Abstract: In human medicine, thyroid storm is a well-recognized condition of acute thyrotoxicosis in which the patient’s metabolic, thermoregulatory, and cardiovascular mechanisms are overwhelmed by excessive circulating levels of thyroid hormone. The etiology is unknown, but multiple precipitating factors have been proposed. Hyperthyroid cats presenting in thyrotoxic crisis have clinical signs similar to those of human thyroid storm patients; however, thyroid storm has not yet been fully characterized in veterinary medicine. Early recognition and prompt, appropriate treatment of this life-threatening condition are essential to obtaining a favorable outcome.

Hyperthyroidism is defined as an endocrine disorder characterized by thyroid hyperfunction. Thyrotoxicosis, although often used interchangeably with hyperthyroidism, refers to a clinical spectrum of disease ranging from an uncomplicated syndrome characterized by mild clinical signs to an acute, life-threatening form known as thyroid storm.1–4 Human patients with hyperthyroidism secondary to Graves disease or toxic multinodular goiter may infrequently experience thyroid storm or thyrotoxic crisis.4,5 Rarely, thyroid storm occurs in patients without hyperthyroidism. In veterinary medicine, the syndrome of thyroid storm has yet to be fully described. As hyperthyroidism is a commonly recognized endocrine disorder in cats, hyperthyroid cats are the veterinary patients most likely to present with clinical signs of thyrotoxic crisis or thyroid storm.6

In humans, thyroid storm is defined as organ dysfunction and decompensation secondary to exposure to high concentrations of serum thyroid hormone.5,7 Its exact incidence in human and veterinary medicine is difficult to estimate because no definitive and universally accepted criteria exist for establishing a diagnosis.5,7 The mortality rate among human thyroid storm patients is approximately 30%.3 The mortality rate among feline thyroid storm patients is unknown but may approach similar, if not higher, levels. Recognition of thyroid storm through observation of compatible clinical signs and identification of predisposing factors is critical to reversing this potentially life-threatening syndrome.

Physiology

The thyroid hormones, thyroxine (T4, a prohormone) and triiodothyronine (T3), have a wide variety of physiologic effects, including increasing the metabolic rate of most tissues, enhancing the catecholamine response, acting as positive inotropes and chronotropes, exerting catabolic effects on muscle and adipose tissue, and aiding in normal growth and development. The synthesis and secretion of these hormones are controlled by thyroid-stimulating hormone, which is secreted by the ante-
rior pituitary gland in response to thyrotropin-releasing hormone, which is produced and secreted by the hypothalamus. Although $T_3$ is more potent than $T_4$, most thyroid hormone is secreted in the form of $T_4$. Peripheral monodeiodination controls thyroid hormone effects by converting $T_4$ to $T_3$. Most thyroid hormone (~99%) in the bloodstream is bound to specific $T_4$-binding proteins and is, therefore, metabolically inactive; it becomes unbound before entering cells, where it exerts its effects through nuclear receptor binding. Unbound $T_4$ and $T_3$ suppress the release of thyroid-stimulating and thyrotropin-releasing hormone through negative feedback.5,8

Pathophysiology

Although the exact causes of thyroid storm are not yet elucidated, five pathophysiologic mechanisms have been proposed: (1) high circulating levels of thyroid hormones, (2) dramatic changes in thyroid hormone levels, (3) increased cellular sensitivity to thyroid hormones, (4) increased tissue sensitivity to sympathetic activation, and (5) a precipitating event.5,7 Intuitively, high circulating thyroid hormone levels would seem to be an important cause of thyroid storm; however, studies in humans have shown no difference in mean serum $T_4$ concentrations between patients with thyroid storm and those with uncomplicated thyrotoxicosis.1,9 A rapid increase in free thyroid hormone availability, leading to an acute rise in serum thyroid hormone, may prove to play a more important role.1,7,10 Impaired binding affinity and/or decreased binding protein concentration have both been implicated as causes of increased serum levels of free $T_4$ and free $T_3$.9

Increased sensitivity to thyroid hormone at the cellular level is another factor thought to precipitate thyroid storm.7 Nonthyroidal illnesses characterized by sepsis, hypoxemia, lactic acidosis and ketoacidosis, and hypovolemia have been associated with increased cellular sensitivity to thyroid hormone.5 The pathophysiologic mechanisms are poorly understood but may be associated with decreased thyroid hormone clearance and/or abnormalities associated with nuclear acid receptor binding.4

Additionally, because thyroid storm is similar to a hyperadrenergic state, increased sympathetic activation through interaction between the adrenergic system and excessive circulating thyroid hormone has been suggested as a precipitating event.1,5,7 This theory is supported by the marked improvement often seen in thyroid storm patients after therapeutic blockade of the $\beta$-adrenergic system.1,5 Serum and urine catecholamine levels in human patients with thyrotoxicosis have been shown to be within normal limits or even below the reference interval.1,5,7 Although the mechanism is not completely understood, it may be that the excess circulating thyroid hormone does not cause an increase in catecholamine release but rather increases adrenergic receptor expression or intensifies its effects via postreceptor pathways.7 This could result in the signs of adrenergic overstimulation despite normal catecholamine levels.

In human medicine, precipitating events have been documented in approximately 98% of cases.5 Known precipitants of thyroid storm include thyroidal and nonthyroidal surgery, infection and other nonthyroidal illness (e.g., diabetic ketoacidosis, trauma, vascular accidents, emotional stress), administration of iodine-containing agents, vigorous palpation of the thyroid, and sudden withdrawal of antithyroid medication.5,5,1 Trauma has been found to predispose patients to thyroid storm through the release of cytokines, leading to activation of the sympathetic nervous system as well as increased free thyroid hormone fractions due to reduced protein binding.12

Clinical Presentation

The clinical signs of thyroid storm reflect severe hypermetabolism. In humans, the diagnosis of thyroid storm is based largely on observation of four major categories of clinical signs: (1) central nervous system dysfunction, including agitation, seizures, and coma; (2) fever; (3) gastrointestinal and/or liver dysfunction; and (4) cardiovascular abnormalities ranging from sinus tachycardia to atrial fibrillation and congestive heart failure.7 Most of the clinical signs associated with thyroid storm resemble those of a hyperadrenergic state. The same clinical signs are observed in human patients with uncomplicated thyrotoxicosis but to a much milder degree.4
Feline patients with thyroid storm may have clinical signs similar to those of human thyroid storm patients, including heart disease secondary to increased cardiac output due to increased metabolic demand. Heart disease in these patients is characterized by arrhythmias, murmurs, gallop sounds, vascular accidents, pulmonary edema, or pleural effusion. Additional clinical signs may include neurologic dysfunction, hypertension, acute respiratory distress, dehydration and hypovolemia, gastrointestinal signs, and hypokalemic myopathy, predominantly characterized by extreme weakness and neck ventroflexion. As this syndrome is more frequently recognized in feline patients, the clinical picture will become more defined.

**Diagnosis**

The diagnosis of thyroid storm in human patients is often based on a history of hyperthyroidism and compatible clinical signs and/or resolution of clinical signs with appropriate treatment. Burch and Wartofsky’s scoring system, developed in 1993 as an ancillary diagnostic tool, is used to distinguish human patients with uncomplicated thyrotoxicosis from those with thyroid storm. Points are assigned based on the severity of clinical signs. A score of 45 or greater is considered highly suggestive of impending or current thyroid storm. We have created a scoring system based on the Burch and Wartofsky system that may be used to aid in the diagnosis of feline thyroid storm or to anticipate impending storm in at-risk patients (BOX 1). Often, response to treatment may be the only means of obtaining a diagnosis.

Laboratory test results, including routine blood work and measurement of total and free T₄, are consistent with hyperthyroidism and cannot be used to distinguish a cat with uncomplicated hyperthyroidism from a cat with thyroid storm. In addition, thyroid function tests are of no value in the veterinary emergency room setting because rapid results are not available. Nonspecific clinicopathologic changes consistent with hyperthyroidism and thyroid storm may include mild erythrocytosis, macrocytosis secondary to increased oxygen-carrying capacity demand, mild hyperglycemia secondary to catecholamine-mediated insulin antagonism, a stress leukogram secondary to increased circulating catecholamines, and mildly elevated liver enzymes, including alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, and aspartate aminotransferase. Mild to severe hypokalemia may also be noted.

Several mechanisms have been proposed for hyperthyroidism-induced hypokalemia. Hyperthyroidism can promote potassium losses through the kidneys via increased proximal tubule reabsorption due to increased renal blood flow and glomerular filtration. Polyuria associated with hyperthyroidism also results in renal potassium wasting via losses into the urinary filtrate from the distal nephron. Polyuria due to concurrent chronic kidney disease can further exacerbate renal potassium losses in hyperthyroid cats.

**Treatment**

Rapid, aggressive therapeutic intervention should be directed toward four main treatment goals: inhibition of the deleterious peripheral effects of thyroid hormones, inhibition of hyperactive thyroid tissue, provision of supportive care, and identification and treatment of precipitating factors.
Feline Thyroid Storm

Precipitating causes should be ruled out through a thorough diagnostic evaluation, including a complete blood count, serum chemistry, urinalysis, FeLV/FIV testing, blood pressure measurement, fundic examination, and imaging; other diagnostic tests may also be indicated.

Inhibition of Peripheral Effects of Thyroid Hormone

The mainstay of treatment directed toward the inhibition of the peripheral effects of thyroid hormones is β-adrenergic blockade, unless contraindicated (i.e., in patients with pulmonary disease and/or severe congestive heart failure not associated with thyrotoxicosis), because β blockers have a rapid onset of action and the potential to reverse clinical signs of thyroid storm. In humans, propranolol is thought to act as a weak inhibitor of the peripheral conversion of $T_4$ to $T_3$. This mechanism in cats is poorly understood and requires further investigation. Propranolol is a nonselective β blocker and, therefore, is contraindicated in cats with asthma or congestive heart failure. It has poor bioavailability and requires frequent dosing because of its rapid hepatic metabolism, but it may be beneficial in cases of thyroid storm because it can be administered intravenously.

Atenolol, a selective β1 blocker, requires only once-daily dosing because of enhanced oral bioavailability, making it a more appropriate choice to treat feline thyroid storm. A rapid-onset, short-acting β blocker like esmolol may be used initially in the emergency setting while monitoring the patient for improvement or deterioration.

Inhibition of Thyroid Hyperactivity

The preferred antithyroid drug, methimazole, is a thionamide used to decrease circulating thyroid hormone concentrations by blocking $T_4$ synthesis through inhibition of tyrosine residue organification. Methimazole may be administered orally, rectally, or transdermally. However, it has no effect on

### TABLE 1

| Medications for Treating Cats With Thyroid Storm$^{2,13,14,22,23}$ |
|-----------------|-----------------|-----------------|
| **Drug**        | **Dosage/Route** | **Mechanism of Action** |
| **Antithyroid drugs** |                 |                             |
| Methimazole     | 2.5–5 mg PO, per rectum, or transdermally q12h | Inhibits thyroid hormone synthesis |
| Potassium iodate| 25 mg PO q8h    | Inhibits preformed thyroid hormone release |
| Iopanoic acid  | 100–200 mg PO q24h | Inhibits preformed thyroid hormone synthesis; blocks peripheral conversion of $T_4$ to $T_3$ |
| **Inhibition of peripheral effects** |                 |                             |
| Propranolol     | 0.02 mg/kg IV slowly (may repeat up to four times); 2.5–5 mg PO q8–12h | Antagonizes hyperadrenergic effects with or without inhibiting peripheral conversion of $T_4$ to $T_3$ |
| Atenolol        | 1–3 mg/kg PO q12–24h | Antagonizes hyperadrenergic effects |
| Esmolol         | Loading dose: 200–500 μg/kg IV over 1 min; IV CRI: 25–200 μg/kg/min | Antagonizes hyperadrenergic effects |
| Dexamethasone sodium phosphate | 0.1 mg/kg IV q12–24h | Inhibits peripheral conversion of $T_4$ to $T_3$ |
| **Supportive care** |                 |                             |
| Potassium gluconate | ¼ tsp (2 mEq) per 4.5 kg in food q12h | Potassium supplementation |
| Vitamin B12 (B complex) | 1 mL IV (in fluids), IM, or SC | Vitamin B12 supplementation |
| Low-dose aspirin | 5 mg/cat PO q72h | Anticoagulation |
| Unfractionated heparin | 200–400 U/kg SC q8h until aPTT = 1.5–2 × baseline | Anticoagulation |

In patients with normal renal function. aPTT = activated partial thromboplastin time.
the amount of preformed thyroid hormone in active thyroid cells. Medications that can be used to block the release of preformed thyroid hormone from the thyroid include iodine preparations such as iopanoic acid and potassium iodate. Iopanoic acid also inhibits the peripheral conversion of T4 to T3. Methimazole should be given 1 hour before administration of iodine preparations because iodine therapy can transiently increase the release of thyroid hormone, resulting in a worsening of the thyrotoxic state.

Supportive Care

Supportive care should begin with correction of dehydration along with aggressive potassium and glucose supplementation for hypokalemic and hypoglycemic patients. Cooling fluids should be administered to hyperthermic patients. Blood exchange methods (peritoneal dialysis, plasmapheresis, hemodialysis) have been used in human patients with severe thyroid storm; however, the expense associated with these treatment modalities may make them impractical in veterinary medicine. Glucocorticoids are used in human medicine to decrease thyroid hormone release and to inhibit peripheral conversion of T4 to T3; these agents are controversial in veterinary medicine and require further investigation.

Identification and Treatment of Precipitating Causes

Preventive measures to guard against thyroid storm are important. Because surgery has been reported to be one of the most common precipitating causes of thyroid storm in human patients, pre- and perioperative treatment may be indicated for known hyperthyroid feline patients undergoing surgery. A euthyroid state should be ensured before surgery, and the administration of β blockers may prevent the development of thyroid storm postoperatively. Another known precipitant of thyroid storm, abrupt withdrawal of antithyroid medication, may be addressed by the use of a β blocker if methimazole is to be discontinued before iodine 131 (¹³¹I) therapy. After resolution of thyroid storm (if one occurs) and clinical stabilization, ¹³¹I therapy may be considered.

Conclusion

Thyroid storm is a severe, potentially fatal syndrome described in human medicine that is characterized by multiorgan decompensation after exposure to excessive circulating levels of thyroid hormones. While further investigation regarding the prevalence of thyroid storm in hyperthyroid cats presenting on an emergency basis is warranted, hyperthyroid cats may present with signs compatible with thyroid storm. The clinical manifestations of thyroid storm are more readily treatable when recognized early; therefore, rapid recognition and appropriate treatment are mandatory to ensure patient survival.

Key Points

- Thyroid storm is a life-threatening multisystemic disease that may occur in cats with hyperthyroidism. Early recognition and immediate intervention are critical to achieve a successful outcome.
- Treatment of thyroid storm is directed toward inhibition of peripheral effects of thyroid hormone, inhibition of hyperactive thyroid tissue, provision of supportive care, and identification and treatment of precipitating causes.

References

1. Which statement regarding thyroid storm in human patients is true?
   a. It is always associated with hyperthyroidism.
   b. A precipitating event is generally not identified.
   c. Clinical signs are associated with hypometabolism.
   d. The clinical signs are the same as for uncomplicated thyrotoxicosis but more severe.

2. ______ is not a treatment option for asthmatic cats with thyroid storm.
   a. Propanolol
   b. Methimazole
   c. Potassium supplementation
   d. Atenolol

3. Which is not thought to be an underlying mechanism of thyroid storm?
   a. increased sympathetic activation
   b. increased sensitivity to thyroid hormone
   c. rapid increases in free T4
   d. decreased conversion of T4 to T3

4. The clinical signs associated with thyroid storm do not include
   a. gastrointestinal signs.
   b. fever.
   c. central nervous system signs.
   d. upper respiratory signs.

5. Most thyroid hormone in the blood is in the form of
   a. free T3.
   b. free T4.
   c. protein-bound T4.
   d. protein-bound T3.

6. Possible precipitating factors for thyroid storm include
   a. methimazole treatment.
   b. intravenous fluid therapy.
   c. trauma.
   d. β blockade.

7. Diagnostic criteria for thyroid storm include
   a. appropriate clinical signs.
   b. hyperthyroidism.
   c. resolution with appropriate treatment.
   d. all of the above

8. Appropriate therapy for thyroid storm does not include
   a. β blockade.
   b. β agonists.
   c. methimazole.
   d. potassium iodate.

9. Measures to prevent thyroid storm might include
   a. vigorous palpation of the thyroid before 131I therapy.
   b. discontinuation of methimazole immediately before surgery.
   c. administration of atenolol before discontinuing methimazole in preparation for 131I therapy.
   d. treatment with a β agonist immediately before surgery.

10. Impending or current thyroid storm may be diagnosed based on
    a. the presence of clinical signs in three or more organ systems.
    b. a history of hyperthyroidism.
    c. the presence of mild clinical signs.
    d. a history of recent thyroid surgery.