

Critical issues in endocrinology

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Endocrine emergencies are commonly encountered in the intensive care unit (ICU). This article focuses on several important endocrine emergencies, including diabetic hyperglycemic states, adrenal insufficiency, myxedema coma, thyroid storm, and pituitary apoplexy. Other endocrine issues that are related to intensive care, such as intensive insulin therapy, relative adrenal insufficiency, and thyroid function test abnormalities also are covered in detail. Because of space limitations, additional endocrinologic emergencies including hypoglycemia, calcium disorders, and fluid and electrolyte disorders are not included (for reviews see references [1–7]).

Critical issues in metabolism

Diabetic hyperglycemic crises: diabetic ketoacidosis and hyperosmolar hyperglycemic states

Diabetic hyperglycemic crises are commonly encountered in the ICU. Diabetic ketoacidosis (DKA) occurs with an annual incidence of four to eight episodes per 1000 diabetic patients [8,9]. It accounts for more than 100,000 yearly hospital admissions [10], with total costs (at more than \$13,000 per admission) that exceed \$1.3 billion per year [11]. The incidence and economic impact of hyperosmolar hyperglycemic states (HHS) are more difficult to ascertain, because of a lack of population-based studies. Although hospital admission rates for HHS are likely lower than those for DKA [10], the growing type 2 diabetes epidemic suggests that the incidence of HHS is increasing.

The underlying mechanism for DKA and HHS is the reduced net activity of circulating insulin, usually with concurrent stimulation of counter-regulatory hormone activity (eg, glucagon, catecholamines, glucocorticoids [GC]). As shown in Fig. 1, these hormonal changes lead to increased glucose production and decreased peripheral glucose use. Hyperglycemia ensues, which leads to a vigorous osmotic diuresis which precipitates volume contraction and severe electrolyte losses [12]. In the setting of absolute insulin deficiency (ie, DKA), accelerated lipolysis and fatty acid oxidation also generate ketoacidosis [13]. In general, DKA afflicts patients who have type 1 diabetes, whereas HHS occurs in patients who have type 2 diabetes; however, there is substantial overlap between these two clinical syndromes. In clinical practice, HHS can present with variable degrees of ketosis and acidosis. Conversely, DKA is being seen with increasing frequency in patients who have type 2 diabetes, with a predilection for obese African Americans [14].

Most hyperglycemic crises have an identifiable precipitating event. Infections trigger up to 50% of cases [10]. Pneumonia, urinary tract infections (UTIs), and sepsis are common precipitants, as are common viral triggers, such as gastroenteritis and upper respiratory infections. Inadequate insulin treatment, including medication noncompliance and insulin pump failure, accounts for an additional 20% to 40% of cases [10]. Table 1 lists some of the more common precipitants for diabetic hyperglycemic crises.

Diagnosis

The presence of DKA or HHS is suggested by a history of polyuria, polydipsia, nausea, vomiting, or dehydration in the setting of known diabetes. DKA/HHS may also be the initial presentation of new diabetes. Because of the discomfort that is induced by acidosis, DKA typically evolves within 24 hours,

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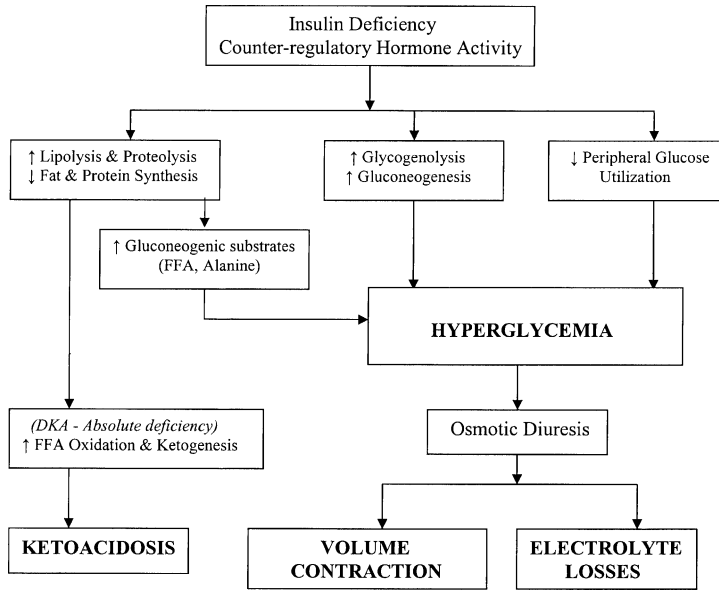


Fig. 1. Pathogenesis of diabetic hyperglycemic states.

whereas HHS may progress over several days [15]. For this reason, patients who have HHS typically present with more severe dehydration and electrolyte disturbances. Focal neurologic symptoms or seizures may be seen in severe cases [16]. On physical examination, patients who have hyperglycemic crises present with

variable degrees of lethargy, mental status changes, and dehydration; the latter is suggested by decreased skin turgor, dry mucous membranes, tachycardia, and orthostatic hypotension. Abdominal pain is common in DKA and may reflect delayed gastric emptying or intestinal ileus [17]; this symptom is less commonly seen in HHS. The presence of ketoacidosis is suggested by the presence of “acetone breath” or rapid, deep Kussmaul respirations.

Table 1
Known precipitants of diabetic hyperglycemic crises

% of Cases	Precipitating event
30–50%	Infections: Viral infections, pneumonia, UTI, sepsis
20–40%	Inadequate insulin therapy
3–6%	Myocardial ischemia/infarction
<2%	Cerebrovascular accident
	Intracranial bleeding
	Pulmonary embolus
	Intestinal thrombosis or obstruction
	Acute pancreatitis
	Alcohol intoxication
	Acute renal failure, peritoneal dialysis
	Hyperthermia or hypothermia
	Severe burns
	Endocrine disorders: thyroid storm, Cushing’s syndrome
	Total parenteral nutrition
	Drugs: β -blockers, calcium channel blockers, diuretics, corticosteroids, antipsychotics, phenytoin, cimetidine

The diagnosis of hyperglycemic crises is usually straightforward. The presence of hyperglycemia in the proper clinical setting should trigger the clinician to test for serum and urine ketones and to obtain arterial blood gases. Follow-up serologic evaluation should include a complete blood count with differential, chemistries (including divalent cations), serum osmolality, liver and pancreatic function tests, and cardiac enzymes. Bacterial cultures of blood, urine, and other sources should be obtained, along with a urinalysis, chest radiograph, and 12-lead ECG. A full septic work-up should be considered in all patients, particularly infants. Recent laboratory criteria that are endorsed by the American Diabetes Association (ADA) for the diagnosis of DKA and HHS [18] are displayed in Table 2. In general, DKA is diagnosed when plasma glucose is greater than 250 mg/dL and arterial pH is less than 7.30 in the setting of detectable urine/serum ketones. DKA severity may be graded using pH, bicarbonate, and other clinical criteria (see Table 2). HHS is diagnosed when plasma glucose is greater

Table 2
Laboratory diagnosis and classification of DKA and HHS

	Mild DKA	Moderate DKA	Severe DKA	HHS
Plasma glucose (mg/dL)	>250	>250	>250	>600
Serum osm (mosm/kg)	Variable	Variable	Variable	>320
Urine/serum ketones	Positive	Positive	Positive	Weak/negative
Arterial pH	7.25–7.30	7.00–7.24	<7.00	>7.30
Serum HCO ₃ ⁻ (mEq/L)	15–18	10–15	<10	>15
Anion gap (mEq/L)	>10	>12	>12	<12

From Kitabachi AE, et al. Technical review. Management of hyperglycemic crises in patients with diabetes. Diabetes Care 2001;24:131–55; with permission.

than 600 mg/dL and serum osmolality is greater than 320 mosm/kg. The term “HHS” [15] is now preferred over “hyperglycemic hyperosmolar nonketotic coma” to emphasize two important clinical points: (1) mental status changes usually occur in the absence of frank coma, and (2) some degree of ketosis may be present in HHS.

Management

The clinical management of diabetic hyperglycemic crises is complex, and requires frequent attention to details regarding hydration, electrolyte repletion, and acid-base status. For this reason, patients who have DKA or HHS are best managed in an ICU setting. The initial goals of therapy for both syndromes are to replace volume and electrolyte deficits. Hyperglycemia should be corrected slowly. A modification of the ADA-endorsed treatment algorithm for DKA/HHS [18] is presented in Fig. 2. The five major components of therapy are considered below.

Volume replacement. Restoration of intravascular volume is the first goal of therapy, to correct tissue hypoperfusion, improve glomerular filtration (restoring renal glucose and ketone clearance), and reverse insulin resistance. DKA and HHS may present with massive total-body water deficits, up to 10 to 12 L [15,19]. Although water losses generally exceed the loss of salts, volume replacement should typically begin with isotonic saline (0.9% NaCl). Intravenous (IV) fluid regimens vary, but it is standard to administer one liter of saline within the first 30 to 60 minutes, followed by a continuous infusion of 250 to 500 mL/hour [20] as guided by clinical and laboratory parameters. During volume replacement for DKA, after blood glucose (BG) levels have fallen below 250 mg/dL, dextrose should be added to the IV fluids, to minimize the risks of cerebral edema and hypoglycemia during continued IV insulin therapy. In pediatric patients, hypotonic fluids (eg, 0.45% NaCl) should generally be avoided because they can precipitate cerebral edema through accelerated fluid shifts into the brain [12].

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Insulin. Insulin therapy is an essential component of therapy for DKA, and is useful in most cases of HHS. Although severe insulin resistance is present in both conditions, supraphysiologic insulin doses are not recommended, because they can result in hypokalemia, hypophosphatemia, or delayed hypoglycemia [21,22]. Standard insulin therapy for DKA uses an IV bolus of 0.15 U/kg of regular insulin, followed by a continuous insulin infusion of 0.1 U/kg/hour [18]. Smaller insulin doses may be used for treating HHS. In some cases of HHS, insulin may not be required to lower BG levels, because tissue perfusion and insulin sensitivity may be restored by volume restoration alone. Ideally, BG levels should decrease by 50 to 75 mg/dL/hour [18]. To achieve this steady decline, it is essential to monitor BG hourly during the early hours of therapy. After BG is less than 250 mg/dL (and ketoacids have been cleared, in DKA), subcutaneous (SQ) insulin therapy can be initiated. In patients who have DKA, it is best to overlap IV and SQ insulin therapy by 1 to 2 hours, to prevent recurrent ketonemia. Following the restoration of normoglycemia, long-term diabetes management may be slowly (re)initiated.

Potassium. Aggressive potassium repletion is critically important during therapy for DKA or HHS. Hypokalemia can result in weakness, muscle cramps, and nausea. Intracellular potassium depletion may also trigger dangerous cardiac arrhythmias. At the time of presentation, most patients who have DKA/HHS have severe total body potassium deficits, on the order of 3 to 6 mEq/kg. Admission potassium levels may be low, normal, or even high, especially in the presence of acidosis or renal insufficiency [23]. After therapy for DKA/HHS has been initiated, serum potassium levels often decrease precipitously, because of an insulin-mediated intracellular shift of potassium ions. In addition, IV saline therapy dilutes circulating potassium

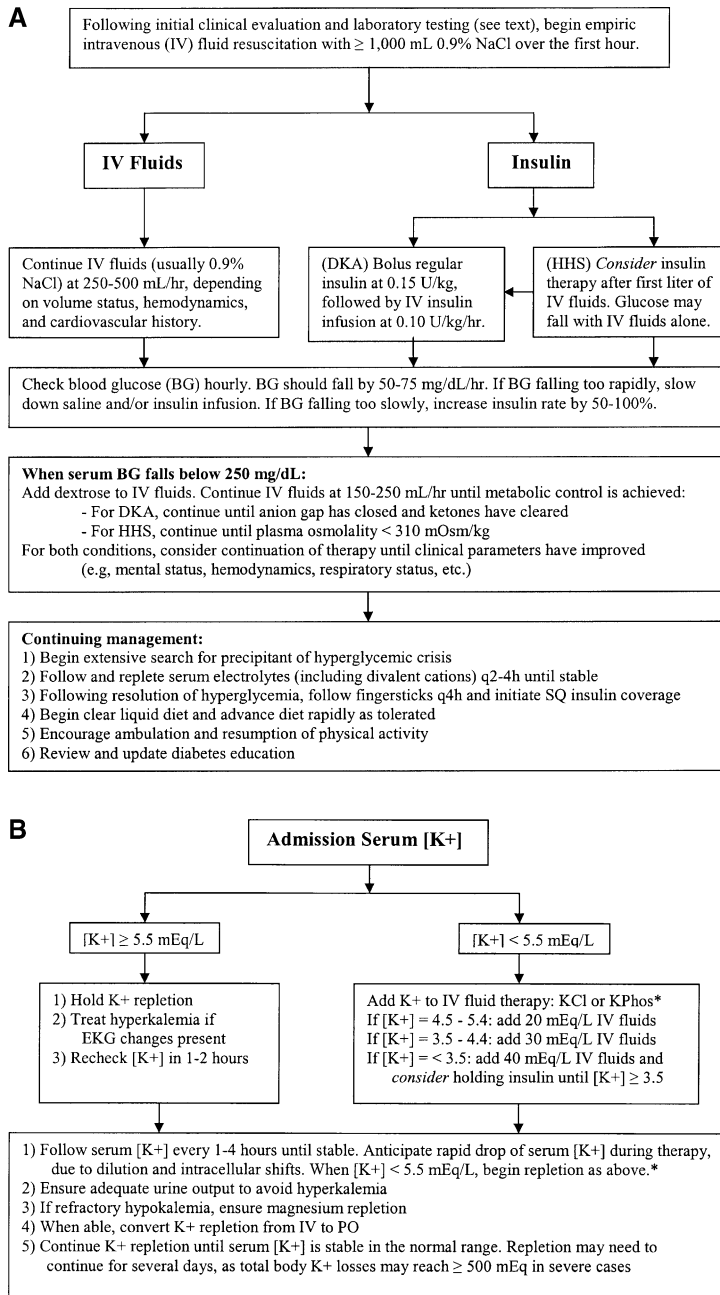


Fig. 2. (A) Management of adult patients who have diabetic hyperglycemic states. Volume repletion and insulin therapy. (B) Management of adult patients who have diabetic hyperglycemic states. Potassium repletion. *K⁺ repletion should be started after the initial fluid resuscitation with at least 1000 mL of isotonic saline. (C) Management of adult patients who have diabetic hyperglycemic states. Bicarbonate therapy.

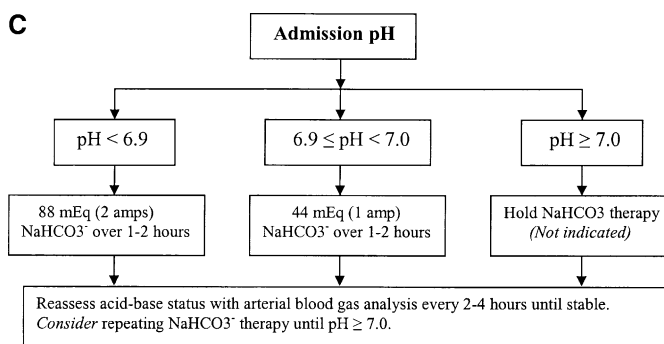


Fig. 2 (continued).

and stimulates urinary potassium excretion [24]. Hypokalemia on presentation demands aggressive potassium repletion; in such cases, insulin therapy should be withheld until potassium levels exceed 3.3 mg/dL [25]. “Normal” potassium levels should also be supplemented early during therapy, in anticipation of therapy-induced potassium shifts [18]. In patients who have abnormal potassium levels (high or low), frequent ECG monitoring is recommended throughout the early phases of therapy.

Phosphate. Like potassium levels, serum phosphate levels may be falsely elevated on presentation because of extracellular shifts. Complications of hypophosphatemia include respiratory and skeletal muscle weakness, impaired cardiac output, and hemolytic anemia [26]. Hypophosphatemia may also hamper oxygen delivery to peripheral tissues [27]. Although prophylactic phosphate repletion is usually unnecessary, prompt recognition and treatment of phosphate deficits are important [28,29]. IV phosphate repletion may be indicated if serum levels decrease to less than 1.0 to 1.5 mg/dL, whereas oral repletion is usually adequate for mild hypophosphatemia. To prevent hypocalcemia, calcium and magnesium levels should be carefully monitored in all patients who receive phosphate therapy.

Bicarbonate. In most patients who have DKA, ketoacids clear spontaneously with standard therapy, because insulin suppresses lipolysis and ketogenesis, whereas the restoration of plasma volume improves renal ketone clearance. For these reasons, the routine use of alkali therapy for DKA is not recommended (see references [18,30,31]). In severe cases ($\text{pH} < 7.0$), bicarbonate therapy may be used to stimulate cardiac inotropy and reverse peripheral vasodilatation. Bicarbonate should be used with extreme caution because it can precipitate hypokalemia and may impair oxygen delivery to peripheral tissues. In addition, alkalosis may develop as patients recover from ketoacidosis.

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In most patients, acid-base status will improve with volume restoration and insulin therapy alone. If bicarbonate is used, it should be administered slowly and in small doses. 1 amp (44 mEq) may be given over 1 hour for pH less than 7.0, whereas 1 to 2 amps may be used if pH is less than 6.9 [18]. Following the administration of bicarbonate, arterial pH (and serum potassium) levels should be monitored at least every 2 hours until pH exceeds 7.0, at which time alkaline therapy should usually be discontinued. Continuous infusions of bicarbonate-containing IV fluids are rarely required.

While treating DKA or HHS, clinicians should be cognizant of therapy-related complications, including hypoglycemia, hypokalemia, and hypophosphatemia. Precautions to avoid these common complications were described. Two rare, but potentially fatal, complications deserve special mention. Cerebral edema is associated with overaggressive correction of hyperglycemia and hypotonic fluid therapy [32,33]. This complication, which is more common in the pediatric population, is believed to result from osmotically driven fluid shifts into the central nervous system (CNS) [34]. Clinically, cerebral edema presents with lethargy, headache, and progressive neurologic deterioration. Emergent neurosurgical consultation is recommended in all cases. The acute respiratory distress syndrome (ARDS), characterized by noncardiogenic pulmonary edema and an increased alveolar-arterial oxygen gradient, has also been attributed to rapid reductions in osmotic pressure [35]. Affected patients present with respiratory distress, hypoxia, and radiographic evidence of pulmonary edema. Because high

IV fluid infusion rates are associated with cerebral edema and ARDS, fluid administration (and correction of hyperglycemia) must be slowed in patients who have either condition [12].

Hyperglycemia and intensive insulin therapy in critically ill patients

Stress hyperglycemia (used herein to denote stress-induced elevations in [BG] and free fatty acid [FFA] levels) occurs in most critically ill patients [36,37]. Severe stress or critical illness induces several alterations in carbohydrate and fatty acid metabolism, including increased hepatic gluconeogenesis, peripheral insulin resistance, and the liberation of FFAs from adipose stores [37]. In a variety of clinical settings, stress hyperglycemia was associated with adverse clinical outcomes. After myocardial infarction (MI), for example, hyperglycemia predicts increased rates of congestive heart failure, cardiogenic shock, and death [38,39], whereas high FFA levels have been associated with excess cardiac arrhythmias and mortality [40,41]. Following acute stroke, stress hyperglycemia also was associated with increased mortality and with diminished neurologic recovery [42]. In patients who were admitted to an ICU, impaired glucose and lipid metabolism is associated with increased severity of illness and decreased survival [43].

Several pathophysiologic mechanisms have been proposed to explain the relationship between stress hyperglycemia and adverse clinical outcomes. First, stress hyperglycemia occurs in the setting of peripheral insulin resistance [37]. Such conditions limit the ability of tissues to use metabolic fuels and permit the local accumulation of FFAs, which can damage cell membranes and impair tissue performance (see references [37,41,44]). Hyperglycemia may also precipitate an osmotic diuresis, which reduces vascular volume and results in decreased cardiac output and impaired tissue perfusion [45]. Hyperglycemia also has been associated with several immune system abnormalities, including impaired leukocyte chemotaxis [46], impaired phagocytosis [47,48], and decreased immunoglobulin function and complement fixation [49].

Stress hyperglycemia typically occurs in the setting of excess glucagon, cortisol, and catecholamine release [50]. Any or all of these counter-regulatory hormones may contribute to adverse clinical outcomes during critical illness. Finally, stress hyperglycemia may simply be a marker for previously undiagnosed impaired glucose tolerance or diabetes; patients who have either condition are known to have an increased prevalence of cardiovascular disease [51]. Thus, patients who exhibit hyperglycemia during stress may

simply be at increased baseline risk for adverse cardiovascular outcomes.

Until recently, few studies have examined the specific impact of glycemic control on short-term clinical outcomes during intensive care. In the mid-1990's, the diabetes mellitus insulin-glucose infusion in acute myocardial infarction (DIGAMI) study [52,53] showed that the use of an inpatient insulin-glucose infusion (followed by an intensive outpatient insulin regimen) reduced mortality in diabetic patients following acute MI. The DIGAMI study examined predominantly long-term outcomes, however, and was not truly a study of intensive inpatient insulin therapy. In 1999, Furnary et al [54] reported reductions in deep sternal wound infections following the introduction of intensive BG control; however, this was a retrospective study and was limited by the use of historical controls. In 2000, Lazar et al [55] published a prospective, randomized, controlled trial of 40 diabetic patients who were undergoing coronary surgery, and reported that glucose-insulin-potassium infusions (which lowered BG levels) improved cardiac index, shortened duration of ventilatory support, and shortened hospital stay. This study, although convincing, was not powered to detect significant differences in many other important clinical outcomes.

In 2001, Van den Berghe et al [56] published a large, prospective, randomized controlled trial of intensive BG control in 1548 patients admitted to a surgical ICU in Leuven, Belgium. The status of two thirds of the patients that were enrolled in this study was postcardiac surgery. Upon admission, patients were randomized to either "conventional" (IV insulin drip if BG > 215 mg/dL, target BG = 180–200 mg/dL) or "intensive" (IV insulin drip if BG > 110 mg/dL, target BG = 80–110 mg/dL) insulin therapy. Intensive therapy reduced ICU mortality by 42%, and dramatically reduced the risk for several other morbid clinical outcomes, including prolonged ICU stay, prolonged need for ventilatory support, need for dialysis, septicemia, and critical illness polyneuropathy (Fig. 3). The mortality benefits seen in the Leuven study applied exclusively to patients who remained in the ICU for more than 5 days, and primarily reflected a reduction in deaths from multiple-organ failure with sepsis, regardless of pre-existing diabetes [56,57]. The Leuven study strongly supports the implementation of intensive BG control in cardiothoracic ICUs. Because the benefits obtained seemed to be mediated by reduced infectious complications, these benefits should apply to patients who are admitted to other types of ICUs, as well. Whether the Leuven study results can be generalized to other ICU populations (eg, medical ICU patients) remains to be established, however.

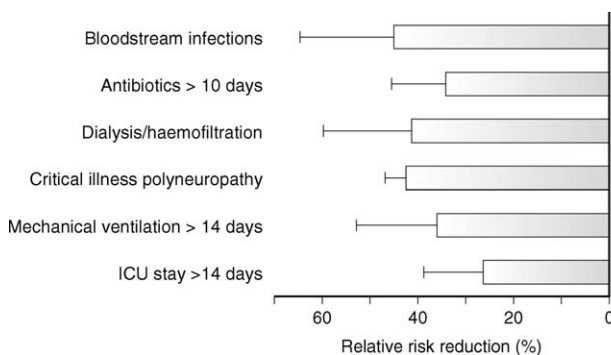


Fig. 3. Relative risk reductions for key measures of ICU morbidity in the Leuven study. * $P < 0.01$, † $P < 0.0001$. Error bars: 95% confidence intervals. Adapted from Van den Berghe G. Beyond diabetes: saving lives with insulin in the ICU. *Int J Obesity* 2002;26(Suppl 3):S6; with permission.

Based on the available data, we strongly endorse the standardized implementation of intensive infusion protocols in critically ill patients. Patients who have a history of diabetes should be targeted for intensive therapy. In addition, four common ICU interventions — corticosteroids, vasopressors, enteral nutrition, and parenteral nutrition — also predispose to poor BG control in the ICU [58]. Patients who receive any of these four interventions should be monitored as frequently as patients who have known diabetes for the presence of hyperglycemia, and should be treated as aggressively. In terms of achieving tight BG control, we recognize that levels of 80 to 110 mg/dL are difficult to achieve practically and safely in most current ICUs (mostly because of staffing issues). For this reason, we currently endorse more conservative target BG levels of 100 to 139 mg/dL, which can be safely and reliably achieved using a standard insulin infusion protocol [59]. These intensive protocols can be implemented (and readily accepted) by a busy ICU nursing staff without the need for subspecialty consultation. In the future, we predict that the development of continuous glucose monitoring strategies in the ICU [60] will promote tighter BG control. Ultimately, such advances would likely contribute to improved patient outcomes during ICU care.

Critical issues in adrenal disease

Acute adrenal insufficiency: Addisonian crisis

Clinical presentation

When present as a chronic condition, adrenal insufficiency can be difficult to diagnose. Nonspecific historical features, including chronic fatigue, depression, weakness, anorexia, nausea, diarrhea, or or-

thostatic hypotension may suggest the diagnosis. Clinically, primary adrenal insufficiency may present with hyperpigmentation (due to excess corticotropin [ACTH] production), hyponatremia, or hyperkalemia (due to mineralocorticoid [MC] deficiency). If present, adrenalitis may be found in association with other autoimmune diseases, including vitiligo, thyroiditis, and type 1 diabetes [61]. Secondary adrenal insufficiency, due to hypothalamic-pituitary disease, may be associated with headaches, visual symptoms, or other pituitary hormone deficiencies, including hypothyroidism, hypogonadism, growth hormone deficiency, or diabetes insipidus [61].

Acute adrenal insufficiency, unlike the chronic disease, presents with rapid, dramatic clinical deterioration, with cardinal signs including fever, abdominal pain, neuropsychiatric manifestations, and hemodynamic instability [62]. Addisonian crises may occur in patients who have chronic adrenal insufficiency in whom steroid therapy is interrupted, or in the setting of superimposed stress or illness. Acute decompensation may also occur in the setting of sudden adrenal injury, most often as a result of hemorrhage, infection, or inflammation [63]. Pituitary injury can also lead to adrenal insufficiency; in this situation, however, the clinical presentation is usually less severe and hyperkalemia is absent because of intact MC secretion from the adrenal glands. An extensive differential diagnosis for adrenal insufficiency (acute and chronic forms) is provided in Box 1.

Diagnosis

Laboratory evaluation for chronic adrenal insufficiency is a complex and controversial issue and is reviewed elsewhere [61,64]. If Addisonian crisis is suspected, an emergent “stress” cortisol level should be obtained, followed by empiric coverage with

Box 1. Differential diagnosis for adrenal insufficiency

Primary adrenal insufficiency

Hemorrhage

Waterhouse-Friderichsen syndrome (Septicemia, DIC)

Idiopathic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura

Heparin-induced thrombocytopenia

Antiphospholipid antibody syndrome

Systemic lupus erythematosus

Anticoagulation (Heparin, Warfarin)

Infections

Mycobacterium tuberculosis (HIV)-related infections

Primary HIV infection

Cytomegalovirus

Mycobacterium avium intracellulare

Cryptococcus neoformans

Toxoplasmosis gondii

Kaposi's sarcoma

Fungal infections

Histoplasma capsulatum

Blastomyces dermatitidis

Coccidioides immitis

Metastases

Solid tumors: lung, breast, gastric

Malignant melanoma

Lymphoma

Autoimmune

(Isolated) autoimmune adrenalitis

Polyglandular autoimmune syndrome type 1

Adrenalitis, hypoparathyroidism, mucocutaneous candidiasis

Polyglandular autoimmune syndrome type 2 (Schmidt's syndrome)

Adrenalitis, thyroiditis, type 1 diabetes mellitus

Genetic

Congenital adrenal hyperplasia (classic)

Congenital adrenal hypoplasia

Familial GC deficiency
Adrenoleukodystrophy
Adrenomyeloneuropathy

Drugs

Etomidate, ketoconazole, metyrapone, aminoglutethamide, mitotane (*inhibited steroid synthesis*)

Phenytoin, phenobarbital, rifampin (*increased steroid catabolism*)

Hypothermia

Secondary adrenal insufficiency

Exogenous corticosteroid therapy

Hypothalamic/pituitary disease:

Tumor: craniopharyngioma, pituitary adenoma/carcinoma

Infiltrative diseases: hemochromatosis, sarcoidosis, amyloidosis, histiocytosis

Autoimmune: lymphocytic hypophysitis

Hemorrhage: pituitary apoplexy

Postpartum pituitary necrosis (Sheehan's syndrome)

Postsurgical hypopituitarism

Posttraumatic hypopituitarism

Postradiation hypopituitarism

"Empty sella syndrome"

Isolated ACTH deficiency

"stress-dose" steroids (see later discussion) until the results have returned. For years, "conventional wisdom" has held that "normal" cortisol responses to stress exceed 20 mg/dL. This historical threshold was based primarily on responses in healthy patients, however, to either supraphysiologic doses (250 µg) of corticotropin or insulin-induced hypoglycemia [65,66]. More recently, 25 µg/dL has been advocated as an "adequate" cortisol response to stress [67]. This new threshold was proposed based on observations that during critical illness, mean cortisol values generally exceed 45 µg/dL [68–70], whereas fewer than 10% of patients mount a cortisol response that is less than 25 µg/dL [66]. At the present time, controversy surrounds the definition of a "normal" cortisol response to stress and the proper use of adrenocortical diagnostic testing during critical illness [71].

The "high-dose" (250 µg) corticotropin stimulation test (CST) is most commonly used to diagnose adrenal insufficiency in the ICU [64,65]. This test

raises circulating ACTH levels to 60,000 pg/mL, which is far higher than the 100 pg/mL concentrations that are required to maximally stimulate the adrenal cortex under basal conditions [72]. For this reason, the high-dose test may lack sensitivity [73,74]. The “low-dose” (1 µg) CST more closely approximates physiologic hypothalamic-pituitary-adrenal (HPA) responses to stress, and is preferred by some investigators for outpatient evaluations of the adrenal axis, especially when pituitary disease is suspected [75–77]. In select patients who have critical illness, the low-dose CST may offer superior sensitivity [78] and was advocated by some investigators [63,79]. Overall experience with the low-dose CST in patients in the ICU is lacking. Because critical illness may be associated with adrenal resistance to ACTH [71,80] or target tissue resistance to steroid activity [81], the use of the low-dose CST in this setting cannot be fully endorsed at the present time. At our institution, we recommend a high-dose CST as first-line testing for adrenal insufficiency in critically ill patients. In the setting of severe illness, “random” cortisol levels that are less than 20 to 25 µg/dL may adequately establish the diagnosis.

In outpatients, the HPA axis may be assessed using the insulin tolerance test [64], the overnight metyrapone test [82], or stimulation with corticotropin releasing hormone (CRH) [64,83]. During critical illness, insulin-induced hypoglycemia and metyrapone testing pose undue risk and should not be performed. The CRH test has not been validated in patients in the ICU, although it may be useful in distinguishing hypothalamic from pituitary disease [84]. In the setting of Addisonian crisis, after the laboratory diagnosis has been established, CT imaging should be used to examine the adrenal glands. If the clinical picture suggests secondary adrenal insufficiency (ie, lack of hyperkalemia, known pituitary hormone deficiencies, visual field deficits), an MRI of the sella turcica should be obtained. In the presence of adrenal hemorrhage, a hematocrit, platelet count, coagulation studies, and additional specific diagnostic tests (eg, antiphospholipid antibody, lupus anticoagulant) may be useful in establishing the underlying diagnosis.

Treatment

Therapy for acute adrenal insufficiency consists of “stress-dose” GC therapy, typically given as hydrocortisone 100 mg IV every 6 to 8 hours (or its equivalent). MC therapy should be considered if primary hypoadrenalism is suspected, but is not required for hypothalamic-pituitary disease. Patients who have hypotension should receive aggressive volume repletion; in general, dextrose should be added to all IV fluids, because of a high incidence of associated

hypoglycemia. During the initial phase of therapy, aggressive hemodynamic or respiratory support may be required. Emergent treatment of severe electrolyte abnormalities (hypokalemia, hyponatremia) may be indicated as well.

If chronic GC replacement therapy is required, typical oral regimens include hydrocortisone, 20 to 30 mg/day or prednisone, 5 to 7.5 mg/day, usually in divided doses. Dose adjustments for GC replacement are symptom-guided. For primary adrenal insufficiency, chronic MC replacement may be required, usually provided as oral fludrocortisone in doses of 50 to 200 µg/day. MC dosing should be guided by measurements of blood pressure, sodium, and potassium. Plasma renin activity, which should be maintained in, or slightly above, the high-normal range, may be helpful in certain cases. Occasionally, patients who are taking hydrocortisone may do well without specific MC therapy, because hydrocortisone has some intrinsic MC activity. With prednisone and other pure GCs, specific MC replacement is nearly always required for primary hypoadrenalism.

Chronic adrenal insufficiency: “stress dosing” of steroids during critical illness

In patients who have a history of chronic adrenal insufficiency (including patients on long-term steroid therapy), GC supplementation is recommended during times of significant stress, including surgery and critical illness. Precise recommendations for perioperative GC coverage have been hampered by a lack of prospective studies. Recent publications suggested that even major surgery may not significantly increase GC requirements [85,86]. In a 1994 surgical consensus article [87], recommendations for hydrocortisone were 25 mg/day (or its equivalent) during minor surgery (eg, laparoscopic surgery), 50 to 75 mg/day during moderate surgery (eg, hysterectomy), and 100 to 150 mg/day during major surgery, including cardiopulmonary bypass and major abdominal operations. Postoperatively, “stress” doses are recommended for only 1 to 3 days in the absence of complications or nonsurgical illness [87].

Similar guidelines could be reasonably applied to patients in a medical ICU, with “stress-dose” GC coverage (≥ 150 mg/day hydrocortisone or equivalent) throughout the critical phase of illness. “Maximal” GC doses (300–400 mg/day hydrocortisone or equivalent) may be preferable in patients who have pressor-resistant hypotension, or in other clinical situations (eg, septic shock, see later discussion) where ACTH or GC resistance is suspected [88]. Following the resolution of critical illness or following recovery

from surgery, tapering of steroid doses is generally recommended. One reasonable approach is to drop GC doses by 25% to 50% per day until maintenance doses are resumed. Slower tapers may be preferred in patients who have a history of more severe or prolonged illness.

Relative adrenal insufficiency in septic shock

In recent years, there has been renewed interest in using corticosteroid therapy for the treatment of patients who have septic shock. Corticosteroids are essential in maintaining normal metabolic, hemodynamic, and immune function. During times of severe stress (eg, septic shock), the HPA axis should be maximally stimulated. Multiple factors may contribute to “relative” hypoadrenalism during septic shock, however, including adrenal injury (eg, infection, hemorrhage), hypoperfusion, or the use of centrally active pharmacologic agents, such as opiates and sedatives [67]. Adrenocortical responses to ACTH are often blunted in critically ill patients [71,80]. This phenomenon may be partially explained by near-maximal stimulation of the adrenal cortex during stress, but may also reflect reduced adrenal cortisol production or reduced adrenal sensitivity to ACTH [80]. In the setting of septic shock, cytokines and other inflammatory mediators suppress the HPA axis [89–91]. Evidence for reversible adrenal failure during septic shock comes from Briegel et al [92], who performed high-dose CSTs in 20 patients who had septic shock, during acute illness and following recovery. Defining 25 $\mu\text{g}/\text{dL}$ as an “adequate” cortisol response, 13 of the 20 patients demonstrated relative adrenal insufficiency in the ICU. Following recovery, CST responses returned to normal in most patients.

In critically ill patients, extreme cortisol levels (low and high) have been associated with increased severity of illness and increased mortality [93,94]. Presumably, low cortisol levels indicate adrenal insufficiency, whereas high levels are associated with increased severity of illness. Impaired adrenal responses to ACTH have also been linked to increased mortality [95]. In 2000, Annane et al [96] tested the high-dose CST in patients who had septic shock as a means of determining prognosis. Patients who had baseline cortisol levels that were 34 $\mu\text{g}/\text{dL}$ or less and an intact cortisol response during the high-dose CST ($>9 \mu\text{g}/\text{dL}$) had the best clinical outcomes, with a 28-day mortality rate of only 26%. Patients who had high baseline cortisol levels ($>34 \mu\text{g}/\text{dL}$) and a blunted CST response ($\leq 9 \mu\text{g}/\text{dL}$) fared the worst, with a 28-day mortality rate of 82% (Fig. 4). For any given baseline cortisol level, blunted CST responses ($\leq 9 \mu\text{g}/\text{dL}$) imparted a poor prognosis [96]. These results lend support to the routine use of the high-dose CST in patients who have septic shock, to provide prognostic information and to guide adjunctive steroid therapy. These data have an alternate interpretation, however; patients who had the most severe illness (and, therefore, the poorest prognosis) may simply have maximized their steroid output, which resulted in a “failed” CST.

Because relative adrenal insufficiency is common in patients who have septic shock, and because blunted adrenal responses to a high-dose CST confer a poor prognosis, an obvious question arises: Does steroid supplementation improve outcomes in patients who have septic shock? Earlier studies that examined the use of steroids in septic shock showed no survival benefit [97–100]. These studies used short-term, supraphysiologic steroid doses in unselected ICU

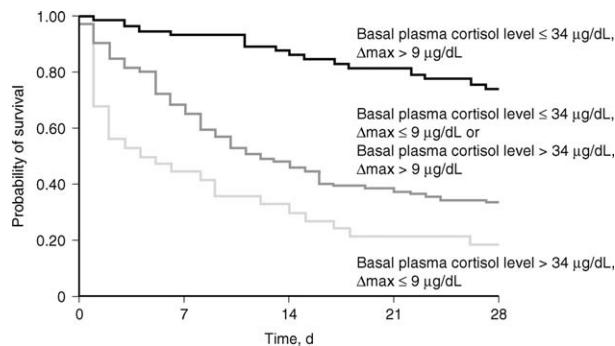


Fig. 4. Survival curves of patients who are admitted to the ICU with septic shock, when considered by basal plasma cortisol levels and the maximum response to a 250- μg corticotropin stimulation test. (From Annane D, Sebille V, Troche G, Raphael JC, Gajdos P, Bellissant E. A three-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotrophin. JAMA 2000;283:1044; with permission.)

populations, however. More recent studies, that invoked the concept of “relative adrenal insufficiency” (ie, pressor-dependent hyperdynamic shock) demonstrated beneficial clinical effects of steroid therapy during septic shock, including reduced need for vasopressors, faster weaning from mechanical ventilation, and improved survival [101–104]. GCs are required for proper functioning of adrenergic receptors. Although sepsis impairs adrenergic responses [101], steroid therapy seems to restore adrenergic tone, thus restoring hemodynamic responsiveness to adrenergic stimuli [105,106].

In 2002, Annane et al [107] published a large, placebo-controlled, randomized, double-blind, multicenter trial that was performed in 300 patients who had septic shock. In this study, treatment with hydrocortisone (50 mg, IV every 6 hours) and fludrocortisone (50 µg/d po) reduced mortality in patients with septic shock by 16%. The benefits were restricted to patients who had “relative” adrenal insufficiency, which was defined as a cortisol response 9 µg/dL or less to a high-dose (250 µg) CST. In this study, “nonresponders” (CST response \leq 9 µg/dL) had an average baseline cortisol level of 21 µg/dL (mean CST response 1 µg/dL), whereas responders had a mean level of 30 µg/dL (mean CST response 22 µg/dL). This suggested that higher baseline cortisol levels were associated with more vigorous CST results. Although these investigators’ definition of relative adrenal insufficiency and their choice of treatment doses can be questioned, it seems clear that the use of steroids in the setting of relative adrenal insufficiency conferred clinical benefit. Based on this and other studies [108], we believe that screening for relative adrenal insufficiency is warranted in patients in the ICU who have septic shock. The optimal means of diagnosis and treatment remain to be established.

Based on the available data, we recommend obtaining a screening “stressed” cortisol level in all patients who have septic shock upon admission. Because critically ill patients lose their diurnal variation in cortisol production [94,109], morning cortisol levels are not required and may delay the diagnosis. A “stressed” cortisol level of less than 20 µg/dL suggests relative hypoadrenalism and physiologic steroid therapy should be considered (see later discussion). If cortisol levels exceed 20 µg/dL, a high-dose CST should be performed; nonresponders (cortisol response \leq 9 µg/dL) should also be considered candidates for steroid therapy unless baseline levels exceed 34 µg/dL [108]. In the ICU setting, hydrocortisone is the preferred GC because it possesses some intrinsic MC activity. Because patients who have septic shock are usually receiving continuous IV fluids, the use of

specific MC therapy (ie, fludrocortisone) seems unwarranted and could contribute to fluid overload, congestive heart failure, or hypokalemia. Current evidence suggests little risk from the use of low-dose MC therapy in patients in the ICU, however [107].

If a patient “passes” the CST test on admission, longitudinal testing should be considered (on a case-by-case basis) because HPA activation may decline as critical illness progresses [110]. This decline may be driven by a change in hypothalamic-pituitary sensitivity to circulating GCs or by a change in adrenal sensitivity to ACTH stimulation [71]. Finally, in all patients who have documented adrenal insufficiency in the ICU, repeat testing is recommended following the resolution of critical illness, to exclude chronic adrenal insufficiency.

Critical issues in thyroid disease

Thyroid function tests in the ICU: the “nonthyroidal illness syndrome”

The interpretation of thyroid function tests (TFTs) in the ICU can be difficult because thyroid hormone (TH) concentrations are affected by a wide variety of nonthyroidal stresses, including sepsis [111,112], HIV/AIDS [113,114], malignancy [115,116], myocardial infarction [117], major surgery [118,119], and severe malnutrition [120,121]. In addition, common ICU medications, including dopamine [122], corticosteroids [123], amiodarone [124], and iodinated radiocontrast agents can also affect thyroid physiology. In the ICU, clinicians frequently encounter the “sick euthyroid syndrome” [125] or “nonthyroidal illness syndrome” (NTIS) [126] which is characterized by low TH levels in the setting of systemic illness. Because patients in the ICU are usually catabolic, it was suggested that the low TH concentrations that are observed during nonthyroidal illness (NTI) are a physiologic response to stress and serve to decrease unnecessary energy expenditure [127]. Because the magnitude of the TH disturbance is associated with disease severity [117] and mortality [128,129], however, the NTIS also may represent a maladaptive response that threatens tissue function.

Critical illness can induce many abnormalities of the hypothalamic-pituitary-thyroid axis, including diminished thyrotropin (TSH) release, reduced levels of tri-iodothyronine (T3) or thyroxine (T4), reduced thyroid binding globulin (TBG) levels, and peripheral TH resistance. Although NTI can produce a wide variety of TFT abnormalities, most patients fall into a “continuum” of three NTI syndromes: (1) low T3,

(2) low T3 and low T4, and (3) low T3, low T4, and low TSH. The classic biochemical progression of TFT abnormalities during NTI is shown in Fig. 5.

Low T3 syndrome

The low T3 syndrome is the most common form of NTIS and occurs in up to 70% of hospitalized patients [126]. During severe illness, T3 levels usually decrease within 24 hours [130] because of reduced extrathyroidal conversion of T4 to T3 (ie, decreased 5'-deiodinase activity) and increased production of reverse T3. GCs, amiodarone, and iodinated radiocontrast agents may also contribute to reduced peripheral TH conversion. In the low T3 syndrome, levels of TSH, total T4, and free T4 are usually normal, although transient elevations in free T4 may be seen (see Fig. 5). In the low T3 syndrome, the magnitude of TH deficit has been associated with illness severity [118] and mortality following ICU admission [129].

Low T3 and low T4 syndrome

In patients who have more severe or more prolonged systemic illness, total T4 levels may decrease, as well. Although less common than isolated T3 deficiency, the “low T3-T4 syndrome” occurs in up to 50% of patients who are admitted to ICUs. Despite depressed total T4 levels, free T4 levels are usually normal (or may be elevated) in this setting; however, free T4 levels may also be depressed in patients who are treated with dopamine or corticosteroids. Proposed mechanisms for the low T3 and low T4 syndrome include decreased TH production, TBG deficiency, circulating inhibitors of TH binding (eg, free fatty acids), and altered TH metabolism [126]. Cytokines, including interleukin (IL)-1, IL-6, and tumor necrosis factor- α , may also be involved in the pathogenesis [131]. As with the low T3 syndrome, the magnitude of

the T3/T4 deficit correlates with illness severity and poor clinical prognosis [128].

Low T3, low T4, and low TSH syndrome

Although TSH elevations have been reported with NTIS [132], most affected patients have TSH levels that are in the normal or low-normal range. Patients who have more severe illness (or patients who receive dopamine or corticosteroids) may have low or even undetectable TSH levels. The finding of low TSH with low T3/T4 suggests an altered hypothalamic-pituitary response to TH [133]. During recovery from critical illness, elevated TSH levels may be seen [134], which likely reflect the restoration of the normal hypothalamic-pituitary response to low TH levels. Such TSH elevations are typically modest. TSH levels that exceeded 20 mU/L suggest primary hypothyroidism.

Diagnosing NTIS can be challenging. When thyroid function is examined in the ICU, we recommend obtaining a complete thyroid panel, including levels of total T4, free T4 (or a calculated free thyroxine index), total T3, and TSH. During critical illness, the presence of low T3 or low T4 levels with a normal or low TSH is strongly suggestive of NTI; however, true hypothyroidism can produce similar TFT results. TSH levels may be high, normal, or low in the setting of NTI. If TSH at least 20 mU/L, primary hypothyroidism is likely. If TSH is normal or only mildly elevated (<20 mU/L), the presence of low free T4 levels, a thyroid goiter, or antithyroid antibodies suggest primary hypothyroidism. Finally, if TSH levels are low, anterior pituitary hormone status should be further assessed. Low (or low-normal) cortisol levels and abnormalities in prolactin secretion suggest pituitary dysfunction. It should be remembered that transient hypogonadotropic hypogonadism is extraordinarily common in critically ill patients. Therefore, assess-

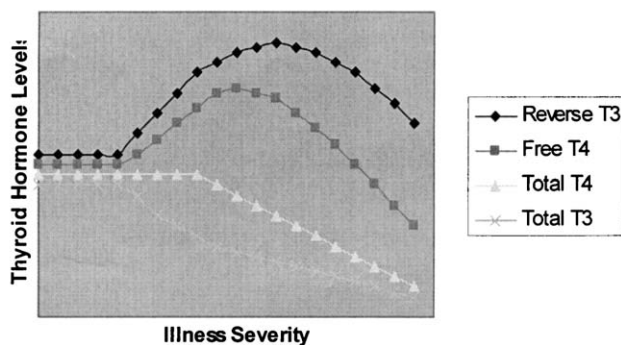


Fig. 5. Thyroid function tests in the nonthyroidal illness syndrome.

ment of the gonadal axis is usually not helpful in this setting. Unfortunately, the measurement of reverse T3 is not helpful in clarifying thyroid status [135]. As a general rule, establishing the diagnosis of the NTIS based on a single day's TFTs is not advisable. Most often, repeat TFT interpretation in the setting of an evolving clinical course is required to firmly establish the diagnosis.

Because NTIS is associated with increased mortality, it is important to establish whether TH replacement improves outcomes in critically ill patients. Studies that examined this question have yielded conflicting results. In patients who were undergoing coronary bypass procedures, T3 improved cardiac output [136] and may reduce mortality [137]. In contrast, other studies in patients who were undergoing coronary bypass [138] and in medical ICU patients [139] failed to show clinical benefit with T3 therapy. In light of the disparate evidence and considering that intracellular hypothyroidism may be protective during critical illness, TH therapy is not currently recommended for most patients who have NTIS. If primary hypothyroidism is suspected in the ICU, TH therapy should be initiated, with the immediate goal of increasing TH levels into the normal range. If secondary hypothyroidism is suspected, "stress-dose" steroid therapy should accompany TH replacement until adrenal insufficiency can be definitively ruled out.

Critical hypothyroidism: "myxedema coma"

The term "myxedema coma" often is used to describe clinically severe hypothyroidism. This term is often a misnomer, however, because most patients who have severe hypothyroidism present with neither myxedema nor a comatose state. Instead, critical hypothyroidism is characterized by progressive dysfunction of the cardiovascular, respiratory, and CNS. If not rapidly recognized and treated, the mortality rate that is associated with this condition is exceedingly high.

Myxedema coma occurs most commonly during the winter months, when thermoregulatory stressors are at maximum levels. Common precipitants include hypothermia, trauma, burns, surgery, stroke, sepsis, and severe infections. Medications, including anesthetics, sedatives, narcotics, diuretics, and β -blockers have also been implicated [140]. Typically, patients are older and have known hypothyroidism; however, myxedema coma can be the initial presentation of hypothyroidism. Cardinal findings include defective thermoregulation (hypothermia) and altered mental status; additional clinical features include bradycardia, hypotension, hypoventilation, and hyponatremia. If present, "myxedema" is characterized by generalized

skin and soft tissue swelling, often with associated periorbital edema, ptosis, macroglossia, or cool, dry skin. Additional clinical features of myxedema coma are summarized in Table 3.

The diagnosis of myxedema coma requires confirmation with low (or undetectable) levels of T4 (total and free) and T3. TSH levels are usually elevated, but may be normal (or even low) in the setting of hypothalamic-pituitary disease or advanced critical illness (eg, NTIS). Additional laboratory findings include normocytic anemia, hyponatremia, hypoglycemia, azotemia, and elevated creatine kinase levels. Hypoxia, hypercapnia, and respiratory acidosis are common findings on arterial blood gas analysis.

The treatment of myxedema coma involves general supportive measures, correction of physiologic derangements, and immediate intravenous replacement of TH. Patients should be treated in an ICU setting, with intensive cardiac, hemodynamic, and blood glucose monitoring. Mechanical ventilation may be required. In patients who have severe hypotension, vasopressor therapy should be considered, although pressors should generally be avoided in borderline cases because they can exacerbate cardiac arrhythmias. To correct hypothermia, a warm room temperature and blankets should be used in most cases because rapid rewarming, and its associated peripheral dilatation, may precipitate hypotension and cardiovascular collapse. Ultimately, normal thermoregulation should be rapidly restored by the administration of thyroid hormone. If present, severe hyponatremia may be treated with hypertonic saline, with or without loop diuretics. Hypoglycemia should be treated with a continuous intravenous dextrose infusion, with frequent attention to sodium levels if hypotonic solutions

Table 3
Clinical manifestations of myxedema coma

Organ system	Clinical features
Skin and soft tissue	Generalized swelling; edema; periorbital edema; ptosis; cool, dry skin; Coarse, sparse hair; Macroglossia; hoarseness
Neurologic	Hypothermia, Lethargy, altered mental status, Psychosis, Seizures, Delayed reflex relaxation
Cardiovascular	Bradycardia, hypotension
Respiratory	Depressed ventilatory drive, hypoventilation, hypoxia, hypercapnea
Gastrointestinal	Constipation, abdominal distention paralytic ileus, megacolon
Hematologic	Anemia blunted stress leukocytosis
Renal and Electrolyte	Hyponatremia decreased glomerular filtration rate

are used. Finally, precipitating factors should be actively pursued. If no obvious precipitants are identified, broad-spectrum antibiotic therapy should be considered until infection has been ruled out, because severe hypothyroidism can blunt the normal leukocyte response to infection.

The proper initiation of TH therapy during myxedema coma is controversial, particularly with regards to the selection and dosing of TH used. In vivo, T3 is the active hormone; circulating T4 is converted to T3 by peripheral deiodinase activity. Because deiodinase activity is suppressed during severe hypothyroidism [125], some investigators advocate intravenous T3 replacement therapy [141], which offers a more rapid onset of action. Parenteral T3 is expensive and difficult to obtain, however, and may be associated with cardiac arrhythmias and increased mortality [142]. At our institution, the routine use of intravenous T3 is not generally recommended.

Most investigators recommend initiating therapy with intravenous T4 alone [143,144], with loading doses of 200 to 500 µg followed by 50 to 100 µg/day. Higher loading doses do not seem to offer additional benefit [145]. If combination T3/T4 therapy is used, loading doses of approximately 4 µg/kg of T4 and 10 µg of T3 may be used, followed by maintenance doses of T4 (50–100 µg daily) and T3 (10 µg, every 8 hours) until pills are initiated [140]. Whatever the regimen, subsequent TH dosing should be guided by the frequent measurement of free T4 and TSH levels.

Along with TH, most investigators recommend the concurrent administration of “stress-dose” corticosteroid therapy for myxedema coma (see references [140,143,144]), in case of concurrent adrenal insufficiency as might be seen in hypopituitarism or polyglandular autoimmune disease. Hydrocortisone, 50 to 100 mg (or its equivalent), IV, should be administered every 6 to 8 hours. Support for this practice is provided by the observation that cortisol responses to stress are blunted during severe hypothyroidism [145]. Cortisol levels should be drawn before therapy is initiated; if appropriately elevated (>25 µg/dL), corticosteroid therapy may be safely discontinued. If cortisol is either low or suboptimally elevated (<25 µg/dL), steroid therapy should be continued until the critical phase of illness has resolved. At a later time, corticotropin stimulation testing can be performed to sort out cases of true hypoadrenalism. Guidelines for the treatment of myxedema coma are summarized in Box 2.

During treatment for myxedema coma, hemodynamic parameters typically improve within 24 hours, whereas normal thermoregulation is restored within 2 to 3 days. Initial body temperatures that are below 93°F or which do not respond to therapy within 3 days

Box 2. Therapy for myxedema coma

Initiate supportive therapy

- Hypoventilation: oxygen therapy, mechanical ventilation
- Hypotension: saline therapy, blood transfusions (if severe anemia)
- Avoid vasopressors if possible (may worsen risk for arrhythmia)
- Hypothermia: passive rewarming (warm room, simple blankets)
- Avoid active rewarming if possible (may precipitate vascular collapse)
- Hyponatremia: saline, free water restriction
- If severe, consider hypertonic saline ± diuresis
- Hypoglycemia: intravenous dextrose infusion (D5NS)

Thyroid hormone replacement

- Initial replacement: Levothyroxine (T4): 200 to 500 Mg, IV
- Consider concurrent Liothyronine (T3): 10 Mg, IV
- Follow-up replacement (until able to take po): T4 50 to 100 Mg, IV, every day
- Consider concurrent T3 replacement: 10 Mg, IV, every 8 hours

Corticosteroid therapy

- Draw baseline cortisol level
- Give hydrocortisone, 100 mg, IV (or equivalent) every 6 to 8 hours
- Follow-up steroid therapy:
 - If initial cortisol level at least 25 Mg/dL, consider discontinuing steroid therapy
 - If initial cortisol level is less than 25 Mg/dL, continue steroid therapy and perform corticotropin stimulation testing after critical illness has resolved

are associated with a poor prognosis [142]. Additional factors that are associated with poor prognosis include advanced age, bradycardia, hypotension, and cardiac complications, including myocardial infarction and congestive heart failure [142,146]. With advances in intensive therapy, the overall mortality rate seems to have decreased to less than 20% [146].

Critical hyperthyroidism: “thyroid storm”

The term “thyrotoxicosis” is often used to describe the hypermetabolic state that results from elevated circulating levels of TH. Thyrotoxicosis may present with a variety of hyperadrenergic clinical manifestations, including hyperactivity, nervousness, tremor, heat intolerance, palpitations, and unexplained weight loss. Diagnostic considerations in patients who have thyrotoxicosis are listed in **Box 3**. TS most commonly occurs in Graves’ disease, which is associated with the highest TH levels. The progression of thyrotoxicosis into life-threatening “thyroid storm” (TS) involves severe thermoregulatory dysfunction (high fever), mental status changes, and evidence of multi-organ dysfunction, including adrenergic crisis (tachycardia, hypertension) and gastrointestinal hypermotility. Several different diagnostic criteria for TS have been proposed [147–149]. An “apathetic” form of critical hyperthyroidism that lacks the classic adrenergic signs, has also been described [150,151]. Because of the life-threatening nature of true TS, early diagno-

Table 4

Clinical manifestations of thyroid storm

Organ system	Clinical features
Skin and soft tissue	Lid lag; proptosis (Graves’ disease); warm, moist skin; hyperhidrosis
Neurologic	Hyperthermia, lethargy, altered mental status, psychosis, seizures, hyperkinesis, hyperreflexia
Cardiovascular	Tachycardia, arrhythmia (eg, atrial fibrillation), systolic hypertension, wide pulse pressure, high-output congestive heart failure
Respiratory	Dyspnea, tachypnea
Gastrointestinal	Abdominal pain, nausea, vomiting, diarrhea

sis and intervention is crucial to prevent morbidity and mortality.

Many cases of TS are associated with a precipitating thyroid event, including thyroid surgery, withdrawal of antithyroid drugs, radioiodine therapy, or the administration of iodinated radiocontrast dyes. In patients who have pre-existing thyrotoxicosis, TS can also be precipitated by systemic insults, including surgery, trauma, parturition, stroke, MI, diabetic ketoacidosis, or severe infections. Cardinal symptoms of TS include thermoregulatory dysfunction, altered mental status, and multi-organ system dysfunction, as shown in **Table 4**.

The diagnosis of TS is suggested by elevated TH levels and suppressed TSH in the proper clinical setting. The magnitude of TH elevation does not correlate well with illness severity [152,153]. In the ICU, TH levels may be elevated following the administration of amiodarone or iodinated radiocontrast agents; TSH may or may not be affected by these interventions. In addition, low TSH levels may reflect severe NTIS or may follow the administration of dopamine or corticosteroids. Signs of chronic hyperthyroid states, such as goiter or ophthalmopathy, may also suggest the diagnosis of TS. Although rarely required, increased iodine uptake during nuclear thyroid testing also can be used to support the diagnosis.

The management of TS is complex, and is summarized in **Box 4**. Initial management can be broken down into four goal-directed components: (1) supportive therapy, (2) blocking TH synthesis and release (and peripheral TH conversion), (3) blocking the peripheral effects of TH, and (4) identifying and treating the precipitating event. Supportive therapy for TS involves respiratory support, hemodynamic support, sedation, and management of hyperthermia. Phenobarbital may be preferred for sedation in this setting

Box 3. Differential diagnosis of thyrotoxicosis

Common causes

- Graves’ disease
- Solitary toxic adenoma
- Toxic multinodular goiter
- Thyroiditis: (early) Hashimoto’s, silent, subacute, postpartum
- Thyrotoxicosis factitia: exogenous TH intake

Rare causes

- TSH-secreting pituitary adenoma
- Thyroid carcinoma
- Struma ovarii - teratoma
- Hydatidiform mole (secretes human chorionic gonadotropin)

Box 4. Management of thyroid storm*Initiate supportive therapy*

- Tachypnea: oxygen therapy, mechanical ventilation
- Hypertension: C-blockade (see below), nitroprusside
- Hyperkinesis: benzodiazepines, barbiturates
- Hyperthermia: IV fluids, cooling blanket, antipyretics

Block thyroid hormone synthesis and release

- Thioureas: block new hormone synthesis
 - Propylthiouracil (PTU): load 600 to 1000 mg, then 1200 mg/d, given as 200–300 mg PO q4-6h
 - Methimazole (tapazole): load 60 to 100 mg, then 60 to 120 mg/d, 20 to 30 mg, po, every 6 to 8 hours
- Inorganic iodine: blocks the release of preformed hormone. (Note: the use of inorganic iodine will necessitate a delay if radioactive iodine therapy is used later.)
 - Saturated solution of potassium iodide: five drops (250 mg), po, every 6 to 12 hours
 - Lugol's solution: four to eight drops, po, every 6 hours
 - Iodate (contrast dye): 0.5 to 1.0 g, po, every 12 hours
 - Iohexol (contrast dye): 0.6 g, IV, every 12 hours
 - Lithium carbonate: 1200 mg/d, po, every 6 to 8 hours

Block peripheral conversion of T4 to T3
PTU

- Corticosteroids: Hydrocortisone 100 mg, IV, every 6 to 8 hours (or equivalent)
- Propranolol
- Iodate, Iohexol

Block peripheral effects of thyroid hormone

- C-adrenergic blockers
 - Propranolol: 0.5 to 1.0 mg, IV, every 2 to 3 hours, or 40 to 80 mg, po, every 4 to 8 hours

- Esmolol: 250 to 500 Mg/kg, IV load, then 50 to 100 Mg/kg/min IV
- Reserpine: 2.5 to 5 mg, IM, every 4 hours
- Guanethidine: 30 to 40 mg, po, every 6 hours
- TH Removal: plasmapheresis, plasma exchange, charcoal plasma perfusion, peritoneal dialysis
- Identify and treat underlying cause*
- Definitive therapy* (should preferably occur after patient is rendered euthyroid using standard medical therapy)
 - Radioactive iodine
 - Surgical thyroidectomy

because it stimulates metabolic clearance of TH by inducing hepatic microsomal enzymes. TS-related hyperthermia may be treated with cool IV fluids, antipyretics, or the use of cooling blankets.

An early step in the treatment of TS is to establish complete blockade of new TH synthesis with thioureas. Initial blockade of iodine organification begins within 1 hour of treatment. Propylthiouracil (PTU) remains the drug of choice for TS because it offers the advantage of inhibiting peripheral conversion of T4 to T3 (methimazole does not). For TS, PTU is administered as a 600 to 1000 mg loading dose, followed by 1200 mg/d in four to six divided oral doses. Methimazole, the more potent thiourea, is an acceptable alternative; it is given as a loading dose of 60 to 100 mg, followed by a daily dose of 60 to 120 mg in three or four divided doses. If the oral route is unavailable, both thioureas may be administered rectally [154,155]. Although a history of thiourea-related agranulocytosis contraindicates therapy, thioureas should be continued in cases of mild adverse drug reactions (eg, rash, urticaria, mild transaminase elevations) until the critical stage of TS has resolved. As thyrotoxicosis improves, thiourea dosages can be gradually lowered to more standard ranges: PTU, 100 to 600 mg/day or methimazole 5 to 20 mg/day.

Although thioureas are effective in blocking new TH synthesis, they do not block the release of preformed thyroid hormone. This task can be accomplished by using inorganic iodine, which directly inhibits the release of TH from the gland. Iodine therapy should ideally be administered 2 hours after thioureas, to allow for organification blockade. Com-

mon dosage formulations for inorganic iodine include saturated solution of potassium iodide (five drops, po, two to four times per day) and Lugol's solution (four to eight drops, po, three times per day). Iodinated contrast dyes, including ipodate and iohexol, are also effective [156,157]. In addition to blocking TH release, these radiocontrast agents also impair peripheral T4 deiodination to T3 and may antagonize TH binding to nuclear receptors [149]. Lithium therapy (300 mg, po, every 6 hours) may also be used to block preformed TH release, either alone or in combination with iodine; toxicity may limit its widespread clinical application. "Stress-dose" corticosteroids (IV hydrocortisone, 100 mg, three or four times per day or equivalent) are also effective in blocking peripheral deiodination. In cases of Graves' disease, steroids may also decrease TH release by way of immunomodulatory effects.

Blocking the peripheral action of TH is another important component of therapy for TS. β -blockers (eg, propranolol 40–80 mg, po, every 4 to 8 hours) are effective for reducing the tachycardia, hypertension, and adrenergic symptoms that are associated with thyrotoxicosis. If oral propranolol is ineffective in controlling symptoms, therapeutic options include IV propranolol and esmolol [158,159]. Reserpine and guanethidine, although effective [148,160,161], are rarely used because of adverse effects, including hypotension and CNS depression. In life-threatening cases, when medical therapy has proven ineffective, plasmapheresis [162], plasma exchange [163], charcoal plasma perfusion [164], and peritoneal dialysis [165] have all been successfully used to remove circulating TH.

Following the initiation of supportive therapy and TH blockade, clinical and biochemical improvement should occur within 24 hours, although full recovery from TS may take several days to weeks [166,167]. Mental status is a reasonable indicator of response to therapy, as are improvements in thermoregulation, tachycardia, and hemodynamic derangements. Failure to improve these parameters within the first few days of therapy portends a poor prognosis [167].

After the critical phase of TS has passed, definitive antithyroid therapy should be considered. Because of the recent administration of inorganic iodine and concerns over excess TH release during therapy, radioactive iodine plays no role in the acute management of TS. In rare cases, definitive therapy with thyroidectomy may be considered during acute, life-threatening TS; however, peri-operative clinical management can be exceedingly difficult and cardiovascular or neurologic complications may occur [168,169]. In most cases, medical therapy should be used to "cool off" patients who have TS for weeks to months before

definitive treatment. Overall, with advances in diagnosis and treatment, mortality from TS that was nearly 100% in early series [170] may now be less than 20% to 30% (see references [148,171,172]).

Critical issues in pituitary disease

Pituitary apoplexy

The term "pituitary apoplexy" describes the life-threatening clinical syndrome that results from the sudden infarction of, or hemorrhage into, the pituitary gland [173]. Typically, apoplexy occurs in the setting of a pre-existing pituitary adenoma, but it can strike normal glands as well [174]. Most cases of apoplexy present without a known history of tumor [175] (ie, apoplexy is often the initial presentation of a pituitary adenoma). Clinical factors that may precipitate apoplexy include head trauma, radiation therapy, anticoagulation, bromocriptine therapy, and dynamic pituitary function testing. Diabetes mellitus, hemodialysis, and the peri-partum state may also predispose to pituitary hemorrhage [176].

The clinical presentation of pituitary apoplexy is extremely variable and ranges from mild, simple headache to sudden coma and circulatory collapse. The clinical severity is determined largely by the extent of pituitary hemorrhage, necrosis, and local edema. Although pituitary hemorrhage can present with acute, subacute, or chronic symptoms, the term "apoplexy" is best reserved for life-threatening, clinical presentations. Apoplexy most commonly presents with a sudden, severe headache, often in a frontal or retro-orbital distribution [177,178]. Extravasation of blood and necrotic sellar contents into the subarachnoid space may lead to leptomeningeal irritation [176], which produces a meningitis-like clinical syndrome of fever, meningismus, nausea, vomiting, and altered mentation. If present, mental status changes are often followed by rapid clinical deterioration [179].

Apoplectic signs and symptoms are determined mostly by the direction and degree of sellar extension (Table 5). Upward expansion may compress the optic chiasm and optic nerves and lead to visual field deficits or complete visual loss [178]. Olfactory nerve damage has also been reported [180], whereas compression of the hypothalamus may lead to abnormal thermoregulation (fever), disturbed respiration, hypertension, or malignant cardiac arrhythmias [180]. Lateral sellar expansion into the cavernous sinus can damage the internal carotid artery (ICA) or local cranial nerves (CNs) III, VI, V₁, V₂, and VI, which leads to ophthalmoplegia, diplopia, ptosis, pupillary defects, or

Table 5
Clinical features of pituitary apoplexy as considered by anatomic tissue disruption

Mechanism (affected structures)	Clinical presentation	% of cases
Local effects		
Sella turcica, dura, meninges	Headache	76%
	Nausea, vomiting	21%
	Altered mentation	19%
	Meningismus	17%
Superior		
Optic chiasm, optic nerves	Visual field deficits, blindness	62%
Olfactory nerve	Disturbed smell, anosmia	rare
Hypothalamus	Disturbed autonomic regulation	2%
Lateral (cavernous sinus)		
Internal carotid artery	Altered mentation, seizures, hemiparesis	4%
Oculomotor nerve (CN III)	Ophthalmoplegia, diplopia, ptosis, mydriasis	40% ^a
Trochlear nerve (CN IV)	Ophthalmoplegia, diplopia	40% ^a
Abducens nerve (CN VI)	Ophthalmoplegia, diplopia	40% ^a
Ophthalmic/maxillary branches, Trigeminal nerve (CN V ₁ , V ₂)	Facial pain, corneal anesthesia	40% ^a
Inferior (sphenoid sinus)		
Sphenoid sinus	Epistaxis, CSF rhinorrhea	rare

^a CN (cranial nerve) palsies are present in approximately 40% of cases. There is no available breakdown of frequency by individual cranial nerve involvement.

Modified from Rolih CA, Ober KP. Pituitary apoplexy. *Endocrinol Metab Clin N Am* 1993;22:291–302; with permission.

facial pain. CN palsies occur in more than 40% of cases. In rare cases of associated ICA spasm, apoplexy can produce seizures, hemiplegia, and other acute signs of cerebrovascular occlusion [181,182]. With inferior expansion into the sphenoid sinus, epistaxis or cerebral spinal fluid (CSF) rhinorrhea have been reported.

Pituitary hormone deficiency is a common consequence of apoplexy. Hypogonadism, growth hormone (GH) deficiency, and prolactin disturbances all occur in more than two thirds of cases, but each of these entities has little clinical consequence in the acute setting [183]. Acute adrenal insufficiency, which is also found in two thirds of cases, can be life-threatening and should usually be treated empirically. Hypothyroidism is found in 42% of cases and may

have clinical significance during a subacute course; however, the long half-life of circulating thyroxine typically precludes an immediate clinical impact. Diabetes insipidus (DI), which results from damage to the posterior pituitary gland, occurs in only 4% of cases [183]. When present, DI presents with polyuria, polydipsia, and hyperosmolar hyponatremia.

The key step in diagnosing pituitary apoplexy is to consider its presence. More common CNS disorders, including CNS tumors, cerebrovascular accidents (CVA), subarachnoid hemorrhage (SAH), ICA aneurysms, and bacterial meningitis, can mimic its clinical presentation. When apoplexy is suspected, the initial serologic work-up should include a complete blood count (with differential), coagulation studies, and electrolytes, as well as a baseline cortisol level and TFTs. Lumbar puncture, although frequently performed to “rule out” bacterial meningitis and SAH, are unreliable in distinguishing these diseases, because pleocytosis, high red blood cell counts, xanthochromia, and high CSF protein can be seen in any of these conditions [184]. In the end, radiologic studies are required to confirm the diagnosis of pituitary apoplexy. During an acute event, CT is the preferred modality [185] because it can rapidly confirm the presence of acute pituitary bleeding. In the subacute setting, MRI offers superior sensitivity and anatomic detail [186,187].

The clinical management of pituitary apoplexy involves supportive management, “stress-dose” corticosteroid therapy, and rapid neurosurgical consultation. Following cardiopulmonary and hemodynamic stabilization, electrolyte and hydration status should be monitored carefully for the development of DI. Hyponatremia also is commonly seen, usually in the setting of inappropriate antidiuretic hormone secretion, secondary hypoadrenalism, or secondary hypothyroidism. Because of the high incidence of adrenal insufficiency, empiric “stress-dose” corticosteroid therapy (hydrocortisone 100 mg, IV, every 6 to 8 hours; dexamethasone, 4 mg, IV, every 8 hours or equivalent) should be rapidly administered in all cases. Steroids may also help to reduce intracranial swelling. Finally, emergent neurosurgical consultation is recommended in most cases.

Transsphenoidal decompression has been the preferred neurosurgical approach for pituitary apoplexy [178]. Absolute surgical indications include obtundation, coma, or a rapidly deteriorating clinical course [179]; visual loss is also frequently cited as a surgical indication [188]. Most patients who have stable mental status and minimal (or absent) visual impairment will recover without surgery [189]. In addition, isolated ophthalmoplegias often resolve with expectant man-

agement [175,189]. Given the growing recognition of subacute and chronic presentations of pituitary injury, there is growing comfort with conservative (nonsurgical) management in milder apoplexy cases. Recent evidence, however, suggests that early surgical decompression may lessen the need for long-term hormonal replacement therapy [187,190] and may reduce the risk of recurrent apoplexy or pituitary tumor growth [187].

Because of the rarity of true pituitary apoplexy, morbidity and mortality data for this syndrome are difficult to ascertain. Severe cases carry a high mortality rate, however, which highlights the importance of early diagnosis and treatment.

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