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Use of a probioitic to decrease enteric hyperoxaluria

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Background. Patients with inflammatory bowel disease have a 10- to 100-fold increased risk of nephrolithiasis, with enteric hyperoxaluria being the major risk factor for these and other patients with fat malabsorptive states. Endogenous components of the intestinal microflora can potentially limit dietary oxalate absorption.

Methods. Ten patients were studied with chronic fat malabsorption, calcium oxalate stones, and hyperoxaluria thought to be caused by jejunoileal bypass (1) and Roux-en-Y gastric bypass surgery for obesity (4), dumping syndrome secondary to gastrectomy (2), celiac sprue (1), chronic pancreatitis (1), and ulcerative colitis in remission (1). For 3 months, patients received increasing doses of a lactic acid bacteria mixture (Oxadrop®, VSL Pharmaceuticals), followed by a washout month. Twenty-four–hour urine collections were performed at baseline and after each month.

Results. Mean urinary oxalate excretion fell by 19% after 1 month (1 dose per day, $P < 0.05$), and oxalate excretion remained reduced by 24% during the second month (2 doses per day, $P < 0.05$). During the third month on 3 doses per day oxalate excretion increased slightly, so that the mean was close to the baseline established off treatment. Urinary oxalate again fell 20% from baseline during the washout period. Calcium oxalate supersaturation was reduced while on Oxadrop®, largely due to the decrease in oxalate excretion, although mean changes did not reach statistical significance.

Conclusion. Manipulation of gastrointestinal (GI) flora can influence urinary oxalate excretion to reduce urinary supersaturation levels. These changes could have a salutary effect on stone formation rates. Further studies will be needed to establish the optimal dosing regimen.

Patients with inflammatory bowel disease have a risk of nephrolithiasis that is 10 to 100 times that of the normal population, ranging from 1% to 25% [1]. Enteric hyperoxaluria has also been documented in other malabsorptive states, including after jejunoileal bypass for obesity [2–4], after gastric ulcer surgery [3], and in the setting of chronic mesenteric ischemia [3]. Patients often have multiple stones, and nephrolithiasis is more commonly observed with ileocolonic disease (9–17%) compared to ileal (6–8%) or colonic disease (3–5%) alone. Renal stones are primarily composed of calcium oxalate when the ileum is involved (e.g., ileocolonic Crohns disease), and uric acid when patients have copious diarrhea or small bowel ostomies [1]. Contributing factors include a low urinary citrate concentration, decreased urine volumes, and a low urinary pH, all due to diarrhea and consequent loss of fluid and bicarbonate in the stool. In addition, when the colon is intact, the percentage of oxalate absorbed from the gut and, hence, the absolute amount excreted in urine can be markedly increased [5], and in general, the degree of hyperoxaluria correlates with steatorrhea [6].

Unfortunately, few satisfactory treatments for enteric hyperoxaluria are available. Typical strategies include dietary restriction of oxalate to limit its delivery to the colon, low fat diets to limit malabsorption and distal colonic effects of fatty acids and bile acids [7, 8], oral calcium to bind oxalate [2], and bile acid sequestrants like cholestyramine [6, 7]. Dietary restriction of oxalate is not always entirely effective because many patients cannot readily identify causative dietary constituents [9]. In its entirety, such a regimen is quite arduous and, even if compliance is achieved, not always effective.

Investigators have previously demonstrated that components of the endogenous digestive microflora can utilize oxalate, potentially limiting its absorption from the intestinal lumen [10]. A recent preliminary study found that a preparation of lactic acid bacteria degraded oxalate in vitro and reduced urinary oxalate excretion when given by mouth [11]. Therefore, the current study was performed to determine if that same preparation (Oxadrop®) can reduce urinary oxalate excretion in patients with enteric hyperoxaluria, and if so, determine the minimal effective dose.

Key words: calcium oxalate, lactobacilli, fat malabsorption, nephrolithiasis.

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METHODS

Oxadrop®

Lactic acid bacteria are normal intestinal commensals, and are ubiquitous in fermented and nonfermented foods. The Food and Drug Administration (FDA) classifies them as "generally regarded as safe" (GRAS) and permits them as food additives (FDA). In clinical trials performed with Oxadrop® [11], or the very similar preparation VSL#3 [12], there have been no adverse events noted, and no case of clinical infection has been traced to ingested probiotic lactic acid bacteria in a normal host [13], although caution may be required for immunocompromised hosts [14]. Each gram of the mix (Oxadrop®) contains 2×10^{11} bacteria (*Lactobacillus acidophilus*, *L. brevis*, *Streptococcus thermophilus,* and *Bifidobacterium infantis*). The different strains are mixed in a 1:1:4:4 ratio and prepared as a granulate. The organisms were chosen based on their ability to degrade oxalate in vitro, and Oxadrop® is slightly different than the more widely studied VSL#3 [12], which contains 3 of the above 4 bacterial species with the exception of *L. brevis*, as well as 3 other species of *Lactobacillus*, and 2 other species of bifidobacteria.

Patient population

Patients with nephrolithiasis, clinical signs of fat malabsorption, and apparent enteric hyperoxaluria were recruited for study from the Mayo Renal Stone Clinic. Men and women age 18 or greater with the presence of hyperoxaluria (>0.5 mmol/L/day; >45 mg/day) and a gastrointestinal disorder associated with fat malabsorption were eligible. Clinical malabsorptive syndromes considered included inflammatory bowel disease in remission, celiac sprue, gastrointestinal resection resulting in short bowel syndrome (e.g., jejunoileal or gastric bypass for obesity; antrectomy, vagotomy, and pyloroplasty for gastric ulcers), or chronic pancreatitis. Stone history was confirmed by the presence of radiopaque stones on x-ray, or a history consistent with passage of a stone, stone surgery, or ESWL in the last 2 years. Stone composition was confirmed either by stone analysis demonstrating more than 50% calcium oxalate, or by radiographic demonstration of a calcific renal stone in the presence of hyperoxaluria. Patients with immunosuppression (receiving chemotherapy, known HIV infection, using oral prednisone or other immunosuppressants) were not eligible. Patients completing a course of oral or parenteral antibiotics less than 2 weeks before initiation of the study were not eligible, and patients who required a course of antibiotics during the period of preparation administration were withdrawn from the study and excluded from the final analysis.

Patients were maintained on previous doses of oxalate binders (e.g., calcium), diet prescriptions (e.g., low oxalate diet), or other stone prevention treatments (e.g., citrate). While the diet was not specifically controlled, patients were asked to maintain a similar diet during all 2-day urine collections. After informed consent was obtained, 2 baseline 24-hour urines were collected on consecutive days. Patients then began taking 1 packet (4 g) of the study preparation Oxadrop® daily. The preparation was mixed in a glass of cold beverage including water, orange juice, or tea. It was not to be mixed with milk which could serve as a substrate for growth. The dose was taken 1 to 2 hours after dinner, or the major meal of the day. At the end of the 4-week period of drug administration, 2 repeat 24-hour urines were collected (days 27–28). Then the dose of Oxadrop® was increased to 2 packets daily, taken together 1 to 2 hours after dinner, or the major meal of the day. At the end of an additional 4 weeks (week 8), 2 repeat 24-hour urines were collected (days 55–56). Finally, the dose of Oxadrop® was increased to 3 packets a day (as a single dose 1–2 hours after dinner, or the major meal of the day) for 4 more weeks. At the end of this period (week 12), 2 more 24-hour urines were collected (days 83–84). Two final urine collections were done 4 weeks later off the preparation.

Urine chemistries

Twenty-four–hour urinary concentrations of oxalate, calcium, and other determinants of supersaturation were mailed to Litholink Corporation (Chicago, IL, USA) for analysis. Supersaturations were calculated using the EQUIL2 program [15].

Statistics

Group means and distributions at each time period were compared by paired *t* test using JMP software (SAS Institute, Inc., Cary, NC, USA). P values < 0.05 were accepted as significant.

RESULTS

Causes of enteric hyperoxaluria were bypass surgery for obesity [jejunoileal bypass (1) and Roux-en-Y gastric bypass surgery (4)], dumping syndrome secondary to gastrectomy (2), celiac sprue (1), chronic pancreatitis (1), and ulcerative colitis in remission (1). Although both men and women were eligible and recruited, only a group of men ages 51 to 69 elected to enroll in this pilot study.

In 7 of the 10 patients urine oxalate excretion fell or remained stable after 1 month of treatment using 1 dose of Oxadrop® per day (mean decrease 19%) (Table 1 and Fig. 1). This drop remained relatively stable during the second month on 2 doses per day (mean decrease 24%). During the third month on 3 doses per day, urine oxalate increased in 4 of 10 patients so that the mean was then 2% below baseline. Interestingly, oxalate excretion once again slightly fell after the 1-month washout period

Table 1. Summary of mean urinary changes for 10 enteric hyperoxaluric patients before, during and after one month on 3 doses of Oxadrop®

Urine parameter	Baseline	Month 1 (1 packet QD)	Month 2 (2 packets QD)	Month 3 (3 packets QD)	Washout
Oxalate *mg*	91 (48)	74 (30)[a]	69 (36)[a]	89 (51)	73 (41)[a]
Oxalate/creatinine ratio	0.049 (0.021)	0.040 (0.015)[a]	0.039 (0.019)[a]	0.044 (0.018)	0.038 (0.016)
ss CaOx	8.14 (4.63)	7.97 (3.90)	7.02 (3.19)[b]	7.60 (3.34)	7.90 (3.24)
Volume *L*	2.22 (0.61)	2.07 (0.84)	1.87 (0.61)[a]	2.00 (0.64)	1.93 (0.68)[b]
Calcium *mg*	154 (91)	143 (49)	129 (82)[b]	138 (85)	152 (81)
Citrate *mg*	549 (387)	512 (374)	557 (361)	543 (338)	521 (401)
pH	6.24 (0.48)	5.96 (0.46)[a]	5.99 (0.54)[a]	5.85 (0.43)[a]	5.85 (0.37)[a]
Urate *g*	0.67 (0.28)	0.58 (0.19)[a]	0.63 (0.27)	0.64 (0.26)	0.69 (0.26)
Sodium *mEq*	244 (84)	212 (54)[a]	191 (59) [a]	222 (68)	211 (84)
Potassium *mEq*	86 (34)	76 (37)[a]	71 (27)[a]	79 (27)	68 (26)[a]
Magnesium *mg*	119 (49)	122 (39)	104 (40)[a]	123 (37)	106 (52)
Sulfate *mEq*	42 (15)	42 (12)	44 (11)	43 (11)	43 (12)
Ammonium *mmol/L*	57 (34)	69 (48)	58 (41)	66 (44)	63 (31)
Phosphorous *g*	1.09 (0.38)	0.99 (0.35)	1.03 (0.30)	1.22 (0.45)	1.03 (0.33)
ss CaP	0.75 (0.48)	0.68 (0.72)	0.60 (0.48)	057 (0.52)	0.61 (0.53)
ss Urate	0.56 (0.49)	0.91 (0.80)	1.07 (0.96)	1.12 (0.886)	1.17 (0.93)
Creatinine *mg*	1883 (498)	1876 (481)	1804 (438)	1992 (497)	1883 (477)

Values are mean (SE).
[a] $P < 0.05$.
[b] $P < 0.10$ vs. baseline.

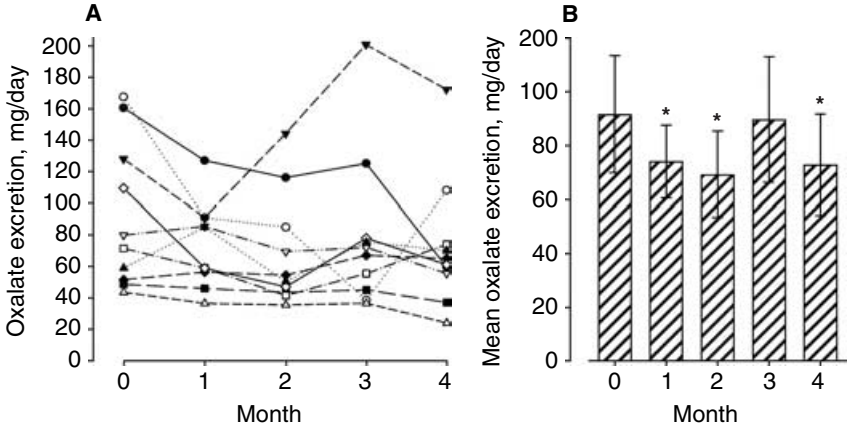

Fig. 1. Changes in urinary oxalate excretion on Oxadrop®. Ten patients with enteric hyperoxaluria were treated with Oxadrop® in increasing doses for 3 months preceded by a baseline value (month 0) and followed by a washout period (month 4). Each patient is represented by an individual line in (*A*) with mean values in (*B*). Oxalate excretion fell in 7 of 10 patients after the first month on 1 dose per day (mean decrease 19% from baseline), was reduced in 8 of 10 after 2 months on 2 doses per day (mean decrease 24% from baseline), but increased toward baseline levels in 4 patients after month 3 on 3 doses per day (mean decrease 2% from baseline). During the washout phase oxalate fell slightly in 5 of 10 patients for a mean decrease of 20% from baseline. Each point in (A) is the average of 2 consecutive 24-hour urine collections. Each value in (B) is mean ± 95th percentile, $^*P <$ 0.05 vs. baseline (month 0).

so that the mean was 20% less than during the baseline. Results expressed as oxalate:creatinine ratio, to correct for variations in urine collection, were largely similar, although the percentage decrease at month 3 was slightly more (Fig. 2). Urinary calcium oxalate supersaturation fell throughout the study, mostly due to changes in oxalate excretion, although results did not reach statistical significance (Fig. 3), perhaps because a slight fall in urine volume partially offset the fall in urine oxalate during months 1 and 2 (Table 1). Uric acid supersaturation rose slightly on the higher doses of Oxadrop® due to a slight fall in urinary pH, but was still below the reference mean for normals in our lab (2.04), suggesting the risk for uric acid stones was not significantly increased.

Adverse events

No adverse events were noted in patients while on the study preparation. Two subjects withdrew within the first month of the protocol; one that received a course of antibiotics to treat a respiratory syndrome, and the other due to poor compliance with dosing and follow-up testing. Their data were not included.

DISCUSSION

These results suggest that manipulation of gastrointestinal flora in patients with fat malabsorption using Oxadrop® can influence oxalate absorption and, hence, urinary oxalate excretion, and reduce urinary supersaturation levels. Because stone formation parallels supersaturation, we predict these changes would have a salutary effect on stone formation rates. The results also suggest that there is an optimal dose, and that it might be possible to give too much of the agent. Therefore, careful dosing studies will be required in the future.

In patients with gastrointestinal diseases associated with fat malabsorption, 2 mechanisms of increased colonic oxalate uptake are commonly purported. (*1*) Bile

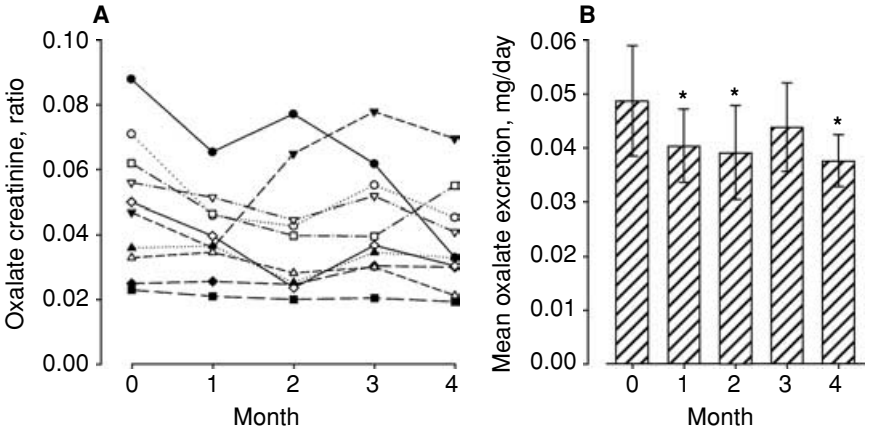

Fig. 2. Changes in urinary oxalate: creatinine ratio on Oxadrop®. Ten patients with enteric hyperoxaluria were treated with Oxadrop® in increasing doses for 3 months preceded by a baseline value (month 0) and followed by a washout period (month 4). Each patient is represented by an individual line in (*A*) with mean values in (*B*). Oxalate-creatinine ratio fell in 7 of 10 patients in the first month on 1 dose per day (mean decrease 18% from baseline), was reduced in 8 of 10 after month 2 on 2 doses per day (mean decrease 21% from baseline), and increased toward baseline levels in 5 patients after month 3 on 3 doses per day (mean decrease 10% from baseline). During the washout phase oxalate-creatinine ratio again fell slightly in 6 of 10 patients for a mean decrease of 22% from baseline. Each point in (A) is the average of 2 consecutive 24-hour urine collections. Each value in (B) is mean ± 95th percentile, $^*P < 0.05$ vs. baseline (month 0).

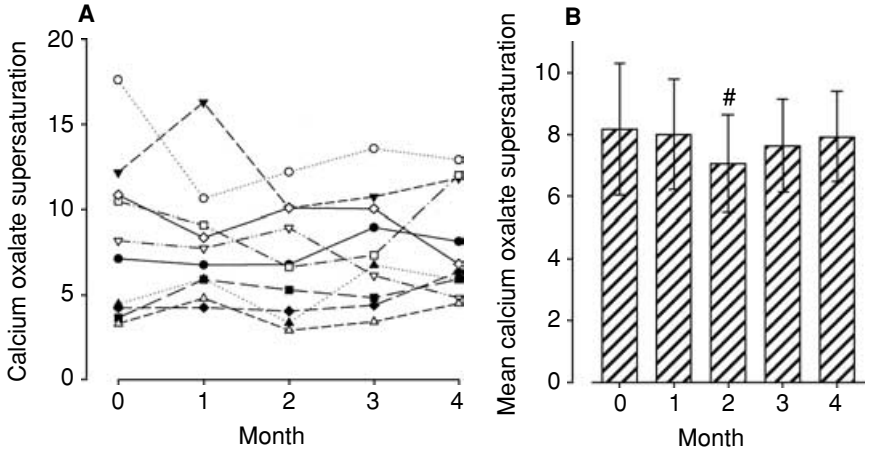

Fig. 3. Changes in urinary calcium oxalate supersaturation on Oxadrop®. Ten patients with enteric hyperoxaluria were treated with Oxadrop® in increasing doses for 3 months preceded by a baseline value (month 0) and followed by a washout period (month 4). Each patient is represented by an individual line in (*A*) with mean values in (*B*). Overall calcium oxalate supersaturation was relatively flat in many patients, but the mean for the group did fall slightly, especially at month 2 (decreased 14% from baseline). Each value in (B) is mean ± 95th percentile, $\#P < 0.10$ vs. baseline (month 0).

salt malabsorption due to the ileal disease resulting in fat malabsorption. The increased colonic fats then bind to free calcium, increasing unbound oxalate that is able to cross the colonic mucosa. (*2*) Colonic permeability is increased by malabsorbed fatty acids and bile acids, perhaps induced by changes in epithelial tight junctions, allowing oxalate to pass from the intestine into the blood stream. Unabsorbed bile acids may also exert damaging effects on intestinal oxalate-metabolizing bacteria, thereby increasing oxalate available for absorption [10]. Regardless of the mechanism, in malabsorptive states the percentage of oxalate absorbed from the gut and excreted in urine can be markedly increased, and hyperoxaluria correlates with steatorrhea [6]. Additional factors that contribute to stone formation include a low urinary pH, low urinary citrate concentration, and decreased urine volumes, due to the diarrhea and consequent loss of fluid and bicarbonate in the stool.

The relative importance of hyperoxaluria as a cause of idiopathic calcium oxalate stone disease remains controversial, especially in relationship to hypercalciuria. However, many studies have identified mild hyperoxaluria in a subset of these patients [16]. In addition, it has been speculated that the normal urinary range, small changes in oxalate concentration could influence supersaturation with respect to calcium oxalate far more than changes in calcium concentrations [16], although recent studies suggest that both ions are equally important determinants [17]. Further, it is relatively easy to initiate calcium oxalate crystallization by addition of oxalate to urine in vitro [18]; therefore, relatively modest effects on urinary oxalate excretion, if sustained, could have more significant clinical effects on crystal growth and stone formation rate.

For patients with idiopathic calcium oxalate stones and mild hyperoxaluria, the mechanisms that mediate increased oxalate excretion are poorly understood. On a typical Western diet, only about 10% of ingested oxalate is typically absorbed, and this is thought to constitute about one third of the total urinary oxalate, the other two thirds being synthesized by the liver [19]. However, the

contribution of dietary oxalate to urinary oxalate could vary widely among individuals because dietary oxalate can vary from 70 to 930 mg/day on a typical Western diet, to as much as 2000 mg while ingesting certain highly vegetarian diets [20]. Factors known to influence the percentage of this dietary oxalate that is absorbed include the availability of free calcium and magnesium ions that can complex with oxalate and decrease its rate of absorption, and the presence of free fats in the distal colon, which can form soaps with calcium and thereby increase concentration of free oxalate [20]. Recent [21, 22] and older [23–25] studies also support the hypothesis that increased gastrointestinal absorption of oxalate due to factors independent of diet could mediate hyperoxaluria in a subgroup of calcium oxalate stone formers. There is evidence that specific energy-dependent transporters might mediate both net oxalate absorption, as well as oxalate excretion [26]. The latter might be particularly critical in eliminating excess oxalate when renal function is reduced [27].

Previous studies have shown that components of the endogenous digestive microflora can utilize oxalate, potentially limiting its absorption from the intestinal lumen [10]. *Oxalobacter formigenes* contains 2 enzymes [formyl coA transferase (frc) and oxalyl-coenzyme A decarboxylase (oxc)] that allow it to utilize oxalate as an energy source, in the process converting it to formate and CO_2, as well as a specific oxalate/formate antiporter (OxlT) [28]. Epidemiology suggests that colonization with *O. formigenes* could be an important determinant of urinary oxalate excretions [29, 30]. The lactic acid bacteria that constitute Oxadrop® have been shown not to contain the OxlT gene [11]. Nevertheless, the bacteria in Oxadrop® can degrade small amounts of oxalate in vitro, and in a small group of mildly hyperoxaluric stone formers, oral administration of this preparation (1 packet daily) decreased urinary oxalate excretion by 40% after 1 month (mean 55.5 mg to 33.5 mg/day, $P < 0.05$) [11]. Although the mechanism by which Oxadrop® reduced urinary oxalate excretion in this study is not clear, it could act via many potential pathways, for example, by improving gastrointestinal barrier function and reducing paracellular oxalate fluxes, directly degrading oxalate, or by changing activity of oxalate transporters.

Although the percentage decrease in urinary oxalate excretion was lower in our study than the previous one in idiopathic calcium oxalate stone formers [10], the absolute decrease was similar (e.g., 22 mg/day on 2 doses per day; Table 1). Therefore, the metabolic capacity of the collection of bacteria contained in Oxadrop® could have an upper limit, or reducing gastrointestinal oxalate absorption could be more difficult in patients with true enteric hyperoxaluria. These results also suggest that timing of administration may be important. In the earlier study by Campieri et al [10], the preparation was administered twice daily before meals, whereas in ours it was administered once daily several hours after the major meal. Our premise was that the preparation acted to colonize the large intestine, and that timing of administration was not an important variable. However, it is possible that coadministration with food may be beneficial, and that perhaps the bacteria can degrade oxalate in the intestine during transit.

Lactic acid bacteria are currently classified as nonpathogenic bacteria, which are permitted in food by the Food and Drug Administration**.** A preparation slightly different from Oxadrop® (VSL#3®) has recently been shown to be safe and effective in the treatment of pouchitis, the major long-term complication after ileal pouch-anal anastomosis for ulcerative colitis [12]. Caution may, however, be required when these or similar probiotic preparations are used in the very young with immature immune systems [14] or immunocompromised patients [31]. In addition to treatment of chronic gastrointestinal inflammation associated with inflammatory bowel disease, preparations of lactobacilli have been successfully used for treatment of acute infectious diarrhea [32].

Although the current results suggest that manipulation of gastrointestinal flora in patients with enteric hyperoxaluria using Oxadrop® can influence oxalate absorption and, hence, urinary oxalate excretion, the effect was relatively small such that urinary supersaturation levels fell but the change was not statistically significant. Further, urinary oxalate rose on the highest Oxadrop® dose, so that there may be an optimal dose, and that it might be possible to give too much of this probiotic. This observation underlines the importance of careful dosing studies. All patients were asked to maintain a standard low oxalate diet; however, diet was not controlled in this study. Oxalate absorption in enteric hyperoxaluria is likely to be dependent on diet composition, and indeed in our paired urine collections variability in 24-hour oxalate excretion was 20.2 ± 14.9% (mean ± SD), compared to 12.5 ± 11.1% for creatinine. Therefore, in future trials, carefully controlling the diet might decrease variability and improve the ability to detect significant effects in smaller patient populations such as this.

CONCLUSION

Hyperoxaluria is often a contributing factor to renal stone formation, an extremely common and costly health condition in the United States. Certain patients with chronic gastrointestinal disease have more extreme hyperoxaluria that can result not only in stones, but renal scarring and failure. In both groups of patients, increased absorption of oxalate across the gastrointestinal tract is likely pathogenic. Probiotics can improve gastrointestinal health, and the current and previous [11] studies suggest that such a strategy may decrease oxalate levels in

the urine of hyperoxaluric individuals. If these results are confirmed in a larger population of patients in a placebo-controlled trial, longer-term treatment trials with stone-forming rate as an outcome would be indicated.

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