

A Pilot Study to Assess Tolerability of Early Enteral Nutrition via Esophagostomy Tube Feeding in Dogs with Severe Acute Pancreatitis

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Background: The putative role of the gut in amplification of systemic inflammation in acute pancreatitis is gaining credence, and intraluminal nutrition has been shown to decrease inflammation in experimental models of pancreatitis. Prepyloric feeding often is used in people with acute pancreatitis, but has not been evaluated in dogs.

Hypothesis: Early intervention with enteral nutrition (EN) delivered proximal to the pylorus will be well tolerated in dogs with acute pancreatitis and provide justification for further larger trials.

Animals: Ten dogs with severe acute pancreatitis in an open-label, prospective pilot study.

Methods: Dogs were treated with plasma transfusion and standard care, and then consecutively assigned to receive either EN via esophagostomy tube feeding or parenteral nutrition (PN). Outcome was used to determine optimal study size for future studies, and complications were compared between the 2 groups.

Results: A significantly greater number of vomiting or regurgitating episodes occurred in dogs receiving PN. The dogs receiving EN did not demonstrate any noticeable postprandial pain. There were more catheter-related complications in the PN group. There was no difference in outcome between the 2 treatments, and 43 dogs for each treatment would be required in future studies to determine a difference in outcome.

Conclusions and Clinical Relevance: Early EN delivered proximal to the pylorus is well tolerated in dogs with severe pancreatitis and resulted in fewer complications than PN. Prospective trials in a larger cohort are justified to fully establish the potential benefit of early EN, preferably compared with minimal enteral nutrition.

Key words: Nutrition-small animal; Pancreatic necrosis; Total parenteral nutrition.

Acute pancreatitis has a high mortality rate in dogs, and surviving animals often require intensive treatment and hospitalization.^{1–3} Apart from general recommendations regarding correction of fluid, electrolyte, and acid-base abnormalities, there remains a paucity of information regarding specific management of acute pancreatitis in dogs.

Nutritional management of acute pancreatitis is difficult because of the presence of substantial catabolism, pancreatic necrosis, increased metabolic demands, and complications of ileus.⁴ Historically, the nutritional recommendation for management of acute pancreatitis has been “strict pancreatic rest,” in the belief that fasting results in no feedback that will further stimulate exocrine pancreatic secretion, thus protecting against autodigestion to some extent.² However, this theory has been

Abbreviations:

EN	enteral nutrition
PN	parenteral nutrition

questioned, because it has been extrapolated from studies of healthy people and has not been proven in dogs. In fact, 3 experimental studies have suggested that there is minimal to no negative pancreatic feedback in dogs given nutrition in both the jejunum and duodenum.^{5–7} It also has been demonstrated in experimental models in rodents and in people with naturally occurring disease that exocrine pancreatic secretion is in fact decreased during pancreatitis, and the decrease is most prominent in severe inflammation.^{8,9}

In people and in studies using animal experimental models, fasting leads to intestinal mucosal atrophy, increased rate of enterocyte apoptosis, decreased glutamine and arginine transport, changes in mucin composition of goblet and deep crypt cells, and a breakdown in the intestinal barrier resulting in increased intestinal permeability.^{10–14} Additionally, the gut itself may either start or contribute to the systemic inflammatory response in acute pancreatitis.¹⁵ Intraluminal nutrition is the most potent stimulator of intestinal mucosal regeneration because of stimulation of growth factors and mucosal blood flow. In addition, enteral nutrition (EN) may decrease splanchnic cytokine production, modulate the acute phase response, decrease catabolism, and preserve protein.¹⁶

Experimental models of pancreatitis in dogs have shown a benefit of early intraluminal nutrition compared with parenteral nutrition (PN) in decreasing bacterial

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translocation and down-regulating the severity of inflammation.^{17–19} There also have been several clinical trials in people demonstrating benefit in early EN compared with PN for treatment of acute pancreatitis, with fewer infectious complications, and in severe cases improved outcome and decreased length of hospitalization.^{20–27} However, meta-analysis of these studies does not show a clear benefit of early EN compared with PN, and there are no well-constructed randomized-controlled trials comparing EN to nothing PO.^{20,26} More recent studies in people also suggest that gastric feeding (rather than jejunal) is well tolerated and safe, with no exacerbation of pain.^{24,25,27}

A previous paper determined that there was no statistical difference in the indirectly measurable pancreatic response to diets of variable fat content in healthy dogs.²⁸ This, along with the changing paradigm of feeding in people with severe acute pancreatitis, formed the background to this pilot study evaluating the tolerability of giving EN proximal to the pylorus in dogs with severe pancreatitis.

Materials and Methods

Animal Selection

Ten dogs with a diagnosis of acute pancreatitis were recruited into the study within 12–24 hours of admission to Murdoch University Veterinary Hospital. The study was approved by the Murdoch University Animal Ethics Committee. Informed, signed owner consent was obtained.

The diagnosis of acute pancreatitis was based on a combination of clinical signs (abdominal pain, vomiting), serum canine pancreatic lipase > 200 µg/L and, in all dogs, the presence of appropriate pancreatic changes on abdominal ultrasonography performed by a board-certified radiologist with a curvilinear 8 MHz or linear 15 MHz probe.^a These ultrasonographic changes included diffuse enlargement of the pancreas, hyperechoic mesentery surrounding the pancreas, and variable pancreatic hypoechogenicity as published previously.^{1,29,30} Dogs were excluded if other disease that could cause secondary pancreatic inflammation, such as septic peritonitis or pancreatic neoplasia, were evident during or after completion of the study, with a follow-up period of 2–4 years. Dogs had to weigh > 10 kg to comply with the volume of blood sampling required, and not have concurrent diabetic ketoacidosis. Only dogs that showed substantial consequences of their disease (eg, dehydration, pain, hypovolemia, persistent vomiting, other systemic effects) necessitating hospitalization and IV fluid therapy were recruited.

Initial Patient Assessment and Treatment

Historical and clinical information including signalment, potential inciting factors, previous medical history, physical examination findings, days of clinical illness preceding admission, days fasting, and the clinical severity score as published previously were recorded for each dog on admission (Day 0).³¹ After recruitment into the study, all dogs had baseline hematology, biochemistry (including glucose, cholesterol, lipase, and amylase), electrolytes, and urinalysis performed.

All dogs received IV fluid therapy (with crystalloids with appropriate electrolyte supplementation) calculated to correct dehydration and ongoing losses on an individual basis. Antiemetic medication (metoclopramide,^b 1–2 mg/kg/d constant rate infusion) and analgesia (including fentanyl continuous rate infusion and patches, methadone, tramadol, lignocaine continuous rate infusion,

and morphine via epidural) also could be administered based on individual requirements. These treatments were initiated before inclusion into the study for all dogs. Within the first 12 hours of admission to the study, a nasoesophageal feeding tube was inserted and a low-rate (0.5 mL/kg/h) infusion of a balanced electrolyte solution^c was started in all dogs. Fresh frozen plasma (10 mL/kg/d) was administered to each dog for the first 2 days of the study. Antibiotics (ampicillin^d 25 mg/kg IV q8h and metronidazole^e 10 mg/kg IV q12h) were to be given if dogs had a neutrophil count < 2.0 × 10⁹/L or a left shift in combination with pyrexia (rectal temperature > 39°C), unless another specific indication was present. Additional antiemetic (prochlorperazine^f) therapy could be administered if clinically indicated.

Treatment Groups

Dogs were consecutively assigned to 1 of 2 treatment groups, PN or EN via esophageal tube feeding within the first 12–24 hours of admission, as described below. The first 24 hours of the study protocol was designated Day 1, with continuation in the study until the end of Day 3. After that time, treatment decisions including nutritional intervention were based entirely on individual dog requirements and not on the basis of the treatment assignment during the study.

All dogs were anesthetized with IV alfaxan^g (1–2 mg/kg) and inhalational isoflurane^h with full anesthetic monitoring. A brief endoscopic examination of the esophagus was performed to subjectively assess the presence of moderate to severe esophagitis, to account for esophagitis as a confounding factor for causing regurgitation or lack of tolerability for EN in individual dogs. This was done both at the time of the endoscopy and retrospectively with blinded review of the recordings by two of the authors (C.S.M., F.E.J.).

The dogs receiving PN had double-lumen jugular 16 G catheters inserted under sterile conditions and the dogs then were recovered from anesthesia. PN administration was started within 2 hours of anesthetic recovery, at a rate of 50% resting energy requirements (RER) on Day 1 and 100% on Day 2. For every 100 kcal of calculated RER, an additional 4 g of protein (14 kcal) was added. This meant that 17.5% of the calories were supplied as lipid and 70.2% as 50% dextrose, along with 12.3% amino acid solution. Full asepsis was used when checking the jugular catheter site daily.

The dogs receiving EN had large gauge (14–16 Fr) single lumen feeding tubes inserted in the esophagus and secured externally before recovery from anesthesia. Dogs were fed within 2 hours of recovery. A total of 1/3 of their daily calculated calories (RER × 1.25) was fed, divided every 6 hours on Day 1, 2/3 on Day 2, and 100% on Day 3. They were fed a low-fat commercial dog foodⁱ with a fat content of 1.7% (1.9 g) per 1,000 kcal. This diet was supplemented with commercial enteric-coated pancreatic enzymes^j at 5,000 U/feed if body weight < 15 kg, 10,000 U/feed body weight 15–30 kg, or 25,000 U/feed if body weight > 30 kg. Medium chain triglyceride oil^k (C₈ and C₁₀ fatty acids composition > 95%) also was supplemented at 1.0 mL/kg/d in divided doses, as established in a previous study to minimize pancreatic response.²⁸

Monitoring

Full daily clinical records were kept for each dog, including results of physical examination, clinical severity score as published previously, presence of any complications, vomiting, or regurgitation events (these were not differentiated as they were not always observed), baseline clinicopathologic data, and body weight.³¹ Daily pain score by 1 of 2 authors (C.S.M. or F.E.J.) was recorded from admission until Day 3, and used to modulate analgesic therapy. The pain score ranged from 0 to 10, adapted from previously published criteria, with a score of 2 indicating mild discomfort,

7 moderate to severe pain, and 10 severe pain causing substantial alterations in mentation.³²

Blood was collected into plain and EDTA containers daily via cephalic or jugular venipuncture before the start of nutritional support at admission into the study (Day 1) until completion of study (Day 3) in all dogs and on Day 1, 5–10 minutes after the 1st feed in the EN dogs. Blood was collected into chilled tubes, stored on ice to allow clotting and then centrifuged at 10°C at 5,000 rpm for 5 minutes before harvesting sera or plasma and storing at –18°C.

Serum samples were shipped on dry ice for measurement of canine trypsin-like immunoreactivity^l (cTLI), canine pancreatic-specific lipase^m (s-CPL), and C-reactive proteinⁿ (CRP), which all were measured at the same laboratory by enzyme-based assays that have been validated previously in dogs.^{33,34} Reference intervals for these markers in dogs are 5.7–45.2, 0–200 µg/L, and 0–7.6 mg/L, respectively. Frozen plasma and serum samples were transported for measurement of gastrin^o at a local laboratory. A previous study had established a reference range for gastrin in healthy dogs of <5–16 pg/mL and results <4.77 pg/mL were recorded as 4.77.²⁸ Additional aliquots of serum were shipped on dry ice for measurement of serum pancreatic elastase-1 (PE-1).^p Gastrin, cTLI, and s-CPL were measured at all time points in all dogs. CRP and elastase were measured at all time points, except the postfeed sample in dogs from the EN group.

Statistical Analyses

Differences in clinical severity scores, esophagitis, duration of clinical signs preceding hospitalization, and blood marker concentrations (cTLI, s-CPL, gastrin, CRP, and PE-1) between the 2 treatment groups at admission were assessed by 1-way ANOVA analysis. The number of vomiting or regurgitation episodes and the number of days each animal was hospitalized both were analyzed by a Poisson model for an effect of treatment. Significance of the estimated β -coefficient was determined at $P < .05$. The β estimate was exponentiated to determine the ratio of the incidence of events. The proportion of dogs surviving after each treatment was compared by Fisher's exact test with significance determined at $P < .05$ by a 2-sided probability. In the face of a nonsignificant result, the sample size required to prove this difference with 95% confidence interval at a statistical power of 80% was determined. PROC GENMOD and PROC FREQ were used for all analysis.^q

Results

There were 4 neutered females and 6 neutered males in the study. The median age was 7 years, with a range of 2–11. The median body weight was 26.1 kg, with a range of 14.8–48.6 kg. There were 3 cross breeds and 1 each of Siberian Husky, Beagle, Bull Terrier, Weimeraner, Golden Retriever, Border Collie, and Rhodesian Ridgeback. All dogs that survived this episode ($n = 9$) were still alive at 2-year follow-up, some up to 4 years. No dog received PN after the initial 3-day period. One dog had hyperlipidemia on admission that persisted after recovery, and required ongoing management, and may have contributed to the development of acute pancreatitis. This dog received EN. No underlying cause was definitively identified in the other 9 dogs, but dietary indiscretion was suspected in 2. No abnormalities in serum glucose concentration were present in any dog at any time point. All dogs had serum canine pancreatic lipase >300 µg/L, with 8 having concentration >800 µg/L. The median, mean, and range for clinical severity score, duration of signs before admission into the study, serum C-RP

concentrations, and concentrations for gastrin, cTLI, PE-1, and s-CPL are presented in Table 1. There was no significant difference between treatment groups for any of these variables.

All dogs in the EN group survived, whereas 1 dog in the PN group died. The proportion surviving was not different between treatments ($P = 1.0$). Using this result of a binomial proportion of survival of 5/5 versus 4/5, the calculated sample size to conclude a difference with 95% confidence interval (at 80% power) would be 43 in each group. If the number of controls (PN) versus treated (EN) was 2 : 1, the sample size required decreases to 35, with 70 controls.

Adverse reactions or complications occurred in 3 dogs in the EN group, but were considered mild or short term. These included abdominal pain refractory to increasing analgesic modalities for the first 36 hours of the study (1 dog), urinary tract infection (1 dog), pyoderma (1 dog), and esophagostomy tube site infection (the same 3 dogs). The tube site infections were considered mild except in the 1 dog that had preexisting severe pyoderma. Discontinuation of tube feeding was not required in any dog. The 3 dogs in this group with documented infection all received cephalexin.^f The dog with refractory pain (pain scores were Day 0: 8, Day 1: 4, Day 2: 1) did not demonstrate any exacerbation of the pain after tube feeding, and the pain decreased substantially by Day 2. Analgesics used in this dog initially were buprenorphine, then methadone along with fentanyl continuous rate infusion, and then combined fentanyl and lignocaine continuous rate infusion. Analgesia was not necessary after Day 3. In the PN group, jugular phlebitis occurred in 4 dogs, with 1 severe enough to cause caval syndrome and require removal of the catheter on Day 3. One dog had refractory abdominal pain and a pancreatic pseudocyst that developed after the treatment trial had been completed (Day 4) and required percutaneous ultrasound-guided drainage. The dog in this group that died developed extrahepatic bile duct obstruction and pleural effusion. One dog had no complications.

In the EN group, only 1 dog had 3 episodes of vomiting or regurgitation over 7 days of hospitalization, whereas in the PN group 3 dogs had 33 episodes (1 had 22 in 6 days of hospitalization, 1 had 9 in 10 days, and 1 had 2 in 5 days). There was a significant effect of treatment on the number of vomiting or regurgitation episodes ($P < .001$), with the ratio of the incidence of episodes for parenteral versus EN estimated at 11.0 (95% confidence interval 3.4–35.8).

Discussion

This pilot study supports the notion that early EN delivered proximal to the jejunum is well tolerated in dogs with severe pancreatitis. It may also be considered that PN could be detrimental in dogs with acute pancreatitis because of the high number of complications, but this may be an institutional bias as there were fewer complications in the EN group than the PN group. The complications and adverse effects seen with PN were all related to catheter sepsis, and none with the composition

Table 1. Summary of clinical information in the 2 treatment groups (n = 5 each group) on admission into the study.

Treatment group	Days of Clinical Signs before Admission		Clinical Severity Index		Pain Score		C-Reactive Protein (mg/L)		S-CPL ($\mu\text{g/L}$)		cTLI ($\mu\text{g/L}$)		Gastrin (pg/mL)	
	EN	PN	EN	PN	EN	PN	EN	PN	EN	PN	EN	PN	EN	PN
Minimum	1	1	1	1	5	3	45.3	35.3	316.0	960.0	9.9	12.8	4.77	0.9
Maximum	4	5	6	4	8	6	173.8	330.4	1001.0	1001.0	27.8	33.0	14.1	21.8
Mean	1.9	3	3.2	1.8	6.2	4.2	79.3	158.2	708.8	990.4	18.7	23.9	4.77	7.7
Median	1.5	4	3	1	6	4	52.6	109.1	851.0	1001.0	16.2	24.0	4.77	3.5

EN, enteral nutrition; PN, parenteral nutrition; S-CPL, specific canine pancreatic lipase; cTLI, canine trypsin-like immunoreactivity; PE-1, serum canine pancreatic elastase.

of the infusion. None of the PN group had hyperglycemia, hyperlipidemia, refeeding syndrome, or hypervolemia at any point, all of which have been associated with a poor outcome in critical care settings in both people and animals.^{4,35,36} The 1 dog that had pre-existing hyperlipidemia was in the EN group. Because of this, it would seem logical to assume that any benefits seen with EN are because of direct nutritional delivery to the intestinal lumen rather than total caloric input alone. The additional RER administered to the PN group (14%) and the EN group (25% by Day 3) is unlikely to have had detrimental effects, because RER is only an estimate of daily caloric requirements that may vary from measured direct calorimetric energy requirements as much as 25% in individual patients.³⁷

One major argument against prepyloric (or gastric) feeding in pancreatitis is that it will be poorly tolerated because of decreased intestinal motility. Certainly in our population of dogs this was not the case. There were significantly more vomiting or regurgitation episodes in the PN group than in the EN group. This could be attributable to differences in patient selection; however, case allocation was consecutive, there was no difference identified between groups at onset of the study, and no animal was selected for the study on the basis of the prospective treatment group. Additionally, all animals had decreased gut sounds on admission. EN may improve gut health to a point that minimizes ileus and vomiting, although this could not be conclusively determined from this study. Although prokinetic agents such as cisapride were allowed by the study protocol, they were not needed in any animal. Initially, all animals had metoclopramide constant rate infusion as part of their treatment, and there may have been a prokinetic benefit conferred from this treatment. This prokinetic treatment was given to all dogs, and consequently is unlikely to have influenced the frequency of vomiting or regurgitation between groups. There were similar degrees of esophagitis visible grossly in both groups, but no statistical comparison was made because of the poor sensitivity of detecting esophageal inflammation on visual assessment.

Another argument against feeding proximal to the jejunum is the possible development of pancreatic pain. There was no temporally associated abdominal pain observed when feeding was commenced in any of the EN dogs. One dog in the EN group had substantial pain on admission that was initially refractory to increasing analgesia, but this declined rapidly after Day 2 while still receiving EN, and did not appear directly associated with feeding. All analgesia could be discontinued in this dog by Day 4. Also, the dog that developed an acute pancreatic fluid collection (previously called a pseudocyst) was in the PN group. One possible hypothesis for acute fluid collection is increased and persistent pancreatic enzyme leakage, and so if stimulation of the pancreas in acute pancreatitis is increased with intraluminal nutrition, development of acute fluid collections could be expected to be more likely in a dog given EN.

Another argument against prepyloric feeding is that it will increase pancreatic secretion by food stimulus within the duodenum. None of the dogs in the EN group

showed any adverse effects from feeding. The need to avoid stimulus of the duodenum in acute pancreatitis does not appear to be upheld by this study.

Currently, the recommendations of many gastroenterology societies in human medicine is to supply EN early in severe (but not mild) pancreatitis because there is a reduction in mortality and infectious complications.^{38–42} There is still extensive debate about the advisability of these recommendations.

In this study, we primarily wanted to evaluate 2 methods of interventional nutrition, and all dogs received a high level of baseline care. This care included plasma transfusion and trickle esophageal electrolyte administration, so that any difference between the 2 groups could be attributed to the interventional nutrition alone. It is questionable whether plasma transfusion actually confers a positive benefit, as was recently proposed in 1 retrospective study of dogs with pancreatitis.⁴³ However, a prospective comparison between animals with similar degrees of disease severity is needed before a definitive determination can be made about whether or not plasma administration provides any benefit in dogs with pancreatitis.

A limitation of the current study was the fact that study observers were not blinded to the treatment groups, leading to the possibility that bias may have influenced results. Given that the 2 treatment modalities were so different, it proved difficult to adequately blind the clinicians involved. To overcome this in the future, it is suggested that treatment groups be randomly assigned and not known to the observer until the patient has been recruited into the study. This will remove the bias of sequential treatment group assignment, as a clinician may not actively recruit a dog into the study if he or she feels the treatment is not suitable for that animal.

Relying on ultrasound examination for diagnosis may have meant that some dogs with pancreatitis that were presented to the center were not recruited for this study. However, this study was aimed at assessing efficacy of treatment in severely affected dogs, and false-positive diagnoses were unlikely in this group. All of the surviving 9 dogs were still alive 2–4 years later, and the nonsurviving dog had a full postmortem examination that did not identify any changes unrelated to severe pancreatitis, and diseases such as pancreatic neoplasia or septic peritonitis seemed extremely unlikely.

The diet chosen in this study was based on a previous study that assessed which dietary combination led to minimal pancreatic stimulation in healthy dogs.²⁸ Extrapolation of this diet to dogs with pancreatic disease is not supported, nor indeed is it known if dietary modification is even necessary if there is minimal pancreatic stimulation during acute pancreatitis. As there were no adverse effects associated with feeding, it can only be concluded that the diet used was not detrimental. There may be additional or unknown benefits from adding supplements such as fiber, probiotics, ω -3 fatty acids, or glutamine, as has been suggested in some studies in people.^{44–47}

Certainly, the optimal treatment of pancreatitis cannot rely on a single modality, nor does this pilot study suggest that early EN necessarily is beneficial in severe

pancreatitis. Rather, this study is an initial step in trying to establish the best nutritional options for dogs with pancreatitis. It would seem logical from the data from humans and dogs to restrict the use of interventional EN to dogs with severe disease, but the optimal timing and type of nutrition is yet to be established. It was calculated that 35–43 dogs would need to be treated with EN in a prospective study to determine whether there is a statistical difference in survival or days between PN and early EN. Future studies also should assess the number of days intensive management is required or the number of days until voluntary food intake occurs between the 2 groups.

The authors feel that because of the high number of technical complications and adverse catheter effects that PN should be reserved for those dogs that cannot support any form of EN after a period of 4–5 days of anorexia. Because esophagostomy tube feeding is well tolerated, a study comparing this method to minimal EN in severely affected animals should be undertaken, with similar numbers of dogs to be recruited as calculated.

Footnotes

^a Sequioa 512, Acuson, Munich, Germany

^b Metomide, Delvet Pty Ltd, Seven Hills, NSW, Australia

^c Lectade, Jurox Pharmaceuticals, Rutherford NSW, Australia

^d Ampicillin, Aspen Pharmcare Pty Ltd, St Leonard's, NSW, Australia

^e Metronidazole, Baxter Healthcare, Toongabbie, NSW, Australia

^f Stemetil Aventis Pharma, Lane Cove, NSW, Australia

^g Alfaxan, Jurox Pharmaceuticals

^h Isoflurane, Veterinary Companies of Australia Pty Ltd, King's Park, NSW, Australia

ⁱ Digestive Low-Fat tinned diet, Royal Canin, Bristol, UK

^j Creon, Solvay Pharmaceuticals, Pymble, NSW, Australia

^k MCT oil, SHS International Ltd, Liverpool, UK

^l cTLI: Commercial radioimmunoassay; Canine TLI Assay, Diagnostic Products Corporation, Los Angeles, CA. Testing performed by the Gastrointestinal Laboratory, Department of Small Animal Medicine and Surgery, College of Veterinary Medicine, Texas A&M University, College Station, TX

^m spec CPL, Idexx. Enzyme-linked immunosorbent assay; Gastrointestinal Laboratory

ⁿ CRP measured by solid phase sandwich assay performed by the Gastrointestinal Laboratory

^o Gastrin enzyme-labeled immunometric assay performed by Path-West Laboratory Medicine WA, Royal Perth Hospital, Western Australia

^p Canine serum pancreatic-elasticase 1 enzyme immunoassay, performed by ScheBo Biotech AG, Geissen, Germany

^q SASv9.1, SAS Institute, Cary, NC

^r Cefazolin injectable, Mayne Pharma Pty Ltd, Mulgrave, VIC, Australia

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