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 pathologic 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 intraluminal 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,
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>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>37/41 (90)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>29/38 (76)</td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>9/66 (14)</td>
<td></td>
</tr>
</tbody>
</table>

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

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

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

NOTE. Adapted from Louie et al. [33]. Data for tolevamer have been deleted. *P < .05.
The conclusion of both studies [32, 33] is that vancomycin is the preferred drug for the treatment of seriously ill patients with CDI. To be fair, no conclusion could be reached for patients with mild or moderate disease on the basis of the data provided, although both studies showed a trend favoring vancomycin, which suggests that a sufficient sample size would achieve statistical significance 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].

RETROSPECTIVE REVIEW OF THE EXPERIENCE IN PREMIER HOSPITALS

A review of the database for CDI for the period 2004–2005 among Premier hospitals, based on a total of 32,325 cases of CDI, was reported at the 2007 meeting of the European Society of Clinical Microbiology and Infectious Diseases [34]. These cases were analyzed by treatment with metronidazole versus vancomycin for length of hospital stay, death, cost of pharmaceutical agents, and total hospital costs. The results are shown in table 3 and indicate that treatment with vancomycin was associated with a statistically significant better outcome in terms of length of hospital stay, mortality, and total hospital costs.

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>
<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>
</tbody>
</table>

NOTE. Adapted from Lahue et al. [34].

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

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