**Retrospective evaluation of refeeding syndrome in cats: 11 cases (2013-2019)**

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**Abstract**

**Objectives**

To describe the clinicopathological findings, management and outcome of cats with refeeding syndrome (RS) following prolonged starvation.

**Methods**

Records from four referral hospitals were searched between May 2013 and November 2019 and retrospectively evaluated. Inclusion criteria were the presence of a risk factor for RS such as severe weight loss or emaciation following a period of presumed starvation, hypophosphataemia or a delta phosphorous exceeding 30% reduction following refeeding, being treated on the basis of a clinical diagnosis of RS and one or more derangement of hypokalaemia, hypoglycaemia or hyperglycaemia.

**Results**

Eleven cats were identified, which had been missing for a median of 6 (3-104) weeks. Mean percentage weight loss was 46 (±7) % (n=8). Eight of eleven cats developed hypophosphataemia with a mean delta phosphorous of -47% (± 9). All cats were documented to be hypokalaemic. During hospitalisation, 10/11 cats developed hyperglycaemia and 7/11 cats developed hypoglycaemia. Cardiovascular, gastrointestinal and neurological signs were common. Eight of eleven cats displayed new or progressive neurological deficits after refeeding, including mentation changes and cerebellar dysfunction. All cats became anaemic and 7 cats required a blood transfusion. Eight cats survived to discharge after a mean of 14 (±4) days of hospitalisation. Six cats developed AKI (IRIS stage 1). The presence of AKI (P=0.024) was associated with non-survival, and maximum bilirubin concentration was significantly higher in non survivors (P=0.018).

**Conclusions and relevance**

Cats with RS in this cohort had been missing, presumed starved, for more than 3 weeks. In addition to hypophosphataemia and hypokalaemia, altered glucose homeostasis and organ damage involving the liver and kidneys were common. Cats with RS appear to have a good prognosis, but prolonged intensive care is required.

# **Introduction**

Refeeding syndrome (RS) is a complex condition that occurs following the reintroduction of nutrition after prolonged starvation or malnourishment. 1 It can occur in people and cats regardless of whether feeding is enteral or parenteral 2, 3 and appears also to occur in ruminants 4 and horses. 5 It is characterised by multiple metabolic derangements, most notably hypophosphataemia, hypokalaemia, and hypomagnesaemia. Thiamine deficiency, altered glucose homeostasis and fluid shifts are also common. 1, 6, 7

The dyselectrolytaemias observed in RS are thought to develop as a consequence of the rapid shift between catabolic and anabolic metabolism that occurs in response to insulin release associated with refeeding. This increases intracellular demand for phosphorus, potassium and magnesium, causing a critical decline in their circulating concentrations. Cellular thiamine demand also increases in response to refeeding as it acts as a cofactor for enzymes such as pyruvate dehydrogenase and alpha ketoglutarate dehydrogenase. 8 Total body reserves of potassium, magnesium, phosphorous and thiamine are already depleted in states of chronic starvation so the sudden increase in demand creates a marked imbalance with clinically apparent deficiencies. Both impaired glucose tolerance and hypoglycaemia are described in people and in cats with RS. 3, 6, 9, 10

In people, this combination of abnormalities is often associated with neurological, cardiovascular, gastrointestinal and haematological abnormalities including tremors, encephalopathy, arrhythmias, heart failure, anorexia, vomiting and haemolysis.1, 10, 11 In the most severe cases, multi organ failure and death can occur. Refeeding syndrome typically develops two to five days after nutrition has been reinstated,12 although signs can be observed within hours of refeeding or delayed for up to ten days. 3, 10

Refeeding syndrome has been infrequently reported in veterinary literature. 3, 6 This study aimed to describe the characteristic clinicopathological findings associated with starvation associated RS in 11 cats, to better characterise disease presentation and outcome.

# **Materials & Methods**

Computerised records from four referral populations (masked for review1) of client-owned cats were searched between May 2013 and November 2019 inclusive for the term “refeeding” or stems “malnourish-”, or “starv-” to retrospectively identify cats that were treated for RS.

Cases were included if they satisfied all of the following criteria:

* There was a risk factor for development of refeeding such as severe weight loss or emaciation following a period of presumed starvation
* They were documented hypophosphataemic or had a delta phosphorous exceeding a 30% reduction during hospitalisation following refeeding
* They had one or more of the following abnormalities documented: hypokalaemia, hypoglycaemia or hyperglycaemia
* They were treated on the basis of a clinical diagnosis of RS.

Cases were excluded if medical records were incomplete.

Data collected included signalment, body condition score (BCS), length of presumed starvation and percentage body weight loss (calculated using the last recorded weight in each cat’s clinical history prior to starvation and their weight on admission). Date of refeeding was taken as the day of the first documented alimentation after starvation. Clinicopathological data not limited to phosphorus, potassium, sodium and glucose concentrations were collected, in addition to blood gases, packed cell volume (PCV) changes over time and blood component therapy administration. Delta phosphorous ( was defined as the maximum drop in phosphorus documented after refeeding. Delta sodium ( was defined as the highest sodium minus the lowest sodium recorded. Where available, rates of nutrient supplementation and percentage of resting energy requirement (RER [defined as RER = 70 x (current body weight in kg)0.75 kcal]) provided were recorded. The initial caloric target was defined as the first documented, intentional, proportion of RER delivered during hospitalisation. Case notes were explored for clinical evidence of cardiovascular, gastrointestinal and neurological dysfunction following refeeding, as well as haematological abnormalities, and comorbidities. If neurological abnormalities were observed prior to refeeding these were also recorded. Tachycardia was defined as heart rate 240 beats per minute, bradycardia was defined as <140 beats per minute, hypertension was defined as systolic blood pressure of 180mmHg, hypotension was defined as a systolic blood pressure of <90mmHg, hypovolaemia was documented when clinical examination and response to fluid resuscitation were consistent with this. Haematological analyses were assessed to identify the aetiology of any anaemia. Length of hospitalisation and outcomes were recorded. All data related to the entire treatment period after initial presentation, including prior to referral.

## **Statistical Analysis**

All continuous data was assessed for normality using a Shapiro–Wilk test and histogram inspection; descriptive data was calculated as appropriate using commercially available software (Prism, Version 8 (GraphPad Software, Inc)). Where a value was not available, the case was excluded from analysis for that particular variable. Continuous variables were compared using a student’s t-test for parametric data, and a Mann-Whitney U test for non-parametric. A Fisher’s exact test was used to compare categorical data.

**Results**

Eleven cases were identified, with a mean age of 83 (±40) months. Table 1 details individual case signalment and BCS on presentation. All cats were reported to be in good health prior to going missing, with no clinically relevant underlying disease. Cats had been missing for a median of 6 (3-104) weeks (n=11) prior to presentation, with a mean percentage weight loss of 46 (±7) % (n=8). All cats ate voluntarily within 2 days of being found.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Cat** | **Age (months)** | **Sex (M/F)** | **Breed** | **Missing (weeks)** | **BCS** | **Weight loss (%)** | **Lowest phosphate (mmol/L) (RI)** | **ΔNa (mmol/L)** | **Highest ALT (U/L) (RI) and day post refeeding** | **Highest total bilirubin (umol/L)**  **(RI)** | **AKI (Y/N)** | **Transfusion type** | **Nutrition route** | **Total hospitalisation (days)** | **Outcome** |
| 1 | 137 | MN | DSH | 6 | 1.5/9 | 48 | 0.72 (1.1-2.74) | 20.00 | 439 (20-100) (5) | 154 (2-10) | Y | pRBC (feline) | Oral, syringe, PN | 10 | CPA |
| 2 | 36 | FN | DSH | 4 | 1/9 | N/A | 0.97 (1-2.42) | 23 | 833 (12-130) (1) | 148 (0-15) | N | pRBC (feline) | Oral + NG | 15 | Discharge |
| 3 | 84 | MN | DSH | 7 | 2.5/9 | 46 | 1.02 (1.1-2.74) | 15 | 96 (12-130) (1) | 8 (2-10) | N | N/A | Oral, PN | 19 | Discharge |
| 4 | 64 | MN | DLH | 3 | 2/9 | 46 | 0.75 (0.92-2.16) | 7 | 218 (20-100) (9) | 31 (2-10) | N | whole blood (feline) | Oral, PN | 18 | Discharge |
| 5 | 91 | FN | BSH | 6 | 3/9 | N/A | 0.88 (1.1-2.74) | 16 | 569 (12-130) (1) | 39 (2-10) | Y | N/A | Oral only | 15 | Discharge |
| 6 | 100 | FN | DLH | 6 | 2/9 | 33 | 0.56 (1.1-2.74) | 14 | 188.6 (5-60) (4) | 7 (2-10) | N | N/A | Oral only | 14 | Discharge |
| 7 | 84 | MN | DSH | 104 | 1/9 | N/A | 0.81 (1.1-2.74) | 23 | 153.3 (5-60) (3) | 283 (2-10) | Y | pRBC (xeno) pRBC (feline) | Oral and NG | 22 | Euthanasia |
| 8 | 42 | FN | DSH | 7 | n/a | 50 | 0.65 (1-2.42) | 13 | 399 (20-100) (1) | 7 (0-15) | N | N/A | Oral only | 8 | Discharge |
| 9 | 19 | FN | DSH | 3 | 1/9 | 55 | 1 (1-2.42) | 10 | 130 (12-130) (3) | 2 (0-15) | Y | whole blood (feline) | Oral only | 9 | Discharge |
| 10 | 138 | FN | DSH | 6 | 2/9 | 39 | 1.03 (1-2.42) | 18 | 281 (12-130) (13) | 55 (0-15) | N | whole blood (feline) | Oral, (syringe) NG and O tube | 18 | Discharge |
| 11 | 115 | FN | Russian Blue | 6 | 1/9 | 54 | 1.82 (1.1-2.74) | 20 | >1000 (12-130) (1) | 60 (2-10) | Y | Feline pRBC | Oral, O tube and PN | 11 | Euthanasia |

**Table 1. Clinicopathological findings, management and outcome**

**RI = reference interval; BCS = body condition score; AKI = acute kidney injury; pRBC = packed red blood cells; PN = parenteral nutrition; NG = nasogastric; CPA = cardiopulmonary arrest; Xeno = xenotransfusion dog to cat**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Cat** | **Cardiovascular** | **Gastrointestinal** | **Neurological** | **RBC abnormalities** | **Comorbidities** |
| 1 | Hypotension, hypertension, hypovolaemia, ventricular tachycardia, bradycardia, CPA | Inappetence after initial appetence, diarrhoea, vomiting, | Before refeeding: Vision loss, mydriasis. After refeeding: seizure, obtundation, ataxia, cervical ventroflexion (k+ 3.1mmol/L) | Heinz bodies | AKI (IRIS grade 1) |
| 2 | Tachycardia, hypotension | Inappetence after initial appetence, diarrhoea, melaena | Before refeeding: (owner reported) vision loss. After refeeding: none | No specific abnormalities detected | None |
| 3 | Bradycardia | Inappetence after initial appetence, vomiting | Before refeeding: left head tilt. After refeeding: Intention tremor, hypermetria, wide-based stance, head pressing | Haemolysed serum, Heinz bodies, ghost cells, spherocytosis, ISAT positive, Coomb's negative | Skin wounds, immune mediated haemolytic anaemia (primary) developed in hospital. |
| 4 | Hypotension, bradycardia, CPA | Vomiting | Before refeeding: obtundation, vision loss. After refeeding: obtundation recurred, seizure (post CPA). | Heinz bodies, echinocytosis, ghost cells, macrocytosis | Skin wounds |
| 5 | Hypertension | Inappetence after initial appetence, diarrhoea | Before refeeding: Head tremors. After refeeding: cervical ventroflexion (K+ 3.7 mmol/L), obtundation, vestibular ataxia, nystagmus | No specific abnormalities detected | AKI (IRIS grade 1) |
| 6 | Bradycardia | Inappetence after initial appetence, diarrhoea | Before refeeding: loss of vision, mydriasis. After refeeding: none | Haemolysed serum, macrocytosis, Heinz bodies | None |
| 7 | Intermittent ventricular premature complexes | Inappetence after initial appetence, vomiting | Before refeeding: cervical ventroflexion (K+ 3.2 mmol/L). After refeeding: Intention tremors, seizure, stupor | Macrocytosis, basophilic stippling, Heinz bodies, elliptocytosis | Skin wounds, AKI (IRIS grade 1). |
| 8 | Tachycardia | Inappetence after initial appetence | Before refeeding: none After refeeding: none | No external haematology performed | None |
| 9 | Bradycardia, hypotension, hypovolaemia | Melaena | Before refeeding: none. After refeeding: hyperaesthesia, cerebellar ataxia | No external haematology performed | Skin wounds, AKI (IRIS grade 1) |
| 10 | Hypotension, tachycardia | Inappetence after initial appetence, diarrhoea, hypersalivation | Before refeeding: none. After refeeding: Intention tremors, ataxia (uncharacterised), cervical ventroflexion (K+ 3mmol/L) | No specific abnormalities detected | AKI (IRIS grade 1), O-tube site infection, hepatic lipidosis on FNA |
| 11 | Hypotension, bradycardia, hypertension, systolic dysfunction, ventricular premature complexes, ST segment elevation | Melaena, inappetence after initial appetence, gastrointestinal stasis, regurgitation | Before refeeding: none. After refeeding: obtundation progressing to coma, hypoventilation | Echinocytosis, elliptocytosis | Skin wounds, skull fractures, femoral and pelvic fractures, O-tube site infection. AKI (IRIS grade 1) |

**Table 2. Organ system abnormalities and comorbidities**

**AKI = acute kidney injury; CPA = cardiopulmonary arrest; ISAT = in saline agglutination test**

**Nutrients**

No cats were hypophosphataemic on initial evaluation of electrolytes. Eight out of eleven cats developed hypophosphataemia during hospitalisation, with the lowest phosphorous occurring a median of 5 (1-13) days following refeeding. The mean delta phosphorous was -47% (± 9) occurring over a median of 1 (0.5-7) days. Phosphorous was supplemented intravenously for a mean of 6 (± 3) days.

A mean lowest plasma potassium concentration of 2.6 (±0.4) mmol/L, occurred a mean of 7 (±6) days after refeeding and cats were supplemented with potassium intravenously for a median of 7 (4-19) days.

Ten out of eleven cats were documented to be hyperglycaemic during hospitalisation, and 7/11 cats were documented to be hypoglycaemic. In those documented hypoglycaemic, all cats received dextrose supplementation for a mean of 3 (±2) days. The highest level of IV glucose supplementation documented was 0.45g/kg/hr for several hours (10% dextrose at a rate of 4.5 ml/kg/h). Sepsis was considered a contributory cause of hypoglycaemia in one case (cat No. 1). There was no pattern in the development or progression of hypo- or hyperglycaemia, and no cats received insulin therapy.

Ten cats received intravenous magnesium supplementation for a mean of 6 (± 3) days. All cats received thiamine supplementation (injectable in 9/11 cases, oral in the remaining 2). Thiamine supplementation ranged between 25 and 100 mg daily, with a mean length of supplementation of 7 (±4) days. Calcium gluconate was supplemented as a continuous rate infusion for 3 and 9 days in cats 9 and 11, respectively.

**Cardiovascular, gastrointestinal and neurological clinical signs**

All cats showed clinical evidence of dysfunction of at least two of the three evaluated organ systems. (**Table 2**). Every cat developed cardiovascular abnormalities, the most frequent being hypotension (n=6). Every cat developed gastrointestinal abnormalities, the most frequent being inappetence after initial appetence (n=9). Six cats displayed neurological deficits prior to refeeding, most frequently vision loss (n=4). Eight of eleven cats displayed new or progressive neurological deficits after refeeding, including mentation changes (n=6) and cerebellar dysfunction (n=4) (**Table 2**). In surviving cats, all neurological clinical signs had resolved or were resolving at discharge.

**Anaemia and haematological findings**

No cats were anaemic on presentation, with a median (range) PCV of 29 (26-44) %. All cats became anaemic with the lowest PCV documented a mean of 8 (±5) days following refeeding. Heinz bodies were detected in 5/9 cats for which an external haematology was available. Additional red blood cell abnormalities are described in **Table 2**. Seven cats required a blood transfusion a mean of 8 (±6) days after refeeding. Four cats received a type specific packed red blood cell transfusion, three cats received type specific whole blood, and one cat received a xenotransfusion in addition to a feline packed red blood cell transfusion.

**Comorbidities**

Table 2 details the comorbidities identified. Skin wounds were present in 5/11 cats. Nine of eleven cats had biochemical (increased ALT activity) evidence of a hepatopathy documented. However, four of these were highest on presentation and five had increased since refeeding. One cat had hepatic lipidosis documented on fine needle aspirate cytology. Six out of 11 cats developed AKI (IRIS stage 1) 13 in hospital.

Blood gas analyses were available for review in 9 cases. When acidaemia or alkalaemia were documented, the most common abnormality was a metabolic alkalosis with alkalaemia in four cats, developing twice on day 2, once on day 3 and once on day 9 after refeeding. Additional blood gas abnormalities identified by the traditional Henderson-Hasselbach based approach included respiratory acidosis with acidaemia in two cats, metabolic acidosis with acidaemia in two cats, a mixed-origin acidaemia in one cat, and respiratory alkalosis with alkalaemia in one cat.

**Nutrition**

All cats ate voluntarily initially, with four cats eating entirely voluntarily throughout hospitalisation. Four cats received additional parenteral nutrition, and four cats were fed by nasogastric or oesophageal feeding tube. (**Table 1**). The median initial caloric target in hospital was 10 (5-40) %. Where delivery of 100% RER was achieved intentionally (n=9), it occurred 13 (±5) days after initial refeeding.

**Outcome**

Eight of 11 cats survived to discharge, one of which underwent CPA with successful return of spontaneous circulation. One cat died and two were euthanased (**Table 1**). Euthanasia was performed in both cases due to a protracted course of critical illness and financial considerations after 11 and 22 days in hospital. Surviving patients were hospitalised for a mean of 14 (±4) days. The presence of AKI (P=0.024) was associated with non-survival, and maximum bilirubin concentration was significantly higher in non survivors (P=0.018). ALT concentration (0.497), (0.678) and (P=0.055) had no association with outcome.

**Discussion**

## This study documents the clinicopathological changes in chronically starved, missing cats that developed RS, and management of these cats in primary care and referral practice.

**Starvation and weight loss**

No case had any previous relevant medical history or underlying disease, being reported in good health prior to going missing and having been presumptively starved. However, with regards cat no. 7 which was missing for 2 years, a more complete investigation would have been necessary to completely exclude, for example, an underlying enteropathy as a contributor to chronic malnourishment.

Broadly, protein catabolism during starvation progresses through three phases: rapid initial depletion, a subsequent more gradual phase during which lean muscle mass is preserved in favour of fat mobilisation and ketone body production, and a final, pre-terminal rapid depletion of body protein. It is possible that protein catabolism in the cat persists at an accelerated rate compared to other species 14 although this is disputed. 15 Nonetheless, there appears to be a ‘point of no return’ after which a complete recovery is not possible, usually during or after the second wave of protein catabolism. Death is likely to occur when protein loss reaches 50% of normal. 16 Three of 11 cats in this study had lost over 50% of their body weight, two of which survived to discharge; it appears that cats can survive after 50% weight loss.

**Phosphorous**

Degree of malnutrition has been correlated with severity of hypophosphataemia in people. In this same study 81% of the anorexia nervosa (AN) patients monitored during refeeding developed their phosphorous nadir within the first week, but for some the nadir occurred as late as 14 or 20 days into hospitalisation. 17 A delta phosphorus decrease of -30% or more in this current study was deemed significant based on previous use, and similar absolute or relative reductions utilised for diagnostic purposes. 18, 19 The timescale to lowest phosphorous after refeeding was 5 (1-13) days, suggesting that hypophosphataemia may develop acutely or later in hospitalisation, as is recognised in people. However, it is also possible that renal phosphate loss secondary to intravenous fluid therapy contributed to hypophosphataemia. 20, 21

**Potassium**

Hypokalaemia observed in RS is attributable to transcellular movement superimposed on chronically reduced intake. 22 Hypokalaemia may cause derangements in electrochemical membrane potentials, including delayed ventricular depolarisation, prolongation of action potentials and increased automaticity, potentiating the development and persistence of cardiac arrhythmias of both ventricular and supraventricular origin. 22 All three non-survivors had specific arrhythmias documented in this study, perhaps suggesting an association with illness severity, or that with continuous ECG monitoring of more stable patients, arrhythmias may appear more prevalent in cats with RS.

Cervical ventroflexion can be seen in hypokalaemic cats as a consequence of muscle weakness and the absence of a nuchal ligament. Forelimb hypermetria and a broad-based hindlimb stance are also possible. 22 Three cats in this study displayed cervical ventroflexion despite normal or only marginally low plasma potassium concentration at the time (**Table 2**). This was potentially attributable to thiamine deficiency.

**Thiamine**

Thiamine is a key co-enzyme in the metabolism of carbohydrates and supply often becomes deficient after refeeding due to increased cellular demand. The inhibition of carbohydrate metabolism in a thiamine-depleted state can cause energy deficits, neuronal dysfunction and necrosis affecting multiple sites including the oculomotor, vestibular and lateral geniculate nuclei. 23 Reported clinical signs include vestibular ataxia, mentation changes, cervical ventroflexion and mydriasis with absent menace responses, with potential progression to coma and death. 24 This spectrum of neurological deficits was appreciated in the cats of this study (**Table 2**). One cat (Cat No. 7) displayed cervical ventroflexion prior to refeeding, and four cats had apparent vision loss, supporting the notion that starvation without refeeding may result in clinical signs of thiamine deficiency. 23 However, signs are likely to worsen on refeeding without supplementation as suggested by the development of cervical ventroflexion, vestibular signs, or both in six cats.

Absolute confirmation of thiamine deficiency is difficult, so a presumptive diagnosis is often made based on clinical signs and response to supplementation. In this study, all cats were supplemented with thiamine and this is also recommended in AN patients being refed. 25

**Glucose**

Hyperglycaemia is often referred to but rarely documented in people with RS. 9, 12 Hypophosphataemia has been linked to impaired glucose homeostasis in both hyperglycaemic and normoglycaemic states and this is thought to be a consequence of diminished tissue sensitivity to insulin. 26 Carbohydrate provision and critical illness may perhaps put cats at greater risk of hyperglycaemia, 27 but both hypoglycaemia and hypoglycaemia are reported 3, 6 and both abnormalities were demonstrated in this study. In people, hypoglycaemia has been reported upon refeeding in 36-44% of AN patients, with 12% observed to have severe, protracted hypoglycaemia lasting a median of eight days. 9 Likely explanations for persistent hypoglycaemia include excessive insulin secretion, minimal capacity for glycogenolysis or sepsis. Considering the likely hyperinsulinaemia, dextrose restriction and avoidance of dextrose bolus therapy would seem prudent but in the author’s experience this is difficult, and escalation appears very much to perpetuate hypoglycaemia.

**Magnesium**

Magnesium deficits are often a consequence of reduced dietary intake with concurrent excessive gastrointestinal or renal losses 28 but they are common in RS due to depleted reserves and a sudden increase in demand for magnesium.

In veterinary species hypomagnesaemia can cause ventricular and supraventricular arrhythmias, seizures, and hypertension. 29 In people, severe magnesium deficiency can result in cardiac arrhythmias, anorexia, tremors, seizures, weakness and ataxia. 30 All of these clinical signs have been observed in the cats in this study, although their aetiologies are likely multifactorial. Unfortunately, neither total nor ionised magnesium assays were commonly performed in the cats of this study, and interpretation is difficult due to a lack of reference intervals.

**Organ dysfunction and comorbidities**

In people there is ongoing debate over whether hepatic injury in refed patients is due to autophagy during the starvation phase or lipidosis during refeeding. In these cats, a biochemical hepatopathy was appreciable both on presentation and on refeeding (**Table 2**), supporting both aetiologies. One cat (cat No. 10) had hepatic lipidosis confirmed and this may well have been an unappreciated comorbidity in other cases.

The documentation of AKI in six cases is novel and underlines the importance of extremely careful attention to fluid balance and dyselectrolytaemias. The mechanism is unclear but could involve oxidative damage, ischaemia-reperfusion injury, cellular hypoxia and iatrogenic damage via overzealous fluid therapy or positive fluid balance.

# Broadly, the neurological deficits observed were likely attributable to a combination of metabolic aetiologies including thiamine deficiency, hypophosphataemia-associated ATP depletion, hypokalaemia and cellular hypoxia. Their resolving nature is also consistent with this, but vascular events cannot be completely excluded. Interestingly, four cats developed evidence of cerebellar dysfunction, including cerebellar ataxia and intention tremors, after refeeding. This does not appear to have been reported previously but may be consistent with Wernicke’s encephalopathy in people with thiamine deficiency. 31

The evidence of oxidative damage to RBCs, progressive hepatocellular injury and an association between hyperbilirubinaemia and a poor outcome warrant further mechanistic investigations but may support the use of antioxidant medications in such patients. It should also be noted that haemolysis of administered transfusions confounds the interpretation of hyperbilirubinaemia, particularly in cat No. 7 which received a xenotransfusion. 32

**Acid-Base**

This study also documents the presence of a presumptive refeeding alkalosis in 4 cats. Both metabolic alkaloses and acidoses, as well as respiratory alkaloses are described in people with RS, 1 but to date, no veterinary evidence appears to exist.

**Anaemia**

Haemolytic anaemia is possible in RS as a consequence of decreased intraerythrocytic ATP concentrations due to phosphorus depletion. Glycolysis is the only method of erythrocytic ATP generation, multiple steps of which are stimulated by phosphorus. 31 ATP depletion causes increased cellular fragility, shorter erythrocyte lifespan and subsequent haemolysis, although clinical evidence of this is not common. 34, 35 A previous study of hypophosphataemic cats with associated haemolytic anaemia noted decreases in PCV within 24 to 48 hours of hypophosphataemia first being documented. 36 Cats are thought to be particularly prone to severe hypophosphataemia-associated haemolysis, in conjunction with having haemoglobin that is particularly vulnerable to oxidation, denaturation and subsequent Heinz body formation. 37 Once formed, Heinz bodies may contribute to erythrocyte fragility and perpetuate haemolysis.

# Development of anaemia in the cats of this study is likely multifactorial and not solely attributable to hypophosphataemic haemolytic crises. The timing of lowest phosphorous did not coincide with the lowest PCV documented. Two cats had haemolytic serum reported; one cat (No. 3) had developed immune mediated haemolytic anaemia in hospital and the other (No. 6) had the lowest phosphorous of the study recorded at 0.56mmol/L at the time (**Table 1**). The immune mediated haemolytic anaemia was considered primary, but a drug-induced secondary process could not be excluded. It is likely that oxidative damage evidenced by Heinz bodies in 5 cats is also a factor, while fluid resuscitation and hospital acquired anaemia are also possibilities. 38

Alimentation associated hypophosphataemia is reported in cats, 39 while refeeding associated alkalosis and hypokalaemia are also anecdotally seen in patients that are refed after shorter periods of starvation, suggesting a spectrum of disease that is continuous with the cats in this study, and which includes a mild disease phenotype without organ dysfunction.

**Study limitations.**

This study is limited by its retrospective nature in several ways. The length of illness and reliance on thorough medical record keeping in patients with varying illness severity reveals differences in levels of monitoring and documentation with the potential for under-reporting. It is possible that more cats developed hepatic lipidosis than was recognised and this would be a key area to explore in future studies. Although subjective, the availability of muscle condition scoring may have permitted stratification according to the degree of malnutrition and should be recorded for that purpose in populations such as this.

It is not possible to completely exclude an effect of comorbidities on clinical findings associated with RS in this study. For example, five cats had skin wounds as evidence of trauma, three of which developed an AKI. Nonetheless, the fact that missing, starved cats with RS often have concurrent evidence of trauma is an important finding which differentiates RS in cats from RS in people with AN.

It can be difficult to accurately characterise neurological clinical signs retrospectively, especially if complete, specialist neurological exams had not been performed or repeated. It may have been possible to more precisely attribute clinical signs to deficiencies if these were consistently and sequentially performed, or may be possible in future analyses. This would be key to interrogating the starvation-associated and the refeeding-associated neurological signs.

**Conclusion**

Refeeding syndrome is an uncommon condition necessitating prolonged intensive care, although cats appear to have a reasonable prognosis when aggressively managed. The observed clinical signs can provide an evidence base for diagnostic criteria in feline RS. As expected, cardiovascular, gastrointestinal and neurological clinical signs appear common in cats with RS, and a requirement for blood transfusion is common.

Despite the multifaceted, spectral nature of this disease, the defining clinicopathological changes in cats with RS appear to be hypokalaemia, hypophosphataemia and abnormal glucose homeostasis. Further work to stratify starved cats according to risk of RS is required, as well as efforts to predict the severity of the syndrome itself.

**Conflicts of Interest**

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article

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**Ethical Approval**

This work involved the use of non-experimental animals only (including owned

or unowned animals and data from prospective or retrospective studies).

Established internationally recognised high standards (‘best practice’) of individual

veterinary clinical patient care were followed. Ethical approval from a committee

was therefore not necessarily required

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**Informed Consent**

This work did not involve the use of animals and therefore informed consent was

not required. No animals or humans are identifiable within this publication, and therefore additional informed consent for publication was not required.

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