Fatal Waterhouse-Friderichsen Syndrome in Two Post-operative Colics

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Objective- This report documents fatal Waterhouse-Friderichsen Syndrome following exploratory abdominal surgery and severe endotoxemia in two horses.

Study Design: Clinical Case Report

Animals: A 14-year-old (544 kg) Tennessee Walking Horse gelding and a 16-year-old (499 kg) Quarter Horse mare that presented for emergency acute abdominal pain resulting in celiotomy.

Results. The horses represented in this case study demonstrated signs of progressive hypovolemic shock in the face of aggressive fluid therapy with continual hyposthenuria. Horses furthermore demonstrated progressive hypovolemia with hemoconcentration, persistent tachycardia, and prolonged CRT. After prolonged hypovolemia both horses developed azotemia. The loss of adrenocortical function was identified with the plummeting hypoglycemia (40 gm/dL rr 60-120 gm/dL) and loss of homeostatic mechanisms. Both horses were euthanized due clinical deterioration and to failure to respond to treatment.

Conclusion: Waterhouse-Friderichsen Syndrome is an irreversible, fatal condition in horses.

Introduction:

The adrenal gland is vital in maintaining normal cardiovascular status, fluid balances, metabolism, inflammation and reproductive function.[1] Emerging evidence in both human and veterinary medicine suggests that transient, reversible adrenocortical dysfunction resulting in cortisol insufficiency frequently develops during critical illness.[2-5] This syndrome is termed relative adrenal insufficiency (RAI) or critical illness-related corticosteroid insufficiency (CIRCI), and can contribute substantially to morbidity and mortality associated with the primary cause of shock.[3-5] Irreversible adrenocortical injury, identified as Waterhouse-Friderichsen Syndrome (WFS) in humans is the occurrence of acute hemorrhagic necrosis resulting in permanent adrenocortical dysfunction.[6] Adrenal hemorrhage is believed to occur due to the increased adrenocorticotropic hormone (ACTH) stimulation that induces an increase in arteriolar blood flow to the adrenal glands while the catecholamines involved in critical illnesses cause a venous constriction, resulting in arteriolar thrombosis and frank parenchymal hemorrhage.[2] In humans, WFS is typically caused by an overwhelming bacterial meningitis and sepsis leading to hypotension and shock.[2-4, 7-12] Adrenal hemorrhage secondary to sepsis has been described as a histopathological finding seen in calves, primates, and rabbits.[13-15] Similar histopathological findings were described in horses documenting massive to patchy adrenal hemorrhages after acute death associated with diarrhea and diagnosed as a complication of "Colitis X".[16] However, WFS has not been reported in horses. The following case report documents fatal WFS in two horses following colic surgery and sepsis.

Case 1:

A 14-year-old (544 kg) Tennessee Walking Horse gelding was referred for severe abdominal pain. On presentation, the horse was severely painful, tachycardic (70 bpm), and hypothermic (97.8°F) with absent borborygmi in all four quadrants. The patient was dehydrated with tacky mucous membranes and prolonged capillary refill time (CRT) of >3 seconds. Intravenous fluid therapy was initiated with one liter of hypertonic saline followed by 10 liters of lactated ringer's solution (LRS). Bloodwork demonstrated moderate hemoconcentration with a packed cell volume (PCV) (45.0%, rr 26-42%), hyperglycemia (160 mg/dL, rr 60-122 mg/dL), and hypocalcemia (10.3 mg/dL, rr 11.2-13.6 mg/dL). A brief abdominal ultrasound demonstrated an edematous large colon (wall thickness of 13-15 mm) and a gas distended cecum. Rectal palpation was not performed due to severe unrelenting pain, and the horse was recommended for surgery.

Prior to surgery, antimicrobials of potassium penicillin G (Pfizerpen[a], 22,000 IU/kg intravenously [IV]) and gentamicin (GentaFuse[b], 6.6 mg/kg IV) were administered. The horse was induced with xylazine (X-ject E injection[c], 0.2 mg/kg IV.), butorphanol (Torbugesic[d], 0.01 mg/kg IV) and ketamine (Ketaset[e], 2.2 mg/kg IV.) and diazepam (Valium[f], 0.2 mg/kg IV). In surgery, the small intestines were distended with gas, the ileum was mildly impacted, and the large colon was severely discolored to dark red and gas distended. A 360 degree large colon volvulus was corrected, and a pelvic flexure enterotomy was performed. The ventral colon was edematous, thick, and firm to the touch, and had an 8 cm X 6 cm area of petechial hemorrhage.

During surgery, the patient had marked bradycardia (6-12 bpm) and severe hypotension (MAP of 40-60 mmHg) for the majority of the surgery. A dobutamine constant rate infusion (CRI) (DOBUTamine[g] 0.5-1 mcg/kg/min IV), 50 total mgs of ephedrine (Ephedrine Sulfate

Injection, USP[h]), a 500mL bolus of colloids (6% Hetastarch[i]), and a 1 liter bolus of hypertonic saline were used to treat the cardiovascular depression during surgery. The patient was markedly acidotic (pH 7.23, rr 7.35-7.45) and hyperglycemic at the start of surgery (246 mg/dL, rr 60-122 mg/dL). All cardiac depression and decreased perfusion parameters were improved before surgery was completed, and recovery was uneventful.

Immediately following recovery, the horse was mildly tachycardic (56 bpm) with injected mucous membranes and a toxic line. Postoperative medical treatment included twice maintenance fluids, a lidocaine CRI (Lidocaine 2%[j], 50 ug/kg/min IV), potassium penicillin (22,000 IU/kg IV every 6 hours), gentamicin (6.6 mg/kg IV every 24 hours), flunixin meglumine (Banamine[k], 1.1 mg/kg IV every 12 hrs), and polymyxin B (Polymixin B for Injection, USB[l] 5000 units/kg IV every 8 hours).

Twelve hours after surgery, the patient was moderately leukopenic (3.6 K/uL, rr 5-11.9 K/uL) and still hypovolemic with a mildly increased PCV (43%, rr 26-42%), a moderately decreased plasma protein (4.9 g/dL, rr 6.8-7.9 g/dL), and a mildly increased creatinine (2.1 mg/dL, rr 1.2-1.9 mg/dL).

Eighteen hours following surgery, the patient developed signs of post-operative ileus, apparent by elevations in heart rate with mild colic signs and nasogastric reflux. A metoclopramide CRI (Metoclopramide Injection[m] 0.04 mg/kg/hour IV) was initiated, as well as antioxidant therapy of 490 grams of dimethyl sulfide (DMSO[n]) diluted in 5 liters LRS every 12 hours. The NG tube remained in place and was evaluated for reflux every 2 hours. Fluid therapy was increased to 4 L/hr. to account for on-going losses, and the patient began urinating hourly.

Twenty-four hours post-operatively, the patient declined. The patient was hypovolemic and pollakiuria in the face of aggressive fluid therapy with the following abnormalities:

hemoconcentration (PCV 43.0%, rr 26-42%), elevated creatinine (2.1 mg/dL, rr 1.2-1.9 mg/dL), mildly decreased plasma protein (4.9 g/dL, rr 6.8-7.9 g/dL), and mild leukopenia (3.6 K/uL, rr 5-11.9 K/uL).

Thirty-six hours following surgery, the patient was tachycardic (76 bpm) and depressed. Mucous membranes were injected dark red with a CRT > 3 seconds. Blood gas analysis was markedly acidotic (pH 7.15, rr 7.35-7.45) and severely hypoglycemic (39 mg/dL, rr 60-122 mg/dL), with significant elevations in lactate (18 /mmol, rr 0-2 /mmol). The horse was administered 200 mL of Karo syrup via the nasogastric tube for treatment of the hypoglycemia. Chloramphenicol therapy (Viceton^{o}, 50 mg/kg bwt *per os*) was initiated for treatment of worsening sepsis.

Forty-eight hours flowing surgery, blood work was repeated demonstrating worsening hemoconcentration, (PCV 44.0%, rr 26-42%), increased creatinine (3.0 mg/dL, rr 1.2-1.9 mg/dL), marked leukopenia (2.2 K/uL, rr 5-11.9 K/uL) characterized by a moderate neutropenia (1188 /uL, rr 2260-8580 /uL). Blood chemistry showed a mild hypernatremia (152.2 mmol/L, rr 132-146 mmol/L), mild hyperchlorinemia (109.2 mmol/L, rr 98-106 mmol/L), moderate decrease in total carbon dioxide (10.1 mmol/L, rr 24-32 mmol/L), markedly increased anion gap (36 mmol/L, rr 6-16 mmol/L), and severe hypoglycemia (40 mg/dL, rr 60-122 mg/dL). Urinalysis showed hyposthenuria (urine specific gravity (USG) 1.015 rr 1.025-1.060), aciduria (pH 6.0, rr 7.5-8.5), hematuria, and trace proteinuria. Due to the continued deterioration of the patient with evidence of multiple organ failure, the horse was humanely euthanized.

Post-mortem necropsy revealed numerous, widely disseminated petechial to ecchymotic hemorrhages along the surface of the abdominal and thoracic cavity. The lungs were mottled, dark red to pink, and soft, and on histopathologic evaluation, the lungs were severely congested

with blood, consistent with severe, acute pulmonary congestion. Aerobic culture of lung samples showed mixed gram positive and gram negative growth of organisms that included: *Escherichia coli* (hemorrhagic), *Aeromonas hydrophila*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, and *Enterococcus faecium*. The surface of the ventral and dorsal large colon was mottled pale tan to dark red to green. A sharply demarcated, approximately 5 cm in diameter area of necrosis was present in the wall of the cecum at the junction of the cecum and the ventral colon. The mucosal surface of the large colon and cecum was dark red to green and covered with fibrin, with mild edema in the walls of the cecum and large colon. The kidneys were grossly and histologically normal. There was bilateral, moderate, acute hemorrhage of the zona glomerulosa of the adrenal glands. Histologically, there were multiple areas of hemorrhagic necrosis within the adrenal glands, particularly along the superficial margins, characterized by hypereosinophilia, loss of cellular detail, nuclear pyknosis and karyorrhexis, and the disassociation of cells from the underlying basement membrane indicative of WFS. These findings were consistent with diffuse, necrosuppurative colitis of the large colon with severe endotoxemia.

Case 2:

A 16-year-old (499 kg) Quarter Horse mare that presented on emergency for signs of colic. On presentation, she was painful, tachycardic (88 bpm), tachypneic (76 bpm), with a mild fever (102.1°F), toxic mucus membranes, and approximately 10% dehydrated. Eight liters of net reflux were obtained after passing a nasogastric tube. Upon rectal exam, a right dorsal displacement was diagnosed. Multiple loops of mild to moderately distended small intestine were also palpable. The mare was leukopenic (3.3/uL, rr 5.0-11.9/uL), with a degenerative left shift (segmented 2282/uL, rr 2500-6000/uL, and bands 228.2/uL, 0-100/uL) and an increased PCV (60%, rr 26-42%). A blood chemistry analysis showed that the patient had a moderate hypochloremia (88.8 mmol/L, rr 98-106 mmol/L), mild hypomagnesemia (1.2 mg/dL, rr 1.6-2.5 mg/dL), mild hypocalcemia (9.2 mg/dL, rr 11.2-13.6 mg/dL), moderately increased anion gap (36 mmol/L, rr 6-16 mmol/L), mild hyperglycemia (188 mg/dL, rr 60-122 mg/dL), and marked azotemia with increased creatinine (5.2 mg/dL, rr 1.2-1.9 mg/dL) and blood urea nitrogen (BUN) (40 mg/dL, 10-24 mg/dL).

Exploratory laparotomy was recommended due to the severity of pain and clinical signs. Preoperative antibiotics included gentamicin (6.6 mg/kg bwt IV) and enrofloxacin (Baytril 100[p], 7 mg/kg bwt IV); as well as ketoprofen (Ketofen[q], 2.2 mg/kg bwt IV) for analgesia. Xylazine (0.2 mg/kg bwt IV) and butorphanol (0.02 mg/kg bwt IV) were used as preanesthetic medications, and ketamine (2.8 mg/kg bwt IV) and diazepam (0.1 mg/kg bwt IV) were used as induction agents for surgery.

A ventral midline celiotomy was performed diagnosing a right dorsal colon displacement with fulminant enteritis. Following recovery, a nasogastric tube placed, and the horse was

refluxed every 2 hours. Treatments included fluid therapy, prokinetic therapy, and 490 grams DMSO IV diluted in 1 liter of LRS.

Three hours following surgery, the patient became uncomfortable, restless, and showing signs of colic. The mare was tachycardic (80 bpm) with toxic mucous membranes. She was hemoconcentrated (PCV 45%, rr 26-42%) and had become severely hypoglycemic (40 mg/dL, rr 60-122 mg/dL), hypernatremic (147.5 mmol/L, rr 132-146 mmol/L), hyperkalemic (4.8 mmol/L, rr 2.4-4.7 mmol/L), hyperchloremic (106.2 mmol/L, rr 98-106 mmol/L), hypocalcemic (8.5 mg/dL, rr 11.2-13.6 mg/dL) and acidotic with low bicarbonate (17.9 mEq/L, rr 24-32) and increased anion gap (28 mmol/L, rr 6-16 mmol/L). The mare was azotemic with an increased BUN (46 mg/dL, rr 10-24 mg/dL) and creatinine (5.58 mg/dL, rr 1.2-1.9 mg/dL). She had a worsening leukopenia (1.8 K/uL, rr 5-11.9 K/uL) characterized by a marked degenerative left shift (segmented 746.2 /uL, rr 2500-6000 /uL, and bands 109.2 /uL, rr 0-100/uL). Urine analysis revealed hyposthenuria (USG 1.008, rr 1.025-1.060) and an increased urine protein/creatinine ratio (urine total protein 13.8 mg/dL and urine total creatinine 15.9 mg/dL for a ratio of 0.87, rr < 0.4).[17] Due the horse's acute deterioration and increase in pain, the owner elected to humanely euthanize 6 hours following recovery.

A post-mortem necropsy was performed, which revealed peracute superficial mucosal necrosis with segmental jejunal volvulus and venous infarction in the small intestine. This jejunal volvulus was considered peracute, which led to necrosis of the mucosa with bacterial invasion into the bloodstream that initiated endotoxemia. The kidneys showed severe, acute, diffuse tubular injury, likely as a result of hypoxia secondary to endotoxemic shock. These pathologic signs likely caused the clinical signs of acute renal failure. The large colon had mild, acute mucosal hemorrhage of the pelvic flexure, and the rectum showed fibrinous proctitis. The

adrenal glands showed moderate, acute, multifocal cortical hemorrhage with necrosis, particularly in the zona fasciculata, consistent with fatal WFS.

Discussion:

The horses represented in this case study demonstrated signs of progressive shock in the face of aggressive fluid therapy with continued pollakiuria and hyposthenuria. Both horses demonstrated progressive hypovolemia with worsening hemoconcentration, persistent tachycardia, and abnormal perfusion parameters despite fluid therapy, and eventually developed azotemia after prolonged hypovolemia. It was the authors experience that we did not identify the loss of mineralocorticoid dysfunction until the plummeting hypoglycemia was identified in horse 1, which made the recognition of this condition in horse 2 more readily apparent. Waterhouse-Friderichsen Syndrome is a fatal, irreversible disease, and early recognition of patients at risk for adrenal insufficiency may improve survival.

Critical illness-related corticosteroid insufficiency has been extensively investigated in foals. A depressed adrenal response, evidenced by an increased ACTH concentration (>153 pg/mL), was shown to be a negative prognostic indicator in septic foals.[18] Also, a lower cortisol concentration was associated with an increased mortality in septic foals.[18] It was also shown that the ACTH/cortisol ratios were higher in septic foals that died than septic foals that survived or healthy foals. [18-20]

In adult horses with Systemic Inflammatory Response Syndrome (SIRS), there is a reduction in both glucocorticoid receptor density and affinity, leading to an overall resistance to glucocorticoids.[21] This indicates that even a normal adrenal response may be inadequate in SIRS, and these horses may benefit from exogenous glucocorticoids. [21] Inflammatory mediators in sepsis have been shown to directly inhibit cortisol synthesis and the tissue response to glucocorticoids in humans, and in human medicine, the treatment of suspected adrenal insufficiency includes vasopressor therapy and moderately supraphysiologic steroid therapy to

211 overcome the tissue steroid resistance that occurs in sepsis. [4] It is recommended in human
212 medicine that adrenal insufficiency testing should be performed, such as a baseline cortisol and a
213 corticotropin test, but in septic shock, steroid therapy should be initiated in suspected cases at
214 testing and stopped if the results do not indicate adrenal insufficiency.[4] For adrenal function
215 testing in horses, a low dose ACTH stimulation test has been standardized in healthy horses
216 (cosyntropin at 0.1 μg/kg with a peak cortisol concentration 30 minutes after administration), but
217 its application in horses with adrenal insufficiency has not yet been evaluated.[22]

218 Although the use of steroids in horses may be controversial, and the use of steroids in a
219 septic horse may seem contraindicated, there was reduced mortality and duration of vasopressor
220 therapy in human patients with sepsis and clinical adrenal insufficiency in the intensive care unit
221 that were treated with steroid therapy.[4] Clinical signs of adrenal insufficiency in humans that
222 would be expected with decreased aldosterone, such as hyperkalemia and hyponatremia, can be
223 seen, but are not commonly seen in human intensive care medicine as fluid resuscitation
224 compensates for these issues.[4] In a case series of forensic autopsies in humans, pathologists
225 identified cases of undiagnosed WFS during autopsies with clinical histories of sepsis, and
226 strongly suggest that the morbidity and mortality of these patients can be decreased with early
227 diagnosis and treatment.[23]

228 Alterations in the adrenal axis results in the clinical signs of hypotension despite
229 aggressive treatment, as well as the plummeting blood glucose levels seen in these cases. The
230 adrenal insufficiency seen in these cases lead to the inability to conserve fluids and concentrate
231 urine and to persistent hypovolemia and later azotemia. In horses with WFS, in our experience,
232 severe hypoglycemia is a poor prognostic indicator, and is indicative of irreversible adrenal

hemorrhage and insufficiency. This case report documents fatal Waterhouse Friderichsen Syndrome in two horses that rapidly decompensated following colic surgery and sepsis.

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Manufacturer information:

a. Pfizerpen, Roerig, New York, NY, USA
b. GentaFuse, Henry Schein Animal Health, Dublin, OH, USA
c. X-ject E injection, Henry Schein, Dublin OH
d. Torgugesic, Zoetis Inc., Kalamazoo, MI, USA
e. Ketaset, Zoetis Inc., Kalamazoo, MI, USA
f. Valium, Hospira, Inc., Lake Forest, IL, USA
g. DOBUTamine, Hospira, Inc., Lake Forest, IL
h. Ephedrine Sulfate Injection, USP, Akron, Inc., Lake Forest, IL, USA
i. 6% Hetastarch, Hospira, Inc., Lake Forest, IL, USA
j. Lidocaine 2% Distributed by MWI, Boise, ID 83705, USA
k. Banamine, Intervet International B.V., Boxmeer, AN, Netherlands
l. Polymyxin B X-Gen Pharmaceuticals, Inc., Big Flats, NY, USA
m. Metoclopramide-Teva Parenteral Medicines, Inc., Irvine, CA, USA
n. DMSO, Neogen Corporation, Lexington, KY, USA
o. Viceton, Osborn made by Bimeda Inc, Le Sueur, MN, USA
p. Baytril 100, Bayer HealthCare LLC, Shawnee Mission, KS, USA
q. Ketofen, Zoetis Inc., Kalamazoo, MI, USA