Case Report

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Critical illness-related corticosteroid insufficiency in a dog with septic shock

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Abstract

Objective – To describe a case of hydrocortisone-responsive hypotension and critical illness-related corticosteroid insufficiency (CIRCI) in a dog with septic shock.

Case Summary – A dog with aspiration pneumonia developed septic shock with pressor-refractory hypotension. A standard ACTH stimulation test was performed that showed a blunted cortisol response consistent with CIRCI. Reversal of shock was achieved within 2 hours of hydrocortisone administration, and complete weaning from pressors was accomplished over the subsequent 8 hours. The patient recovered and was discharged from the hospital. An ACTH stimulation test performed 1 month after hospital discharge showed normal adrenal responsiveness consistent with resolution of CIRCI.

New or Unique Information Provided – This case is the first published report of hydrocortisone-responsive hypotension and transient CIRCI associated with naturally occurring septic shock in a dog.

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Introduction

Hypothalamic-pituitary-adrenal (HPA)-axis dysfunction is common in humans with severe sepsis or septic shock.[1–5] This endocrine dysfunction is associated with pressor-refractory hypotension[6–8] and death.[5,9,10]

There is little information in the veterinary literature about HPA-axis dysfunction in critically ill dogs and cats. One prospective study of 20 cats sequentially admitted to an intensive care unit failed to demonstrate HPA-axis dysfunction in any cat.[a] Another prospective, multicenter study of 19 septic cats identified a blunted cortisol response to a standard ACTH stimulation test in septic cats compared with healthy controls. However, the investigation was unable to demonstrate an association between this blunted cortisol response and survival.[b] A recent case report[11] documented adrenal insufficiency in a cat with systemic inflammatory response syndrome secondary to blunt trauma. The cat in that report had fluid-refractory hypotension, a blunted cortisol response to an ACTH stimulation test, and clinical improvement after initiation of glucocorticoid therapy.

There is conflicting information in the veterinary literature regarding the occurrence of HPA-axis abnormalities in critically ill dogs. One prospective study of 20 dogs sequentially admitted to an intensive care unit found normal or elevated serum cortisol concentrations at baseline and after ACTH stimulation in all dogs.[12] One retrospective investigation of 42 critically ill dogs identified a poor cortisol response to a standard ACTH stimulation test in 4 animals; all 4 dogs were septic, and all of them died.[c] In a recent prospective study, 15 of 33 (45%) septic dogs had poor adrenal responsiveness that was associated with hypotension, decreased survival to discharge, and decreased 28-day survival.[13] To the authors' knowledge, this is the first clinical report of hydrocortisone-responsive hypotension associated with poor adrenal responsiveness in a dog with septic shock.

Case Summary

A 15-month-old castrated male Standard Poodle, weighing 27 kg, was presented to the William R. Pritchard Veterinary Medical Teaching Hospital at the University of California, Davis for evaluation of vomiting

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and aspiration pneumonia. Five days before presentation, the dog had vomited pieces of magazine. The patient was then boarded at a kennel for 3 days, where no abnormalities were noted. The owner retrieved the dog from the boarding facility 2 days before presentation at our hospital; at that time the dog had a soft cough and was vomiting. He was taken to his local veterinarian the following morning and found to be febrile, with a rectal temperature of 41°C (106.0°F). Diagnostic testing[d,e] at that veterinary clinic showed a mild thrombocytopenia of 145×10^9L (reference interval, 175–500 $\times 10^9$L), a normal WBC of 9.0×10^9L (reference interval, 5.5–16.9 $\times 10^9$L), and a neutrophil count of 5.7×10^9L (reference interval, 2.0–12.0 $\times 10^9$L). Thoracic radiographs showed severe interstitial to alveolar infiltrates in the right middle and left cranial lung lobes, compatible with aspiration pneumonia. The dog was treated with a bolus of isotonic crystalloid solution[f] (400 mL, IV), ampicillin[g] (23 mg/kg, IV, q 8 h), and enrofloxacin[h] (5 mg/kg, IM, q 12 h). The dog was hospitalized at a local emergency clinic overnight, where he continued to be tachypneic (50/min), dyspneic, and febrile (40.3°C [104.5°F]). The pulse oximeter reading (SpO_2) was 82% with the patient breathing room air. A CBC[i] performed at the emergency clinic showed a leukopenia of 1.1×10^9L (reference interval, 5.7–16.3 $\times 10^9$L) with 0.64×10^9L moderately toxic neutrophils (reference interval, 3.0–11.50 $\times 10^9$L), and 109×10^9L platelets (reference interval, 164–510 $\times 10^9$L). A prothrombin time[j] was 15 seconds (reference interval, 12–17 s), an activated partial thromboplastin time[k] was 117 seconds (reference interval, 59–87 s), and the plasma D-dimer[l] concentration was 250–500 μg/L (200–500 ng/mL) (reference interval, <250 μg/L [<250 ng/mL]). Oxygen was administered at 8 L/min through bilateral nasal cannulae. Enrofloxacin (8.5 mg/kg, IV, q 24 h) was continued, and ticaricillin/clavulanic acid[m] (43 mg/kg, IV, q 8 h) and an isotonic crystalloid solution[n] (130 mL/h, IV) were instituted. Two units of canine fresh frozen plasma were administered for suspected disseminated intravascular coagulation. Overnight the dog remained febrile and hypoxemic with SpO_2 readings between 81% and 90%, while receiving supplemental oxygen. The dog continued to vomit and regurgitate, and was referred to the William R. Pritchard Veterinary Medical Teaching Hospital for further evaluation.

At presentation to our hospital, the dog was moderately obtunded with a rectal temperature of 40.6°C (105.0°F), weak femoral pulses, and a heart rate of 130/min. He had a respiratory rate of 50/min with increased respiratory effort and decreased cranioventral bronchovesicular sounds bilaterally. Based on the suspicion of infection and the presence of systemic inflammatory response syndrome, the dog was diagnosed with sepsis secondary to aspiration pneumonia.

A CBC[o] showed a leukopenia of 5.7×10^9/L (reference interval, 6.0–13.0 $\times 10^9$/L) with a degenerative left shift (3.54×10^9/L bands and 1.31×10^9/L mature neutrophils [reference interval, 3.0–10.5 $\times 10^9$/L]). All components of a serum biochemistry panel[p] were within the reference intervals. The serum sodium concentration was 145 mmol/L (reference interval, 145–154 mmol/L) and the serum potassium concentration was 3.5 mmol/L (reference interval, 3.5–5.3 mmol/L). Ultrasonographic examination of the abdomen showed no significant abnormalities; both adrenal glands were normal in size, shape, and echogenicity. Thoracic radiographs showed severe consolidation of the right cranial, middle, and caudal lung lobes, and the left cranial lung lobe. An arterial blood gas while the patient was breathing room air showed a PaO_2 of 53.3 mm Hg (reference interval, 80–100 mm Hg) with a PaO_2:FiO_2 (P:F) ratio of 253 (reference interval, >400). The dog was placed in an oxygen cage with 70% FiO_2, and broad-spectrum antimicrobial therapy was continued (ticarcillin/clavulanic acid, 50 mg/kg, IV, q 8 h; enrofloxacin, 5 mg/kg, IV, q 12 h; metronidazole,[q] 7.5 mg/kg, IV, q 12 h). Over the next 5 hours, the dog's dyspnea and pulmonary function worsened (P:F, 69.9). Based on this finding, we induced anesthesia using midazolam[r] (0.25 mg/kg, IV), oxymorphone[s] (0.03 mg/kg, IV), and propofol[t] (2 mg/kg, IV). The dog was endotracheally intubated, and placed on a mechanical ventilator[u] in a pressure assist/control mode. Light anesthesia was maintained with IV constant rate infusions (CRI) of oxymorphone (0.01 mg/kg/h), midazolam (0.1–0.3 mg/kg/h), and pentobarbital[v] (1–5 mg/kg/h). No diagnostic airway washes were performed due to the patient's unstable condition and that institution of antimicrobials had taken place in the previous 24 hours and had not had sufficient time to change the clinical course of the patient's condition.

At the institution of positive-pressure ventilation, arterial serum lactate concentration was 5.3 mmol/L (reference interval <1 mmol/L), and 1 L of isotonic crystalloid[f] was administered as an IV bolus. An arterial catheter was placed for continuous direct monitoring of peripheral arterial blood pressure. Following the fluid bolus, the dog's mean arterial pressure (MAP) was 75–80 mm Hg (normal 60–100 mm Hg) and his arterial serum lactate concentration decreased to 3.5 mmol/L, with a urine output of 2 mL/kg/h (normal 1–2 mL/kg/h). One hour after institution of positive pressure ventilation, the dog's MAP dropped to 50 mm Hg. Central venous pressure was not available at that time, but the patient had a positive fluid balance of 1.3 L. The dog

had a prolonged activated clotting time[w] of 140 seconds (reference interval, 60–120 s). Therefore, fresh frozen canine plasma[x] was bolused intravenously to a total volume of 355 mL (13 mL/kg). The MAP showed no improvement after plasma administration so dopamine[y] (7.5 μg/kg/min, IV) was instituted. In addition, the patient remained on a plasma infusion (2.5 mL/kg/h, IV) and isotonic crystalloid solution[f] (5 mL/kg/h, IV). Thirty minutes after initiating dopamine, the MAP remained 50 mm Hg. At that time, a standard 1-hour ACTH stimulation test[z] was performed using 250 μg cosyntropin[aa] IV. While awaiting results of the ACTH stimulation test, and approximately 5 hours after starting the dopamine CRI, hydrocortisone[bb] (0.5 mg/kg, IV) was administered. Within 2 hours of the first dose of hydrocortisone, the dog's MAP increased to 70 mm Hg and remained $\geq$75 mm Hg while receiving dopamine (5 μg/kg/min). The arterial serum lactate concentration dropped to 1.4 mmol/L. The dopamine CRI was discontinued 8 hours after the administration of the first hydrocortisone dose, and the dog's MAP remained above 80 mm Hg without further pressor support for the remainder of hospitalization. Hydrocortisone was continued at a dosage of 0.5 mg/kg, IV, every 6 hours, for 4 days. The dosage was then decreased to 0.5 mg/kg, IV, every 8 hours, on day 5, and further reduced to every 12 hours administration on day 8. The results of the ACTH stimulation test were available 3 days after initiation of hydrocortisone therapy, and showed a baseline serum cortisol concentration of 0.16 μmol/L (5.6 μg/dL) and post-stimulation serum cortisol concentration of 0.15 μmol/L (5.5 μg/dL) (δ cortisol = −0.01 μmol/L [−0.1 μg/dL]).

Four days after the initiation of positive pressure ventilation the P:F ratio had increased to 313, indicating marked improvement in the patient's lung function. The dog was weaned from mechanical ventilation and placed in an oxygen cage with an oxygen concentration between 40% and 60%. On the sixth day of hospitalization, the dog no longer required supplemental oxygen, and had a PaO_2 of 95 mm Hg while breathing room air.

The patient's gastrointestinal signs of vomiting and regurgitation were treated with the following: metoclopramide[cc] (1 mg/kg/d, IV), ondansetron[dd] (0.6 mg/kg, IV, q 24 h), famotidine[ee] (0.5 mg/kg, IV, q 12 h), a nasogastric tube with intermittent gastric suction, and sucralfate[ff] (1 g, PO, q 8 h). The dog received total parenteral nutrition with gradual weaning to an enteral low fat diet.[gg] The patient's gastrointestinal signs were suspected to be due to gastroenteritis from dietary indiscretion and resolved with supportive therapy over the course of hospitalization.

The patient was discharged 11 days after presentation on broad-spectrum antimicrobials (amoxicillin/clavulanic acid,[hh] 14 mg/kg, PO, q 12 h; enrofloxacin, 5 mg/kg, PO, q 12 h, metronidazole, 10 mg/kg, PO, q 12 h), gastric protectants (famotidine, 1 mg/kg, PO, q 24 h; sucralfate, 1 g, PO, q 8 h), a low-fat diet,[gg] and saline nebulization with coupage every 8 hours daily.

Four weeks following hospital discharge, the dog was bright and active, and reported to be doing well at home. Thoracic radiographs, a CBC, a serum biochemistry panel, and a standard 1-hour ACTH stimulation test were performed. Thoracic radiographs showed resolving aspiration pneumonia. The CBC and serum biochemistry panel were within normal limits. The baseline serum cortisol concentration was 0.03 μmol/L (1.1 μg/dL) and the post-stimulation serum cortisol concentration was 0.32 μmol/L (11.3 μg/dL) (δ cortisol = +0.29 μmol/L [+10.2 μg/dL]).

Discussion

Dysfunction of the HPA axis leading to adrenal insufficiency has been described in humans with severe sepsis or septic shock.[1–5] Patients with this type of adrenal insufficiency do not have the absolute adrenal insufficiency seen in classic hypoadrenocorticism (Addison's disease). Rather, these patients produce cortisol, but the production or adrenal reserve of the hormone may be inadequate for the degree of illness. This syndrome is associated with pressor-refractory hypotension[6–8] and death.[5,9,10] Because it is not classic hypoadrenocorticism and because endogenous serum cortisol concentration is not usually low, this syndrome has been described in the literature as a relative adrenal insufficiency.[1,5,8,14] The term relative adrenal insufficiency has come under criticism because the name implies that the adrenal glands are abnormal (primary adrenal dysfunction). The adrenal insufficiency seen in critical illness can also be due to hypothalamic or pituitary dysfunction (secondary adrenal dysfunction). Additionally, alterations in glucocorticoid transport or a decreased affinity for glucocorticoids at the level of glucocorticoid receptors may play a role.[3] Hence, it has been recommended that the syndrome be renamed to critical illness-related corticosteroid insufficiency (CIRCI).[15]

The pathophysiology of CIRCI is unknown. The syndrome has many possible underlying causes, and one or many pathophysiologic mechanisms may be responsible in any given individual. One theory involves suppression of the HPA axis by inflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor-α.[6,16,17] Adrenal insufficiency in humans with sepsis has also been associated with hemorrhage or microvascular thrombi in the adrenal glands.[6] Endotoxin has also been found to decrease glucocorticoid

receptor affinity for cortisol and to cause downregulation of these receptors.[3] The exact cause of CIRCI in this dog was unknown. Cytokine-mediated suppression of the HPA axis seems more likely than diffuse, bilateral adrenal hemorrhage or thrombosis, as there were no electrolyte abnormalities to suggest aldosterone deficiency, and no evidence of adrenal hemorrhage visualized during the ultrasonographic examination.

The best method to identify CIRCI is unknown. The most common method used in humans is to determine the difference between the serum cortisol concentration at baseline and after a standard ACTH stimulation test using 250 μg of cosyntropin. The value obtained by subtracting the baseline serum cortisol concentration from the stimulated serum cortisol concentration is called δ cortisol, and a value $<0.25\,\mu mol/L$ ($<9\,\mu g/dL$) has been associated with pressor-refractory hypotension[6–8] and death[5,9,10] in human beings. The δ cortisol method in response to 250 μg of cosyntropin is used most commonly for the diagnosis of HPA-axis dysfunction in critically ill humans because of its prognostic value and the ease of the test, and it has been validated using the more cumbersome gold standard of the metyrapone stimulation test.[5] Other methods that have also been evaluated to identify HPA-axis dysfunction in critically ill humans include baseline serum cortisol concentration, ACTH-stimulated serum cortisol concentration, the ratio between endogenous plasma ACTH concentration and baseline serum cortisol concentration, and combinations of these methods.[1,2,14,18] In addition, some authors have evaluated an ACTH stimulation test using the more physiologic cosyntropin dose of 1 μg per adult human being, and have identified a greater number of patients with δ cortisol $<0.25\,\mu mol/L$ ($<9\,\mu g/dL$) using this method.[19,20] However, no study has shown that this more sensitive testing method has greater prognostic value than the less sensitive 250 μg ACTH stimulation test, and therefore the low-dose ACTH stimulation test has not gained wide acceptance. One study of septic dogs found that a δ cortisol of $<0.08\,\mu mol/L$ ($<3\,\mu g/dL$) in response to a standard 1-hour ACTH stimulation test using 250 μg of cosyntropin was associated with hypotension and decreased survival.[13] The dog in the current report had a δ cortisol of $-0.01\,\mu mol/L$ ($-0.1\,\mu g/dL$) in response to 250 μg of cosyntropin, consistent with CIRCI.

Hydrocortisone is recommended for treatment of pressor-refractory hypotension in humans.[21] It has been shown to improve pressor response to alpha agonists in patients with septic shock,[1,22] and its use has been associated with blood pressure stabilization and earlier vasopressor weaning.[18,23–27] Hydrocortisone is structurally identical to endogenous cortisol in both dogs and humans.[28] It has some intrinsic mineralocorticoid activity that may support intravascular volume[8,29] and a short duration of HPA-axis suppression.[21] Based on this information, hydrocortisone was chosen over other glucocorticoids for the dog in this case report. Within 8 hours of initiation of replacement hydrocortisone therapy, the dog was weaned from vasopressor support and maintained a normal blood pressure. This clinical response is consistent with the rapid shock reversal noted in some humans after administration of hydrocortisone; the literature reports improved mean arterial blood pressure within 24 hours[27] and discontinuation of vasopressor support in as little as 2 days after initiation of the drug.[8,23,24,27]

This dog received hydrocortisone 0.5 mg/kg, IV, every 6 hours (2 mg/kg/d). This hydrocortisone dose is approximately equivalent to a prednisone dose of 0.5 mg/kg/d.[28] The doses of hydrocortisone used in humans range from 2.9 to 4.3 mg/kg/d, and are therefore called *physiologic*, *stress*, *replacement*, or *low* doses.[23–25] Some studies suggest that low-dose hydrocortisone improves survival in human septic shock patients with CIRCI such that their outcomes are similar to those of patients with normal HPA-axis function.[8,24,25,29] This dog received intermittent boluses rather than a CRI of hydrocortisone due to ease of administration. In humans, both bolus[8,27] and CRI[23–25] administration has been described. Studies have not been performed to determine the superiority of either technique.

The dog in this study was weaned from hydrocortisone over a 6-day period. The patient was then discharged with no additional exogenous glucocorticoid therapy, and continued to improve. The best approach for tapering glucocorticoid supplementation after use in critical illness is unknown. In humans, glucocorticoid weaning is generally performed over several days.[8,24] Glucocorticoid supplementation should be decreased only once the patient is stable and improving, as hydrocortisone withdrawal before resolution of septic shock has resulted in hemodynamic deterioration.[2] In dogs, it seems reasonable to consider glucocorticoid weaning once the patient begins to eat voluntarily, or a few days before anticipated discharge.

An ACTH stimulation test was performed in this dog 1 month after hospital discharge, which was several weeks after discontinuation of glucocorticoid therapy. The convalescent ACTH stimulation test was essential to confirm that the adrenal hyporesponsiveness noted during the septic shock episode was in fact CIRCI rather than classic hypoadrenocorticism, particularly because hypoadrenocorticism appears to be prevalent in Standard Poodles.[3] The normal convalescent ACTH stimulation test confirmed that this dog did not have classic hypoadrenocorticism but rather experienced a

transient HPA-axis abnormality. Humans with CIRCI have been shown to recover HPA-axis function after resolution of critical illness.[14] It is possible that this dog, who may be at increased risk for adrenal disease,[30] may also have been at increased risk of developing CIRCI; however, no association has been shown between CIRCI and classic hypoadrenocorticism in humans.

In their landmark report published in 2002,[8] Annane et al described the results of a multicenter, randomized, double-blind, placebo-controlled trial that included 300 patients with septic shock. These patients were administered a standard 250 μg ACTH stimulation test and divided into 2 treatment groups: 1 receiving hydrocortisone (50 mg, IV, q 6 h) and fludrocortisone (50 μg, PO, q 24 h), and 1 receiving a placebo. This study found a significant improvement in the 28-day survival in patients with δ cortisol $<0.25\,\mu mol/L$ ($<9\,\mu g/dL$) that received corticosteroids compared with those patients that received placebo. There was no difference between the hydrocortisone and the placebo groups in the frequency of adverse events.

Findings of the 2002 report were brought into question after results of a more recent investigation by the CORTICUS study group were published in early 2008.[31] The CORTICUS trial is the largest multicenter, randomized, double-blind, placebo-controlled study to date about HPA-axis function in septic shock, and included 499 patients. All patients underwent a standard 250 μg ACTH stimulation test, and were then divided into 2 treatment groups: 1 receiving hydrocortisone therapy and the other a placebo. The CORTICUS study found no significant difference in the 28-day survival of humans that were responders to ACTH stimulation compared with nonresponders, nor in patients treated with hydrocortisone compared with placebo. The trial did, however, find that treatment with hydrocortisone resulted in a faster time to reversal of shock in all treated patients, regardless of δ cortisol. Adverse events such as superinfections or new infections were observed more frequently in the hydrocortisone group than in the placebo group. Therefore, results of the CORTICUS trial call into question the relationship between adrenal responsiveness and hydrocortisone's effects on systemic blood pressure.

The marked disparity in results between the 2 studies is likely due in part to a difference in the degree of illness in the populations. Based on a higher median Simplified Acute Physiology Score II score and a higher mortality rate in its placebo group, Annane and colleagues's study population was more critically ill than the CORTICUS study population. The Annane and colleagues study required enrollment within 8 hours, whereas the CORTICUS trial allowed enrollment for up to 72 hours, after development of septic shock. Patients that survive the first 72 hours of septic shock may be more likely to survive in general. The disparity in inclusion criteria may therefore have biased the CORTICUS trial toward enrolling a more stable patient population less likely to benefit from hydrocortisone.

Additionally, the CORTICUS trial was conducted after publication of the first Surviving Sepsis Campaign Guidelines,[21] in which hydrocortisone was 'recommended in patients with septic shock who, despite adequate fluid replacement, require[d] vasopressor therapy to maintain adequate blood pressure.' Therefore, many physicians may have excluded their sickest patients from the CORTICUS trial so they could administer hydrocortisone to those at a higher risk of developing CIRCI, in accordance with these guidelines. Such exclusion would have resulted in confounding by indication, and would have severely biased the results of the CORTICUS trial.

The survival benefit of hydrocortisone in these 2 studies was also different. The more critically ill population in the Annane and colleagues study was treated with hydrocortisone after a shorter delay, suggesting that there may be a greater benefit in hydrocortisone treatment soon after the onset of septic shock. The CORTICUS study also demonstrated via the placebo group that patients who live up to 72 hours with septic shock are more likely to live in general and less likely to benefit from the hydrocortisone. The inclusion of patients treated with etomidate, an adrenal suppressive anesthetic drug, may have also resulted in a more obvious benefit for patients in the Annane and colleagues study. The addition of fludrocortisone in the Annane et al study may also have enhanced treatment efficacy. Fludrocortisone may increase survival by increasing vascular volume; however, no additional research on supplemental mineralocorticoids has been done in patients with CIRCI. The increase in adverse side effects seen in the CORTICUS trial may have been due to administration of hydrocortisone to less critically ill patients, in which the side effects may have been more notable than the benefits.

Decreased time to shock reversal after administration of hydrocortisone was noted in both studies. This consistent finding suggests a population of patients with pressor-resistant hypotension that will respond to low-dose hydrocortisone administration, regardless of their HPA-axis function. Yet the absence of a true diagnosis of CIRCI in the patients in the CORTICUS trial suggests that this hydrocortisone-responsive hypotension may be a separate condition.

The dog in this report was found to have CIRCI associated with hydrocortisone-responsive hypotension.

CIRCI has also been identified in other critically ill dogs. In canine[c],[13] studies, the patients with blunted cortisol responses to ACTH administration were also diagnosed with systemic inflammatory response syndrome or sepsis. This dog exhibited a reversal of shock after administration of hydrocortisone. This condition is seen in patients with CIRCI, but based on the findings from the CORTICUS trial, the exact relationship between HPA-axis function and hydrocortisone-responsiveness is unknown. This case report is, to the authors' knowledge, the first description of a dog with both CIRCI and hydrocortisone-responsive hypotension. Further investigation is warranted to determine the incidence and character of CIRCI in critically ill veterinary patients, and to evaluate the effects of low-dose hydrocortisone in patients with pressor-resistant hypotension.

Footnotes

[a] Prittie JE, Barton LJ, Peterson ME, et al. Hypothalmo-pituitary-adrenal (HPA) axis function in critically ill cats (abstr). J Vet Emerg Crit Care 2003;13(3):165.
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[c] Shaw SP, Chan DL, de Laforcade AM, Rozanski EA. Relative adrenal insufficiency in critically ill dogs. J Vet Emerg Crit Care 2005;15(S1);S7.
[d] Lasercyte Hematology analyzer, IDEXX Laboratories Inc, Westbrook, ME.
[e] SNAP 3DX test, IDEXX Laboratories Inc.
[f] Lactated Ringers Solution, Baxter Healthcare Corp, Deerfield, IL.
[g] Ampicillin, Abraxis Pharmaceuticals, Schaumburg, IL.
[h] Baytril, Bayer Healthcare, Shawnee Mission, KS.
[i] CBC, IDEXX laboratories Inc, Sacramento, CA.
[j] Prothrombin time, Coag analyzer, IDEXX Laboratories Inc.
[k] Activated partial thromboplastin time, Coag analyzer, IDEXX Laboratories Inc.
[l] D-dimer, IDEXX laboratories.
[m] Timentin, GlaxoSmithKline, Research Triangle Park, NC.
[n] 0.9% Sodium chloride, Baxter Healthcare Corp.
[o] CBC, University of California Davis Clinical Pathology Service, Davis, CA.
[p] Serum biochemistry panel, University of California Davis Clinical Pathology Service.
[q] Metronidazole, Hospira Inc, LakeForest, IL.
[r] Midazolam HCL, Bedford Laboratories, Bedford, OH.
[s] Oxymorphone, Endo Laboratories, Chadds Ford, PA.
[t] Propofol, AstraZeneca Pharmaceuticals, Wilmington, DE.
[u] Respironics Esprit ventilator, Respironics Inc, Carlsbad, CA.
[v] Pentobarbital, Abbott Laboratories, North Chicago, IL.
[w] ACT II, Medtronic Inc, Minneapolis, MN.
[x] Fresh frozen plasma, University of California Davis Blood Bank, Davis, CA.
[y] Dopamine, American Regent Inc, Shirley, NY.
[z] ACTH stimulation, IDEXX laboratories.
[aa] Cortrosyn, Amphastar Pharmaceuticals Inc, Rancho Cucamonga, CA.
[bb] Hydrocortisone sodium succinate, Pharmacia and Upjohn Co, New York, NY.
[cc] Metoclopramide, Hospira Inc.
[dd] Ondansetron, Bedford Laboratories.
[ee] Famotidine, Baxter Healthcare Corp.
[ff] Sucralfate, TEVA Pharmaceuticals, Sellersville, PA.
[gg] Digestive Lowfat LF, Royal Canin, St Charles, MO.
[hh] Clavamox, GlaxoSmithKline.

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