A Randomized, Double-blind Trial of Lactobacillus GG Versus Placebo in Addition to Standard Maintenance Therapy for Children with Crohn's Disease

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Abstract: Probiotics are widely used by patients with Crohn's disease (CD) in an attempt to improve their health, but few controlled studies have been done to evaluate the efficacy of these therapies. We conducted a randomized, placebo-controlled trial of the probiotic *Lactobacillus rhamnosus* strain GG (LGG) to see if the addition of LGG to standard therapy prolonged remission in children with CD. Concomitant medications allowed in the study included aminosalicylates, 6-mercaptopurine, azathioprine, and low-dose alternate day corticosteroids. Seventy-five children (age range, 5–21 yr) with CD in remission were randomized to either LGG (n = 39) or placebo (n = 36) and followed for up to 2 years. The median time to relapse was 9.8 months in the LGG group and 11.0 months in the placebo group (P = 0.24); 31% (12/39) of patients in the LGG group developed a relapse compared with 6/36 (17%) of the placebo group (P = 0.18). The LGG was well tolerated, with a side effect profile comparable with placebo. This study suggests that LGG does not prolong time to relapse in children with CD when given as an adjunct to standard therapy.

Key Words: Child, Crohn's disease, inflammatory bowel disease, lactobacillus, probiotics

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Crohn's disease (CD) is a chronic disease characterized by relapsing episodes of small and large bowel inflammation; approximately 20% of patients develop CD in childhood or adolescence.[1,2] Therapy often involves induction of remission with corticosteroids and maintenance therapy with a combination of aminosalicylates and immunomodulators.[3,4] Whereas induction of remission in CD may initially be achieved with corticosteroids, maintenance therapy for CD is often less successful. Patients treated with long-term corticosteroids may experience a number of complications, including growth failure or osteopenia.[5] Aminosalicylates (e.g., sulfasalazine, mesalamine) may be used to maintain remission, but at best, have a modest effect, with a more than 50% relapse rate after 1 year.[6] 6-mercaptopurine (6-MP) and azathioprine are more effective as maintenance agents, but these medications have the potential complications of leukopenia, infection, pancreatitis, hepatitis, and increased risk of malignancy.[7,8] Therefore, currently available maintenance therapies for CD have either limited efficacy or an adverse event profile unacceptable to many patients.

Clinical and laboratory studies support the concept that CD occurs in a genetically predisposed host, when the mucosal immune system is activated by an environmental, dietary, or infectious antigen.[9] Studies have shown that between 25% and 50% of patients with CD carry mutations in the *NOD2/CARD15* gene; these mutations may alter the host's immune response to

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bacterial flora.[10,11] The patient's endogenous bacterial flora may initiate a cascade, resulting in intestinal injury by secreting inflammatory mediators such as lipopolysaccharide, which may activate the host's innate immune system and initiate the aberrant immune response.[12,13] In support of this hypothesis, therapies that modify the bacterial microenvironment (e.g., antibiotics, elemental diet, and fish oil) may induce or maintain remission in CD.[14–16]

Alternative and complementary therapies such as probiotics are used by approximately 40% of adults and children with inflammatory bowel disease, but there are few clinical trials studying these agents.[17] The probiotic VSL#3, consisting of 8 different bacterial species, has been shown to be effective in preventing pouchitis in adults having undergone ileal pouch anal anastomosis.[18,19] Lactobacillus GG (LGG), another commonly available probiotic, has been shown to be effective in the treatment of rotavirus and antibiotic-associated diarrhea.[20–22] Our group aimed to evaluate the efficacy of LGG as an adjunct to standard maintenance therapy in children with CD.

MATERIALS AND METHODS

Patients 5 to 21 years of age were recruited from 11 pediatric gastroenterology academic medical centers across the United States between September 1999 and February 2002. Patients were required to have small bowel, colonic, or perianal CD confirmed radiographically and/or endoscopically either at entry into the study or within the preceding 5 years. The patient was required to be in remission, with remission defined as a pediatric CD activity index (PCDAI) score of less than or equal to 10 during the 2 months before enrollment in the study.[23] Concomitant maintenance medications allowed at study entry included aminosalicylates, 6-MP, azathioprine, and low-dose alternate day corticosteroids (<0.5 mg/kg every other day). Exclusion criteria were abdominal or perirectal abscess within the past 2 months; documented intestinal stricture or abscess thought to require imminent surgery; antibiotic use for a period of more than 14 consecutive days in the 2 months before enrollment; toxic megacolon or fulminant colitis within 6 months before screening; concurrent use of exclusive elemental diet at enrollment; history of allergic reaction to Lactobacillus or other probiotic therapies; use of any probiotic bacterial supplement within the past 30 days; or concurrent use of other immunomodulating agents (e.g., methotrexate, cyclosporine, tacrolimus, infliximab). Informed consent was obtained from each patient under a protocol approved by the Institutional Review Boards of the participating centers.

Patients agreeing to participate in the study were randomized to a study drug containing either LGG, 1 capsule (containing at least 10^{10} bacteria and 295 mg inulin) twice per day, or an identical capsule containing 355 mg inulin (placebo). This dosage was selected because it has been used in a number of clinical studies of acute diarrhea and in an open label pilot trial of children with CD and because prior studies suggested colonization of the bowel by LGG at this dose.[20,24,25] Capsules and placebo were supplied by ConAgra Foods (Omaha, Nebr.) after being compounded at Garden State Nutritionals (West Caldwell, N.J.). The first 22 patients were randomized as a single block, using a 1:1 randomization. The randomization of subsequent patients was stratified by center, using a permuted block 1:1 randomization for each site. Patients participating in the study were instructed to take the study drug either for 2 years or until clinical relapse was documented. Study investigators evaluated subjects every 3 months, at which time history, physical examination, and laboratory studies were performed. During these visits, pill counts were used to determine compliance with study medication. Stool cultures to analyze for bacterial colonization were performed at baseline, 3 months, 1 year, and 2 years after enrollment, or at time of relapse. Clinical relapse of CD was defined as the occurrence of any of the following: PCDAI score of greater than 30 points on any single visit or a PCDAI score greater than 15 points on any 2 consecutive visits more than 1 week apart; need for corticosteroid or other rescue therapy for active CD; or need for surgery or hospitalization for a complication of CD (e.g., fistula, stricture, or abscess).[23]

Fecal Microbiological Assays and Stool Specimen Handling

Stool samples obtained from the patient were stored frozen in commercially available media (Meridian Diagnostics) and analyzed by the laboratory of one of the authors (B.G.). Samples were plated on blood agar under aerobic and anaerobic conditions to isolate total aerobes and anaerobes. Aerobes were incubated in an aerobic incubator at 37°C for up to 48 hours. Anaerobes were incubated in an anaerobic chamber at 37°C. The anaerobic chamber contained the following: 85% N_2, 5% CO_2, and 10% H_2. Lactobacillus counts were determined by using lactobacillus-selective agar. Verification of lactobacillus was established by biochemical testing using API strips.

Statistical Analysis

Baseline continuous variables were compared using 2-sample *t* tests, and baseline and outcome categorical variables were compared using the χ^2 or Fisher exact test. The primary a priori endpoint used in the study was time to clinical relapse, using the definition of relapse described earlier. To compare time to relapse between the 2 groups, Kaplan-Meier curves were constructed, and univariate survival analysis (LGG versus placebo) was performed using the log-rank test. The secondary endpoint was the proportion of patients in each group exhibiting a clinical relapse; for this endpoint, the χ^2 method was used to compare binomial proportions between treatment groups. For both analyses, a statistically significant difference between groups was set at a 2-tailed α level of 0.05. The a priori power calculation was

done for the comparison of the 2 proportions, because we had insufficient information on the median time to relapse in the LGG versus placebo group and comparison of 2 proportions typically provides a greater power for comparison of survival curves. The initial sample size calculation was based on an estimated 25% relapse rate at 2 years in the LGG group and a 50% relapse rate in the placebo group. A sample size of 66 patients per group was predicted to provide 80% power to detect a difference between the 2 groups, using the χ^2 test and a 2-sided P value of 0.05 (nQuery Advisor version 3; Statistical Solutions, Saugus, Mass.).

An independent Data and Safety Monitoring Board (DSMB; consisting of 1 adult gastroenterologist, 1 pediatric gastroenterologist, and 1 statistician) monitored the study and planned to conduct one interim analysis for efficacy during the study. Group sequential monitoring was planned to stop the study if large treatment differences appeared before the end of the study, and the method of stochastic curtailing was planned to stop the study early if there was little chance of finding a significant difference between groups. The effect of an O'Brien Fleming rule on the sample size for the study was examined. Assuming a single interim data analysis when one-half of the patients had completed the study, the null hypothesis was rejected if $P < 0.003$ ($|Z| > 2.96$); the null hypothesis was accepted if $P > 0.73$ ($-0.35 < Z < 0.35$).

RESULTS

Study Population

Seventy-five patients were recruited for the study and randomized to LGG or placebo. Thirty-nine patients were randomized to receive LGG, and 36 patients were randomized to placebo at the time that the DSMB stopped the study for lack of efficacy and difficulty in recruiting study subjects. Characteristics of the study population are given in Table 1. Of note, at baseline, 9 patients (3/27; 8%) providing specimens in the LGG group and 6/24 (25%) providing specimens in placebo group ($P = 0.28$) had greater than or equal to 10^5 of *Lactobacillus* spp. in their stool.

Results of the Interim Analysis by the DSMB

Interim data were reviewed by the DSMB 42 months after the initiation of the study, after 75 patients had been enrolled. The study was stopped both because of slow recruitment and because the interim analysis suggested lack of efficacy. It was determined by the DSMB that even if the target recruitment was reached, a treatment effect would almost certainly not be identified.

Data were available on 71 subjects at the DSMB meeting and analyzed for both safety and efficacy. The DSMB concluded that there was no difference in adverse events in the 2 groups ($P = 0.36$). Based on the lack of difference between the 2 groups in time to relapse ($P = 0.10$, with the placebo arm having the longer time to relapse) and the increasing difficulty of recruiting subjects on the allowed medications because of changes in treatment of pediatric CD during the study (e.g., the increasing use of infliximab), the DSMB recommended closure of the study. The 28 study subjects who were active in the study at that time were asked to return for a final close out visit and all were withdrawn from therapy.

LGG Does Not Prolong Time to Relapse over Standard Therapy

In the final data set of 75 patients, median (interquartile range) follow-up for the LGG group was 9.8 months (3.1–16.1 mo) and for the placebo group was similar at 11.7 months (4.0–19.1 mo; $P = 0.24$). Median time to relapse was similar for the 2 study groups (LGG group, 11.6 mo, interquartile range 7.9–15.3 mo; placebo group, 12.8 mo, interquartile range 8.3–17.4 mo; $P = 0.37$; Fig. 1). The proportion of patients relapsing is shown in Table 2 and is not different between the 2 groups ($P = 0.18$). Microbiologic analysis was conducted to assess the ability of the Lactobacillus (not LGG specifically) to colonize the gastrointestinal tract. At 3 months, 10 patients had been discontinued from the study (6 in the LGG group, 4 in the placebo group). Of the remaining 65 patients, 30 provided fecal specimens at 3 months: 1 of 15 (7%) in the LGG group and 3 of 15 (20%) in the placebo group had greater than or equal to 10^5 of *Lactobacillus* spp. in their stool ($P = 0.60$).

Adverse Events, Dropouts, and Noncompliance

The study drug was well tolerated, with only 15 of the 75 subjects reporting any adverse events (18% in the LGG group and 21% in the placebo group; $P = 0.78$; Table 2). During the study period, 2 patients in the LGG group were hospitalized (serious adverse events) for complications thought to be secondary to CD (not caused by LGG): perianal abscess and perirectal abscess. Both patients were treated with antibiotics and surgical drainage. Three patients (4% of the total) withdrew from the study for adverse events thought to be related to study medication (2 in the LGG group reported vomiting and inability to tolerate the medication, and 1 in the placebo group reported mild diarrhea). Ten patients (13% of the total) reported adverse events that were not attributed to study medication, and all patients continued with study therapy (3 in the LGG group: 1 with nausea, vomiting, ankle swelling and relapse, 1 with abdominal pain, and 1 with diagnosis of an eating disorder; 7 in the placebo group: 2 with abdominal pain, 1 with a sore throat, 1 with appearance of cervical lymph nodes, headache, dizziness, and relapse, 1 with headaches and relapse, 1 with nausea and fatigue, and 1 with difficulty ambulating and relapse). Five patients (7% of the total) withdrew because medications not allowed in the study protocol were prescribed (4 in the LGG group and 1 in the placebo group).

Fourteen patients (19% of the total) prematurely dropped out of the study because of noncompliance: 8 patients (21%) in

TABLE 1. Baseline Characteristics of the 75 Children Enrolled in the Study

Characteristics	LGG Group (n = 39)	Placebo Group (n = 36)	*P*
Study site			0.99
Columbia	5 (13%)	7 (19%)	
Omaha	6 (15%)	5 (14%)	
Boston	5 (13%)	4 (11%)	
Seattle	5 (13%)	3 (8%)	
Philadelphia	5 (13%)	3 (8%)	
Michigan	4 (10%)	3 (8%)	
Texas	4 (10%)	3 (8%)	
Wisconsin	3 (8%)	4 (11%)	
Maryland	1 (3%)	2 (5%)	
Jacksonville	1 (3%)	1 (3%)	
Morristown	0 (0%)	1 (3%)	
Demographics			
Age (years; median, interquartile range)	14.8 (13.1–18.1)	14.9 (13.4–16.4)	0.96
Sex			0.48
Male	26 (67%)	21 (58%)	
Female	13 (33%)	15 (42%)	
Race			0.27
White	36 (92%)	28 (78%)	
Hispanic	1 (3%)	2 (6%)	
African American	2 (5%)	4 (11%)	
Other	0 (0%)	2 (5%)	
Weight	55.3 (42.2–63.0)	52.6 (38.8–63.2)	0.38
Details of CD			
Age of onset of CD (years; median, interquartile range)	11.8 (10.2–13.0)	12.3 (10.1–14.1)	0.54
Duration of CD (months; median, interquartile range)	29.6 (15.1–51.2)	25.0 (13.5–43.1)	0.35
Number of flares since diagnosis			0.81
0–2	25 (68%)	22 (65%)	
>2	12 (32%)	12 (36%)	
Disease phenotype			
Mucosal	30 (79%)	28 (80%)	1.00
Stricturing	3 (8%)	2 (6%)	
Perforating	5 (13%)	5 (14%)	
Location of CD			0.16
Small bowel only	6 (17%)	1 (3%)	
Large bowel only	5 (14%)	6 (17%)	
Both	25 (69%)	28 (80%)	
Prior surgery	4 (10%)	8 (22%)	0.22
Medications			
Aminosalicylates	32 (89%)	28 (82%)	0.51
Azathioprine or 6-MP	22 (65%)	21 (66%)	1.00
Alternate day steroids	6 (19%)	6 (21%)	1.00
PCDAI (median, interquartile range)	2.5 (0–5)	2.5 (0–5)	0.89

the LGG group and 6 patients (17%) in the placebo group. The most common reason cited for noncompliance was the desire to not take additional medication. At 3 months, data were available on 36 of the 65 patients still enrolled in the study. In the members of the LGG group providing data on compliance, median compliance was 94% (interquartile range, 88%–99%), and in the placebo group members providing data on compliance, median compliance was 93% (85%–97%; $P = 0.51$).

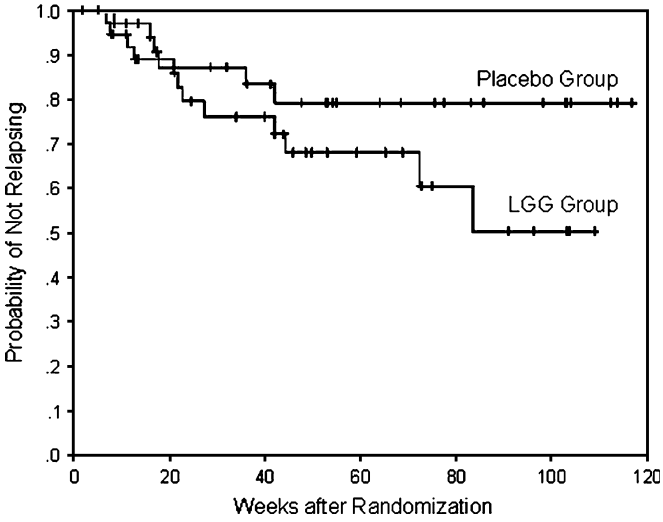

FIGURE 1. Survival curve showing the probability of staying relapse free during the duration of the study. Individual tick marks represent censored patients (patients who did not develop a relapse or an adverse event, necessitating withdrawal at the time of the study was stopped). The 2 curves and median survival times were not significantly different by the log-rank test.

Because the study was stopped by the DSMB, there are insufficient data to report on compliance at other time intervals.

We had originally planned to evaluate whether either a history of surgery or use of 6-MP/azathioprine were potential confounding variables affecting relapse of CD. In the total of 18 patients who relapsed, 33% had prior surgery, 22% had not (odds ratio, 1.7; 95% confidence interval, 0.5–6.5; $P = 0.43$). In this same population, 20% were on 6-MP/azathioprine and 35% were not (odds ratio, 0.5; 95% confidence interval, 0.2–1.5; $P = 0.22$). Because we did not identify that either surgery or 6-MP/azathioprine use was independent predictors on univariate analysis, we did not pursue further multivariate analysis using the Cox proportional hazards model.

DISCUSSION

Probiotics have been defined as organisms that, when ingested, may have beneficial effects on human health. A myriad of different probiotic preparations are sold through pharmacies, supermarkets, and health food stores. The majority of these preparations are marketed directly to patients without any published clinical studies. Organisms present in probiotic preparations include *Lactobacillus* sp., *Bifidobacterium* sp., and *Streptococcus* sp. *Saccharomyces boulardii*, a yeast probiotic, has been shown to prevent recurrences of *Clostridium difficile* infection, and open-label trials suggest efficacy in inflammatory bowel disease.[26–28] In children, the best studied probiotic preparation is LGG. Clinical trials have shown the efficacy of this preparation in reducing the severity of acute diarrhea, decreasing antibiotic associated diarrhea, and reducing the development of atopic disease in at-risk infants.[20,22,29] Finally, the addition of LGG to a prednisone regimen improved

TABLE 2. Outcomes and Adverse Events for the 75 Children Enrolled in the Study

	LGG Group (n = 39)	Placebo Group (n = 36)	*P*
Outcome			
Relapse occurred	12 (31%)	6 (17%)	0.18
Relapse did not occur	27 (69%)	30 (83%)	
Completed 24 months of study	2 (5%)	5 (14%)	
Stopped after DSMB meeting	11 (28%)	17 (47%)	
Withdrew	14 (36%)	8 (22%)	
Withdrawn because of noncompliance	8 (21%)	6 (17%)	
Withdrew because of use of medications not allowed by the study (but not relapse)	4 (10%)	1 (3%)	
Withdrawn because of adverse event	2 (5%)	1 (3%)	
Adverse events			
No adverse event reported	33 (82%)	28 (79%)	0.78
Adverse event	7 (18%)	8 (21%)	
Serious adverse event—hospitalization for relapse—withdrawn from study	2 (5%)	0 (0%)	
Adverse event resulting in withdrawal from study	2 (5%)	1 (3%)	
Adverse event and relapse resulting in withdrawal from study	1 (3%)	3 (8%)	
Adverse event and use of medications not allowed by the study	1 (3%)	1 (3%)	
Adverse events not resulting in withdrawal from the study	1 (0%)	3 (8%)	

gut permeability and decreased disease activity in a series of 4 children with CD.[25] For these reasons, we elected to study LGG in the prevention of relapse in CD.

In our study, we were unable to show that LGG prolonged remission time in patients with CD already in remission on standard therapy. The time to relapse and proportion of patients relapsing was essentially identical in both LGG and placebo groups. There were very few reported adverse events attributable to study medication, suggesting that this preparation is safe and well tolerated. We also did not identify any reliable correlation between medication intake, clinical status, and fecal colonization with lactobacillus. However, children with CD in remission enrolled into this study were reluctant to take additional supplemental therapy for a prolonged period of time. Thus, there was a high dropout rate related to unwillingness to follow the study protocol, which would bias the study in favor of the null hypothesis.

The most likely explanation for our results is that LGG is simply ineffective as an adjunct maintenance agent in patients with CD.[30] In support of this statement, a smaller study by Schultz et al[30] evaluating LGG as a maintenance agent showed similar times to relapse in the LGG and placebo groups. In addition, a placebo-controlled study by Prantera et al[31] evaluating LGG in the prevention of postoperative recurrence in patients with CD also showed no efficacy. Another explanation is that both the placebo and LGG preparations contained inulin, a prebiotic that has been known to modify bacterial flora.[32] However, the amount of inulin in these capsules was very small compared with the dosage of inulin used as a prebiotic in human studies. Thus, whereas we cannot completely exclude a beneficial prebiotic effect of the inulin or the trace amounts of LGG in the placebo, it is unlikely this low dose of inulin had a biologic effect.

The purity and viability of probiotic preparations is not well standardized secondary to the lack of FDA oversight in the marketing of these compounds. Because the LGG and inulin placebo were compounded in the same facility, we studied the possibility that the placebo could contain LGG by conducting a post hoc microbiologic analysis on capsules that had previously been dispensed to 27 patients in enrolled in the study. Only patients who had available capsules were included in this analysis. All of the 15 patients randomized to active LGG had appropriate amounts of LGG in their capsules. Six of the 12 patients randomized to placebo had undetectable LGG ($<10^2$ colony forming units/g). However, we identified low amounts of LGG (10^3–10^4 colonies/g) in 5/12 capsules retrieved from patients randomized to receive placebo capsules. The amount of LGG in these placebo capsules was less than one millionth the dose (10^4 colonies compared with 10^{10} colony forming units/g in the active capsule), therefore we do not believe the minute dose of probiotic we found in some of the placebo capsules is capable of a biologic effect. However, we did identify 1 subject who was randomized to placebo who had significant amounts of LGG (10^9 colony forming units/g) on post hoc analysis. This patient most likely received active drug when they were assigned placebo and most likely reflects an error in labeling of the study capsules. Thus, issues with manufacturing of the placebo in our study could bias this study toward the null hypothesis. However, the same placebo has been used in other published studies that have shown significant differences between LGG and placebo.

There are other explanations for our results. The patients selected for this study were somewhat healthy, with a prolonged remission period and a lower risk of relapse. Patients were allowed to stay on concomitant therapies during this study, and the efficacy of the concomitant treatments could potentially mask any effect of the LGG. Whereas allowing concomitant medications was a drawback of the study design, the individuals planning the study decided that it was not feasible or ethical to withdraw maintenance medication from children in remission. We also did not conduct a dose-ranging study before this trial; the dosage used has been shown to colonize healthy volunteers, and this dosage has been widely used in adult and pediatric clinical trials.[21,24] However, there is a possibility that patients with CD may be more resistant to colonization with this organism and thus might require a different dosage. Given the inconsistent colonization of fecal flora with lactobacilli in patients randomized to study drug in our study, future investigators studying LGG may wish to consider additional dose-response pilot studies in individuals with CD.

Administering probiotics to interleukin-10–deficient mice with bowel inflammation decreases levels of proinflammatory cytokines (e.g., tumor necrosis factor α, interleukin-12) and reduces intestinal inflammation.[33,34] Despite promising results with animal models, the efficacy of probiotics in humans with inflammatory bowel disease is mixed. The probiotic VSL#3, a preparation consisting of 8 different bacterial species, seems to be effective in the treatment of pouchitis. In a placebo-controlled trial randomizing patients to VSL#3 or placebo for the first year after ileoanal pouch creation, 2 of 20 patients in the VSL#3 group, compared with 8 of 20 patients treated with placebo, experienced a pouchitis episode.[19] A subsequent study suggested that 85% of patients with recurrent pouchitis treated with VSL#3, compared with less than 10% of placebo-treated patients, stayed in remission and had higher quality-of-life scores.[18] Small open-label trials of *Saccharomyces boulardii* in humans with ulcerative colitis and CD suggested that this probiotic may be useful as adjunctive maintenance therapy, but definitive placebo-controlled studies have not been performed.[27,28] One recent open-label trial also suggested that LGG may delay or prevent the onset of pouchitis.[35] Our study does not support a role for LGG as adjunctive therapy in stable patients with CD already on maintenance medication. However, additional placebo-controlled studies are necessary to further delineate the potential of probiotics in patients with CD.

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