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CASE REPORT

Waterhouse–Friderichsen syndrome in a cat with *Klebsiella* spp. infection

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Abstract

Objective: To describe a case of Waterhouse–Friderichsen syndrome of adrenocortical failure in a cat with *Klebsiella* spp. infection.

Case Summary: A 12-year-old male neutered domestic short-haired cat was referred for respiratory failure requiring mechanical ventilation. The cat remained comatose despite successful weaning from the ventilator and developed a *Klebsiella pneumoniae* pneumonia. On day 4 of hospitalization, the cat acutely deteriorated with profound hypotension, azotemia, and hyperkalemia, which rapidly progressed to cardiac arrest. Necropsy findings revealed massive adrenal hemorrhage and intralesional bacteria, termed Waterhouse–Friderichsen syndrome. Waterhouse–Friderichsen syndrome was suspected to have been the cause of acquired adrenocortical insufficiency and sudden death of the cat.

New or Unique Information: To the authors' knowledge, this is the first report of sepsis causing Waterhouse–Friderichsen syndrome in a veterinary species.

1 | CASE SUMMARY

A 12-year-old male neutered domestic short-haired cat was referred to a tertiary care veterinary hospital for further management of dyspnea post trauma. The cat presented to the primary care veterinarian 2 days prior with motor vehicle–related blunt trauma. At presentation to the referring veterinarian, the cat was dyspneic and had oral bleeding but was able to ambulate. Initial treatment included methadone (0.3 mg/kg intravenously, IV) and flow by-oxygen. A radiograph revealed pneumothorax and pulmonary contusions. Hematology and biochemistry profiles revealed a mild increased alanine transaminase activity (267 U/L; reference interval [RI]: 12–130 U/L) and hyperglycemia (glucose = 9.28 mmol/L [167 mg/dL]; RI: 3.95–8.84 mmol/L [71.1–159 mg/dL]). Twenty-one milliliters of air was removed via needle thoracocentesis from the left hemithorax. Further supportive treatment consisted of oxygen therapy via oxygen tent, methadone, compounded sodium lactate crystalloid fluids, and a single dose of potentiated amoxicillin. Forty-eight hours later, the cat's respiratory effort deteriorated, and the cat was referred for further assessment.

Upon admission to the ICU, the cat was alert, ambulatory, and responsive. The heart rate was 220/min and the systolic blood pressure was 90 mm Hg using doppler sphygmomanometry.[a] The cat was dyspneic with reduced lung sounds bilaterally, which was consistent with pneumothorax. Needle thoracocentesis removed 20 mL of air from the right hemithorax and 1 mL from the left hemithorax.

Abbreviations: AKI, acute kidney injury; CIRCI, critical illness-related corticosteroid insufficiency; CT, computed tomography; MV, mechanical ventilation; RI, reference interval

TABLE 1 Venous blood gas, acid base and electrolyte analysis at various time points of hospitalization in a cat with suspected Waterhouse–Friderichsen syndrome

	0[a]	12 hours[b]	1 day[c]	2 days[d]	3 days[e]	6 days[f]	Reference interval
pH	7.28	7.29	7.29	7.1	7.30	7.33	7.35–7.47
$PvCO_2$ (mm Hg)	–	69.3	53.6	79.8	52.4	34.8	37–47
Lactate (mmol/L)	1.1	0.8	0.8	0.7	1.1	3.5	0.6–2.5
Base excess	–	0.9	−0.2	0.7	−0.3	−6.7	
Sodium (mmol/L)	147	147	147	149	146	142	140–153
Chloride (mmol/L)	–	115	115	112	115	114	106–120
Potassium (mmol/L)	3.3	3.5	3.5	4	3.2	6.4	3.6–4.6
Creatinine (μmol/L) [mg/dL]	–	72 [0.81]	92 [1.04]	–	128 [1.44]	273 [309]	50–140 [0.57–158]
Glucose (mmol/L) [mg/dL]	9.8 [176]	9.6 [172]	9.0 [162]	15.3 [275.4]	15.3 [275]	12.7 [228]	4.7–7.3 [84.7–131]

Note: – denotes missing information.
[a]At time of admit.
[b]Point of initiation of mechanical ventilation.
[c]During mechanical ventilation.
[d]Intubated but off anesthetic drugs and ventilatory support.
[e]Extubated 12 hours posttermination of anesthetic drugs.
[f]Immediately prearrest.

Initial emergency database including venous blood gas analysis[b] revealed an acidemia and hyperglycemia (Table 1). Hematology[c] revealed a mild anemia (0.23 L/L [23.2%]; RI: 0.24–0.35 L/L [24–35%]) and neutrophilia (17.74 × 10^9/L; RI: 2.5–12.5 × 10^9/L) with no bands present. Biochemical[d] changes included mild hypoalbuminemia (22.9 g/L [2.9 g/dL]; RI: 25–45 g/L [2.5–4.5 g/dL]) and increased alanine transaminase (242 U/L; RI: 5–60 U/L) and creatine kinase (71,788 U/L; RI: 57–574 U/L) activities. Focused thoracic ultrasound revealed diffuse confluent B-lines.

Oxygen therapy was provided using a commercial oxygen kennel[e] (FiO_2 0.6). Analgesia was initially provided with fentanyl[f] (5 μg/kg/h IV) and ketamine[g] (0.3 mg/kg/h IV) was added due to persistent tachypnea and increasing pain score. Repeat venous blood gas 12 h later revealed hypercapnia (Table 1). Due to hypercapnia and concern for respiratory fatigue, the cat was anesthetized with midazolam,[h] fentanyl, and propofol[i] and mechanical ventilation (MV)[j] was initiated. MV was initiated using an assisted pressure-controlled mode with a positive end-expiratory pressure of 5 cm H_2O, tidal volume of 8 mL/kg, and an FiO_2 of 0.8. General anesthesia was maintained using IV infusions of midazolam (0.2–0.25 mg/kg/h), fentanyl (2–4 μg/kg/min), and propofol (0.1--0.2 mg/kg/min). Monitoring consisted of urine output volume, multiparameter monitoring (capnography, pulse oximetry, continuous electrocardiography[k]), and indirect doppler blood pressure monitoring.

Computed tomography (CT) [l] of the head, thorax, and abdomen was performed. Multiple injuries were identified including thoracic vertebrae (T) 3–9 dorsal spinous fractures, left-sided T6 dorsal compartment fracture, left-sided T10 rib fracture, and bilateral T8 and T9 fractures with fragments of rib 9 penetrating lung, marked multifocal lung changes consistent with contusions, small volume pleural effusion, subcutaneous emphysema, a renal infarct, bilateral comminuted nonarticular scapular fractures, and a mandibular symphyseal fracture. An incidental finding included previously sustained, healed pelvic fractures. The scapular fracture was considered nonsurgical and the mandibular symphyseal fracture was repaired with an encircling orthopedic cerclage wire.

$PvCO_2$ improved while the cat received MV (Table 1) and the arterial oxygen saturation ranged between 96% and100% on FiO_2 0.4. Twenty-four hours after initiating MV, the ventilator mode was changed to synchronized intermittent mandatory ventilation with a low level of pressure support (2 cm H_2O) in preparation for weaning. The following day, prior to weaning, an esophagostomy tube and an epidural catheter were placed for optimal nutritional and analgesia management. The epidural catheter was placed under fluoroscopic guidance. At the time of placement of the epidural catheter, CSF was retrieved at the lumbosacral space. The catheter was therefore replaced more caudally at the sacrococcygeal site as a result. Ropivacaine[m] (0.04 mg/kg) and preservative free morphine[n] (0.1 mg/kg) were administered epidurally. Ropivacaine dosing was then continued every 6 hours.

After these procedures, all IV anesthetic drugs were discontinued and ventilatory support was removed. The cat remained intubated and was spontaneously ventilating but remained comatose. This state persisted despite reversal of the midazolam and the opioids with flumazenil[o] and naloxone,[p] respectively. The cat was hemodynamically stable and oxygenating well with an arterial oxygenation saturation of 98% on FiO_2 0.4. On neurological assessment, it had pupillary light reflexes but an absent gag. Due to worsening respiratory acidosis (Table 1), MV was re-initiated without any anesthetic drugs. The ventilator mode was synchronized intermittent mandatory ventilation with a low level of pressure support (2 cm H_2O).

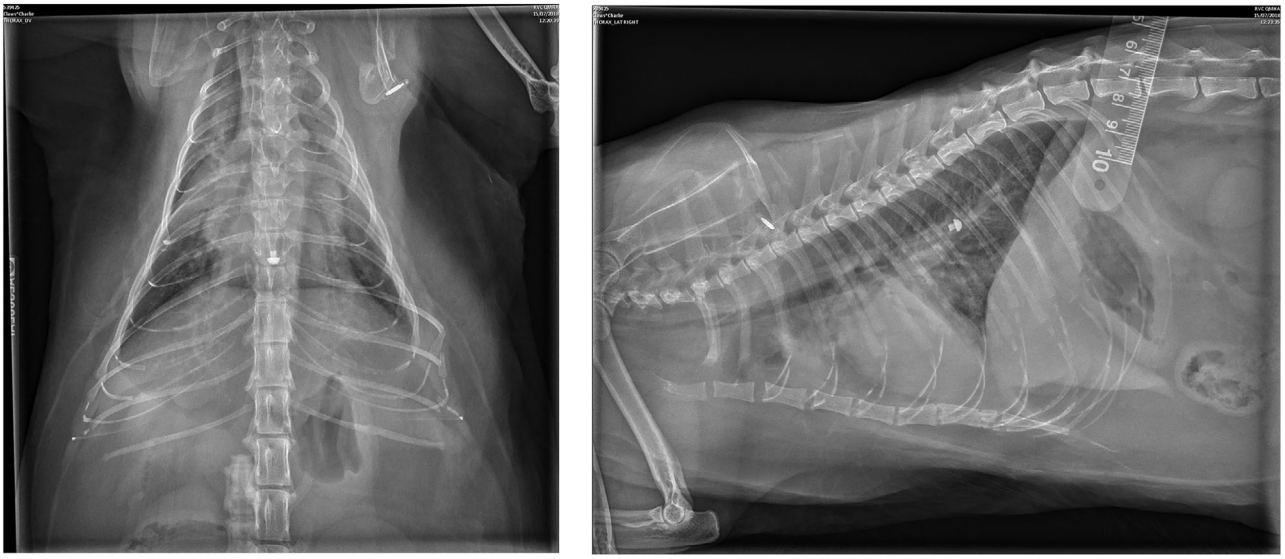

FIGURE 1 (A) Dorsoventral radiograph: Consolidation of the right middle and left cranial lung lobes consistent with aspiration pneumonia and small volume pneumothorax in a cat diagnosed with Waterhouse–Friderichsen syndrome after a motor vehicle accident. (B) Right lateral radiograph: Consolidation of the right middle and left cranial lung lobes consistent with aspiration pneumonia and small volume pneumothorax in a cat diagnosed with Waterhouse–Friderichsen syndrome after a motor vehicle accident

Due to a persistent comatose state, no further sedative drugs were administered systemically but ropivacaine (0.04 mg/kg) was continued epidurally every 6 hours. Twelve hours later, the cat regained a gag and was extubated but remained comatose. $PvCO_2$ was 52.4 mm Hg at the time of extubation (Table 1). The cat was placed in an oxygen kennel (FiO_2 0.4) and was managed with compounded sodium lactate IV fluids (4 mL/kg/h) with 40–60 mEq/L potassium chloride supplementation[q] and ropivacaine (0.04 mg/kg epidurally q 6 h). The cat's systolic blood pressure dropped to 70 mm Hg and did not respond to a 5 mL/kg crystalloid bolus. Norepinephrine[r] (0.1–0.2 μg/kg/min IV) was therefore initiated. Twenty-four hours later, lung auscultation revealed harsh lung sounds. Thoracic radiographs were performed, which revealed consolidation of the right middle and left cranial lung lobes with persistent small volume pneumothorax (Figures 1A and 1B). An endotracheal wash was performed. Cytology revealed evidence of intracellular rods consistent with bacterial pneumonia. Antimicrobials (20 mg/kg potentiated amoxicillin[s] IV every 8 hours) were initiated pending culture and bacterial sensitivity results. Parenteral nutrition[t] was initiated at 1 mL/kg/hr alongside the fluid therapy. Seven hours later the cat had increased respiratory effort. Thoracic focused ultrasound revealed diffuse pulmonary B-lines and an enlarged left atrium. A single dose of 2 mg/kg furosemide[u] was administered IV and the fluid rate was reduced. Twenty-four hours later the cat's cardiovascular status improved. Norepinephrine was discontinued but the cat remained comatose. Epidural administration of the ropivacaine was therefore discontinued over the following 24 hours. No significant improvement in neurological status was seen.

Three days post anesthesia, an MRI[v] of the brain and cervical, thoracic and lumbosacral spine was performed to investigate the poor neurological recovery. The symphyseal wire was removed prior to the MRI. The MRI revealed no gross abnormalities of the brain or spinal cord. Supportive care including fluid therapy, parenteral nutrition and esophagostomy tube feeding were continued. Epidural ropivacaine was re-initiated but extended to every 12 hours and methadone[w] (0.05 mg/kg IV every 6 hours) was started alongside a single dose of meloxicam[x] (0.2 mg/kg IV).

Bacterial culture and sensitivity results from the endotracheal wash revealed profuse growth of *Klebsiella pneumoniae* resistant to potentiated amoxicillin. Potentiated amoxicillin therapy was discontinued and trimethoprim/sulfonamide[y] (15 mg/kg via the esophagostomy tube every 12 hours) was substituted based on bacterial culture and sensitivity results.

Five days after discontinuing anesthetic drugs, the cat's neurological status began to improve; it could respond to auditory stimuli and was able to move its head. During the same time period its respiratory effort increased, and thoracic auscultation revealed bilateral harsh lung sounds. Focused thoracic ultrasound revealed a subjectively enlarged left atrium and small volume pleural effusion. A single dose of furosemide (0.5 mg/kg IV) was given for suspected fluid overload. On day 6 post termination of anesthetic agents the cat became acutely hypotensive (40 mm Hg systolic) with a symptomatic bradycardia (80/min) with premature atrial complexes. A single dose of atropine[z] (0.02 mg/kg IV) was given. A venous blood gas at the time revealed a metabolic acidosis, moderate azotemia and hyperkalemia (Table 1). Fluid therapy was stopped and calcium gluconate[aa] (0.5 mL/kg IV) was given. The heart rate improved initially but then reduced again and another dose of calcium gluconate alongside 0.25 IU/kg IV soluble insulin[ab] and 0.25 g/kg glucose[ac] IV was given. Within thirty minutes the cat experienced a cardiac arrest and the owner declined resuscitation.

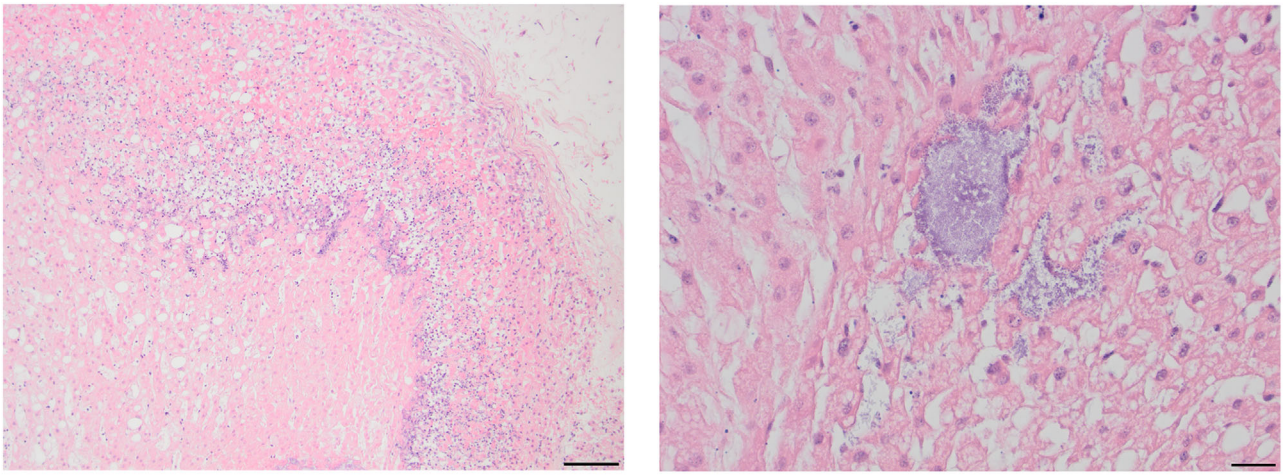

FIGURE 2 (A) Histopathology of the adrenal cortex: coalescing regions of coagulative necrosis centered on the corticomedullary junction in a cat diagnosed with Waterhouse–Friderichsen syndrome (×100 [bar = 100 μm]). (B) Histopathology of the adrenal cortex: multifocal colonies of short rod-shaped bacteria within the necrotic cortex in a cat diagnosed with Waterhouse–Friderichsen syndrome (×400 [bar = 20 μm])

A postmortem examination was performed. Gross findings included multiple rib fractures, a mandibular symphyseal fracture, serosanguinous pleural effusion, reddening of the spinal cord with epidural hemorrhage at L1-L4 and multiple renal infarcts. Microscopic findings included edema of the lungs with alveolar histiocytosis and type II pneumocyte hyperplasia, hepatocellular degeneration and necrosis and severe necrotizing adrenalitis with diffuse severe cortical hemorrhage and intralesional bacteria (Figures 2A and 2B). The adrenal lesions were consistent with Waterhouse–Friderichsen syndrome. The brain was macroscopically and microscopically unremarkable. Culture of the epidural catheter grew *K. pneumoniae*.

2 | DISCUSSION

This report describes a case of Waterhouse–Friderichsen syndrome in a cat resulting in presumed adrenocortical insufficiency and death. Acute hemorrhagic necrosis of the adrenal gland and clinical adrenal insufficiency termed Waterhouse–Friderichsen syndrome is a rarely reported condition in people that is associated with a high morbidity and mortality.[1] The condition has primarily been considered as a complication of meningococcal sepsis, but has been associated with other bacterial pathogens including *Streptococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli*, *K. pneumoniae*, *Pasteurella multocida*, and *Acinetobacter calcoaceticus*.[2–5] In this case, *K. pneumoniae* was cultured from the endotracheal wash and on the epidural catheter and therefore most likely represented the bacteria identified in the adrenal gland and the cause of the acute adrenocortical crisis.

Other reported causes of adrenal hemorrhage include stress, trauma, corticotrophin therapy, hypotension, and coagulopathy.[6] In this cat, relevant causal factors of the adrenal hemorrhage include trauma and hypotension. The temporal pattern of events between onset of trauma, the initial moderate hypotensive period, and the cat's clinical deterioration makes them unlikely causes of the massive adrenal hemorrhage seen at necropsy. Furthermore, absence of CT findings suggestive of adrenal hemorrhage at the time of CT makes trauma an unlikely trigger.[7]

Antemortem findings of acute adrenal hemorrhage in people include abdominal pain, pyrexia, and endocrinopathies. Suggested criteria for antemortem diagnosis are evidence of bilaterally enlarged and hyperdense adrenal glands on CT and demonstration of adrenocortical failure on hormonal evaluation.[7,8] In the majority of cases, Waterhouse–Friderichsen syndrome is only identified at necropsy due to rapid progression of signs resulting in hypotension and cardiac arrest.[3] Necropsy findings of cases with Waterhouse–Friderichsen syndrome include gross identification of massive adrenal hemorrhage and microscopic findings of hemorrhages localized to the corticomedullary junction and infarction of the cortex.[3] In this cat, Waterhouse–Friderichsen syndrome was diagnosed on microscopic examination by the presence of adrenal hemorrhage and intralesional bacteria on necropsy with documented *Klebsiella* spp. infection.

The exact mechanism of adrenal hemorrhage in sepsis has not been elucidated. However, specific anatomic and physiological factors of the adrenal gland are thought to contribute. These include a high rate of blood flow to the adrenal gland, which is further stimulated by ACTH release, and an arterial network that abruptly transitions to a capillary plexus that is drained by a single central vein. All of these features can result in increased venous or arterial pressure and subsequent hemorrhage. This is further compounded by platelet aggregation and thrombosis secondary to increased catecholamine release from the adrenal medulla.[3,9,10]

Primary hypoadrenocorticism, defined as the deficiency of glucocorticoid and/or mineralocorticoid secondary to destruction of the adrenal gland, is predominantly described in dogs as a result of

immune-mediated destruction of the adrenal gland and has less commonly been associated with neoplasia, granulomatous disease, and hemorrhage.[11–13] Primary hypoadrenocorticism has rarely been reported in cats.[14] Antemortem biochemical findings reported to be supportive of a diagnosis of hypoadrenocorticism include azotemia, hyponatremia, hyperkalemia, Na:K ratio < 26, and ECG findings including sinus bradycardia and atrial premature complexes.[11,15] These clinicopathological findings can also be seen with acute kidney injury (AKI). Therefore, in light of cat's age, presence of renal infarctions, and meloxicam use, AKI was also considered as a differential alongside an adrenocortical crisis. However, necropsy findings were not compatible with AKI.

Adrenal hemorrhage can lead to adrenal dysfunction and has been previously considered as one of the many etiological causes of critical illness-related corticosteroid insufficiency (CIRCI).[16] The Society of Critical Cate Medicine characterized CIRCI as a dysregulated systemic inflammation resulting from inadequate intracellular glucocorticoid-mediated activity for the severity of the patient's critical illness, whereas the Surviving Sepsis Campaign's clinical diagnosis for CIRCI is vasopressor-resistant shock responsive to hydrocortisone supplementation.[17–19] CIRCI has been identified in dogs with sepsis and there are 2 case reports of suspected CIRCI in cats; 1 cat with polytrauma, and the other in septic shock.[20–22] The cat with septic shock had persistent hypotension unresponsive to fluid therapy and vasopressors but responded to hydrocortisone. This cat had normal electrolyte levels, normal electrocardiogram, high basal cortisol levels, and diffuse adrenocortical hyperplasia on necropsy.[22] In contrast, the cat in this report developed a sudden profound hypotension, azotemia, and hyperkalemia with a sodium to potassium ratio of 22:1 and atrial premature complexes. There is no current consensus regarding the identification of CIRCI in veterinary medicine; however, clinical signs are usually vague and hyponatremia and hyperkalemia are uncommon.[23] In the authors' opinion, the rapidity of decline in a previously hemodynamically stable animal was more consistent with a peracute primary adrenocortical crisis than CIRCI. A basal cortisol, adrenocorticotrophin hormone stimulation, and response to treatment with hydrocortisone would have been required to confirm the diagnosis of adrenocortical dysfunction antemortem. Unfortunately, the cat's condition deteriorated over a short time period making further diagnostics or interventions not possible.

The reason for the cat's persistent coma despite cessation of all anesthetic drugs remains unknown. There were no gross or histopathological findings suggestive of hemorrhagic or ischemic injury and therefore drug-induced narcosis remains possible. This theory is supported by a single-case report of a woman experiencing a 36-hour coma after accidental subarachnoid injection of local anesthetic with an opioid.[24] During placement of the epidural catheter, CSF was encountered at the lumbosacral site, indicating penetration of the subarachnoid site. The epidural catheter was replaced further caudally at the sacrococcygeal site. Both ropivacaine and morphine were administered epidurally at the time of initial placement and then only ropivacaine was continued. The cat's neurological status did improve slowly. This could be consistent with intrathecal administration of anesthetic drugs leading to ascending spinal anesthesia and subsequent coma.

3 | CONCLUSION

To the authors' knowledge, this is the first report in veterinary medicine of bilateral massive adrenal hemorrhage, termed Waterhouse–Friderichsen syndrome secondary to sepsis. This condition led to a rapid clinical deterioration and cardiac arrest in this cat. Awareness of this condition may allow for earlier recognition and appropriate treatment of this syndrome antemortem.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ENDNOTES

[a] Vet BP Doppler Kit, Burtons Veterinary Equipment, Marden, UK.
[b] NOVA Stat Profile pHOx Ultra, Nova Biomedical Corporation, Waltham, MA.
[c] CBC4 Advia 2120i Haematology System, Siemens Healthcare Ltd., Camberley, UK.
[d] Lab 600, Instrumentation Laboratory, UK.
[e] Oxygen kennel, Plas Labs ICS II, Lansing, MI.
[f] Fentanyl citrate, Eurovet Animal Health, Bladel, The Netherlands.
[g] Ketamine hydrochloric acid, Animal Care Ltd., York, UK.
[h] Midazolam hydrochloride, Roche Products Ltd., Welwyn Garden City, UK.
[i] Propofol, Norbrook Laboratories Ltd., Newry, UK.
[j] 9 Nellcor Puritan Bennett 840 Ventilator System, Puritan-Bennett Corporate, Pleasanton, CA.
[k] Mindray beneview T8 Multiparameter, SOMA Technology, Bloomfield, CT.
[l] 10 16-slice MDCT scanner MX 8000 IDT, Philips Medical Systems, Surrey, UK.
[m] Naropin, Aspen Ltd., Dublin, Ireland.
[n] Morphine sulfate, Martindale Pharma, Brentwood, UK.
[o] Flumazenil, Hameln Pharmaceuticals Ltd., Gloucester, UK.
[p] Naloxone, Hameln Pharmaceuticals Ltd., Gloucester, UK.
[q] Potassium chloride supplement, Hameln Pharmaceuticals Ltd., Gloucester, UK.
[r] Noradrenaline, Hospira UK Ltd., Hurley, UK.
[s] Co-amoxiclav, Bowmed Ibisqus Ltd., Wrexham, UK.
[t] Fresenius Kabi Ltd., Cheshire, UK.
[u] Dimazon 5%, Intervet Ltd., Milton Keynes, UK.
[v] 1.5 Tesla Unit, Intera Pulsar System, Philips Medical Systems, Surrey, UK.
[w] Synthadon, Animalcare Ltd., York, UK.
[x] Metacam, Boehringer Ingelheim, Ingelheim am Rhein, Germany.
[y] Co-Trimoxazole paediatric suspension, Aspen Pharmacare, Berkshire, UK.
[z] Atrocare, Animalcare Ltd., York, UK.
[aa] Calcium gluconate, Hameln Pharmaceuticals Ltd., Gloucester, UK.
[ab] Actrapid, Novo Nordisk, Bagsværd, Denmark.
[ac] Glucose 50%, Hameln Pharmaceuticals Ltd., Gloucester, UK.

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