Myxedema coma

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Feb 2016. | This topic last updated: Jun 03, 2015.

INTRODUCTION — Myxedema coma is defined as severe hypothyroidism leading to decreased mental status, hypothermia, and other symptoms related to slowing of function in multiple organs. It is a medical emergency with a high mortality rate. Fortunately, it is now a rare presentation of hypothyroidism, likely due to earlier diagnosis as a result of the widespread availability of thyroid-stimulating hormone (TSH) assays.

Early recognition and therapy of myxedema coma are essential. Treatment should be begun on the basis of clinical suspicion without waiting for laboratory results. Important clues to the possible presence of myxedema coma in a poorly responsive patient are the presence of a thyroidectomy scar or a history of radioiodine therapy or hypothyroidism. A history obtained from family members often reveals antecedent symptoms of thyroid dysfunction followed by progressive lethargy, stupor, and coma.

The clinical presentation, diagnosis, and treatment of myxedema coma will be reviewed here. The diagnosis and treatment of hypothyroidism are reviewed separately. (See "Disorders that cause hypothyroidism" and "Clinical manifestations of hypothyroidism" and "Treatment of hypothyroidism".)

PATHOGENESIS — Myxedema coma can occur as the culmination of severe, long-standing hypothyroidism or be precipitated by an acute event such as infection, myocardial infarction, cold exposure, or the administration of sedative drugs, especially opioids.

The demographics of patients who develop myxedema coma are those of hypothyroidism in general, with older women being most often affected. Myxedema coma can result from any of the usual causes of hypothyroidism, particularly chronic autoimmune thyroiditis, because of its often insidious course compared with post-surgical or post-ablative hypothyroidism (see "Disorders that cause hypothyroidism"). It can occur in patients with secondary hypothyroidism, and there are case reports of its occurrence in patients with lithium- or amiodarone-induced hypothyroidism [1-3].

CLINICAL PRESENTATION — The function of virtually every organ system and the activity of many metabolic pathways are slowed in severe hypothyroidism. The hallmarks of myxedema coma are decreased mental status and hypothermia, but hypotension, bradycardia, hyponatremia, hypoglycemia, and hypoventilation are often present as well. Puffiness of the hands and face, a thickened nose, swollen lips, and an enlarged tongue may occur secondary to nonpitting edema with abnormal deposits of mucin in the skin and other tissues (myxedema).

The possibility of a precipitating infection or other acute illness should always be considered; it is important to appreciate, however, that the patient may not have a febrile response to infection (table 1).

Neurologic manifestations — Despite the name myxedema coma, patients frequently do not present in coma, but do manifest lesser degrees of altered consciousness [4]. This usually takes the form of confusion with lethargy and obtundation. Alternatively, a more activated presentation may occur with prominent psychotic features, so-called myxedema madness [5]. Untreated, patients will progress to coma.

Focal or generalized seizures may occur, sometimes due to concomitant hyponatremia, and status epilepticus has been reported [6,7]. In the absence of seizures, electroencephalogram (EEG) findings are nonspecific with slowing and decreased amplitude, rarely with triphasic waves [8]. When cerebrospinal fluid is obtained (usually to rule out infection in a patient with fever and mental status changes), modest elevation of protein levels (<100 mg/dL) may be seen [8].
Hyponatremia — Hyponatremia is present in approximately one-half of patients with myxedema coma. It can be severe and may contribute to the decrease in mental status. Most, but not all, patients have an impairment in free water excretion due to inappropriate excess vasopressin secretion or impaired renal function [9]. The low serum sodium concentration is reversible after treatment of the hypothyroidism. (See "Causes of hyponatremia in adults", section on 'Hypothyroidism'.)

Hypothermia — Hypothermia is present in many patients with myxedema coma. It is due to the decrease in thermogenesis that accompanies the decrease in metabolism.

The low body temperature may not be recognized initially because many automatic thermometers do not register frankly hypothermic body temperatures. If a low temperature is found, the thermometer itself should be checked to avoid an incorrect measurement. The severity of the hypothermia is related to mortality in severe hypothyroidism; the lower the temperature, the more likely a patient is to die.

Hypoventilation — Hypoventilation with respiratory acidosis results primarily from central depression of ventilatory drive with decreased responsiveness to hypoxia and hypercapnia [10]. Other contributing factors include respiratory muscle weakness, mechanical obstruction by a large tongue, and sleep apnea. (See "Clinical manifestations and diagnosis of obesity hypoventilation syndrome".)

Some patients require mechanical ventilation (see "Control of ventilation"). Airway management may be complicated by myxedematous infiltration of the pharynx [11]. Recovery from ventilatory depression may take as long as three to six months after treatment of hypothyroidism [4].

Hypoglycemia — Hypoglycemia may be caused by hypothyroidism alone or, more often, by concurrent adrenal insufficiency due to autoimmune adrenal disease or hypothalamic-pituitary disease. The presumed mechanism is decreased gluconeogenesis, but starvation and infection can contribute. (See "Clinical manifestations of adrenal insufficiency in adults".)

Cardiovascular abnormalities — Thyroid hormone plays a role in blood pressure homeostasis. Hypothyroid patients have diastolic hypertension, even though cardiac output is reduced, and a narrowed pulse pressure. Severe hypothyroidism is associated with bradycardia, decreased myocardial contractility, a low cardiac output, and sometimes hypotension [12]. Overt congestive heart failure is quite rare in the absence of preexisting cardiac disease. This is probably due to the lower tissue demands for oxygenation and cardiac output in hypothyroidism. (See "Cardiovascular effects of hypothyroidism".)

Pericardial effusion may be present. Its clinical manifestations include diminished heart sounds, low voltage on electrocardiogram, and a large cardiac silhouette on chest radiograph; however, ventricular function is rarely compromised. (See "Constrictive pericarditis".)

All of the cardiac abnormalities are reversible with thyroid hormone therapy [13].

DIAGNOSIS — The diagnosis of myxedema coma is initially based upon the history, physical examination, and exclusion of other causes of coma (see "Stupor and coma in adults", section on 'Diagnosis'). The diagnosis should be considered in any patient with coma or depressed mental status who also has hypothermia, hyponatremia, and/or hypercapnia [4]. Additional clues to the possible presence of myxedema coma in a poorly responsive patient are the presence of a thyroidectomy scar or a history of radioiodine therapy or hypothyroidism.

A diagnostic scoring system for myxedema coma has been proposed based on 21 patients diagnosed with myxedema coma [14]. The scoring system gives points for the degree of hypothermia; lethargy, obtundation, stupor, or coma; anorexia, reduced intestinal mobility, or paralytic ileus; the presence of a precipitating event; the degree of bradycardia, electrocardiogram (ECG) changes, pericardial or pleural effusions, cardiomegaly or hypertension; and hyponatremia, hypoglycemia, hypoxemia, hypercapnea or reduced glomerular filtration rate (GFR). Although some clinicians may find this scoring system useful, it is limited by the small number of patients from which it was derived.
If the diagnosis of myxedema coma is suspected, a blood sample should be drawn for measurement of serum thyroid-stimulating hormone (TSH), free thyroxine (T4), and cortisol before therapy with a glucocorticoid and thyroid hormone are initiated. Ideally, cortisol should be measured before and after corticotropin administration. (See "Diagnosis of adrenal insufficiency in adults".)

Most patients with myxedema coma have primary hypothyroidism, with high serum TSH and low free T4 values. On the other hand, a normal or low serum TSH value in a patient with a low free T4 value indicates that the hypothyroidism is secondary to hypothalamic or pituitary dysfunction. (See "Disorders that cause hypothyroidism".)

**TREATMENT** — Although in many clinical settings the results of serum thyroid-stimulating hormone (TSH) measurements are rapidly available, in circumstances where laboratory confirmation of hypothyroidism is delayed, treatment should be instituted in patients with presumed myxedema coma without waiting for laboratory confirmation.

Myxedema coma is an endocrine emergency and should be treated aggressively. The mortality rate remains high at 30 to 40 percent [15-17], with older patients and those with cardiac complications, reduced consciousness, persistent hypothermia, and sepsis being at greatest risk [16,18]. Treatment consists of thyroid hormone, supportive measures, and appropriate management of coexisting problems such as infection (table 2).

In addition, until the possibility of coexisting adrenal insufficiency has been excluded, the patient must be treated with glucocorticoids in stress doses (eg, hydrocortisone given intravenously, 100 mg every eight hours). (See "Treatment of adrenal insufficiency in adults".)

**Thyroid hormone** — The optimal mode of thyroid hormone therapy in patients with myxedema coma is controversial, largely because the condition is so rare that there are no clinical trials comparing the efficacy of different treatment regimens. We prefer to give both hormones because the biologic activity of T3 (triiodothyronine, liothyronine) is greater, and its onset of action is more rapid, than T4 (levothyroxine). An additional consideration is that the conversion of T4 to T3 is impaired due to both hypothyroidism and any concurrent nonthyroidal illness. The decrease in T4 to T3 conversion may be a protective adaptation in the face of severe illness. Therefore, proper dosing of T3 is important. High serum T3 concentrations during treatment have been correlated with mortality [15].

T4 should be given intravenously, when available, because gastrointestinal absorption may be impaired [19]. We typically administer T4 in a loading dose of 200 to 400 mcg followed by a daily dose of 1.6 mcg/kg thereafter, initially intravenously and, when feasible, orally (table 2). Given the 10 L volume of distribution for T4, this will raise the total serum T4 level by 2 to 4 mcg/dL. The lower end of the dosing range is preferred in lighter and older patients and those at risk for cardiac complications (myocardial infarction, arrhythmia). T3 may be given simultaneously in a dose of 5 to 20 mcg, followed by 2.5 to 10 mcg every eight hours, depending upon the patient’s age and coexistent cardiac risk factors. T3 is continued until there is clinical improvement and the patient is stable. Chronic therapy is discussed elsewhere. (See "Treatment of hypothyroidism".)

While increasing serum thyroid hormone concentrations rapidly carries some risk of precipitating myocardial infarction or atrial arrhythmias, this risk must be accepted because of the high mortality of untreated myxedema coma. In one randomized trial of 11 patients, those who received a 500 mcg loading dose of T4, followed by 100 mcg daily, had a lower mortality than those treated with 100 mcg daily without a loading dose (one of six died compared with three of five who did not receive the loading dose); however, the difference did not reach statistical significance [20].

There is disagreement about the preferred thyroid hormone regimen, but both very high (T4 >500 mcg, T3 ≥75 mcg) and very low doses seem less effective than intermediate doses [18]. Whether patients with myxedema coma should be treated with T4, T3, or both is controversial [4]. Some experts favor administration of T3, while others favor T4, preferring that T3 production be governed by the activity of 5’-deiodinase in the patient, while others prefer a combination of T4 and T3 [4,19,21-23].
Glucocorticoids — Patients with secondary hypothyroidism may have associated hypopituitarism and secondary adrenal insufficiency. In addition, patients with autoimmune-mediated primary hypothyroidism may have concomitant primary adrenal insufficiency. (See "Diagnosis of hypopituitarism" and "Causes of primary adrenal insufficiency (Addison's disease)", section on 'Autoimmune adrenalitis'.)

Until the possibility of coexisting adrenal insufficiency has been excluded, the patient must be treated with glucocorticoids in stress doses (eg, hydrocortisone given intravenously, 100 mg every eight hours). (See "Diagnosis of adrenal insufficiency in adults" and "Treatment of adrenal insufficiency in adults".)

Supportive measures — Supportive measures are extremely important in the treatment of patients with myxedema coma and, in the first day or so, may make the difference between survival and death. These measures include treatment in an intensive care unit, mechanical ventilation if necessary, judicious administration of intravenous fluids including electrolytes and glucose, correction of hypothermia, and treatment of any underlying infection.

- Dilute fluids should be avoided in hyponatremic patients to prevent a further reduction in the plasma sodium concentration. (See "Overview of the treatment of hyponatremia in adults".)
- Hypotension, if present and not caused by volume depletion, will be corrected by thyroid hormone therapy over a period of hours to days. Severe hypotension that does not respond to fluids should be treated with a vasopressor drug until the T4 has had time to act. (See "Evaluation of and initial approach to the adult patient with undifferentiated hypotension and shock", section on 'Initial approach'.)
- Passive rewarming with a blanket is preferred for correction of hypothermia. Active rewarming carries a risk of vasodilatation and worsening hypotension. (See "Hypothermia in children: Management" and "Accidental hypothermia in adults", section on 'Management'.)
- As with any critically ill, comatose patient, empiric administration of antibiotics should be considered until appropriate cultures are proven negative.

SUMMARY AND RECOMMENDATIONS

- Myxedema coma is defined as severe hypothyroidism leading to slowing of function in multiple organs. It is a medical emergency with a high mortality rate. Fortunately, it is now a rare presentation of hypothyroidism, likely due to earlier diagnosis as a result of the widespread availability of thyroid-stimulating hormone (TSH) assays. (See 'Introduction' above.)
- The hallmarks of myxedema coma are decreased mental status and hypothermia, but hypotension, bradycardia, hyponatremia, hypoglycemia, and hypoventilation are often present as well. (See 'Clinical presentation' above.)
- If the diagnosis of myxedema coma is suspected, a blood sample should be drawn for measurement of serum T4 (thyroxine), TSH, and cortisol (ideally before and after corticotropin administration) before therapy with a glucocorticoid and thyroid hormone are initiated. The serum T4 concentration is usually very low. The serum TSH concentration may be high, indicating primary hypothyroidism, or low, normal, or slightly high, indicating central hypothyroidism. (See 'Diagnosis' above and "Diagnosis of and screening for hypothyroidism in nonpregnant adults" and "Central hypothyroidism".)
- Patients with myxedema coma should be treated aggressively, because the mortality rate approaches 40 percent (table 2). In circumstances where laboratory confirmation of hypothyroidism is delayed, treatment with thyroid hormone and glucocorticoids should be instituted without waiting for laboratory confirmation. (See 'Diagnosis' above.)
- For patients with myxedema coma, we suggest combined therapy with T4 (levothyroxine) and T3 (triiodothyronine, liothyronine) rather than T4 alone (Grade 2C). We suggest an initial dose of 200 to 400 mcg T4 intravenously, followed by daily intravenous doses of 50 to 100 mcg until the patient can take T4 orally.
T3 is given intravenously at the same time; the initial dose is 5 to 20 mcg, followed by 2.5 to 10 mcg every eight hours depending upon the patient’s age and coexisting cardiovascular disease. T3 is continued until there is clinical improvement and the patient is stable. (See ‘Treatment’ above.)

● Until coexisting adrenal insufficiency can be excluded, the patient should be given high-dose glucocorticoid therapy (hydrocortisone 100 mg intravenously every eight to twelve hours for two days, then lower doses). (See ‘Glucocorticoids’ above.)

● Supportive measures are extremely important, including mechanical ventilation, appropriate fluid replacement, and correction of hyponatremia and hypothermia. In addition, there is often an associated illness that must be treated, such as infection, or gastrointestinal bleeding. (See ‘Supportive measures’ above.)

Use of UpToDate is subject to the Subscription and License Agreement.

REFERENCES


### Clinical features of myxedema coma

<table>
<thead>
<tr>
<th>Decreased mental status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothermia</td>
</tr>
<tr>
<td>Bradycardia</td>
</tr>
<tr>
<td>Hyponatremia</td>
</tr>
<tr>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Hypotension</td>
</tr>
<tr>
<td>Precipitating illness</td>
</tr>
</tbody>
</table>

Graphic 54836 Version 1.0
<table>
<thead>
<tr>
<th>Treatment of myxedema coma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Draw serum for T4, TSH, and cortisol.</td>
</tr>
<tr>
<td>Administer levothyroxine 200 to 400 mcg (0.2 to 0.4 mg) intravenously followed by daily doses of 50 to 100 mcg, and triiodothyronine 5 to 20 mcg intravenously followed by 2.5 to 10 mcg every eight hours.</td>
</tr>
<tr>
<td>Change to an equivalent oral dose of levothyroxine when the patient can tolerate oral medications. (Oral dose = intravenous dose ÷ 0.75).</td>
</tr>
<tr>
<td>Supportive measures:</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
</tr>
<tr>
<td>Fluids and vasopressor drugs to correct hypotension</td>
</tr>
<tr>
<td>Passive rewarming</td>
</tr>
<tr>
<td>Intravenous dextrose</td>
</tr>
<tr>
<td>Stress-doses glucocorticoids</td>
</tr>
<tr>
<td>Consider empirical antibiotic treatment</td>
</tr>
<tr>
<td>Monitor for arrhythmias and treat when indicated</td>
</tr>
</tbody>
</table>

T4: thyroxine; TSH: thyroid-stimulating hormone.

Graphic 61507 Version 2.0
Disclosures

Disclosure: Douglas S Ross, MD Consultant/Advisory Board: Bayer/Onyx Pharmaceuticals [Thyroid cancer (Sorafenib)]; Eisai Inc. [Thyroid cancer (Lenvatinib)]. David S Cooper, MD Nothing to disclose. Jean E Mulder, MD Nothing to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy