Clinical Pharmacy Program Guidelines for Dificid

<table>
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<tr>
<th>Program</th>
<th>Prior Authorization</th>
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<tr>
<td>Medication</td>
<td>Dificid (fidaxomicin)</td>
</tr>
<tr>
<td>Pharmacy and Therapeutics</td>
<td>10/2016</td>
</tr>
<tr>
<td>Approval Date</td>
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<td>Effective Date</td>
<td>1/1/2016</td>
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1. **Background:**

**Clostridium difficile-Associated Diarrhea**

Dificid is indicated in adults (greater than or equal to 18 years of age) for treatment of Clostridium difficile-associated diarrhea (CDAD). To reduce the development of drug-resistant bacteria and maintain the effectiveness of Dificid and other antibacterial drugs, Dificid should be used only to treat infections that are proven or strongly suspected to be caused by Clostridium difficile.

**Clinical Practice Guidelines**

*Society for Healthcare Epidemiology of America/Infectious Diseases Society of America (2010 update) [5, A]*

a. Discontinue therapy with the inciting antimicrobial agent(s) as soon as possible, as this may influence the risk of *C. difficile* infection (CDI) recurrence (A-II).

b. When severe or complicated CDI is suspected, initiate empirical treatment as soon as the diagnosis is suspected (C-III).

c. If the stool toxin assay result is negative, the decision to initiate, stop, or continue treatment must be individualized (C-III).

d. If possible, avoid use of peristaltic agents, as they may obscure symptoms and precipitate toxic megacolon (C-III)

e. Metronidazole is the drug of choice for the initial episode of mild-to-moderate CDI. The dosage is 500 mg orally 3 times per day for 10 to 14 days (A-I).

f. Vancomycin is the drug of choice for an initial episode of severe CDI. The dosage is 125 mg orally 4 times per day for 10 to 14 days (B-I).

g. Vancomycin administered orally (and per rectum, if ileus is present) with or without intravenously administered metronidazole is the regimen of choice for the treatment of severe, complicated CDI. The vancomycin dosage is 500 mg orally 4 times per day and 500
mg in approximately 100 mL normal saline per rectum every 6 hours as a retention enema, and the metronidazole dosage is 500 mg intravenously every 8 hours (C-III).

h. Consider colectomy for severely ill patients. Monitoring the serum lactate level and the peripheral blood WBC count may be helpful in prompting a decision to operate, because a serum lactate level rising to 5 mmol/L and a WBC count rising to 50,000 cells/µL have been associated with greatly increased perioperative mortality. If surgical management is necessary, perform subtotal colectomy with preservation of the rectum (B-II).

i. Treatment of the first recurrence of CDI is usually with the same regimen as for the initial episode (A-II) but should be stratified by disease severity (mild-to-moderate, severe, or severe complicated), as is recommended for treatment of the initial CDI episode (C-III).

j. Do not use metronidazole beyond the first recurrence of CDI or for long-term therapy because of potential for cumulative neurotoxicity (B-II).

k. Treatment of the second or later recurrence of CDI with vancomycin therapy using a tapered or pulse regimen is the preferred next strategy (B-III).

l. No recommendations can be made regarding prevention of recurrent CDI in patients who require continued antimicrobial therapy for the underlying infection (C-III).

2. Coverage Criteria:

A. Authorization Criteria

1. Diagnosis of Clostridium difficile-associated diarrhea (CDAD), also known as C. difficile pseudomembranous colitis [1, 2, B]

   AND

2. One of the following:

   a. Both of the following: [5, 19, C]
      (1) Patient has mild-moderate CDAD

      AND

      (2) History of failure, contraindication, or intolerance to oral Vancocin (vancomycin)*

      OR

   b. Patient has CDAD [5, 19, C]

      OR
c. For continuation of prior Dificid therapy

Authorization will be issued for 10 days.

“Educational Statement” OR “Additional Information”- if necessary, put before #3. OR evaluate if can put info in Background Section.

3. Endnotes

A. The Clinical Practice Guidelines for Clostridium difficile Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) offer recommendations for the treatment of C. difficile infection. The guidelines make recommendations for treatment based on whether the infection is an initial episode, first occurrence, or second recurrence. Treatment is also based on severity of the infection as mild to moderate, severe, and severe and complicated infection. These guidelines provide recommendations that are, in part, based on the comparative efficacy of metronidazole and oral vancomycin. The place in therapy of Dificid is not defined within the SHEA/IDSA guidelines because this agent was not FDA-approved at the time these guidelines underwent revision. [5]

B. Severity of infection: There is no specific guidance in regards to use of Dificid and severity of C. difficile infection. In the Louie 2011 study, inclusion criteria were: age 16 years and older, diagnosis of C. difficile infection (defined by the presence of diarrhea), and C. difficile toxin A, B, or both in a stool specimen obtained within 48 hours before randomization. Although the severity of infection for each patient was noted by the authors, no further analysis was done to define severity of infection with the use of Dificid. Until further data is available, it is not possible to define criteria for the use of Dificid based on severity of infection. [2, 6, 7]

C. Severity of disease and choice of drug for treatment: Three factors may indicate a severe or complicated course and should be considered when initiating treatment: age, peak white blood cell (WBC) count (leukocytosis), and peak serum creatinine level. Complications are more common among patients with a WBC count greater than or equal to 15,000 cells/?L than among those with a normal WBC count, and the disease is truly catastrophic in patients with a WBC count greater than or equal to 50,000 cells/?L. An elevated serum creatinine level may indicate severe diarrhea with subsequent dehydration or inadequate renal function. A recent randomized, double-blind, placebo-controlled trial (Zar et al 2007) demonstrated that treatment of CDI with either oral vancomycin at a dosage of 125 mg qid for 10 days or metronidazole 250 mg qid for 10 days resulted in comparable clinical cure rates in patients with mild disease (98% vancomycin vs. 90% metronidazole), while vancomycin was statistically superior to metronidazole in the subset of patients with severe CDI (97% vs. 76%; p = 0.02). Severe CDI was assessed using a severity score incorporating six clinical variables (eg, age > 60 years, WBC count > 15,000 cells/?L, albumin level < 2.5 mg/dL). Clinical symptoms recurred in 15% of patients treated with metronidazole and 14% treated with vancomycin. [19]
D. History of failure (as defined by unresolved CDAD infection): Failure to oral Vancocin is defined as a course of therapy to which a patient has an inadequate response and has an unresolved CDAD infection. Failure is not defined by development of a recurrent episode.

4. References:

8. Per clinical consult with infectious disease, pediatric infectious disease, and gastroenterology and internal medicine specialists, August 23, 2011.
<table>
<thead>
<tr>
<th>Date</th>
<th>Change</th>
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<tbody>
<tr>
<td>Sept 2011</td>
<td>New Guideline</td>
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<tr>
<td>Dec 2011</td>
<td>Revised indications section II.A.</td>
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<tr>
<td></td>
<td>Clarified the precursor use of vancomycin must be the oral formulation</td>
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<tr>
<td></td>
<td>in section III.A.3 of guideline.</td>
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<tr>
<td>Sept 2012</td>
<td>Criteria have been revised to allow patients diagnosed with CDAD to</td>
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<td></td>
<td>receive Dificid if they are “at high risk for CDAD recurrence.”</td>
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<tr>
<td></td>
<td>Removed criteria under patients with severe CDAD: “History of failure</td>
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<td>(as defined by unresolved CDAD infection), contraindication, or</td>
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<td></td>
<td>intolerance to oral Vancocin (vancomycin)”</td>
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<tr>
<td>June 2014</td>
<td>Annual Review</td>
</tr>
<tr>
<td>December 2015</td>
<td>Full revision to Dificid clinical criteria. Removed the following</td>
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<tr>
<td></td>
<td>requirements: New CDAD infection, previous metronidazole therapy</td>
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<td>requirement for mild-moderate CDAD, and high risk of recurrence.</td>
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<tr>
<td></td>
<td>Also updated criteria to align with current template.</td>
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<tr>
<td>October 2016</td>
<td>Annual review. Updated policy template.</td>
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