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Review Article

Palatability and Clinical Effects of an Oral Recuperation Fluid During the Recovery of Dogs With Suspected Parvoviral Enteritis

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Dogs infected with canine parvovirus (CPV) can develop severe enteritis that requires supportive care until voluntary food and water consumption return. An oral recuperation fluid (ORF) may assist in the overall recovery from CPV. The hypotheses of the study were that dogs with naturally infected CPV would prefer the ORF to water and that dogs consuming the ORF would have a more rapid return to voluntary appetite and improved caloric intake during the initial recovery period compared with dogs consuming water. A total of 28 dogs with CPV were enrolled. Dogs were excluded if voluntary food or water intake was present at the time of study enrollment. Dogs were randomized to either an ORF or water group. The designated fluid was offered twice daily, followed by offering the opposite fluid 1 hour later if the designated fluid was refused. Dogs also received a standardized supportive treatment protocol. Beginning on day 2, all dogs were offered a gastrointestinal diet q8h, staggered with the fluid intake trials. A total of 40% (6/15) of dogs with CPV consumed the ORF as their designated fluid, and 31% (4/13) of dogs with CPV consumed water as their designated fluid ($P = .71$). For those dogs who refused their designated fluid, 56% (5/9) of the dogs consuming ORF ultimately consumed water, and 22% (2/9) of the dogs consuming water also consumed the ORF ($P = .33$). Dogs who consumed the ORF demonstrated a more rapid return to voluntary appetite (median = 1.5 days [range: 1-3]) compared with those that consumed water (median = 4.25 days [range: 1.5-5.5], $P = .01$) or neither fluid (median = 2 days [range: 1.5-5.5], $P = .03$). Additionally, those dogs consuming the ORF demonstrated greater caloric intake [median = 100% resting energy requirement (RER), range: 61%-100%] compared with those that consumed water (median = 19% RER; range: 9%-100%; $P = .004$) or neither fluid (median = 37% RER; range: 3-100; $P = .05$). This study suggests that some dogs with CPV voluntarily consume an ORF during the recovery phase of their illness and that consumption of the ORF may foster a more rapid return of voluntary appetite as well as improved caloric intake. Additional studies are warranted to further assess additional effects of this ORF during recovery from CPV.

Introduction

Canine parvovirus (CPV) replicates in the highly proliferative germinal epithelial cells of the intestinal crypts, resulting in villous atrophy and collapse. Acute enteritis affects the small intestine's ability to maintain fluid and protein balance, subsequently leading to dehydration and hypovolemic shock. Clinical manifestations of CPV are largely related to the gastrointestinal tract and include anorexia, lethargy, vomiting, and diarrhea.[1]

Treatment of CPV-infected dogs is supportive in nature and consists of intravenous (IV) fluids, control of emesis, antimicrobials, analgesia, and early enteral nutrition. Older recommendations for treatment of CPV included withholding of food for 3-7 days, theoretically allowing for a quiescent period as enterocytes undergo repair.[2,3] Subsequent studies found that withholding nutrition in critically ill patients results in increased intestinal permeability and decreased intestinal absorptive abilities.[4-6] A study by Mohr et al concluded that CPV-infected dogs who were administered enteral nutrition 12 hours after the admission exhibited more rapid clinical improvements compared with those that were kept nil per os. Noted improvements in those administered enteral nutrition included improved attitude, faster return to appetite, and decreased length of hospitalization.[7] Current recommendations for treatment of dogs with CPV now include early enteral nutrition to provide enterocytes with the nutrients necessary for intestinal tract repair, regeneration, and function.[8]

The commercially available oral recuperation fluid (ORF) studied here (Viyo Recuperation, Viyo International, Antwerp, Belgium) was formulated to nutritionally assist dogs during the recovery phase of illness. Nutrients contained within the ORF that may aid in gastrointestinal tract healing and integrity include prebiotics, omega 6/3 fatty acids, and the essential amino acids glutamine, arginine, and taurine. Several studies have identified the benefits of these amino acids in intestinal immune function, mucosal morphology, and mucosal permeability.[9-14] The ORF may also encourage voluntary appetite and increase caloric intake, as

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Partial results of this study have been presented in a poster abstract form at the 2015 Colorado State University College of Veterinary Medicine and Biomedical Sciences Research Day in Fort Collins, CO, and the 2015 American College of Veterinary Internal Medicine Forum in Indianapolis, IN.

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demonstrated in healthy dogs recovering from routine surgical sterilization procedures.[15] The postoperative healing period lasts up to 14 days, suggesting that extended administration of supplementation may also be of benefit.[16,17]

This prospective study assessed the palatability and clinical effects of an ORF in dogs naturally infected with CPV. The first hypothesis tested was that dogs recovering from CPV infection would prefer to ingest an ORF when compared to water. Additionally, the authors hypothesized that CPV-infected dogs who consumed the ORF would have an improved clinical outcome, measured as (1) more rapid return of appetite and (2) greater caloric intake during the first 24 hours of voluntary food ingestion, when compared with dogs who consumed water.

Methods

Study Population

The protocol, as described below, was applied to shelter dogs housed in either an open admission shelter ($n = 22$) in north-central Colorado or in the isolation unit at Colorado State University ($n = 6$). Each of the 28 dogs had clinical signs consistent with CPV infection (e.g., lethargy, anorexia, vomiting, diarrhea) and was enrolled following confirmation of CPV antigen in feces using an enzyme-linked immunosorbent assay test (SNAP Parvo Test, Idexx, Westbrook, ME). Dogs were excluded if treatments were administered before study enrollment, if comorbidities capable of affecting the clinical outcome or length of hospitalization (e.g., intussusception, canine infectious respiratory disease syndrome) were detected, if behavioral aggression was exhibited that would prohibit study involvement, or if voluntary appetite or water intake was present at the time of study enrollment. The study was approved by the participating shelter and the Institutional Animal Care and Use Committee (IACUC) at Colorado State University.

Data Collection

Information collected by the shelter staff upon study enrollment included estimated age, sex, estimated breed, and any known medical history (e.g., vaccination or deworming) before shelter ownership. Recorded baseline parameters included body weight, rectal temperature, heart rate, respiration rate, dehydration status using a clinical scoring system,[18] packed cell volume, total solids concentration, blood glucose concentration, and total neutrophil count. Additionally, a clinical severity score (CSS) was assigned using an integrated system of a comprehensive CSS[7] and an internally modified visual analog scale for pain.[19,20] Visceral pain was assessed every 8 hours (q8h) using a modified visual analog scale pain scoring system developed for internal use. Data collected once daily (q24h) included body weight (kg), CSS (0-12), packed cell volume/total solids concentration, and blood glucose concentration. Information recorded every 12 hours included rectal temperature, heart rate, respiration rate, and percent dehydration.

Experimental Design

All dogs were hospitalized in an isolation unit. An IV catheter was placed immediately and if needed, fluid resuscitation was performed at the discretion of the clinician. Once fluid deficits were corrected, maintenance IV fluid therapy was administered at a rate of 120 mL/kg/day using an isotonic fluid (Lactated Ringers Solution, Abbott Laboratories, North Chicago, IL; PLASMA-LYTE, Abbott Laboratories, North Chicago, IL) supplemented with 20 mEq/L of potassium chloride (Potassium chloride, APP Pharmaceuticals, Schaumburg, IL). Dextrose supplementation (Dextrose, Hospira, Inc, Lake Forest, IL) was added to the base fluids of hypoglycemic dogs (≤ 60 mg/dL) to provide a continuous rate infusion of 2.5%-5% dextrose. Colloidal fluids (VetStarch, Abbott Laboratories, North Chicago, IL) were provided if a dog demonstrated elevated heart rate and was unresponsive to isotonic crystalloids or analgesia. Dogs were maintained on IV fluids until demonstration of voluntary food consumption. Once voluntary appetite was observed, the IV catheter was removed and 30 mL/kg of subcutaneous crystalloids was administered q24h until the dog was observed to be drinking consistently. Dogs also were administered cefoxitin (Cefoxitin, Apotex Corporation, Weston, FL) at 22 mg/kg IV q6h and maropitant (Maropitant citrate (Cerenia), Zoetis Inc, Florham Park, NJ) at 1 mg/kg IV q24h while hospitalized. After dogs were voluntarily eating, the antibiotic and antiemetic were administered subcutaneously for an additional 24 hours. Determination of the need for analgesia, additional antiemetics, gastric acid suppressants (Famotidine, West-Ward, Eatontown, NJ), or other rescue interventions was assessed q8h for the duration of the study. These interventions were administered at the discretion of the primary clinician.

Using a computer-generated Excel sheet (Microsoft Excel, Redmond, WA), qualifying dogs were randomized at admission (day 0) to be offered either the ORF or water as the primary oral fluid. Each dog was offered a fixed amount of the designated fluid twice per day at 10:00 AM and 3:00 PM; each fluid offering was considered a “feeding period.” The fluid amount was determined based upon body weight and manufacturer recommendations (10 mL of ORF [or water] if 0-10 kg; 15 mL ORF [or water] if 10-25 kg; 20 mL ORF [or water] if >25 kg). The dog was directly observed, and fluid acceptance (yes/no; minimum of >5 mL) and the volume of fluid consumed (mL) within 5 minutes were recorded. For dogs who did not consume their assigned primary fluid, a crossover trial with the opposite fluid was offered 1 hour later, at 11:00 AM and 4:00 PM. Secondary acceptance (yes/no) and volume consumed (mL) within 5 minutes were recorded. Dogs were maintained nil per os until day 2 of hospitalization, excluding the oral fluid trials, to allow for control of vomiting and nausea before further nutritional interventions.

Beginning day 2 of hospitalization, every 8 hours and staggered with the predetermined fluid trials, dogs were provided a measured amount of gastrointestinal canned food (Hill's i/d, Hill's Pet Nutrition, Topeka, KS). Amount of food provided was based upon the calculated resting energy requirement [RER; $30 \times (BW_{kg}) + 70$]. Food ingested within a 10-minute period was recorded as kilocalories (kcal) consumed. Total amount of kcals consumed in a 24-hour period was also recorded as a daily percentage of RER (%RER). Dogs were discharged from the study 24 hours after restoration of voluntary appetite. At the completion of the study, survival (yes/no), length of hospitalization (days), number of feeding periods until return of voluntary appetite, and caloric intake (%RER) in the first 24 hours following restoration of voluntary appetite were recorded.

Statistical Methods

Descriptive statistics were calculated, and categorical data were expressed as frequencies, whereas continuous data were expressed as median, mean, and range. Preference for the ORF or water, as a primary or crossover (secondary) fluid, was compared using the two-tailed Fisher's exact test. The Wilcoxon rank sum test was used to compare CSS on day 0 between treatment groups. Improvement in clinical outcome was defined by rapidity of appetite return and amount of food consumed within the first 24 hours of appetite return. Rapidity of appetite return was assessed using 3 parameters: (1) number of feeding periods from day 0 until appetite return; (2) number of feeding periods from first day of fluid consumption until appetite return; and (3) probability of eating. Amount of food consumed was expressed as caloric intake (%RER) in the first 24 hours following restoration of voluntary appetite.

Other individual factors potentially associated with these outcomes were also evaluated. These variables included age category (<4 months; 4-12 months; and >12 months), breed categories (toy vs. mixed/large breed), and the following baseline data on day 0: CSS, blood neutrophil count ($\times 10^3/\mu L$) and neutrophil category (below, within, or above reference interval). These variables were screened for associations with the first outcome of interest, rapidity of appetite return, using a univariable survival analysis (Kaplan Meier), and if the *P* value was $< .25$ these variables were included in a multivariable Cox proportional hazards model to control for potential confounding. Time to event was defined as number of feeding periods from day 0 to appetite return or removal from study. Variables were screened for associations with the second outcome of interest, amount of food consumed, using univariable regression analyses, and the Wilcoxon rank sum test, and if the *P* value was $< .25$, these variables were included in multivariable regression analyses. All analyses were conducted with commercially available statistical software (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP). For all analyses, values of $P \leq .05$ were considered statistically significant.

Results

A total of 28 dogs were enrolled between June and November 2014 and were randomized into the ORF ($n = 15$) or water ($n = 13$) group. The breeds estimated by staff included Chihuahua mix ($n = 12$), Labrador Retriever mix ($n = 5$), Shepherd mix ($n = 4$), and 1 each of Pitbull mix, Staffordshire mix, terrier mix, Golden Retriever mix, Husky, Maltese, Pomeranian, Poodle, and Shih Tzu. Dogs presented with similar clinical degree of illness, measured by CSS on day 0. When evaluating baseline CSS measurements between the ORF and water groups on day 0, there was no difference observed ($P = .8$).

Of the 28 dogs, 24 dogs (86%) completed the study, 3 dogs (11%) were euthanized due to deteriorating clinical status, and 1 dog (3%) was removed from the study owing to personal issues, leading to a treatment scoring period being missed. Only 1 dog (randomized to the ORF group but consumed neither fluid) received additional treatments during the study, including famotidine IV (1 mg/kg Q12h on days 4 and 5), hetastarch (2 mL/h on day 4), and 150 mL/kg/day maintenance fluids.

Of the 15 dogs randomized into the ORF group, the ORF was accepted as the primary fluid by 6 of 15 (40%); 5 of the other 9 dogs (56%) voluntarily consumed water as the secondary fluid during the crossover trial. Of the 13 dogs randomized into the water group, the water was accepted as the primary fluid by 4 of 13 (31%); 2 of the other 9 dogs (22%) voluntarily consumed the ORF as their secondary fluid in the crossover trial. When the primary and secondary fluid preferences were combined, 8 of 28 dogs (29%) drank the ORF, 9 of 28 dogs (32%) drank water, and 11 of 28 dogs (39%) drank neither fluid. When the results of the ORF and water groups were compared, there was no difference in which fluid was primarily ($P = .7$) or secondarily ($P = .3$) accepted. Of the 4 dogs (14%) removed from the study, only 1 dog drank either fluid (water or ORF), and that dog was ultimately euthanized.

When evaluating time interval (measured as feeding periods) from day 0 until return of appetite, those 8 dogs consuming the ORF demonstrated faster return to appetite (median = 3.0 periods, range: 2-6) when compared with the 8 dogs who consumed water and completed the study (median = 8.5 periods, range: 3-11 [$P = .005$]), and also when compared with the 8 dogs who drank neither fluid and completed the study (median = 4 periods, range: 3-11 [$P = .03$]) (Fig 1). When evaluating feeding periods from the day of first fluid intake (ORF vs. water) until return of appetite, those dogs consuming the ORF demonstrated faster return to appetite (median = 3.0 periods, range: 2-4) when compared with dogs who consumed water (median = 7 periods, range: 2-10 [$P = .001$]) (Fig 2).

The probability of eating was 15 times more likely if the dog drank the ORF instead of water ($P = .01$). When adjusting for neutrophil counts on day 0, the probability of eating was 4.3 times more likely to occur if the dog drank the ORF instead of water ($P = .1$).

When evaluating %RER consumed in the first 24 hours, the dogs consuming the ORF demonstrated greater caloric intake (median = 100% RER, range: 61-100) when compared with those dogs consuming water (median = 19% RER; range: 9-100; $P = .004$). Dogs consuming neither fluid ingested significantly less calories (median = 37% RER, range: 3-100) during the first 24

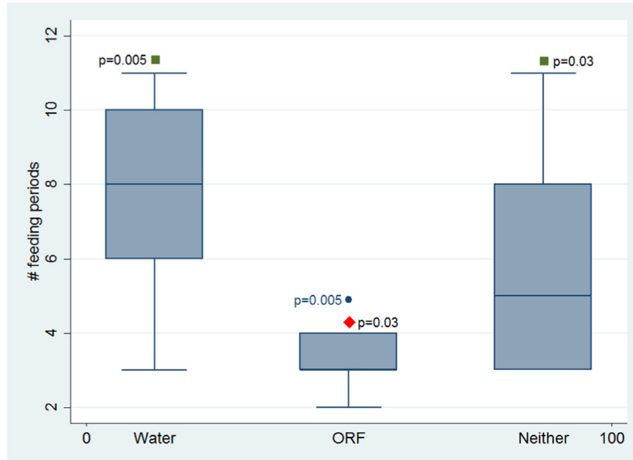

Fig 1. Feeding periods from day 0 until return to appetite. Dogs who consumed the ORF had more rapid return to appetite (median = 3, range: 2-6) compared with dogs who consumed water (median = 8.5; range: 3-11; $P = .005$) or neither (median = 4; range: 3-11; $P = .03$).

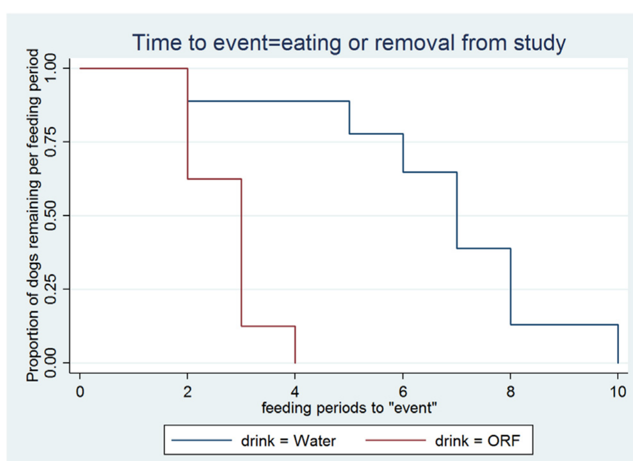

Fig 2. Feeding periods from the day of first ORF or water intake until return to appetite. Dogs who consumed the ORF demonstrated a more rapid return to appetite (median = 3, range: 2-4) compared with dogs who consumed water (median = 7; range: 2-10; $P = .001$).

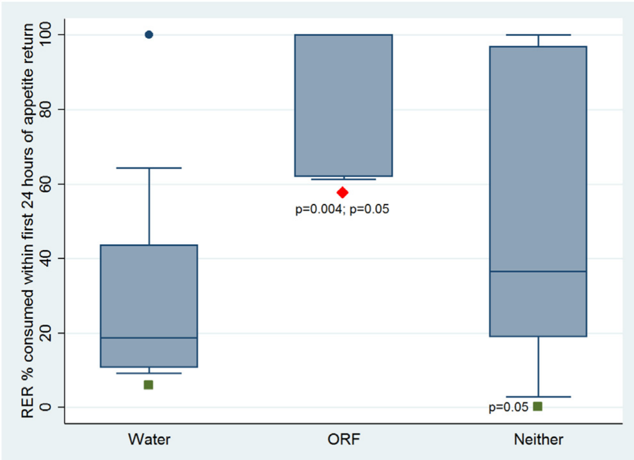

Fig 3. RER (%) consumed in first 24 hours of appetite return among dogs who consumed the ORF, water, or neither fluid. Dogs who consumed the ORF demonstrated a higher RER (median = 100%, range: 61%-100%) compared with those who consumed water (median = 19%, range: 9%-100%, P = .004), or neither fluid (median = 37%; range: 3%-100%; P = .05).

hours of voluntary appetite when compared with dogs consuming the ORF (P = .05) (Fig 3).

When adjusting for neutrophil counts on day 0, and age group, there was no statistically significant difference in %RER consumed during the first 24 hours of appetite return when comparing with those who consumed the ORF, water, or neither. After adjusting for neutrophil group and age group, those who consumed the ORF had a 26% greater %RER intake vs. those who consumed water (P = .29), and a 36% greater %RER intake vs. those who consumed neither (P = .11).

Discussion

The importance of early enteral nutrition during recovery from CPV enteritis has been established in dogs.[7] Dogs with CPV in the current study demonstrated a more rapid return of appetite and greater caloric intake if the ORF was consumed. Some of the dogs consuming the ORF ingested 100% of their prescribed RER within the first 24 hours of appetite return. These data support the use of an ORF during the recovery phase of CPV, as the ORF might help to stimulate appetite return and increase food consumption, which might speed clinical resolution of the disease.

Providing the gastrointestinal tract with essential nutrients assists with local immunity as well as restoration of enterocyte structure and function. Although not evaluated in this study, consumption of an ORF might enhance maintenance of proper hydration status and provide essential nutrients (e.g., glutamine, arginine) that assist with gastrointestinal tract recovery. Glutamine improves intestinal mucosal morphology, enhances GIT immune function, increases enterocyte proliferation, and decreases production of inflammatory cytokines.[9,10,21] Arginine enhances gastrointestinal immune function, supports the intestinal microvasculature, and decreases inflammatory cytokines.[10,21] These amino acids are likely integral to gastrointestinal tract recovery in dogs with CPV and should be investigated in future studies.

Other studies have identified benefits in administering similar solutions in dogs. One study evaluated the use of an ORF in non-CPV dogs with mild-to-moderate dehydration due to hemorrhagic diarrhea.[22] This study found that rehydration therapy was effective and safe in this population. A more recent study, involving a population of healthy dogs undergoing routine sterilization, found that dogs preferred an ORF to water during the perioperative period.[15] In that study, for dogs who demonstrated a preference, 87% of preoperative and 98% of postoperative dogs chose the ORF over water. These studies further support the role of an ORF in the veterinary setting and should be considered for select populations.

The current study documented intake of an ORF or water on a voluntary basis; dogs were not force fed either fluid during the recovery period. It is unknown if provision of an ORF starting at study admission, either through syringe feeding or placement of a nasoesophageal tube, would change the outcome variables of the current study (i.e., faster return of voluntary appetite or greater caloric intake). Additionally, to determine the effect of fluid intake on these variables, dogs in this study were not provided supplemental enteral nutrition. Most veterinary clinicians prescribe enteral nutrition within the first 24-48 hours of hospital admission, either through syringe feeding or feeding tube placement. This study simply offered food 3 times daily, rather than taking a more aggressive nutritional approach. Although this is typical of nutrition management in a high-volume shelter setting, it may not be reflective of nutrition practices in other veterinary hospital settings. Whether there is benefit to continuing the ORF for up to 14 days (as suggested in the postoperative healing period)[16,17] during the recovery from CPV would need to be evaluated in future studies.

Dogs with a normal or high neutrophil count on study admission demonstrated a more rapid return of appetite as well as increased caloric intake. White blood cell parameters on hospital admission have been associated with outcome in dogs with CPV.[23] However, even after controlling for the effects of the neutrophil counts, clinical outcome (rapidity of appetite return and %RER) was still improved, approaching significance, in ORF dogs vs. those who consumed water or neither fluid. The current study only determined CSSs and complete blood count values upon study enrollment and did not follow these parameters through the course of treatment. It would be helpful to track such parameters throughout the hospitalization and determine their association with fluid preference, return of appetite, and caloric consumption.

Age group was significantly associated with %RER; however, age group was not significantly associated with rapidity of appetite return nor probability of appetite return. We consider this a spurious finding of minimal clinical significance, likely due to individual variability within the small sample size.

Other limitations of the current study include those inherent to the shelter population. Historical and medical background (including vaccination and deworming status) was largely unknown for most dogs. Additionally, duration of illness before shelter presentation could not be determined. Dogs were treated with a standard, simplified treatment protocol that could accommodate shelter staffing needs and time constraints. A more standardized patient population, as well as use of a more intensive treatment protocol, may have altered the results of the current study. Additionally, voluntary food intake was only tracked for the first 24 hours following return of appetite. It is unknown if the beneficial effects of an ORF on caloric intake would extend past 24 hours; this could be considered in future studies.

A final limitation was a lack of statistical difference when comparing the number of dogs who ultimately accepted the ORF to the number of dogs who accepted water. This may be due to sample size, a true lack of preference while severely ill, or other environmental or individual factors that affect a dog's fluid preference. Although previous studies demonstrated a preference for an ORF compared to water[15] in healthy dogs, those findings were not repeated in the current study. Patient illness was considerably worse in this setting and likely affected the results. Additional studies that account for patient population size, clinical status of those patients, and treatment interventions would help elucidate whether dogs with CPV would ultimately prefer drinking an ORF compared to water. This preference may vary based upon the phase of recovery as well.

Conclusion

Dogs with CPV that ingested an ORF demonstrated a faster return to voluntary food intake, as well as increased caloric intake during the first 24 hours of appetite return. An ORF may also help with gastrointestinal health during CPV recovery; however, additional studies are warranted to determine its cellular and immune benefits. Clinicians should consider an ORF as part of the larger therapeutic plan when treating CPV to assist with enteral feeding and return of voluntary appetite.

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