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Founding Member, Mass General Brigham

Hot Topics in Infectious Diseases

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HARVARD MEDICAL SCHOOL
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CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

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- Research interests: Invasive fungal infection and HBV in immunocompromised patients

Disclosures

- I have research funding from Cidara, F2G, Scynexis and GSK
- I have been a consultant for F2G, Melinta, Pfizer, Roche and Seres therapeutics

What's New in Infectious Diseases?

- Formidable New & Old Bugs
  - COVID-19
  - Avian influenza
  - Multi-drug resistant organisms
  - Powassan and other vector-borne illnesses
- New Antimicrobials
  - Ibrexafungerp 2021
  - Oteseconazole 2022
  - Fecal microbiota, live-jslm 2022
  - Rezafungin 2023
  - SER-109 2023
  - Sulbactam-durlobactam 2023
  - Cefepime-enmetazobactam 2024
  - Ceftobiprole 2024
- New Problems
  - Impact of climate change on infection
- New Guidelines for Testing and Management
  - New Fever in Critically Ill Patients 2023
  - Diabetic Foot Infection 2023
  - Antimicrobial resistance 2023
  - Hepatitis C 2023
  - C. difficile 2021
- New Approach to Old Problems
  - Oral antibiotics for serious invasive infection
  - Shorter antimicrobial courses for bloodstream infection
- New Diagnostic Tools
  - Next generation sequencing

New Problems:

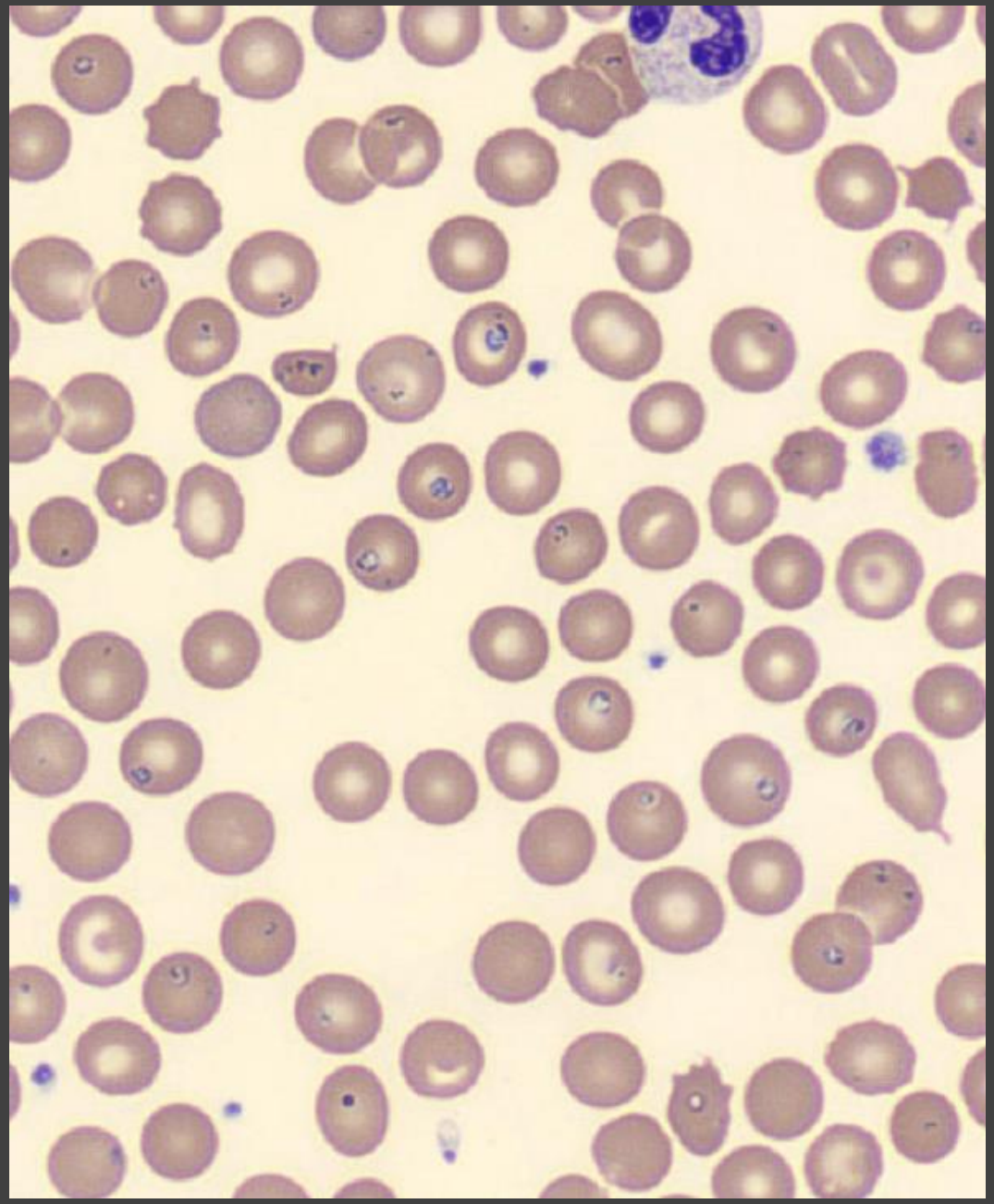
Impact of climate change on infection

Clinical Case

- 68-year-old man with diffuse large B cell lymphoma s/p 6 cycles of R-CHOP chemotherapy 4 months ago presents the first week of January with malaise, dyspnea on exertion and sweats that have progressed for the last 2 weeks
  - His daughter notes that he looks yellow
- Past medical history is notable for lymphoma as above, hypertension, hyperlipidemia and asplenia (MVA at age 18)
- Medications include atorvastatin, amlodipine and lisonopril
- Social history is notable for living in the suburbs of Boston. Retired engineer. Two pet Labradors that he walks in a nearby nature reserve daily. Just returned from a holiday vacation to Hawaii for 10 days.

Examination & Labs

- Exam
  - Notable for a fatigued appearing man with pale conjunctiva
  - Mild tachycardia with regular rhythm
  - Clear lungs but is tachypneic
- Labs
  - WBC 4.2, HCT 24, PLT 301
    - Differential sent…
  - Cr 1.4, AST 111, ALT 34, T Bili 2.9
  - LDH 1102



The likely cause of his illness is:

A. Malaria
B. Leptospirosis
C. Babesia
D. Oroyo fever (Bartonella bacilifomis)
E. Dengue fever

Climate change and Infection

- Climate change has the potential to have broad reaching impacts on human infection
- Knowledge of some changes we see now can help with prevention and early diagnosis

Table. Impact of Climate-Related Changes on Infectious Disease Epidemiology

Disease type	Climate-related change	Effect on infectious disease epidemiology	Examples
Vector-borne diseases	Shorter, warmer winters Longer summers Expanding range of vectors, eg, mosquitoes and ticks Changes in precipitation patterns	Increased disease incidence Expanding seasonality into winter months Expanding geographic range, primarily northward and westward Increased likelihood of onward transmission	Babesiosis Lyme disease Anaplasmosis Powassan virus Ehrlichiosis Dengue Zika virus Chikungunya virus Malaria
Zoonotic diseases	Changes in animal migration patterns, natural ranges, and population density Habitat destruction Increased interaction between different animal species Increased human-animal interaction	Increased cross-species transmission events Emergence of novel human pathogens Increased disease incidence Expanding geographic range	Avian influenza (H5N1) Plague Hantavirus Tularemia Emerging coronaviruses
Fungal diseases	Expanded thermotolerance in fungal organisms New favorable environments for endemic fungi	Emergence of novel human pathogens Expanding geographic range of endemic mycoses	*Candida auris* *Sporothrix brasiliensis* *Coccidioides* *Histoplasma* *Blastomyces*
Waterborne diseases	Rise of sea level Extreme weather events Flooding-induced strain on water infrastructure Changes in precipitation patterns Changes in coastal water temperature	Increased disease incidence after storms Expanding seasonality Expanding geographic range, primarily northward	*Campylobacter* *Escherichia coli* *Cryptosporidium* *Vibrio* species

Phillips MC, LaRocque RC, Thompson GR. JAMA 2024; doi: 10.1001/jama.2023.27724

How might climate change impact fungal infection?

- Humans have two major defenses against invasive fungal infection:
  1. Relatively high body temperature (we're warm-blooded!)
  2. Immune defenses
- Warm ambient temperatures and particularly the number of days with excessive heat can select for environmental fungi that rapidly adapt to survive at warmer temperatures
  - Fungi that survive at warmer temperatures can be better suited to cause human infection
  - The first potential example of this: *Candida auris*, which has significant thermotolerance (grows well at 37°C), emerged on different continents ~2010
    - This organism can cause difficult-to-treat infection in a vulnerable population (ICU in particular) and is typically multidrug resistant
  - Other fungi not known to cause human infection now could adapt and cause new syndromes

Casadevall A. Nat Microbiol. 2023;8:2217-2219.
Seidel D, et al. Lancet Microbe. 2024; doi.10.1016/S2666-5247(24)00039-9

Climate change & Fungi: Distribution & Disasters

- Distribution
  - The distribution of endemic mycoses i
  - Modeling studies have suggested that the Ohio river valley has expanded to
  - Modelling studies have also suggested the Northwest US
- Increased natural disasters m[illegible] lea difficult invasive fungal i[illegible]ction

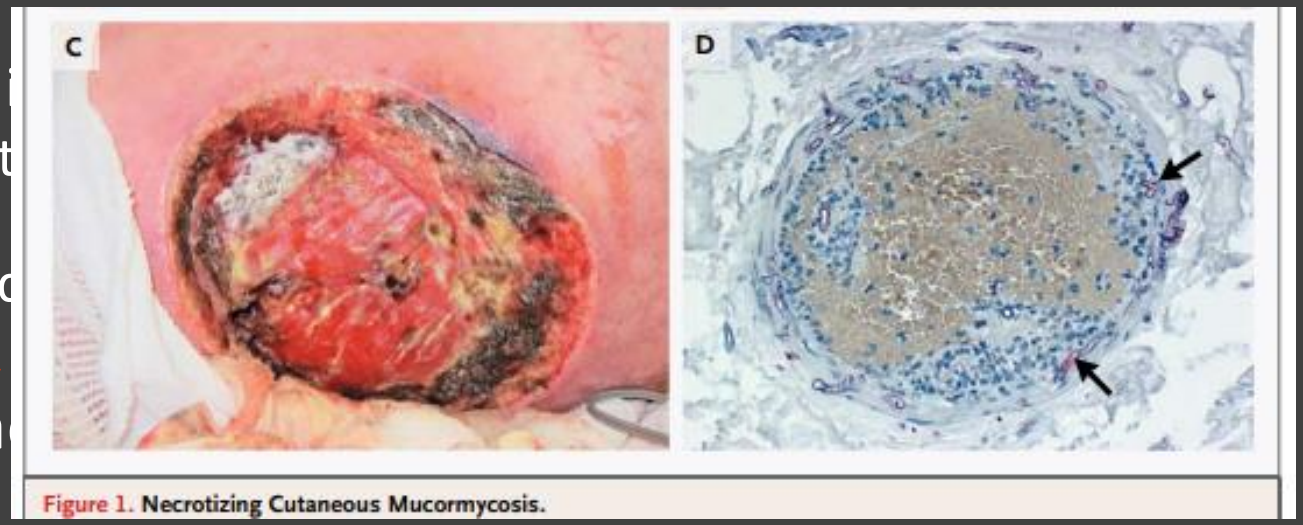


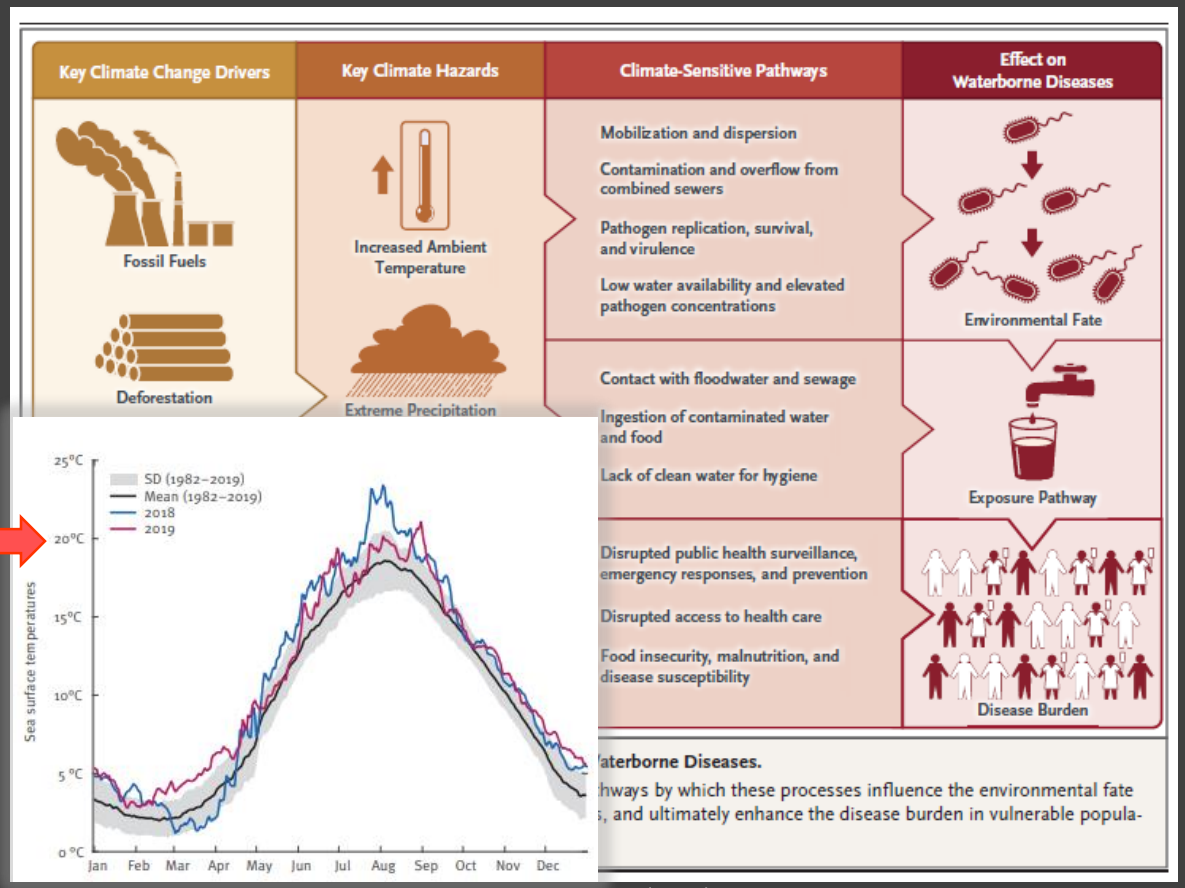
Figure 1. Necrotizing Cutaneous Mucormycosis.

  - **Tornado eg:** Joplin, Missouri 2011: following a severe tornado (winds >200 miles per hour) a cluster of cutaneous mucormycosis was reported in 13 injured individuals due to *Apophysomyces trapeziformis*
  - **Wildfire eg:** Wildfire smoke contains microbes including fungal spores
    - Mulliken et al. studied the association between wildfire smoke and California hospital admissions for Coccidioides and Aspergillus and found that Coccidioides admissions rose 20% in the month following smoke exposure based on smoke plume data

Seidel D, et al. Lancet Microbe. 2024; doi.10.1016/S2666-5247(24)00039-9.
Fanfair RN, et al. N Engl J Med 2012;367:2214-25.
Mulliken JS, et al. Lancet Planet Health 2023; 7: e381–86

Waterborne Infection and Climate Change

- Climate change has impacted movement of water between earth & atmosphere
  - Increased evaporation has increased atmospheric water vapor
- This can favor certain waterborne pathogens:
  - Some thrive with increased flooding or sea level surges due to dispersion and contamination (fecal pathogens, leptospirosis)
  - Some thrive in warmer water directly (Salmonella, vibrio, amoeba) or indirectly (Legionella in air conditioning units)
- Eg: Vibrio infection has increased globally
  - Outbreak of domestically acquired infections in Germany in 2018-2019 associated with increased temperatures in Baltic Sea
  - In Maryland there was 39% increase in average Vibrio infection incidence from 2006-12 vs. 2013-19
    - Same research group showed linear relationship between water temperature and V. vulnificus presence in Chesapeake



Semenza JC, Ko AI. N Engl J Med2023;389:2175-87
Brehm TT et al. Euro Surveill 2021; doi: 10.2807/1560-7917.ES.2021.26.41.2002041
Brumfield KD et al. Appl Environ Microbiol. 2023; doi: 10.1128/aem.00307-23
Morgado ME, et al. Environ Res 2024; doi: 10.1016/j.envres.2023.117940.

Summary thoughts on climate and infection

- How does it help us to understand how climate change may impact infectious diseases risk?
  - Climate change literature can feel heavy and leave providers feeling helpless
  - However, regardless of one's stance on climate change, knowledge is helpful!
    - Natural disasters can be associated with increased waterborne and invasive fungal infection so knowledge can lead to earlier diagnosis and better outcomes
    - Travel advice with awareness of shifting epidemiology (e.g. increased vibrio risk in areas previously with cooler water) can be helpful for infection prevention and earlier recognition of infection
      - This includes checking available public health resources about infection risk in certain locations even domestically

Updated Guidelines

Changes in *C. difficile* management

Clinical Case

- 76-year-old woman with COPD presents with recurrent profuse diarrhea and dehydration for 1 day
  - Recent medical history notable for community acquired pneumonia and COPD flare requiring admission 4 mo ago
    - Treated with levofloxacin and steroid pulse
    - Diarrhea developed at end of hospital stay→ stool testing positive for C. difficile
    - Treated with oral metronidazole for 14 days total (10 days of course after levofloxacin course had ended)
  - Diarrhea relapsed 2 more times, each within 2 weeks of stopping C. difficile treatment
    - First relapse treated with oral vancomycin x 10 days
    - Second relapse treated with 6 week taper oral vancomycin
      - Course ended 12 days ago

Clinical Case

- Past medical history is notable for COPD and treated breast cancer Medications: tiotropium, albuterol inhaler, Saccharomyces boulardii (“Florastor”), and tamoxifen
- Exam is notable for a thin elderly woman with dry mucous membranes; cardiovascular notable for tachycardia; abdomen is soft without significant tenderness
- Labs are notable for a WBC 15 and Cr 1.2
- She is admitted for hydration and assessment
- Stool testing is positive for C. difficile toxin and antigen

How should this recurrent episode of C. difficile be treated?

A. Oral metronidazole for 10-14 days
B. Fidaxomycin for 10 days
C. “Stool transplant”
D. Oral vancomycin for 10 days given with bezlotoxumab x1
E. Oral vancomycin taper for 6 weeks (again)

Clostridiodes difficile: Basics

- When and why did the name change?
  - *Clostridium difficile* changed names in 2016 based on microbiologic differences with other Clostridia
  - Trivia: it was originally assigned to a different genus that would have resulted in the name *Peptoclostridium difficile*→ careful thought led to name of new genus instead
- The incidence of *C. difficile* infection (CDI) decreased between 2011 and 2017, mostly related to a decrease in healthcare-associated infection
  - Burden of community acquired infection did not decline --accounts for ~50% of CDI
  - Also, no decline in risk of first relapse noted
  - Hospitalization for CDI declined
- Relapse after first course of treatment is common
  - Historically relapse is 13.5% among community-associated cases and 20.9% among healthcare-associated case

Editorial; Lancet Infect Dis. 2019;19:449.
Guh Y, et al. N Engl J Med 2020;382:1320-30.
Lessa FC, et al. N Engl J Med 2015;372:825-34

Recurrent C. difficile

- Why does C. difficile recur?
  - Active antibiotics (oral vancomycin, fidaxomicin) kill toxin producing bacteria but do not kill the spore form of C. difficile
  - Once antibiotics end the spore can germinate into toxin-producing bacteria
  - Alterations in microbiome from broad-spectrum antibiotics can favor spore germination
- Potential solutions to this conundrum
  - Shift to tailored antimicrobials (fidaxomicin>vancomycin>>metronidazole)
  - Tapered and pulsed vancomycin/fidaxomicin
  - Fecal microbiota transplantation (FMT)
    - Spore-based therapies (FMT 2.0)
  - Monoclonal antibodies
- Guidelines for CDI management updated in 2021 to better address high recurrence rate

P Feuerstadt, et al. N Engl J Med 2022;386:220-9
Johnson S, et al. Clin Infect Dis 2021;73:e1029-44.

Clinical Presentation	Recommended and Alternative Treatments	Comments
Initial CDI episode	Preferred: Fidaxomicin 200 mg given twice daily for 10 days	Implementation depends upon available resources
	Alternative: Vancomycin 125 mg given 4 times daily by mouth for 10 days	Vancomycin remains an acceptable alternative
	Alternative for nonsevere CDI, if above agents are unavailable: Metronidazole, 500 mg 3 times daily by mouth for 10–14 days	Definition of nonsevere CDI is supported by the following laboratory parameters: White blood cell count of 15 000 cells/μL or lower and a serum creatinine level <1.5 mg/dL
First CDI recurrence	Preferred: Fidaxomicin 200 mg given twice daily for 10 days, OR twice daily for 5 days followed by once every other day for 20 days	…
	Alternative: Vancomycin by mouth in a tapered and pulsed regimen	Tapered/pulsed vancomycin regimen example: 125 mg 4 times daily for 10–14 days, 2 times daily for 7 days, once daily for 7 days, and then every 2 to 3 days for 2 to 8 weeks
	Alternative: Vancomycin 125 mg given 4 times daily by mouth for 10 days	Consider a standard course of vancomycin if metronidazole was used for treatment of the first episode
	Adjunctive treatment: Bezlotoxumab 10 mg/kg given intravenously once during administration of SOC antibiotics[a]	Data when combined with fidaxomicin are limited. Caution for use in patients with congestive heart failure[b]
Second or subsequent CDI recurrence	Fidaxomicin 200 mg given twice daily for 10 days, OR twice daily for 5 days followed by once every other day for 20 days	…
	Vancomycin by mouth in a tapered and pulsed regimen	…
	Vancomycin 125 mg 4 times daily by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days	…
	Fecal microbiota transplantation	The opinion of the panel is that appropriate antibiotic treatments for at least 2 recurrences (ie, 3 CDI episodes) should be tried prior to offering fecal microbiota transplantation
	Adjunctive treatment: Bezlotoxumab 10 mg/kg given intravenously once during administration of SOC antibiotics[a]	Data when combined with fidaxomicin are limited. Caution for use in patients with congestive heart failure[a]
Fulminant CDI	Vancomycin 500 mg 4 times daily by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of vancomycin. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal vancomycin, particularly if ileus is present	Definition of fulminant CDI is supported by: Hypotension or shock, ileus, megacolon

Johnson S, et al. Clin Infect Dis 2021;73: e1029-44

Fidaxomicin– First Line

- A macrocyclic antibiotic with minimal absorption
  - Active against C. difficile but limited activity against common GI flora like Bacteroides spp.
- FDA approved for treatment of CDI in 2011 on basis of favorable study results
  - Louie et al. performed a randomized blinded trial of fidaxomycin vs. oral vancomycin for treatment of CDI in 629 people
    - Treatment duration: 10 days
    - Study outcomes: clinical cure 2 days after treatment, recurrence within 4 weeks, and cure without recurrence

Louie TJ, et al. N Engl J Med 2011;364:422-31.
Cornely OA, et al. Lancet Infect Dis 2012;12:281-9.
Guery B, et al. . Lancet Infect Dis. 2018;18:296-307

Fidaxomicin

- In subgroup analysis those with non-NAP1 strain who were treated with fidaxomicin were significantly less likely to relapse (7.8% vs. 25.5%)
- No difference in the relapse rate of those with NAP1 strain of C. difficile

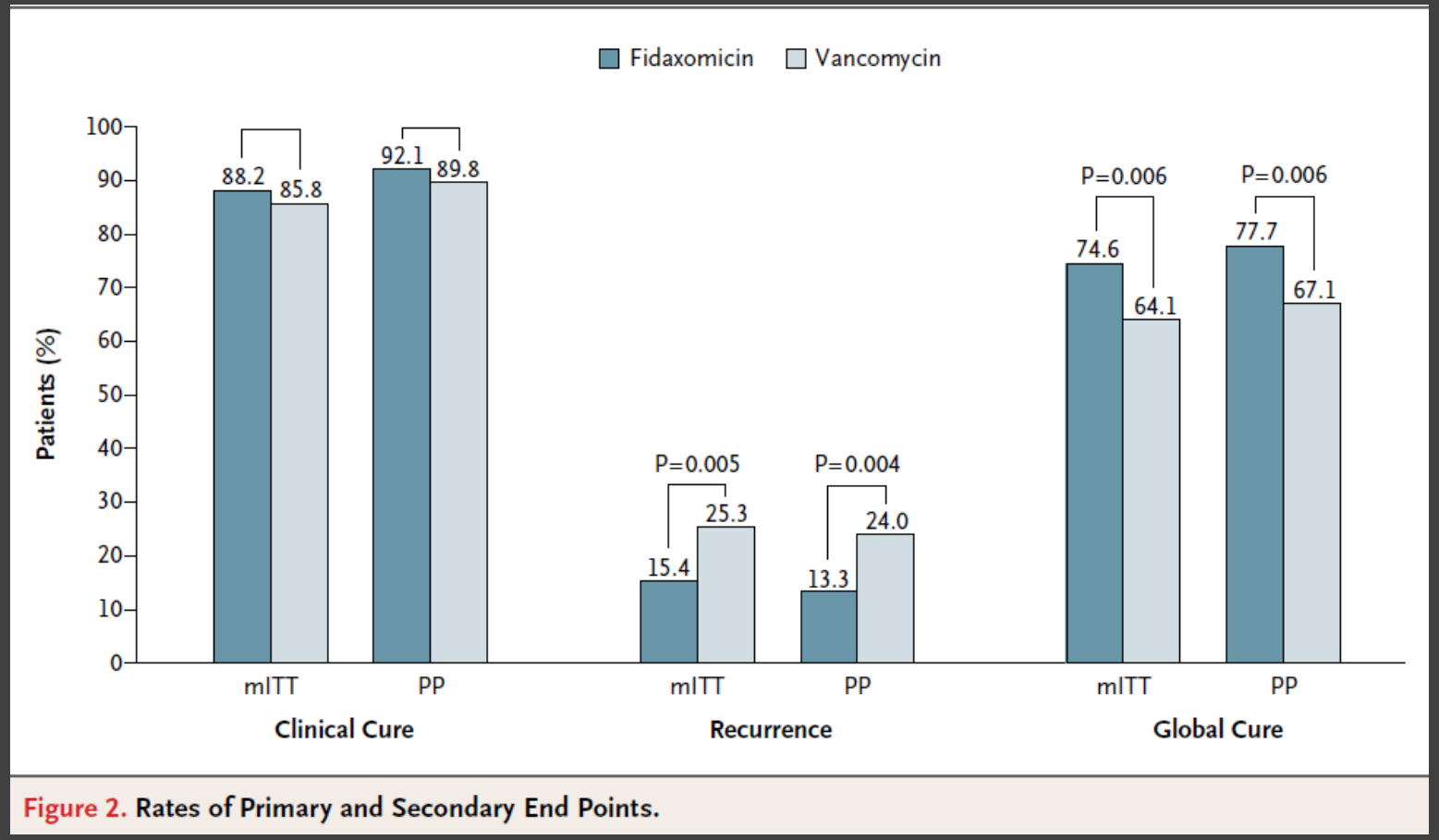


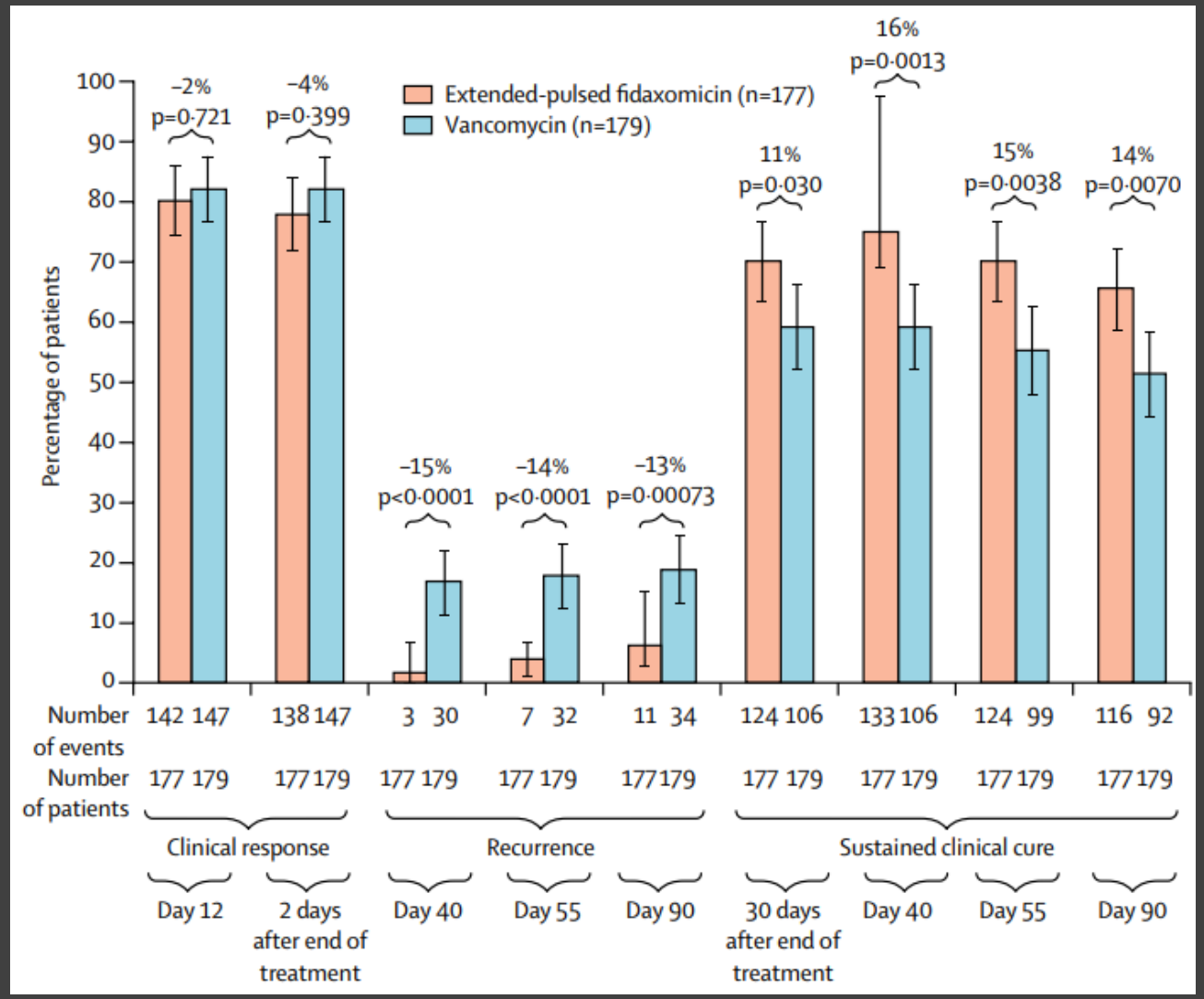
Figure 2. Rates of Primary and Secondary End Points.

Louie TJ, et al. N Engl J Med 2011;364:422-31.

Other considerations with Fidaxomycin

Tapered dosing?

- EXTEND study assessed response in adults >60 with CDI
  - Vancomycin x10d vs. fidaxomicin 200 mg BID x5d then 200 mg Q48hours through day 25
  - Notable for exceedingly low recurrence rates



Guery B, et al. . Lancet Infect Dis. 2018;18:296-307
Goodrx.com; accessed 4/23/2024

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Cost

- The approximate cost of fidaxomicin 200 mg po BID x10 days is ~$4800
- The approximate cost of oral vancomycin 125 mg po 4 times per day x10 days is ~ $50

Guery B, et al. . Lancet Infect Dis. 2018;18:296-307
Goodrx.com; accessed 4/23/2024

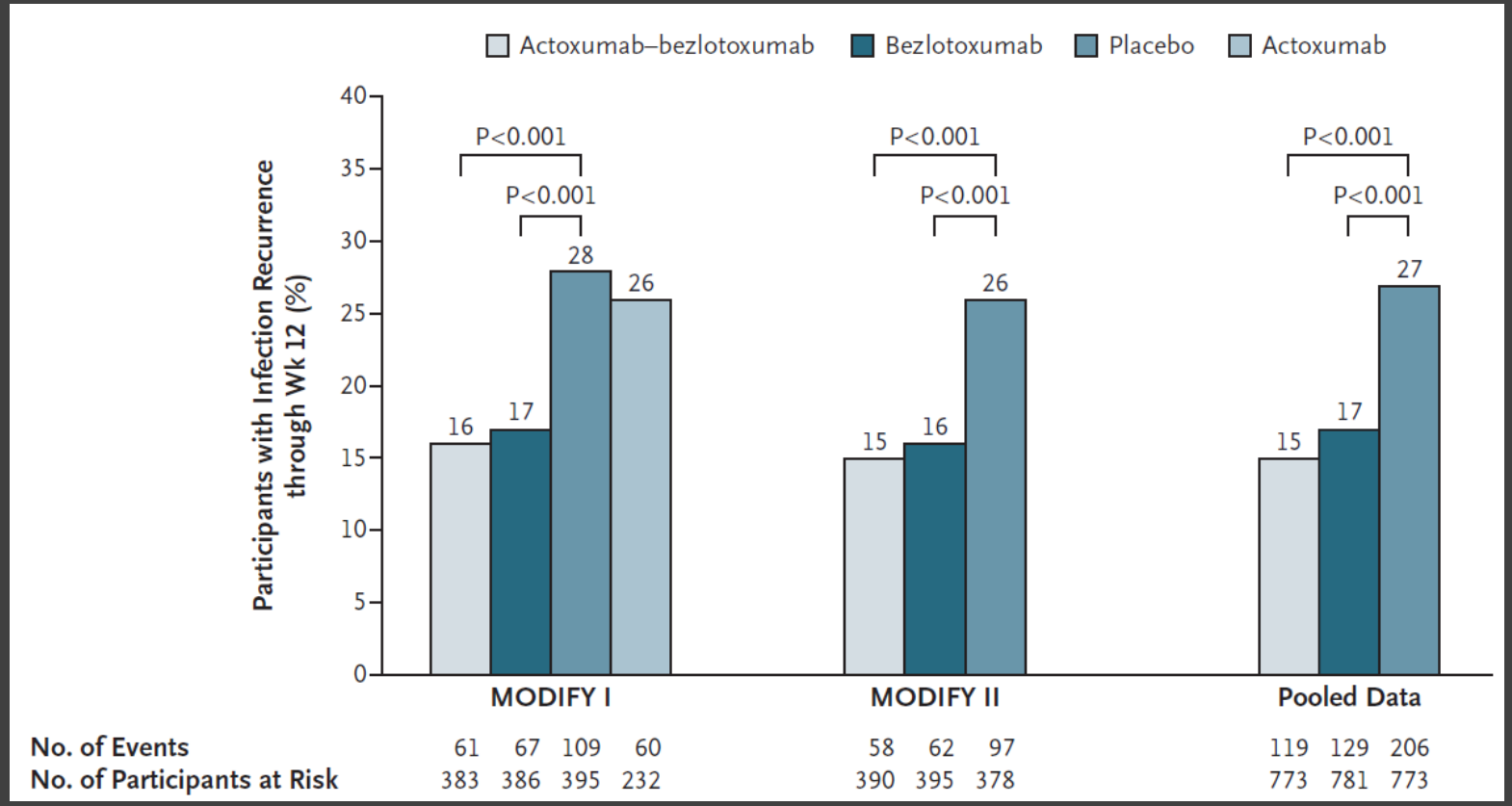
Bezlotoxumab— Adjunctive

- Human monoclonal antibody to toxin B of C. diff
  - Blocks binding of toxin B to cells
- Approved by FDA for management of CDI based on two placebo-controlled studies in 2016
  - Studies included actoxumab, antibody to Toxin A
- Studies included 2580 patients with CDI treated with standard antibiotics and study drug (infused hour x1)
  - MODIFY I: randomize to bezlotoxumab vs. actoxumab + bezlotoxumab vs. actoxumab vs. placebo
  - MODIFY II: randomize to bezlotoxumab vs. actoxumab + bezlotoxumab vs. placebo
  - Study Outcomes: New CDI within 12 weeks after therapy

Wilcox MH, et al. N Engl J Med. 2017;376:305-17
Bartlett JG. N Engl J Med. 2017;376:381-2.

Bezlotoxumab

- Number needed to treat to prevent one episode recurrent CDI was 10, but declined to 6 among patients older than 65 and those with previous CDI
- Adverse events similar between placebo and bezlotoxumab groups
  - More serious adverse events seen in patients with baseline heart failure who received bezlotoxumab



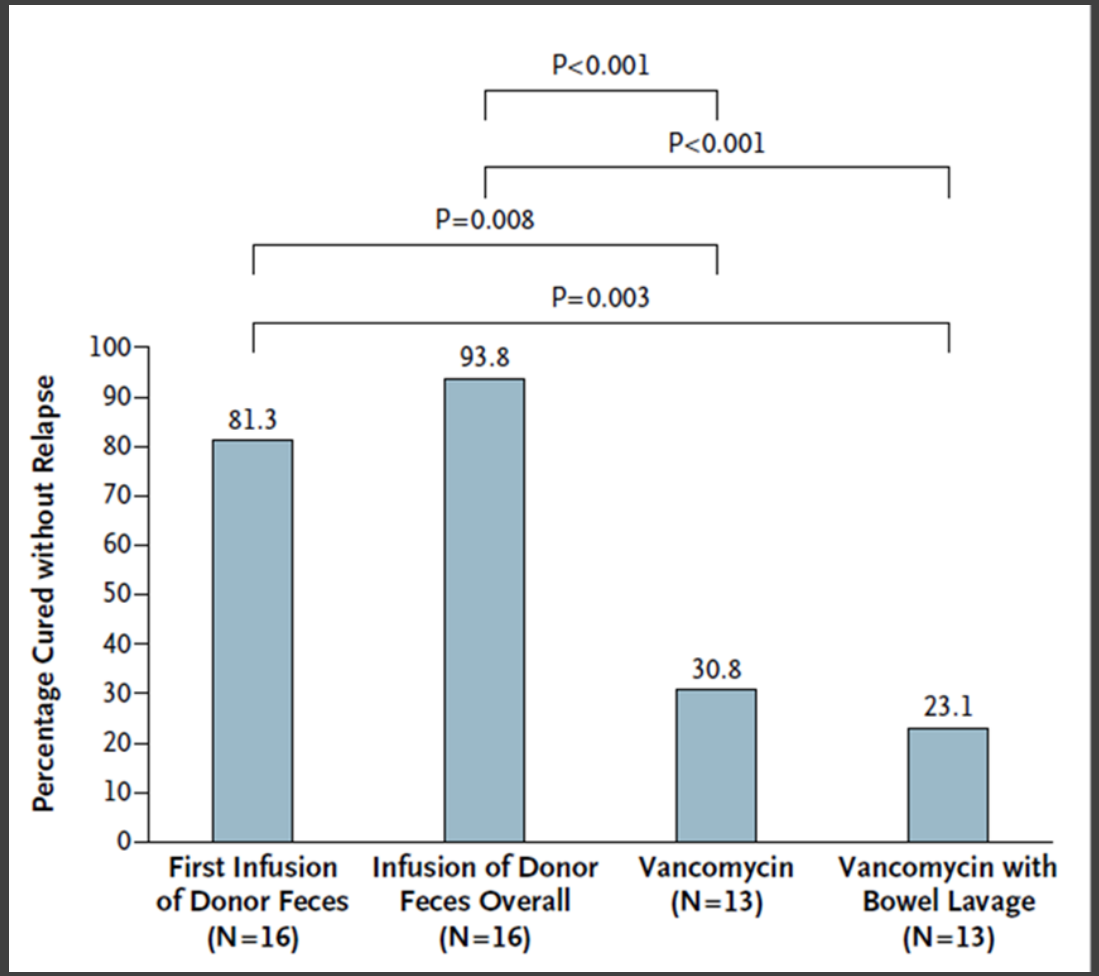
- In a post-hoc analysis patients with a risk factor for recurrence including age >65, at least 1 recurrence, immunocompromise or severe C. diff were more likely to benefit
  - Patients with 3 or more risk factors benefitted most and patients with no risk factors did not benefit

Wilcox MH, et al. N Engl J Med. 2017;376:305-17
Gerding DN, et al. Clin Infect Dis 2018;67:649–56
Johnson S, Gerding DN. Clin Infect Dis 2019;68:699–704

FMT: use of healthy donor stool to restore depleted/altered microbiota

Supporting Evidence

- In 2013 van Nood, et al. performed randomized study of FMT (by NGT) in adults with recurrent CDI after appropriate antibiotic course
  - Compared vancomycin 4 days then bowel lavage & infusion of donor stool vs. 14 days oral vancomycin vs. 14 days oral vancomycin with bowel lavage



Van Nood E, et al. N Engl J Med 2013;368:407-15.
DeFillip Z, et al. N Engl J Med 2019; 381:2043-50.
Alang N, Kelly CR,. Open Forum Inf Dis.2015 : 10.1093/ofid/ofv004
https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/safety-alert-regarding-use-fecal-microbiota-transplantation-and-additional-safety-protections

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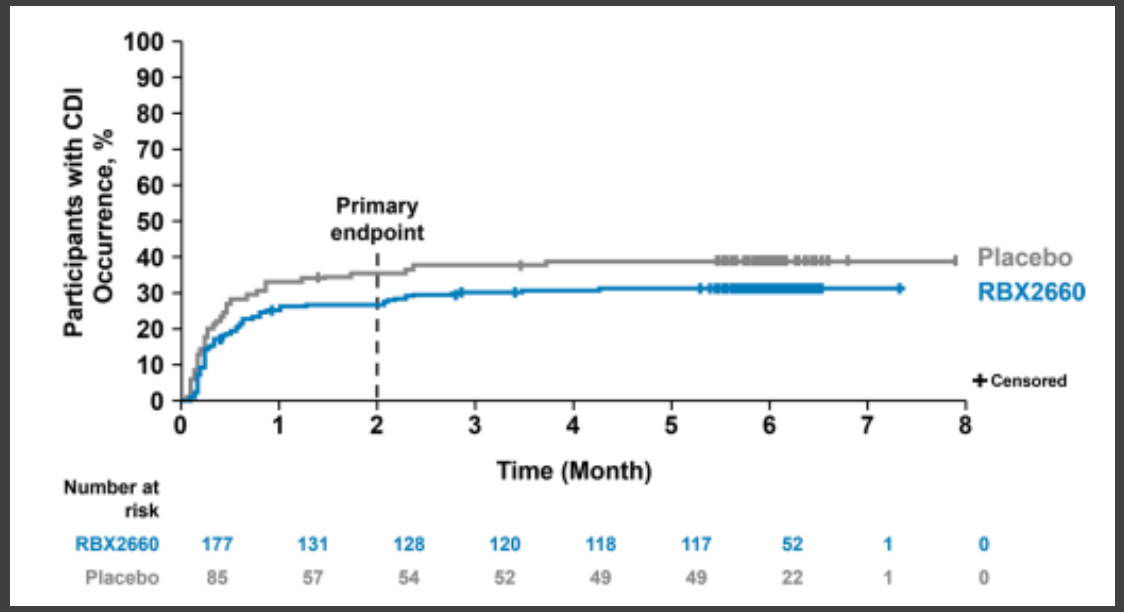
Potential Risks

- The donor problem: FMT can potentially transmit
  - Blood-borne pathogens
  - Enteric pathogens (eg. Bacteria, parasites and viruses), COVID
  - Food allergens
- Other risks include impact on metabolic status
  - Unintentional weight gain reported

Van Nood E, et al. N Engl J Med 2013;368:407-15.
DeFillip Z, et al. N Engl J Med 2019; 381:2043-50.
Alang N, Kelly CR,. Open Forum Inf Dis.2015 : 10.1093/ofid/ofv004
https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/safety-alert-regarding-use-fecal-microbiota-transplantation-and-additional-safety-protections

FMT enema: RBX2660

- Live “biotherapeutic” agent that is FDA approved for prevention of recurrent CDI in adults with relapsed CDI
- Khanna, et al. reported a randomized blinded trial of RBX2660 vs. placebo
  - Analysis combined previous phase 2 and new phase 3 data with Bayesian modeling
- Study included adults with ≥2 episodes of CDI with another episode of CDI for which standard antibiotics were prescribed
- Primary endpoint no recurrence within 8 weeks

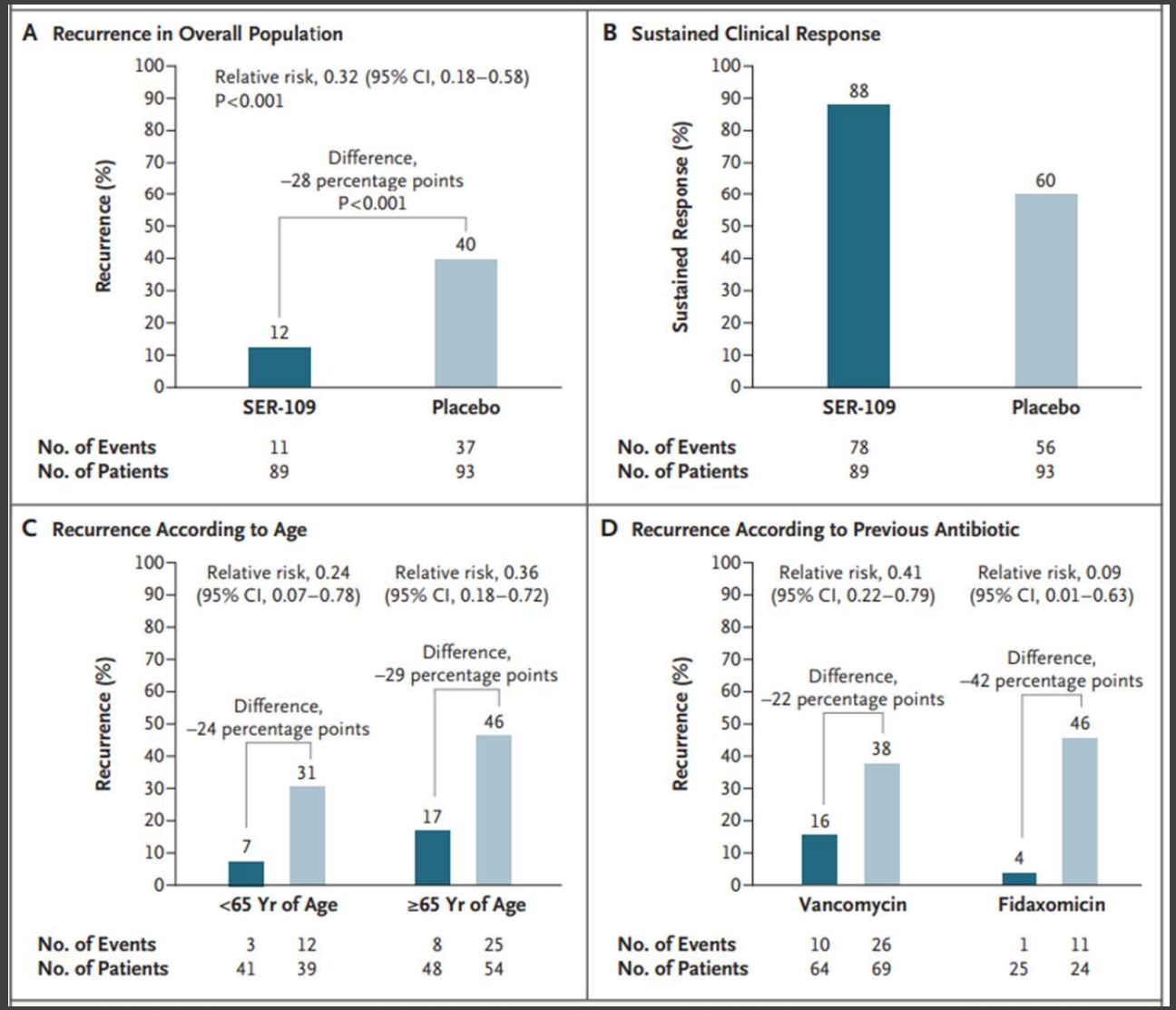


- Treatment success achieved in 70% vs. 58% in RBX2660 vs. placebo and the difference was sustained over 6 months
- Adverse events were most common in first two weeks and were most often mild GI symptoms
  - There were more adverse events in the RBX2660 group than placebo
- Cost: ~$9000 for a single dose

Khanna S, et al. Drugs 2022;82:1527–1538
Goodrx.com; accessed 4/23/2023

FMT 2.0: Spore-based therapies—SER-109

- FDA approved for prevention of recurrent CDI in adults with recurrent CDI
- Feuerstadt et al. reported results of a phase III trial of SER-109
  - SER-109 is encapsulated spores isolated from donor stool after processing with ethanol (improved safety of product)
- Study included adults with **≥ 3 episodes** CDI within 1 year treated with 10-21 days of standard antibiotics
- Randomized to SER-109 (4 capsule po daily x3 days) vs. placebo
- Primary outcome: C. diff recurrence within 8 weeks of therapy
- Single arm phase III study showed recurrence rates of 8% in patients with first relapse
- Cost: ~$19,000 for a single course



P Feuerstadt, et al. N Engl J Med 2022;386:220-9
Sims MD, et al. JAMA Network Open. 2023;6:e2255758
https://www.drugs.com/price-guide/vowst; accessed 4/23/2024

New Antimicrobials

Ibrexafungerp and Oteseconazole

Clinical Case

- 42-year-old healthy woman presents for follow up after completing her most recent treatment course for vulvovaginal candidiasis (VVC) with intravaginal teraconazole cream
  - Her symptoms have resolved completely
  - She reports that this was the third time she has had VVC in the last year and she asks if there is a way to prevent future recurrence
- Past history is notable for symptomatic fibroids s/p hysterectomy 1 year ago and obesity
- Medications include a multivitamin
- Social history is notable for being sexually active with her male partner

Optimal treatment for recurrent VVC for this patient includes:

A. Start Fluconazole 150 mg po weekly x 6 months
B. Treat the partner for yeast infection
C. Start Ibrexafungerp 300 mg po BID x 2 doses given weekly for 6 months
D. Start Oteseconazole 150 mg po daily x7 days followed by weekly x 11 weeks
E. Terbinafine 250 mg po daily x12 weeks

Vulvovaginal candidiasis (VVC)

- VVC is a common diagnosis impacting 75% of women at least once during their lifetime
  - Most common microbiological cause: C. albicans >85%
  - Some research suggests women with higher BMI and black women are disproportionately affected
- Gold standard diagnosis is culture-based, but clinical diagnosis or use of wet prep is common
  - Newer PCR-based assays available with good sensitivity, but not all commercial assays available are FDA cleared
- Treatment options include various azole antifungal formulations
  - Special considerations: treatment in pregnancy limited to topical therapies– fluconazole associated with craniofacial and cardiac congenital abnormalities

Table 1. Recommended Regimens for Treatment of Vulvovaginal Candidiasis

Regimen	Dosing
Over-the-counter intravaginal agents:	
Clotrimazole 1% cream	5 g intravaginally daily for 7–14 days
Clotrimazole 2% cream	5 g intravaginally daily for 3 days
Miconazole 2% cream	5 g intravaginally daily for 7 days
Miconazole 4% cream	5 g intravaginally daily for 3 days
Miconazole 100 mg vaginal suppository	One suppository daily for 7 days
Miconazole 200 mg vaginal suppository	One suppository for 3 days
Miconazole 1200 mg vaginal suppository	One suppository for 1 day
Tioconazole 6.5% ointment	5 g intravaginally in a single application
Prescription intravaginal agents:	
Butoconazole 2% cream (single dose bioadhesive product)	5 g intravaginally in a single application
Terconazole 0.4% cream	5 g intravaginally daily for 7 days
Terconazole 0.8% cream	5 g intravaginally daily for 3 days
Terconazole 80 mg vaginal suppository	One suppository daily for 3 days
Oral agent:	
Fluconazole 150 gm	Single dose

Nyirjesy P, et al. Clin Infect Dis 2022;74:S162–8.
Workowski KA, et al. MMWR Recomm Rep. 2021;70:1–187
Sobel JD, et al. NEJM Evid 2022;1
Sobel JD. Clin Infect Dis. 2023;76:783-5.
Goje O, et al. J Womens Health. 2023;32:178-183.

Recurrent VVC

- Definition of recurrent VVC: 3 or more episodes of VVC in 12-months
  - Less common than VVC but difficult to treat
- Treatment is typically a prolonged fluconazole course 150-200 mg given every 72 hours for 3 doses
- Suppressive therapy aimed at reducing colonization can be used
  - Fluconazole 150 mg po weekly x 6 months
  - Fluconazole 200 mg weekly x2 months followed by every other week for 4 months then monthly
- Recurrence is common after suppression ends
- Infection with resistant Candida species (*C. glabrata*) or development of resistance can be a problem
- This condition is particularly difficult to manage in pregnancy

Sobel JD, et al. NEJM Evid 2022;1
Sobel JD. Clin Infect Dis. 2023;76:783-5.
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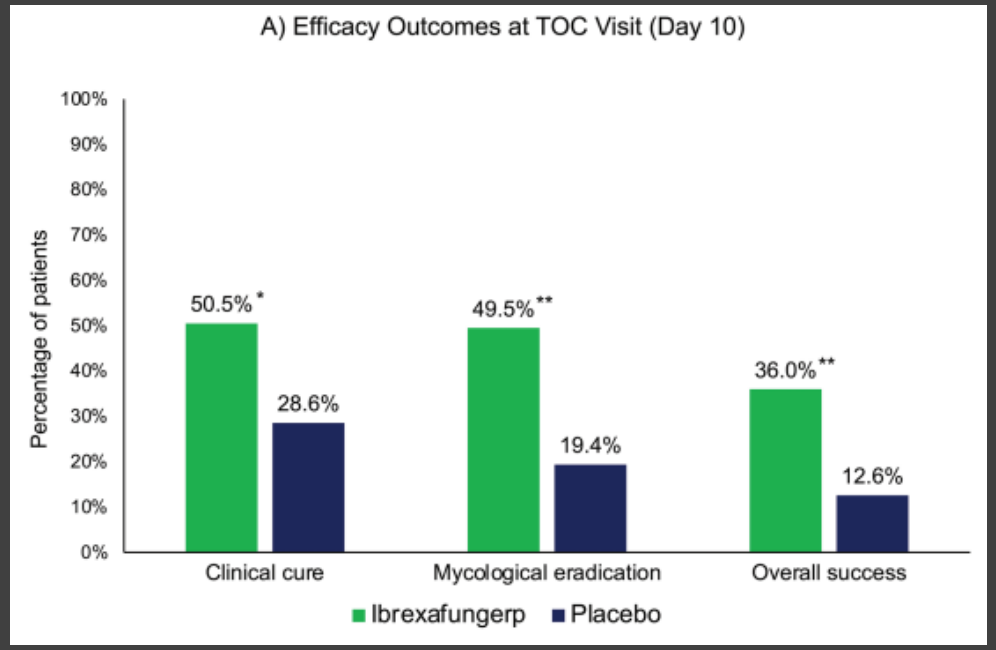
Workowski KA, et al. MMWR Recomm Rep. 2021;70:1–187

Ibrexafungerp

- Fungicidal oral antifungal agent that inhibits glucan synthetase (inhibits cell wall production) with spectrum of similar to echinocandins
- FDA approved for treatment of:
  - Episodic VVC (2021) based on two clinical trials
    - VVC treated with ibrexafungerp 300 mg po BID x1 day
  - Recurrent VVC (2022)
    - Recurrent VVC treated with ibrexafungerp 300 mg po BID on day 1 followed by weekly dosing for 24 weeks
- Why is the cure rate so low?
  - FDA changed VVC clinical trial parameters in 2019 to require **placebo** comparison and 'complete' clinical response
  - Unclear how this works relative to fluconazole (older studies used different parameters)
- Side effects include diarrhea, nausea and other GI symptoms that appear to be dose-dependent
- Precautions
  - Unclear if it is safe in pregnancy
  - It's expensive—$530-$608 for single 1 day course



	Ibrexafungerp	Placebo
ITT- no mycologically proven, presumed or suspected rVVC	n=130	n= 130
24 weeks	**65%**	**53%**
36 weeks	**58%**	**46%**
Per Protocol- no mycologically proven recurrence	n=94	n=88
24 weeks	**82%**	**73%**
36 weeks	**73%**	**68%**

Schwebke JR, et al. Clin Infect Dis 2022;74:1979–5.
Goje O, et al. J Womens Health. 2023;32:178-183.
Goje O, et al. IDSOG Annual Meeting. 4 August 2022, Boston, MA.
https://www.goodrx.com; 4/20/2024

Oteseconazole

- Tetrazole antifungal with more targeted activity against fungal CYP51 (ergosterol synthesis enzyme) than other azoles
  - Broader spectrum of activity against resistant Candida spp.
  - LONG half life (138 days)
- FDA approved for recurrent VVC based on two similar trials
  - Participants: ≥3 VVC episodes in 12 months with new episode treated with fluconazole induction followed by:
    - Oteseconazole 150 mg daily x7 days then weekly for 11 weeks *or* Placebo
  - No significant safety concerns
- Non-FDA approved indication
  - Recent Chinese study assessed oteseconazole vs. fluconazole for severe VVC →superior
- Precautions
  - Not known to be safe for pregnancy/people of childbearing potential→ contraindicated
  - Expensive ($2812-3232 for 6 months)

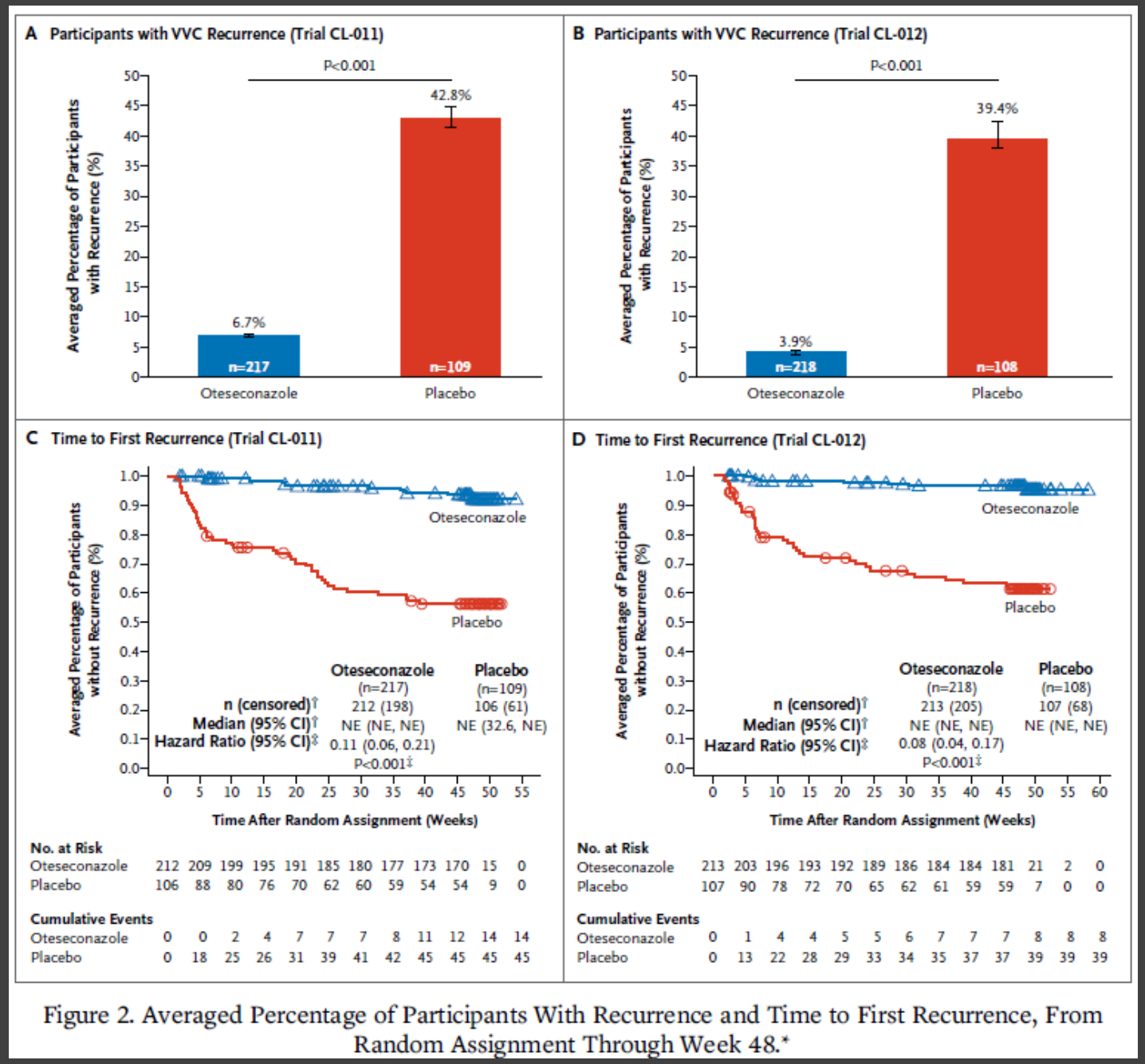


Figure 2. Averaged Percentage of Participants With Recurrence and Time to First Recurrence, From Random Assignment Through Week 48.*

Sobel JD, et al. NEJM Evid 2022;1.
Wang X, et al. Antimicrob Agents Chemother 2024; doi: 10.1128/aac.00778-23
https://www.goodrx.com; accessed 4/21/2024

Disclosures

- I have research funding from Cidara, F2G, Scynexis and GSK
- I have been a consultant for F2G, Melinta, Pfizer, Roche and Seres therapeutics

Selected References

- Climate change and infection
  - Phillips MC, LaRocque RC, Thompson GR. JAMA 2024; doi: 10.1001/jama.2023.27724
  - Semenza JC, Ko AI. N Engl J Med2023;389:2175-87
- *Clostridiodes difficile* infection
  - Johnson S, et al. Clin Infect Dis 2021;73:e1029-44
- New drugs for vulvovaginal candidiasis
  - Sobel JD. Clin Infect Dis. 2023;76:783-5.