JOURNAL OF
Veterinary Emergency
AND Critical Care

Original Study

Journal of Veterinary Emergency and Critical Care **27**(1) 2017, pp 52–65
doi: 10.1111/vec.12561

Evaluation of an outpatient protocol in the treatment of canine parvoviral enteritis

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Abstract

Objective – To compare 2 treatment protocols (standard in-hospital versus modified outpatient) in affecting the duration of treatment or survival of dogs with parvoviral enteritis.
Design – Prospective, randomized study.
Setting – University teaching hospital.
Animals – Client-owned dogs with naturally acquired parvovirus were randomized to receive either an inpatient ($n = 20$) or outpatient ($n = 20$) treatment protocol.
Interventions – Both groups received intravenous (IV) fluid resuscitation and correction of hypoglycemia at hospital admission. Following stabilization, basic inpatient interventions included administration of IV fluids, administration of cefoxitin (22 mg/kg IV q 8 h), and maropitant (1 mg/kg IV q 24 h). Basic outpatient interventions (provided in-hospital) included administration of subcutaneous (SC) fluid (30 mL/kg q 6 h), administration of maropitant (1 mg/kg SC q 24 h) and cefovecin (8 mg/kg SC once). Using daily electrolyte and glucose evaluations, dextrose and potassium supplementation was provided intravenously (inpatients) or orally (outpatients) as indicated. Rescue criteria were used in both groups for analgesia and nausea. All dogs were syringe fed a commercial canine convalescence diet (1 mL/kg PO q 6 h) until voluntary appetite returned.
Measurements and Main Results – Protocol success, defined as survival to hospital discharge, was 90% (18/20) for the inpatient group compared to 80% (16/20) for the outpatient group ($P = 0.66$). There was no difference detected in duration of hospitalization for inpatient dogs (4.6 ± 2 days) versus outpatient dogs (3.8 ± 1.8 days, $P = 0.20$). Metabolic disturbances were frequent in the outpatient group, with 50% of dogs requiring dextrose supplementation and 60% of dogs requiring potassium supplementation.
Conclusions – An outpatient protocol may be a reasonable alternative for dogs that cannot receive standard in-hospital treatment for parvoviral enteritis. Diligent supportive care and monitoring are still required to optimize treatment of dogs with parvoviral enteritis in an outpatient setting.

(J Vet Emerg Crit Care 2017; 27(1): 52–65) doi: 10.1111/vec.12561

Keywords: cefovecin, maropitant, outpatient

Abbreviations

CBC	complete blood count
CPV	canine parvovirus
IP	inpatient protocol
OP	outpatient protocol
PCV	packed cell volume
SC	subcutaneous
TPP	total plasma protein
VAS	visual analog scale

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Funded by Zoetis Animal Health.

The authors declare no other conflicts of interest.

Results of this study have been presented in oral abstract form at the 2013 American College of Veterinary Internal Medicine Forum in Seattle, WA; at the 2013 Colorado Veterinary Medical Association Conference in Loveland, CO; and at the 2014 Colorado State University College of Veterinary Medicine and Biomedical Sciences Research Day in Fort Collins, CO.

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Submitted October 10, 2014; Accepted June 03, 2015.

Introduction

Canine parvovirus (CPV) is a highly contagious, nonenveloped, single-stranded DNA virus from the family *Parvoviridae* that primarily targets the highly proliferative germinal epithelium of the small intestine in young dogs.[1–5] Mortality rates for CPV are reported between 9% for aggressively treated populations and up to 91% for untreated patients.[4,6,7] The standard of care for treatment of CPV involves hospitalization with

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intravenous (IV) fluid therapy to correct and prevent dehydration and hypovolemia. Additional therapies may include antiemetics, antimicrobials, and early enteral nutrition.[4,8]

Hospitalization can be cost prohibitive for owners and may influence their decision to euthanize, or attempt their own version of outpatient protocol (OP) therapy.[9] Veterinarians are often presented with the challenge to provide lower cost care to these dogs while still preserving the doctor-client relationship. The objective of this study was to determine if a veterinarian-based modified outpatient treatment protocol could be used in cases of CPV, and if dogs treated with this protocol would have a similar clinical response to treatment and overall outcome when compared to those managed with an inpatient treatment protocol.

Materials and Methods

This prospective, randomized clinical trial was advertised to the greater area for clients that could not afford hospitalization and treatment of their CPV-affected dogs. Complete enrollment was achieved between June 4 and August 11, 2012. Dogs were considered eligible for study inclusion if they had never received a CPV vaccination, were demonstrating clinical signs consistent with CPV (eg, lethargy, vomiting, or diarrhea), tested positive for CPV via enzyme-linked immunosorbent assay (ELISA),[a] and they had not received any treatment at another veterinary facility. All levels of clinical severity relating to CPV infection were considered eligible for study inclusion. Dogs were excluded from the study if they had identifiable comorbidities upon hospital presentation that could influence outcome (eg, intussception, concurrent infection), displayed a temperament that would affect study participation, or if owners were not comfortable with their dog potentially receiving OP therapy. Informed owner consent was obtained prior to study enrollment. Owners received a verbal explanation from the lead investigators regarding the study goals and how the 2 treatment groups differed prior to enrollment. This was followed up with an explanation in writing on the client consent form. Owners were blinded as to which group their dog was enrolled in until after hospital discharge, but would receive daily status updates. Owners were financially responsible for only the initial examination fee and ELISA parvoviral test. Any costs thereafter related to supplies, treatment, and diagnostics were covered by the study. The protocols used were approved by the Institutional Animal Use and Care Committee prior to study initiation.

Baseline data obtained from each dog included their age, sex, breed, duration of clinical signs prior to hospital presentation, pertinent medical history, baseline vital parameters (eg, temperature, pulse and respiration), hydration status (% dehydration),[10] body weight (kg), physical examination findings, and baseline clinical scoring using 2 systems (a comprehensive clinical severity score and an internally modified visual analog scale [VAS] for pain [Appendix 1]).[8,11,12] Whole blood was collected for a baseline complete blood count (CBC), venous blood gas with electrolytes, and packed cell volume and total plasma protein (PCV, TPP).[b,c] A fecal sample was also collected for double centrifugal fecal flotation using Sheather's sugar solution.[d]

All dogs had a peripheral IV catheter placed at hospital admission, followed by intravascular volume resuscitation with crystalloid fluids,[e] (15–45 mL/kg IV). The volume of resuscitation fluid provided to each dog was determined using clinical examination and the estimated fluid deficit present.[10,13,14] Additional IV fluid resuscitation, using crystalloids or colloids,[f] (2–5 mL/kg IV), could be administered at the discretion of the lead clinician. The type and volume of fluids used during resuscitation was recorded for each dog. If low blood glucose concentration was identified on the initial electrolyte and metabolic panel, a bolus of 25% dextrose[g] (1–2 mL/kg IV)[15] was supplemented based upon the degree of hypoglycemia. The electrolyte panel was then rechecked to confirm resolution of hypoglycemia. External warming was also initiated during cardiovascular resuscitation to maintain a rectal temperature >37.2°C (99°F). Once a dog exhibited adequate improvement in perfusion parameters (eg, heart rate, pulse quality, mentation, mucous membrane color, capillary refill time, plasma lactate concentration) to indicate appropriate stabilization, it was then transitioned into its designated treatment protocol.

Dogs were randomized using a computer-generated program[h] and assigned to either the inpatient protocol (IP) or OP treatment group. All dogs, regardless of treatment group, remained in the hospital for the duration of the treatment protocol. This allowed for close monitoring, daily blood work, and high treatment compliance during the course of both IP and OP treatment protocols.

The IP group, representative of the current standard in-hospital treatment, received IV crystalloid fluids[e] a base rate of 120 mL/kg/day.[10,16] The amount of 120 mL/kg/day was derived from doubling an older version of maintenance fluids (40–60 mL/kg/day) with the intent of providing an adequate initial amount of fluid support across different ages and body weights. Estimated ongoing losses (dictated by the volume and frequency of vomiting/diarrhea) were added to this base rate throughout hospitalization; correction of dehydration using a standard calculation was also performed over the first 24 hours.[16] A standardized dose of 20 mmol/L (mEq/L) KCl[i] was added to maintenance fluids to bring the total to 25 mmol/L (mEq/L) of potassium,

with additional supplementation added as needed using the dog's daily blood potassium concentration and a corresponding chart.[10,17] Additional IP treatments included antimicrobial (22 mg/kg cefoxitin[j] IV q 8 h) and antiemetic (maropitant[k] 1 mg/kg IV q 24 h) therapies. Further treatments could be prescribed according to the primary clinician and subsequently recorded within the medical record. Dogs were first offered a commercial canine convalescence diet[l] (1 mL/kg PO) every 6 hours then syringe fed if they demonstrated no voluntary appetite. Syringe feeding involved placing 1–3 mL of diet at a time onto the tongue and allowing the dog a chance to swallow. When the patient was no longer receptive to this or exhibited any worsening nausea, it was stopped until the next scheduled feeding attempt.

The OP protocol modified the above IP treatments to facilitate potential home administration for future care settings. Outpatient dogs also received 120 mL/kg/day of crystalloid fluids, but route of delivery was 30 mL/kg subcutaneous (SC) every 6 hours. Volume of fluids required to correct dehydration was calculated using the previously mentioned formula; this volume was then divided by 4 and added onto each SC fluid treatment for the first 24 hours. Fluids were primarily administered over the scapular region, alternating between left and right sides. In an effort to maintain simplicity and extrapolation to a true home protocol, ongoing losses were not calculated or provided during hospitalization; additives were also not provided within the fluids. In order to promote SC fluid absorption, rectal temperature was closely monitored every 6 hours and external heat support provided to maintain body temperature >37.2°C (99° F). Additionally, if a large portion or the entire previous dose of SC fluids remained when time for the next treatment, only a partial dose of SC fluids was administered, or fluids were completely withheld. Additional OP treatments included antimicrobial (8 mg/kg cefovicin[m] SC once) and antiemetic (maropitant 1 mg/kg SC q 24 h) drugs. Further treatments could be prescribed according to the primary clinician and subsequently recorded within the medical record. Dogs were first offered a commercial canine convalescence diet (1 mL/kg PO) every 6 hours, then syringe fed if they demonstrated no voluntary appetite, as described previously for the IP group.

Rescue protocols were established for any dog that was determined to have uncontrolled pain or nausea. While maropitant was anticipated to provide some visceral analgesia, pain was assessed using the modified VAS scale every 12 hours, or more frequently if indicated, and buprenorphine[n] (0.02 mg/kg IV for IP, SC for OP) administered once to any dog that exhibited a pain score ≥5.[18,19] This dose could be repeated during hospitalization as numerically indicated by the modified VAS scale. Dogs that exhibited ≥3 episodes of vomiting in a 6-hour period while receiving maropitant were provided a one-time dose of ondanestron[o] (0.5 mg/kg IV for IP, SC for OP). This dose could also be repeated during hospitalization as indicated using the same vomiting criteria. Any additional rescue interventions required approval by the study investigators prior to administration and were subsequently documented in the medical record.

Electrolyte supplementation was provided to both groups based upon results of daily electrolyte panels. Blood glucose concentration could be checked more frequently than every 24 hours if a clinical suspicion of hypoglycemia existed. Glucose supplementation was provided to dogs whose blood glucose concentration was <4.44 mmol/L (80 mg/dL). Hypoglycemic IP dogs received a 25% dextrose bolus IV, followed by an additional 2.5–7.5% dextrose continuous rate infusion within the maintenance fluid bag. Hypoglycemic OP dogs received 1–5 mL of high fructose corn syrup[p] bucally every 4–6 hours.[20] Potassium supplementation was provided to dogs with a potassium concentration <3.4 mmol/L (mEq/L). Hypokalemic IP dogs received an additional amount of KCl added to their maintenance fluid bag, using the previously mentioned sliding scale.[17] Hypokalemic OP dogs received 2 mmol/L(mEq)/4.5 kg of oral potassium supplement[q] every 4–6 hours per package insert instructions. Supplementation of dextrose or potassium was discontinued when electrolyte abnormalities resolved and the dog's voluntary food consumption was consistent to maintain values within the normal range.

For ethical reasons, dogs randomized to the OP group that developed clinical signs severe enough to consider having failed the protocol were subsequently transitioned to the IP protocol. Criteria for OP protocol failure included hyperlactatemia (≥4 mmol/L), decline in mentation (eg, stuporous, obtunded), a fever of >40°C (104°F), and progressive dehydration (defined as loss of ≥10% of body weight admission or after 2 serial measurements of ≥8% dehydration). Any other subjective criteria of concern that would sway the attending clinician toward transition could also be considered, but those justifications had to be clearly documented within the medical record.

For each day of treatment, dogs received a physical examination, CBC, PCV/TPP, and venous blood gas with electrolytes. Data recorded every 24 hours included the results of those tests in addition to the dog's body weight, daily clinical severity score, presence/absence of voluntary appetite, total number of kilocalories consumed, percentage of daily resting energy requirement consumed, total volume of parenteral fluids administered, use of rescue analgesics or antiemetics, and other medications administered. Every 12 hours, each dog's hydration status (% dehydration) and visceral pain score

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were recorded. Every 6 hours, each dog's temperature, pulse, and respiration values were recorded.

Dogs in both groups were considered ready for hospital discharge once vomiting had resolved, they were drinking and euhydrated, voluntary appetite had returned, and CBC parameters indicated a rebound from their neutrophil nadir. Data recorded at hospital discharge for each dog included survival, length of hospitalization, days until clinical severity score was ≤2, days until return to voluntary appetite, total volume of resuscitation (mL/kg) and maintenance fluids (mL/kg/day) administered, amount of hospitalized time documented to have ≥5% and ≥7% dehydration, and percent change in body weight from hospital admission.

Statistical methods

Statistical analysis and graphing was performed with commercially available computer programs.[r,s] Datasets were assessed for normality using Shapiro–Wilk testing. Two-sided *t*-tests, including Mann–Whitney when applicable for non-Gaussian distribution, were used to compare the 2 groups in regards to age, body weight at admission, duration of clinical signs prior to hospitalization, and total duration of hospitalization. Baseline information regarding CBC results (total nucleated cell count, lymphocytes, monocytes, segmented neutrophils, bands, and platelets), blood electrolytes (Na^+, Cl^-, K^+, glucose, and lactate concentrations), PCV/TPP, vital parameters (temperature, pulse, and respiration), clinical severity score, % dehydration, and pain score were also compared using two-sided *t*-tests. Further analysis using two-sided *t*-tests looked at the percentage of hospitalized time dogs were ≥5% and ≥7% dehydrated, volume of resuscitation (mL/kg) and maintenance (mL/kg/day) fluids administered, number of days until clinical severity score was ≤2, total number of hospitalized days of documented hypoglycemia or hypokalemia, as well as number of days until resolution of hypoglycemia or hypokalemia. All tests were evaluated at a 0.05 significance level with no error rate correction for multiplicity.

Fisher's exact test for equality was incorporated when looking at the overall success of a treatment protocol (defined as completion of the assigned protocol, including survival and hospital discharge), the number of dogs that developed hypoglycemia or hypokalemia during hospitalization for each protocol, and the number of dogs that required a rescue antiemetic or analgesic during hospitalization for each protocol. Chi-square testing was utilized to examine pain score results between the 2 groups. To compare any differences in gender between the 2 groups, an adjusted Wald test was incorporated into the analysis. For analysis of potassium supplementation between the IP group and both OP subgroups (treated vs. untreated hypokalemia), ANOVA testing was used to compare the 3 sample groups.

Mixed models were utilized to compare changes over time between the 2 groups, and the effect of treatment over time for those values between the 2 groups [Outcome = $\beta_0 + \beta_1 \times$ day $+ \beta_2 \times$ treatment $+ \beta_3 \times$ day $\times$ treatment $+ \beta_4 \times$ case(treatment)]. Only days 0–4 were analyzed, as those days represented the time when the majority of dogs were still enrolled in the study. Variables analyzed over time using mixed model from day 0 to day 4 included CBC results (total nucleated cell count, lymphocytes, monocytes, segmented neutrophils, bands, and platelets), vital parameters (temperature, pulse, and respiration), clinical severity score, hydration status (% dehydration), maintenance fluids (mL/kg/day), pain score, blood electrolytes (Na^+, Cl^-, K^+, glucose, and lactate concentrations), PCV/TPP, and body weight (kg). Odds ratio testing for neutropenic patients was accomplished using the Breslow–Day test and Cochran–Mantel–Haenszel chi-square test.

Results

A total of 40 dogs total were enrolled in the study over a 9-week period and randomized to receive either the IP ($n = 20$) or OP ($n = 20$) protocol. The IP group included 10 intact males and 10 intact females; the OP group consisted of 10 intact males, 1 castrated male, and 9 intact females. There was no significant difference in gender between the 2 groups ($P = 0.76$). The median age did not differ significantly between the groups ($P = 0.28$). Median age for the IP group was 3.0 months (range 1.5–30 months) and 4.5 months (range 1.75–15 months) for the OP group. The median weight of the IP group was 3.9 (0.89–21 kg) versus 3.8 (1.17–19.59 kg) for the OP group ($P = 0.75$). The median number of days for duration of clinical signs prior to presentation for the IP group was 1.5 (1–4) and 1.0 (1–4) for the OP group ($P = 0.54$). A variety of breeds were represented in the study with the majority of dogs being mixed breed. Dog breeds were categorized into overall groups based upon their predominant breed conformational characteristics. Breeds represented within the IP group included Chihuahuas (4/20, 20%), Pit Bulls (4/20, 20%), Hounds (3/20, 15%), Miniature Poodles (2/20, 10%), Pugs (2/20, 10%), and 1 each of Terrier, Maltese, German Shepherd, Standard Poodle, and Great Dane (1/20, 5%). Breeds represented in the OP group included Chihuahuas (5/20, 25%), Hounds (3/20, 15%), Labrador Retrievers (2/20, 10%), and 1 each of Pit Bull, Siberian Husky, Terrier, Miniature Poodle, Border Collie, Australian Heeler, Maltese, Boxer, and Miniature Pinscher (1/20, 5%).

There was no difference in multiple baseline characteristics assessed between groups at hospital presentation

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Table 1: Baseline measured variables (mean with standard deviation for normally distributed data, and median with corresponding ranges for nonnormally distributed data to a 95% confidence interval) between inpatient and outpatient groups

Measured variable	Inpatient	Outpatient	*P* value
Clinical severity score	6.90 ± 1.65	7.05 ± 2.09	0.80
Dehydration (%)	7.35 ± 1.69	6.40 ± 1.50	0.07
Resuscitation fluids (mL/kg)	24 (22–78)	26.50 (22–90)	0.91
Nausea	0.0 (0–3)	0.5 (0–3)	0.43
Pain	2.85 ± 1.23	2.95 ± 1.05	0.78
Pulse (beats per minute)	142.40 ± 35.43	135.40 ± 30.26	0.50
Respirations (breaths per minute)	47.90 ± 15.97	47.40 ± 14.81	0.92
Temperature (°C)	38.63 ± 0.67	37.97 ± 0.90	0.69
Packed cell volume (%)	45.15 ± 7.10	49.20 ± 10.16	0.15
Total protein (mg/dL)	5.15 ± 0.72	5.60 ± 0.84	0.08
Total nucleated cell count ($\times 10^9$/L)	7.67 ± 5.27	6.78 ± 3.76	0.54
Lymphocytes ($\times 10^9$/L)	1.09 ± 0.63	0.85 ± 0.46	0.17
Monocytes ($\times 10^9$/L)	0.3 (0–1.1)	0.25 (0–1.4)	0.91
Segmented neutrophils ($\times 10^9$/L)	6.06 ± 5.02	5.32 ± 3.74	0.59
Bands ($\times 10^9$/L)	0.0 (0.0–1.2)	0.05 (0.0–1.4)	0.46
Platelets ($\times 10^9$/L)	351.55 ± 126.4	334.30 ± 112.68	0.65
Chloride (mmol/L)	107 (94–111)	106.5 (93–112)	0.50
Glucose (mmol/L) (mg/dL)	6.25 ± 1.51 112.55 ± 27.17	5.58 ± 1.70 100.55 ± 30.59	0.19
Potassium (mmol/L)	3.60 ± 0.41	3.51 ± 0.50	0.52
Lactate (mmol/L)	1.77 ± 0.69	1.80 ± 0.67	0.87
Sodium (mmol/L)	138.30 ± 3.57	139.05 ± 3.49	0.50

(Table 1). Fecal results were available for 29 dogs and only 3/29 (10%) dogs were positive for intestinal parasites. One dog from the IP group had confirmed *Toxicara canis*, and 1 dog from each group had *Cystoisospora ohioensis*-like oocysts (Coccidia).

Overall success rate of the IP protocol was 90% (18/20); 2 IP dogs died during hospitalization due to their disease. Overall success rate for the OP protocol was 80% (16/20) and did not differ from the IP group ($P = 0.66$). Two OP dogs died during hospitalization due to their disease, a third dog was euthanized just prior to imminent cardiopulmonary arrest, and the fourth dog was transferred to the IP group after developing a severe fever and hence qualifying as a failure of the OP protocol. The dog that was transferred to the IP protocol

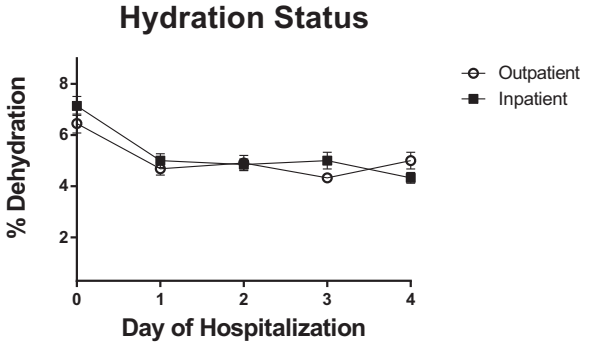

Figure 1: Mean and standard error of hydration status from days 0–4 for both groups. Over this time there was a significant decrease in dehydration for both groups ($P < 0.01$), but no significant difference between treatment groups ($P = 0.29$).

ultimately survived. Mean duration of hospitalization was not significantly different between the IP (4.5 ± 2 days) and the OP (3.8 ± 1.8 days) groups ($P = 0.20$). All nonsurvivors from both groups weighed ≤4 kg. All 4 dogs that failed the OP protocol and 1 IP nonsurvivor were ≤4 months old. Of the 35 dogs that survived, 26 were enrolled in a follow-up nutritional study. Owners were contacted daily for 5 consecutive days for data collection purposes and only 1 dog was lost to follow-up. Twenty-five dogs were reported to be alive and doing well at home at the end of the 5-day follow-up.

While the volume of resuscitation fluids required between the groups at admission did not differ ($P = 0.91$), the volume of maintenance fluids administered during hospitalization was significantly higher for the IP group (135 ± 29 mL/kg/day) compared to the OP group (92 ± 30 mL/kg/day, $P < 0.01$). Despite this finding, there was no clinically appreciable difference in hydration status (determined as % dehydration) between groups during hospitalization (Figure 1). Inpatient dogs were found to be ≥5% dehydrated for 39% of their hospitalization time, versus 35% for OP dogs ($P = 0.72$). Both IP and OP dogs were found to be ≥7% dehydrated for only 10% of their hospitalization time ($P = 0.92$). Overall, dehydration levels decreased significantly ($P < 0.01$) over time for both groups (Figure 1). When evaluating PCV and TPP, there were significant decreases noted for both groups over time ($P < 0.01$ for both values), with PCV showing a more significant decrease over time ($P = 0.01$) in the IP group (Figure 2).

For electrolyte changes, there was a significant change over days 0–4 in both groups regarding glucose ($P < 0.01$), potassium ($P < 0.01$), and sodium ($P = 0.03$) concentrations (Figure 3). Of those, potassium showed a greater increase in the IP group compared to the group over the first 4 days of hospitalization ($P = 0.02$).

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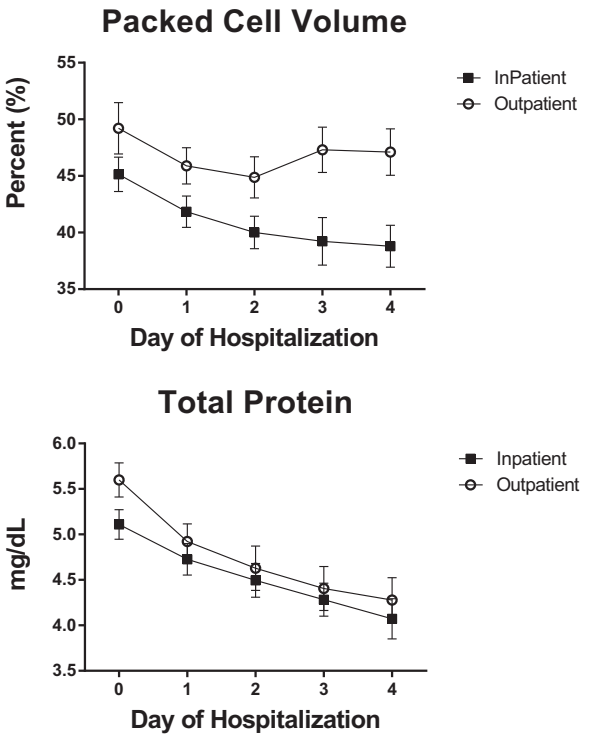

Figure 2: Mean and standard errors of PCV and total protein results over days 0–4 for both groups. Both values showed a significant decrease over days 0–4 within each group ($P < 0.01$), while PCV showed a more significant decrease over time ($P = 0.01$) for the inpatient protocol (IP) group.

Chloride also differed between treatments groups, with the IP group exhibiting a higher rate of increase during hospitalization ($P = 0.03$). Plasma lactate concentration significantly differed overall between the treatment protocols ($P = 0.03$) and between the protocols over time ($P = 0.03$). Overall, the IP group demonstrated lower plasma lactate concentrations compared to the OP group. The OP group showed nearly no changes in lactate concentrations over days 0–2, but then experienced slight increases over days 3–4 (Figure 3).

When reviewing CBC data, there was a significant change over time for lymphocytes ($P < 0.01$), segmented neutrophils ($P < 0.01$), platelets ($P < 0.01$), and monocytes ($P < 0.01$) for both groups. Lymphocytes ($P < 0.01$) and monocytes ($P < 0.01$) increased over time for both groups with a greater overall increase in the OP group compared to the IP group. Nucleated cell counts dropped more significantly over days 0–4 in the IP group ($P = 0.01$, Figure 4). Segmented neutrophils decreased significantly over time for both groups ($P < 0.01$) with a greater decrease seen in the IP group (Figure 4). Lymphocytes ($P = 0.01$), nucleated cells ($P = 0.01$), and monocytes ($P < 0.01$) had a significant difference in numbers between groups over days 0–4 (Figure 4). The average odds ratio between groups indicated that the IP group was 1.8 times more likely to be neutropenic, but this was not significantly different from the OP group for each day ($P = 0.82$) or across the duration of hospitalization ($P = 0.07$). Neutropenia (defined as $<2.6 \times 10^9$/L [$2.6 \times 10^3/\mu$L]) was present in all nonsurvivors at the time of death and in the 1 OP that was transitioned to the IP protocol (Table 2). While bands did noticeably increase in the OP group on day 4, there was no significant difference found compared to the IP group ($P = 0.70$).

When comparing the need for electrolyte supplementation, a higher proportion ($P = 0.04$) of IP dogs (17/20, 85%) required dextrose supplementation when compared to the OP dogs (10/20, 50%). Following dextrose supplementation, resolution of hypoglycemia occurred more rapidly ($P = 0.04$) in the IP group (1.2 days; 95% CI 0.8–1.6) compared to the OP group (2.0 days; 95% CI 1.4–2.6). For potassium supplementation, 10/20 (50%) of the IP dogs required adjustment to the standard 20 mmol (mEq) KCl/L additive in the maintenance fluids, which was not significant ($P = 0.75$) compared to the 12/20 (60%) of OP dogs that required oral potassium supplementation. Hypokalemia in the IP group resolved over 1.5 ± 0.83 days. Of the 12 dogs in the OP group with hypokalemia, 7 dogs were inadvertently not provided oral supplementation, leaving only 5 dogs that did receive treatment. For the 5 OP dogs that did receive supplementation, their time to resolution was 2 ± 0.8 days, versus 2.3 ± 1.0 days for the 7 OP dogs that did not receive potassium supplementation. There was no significance in the amount of time until resolution of hypokalemia between the IP, supplemented OP, and nonsupplemented OP groups ($P = 0.32$).

Rescue medications were used in both groups, but their overall use was low. There was no difference ($P = 1.0$) in the number of IP dogs requiring buprenorphine during hospitalization (4/20, 20%) compared to the OP dogs (3/20, 15%). The OP group had 5/74 total hospital days of buprenorphine use, which was not significantly different to the 10/97 total hospital days required for the IP group ($P = 0.42$). Ondansetron was required for 6/20 (30%) dogs of the IP group and 2/20 (10%) dogs in the OP group during hospitalization ($P = 0.24$). The OP group had 3/74 total hospital days of ondansetron use, which was significantly ($P = 0.02$) lower compared to the 15/97 total hospital days required for the IP group. Additional medications administered at clinician discretion in response to overall patient status were utilized by the IP group only and they included colloids (5/20), famotidine[t] (3/20), mirtazapine[u] (1/20), ampicillin-sublactam[v] (1/20), and Desitin[w] topical (1/20). No OP dogs required additional medications outside the approved protocol.

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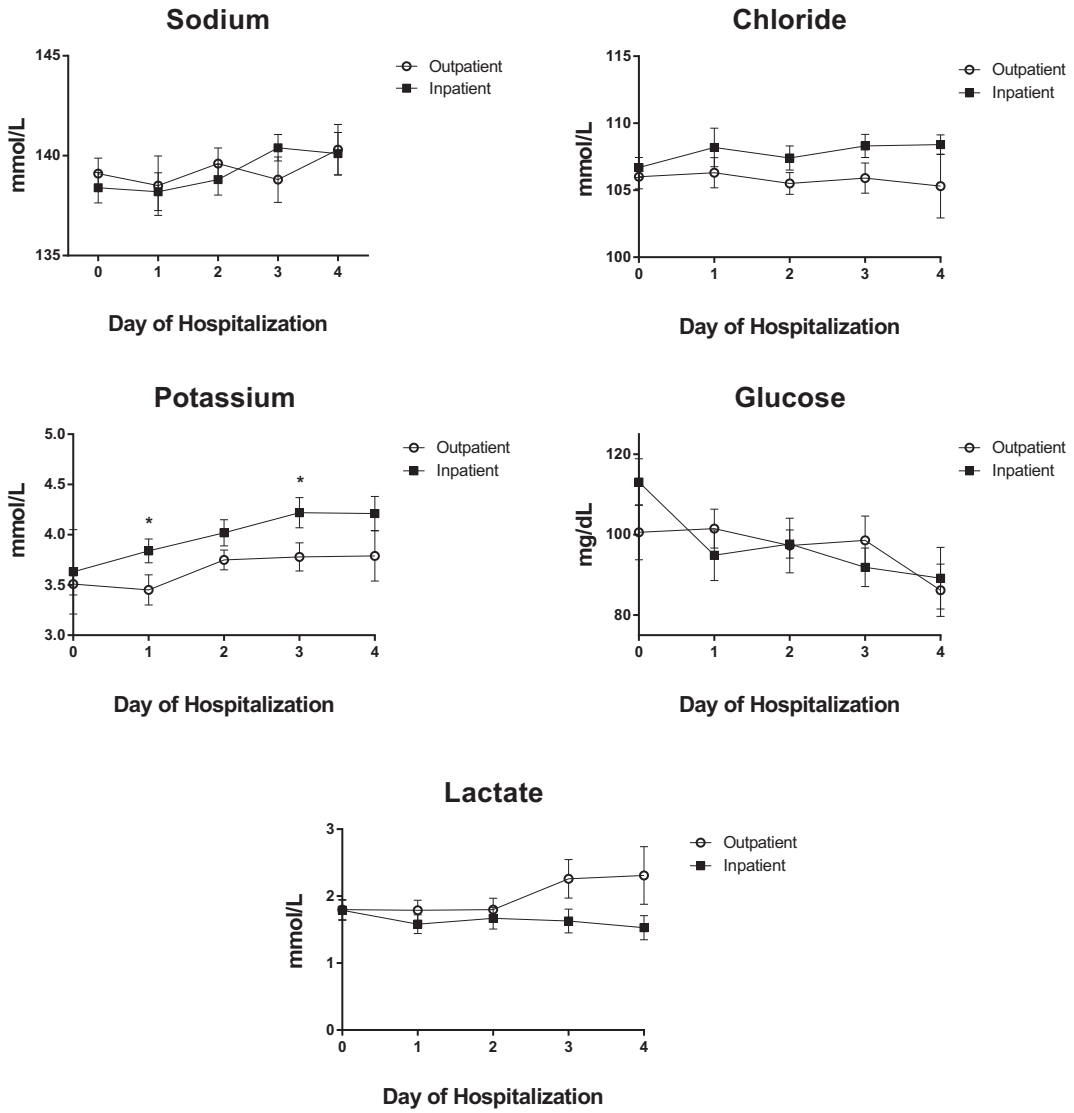

Figure 3: Mean and standard errors of electrolyte results over time for both groups. Sodium concentration ($P = 0.03$), glucose concentration ($P < 0.01$), and potassium concentration ($P < 0.01$) all showed significant changes over days 0–4 regardless of group. Of those, potassium concentration showed a greater increase in the IP group ($P = 0.02$). There was significant difference between both groups for potassium concentration on day 1 ($P = 0.03$) and day 3 ($P = 0.04$) as indicated by $*$. Chloride concentration also differed between treatments groups, with the IP group exhibiting a higher rate of increase during hospitalization ($P = 0.03$). Blood lactate concentration was significantly different between the treatment protocols ($P = 0.03$) and between the protocols over days 0–4 ($P = 0.03$), with a greater decrease observed in the IP group. No significant difference in lactate was found directly between groups on days 3 and 4 via *t*-test analysis.

The total number of kilocalories consumed and percent of resting energy requirements met showed a significant increase over time for both groups ($P = 0.0015$ and $P \leq 0.001$, respectively), but there was no significant difference between the 2 groups.

Discussion

The scientific data available to guide veterinarians on appropriate treatment of CPV overwhelmingly focus on inpatient care, with few evaluated options available for possible OP care in cases influenced by owner financial constraints. To the authors' knowledge, this is the first study aimed to determine if a standardized OP protocol could be applicable to a certain subpopulation of patients that would otherwise be allowed to succumb to the disease at home, or be euthanized due to owner financial constraints.

Analysis of baseline admission data indicated the IP and OP treatment groups were similar across a wide

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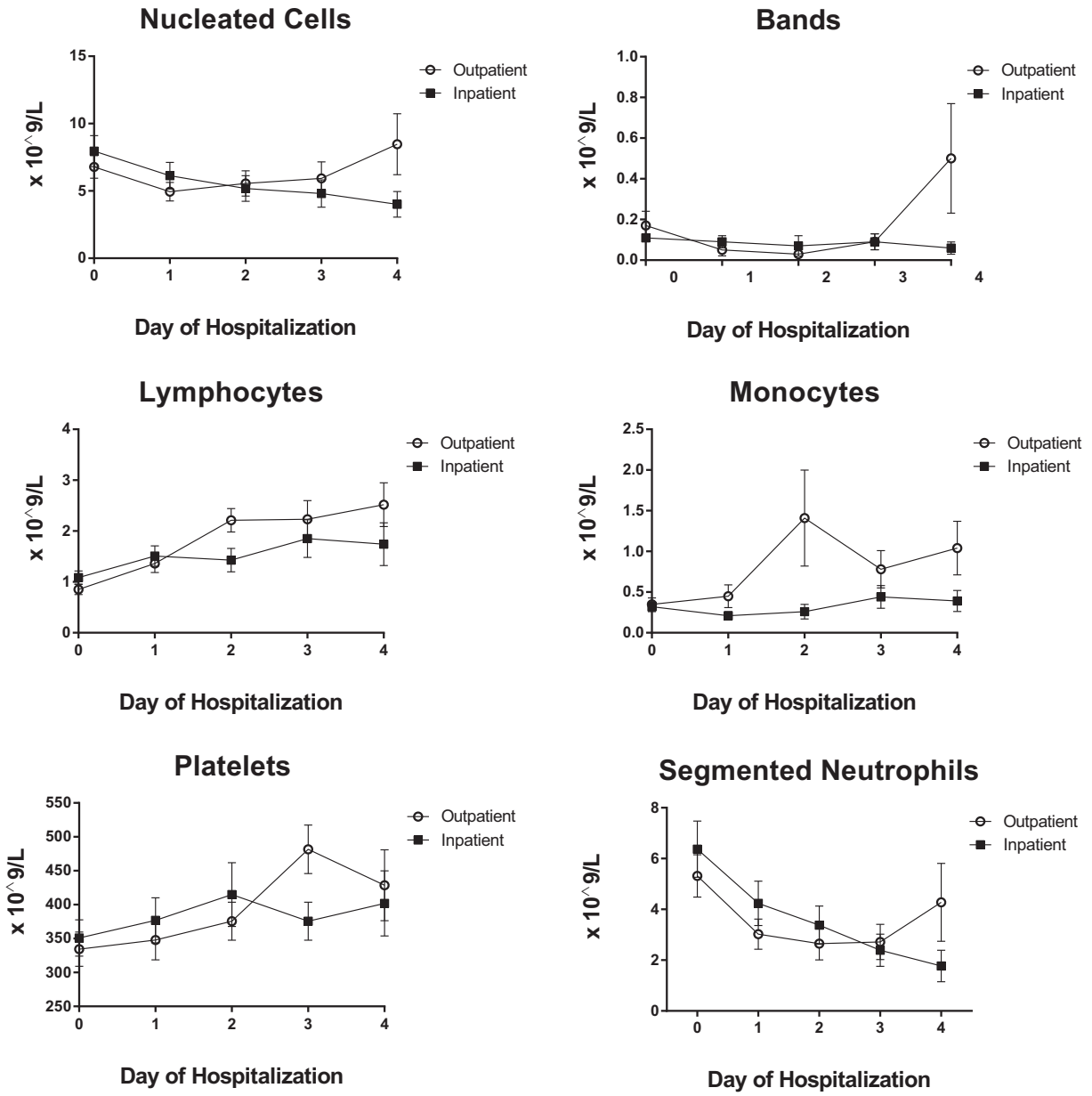

Figure 4: Mean and standard errors of complete blood count results over time for both groups. Lymphocytes ($P < 0.01$), segmented neutrophils ($P < 0.01$), and monocytes ($P < 0.01$) showed significant change over days 0–4 for both groups. Total nucleated cell counts dropped more significantly over days 0–4 for the IP group ($P = 0.01$). The OP group showed a greater increase in lymphocytes ($P = 0.01$) and monocytes ($P < 0.01$) compared to the IP group. For each variable, days in which there was no overlap of standard error bars were assessed via *t*-test and no significant difference between groups was appreciated.

representation of variables at hospital admission. Overall, there was no significant difference between the 2 groups when comparing protocol success, duration of treatment, or quality of clinical recovery (assessed through a number of variables including hydration, pain, and clinical severity scoring). This would suggest that a standardized OP protocol does have the ability to serve as an alternative to standard in-hospital therapy; however, success of an OP protocol still requires diligent monitoring and follow-up assessments by a veterinarian to ensure the dog is responding appropriately and does not require further intervention.

When deciding what patient demographics would be least suited for an OP protocol, our study found that nonsurvivors from both groups all weighed ≤4 kg. Statistical analysis of body weight in relation to protocol

Table 2: Proportion of neutropenic dogs each day of the study compared to total dogs that were either still in the study or had data available for analysis. Inpatients were 1.8 times more likely to be neutropenic but this did not reach statistical significance

	Outpatient group		Inpatient group	
	Neutropenic	Total dogs	Neutropenic	Total dogs
Day 0	3	20	5	20
Day 1	7	19	10	20
Day 2	7	17	8	19
Day 3	8	16	13	18
Day 4	4	7	11	13

success was not possible due to small sample size and variation in breed size. All 3 nonsurvivors from the OP group, as well as the dog that was transitioned to the IP group, were also ≤4 months of age. Again, statistical analysis of age in relation to protocol success was not possible due to the small sample size but trends from this study would suggest that younger dogs or dogs of low body weight may not tolerate OP care and therefore would not serve as ideal candidates for an OP protocol.

Appropriate fluid therapy is necessary for successful management of CPV, regardless of protocol.[4] For both treatment groups, initial IV fluid resuscitation at hospital admission was paramount for stabilizing cardiovascular status and improving perfusion parameters. Absorption of SC fluids is less effective in a severely dehydrated patient due to peripheral vasoconstriction, but if the effort is made to first address the intravascular aspect of hypovolemia and hypoperfusion, improvement for the rate of absorption for future SC fluid administration can be achieved relatively quickly.[16]. The authors believe that maintaining normothermia was an important factor in facilitating absorption of SC fluids, and that close monitoring of rectal temperature with appropriate heat support should be provided in the OP setting. Hypothermic animals can experience peripheral vasoconstriction resulting in decreased SC absorption and dispersion.[10] The importance of monitoring rectal temperature in order to provide appropriate external temperature conditions should be discussed with owners and addressed to meet their individual capabilities (eg, heat lamps, warm water bottles, keeping puppies clean, and dry).

The volume of maintenance fluids administered during treatment was greater for the IP group, likely because this group received additional fluids to replace gastrointestinal losses. Additionally, there were multiple times when fluid administration was decreased or withheld in the OP group due to incomplete absorption. Interestingly, the amount of time that dogs in each group were documented to have ≥5% or ≥7% dehydration was not significantly different. Although a standardized scoring system was used to determine percent dehydration, this is still a subjective measurement based on clinical appearance and percent dehydration was not always scored by the same individual. Areas of SC fluid administration were avoided for skin tent measuring in favor of areas such as the supraorbital region, but lingering fluid pockets could have falsely misrepresented skin tent scoring. Also, given the ordinal nature of the data and their fairly narrow range, being able to find a significant difference with the small number of subjects in this study is difficult. PCV and blood lactate concentration are more objective measurements of hydration and perfusion, respectively. These variables underwent more significant decreases over time in the IP group, suggesting that the IP protocol was more effective in maintaining appropriate fluid balance, despite a lack of difference in hydration status between groups. The OP group did experience a small increase in plasma lactate concentration on days 3–4 of hospitalization, but the clinical relevance of this was unknown. On day 4, 16/20 of the OP dogs were still active in the study with 8 of them registering lactate concentrations above 2.0 mmol/L. Despite this, 4 of those 8 dogs were discharged on day 4 due to improved clinical status, while 1 of the 8 dogs died later that day.

Potassium and dextrose supplementation was frequently required in both groups, indicating a need for close monitoring of blood electrolytes when using either protocol. The IP group displayed a higher incidence of hypoglycemia and subsequently required more dextrose supplementation when compared to the OP group. Hypoglycemia is often regarded as a marker for sepsis that results from decreased intake, decreased hepatic function, and noninsulin-mediated increase in consumption during infection.[15] One study reported 26% of its patient population developed hypoglycemia which is much lower than our study population, especially compared to the IP group.[21] This finding may indicate that, although baseline data found the 2 groups to be similar at hospital admission, the IP group could have been more severely affected by CPV.

Other findings from this study may also support the suspicion of a more debilitated IP group. The number of days until resolution of hypokalemia was equal between the groups, despite the IP group receiving an additional baseline dose of supplemental potassium (20 mmol/L [mEq/L]). While this could reflect high degree of potassium lost through the gastrointestinal tract, consideration for increased diuresis and associated potassium wasting from higher fluid rates cannot be overlooked. IP dogs also received more days of rescue antiemetic use due to increased frequency of vomiting compared to OP dogs. Finally, the OP group showed a greater increase in lymphocyte and monocyte counts during the course of treatment compared to the IP group, and the IP

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group had a statistically greater decrease in total nucleated cell count over time. One study has shown that more severely affected CPV dogs will have a greater decrease in total nucleated cell counts over the first 72 hours and less severely affected dogs will show an increase in lymphocyte counts.[2] If IP dogs were indeed more severely affected during this study, it could have positively biased OP dogs to a more favorable overall outcome (ie, survival). The authors therefore speculate the OP protocol may be more appropriate for less severely affected dogs until larger prospective studies can be performed.

A majority of dogs overall in this study (22/40, 55%) exhibited hypokalemia that required either oral supplementation or adjustments to IV supplementation. Our study showed that oral potassium supplementation can be an effective route of administration in CPV dogs, but also showed that hypokalemia will resolve without supplementation. Withholding supplementation is not recommended by the authors despite our findings due to the potential adverse effects of hypokalemia such as neuromuscular weakness, lethargy, muscle cramps, anorexia, vomiting, decreased bowel motility, respiratory paralysis, and sudden cardiac death. In future situations, it would be reasonable to institute prophylactic potassium supplementation of all outpatients given the high number of dogs that exhibited hypokalemia.

Antiemetic administration is important during the course of CPV therapy and should be included when prescribing an OP protocol. Continuous vomiting caused by CPV serves as a major source of fluid loss and can negatively affects voluntary appetite.[22] Maropitant offers CPV dogs consistent and effective antiemesis that can help decrease ongoing fluid losses. With its once daily dosing, it also provides a convenience factor that is ideal for both inpatients and outpatients. It is labeled for once daily use up to 5 consecutive days due to concerns for accumulation, but 1 study has shown it can be given up to 14 consecutive days in healthy dogs with few to no side effects.[23,24] In the current study, 8 dogs received maropitant longer than 5 days with no adverse effects noted.

Maropitant is not currently labeled for IV use in dogs. Slow IV infusion of maropitant has been researched and is considered safe.[18,19] It also appears to have a faster onset of action than the estimated 45 minutes for the SC route.[25] Pharmacokinetics indicate that the half-life of maropitant is longer for the SC route compared to the IV route, and plasma levels of maropitant are higher after 24 hours for the SC route compared to the IV route.[23] The difference seen in the need for rescue antiemetics between the 2 groups may possibly be related to the pharmacokinetics of the route of administration, but timing of rescue antiemetic administration did not suggest that decreased plasma levels of maropitant would have been a contributing factor to breakthrough vomiting. Following the recommended route of SC administration in an OP protocol was found to be effective in our population.

Maropitant is labeled for use in dogs >8 weeks in age mainly because bone marrow hypoplasia was observed in younger dogs at higher than the recommended doses during clinical trials.[x] Ten dogs from our study, 3 from the OP group and 7 from the IP group, were <8 weeks of age and all received 1 mg/kg doses of maropitant daily. Evidence of bone marrow hypoplasia is difficult to ascertain in these dogs due to the critical nature of their illness and CPV's inherent suppressive effect on the lymphoproliferative tissue of the bone marrow. The greater benefit of maropitant's potency at decreasing emesis and preventing worsening dehydration from gastrointestinal losses in these critically ill dogs was weighed in favor of withholding the drug for bone marrow hypoplasia concerns in our dogs. Overall, maropitant in these younger patients seemed to be well tolerated but clinicians should be cognizant of label warnings when prescribing it to CPV patients. Maropitant has also been found to have some visceral analgesic properties, which may have contributed to the low use of rescue analgesics in this population.[18,19]

All dogs in this study were treated with parenteral antimicrobials due to the risk of bacterial translocation and sepsis. Inpatient dogs received cefoxitin, a cephamycin group cephalosporin that has better efficacy against anaerobic bacteria and gram-negative bacilli than other members of that drug class, and is appropriate for enteric organisms.[25] This antimicrobial is used at multiple dose variations and frequencies of every 6–8 hours depending on the type of infection being treated.[26,27] Our choice of 22 mg/kg IV every 8 hours falls within the acceptable range for treatment of bacteremia. Antimicrobial therapy in the OP group was achieved using cefovecin, a long-acting, injectable third-generation cephalosporin that has good activity against streptococci, *Staphylococcus* species, and gram-negative bacilli.[26] It is given subcutaneously and provides effective plasma levels of the drug over a period of 14 days. While it has been approved for use in skin or soft tissue infections in small animals, its efficacy for treatment of other infection types aside from urinary tract infections is not yet established.[28]

A recent article published after completion of our study showed that cefovecin decreased the overall population of intestinal *Escherichia coli* over the first 72 hours in healthy Beagles, but led to an increase in cefovicin-resistant *E. coli* populations over 28 days. It appeared to selectively favor *E. coli* producing plasmid-borne CMY-2 beta-lactamase that resulted in populations exhibiting cross-resistance to β-lactams. Cefovecin does not provide coverage against *Enterococcus* species and Lawrence et al demonstrated that, while there is an increase in fecal

Enterococci population during treatment with cefovecin due to disruption of normal gut flora, it does not cause an increase in resistant populations.[29] These findings are similar to other studies examining the effects of other cephalosporins on gastrointestinal flora.[30]

The clinical application of these findings is not yet known for critically ill animals, but it does suggest CPV dogs could benefit in the short term over the first 72 hours for treatment of translocation of *E. coli* populations before resistance becomes a possible issue. If the blood-gut barrier is reestablished effectively enough before the 72-hour mark after treatment, then the risk of translocation of resistant bacteria would be less of a concern. Future studies regarding the use of cefovecin in CPV dogs could consider monitoring for development of resistant fecal flora. Cefovecin was chosen for this study because it provides a convenient, one-time injection that owners would not have to repeat at home. While it appeared to provide effective coverage to our OP group, other SC or intramuscular antibiotic therapy options such as cefoxitin may be considered.

Early enteral nutrition was implemented in both groups by offering a commercial canine convalescence diet every 6 hours. If dogs would not voluntarily eat, a syringe was used to place 1–3 mL on the tongue at a time and they were offered a chance to swallow voluntarily. They were syringe fed until the prescribed volume was reached, they refused to swallow, or exhibited any worsening nausea. Providing early enteral nutrition has been shown to decrease intestinal permeability, increase weight gain, and demonstrate earlier clinical improvement when compared to starved CPV patients.[8] No feeding tubes were utilized in order to mimic the type of feeding assistance owners would be able to do at home. Care must be taken when syringe feeding to minimize the risk of aspiration pneumonia or further worsen nausea in CPV patients.

None of the dogs developed complications with syringe feeding and there was no significant difference between the 2 groups in regard to the amount of time before dogs reached full consumption of their prescribed daily caloric requirements. There was also no difference in the percent body weight change between groups, or between admission and discharge within a group. This would suggest that as long as there is proper implementation of fluid and antiemetic therapy, owners could reach a target amount of nutrition to feed their pets at home relatively quickly and enhance the odds of recovery.

There are several important limitations of this study. All dogs, including those receiving OP therapies, received ongoing treatment within a hospital setting with continuous care provided by trained veterinary personnel. This approach was adopted in an effort to fully assess the efficacy of an OP protocol in a controlled setting and ensure treatment compliance for appropriate data collection. The authors understand that the outlined level of care and ability to appropriately monitor or recognize concerning physical exam parameters is not to be automatically expected from every client, and a great deal of time would need to be devoted to client education before a CPV dog could be released for OP care at home. For instance, while SC fluids were prescribed every 6 hours, numerous dogs had not absorbed enough of their previous dose to warrant receiving the next full dose on time, or doses were postponed, and this would be an important point of discussion with owners to recognize at home. Veterinary medicine already provides support for home therapy of conditions like chronic kidney disease and diabetes mellitus. It is feasible that certain owners would be able to grasp the fundamentals of care such as SC fluids, giving oral supplements, syringe feedings and injections for CPV dogs, but selection of the appropriate OP client population should be left to the discretion of the attending veterinarian. If it is determined that clients would not be able to handle such responsibilities, it is reasonable this OP protocol could be adopted by veterinary staff to be done in-hospital for financially restricted clients. The cost savings benefit of this approach would ultimately vary from clinic to clinic based upon individual pricing systems.

A further limitation of this study that may have introduced preferential bias is veterinary personnel were not blinded to which treatment group each dog belonged. Because owner finances did not influence treatment options, and we utilized a rotating staff so that no one individual consistently worked with one group over the other, the authors feel this minimized the chance for preferential bias. Also, nursing staff members were able to fully devote their time to each CPV patient, regardless of the protocol group. Focus for future studies to assess the true effectiveness of this OP protocol could involve a shelter setting, or sending client-owned dogs home to receive their supportive care while still obtaining daily, follow-up veterinary care (eg, brief examination, assessment of blood glucose, electrolytes, and PCV/TPP) to document progress. Repeat monitoring and assessments by veterinary personnel over a period of days could still become cost restrictive to many clients, but the authors would consider this approach to be best-practice in order to ensure dogs are responding appropriately to therapy. If a dog is not responding well to OP treatment, immediate transfer to a hospitalized setting or euthanasia might be indicated. When considering differences in treatment costs between the 2 study groups, specific data were not collected but we estimate that strict adherence to our OP protocol over 4–5 days of treatment would be roughly a third of the cost as compared to the expense of in-hospital care at our facility.

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A lack of statistical significance between the 2 protocol groups when evaluating a number of outcome variables is likely a reflection of the small sample size. The decision to enroll a total of 40 dogs was based upon a power calculation expecting 90% success using the IP protocol and 50% success using the OP protocol. The unanticipated survival of a majority of OP dogs likely contributed to a subsequent lack of statistical difference in protocol success. Twenty dogs in each group is a meaningful number by clinical standards, but it may have inhibited the ability to more accurately assess the protocol if the OP group was less severely affected by CPV than the IP group, and therefore survival may have been positively biased for the OP group. This possible limitation, along with the demographics of dogs that did not survive, would support the notion that an OP protocol would preferentially be considered as a cost-conscious alternative for CPV dogs that are older (>4 months), of higher body weight (>4 kg), and less severely affected by CPV.

In conclusion, an outpatient treatment protocol for CPV performed well in a controlled setting when compared to a standard in-hospital protocol. Although outpatient care should not be considered an automatic substitute for in-hospital treatment, it may be considered as a cost-conscious alternative in older dogs with less severe cases of CPV that have owners who can commit to the responsibilities of care. Regular examination by a veterinarian, diligent supportive care, and routine monitoring of blood work is still required to optimize treatment success.

Acknowledgments

That authors would like to thank Dr. Karen Copeland, for her assistance in statistical analyses.

Footnotes

[a] SNAP Parvo Test, Idexx, Westbrook, ME.
[b] Advia 120 Hematology System, Siemens Healthcare Diagnostics, Inc, Newark, DE. Manual differentials using Wright-Geimsa stain was verified by a DACVP.
[c] ABL 800 Flex Blood Gas Analyzer, Radiometer, Bronshoj, Denmark.
[d] Sheather's sugar solution, Jorgensen Labs, Loveland, CO.
[e] Normosol-R, Abbott Laboratories, North Chicago, IL.
[f] Hetastarch, Abbott Laboratories.
[g] Dextrose, Hospira, Inc, Lake Forest, IL.
[h] Microsoft Excel, Redmond, WA.
[i] Potassium chloride, APP Pharmaceuticals, Schaumburg, IL.
[j] Cefoxitin, Apotex Corporation, Weston, FL.
[k] Maropitant citrate (Cerenia), Pfizer Animal Health, New York, NY.
[l] Hill's a/d, Hill's Pet Nutrition, Topeka, KS.
[m] Cefovecin sodium (Convenia), Zoetis Inc, Kalamazoo, MI.
[n] Buprenorphine, Reckitt Benckiser Pharmaceuticals, Inc, Richmond, VA.
[o] Ondansetron, West-Ward, Eatontown, NJ.
[p] Karo simple syrup, ACH Food Companies, Inc., Memphis, TN.
[q] Tumil-K (potassium gluconate),Virbac Animal Health, Fort Worth, TX.
[r] JMP Pro 10, SAS Institute, Cary, NC.
[s] GraphPad Prism Version 6.04, GraphPad Software, Inc, San Diego, CA.
[t] Famotidine, West-Ward.
[u] Mirtazapine, Aurobindo Pharma USA, Inc, Dayton, OH.
[v] Ampicillin-Sublactam (Unasyn), West-Ward.
[w] Desitin, Johnson&Johnson, Skillman, NJ.
[x] Freedom of Information Survey. Original New Drug Survey NADA 141–263; Pfizer, Inc, Cerenia; January 29, 2007.

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Appendix 1: Internally modified VAS pain score criteria

Score	Interpretation	Description
0	No pain	• Displaying normal behavior • Running, playing, eating, jumping, walking normally • Affectionate response to caregiver • Normal heart rate
1	Maybe mild discomfort	• Appears to be normal, but condition is not as clear cut as above • Heart rate may be normal or slightly increased due to excitement
2	Mild discomfort	• May have difficulty jumping or rising, or resist palpation of the abdomen, but otherwise shows no other signs of discomfort • Not depressed • Respiratory and/or heart rate may be increased • Wags tail during interaction with caregiver
3	Mild pain or discomfort	• Guards abdomen (may be slightly tucked up) • Slightly depressed • Cannot get comfortable or may tremble or shake
4	Mild to moderate pain	• Painful abdomen, or pain when stretching legs • Looks, licks, or chews at the painful area • Sits or lies in the abnormal position and not look relaxed • Trembles or shakes • Respiratory rate may be increased or shallow • Whimpers • Slow to rise or unable to jump • Tail hangs down • Somewhat depressed in response to caregiver
5	Moderate pain	• Depressed and reluctant to move • Maybe or attempt to bite when the caregiver approaches the painful area • Trembles or shakes with the head down • May vocalize • Painful abdomen • Ears may be pulled back • Lies down but doesn't really sleep
6	Increased moderate pain	• Vocalizes or whines frequently without provocation and when attempting to move • Heart rate and respiratory rate may be increased. May take deeper breaths • Pupils may be dilated

(*Continued*)

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Score	Interpretation	Description
7	Moderate to severe pain	• Includes signs from 5 and 6 • Very depressed and not concerned with its surroundings but usually responds to direct voice • Urinates and defecates without attempting to move • May cry out spontaneously or continually whimper. Occasionally, an animal at level 7 does not vocalize.
8	Severe pain	• Signs as for level 7 • Vocalizing may be more of a feature, or the patient is so consumed with pain that it does not notice another presence and just lies there • May thrash around in the cage intermittently
9	Severe to excruciating pain	• As in level 8, but patient in hyperesthetic • When any part of the body in proximity to the abdomen is touched, the patient trembles involuntarily due to severe inflammatory pain
10	Almost comatose	• As in level 9, but patient emits piercing scream or is nearly comatose • Hyperesthetic/hyperalgesic • The whole body is trembling, and pain is elicited wherever the patient is touched

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