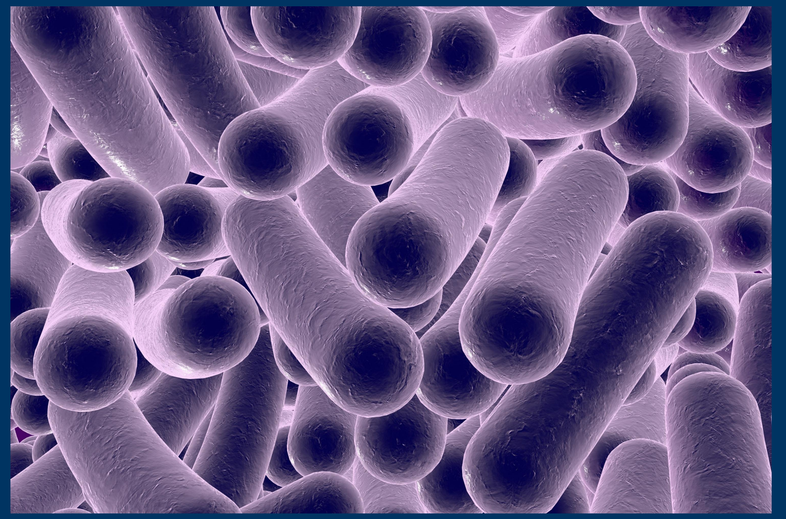


Clostridia & C. Diff Infections

The Crazy World of Clostridia

Ryan Monahan, FDN-P Level III, NBC-HWC, Certified AIP Coach

Clostridium Difficile

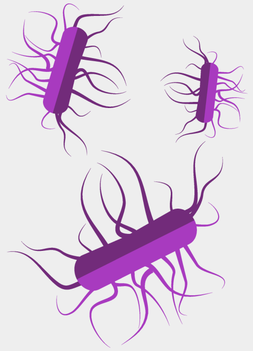
A Brief Overview…

Kingdom: Bacteria

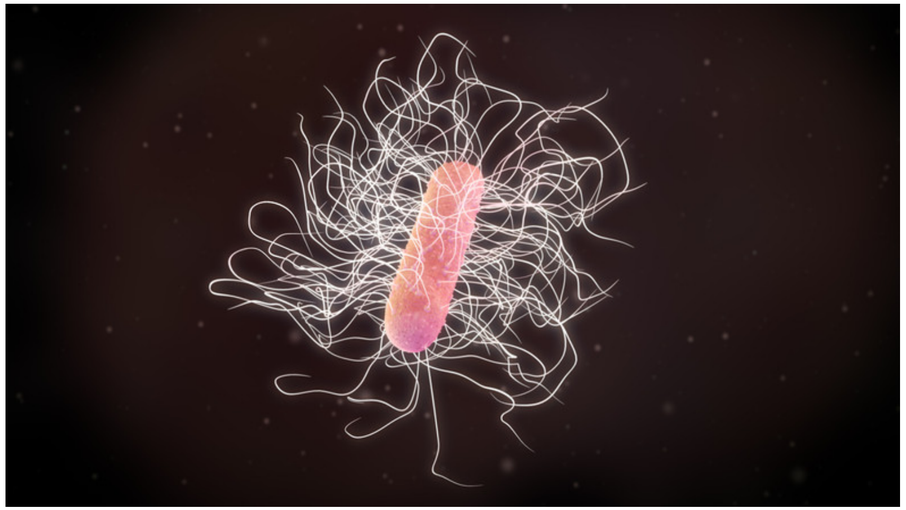
Class: Clostridia

Genus: Clostridium

Species: Clostridium difficile



- **Clostridioides difficile, formerly known as Clostridium difficile**, is a bacterium that can cause a range of illnesses, from mild diarrhea to life-threatening inflammation of the colon.
- Anaerobic, spore-forming, gram-positive bacterium that is commonly found in the environment, particularly in soil, water, and animal feces.
- According to ***BMC Infectious Diseases,*** CDI affects approximately 500,000 patients annually in the United States. CDI is the **leading cause of antibiotic- and healthcare-associated infective diarrhea in the United States**.
- **Symptoms** of CDI include **watery diarrhea, fever, abdominal pain, and nausea**. In severe cases, CDI can cause colitis (inflammation of the colon) and even sepsis (a life-threatening bloodstream infection).
- Conventional treatment for CDI involves antibiotics that target C. difficile (such as metronidazole, vancomycin, and fidaxomicin). In some cases, fecal microbiota transplantation (FMT) may be used to restore the balance of gut bacteria.
- Prevention involves good hygiene practices, such as hand-washing with soap and water (alcohol-based hand sanitizers do not kill C. difficile spores). Probiotics and prebiotics may also help to prevent CDI.
- Interestingly, some studies have suggested that C. difficile may have a role in regulating the gut microbiome. For example, it has been shown to produce compounds that inhibit the growth of other harmful bacteria, such as Salmonella and E. coli. Additionally, C. difficile infection may trigger the immune system to produce antibodies that provide some protection against future infections.

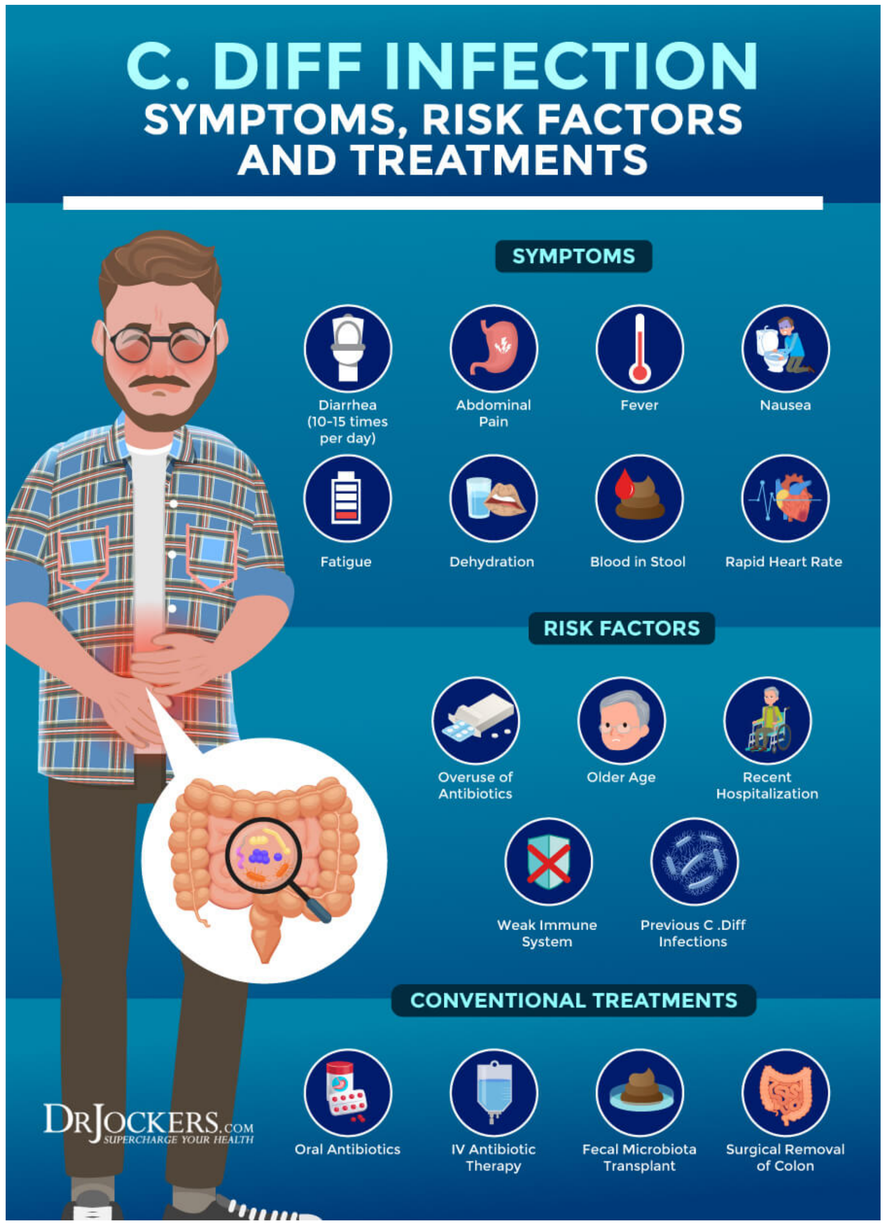


Clostridium Difficile

Common Symptoms

- Diarrhea
- Abdominal pain
- Cramping
- Inflammation
- Leaky gut
- Food sensitivities
- Joint pain
- Brain fog
- Poor memory
- ADD
- Depression
- Adrenal fatigue
- Hormonal imbalance
- Endotoxemia (LPS)
- Liver dysfunction
- Neuro-inflammation
- Pseudomembranous colitis
- Fever

- **Very common to feel “lousy” mentally speaking**



Clostridium Difficile

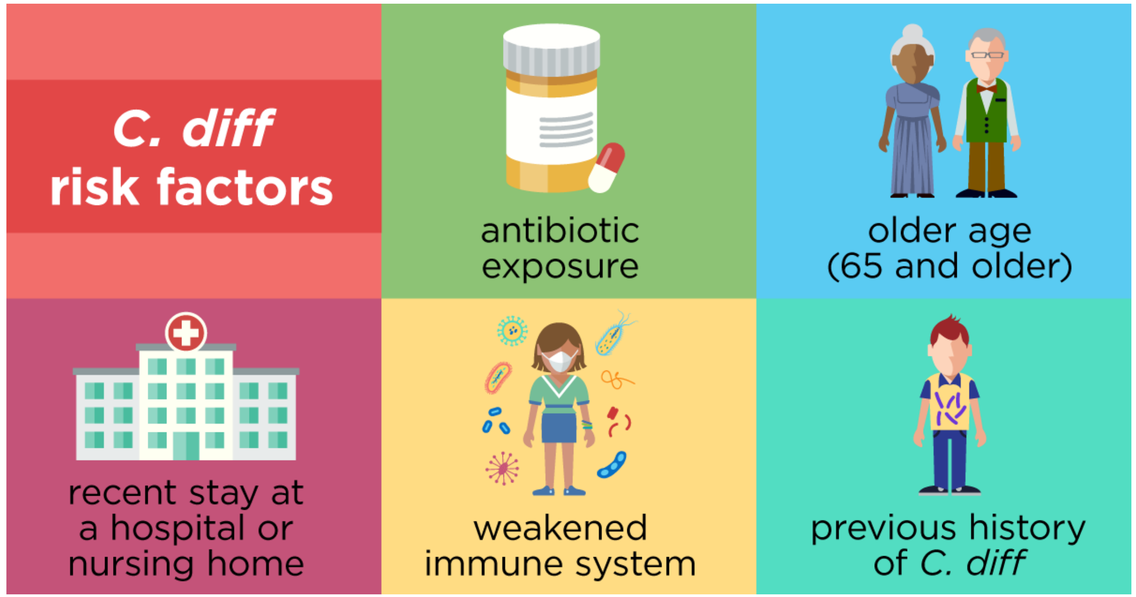
How Do We Pick it Up?

- C. difficile infections are commonly acquired in healthcare settings, where **antibiotics (esp. clindamycin) and other medical interventions can disrupt the balance of gut bacteria and allow C. difficile to grow unchecked**.
- Can survive on surfaces for months (toilet seats for example!!), making it highly contagious - can be spread via a healthcare workers after forgetting to wear gloves
- Can be transmitted via fecal-oral transmission
- "Many patients are also impacted by **recurrent C. difficile infections** (rCDI); up to 35% of index CDI will recur and of these up to 60% will further recur with multiple recurrences observed. The range of outcomes adversely affected by rCDI is significant and current **standard of care does not alter these recurrence rates due to the damaged gut microbiome and subsequent dysbiosis**."
  - - ***BMC Infectious Diseases, March 2023***

Abstract

Clostridioides difficile infection (CDI) affects approximately 500,000 patients annually in the United States, of these around 30,000 will die. CDI carries significant burdens including clinical, social and economic. While healthcare-associated CDI has declined in recent years, community-associated CDI is on the rise. Many patients are also impacted by recurrent *C. difficile* infections (rCDI); up to 35% of index CDI will recur and of these up to 60% will further recur with multiple recurrences observed. The range of outcomes adversely affected by rCDI is significant and current standard of care does not alter these recurrence rates due to the damaged gut microbiome and subsequent dysbiosis. The clinical landscape of CDI is changing, we discuss the impact of CDI, rCDI, and the wide range of financial, social, and clinical outcomes by which treatments should be evaluated.

Source: "The burden of CDI in the United States: a multifactorial challenge" *BMC Infectious Diseases*, March 2023



PPI Use & Risk

How Do We Pick it Up?

Innov Pharm. 2021; 12(1): 10.24926/iip.v12i1.3439.
Published online 2021 Mar 9. doi: 10.24926/iip.v12i1.3439
PMCID: PMC8102963
PMID: 34007671

The Positive Association between Proton Pump Inhibitors and Clostridium Difficile Infection

Dania Tawam, PharmD Candidate, Michael Baladi, PharmD Candidate, Paiboon Jungsuwadee, PhD, Grace Earl, PharmD, and Jayoung Han, PhD

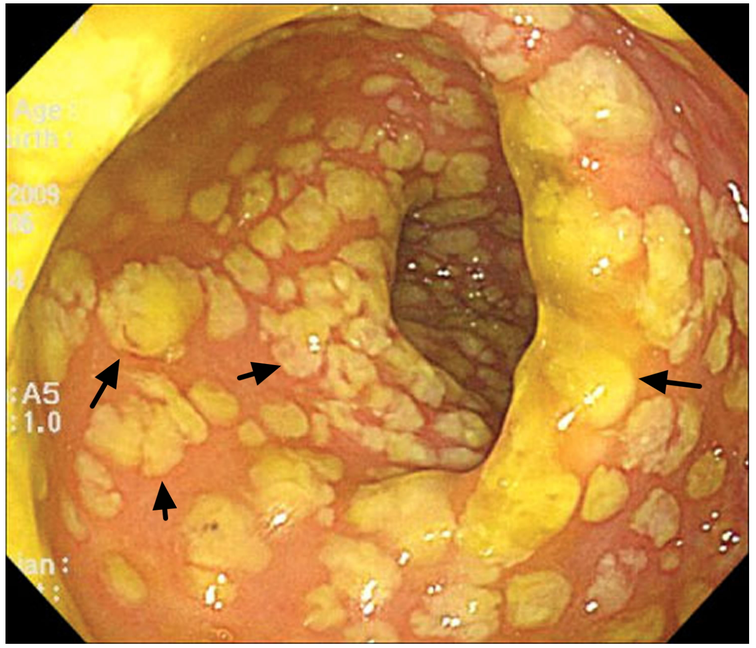
- **Proton Pump Inhibitors** are one of the most commonly prescribed drugs in the United States, with an estimated **15 million** (about 4.5%) Americans taking them regularly.
- Between 1999 and 2012, the number of prescriptions for PPIs in the United States increased from **59 million to 157 million**.
- A **2020 study published in JAMA Internal Medicine found that over 50% of long-term PPI users in the United States had no appropriate indication for their use**, suggesting that many people may be taking PPIs unnecessarily
  - https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2769371
- "Recently, the **FDA issued a warning with respect to the utilization of PPIs and risk of developing Clostridium difficile infections** (CDI). The most commonly known medications to cause CDI are antibiotics. However, **available studies suggest an association and increase in risk for CDI with PPI use** as well.
- Eight meta-analyses and systematic reviews met the inclusion criteria. They included studies conducted in the US, Europe, Asia and Canada on inpatient and outpatient adults. The final **result for all 8 studies showed a statistically significant association between PPIs and CDI ranging from mild to high risk.**

Clostridium Difficile

What Are Toxin A & B?

Pathogens			
Bacterial Pathogens	Result		Normal
Campylobacter	**<dl**		<1.00e3
C. difficile, Toxin A	**1.80e2**		<1.00e3
C. difficile, Toxin B	**7.26e4**	**High**	<1.00e3
Enterohemorrhagic E. coli	**<dl**		<1.00e3
E. coli O157	**<dl**		<1.00e3
Enteroinvasive E. coli/Shigella	**<dl**		<1.00e2
Enterotoxigenic E. coli LT/ST	**<dl**		<1.00e3
Shiga-like Toxin *E. coli* stx1	**<dl**		<1.00e3
Shiga-like Toxin *E. coli* stx2	**<dl**		<1.00e3
Salmonella	**<dl**		<1.00e4
Vibrio cholerae	**<dl**		<1.00e5
Yersinia enterocolitica	**<dl**		<1.00e5

- **NOTE**: C. Diff exists the gut environments of most healthy hosts. As the expression goes, “the poison is in dose” - in other words, its ***overgrowth*** of clostridia species that is associated with disease and dysfunction
- **C. Diff Toxins A & B are some of the most toxic substances known to the human body**, even more toxic than LPS (lipopolysaccharide)
- **Toxin A** - Enterotoxin
  - Associated with watery diarrhea, often foul smelling
  - Binds to brush border of intestines, which results in inflammation due to recruitment of neutrophils into the ileum.
  - Neutrophils cause damage the brush border and mucosal barrier cells, resulting in leaky gut / intestinal permeability leading to leaky gut and diarrhea
- **Toxin B -** Cytotoxin
  - ***Cyto*** literally means ***cell***, therefore cytotoxin means toxic to our cells
  - Toxin B disrupts the cytoskeletons of our cells
  - Works be **depolymerizing** (break down into smaller units) the protein **actin**
  - This leads to **enterocyte death** and **necrosis** (cell death), which is like killing the cells from the inside out
  - Toxin B is more associated with **Pseudomembranous Colitis** - results in a membrane or coating form on the colon
  - This **“pseudo-membrane”** can actually block water reabsorption and lead to diarrhea



Clostridium Difficile

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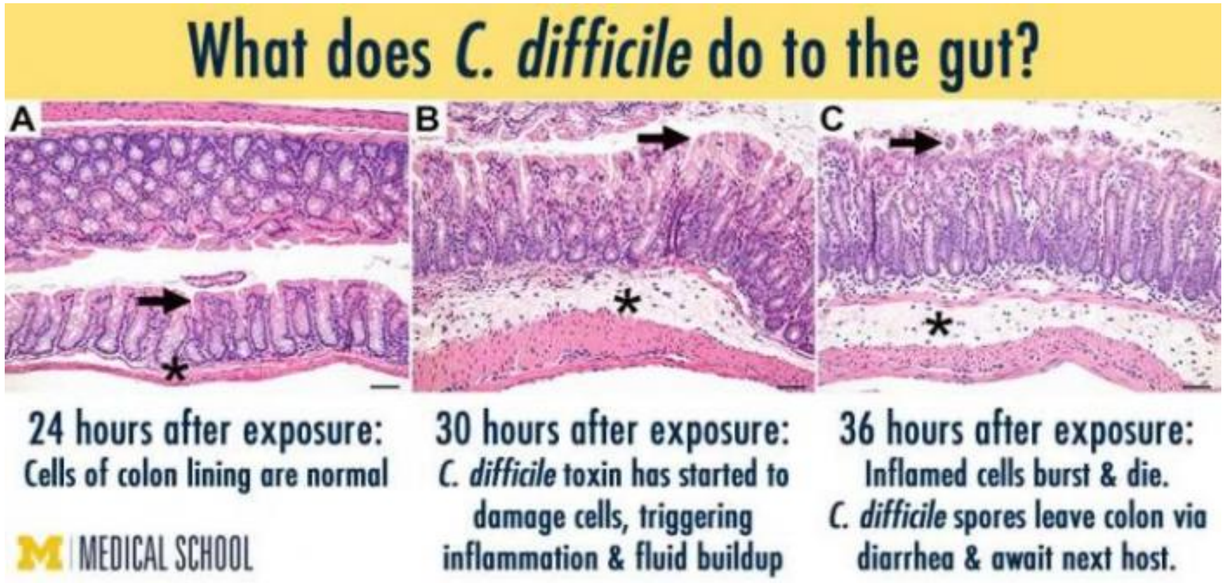

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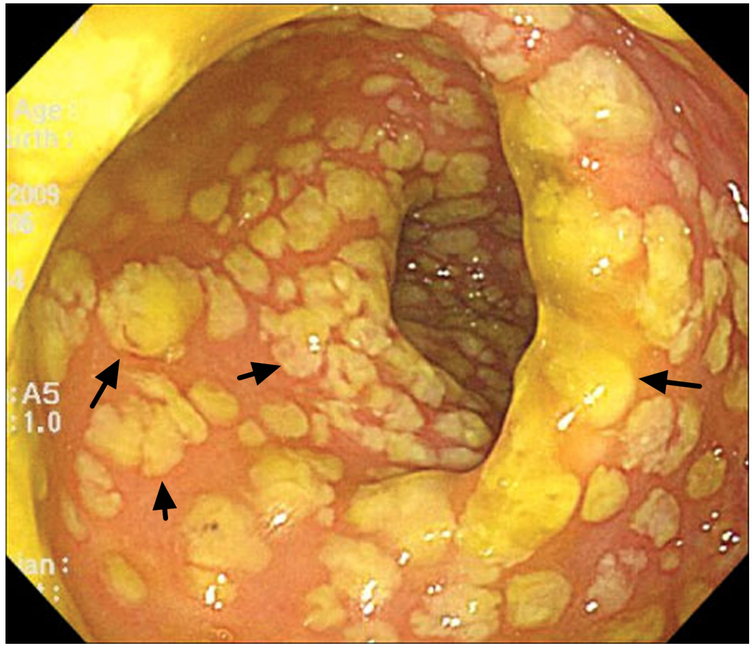


C. Diff & Anxiety

The Gut-Brain Axis

Research article | Open Access | Published: 07 May 2013

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

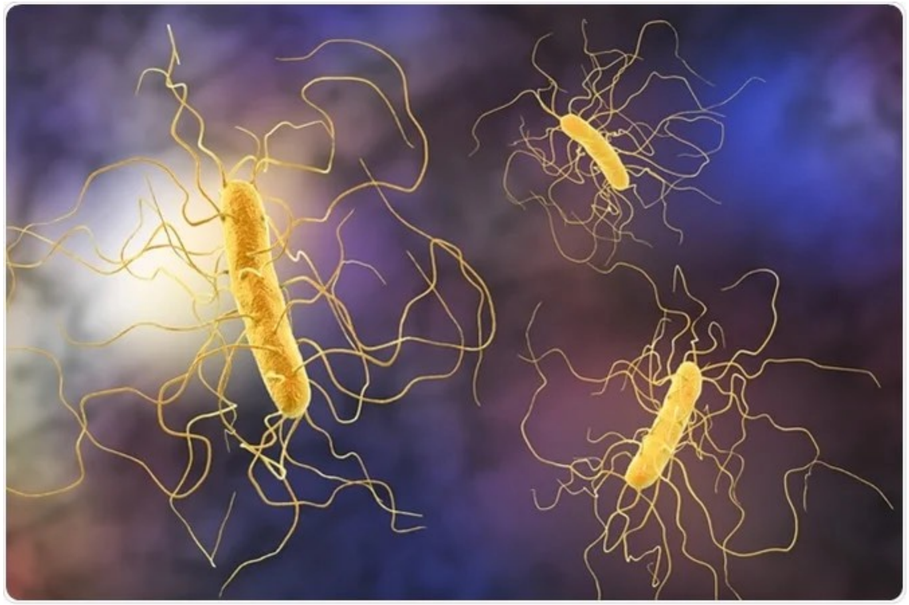
Mary AM Rogers, M Todd Greene, Vincent B Young, Sanjay Saint, Kenneth M Langa, John Y Kao & David M Aronoff

BMC Medicine **11**, Article number: 121 (2013) | Cite this article

23k Accesses | **59** Citations | **130** Altmetric | Metrics

BMC Medicine, 2013

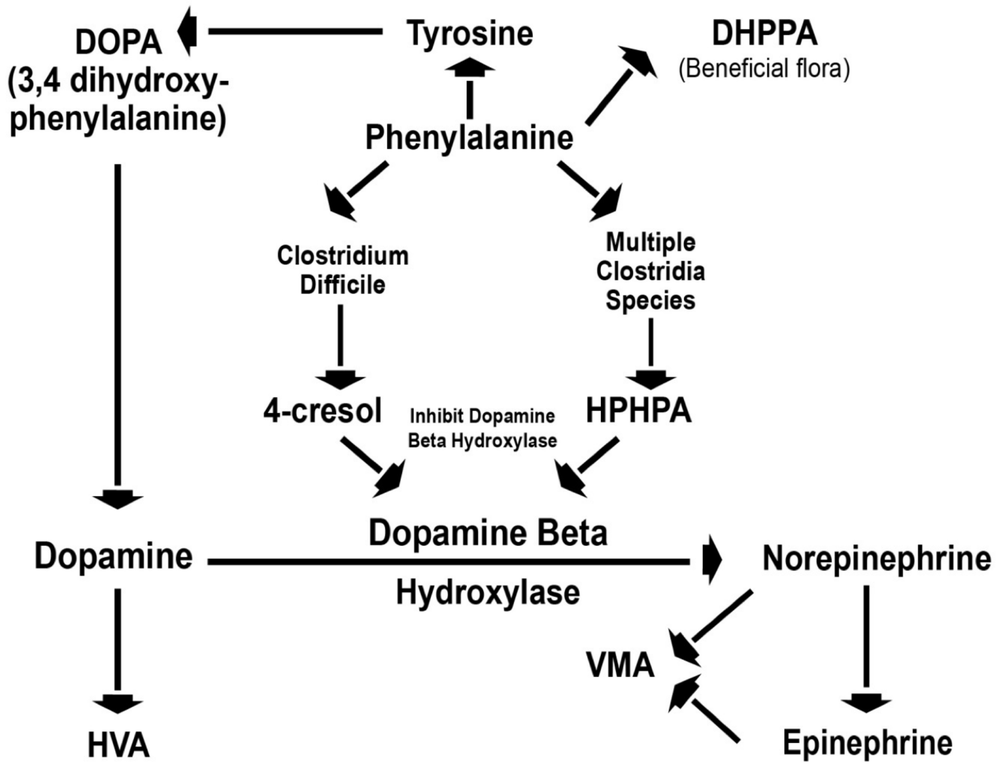
- **"It has been suggested that the mechanisms underlying the brain–gut axis may be bidirectional."**
- "In a 12-year prospective study, the relationship between anxiety, depression, and functional GI disorders appeared to be bidirectional, in that **psychiatric disorders predicted GI disease and vice versa**. A population-based longitudinal study in the Netherlands found similar results; the risk of developing severe bowel disease was significantly higher in individuals with previous depression, and the risk of developing depression was significantly higher in individuals who had previously experienced severe bowel disease."



C. Diff & Anxiety

Quick Stats…

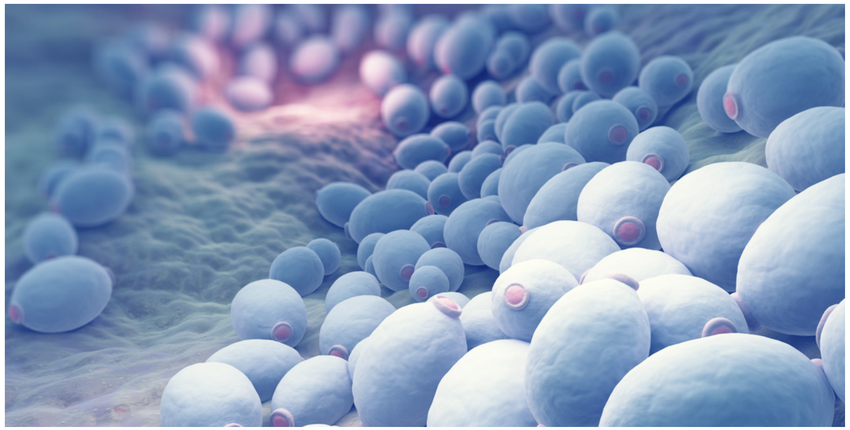
- From a functional perspective, **Clostridium Difficile and other related species are notorious for inhibiting the breakdown and elimination of Dopamine**
    - **Mechanism:** Certain metabolites produced by clostridium - namely 4-Cresol and HPHPA - inhibit the enzyme DBH (Dopamine Beta Hydroxylase) which is normally responsible for the clearance of dopamine
- This leads to either poor dopamine clearance and/or high dopamine levels
- **High dopamine** = anxiety, overwhelm, difficulty winding down from stress
- **NOTE**: Dopamine is a not so distant cousin to norepinephrine (adrenaline), which are both in the same family of neurotransmitters known as **catecholamines**



C. Diff & S. Boulardii

S. Boulardii C. Diff Protocol in Practice

- Saccharomyces Boulardii is a **probiotic yeast**
- Many studies looking at the use of S. Boulardii promote its use ***alongside*** antibiotics
- “While discontinuation of antimicrobial agents and antibiotic treatment of the infection remain the cornerstone of therapy, the use of probiotics, especially **Saccharomyces boulardii, and more recently of fecal microbiota transplantation have become valid forms of prevention and/or therapy and are here critically examined.**”



Clostridium difficile Colitis Prevention and Treatment

Meltem Dinleyici [1], Yvan Vandenplas [2]

Affiliations + expand

PMID: 30689174 DOI: 10.1007/5584_2018_322

Abstract

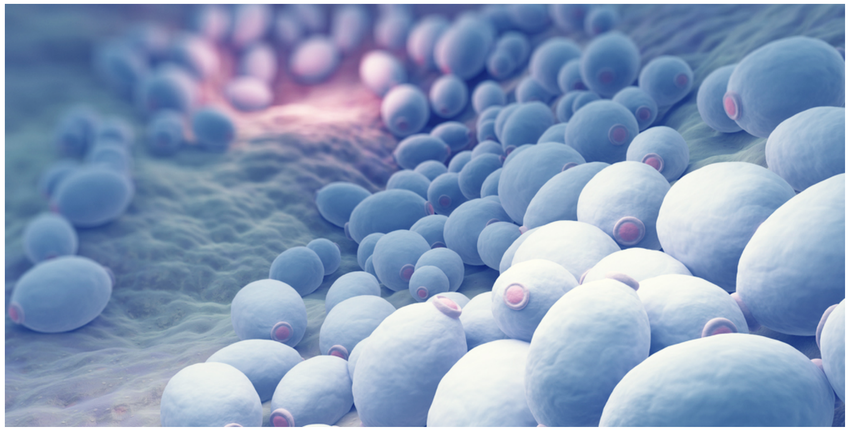
Clostridium difficile (C. diff) is the most common causative agent of antibiotic-associated diarrhea and colitis. This spore-forming, obligate anaerobic, gram-positive bacillus is becoming responsible for an increasing number of infections worldwide, both in community and in hospital settings, whose severity can vary widely from an asymptomatic infection to a lethal disease. While discontinuation of antimicrobial agents and antibiotic treatment of the infection remain the cornerstone of therapy, the use of probiotics, especially Saccharomyces boulardii, and more recently of fecal microbiota transplantation have become valid forms of prevention and/or therapy and are here critically examined.

Advances in Experimental Medicine and Biology, 2019

C. Diff & S. Boulardii

S. Boulardii C. Diff Protocol in Practice

- “This study was designed to assess the efficacy and safety of **Saccharomyces cerevisiae variant boulardii CNCM I-3799 in the management of acute diarrhea in children**.”
- 100 infants ranging between 3-36 months of age with acute diarrhea were randomly assigned to an S. Boulardii probiotic group and were given the probiotic for 5 days
- Results: The administration of S. boulardii CNCM I-3799 was associated with **beneficial effects on duration and severity of diarrhea.** The time of **recovery from diarrhea was significantly shorter in the probiotic group compared with the placebo group.**



Randomized Controlled Trial > Pediatr Infect Dis J. 2020 Nov;39(11):e347-e351.
doi: 10.1097/INF.0000000000002849.

A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Saccharomyces boulardii in Infants and Children With Acute Diarrhea

Florian Mourey [1], Varun Sureja [2], Dharmeshkumar Kheni [2], Parthiv Shah [3], Devang Parikh [4], Unmesh Upadhyay [5], Milan Satia [6], Dhara Shah [6], Charlotte Troise [1], Amélie Decherf [1]

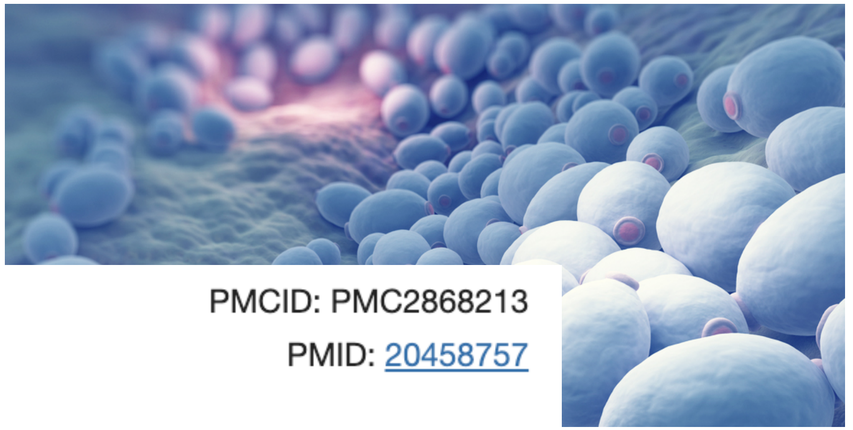
Affiliations + expand

PMID: 32796401 PMCID: PMC7556239 DOI: 10.1097/INF.0000000000002849

Pediatric Infectious Disease Journal, Nov 2020

C. Diff & S. Boulardii

S. Boulardii C. Diff Protocol in Practice



World J Gastroenterol. 2010 May 14; 16(18): 2202–2222.
Published online 2010 May 14. doi: 10.3748/wjg.v16.i18.2202

PMCID: PMC2868213
PMID: 20458757

Systematic review and meta-analysis of *Saccharomyces boulardii* in adult patients

Lynne V McFarland

- Of **31 randomized, placebo-controlled treatment arms in 27 trials** (encompassing 5029 study patients), **S. boulardii was found to be significantly efficacious and safe in 84% of those treatment arms**. A meta-analysis found a significant therapeutic efficacy for S. boulardii in the prevention of antibiotic-associated diarrhea (AAD).
- In adults, **S. boulardii can be strongly recommended for the prevention of AAD and the traveler's diarrhea**. Randomized trials also support the use of this yeast probiotic for prevention of enteral nutrition-related diarrhea and reduction of Helicobacter pylori treatment-related symptoms.
- **S. boulardii shows promise for the prevention of C. difficile disease recurrences**; treatment of irritable bowel syndrome, acute adult diarrhea, Crohn's disease, giardiasis, human immunodeficiency virus-related diarrhea; but more supporting evidence is recommended for these indications.
- **The use of S. boulardii as a therapeutic probiotic is evidence-based for both efficacy and safety for several types of diarrhea**.

The D.R.E.S.S. Approach

S. Boulardii C. Diff Protocol in Practice

- Saccharomyces Boulardii is a **probiotic yeast**
- **NOTE:** Many studies looking at the use of S. Boulardii promote its use ***alongside*** antibiotics; however, in clinical practice, I have observed dozens of cases where S. Boulardii was effective at eradicating C. Diff
    - One reason I suspect this to work so effectively is due to **S. Boulardii's ability to boost the gut immune response by supporting Secretory IgA**
- **60 DAY REVERSE TITRATION PROTOCOL**:
    - This involves starting at a much higher dose of Saccharomyces Boulardii and gradually ramping down the dose
    - Use any preferred S. Boulardii product, most are a standard 5 Billion CFU per capsule
        - **12 caps/day - 2 weeks**
            - **4 caps 3x/day**
        - **9 caps/day - 2 weeks**
        - **6 caps/day - 2 weeks**
        - **4 caps/day - 2 weeks**
- In my experience, I have seen a much higher percentage of those with C. Diff or clostridia-related infections in those that have experienced mold illness due to exposure to water damaged buildings
- I suspect the mechanism here to be the highly immune suppressive nature of mycotoxins opening the door to other infections "joining the party"
- If we're not addressing the health of the client holistically (especially with diet, stress reduction, supporting gut immune health, 100% removal of gluten and other inflammatory foods), the client may not stand a chance at eradicating C. Diff and may be more likely to relapse