

# Recurrent C. diff: is it time to change?

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# Disclosures

- None, other than I don't appreciate having to call it *clostridioides* instead of *clostridium*



# Case 1

- 90 year old male with a history of diarrhea dating back to 2022 who is admitted for ongoing diarrhea
- He also has a history of pharyngeal dysphagia requiring dilations and PEG placement and he receives tube feeds
- He had a colonoscopy in 2022 that was normal other than polyps with plan for repeat colonoscopy in 2025 but it was cancelled because he ate
- He was admitted 3 weeks ago for report of worsening diarrhea, C. diff PCR +, toxin negative, multiplex PCR panel also + for shigella and norovirus
- He was given 10 days of PO vancomycin without improvement and was seen again in the ER 2 weeks later, C. diff and multiplex PCR at that time negative
- Today he continues to complain of watery diarrhea, 5-8 episodes a day, abdominal cramping, poor PO intake, weakness, fecal incontinence

# Repeat testing for C. diff – what is recommended by IDSA?

- “Do not perform repeat testing (within 7 days) during the same episode of diarrhea...”
- “For symptomatic patients with a high clinical suspicion of CDI but a negative CDI test, particularly those in whom symptoms worsen, repeat testing should be considered.”
  - Recommendations are based on this study: Cardona DM, Rand KH. Evaluation of repeat Clostridium difficile enzyme immunoassay testing. J Clin Microbiol. 2008 Nov;46(11):3686-9
  - Toxin EIA, 8,256 tests from 3,112 patients
  - Of the 3,749 initially negative patient tests, 96 were positive upon repeat testing within 10 days of the first test. Of repeat tests, 0.9% repeated on day 0 (same day as the first test), 1.8% on day 1, 3.8% on day 2, 2.6% on day 3, 5.4% on days 4 to 6, and 10.6% on days 7 to 10 were positive.
  - Of initially positive patients, 91% were positive upon repeat testing on day 0, 75% on day 1, and 58% on day 2, to a low of 14% on days 7 to 10
- “Empiric treatment, that is without confirmatory testing of suspected recurrence, is discouraged, as this may be unnecessary and indeed possibly harmful to microbiome restoration.”

# Repeat testing

- “Ideally, in the absence of clear changes to the clinical presentation of suspected CDI (ie, change in character of diarrhea or new supporting clinical evidence), repeat testing should not be performed.”
- “Given that recurrent CDI occurs commonly, a recurrence of symptoms following successful treatment and diarrhea cessation should be assessed by repeat testing.”
- “Last, there is no clinical value in repeat CDI testing to establish cure; >60% of patients may remain *C. difficile* positive even after successful treatment.”
- IDSA also notes that many who are felt to have recurrent CDI do not have recurrent disease despite high rates of repeated infection
- In summary:
  - If you have negative initial testing but a high clinical suspicion of CDI, consider repeating
    - Hospitals discourage this due to HAI concerns
    - This recommendation was based on a study with single step testing and the study itself recommended against repeat testing
  - If you have recurrence of symptoms more than 7 days after the completion of therapy, repeat testing is reasonable
  - Do not repeat testing for cure
  - Studies about repeat testing are primarily looking at EIA testing alone – the sensitivity of this test is known to be poor, combination testing is preferred



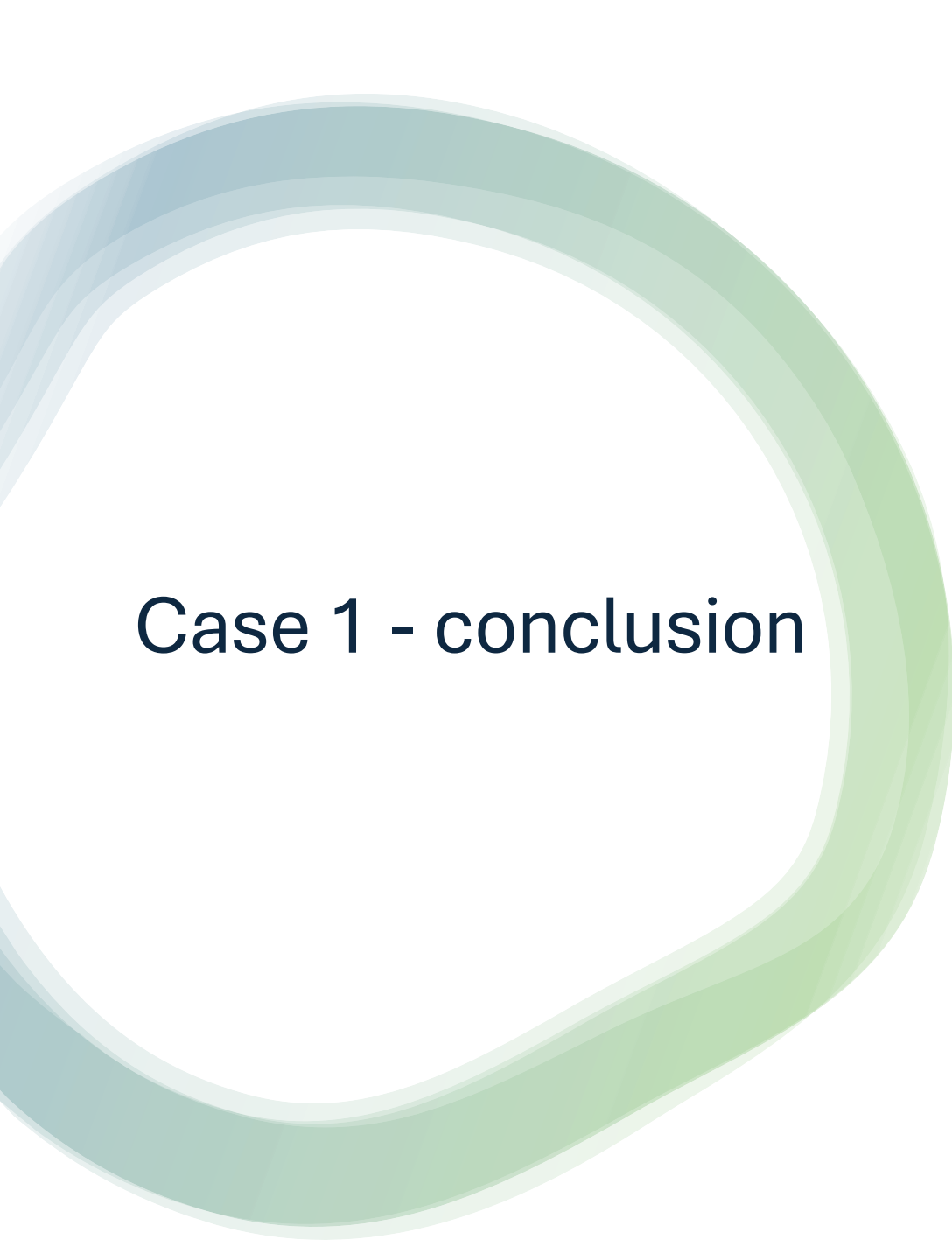
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## How does repeat testing impact how we counsel patients?

- Appropriately obtained testing helps direct next steps in management
- Negative testing can avoid unnecessary antibiotics
- Testing indicating colonization can help triage potential recurrences when future antibiotics are required
  - Continued colonization may help indicate the need for prophylaxis
    - Maraolo et al. review and meta analysis revealed that oral vancomycin ppx provides a protective effect for those at high risk of either primary or recurrent CDI
    - Keating et al. in JAMA 2025, RCT of 81 patients, 43% rCDI in vancomycin group vs 57% in control, study underpowered
- Continued positive PCR with negative GDH/antigen testing (colonization) can cause patient anxiety; providers should be cautious with repeated testing in this setting
  - Discussion with family/caregivers may be prudent

# How often should we be recommending repeat testing?

- Guidelines would suggest *not* for ongoing diarrhea, yet proving lack of colonization (when off antibiotics) is very helpful
- Barbut F, et al. Epidemiology of recurrences or reinfections of Clostridium difficile-associated diarrhea. J Clin Microbiol. 2000 Jun;38(6):2386-8
  - New acquisition could occur as quickly as 10 days (for same or new strains) but as far out as 6 months (for same strains)
  - This would suggest that repeated testing several times within a year, depending on symptoms, might be reasonable



## Case 1 - conclusion

- Primary team decided to repeat stool testing for C diff and multiplex panel – both are negative
- Cholestyramine is restarted
- Recommended for outpatient GI follow up for repeat colonoscopy



## Case 2

- 57 year old female with history of SMA syndrome and prior cholecystectomy and gastrojejunostomy for duodenal stricture who is referred for recurrent CDI
- Diarrhea started abruptly 6 months ago after a course of antibiotics for cystitis
- Diarrhea is watery, multiple episodes per day with fecal incontinence; she has associated poor PO intake, weight loss, and depression
- Initial PCR testing was positive and she was given a course of vancomycin without symptomatic improvement; over the course of the next two months she received ongoing courses of vancomycin and fidaxomicin without improvement
- 4 months ago she received Rebyota with 1 week of symptomatic resolution then recurrence
- 2 weeks ago she completed a course of Vowst without symptomatic improvement

# What constitutes recurrent CDI?

- Defined as an episode of CDI occurring within 8 weeks of a previous episode when there was documented return to normal.
  - Increasing age, PPI/H2 blockers, severe underlying disease, ongoing use of antibiotics, inability to mount an immune response all noted to be a risk factor for recurrence
- 15% to 30% of patients who initially respond to antimicrobial therapy experience recurrence
  - One study looking at 18 patients with recurrence demonstrated new strains in 33%
  - Second study looking at 93 patients with recurrence demonstrated new strains in 48%
  - Other estimates are up to 75% of recurrences are with new strains
  - Conclusion that recurrence (rather than relapse) may be underestimated as patients may clear and acquire the same strain
  - Delayed recurrence (beyond 8 weeks) occurs in ~ 20% of patients
- After the first recurrence has improved, the risk of further recurrence significantly increases.
  - A second recurrence rate of 40% has been reported among patients with resolved first recurrence.
  - The subsequent recurrence rate of patients who have already recurred more than twice is approximately 45% to 65%.

# Why are we recurring?



## **Our population is aging**

Several studies have demonstrated that age > 65 increases the chance of recurrence



## **Antimicrobial stewardship in the community has been poor**

From 2000-2015 there was a 39% increase in antibiotic consumption/1000 individuals/day

Globally, more people can afford antibiotics; physician education around responsible use has not considerably increased

Increasing antibiotic use in agriculture changes ongoing human antibiotic exposure

- One study estimated <102.218 ng/kg bw/day of antibiotic from food exposure which individually may be negligible but cumulative exposure has noticeable impact

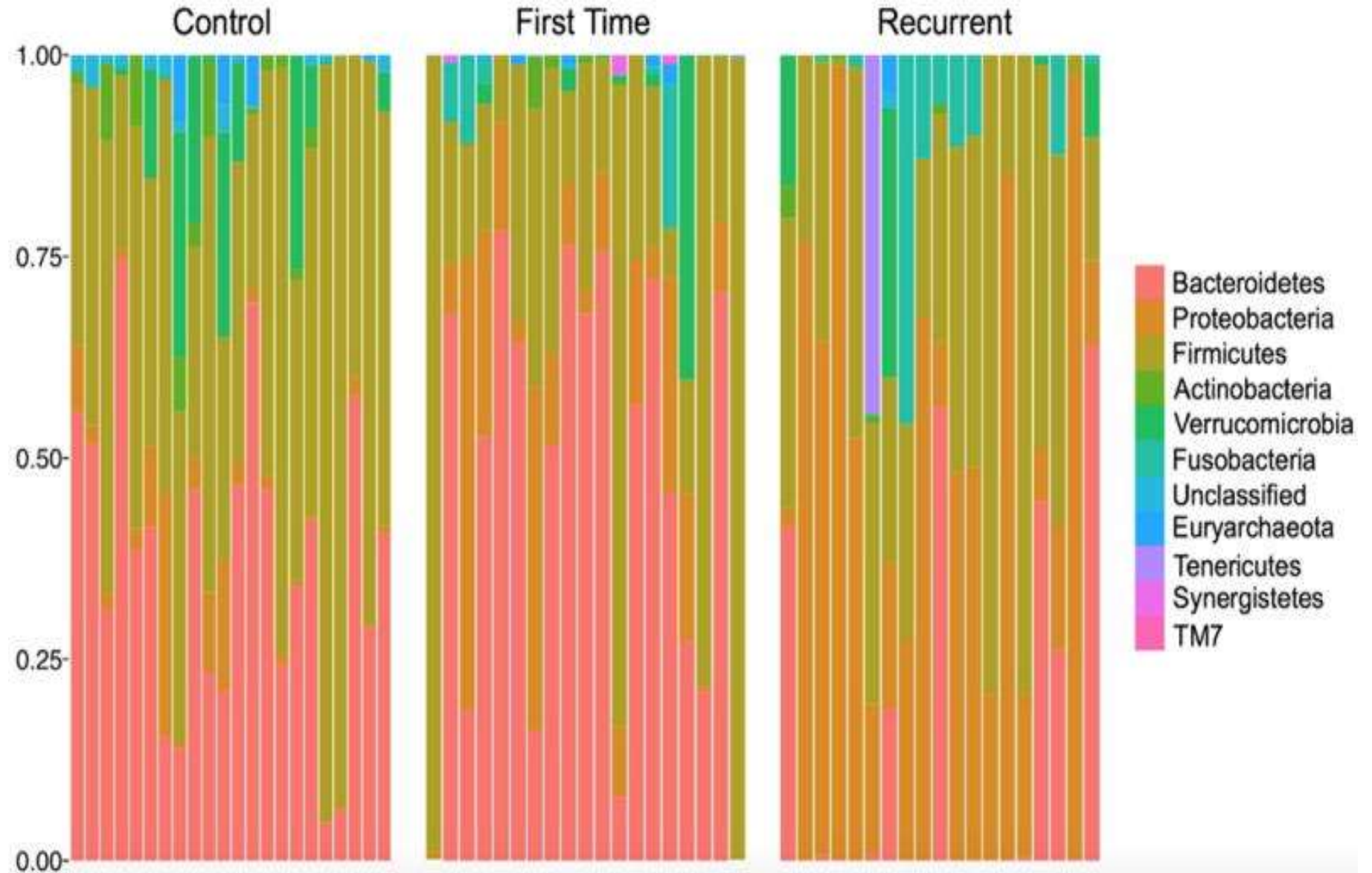


# Why are we recurring?

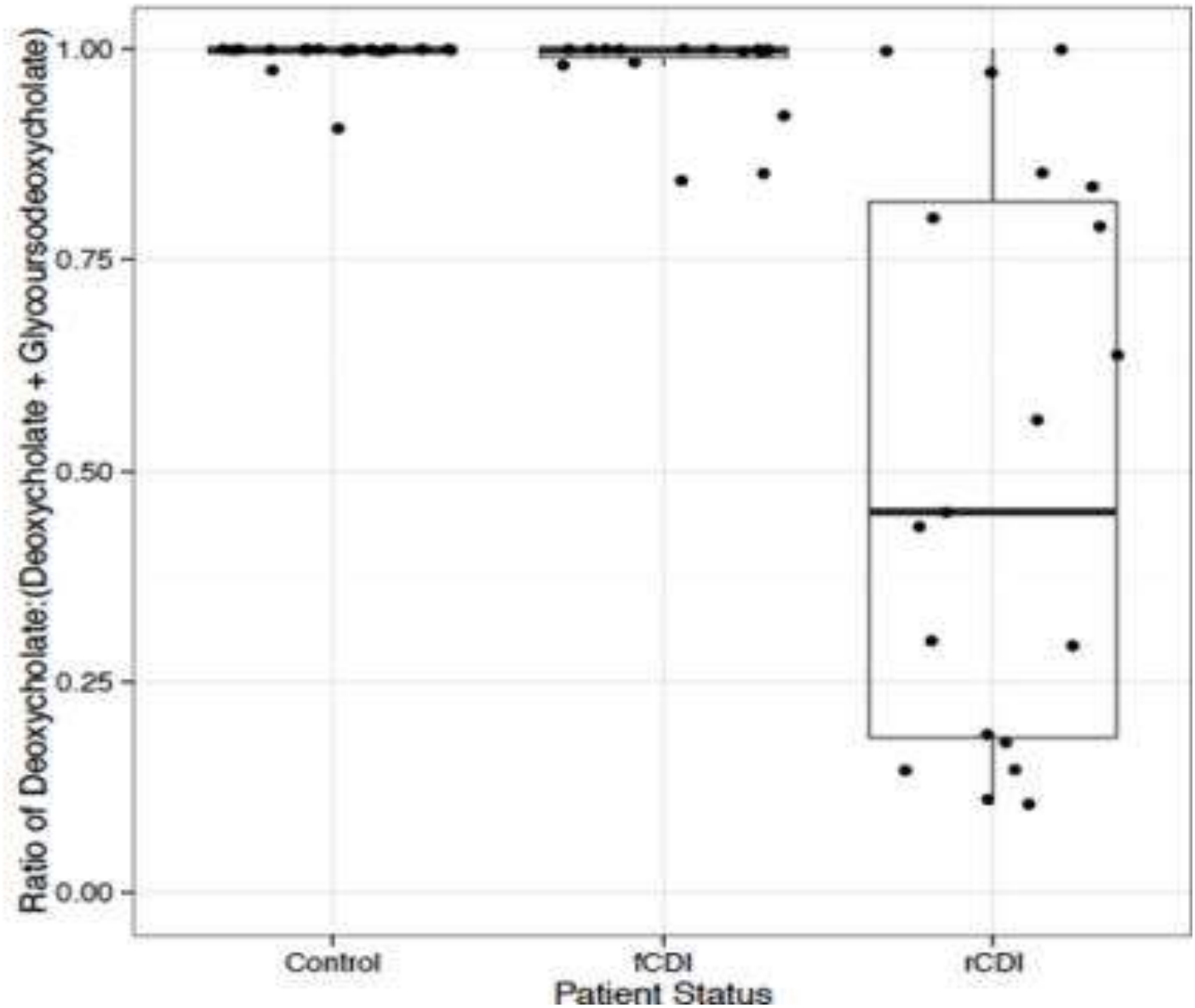
- Alterations in the gut: bile acids and diet
  - Allegretti JR, et al. demonstrated that antibiotics alter gut flora leading to inability to convert primary to secondary bile acids
    - 2ary bile acids were significantly elevated in control patients compared to CDI patients
    - 2ary bile acids were significantly elevated in initial infection compared to recurrence
    - 1ary bile acids were significantly elevated and 2ary bile acids were significantly lower in rCDI patients compared to controls
  - Alterations in diet can impact this as well
    - Low fat, high fiber diets may decrease fecal bile acids in humans – the opposite has been demonstrated in murine studies
    - A randomized controlled trial by Deehan et al. comparing the effects of 3 resistant starches (maize, potato, and tapioca) showed dose-dependent increases in butyrate and propionate in persons who consumed maize or tapioca
      - Butyrate has been demonstrated in mouse models and humans to be protective against CDI
  - Probiotics are controversial
    - Foley MH, et al. 2025. Differential modulation of post-antibiotic colonization resistance to *Clostridioides difficile* by two probiotic *Lactobacillus* strains – one strain improved CDI resistance while the other promoted infection in a mouse model
    - Suez J, et al. Post-Antibiotic Gut Mucosal Microbiome Reconstitution Is Impaired by Probiotics and Improved by Autologous FMT. *Cell*. 2018 Sep 6;174(6):1406-1423.e16 - probiotics delayed microbiome stabilization.

## Changes in stool flora between controls, first CDI and recurrent CDI

Allegretti JR, et al. Recurrent *Clostridium difficile* infection associates with distinct bile acid and microbiome profiles. *Aliment Pharmacol Ther.* 2016 Jun;43(11):1142-53.

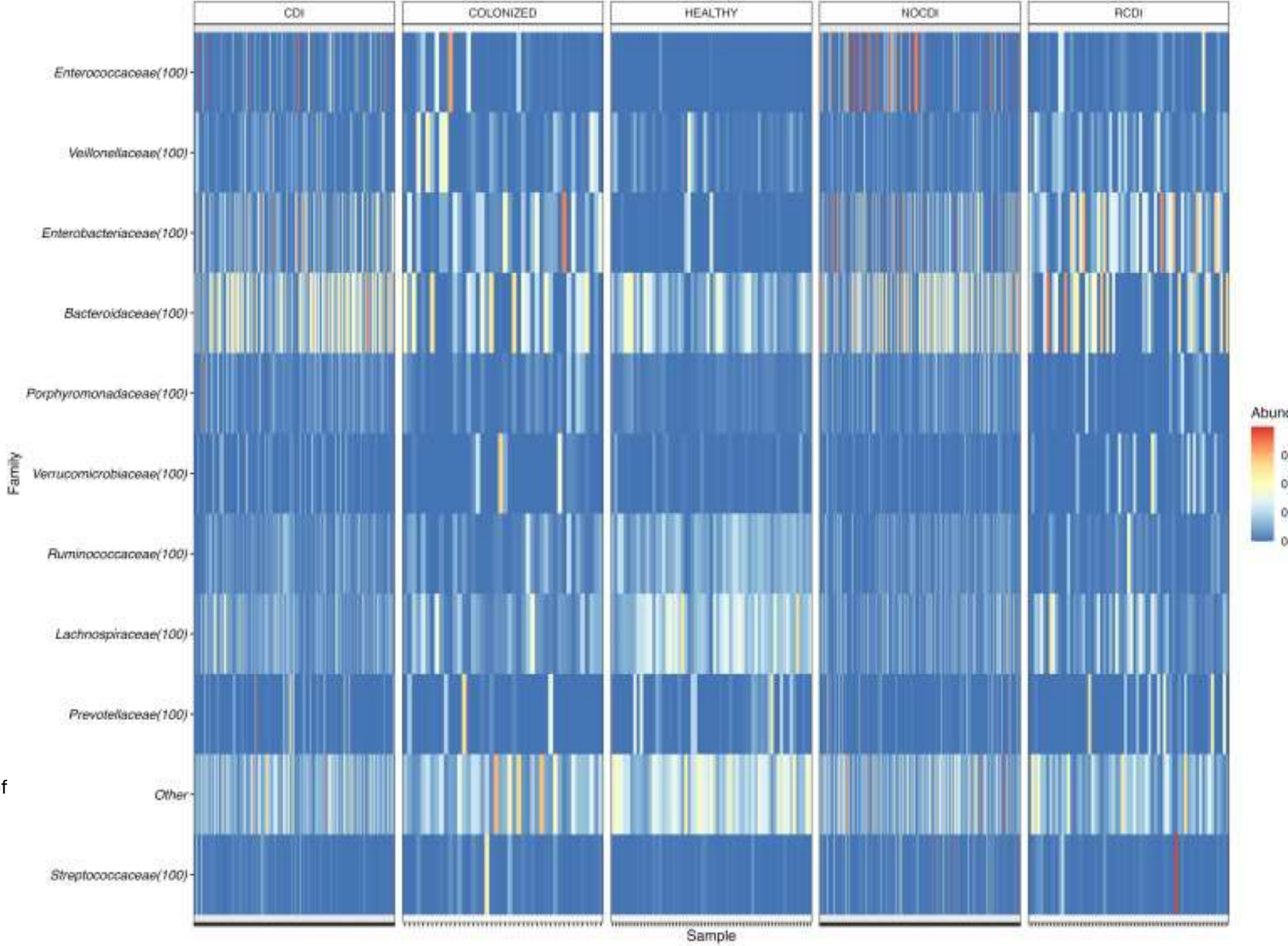


Ratio of deoxycholate to glyoursodeoxycholate and deoxycholate, which was found to be the most important predictor variable in the random forest model.



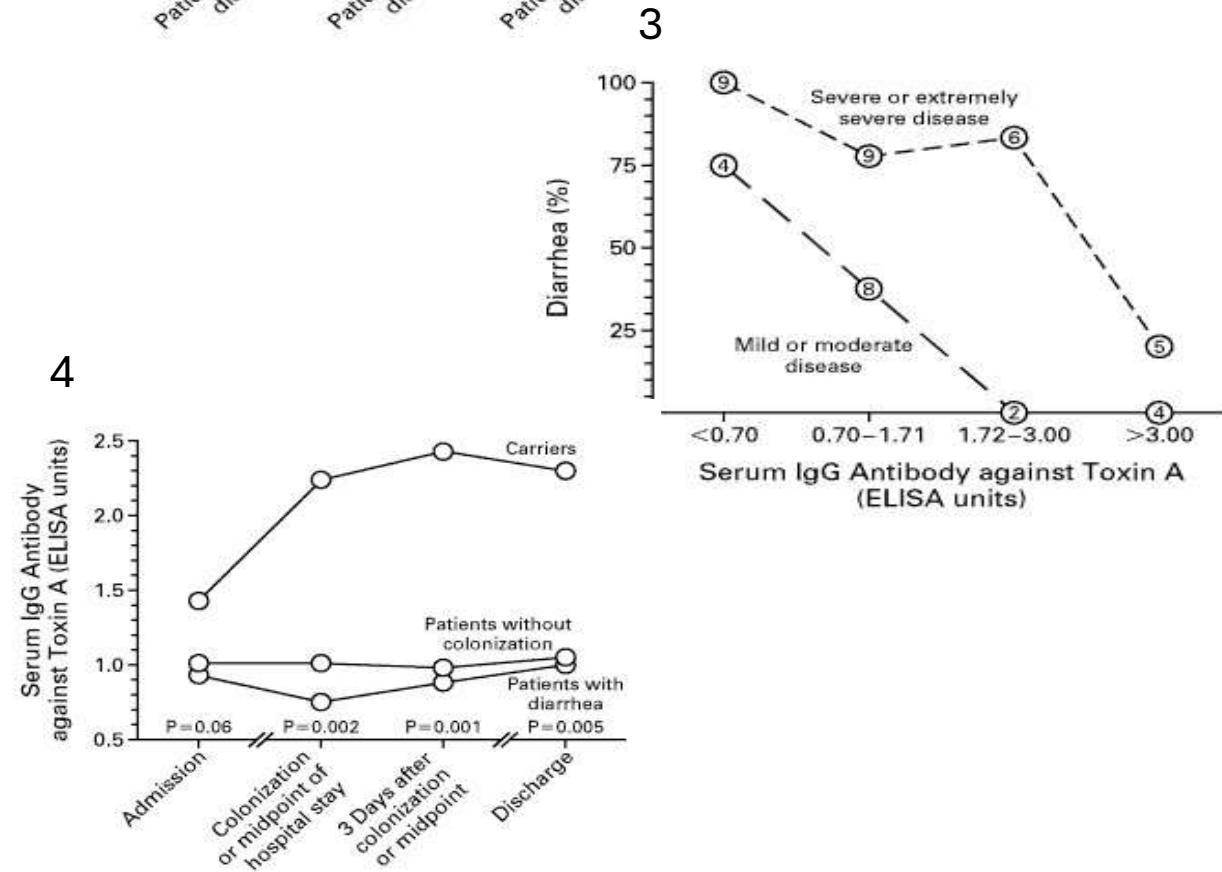
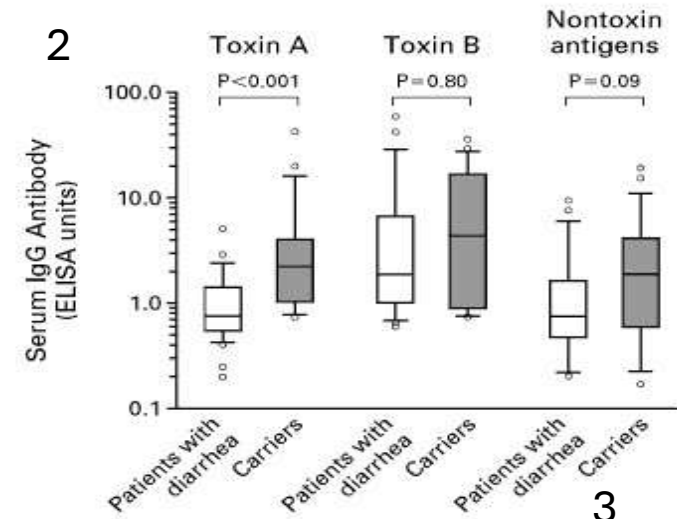
Heatmap of family relative abundance in each sample, demonstrating the most significant biomarkers for CDI (*Bacteroides*, *Proteus*, *Paraprevotella*, *Robinsoniella*), R-CDI (*Veillonella*, *Fusobacterium*, *Lactobacillus*, *Clostridium sensu stricto* I), and colonization by *C. difficile* (*Parabacteroides*, *Faecalicoccus*, *Flavonifractor*, *Clostridium XVIII*)

Vázquez-Cuesta et al. Characterization of the gut microbiome of patients with *Clostridioides difficile* infection, patients with non-*C. difficile* diarrhea, and *C. difficile*-colonized patients. Front Cell Infect Microbiol. 2023 Apr 12;13:1130701.

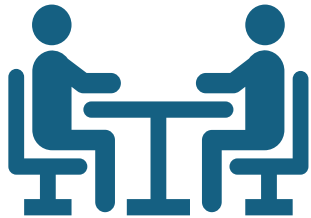


# Why are we recurring?

- Our population has higher immune senescence and suppression, thus the ability to mount serum and fecal antibodies is impacted
  - Two studies demonstrating pre-existing anti-toxin B IgG decreases chance of relapse
  - Serum anti-toxin A IgG was associated with asymptomatic colonization vs disease; also prevented severe disease (2, 3, 4)
  - Bezlotuximab is now off the market - prior studies with IVIG alone didn't show much benefit
  - IgA targeting of stool colonies differs between CDI and healthy patients
  - Secretory IgA promotes bacterial clumping and decreased cytotoxicity
- Genetic susceptibility may also play a role
  - Ferar et al. Performed genetic evaluation of > 19,000 patients and found strong evidence for genetic variation in the DRB locus of the MHC (HLA) II region that predisposes individuals to CDI



# Why are we recurring?



## **Household contacts were significantly associated with community acquired disease**

Asymptomatic carriers aren't quantified and may contribute more than we estimate to new and repeat infections

- CDI incidence among insurance enrollees exposed to a recently hospitalized family member was 73% greater than enrollees not exposed



## **Household surfaces are reservoirs similar to hospital surfaces**

Environmental cultures detected *C. diff* on  $\geq 1$  surface in 8/8 (100%) peri-FMT households, versus 3/8 (38%) post-FMT households and 3/8 (38%) control households ( $P = 0.025$ ).

The most common *C. difficile*-positive sites were the vacuum (11/27; 41%), toilet (8/30; 27%), and bathroom sink (5/29; 17%).

- Computer, bathroom switch, microwave, refrigerator, remote control, telephone all had positive results but at lower percentages



# Why are we recurring?

- What happens in murine models, in vitro, and in vivo are in opposition
  - Huang X, et al. 2025. *Clostridioides difficile* colonization is not mediated by bile salts and utilizes Stickland fermentation of proline in an *in vitro* model. mSphere 10:e01049-24.
    - 12 healthy participants, given 6 different antibiotics, then stools analyzed in a flow model simulating the colon
    - Antibiotics disrupted microbiota but did not impact susceptibility to CDI
    - Increases in primary bile salts were seen but this did not impact susceptibility to CDI and bile salts were not required to prevent colonization
    - Stickland fermentation, however, stuck out as a reason for lack of colonization
  - A separate study disputes the findings of antitoxin IgG, indicating IgG has no bearing on outcomes
- We still don't understand the disease well enough to prevent relapse

# In summary:



DATA SUGGESTS THAT  
REACQUISITION, RATHER  
THAN FAILURE TO CLEAR,  
MAY BE RESPONSIBLE FOR  
MOST CASES



AGING POPULATION WITH  
MORE COMORBIDITIES AND  
MEDICATIONS THAT ALTER  
GUT FLORA INCREASE THE  
RISK OF POOR IMMUNE  
RESPONSE



CLEANING PRACTICES AND  
FAMILY RESERVOIRS MAY BE  
ADDING TO THE BURDEN OF  
DISEASE FOR SOMEONE  
WHO MOUNTED A POOR  
RESPONSE INITIALLY



WE DON'T REALLY  
UNDERSTAND THE  
UNDERLYING MECHANISMS  
OF WHO WILL DEVELOP  
SYMPTOMS AND  
RECURRENCE



UP TO 25% OF PEOPLE WILL  
DEVELOP POST-INFECTIOUS  
IBS WHICH IS DIFFICULT TO  
DISCERN FROM REPEAT  
INFECTION

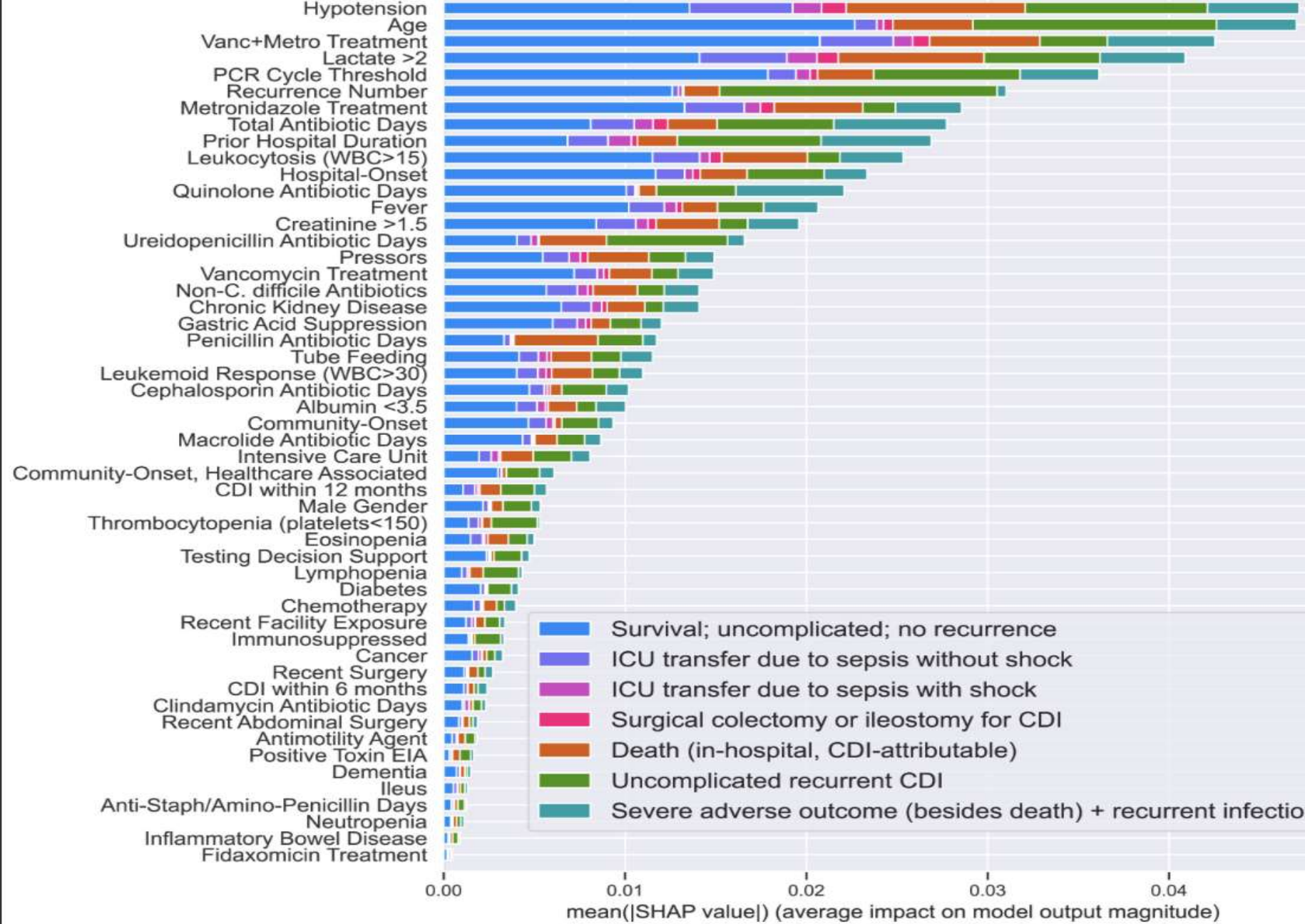
# Calculating who will recur

- ATLAS score – used to predict response to therapy as well as mortality
  - Age, abx use, WBC, albumin, Cr; each gets a score of 0-2 and scores are totaled
  - Provides a ‘cure rate’ and a ‘mortality’ percentage
    - Scores  $\leq 3$  89-96% cure rate with  $<3\%$  mortality
    - Scores  $\geq 7$  have 50% or less change of cure with 14-56% mortality
- DASC score - used to predict risk of recurrence
  - Antibiotic spectrum coverage (ASC) score, which quantifies activity of antibiotics among 16 biological categories, multiplied by the number of days of treatment
  - Combined with ATLAS score, DASC score 30 days prior to treatment of CDI helped predict recurrence
- Score for recurrence
  - Scores  $\geq 2$  accuracy of 79%

TABLE 1.. Clinical prediction rule for recurrent *Clostridium difficile* infection [34]

| Risk factor                                                               | Score |
|---------------------------------------------------------------------------|-------|
| Age >65 years                                                             | 1     |
| Severe underlying disease (Horn index score of 3 or 4) <sup>a</sup>       | 1     |
| Additional antibiotic use                                                 | 1     |
| Add one point for each risk factor present to determine score (range 0-3) |       |

| ASC Score | Antibiotic                                                                                                                                       |
|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| 1         | None                                                                                                                                             |
| 2         | Dicloxacillin, nafcillin, oxacillin, metronidazole, tinidazole                                                                                   |
| 3         | Penicillin G, penicillin V, cefadroxil, cefazolin, cefixime, cephalixin, erythromycin                                                            |
| 4         | Aztreonam, cefdinir, cefpodoxime, cefprozil, cefuroxime                                                                                          |
| 5         | Quinupristin-dalfopristin, rifampin, amoxicillin, ampicillin, cefiderocol, clarithromycin, dalbavancin, telavancin, vancomycin                   |
| 6         | Polymyxin B, colistin, linezolid, tedizolid, azithromycin, daptomycin, clindamycin, oritavancin, cefotetan, ceftazidime, ceftriaxone, cefotaxime |
| 7         | Tetracycline, doxycycline, lefamulin, piperacillin, nitrofurantoin, sulfamethoxazole-trimethoprim, ceftaroline, amoxicillin-clavulanate          |
| 8         | Minocycline, fosfomycin, cefepime, ceftolozane-tazobactam, ceftazidime-avibactam, ampicillin-sulbactam, amikacin                                 |
| 9         | Chloramphenicol, ofloxacin, norfloxacin, ciprofloxacin, ertapenem, tobramycin, plazomicin, gentamicin                                            |
| 10        | Ticarcillin-clavulanate                                                                                                                          |
| 11        | Gemifloxacin, piperacillin-tazobactam                                                                                                            |
| 12        | Doripenem, imipenem-cilastatin, meropenem, levofloxacin                                                                                          |
| 13        | Imipenem-cilastatin-relebactam, moxifloxacin, meropenem-vaborbactam                                                                              |
| 14        | Delafoxacin                                                                                                                                      |
| 15        | Eravacycline, omadacycline, tigecycline                                                                                                          |
| 16        | None                                                                                                                                             |



Predicting who will  
recur



# What therapies remain for recurrent infection?

## Dietary modifications

- Virgin coconut oil, pomegranate extract, black seeds and myrrh show antimicrobial activity against C diff in vitro
- Prebiotics and probiotics
- Avoidance of tea/coffee vs caffeine
  - Data around increased chronic diarrhea and caffeine
  - One study indicating tea may impact C diff
- Increase fibers and starches, fermented products, avoid red meats; consideration of low FODMAPS diet (benefit for IBS)



# What therapies remain for recurrent infection?

## Medications

- Traditional: Vanc, Flagyl, Fidaxomicin
- Cadazolid and Surotomylin – no longer being produced as no data to support superiority
- Emerging data: Rifaximin, Tigecycline, Ridinilazole
  - Resistance to rifamycins may be increasing; this is currently used as an adjunct therapy
  - No RCTs using tigecycline; some indication that this may be of benefit in severe CDI
    - One study showing no benefit for 30 day mortality but the population in which this was used was quite ill
  - Ridinilazole: no activity against aerobic gram-negative bacteria, *Enterococcus faecalis*, *Streptococcus*, and other gram-positive anaerobes such as *Clostridium perfringens*, *Eggerthella*, and *Fingoldia magna*
- Aprepitant and fremanezumab
  - Drugs for nausea and migraine that target inflammatory pathways in the gut shown to decrease colonization in mice
  - Novel approach targeting inflammation that doesn't impact microbiota – study ongoing
- Oral Immunoglobulin
  - Over the counter product
  - Mostly looked at in pediatric patients with some data to support shortening of symptoms but not specifically for CDI
  - Chiari EF, et. al. Oral Immunotherapy With Human Secretory Immunoglobulin A Improves Survival in the Hamster Model of *Clostridioides difficile* Infection. *J Infect Dis.* 2021 Oct 28;224(8):1394-1397 – co-administered with vanc

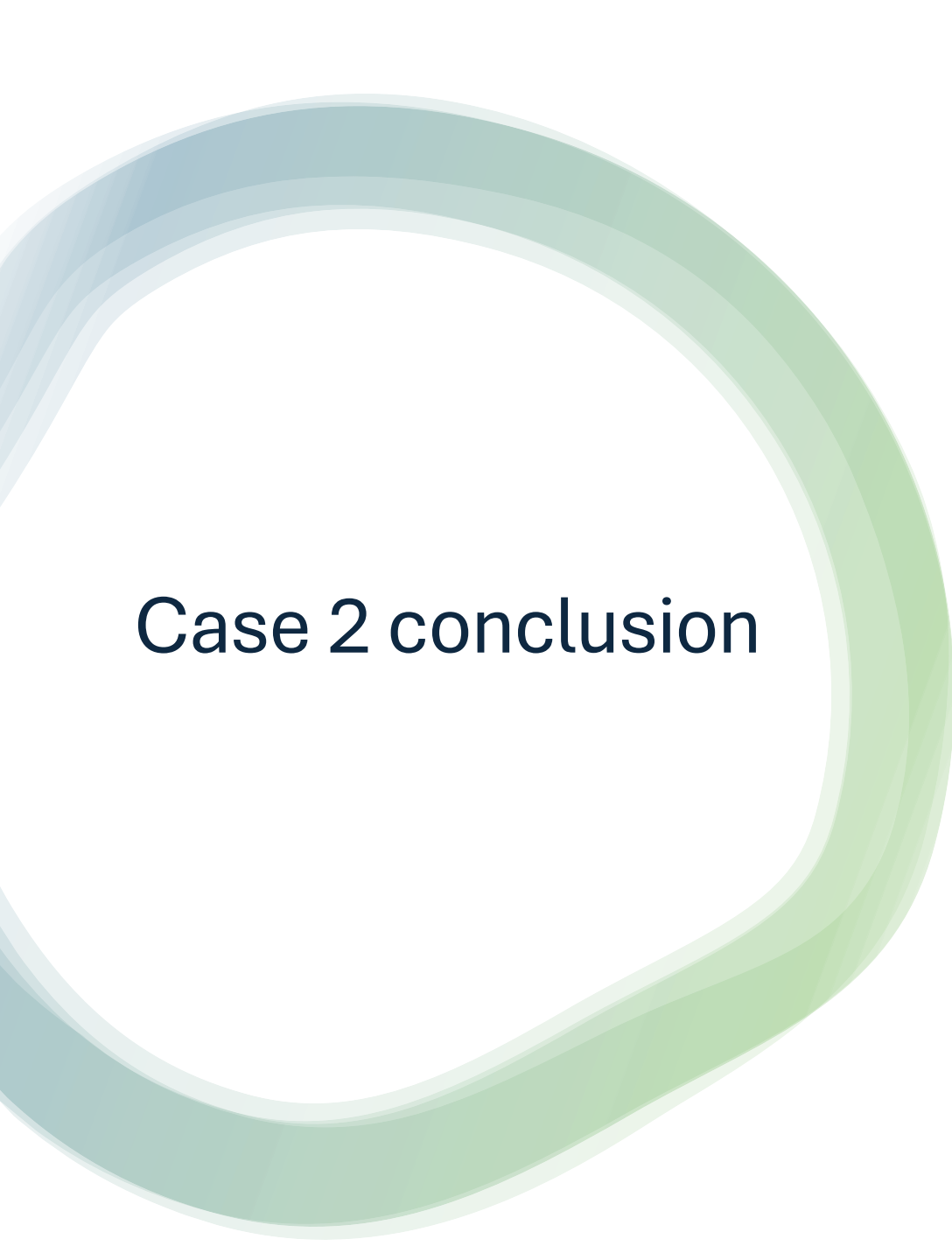


# What therapies remain for recurrent infection?

- Microbiota
  - Rebyota – office or home administered fecal material
  - Vowst – capsules with firmicutes spores
  - FMT
    - FMT for primary treatment proved non-inferior to vancomycin
- Surgery
  - Reserved for fulminant disease but can be considered in ongoing recurrence
  - Loop ileostomy with vanc enema showed equivocal outcomes to colectomy and lower morbidity
- Antimotility agents
  - There is data to support benefit of AAs while on concurrent C diff therapy
  - 339 hematologic malignancy patients, 27% received AAs (mostly loperamide), 2 adverse events (vs 6 in nonAA group) neither of which were megacolon, early use of AAs correlated with fewer diarrhea days
  - 55 patients with CDI given AAs, adverse events noted when AAs given alone before initiation of antimicrobials
- Spontaneous clearance
  - No studies looking at supportive care alone for mild infection
  - However, mild cases may develop and remit after stopping antibiotics and those patients never present to care

# What is the role of colonoscopy?

- Not recommended as a primary screening tool
- Helpful if other pathologies are at play
  - Can help rule out other diagnoses as well
- Should be requested in settings of ongoing diarrhea where CDI is not the clear diagnosis or is not responding to therapy
- More frequent repeats may help uncover pathologies when diarrhea persists
- Other etiologies of pseudomembranes: Behcet's disease, collagenous colitis, inflammatory bowel disease, ischemic colitis, other infections (SA, kleb, CMV, covid, entamoeba), cocaine, NSAIDs, amphetamines, voriconazole



## Case 2 conclusion

- Repeat PCR testing was negative for CDI
- Colonoscopy was performed, benign polyp that was biopsied but no other acute findings and path was negative
- Diarrhea persisted, 1 tab of Imodium per day was not improving symptoms
- Dietary changes implemented, increased Imodium and added Lomotil
- Several days of normal stools while using lomotil



## Case 3

- 51 year old male with history of PTSD related to prior military service who is referred for recurrent C diff
- He reports battling CDI x 3 years with no improvement with various therapies, though he has not undergone FMT or used a similar product
- Current symptoms are intermittent bouts of diarrhea associated with extreme depression and fatigue, borderline suicidal ideation
- Last C diff testing was PCR+, toxin -, 2 years ago

# What therapies may have utility when it's non-CDI diarrhea?

Antimotility  
agents

SSRIs or TCAs

- Studies showing benefit in IBS – extrapolate to pIBS

Probiotics and  
prebiotics

Rifaximin

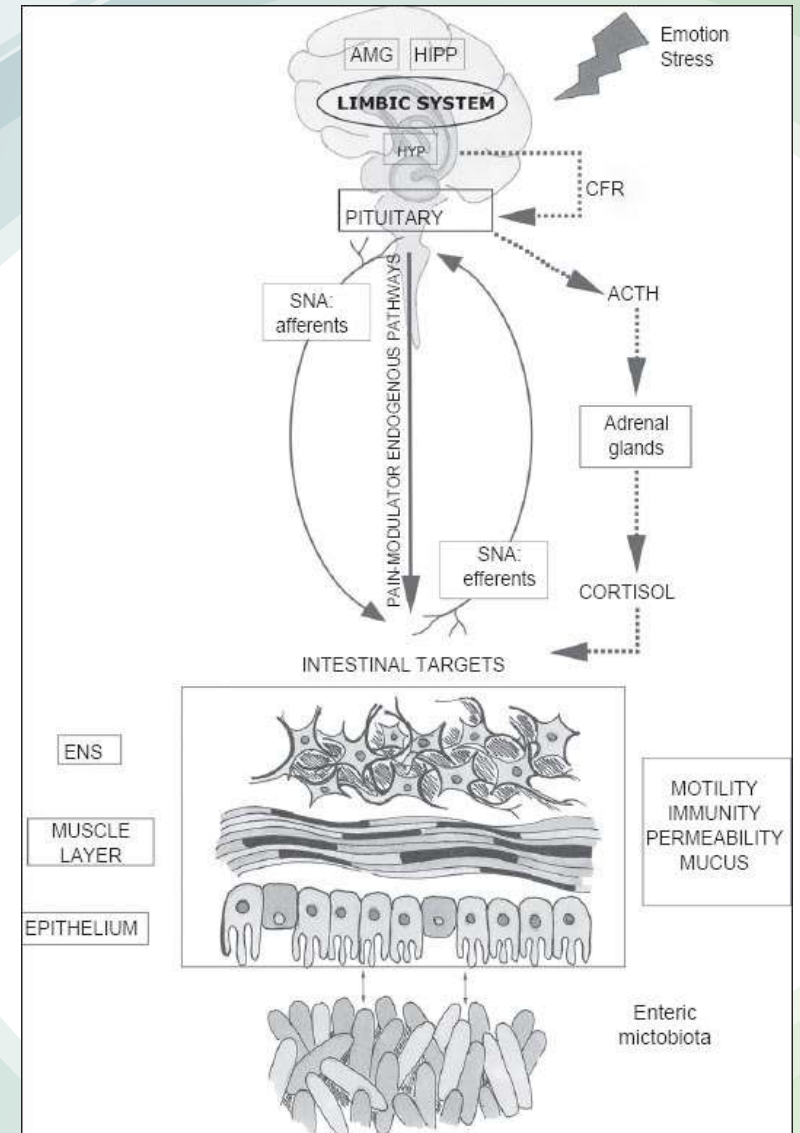
CBT

- CBT + exercise showed benefit for IBS-D patients

Could FMT or  
other biome  
agents play a  
role?

# What is the mental/emotional toll of CDI and how can we help?

- Gut/brain axis
  - Signals between the brain and gut are impacted by the microbiome
  - Evidence indicating the microbiome may help the development of the CNS
  - Mental health may be impacted by the microbiome



# Post-infectious mental health

- Boustany A, et al. found that antidepressants may lead to dysbiosis, increasing CDI risk, in people with mental health issues related to dysbiosis
  - Separate study found that pre-existing depression increased the risk of CDI; mirtazapine and trazodone use in hospital greatly increased OR of CDI
- S Turcan et al. compared anxiety and depression in patients with CDI vs IBD and noted 86% of CDI cases with depression compared to 57% in the IBD group

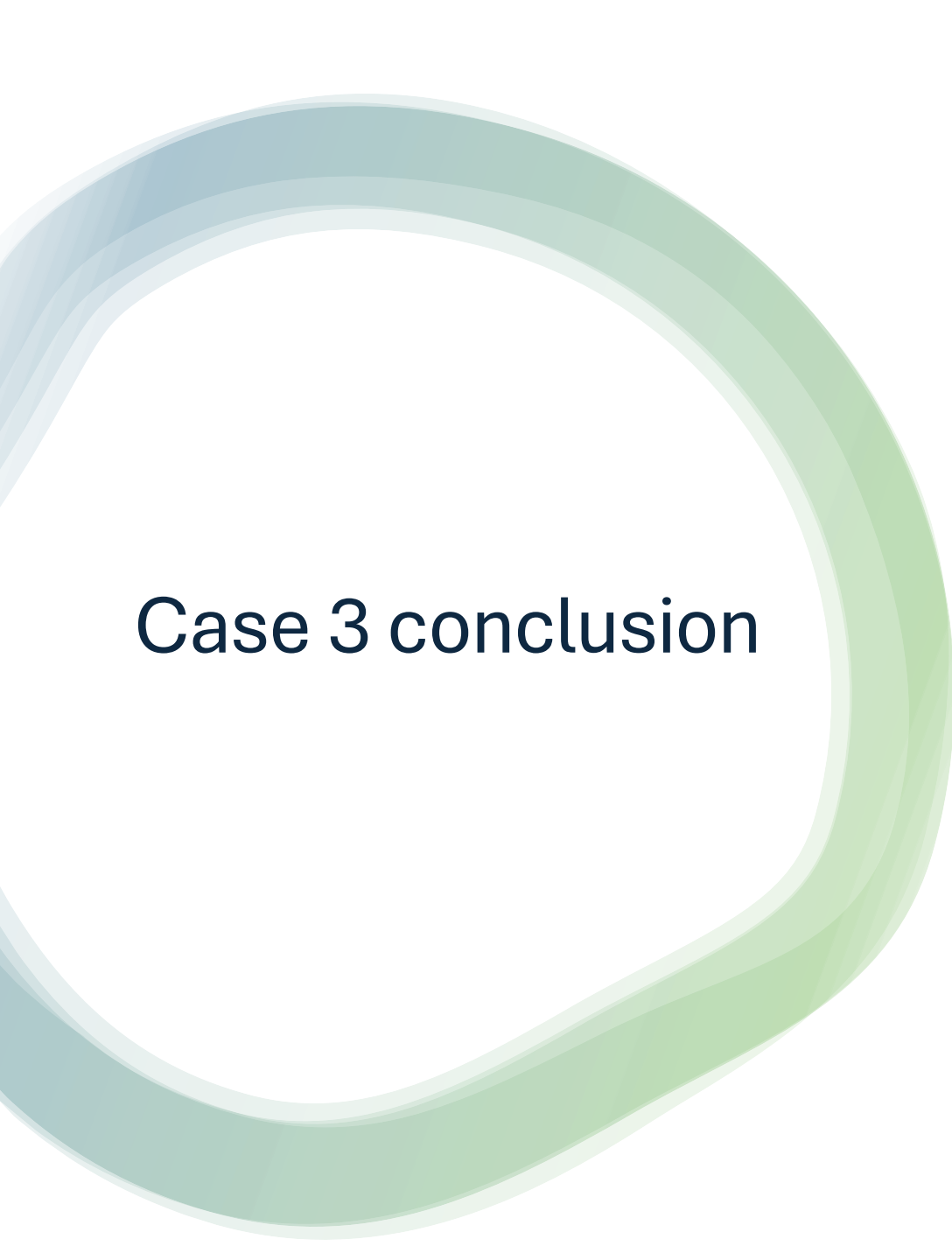


## Guest Blog on Peggy Lillis Website: The lasting impact of C. diff

There is something that all C. diff survivors know, and you can't always see it. We may look "normal," even healthy. We may seem to be thriving, and little of what is happening underneath shows through. Or we may appear weak and frail, and one could assume there is some pain, some suffering, some lingering discomfort. But in reality, there is a far deeper experience happening than may appear on the surface. What we know is this: C. diff has deep and lasting effects on our lives long after the last test comes back negative. ...a hugely important and lasting complication of C. diff is the emotional state in which it leaves the patient, cured or not. At first, even with a diagnosis of eradication, there is a lingering doubt about whether it is really gone, especially when so many of the physical aspects remain. There is anger, so much anger. Anger at the doctors, the hospital where you were infected, the inability to get well, the fact that you caught it in the first place. I even blamed myself for deciding to get the surgery at all! There is frustration. This can be directed at doctors, nurses, your insurance company, your family and friends, or anyone who happens to be connected with your care. Because there are so many roadblocks to diagnosis and treatment, a deep sense of mistrust of doctors and hospitals can remain with you indefinitely. Then there is fear, and a lot of it. The first time, and every time after, you have diarrhea, you immediately suspect a relapse. You are constantly afraid it's come back, and this time you will die. I will still wake up in a cold sweat in the middle of the night thinking I still have C. diff and freeze in terror. I will cry and shake and ruminate over every surface I touched that day and how many times I washed my hands and if it was long enough. Did I eat off a fork I didn't personally wipe off? The weight of the experience in its entirety will cause me to collapse with an anxiety attack, unable to leave my house that day.

# What else should we be considering for patients with chronic diarrhea?

- IBS and pIBS
  - Diagnosis of exclusion, questionnaires about symptoms
- IBD
  - Colonoscopy
  - Fecal leukocytes, blood, calprotectin, lactoferrin (the latter can replace leukocytes)
- Microscopic colitis
  - Colonoscopy
- Celiac
  - Small intestinal bx and tissue transglutaminase
- Pancreatic insufficiency
  - Fecal chymotrypsin and elastase
  - Fecal fat
- Bile acid and/or other malabsorption
  - Fecal fat
  - Fecal electrolytes
  - $290 \text{ mOsm/kg} - 2(\text{Na}[\text{feces}] + \text{K}[\text{feces}])$ . If the result of the above formula is less than 50 mOsm/kg, then the diarrhea is secretory. If the result is greater than 75 mOsm/kg, then the diarrhea is osmotic
- Hyperthyroidism
  - TSH/T4
- Dietary issues or medications
  - History and physical



## Case 3 conclusion

- Repeat testing was PCR negative
- Recommended SSRI initiation and dietary modifications

# Conclusions

- We should be repeating testing more frequently than we are
  - Empiric therapy has downsides and many 'relapses' are not, in fact, CDI
- We should request colonoscopy sooner in the course
  - IBD happens and initial CDI can predispose
- We should collaborate with our GI colleagues to expedite workup of other etiologies, including non-infectious causes
- We should consider the impact of ongoing spore colonization within homes and counsel patients, as well as families, about cleaning
- We should be less afraid of antimotility agents, especially when C. diff eradication is confirmed
- We should consider the link between mental health and CDI, as well as the emotional toll of infection, and work to provide support

# References

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