Putative precipitating factors for hepatic encephalopathy in dogs: 118 cases (1991–2014)

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Objective—To elucidate the relationship between plasma ammonia concentration and severity of hepatic encephalopathy and determine whether factors that precipitate hepatic encephalopathy in humans are associated with the presence of clinical signs of hepatic encephalopathy in dogs previously treated for the disease.

Design—Retrospective case series.

Animals—118 dogs with hepatic encephalopathy.

Procedures—The medical records database of a veterinary teaching hospital was searched for records of dogs in which hepatic encephalopathy was diagnosed between October 1, 1991, and September 1, 2014. Hepatic encephalopathy severity was graded on a 5-point scale, and the correlation between disease severity and plasma ammonia concentration was determined. Respective associations between hepatic encephalopathy and systemic inflammatory response syndrome, gastrointestinal hemorrhage, dietary indiscretion, furosemide treatment, azotemia, hypokalemia, hyponatremia, alkalosis, and hyperammonemia were assessed by Fisher exact tests followed by multivariable logistic regression.

Results—Severity of hepatic encephalopathy at hospital admission was not significantly correlated with plasma ammonia concentration. Dogs treated for hepatic encephalopathy prior to hospital admission were significantly less likely to have clinical signs of the disease at hospital admission, compared with dogs that were not treated for the disease (OR, 0.36; 95% confidence interval, 0.17 to 0.78). None of the putative precipitating factors for hepatic encephalopathy were significantly associated with the presence of clinical signs of the disease at hospital admission.

Conclusions and Clinical Relevance—Results indicated that hepatic encephalopathy treatment alleviated clinical signs of the disease. Further investigation is necessary to identify precipitating factors for hepatic encephalopathy in dogs. (J Am Vet Med Assoc 2015; 247:176–183)
available, whereas in human medicine, diagnosis of hepatic encephalopathy is not dependent on measurement of plasma ammonia concentration. \(^1\)

Several factors are known to precipitate hepatic encephalopathy in human patients. Identifying and addressing those precipitating factors are important for patient management because the prognosis for patients with \(\geq 1\) precipitating factor is worse than that for patients without precipitating factors. \(^6\) In previous studies, 354 of 404 (88%) \(^6\) and 45 of 50 (90%) \(^7\) human patients with hepatic encephalopathy had at least 1 precipitating factor. Precipitating factors most commonly associated with hepatic encephalopathy in human patients include gastrointestinal bleeding (18% to 76% of patients), constipation (3% to 52%), diarrhea (12% to 48%), infection (3% to 32%), hypokalemia (9% to 70%), hyponatremia (25% to 38%), and excess dietary protein intake (9% to 52%). \(^7,8\) Hepatic encephalopathy has been described in dogs with CPSS or APSC secondary to portal hypertension. \(^10\) Factors proposed to precipitate hepatic encephalopathy in dogs include gastrointestinal hemorrhage, hypokalemia, hyponatremia, high-protein diets, and alkalosis. \(^31\) Results of a study \(^12\) of dogs with CPSS suggest that hyperammonemia and SIRS, but not hyponatremia, were associated with hepatic encephalopathy. To our knowledge, studies to elucidate the association between hepatic encephalopathy and other putative precipitating factors in dogs are lacking. The objectives of the study reported here were to elucidate the relationship between plasma ammonia concentration and the severity of hepatic encephalopathy in dogs and to determine whether there is an association between factors that precipitate hepatic encephalopathy in humans and the presence of clinical signs of hepatic encephalopathy at hospital admission in dogs previously treated for the disease.

**Materials and Methods**

Case selection—The computerized medical record database at the Texas A&M Veterinary Medical Teaching Hospital was searched for records of dogs in which hepatic encephalopathy was diagnosed between October 1, 1991, and September 1, 2014. An investigator (JAL) reviewed all identified records to verify the diagnosis of hepatic encephalopathy and ensure that each dog met the inclusion criteria for the study. Hepatic encephalopathy was diagnosed on the basis of clinical findings; the exclusion of other causes of encephalopathy; evidence of hepatic dysfunction or insufficiency as determined by results of serum biochemical analysis, CBC, urinalysis, diagnostic imaging (typically abdominal ultrasonography or portal scintigraphy); and response to treatment. Plasma ammonia and serum bile acid concentrations were also evaluated when available. A dog was excluded from the study if its medical record was unavailable for review or it did not meet the criteria for hepatic encephalopathy.

Medical records review—Signalment, history (including previous treatments), cause of hepatic encephalopathy, and results of the physical examination performed at hospital admission, serum biochemical analysis, CBC, diagnostic imaging, and plasma ammonia concentration (when available) were extracted from the record of each dog enrolled in the study. Laboratory test results were evaluated only if the samples were collected within 24 hours after hospital admission. For dogs that were admitted to the teaching hospital on multiple occasions, information was evaluated only from the admission during which hepatic encephalopathy was initially diagnosed. When possible, the cause of hepatic encephalopathy was classified in accordance with a slightly modified version of a classification scheme \(^1\) used for human patients in which the definition of type C hepatic encephalopathy was broadened to include all types of intrinsic hepatocellular disease rather than just cirrhosis. Specifically, type A hepatic encephalopathy was defined as acute liver failure in the absence of preexisting hepatic disease, type B hepatic encephalopathy was defined as a portosystemic bypass without intrinsic hepatocellular disease (eg, CPSS), and type C hepatic encephalopathy was defined as intrinsic hepatocellular disease and portal hypertension or acquired portosystemic shunting.

When sufficient information was available for dogs that had been previously treated for hepatic encephalopathy, the severity of hepatic encephalopathy historically and the severity at the time of hospital admission were graded in accordance with a previously described 5-point scale. \(^13\) The historical hepatic encephalopathy grade generally represented the most severe clinical sign recorded in the patient's history. Briefly, grade 0 was assigned to dogs with no clinical signs of hepatic encephalopathy; grade 1 was assigned to dogs with mildly impaired mobility, apathy, or both; grade 2 was assigned to dogs with severe apathy, mild ataxia, or both; grade 3 was assigned to dogs with hypersalivation, severe ataxia, head pressing, blindness, circling, or any combination of those signs; and grade 4 was assigned to dogs with seizures or that were in a stupor or coma.

The prevalence of factors such as SIRS, gastrointestinal hemorrhage, dietary change or indiscretion, constipation, furosemide treatment, hypokalemia, hyponatremia, alkalosis, and azotemia that are known to precipitate hepatic encephalopathy in human patients \(^3\) was recorded for each dog on the basis of the patient's history and physical examination findings at the time of its first admission to the teaching hospital. Systemic inflammatory response syndrome was diagnosed when at least 2 of the following 4 criteria were met: body temperature \(\geq 39.7°C (103.5°F)\) or \(\leq 37.8°C (100.0°F)\), heart rate \(\geq 160\) beats/min, respiratory rate \(\geq 40\) breaths/min, and WBC count \(\geq 12,000\) or \(\leq 4,000\) cells/µL or \(\geq 10%\) band neutrophils. \(^16\) Results of serum biochemical analysis for samples obtained only within 24 hours after the first hospital admission were used to determine the prevalence of hyperammonemia, hyponatremia, alkalosis, and azotemia. When available, the plasma ammonia concentration measured within 24 hours after the first hospital admission was also recorded.

**Statistical analysis**—The distributions of continuous variables were evaluated for normality by visual inspection of frequency histograms and the Kolmogorov-Smirnov test. Results for variables that were not normally distributed were expressed as the median (range), and results for normally distributed
variables were expressed as the mean ± SD. For each historical finding, physical examination result, and precipitating factor, the prevalence within the study population was expressed as the percentage. The historic hepatic encephalopathy severity grade was compared with the hepatic encephalopathy severity grade at the time of hospital admission by use of the Wilcoxon signed rank test. The correlation between plasma ammonia concentration and the hepatic encephalopathy severity grade was assessed with the Spearman rank correlation coefficient (r). A statistical software program was used for all analyses, and values of P < 0.05 were considered significant.

To investigate the relationship between potential precipitating factors for hepatic encephalopathy and the presence of clinical signs of the disease at the time of hospital admission, the study population was divided into 2 groups (ie, dogs with and without clinical signs of hepatic encephalopathy during the initial physical examination at hospital admission). The respective frequencies of prior treatment for hepatic encephalopathy, SRS, gastrointestinal hemorrhage, dietary change or indiscretion, constipation, furosemide treatment, hypokalemia, hyponatremia, alkalosis, azotemia, and hyperammonemia were compared between the 2 groups by use of the Fisher exact test. Variables with P < 0.2 for the Fisher exact test were included in a multivariable logistic regression model in which the outcome of interest was modeled as the presence of clinical signs of hepatic encephalopathy at hospital admission. The final model was constructed by backward stepwise elimination, and only variables with P < 0.05 were retained in the model. The OR and 95% CI for each variable were calculated. These analyses were performed with another statistical software program.

**Results**

**Dogs**—The database search revealed that 170 dogs were assigned the diagnostic code for hepatic encephalopathy between October 1, 1991, and September 1, 2014. Forty dogs were excluded from the study because their medical records were incomplete or unavailable for review. An additional 12 dogs were excluded from the study because review of their medical records revealed that there was insufficient evidence to diagnose hepatic encephalopathy. Thus, 118 dogs met the criteria for diagnosis of hepatic encephalopathy and were enrolled in the study, of which 46 (39%) were spayed females, 17 (14%) were sexually intact females, 31 (26%) were castrated males, and 24 (20%) were sexually intact males. The median age of dogs at the time of onset of clinical signs was 24 months (range, 1 to 186 months), and the median age of dogs at the time of admission to the teaching hospital was 32 months (range, 2 to 186 months). The breeds most commonly represented in the study population were Yorkshire Terrier (n = 17 [14%]), Miniature Schnauzer (19 [16%]), Chihuahua (7 [6%]), Labrador Retriever (6 [5%]), Poodle (6 [5%]), Pug (4 [3%]), Dachshund (4 [3%]), Cocker Spaniel (3 [3%]), and Pomeranian (3 [3%]).

**Examination findings**—The cause of hepatic encephalopathy was unknown because of incomplete diagnostic evaluation for 16 (14%) dogs. Type A hepatic encephalopathy was not diagnosed in any of the dogs, whereas types B and C hepatic encephalopathy were diagnosed for 73 (62%) and 29 (25%) dogs, respectively. Of the 73 dogs with type B hepatic encephalopathy, the disease was attributed to CPSS in 70 (96%), an arteriovenous fistula and APSC in 2 (3%), and microvascular dysplasia in 1 (1%). Of the 29 dogs with type C hepatic encephalopathy, the disease was attributed to intrinsic hepatocellular disease with APSC in 24 (83%) and intrinsic hepatocellular disease without evidence of APSC identified during abdominal ultrasonography in 2 (7%); the remaining 3 (10%) dogs had intrinsic hepatocellular disease but did not undergo diagnostic imaging for evaluation of APSC. Overall, 96 of the 102 (94%) dogs in which the cause of hepatic encephalopathy was identified had some type of macroscopic porto-systemic shunting.

The most frequently recorded historical clinical signs were lethargy (n = 32 [27%] dogs), altered behavior (31 [26%]), obtundation (29 [25%]), ataxia (28 [24%]), seizures (26 [22%]), head pressing (22 [19%]), ptalism (22 [19%]), vomiting (21 [18%]), blindness (20 [17%]), circling (15 [13%]), shaking or twitching (14 [12%]), and anorexia or hyporexia (13 [11%]). At the time of hospital admission, abnormal neurologic findings were recorded for 56 (47%) dogs, and the most frequently recorded clinical signs were obtundation (n = 30 [25%]), ataxia (23 [19%]), paresis (9 [8%]), conscious proprioceptive deficits (8 [7%]), seizures (6 [5%]), stupor or coma (5 [4%]), circling (4 [3%]), abnormally delayed menace response (4 [3%]), and tremors (3 [3%]), as well as blindness, abnormally decreased pupillary light response, head pressing, ptalism, head tilt, and anisocoria (2 [2%] each).

The frequency distributions of hepatic encephalopathy severity grades before (historical) and at the time of hospital admission for the study population were summarized (Table 1). A hepatic encephalopathy severity grade at the time of hospital admission could not be assigned to 2 of the 118 dogs because the medical records for those dogs contained insufficient information. The
median historical severity grade (3; range, 0 to 4) was significantly ($P < 0.001$) greater than the median severity grade at hospital admission (1; range, 0 to 4). For each of 116 dogs, the medical record maintained by the referring veterinarian prior to the patient's admission to the teaching hospital was available for review, and 50 (43%) dogs were treated for hepatic encephalopathy prior to referral to the teaching hospital.

Plasma ammonia concentration was determined within 24 hours after hospital admission for 83 of 118 (70%) dogs. The median plasma ammonia concentration was 179 µg/mL (range, 15 to 1,350 µg/mL; reference limit, < 50 µg/mL), and 77 (93%) dogs had hyperammonemia. Plasma ammonia concentration was not significantly correlated with either the historical hepatic encephalopathy severity grade ($r_s = 0.16$; $P = 0.156$) or the hepatic encephalopathy grade at the time of hospital admission ($r_s = 0.22$; $P = 0.052$; Figure 1).

Precipitating factors for hepatic encephalopathy—Information regarding some precipitating factors for hepatic encephalopathy was unavailable for some dogs; therefore, the denominator used for determining the prevalence varied among the precipitating factors. The putative precipitating factors for hepatic encephalopathy prevalent in dogs at the time of hospital admission were SIRS (prevalence, 14% [16/116]), hypokalemia (7% [7/105]), alkalosis (5% [5/103]), hypokalemia (9% [5/105]), dietary change or indiscretion (3% [4/118]), furosemide treatment (3% [4/118]), azotemia (3% [3/107]), gastrointestinal hemorrhage (2% [2/118]), and constipation (1% [1/118]). Thirty-six of the 118 (31%) dogs had at least 1 putative precipitating factor for hepatic encephalitis at the time of hospital admission.

Of the 116 dogs for which sufficient information was available to assign a hepatic encephalopathy grade at the time of admission to the hospital, 59 (51%) and 57 (49%) did and did not, respectively, have clinical signs of hepatic encephalopathy recorded during the initial physical examination at the time of admission. Fisher exact test results revealed that prior treatment for hepatic encephalopathy (OR = 0.014) and hyperammonemia (OR = 0.023) were significantly associated with whether dogs did or did not have clinical signs of hepatic encephalopathy at the time of hospital admission (Table 2).

![Figure 1](image_url)

**Table 2**—Frequency distributions of various putative precipitating factors for hepatic encephalopathy for the dogs of Table 1 that did (n = 59) and did not (n = 57) have clinical signs of the disease at the time of admission to a veterinary teaching hospital.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Dogs with clinical signs at admission*</th>
<th>Dogs without clinical signs at admission†</th>
<th>OR (95% CI)$\dagger$</th>
<th>$P$ value§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior treatment for hepatic encephalopathy</td>
<td>18 (32)</td>
<td>32 (56)</td>
<td>0.36 (0.17–0.78)</td>
<td>0.014</td>
</tr>
<tr>
<td>SIRS</td>
<td>11 (19)</td>
<td>5 (9)</td>
<td>2.49 (0.80–7.69)</td>
<td>0.176</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>1 (2)</td>
<td>3 (5)</td>
<td>0.31 (0.03–3.08)</td>
<td>0.360</td>
</tr>
<tr>
<td>Dietary change or indiscretion</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>0.97 (0.08–15.83)</td>
<td>1.000</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>2.95 (0.12–73.35)</td>
<td>1.000</td>
</tr>
<tr>
<td>Furosemide treatment</td>
<td>2 (4)</td>
<td>4 (7)</td>
<td>2.35 (0.44–12.71)</td>
<td>0.443</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>4 (7)</td>
<td>1 (2)</td>
<td>8.65 (0.45–165.00)</td>
<td>0.117</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>5 (9)</td>
<td>2 (4)</td>
<td>6.68 (0.01–3.77)</td>
<td>0.689</td>
</tr>
<tr>
<td>Azotemia</td>
<td>3 (5)</td>
<td>0 (0)</td>
<td>6.87 (0.35–136.40)</td>
<td>0.244</td>
</tr>
<tr>
<td>Hyperammonemia</td>
<td>45 (86)</td>
<td>33 (58)</td>
<td>9.55 (1.12–81.41)</td>
<td>0.023</td>
</tr>
</tbody>
</table>

*Values represent the number (percentage) of dogs unless otherwise indicated.

*The denominator for the percentage is 57 for prior treatment for hepatic encephalopathy, SIRS, and furosemide treatment; 59 for hypokalemia, hyponatremia, and azotemia; 53 for alkalosis; and 46 for hyperammonemia. The denominator for the percentage is 51 for azotemia; 48 for hypokalemia, hyponatremia, and alkalosis; and 40 for hyperammonemia. ORs were calculated by univariable analysis, and the referent was dogs without clinical signs of hepatic encephalopathy at hospital admission. If Fisher exact test, CI was calculated by adding 0.5 to each group of dogs.
assessed in the multivariable logistic regression model included prior treatment for hepatic encephalopathy, SIRS, hypokalemia, and hyperammonemia. Hypokalemia, SIRS, and hyperammonemia were sequentially eliminated from the model, and the final model included only prior treatment for hepatic encephalopathy. Dogs with clinical signs of hepatic encephalopathy at the time of hospital admission were significantly (P = 0.009) less likely to have been previously treated for the disease than were dogs without clinical signs of hepatic encephalopathy at the time of hospital admission (OR, 0.36; 95% CI, 0.17 to 0.78).

**Discussion**

In the present study, most of the 118 dogs treated for hepatic encephalopathy at a veterinary teaching hospital between October 1, 1991, and September 1, 2014, had type B hepatic encephalopathy, followed by type C hepatic encephalopathy. Although 36 (31%) of those dogs had at least 1 putative precipitating factor for hepatic encephalopathy at the time of hospital admission, none of the precipitating factors evaluated were significantly associated with the presence of clinical signs of hepatic encephalopathy at hospital admission. Dogs that were treated for hepatic encephalopathy prior to hospital admission were less likely to have clinical signs of the disease at hospital admission than were dogs that were not treated for hepatic encephalopathy prior to hospital admission.

In human patients, type C hepatic encephalopathy, which is associated with cirrhosis and portal hypertension or acquired portosystemic shunting, is more common than type B hepatic encephalopathy, which is associated with portosystemic bypass in the absence of intrinsic hepatocellular disease. Conversely, most of the dogs in the present study in which the cause of hepatic encephalopathy was identified (n = 102) had type B hepatic encephalopathy (73 [72%]), which was generally attributable to CPSS (70/73 [96%]), whereas the remaining dogs (29 [28%]) had type C hepatic encephalopathy, which was generally attributable to portal hypertension and the development of APSC (24/29 [83%]). Some dogs with intrinsic hepatocellular disease (type C hepatic encephalopathy) were not evaluated for APSC, and in others, APSC was not detected during diagnostic imaging but may have been present (ie, false-negative diagnostic imaging results). Therefore, it is likely the prevalence of APSC was underestimated for the dogs of the present study. Macroscopic portosystemic shunting secondary to CPSS or APSC was identified in 96 of the 102 (94%) dogs in which the cause of hepatic encephalopathy was identified; however, it is likely this is also an underestimate of the true prevalence of macroscopic portosystemic shunting in the study population. Regardless, the results of the present study were similar to those of another study, in which abdominal ultrasonography was used to identify the cause of hyperammonemia in 90 dogs. In that study, 61 (68%) dogs had CPSS, 17 (19%) dogs had APSC (including arteriovenous fistulae), and 11 (12%) dogs had no macroscopic portosystemic shunting detected. Although type A hepatic encephalopathy associated with acute hepatic failure was not diagnosed in any dogs of the present study, it has been reported in dogs.

The most commonly reported historical and clinical findings (lethargy, altered behavior, obtundation, ataxia, seizures, head pressing or tilt, ptalism, vomiting, blindness, circling, shaking or twitching, anorexia or hyporexia, abnormally delayed menace and pupillary light responses, anisocoria, conscious proprioceptive deficits, and stupor or coma) for the dogs of the present study were similar to those that have been described previously. In human medicine, seizures are rarely associated with hepatic encephalopathy; however, seizure activity was recorded for a substantial proportion (26/118 [22%]) of dogs in the present study. The apparent difference in the incidence of seizure activity between humans and dogs with hepatic encephalopathy might be a reflection of the fact that hepatic encephalopathy is generally diagnosed at an earlier stage in human patients than it is in dogs. Human patients with subclinical hepatic encephalopathy perform poorly on specialized psychometric tests, but do not have an impaired mental status or abnormal neurologic examination findings. Unfortunately, there is currently no way to diagnose subclinical hepatic encephalopathy in dogs, and the disease is detected only after clinical signs become apparent. Therefore, it is likely that hepatic encephalopathy is underdiagnosed in dogs.

For the dogs of the present study, the median hepatic encephalopathy severity grade before hospital admission (median grade, 3) was worse than that at hospital admission (median grade, 1). This finding was not surprising because 30 of the 116 (43%) dogs that were assigned a hepatic encephalopathy severity grade both before and at hospital admission were treated for the disease prior to being admitted to the veterinary teaching hospital. Also, dogs that were not treated for hepatic encephalopathy prior to hospital admission were approximately 3 times as likely to have clinical signs of hepatic encephalopathy at the time hospital admission, compared with dogs that were treated for the disease prior to hospital admission.

The protocols used to treat the dogs of the present study for hepatic encephalopathy prior to admission to the veterinary teaching hospital varied but generally included antimicrobials, lactulose, and some type of dietary intervention. Unfortunately, it was not possible to assess the efficacy of individual interventions because of the extent that protocols varied. However, the findings of the present study suggested that medical management strategies commonly used to treat dogs with hepatic encephalopathy are effective, at least in the short term.

In the present study, venous plasma ammonia concentration was measured within 24 hours after hospital admission for 83 dogs, of which 78 (94%) had hyperammonemia (ammonia concentration ≥ 50 µg/mL). This suggested that most but not all dogs with hepatic encephalopathy have hyperammonemia, a finding that supported the results of another study that involved dogs with hepatic encephalopathy. However, we could not estimate the sensitivity of the presence of ammonia for detecting dogs with hepatic encephalopathy from our data because the presence of hyperammon-
Hyponatremia was used as an inclusion criterion for the study. Consequently, the sensitivity of hyperammonemia for detecting hepatic encephalopathy calculated from the data of the present study would likely be overestimated. Also, at the time of hospital admission, many dogs were receiving lactulose and various antimicrobials, which might have reduced the absorption of ammonia from the intestine at the time the blood sample used to measure plasma ammonia concentration was obtained. Although there was a weak positive correlation ($r = 0.22$) between venous plasma ammonia concentration and the hepatic encephalopathy severity grade at the time of hospital admission, that correlation did not quite reach significance ($P = 0.052$). Results of another study$^4$ that involved dogs indicate that there is a positive correlation between hepatic encephalopathy severity and both arterial and venous plasma ammonia concentrations. It is possible that the enrollment of additional dogs with hepatic encephalopathy or dogs without a history of hepatic encephalopathy in the present study would have enabled us to detect a significant correlation between plasma ammonia concentration and hepatic encephalopathy severity. Results of studies$^{15}$ that involved human patients suggest there is a moderate to strong positive correlation between arterial plasma ammonia concentration or partial pressure and the severity of hepatic encephalopathy. Interestingly, results of another study$^{16}$ suggest only a weak correlation between venous plasma ammonia concentration and the severity of hepatic encephalopathy in human patients. Arterial ammonia concentration is generally higher than venous ammonia concentration and may better reflect the ammonia concentration in the cerebrum.$^2$ Ammonia in its gaseous form readily enters the brain; therefore, the correlation between the severity of hepatic encephalopathy and the pH-dependent partial pressure of gaseous ammonia is better than the correlation between the severity of hepatic encephalopathy and total arterial ammonia concentration.$^3$ Because the ranges for plasma ammonia concentration among patients with different hepatic encephalopathy severity grades (including those with a severity grade of 0, or no clinical signs of the disease) overlap, measurement of plasma ammonia concentration is of limited value for detection of individual patients with hepatic encephalopathy.$^4$ Hence, even though ammonia has a critical role in the pathogenesis of hepatic encephalopathy, other factors such as inflammatory mediators, neurosteroids, and manganese are also important.$^3$ Dogs with CPSS and clinical signs of hepatic encephalopathy often have serum C-reactive protein concentrations that are increased from reference limits.$^17$ Additionally, dogs with CPSS$^18$ or primary hepatitis$^19$ frequently have blood manganese concentrations that are increased from reference limits.

Thirty-six of the 118 (31%) dogs of the present study had at least 1 putative precipitating factor for hepatic encephalopathy at the time of hospital admission. The precipitating factors for hepatic encephalopathy that were most commonly recorded for the dogs of the present study were SIRS, hyponatremia, alkalosis, hypokalemia, dietary change or indiscretion, fluoride treatment, azotemia, gastrointestinal hemorrhage, and constipation. The prevalences of those precipitating factors in the dogs of the present study were generally lower than the prevalences of those factors in human patients with hepatic encephalopathy, likely because the most common cause of hepatic encephalopathy in dogs is CPSS, whereas the most common cause of hepatic encephalopathy in humans is cirrhosis, and patients with cirrhosis tend to have more systemic complications.$^3$

Results of another study$^{12}$ indicate that SIRS is associated with hepatic encephalopathy in dogs with CPSS, and SIRS (prevalence, 14% [16/116]) was the most commonly recorded precipitating factor for hepatic encephalopathy in the dogs of the present study. The criteria used to diagnose SIRS in the present study were more stringent than those used in another study$^{20}$ because we decided it would be preferable to be conservative and reduce the chance for false-positive SIRS diagnoses, which might have contributed to the fairly low prevalence of SIRS in the present study. A variety of mechanisms have been proposed for how inflammation and infection could precipitate hepatic encephalopathy. A synergistic relationship between ammonia and inflammatory cytokines might alter cerebral neurotransmission and increase the permeability of the blood-brain barrier.$^{21}$ Also, dogs with CPSS have higher serum C-reactive protein$^{17}$ and plasma interleukin-6 concentrations$^{22}$ than do dogs without CPSS. Hyponatremia (7/105 [7%]) and hypokalemia (5/105 [5%]) were the next most common precipitating factors for hepatic encephalopathy recorded for the dogs of the present study. Hyponatremia is believed to precipitate hepatic encephalopathy by exacerbating the low-grade cerebral edema caused by ammonia dysmetabolism.$^{23}$ Hypokalemia causes extracellular alkalosis, which can lead to the trapping of ammonium ions within the cells of the cerebral cortex.$^{11}$

The putative precipitating factors for hepatic encephalopathy evaluated in the present study were chosen on the basis of known precipitating factors for hepatic encephalopathy in humans. For the dogs of the present study, none of those precipitating factors for hepatic encephalopathy were significantly associated with the presence of clinical signs of the disease at the time of hospital admission. However, these findings are specific for the study population and should not be extrapolated to a population that includes dogs with and without a history of hepatic encephalopathy. Thus, the precipitating factors for hepatic encephalopathy evaluated in the present study might instead be comorbid disorders that are not involved in the pathogenesis of hepatic encephalopathy in dogs. The results of the present study differ from those of a retrospective study$^{12}$ of dogs with CPSS in which SIRS and hyperammonemia, but not hyponatremia, were associated with hepatic encephalopathy. That study$^{12}$ differed from the present study in that the dogs with CPSS did not have a history of hepatic encephalopathy, which may account for the conflicting results between the 2 studies. Furthermore, the prevalences of the putative precipitating factors for hepatic encephalopathy in the present study population were fairly low, which could suggest that the study had insufficient power to detect an association between the precipitating factors for hepatic encephalopathy and
the presence of clinical signs of the disease at hospital admission. Conversely, it is possible that there is no association between the putative precipitating factors and the presence of clinical signs of hepatic encephalopathy because those factors are not as critical for the development of hepatic encephalopathy in dogs as they are in humans. Nevertheless, we believe that it is prudent for clinicians to evaluate dogs for the putative precipitating factors for hepatic encephalopathy and manage those factors whenever possible.

The present study had several limitations. As with any retrospective study, our ability to identify dogs that met the criteria for study enrollment and accurately evaluate those dogs was dependent on the correct and complete recording of each subject's history, physical examination findings, and diagnostic test results in its medical record. It is possible that the prevalence of dogs with clinical signs of hepatic encephalopathy at the time of hospital admission was underestimated. Also, the retrospective assignment of hepatic encephalopathy severity grades was difficult because the disease is episodic in nature, and it is possible that clinical signs were not at their worst when the dogs were examined at the veterinary teaching hospital, which could have led to underestimation of severity grade. Underestimation of the hepatic encephalopathy severity grade would have limited our ability to detect a correlation between the plasma ammonia concentration and the severity grade. To minimize the potential effect from underestimation of the hepatic encephalopathy severity grade, we assigned each dog 2 severity grades, 1 that was based on the patient's history provided by the owner and referring veterinarian and another that was based on the patient's initial physical examination findings at the time of hospital admission. Additionally, the diagnostic testing protocol was not standardized. Therefore, evaluation for portosystemic vascular anomalies varied among dogs, and we were unable to determine the cause of hepatic encephalopathy in some dogs. Ideally, a prospective study should be performed in which each patient undergoes a standardized comprehensive evaluation (eg, CT angiography for identification of portosystemic vascular anomalies and histologic evaluation of a liver biopsy specimen for assessment of intrinsic hepatocellular disease). Although the prevalences of the putative precipitating factors were determined at the time of or within 24 hours after admission to the veterinary teaching hospital to ensure that dogs were assessed for the presence of hepatic encephalopathy as close to hospital admission as possible, it is possible that plasma ammonia or serum electrolyte concentrations changed between the time that the initial physical examination was performed and the time that the blood samples were obtained for analyses. Finally, because of the retrospective nature of the study, evaluation of the putative precipitating factors for hepatic encephalopathy was not standardized. Some factors, such as hypokalemia, are easy to detect, whereas others, such as gastrointestinal hemorrhage, are difficult to diagnose. Consequently, the presence of some factors may have been non-differentially misclassified, which would have shifted the ORs for those factors toward the null and potentially caused a type II error. Further studies are necessary to better elucidate the precipitating factors for hepatic encephalopathy in dogs.

Results of the present study indicated that type B hepatic encephalopathy subsequent to CPSS was the most common cause of hepatic encephalopathy in dogs with a history of the disease, followed by type C hepatic encephalopathy subsequent to APSC. Thirty-six of 118 (31%) dogs had at least 1 putative precipitating factor for hepatic encephalopathy; however, there was no significant association between any of those factors and the presence of clinical signs of hepatic encephalopathy at the time of hospital admission. Dogs treated for hepatic encephalopathy prior to hospital admission were less likely to have clinical signs of the disease at the time of hospital admission. Further investigation into the pathogenesis of hepatic encephalopathy in dogs is needed.

a. Prism, version 5, GraphPad Software Inc, La Jolla, Calif.
b. PROC LOGISTIC, SAS, version 9.4, SAS Institute Inc, Cary, NC.

References
17. Gow AG, Marques AI, Yool DA, et al. Dogs with congenital porto-systemic shunting (cPSS) and hepatic encephalopathy have higher serum concentrations of C-reactive protein than asymptomatic dogs with cPSS. *Metab Brain Dis* 2012;27:227–229.

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**From this month’s *AJVR***

**Comparison of axillary and rectal temperatures for healthy Beagles in a temperature- and humidity-controlled environment**

Justin C. Mathis and Vicki L. Campbell

**Objective**—To compare axillary and rectal temperature measurements obtained with a digital thermometer for Beagles in a temperature- and humidity-controlled environment.

**Animals**—26 healthy Beagles (17 sexually intact males and 9 sexually intact females).

**Procedures**—Dogs were maintained in a temperature- and humidity-controlled environment for 56 days before rectal and axillary temperatures were measured. Axillary and rectal temperatures were obtained in triplicate for each dog by use of a single commercially available manufacturer-calibrated digital thermometer.

**Results**—Mean rectal and axillary temperatures of Beagles maintained in a temperature- and humidity-controlled environment were significantly different, with a median $\pm$ SD difference of 1.4° $\pm$ 0.15°C (range, 0.7° to 2.1°C). Mean rectal and axillary temperatures were 38.7°C (range, 37.6° to 39.5°C) and 37.2°C (range, 36.6° to 38.3°C), respectively.

**Conclusions and Clinical Relevance**—Results of this study indicated that the historical reference of a 0.55°C gradient between rectal and axillary temperatures that has been clinically used for veterinary patients was inaccurate for healthy Beagles in a temperature- and humidity-controlled environment. Rectal and axillary temperatures can be measured in veterinary patients. Reliable interpretation of axillary temperatures may accommodate patient comfort and reduce patient anxiety when serial measurement of temperatures is necessary. Further clinical studies will be needed. (*Am J Vet Res* 2015;76:632–636)