Oops… I C-Diffed again. Primary Prophylaxis for Clostridioides Difficile Infections in Hematopoietic Stem Cell Transplant Patients

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Learning Objectives:
1. Review the importance and pathophysiology of Clostridioides difficile infections (CDI)
2. Understand the background, process, and risks of hematopoietic stem cell transplantations (HSCT)
3. Recognize the relevance and consequences of CDI in the HSCT setting
4. Evaluate the literature supporting primary prophylaxis of CDI in HSCT patients
5. Formulate an evidence-based recommendation for prevention of CDI in HSCT patients
1. **Clostridioides difficile infection (CDI)**
   a. **Background**\(^1\)
      i. Formerly known as *Clostridium difficile*
      ii. CDI is identified by the Centers for Disease Control and Prevention (CDC) as an urgent health threat
         1. 500,000 infections annually
         2. 15,000 deaths annually
      iii. Contributes to roughly $6.3 billion in healthcare costs annually\(^3\)
      iv. All antibiotics have a warning for increased risk of CDI, with clindamycin having a boxed warning
   b. **Pathophysiology (Figure 1)**\(^1,4-7\)
      i. The gastrointestinal (GI) tract contains more than 1,000 species of organisms as part of the normal flora
      ii. The GI microbiota provides colonization resistance against pathogenic organisms
      iii. Antibiotics kill normal GI flora along with the targeted pathogens
      iv. Disruption of normal GI flora leads to a loss in colonization resistance allowing for an overgrowth of organisms resistant to the antibiotics
      v. *C. difficile* exposure and colonization
         1. *C. difficile* is present in normal GI flora
            a. Gram positive, spore-forming, obligate anaerobic organism
         2. Gut microbiome offers protection against CDI
         3. *C. difficile* is resistant to many antibiotics and spores become activated and infectious
      vi. *C. difficile* secretes toxins (toxin A and toxin B)
         1. Compromise intestinal epithelium leading to loss of barrier integrity
         2. Increases inflammatory response causing fluid secretion and mucosal injury

![Figure 1. Pathophysiology of CDI](image)
Table 1. Risk Factors for Developing CDI

- Recent antibiotic exposure
- Hematopoietic stem cell transplantation
- Extended duration of antibiotic use
- Recent hospitalization
- Age > 65 years
- Severe comorbid illness
- Cancer chemotherapy
- Acid-suppressing medication use
- GI surgery
- Long term care facility residency

Table 2. CDI Symptoms and Complications

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watery profuse diarrhea</td>
<td>Toxic megacolon</td>
</tr>
<tr>
<td>Fever</td>
<td>Bowel perforation</td>
</tr>
<tr>
<td>Abdominal cramping</td>
<td>Peritonitis</td>
</tr>
<tr>
<td>Nausea</td>
<td>Sepsis</td>
</tr>
<tr>
<td>Anorexia</td>
<td>Death</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td></td>
</tr>
</tbody>
</table>

Clinical presentation\(^1,9-10\)

i. Asymptomatic colonization can occur in 10-30% of hospitalized patients
ii. It is important to differentiate between colonization and CDI
iii. CDI can range from mild to severe and can be potentially fatal
   1. Severe infections include leukocytosis with a WBC count >15,000 cells/mL or SCr >1.5 mg/dL.

Diagnosis\(^1,9,11-12\)

i. Testing should be performed in patients with new unexplained diarrhea
   1. ≥3 unformed stools in 24 hours
ii. Multistep testing should include symptoms and laboratory findings, radiographic evidence, or endoscopy
   1. Positive toxin production
   2. Endoscopy confirming pseudomembranous colitis
      a. Estimated to only be seen in about half of patients
iii. Toxin must also be present with active diarrhea
   1. Can be detected up to 30 days after treatment\(^13\)
   2. Test for cure not recommended
Table 3. Testing Recommendations for CDI\textsuperscript{12,13}

<table>
<thead>
<tr>
<th>Detection</th>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clostridio\textit{j}des difficulte</strong> presence</td>
<td>Laboratory stool test</td>
<td>High</td>
<td>Low</td>
<td>• Takes 2-3 days</td>
</tr>
<tr>
<td></td>
<td>Glutamate dehydrogenase (GDH) antigen</td>
<td>High</td>
<td>Low</td>
<td>• Must be combined with toxin test</td>
</tr>
<tr>
<td><strong>Toxin presence</strong></td>
<td>Enzyme immunoassay (EIA)</td>
<td>Low</td>
<td>Moderate</td>
<td>• Simple</td>
</tr>
<tr>
<td></td>
<td>Nucleic acid amplification test (NAAT)</td>
<td>High</td>
<td>Low</td>
<td>• Should be followed by EIA detecting toxin A and B or toxin B</td>
</tr>
<tr>
<td></td>
<td>Polymerase chain reaction (PCR)</td>
<td>High</td>
<td>High</td>
<td>• Quick turnaround</td>
</tr>
<tr>
<td></td>
<td>Toxigenic cultures</td>
<td>High</td>
<td>Low</td>
<td>• Not frequently performed (labor intensive)</td>
</tr>
</tbody>
</table>

e. Differential diagnosis\textsuperscript{1,14}
   i. Osmotic diarrhea
   ii. Inflammatory bowel disease
   iii. Infection with another pathogen
   iv. Chemotherapy induced diarrhea
   v. Graft vs. host disease (GvHD)

f. Prevention\textsuperscript{15-17}
   i. Hand hygiene
      1. Spores are not killed by alcohol
      2. Use soap and water
   ii. Antibiotic stewardship
      1. De-escalation whenever appropriate
      2. Proper duration of antibiotic therapies
   iii. Contact precautions
      1. Signs for contact precautions
      2. Use of gowns and gloves during patient encounters
      3. Cleaning of patient rooms and equipment
      4. Chlorhexidine bathing
      5. Private room and dedicated toilet
   iv. Avoid gastric acid suppression

 g. Treatment\textsuperscript{1}
   i. Discontinuation of offending antibiotics when possible
Table 4. Recommendations for the Treatment of CDI in Adults Based on IDSA 2017 Guidelines

| Initial episode non-severe | • Vancomycin 125 mg PO four times daily for 10 days  
• Fidaxomicin 200 mg PO twice daily for 10 days  
• Alternative: metronidazole 500 mg PO three times daily for 10 days |
|---------------------------|------------------------------------------------------------------|
| Initial episode severe    | • Vancomycin 125 mg PO four times daily for 10 days  
• Fidaxomicin 200 mg PO twice daily for 10 days |
| Initial episode fulminant | • Vancomycin 500 mg PO/NG tube four times daily AND metronidazole 500 mg IV three times daily  
• Consider rectal instillation of vancomycin |
| Second or subsequent episode | • Vancomycin 125 mg PO four times daily for 10 days  
• Vancomycin prolonged tapered therapy  
• Vancomycin 125 mg PO four times daily followed by rifaximin  
• Fidaxomicin 200 mg PO twice daily for 10 days  
• Fecal microbiota transplantation |

Cost of Full Course of First Line CDI Treatments Based on Average Wholesale Price

<table>
<thead>
<tr>
<th>Drug</th>
<th>Wholesale Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin liquid (IV formulation compounded as oral liquid)</td>
<td>$52</td>
</tr>
<tr>
<td>Vancomycin capsules</td>
<td>$1,273</td>
</tr>
<tr>
<td>Fidaxomicin tablets</td>
<td>$3,360</td>
</tr>
</tbody>
</table>

2. Hematopoietic Stem Cell Transplantation (HSCT)
   a. Background
      i. Process by which normal hematopoiesis and/or lymphopoiesis is established by the infusion of ex vivo pluripotent stem cells
      ii. Infusion of stem cells typically occurs following administration of chemotherapy and/or radiation to the recipient
      iii. The most severe toxicity with chemotherapy regimens used in myeloablative therapy is myelosuppression
         1. HSCT allows dose intensification of chemotherapy by 3 to 10 fold over standard dose
      iv. Donor source can be autologous or allogeneic dependent upon the malignancy treated and patient characteristics
      v. Autologous
         1. Infusion of patient’s own stem cells
         2. Serves to rescue the patient from myelosuppressive effects
         3. Faster immune reconstitution
         4. Lower infection risk and no graft-versus-host disease (GvHD)
   vi. Allogeneic
      1. Infusion of donor stem cells
      2. Replaces a missing or abnormal hematopoietic or lymphoid component in non-malignant disorders
      3. Rescues recipient from myeloablative therapy given for treatment of malignant disease
4. Establishes graft-versus-leukemia (tumor) effect mediated by donor cell recognition and destruction or inhibition of residual host malignant cells
5. Increased risk of infections due to prolonged immunosuppression
6. High risk of GvHD

<table>
<thead>
<tr>
<th>Table 5. Indications for HSCT&lt;sup&gt;21&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Acute myeloid leukemia (AML)</td>
</tr>
<tr>
<td>• Acute lymphoblastic leukemia</td>
</tr>
<tr>
<td>• Myelodysplastic syndromes</td>
</tr>
<tr>
<td>• Myeloproliferative neoplasms</td>
</tr>
<tr>
<td>• Chronic myeloid leukemia</td>
</tr>
<tr>
<td>• Peripheral T-cell lymphoma</td>
</tr>
<tr>
<td>• Follicular lymphoma</td>
</tr>
<tr>
<td>• Diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td>• Neuroblastoma</td>
</tr>
<tr>
<td>• Nonmalignant inherited and acquired marrow disorders</td>
</tr>
<tr>
<td>• Autoimmune diseases</td>
</tr>
</tbody>
</table>

b. HSCT process<sup>20,22-25</sup>

i. Mobilization
   1. Movement of stem cells from the bone marrow into the blood through use of granulocyte-colony stimulating factors

ii. HSCT collection
   1. Bone marrow harvest
      a. Procured through multiple needle aspirations

Figure 3. HSCT Process<sup>22</sup>
2. Peripheral blood stem cell harvest
   a. Apheresis machine is used, which separates stem cells from other blood parts
3. Umbilical cord harvesting
4. Agents are then cryopreserved for processing and storage

iii. Conditioning
   1. Myeloablative
      a. Causes irreversible cytopenia
      b. Stem cell support is mandatory
      c. Standard of care for AML patients
      d. Lower rates of relapse
   2. Non-myeloablative
      a. Causes minimal cytopenia
      b. Given with or without stem cell support
      c. Involves minimization of anti-tumor intensity and maximization of immunosuppression
   3. Reduced-intensity regimens
      a. Can cause cytopenia of variable durations
      b. Should be given with stem cell support
   4. Non-myeloablative and reduced-intensity regimens aim to exploit the premise of allogeneic HSCT, providing graft-versus-leukemia or graft-versus-tumor effects while also reducing toxicity
      a. Higher rates of relapse and transplant rejection
   5. Intensity is dependent on type of malignancy, transplant, and patient risk factors

iv. Immunosuppression
   1. Required only for allogeneic HSCT
   2. Prevention of graft rejection
      a. Eradicates host immune system to allow acceptance of donor cells
   3. GvHD prevention
      a. Calcineurin inhibitors with short course methotrexate
      b. Post-transplant cyclophosphamide in select regimens
         i. Often utilized leading to more prolonged immunosuppression

v. Infusion of stem cells
   1. Day of infusion is referred to as Day 0

vi. Recovery/engraftment
   1. Transplanted stem cells begin production of platelets, red blood cells, and white blood cells
   2. Sustained ANC >0.5 x 10^9/L for three consecutive days and a platelet count >20 x 10^9/L

c. Complications of HSCT
   i. Nausea and vomiting
      1. Managed with NK-1-receptor antagonists, 5-HT3 receptor antagonists, and corticosteroids
ii. Mucositis
   1. Painful inflammation and ulceration of the mucous membranes lining the digestive tract
   2. Managed with good oral hygiene, cryotherapy, and palifermin
   3. Increased risk of mucosal barrier breakdown leading to translocation of gastrointestinal flora into the blood

iii. GvHD
   1. Condition that may develop in allogeneic HSCT where graft views recipient’s tissue as foreign and “attacks” the recipient’s tissues
   2. Clinical features determine whether classification is acute or chronic
   3. Approximately 35-50% of recipients develop acute GvHD
   4. Leading cause of non-relapse mortality in allogeneic HSCT patients
   5. Benefits include graft-versus-tumor and graft-versus-leukemia effects (refer to Figure 4)
   6. Characterized by erythema, maculopapular rash, nausea, vomiting, profuse diarrhea, ileus, or anorexia
   7. Risk factors
      a. Degree of mismatch between donor and recipient
      b. Intensity of conditioning regimen
      c. Stem cell source
      d. Age of patient/donor
      e. Prophylaxis regimen
      f. CMV Status
   8. Managed with immunosuppression, steroids, and monoclonal antibodies

![Figure 4. Prognosis of Patients that Develop GvHD](image-url)
9. GI microbiome plays an important role in GvHD\textsuperscript{29,30}
   a. Intestinal bacteria contribute to health of host through a variety of functions
   b. Multiple studies have demonstrated that decreased microbiota diversity leads to reduced overall survival
   c. Allogeneic HSCT recipients have a disruption in their microbiome due to many infectious and inflammatory processes
   d. Neutropenic fever treatment with anaerobic coverage is associated with increased risk for GvHD\textsuperscript{29}
   e. Presence of anaerobic species \textit{Blautia}, is associated with reduced GvHD-related mortality and improved overall survival\textsuperscript{30}
   f. When combined with other risk factors, allogeneic patients are often at higher risk of GvHD

iv. Infection\textsuperscript{20,25,31}
   1. Risk mainly related to time since transplant and presence/absence of GvHD
   2. Patients may experience a period of profound pancytopenia spanning days to weeks depending on the stem cell dose, donor source, and conditioning regimen intensity

![Figure 5. Timing of Immune Reconstitution in HSCT\textsuperscript{25}](image)

3. Risk factors for infection
   a. Immunosuppression
   b. GvHD
   c. Age
   d. Comorbidities
   e. Pathogen exposure/colonization
4. Recommended prophylaxis should include antibacterial, antiviral, and antifungal agents
5. Antibacterial prophylaxis is recommended to be continued until recovery from neutropenia
   a. Length of prophylaxis varies
   b. Agents should be broad spectrum
   c. American Society of Blood and Bone Marrow Transplantation Guidelines strongly recommend broad spectrum agents in adult HSCT patients with anticipated neutropenic period of 7 days or more
   d. Prophylaxis with fluoroquinolones has been shown in large meta-analyses to decrease gram-negative infections, infection-related complications, and mortality in neutropenic patients

6. Oncology patients are at higher risk for vancomycin resistant enterococcus (VRE) bloodstream infections
   a. Colonization with VRE and antibiotic use lead to domination of the GI flora
   b. Mucosal lining damaged from chemotherapy allows for translocation of VRE into the bloodstream

3. **CDI and HSCT patients**
   a. Background
      i. Infection remains a major cause of morbidity and mortality in HSCT patients
      ii. CDI rates in HSCT patients are as high as 33%
         1. Recurrence rates up to 41% in HSCT population
         2. Compared to ~1% of overall U.S. population
         3. Identified as an independent risk factor for increased mortality
      iii. Most risk factors for allogeneic HSCT patients are not modifiable
         1. Patients must maintain antibiotic prophylaxis during neutropenia
      iv. No specific recommendations for CDI treatment in HSCT patients due to scarcity of data
      v. Mortality rate of CDI patients in HSCT is similar to non-HSCT population
         1. Complications of CDI are often devastating in this patient population
   b. Why are CDI rates higher in HSCT patients?
      i. Chemotherapy damages mucosal lining
         1. Grade ≥2 mucositis
      ii. Reactivation of Cytomegalovirus
      iii. Reactivation of Herpesviridae
      iv. Chemotherapeutics may have antimicrobial properties
      v. Ubiquitous use of fluoroquinolone prophylaxis
      vi. Prolonged neutropenia
      vii. Prolonged broad-spectrum antibiotic use for treatment of febrile neutropenia
      viii. Prolonged hospitalizations
   c. Importance
      i. Immunosuppressed patients are often excluded in clinical trials, which makes treatment guideline recommendations difficult to use
         1. Typically treat CDI in immunosuppressed patients similarly to non-immunosuppressed patients
      ii. CDI rates in allogeneic HSCT are double that of autologous HSCT
iii. Studies have shown no difference in all-cause mortality when comparing patients with CDI versus uninfected allogeneic HSCT patients.4

iv. Early CDI during allogeneic HSCT is correlated with increased risk of GI GvHD by more than 3-fold.4
   1. Preparative regimens cause damage to the tissues
   2. Proinflammatory cytokines promote antigen-presenting cells to activate donor T cells, which causes a cascade of cytotoxicity
   3. Theorized that local infection of the gut may further destroy epithelial integrity augmenting responses during a cycle of inflammation

Figure 6. Rates of GvHD in allogeneic HSCT patients with and without CDI.4

4. Higher rates of GvHD grade II or higher in patients with CDI
   a. Unable to associate higher GvHD rates due to infection itself or treatment with vancomycin leading to disruption of gut microbiome

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Untreated 5-year GVHD-related mortality (n)</th>
<th>Treated 5-year GVHD-related mortality (n)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atovaquone (PO)</td>
<td>14.1% (772)</td>
<td>19.1% (85)</td>
<td>0.496</td>
</tr>
<tr>
<td>Aztreonam (IV)</td>
<td>14.2% (793)</td>
<td>17.5% (64)</td>
<td>0.777</td>
</tr>
<tr>
<td>Cefepime (IV)</td>
<td>14.6% (705)</td>
<td>13.8% (152)</td>
<td>0.980</td>
</tr>
<tr>
<td>Ciprofloxacin (IV)</td>
<td>14.4% (533)</td>
<td>14.7% (322)</td>
<td>0.862</td>
</tr>
<tr>
<td>Imipenem-clastatin (IV)</td>
<td>13.1% (709)</td>
<td>21.5% (148)</td>
<td>0.025</td>
</tr>
<tr>
<td>Metronidazole (IV)</td>
<td>14.0% (779)</td>
<td>18.6% (78)</td>
<td>0.197</td>
</tr>
<tr>
<td>Metronidazole (PO)</td>
<td>14.0% (801)</td>
<td>20.8% (56)</td>
<td>0.206</td>
</tr>
<tr>
<td>Piperacillin-tazobactam (IV)</td>
<td>11.9% (557)</td>
<td>19.8% (300)</td>
<td>0.007</td>
</tr>
<tr>
<td>Sulfamethoxazole-trimethoprim (IV)</td>
<td>14.8% (769)</td>
<td>12.9% (88)</td>
<td>0.625</td>
</tr>
<tr>
<td>Sulfamethoxazole-trimethoprim (PO)</td>
<td>14.6% (727)</td>
<td>12.8% (130)</td>
<td>0.522</td>
</tr>
<tr>
<td>Vancomycin (IV)</td>
<td>13.4% (408)</td>
<td>15.6% (449)</td>
<td>0.579</td>
</tr>
<tr>
<td>Vancomycin (PO)</td>
<td>14.4% (796)</td>
<td>17.3% (61)</td>
<td>0.942</td>
</tr>
</tbody>
</table>

Figure 7. Effects of antibiotic exposure on increased 5-year GVHD-related mortality.43
5. Oral vancomycin does not have an increased risk of GvHD related mortality in allogeneic patients
d. Colonization\textsuperscript{37,44,45}
   i. Transmission is likely spread from person to person via the fecal-oral route
   ii. Asymptomatic colonization with toxigenic \textit{C. difficile} has been found predictive of CDI in HSCT patients
      1. Develop CDI within 2 weeks of hospital admission
   iii. Prevalence of asymptomatic colonization among HSCT adults is estimated between 3-26\%\textsuperscript{45}
   iv. Colonization with non-toxigenic \textit{C. difficile} has appeared protective\textsuperscript{44}
   v. Studies suggest avoiding broad spectrum antibiotics that alter GI microbiome due to risks leading to GvHD\textsuperscript{46,47}

4. \textbf{Secondary prophylaxis for CDI (Table 6)}\textsuperscript{48-53}
   a. Due to high morbidity and costs associated with CDI, studies have assessed the efficacy of oral vancomycin as secondary prophylaxis in high-risk populations
   b. Oral vancomycin 125 mg once daily for the duration of antimicrobial treatment may be considered if secondary prophylaxis is implemented\textsuperscript{1}
      i. Optimal dosing strategy has not been defined- studies currently ongoing\textsuperscript{46}

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Methods</th>
<th>Findings</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Carignan et al. (2016)\textsuperscript{59} | Multi-center retrospective cohort study | Vancomycin 125 mg PO QID vs. no prophylaxis | Vancomycin is an effective strategy for secondary prevention for those re-exposed to antibiotics | • Non-heterogeneity among patient population  
• Lack of standardized follow-up for recurrence in days off vancomycin  
• Patients on metronidazole for non-CDI indications  
• Unclear medication review + treatment doses |
| N=551            |                                      |                             |                                                                          |                                                                             |
| Van Hise et al. (2016)\textsuperscript{60} | Retrospective single-center cohort study | Vancomycin 125-250 mg PO BID vs. no prophylaxis | Vancomycin may be effective at preventing CDI recurrence in patients who require antibiotic therapy | • Surveillance duration only 4 weeks  
• Did not study changes in fecal flora |
| N=223            |                                      |                             |                                                                          |                                                                             |
| Splinter et al. (2018)\textsuperscript{51} | Retrospective cohort study assessing use in renal transplant patients | Vancomycin 125 mg PO BID vs. no prophylaxis | No instances of CDI in the treatment group vs. 2 in control group | • Difference not statistically significant  
• No follow-up after vancomycin discontinuation  
• Small sample size  
• Lack of randomization |
| N=29             |                                      |                             |                                                                          |                                                                             |
Knight et al. (2019)\textsuperscript{52}  
N=91

| Retrospective single-center cohort study | Vancomycin 125-250 mg PO QID vs. no prophylaxis | Vancomycin as secondary prophylaxis appears to reduce the risk of recurrent CDI for up to 12 months without increasing VRE infections | • Variable antibiotic exposure within groups  
• Unmatched prophylaxis strategies  
• Used treatment doses for prophylaxis |

Morrisette et al. (2019)\textsuperscript{53}  
N=50

| Retrospective cohort study assessing use in HSCT patients | Vancomycin 125 mg PO BID continuing 7 days after antibiotic discontinuation vs. no prophylaxis | Decreased incidence of recurrent CDI with no increase in VRE infections | • Lengthy duration of prophylaxis  
• Concurrent major prevention strategies may have skewed CDI to decrease |

c. Studies had similar limitations  
   i. Lacked consistent and defined patient follow up  
      1. No detection of late-recurrences  
      2. May have been detected in Carignan study  
   ii. Potentially missed patients who were treated at different hospital systems  
   iii. Earlier studies did not investigate the impact of resistant organism acquisition  
   iv. Adverse effects not reported  

d. All five studies demonstrate that oral vancomycin appears to be effective at reducing the risk of CDI recurrence in high-risk patients

5. **Abstract (Table 7)**
   a. Secondary prophylaxis studies have led to preliminary investigation questioning the safety and efficacy of primary CDI prophylaxis in HSCT patients

**Table 7. Does Oral Vancomycin Prophylaxis for *Clostridium Difficile* Infection Improve Allogeneic Hematopoietic Stem Cell Transplant Outcomes?**

<table>
<thead>
<tr>
<th>Background</th>
</tr>
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</table>
| • Allogeneic HSCT patients are at high risk for CDI  
• No guideline recommendations utilizing antimicrobial prophylaxis for CDI in allogeneic HSCT patients  
• Hackensack University Medical Center used oral vancomycin prophylaxis in this population |

<table>
<thead>
<tr>
<th>Methods</th>
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</table>
| • Retrospective medical record review of HSCT patients between January 2013 and December 2014 with at least one readmission within one year  
• Collected data on allogeneic HSCT related information, prophylactic oral vancomycin usage, antimicrobial exposures, GvHD development, VRE bacteremia, mortality, and occurrence of CDI during hospital stay  
• Primary objective: evaluate the development of CDI  
• Secondary objectives: occurrence of GvHD, VRE bacteremia, and death |
• Group A: patients with documented CDI history who received vancomycin prophylaxis
• Group B: patients with documented CDI history who did not receive vancomycin prophylaxis
• Group C: patients without documented CDI history who did not receive prophylactic vancomycin

<table>
<thead>
<tr>
<th></th>
<th>CDI</th>
<th>VRE bacteremia</th>
<th>GvHD</th>
<th>Death within 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group A (n=12)</strong></td>
<td>2 (17%)</td>
<td>3 (25%)</td>
<td>12 (100%)</td>
<td>6 (50%)</td>
</tr>
<tr>
<td><strong>Group B (n=7)</strong></td>
<td>1 (14%)</td>
<td>0 (0%)</td>
<td>4 (57%)</td>
<td>1 (14%)</td>
</tr>
<tr>
<td><strong>Group C (n=161)</strong></td>
<td>17 (11%)</td>
<td>15 (9%)</td>
<td>120 (75%)</td>
<td>55 (34%)</td>
</tr>
</tbody>
</table>

**Conclusion**
- “The possible influence of oral vancomycin prophylaxis on outcomes in allogeneic HSCT patients remains unknown”
- Missing group for patients without documented CDI history who received vancomycin prophylaxis
- 109 patients were excluded due to not being readmitted within one year
- Hypothesis generating

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**Clinical Questions: Should HSCT patients receive primary prophylaxis for CDI? If so, which agent should they receive?**


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<td>17 (11%)</td>
<td>15 (9%)</td>
<td>120 (75%)</td>
<td>55 (34%)</td>
</tr>
</tbody>
</table>

**Objective**
To evaluate the use of prophylactic oral vancomycin and incidence of CDI in allogeneic HSCT patients

**Methods**
Retrospective, single center, cohort study between April 2015 and November 2016 at the Hospital of the University of Pennsylvania

**Patient Population**

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients receiving allogeneic HSCT</td>
<td>Allergy or intolerance to vancomycin</td>
</tr>
</tbody>
</table>

**Intervention**
Vancomycin 125 mg twice daily starting on the day of inpatient admission and continuing until the day of discharge compared to a cohort of unexposed patients between April 2015 and December 2015

**Outcomes Evaluated**

<table>
<thead>
<tr>
<th>Primary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Association between oral vancomycin prophylaxis and CDI diagnosis from time of inpatient admission to hospital discharge</td>
</tr>
</tbody>
</table>
**Secondary**
- Acute and chronic GvHD
- Relapse, non-relapse mortality, overall survival
- Incidence of VRE bloodstream infections

**Statistics**
- Utilized X² or Fisher’s exact test for categorical variables
- Wilcoxon rank-sum was used for continuous variables
- Calculations were performed using Stata v15.1
- A 2-tailed P value <0.05 was considered to be significant

**Results**
- Total of 145 patients were included in the study
- No cases of CDI in patients that received prophylaxis (0/90)
- CDI occurred in 11/55 (20%) patients that did not receive prophylaxis (P<0.001)
- Oral vancomycin prophylaxis was not associated with a higher risk of acute grades 2-4 GvHD

**Author’s Conclusions**
Prophylaxis with oral vancomycin is highly effective in preventing CDI in allogeneic HSCT patients without increasing the risk of GvHD, VRE bloodstream infections, or disease relapse.

**Reviewer’s Critique**

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Targets a population often not included in studies</td>
<td>Retrospective, single cohort</td>
</tr>
<tr>
<td>No significant baseline differences</td>
<td>Small sample size for rare outcomes</td>
</tr>
<tr>
<td>Reported the days of broad spectrum gram-negative antibiotic exposure</td>
<td>Additional preventative measures unspecified</td>
</tr>
<tr>
<td>Followed patients for incidence of CDI and GvHD after discharge</td>
<td>No analysis on changes in the gut microbiota</td>
</tr>
<tr>
<td></td>
<td>No routine screening for VRE</td>
</tr>
<tr>
<td></td>
<td>Time periods for comparator groups were not aligned</td>
</tr>
<tr>
<td></td>
<td>Lack of difference in length of hospitalization, GvHD rates, and survival outcomes</td>
</tr>
<tr>
<td></td>
<td>Lengthy prophylaxis period</td>
</tr>
</tbody>
</table>

**Take-home Points**
- Demonstrated vancomycin as a viable option for prophylaxis against CDI in allogeneic HSCT patients
- Vancomycin use did not increase GvHD rates, VRE bloodstream infections, or relapse
- Risks for GvHD and VRE still unclear within small study population size
- GvHD rates were also not lowered as would be expected with decrease in CDI
- Lack of differences between groups raises question if early identification and treatment of CDI is just as effective as prophylaxis
- Further studies needed to assess the efficacy and safety of vancomycin prophylaxis

### Objective
To examine the efficacy and safety of fidaxomicin as prophylaxis against CDI in patients undergoing autologous or allogeneic HSCT and receiving fluoroquinolone prophylaxis during neutropenia

### Methods
Randomized, double-blind, placebo-controlled study at 42 centers in North America

#### Patient Population

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ≥18 years old</td>
<td>• Active CDI</td>
</tr>
<tr>
<td>• Undergoing HSCT</td>
<td>• Fulminant colitis</td>
</tr>
<tr>
<td>• Planned fluoroquinolone prophylaxis during neutropenia</td>
<td>• Toxic megacolon, or ileus</td>
</tr>
<tr>
<td></td>
<td>• Receipt of a cord blood transplant</td>
</tr>
<tr>
<td></td>
<td>• History of inflammatory bowel disease</td>
</tr>
<tr>
<td></td>
<td>• Pregnant or breast-feeding</td>
</tr>
<tr>
<td></td>
<td>• Current use of any drugs potentially useful in the treatment of CDI</td>
</tr>
</tbody>
</table>

#### Intervention
Randomized to receive daily fidaxomicin or matching placebo within two days of starting conditioning or at fluoroquinolone initiation until seven days after neutrophil engraftment or completion of fluoroquinolone prophylaxis

#### Outcomes Evaluated

**Primary**
- Prophylactic failure of fidaxomicin vs. placebo through 30 days
  - Confirmed CDI
  - Use of antibiotics potentially effective against CDI (metronidazole)
  - Missing CDI assessments (due to death, AE, or any other reason)

**Secondary**
- CDI incidence 30, 60, and 70 days after study medication discontinuation
- Time to onset CDI
- Treatment-emergent adverse effects
- All-cause mortality
- Gastrointestinal hemorrhagic events
- Time to neutrophil engraftment
- Acute GvHD

#### Statistics
- Used modified intention-to-treat analysis
- 1-sided Wald test for a difference in proportions
### Results

- 611 patients enrolled, 600 patients received at least 1 dose of a study drug
- Study completed by 227 fidaxomicin recipients and 218 placebo recipients
- Prophylactic failure through 30 days occurred in 28.6% of fidaxomicin-treated patients and 30.8% of placebo (P=0.278)
- Incidence of confirmed CDI for both autologous and allogeneic HSCT patients was lower in the prophylaxis group than placebo at 30 days post treatment (6.4 vs 14.6% allogeneic and 2.8 vs 8.0% in autologous)
- The incidence of confirmed CDI was lower in the placebo group through 60 days after the study treatment ended (5.6 vs 10.7%; P=0.0014)

### Author's Conclusions

Prophylaxis of CDI with fidaxomicin can reduce the incidence of confirmed CDI in the HSCT population

### Reviewer's Critique

**Strengths**

- Randomized, double-blind, placebo controlled
- Clear on methods used for prophylaxis
- Appropriate diagnosis of CDI
- Baseline characteristics matched between two groups
- Included autologous and allogeneic patients
- Sensitivity analysis determined *a priori*

**Limitations**

- Primary analysis not met
- Stringent failure qualifications may have led to lack of difference
- Microbiota changes were not assessed
- Only 64% of patients completed study treatment and follow-up
- Lower than expected incidence of confirmed CDI

### Take-home Points

- Prophylactic failure was similar in fidaxomicin and placebo groups
- Fidaxomicin was shown to be a reasonable option for CDI after *a priori* analysis was performed
- The sensitivity analysis showed a significant decrease of confirmed CDI in the fidaxomicin group, but the overall incidence was much lower than expected
- Questionable utility due to high cost and unmet primarily analysis of this study
- Further studies assessing the safety and efficacy of fidaxomicin are warranted

### 6. Future Directions

- **ID Week abstracts**
  - Many hospitals have implemented vancomycin 125 mg PO once or twice daily as secondary prophylaxis in high risk patients with favorable results
- **Current studies ongoing to determine best practices for CDI prophylaxis**

### 7. Summary of Evidence

- **Pros to primary prophylaxis for CDI**
  - Protective for CDI and improvement in morbidity and mortality
  - CDI is associated with increased rates of GvHD
    - GvHD is the leading non-relapse cause of death
2. However, unable to distinguish occurrence of CDI or CDI treatment as cause for GvHD
3. Vancomycin use is not associated with increased rates of GvHD-related mortality
   iii. Leads to decrease in relapse of malignancy
b. Cons to prophylaxis for CDI
   i. Unclear long-term effects
      1. VRE infections
      2. Increased rates of GvHD due to disruption of microbiome

8. **Recommendations**
a. Who, if any, should get primary prophylaxis?
   i. Due to the unknown consequences of prophylaxis, I limit the utility to only allogeneic HSCT patients who are colonized with *C. difficile* due to their increased risk of GvHD with CDI
      1. Routine screening for allogeneic patients
         a. GDH testing performed with admission labs
         b. Weekly screening thereafter
   ii. I do not recommend primary prophylaxis in autologous HSCT patients
      1. Rates of CDI are much lower in autologous patients
      2. Virtually no GvHD in autologous patients
b. If primary prophylaxis is given, vancomycin should be preferred over fidaxomicin due to:
   i. Higher cost associated with fidaxomicin
   ii. Apparent risk reduction with vancomycin
      1. ARR 20% with vancomycin use
      2. ARR 8.4% with fidaxomicin use
      3. It would be ideal to conduct a head-to-head comparison of efficacy with vancomycin or fidaxomicin in HSCT patients to better determine preferred agent
   iii. Reserving fidaxomicin as an option to patients that develop CDI with vancomycin prophylaxis or vancomycin-resistant CDI
c. When and how to administer:
   i. Dose of vancomycin 125 mg PO BID starting at time of antibiotic initiation until discontinuation of antibiotic therapy
d. Maintain high-level antimicrobial stewardship techniques
   i. Minimizing antibiotic exposure (particularly fluoroquinolones in our HSCT patients)
   ii. Improve prevention practices
e. More studies are warranted to determine the safety and efficacy of primary prophylaxis of CDI before it is routinely incorporated into the transplant setting for all donor types
References


