The Case for Vancomycin as the Preferred Drug for Treatment of Clostridium difficile Infection

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(See the IDSA lecture by Pepin on pages 1493–8)

Antibiotic-associated diarrhea became a well-recognized complication of antibiotic use shortly after the introduction of these agents in the early 1950s. Staphylococcus aureus was the presumed pathogen, pseudomembranous enterocolitis was the characteristic pathological lesion, and oral vancomycin became the standard method of treatment [1–4]. In 1974, Tedesco et al. [4] published the seminal report on “clindamycin colitis,” showing a 10% rate of pseudomembranous colitis associated with clindamycin use, but a notable observation in the study was that S. aureus, the presumed etiologic agent of this disease, could not be detected, despite the ease of growing it on selective media. This prompted subsequent studies to search for an alternative etiologic agent.

Much of the early work was done with the hamster model, because clindamycin, as well as many other antibiotics, almost invariably caused a lethal cecitis that resembled the lesions found in patients. One of the first clues to a bacterial etiology in this model was the observation that clindamycin-induced disease could be prevented with oral vancomycin [5, 6]. The search for the alternative etiologic agent led to the detection of Clostridium difficile as the putative agent [7], and vancomycin was approved by the US Food and Drug Administration (FDA) for this indication; it quickly became standard therapy [8]. During the early 1980s, there were 3 important additional observations relevant to treatment: (1) the standard dose of vancomycin was reduced from 500 mg administered 4 times daily to 125 mg administered 4 times daily, (2) metronidazole appeared to be effective, and (3) both drugs were associated with relatively high rates of relapse after treatment was discontinued [8–12].

During the past 20 years, there has been intermittent progress in developing alternative antibiotics for the treatment of C. difficile infection (CDI), including bacitracin, fusidic acid, and teicoplanin. All of these worked, but vancomycin and metronidazole emerged as the clear favorites for clinicians. Metronidazole was sometimes favored, because it is less expensive, avoids “vancomycin abuse,” and is possibly less likely to lead to the development of vancomycin-resistant enterococci. Nevertheless, vancomycin had the advantage of a long history of use and, for an intralumenal pathogen, great pharmacological characteristics; it remains the only drug that has been approved by the FDA for this indication, and the drug had virtually no apparent adverse effects, other than the bad taste of the intravenous formulation that was given by mouth as standard practice in the early 1980s. The debate on the relative merits of these 2 drugs continues. This article will summarize the case for vancomycin, which has quite recently become a robust, one-sided argument, based on clinical trials that show compelling evidence that it is the preferred drug for patients with serious disease and, possibly, for all patients who need treatment.

THE ISSUES

The issues raised in this report concern the pharmacology of vancomycin versus metronidazole, the in vitro activity of these drugs against C. difficile, clinical trials,
The issue of vancomycin-resistant enterococci promotion is debated, because it appears that both metronidazole and vancomycin may be responsible [21]. My view is that there is no consensus on this issue, and the topic should be the subject of a different debate.

Relapse of CDI is a complication of treatment with either metronidazole or vancomycin. The rates of relapse are approximately the same for each drug (15%-25% of cases), and there has not been a convincing or consistent demonstration of the superiority of either agent in the multitude of trials that have been performed to date [10, 12, 22–28].

FDA approval applies to oral vancomycin, indicating that it has undergone a standard FDA review with a placebo-controlled trial to demonstrate efficacy. Metronidazole has not undergone such a review. This may be an important issue for some, but there are many antibiotics that have become standards for selected infections without completing the FDA approval process, and based on this precedent, this now appears to be a relatively weak argument in favor of vancomycin.

### PHARMACOLOGY

CDI is characterized by *C. difficile* colonization in the colon, with production of toxin when spores are transformed to the vegetative form, resulting in the production of both toxin A and toxin B. Both toxins are thought to be important in the pathophysiology of CDI. This is a toxin-mediated disease, and the putative agent, *C. difficile*, neither invades the intestinal wall nor causes bacteremia. It has been identified at other anatomical sites, but it does not appear to produce toxin at these sites and does not have any distinguishing features that are clinically important [29]. The conclusion is that the antibiotic needs to be in the colonic lumen, because that is where *C. difficile* is located and toxin is produced. In this regard, oral vancomycin is the perfect drug, because it is not absorbed, serum levels are virtually nil, and colonic levels are very high (often 500–1000 μg/mL, which is several hundred-fold higher than the highest MIC measured for *C. difficile*) [23, 30]. Metronidazole, by contrast, is virtually 100% absorbed in the small bowel, so that levels in the colonic lumen are extremely low and are often undetectable [31]. To be fair, there may be low levels measured in the presence of diarrhea, and there is the possibility of back diffusion from the serum across the colonic mucosa, but this is quite inconsistent [31]. Of interest is the observation that metronidazole is possibly the most potent anti-anaerobic bacterial antibiotic available; anaerobes account for ~99.9% of the colonic flora, but oral metronidazole has little or no important impact on that flora when given to healthy persons. There is a message in this observation.

### PROSPECTIVE CLINICAL TRIALS

The prospective studies to address the issue of the relative merits of vancomycin versus metronidazole provide the most compelling support for selective use of vancomycin. There are some older studies that fail to show a difference in response rates or relapse rates, but the number of participants in these studies was relatively small, and the conclusions of such studies was,

### Table 1. Vancomycin versus metronidazole for treatment of *Clostridium difficile* infection.

<table>
<thead>
<tr>
<th>Outcome, by severity of disease</th>
<th>Proportion (%) of patients</th>
</tr>
</thead>
</table>
|                               | Metronidazole | Vancomycin | *P*
| Cure                          | 37/41 (90) | 39/40 (98) | .36 |
| Relapse                       | 9/66 (14) | 5/69 (7) | .27 |

**NOTE.** Adapted from Zar et al. [32].

### Table 2. Vancomycin versus metronidazole for treatment of *Clostridium difficile* infection.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Proportion (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>109/133 (82)</td>
</tr>
<tr>
<td>Mild</td>
<td>23/27 (85)</td>
</tr>
<tr>
<td>Moderate</td>
<td>58/73 (80)</td>
</tr>
<tr>
<td>Severe</td>
<td>28/33 (85)</td>
</tr>
<tr>
<td>Relapse</td>
<td>27/103 (23)</td>
</tr>
</tbody>
</table>

**NOTE.** Adapted from Louie et al. [33]. Data for tolevanam have been deleted.

* *P* < .05.
consequently, limited. The largest studies have been reported in the past year and show convincing evidence that treatment with vancomycin is superior to treatment with metronidazole in patients who are judged to be seriously ill [32].

The study reported by Zar et al. [32] was a prospective study of vancomycin (125 mg administered 4 times per day for 10 days) versus metronidazole (250 mg administered 4 times per day for 10 days) in patients with CDI who were stratified by severity of illness and monitored for response. Severe disease was defined as pseudomembranous colitis or 2 of the following characteristics: age >60 years, serum albumin level <2.5 mg/mL, peripheral leukocyte count >15,000 cells/mL, and temperature >38.3°C. Cure was defined as the absence of diarrhea on day 6 and a toxin assay result negative for *C. difficile* on day 6 and day 10. Failure was defined by the need for a colectomy, death after 5 days, relapse within 21 days after the end of therapy, or the failure to achieve the definition of cure. Results of the study are shown in table 1, which shows a trend (90% vs. 98%) favoring vancomycin that was not statistically significant for this category as well. It is quite possible that many of the patients judged to have mild disease would have done well simply with discontinuation of treatment with the implicated antibiotic. This was a common ploy when the toxin test was done with use of the cytotoxin assay, which necessitated a 24–48-h delay in reported results. Approximately one-third of patients were never given either drug, because their condition improved sufficiently as a result of discontinuation of the inducing agent before toxin assay results were reported. This conclusion is supported by a Cochrane Library review, which states that “current evidence leads to uncertainty if mild CDI needs to be treated” [35, p. 2].

**CONCLUSIONS**

Until 2007, the debate on the relative merits of vancomycin versus metronidazole had been largely limited to the theoretical advantage of vancomycin based on historical precedent, FDA approval, and pharmacology. The renewed interest in *C. difficile* has spawned great interest in CDI, and larger and more comprehensive studies are now available. The 2 prospective trials [29, 30] show clear evidence of the superiority of vancomycin therapy in patients with severe disease and show trends toward superior outcome in those with mild disease. The review from the Premier hospitals shows some substantial additional benefits, including length of stay, total hospital costs, and mortality. There seems to be little doubt that vancomycin is the best drug for patients with severe or severe and complicated CDI, although the remaining challenges include getting the drug to

### Table 3. Retrospective review of vancomycin versus metronidazole for treatment of 32,325 cases of *Clostridium difficile* infection.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Metronidazole</th>
<th>Vancomycin</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of hospital stay, mean days</td>
<td>12.8</td>
<td>11.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mortality rate, %</td>
<td>7.9</td>
<td>6.8</td>
<td>.02</td>
</tr>
<tr>
<td>Length of stay in the intensive care unit, mean days</td>
<td>23.2</td>
<td>17.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pharmacy cost, mean value</td>
<td>$2439</td>
<td>$2492</td>
<td>.5</td>
</tr>
<tr>
<td>Hospital cost, mean value</td>
<td>$16,953</td>
<td>$14,718</td>
<td>&lt;.001</td>
</tr>
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**NOTE.** Adapted from Lahue et al. [34].
the site of infection in those with ileus and the continuing problem of relapse. For patients with mild disease, there is some question about the need for an antibiotic, and metronidazole may be the preferred agent when no antibiotic is needed.

Acknowledgments

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References