 unformed stools in 24hrs
  - takes the shape of the container

Cramping, fever, ileus, shock

- severe
  - WBC >15K, creatinine >1.5mg/dL
- fulminant
  - shock, ileus, megacolon
- surgical indications
  - multiorgan failure
  - lactate >5mmol/L, WBC >50K
  - ongoing shock (pressors, AMS)
  - <u>early surgery improves survival</u>



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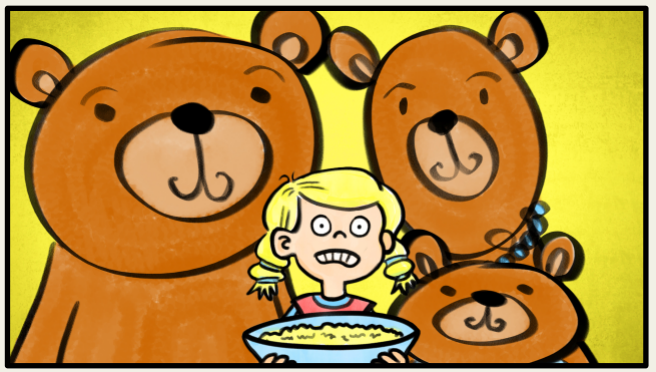

The Tests

- toxigenic culture
  - “gold standard” but time consuming
- toxin A/B
  - enzyme-linked immunoassay (EIA)
  - not sensitive enough
- glutamate dehydrogenase (GDH)
  - immunoassay detecting “common antigen”
  - too sensitive (NPV >95%, PPV <50%)
    - ie, detects nontoxigenic strains
- nucleic acid amplification (NAAT)
  - often loop mediated isothermal amplification (LAMP)
  - too sensitive (NPV >95%, PPV <50%)
    - ie, detects the gene even if toxin not present

McDonald et al CID 2018

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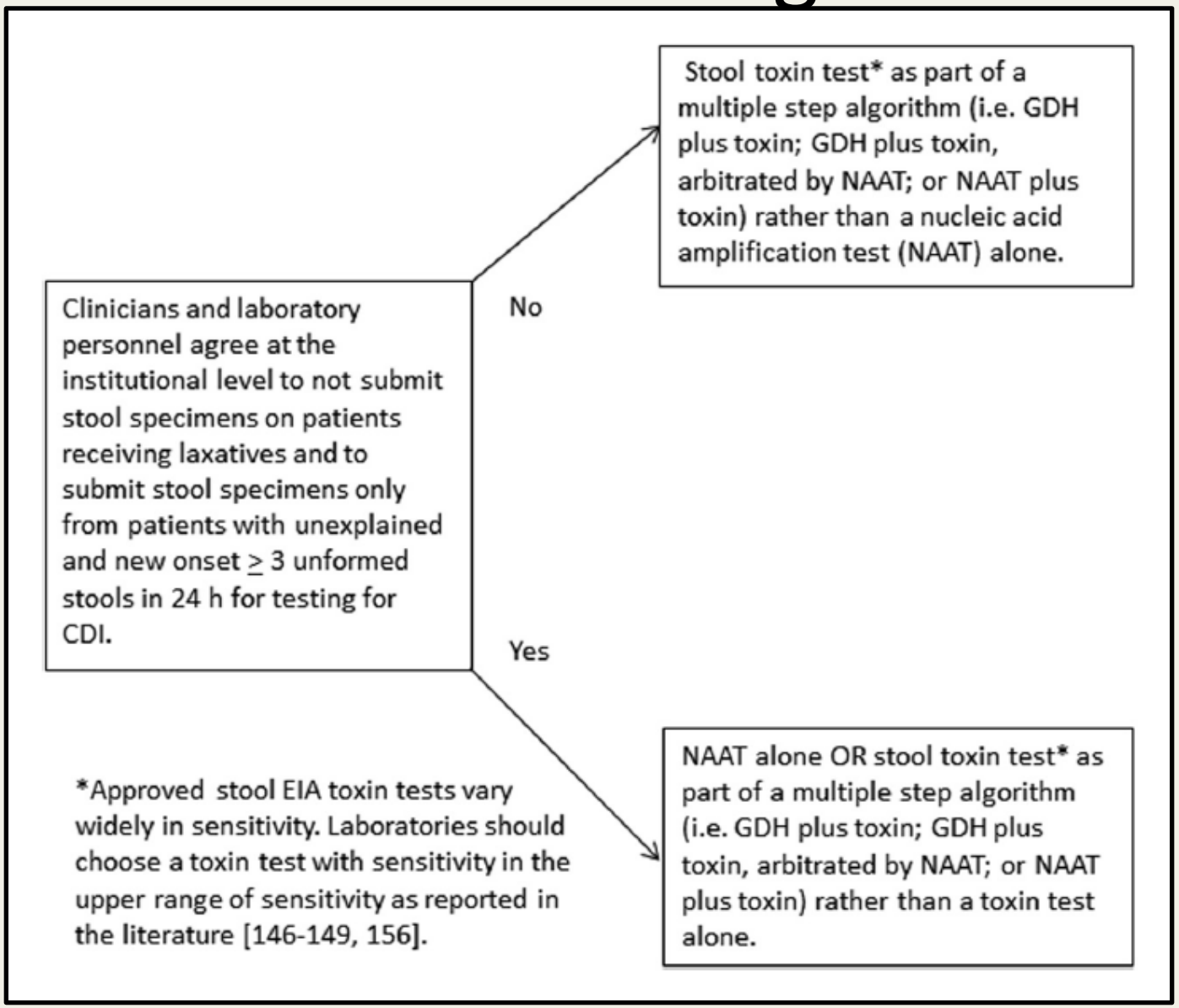

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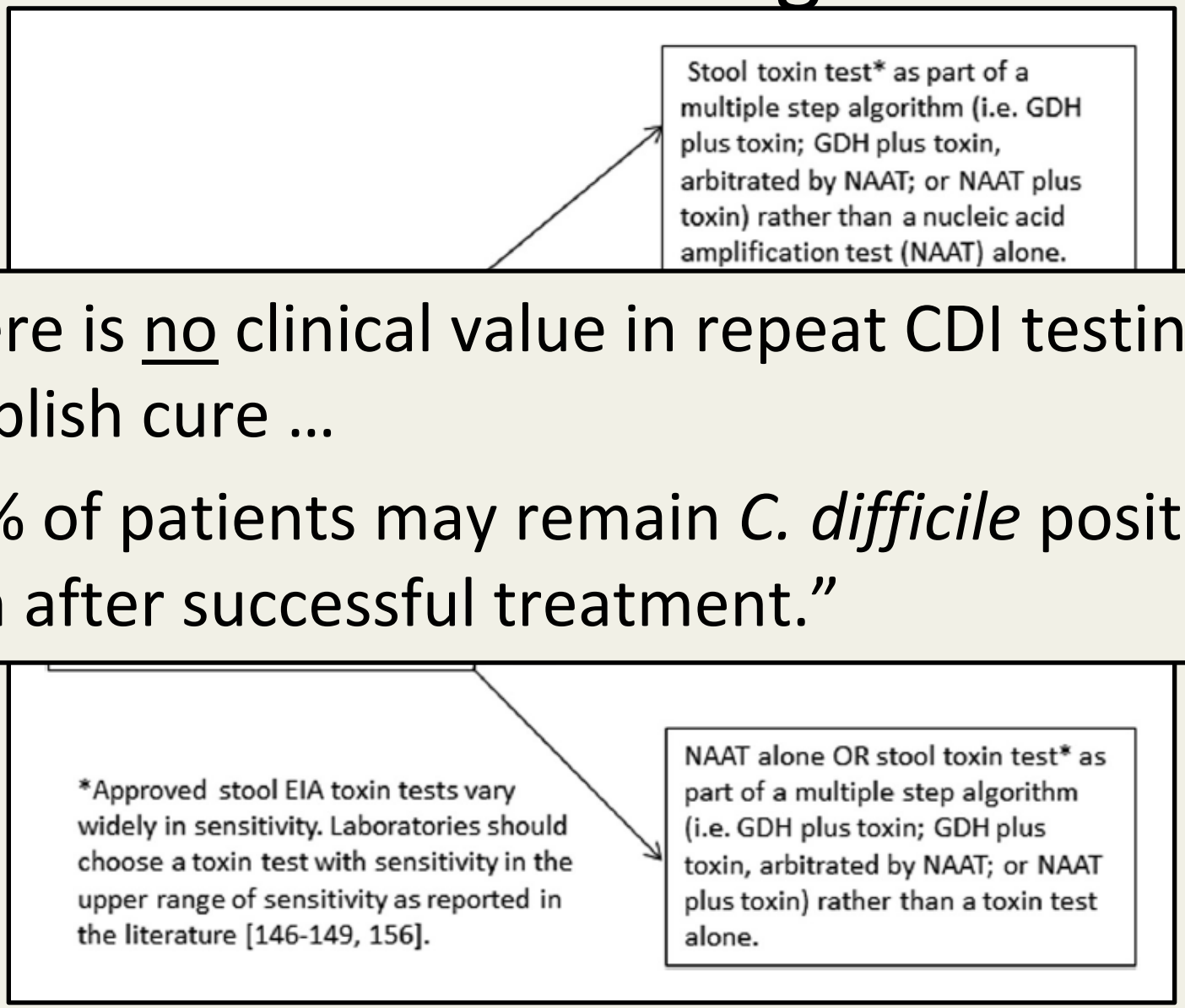

“There is no clinical value in repeat CDI testing to establish cure …

>60% of patients may remain *C. difficile* positive even after successful treatment.”

McDonald et al CID 2018

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Hot on the Case!

79 yo female nursing home resident

- remote prior left THA, PCN “allergy”
- mild C. difficile (clindamycin)
- treated with vancomycin x 10 days
- hospitalized now 4 weeks later
- cramping diarrhea, WBC 13K, creatinine 1.1
- C. difficile NAAT+
- generally well appearing with reassuring abd exam

A. vancomycin PO x 10 days
B. vancomycin PO “taper” x weeks
C. fidaxomicin PO x 10 days
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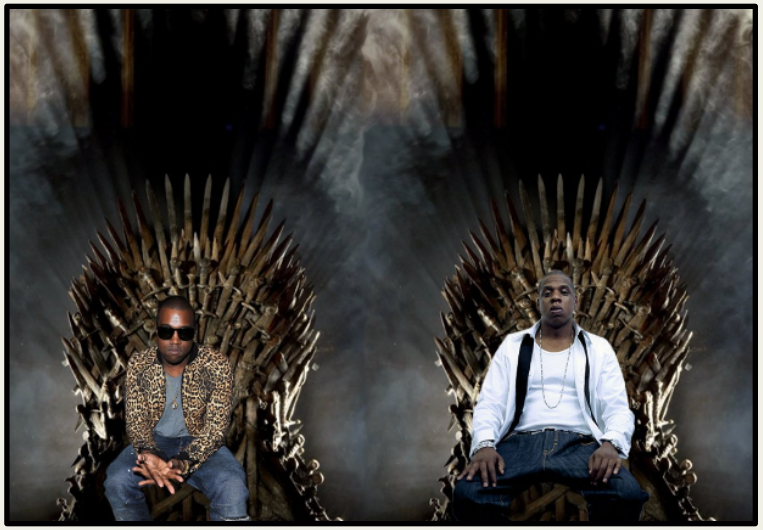
The Punchline

Table 1. Recommendations for the Treatment of *Clostridium difficile* Infection in Adults

Clinical Definition	Supportive Clinical Data	Recommended Treatment[a]	Strength of Recommendation/ Quality of Evidence
Initial episode, non-severe	Leukocytosis with a white blood cell count of ≤15000 cells/mL and a serum creatinine level <1.5 mg/dL	• VAN 125 mg given 4 times daily for 10 days, OR	Strong/High
		• FDX 200 mg given twice daily for 10 days	Strong/High
		• Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days	Weak/High
Initial episode, severe[b]	Leukocytosis with a white blood cell count of ≥15000 cells/mL or a serum creatinine level >1.5 mg/dL	• VAN, 125 mg 4 times per day by mouth for 10 days, OR	Strong/High
		• FDX 200 mg given twice daily for 10 days	Strong/High
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	• VAN, 500 mg 4 times per day by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of VAN. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal VAN, particularly if ileus is present.	Strong/Moderate (oral VAN); Weak/Low (rectal VAN); Strong/Moderate (intravenous metronidazole)
First recurrence	…	• VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR	Weak/Low
		• Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (eg, 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks), OR	Weak/Low
		• FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode	Weak/Moderate

McDonald et al CID 2018

Watch the Throne



How did metronidazole fall?

- clinical cure
  - 84% vs 97% vancomycin
    - Zar et al CID 2007
  - 73% vs 81% vancomycin
    - Johnson et al CID 2014
- recurrence
  - 13% vs 9% vancomycin
    - Siegfried et al Infect Clin Dis Pract 2016

McDonald et al CID 2018

Watch the Throne

How did fidaxomicin threaten the throne?

- two RCTs (n=1105)
  - Louie et al NEJM 2011
  - Cornely et al Lancet Infect Dis 2012
- clinical cure (10d)
  - 88% vs 86% vancomycin
- recurrence (25d)
  - 71% vs 57% vancomycin
- excluded fulminant *C. difficile* infection

McDonald et al CID 2018

Watch the Throne

Fidaxomicin (new class of macrocyclic antibiotics)

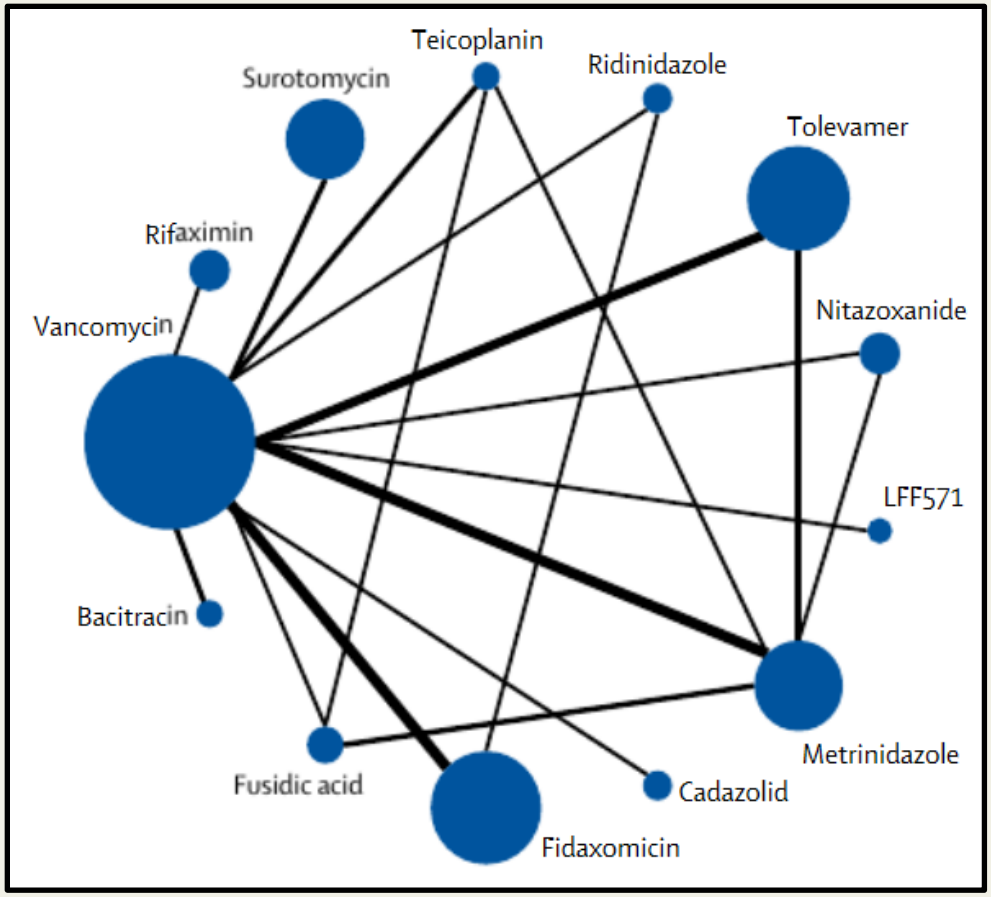
- inhibits bacterial RNA polymerase
- low systemic but high fecal concentration
- relatively narrow spectrum
  - less effect on commensal flora (eg, *Bacteroides*)

Soriano and Johnson IDCNA 2015

Watch the Throne

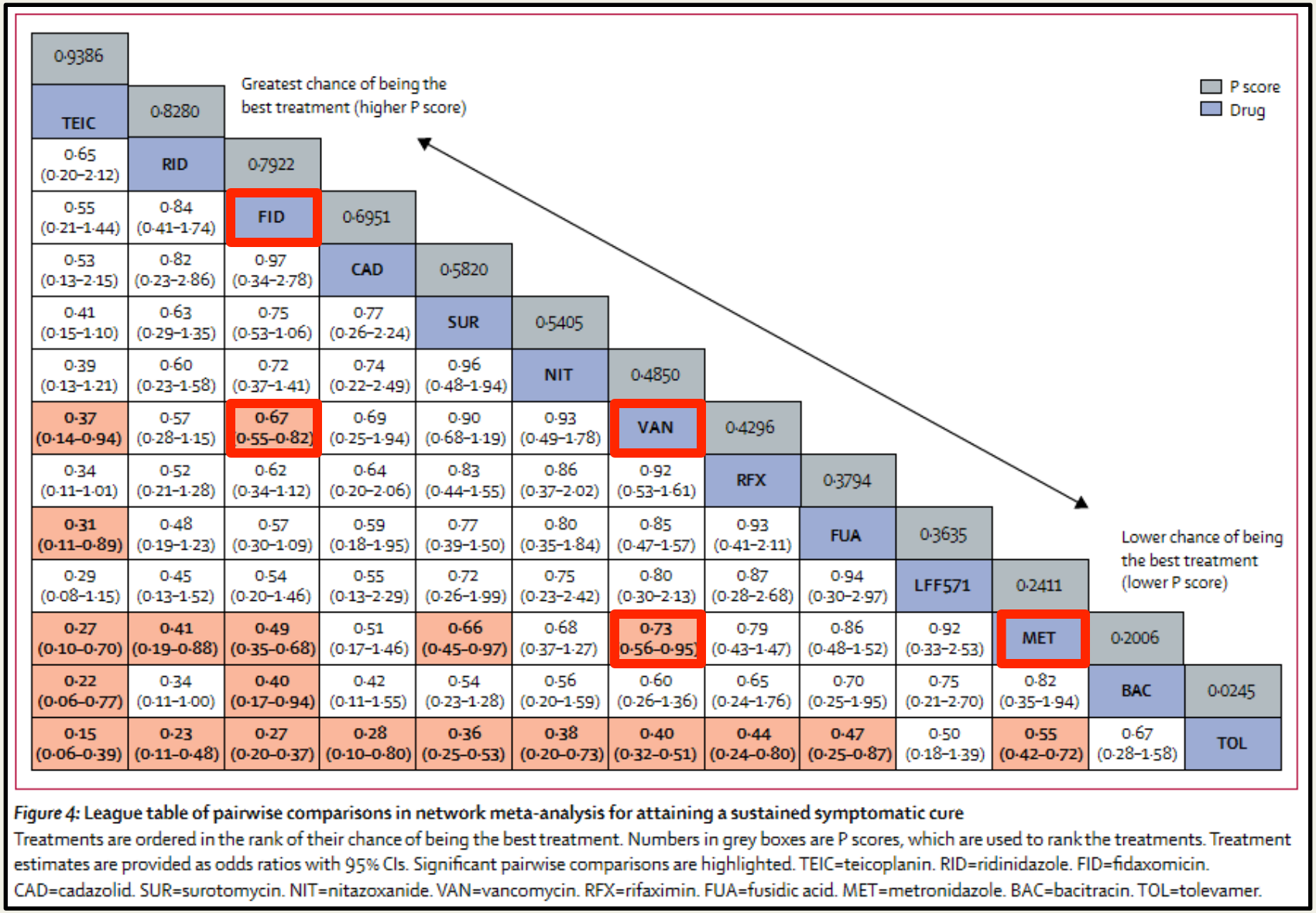
"Random effects network meta analysis"

- 24 trials included (n=5361) with 13 treatments



Beinortas et al Lancet Infect Dis 2018

Watch the Throne



0·9386											
TEIC	0·8280										
0·65 (0·20–2·12)	RID	0·7922									
0·55 (0·21–1·44)	0·84 (0·41–1·74)	FID	0·6951								
0·53 (0·13–2·15)	0·82 (0·23–2·86)	0·97 (0·34–2·78)	CAD	0·5820							
0·41 (0·15–1·10)	0·63 (0·29–1·35)	0·75 (0·53–1·06)	0·77 (0·26–2·24)	SUR	0·5405						
0·39 (0·13–1·21)	0·60 (0·23–1·58)	0·72 (0·37–1·41)	0·74 (0·22–2·49)	0·96 (0·48–1·94)	NIT	0·4850					
0·37 (0·14–0·94)	0·57 (0·28–1·15)	**0·67 0·55–0·82)**	0·69 (0·25–1·94)	0·90 (0·68–1·19)	0·93 (0·49–1·78)	VAN	0·4296				
0·34 (0·11–1·01)	0·52 (0·21–1·28)	0·62 (0·34–1·12)	0·64 (0·20–2·06)	0·83 (0·44–1·55)	0·86 (0·37–2·02)	0·92 (0·53–1·61)	RFX	0·3794			
0·31 (0·11–0·89)	0·48 (0·19–1·23)	0·57 (0·30–1·09)	0·59 (0·18–1·95)	0·77 (0·39–1·50)	0·80 (0·35–1·84)	0·85 (0·47–1·57)	0·93 (0·41–2·11)	FUA	0·3635		
0·29 (0·08–1·15)	0·45 (0·13–1·52)	0·54 (0·20–1·46)	0·55 (0·13–2·29)	0·72 (0·26–1·99)	0·75 (0·23–2·42)	0·80 (0·30–2·13)	0·87 (0·28–2·68)	0·94 (0·30–2·97)	LFF571	0·2411	
0·27 (0·10–0·70)	**0·41 (0·19–0·88)**	**0·49 (0·35–0·68)**	0·51 (0·17–1·46)	**0·66 (0·45–0·97)**	0·68 (0·37–1·27)	**0·73 0·56–0·95)**	0·79 (0·43–1·47)	0·86 (0·48–1·52)	0·92 (0·33–2·53)	MET	0·2006
0·22 (0·06–0·77)	0·34 (0·11–1·00)	**0·40 (0·17–0·94)**	0·42 (0·11–1·55)	0·54 (0·23–1·28)	0·56 (0·20–1·59)	0·60 (0·26–1·36)	0·65 (0·24–1·76)	0·70 (0·25–1·95)	0·75 (0·21–2·70)	0·82 (0·35–1·94)	BAC
0·15 (0·06–0·39)	**0·23 (0·11–0·48)**	**0·27 (0·20–0·37)**	**0·28 (0·10–0·80)**	**0·36 (0·25–0·53)**	**0·38 (0·20–0·73)**	**0·40 (0·32–0·51)**	**0·44 (0·24–0·80)**	**0·47 (0·25–0·87)**	0·50 (0·18–1·39)	**0·55 (0·42–0·72)**	0·67 (0·28–1·58)

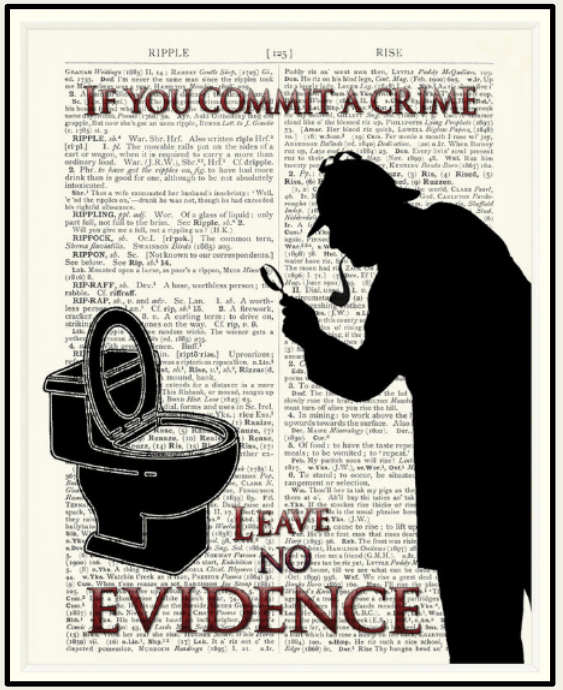
0·0245
TOL

Figure 4: **League table of pairwise comparisons in network meta-analysis for attaining a sustained symptomatic cure**

Treatments are ordered in the rank of their chance of being the best treatment. Numbers in grey boxes are P scores, which are used to rank the treatments. Treatment estimates are provided as odds ratios with 95% CIs. Significant pairwise comparisons are highlighted. TEIC=teicoplanin. RID=ridinidazole. FID=fidaxomicin. CAD=cadazolid. SUR=surotomycin. NIT=nitazoxanide. VAN=vancomycin. RFX=rifaximin. FUA=fusidic acid. MET=metronidazole. BAC=bacitracin. TOL=tolevamer.

Beinortas et al Lancet Infect Dis 2018

Think Outside the Bowl



C. difficile Checklist

- stop the offending antibiotic
- stop unnecessary PPIs
  - “a clinical association” but not causal

Ancillary therapy

- probiotics
  - “insufficient data … for primary prevention”
  - “for the prevention of recurrence … none has demonstrated … reproducible efficacy”
- IVIG if not responding
  - “no controlled trials have been performed”
- bezlotoxumab

McDonald et al CID 2018

Bezlotoxumab

The NEW ENGLAND JOURNAL of MEDICINE

MODIFY I and MODIFY II

- two double-blind phase 3 RCTs (n=2655)
- primary and recurrent CDI
  - bezlotoxumab vs actoxumab + bezlotoxumab vs placebo
  - single infusion + “standard of care”
    - ≈ split between vancomycin or metronidazole (little fidaxomicin)

Sustained cure 64% (alone) vs 54% (placebo)

- no change in rates for initial cure vs placebo

Wilcox et al NEJM 2017

Bezlotoxumab

The NEW ENGLAND JOURNAL of MEDICINE

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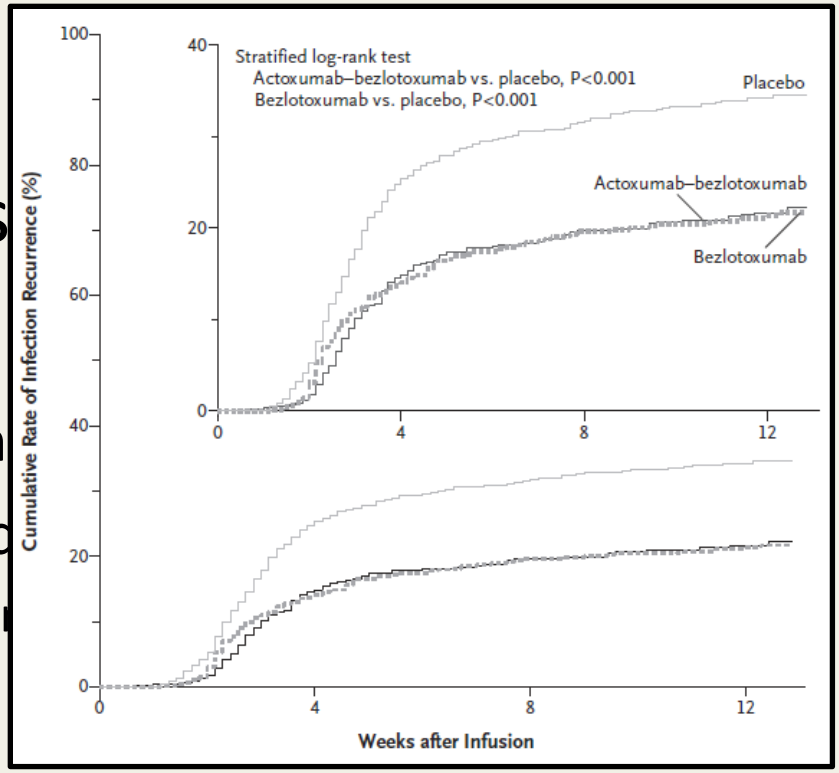

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Wilcox et al NEJM 2017

Hot on the Case!

Your patient is back again.

Rate of 1st recurrence ≈15-30%

- recurrent CDI ≈ 33% increased 180d mortality

What is the rate of 2nd recurrence?

A. 0-20%
B. 20-40%
C. 40-60%
D. 60-80%

Gil et al Future Microbiol 2018

Hot on the Case!

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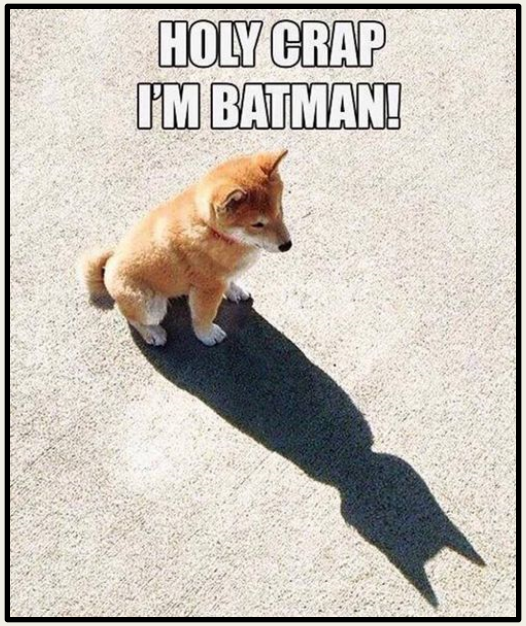

Gil et al Future Microbiol 2018

The Punchline

Table 1. Recommendations for the Treatment of *Clostridium difficile* Infection in Adults

Clinical Definition	Supportive Clinical Data	Recommended Treatment[a]	Strength of Recommendation/ Quality of Evidence
Initial episode, non-severe	Leukocytosis with a white blood cell count of ≤15000 cells/mL and a serum creatinine level <1.5 mg/dL	• VAN 125 mg given 4 times daily for 10 days, OR	Strong/High
		• FDX 200 mg given twice daily for 10 days	Strong/High
		• Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days	Weak/High
Initial episode, severe[b]	Leukocytosis with a white blood cell count of ≥15000 cells/mL or a serum creatinine level >1.5 mg/dL	• VAN, 125 mg 4 times per day by mouth for 10 days, OR	Strong/High
		• FDX 200 mg given twice daily for 10 days	Strong/High
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	• VAN, 500 mg 4 times per day by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of VAN. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal VAN, particularly if ileus is present.	Strong/Moderate (oral VAN); Weak/Low (rectal VAN); Strong/Moderate (intravenous metronidazole)
First recurrence	…	• VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR	Weak/Low
		• Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (eg, 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks), OR	Weak/Low
		• FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode	Weak/Moderate

McDonald et al CID 2018

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Initial episode, severe[b]	Leukocytosis with a white blood cell count of ≥15000 cells/mL or a serum creatinine level >1.5 mg/dL	• VAN, 125 mg 4 times per day by mouth for 10 days, OR	Strong/High
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First recurrence	…	• VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR	Weak/Low
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		• FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode	Weak/Moderate
Second or subsequent recurrence	…	• VAN in a tapered and pulsed regimen, OR	Weak/Low
		• VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR	Weak/Low
		• FDX 200 mg given twice daily for 10 days, OR	Weak/Low
		• Fecal microbiota transplantation[c]	Strong/Moderate

McDonald et al CID 2018

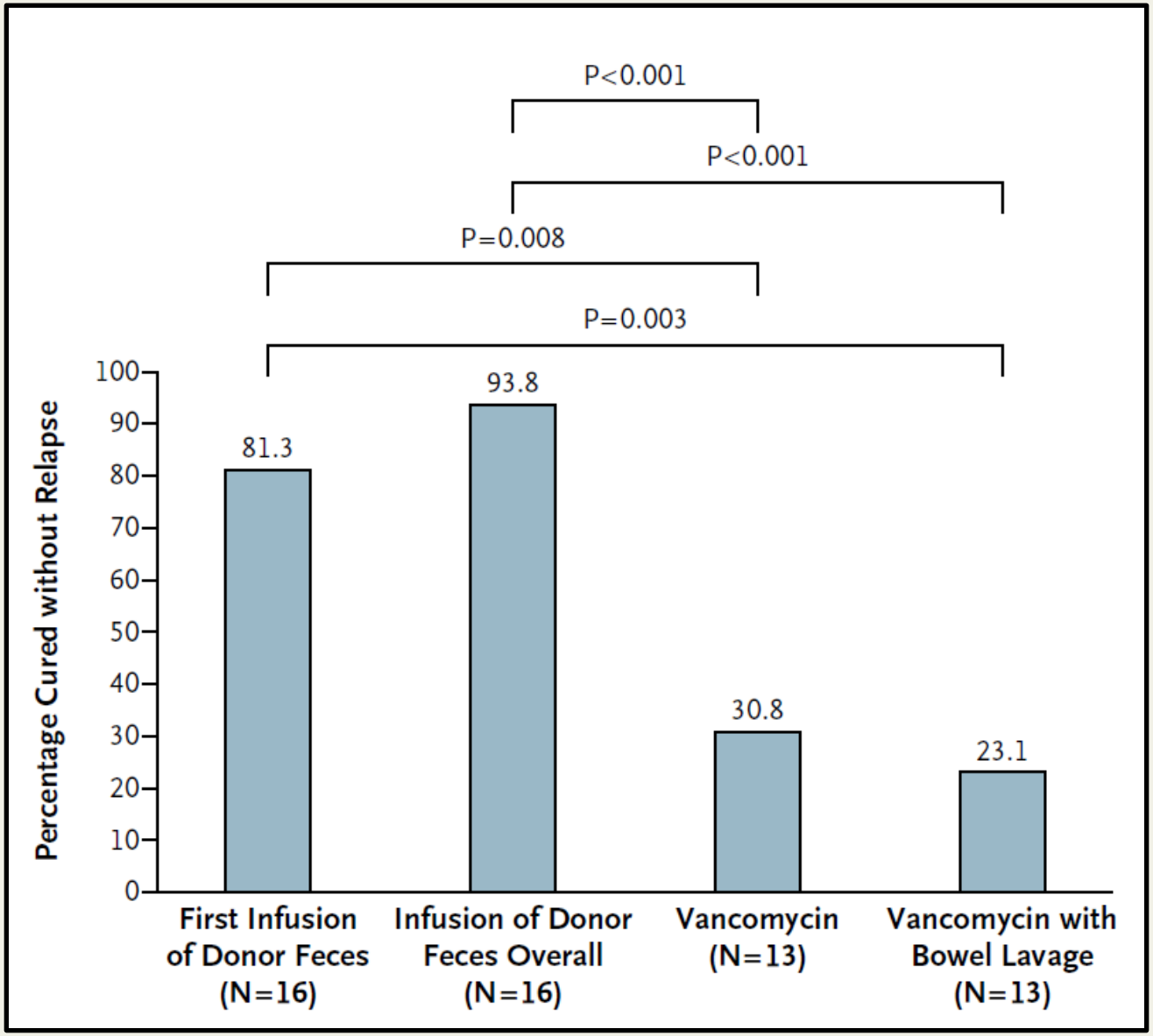
“I’ve Got Good News and Bad News”

Fecal Microbiota Transplant

- >2000 cases reported since 2016
- Van Nood et al NEJM 2013
  - unblinded RCT (n=43)
  - ≥2 recurrences
  - vancomycin vs vancomycin + bowel lavage vs FMT
  - 81% sustained response after 1st infusion
    - received vancomycin x 4d and bowel lavage prior to FMT
    - study terminated prior to 10 week primary endpoint
- methods
  - colonic administration
    - “highest success rates (80-100%)”
  - nasoduodenal tube
  - “the crapsule”

Van Nood et al NEJM 2013
McDonald CID 2018

Hard Data



Van Nood et al NEJM 2013

What's the Catch?

Safety Data

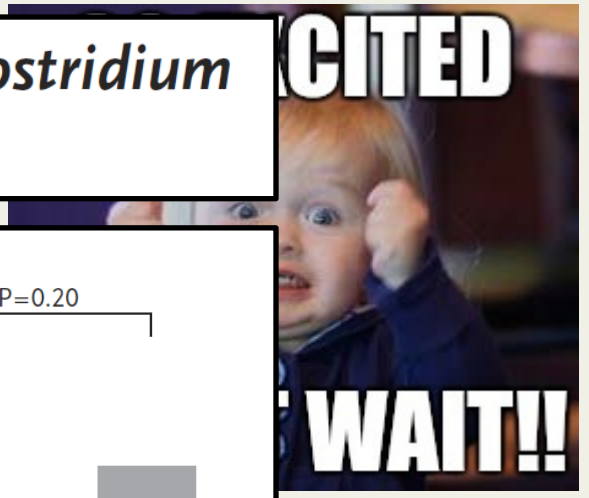
- risks associated with colonoscopy
- two patients contracted norovirus
  - though generally safe even in immune compromised

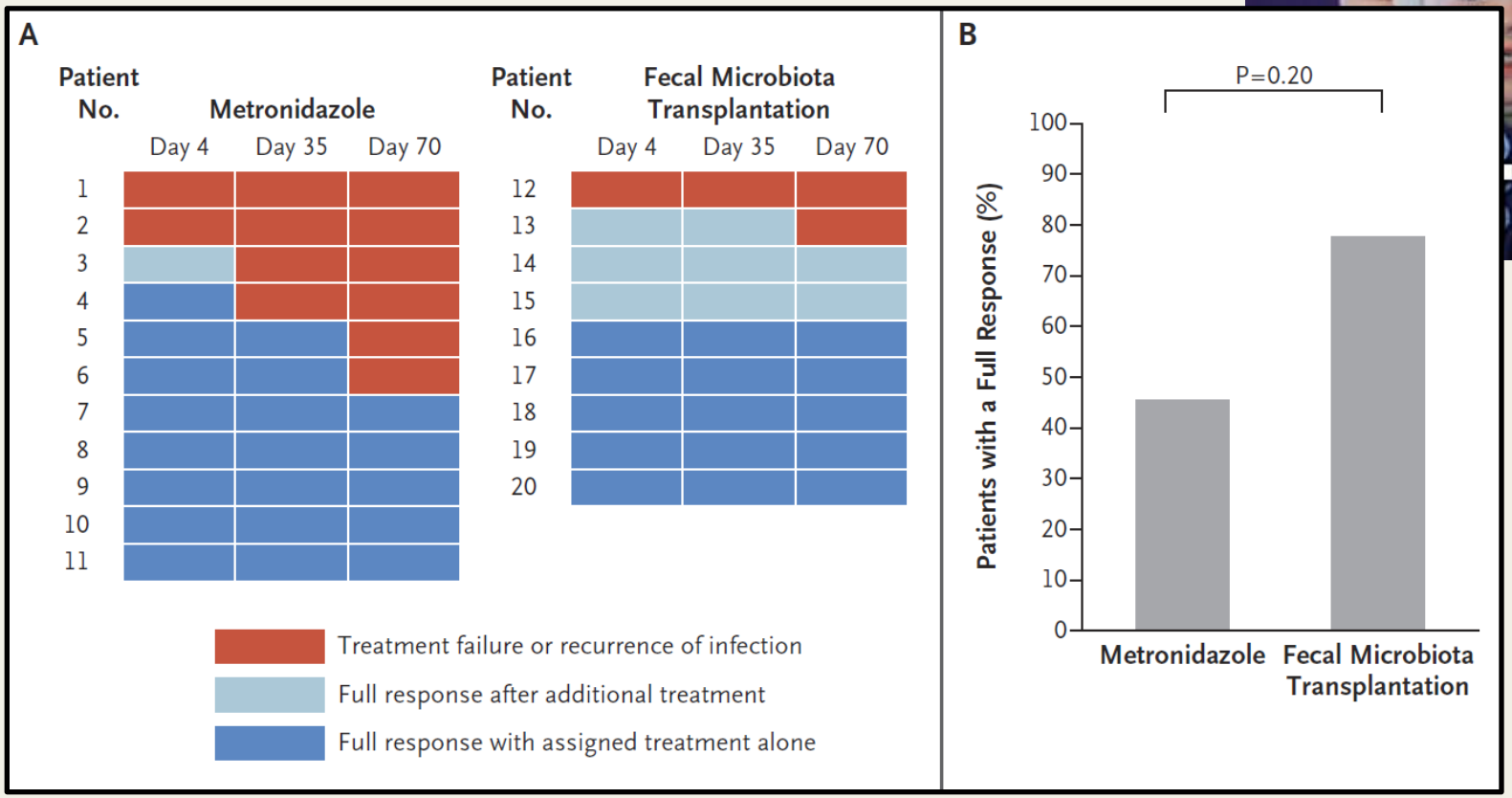
Logistics

- finding a provider
- finding a donor
  - some specialists have access to "stool banks"
    - cost ≈ $250 (statistic courtesy of Dr. Dawn Beaulieu)
- covering cost of screening (falls to the donor!)
  - stool: *C. difficile*, culture, O&P, *Giardia* +/- *Cryptosporidium*
  - serum: HIV, HAV, HBV, HCV, syphilis and TB screen

Van Nood et al NEJM 2013
McDonald CID 2018

Fecal Microbiota Transplantation for Primary *Clostridium difficile* Infection

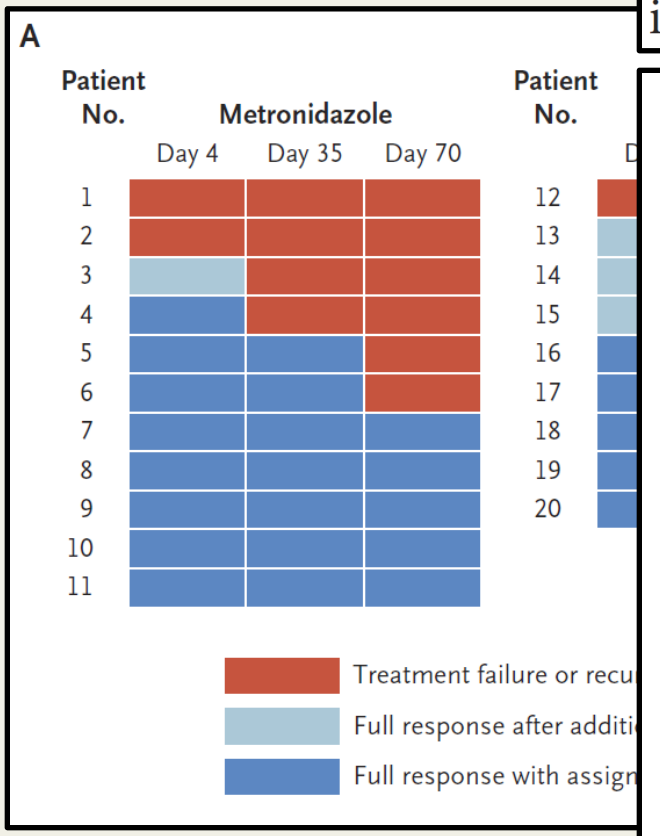


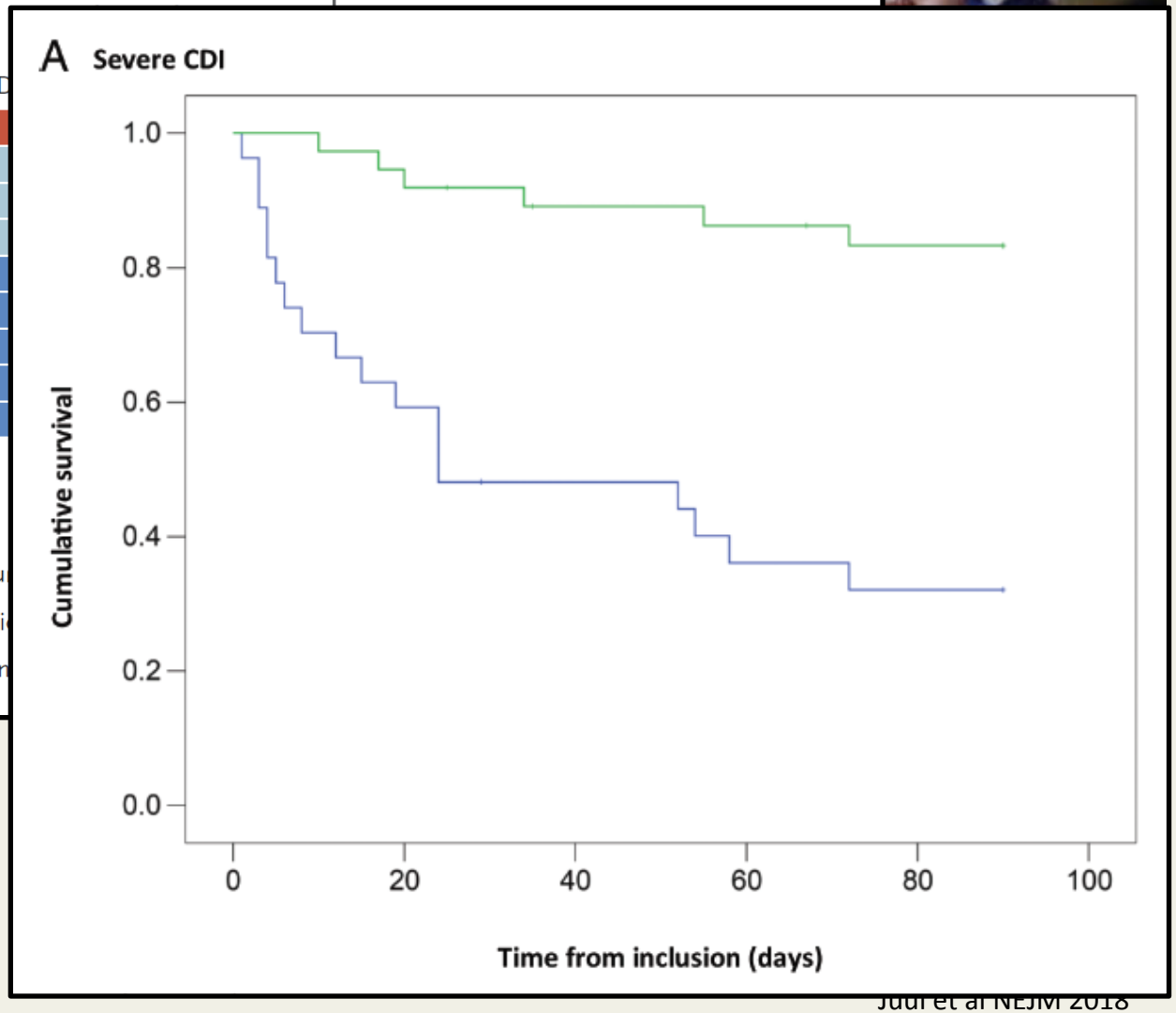


Juul et al NEJM 2018
Hocquart et al CID 2018

Fecal Microbiota Transplantation for Primary *Clostridium difficile* Infection

Early Fecal Microbiota Transplantation Improves Survival in Severe *Clostridium difficile* Infections





Juul et al NEJM 2018
Hocquart et al CID 2018

TGIF

Careful with antibiotics.

C. difficile:

- "Easy to treat, hard to cure."

Therapeutic updates:

- metronidazole no longer 1st line
- fidaxomicin 1st line with oral vancomycin

Find a FMT provider near you.

Questions?

matthew.h.greene@vumc.org