Vancomycin for the Treatment of *Clostridium difficile* Infection: For Whom Is This Expensive Bullet Really Magic?

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The epidemiology, clinical severity, and case-fatality ratio of *Clostridium difficile* infection (CDI) changed dramatically with the emergence of a toxin hyperproducing strain (BI/NAP1/027) in North America and Europe in 2000. For the treatment of CDI, metronidazole and vancomycin remain the 2 most commonly used drugs. The 3 randomized controlled trials published thus far, as well as the upcoming televamer trial, use intermediate outcomes, rather than the outcomes that now preoccupy clinicians: the frequency of complications or recurrence. The major advantage of metronidazole is its low price. The major advantage of orally administered vancomycin is its more favorable pharmacokinetics. Facilitating vancomycin-resistant enterococci colonization and/or infection is a potential drawback of both drugs. Pending the development of a prospectively validated scoring system, members of the Infectious Diseases Society of America/Society for Healthcare Epidemiology of America expert committee will define severe CDI as present in any patient with a leukocyte count \( \geq 1.5 \) times the baseline value, or a leukocyte count \( \geq 15,000 \) cells/mm\(^3\) or a creatinine level increased by \( \geq 50\% \) from baseline. For patients with mild-to-moderate CDI (defined by a leukocyte count \( < 15,000 \) cells/mm\(^3\) and a creatinine level \( < 1.5 \) times the baseline value), there is no evidence that treatment with vancomycin is superior to treatment with metronidazole (even for intermediate outcomes), and metronidazole therapy should be preferred. For patients with severe CDI who are not infected with BI/NAP1/027, there is reasonable evidence that the better pharmacokinetics of vancomycin translate into a lower probability of complications. For those patients who are infected with BI/NAP1/027, the superiority of vancomycin therapy remains to be proven. In practice, because it is not yet possible to rapidly type the strains, all patients with severe CDI should be treated with vancomycin. Future trials should use complicated CDI and recurrences as their primary outcomes.

HISTORICAL PERSPECTIVE

In March 1978, John Bartlett and colleagues published the first article that established the etiological role of *Clostridium difficile* toxins in causing pseudomembranous colitis [1]. Four months later, they reported on the use of oral vancomycin in 9 patients, all of whom had a good clinical response, and documented high fecal levels of vancomycin [2]. Similar results were reported shortly thereafter by a British group [3]. During the same year, the first reports of treatment of *C. difficile* infection (CDI) with metronidazole appeared [4, 5]. At the end of 1983, the results of the first randomized trial comparing metronidazole (42 patients) and vancomycin (52 patients) were published [6]. The groups did not differ with respect to mean time to resolution of diarrhea, frequency of treatment failure (which occurred in 2 patients, both of whom had received metronidazole), or relapses. This was before power, sample
size estimates, and β-type error became a collective preoccupation, and it was concluded that both treatments were equivalent [6].

The field of CDI treatment then entered a hibernation phase that lasted >20 years. Additional case series were published, treatments other than metronidazole or vancomycin came and went (e.g., bacitracin, fusidic acid, teicoplanin, and colestipol), and a second small, 4-arm, randomized controlled trial was conducted (with 31 patients per arm) which, predictably, did not show differences between metronidazole and vancomycin therapy [7]. Use of vancomycin for the treatment of CDI decreased when, in 1995, the Hospital Infection Control Practices Advisory Committee recommended avoiding it as much as possible, in the hope of reducing the selection pressure for the emergence of vancomycin-resistant enterococci [8]. The Society for Healthcare Epidemiology of America position paper stated that both drugs were effective and that “metronidazole is less expensive and may be preferable to avoid vancomycin resistance in other nosocomial bacterial species” [9, p. 473]. Two years later, the American College of Gastroenterology also recommended metronidazole for most patients, with the exception of small subgroups, such as those critically ill with CDI [10]. Throughout that period, CDI was considered to be a generally trivial condition, and there was little interest in evaluating novel therapeutic approaches, despite the shortcomings associated with available drugs, especially the high frequency of recurrences.

Around 2000, somewhere in the United States, 1 specific strain of *C. difficile*—to be designated BI/NAP1/027—became resistant to all fluoroquinolones and, probably because of a 1–base pair deletion in its tcdC gene, became a hyperproducer of toxins A and B [11]. Compared with historical strains, these changes enhanced its transmission within and between hospitals, and BI/NAP1/027 spread very effectively. In 2002, it was introduced into Montreal, Canada, in the province of Quebec, and spread from there to dozens of hospitals, presumably via transfer of patients or via health care workers who provided care in >1 institution [12, 13]. Incidence of nosocomial CDI increased dramatically: at the worst of the epidemic, ≥4% of all patients who were admitted into several hospitals of Quebec acquired nosocomial CDI. Between 14% and 17% of patients with nosocomial CDI died as a direct or indirect consequence of infection [13, 14]. In Quebec, mortality in which CDI was the main cause of death increased from 85 cases in 2000 to 691 cases in 2004 [15]. BI/NAP1/027 spread throughout the United States, where the incidence of CDI more than doubled and CDI mortality quadrupled [16–18], but it also spread throughout Western Europe [19]. At last, this crisis gave a new impetus to the development of novel drugs for the treatment of CDI and prompted a reassessment of the comparative efficacy of metronidazole and vancomycin.

**IN VITRO SUSCEPTIBILITY**

Metronidazole resistance in *C. difficile* is rare, and the MICs of nearly all strains are ≤2.0 mg/L [20, 21]. In a report from Spain, the MIC₉₀ of 415 isolates was 4.0 mg/L, and 6% of isolates had MICs ≥32 mg/L [22], but this was not confirmed by further work. The MIC₉₀ of vancomycin against *C. difficile* is 1.0–2.0 mg/L, and the highest MIC ever reported is 16 mg/L [20, 21]. There is no evidence that the epidemic BI/NAP1/027 strain or other recent North American isolates are more resistant to vancomycin or metronidazole than are nonepidemic strains or historical isolates [13, 23–25].

**PHARMACOKINETICS**

Orally administered metronidazole is absorbed rapidly and almost completely; only 6%–15% of its metabolites are excreted in stools. Fecal concentrations of metronidazole reflect its secretion in the colon, and levels decrease rapidly after treatment of CDI is initiated, from 9.3 μg/g in watery stools to 1.2 μg/g in formed stools [26]. When metronidazole is administered intravenously, fecal levels are at least as high as and perhaps even higher than when the drug is given orally [26, 27]. Metronidazole is undetectable in stools of asymptomatic *C. difficile* carriers [28], and administering courses longer than 14 days seems to be irrational, particularly if diarrhea has resolved. In contrast, vancomycin is poorly absorbed, so that fecal concentrations following oral administration (at a dosage of 125 mg administered 4 times daily) are generally >1000 μg/g [28]. Vancomycin fecal levels are maintained throughout treatment. Thus, the ratio of fecal levels divided by the MIC is 2 orders of magnitudes higher with vancomycin treatment than with metronidazole treatment.

It normally requires <6 h for nutriments to travel from the mouth to the ileo-caecal valve. In patients with some degree of ileus, this interval will be longer, but whether this becomes clinically relevant with regard to the delivery of vancomycin to the colon is unknown. In comparison, orally administered metronidazole peaks 1–2 h later and will quickly reach the colonic wall. However, we do not know how long it takes for metronidazole to be secreted into the colonic lumen.

**ADVERSE EFFECTS**

Adverse effects are not a major issue when selecting between metronidazole or vancomycin for patients with CDI. The most common adverse effect of metronidazole therapy is gastrointestinal intolerance, but in patients with CDI, it is difficult to determine whether nausea is caused by the drug or by the underlying illness. If given for a long duration, metronidazole can cause polyneuropathy, which is another reason to avoid long courses of therapy. When administered orally, little van-
VANCOMYCIN-RESISTANT ENTEROCOCCI

CDI and colonization and/or infection with vancomycin-resistant enterococci (VRE; or methicillin-resistant *Staphylococcus aureus*) share many risk factors: increased age, extended hospital stay, presence of numerous comorbidities, tube feeding, and the administration of antibiotics, such as cephalosporins and fluoroquinolones [29]. It is thus not surprising that these pathogens often coexist in some patients, as has been demonstrated repeatedly [30, 31].

Whether intravenously or orally administered vancomycin promotes the emergence of vancomycin-resistant enterococci was reviewed 10 years ago by Dale Gerding [32]. An association between intravenously administered vancomycin and VRE colonization or infection was documented in 9 of the 10 studies then available [32]. Orally administered vancomycin was associated with VRE in 3 of the 4 small studies that stratified risk by route of administration. Metronidazole was also associated with VRE [32]. Although this could have been a consequence of the concomitant administration of other antibiotics that themselves select for VRE (e.g., third-generation cephalosporins and fluoroquinolones), treatment with anti-anaerobic agents promotes high-density colonization with VRE [33].

A meta-analysis found substantial heterogeneity between studies: those that used patients with vancomycin-susceptible enterococci as control subjects yielded much stronger associations between administration of vancomycin and VRE than did those that used patients without VRE (many without any enterococcal colonization or infection at all) as control subjects, and the funnel plot suggested publication bias [34]. More recently, in a large case-control study that adjusted for multiple confounding factors, including duration of hospital stay and administration of other antibiotics, VRE was associated with prior use of metronidazole, third-generation cephalosporins, and long courses of fluoroquinolones; surprisingly, VRE was not associated with the use of either intravenous or oral vancomycin [31]. Control subjects consisted of a mix of patients documented not to have VRE and patients not tested at all; therefore, there must have been at least some misclassification bias.

The only study that specifically looked at the frequency of VRE colonization in patients who were given oral vancomycin for the treatment of CDI was performed in a hospital with a low overall incidence of VRE colonization [35]. At the population level, the use of oral vancomycin has increased dramatically in Quebec and in parts of the United States since 2002. In Quebec, a provincial surveillance system for VRE documented that the number of cases increased from 106 in 2002 to 275 in 2003 and 554 in 2004, in parallel with the increasing use of oral vancomycin for CDI [36]. However, the availability of novel antibiotics active against VRE (e.g., daptomycin and tigecycline) attenuated the potentially devastating clinical impacts of this pathogen.

COSTS

The major advantage of metronidazole over vancomycin is its much lower price. Cost of a 10-day course of metronidazole is $20, whereas the cost of a 10-day course of oral vancomycin (Vancocin; ) increased from $300 to $600 when the drug became more widely used in the United States. In hospitals, this issue can be avoided by administering the generic intravenous formulation of vancomycin, reducing the price of a 10-day course to $45. There is no reason to believe that such an approach would alter fecal levels of the drugs. However, community pharmacies do not stock intravenous vancomycin and would not be interested in manipulating the product so that it could be taken orally. It is possible that generic formulations of oral vancomycin will reach the US market within the next few years.

This having been said, if vancomycin therapy were truly superior to metronidazole therapy in avoiding complications, it could be inferred, even without a formal cost-efficacy analysis, that the additional costs incurred by vancomycin therapy would be compensated by savings on the management of CDI complications. Obviously, the cost per patient with CDI requiring admission to the intensive care unit must be in the 5-digit range.

MARKERS OF SEVERITY

What is complicated CDI? Most clinicians would agree that this must include cases in any patient who either (1) dies as a direct or indirect consequence of CDI, be it during the initial episode or during a recurrence; (2) requires admission to the intensive care unit for the care of CDI; (3) develops hypotension or shock (hypovolemic or septic); or (4) develops megacolon, perforation, or some other indication for an emergency colectomy. These are the main outcomes that clinicians want to avoid by using a putatively better treatment, and this definition will be used herein. Other outcomes of relevance include the prolongation of hospital stay, costs of an episode of nosocomial CDI, and the frequency of recurrences. Unfortunately, many therapeutic trials have used softer, intermediate outcomes, such as presence of diarrhea or a positive toxin assay result on a specified therapy day.

A number of markers have been identified as predictive of complicated CDI in retrospective studies [12, 37]. First, the incidence of CDI increases with age, as does the frequency of complications and the case-fatality ratio. Second, a high leukocyte count, which reflects the severity of colonic inflammation, is strongly associated with complications. Third, the
severity of diarrhea, measured either clinically (e.g., number of stools per 24 h) or biochemically (an increasing creatinine level) correlates with complicated CDI.

It is thus surprising that no simple scoring system has yet been validated prospectively. In a recently published trial, researchers used a score combining age >60 years, temperature >38.3°C, albumin level <2.5 mg/dL, and leukocyte count $\geq 15,000$ cells/mm$^3$, giving 1 point for each characteristic and giving 2 points if pseudomembranous colitis was seen on endoscopic examination or if the patient required admission to the intensive care unit [38]. Severe CDI was defined as a score $\geq 2$. However, the authors provided no information on how these variables individually or collectively correlated with complicated CDI. Pending the development of a prospectively validated scoring system, members of the Infectious Diseases Society of America/Society for Healthcare Epidemiology of America expert committee are going to define severe CDI as occurring in any patient with a leukocyte count $\geq 15000$ cells/mm$^3$ or a creatinine level increased by $\geq 50\%$ from baseline. This is meant to have high sensitivity for identifying patients at risk for complications, while accepting a lower specificity.

**COMPARATIVE EFFICACY OF METRONIDAZOLE AND VANCOMYCIN**

For patients with mild-to-moderate CDI, there is no evidence from randomized controlled trials that treatment with vancomycin is superior to treatment with metronidazole. In a recently published, small, randomized controlled trial that enrolled patients from 1994 through 2002 (i.e., before the emergence of BI/NAP1/027) and used a soft outcome (no diarrhea and negative toxin assay results on day 6 and day 10 of therapy), no difference was seen between vancomycin therapy and metronidazole therapy for patients with mild disease (i.e., those with a score of 0–1) [38]. Similarly, in the tolevamer versus vancomycin versus metronidazole trial, whose preliminary results were presented at the 2007 Interscience Conference on Anti-microbial Agents and Chemotherapy, no difference was seen between treatment with metronidazole and treatment with vancomycin for patients with mild-to-moderate CDI, with the outcome being defined as resolution of diarrhea and abdominal discomfort by day 10 of therapy [39].

Both studies showed a better outcome with vancomycin therapy in patients with severe CDI, defined as a score $\geq 2$ [38] or as having either a leukocyte count $\geq 20,000$ cells/mm$^3$, $\geq 10$ bowel movements per day, or severe abdominal pain [39]. However, these studies did not prove that treatment with vancomycin reduced the frequency of complicated CDI or of recurrences. The first study was conducted before the emergence of BI/NAP1/027 [38]. In the tolevamer trial, isolates were typed, and it will be interesting to stratify analysis according to genotypes.

Even if they are intrinsically inferior to randomized controlled trials, because of the eternal problem of residual confounding, observational studies can provide useful information pending the results of large randomized controlled trials that will use a hard outcome. We recently extended our retrospective review of all 1616 cases of CDI treated in a single academic center in Canada from 1991 through 2006 [37]. Adjusting for the same confounding variables (age, immune status, hospital acquisition, peak leukocyte count, and peak creatinine level), administration of vancomycin as the initial treatment was associated with a lower probability of developing complicated CDI, compared with initial treatment with metronidazole, for the 1991–2002 period, before BI/NAP1/027 was introduced in our hospital (adjusted OR [AOR], 0.21; 95% CI, 0.05–0.99). However, for the 2003–2006 period, when BI/NAP1/027 was the predominate strain, use of vancomycin rather than metronidazole as the initial treatment no longer impacted on the risk of complicated CDI (AOR, 0.90; 95% CI, 0.53–1.55), after adjustment for the very same confounding factors. Interaction (i.e., effect modification) was present (i.e., the AOR for 1991–2002 significantly differed from the AOR for 2003–2006). Restricting analysis to 2003–2006, adjusting for the same confounders and using the same outcome, the AOR of vancomycin versus metronidazole was the same whether the patient fulfilled the Infectious Diseases Society of America/Society for Healthcare Epidemiology of America criteria of severity (AOR, 0.90; 95% CI, 0.49–1.65) or not (AOR, 0.92; 95% CI, 0.28–3.02).

The emergence of BI/NAP1/027 is the most obvious difference between the 2 periods, potentially accounting for this epidemiological interaction. What could have happened? It may be that, in patients infected with BI/NAP1/027, production of toxins A and B was so rapid and overwhelming [40] and the effect so immediate in patients with no preexisting immunity that, by the time orally administered vancomycin reached the colonic lumen in patients with some degree of ileus, it was too late to make any difference.

Recent reports from Canada and the United States suggested that the risk of postmetronidazole recurrences was increasing [12, 23]. However, extending the observation through 2006, an interesting phenomenon was documented [37]. After metronidazole treatment, the frequency of recurrences was 20% in 1991–2002, increased to 45% in 2003–2004, and then decreased to 35% in 2005–2006. After vancomycin treatment, the frequency of recurrences was 20% in 1991–2002, 39% in 2003–2004, and 23% in 2005–2006. The fact that the same temporal trend was seen with 2 completely unrelated drugs, in the absence of any change in their in vitro activity, suggests that a substantial fraction of the frequent recurrences in 2003–2004 corresponded to reinfections during a period when in-hospital exposure to *C. difficile* spores was very high.
CONCLUSIONS

The major advantage of metronidazole is that it is cheap. The major advantage of orally administered vancomycin lies in its more favorable pharmacokinetics. Although it is perhaps counterintuitive, facilitating VRE colonization and/or infection is a potential drawback of both drugs and cannot be used as an argument in favor of one drug over the other.

For patients with mild-to-moderate CDI, metronidazole therapy should be preferred, because it is 20 times cheaper than vancomycin therapy, and no study has documented any difference, even in intermediate outcomes. Pending the availability of a prospectively validated scoring system, mild-to-moderate CDI can be defined according to the Infectious Diseases Society of America/Society for Healthcare Epidemiology of America guidelines (i.e., a leukocyte count <15,000 cells/mm³ and a creatinine level <1.5 times the baseline value).

For patients with severe CDI who are not infected with BI/NAP1/027, there is reasonable evidence that the better pharmacokinetics of vancomycin translate into a lower probability of complications. For those patients who are infected with BI/NAP1/027, the superiority of vancomycin therapy remains to be proven. In practice, because it is not yet possible to rapidly type the strains, all patients with severe CDI should be treated with vancomycin.

There is a need for a simple and large study in which intravenous metronidazole and oral vancomycin would be compared head-to-head in patients with severe CDI, using complicated CDI as the primary outcome and with stratification according to strain type. Until then, we may use the golden bullet, but we do not know for sure whether it is magic, and that should not deter us from trying to find better bullets.

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References