Update on the Treatment of Clostridium difficile Infections

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Disclosure
• The presenters have no actual or potential conflicts of interest related to this presentation.

Objectives
• At the completion of this activity, the participant will be able to:
  • Recall the pathophysiology of CDIs
  • Formulate an empirical treatment regimen based upon presentation
  • Develop a treatment regimen for patients with recurrent infections
  • Investigate non-traditional methods of treating CDIs

Definitions
• CDI - Clostridium difficile infection
• CDAD – Clostridium difficile associated diarrhea
• PC – pseudomembranous colitis
• FMT – fecal microbiota transplantation

Epidemiology
• Increase in incidence of 400% during the past 10 years
• 3rd most common nosocomial infection
• Four-fold increase in CDI related mortality between 1999 and 2011
• 700,000 new cases each year in the US
• Increase in infection severity
• Increased hospital cost and length of stay
• Increase in number of community-associated cases

Clostridium species
• Gram-positive bacilli
• Obligate anaerobes
• Spore-forming
  • Allows survival in environmental extremes
• Ubiquitous in the environment
  • Commonly found in soil
• All species produce exotoxins
  • Important for pathogenesis
**Clostridium species**

- *C. difficile*
  - Gastrointestinal disturbances, CDAD, PC
- *C. perfringens*
  - Gas gangrene
- *C. botulinum*
  - Food poisoning
- *C. tetani*
  - Tetanus

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**Clostridium 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

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**Clostridium 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

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**Clostridium difficile**

**CDI**

- Risk factors for infection
  - Recent use of antimicrobials (usually broad-spectrum)
    - Usually broad-spectrum agents, but can occur with narrow-spectrum agents
  - Age >65 years
  - Underlying immune suppression
  - Increasing incidence seen in:
    - Peripartum women
    - Otherwise healthy, community-dwelling persons
CDI

- Signs/Symptoms:
  - Watery diarrhea
  - Severe abdominal pain/cramps
  - Nausea/vomiting
  - Fever
  - Anorexia
  - Malaise

- Serious Complications:
  - PC
  - Toxic megacolon

CDI

- Why the sharp increase in incidence?
  - Increased use of broad-spectrum antimicrobials
  - Emergence of hyper-virulent strains
    - NAP1/BI/027
  - Increase in number of at-risk patients
    - Patients are living longer lives
      - More people >65 years of age
      - Advances in medical treatment
        - Patients with immunological abnormalities are living longer lives

CDI

- Antimicrobials associated with infection:
  - Clindamycin
  - Cephalosporins
    - 2nd, 3rd, and 4th generation
  - Extended-spectrum penicillins
  - Fluoroquinolones
    - Moxifloxacin
  - Aminopenicillins
    - Community-associated CDI

CDI Guidelines

- Published May 2010
- 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
- NOTE: New guidelines projected Spring 2016

CDI Guidelines

- Diagnosis:
  - Testing should only be performed on diarrheal (unformed) stool
  - Testing in asymptomatic patients (including a test of cure) is not useful
  - Cell cytotoxin assay testing is clinically highly useful though not sensitive, but should be utilized
  - Enzyme immunoassay (EIA) is rapid but less sensitive than cytotoxin assay
  - Gold standard: stool cultures
    - Very slow turnaround time – only use for epidemiological studies

CDI Guidelines

- 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
CDI Guidelines

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

- **Treatment:**
  - D/C use of suspected antimicrobial ASAP
    - Less likely to have recurrence of infection
  - Begin treatment immediately if severe or complicated CDI is suspected
  - If toxin assay is negative, treatment decisions must be individualized
  - Do not use antiperistaltic agents
    - Can hide symptoms
    - Associated with toxic megacolon

- **DOC for mild/moderate infections:**
  - Metronidazole 500 mg PO TID for 10-14 days

- **DOC for severe infections:**
  - Vancomycin 125 mg PO QID for 10-14 days

- **DOC for severe, complicated infections**
  - Vancomycin 500 mg PO QID + metronidazole 500 mg IV Q8H
    - Can also ADD rectal vancomycin if ileus is present
  - Treatment for 1st episode of recurrence is the same as initial therapy

- **Vancomycin**
  - Glycopeptide antibiotic
  - MOA: inhibition of cell-wall synthesis
  - Very large, polar molecule
    - Only effective against gram-positive organisms
  - Commonly used in the inpatient setting for management of severe gram-positive infections
    - Requires therapeutic drug monitoring (TDM)
  - Oral formulation stays in the GI tract
    - Does not cross into the bloodstream
    - No TDM

- **Surgical intervention (colectomy):**
  - Use only if severely ill
  - Increased perioperative mortality associated with:
    - Serum lactate 5 mmol/L
    - WBC 50,000 cells/mm³
    - Monitor these labs closely
  - If surgical intervention is utilized, perform subtotal colectomy with preserved rectum

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Vancomycin
- Historically, considered the DOC for the management of CDI
- Highly effective for the treatment of CDIs
- 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

Metronidazole
- Nitroimidazole antimicrobial
- MOA: inhibition of protein synthesis via DNA interaction that results in a loss of the helical DNA structure and strand breakage
- Only effective for anaerobic organisms
- Available in IV, PO, and topical formulations
- Used extensively in both the inpatient and outpatient settings for a wide variety of disease states

Metronidazole
- Two different trials have shown oral metronidazole to be equally efficacious to oral vancomycin for the treatment of CDI
- Oral metronidazole considerably cheaper than oral vancomycin
- Lower fecal concentrations achieved than oral vancomycin
  - Low levels of resistance might theoretically lead to treatment failures
  - Recommended as first-line treatment for first episode of CDIs

Fidaxomicin
- First approved for use in May 2011
- Macrolide antimicrobial
- Bactericidal
- MOA: suppression of RNA synthesis, thus inhibiting bacterial protein transcription and ultimately protein synthesis
- Lower MIC in vitro for C. difficile compared to metronidazole or vancomycin

Fidaxomicin
- Spectrum of activity:
  - More potent for Clostridium species compared to other bacteria
  - Also displays activity against other gram-positive species
    - Modest activity against Staphylococcus and Enterococcus, including VRE
  - NO activity against:
    - Gram-negatives
    - Yeasts

Fidaxomicin
- 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
**Fidaxomicin**

- Blocks toxin production in *Clostridium* species
- May also inhibit sporulation
- When compared to vancomycin, fidaxomicin showed equal efficacy for treatment of CDI
- Fidaxomicin was superior to vancomycin in preventing recurrence of CDI
- Usual dose: 200 mg PO BID for 10 days

**Fidaxomicin**

- Adverse effects:
  - Comparable to oral vancomycin
  - Bone marrow suppression (?)
  - Pregnancy category B
- Disadvantages:
  - Cost
  - Less clinical experience compared to metronidazole and vancomycin

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**Fidaxomicin**

- Place in therapy:
  - Will almost certainly be included in the updated guidelines

**Fecal transplantation**

- Fecal microbiota transplantation (FMT)
  - Goal is to restore the microflora of the intestinal tract to a diseased recipient from a healthy individual
  - Various ways of accomplishment:
    - Enema
    - Oral capsule
    - Gastric tube
  - Appears highly effective for recurrent CDIs

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**Fecal transplantation**

- Traditionally thought of as a “last-line” approach to management
- 2013 randomized controlled trial showed FMT to be superior to vancomycin for the treatment of recurrent CDI
- May be more cost effective compared to repeated courses of antibiotics for treatment
- Would likely be associated with decreased antimicrobial resistance

**Fecal transplantation**

- Not assessed in the current CDI treatment guidelines
- Currently, FMT is being used in patients who have multiple recurrent episodes of CDI or those who have severe disease where antibiotics appear to be ineffective
- Updated guidelines will likely make a recommendation for use of FMT
Question 1
- D.B. is a 60 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. diff. Which of the following is the most appropriate management for D.B. at this time?
  - A) Vancomycin 250 mg PO QID for 14 days
  - B) Metronidazole 500 mg PO TID for 10 days
  - C) Vancomycin 125 mg PO QID for 10 days
  - D) Fidaxomicin 200 mg PO BID for 10 days

Question 2
- S.G. is a 48 year old male who has had 9 episodes of CDI during the past 3 years. He has been treated with metronidazole, vancomycin, and fidaxomicin multiple times. What would be the most appropriate management for the patient at this time?

Question 3
- Which of the following drugs would theoretically be the most effective option for the treatment of CDI based on MOA, pharmacokinetic, and pharmacodynamic properties?
  - A) Metronidazole
  - B) Vancomycin
  - C) Fidaxomicin
  - D) None of the above

Question 4
- I.O. is a 32 year old female who is currently experiencing a second recurrence of CDI. Both of the prior infections were treated with oral metronidazole. What would be the most appropriate treatment option at this time?
  - A) Another course of metronidazole
  - B) Oral vancomycin in a pulsed regimen
  - C) Vancomycin plus metronidazole
  - D) FMT

Question 5
- H.B. is a 70 year old who presents to the hospital with a severe first episode of CDI. What would be the most appropriate management for him at this time?
  - A) Vancomycin 250 mg PO QID for 14 days
  - B) Metronidazole 500 mg PO TID for 10 days
  - C) Vancomycin 125 mg PO QID for 10 days plus fidaxomicin 200 mg PO BID for 10 days
  - D) Vancomycin 500 mg PO QID plus metronidazole 500 mg IV

QUESTIONS???