Higher Risk Of Recurrence And Death From Clostridium difficile Infection After Initial Therapy With Metronidazole

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Abstract

It is controversial whether initial therapy of Clostridium difficile colitis with metronidazole is associated with higher rates of recurrence or death, compared to vancomycin. In this retrospective cohort of 1309 hospitalized patients, patients had a higher risk of recurrence and death with metronidazole therapy compared to vancomycin therapy (14% vs. 7%, p<0.025 for recurrence; 18% vs. 11%, p<.05 for death).

BACKGROUND

Recent reports suggest that the incidence and severity of Clostridium difficile colitis are increasing in North America. Despite these worrisome trends, optimal first-line treatment of the disease is poorly defined. Vancomycin and metronidazole are widely used in the United States for the initial treatment of C. difficile infection, although only vancomycin is FDA-approved for this indication. Two earlier randomized studies concluded that vancomycin and metronidazole had similar efficacy in treating the disease, and a recent Cochrane review came to the same conclusion [1,2,3]. However, given the cost of oral vancomycin and its potential to disseminate vancomycin-resistant enterococci, metronidazole has widespread endorsement as first-line therapy by the Society for Healthcare Epidemiology of America (SHEA), the American Society for Health-System Pharmacists (ASHP), the American College of Gastroenterology (ACG), the Centers for Disease Control (CDC) and the Healthcare Infection Control Practices Advisory Committee (HICPAC). All guidelines agree that vancomycin be reserved for the critically ill, or for patients failing or intolerant of metronidazole [4,5,6,7].

Despite data showing therapeutic equivalency of vancomycin and metronidazole in C. difficile colitis, infectious diseases specialists have always had reservations about the efficacy of metronidazole in this condition [8]. Recent literature suggests the efficacy of metronidazole as first-line therapy may be waning. In an observational study, Musher et al found that only 50% of patients initially treated with metronidazole had symptom resolution without recurrence. Of the remaining, half continued to have symptoms despite 10 days of treatment, and the other half had a recurrence within 90 days. The mortality of initial responders versus non-responders was 33% vs. 21% respectively [9]. In another observational study, Pepin et al. found in patients initially treated with metronidazole, the 60-day recurrence rate increased from 21% to 47% from 1991-2002 to 2003-2004 [10]. These studies were limited by their single institution designs and relatively small sample sizes. An additional limitation of the Quebec study is that the higher failure rates may reflect a more virulent strain of C. difficile than is commonly encountered in the United States. This study sought to corroborate whether initial therapy with metronidazole confers a higher risk of recurrence or death than initial therapy with vancomycin, looking at a cohort of patients with a low prevalence of the emerging, more virulent C. difficile strains.

METHODS

A retrospective cohort was identified of all patients at Brigham and Women's Hospital hospitalized between 1997 and 2004 with an ICD9 diagnosis for C. difficile (008.45). Brigham and Women's Hospital is a 747-bed nonprofit teaching affiliate of Harvard Medical School and a founding member of Partners HealthCare System located in Boston, Massachusetts. The patients for the cohort were identified through the Partners HealthCare System Research Patient Database Repository (RPDR). The RPDR is an inclusive Partners Health System administrative database that contains over 2.5 million patients and 550 million records from patient encounters. Data from the Partners Health patient

billing system is directly downloaded into RPDR and is 100% complete and accurate. The database contains demographics, laboratory values, inpatient medications, and diagnosis codes. The subjects were identified by inpatient hospitalizations associated with a C. difficile ICD9 code (008.45). The subject was then linked to their demographics, medications, and admission / discharge date. The subject was considered to have received first line metronidazole (or vancomycin) if therapy was started at least 24 hours before initiation of the other agent. Subjects were excluded if they received both vancomycin and metronidazole therapy within 24 hours of each other. Recurrence was defined as any subsequent hospital stay associated with another C. difficile ICD9 code occuring at least 2 weeks after the index admission, but within 6 months. Death was included if it occurred in the hospital, or within 4 weeks of hospital discharge. Baseline demographics were compared by t-test or chi-square (for continuous and categorical variables respectively). Recurrence risk and death rates were calculated as simple percentages, and differences between the treatment groups were compared by chi-square. P values <.05 were considered signficant. IRB approval was granted through the Partners Healthcare system.

RESULTS

There were a total of 1016 individual subjects with a C. difficile ICD9 code between 1997 and 2004 that were treated with either vancomycin or metronidazole. Of these, 851 (84%) were treated first line with metronidazole, and 165 (16%) were treated first line with vancomycin. Basic demographics for subjects treated with vancomycin or metronidazole were not significantly different (age, sex, race, and language) (Table 1).

Figure 1

Table 1: Baseline Demographics

	Metronidazole (N=851)	Vancomycin (N=165)	P value
Age (mean)	68 years	67 years	0.38
Sex (% Female)	57%	59%	0.93
Race (% White)	79%	80%	0.95
Language (% English)	94%	94%	0.98

Of the total cohort, 127 (12%) experienced a recurrence, and 170 (17%) died. For patients initially treated with metronidazole or vancomycin, the recurrence rates were 7% and 14% respectively (p<0.025) and death rates were 11% and 18% respectively (p<0.05) (Table 2). Of the 127 patients that had a recurrence, 116 were treated with flagyl and 11 were treated with vancomycin; of those treated with metronidazole, 26 died (23%) versus none of the vancomycin treated patients (p=0.10).

Figure 2

Table 2: Risk of recurrence and death among treatment groups by medication type.

	Metronidazole (N=851)	Vancomycin (N=165)	Totals (N=1016)	P Value
Recurrence	116 (14%)	11 (7%)	127 (12%)	<0.025
Death	152 (18%)	18 (11%)	170 (17%)	<0.05

DISCUSSION

Although C. difficile has become a burgeoning nosocomial problem, the most efficacious first-line treatment strategy is still not well defined. Although metronidazole is heavily endorsed by most major reputable agencies, there are growing concerns of high rates of treatment failures, recurrences, and mortality. In the earliest randomized trial comparing vancomycin to metronidazole, 101 patients showed initial clinical response rates of 92% and 87% respectively [1]. In a similar trial a decade later, 62 patients showed initial clinical response rates of 94% in both groups [2]. Based primarily on these two small studies, a Cochrane review concluded that metronidazole was as effective as vancomycin for symptom resolution [3]. Given concerns of cost and the potential for the spread of vancomycin-resistant enterococci, metronidazole has been endorsed as the treatment of choice in those who can tolerate it and who are not critically ill [4,5,6,7]. However, this study and others have found that initial treatment with metronidazole may confer a worse outcome. Musher et al showed that initial metronidazole treated patients had high rates of symptom persistence and 3-month recurrence, as well as higher mortality in initial non-responders [9]. Pepin et al showed that the risk of recurrence in initial metronidazole treated patients more than doubled from 1991-2002 to 2003-2004 [10]. This study, the largest to date, found that the risk of 6-month recurrence and death were both significantly higher in the initial metronidazole group compared to the initial vancomycin group. Neither this study, nor the two previous studies, controlled for severity of illness. However, since vancomycin is indicated for more critically ill patients, not controlling for severity of illness should bias the results

toward the null, which further strengthens the argument of a true association between initial metronidazole treatment and recurrence.

This study was limited by its single institution design, but as a large urban teaching hospital, our population of patients should be generalizable to many other patient populations. The use of ICD9 codes in identifying patients could also be a limitation of the study, although 2 previous studies, including one from this institution, showed that ICD9 coding for C. difficile has both a high sensitivity and specificity for true disease [11, 12]. The other limitation of this study design was that it only captured inpatient prevalence of the disease and only captured patients admitted or discharged within the cohort time frame. Therefore, cases diagnosed before 1997 with a recurrence in 1997 would not have been captured, and would have been misclassified as an initial episode. Similarly, recurrences occurring in the 6 months after 2004 would have been misclassified as not having a recurrence. However, this should not have biased the results, since both recurrent and no-recurrent disease patients would have had an equal likelihood of being misclassified.

In conclusion, this data supports other recent observational studies that the use of metronidazole as first-line treatment in patients with C. difficile may confer a higher risk of recurrence and death. Prospective studies of vancomycin and metronidazole as first-line therapy in C. difficile are needed, and the potential benefit of vancomycin needs to be balanced against the risk of selecting for nosocomial vancomycin-resistant gram-positive pathogens.

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