PALLIATIVE PEARLS
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# Clostridioides Difficile Infection: Risks, Prevention & Medication Therapy
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**PATIENT CASE**

MK is a 78-year-old female with a primary diagnosis of heart failure and comorbidities of atrial fibrillation, edema, hypothyroidism, anxiety, and depression. She has no known drug allergies and currently resides in a long-term care facility.

**Current medications:**

- Acetaminophen 325 mg; 2 tablets by mouth every 4 hours as needed for fever
- Alprazolam (Xanax®) 0.5mg; 1 tablet by mouth every 2 hours as needed for anxiety
- Carvedilol (Coreg®) 3.125mg; 1 tablet by mouth twice a day (hold for HR < 60 and SBP < 100)
- Levothyroxine (Synthroid®) 137mcg; 1 tablet by mouth every day
- Omeprazole (Prilosec®) 20mg; take 2 capsules (40mg) by mouth every day
- Oxycodone (Oxy IR®) 5mg; 1 tablet by mouth every 2 hours as needed for pain
- Quetiapine (Seroquel®) 25mg; 1 tablet by mouth every 12 hours
- Valsartan (Diovan®) 40mg; 1 tablet by mouth every day (hold for HR < 60 and SBP < 100)
- Warfarin (Coumadin®) 2mg; 1 tablet by mouth every day
- Zolpidem (Ambien®) 5mg; 1 tablet by mouth at bedtime as needed for sleep
- Sennosides/Docusate 8.6/50mg; 2 tablets by mouth every day for constipation (hold for loose stool)

MK was treated for pseudomembranous colitis due to C. *difficile* infection with a 10-day course of Metronidazole (Flagyl®). She completed the antimicrobial course 4 weeks ago and is now presenting with diarrhea consistent with *C. diff* infection.

**OVERVIEW OF *CLOSTRIDIOIDES DIFFICILE* INFECTION[1]**

*Clostridioides* (formerly *Clostridium*) *difficile* infection (CDI) is one of the most common hospital-acquired (nosocomial) infections and is an increasingly frequent cause of morbidity and mortality among older adult hospitalized patients. *C. difficile* colonizes the human intestinal tract after the normal gut flora has been disrupted (frequently in association with antibiotic therapy) and is the causative organism of antibiotic-associated diarrhea and pseudomembranous colitis.

Recurrent *C. difficile* infection is defined by resolution of CDI symptoms while on appropriate therapy, followed by reappearance of symptoms within two to eight weeks after treatment has been stopped.[2]

**RISK FACTORS [3-10]**

- Age (> 80% deaths from CDI are age 65 and older)
- Complicated medical care and extended stays in healthcare settings, especially hospitals and nursing homes
- A weakened immune system
- Previous infection with *C. diff* or known exposure
- Antibiotic therapy (increases risk **7 to 10 times** while taking and during the month after)

**ASSOCIATION OF PROTON PUMP INHIBITOR THERAPY & *C. DIFF* INFECTION**

Proton pump inhibitor (PPI) (e.g., omeprazole) use is associated with an increase in *C. difficile* infections and diarrhea. The FDA and Health Canada have issued warnings that, though evidence is limited for a firm cause and effect relationship, the link between PPIs and *C. difficile* infection cannot be ruled out.[3,4] A population-based cohort study suggested that both PPIs and histamine-2 (H2) blockers (e.g., ranitidine) are associated with an increased risk of *C. difficile* and *Campylobacter* gastroenteritis in both the hospital and community.[6] For every 533 patients receiving a daily PPI in the hospital, at least one will develop *C. difficile.*[7] In addition, a retrospective, cohort study showed PPI use was associated with a 42% increased risk of recurrent *C. difficile* infection within 90 days.[8]

In order to prevent associated infection:

- Ensure PPIs have a clear indication and duration with regular reassessment of necessity
- Use PPIs cautiously in patients at risk for *C. difficile* infection (see "Risks" in section above)
- Consider H2-blockers as alternatives to PPIs when appropriate (risk of *C. diff* is comparatively less)

**PREVENTION WITH USE OF PROBIOTICS [11-15]**

Probiotics are live organisms that provide therapeutic or preventative benefit for the host. The most commonly used probiotics are the lactic-acid producing bacteria *bifidobacteria* and *lactobacilli.* Probiotics also include the yeast *Saccharomyces boulardii.* Probiotics are promoted to strengthen the immune system or recolonize the gut or vagina with beneficial microbes. Accordingly, patients may express interest in using them to protect against infectious disease (e.g., influenza), antibiotic-associated diarrhea, or vaginitis. They are presumed harmless in healthy patients however in rare cases, such as in immunocompromised patients, probiotics can cause infection.

Studies on the use of probiotics for prevention of *C. diff* are sparse and inconsistent. While some suggest they may be effective or ineffective, many studies find insufficient evidence to produce any recommendation. Also, the efficacy of one probiotic product can't be extrapolated to other products. Currently there is no formal guidance for the use of probiotics as a preventative therapy for *C. diff* infections. As such, it is recommended to avoid probiotics in seriously ill patients, as well as those with Crohn's disease, unless there is a medical indication.

**TREATING RECURRENCE [1,16]**

For patients presenting with a first recurrence of *C. diff* infection who were treated with oral fidaxomicin (Dificid®) or metronidazole (Flagyl®) for the initial episode, treatment with oral vancomycin is appropriate:

- Vancomycin 125 mg orally four times daily for 10 days

For patients presenting with a first recurrence of *C. diff* infection who were initially treated with oral vancomycin, treatment with oral vancomycin administered in a pulse-tapered fashion or oral fidaxomicin (Dificid®) are appropriate:

- Fidaxomicin 200 mg orally twice daily for 10 days

- Tapered and pulsed vancomycin. For example:
    - 125 mg orally four times per day for 10 to 14 days, followed by

  - 125 mg orally twice a day for 7 days, followed by
  - 125 mg once a day for 7 days, and then once daily every 2 or 3 days for up to 8 weeks (the doses in this 8-week regimen are considered "pulses" with a goal of preventing *C. difficile* spores from forming while restoring the normal flora)

- Alternative 42-day vancomycin taper may read:
  - 125 mg orally four times per day for 7 days, then
  - 125 mg orally twice a day for 7 days, then
  - 125 mg orally once a day for 7 days, then
  - 125 mg orally every other day for 7 days, then
  - 125 mg orally every three days for 14 days

**PATIENT CASE ASSESSMENT AND PHARMACIST'S RECOMMENDATIONS**

MK presents with *C. diff* infection 4 weeks after initial therapy for *C. diff* infection ended. Being within 2 to 8 weeks of therapy completion, this is considered a recurrence where the initial infection had been treated with Metronidazole (Flagyl®). A regimen of Vancomycin 125 mg orally four times daily for 10 days is recommended.

An additional consideration would be evaluation of the current PPI regimen of Omeprazole 40mg twice daily. When used chronically, PPIs maintain a side effect of decreasing the absorption of certain medications, including antimicrobials. Also, with a reported association between *C. diff* infection and long-term use of PPIs and no compelling indication for MK to remain specifically on a PPI, it is reasonable to suggest 1 or more of the following:

- Holding Omeprazole treatment during antimicrobial treatments now and going forward
- Switching Omeprazole therapy to H2-blocker therapy with Famotidine (Pepcid®) after antibiotic treatment is completed
- Discontinuing acid suppression therapy all together and monitoring MK for return of dyspeptic symptoms

**For additional information on this topic, please review these references:**

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