BRIEF REPORT

Staggered and Tapered Antibiotic Withdrawal With Administration of Kefir for Recurrent *Clostridium difficile* Infection

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Daily administration of the probiotic kefir given in combination with a staggered and tapered antibiotic withdrawal regimen may resolve recurrent *Clostridium difficile* infection as effectively as fecal microbiota transplantation.

Keywords. antibiotic withdrawal; *Clostridium difficile*; diarrhea; kefir; recurrent.

The incidence of *Clostridium difficile* infection (CDI) has increased steadily during the last decade, and CDI is now the most common nosocomial infection in the United States [1]. The majority of patients with CDI respond to treatment with orally administered metronidazole or vancomycin, but 5%–30% of patients fail antibiotic therapy and go on to develop recurrent diarrhea [2]. Risk factors for recurrent CDI include age >65 years, poor nutritional status, recent abdominal surgery, prolonged hospitalization, and recent stay in the intensive care unit (ICU) [2]. Permanent resolution and cure of recurrent CDI presents a significant challenge to the treating physician as no consistent treatment guidelines exist in published literature [3]. Until now, fecal microbiota transplantation (FMT) has been the most successful treatment modality, with success rates of 80%–100% [4–6]. However, for various reasons FMT may be unattainable for those patients who most need the treatment [7, 8]. In 2005, the author implemented a treatment regimen for recurrent CDI utilizing a staggered and tapered antibiotic withdrawal (STAW) regimen combined with regular oral ingestion of the probiotic liquid kefir. Eight patients were treated with STAW between 2005 and 2009, and all successfully resolved their recurrent diarrhea [7].

This article reports the long-term follow-up of the initial 8 patients and 17 subsequent patients with recurrent CDI who were treated with STAW between 1 January 2009 and 31 October 2013. Each CDI recurrence was verified by ≥1 positive stool enzyme immunoassay test results for toxin A and B or polymerase chain reaction for the *tcd*B locus. At the initial evaluation, each patient was asked whether they preferred to be treated with FMT or with an oral antibiotic agent (metronidazole prior to 2007, vancomycin from 2007 onward) administered as STAW combined with regular intake of kefir (Lifeway kefir, Lifeway Foods, Morton Grove, Illinois) (Table 1). All 26 patients opted not to be treated with FMT, either because they were unable to afford the costs associated with FMT (in large part due to the cost of laboratory screening of the potential stool donor), or they preferred to defer FMT until they had failed STAW. Twenty-four patients lived within the St Luke's Hospital catchment area and were treated by the author at St Luke's Hospital or the outpatient clinic. Two additional patients lived outside the upper Midwest (patient 23 in Florida, patient 24 in Florida) and were followed by their local infectious disease physicians who consulted with the author.

The initial treatment goal was to bring the clinical diarrhea under control by continuing ongoing therapy with either metronidazole or vancomycin instituted by the referring physician (Table 1). Each patient was instructed to drink a 5-oz glass of Lifeway kefir with each meal (at least 3 glasses per day), or ad libitum as tolerated. Lifeway kefir is a fermented dairy product with a diverse collection of probiotic agents and can be purchased in many large chain food stores (www.kefir.com). STAW was started once normally formed bowel movements had been established and maintained for at least 7 days (Figure 1). Each antibiotic dose was taken at 72-hour intervals over a 6-week period, with gradual dose reduction every 2 weeks. In addition, patients were instructed to continue to drink kefir for at least 2 months beyond the completion of STAW. Each patient was interviewed by telephone or mail at 90 days postprotocol and at quarterly intervals thereafter for up to 1 year to determine whether diarrhea had recurred. Statistical comparisons of categorical variables were done by χ^2 analysis and $P \leq .05$ was considered statistically significant.

RESULTS

This prospective case series included 25 evaluable patients (21 women and 4 men) with a mean age of 68 years (SD, 14 years).

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Table 1. Demographic and Clinical Information for 25 Patients Who Resolved Their Recurrent *Clostridium difficile* Infection With a Staggered Antibiotic Withdrawal Treatment Program Combined With Lifeway Kefir

Patient/Year	Sex/Age	Index Infection[a]	Prior Antibiotic Treatment[a]	Prior Treatment for Recurrent CDI[b]	Duration of Diarrhea Before STAW[d]	Taper Drug[c]	Outcome
1/2005	89/F	Diverticulitis	Ery, Neo	V, M, M, M	452	M	Cure
2/2005	76/F	CAP	Azi, Cro	M, M, V	88	M	Cure
3/2006	71/F	CAP	Azi, Cro	M, M, M, V, M	32	M	Cure
4/2006	63/F	Diverticulitis	Cro	M, M	65	M	Cure
5/2006	54/M	UTI	Cip	M, V, V, V, M, V	90	V	Cure
6/2006	36/F	Pancreatitis	Pip-tazo	M, V, V, V	127	V	Cure
7/2006	79/F	UTI	Cip	M, V, V, V	260	V	Cure
8/2008	83/M	Cellulitis	Cli	M, M, V, V	68	V	Cure
9/2009	53/F	Empyema	Cfz	M, V	19	V	Cure
10/2009	89/F	CAP, UTI	Cip, Amo	M, V, V, V	354	V	Relapse[d]
11/2009	75/F	CAP	Mox	M, V, V, V, V, V, V	176	V	Cure
12/2010	59/F	Diverticulitis	Cip	M, V, M, M	85	V	Cure
13/2010	78/F	PVE	Ert, Gen	M, V	24	V	Cure
14/2010	57/F	UTI	Cip, Sxt	V, V, V, V	143	V	Relapse[d]
15/2010	75/F	Diverticulitis	Cro	M, V, V, V	197	V	Cure
16/2011	75/F	Sinusitis	Amo-clav	V, V, V	63	V	Relapse[d]
17/2012	62/F	Cellulitis	Cli	M, V, V, V	159	V	Cure
18/2012	67/F	Cellulitis	Cli	V, V, V, V	97	V	Cure
19/2012	82/F	Sepsis	Cro	M, V, V	175	V	Cure
20/2012	77/F	CAP	Cro	V, V, V	210	V	Cure
21/2012	64/M	Diverticulitis	Cip, M	M ×9	2590	V	Relapse[d]
22/2013	72/M	Sinusitis	Amo-clav	M, V	240	V	Cure
23/2013	68/F	Bronchitis	Azi	M, V, F, V	97	V	Cure
24/2013	37/F	Sinusitis	Cfd	M, M, M, V, F, N	310	V	Cure
25/2013	65/F	SCT	Pen VK	M, V, V	215	V	Cure

Abbreviations: Amo, amoxicillin; Amo-clav, amoxicillin-clavulanate; Azi, azithromycin; CAP, community-acquired pneumonia; CDI, *Clostridium difficile* infection; Cfd, cefdinir; Cfz, cefazolin; Cip, ciprofloxacin; Cli, clindamycin; Cro, ceftriaxone; Ert, ertapenem; Ery, erythromycin; F, fidaxomicin; Gen, gentamicin; M, metronidazole; Mox, moxifloxacin; N, nitazoxanide; Neo, neomycin; Pen VK, penicillin VK; Pip-tazo, piperacillin-tazobactam; PVE, prosthetic valve endocarditis; SCT, stem cell transplant; Sxt, trimetohoprim-sulfamethoxazole; UTI, urinary tract infection; V, vancomycin.

[a] Initial infection and antibiotic treatment administered prior to the first episode of *C. difficile* infection.

[b] Specific antibiotic agent chosen for treatment of initial episode of CDI and subsequent episodes of recurrent CDI. Each letter entry indicates 1 course of treatment.

[c] Agent chosen for the staggered and pulsed antibiotic withdrawal regimen.

[d] Clinical relapse and positive stool *C. difficile* test result; no recurrence of diarrhea after a 2-week course of oral vancomycin immediately followed by a 2-week course of rifaximin.

Seven patients were hospitalized at St Luke's Hospital at the time of their initial evaluation; the remaining 18 patients were treated in the Infectious Diseases outpatient clinics. Patient 26 was eliminated from the outcomes evaluation because he failed to follow treatment recommendations after hospital discharge. Table 1 summarizes the demographic characteristics of and the treatment outcomes for the 25 evaluable subjects. The mean number of preprotocol CDI relapses was 4 (range, 1–9), and the median days of diarrhea from the time of the initial diagnosis of CDI until the beginning of STAW was 135 (range, 9–2920 days). During the same period, the 25 patients submitted a combined total of 103 stool samples for *C. difficile* testing for an average of 3.6 (range, 1–9) positive samples per patient. The antibiotic therapy that had been started by the referring physicians prior to STAW included 98 courses of different agents (metronidazole 40 courses, vancomycin 55 courses, fidaxomicin 2 courses, and nitazoxanide 1 course). Patient 23 redeveloped diarrhea (third recurrence) 2 weeks after he had completed a 6-week course of a daily tapered vancomycin, and began STAW 1 week later.

The most common predisposing infectious condition leading to recurrent CDI was a respiratory tract infection, followed by diverticulitis and urinary tract infection (Table 1). Almost one-third of the patients were taking an H2 blocking agent and 4 patients were on active immunosuppressive therapy. Comorbid illnesses that might have predisposed to recurrent

Antibiotic Time Course	Metronidazole Dose/Frequency		Vancomycin Dose/Frequency		Kefir
Weeks 1-2	250 mg Q 6h		125 mg Q 6h		150 mL TID
Weeks 3-4	750 mg Q 72h		375 mg Q 72h		150 mL TID
Weeks 5-6	500 mg Q 72h	**OR**	250 mg Q 72h	**PLUS**	150 mL TID
Weeks 7-8	250 mg Q 72h		125 mg Q 72h		150 mL TID
Weeks 9-15					150 mL TID

Figure 1. Protocol utilizing a staggered and tapered antibiotic treatment regimen for the treatment of recurrent *Clostridium difficile* infection that has failed to respond to standard antibiotic therapy. Abbreviations: Q, every; TID, 3 times daily.

infection included ulcerative colitis, malignant illnesses, previous bowel surgery, and diabetes mellitus. Ceftriaxone was the most common inciting antibiotic precipitating CDI, followed by a fluoroquinolone, azithromycin, clindamycin, and various other agents (Table 1).

None of the 25 patients received additional antibiotics during the course of STAW.

All 25 patients had reestablished normal bowel function with formed bowel movements at the start and completion of STAW. Twenty-one of the 25 patients (84%) remained free of diarrhea during the following 9 months. Twenty patients have remained symptom free for >12 months. Four patients (16%) experienced diarrhea relapse with a positive stool *C. difficile* test between 24 and 45 days after completion of STAW (Table 1). There was no relationship between diarrhea relapse and H2-blocker usage, active immunosuppressive therapy, comorbid conditions, or predisposing infectious illness (P = NS, data not shown). The 4 patients who relapsed permanently resolved their diarrhea after a conventional 2-week course of oral vancomycin 125 mg 4 times daily followed by a 2-week course of rifaximin 200 mg twice daily. All 4 patients remained symptom-free at 12 months of follow-up.

DISCUSSION

Antibiotic treatment of incidental infections may disrupt the ecologic balance in the colon, creating an opportunity for *C. difficile* overgrowth [9]. Many patients are able to resolve CDI after a conventional course of metronidazole or vancomycin. However, antibiotic therapy of CDI may further augment the disruption of the microbiota sufficiently and allow *C. difficile* to persist as antibiotic-resistant spores. There is currently no consensus on best treatment for recurrent CDI [3]. FMT administration has been reported to resolve recurrent CDI on average for >80% of patients [4, 6, 9]. Although FMT is highly effective, the US Food and Drug Administration currently considers it to be investigational therapy, and the Centers for Medicare and Medicaid Services and many third-party payers have been unwilling to pay for FMT. Thus, alternative strategies for the treatment of recurrent CDI are needed.

Oral metronidazole or vancomycin administration will typically halt the growth of vegetative *C. difficile* and temporarily resolve diarrhea, but the resident commensal bacterial flora is negatively affected by the antibiotic action. Thus, a crucial question is how to deplete or rid the colon of retained spores, and at the same time enrich and diversify the microbiota to restore colonization resistance. Despite limited clinical evidence, the recently published Infectious Diseases Society of American/Society for Healthcare Epidemiology of America treatment guidelines recommend tapering and/or pulsed regimens of vancomycin for patients who have sustained ≥2 recurrences of CDI [3]. Patient 23 had failed prior treatment with a course of gradually tapered vancomycin, and in a sense served as his own control. The hypothesis of this report was that intermittent drug dosing would allow spores to germinate during the intraluminal drug-free periods and gradually become depleted, and that kefir administration would enrich and diversify the resident colonic flora. As a result, the pool of spores would become reduced over time to a number low enough to be subdued by the restored colonization resistance. The primary treatment success rate of 84% observed in this case series parallels the success rates reported for FMT and would argue that the elimination of spore

forms, combined with restoration of an enriched and diversified colon microbiota, holds the key to successful resolution of recurrent CDI [6, 9–11]. Even though 4 patients failed to resolve their infection, they all resolved their diarrhea after a conventional 2-week course of vancomycin, followed by 2 weeks of rifaximin [12]. Comorbid conditions, such as chronic H2-blocker therapy, comorbid immunosuppressive illnesses, immunosuppressive therapy, or inflammatory bowel disease (ulcerative colitis), were not associated with STAW treatment failure.

Limitations with this investigation include the retrospective analysis of an uncontrolled study population treated by a single provider and the small number of cases. However, each patient served as his or her own control, as multiple attempts at resolving the recurrent courses of diarrhea had previously been attempted with the same oral antibiotics but without the probiotic component. Furthermore, the relative contributions of STAW and kefir toward resolution of diarrhea cannot be determined by this report, and should be investigated further in future clinical trials. In conclusion, the findings of this preliminary study would argue that STAW and kefir can be as effective as FMT at resolving recurrent *C. difficile* infection.

Notes

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