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Updates in the Treatment of *Clostridioides difficile* Infection

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Disclosure/Conflict of Interest

I, Spencer Durham, have no actual or potential conflict of interest in relation to this program.

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PHARMACIST OBJECTIVES

- Review the pathogenesis of *C.difficile* infections
- Describe the major recommendations of the 2018 *C.difficile* clinical practice guidelines
- Recognize the recommendations of the focused guideline update from 2021
- Given a patient case, identify the appropriate pharmacotherapy treatments for a patient with *C.difficile* infection

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INTRODUCTION

- Catherine Duff
  - Featured patient in the IDSA report "Faces of Antimicrobial Resistance"
- Diagnosed with severe diverticulitis, requiring surgery to remove one-third of her colon
- Subsequently, she developed an abdominal abscess that burst, requiring further surgery and developed subsequent sepsis due to MRSA
- Antibiotics used to treat sepsis caused a *C.difficile* infection (CDI)

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INTRODUCTION

- Ms. Duff subsequently had a total of 8 different episodes of *C.difficile* over several years, each one worse than the last
  - Each time took longer for her to recover
- Experienced up to 30 diarrhea episodes in a day, became bedridden, and lost almost 70 pounds
- Eventually, her doctors told her she would not survive the infection
- Ms. Duff and her husband performed a fecal microbiota transplant (FMT) at home, resulting in rapid improvement
- A subsequent surgery resulted in another infection with resistant *C.difficile*
- Another FMT was performed via colonoscopy, with great success
- Ms. Duff subsequently started The Fecal Transplant Foundation

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CLOSTRIDIOIDES DIFFICILE

- Not generally a component of the normal microflora in adults
- Infection occurs after ingestion of spores or vegetative cells
- Spores are highly resistant to acid, allowing passage through the GI tract
- If normal GI microflora is intact, colonization does not usually occur
- If GI microflora is disrupted, replication will occur
  - Often follows broad-spectrum antibiotic use
- Alcohol-based disinfectants are ineffective
  - Traditional hand washing must be used to remove the bacteria

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CLOSTRIDIOIDES DIFFICILE

- Two exotoxins are associated with active disease
- Toxin A
  - Activates inflammatory cells which release cytokines
  - Causes increased mucosal permeability and loss of fluids
- Toxin B
  - Cytotoxic
  - Causes further damage to GI mucosa after the initial damage from Toxin A
- Hyper-virulent strains (NAP1/BI/027) are emerging

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CLOSTRIDIOIDES DIFFICILE

- Risk factors for infection
  - Recent use of antimicrobials (usually broad-spectrum)
    - Usually broad-spectrum agents, but can occur with narrow-spectrum agents
  - Long-term exposure or exposure to multiple antimicrobials
  - Age >65 years
  - Underlying immune suppression
  - PPI/H2 blocker use
  - Female gender
  - GI tract manipulation
- Traditionally considered a nosocomial infection, but community-associated infections are increasing

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CLOSTRIDIUM DIFFICILE

- Antimicrobials associated with infection

High Risk	Moderate Risk	Low Risk
• Clindamycin • Extended-spectrum cephalosporins • Fluoroquinolones • Ampicillin/amoxicillin	• TMP/SMX • Macrolides • Penicillins	• Vancomycin • Aminoglycosides • Metronidazole

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CLOSTRIDIOIDES DIFFICILE

- Signs and symptoms:
  - Watery diarrhea
    - New onset ≥3 unformed stools in 24 hours
  - Severe abdominal pain/cramps
  - Nausea/vomiting
  - Fever
  - Anorexia
  - Malaise
- Serious complications:
  - Pseudomembranous colitis
  - Toxic megacolon

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TREATMENT OPTIONS

- Pharmacotherapy options
  - Vancomycin
  - Fidaxomicin
  - Metronidazole
  - Rifaximin
  - Bezlotoxumab
- Other treatments
  - FMT

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VANCOMYCIN

- Historically, considered the drug of choice for the management of *C. difficile* infections
- Highly effective for the treatment
  - High stool concentrations
- Most commonly used antibiotic until the mid-1990s
  - Vancomycin-resistant enterococcus (VRE) emerged as an important pathogen
  - Call for more judicious use of vancomycin
  - Metronidazole was shown to be equally effective to vancomycin, so it became the first-line therapy
- Few ADRs with oral formulation – GI disturbances is most common

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METRONIDAZOLE

- Oral metronidazole considerably cheaper than oral vancomycin
- Lower fecal concentrations achieved than oral vancomycin
  - Lower levels of the drug might theoretically lead to treatment failures and increased antimicrobial resistance
  - Clinical trials show comparable results between the two agents
- Recurrence may be more likely in patients treated with metronidazole, especially those ≥ 65 years
- Used a first-line option for many years, but the 2017 guidelines relegated it to being used only when vancomycin or fidaxomicin are not available

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FIDAXOMICIN

- First approved for use in May 2011
  - First new drug approved for *C. difficile* in 31 years
- Lower MIC *in vitro* for *C. difficile* compared to metronidazole or vancomycin
- Prolonged post-antibiotic effect
  - 10 hours
  - Allows for BID dosing
- Poorly absorbed from GI tract, resulting in high fecal concentrations
  - Low systemic absorption, and thus fewer systemic adverse effects
- Minimal effects on other GI flora compared to metronidazole and vancomycin

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FIDAXOMICIN

- Blocks toxin production in *Clostridium* species
- May also inhibit sporulation
- When compared to vancomycin, fidaxomicin showed equal efficacy for treatment of CDIs
- Fidaxomicin was superior to vancomycin in preventing recurrence of CDI
- Now recommended as a first-line treatment option and in recurrent infections

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BEZLOTOXUMAB

- First approved in October 2016
- Monoclonal antibody that binds to *C.difficile* toxin B to neutralize it and prevent damage to the colon
  - One-time infusion of 10 mg/kg
- Indicated to prevent recurrent infections in patients considered high risk
- Must use during an active CDI while taking antibiotics
- Generally well-tolerated, although caution must be used in patients with congestive heart failure
- Not addressed in the 2017 guidelines due to late approval in 2016, but addressed in the 2021 update

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FMT

- Highly effective for the treatment of CDI
- 80-90% successful treatment
- Goal is to restore the microflora of the intestinal tract to a diseased recipient from a healthy individual
- Various ways of administer:
  - Enema
  - Oral capsule
  - Gastric tube
  - Colonoscopy

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FMT

- Although highly efficacious, it is generally reserved for patients who have had repeated infections or those with known antimicrobial resistance
- Considered a medical procedure with associated risks
- Though rare, transmission of a multidrug-resistant organism can occur
- Long-term risks are not well-defined
- More expensive compared to traditional pharmacotherapy options
- Possible concerns with availability

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CLOSTRIDIOIDES DIFFICILE TREATMENT GUIDELINES

- Released February 2018
  - Considered the "2017 guidelines"
- Joint publication of the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Disease Society of America (IDSA)
- Provides recommendations for diagnosis, treatment, infection control, and environmental management
- Several changes from prior guidelines were introduced

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2017 GUIDELINE RECOMMENDATIONS

- Highlight of changes in the updated guidelines
  - Use of metronidazole is no longer recommended except when access to first-line agents is not available
    - Higher rate of recurrence
  - Fidaxomicin introduced as a first-line agent
    - Prior guidelines were released before the introduction of fidaxomicin to the market
  - Fecal microbiota transplantation (FMT) introduced as a potential option for recurrent infections

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2017 GUIDELINE RECOMMENDATIONS

- Diagnosis:
  - Testing should only be performed on diarrheal (unformed) stool
  - Testing in asymptomatic patients (including a test of cure) is not recommended
  - Gold standard: stool cultures
    - Very slow turnaround time – only use for epidemiological studies
  - Diagnosis should be made based on a multistep algorithm that includes a stool toxin test

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2017 GUIDELINE RECOMMENDATIONS

- Infection control measures:
  - Gloves/gowns used at all times
  - Soap and water for hand hygiene
    - NOT alcohol-based hand sanitation products
  - Use private room with contact precautions
    - Maintain at least for duration of diarrhea
  - Remove potential environmental sources for CDI
    - Electronic rectal thermometers

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2017 GUIDELINE RECOMMENDATIONS

- Antimicrobial use restrictions:
  - Use of an antimicrobial stewardship program is useful to reduce the risk of CDI
  - Restrict the use of fluoroquinolones, cephalosporins, and clindamycin
- Use of probiotics is not currently recommended for treatment or prevention
  - Limited data for usefulness
  - Possible risk for bacteremia/sepsis in susceptible populations
    - Neutropenic patients
    - Underlying immune suppression

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2017 GUIDELINE RECOMMENDATIONS

Severity Classification	Criteria
Non-severe	WBC count ≤ 15,000 cells/μL PLUS SCr < 1.5 mg/dL
Severe	WBC count ≥ 15,000 cells/μL OR SCr ≥ 1.5 mg/dL
Fulminant	Hypotension or shock ileus, megacolon

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PATIENT CASE

- DB is a 68-year-old female admitted to the hospital for treatment of community-acquired pneumonia.
- She has been managed for the past week on therapy with levofloxacin 750 mg IV once daily.
- On day 7, she begins experiencing severe diarrhea. A toxin test is positive for *C. difficile*.
- Allergies: NKDA
- Labs: WBC-16.2, SCr-1.4 (1.2 on admission)
- PE:
  - BP-140/86
  - HR-72
  - RR-22
  - Temp-99°F

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PATIENT CASE

How would the severity of DB's current C. *difficile* infection best be characterized?

A. Non-severe
B. Severe
C. Fulminant
D. He is colonized but is not experiencing true infection

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2017 GUIDELINE RECOMMENDATIONS

- Discontinue the suspected antimicrobial ASAP
  - Less likely to have recurrence of infection
- Begin treatment immediately if:
  - Fulminant infection is present, or
  - A significant delay in laboratory confirmation is expected
- Use of antiperistaltic agents (i.e., loperamide) has not been historically recommended, but studies are lacking
- Fluid/electrolyte replacement as needed

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INITIAL TREATMENT

Classification	Treatment
Initial, non-severe	• Vancomycin 125 mg PO QID for 10 days OR • Fidaxomicin 200 mg PO BID for 10 days * Can use metronidazole 500 mg PO TID for 10 days only if above agents are unavailable
Initial, severe	• Vancomycin 125 mg PO QID for 10 days OR • Fidaxomicin 200 mg PO BID for 10 days
Initial, fulminant	Vancomycin 500 mg PO QID + metronidazole 500 mg IV Q8H ADD rectal vancomycin if ileus is present

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TREATMENT

- First recurrence
  - Vancomycin 125 mg PO QID x 10 days
    - If metronidazole was used for initial episode
  - Prolonged or pulsed vancomycin if standard dose was used for initial episode
    - Vancomycin PO 125 mg QID x 10-14 days, then
    - 125 mg BID x 7 days, then
    - Daily x 7 days, then
    - Once every 2-3 days x 2-8 weeks
  - Fidaxomicin 200 mg BID x 10 days
    - If vancomycin was used initially

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TREATMENT

- Second or subsequent recurrence
  - Pulsed or tapered vancomycin
  - Vancomycin 125 mg PO QID for 10 days, followed by rifaximin 400 mg PO TID for 20 days
  - Fidaxomicin 200 mg PO BID for 10 days
  - Fecal microbiota transplantation
    - Antimicrobial treatment should be attempted for at least 2 recurrences (3 total episodes) prior to FMT

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2021 FOCUSED UPDATE

- In 2021, the IDSA and SHEA issued a "Focused Update" on the management of *C.difficle* infections
- This update specifically addresses the use of fidaxomicin and bezlotoxumab
  - Includes information not available at the time of the publication of the 2017 guidelines
- Focuses exclusively on the management of adult patients
- Major recommendations from the 2017 guidelines still apply

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2021 FOCUSED UPDATE

- Fidaxomicin should be used preferentially over vancomycin for first episodes of CDI
  - Guidelines acknowledge that this may not always be possible depending on the availability of resources
  - Oral vancomycin is an acceptable alternative
- Includes data from 2 new trials not available in 2017
- Pooled results show comparable clinical cure between fidaxomicin and vancomycin, but higher sustained clinical response at 4 weeks with fidaxomicin
  - Especially important for patients at high risk of CDI recurrence

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2021 FOCUSED UPDATE

- Fidaxomicin should be preferentially used over standard course vancomycin in cases of recurrent CDI
  - One additional trial is now available
  - Pooled data suggest a fidaxomicin benefit with sustained response at 30 days compared with vancomycin
    - No benefit seen at 90 days
- Standard dose vancomycin or pulsed dose vancomycin are acceptable alternatives
- Pulsed dose vancomycin, vancomycin plus rifaximin, fidaxomicin, or FMT are all options for patients with multiple recurrences

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2021 FOCUSED UPDATE

- Bezlotoxumab should be used as a co-intervention along with standard antibiotics for patients with a recurrent CDI episode within the last 6 months
  - Logistics and feasibility may limit the use of this recommendation
- Could be considered during an initial CDI episode for patients at high risk of recurrence (older adults, immunocompromised, etc.)
- Two randomized controlled trials demonstrate benefit at reducing CDI at 12 weeks
  - No benefit with mortality
- In patients with congestive heart failure, benefits of bezlotoxumab must outweigh the risks of use

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PATIENT CASE CONT.

Which of the following would be the most appropriate treatment of D.B.'s *C. difficile* infection at this time?

A. Metronidazole 500 mg PO TID for 10-14 days
B. Vancomycin 125 mg PO QID for 10 days
C. Vancomycin 500 mg PO QID + metronidazole 500 mg IV Q8H
D. Fidaxomicin 200 mg PO BID for 10 days

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PATIENT CASE CONT.

- Should we consider the addition of bezlotoxumab for this recurrence?
  A. Yes, the patient has had a single recurrence within 6 months of the first
  B. No, the patient must have at least one other recurrence before using bezlotoxumab
  C. Yes, but the bezlotoxumab should be administered after completing the antibiotic course
  D. No, the patient has a contraindication to bezlotoxumab

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PATIENT CASE CONT.

The patient was successfully cured of the CDI, but presented back to his PCP in 4 weeks with severe diarrhea and was diagnosed with a recurrent infection. What would be the most appropriate treatment at this time?

A. Metronidazole 500 mg PO TID for 10-14 days
B. Vancomycin 125 mg PO QID for 10 days
C. Vancomycin 500 mg PO QID + metronidazole 500 mg IV Q8H
D. Fidaxomicin 200 mg PO BID x 10 days

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CLINICAL PEARLS

- Metronidazole is no longer recommended as a first-line option and should only be used when vancomycin or fidaxomicin are not available
- Diagnosis should be made with combination of clinical signs and laboratory testing
  - Patients should not be screened for infection without having signs and symptoms
- Be mindful of this infection whenever patients are on broad-spectrum antimicrobials
- Fidaxomicin should generally
- FMT may be considered after multiple infections

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QUESTIONS???

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