



NOTE

Internal Medicine

Successful outcome after a single endoscopic fecal microbiota transplantation in a Shiba dog with non-responsive enteropathy during the treatment with chlorambucil

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ABSTRACT. A 7-year 6-month-old, castrated male Shiba dog presented with a 1-month history of lethargy, anorexia, vomiting, and frequent watery diarrhea. Weight loss, hypoalbuminemia, anemia, and leukocytosis were detected at the first visit. The dog was diagnosed with non-responsive enteropathy (NRE) based on clinical and histopathological examinations. Since the dog did not respond to the immunosuppressive drugs, fecal microbiota transplantation (FMT) was performed during the treatment with chlorambucil. A single endoscopic FMT into the cecum and colon drastically recovered clinical signs and clinicopathological abnormalities and corrected dysbiosis in the dog. No recurrence or adverse events were observed. The present case report suggests that FMT, possibly together with chlorambucil, might be a treatment option for NRE in Shiba dogs that have poorer prognosis compared with other dog breeds.

KEY WORDS: dysbiosis, fecal microbiota transplantation, hypoalbuminemia, non-responsive enteropathy, Shiba dog

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Inflammatory bowel disease (IBD) in dogs is characterized by idiopathic, chronic mucosal inflammation in the gastrointestinal (GI) tract [27]. Canine IBD, together with antibiotic-responsive enteropathy (ARE) and food-responsive enteropathy (FRE), constitute a group of disorders called chronic enteropathy (CE) [7]. Dysbiosis, defined as an altered composition of the gut microbiota, intestinal barrier dysfunction, genetic factors, inappropriate reactions to dietary components, or some combination of these factors are related to chronic dysregulation of the mucosal immune responses in the small and large intestines of dogs with IBD [9]. Treatment of IBD typically requires immunosuppressive drugs, including glucocorticoids; however, some dogs with IBD do not respond to these drugs, resulting in poor outcomes [7, 11]. Thus, it was recently proposed that canine IBD should be classified as immunosuppressant-responsive enteropathy (IRE) and dogs that did not respond to the immunosuppressants should be categorized as having non-responsive enteropathy (NRE) [7].

Previous studies have shown that Shiba dogs are predisposed to CE and have poorer prognosis compared with other dog breeds [18–20]. The polymerase chain reaction for antigen receptor rearrangement (PARR) analysis revealed that more than half of Shiba dogs with CE were clonality-positive in the intestinal mucosal specimens [17]. In addition, most clonality-positive Shiba dogs exhibited epitheliotropism characterized by marked and dense infiltration of small lymphocytes in the epithelium upon histopathological examination [17]. These findings suggest that the pathogenesis of severe, refractory CE in Shiba dogs might be associated with small cell intestinal lymphoma. However, even in clonality-negative or epitheliotropism-negative Shiba dogs, the median survival times were still shorter than those of other dog breeds [17]. It is, therefore, conceivable that CE in Shiba dogs is a breed-specific disease.

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Fecal microbiota transplantation (FMT) is a treatment performed by introducing fecal microbiota obtained from a healthy individual into the GI tract of a diseased individual [2, 10]. The mechanisms underlying the effects of FMT are not fully understood, but may be associated with enhanced numbers of beneficial microbes, increased microbial diversity, and restoration of normal flora [13]. Published papers, but not conference abstracts, have demonstrated that FMT is effective for the treatment of several GI diseases in dogs, including canine parvovirus infection [22], postweaning diarrhea [4], acute diarrhea [6], and *Clostridium difficile*-associated diarrhea [26]. A previous pilot study reported that repeated oral or endoscopic FMT into the duodenum, ileum, or colon improved GI signs in most but not all of 16 dogs with IBD [3]. Long-term, repeated FMT by rectal enema was also shown to improve GI signs, as well as the fecal microbiome diversity, in a dog with IBD [14]. Similar results have been recently confirmed in nine dogs with IBD [15]. Thus, FMT is considered to be a potential therapeutic option for IBD in dogs. However, it remains unclear whether FMT is effective for hypoalbuminemia, anemia, leukocytosis, and weight loss, which are associated with NRE in dogs.

Here, we report that a single endoscopic FMT into the cecum and colon drastically induced remarkable and persistent recovery of GI signs and clinical and clinicopathological abnormalities and corrected dysbiosis in a Shiba dog with NRE during the treatment with chlorambucil.

A 7-year 6-month-old, castrated male Shiba dog was referred to Tokyo University of Agriculture and Technology Animal Medical Center for evaluation of a 1-month history of lethargy, anorexia, and GI signs, including vomiting and frequent watery diarrhea. The dog had been treated with oclacitinib (Apoquel, Zoetis Japan, Tokyo, Japan) for more than one year by a referring veterinarian because of a history of pruritus and allergic skin disease and had been fed a hypoallergenic, low-fat diet (Medycoat allergencut; Petline, Gifu, Japan). Since hypoalbuminemia (1.6 g/dl; reference interval [RI]: 2.6–4.0 g/dl) and mild ascites were detected in the dog, prednisolone (2 mg/kg, q24 hr, subcutaneous [SC]) was administered for 7 days prior to the current presentation by a referring veterinarian. However, the treatment with prednisolone at the immunosuppressive dose did not improve clinical signs and hypoalbuminemia.

On day 1, the dog showed moderate lethargy and anorexia, vomiting (1 time/week), and frequent watery diarrhea (>5 times/day). Physical examination detected mild dehydration, and the body weight (BW) of the dog was 13.2 kg, indicating weight loss by 2.3 kg for a month. The canine chronic enteropathy clinical activity index (CCECAI) was 17, which was classified as very severe disease [1]. A complete blood count (CBC) showed an increased white blood cell (WBC) count (29.5×10^9 cells/l; RI: $6.0\text{--}17.0 \times 10^9$ cells/l) and a decrease in packed cell volume (PCV; 27.6%; RI: 37–55%). A blood biochemical analysis detected hypoalbuminemia (1.8 g/dl) and hypoproteinemia (3.5 g/dl; RI: 5.0–7.2 g/dl), but other parameters, including basal cortisol (4.5 $\mu\text{g/dl}$; RI: 1.0–6.0 $\mu\text{g/dl}$), total bile acid (preprandial; 6.2 $\mu\text{mol/l}$; RI: ≤ 7.9 $\mu\text{mol/l}$; postprandial; 11.7 $\mu\text{mol/l}$; RI: ≤ 24.5 $\mu\text{mol/l}$) and trypsin-like immunoreactivity (14.3 ng/ml; RI: >5.2 ng/ml), were within RI. Abdominal ultrasound illustrated mild ascites and mild swelling of mesenteric lymph nodes, while thoracic ultrasound did not find any abnormalities including pleural effusion. Inspection for ascites revealed a specific gravity of 1.008 and total protein of 0.3 g/dl, indicating a transudate. A fecal examination did not identify any pathogens, and urinalysis did not reveal proteinuria.

On day 10, to determine the underlying causes of the chronic GI signs, endoscopic examination of the upper and lower GI tract was performed according to our previous reports [16, 21]. Histopathological analysis revealed lymphoplasmacytic enteritis (LPE) and lymphangiectasia in the duodenal, ileal, and colonic mucosae. Although PARR analysis (Canine-Lab, Tokyo, Japan) detected the presence of clonal rearrangement in the *IgH* gene in the duodenal mucosal sample, there were no histopathological findings suggestive of intestinal lymphoma, including intraepithelial lymphocytes.

Figure 1 shows the treatments performed and changes in the clinical and clinicopathological parameters. The dog first received a whole-blood transfusion (20 ml/kg) on day 2 because of non-regenerative anemia and hypoalbuminemia. The dog was administered antibiotics, including metronidazole (Flagyl, Shionogi & Co., Ltd., Osaka, Japan; 15.0 mg/kg, per os [PO], q12 hr) from day 1–44 and enrofloxacin (Baytril, Bayer Yakuhin, Ltd., Osaka, Japan; 6 mg/kg, PO, q12 hr) from day 10–14, day 25–28, and day 44–56. The dog was also given an antidiarrheal (Diabuster, Kyoritsu Seiyaku Corp., Tokyo, Japan; 1–2 tablets, PO, q12 hr) containing berberine tannate, bismuth subnitrate, geranium herb, nutgalls, and scopolia extract, and probiotics (Bioymbuster, Kyoritsu Seiyaku Corp.; 1–2 tablets, PO, q12 hr) containing *Bacillus coagulans*, *Bifidobacterium longuin*, *Lactobacillus acidophilus*, *Streptococcus fecalis*, and pancreatin from day 2–44. Although the clinical and clinicopathological parameters temporarily improved after the initial treatment, possibly because of the whole-blood transfusion, they did not remain stable and became worse on day 22. The poor response to the antibiotic treatments ruled out ARE in the dog. To further assess the presence of FRE, a dietary trial was carried out using two different hypoallergenic foods (Anallergenic and Hypoallergenic; Royal Canin Japon, Inc., Tokyo, Japan) from day 22–37. However, the dog did not respond to the diet trial, thus excluding FRE.

Based on the clinical and histopathological findings, the dog's illness was suspected to be IRE accompanied with protein-losing enteropathy. Thus, on day 37, budesonide (Zentacoart, Zeria Pharmaceutical Co., Ltd., Tokyo, Japan; 0.2 mg/kg, PO, q24 hr) and chlorambucil (Leukeran, Aspen Pharma, Baar, Switzerland; 3.7 mg/m², PO, q24 hr) treatments were initiated. However, these immunosuppressants did not improve the clinical and clinicopathological parameters in the dog; therefore, the dog was diagnosed with NRE. Additional whole-blood transfusions (20 ml/kg) were performed on day 45 and 65 (Fig. 1) because of non-regenerative anemia and hypoalbuminemia. Budesonide was terminated on day 58, whereas chlorambucil was continued upon the owner's request.

On day 81, the dog exhibited severe lethargy, moderate anorexia, further weight loss (11.1 kg), moderate dehydration, vomiting (2–3 times/week), and watery diarrhea (3–5 times/day). Although the WBC count (16.7×10^9 cells/l) from the blood test was within but near the upper limit of the RI, anemia (PCV: 22.1%) and hypoalbuminemia (2.0 g/dl) were detected. The CCECAI was 17. Since the dog did not respond to treatments, including the immunosuppressants, FMT was performed on day 81 by endoscopic administration of feces from a healthy donor dog into the subject. As a donor dog, a 5-year-old, 11.3 kg, sexually intact healthy male beagle maintained for research purposes was used. The donor dog was fed a commercial diet (Science Diet Adult, Hill's-Colgate Ltd., Tokyo, Japan),

and water was provided *ad libitum*. Physical and clinical examinations, including a CBC, serum biochemical analysis, radiography, abdominal ultrasound, and fecal examination, did not identify any abnormalities in the donor dog. In addition, genes of pathogens were not detected in feces of the donor dog by the IDEXX Canine Diarrhea RealPCR Panels (IDEXX Laboratories, Inc., Tokyo, Japan) for *Cryptosporidium* spp., *Giardia* spp., *Clostridium perfringens* α toxin, *Clostridium difficile* toxin A&B, *Campylobacter jejuni*, *Campylobacter coli*, *Salmonella* spp., Canine parvovirus type 2, canine distemper virus, and canine enteric coronavirus. The collection and use of feces from the healthy donor dog was approved by the Institutional Animal Care and Use Committee of Tokyo University of Agriculture and Technology (No. 30-131). The recipient dog was prepared for endoscopic FMT by withholding food for 24 hr. Because the general condition of the recipient dog was not good, the risk associated with anesthesia was concerned. Thus, after written informed consent was obtained from the owner, the endoscopic FMT was performed without anesthesia under the approval and guideline of the Research Ethics Committee of Tokyo University of Agriculture and Technology (No. 0019007). A cecum and colon cleanse using warm saline was conducted thoroughly before FMT under endoscopy. Immediately after collection of naturally excreted feces from the donor dog, 100 g of fresh feces was dissolved in 100 ml of saline. The fecal solution was filtered twice through a medical gauze pad, and approximately 50 ml of fecal solution was obtained. The filtered fecal solution was administered into the cleansed cecum and colon of the recipient dog through the channel of the endoscope. After the administration, the dog was restrained in lateral recumbency for 15 min in order to keep the fecal solution in the cecum and colon of the recipient dog.

The clinical and clinicopathological abnormalities were dramatically recovered after FMT (Fig. 1). On day 85, although the GI signs remained, the lethargy and anorexia had disappeared. On day 87, the stool consistency became soft (3–4 times/day), and no vomiting was observed. On day 98, the stool consistency became normal (2 times/day). Chlorambucil was, therefore, tapered and then discontinued on day 176. The GI signs, leukocytosis, anemia, and hypoalbuminemia did not recur even after cessation of chlorambucil, and further medications were unnecessary. The stool characteristics remained normal on day 288. No adverse events were observed in the dog after FMT.

Fecal microbiota in the Shiba dog and the donor dog was analyzed according to the [Supplementary MATERIALS AND METHODS](#). Before FMT (day 10 and 81), the fecal microbiota of the Shiba dog was predominantly composed of three phyla, including Firmicutes, Bacteroidota, and Proteobacteria, whereas that of the donor dog was composed of five phyla, including Firmicutes, Fusobacteriota, Bacteroidota, Proteobacteria, and Actinobacteriota (Fig. 2A), indicating dysbiosis in the fecal microbiota of the Shiba dog. After FMT, Fusobacteriota and Actinobacteriota appeared in the fecal microbiota of the Shiba dog, and the microbiota became similar to that of the donor dog (Fig. 2A). At the genus level, 22 genera appeared in the fecal microbiota of the Shiba dog after FMT (Table 1). In particular, *Alloprevotella*, *Fusobacterium*, *Megamonas*, *Holdemanella*, *Anaerobiospirillum*, and *Collinsella* appeared at greater than 1% relative abundance on day 87 (Table 1). On the other hand, *Bacteroides*, *Lachnoclostridium*, and *Escherichia-Shigella* had drastically decreased in the fecal microbiota of the Shiba dog, from 56.3%, 7.1%, and 6.8% on day 81 to 4.9%, 0.85%, and 0.15% on day 87, respectively (Table 1). Principal coordinates analysis (PCoA) of compositional dissimilarity showed that the fecal microbiota of the Shiba dog was plotted separately from that of the donor dog (Fig. 2B). A week after FMT (day 87), the fecal microbiota of the Shiba dog became closer to that of the donor dog; however, it got away over time. Notably, the fecal microbiota of the Shiba dog showed little change from day 135 to 288 and was different from that of the donor dog and that of the Shiba dog before FMT (Fig. 2B). This is compatible with the findings that, among the 22 genera that appeared on day 87 in the fecal microbiota of the Shiba dog, only eight genera remained on day 120, and five genera, including *Fusobacterium*, *Megamonas*, *Sutterella*, *Holdemanella*, and *Peptoclostridium*, remained on day 288 (Table 1). Along with the appearance and disappearance of these genera, the alpha diversity (Shannon index and the number of amplicon sequence variant) of the fecal microbiota of the Shiba dog increased on day 87 and decreased until day 120, but gradually increased again through day 288 (Fig. 2C).

The present case report clearly demonstrates that a single endoscopic FMT into the cecum and colon markedly improved CCECAI, GI signs, weight loss, anemia, hypoalbuminemia, and leukocytosis and corrected dysbiosis in a Shiba dog with NRE during the treatment with chlorambucil. Furthermore, no recurrence of the clinical and clinicopathological parameters was observed in the dog after FMT. Previous studies reported that Shiba dogs, the presence of clonal rearrangement upon PARR analysis, anorexia, hypoproteinemia, and the lack of initial response to treatment were associated with poor prognosis in CE and LPE [17–19]. Since the Shiba dog in this report met these qualifications, the dog could have been poor prognosis without FMT. In this case, FMT was performed during the treatment with chlorambucil; therefore, it is possible that FMT and chlorambucil might have additively or synergistically contributed to the clinical improvement. Given the findings in this report, FMT, possibly together with chlorambucil, might be a potential treatment option for dogs with NRE and poor prognosis.

As detailed in this report, we found that a single endoscopic FMT dramatically changed the gut microbiota of the Shiba dog. Previous studies showed that a reduced proportion of Fusobacteriota was one of the features of the gut microbiota in dogs with IBD [14, 15, 24]. Similarly, Fusobacteriota was undetectable in the Shiba dog before FMT. As shown in the compositional analysis of the gut microbiota at the phylum level, Fusobacteriota appeared shortly after FMT and remained until day 288. At the genus level, among the 22 genera that appeared in the Shiba dog shortly after FMT, five genera, including *Fusobacterium*, *Megamonas*, *Sutterella*, *Holdemanella*, and *Peptoclostridium*, had colonized through day 288. We also detected that three genera, including *Bacteroides*, *Lachnoclostridium*, and *Escherichia-Shigella*, had markedly decreased shortly after FMT and remained at low levels through day 288. As revealed in the PCoA, the gut microbiota of the Shiba dog became more similar to that of the donor dog shortly after FMT, but became less similar to that of the donor dog over time. However, considering the long-term improvement in the GI signs and the clinical and clinicopathological parameters in the Shiba dog, it is plausible that persistent colonization by *Fusobacterium*, *Megamonas*, *Sutterella*, *Holdemanella*, and *Peptoclostridium* from the donor dog and decreases in *Bacteroides*, *Lachnoclostridium*, and *Escherichia-Shigella* colonization may be associated with the clinical efficacy of FMT in the Shiba dog.

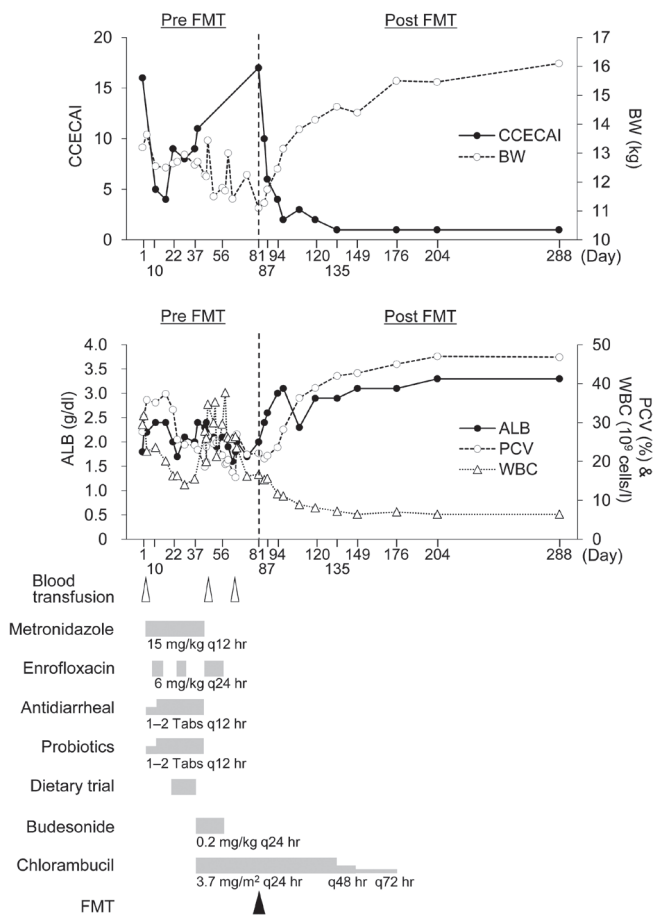


Fig. 1. Changes in canine chronic enteropathy clinical activity index (CCECAI), body weight (BW), plasma albumin levels (ALB), packed cell volume (PCV), and white blood cell counts (WBC) of a Shiba dog that received fecal microbiota transplantation (FMT). Treatments performed, a dietary trial, and administered drugs are shown below the graph.

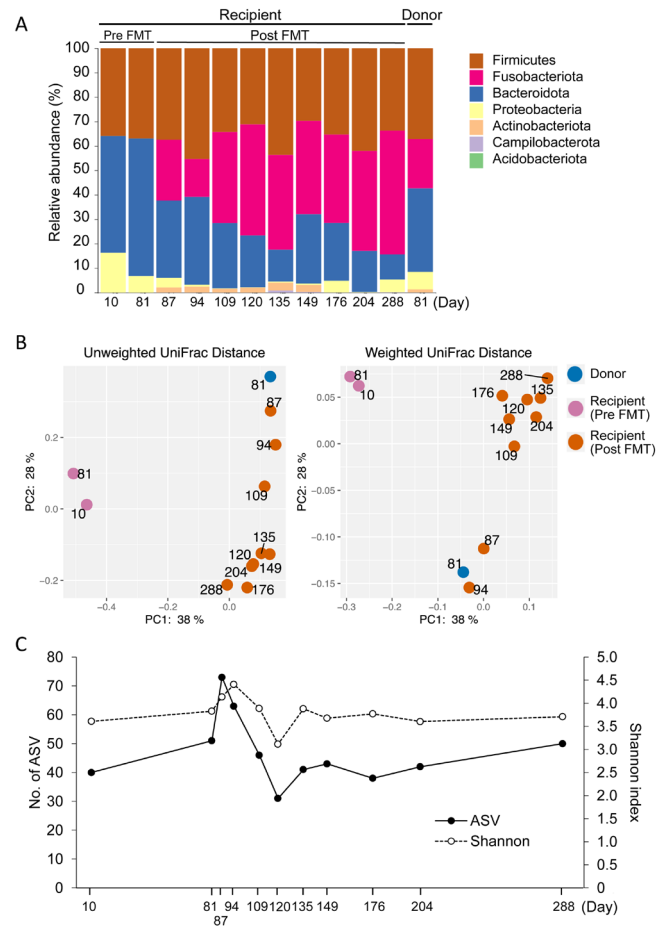


Fig. 2. Compositional changes in the fecal microbiota of a Shiba dog before and after fecal microbiota transplantation (FMT). (A) Composition of the fecal microbiota. (B) Principal coordinates analysis (PCoA) plots based on unweighted and weighted UniFrac distances of the fecal microbiota. The number showed the day. (C) Alpha diversity of the fecal microbiota of the recipient dog. ASV, amplicon sequence variant.

Theoretical guidelines for FMT have been proposed in dogs and cats [5, 23]. However, since clinical data of FMT are limited in veterinary medicine, there is no consensus regarding the effective method and route of fecal administration in dogs. Accumulating evidence indicates that gut microbiota are present more abundantly in the cecum and colon than in the small intestine [8]. We, therefore, performed endoscopic FMT into the cecum and colon after thorough cleansing with saline in this case. As a result, a single FMT induced drastic changes in the gut microbiota and long-term resolution of the clinical and clinicopathological parameters associated with NRE in the dog treated with chlorambucil. Recent reports showed that FMT via rectal enema induced improvement in GI signs and fecal microbiota in dogs with IBD [14, 15]. However, FMT had to be repeated once every 2–3 weeks for months to maintain clinical resolution [14, 15]. For the long-term stabilization of the gut microbiota from the healthy donor, it might be important to select the cecum and colon as the transplant sites and to cleanse the sites thoroughly before FMT in the recipient dog. Further studies are warranted to establish the effective FMT method for long-term management of canine NRE.

Dysbiosis has been reported in dogs with IBD [12, 24, 25]. However, it remains unclear whether dysbiosis is the cause or consequence of NRE in dogs. Since FMT is a direct method for correction of dysbiosis in the GI tract, clinical improvement by FMT suggests that dysbiosis contributes to disease development. In this report, endoscopic FMT changed the gut microbiota and restored the clinical and clinicopathological parameters in the Shiba dog, implying that dysbiosis was the cause of NRE in the dog. FMT may be effective for this type of canine NRE. However, there could be another type of canine NRE in which dysbiosis is the consequence but not the cause of the disease. FMT may not be suitable for this type of NRE. Further investigations are required to prove this hypothesis.

In conclusion, the present case report revealed that a single endoscopic FMT led to long-term recovery of the clinical signs and clinicopathological abnormalities, including hypoalbuminemia and anemia, and dramatic changes in the gut microbiota in a Shiba dog with NRE during the treatment with chlorambucil. The findings in this report suggest that endoscopic FMT into the cecum and colon after thorough cleansing, possibly together with chlorambucil, could be a promising treatment option for canine NRE in

which dysbiosis is associated with disease development. To determine the clinical efficacy and the effective method of FMT for canine NRE, clinical trials should be performed in a larger population of dogs with NRE.

CONFLICT OF INTEREST. Ayaka Shima and Genki Ishihara are employees of Anicom Specialty Medical Institute Inc. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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