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, fuscidic 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,
retrospective reviews, cost, and vancomycin-resistant enterococci promotion. Some of these issues can be dispensed with rather rapidly, because they appear to be beyond debate.

With respect to in vitro activity, both drugs are highly active against *C. difficile*, with median MICs $\approx 0.01$ μg/mL [13–19]; there is 1 report of a 6% rate of resistance to metronidazole from Spain, but this has generally not been the clinical experience elsewhere [16]. It seems fair to conclude that both drugs consistently show good activity against *C. difficile* and that the development of resistance to either drug has not been convincingly shown [10–12].

Cost is substantially less for metronidazole, compared with the oral formulation of vancomycin, which is now available as parvules. The cost per day based on the average wholesale price for oral parvules with 125 mg vancomycin is $\approx $70, compared with $\approx $2 per day for metronidazole [20]. The intravenous form of vancomycin is sometimes given in hospitals; this has a noxious taste, but it has a lower price than that of parvules. The intravenous form of vancomycin is not generally available in outpatient pharmacies, so virtually all outpatient use of this drug will be with parvules.

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 $\approx 99.9\%$ 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>
<thead>
<tr>
<th>Outcome</th>
<th>Proportion (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vancomycin</td>
</tr>
<tr>
<td>Cure, by severity of disease</td>
<td></td>
</tr>
<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 tolevamer have been deleted.

*a* $P<.05$. (CID 2008:46 (15 May) • Bartlett)
mild, moderate, or severe disease; severe disease was defined as pseudomembraneous 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 those with mild disease and shows clear superiority for vancomycin in terms of cure rates for those with severe disease (77% vs. 98%; \( P < .002 \)).

The second trial was actually the largest trial ever performed involving CDI and has been reported in abstract form [33]. This was the phase 3 trial of tolevamer versus vancomycin and metronidazole. The patients were stratified as having either mild, moderate, or severe disease; severe disease was defined as ≥10 bowel movements per day, a peripheral leukocyte count of ≥20,000 cells/mL, or severe abdominal pain. The results are shown in table 2 and favor the superiority of vancomycin in all 3 severity-of-illness categories, but the superiority of vancomycin was statistically significant only in the severe illness group (cure rate, 65% vs. 85%; \( P < .05 \)).

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 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>
</tbody>
</table>

**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**

*Potential conflicts of interests.* J.G.B. has served on the HIV Advisory Boards of Johnson & Johnson, Bristol Myers Squibb, Gilead, Tibotec, GlaxoSmithKline, and Pfizer, has served on the Infectious Diseases Advisory Board of Arpida, and has received a research grant from Gilead.

**References**