BC Provincial Antimicrobial Clinical Expert Group (PACE)

Oral Vancomycin as First-Line for c. diff Infection - Criteria for Use Recommendations

SITUATION

Oral vancomycin and metronidazole are BCHA formulary antibiotics indicated to treat Clostridium difficile infection (CDI). Previously published treatment guidelines recommended oral metronidazole for patients with mild to moderate severity CDI, while oral vancomycin was recommended only for severe CDI (Cohen 2010, Surawicz CM, Debast 2014).

Recent literature has demonstrated the superiority of oral vancomycin over metronidazole regardless of disease severity (Johnson 2014, Ooijevaar 2018). Newly released international treatment guidelines have also recommended the use of oral vancomycin regardless of disease severity (McDonald 2018). The purpose of this SBAR is to evaluate the clinical and budgetary implications of using oral vancomycin first line to treat CDI of any severity (including mild to moderate disease).

BACKGROUND

CDI is a rare complication associated with antibiotic use. For some patients, it is a self-limiting illness with resolution once the offending antimicrobial is discontinued. However, other patients require directed antibiotic therapy to cure the infection. Two agents are available on the BCHA formulary to treat CDI: metronidazole and oral vancomycin. Fidaxomicin, also indicated to treat CDI, is excluded (non-formulary) from the BCHA formulary. Until recently, treatment guidelines from the Infectious Diseases Society of America (IDSA) (Table 1) had divergent CDI recommendations based on severity.

One potential problem with treatment recommendations based on disease severity is that this can lead to patient miscategorization and selection of inappropriate treatment, such as selection of metronidazole for severe disease, possibly leading to poor patient outcomes. This problem was illustrated with a quality improvement project performed at Fraser Health in 2017.

Between April and August 2017, all inpatient CDI cases were reviewed by Infection Prevention and Control (IPC) staff using an algorithm to identify guideline-discordant therapy. At three sites within FHA, patients receiving guideline-discordant therapy were referred by IPC staff to the pharmacist for treatment optimization, usually escalation from oral metronidazole to vancomycin, in consultation with the most responsible physician. In September 2017, following completion of the three month evaluation, all cases meeting criteria for treatment escalation received a chart review. Out of the 38 patients meeting criteria for escalation, 27 (71%) were escalated due to inappropriate use of metronidazole monotherapy. When looking at this in terms of the whole 201 person cohort included, at least 1 in 10 CDI inpatients received inadequate therapy.

<table>
<thead>
<tr>
<th>CDI Severity Category</th>
<th>Treatment Recommendation</th>
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<tbody>
<tr>
<td>Initial Episode, Mild-moderate</td>
<td>metronidazole 500 mg PO TID x 10-14 days</td>
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<tr>
<td>Initial Episode, Severe</td>
<td>vancomycin 125 mg PO QID x 10-14 days</td>
</tr>
<tr>
<td>Initial Episode, Fulminant/Complicated</td>
<td>vancomycin 500 mg PO QID x 10-14 days AND metronidazole 500 mg IV Q8H x 10-14 days Consider adding vancomycin by retention enema QID if ileus present</td>
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Table 1: Previous IDSA treatment guidelines for management of CDI (first episode). See Cohen 2010.
There have been several major publications since the 2010 IDSA guidelines that have shifted thinking with respect to CDI management. Johnson (2014) published the results of two multinational, randomized-controlled trials comparing vancomycin, metronidazole, and a toxin-binding agent tolevamer. Tolevamer, the novel agent under investigation, was inferior to both metronidazole and vancomycin. However, the trials together showed that metronidazole was also inferior to vancomycin. Clinical success for patients receiving vancomycin was 81.1%, dropping to 72.7% for metronidazole (p=0.02). Importantly, patients who had mild or moderate disease who received vancomycin had superior clinical success than those who received metronidazole: 82.7 vs. 78.7% for mild disease and 82.2 vs. 73.9% for moderate disease (P<0.02) implying that vancomycin should be used to treat mild to moderate disease instead of metronidazole.

Furthermore, Stevens (2017) published a retrospective, propensity-matched cohort study from the US Department of Veterans Affairs healthcare network. This is the largest review of CDI treatment with 47,471 patients included. Patients who received vancomycin had lower mortality than those who received metronidazole in the any severity cohort (adjusted relative risk 0.86; 95% CI 0.74 to 0.98). This outcome was primarily driven by the high severity CDI group. Unadjusted mortality was 8.6% in those treated with vancomycin versus 10.6% in those treated with metronidazole in the any severity cohort (P=0.01) – an absolute risk reduction of 2%. Finally, the Nelson (2017) systematic review and meta-analysis of 4 randomized controlled trial found that vancomycin was superior to metronidazole for any severity CDI (RR 0.90, 95% CI 0.84-0.97). The mild disease sub-analysis did not include the Johnson study and metronidazole and vancomycin resulted in similar symptomatic cure.

The IDSA has recently published guidelines on management of Infectious Diarrhea (Shane 2017). In this guideline, the first choice recommendation for CDI is oral vancomycin, with fidaxomicin as an alternative. Metronidazole is noted to second-line therapy for adults with non-severe CDI in cases where oral vancomycin is cost prohibitive.

In February of 2018, the IDSA also released updated CDI treatment guidelines (McDonald 2018). Treatment recommendations are summarized in Table 2. Notably, for non-severe disease (formally called mild to moderate) the first line recommendation is oral vancomycin or fidaxomicin. Oral metronidazole is considered alternative treatment when first line therapies are not available.

Table 2. Updated IDSA treatment guidelines for management of CDI. See McDonald 2018.

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<td>Initial Episode, Mild-moderate (non-severe)</td>
<td>vancomycin 125 mg PO QID x 10 days OR fidaxomicin 200 mg PO BID x 10 days Alternate if above agents are unavailable: metronidazole 500 mg PO TID x 10 days</td>
</tr>
<tr>
<td>Initial Episode, Severe</td>
<td>vancomycin 125 mg PO QID x 10 days OR fidaxomicin 200 mg PO BID x 10 days</td>
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Taken together, the more recent literature, updated treatment guidelines, and experience in Fraser Health support use oral vancomycin over metronidazole as first-line therapy for CDI, regardless of disease severity.
ASSESSMENT

1. BUDGET IMPACT ANALYSIS
Precise budgetary impact cannot be easily ascertained. Given the widespread use of oral metronidazole for indications other than CDI (e.g., intra-abdominal infection), there is no direct way to estimate the budgetary impact of converting all oral metronidazole use for CDI to oral vancomycin use.

(Note: Proprietary costing information has been removed)

2. COST-EFFECTIVENESS EVALUATION
Cost-effectiveness evaluation is detailed for all patients with CDI regardless of severity classification. Figures are derived from local costs and published literature.

Incremental Benefit (Source: Johnson 2014):
Clinical Cure:
Clinical cure with oral metronidazole = 72.7%
Clinical cure with oral vancomycin = 81.1%
Incremental benefit for oral vancomycin versus oral metronidazole = 8.4%
Number needed to treat = 12

Mortality:
Mortality with oral metronidazole = 10.6%
Mortality with oral vancomycin = 8.6%
Incremental benefit for oral vancomycin versus oral metronidazole = 2%
Number needed to treat = 50

3. ANALYSIS
Use of oral vancomycin for CDI first-line regardless of disease severity would cost $945.24 per single extra clinical cure and $3,970 per avoided mortality over use of metronidazole. On the scale of health interventions, this would be a highly cost-effective intervention.

A potential barrier to first-line use of oral vancomycin to treat CDI is the higher financial burden for patients continuing therapy after hospital discharge. Oral metronidazole is less costly than oral vancomycin and is covered by the BC Pharmacare and the Government of Canada, Non-insured Health Benefits (NIHB) programs. Oral vancomycin is covered by both BC Pharmacare and the NIHB program but only if patients meet specific criteria. BC PharmaCare provides coverage for oral vancomycin under Special Authority criteria listed in Table 7. NIHB provides coverage for oral vancomycin under Limited Use Benefits criteria listed in Table 8. Patients who meet these criteria are eligible for up to 14 days treatment with oral vancomycin for CDI. Hospitalized patients who receive oral vancomycin first-line for CDI may not necessarily qualify for BC PharmaCare or NIHB program coverage upon discharge and may need to pay out of pocket or seek reimbursement from 3rd party insurance to cover their prescription costs. This may result in outpatients who cannot afford to pay for an oral vancomycin prescription, either experiencing a delay having their prescription filled or choosing not to fill their prescription, both of which could result in poor outcomes.
Table 9. BC PharmaCare Special Authority Oral Vancomycin Criteria for Use

For the treatment of patients diagnosed with symptomatic *Clostridium difficile* Infection (CDI) that:
1. Are allergic, resistant or intolerant to *metronidazole* 
   OR
2. Have failed to respond to 4-6 days of oral metronidazole at doses of 500 mg three times a day 
   OR
3. Have severe disease\(^i\) and initial doses are prescribed by an infectious disease or gastrointestinal specialist 
   OR
4. Are experience a second recurrence\(^{ii}\) and are recommended vancomycin on consultation from an 
   infectious diseases or gastro-intestinal specialist.

Notes:
\(^i\) Severe is defined as having any of the following symptoms:
- white blood cell count > 15,000 mm\(^3\) and fever
- acute kidney injury with rising serum creatinine ≥ 1.5 times premorbid level or ≥175 
  micromole/litre
- pseudomembranous colitis, hypotension, shock, or megacolon
\(^{ii}\) Recurrence is defined as a subsequent CDI episode occurring within 2-8 weeks of a previous episode 
  from the date of diagnosis.

Table 10. NIHB Program - Oral Vancomycin Limited Use Benefit Criteria

For the treatment of patients diagnosed with symptomatic *Clostridium difficile* infection who:
- are allergic, resistant or intolerant to metronidazole; OR
- have failed to respond to 4-6 days of oral metronidazole at doses of 500mg three times a day; OR
- have severe disease and initial doses are prescribed/recommended by an infectious disease or gastro-intestinal specialist.

RECOMMENDATION

1. Oral vancomycin be used as first-line therapy in hospitalized adult patients with *Clostridium difficile* 
   infection regardless of severity. In patients intolerant or allergic to oral vancomycin, metronidazole 500 
   mg PO TID be used to treat non-severe (mild to moderate) *Clostridium difficile* infection.
2. The Health Authorities, through PACE, advocate for modification of the BC PharmaCare Special Authority 
   criteria to provide coverage for patients discharged from hospital on oral vancomycin.
PACE DECISION

1. Decision

<table>
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<th>Date</th>
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<tr>
<td>June 19, 2018</td>
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PACE endorses the following recommendations:

1. Oral vancomycin be used as first-line therapy in hospitalized adult patients with *Clostridium difficile* infection regardless of severity. In patients intolerant or allergic to oral vancomycin, metronidazole 500 mg PO Q8H be used to treat non-severe (mild to moderate) *Clostridium difficile* infection.

2. The Health Authorities, through PACE, advocate for modification of the BC PharmaCare Special Authority criteria to provide coverage for patients discharged from hospital on oral vancomycin.

Submitted By: Dr. Kevin Afra, Fraser Health Authority – PACE Co-Chair

Date: Original Draft – March 14, 2018
Revised: May 22, 2018, June 13, 2018, June 15, 2018, June 18, 2018, June 21, 2018

References