Impact of oral vancomycin duration on Clostridium difficile infection (CDI) recurrence in patients receiving concomitant non-CDI antibiotics

Shane Salimnejad, PharmD; Maegan Greenland, PharmD, MS, BCPS; Jennifer Schultheis, PharmD, BCPS, BCCCP; Christina Sarubbi, PharmD, BCPS-AQ ID
Duke University Hospital; Durham, North Carolina

**Background**

- Recurrent Clostridium difficile infection (RCDI) is defined as CDI that occurs within eight weeks after the onset of a previous episode, provided the symptoms from the previous episode resolved.¹
- After an initial episode of C. difficile, the rate of RCDI within eight weeks approaches 20 – 30%. After first recurrence, the risk of future recurrence increases to 40 – 65%.² ³
- At Duke University Health System (DUHS), oral vancomycin therapy for an active CDI episode is routinely extended for patients receiving concomitant non-CDI antibiotic therapy. The decision of how long to treat with oral vancomycin past completion of non-CDI antibiotic therapy is largely based on physician preference, but typically spans 0-21 days, with an emphasis on 7, 10, and 14 day regimens.

- The SHEA-IDSA guidelines acknowledge that some providers may prefer to extend CDI therapy for patients concomitantly receiving non-CDI antibiotics, yet provide no recommendations due to a lack of evidence.⁴ This approach is currently unproven, costly, and may adversely alter intestinal flora or promote propagation of vancomycin resistant enterococci (VRE).⁵ Thus, an evaluation of the presumed benefits of prolonged CDI therapy and treatment durations is warranted.

**Objectives**

**Primary Objective**
- To determine whether duration of oral vancomycin therapy for CDI after cessation of concomitant non-CDI antibiotics affects the incidence of RCDI

**Secondary Objectives**
- To determine whether duration of oral vancomycin therapy for CDI after cessation of concomitant non-CDI antibiotics affects hospital readmission rates due to CDI-related complications
- To compare the incidence of RCDI in patients receiving different classes of concomitant non-CDI antibiotics
- To determine whether duration of oral vancomycin therapy for CDI after completion of concomitant non-CDI antibiotics affects all-cause mortality
- To determine whether duration of oral vancomycin therapy for CDI after completion of concomitant non-CDI antibiotics affects time to first RCDI event

**Study Design**
- IRB-approved, single-center, retrospective cohort study
- Recurrence is considered diarrhea which developed within 90 days following the initial CDI episode treatment, requiring a second course of treatment against CDI.

**Methods**

**Inclusion Criteria**

<table>
<thead>
<tr>
<th>Age ≥ 18 years</th>
<th>Patients with &gt; 4 episodes of CDI</th>
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<tr>
<td>Patient hospitalization from July 1, 2013 to August 1, 2016 for ≥ 72 h</td>
<td>Patients receiving fidaxomycin, rifaximin, or rifampin as CDI or non-CDI therapy</td>
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<td>Receiving oral vancomycin for CDI (defined as chart documentation of “loose stools” or “diarrhea” and concurrent positive stool test for C. difficile by polymerase chain reaction)</td>
<td>Patients discharged to a non-DUHS inpatient rehab or skilled nursing facility with independent physician oversight</td>
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**Exclusion Criteria**

| Patients who received the following concomitant non-CDI antibiotics for ≥ 72 h: | Diagnosis of inflammatory bowel disorder (defined as Crohn disease, diverticulitis, diverticulitis, short bowel syndrome, or bacterial gastrointestinal infection with agents other than C. difficile (eg, Salmonella sp.) |
| • Ciprofloxacin, levofloxacin, moxifloxacin | Death during oral vancomycin treatment |
| • Ertapenem, meropenem | Patients who do not receive DUHS follow-up |
| • Piperacillin/tazobactam | Patients receiving fecal microbiota transplant |
| • Ceftazidime | Patients discharged to inpatient hospice |

**Primary Endpoint**
- Incidence of RCDI, evaluated using time from completion of oral vancomycin treatment to first RCDI event

**Secondary Endpoints**
- Hospital readmission rates due to CDI-related complication within 90 days following CDI therapy among patients receiving oral vancomycin for 10 days or less compared to 11-21 days after the completion of non-CDI antibiotics
- Incidence of RCDI among patients receiving classes of concomitant non-CDI antibiotics
- Incidence of all-cause mortality within 90 days following CDI therapy, evaluated by using time from completion of oral vancomycin treatment to death event
- Time to first RCDI event among patients receiving oral vancomycin for 10 days or less compared to 11-21 days after the completion of non-CDI antibiotics

**Data Collection and Analysis**

**Statistical Analysis**
- For primary analysis, patients will be divided into two groups, patients receiving oral vancomycin for 10 days or less and patients with 11-21 days of treatment
- The association of recurrence of CDI with duration of oral vancomycin treatment will be examined with a Cox proportional hazards model
- Adjusted hazard ratio of the two treatment groups will be calculated and Kaplan-Meier survival plot will be created to compare the risk of RCDI between two groups
- For secondary analyses, descriptive statistics will be performed.
- The following RCDI risk factors (co-variates) will be accounted for:
  - Age ≥ 65 years
  - Number of past CDI episodes
  - Antacid use
  - Non-CDI antibiotic use in the 90-day period after completion of oral vancomycin therapy
  - Tube feed use
  - Duration of hospital stay during CDI treatment
  - Oral vancomycin regimen (500 mg four times daily, 125 mg four times daily, taper, or other)
  - Immunocompromised state

**References**


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