Management of Recurrent C. Difficile Associated Diarrhea (CDAD)

October 12, 2006

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Outline

1. Overview of patient case

2. Review C. difficile associated diarrhea (CDAD)
   a. Signs and symptoms
   b. Pathophysiology
   c. Risk factors

3. Evaluate treatment options for CDAD
   a. Initial episodes
   b. Recurrent episodes

4. Apply pharmacy care plan principles to case
Overview of Patient Case
Patient Case: Mrs. K

HPI
- 78 year old female
- Right great toe - red, swollen, painful
- White pus-like discharge oozing from corn

Vitals
- BP 170/88, HR 77
- RR 18, T 35.9°C

Labs
- WBC 6.6, SCr 76

Allergies & Intolerance
- Penicillamine
  - Thrombocytopenia
- Codeine
  - GI upset
Past Medical History

- Rheumatoid arthritis
- Hypertension
- Chronic anemia
- Fibromyalgia
- Osteoarthritis – knees bilaterally
- Infectious colitis / diverticula (2005)
- Intracranial hemorrhage due to aneurysm (2002)
# Medication History

<table>
<thead>
<tr>
<th>Condition</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid Arthritis</td>
<td>Etanercept 25 mg SC 2x / week</td>
</tr>
<tr>
<td></td>
<td>Prednisone 5 mg po OD</td>
</tr>
<tr>
<td></td>
<td>MTX 7.5 mg po 1x / week</td>
</tr>
<tr>
<td></td>
<td>Folic acid 5 mg po OD</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Candesartan 16 mg po OD</td>
</tr>
<tr>
<td></td>
<td>HCTZ 12.5 mg po OD</td>
</tr>
<tr>
<td>Primary Stroke Prevention</td>
<td>ASA EC 81 mg po OD</td>
</tr>
<tr>
<td>Chronic Anemia</td>
<td>Ferrous gluconate 300 mg po OD</td>
</tr>
<tr>
<td>Other</td>
<td>Docusate 100 mg po BID</td>
</tr>
<tr>
<td></td>
<td>Senna 8.6 mg po QHS</td>
</tr>
</tbody>
</table>

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History of Present Illness

7 months ago

- S. aureus osteomyelitis of right great toe
  - Tx - incision and drainage
  - Rx - cloxacillin 2 g Q6H x 8 wks

1 month ago

- Cellulitis of right great toe
  - Rx – clindamycin 300 mg po Q6H
Relevant History

15 days ago

- severe CDAD post-clindamycin treatment
  - Rx – 14 d course:
    - Vancomycin 125 mg po Q6H
    - Metronidazole 500 mg po Q8H

- Patient c/o intolerance to antibiotics
  - Unclear whether patient was compliant
Cultures & Sensitivities

- **Blood (peripheral)**
  - + GPC (CNST)
    - S: Ancef / Clinda / Clox / Erythro / Septra / Vanco

- **Wound Swab (R great toe)**
  - + GPC (S.aureus)
    - S: Ancef / Clox / Septra
    - R: Clinda / Erythro
Diagnostics

- X-Ray (R Foot):
  - R great toe
    - Soft tissue swelling
    - Bone resorption
    - Chronic appearance

- Diagnosis:
  - Osteitis and cellulitis of right great toe
Clinical Course in Hospital

- Rx - Cephalaxein 250 mg po Q6H
  - Result? ↓ erythema of right great toe

- Orthopedics recommends lifelong antibiotic prophylaxis treatment
  - Rx - Cefadroxil 500 mg po BID
Clinical Course in Hospital

1 week post-antibiotic treatment

- Mrs. K experiences “explosive diarrhea”

- WBC 15.0, T 38.8°C

- Stool culture: + C. difficile toxin

- Team wants indefinite metronidazole treatment
Issues

1. C. difficile associated diarrhea (CDAD)

2. Acute cellulitis and osteitis of great toe

3. Rheumatoid arthritis management

4. Prevention of osteoporosis
Review of C. difficile-associated Diarrhea (CDAD)
Infectious Diarrhea

Adapted from IDSA Guidelines for Management of Infectious Diarrhea

Decision tool can be found in Aslam et al. Gastroenterol Clin N Am 2006; 35: 315-335
Antibiotic-Associated Diarrhea

- Unexplained diarrhea that occurs in association with the administration of antibiotics
- Occurs in 3-29% of hospitalized patients

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Incidence Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin-Clavulanate</td>
<td>10-25%</td>
</tr>
<tr>
<td>Cefixime</td>
<td>15-20%</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>5-10%</td>
</tr>
<tr>
<td>Other cephalosporins, quinolones, macrolides, tetracycline</td>
<td>2-5%</td>
</tr>
</tbody>
</table>

Bartlett JG. NEJM 2002; 346(5): 334-339
C. difficile-Associated Diarrhea

- C. difficile is causative organism in:
  - 10-25% of antibiotic-associated diarrhea
  - 50-75% of antibiotic-associated colitis
  - 90-100% of antibiotic-associated pseudomembranous colitis

Significance of CDAD

- ↑ length of hospitalization
  - Often adds up to 2 additional weeks
  - Additional cost of $6 000-10 000 per case

- ↑ mortality
  - 2-5% in otherwise healthy patients
  - 10-20% in elderly or debilitated patients
  - 30-80% in fulminant colitis or toxic megacolon

Mylonakis et al. Arch Intern Med 2001; 161: 525-533
Yassin et al. Mayo Clin Proc 2001; 76: 725-730
Microbiology of C. difficile

- Clostridium difficile
  - Gram positive
  - Anaerobic bacillus
  - Spore forming

- Fecal-oral route of transmission
Reservoirs of C. difficile

- Colonized or infected patients
- Contaminated surfaces
- Hospitals and nursing homes
- Hands of hospital personnel
Clinical Presentation

- Onset varies from 1 day to 6 weeks after antibiotic use

- Variable presentation
  - Watery or mucoid diarrhea
  - ± abdominal pain
  - ± low grade fever
  - ± occult blood
  - ± pseudomembranous colitis
Signs and Symptoms

1/3 of colonized patients are symptomatic

- **Mild to moderate**
  - Lower abdominal cramping
  - No systemic symptoms

- **Moderate to severe**
  - Abdominal distention with pain
  - Ileus, toxic megacolon
  - Systemic systems (fever, nausea, malaise)
  - Profuse diarrhea may or may not be present

Mylonakis et al. Arch Intern Med 2001; 161: 525-533
Pathogenesis

1. Alteration of normal fecal flora
   - Antibiotics, antineoplastics, immunosuppressants

2. Colonization of colon with C. difficile
   - Ingested spores are acid-resistant and germinate in the bowel upon exposure to bile acids

3. Growth and toxin release in the colon
   - C. difficile multiplies and releases Toxin A & B

Poutanen et al. CMAJ 2004; 171(1): 51-58
*Clostridium difficile* spores and vegetative cells are ingested

- **Spores**
- **Vegetative cells**

Most vegetative cells are killed in the stomach, but spores can survive the acid environment

*Clostridium difficile* spores germinate in the small bowel upon exposure to bile acids

Flagella facilitate *C. difficile* movement; a polysaccharide capsule discourages phagocytosis

*C. difficile* multiplies in the colon

Gut mucosa facilitates adherence to the colonic epithelium

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Poutanen et al. CMAJ 2004; 171(1): 51-58
Toxic Effects of C. Difficile

- **Toxin A** – enterotoxin and cytotoxin
  - Induces necrosis and loosens tight junctions of epithelial cells facilitating entry of Toxin B
  - induces inflammation, chemotaxis and fluid secretion

- **Toxin B** – cytotoxin
  - induces inflammation, chemotaxis and fluid secretion
  - 1000x more cytotoxic than Toxin A

- **Binary Toxin** – unknown role in human disease

Poutanen et al. CMAJ 2004; 171(1): 51-58
C. difficile vegetative cells produce toxins A and B and hydrolytic enzymes (1). Local production of toxins A and B leads to production of tumour necrosis factor-alpha and proinflammatory interleukins, increased vascular permeability, neutrophil and monocyte recruitment (2), opening of epithelial cell junctions (3) and epithelial cell apoptosis (4). Local production of hydrolytic enzymes leads to connective tissue degradation, leading to colitis, pseudomembrane formation (5) and watery diarrhea.
Colonization Rates

- Rates proportional to duration of hospitalization and antibiotic exposure
- 3% in healthy adults
- 16-35% in hospitalized patients
- Colonization ≠ Symptomatic Disease
Significance of Immune Response

- Antibody response to toxin A protects against development of diarrhea

- Colonized patients with a high serum Ab response are more likely to be:
  - Protected against diarrhea
  - Asymptomatic carriers

Kyne et al. NEJM 2000; 342: 390-397
Risk Factors

- Increasing age
- Severe underlying illness
- Increasing length of stay in hospital
- Exposure to broad spectrum antibiotics (even 1 dose pre-surgery!)
- Use of antacids / H\textsubscript{2} antagonists / PPIs
- Use of chemotherapy or immunosuppressants
- Use of NG tubes
- GI surgery
- ICU admission

Mylonakis et al. Arch Intern Med 2001; 161: 525-533
Common Inciting Antibiotics

- Clindamycin
- 3rd Generation Cephalosporins
- Fluoroquinolones
- Amoxicillin
- Ampicillin

Mylonakis et al. Arch Intern Med 2001; 161: 525-533
All antibiotics (even vancomycin and metronidazole) can predispose patients to CDAD!!!
Cytotoxin assay is gold standard

Other non-specific markers
- Leukocytosis
- Fecal leukocytes
- Hypoalbuminemia (protein-losing enteropathy)
- Thickening of colonic wall on CT
- Pseudomembranous colitis on colonoscopy
Figure 4. Gross appearance of colon with multiple foci of Clostridium difficile–associated pseudomembranes with characteristic adherent yellow plaques that vary in diameter from 2 to 10 mm and can coalesce to cover large areas of the mucosa.
Goals of Therapy

1. Resolution of diarrhea
2. Prevent spread of C. difficile
3. Minimize risk of relapse or re-infection
General Principles of Treatment

- Isolate patient
- Hand-washing and barrier precautions
- Clean physical environment during symptomatic period

Mylonakis et al. Arch Intern Med 2001; 161: 525-533
General Principles of Treatment

- Discontinue culprit antibiotic if possible
- Give fluid and electrolytes as needed
- Avoid anti-peristaltic and opiate drugs
  - Why?
    - Mask symptoms
    - Promote retention of toxin
    - Risk of toxic megacolon
Are Antibiotics Needed?

- Diarrhea will resolve spontaneously within 48-72 hours of stopping the offending antibiotic in up to 25% of patients.

- Use of antimicrobials indicated when:
  - Moderate to severe diarrhea
  - Persistent diarrhea despite stopping antibiotic
  - Need to continue treating original infection

Mylonakis et al. Arch Intern Med 2001; 161: 525-533
Pharmacological Therapy

1st Line

- Metronidazole 250 mg po QID x 10-14 d
- OR
- Metronidazole 500 mg po BID x 10-14 d

Alternatives

- Vancomycin 125 mg po QID x 10-14 d

Poutanen et al. CMAJ 2004; 171(1): 51-58
Metronidazole vs. Vancomycin

- Metronidazole and vancomycin are equivalent\textsuperscript{1,2} with regards to:
  - Efficacy - both 90-97%
  - Relapse rate - both 10-20%

- Metronidazole is preferred
  - Less expensive than vancomycin
  - Prevent development of VRE

\textsuperscript{1} Wenisch et al. Clin Infect Dis 1996; 22: 813-818
\textsuperscript{2} Teasley et al. Lancet 1983; 2: 1043-1046
When is Vancomycin Used?

- Reserved for:
  - Metronidazole allergy or intolerance
  - Metronidazole failure or resistance
  - Pregnancy or children < 10 years of age

- Vancomycin 125 mg po QID is equivalent to 500 mg po QID with regards to:
  - Efficacy
  - Relapse

IV or PO?

- All antibiotics should ideally be given PO
  - Why? C. difficile is restricted to colonic lumen

- Vancomycin must be given PO
  - Why? drug is not excreted into the colon

- Metronidazole can be given PO or IV
  - Why? Sufficient entero-hepatic circulation
Recurrence

- Recurrence occurs in 25% of cases regardless of therapeutic agent(s) used\(^1\)
  - 50% are relapses of primary infection\(^2,3\)
  - 50% are re-infections\(^2,3\)

- Follow-up C. difficile toxin assay is not indicated
  - unreliable predictor of recurrence
    - 1/3 of patients with treatment success are assay positive\(^1\)

Proposed Mechanisms of Relapse

- Spores of *C. difficile* survive in the colon
  - Subsequent germination in the intestine produces vegetative forms and illness

- Normal flora may take up to 3 months to recover after antibiotic exposure\(^1\)

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\(^1\) McFarland LV. J Med Microbiol 2005; 54: 101-111
Risk Factors for Recurrence

- Age > 65 years
- Severe underlying illness
- ICU admission
- Low serum albumin (< 2.5 g/dL)
- Hospitalization for 16-30 days

Treatment of 1st Recurrence

- Repeat treatment with metronidazole or vancomycin for 14 d

- Studies suggest a relapse rate of 65% after treatment of recurrent disease

Treatment of Multiple Recurrences

- Tapered or pulsed antibiotic therapy
- Adjunctive treatment with probiotics
- Adjunctive treatment with binding resins

Other
- Fusidic acid
- Rifampin
- Bacitracin (not available in Canada)
- Teicoplanin (not available in Canada)
- Intravenous Immunoglobulin (IVIG)
- Human stool “transplants”
Tapered or Pulsed Therapy

- 4-6 weeks of therapy to allow C. difficile spores to germinate and be susceptible to antibiotic
  - controls C. difficile while normal flora is re-established

<table>
<thead>
<tr>
<th>Week</th>
<th>Vancomycin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>125 mg QID</td>
</tr>
<tr>
<td>2</td>
<td>125 mg BID</td>
</tr>
<tr>
<td>3</td>
<td>125 mg every day</td>
</tr>
<tr>
<td>4</td>
<td>125 mg every other day</td>
</tr>
<tr>
<td>5 and 6</td>
<td>125 mg every 3 days</td>
</tr>
</tbody>
</table>

**Fig. 1.** Effectiveness of different treatment strategies for recurrent CDAD. Different vancomycin regimes (bars) compared to the frequency of recurrences (◆) in 200 patients followed for at least 2 months post-treatment. Asterisks indicate one dose every 3 days.
Treatment with Probiotics

- Probiotics repopulate colonic flora and suppress growth of *C. difficile*

- Recent meta-analysis showed probiotics were efficacious in reducing CDAD risk
  - $RR = 0.59$, $95\% CI \, 0.41 – 0.85$, $p = 0.005$
  - Note: Results driven by trials of *S. boulardii*

McFarland LV. Am J Gastroenterol 2006; 101: 812-822
Treatment with Probiotics

- In a RCT of 124 patients, addition of Saccharomyces boulardii decreased relapse risk by 30% in 60 patients with recurrent CDAD
  - 64% vs. 34%, P < 0.05, NNT = 3

- No significant effect in treatment of 64 patients with an initial episode of CDAD

McFarland et al. JAMA 1994; 271: 1913-1918
Treatment with Probiotics

- In a RCT of 168 patients, co-treatment with S. boulardii decreased recurrence rate in patients in the high dose vancomycin (2 g po OD) treatment arm.

Figure 1. Frequency of a subsequent recurrence of *Clostridium difficile* disease (CDD) after treatment with high-dose vancomycin (2 g/day for 10 days) and either *Saccharomyces boulardii* or placebo (1 g/day for 28 days) in adult patients with active CDD.
Treatment with Anion Binding Resins

- Resins bind to C. difficile spores and toxins

- Tx: cholestyramine 4 g po BID-QID

Caution

- Resin binders can bind to oral antibiotics
- Give 1 h before or 4-6 h after antibiotics to prevent false “antibiotic resistance”

Indefinite Prophylaxis?

- Only anecdotal evidence exists for either vancomycin or metronidazole.

- Unanswered questions
  - Efficacy?
  - Development of resistance?
Efficacy of Indefinite Prophylaxis

- Vancomycin may be more efficacious due to sustained levels in the colon

- Metronidazole
  - Well absorbed by the small intestine
  - ↓ fecal levels as ↑ consistency of stool
  - Undetectable levels in healthy individual

- Vancomycin
  - Not absorbed by the small intestine
  - High fecal levels even in the absence of diarrhea
Development of Resistance

- Metronidazole resistance has been reported\(^1\), but is likely rare

- Antimicrobial resistance as the mechanism of relapse has not been documented

- Resistance may not be clinically significant
  - Fecal levels of metronidazole reach up to 500x MIC\(_{90}\)\(^2\)
  - Fecal levels of vancomycin reach up to 3000x MIC\(_{90}\)\(^2\)

Pharmacy Care Plan

DRP

- Mrs. K is experiencing signs and symptoms of recurrent CDAD and requires appropriate antimicrobial therapy

Clinical Outcome

- Resolve signs and symptoms of CDAD

Pharmacotherapeutic Outcome

- Provide optimal antimicrobial drug(s) at the right dose, frequency and duration while minimizing recurrence and resistance
## Pharmacotherapeutic Endpoint

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Degree of Change</th>
<th>Time Frame</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Resolution</td>
<td>4-5 days</td>
</tr>
<tr>
<td>Fever</td>
<td>Resolution</td>
<td>1 day</td>
</tr>
<tr>
<td>WBC</td>
<td>No increase</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>
As discussed:

- Metronidazole alone x 14 d
- Vancomycin alone x 14 d
- Indefinite metronidazole or vancomycin
- Tapered or pulsed vancomycin
- Adjunctive therapy with S. boulardii
- Adjunctive therapy with cholestyramine
- Fecal transplants
Therapeutic Plan

- Tapered vancomycin with **S. boulardii** adjunctive therapy

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<tr>
<td>4</td>
<td>125 mg every other day</td>
</tr>
<tr>
<td>5-6</td>
<td>125 mg every 3 days + <strong>S. boulardii</strong>*</td>
</tr>
<tr>
<td>7-10</td>
<td><strong>S. boulardii</strong>*</td>
</tr>
</tbody>
</table>

* Data on interchangeability of products is lacking – refer to specific product for dosing

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## Therapeutic Endpoints

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Degree of Change</th>
<th>Time Frame</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms of CDAD</td>
<td>Resolution</td>
<td>4-5 days</td>
</tr>
<tr>
<td>Ototoxicity or nephrotoxicity</td>
<td>Prevent</td>
<td>Throughout</td>
</tr>
<tr>
<td>Rash or constipation</td>
<td>Prevent</td>
<td>Throughout</td>
</tr>
<tr>
<td>Symptoms of osteitis and cellulitis</td>
<td>Prevent or Minimize</td>
<td>Throughout</td>
</tr>
</tbody>
</table>
Questions for Discussion

- How do we justify the high cost of vancomycin to patients when optimal treatment of recurrent CDAD is unclear?
  - Is metronidazole taper acceptable?

- Should our goal of therapy be bacteriologic or symptomatic cure?
Issues

1. C. difficile associated diarrhea (CDAD)

2. Acute cellulitis and osteitis of great toe

3. Rheumatoid arthritis management

4. Prevention of osteoporosis
Cellulitis

- Acute, spreading infection of the epidermis and dermis that can spread within the superficial fascia
  - Inflammation with little or no necrosis
  - Erythema and edema of skin

- Common organisms
  - Group A streptococci (S.pyogenes)
  - S.aureus
General Principles of Treatment

- Rapid eradication of the infection with antibiotics for 10-14 days

- Elevation and immobilization of area
Issues

1. C. difficile associated diarrhea (CDAD)

2. Acute cellulitis and osteitis of great toe

3. Rheumatoid arthritis management

4. Prevention of osteoporosis
Rheumatoid Arthritis (RA)

- Chronic, progressive, inflammatory autoimmune disorder characterized by:
  - Polyarticular symmetric joint involvement
  - Joint stiffness, swelling and pain
  - Rheumatoid nodules
  - Abnormal serum rheumatoid factor
  - Systemic manifestations
    - skin, blood vessels, heart, lungs, and muscles
General Principles of Treatment

- Use disease-modifying anti-rheumatic drug (DMARD) within first 3 months of symptom onset

- Anti-TNF or interleukin-1 receptor antagonists can be used in patients who fail other DMARDs
  - Biologic agents induce greater suppression of structural damage progression

- NSAIDs ± steroids for symptomatic relief
  - NSAIDS have no impact on disease progression
Etanercept (Enbrel®)

- Neutralizes TNF-α
  - TNF is essential component of inflammatory process and joint destruction in RA

- Recent meta-analysis suggests that there is increased risk of serious infections with anti-TNF agents (OR 2.0, 95% 1.3-3.1)\(^1\)

- If infection or sepsis occurs, etanercept should be discontinued

Bongartz et al. JAMA 2006; 295: 1775-1785
Other Issues and DRPs

Mrs. K is at risk of infection secondary to use of DMARDs for rheumatoid arthritis
- Etanercept is being HELD until resolution of infection

Mrs. K is experiencing S&Sxs of recurrent cellulitis of the right great toe and requires antimicrobial therapy
- Patient to be discharged on indefinite cefadroxil
Other Issues and DRPs

- Mrs. K is at risk of osteoporosis secondary to RA and corticosteroid use and requires preventative therapy
  - To speak with team regarding use of bisphosphonates, calcium and vitamin D
Update on Mrs. K

- Recent MRI of great toe could not rule out the possibility of acute osteomyelitis
  - Gallium scan is pending

- Orthopedics is being consulted regarding the possibility of amputation
Discussion and Questions

It’s okay... I’ve got diarrhea!