Title: Vancomycin for *C. difficile* Pseudomembranous Colitis: Guidelines and a Clinical Effectiveness Review

Date: 29 February 2008

Context and policy issues:

*Clostridium difficile* is a bacterial enteric pathogen that causes a broad range of clinical disease from asymptomatic colonization or mild diarrhea to life-threatening pseudomembranous colitis (PMC).\(^1\) *C. difficile* associated disease (CDAD) is one of the most common hospital-acquired infections and is a frequent cause of morbidity and mortality among elderly hospitalized patients. Complications include shock, need for colectomy, toxic megacolon, perforation, or death.\(^1\) *C. difficile* colonizes the gastrointestinal tract after the normal gut flora has been altered by antibiotic therapy. Some patients with mild CDAD can be treated symptomatically and with withdrawal of the offending antibiotic.\(^1\) Patients with moderate to severe CDAD require prompt antibiotic treatment, with either oral metronidazole or vancomycin.\(^1\) In the past, due to its higher cost and concerns about the emergence of vancomycin resistance, use of vancomycin has been reserved for cases of intolerance to or treatment failure with metronidazole, patients with severe disease, and for pregnant/lactating women. However, limitations of metronidazole include dose-dependent peripheral neuropathy and gastrointestinal adverse effects.\(^1\)

From December 2002 to December 2005, outbreaks of an unexpectedly large number of CDAD cases (14,000) were reported in Quebec.\(^2,3\) These outbreaks were characterized by a 4.5 fold increase in incidence (35.6 cases per 100,000 people in 1991 versus 156.3 cases per 100,000 people in 2004), an almost 5-fold increase in mortality (4.5% of cases in 1991 versus 22% of cases in 2004), and by a 2.5-fold increase in the number of complicated CDAD cases (7.1% of cases in 1991 versus 18.2% of cases in 2003).\(^2,3\) A number of hypotheses have been put forward to explain these outbreaks, but the strongest evidence so far indicates the emergence of an atypical hypervirulent strain of *C. difficile*.\(^4\) Outbreaks caused by the same strain have subsequently been reported in six Canadian provinces, and can be expected to appear in others in the near future.\(^5\) In light of the increasing prevalence and severity of CDAD in Canada, an assessment of the comparative efficacy of metronidazole versus vancomycin is necessary to
help guide treatment. This report will review the evidence for the clinical effectiveness of vancomycin compared with metronidazole for CDAD. Guidelines and dosing recommendations will also be discussed.

Research questions:

1. What is the clinical effectiveness of vancomycin compared to metronidazole for the treatment of *C. difficile* pseudomembranous colitis?

2. What are the guidelines for vancomycin treatment in patients with *C. difficile* pseudomembranous colitis?

3. What are the dosing and dose tapering guidelines for vancomycin treatment of *C. difficile* pseudomembranous colitis?

Methods:

A limited literature search was conducted on key health technology assessment resources, including Pre-Medline, Medline, Embase, Biosis, CINAHL, UptoDate, Pubmed, the Cochrane Library (Issue 1, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2003 and the January 2008, and are limited to English language publications only. Filters were applied to limit the retrieval to systematic reviews/HTA, guideline, and randomized controlled trial (RCT) studies. This search was supplemented by hand searching the bibliographies of selected papers. Internet links are provided, where available.

Summary of findings:

Health technology assessments

No health technology assessments were identified.

Systematic reviews and meta-analyses

One Cochrane systematic review was identified. The objective of the review was to assess the efficacy of antibiotic therapy for CDAD and to identify the most effective antibiotic treatment for CDAD in adults. Eight different oral antibiotics were investigated: vancomycin, metronidazole, fusidic acid, nitazoxanide, teicoplanin, rifampin, rifaximin, and bacitracin. The review’s primary outcome was symptomatic cure (defined as initial symptomatic resolution without symptomatic recurrence at any time during the follow-up period). The review’s secondary outcomes included initial symptomatic resolution, bacteriologic cure, and initial bacteriologic resolution. Results indicated that metronidazole, vancomycin, bacitracin, teicoplanin, fusidic acid, and rifaximin were equally effective at achieving early symptomatic cure and the secondary outcomes. Only two randomized controlled trials evaluating vancomycin versus metronidazole were included in the review. Details of these trials are discussed in the next section. Pooled analysis of the two trials indicated equivalent efficacy for the primary outcome of symptomatic cure with a relative risk of 1.01 (95% CI 0.87,1.18). Equivalent efficacy of vancomycin and metronidazole was also reported for all the secondary outcomes.
Randomized controlled trials

Three randomized controlled trials (RCTs) comparing the efficacy of vancomycin versus metronidazole for the treatment of CDAD have been published.\textsuperscript{7-9} Details of these trials, including their limitations, are presented in Table 1.

1. Teasley \textit{et al.} prospectively randomized 94 patients to receive oral courses of vancomycin or metronidazole.\textsuperscript{7} The authors defined CDAD as stool being positive for \textit{C. difficile} by culture or cytotoxin assay, or by the presence of pseudo-membranes on endoscopy. Stool was tested for other enteric pathogens, but the authors did not comment on the presence of absence of these pathogens. Treatment failure was defined as persistence of watery stools greater than four times per day after six days of treatment. Relapse following treatment was defined as a recurrence within 21 days of diarrhea (watery stools greater than four times per day for a minimum of 48 hours) in a patient who had responded to 10 days of vancomycin or metronidazole treatment. Results for the number of treatment failures, time to resolution of diarrhea, and number of relapses were not significantly different between the treatment groups. Treatment in one patient in each group was discontinued due to drug intolerance (nausea and vomiting). The authors concluded that metronidazole and vancomycin have equivalent efficacy and relapse rates, and are tolerated to a similar extent.

2. Wenisch \textit{et al.} randomized 119 patients to receive oral courses of vancomycin, metronidazole, teicoplanin, or fusidic acid.\textsuperscript{8} The authors defined \textit{C. difficile} disease as stool positive for cytotoxin or endoscopic evidence of pseudo-membranes or fecal leukocytes. The authors did not perform stool culture on any of the study patients and, therefore, did not exclude the presence of other pathogens in the stool as the cause of diarrhea. Clinical cure was defined as a lack of symptoms (no loose stools, gastrointestinal symptoms, or fever) and normalization of serum levels of C-reactive protein and leukocyte counts. Clinical failure was defined as the persistence of diarrhea after six days of treatment. Clinical relapse was defined as the reappearance of diarrhea and other symptoms during the follow-up period of 30 days after discontinuation of therapy. Consistent with previous results, no significant differences were noted for clinical cure or recurrence of symptoms for patients treated with any of the four antibiotics. Gastrointestinal adverse effects were observed in three patients treated with metronidazole but no adverse effects related to therapy with vancomycin were reported. The authors concluded that considering the costs of treatment, indication of equivalent efficacy suggested that metronidazole should be the drug of choice for \textit{C. difficile} associated diarrhea and that vancomycin should be reserved for patients who cannot tolerate metronidazole or who do not respond to treatment.

3. Zar \textit{et al.} conducted a randomized, double-blind trial comparing vancomycin with metronidazole.\textsuperscript{9} Compared with the two previous trials, a considerably lower dose of vancomycin was used. One hundred and fifty participants were stratified according to disease severity to investigate whether one agent was superior for treating mild or severe disease. Patients with a severity assessment score equal or greater than 2 points were considered to have severe CDAD. One point was given for age >60 years, temperature >38.3°C, albumin level <2.5 mg/dL, or peripheral white blood cell count >15,000 cells/mm\textsuperscript{3} within 48 hours of enrollment. Two points were given for endoscopic evidence of pseudo-membranes or treatment in the intensive care unit (ICU). Participants were enrolled based on a positive result for \textit{C. difficile} toxin or if pseudomembranous colitis (PMC) was demonstrated on endoscopic examination. Stool samples were examined to exclude other infectious causes of diarrhea. Patients were
followed up for 21 days to assess cure, treatment failure, relapse, or intolerance. Cure was defined as diarrhea resolution by the sixth day of treatment in addition to clearance of *C. difficile* toxin from stool specimens obtained on the sixth and tenth days of treatment. Treatment failure was defined as persistence of diarrhea and/or positive result of a *C. difficile* toxin assay after six days of treatment, need for colectomy, or death after five days of therapy. Relapse was defined as recurrence of *C. difficile* toxin positive diarrhea by day 21 after initial cure. Overall, the rate of cure was significantly higher in those patients treated with vancomycin than in those treated with metronidazole. Furthermore, among patients with severe disease, vancomycin therapy resulted in a significantly higher rate of clinical cure than treatment with metronidazole. However, there was no significant difference in the proportion of patients with mild disease who achieved clinical cure with vancomycin or metronidazole. After initial cure, there was no significant difference in the percentage of patients who relapsed when analyzed according to mild or severe disease, or treatment with metronidazole versus vancomycin. One case of gastrointestinal adverse effects resulting in discontinuation of the drug was reported for each treatment group. Factors significantly associated with metronidazole treatment failure were serum albumin level <2.5 mg/dL, presence of PMC, and admission to the ICU. The authors concluded that that vancomycin therapy was superior to metronidazole therapy overall, but the treatment benefit was limited to patients with severe disease.

Methodological issues in this trial may, however, compromise the validity of this conclusion. Firstly, most clinicians and previous clinical trials have used clinical criteria for determining treatment success. Persistence of *C. difficile* toxin in stool specimens despite diarrhea resolution is a well-documented phenomenon of uncertain clinical significance. Furthermore, there is evidence that although vancomycin is associated with higher rates of toxin clearance than metronidazole, this does not translate into a lower risk of recurrence. Therefore, due to its lack of prognostic value, repeat stool toxin assays after resolution of diarrhea is not recommended as a “test of cure”. Secondly, although the markers of severity chosen in this trial relate to markers of poor outcome in other studies, this severity scale has not been prospectively validated in a cohort of patients with CDAD. There may be some benefit to stratifying patients according to formal measures of illness severity such as the APACHE score instead.
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<tr>
<th>Author, Year</th>
<th>Study Design</th>
<th>Participants</th>
<th>Interventions</th>
<th>Results</th>
<th>Conclusions and Limitations</th>
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</table>
| Teasley et al., 1983 | RCT | Patients with *C. difficile* associated diarrhea or colitis | **Vancomycin**
500 mg orally four times daily (n=52)
**Metronidazole**
250 mg orally four times daily (n=42)
Duration: 10 days | **Number of treatment failures:**
Vancomycin: 0
Metronidazole: 2
(p=0.20)
**Mean time to resolution of diarrhea (±SD):**
Vancomycin: 2.8 ± 1.8
Metronidazole: 2.4 ± 1.9
(p=NS)
**Number of relapses:**
Vancomycin: 6
Metronidazole: 2
(p=0.17) | Metronidazole is as effective as vancomycin for the treatment of *C. difficile* associated colitis and diarrhea.
Non-blinded
Small sample size for each treatment group
Unclear allocation concealment
ITT analysis not conducted |

| Wenisch et al., 1996 | RCT | Patients with *C. difficile* associated diarrhea or colitis | **Teicoplanin**
400 mg orally twice daily (n=28)
**Fusidic acid**
500 mg orally three times daily (n=29)
**Vancomycin**
500 mg orally three times daily (n=31)
**Metronidazole**
500 mg orally three times daily (n=31)
Duration: 10 days | **Clinical Cure (%)**
Teicoplanin: 96
Fusidic acid: 93
Vancomycin: 94
Metronidazole: 94
(overall: p>0.05)
(vancomycin vs. metronidazole: p>0.8)
**Recurrence of symptoms (%)**
Teicoplanin: 7
Fusidic acid: 28
Vancomycin: 16
Metronidazole: 16
(overall: p value not reported)
(vancomycin vs. metronidazole: p>0.8) | Metronidazole is the drug of choice for *C. difficile* associated diarrhea.
Non-blinded
Small sample size for each treatment group
ITT analysis unclear due to absence of allocation data for 7 drop outs. |
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<tr>
<td>Zar et al., 2007</td>
<td>RCT</td>
<td>Double-blind, Placebo-controlled</td>
<td>Vancomycin 125 mg orally (liquid) four times daily with placebo tablet (mild n=40) (severe n=31)</td>
<td>Overall rate of cure(%): Vancomycin: 97 Metronidazole: 84 (p=0.006)</td>
<td>Vancomycin is significantly better for treating individuals with severe disease but not those with mild CDAD.</td>
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<td>Patients with C. difficile associated diarrhea or colitis stratified according to disease severity Mild (n=81) Severe (n=69)</td>
<td>Metronidazole 250 mg orally (tablet) four times daily with placebo liquid (mild n=41) (severe n=38)</td>
<td>Clinical cure with severe disease(%): Vancomycin: 97 Metronidazole: 76 (p=0.02)</td>
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<td>Clinical cure with mild disease(%): Vancomycin: 98 Metronidazole: 90 (p=0.36)</td>
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<td>Relapse rate according to severity(%): Mild: 7 Severe: 15 (p=0.15)</td>
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<td>Relapse rate(%): Vancomycin: 7 Metronidazole: 14 (p=0.27)</td>
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</table>

RCT=Randomized controlled trial, SD=Standard Deviation, NS=Non-significant, ITT=Intention-to-treat

Vancomycin for C. difficile Pseudomembranous Colitis
Guidelines and Dosing Recommendations

Formal guidelines published in the 1990s recommend oral metronidazole over oral vancomycin as first-line therapy for non-severe CDAD.\textsuperscript{13-16} Dosing recommendations are outlined in Table 2. Rationale for this recommendation includes the lower cost of metronidazole relative to vancomycin, an attempt to curtail the spread of vancomycin-resistant enterococci (VRE), and the comparable clinical effectiveness of both agents. However, all of these guidelines are based on clinical effectiveness documented in the medical literature before the appearance of the current hypervirulent strain.\textsuperscript{17}

Currently, consensus recommendations for the prevention of recurrent CDAD are unavailable. An initial relapse is not commonly associated with resistance and should thus be treated similarly to the initial episode.\textsuperscript{15} Patients with multiple relapses may benefit from a combination of a tapering dose of vancomycin followed by pulsed dosing.\textsuperscript{1} One recommendation has been oral vancomycin 125 mg four times daily for seven days, tapering to 125 mg twice daily for seven days, then daily for seven days.\textsuperscript{16} Other authors recommend starting oral vancomycin at a higher dose of 500 mg four times daily for 10 days, then tapering.\textsuperscript{19} After the taper has been completed, pulsed dosing begins. Although there is no standard well-studied pulsing regimen, one suggestion has been to give vancomycin 250 mg every two or three days for a total of three weeks.\textsuperscript{20} Others have recommended continued lengthening of the pulsing interval until the vancomycin is given only once every 10 days.\textsuperscript{19} The use of intermittent antibiotic therapy is based upon a theory that \textit{C. difficile} relapse may be due to the presence of persistent spores that survive antibiotic therapy.\textsuperscript{21} Intermittent therapy may allow the spores to germinate on the days when no antibiotics are administered. Once the spores have converted to the toxin-producing forms, they are susceptible to killing when the antibiotics are re-administered.\textsuperscript{21} The effect of these regimens on the occurrence of VRE has not been evaluated.

There is no consensus definition for severe CDAD, nor is there agreement as to the most important clinical indicators that should be used to differentiate severity.\textsuperscript{1} There is no definitive data for the antibiotic management of severe disease. A combination of high dose oral vancomycin in combination with intravenous metronidazole has been suggested.\textsuperscript{1} Intracolonic vancomycin may be considered in patients with toxic megacolon.\textsuperscript{1}

\begin{table}[h]
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\begin{tabular}{|l|l|}
\hline
\textbf{Severity Category} & \textbf{Treatment Regimen} \\
\hline
Non-severe initial episode & Preferred: Metronidazole 500 mg orally three times daily for 10-14 days or Metronidazole 250 mg four times daily for 10-14 days \\
 & Alternative*: Vancomycin 125-500 mg orally four times daily for 10-14 days \\
\hline
Non-severe first relapse & If antibiotics are needed, repeat treatment as in initial episode above with metronidazole as the preferred option \\
\hline
Non-severe subsequent relapse & Tapering and pulsed oral vancomycin (see text) \\
\hline
Severe episode & Metronidazole 500 mg intravenously every eight hours plus Vancomycin 125-500 mg orally four times daily \\
 & Intracolonic vancomycin may be considered in patients with toxic megacolon \\
\hline
\end{tabular}
\caption{Treatment Regimens for CDAD\textsuperscript{1,13-16}}
\end{table}

* Vancomycin is the preferred agent when metronidazole fails to elicit a response after 4-6 days, in pregnant/lactating women, or patient is intolerant to metronidazole.
Limitations

It is likely that the two RCTs that indicated equivalent efficacy between metronidazole and vancomycin for either initial response or rate of relapse may have been underpowered (i.e., the sample sizes were too small) to detect a difference.\(^7,8\) In addition, the time these trials were published (1983 and 1996) may affect the generalizability of these results to current resistance patterns of \(C.\) difficile including the hypervirulent strain. Definition of cure and severity assessment in the third RCT may have affected the accuracy the conclusion that vancomycin is superior to metronidazole for the treatment severe disease.\(^9\)

No randomized trials are available to guide therapy of recurrent disease or CDAD caused by the hypervirulent strain. Furthermore, no studies have yet evaluated VRE fecal colonization and/or carriage in patients receiving vancomycin. Clinically important outcomes including complications (e.g. development of toxic megacolon or the need for colectomy) or mortality have not been assessed due to the short-term follow up of available trials.

Conclusions and implications for decision or policy making:

No major health agency has published treatment guidelines since the appearance of the hypervirulent strain of \(C.\) difficile despite increasing prevalence and severity of the disease. This important deficiency reflects the lack of available evidence. Although data are limited, clinical practice is shifting toward using oral vancomycin as initial therapy for severe CDAD, and some authorities have endorsed vancomycin as the preferred therapy for moderate or severe disease caused by the hypervirulent strain.\(^22\) However, concrete fears of the development of vancomycin resistance among clinically important pathogens, such as \(Staphylococcus aureus\) and the enterococci remain. Therefore, further evidence is needed before vancomycin is universally recommended for use in patients with severe CDAD or CDAD caused by the hypervirulent strain. Moreover, appropriate treatment for patients with multiple relapses of CDAD remains to be determined. Further long-term RCTs comparing vancomycin with metronidazole in patients with severe and refractory CDAD are needed. Clinically important outcomes such as complications, mortality and resistance should be evaluated. In the meantime, clinical experience and expert opinion are needed to help guide the choice of therapy for CDAD.

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