

# Rifaximin Salvage Therapy for Metronidazole-Resistant *Clostridium difficile* Infection—a Prospective Pilot Trial

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## INTRODUCTION

- Incidence and severity of *Clostridium difficile* infection (CDI) have been increasing in North America,<sup>1,2</sup> in part because of hypervirulent strains<sup>3</sup>
- Hypervirulent *C difficile* strains reported in outbreaks were positive for toxins A and B,<sup>4</sup> binary toxin (BT),<sup>4,5</sup> and partial deletions in the *tcdC* gene<sup>5</sup>
- Standard treatments for CDI include oral vancomycin and metronidazole<sup>6</sup>
  - US Centers for Disease Control and Prevention recommend metronidazole as first-line therapy because of the potential for vancomycin-resistant *C difficile* strains<sup>6</sup>
- However, in recent years, more cases of CDI have been unresponsive to metronidazole than in the past<sup>7</sup>
  - In a Canadian teaching hospital between 1991 and 2002, 10% of CDI cases did not respond to metronidazole, whereas 26% of CDI cases diagnosed between 2003 and 2004 were unresponsive<sup>7</sup>
- 6% of *C difficile* isolates were resistant (minimal inhibitory concentration  $\geq 32$   $\mu\text{g/mL}$ ) to metronidazole in a study of 415 isolates obtained from hospitalized adults with their first CDI episode<sup>8</sup>
- Rifaximin<sup>9</sup> is a gut-selective, nonsystemic (<0.4% absorbed) antibiotic that has a placebo-like tolerability profile<sup>9</sup>
  - 7 of 8 patients with CDI did not have recurrence of diarrheal symptoms during a 51- to 431-day follow-up period after rifaximin 400 to 800 mg/d for 2 weeks<sup>9</sup>

## OBJECTIVE

- To evaluate the efficacy of rifaximin in eradicating *C difficile* infection in patients with CDI that was unresponsive to metronidazole

## METHODS

- Patients with mild-to-moderate CDI (5-10 bowel movements a day without sepsis) that was unresponsive to metronidazole (stool samples positive for toxins A and B after oral metronidazole 500 mg three times daily for 5 days) were recruited into the study
  - Patients were excluded if they had a leukocyte count  $>20,000/\text{mm}^3$ , sepsis, abdominal distention, human immunodeficiency virus infection, multi-organ failure, or renal failure
  - Patients who were on ventilator support, receiving chemotherapy, had a recent organ transplant, or had been exposed to vancomycin or rifampicin within the previous 6 weeks were also excluded
- Oral rifaximin (Xifaxan<sup>®</sup>; Salix Pharmaceuticals, Inc, Morrisville, NC) 1200 mg/d for 14 days was administered as salvage therapy immediately after cessation of metronidazole treatment
- Stool samples were obtained immediately after termination of rifaximin therapy (day 14)
- Patients were periodically visited during the 56 days after the end of rifaximin treatment to obtain stool samples and assess treatment compliance
  - Stool samples were also obtained on the last day of follow-up (56 days posttreatment)
- Stool samples were analyzed for the presence of *C difficile* toxin B gene using qualitative real-time polymerase chain reaction (PCR; Quest Diagnostics, Teterboro, NJ) to assess effect of treatment
  - Favorable response to rifaximin was defined as PCR results negative for toxin B gene

- Percentages of patients with resolution of CDI were calculated for intent-to-treat (ITT) and per protocol (PP) populations

## RESULTS

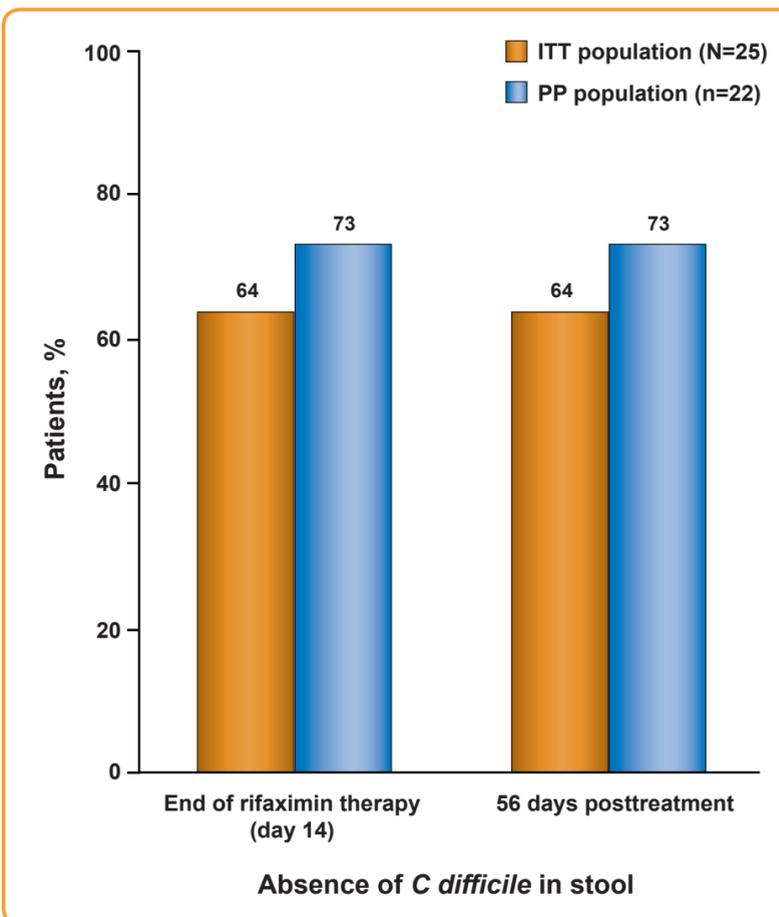
- 25 of 85 patients (29%) screened met exclusion criteria and were included in the ITT population (Table 1)

**Table 1.** Patient Demographics and Characteristics

Parameter	Rifaximin 1200 mg/d (N=25)
Mean age (range), y	59 (48-65)
Male:Female, n	13:12
Race, n (%)	
White	13 (52)
Black	8 (32)
Hispanic	2 (8)
Asian	2 (8)
CDI acquisition, n (%)	
Community	13 (52)
Nursing home	12 (48)
Mean white blood cell count (range), cells/mm <sup>3</sup>	14,000 (6000-18,000)
Hospitalization within 3 months before study initiation, n (%)	12 (48)
Mean creatinine level (range), mg/dL	0.9 (0.2-1.3)
Exposure to PPIs within 3 months of study initiation, n (%)	18 (72)
Antibiotics taken within 3 months of study initiation, n (%)	
Metronidazole	25 (100)
Cephalosporins	3 (12)
Isoxazolyl penicillin	7 (28)

CDI, *C difficile* infection; PPI, proton pump inhibitor.

- 22 of 25 patients (88%) completed rifaximin therapy and were included in the PP population
  - 3 patients terminated treatment because of abdominal distention
- At the end of rifaximin therapy (day 14), 16 of 25 patients (64%) in the ITT population and 16 of 22 patients (73%) in the PP population had stool samples negative for *C difficile* (Figure)



**Figure.** Percentage of patients without *C difficile* infection at the end of rifaximin treatment (day 14) and on a follow-up visit 56 days posttreatment. Stool samples were analyzed for the presence of *C difficile* toxin B gene using qualitative real-time polymerase chain reaction. ITT, intent-to-treat; PP, per protocol.

- At 56 days posttreatment, 64% of patients in the ITT population and 73% of patients in the PP population did not have *C difficile* infection (Figure)
- In general, oral rifaximin was well tolerated, with few reported adverse events (Table 2)

**Table 2.** Adverse Events Reported in the Intent-to-Treat Population

Adverse event	Rifaximin 1200 mg/d (N=25)
During rifaximin treatment, n (%)	
Headache	3 (12)
Belching	3 (12)
Abdominal distention	3 (12)
During 56-day posttreatment, n (%)	
Constipation	2 (8)

## DISCUSSION AND CONCLUSIONS

- Incidence and severity of CDI have been escalating in recent years<sup>1,2</sup>
- Response of CDI to metronidazole has decreased<sup>7</sup>
  - Treatment failures and infection recurrences after metronidazole treatment have been reported in 8% to 50% of patients<sup>7</sup>
- Rifaximin may be an appropriate treatment for mild-to-moderate CDI that is unresponsive to metronidazole, given that 16 of 22 patients with CDI who completed a 14-day course of rifaximin 1200 mg/d (73%) had stool samples negative for *C difficile* after treatment
- Sustained response to rifaximin was observed up to 56 days after cessation of rifaximin therapy in 73% of patients, indicating prolonged eradication of CDI
- Rifaximin 1200 mg/d for 14 days was well tolerated, with only 3 of 25 patients (12%) discontinuing therapy because of an adverse event
- Larger, randomized trials examining the benefit of rifaximin in patients with CDI that is unresponsive to metronidazole are needed to verify these positive preliminary findings

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**References:** 1. Muto CA, Pokrywka M, Shutt K, et al. *Infect Control Hosp Epidemiol.* 2005;26(3):273-280. 2. Pápin J, Valiquette L, Alary M-E, et al. *CMAJ.* 2004;171(5):466-472. 3. McDonald LC, Killgore GE, Thompson A, et al. *N Engl J Med.* 2005;353(23):2433-2441. 4. McEllistrem MC, Carman RJ, Gerding DN, Genheimer CW, Zheng L. *Clin Infect Dis.* 2005;40(2):265-272. 5. Loo VG, Poirier L, Miller MA, et al. *N Engl J Med.* 2005;353(23):2442-2449. 6. Aslam S, Hamill RJ, Musher DM. *Lancet Infect Dis.* 2005;5(9):549-557. 7. Pápin J, Alary M-E, Valiquette L, et al. *Clin Infect Dis.* 2005;40(11):1591-1597. 8. Peláez T, Alcalá L, Alonso R, Rodríguez-Crúexens M, García-Lechuz JM, Bouza E. *Antimicrob Agents Chemother.* 2002;46(6):1647-1650. 9. Scarpignato C, Pelosini I. *Digestion.* 2006;73(suppl 1):13-27. 10. Johnson S, Schriener C, Galang M, Kelly CP, Gerding DN. *Clin Infect Dis.* 2007;44(6):846-848.

\*Rifaximin is indicated for treatment of travelers' diarrhea caused by noninvasive strains of *Escherichia coli*.