Lynn Loriaux   *Editor*

Endocrine Emergencies

Recognition and Treatment

Humana Press

CONTEMPORARY ENDOCRINOLOGY

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Preface

There are only a few books written that address the diagnosis and management of endocrine emergencies. None have been comprehensive, and the most recent one was published in 2006. The purpose of this book is to update the management of endocrine, diabetic, and metabolic emergencies by consensus of experts in the field. We believe that this book will bring the topic areas up to date, set a standard for diagnosis and treatment in each category, and comprehensively cover the area.

Each chapter begins with a Precis that presents, in concentrated form, what the physician needs to know to begin the evaluation and emergency treatment of the known endocrine emergencies. This is followed by an extended discussion of the pathophysiology that can be read after initial treatment has begun.

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Chapter 1
Acute Adrenal Insufficiency

Lynn Loriaux

Précis

1. Clinical setting—Shock resistant to volume and presser resuscitation.
2. Diagnosis

    (a) History: Important complaints include weight loss, syncope, hypoglycemia, fatigue, and unexplained abdominal pain. Recent supraphysiological gluccoid treatment or a history of pituitary or hypothalamic disease including neurosurgery in the skull base and closed head trauma. Adrenal surgery, abdominal trauma, unexplained flank pain associated with anticoagulation, and the antiphospholipid antibody syndromes all increase the likelihood of primary adrenal failure. Medications that interfere with glucocorticoid synthesis, secretion, and action are obvious causes: ketoconzole, metyraprone, and mefipristone (RU-486).

    (b) Physical examination: Fever up to 104°, orthostatic hypotension, weight loss, hyperpigmentation of the skin, vitiligo, purpura, petechia, thrush, and calcification of the cartilage of the external ear are signs that can be associated with adrenal insufficiency.

    (c) Laboratory values: A total plasma cortisol of less than 20 μg/dL, hyponatremia, hypoglycemia, relative lymphocytosis, eosnophilia, pre-renal azotemia, and mild to moderate anion gap metabolic acidosis are common.

    (d) Imaging: Abnormalities of the hypothalamus and pituitary gland, and abnormalities of adrenal size. Bilaterally small adrenal glands can be the result of autoimmune adrenal destruction or adrenal suppression. Large adrenal glands are caused by infection, infarction, infiltration, and hemorrhage.

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3. Treatment—In addition to the standard treatment for shock, the treatment for acute adrenal insufficiency is intravenous replacement of hydrocortisone in a dose that replicates the plasma cortisol levels associated with critical illness. The standard dose is 50 mg hydrocortisone intravenously every 6 h until the crisis is past. If the pretreatment plasma cortisol is greater than 20 µg/dL, the cortisol administration can be discontinued when the crisis resolves. If the pretreatment cortisol level is less than 20 µg/dL, the intravenous dose of hydrocortisone should be reduced to an oral dose of 12–15 mg/m^2/day until the diagnosis of adrenal insufficiency can be confirmed or excluded. It can require 12 h following the first dose of hydrocortisone before for the first glucocorticoid effects are clinically manifest.

The most common untoward side effect of glucocorticoid therapy is failure to discontinue its administration when the crisis is past. Every attempt must be made to stop the administration of glucocorticoid at the earliest possible time to prevent the complications of iatrogenic Cushing's syndrome which can quickly become the dominant clinical problem. Another common error is to conclude that clinical improvement equates with an underlying adrenal insufficiency.

Acute Adrenal Insufficiency

There are two forms of acute adrenal insufficiency. Primary acute adrenal insufficiency is associated with destruction of both adrenal glands. Autoimmunity, infection, infiltration, infarction, and hemorrhage are common etiologies. Both cortisol and aldosterone are deficient. Secondary acute adrenal insufficiency is associated with ACTH deficiency caused by hypothalamic or pituitary dysfunction. Only cortisol is deficient. Aldosterone secretion, regulated by the renin–angiotension system, is normal in secondary adrenal insufficiency.

The clinical syndrome of acute adrenal insufficiency was first described by Lipsett and Pearson [2, 3]. "We have withdrawn cortisone from adrenalectomized patients in the attempt to maintain them without any steroid hormone administration. It soon became apparent that this was not possible. When cortisone was withdrawn, clinical collapse developed promptly. Within 24 h of cortisone withdrawal, the patient complained of malaise, lethargy, anorexia, and weakness. At 48 h, the patient noted giddiness in the upright position and such profound weakness that he was unwilling to leave the bed. At 72 h, the patient was usually unable to take food, and nausea, vomiting, diarrhea, and stupor frequently ensued. The blood pressure fell but not to shock levels as long as the patient remained horizontal. The patient developed a gaunt and ashen appearance, the skin was cold and gray, the pulse weak, and it appeared that death would soon follow. Administration of cortisone at this time brought about dramatic clinical improvement usually within 12 h, so that the patient was ready to eat and to ambulate, and he felt well."

Lipsett and Pearson then differentiated the syndrome of isolated aldosterone deficiency from that of isolated cortisol deficiency. Figure 1.1 shows the clinical

Fig. 1.1 The syndrome of acute mineralocorticoid deficiency produced in an adrenalectomized person. Reprinted from NEJM 254: 511; 1956
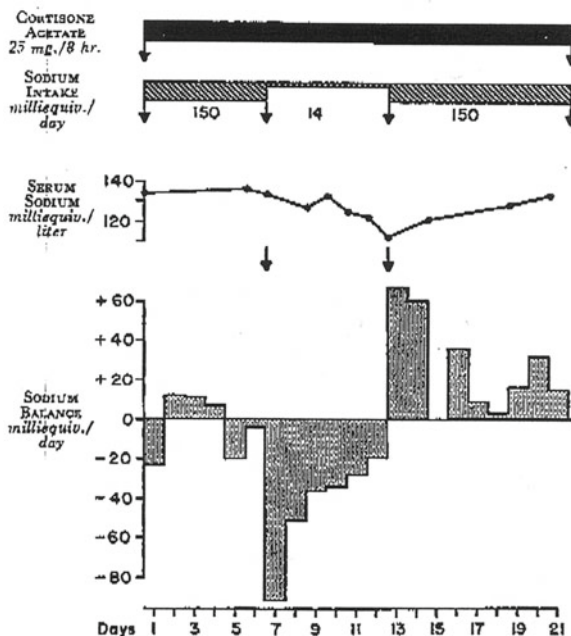
consequences of acute aldosterone deficiency [3]. In this experiment, glucocorticoid is maintained throughout the experimental period, and salt intake is reduced on day 6, simulating aldosterone deficiency. This leads to severe negative salt balance, hyponatremia, and weight loss. "Note the inability to come into sodium balance and the total loss of 273 milliequivalents of sodium (16 g of salt) in 6 days. At the end of this period, the patient was weak, anorectic, lethargic, subject to muscle cramps, and hypotensive. She had lost weight, the blood volume was low, and the serum sodium had dropped." Figure 1.2 shows the pathophysiological changes associated with isolated cortisol deficiency [3]. Cortisol was withdrawn between days 3 and 7, and positive salt balance was maintained by replacing urinary salt loss, effectively replacing mineralocorticoid action. In this situation, serum sodium falls, urine volume decreases, and body weight increases. "After a day or two without cortisone, the patient becomes anorectic and listless and complains of stiffness and aching of the muscles, these symptoms being succeeded by weakness, lethargy, nausea and vomiting, fever, drop in blood pressure and postural hypotension; as the patient becomes severely ill, the systolic blood pressure reaches a level of 60–70 in the upright position and prostration ensues; this is usually accompanied by a high fever (temperature of 103–104 °F). When 100 mg of hydrocortisone is given intravenously, there is a rapid fall in temperature, a rise in blood pressure and a return of a sense of well-being within 12 h. The course outlined can be compressed into 36 h or may take 10 days. The average time for the development of adrenal crisis is 3 or 4 days after withdrawal of cortisone given by mouth" [3].

Fig. 1.2 The syndrome of acute glucocorticoid deficiency produced in an adrenalectomized person. Reproduced from Pearson OH, et al. Clinical and metabolic studies of bilateral adrenalectomy for advanced cancer in man. Surgery 34: 543–544; 1956
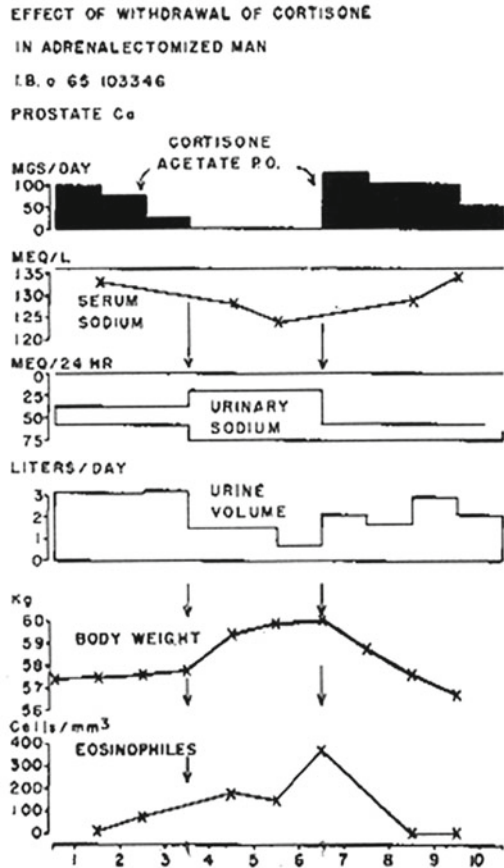
Thus, there are two forms of acute adrenal insufficiency. Both lead to shock. The standard treatment with saline replacement, pressors if needed, and intravenous hydrocortisone effectively treats both forms.

The Adrenal Response to Stress

The first to investigate the response of the adrenal gland to critical illness was Melby and Spink in 1958 [4]. These investigators measured plasma cortisol in 20 patients with sepsis and in 13 normal control subjects. Plasma cortisol in septic patients was elevated, 63 ± 30 µg/dL, compared to 13 ± 4 in normal subjects. More interesting, when Melby divided the septic group into survivors and non-survivors, the plasma cortisol was considerably higher in the non-survivors, 73 ± 34 µg/dL vs. 50 ± 12 µg/dL. This observation has been confirmed in many subsequent studies [5, 6].

Fig. 1.3 The pattern of glucocorticoid excretion in patients with experimental tularemia. Reproduced from Beisel, Braton, Anderson, and Sawyer, Adrenocortical Responses During Tularemia in Human Subjects. J Clin Endo Metab 27: 61, 1967
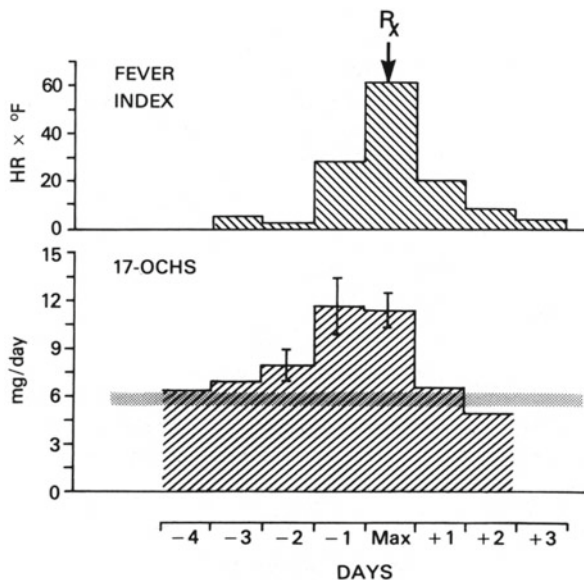
Beisel et al. in 1967 [7] studied the urinary excretion of glucocorticoid metabolites in army recruits with experimentally induced tularemia (Fig. 1.3). Urinary 17-hydroxy steroids doubled during the febrile phase of the illness. This finding was followed by several studies of the response of plasma cortisol to the stress of surgery (Fig. 1.4) [8]. Plasma cortisol typically rises four- or fivefold during surgical stress and then returns to high normal levels on the second postoperative day. Collectively, these studies led to a consensus that elevated cortisol concentrations are essential to the survival of the stressed patient. Nothing in these studies, however, implies that this is true.

The concept that the "stress induced rise in cortisol is needed to survive stress" has been addressed in primates by two studies. The first was done by Udelsman et al. [9] using rhesus monkeys. Udelsman studied four groups of eight or nine adult male monkeys. All were adrenalectomized. All were treated with replacement doses of cortisol and Florinef®. Group four underwent a "sham adrenalectomy." One day before a planned cholecystectomy, the glucocorticoid dose was changed to "ten times normal" in group one, "normal" in group two, and "1/10 normal" in group three. Group four underwent a "sham cholecystectomy." The operations were performed without any additional glucocorticoid. In groups one and two there were no changes in blood pressure, heart rate, or electrolytes. The group three animals, however, did not do well. Three of the nine animals died in the perioperative period (Fig. 1.5). The authors contend that:

> The physiologically replaced group was hemodynamically indistinguishable from either the supraphysiologically replaced or sham-adrenalectomy-placebo group, both before and after cholecystectomy. The mortality rates were identical in the supraphysiologically and physiologically replaced groups (14 %) and were not significantly different from those in the sham-adrenalectomy-placebo group. In contrast, the subphysiologically replaced monkeys developed marked hemodynamic instability, with significant reduction ($P < 0.05$) in
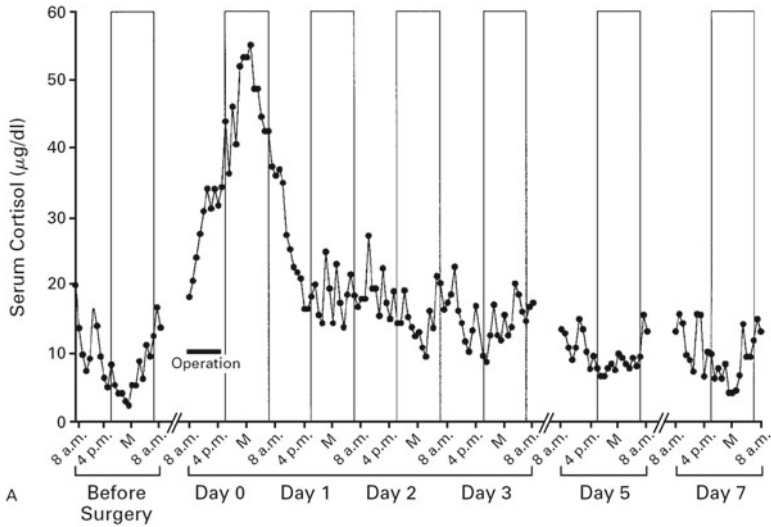
Fig. 1.4 The pattern of cortisol secretion during a major surgical intervention. Reprinted from Lamberts SW, Bruining HA, de Jong FH. Corticosteroid therapy in severe illness. N Engl J Med. 1997 337: 1285–92. Original data reported in Naito Y, Fukata J. Tamai S, et al. Biphasic changes in hypothalamo-pituitary-adrenal function during the early recovery period after major abdominal surgery. J Clin Endocrinol Metab 1991;73:111–117

mean systemic blood pressure, cardiac index, systemic vascular resistance index, and left ventricular stroke work index. Surgical stress amplified this instability and resulted in a 30 % perioperative mortality rate ($P < 0.05$ when compared with that in the sham-treated group). There were no significant changes in body weight, serum electrolytes, serum proteins, or hematologic profiles.

These findings suggest that physiologic glucocorticoid replacement is both necessary and sufficient for primates to tolerate surgical stress. There does not appear to be a hemodynamic advantage to supra-physiologic peri-operative glucocorticoid replacement.

The second study was published by Kehlet and Binder in 1973 [10]. One hundred and four patients chronically treated with glucococorticoid were studied. All had an elective surgical procedure. Seventy-four operations such as colectomy and splenectomy were classified as "major" surgical procedures. The remainder were classified as minor procedures. Fourteen normal individuals underwent minor surgery and served as control subjects. Glucocorticoid therapy was removed 36 h before the scheduled operation. The operations were done without any glucocorticoid supplementation.

Blood pressure and heart rate were measured every 5 min during the operation, and plasma cortisol measurements were made at 1, 4, 7, 12, and 14 h after the beginning of the surgical procedure. Glucocorticoid treatment was reinitiated 72 h after the major procedures.

In the major surgery group, 37 patients had a subnormal cortisol response to surgery. Hypotension occurred in 18 of 74 patients. Twelve of these had a normal
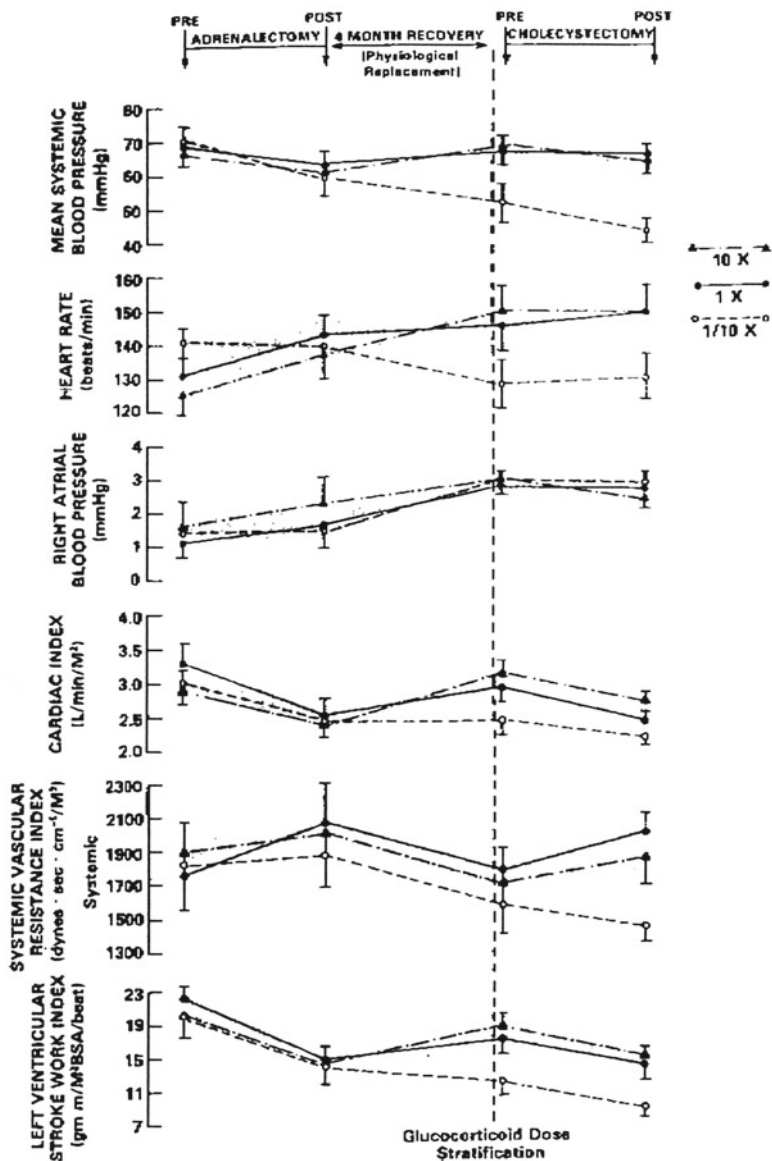
Fig. 1.5 The response of groups of adrenalectomized Rhesus monkeys to surgical stress under conditions. Of normal, ten times normal and, one tenth normal cortisol replacement. Reprinted from Udelsman R, Loriaux L, Chrousos G, Surgical Form 36: 1820; 1985

adrenal response to surgery, six had an attenuated response. All episodes resolved without the administration of glucocorticoids.

The authors conclude that, "Adrenocortical function, as expressed by repeated plasma corticosteroid measurements and the clinical course, were studied in 104

glucocorticoid-treated patients undergoing surgery without supplementary gluco-corticoid administration. Eight patients developed otherwise unaccountable hypotension during surgery but only one patient showed concomitant low plasma corticosteroid values. Eighteen patients had minimal adrenocortical function without accompanying signs of adrenocortical insufficiency. Postoperatively, four patients developed hypotension, which could not be correlated with cortisol deficiency. It is concluded that cortisol is not the prime determinant of blood pressure during and after surgery in glucocorticoid-treated patients, that stress-induced acute adrenocortical insufficiency must be infrequent in these patients."

The data from these two studies suggest that the rise in cortisol associated with stress is a biological marker for the stress but is not needed to survive the stress. It appears that stress can be dealt with physiologically without a rise in plasma cortisol.

Another important lesson from these studies is that the most important thing the physician can do to prevent acute adrenal insufficiency during stress in "at risk" patients is to ensure that adequate glucocorticoid is "on board" 24 h before the stress is introduced. Fifty milligrams of hydrocortisone, by any route, is the usual practice.

Current dogma directs that the dose of cortisol must be doubled for the duration of "significant" stress in patients with known adrenal insufficiency and in patients who have received supraphysiologic glucocorticoid therapy within the last year. This has become the "standard of care" and is unassailable. It may do more harm than good.

It is this concept, a rise in plasma "cortisol is essential for the survival of stress," that leads to the concept of "relative adrenal insufficiency." The reasoning is that, in a given patient, the rise in cortisol may be inadequate for the level of clinical "stress." Since the best test to predict the "adequacy" of the rise of cortisol in response to stress is the Cortrosyn® stimulation test, an abnormal response to Cortrosyn® would define a relative deficiency in the adrenal response to stress. Untreated, it was reasoned, this deficiency could lead to shock and death. Hence, for many years such patients have been treated with "stress doses" of glucocorticoid.

The Cortrosyn® Stimulation Test

The diagnosis of "relative adrenal insufficiency" has rested upon the interpretation of the Cortroysn® stimulation test. The Cortrosyn® stimulation test consists of a 250 μg intravenous dose of Cortrosyn® followed by plasma cortisol measurements at fixed intervals of 30, 45, and 60 min. The "normal response" was developed in "healthy" non-stressed adults. The "basal level" of plasma cortisol is 15 ± 8 μg (± 2SD) μg/dL and the Cortroysn® stimulated levels 32 ± 12 μg/dL (± 2SD) [11]. The bottom of the range of Cortrosyn® stimulated values is generally accepted as 20 μg/dL. An additional measure of "normal" has been the magnitude of the rise of plasma cortisol in response to Cortroysn®. A "Δ" between the basal and stimulated level of less than 5–9 μg/dL, depending on the report, is considered an abnormal response to

the Cortrosyn® stimulation test [12]. A maximally stimulated level of 20 µg/dL or more predicts the ability of the adrenal glands to respond adequately to surgical stress [14]. The "Δ" criterion has not been tested in this way. In addition, it is now clear that as many as one third of normal volunteers will fail the "Δ" criterion, and that the "Δ" in any given test is inversely related to the basal cortisol concentration [13, 14]. For these reasons, most clinicians are uncomfortable with the "Δ" response as a predictor of normal adrenal function. The "Δ" criterion is now rarely applied. As a consequence, the basal value of plasma cortisol is no longer routinely measured. The current test is a 250 µg intravenous bolus of Cortrosyn® followed by plasma cortisol measured at 30, 45, or 60 min after administration (usually 30 and 60 or 45 and 60, not all three).

There are several clinical situations that can complicate the interpretation of the Cortrosyn® test. The first is the acute loss of ACTH secretion. For example, "stalk section" will not reliably result in abnormal values in the Cortrosyn® test for up to 12 days [15]. It takes time for the adrenal glands to atrophy after adrenocorticotrophic hormone stimulation is withdrawn. Second, circulating cortisol is bound to CBG (70 %) and albumin (20 %). Ten percent of circulating cortisol is "free," i.e., not protein bound. It is this "free fraction" that is regulated by ACTH. At a total cortisol level of 20 µg/dL, 4 µg of cortisol is bound to 4 g of albumin. If the plasma albumin level is reduced to 2 g/dL, only 2 µg of cortisol will be albumin bound and the total plasma cortisol level will fall by 2 µg/dL. This will alter the "cut off" value [16] (Fig. 1.6). It is common that critically ill patients have reduced circulating albumin levels. The result is an increased number of false positive tests in the critically ill. This same concept applies to changes in CBG concentrations which cause even bigger changes in total plasma cortisol.

All of the baseline clinical data that we depend upon to interpret the Cortrosyn® stimulation test were determined with a Cortrosyn® dose of 250 µg. This is a maximally stimulating dose that is well out on the "V-max" portion of the dose response curve (Fig. 1.7). If the Cortrosyn® dose is reduced so that it is on the rapidly rising part of the curve, the coefficient of variation of the test increases and the results are less precise [17]. Lower precision is associated with an increased number of "false positive" numbers. The imprecision puts more subjects below the "cut off" point. The tendency has been to think of these "low dose" tests as superior in that more patients with "adrenal insufficiency" are identified. In reality, these are "false positive numbers." This shortcoming is true of every other test of adrenal function—metyrapone, insulin hypoglycemia, CRH, etc. The "gold standard" test remains the 250 µg Cortrosyn® stimulation test. A "1 µg test" has been proposed as better than the 250 µg test for identifying "partially deficient" patients. The results of the 1 µg test have usually been interpreted using the well-established criteria associated with the 250 µg test. One microgram of Cortrosyn®, however, will produce lower plasma cortisol levels than those produced by 250 µg. Figure 1.8 shows the 1 µg test arrayed against the 250 µg criteria [18]. In this case, 95 % of the results of the 1 µg will be interpreted as abnormal.

Finally, the interpretation of the Cortrosyn® stimulation test in stressed patients depends upon criteria developed in non-stressed subjects. When the Cortrosyn® test

Circulating Plasma Cortisol Levels in a Normal Person, A
Stress Person, and a Stresses Person with Hypoalbuminemia.
Approximately 10 percent of cortisol is present in the free
(bioactive) state, unbound to protein; 20 percent is loosely
bound to albumin; and 70 percent is tightly bound to cortisol-
binding globulin. Binding to cortisol-binding globulin is nearly
saturated at plasma cortisol levels in the range of 15 to 18 µg
per deciliter (413.8 to 496.6 nmol per liter). With stress and
hypoalbuminemia, the maximal total cortisol measurement will
fall below that in persons with a normal albumin concentration
and, often, below the traditional cutoff level for the co-
syntropin stimulating test, even though the level of free,
bioactive cortisol is the same in these two groups and is
appropriate for the clinical situation. To convert values to
nanomoles per liter, multiply by 27.6

is applied to stressed patients, as in a medical intensive care unit, the baseline
cortisol value is an ACTH stimulated number (Fig. 1.9). In this situation, the "Δ"
criterion is no longer applicable. If the "Δ" criterion is used to interpret the test,
many, perhaps most, of the patients will appear to have adrenal insufficiency.

Examining one review in which 18 studies are presented is informative [19]. Six
studies used the "maximum value" criterion to diagnose relative adrenal insufficiency.
The "cut off" value for maximum plasma cortisol concentration was between
500 nM (18 µg/dL) and 550 nM (19 µg/dL). Using this "cut off" range, the incidence
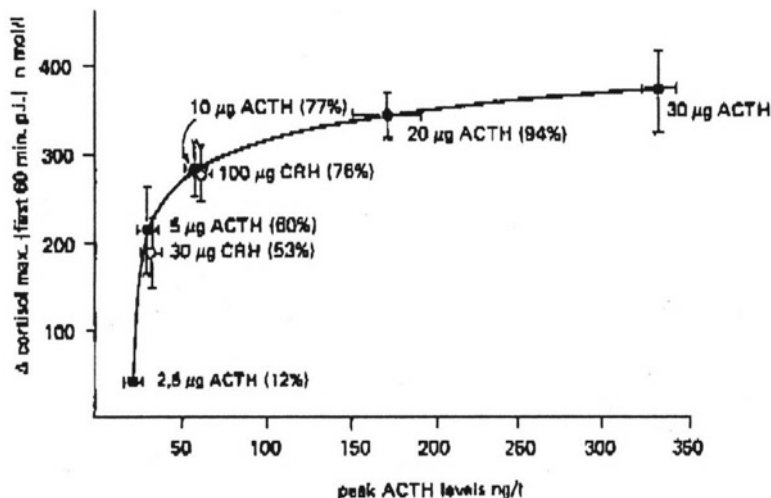
Fig. 1.7 The correlation between maximum serum cortisol and dose of Cortrosyn® (ACTH). Reprinted from Oelker W. Dose response aspects in the clinical assessment of the HPA axis, and the low-dose adrenocorticotropin tests. European J of Endo 135: 27–33; 1998

Fig. 1.8 A comparison of the 250 µg and the 1 µg Cortrosyn® stimulation test. Reprinted from Endocrine Practice 2009
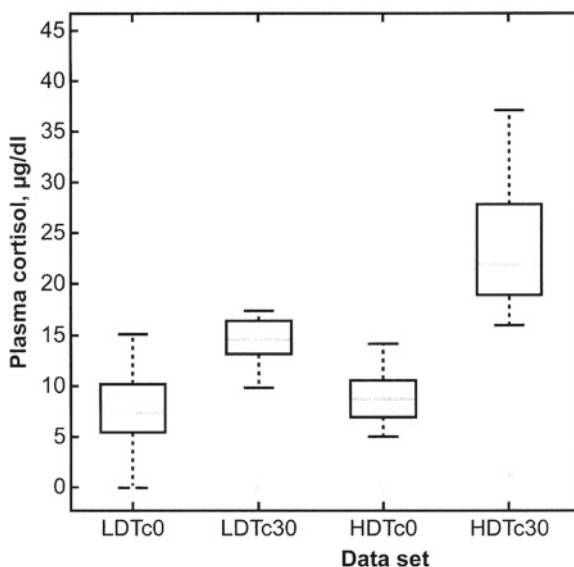
"of relative adrenal insufficiency" in the six studies was 9 %. The remaining studies used the "Δ" criterion. A "Δ" of less than 200 nM (7 µg/dL) to 250 nM (9 µg/dL) was used to make the diagnosis of relative adrenal insufficiency. In these studies, the average incidence of "relative adrenal insufficiency" was 40 %. Depending upon the criteria, interpreting the Cortrosyn® stimulation test in this manner can result in a prevalence of "relative adrenal insufficiency" in the intensive care setting of up to 75 % [1].

The Explanation

Critically ill patients

Endogenous ACTH stimulation yields a false positive "Δ" criterion

Normal subjects

Chronically ill patients

Low albumin yields a false positive "max concentration" criterion
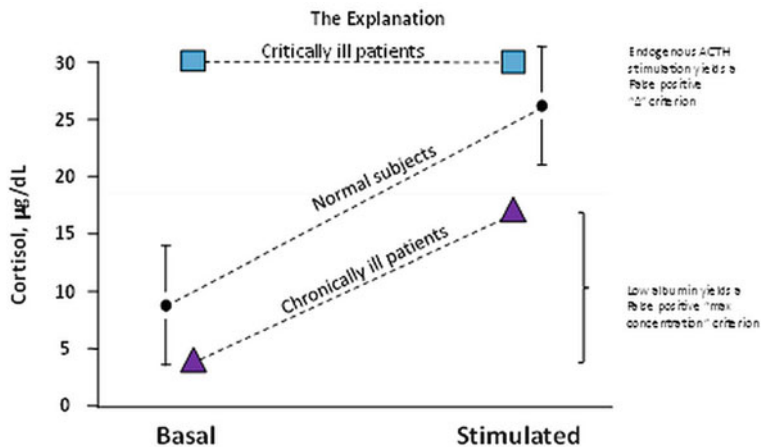
"Normal is a stimulated value greater than 18 μg/dL or a 'Δ' greater than 5-9 μg/dL"

Fig. 1.9 Reponse pattern of cortisol in stressed patients looking at alterations in the "maximum Concentrations" and "Δ" criterion

The "Δ" criterion has led to recommendations such as the following:

"When the result is positive (Cortrosyn® stimulation), there is an immediate need for GC treatment/replacement, without any reservation. A negative or inconclusive result should not, however, prohibit a trial of steroid replacement, especially in patients with a high basal cortisol level, a weak response to ACTH and clinical suspicion of relative adrenal insufficiency" [1]. In other words, the Cortrosyn® stimulation test does not influence the intention to treat with glucocorticoids. Everybody should be treated since all should be suspected of having relative adrenal insufficiency. This recommendation comes very close to the truth of the matter. The results of the Cortrosyn® stimulation test play no role in arriving at this conclusion.

Some studies point to the apparent clinical value of "stress doses" of glucocorticoid in septic patients as evidence for an undiagnosed "relative adrenal insufficiency." The usual "stress dose" of glucocorticoid is 200 mg of hydrocortisone a day. Two hundred milligrams of cortisol is equivalent to 50 mg of Prednisone®. The usual "dose pack" of Prednisone® starts with six 4 mg tablets of Prednisone® a day, about half of the effective glucocorticoid dose of a 200 mg cortisol "stress dose." This dose of cortisol can be very effective in treating diseases with an inflammatory component. It does not follow that patients who respond have adrenal insufficiency.

Recommendations for the Diagnosis of Adrenal Insufficiency in the Critically Ill

The diagnosis of acute adrenal insufficiency is a clinical one: shock poorly responsive to volume and pressor therapy. All patients with this syndrome should be treated with the standard "stress" dose of glucocorticoid. The usual regimen is 200 mg of hydrocortisone given in 50 mg intravenous boluses at 6 h intervals. Treatment should be continued until the hypotension is resolved.

When can the cortisol be discontinued? The most useful tool in making this decision is the total plasma cortisol measured before glucocorticoid treatment is initiated. Patients with values over 20 μg/dL can have the hydrocortisone discontinued over a few days. Those with total plasma cortisol levels less than 20 μg/dL should have the dose reduced over a period of several days to an oral replacement dose of 12–15 mg/m^2 and kept at that dose until primary or secondary adrenal insufficiency can be excluded.

In the opinion of the author, the Cortrosyn® stimulation test is not useful in the management of suspected acute adrenal insufficiency. In fact, as currently interpreted, the test can lead to therapeutic delay or unnecessary prolongation of glucocorticoid therapy. Both have serious downstream complications.

Conclusions

The concept of relative adrenal insufficiency is based on the notion that the adrenal response to stress is needed to survive that stress. This has led to the widespread use of the Cortrosyn® stimulation test to identify these patients. The Cortrosyn® stimulation test, however, is not reliable in this setting. The primary reason is that the standard criteria for interpreting the test, developed in normal unstressed adults, are not applicable to patients with a high level of stress such as "shock." This is particularly true for the "Δ" criterion. Much of the confusion caused by this situation can be resolved by abandoning the Cortrosyn® stimulation test altogether and treating all patients with shock poorly responsive to volume and pressor therapy with stress levels of hydrocortisone. The total plasma cortisol measured before any glucocorticoid therapy is given in the course of the critical illness can be used as a guide for important decisions about when and how to discontinue glucocorticoid therapy when the crisis is past.

These recommendations are at odds with some of the 2008 recommendations of the international task force of the American College of Critical Care Medicine [20]. Recommendation 3 of this group, for example, states that the Cortrosyn® stimulation test is the best way to diagnose adrenal insufficiency associated with critical illness. I do agree, however, with the task force recommendation concerning which patients to treat with hydrocortisone. Patients with "shock" are poorly responsive to volume and pressor therapy. That recommendation also agrees with several recent reviews on the subject [21, 22].

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Chapter 2
Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic Syndrome

Beatrice C. Lupsa and Silvio E. Inzucchi

Précis

1. Clinical setting—Any altered state of well being in the context of significant hyperglycemia in a patient with type 1 (DKA) or advanced type 2 diabetes mellitus (DKA or HHS), particularly during acute illness, may signify one of these diabetic emergencies.
2. Diagnosis

    (a) History: Most patients with diabetic ketoacidosis (DKA) or with hyperosmolar hyperglycemic state (HHS) will have a history of diabetes, and a history of altered insulin dose, infection, significant medical "stress". Antecedent symptoms of polyuria and polydipsia, lassitude, blurred vision, and mental status changes may predominate the clinical picture. With DKA, abdominal pain and tachypnea are often present.
    (b) Physical examination usually reveals an altered sensorium, signs of volume contraction/dehydration (tachycardia, hypotension, dry mucus membranes, "tenting" of the skin); in DKA, the odor of acetone in the breath.
    (c) Laboratory evaluation. The diagnostic criteria for DKA include blood glucose above 250 mg/dL, arterial pH < 7.30, serum bicarbonate < 15 mEq/l

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and moderate degree of ketonemia and/or ketonuria. Patients with HHS present with extreme hyperglycemia (blood glucose > 600 mg/dL), increased osmolality (>320 mOsm/kg) and profound dehydration/volume contraction. The laboratory evaluation of a patient with hyperglycemic emergency should include measurement of blood glucose and hemoglobin A1c, arterial blood gases, serum electrolytes, ketones and osmolality, renal function and urinalysis. A work up for sepsis or other precipitating causes should be initiated if indicated.

3. Treatment

   (a) DKA

      1. Fluid: Estimated fluid deficit is 5–7 liters. Correct with normal saline, 2L in the first 2 hours, the remainder over the next 22 hours.
      2. Insulin: IV bolus of 0.1 U/Kg regular insulin followed by an intravenous infusion of 0.1 U/kg/h. Goal is to reduce plasma glucose by 50–75 mg/dL/h. Initial target plasma glucose is 200–250 mg/dL. Once achieved, reduce insulin rate and provide dextrose to 'clamp' the plasma glucose until acidosis/anion gap resolved.
      3. Acid/base – pH will climb with plasma expansion and insulin administration. Use small amounts of sodium bicarbonate only for severe acidemia (pH <6.9).
      4. Electrolyes: Close monitoring and correction of serum potassium is critical. (If serum potassium <3.5, correct hypokalemia *before* any insulin is given.)
      5. Search for cause: Seek to determine underlying precipitant, such as treatment non-adherence, infection, myocardial infarction, etc.

   (b) HHS

      1. Fluid: Estimated fluid deficits typically larger than in DKA (7–9 liters). Correction/maintenance of plasma volume with normal saline is critical in older patients. Correct rate depends on blood pressure, other signs of volume contraction and any history of underlying cardiovascular disease, especially heart failure.
      2. Insulin: Should be initiated *after* initial saline plasma expansion. IV bolus of 0.1 U/Kg regular insulin followed by an intravenous infusion of 0.1 U/kg/h. Goal is to reduce plasma glucose by 50–75 mg/dL/h. Target plasma glucose is 250–300 mg/dL.
      3. Acid/base- By definition, no major deficits related to HHS itself.
      4. Electrolyes: Derangements not as common as in DKA, but monitoring is still required.
      5. Search for cause: As above.

Introduction

Diabetic Ketoacidosis (DKA) and hyperosmolar hyperglycemic syndrome (HHS) are two acute and life-threatening complications of diabetes requiring prompt recognition and aggressive therapy to optimize clinical outcomes. Although they share certain features, DKA and HHS differ clinically according to the degree of hyperglycemia and the presence of ketoacidosis. The fundamental difference between the two conditions is that a small residual amount of insulin prevents significant ketosis and acidosis in HHS. Descriptive definitions of DKA and HHS and the criteria for classification of the severity of the former are shown in Table 2.1.

Patients with DKA present with hyperglycemia, ketonemia, and metabolic acidosis secondary to absolute or profound relative insulin deficiency. HHS is characterized by a greater severity of plasma glucose elevation, marked increase of plasma osmolality, absent to mild ketosis, and altered mental status. In HHS, residual secretion minimizes ketone body production but is not able to control hyperglycemia. The older terms "hyperglycemic hyperosmolar nonketotic coma" and "hyperglycemic hyperosmolar nonketotic state" have been replaced with the term "hyperglycemic hyperosmolar syndrome (or state)" to reflect the fact that different levels of mentation and ketosis may indeed be present.

Most patients with DKA have type 1 diabetes, which is associated with absolute insulin deficiency. Patients with advanced or severe type 2 diabetes can also be at risk during acute illnesses. HHS occurs almost exclusively in type 2 diabetes patients, who continue to demonstrate some degree of insulin secretion.

Table 2.1 Diagnostic criteria for diabetic ketoacidosis (DKA) and hyperosmolar state (HHS) (Adapted from Kitabchi et al., *Diabetes Care*, 2001 [1])

| | DKA | | | |
	Mild	Moderate	Severe	HHS
Plasma glucose (mg/dL)	>250	>250	>250	>600
Arterial pH	7.25–7.30	7.00–7.24	<7.00	>7.30
Serum bicarbonate (mEq/L)	15–18	10 to <15	<10	>18
Urine ketones[a]	Positive	Positive	Positive	None — small
Serum ketones[a]	Positive	Positive	Positive	None — small
Effective serum osmolality (mOsm/kg water)[b]	Variable	Variable	Variable	>320
Anion gap[c]	>10	>12	>12	Variable, but usually normal
Mental status	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

[a] Nitroprusside reaction method
[b] Calculation: 2 [measured Na (mEq/L)] + glucose (mg/dL)/18
[c] Calculation: $Na^- - (Cl^- + HCO_3^-)$, in mEq/L
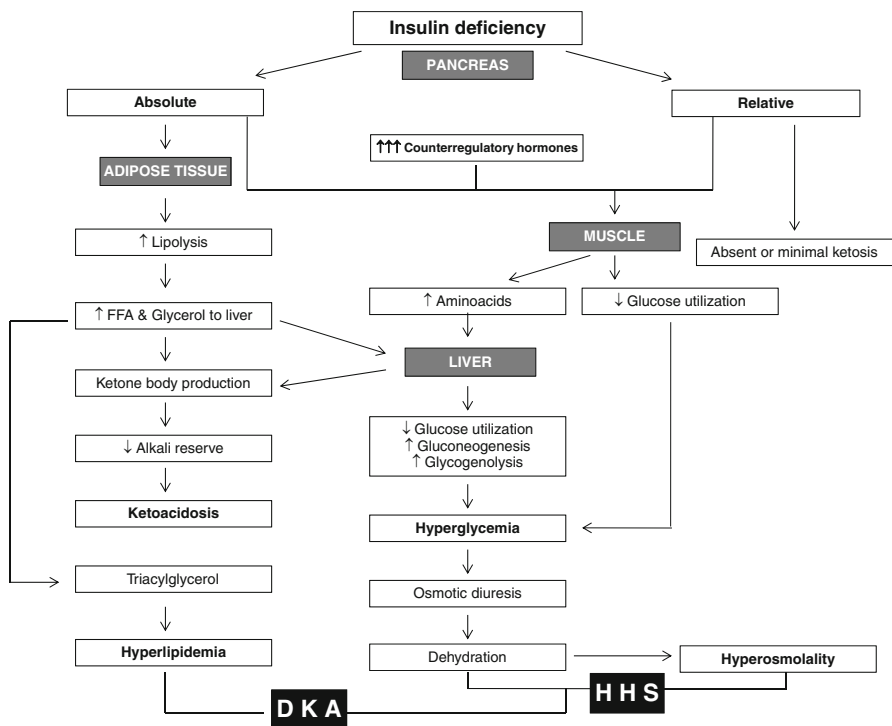
Fig. 2.1 Schematic overview of the pathogenesis of diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome (Adapted from Kitabchi et al., Diabetes Care, 2001 [1]). *DKA* diabetic ketoacidosis, *FFA* free fatty acids, *HHS* hyperosmolar hyperglycemic syndrome

Pathogenesis

The events leading to DKA and HHS are shown in Fig. 2.1. In DKA, absent or severely reduced insulin concentrations, increased insulin-counterregulatory hormones (cortisol, glucagon, growth hormone, and catecholamines), and peripheral insulin resistance result in hyperglycemia and ketosis. Hyperglycemia evolves through decreased glucose utilization by peripheral tissues and accelerated hepatic gluconeogenesis and glycogenolysis [1–4]. Due to increased lipolysis and decreased lipogenesis, abundant circulating free fatty acids are converted to ketone bodies (beta-hydroxybutyrate, acetoacetate, and acetone) by the liver. Beta-hydroxybutyrate and acetoacetate are two relatively strong acids. At physiological pH, these two ketoacids dissociate completely and the excess hydrogen ions bind bicarbonate, resulting in decreased serum [HCO_3^-] concentrations. Ketones thus circulate in the anionic form, leading to the development of the anion gap metabolic acidosis that characterizes DKA. Hyperglycemia-induced osmotic diuresis also leads to dehydration, hyperosmolality, electrolyte losses, and subsequent decreased plasma volume and glomerular filtration. With decline in renal function, glycosuria and ketonuria

are attenuated, further excerbating hyperglycemia, hyperosmolality, and ketoacidosis. Activation of the sympathoadrenal system further counteracts insulin action, heightening all of these features.

HHS is also caused by a reduction in the net effective action of circulating insulin and an increase in counterregulatory hormones, leading to hyperglycemia and hyperosmolality. The key difference between HHS and DKA is that insulin levels in HHS are inadequate to control hyperglycemia, but generally sufficient to prevent significant ketosis, and as a result, acidosis.

Recent studies have shown that patients in hyperglycemic crisis also exhibit a severe pro-inflammatory state characterized by elevated cytokine (tumor necrosis factor-α (alpha), interleukin-β (beta), −6 and −8), C-reactive protein, reactive oxygen species, lipid peroxidation, and plasminogen activator inhibitor-1 [5].

New-onset type 1 diabetes (and, in some circumstances, type 2) can present with DKA. The most common precipitating factors are omission of insulin or inadequate insulin coverage especially during some other acute illness (e.g., gastroenteritis, influenza), severe infections, myocardial infarction, stroke, pancreatitis, or major surgery. Insulin pump malfunction, psychiatric illness, eating disorders, and drug abuse can also be associated with DKA. Administration of medications such as corticosteroids, conventional and atypical antipsychotic drugs, thiazide diuretics, and beta blockers has also been reported to promote the development of DKA.

HHS is seen exclusively in type 2 diabetes and can sometimes be its initial presentation. Infection is the major precipitating factor (pneumonia, pyelonephritis, etc.) occurring in about 50 % of the patients. Other acute illnesses such as myocardial infarction and stroke, which cause the release of counterregulatory hormones, and intra-abdominal processes, including acute pancreatitis can be the stimulus for HHS. Medications associated with DKA also have been associated with HHS. Nonetheless, in about 20 % of patients presenting with hyperglycemic crisis there is no obvious cause—likely due to an abrupt increased insulin requirement for some unidentifiable reason, with superimposed effects of gluco-toxicity, which describes the phenomenon of worsening beta-cell secretion of insulin caused by hyperglycemia itself.

Diagnosis

History and Physical Examination

DKA and HHS are medical emergencies that require urgent recognition and treatment. The initial approach to these patients should include a rapid but thorough history and physical examination with special focus on patency of airways, mental status, state of hydration, cardiovascular and renal integrity, and potential sources of infection.

Table 2.2 Initial laboratory evaluation for DKA and HHS

Metabolic evaluation	Infectious disease evaluation[a]	Others[a]
Glucose	CBC with differential	Electrocardiogram
Serum ketones	Chest X-ray	Urine toxicology panel
Electrolytes (monovalent and divalent: Na^+, K^+, Cl^-, HCO_3^-, Ca^{2+}, PO_4^{3-}, Mg^{2+})	Urine culture	Pregnancy test
Serum osmolality	Blood cultures	
Blood urea nitrogen (BUN) and creatinine	Viral nasal swab	
Arterial blood gases (ABG)		
Liver function tests		
Amylase and lipase		
Hemoglobin A1c		
Urinalysis		

[a]If clinically indicated

The development of DKA is usually relatively acute, occurring in less than 24–48 h, whereas HHS usually evolves over several days to weeks. The typical symptoms of unrestrained hyperglycemia in both syndromes include polyuria, polydipsia, blurred vision, fatigue, weakness, and weight loss. DKA patients usually present with vomiting and abdominal pain probably due to delayed gastric emptying and ileus caused by electrolyte abnormalities and/or acidosis.

Physical findings include poor skin turgor, tachycardia, and hypotension. In DKA, there may be a fruity odor to the breath (from ketosis) as well as rapid, regular, and deep respirations (Kussmaul breathing), the latter representing an effort to mitigate the impact of metabolic acidosis by inducing a compensatory respiratory alkalosis. Patients with HHS can present with focal neurological signs (hemiparesis, hemianopsia) and seizures. Mental status can vary from alertness to lethargy and coma. Serum osmolality is the most important determinant of mental status in HHS. In particular, obtundation and coma may be seen when the effective osmolality exceeds 330 mOsm/kg [6].

Even though infection is a common precipitating factor for hyperglycemic crises, the body temperature can be misleadingly normal or low due to peripheral vasodilation.

Laboratory Findings

The easiest and most urgent laboratory tests are determination of blood glucose by finger stick and urinalysis with reagent strips for ketones and glucose allowing for the detection or at least the strong suspicion of these hyperglycemic crises before the patient is seen. These can be done by the patient at home.

The initial laboratory evaluation of a patient with DKA or HHS should include measurement of blood glucose, arterial blood gases, renal function, serum electrolytes, ketones, serum osmolality, complete blood count with differential, and urinalysis. A work-up for sepsis should be initiated by obtaining blood and urine cultures and a chest X-ray if clinically indicated. Additional tests include EKG and determination of hemoglobin A1c level, the latter to assess for chronicity and degree of hyperglycemia (Table 2.2).

The diagnostic criteria for DKA include blood glucose above 250 mg/dL, arterial pH <7.30, serum bicarbonate <15 mEq/L, and moderate degree of ketonemia and/or ketonuria (Table 2.1) [1]. Hyperglycemia is a key diagnostic criteria of DKA; however, 10 % of DKA patients will have a glucose level below 250 mg/dL [7], sometime due to insulin administration before getting to the hospital decreased nutritional intake and decreased gluconeogenesis due to recent ethanol consumption or advanced liver disease [8, 9].

Accumulation of ketones results in an anion gap metabolic acidosis. The anion gap is calculated by subtracting the major measured anions (chloride and bicarbonate) from the major measured cation (sodium). In the older literature, a level above 14–15 mEq/L was thought to be consistent with an increased anion gap metabolic acidosis. However, most laboratories currently measure sodium and chloride using ion-specific electrodes. Plasma chloride level measured by this method is usually 2–6 mEq/L higher than with prior analytical methods. Therefore, using the ion-specific technique, an anion gap of >10–12 mEq/L would suggest the presence of an anion gap acidosis [10, 11]. Arterial blood gases support the diagnosis with the presence of acidemia.

The key laboratory features of DKA are ketonemia and ketonuria. The ratio between the two main ketoacids, beta-hydroxybutyrate and acetoacetate, depends on the prevailing redox state. In high redox states, such as DKA (as well as lactic acidosis), beta-hydroxybutyrate predominates. Assessment of ketone status is usually performed with the nitroprusside reaction, which provides a semiquantitative measurement of acetoacetate and acetone. However, the nitroprusside reaction does not detect beta-hydroxybutyrate, thus underestimating the severity of ketoacidosis. If available, direct measurement of serum beta-hydroxybutyrate can be helpful in establishing the diagnosis.

Patients with HHS present with extreme hyperglycemia (blood glucose >600 mg/dL), increased osmolality (>320 mOsm/kg), and profound dehydration/volume contraction. The effective serum osmolality is calculated as follows: 2 [measured Na (mEq/L)] + glucose (mg/dL)/18, with normal value being 290 ± 5 mOsm/kg (blood urea nitrogen, which enters the equation for total serum osmolality, is not included here as it is freely diffusible across cell membranes and is therefore not considered an "effective osmole"). Usually in HHS, the anion gap is normal and serum bicarbonate level is over 20 mEq/L. However, some patients can present with mild acidosis, due to the accumulation of ketone bodies in low concentration and/or lactate resulting from generalized hypoperfusion.

Table 2.3 Typical deficits of water and electrolytes in DKA and HHS (Adapted from Kitabchi et al., Diabetes Care, 2006 [29])

	DKA	HHS
Total water (L)	6	8
Water (mL/kg)[a]	100	100–200
Na^+ (mEq/kg)	7–10	5–13
Cl^- (mEq/kg)	3–5	5–15
K^+ (mEq/kg)	3–5	4–6
PO_4^{3-} (mmol/kg)	5–7	3–7
Mg^{2+} (mEq/kg)	1–2	1–2
Ca^{2+} (mEq/kg)	1–2	1–2

[a]Per kilogram of body weight

Both DKA and HHS are associated with large fluid and electrolyte deficits (Table 2.3). The development of dehydration and electrolyte depletion is the result of hyperglycemia, insulin deficiency and, in DKA, keto-anion excretion.

Hyperglycemia causes an osmotic diuresis. During severe hyperglycemia the renal threshold of glucose and ketones is exceeded. The osmotic effect of glucosuria results in impaired water and sodium chloride reabsorption in the proximal tubule and loop of Henle [12]. Insulin deficiency itself may further contribute to fluid and electrolyte losses because insulin stimulates salt and water resorption in the proximal and distal nephron and phosphate reabsorption in the proximal tubule. Ketoacid excretion exacerbates solute diuresis by causing urinary cation excretion in the form of sodium, potassium, and ammonium salts.

The severity of dehydration is greater in HHS than in DKA likely due to more gradual and longer duration of metabolic decompensation and decreased fluid intake. Also, nausea and vomiting (in DKA) and fever, when present, can further contribute to dehydration.

Serum sodium concentration is markedly decreased because of intracellular water shifting to the extracellular compartment in order to equilibrate hyperosmolality. Usually the admission sodium is factitiously low because of the hyperglycemia and hyperlipidemia. The corrected sodium can be calculated by adding 1.6 mEq to the reported sodium value for every 100 mg of glucose over 100 mg/dL. As a result, a normal or high-measured serum sodium in this setting actually indicates severe state of dehydration, as is often the case in patients presenting with HHS.

The patient's serum potassium may be initially elevated due to an extracellular shift of potassium caused by insulin deficiency, acidemia, and hypertonicity, which is falsely reassuring as the total body potassium stores are probably depleted. A low or low-normal potassium level suggests severe total body potassium depletion.

Patients with uncontrolled hyperglycemia are usually in a negative phosphate balance because of phosphaturia caused by osmotic diuresis and the shift of phosphate out of the cell in the setting of acidosis.

Leukocytosis around 10,000–15,000 mm^3 is a common finding in DKA and may not be the result of an infection. This is attributed to stress and elevation in stress hormones. However, leukocytosis above 25,000 mm^3 suggests a septic process and should trigger further evaluation.

Hyperamylasemia has been reported in patients with DKA. It is not always being associated with pancreatitis. The origin of amylase in DKA is usually a non-pancreatic tissue such as the salivary glands. Measuring a lipase level can be useful in the differential diagnosis; however, lipase also can be elevated in the absence of pancreatitis [13]. The mechanisms of increased amylase and lipase levels in DKA are not well defined.

Moderate hypertriglyceridemia is common during episodes of DKA [14]. The deficiency of insulin activates lipolysis in adipose tissue releasing increased free fatty acids, which accelerates the formation of very low density lipoprotein (VLDL) in the liver. In addition, reduced activity of lipoprotein lipase in peripheral tissue decreases the removal of VLDL from the plasma, resulting in hypertriglyceridemia. Severe hypertriglyceridemia and hypertriglyceridemia-induced pancreatitis leading to DKA or HHS are well recognized [15]. Severe hypertriglyceridemia may spuriously lower serum glucose (pseudonormoglycemia) [16] and serum sodium (pseudohyponatremia) [17] in laboratories using volumetric testing and dilution samples with ion-specific electrodes.

Differential Diagnosis

DKA must be differentiated from other conditions that present with ketoacidosis and anion gap metabolic acidosis. Starvation and alcoholic ketoacidosis are not typically associated with hyperglycemia above 200 mg/dL and, usually, the bicarbonate level is greater than 18 mEq/L. Other causes of an anion gap metabolic acidosis include lactic acidosis, acute renal failure, and the ingestion of methanol, ethylene glycol, paraldehyde, and salicylate. The origin of the anion gap can usually be ascertained by assessing the ketone concentrations in the plasma. HHS is difficult to confuse with other conditions, given its narrowly defined diagnostic criteria. Overlap syndromes with features of both DKA and HHS, however, can be encountered in clinical practice. These may occur in patients with a slower development of ketoacidosis and, as a result, more protracted urinary losses of free water, resulting in hyperosmolality.

Treatment

The therapeutic goals of DKA and HHS management include restoration of volume status, correction of hyperglycemia and ketoacidosis (in DKA), correction of electrolyte abnormalities, treatment of precipitating factors, and prevention of the
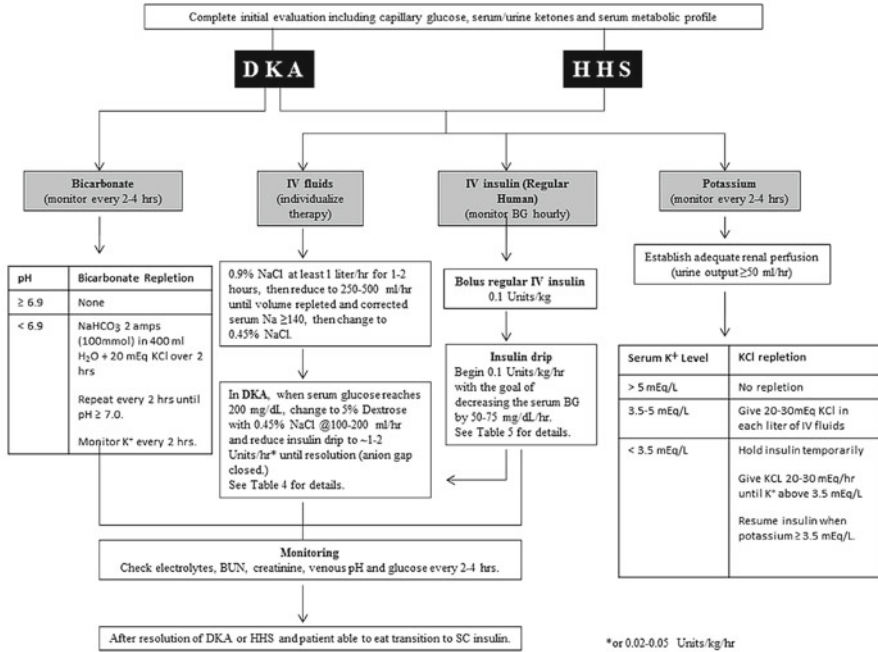
Fig. 2.2 Suggested protocol for management of adult patients with diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome. (Adapted from Kitabchi et al., Diabetes Care, 2009 [18]). *BG* blood glucose, *DKA* diabetic ketoacidosis, *HHS* hyperosmolar hyperglycemic syndrome, *hr* hour, *H₂O* water, *IV* intravenously, *KCl* potassium chloride, *NaCl* sodium chloride, *mEq/L* milliequivalents per liter, *SC* subcutaneous)

complications of DKA and HHS. Adequate intravenous (IV) access is essential with two larger bore IV peripheral lines or a central line. A suggested protocol for the management of patients with DKA and HHS is summarized in Fig. 2.2.

Fluid Therapy

In the emergency room, fluid resuscitation is critical for intravascular, interstitial, and intracellular volume and restoration of renal perfusion. The average fluid loss is approximately 5–7 L in DKA and 7–9 L in HHS (Table 2.3). The IV fluid administration replaces the fluid and electrolyte deficiencies, while simultaneously reducing plasma glucose concentrations and counterregulatory hormones, partially through dilution but also through volume expansion and resultant expansion of plasma volume. IV fluids should be administered *before* starting insulin in HHS, especially in older patients with tenuous cardiovascular status, in order to preserve vascular volume (see below).

Table 2.4 Suggested algorithm for clamping the blood glucose using dextrose-containing IV fluids and IV insulin in DKA

Serum glucose	IV fluid	Insulin infusion
200–250 mg/dL in DKA	Change to D$_5$0.45%NS 100–200 mL/h[a,b]	Reduce insulin drip to 1–2 U/h[b,c]
	100 mL/h ⟶ 1 U/h	
	200 mL/h ⟶ 2 U/h	
If serum glucose increases	Do not reduce IV fluids	Minor increases in insulin infusion rate (~0.5–1 U/h)[d]
If serum glucose decreases	Increase IV fluids	Do not decrease insulin infusion rate

[a] Provides 5–10 g of carbohydrates per hour

[b] Alternative is 0.02–0.05 U/kg/h

[c] Give insulin IV 1 U/h for every 5 g of dextrose IV/h

[d] Highly insulin resistant patients who require large amounts of IV insulin may need as much as 5–10 U of insulin/h. Accordingly, insulin dose adjustments may need to be more aggressive. The insulin dose can likely be reduced gradually as hyperglycemia improves

Normal saline is generally given in the first hour at a rate of 15–20 mL/kg body weight/h or 1–1.5 L in the first hour, although care is required in older patients with underlying cardiovascular disease. After initial stabilization, if the corrected serum sodium is normal or elevated, normal saline can be changed to half-normal saline at a rate of ~250–500 mL/h. If the corrected sodium is low, normal saline can be continued at a similar rate. Fluid replacement should correct the estimated deficit in the first 24 h, with 50 % of fluid resuscitation in the first 8–12 h. In patients with HHS, the change in serum osmolality should not exceed 3 mOsm/kg water/h.

The response to fluid resuscitation is judged by monitoring hemodynamic parameters (blood pressure and heart rate), clinical exam, urinary output, and laboratory values. In patients with renal or cardiac compromise fluid resuscitation should be conducted with caution to avoid fluid overload.

Once the serum glucose is 200–250 mg/dL in DKA, the insulin infusion rate should be reduced to 1–2 U/h and 5 % dextrose should be added to the IV fluids (this is termed the "glucose-insulin clamp" by some authorities). This technique will prevent hypoglycemia but will allow continuation of insulin administration sufficient in amount to resolve the ketoacidosis in DKA (i.e., to close the anion gap). A proposed algorithm for clamping the serum glucose using dextrose-containing IV fluids and IV insulin is outlined in Table 2.4.

Due to concerns that lowering the serum glucose too fast in HHS might promote the development of cerebral edema, some authorities recommend adding 5 % dextrose to the IV fluids when the serum glucose is 250–300 mg/dL until the patient is mentally alert [18]. In the majority of HHS cases, serum osmolality and mental status are normalized by the time the hyperglycemia is corrected, thus the "glucose clamp" will not often be necessary. Indeed, a simple lowering of the insulin infusion rate without the addition of dextrose can be sufficient, even in cases where the mental status remains abnormal.

Table 2.5 Suggested algorithm for adjusting the IV insulin infusion during treatment of the hyperglycemic phase of DKA and HHS

Hourly change in blood glucose (BG)	Action
BG↑	Rebolus (0.1 U/kg) and double insulin rate
BG ↓ by 0–49 mg/dL/h	↑Insulin drip by 25–50 %
BG ↓ by 50–75 mg/dL/h	No change in insulin drip
BG ↓ by >75 mg/dL/h	Hold insulin drip×30 min and restart at 50 % of most recent rate

Insulin Therapy

The only contraindication to insulin therapy is a current serum potassium below 3.5 mEq/L as insulin will worsen the hypokalemia by shifting the potassium into the cells.

The administration of continuous intravenous infusion of regular insulin is the preferred route as it has short half-life, it is easy to titrate, and has a rapid onset and short duration of action. The insulin dose is similar in DKA and HHS. However, as mentioned before, initial volume expansion with crystalloid is recommended (at least 1 L) in the more profoundly dehydrated and older HHS patients. This recommendation is to protect the plasma volume; once insulin is administered, the consequent fall in circulating glucose concentrations will lead to an intracellular shift of water from the plasma compartment which can result in a precipitous drop in systemic blood pressure. Insulin treatment usually starts with an IV bolus of 0.1 U/kg body weight followed by a 0.1 U/kg body weight/hour continuous infusion. The goal of insulin therapy is to decrease serum glucose by 50–75 mg/dL/h. Overly aggressive reduction of glucose may result in brain edema. A suggested algorithm for adjusting the IV insulin drip during DKA and HHS treatment can be found in Table 2.5. Glucose levels should be monitored every 1 h initially, and once stabilized, every 2–3 h.

Treatment of patient with mild to moderate DKA with subcutaneous rapid-acting analogs (lispro, aspart) every 1–2 h in non-intensive care unit has been shown to be effective in several studies [19, 20]; however, until these studies are confirmed outside the research setting, the vast majority of patients with DKA and HHS should be treated with intravenous regular insulin. Preferably, patients with these hyperglycemic emergencies should be managed in an intensive care setting, mainly due to the requirements to continuous patient monitoring, frequent blood testing and reporting, and rapid titration of therapy that may be required.

Potassium Replacement

Potassium replacement is critical in managing patients with DKA and HHS. Renal and gastrointestinal losses contribute to a marked potassium deficit in most patients. Despite the total body potassium deficit, the serum potassium concentration can be

normal or elevated at presentation due to the acidosis, the insulin deficiency, and the hyperosmolality, all of which cause a potassium shift from the intracellular to the extracellular space. Administration of insulin results in a significant shift of potassium into the cells and a fall in the serum potassium level. To prevent hypokalemia, potassium chloride is usually added to the IV fluids if the serum potassium is below the upper level of normal for the particular lab (5.0–5.2 mEq/L) and there is a good urinary output (>50 mL/h). Careful monitoring of the serum potassium is a critical part in the management of all hyperglycemic emergencies. Ideally, the serum potassium should be measured every 2–4 h (along with other electrolytes) and maintained between 4 and 5 mEq/L. To avoid cardiac and respiratory complications, patients who are hypokalemic prior to the initiation of treatment should not receive insulin until the potassium level is above 3.5–4.0 mEq/L. Such patients should receive aggressive potassium replacement (20–30 mEq/h) until potassium level is above 3.5–4.0 mEq/L (see Fig. 2.2 for details).

Phosphate Replacement

At presentation, serum phosphate is often normal or high in spite of whole-body phosphate deficit due to movement of phosphate out of the cells. As with potassium balance, phosphate concentration decreases with insulin therapy. However, the fall in serum phosphate level during DKA treatment is usually self-limited, asymptomatic, and does not require treatment. Prospective randomized trials of patients with DKA failed to show any benefit associated with supplementation [21] and phosphate replacement can have adverse effects such as hypocalcemia and hypomagnesemia [22]. Thus, phosphate replacement is not routinely recommended; however, it should be considered in patients at risk for cardiac dysfunction, hemolytic anemia, and respiratory depression or when the phosphate concentration is below 1 mg/dL. When needed, potassium phosphate 20–30 mEq/L can be added to the replacement fluids. The rate of phosphate replacement should not exceed 4.5 mmol/h [23]. Because of the risk of hypocalcemia, serum calcium and phosphate levels should be monitored during phosphate infusion. No studies are available on the use of phosphate in treatment of HHS. Phosphate levels should be tested but less frequently than routine electrolytes, perhaps every 8–12 h.

Bicarbonate Therapy

Bicarbonate use in DKA remains controversial. Treatment with insulin inhibits lipolysis and ketoacid production and promotes keto-anion metabolism. Because protons are consumed during keto-anion metabolism, bicarbonate is regenerated leading to partial correction of metabolic acidosis with insulin therapy and volume expansion alone. However, severe acidosis can lead to impaired cardiac contractility, cerebral vasodilatation, and severe gastrointestinal complications.

A randomized trial of 21 DKA patients with an admission arterial pH between 6.9 and 7.1 showed no difference in morbidity and mortality with bicarbonate use [24]. Not surprisingly, there are no prospective randomized trials on the use of bicarbonate in DKA patients with an arterial pH less than 6.9. Potential side effects of bicarbonate therapy include hypokalemia, worsening intracellular acidosis (as a result of increased carbon dioxide production), delayed keto-anion metabolism, and development of paradoxical central nervous system acidosis [25–27].

Nonetheless, because severe acidosis may result in significant adverse cardiovascular effects, it is recommended that patients with pH values <6.9 should receive 100 mmol of sodium bicarbonate (2 ampules) in 400 mL sterile water with 20 mEq potassium chloride at a rate of 200 mL/h for 2 h until the pH is >7. If the pH is still <7, the bicarbonate infusion can be repeated every 2 h until the pH is >7. Hypokalemia, if present, must be corrected before any bicarbonate administration. Profound acidosis can require a continuous bicarbonate infusion.

Search for Precipitating Factors

Infection is a major precipitating factor for hyperglycemic emergencies. Hence, it is important to search for underlying infections. If indicated, chest X-ray and blood and tissue cultures should be obtained. Appropriate antibiotic treatment should be initiated if a bacterial infection is identified.

Resolution of DKA and HHS

Criteria for resolution of DKA includes a serum glucose <200 mg/dL and two out of the following criteria: serum bicarbonate ≥15 mEq/L, a venous pH >7.3, and a calculated anion gap ≤12 mEq/L. Resolution of HHS includes normal serum osmolality (<315 mOsm/kg), and normal mental status [18]. Please note that the serum bicarbonate may still be low even after DKA resolution due to an "expansion" non-gap acidosis associated with aggressive IV crystalloid repletion. Thus, the anion gap is the best indicator of DKA resolution.

Transition to Subcutaneous Insulin

If the DKA or HHS has resolved but the patient is to remain NPO, IV insulin and fluid replacement should be continued. However, if the patient is able to eat, subcutaneous insulin can be started, although this may be most conveniently done in conjunction with the patient's next planned meal. As the IV insulin has a very short half-life, in order to prevent the recurrence of hyperglycemia and acidosis, it is important to overlap for 1–2 h the subcutaneous and IV insulin. If the patient has a history of type 1 diabetes mellitus, patient's routine therapy can be resumed

as long as an inadequate home regimen was not the reason for the hyperglycemia crisis. In newly diagnosed patients, a multidose insulin regimen should be started at a dose of 0.5–0.8 U/kg/day, the higher end of this range reserved for patients who have substantial degrees of insulin resistance as reflected by the insulin infusion requirements, prior history, body weight, and other physical features, such as acanthosis nigricans. Typically, however, the recent insulin infusion rates are not helpful in determining subcutaneous insulin doses, since they may be rapidly fluctuating, and with the resolution of gluco-toxicity, insulin requirements can be quite valuable.

A variety of subcutaneous insulin regimens are available from relatively straightforward (twice per day pre-mixed insulins) to relatively complex (e.g., long acting insulin in the evening and rapid-acting insulin with meals, the so-called *basal-bolus* strategy). The latter is likely to result in the best glycemic control, although it requires more understanding and participation by the patient. The use of insulin sliding scale alone should be discouraged, even as a transition, as it cannot provide the necessary insulin requirement in patients recovering from hyperglycemic crisis. Fingerstick glucose measurements before each meal and at night should be done after discontinuing the IV insulin to correct for possible fluctuations in insulin needs while in the hospital.

Complications

Hypoglycemia and hypokalemia are the most common iatrogenic complications during treatment for DKA and HHS. These can be prevented by very close monitoring (every 2–4 h) of potassium level and appropriate supplementation, adjustment of insulin dose, and use of dextrose-containing IV fluids.

Hyperchloremic non-anion gap metabolic acidosis is commonly seen after the resolution of DKA. It is usually explained by the high dose of chloride administered in IV fluids. This acidosis is self-limited and has no adverse clinical effects. Patients usually require several days to recover as the kidneys readjust bicarbonate production and acid secretion. The persistently low bicarbonate level due to hyperchloremic metabolic acidosis can be distinguished from persistent DKA due to inadequate insulin treatment by following the anion gap.

Cerebral edema is an uncommon but very serious complication of DKA and HHS treatment, associated with high mortality. For unclear reason, it is seen more commonly in children with DKA. Symptoms of cerebral edema include headache, lethargy, popillary changes, seizures, bradycardia, and cardiac arrest. The underlying mechanisms are not completely understood. Rapid decline in plasma osmolality and brain ischemia have been proposed as contributing mechanisms. Prevention of cerebral edema may be achieved by avoiding overzealous hydration and by maintaining plasma glucose ~200 mg/dL in DKA until the anion gap is closed. Patients should be carefully monitored for changes in mental and neurologic status.

Manitol infusion and mechanical ventilation are suggested for treatment of cerebral edema [28].

Noncardiogenic pulmonary edema can develop in DKA patients from excessive fluid replacement, even in patients without renal or cardiac problems. Pulmonary rales and an increased alveolar-arterial gradient should prompt a decrease in IV fluid rate and initiation of continuous pulse oxymetry.

Prevention

Many cases of DKA and HHS can be prevented by better access to medical care, proper patient education, and effective communication with healthcare provider during an intercurrent illness. Patients and their families should receive education about managing sick days. The use of urine ketone testing or combined home glucose-ketone meters can allow early recognition of impending ketoacidosis and possibly prevent hospitalization for DKA.

One of the most common precipitating factors for hyperglycemic crisis is discontinuation of insulin for economic reasons. This suggests that the current mode of providing health care has significant limitations. Thus, resources need to be directed towards funding better access to medical care and educational programs tailored to individual needs.

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Chapter 3
Hypoglycemia

Philip E. Cryer

Précis

1. Clinical setting—A patient with some combination of neurogenic symptoms (sweating, hunger, tremor, palpitations), neuroglycopenic manifestations (confusion, aberrant behavior, seizure, coma), and signs of sympathoadrenal activation (pallor, diaphoresis) [1, 2].

2. Diagnosis

   (a) Important findings include a history of hypoglycemic or hyperglycemic episodes, a confirmed diagnosis of diabetes, medications used to treat hypoglycemia, alcohol abuse, liver, kidney, and pituitary disease, and a history of bariatric surgery.

   (b) Physical examination—vital signs (tachycardia) mental status (delirium, obtundation) and the "gag" reflex should be assessed.

   (c) Laboratory findings—the key laboratory measurement is a capillary blood plasma glucose of less than 55 mg/dL.

3. Treatment

   (a) In the medical setting (office or hospital): intravenous glucose is the standard initial treatment regardless of cause. An initial dose of 25 g of glucose as an intravenous bolus is recommended [5]. This should be followed by an intravenous infusion of glucose at a rate of 20 mg/kg/min until hypoglycemia is corrected [8]. In sulfonylurea-induced hypoglycemia infusion of the somatostatin analogue octreotide can be used to suppress insulin secretion [9].

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(b) In the home setting, most episodes of hypoglycemia can be treated with oral carbohydrate in the form of glucose tablets, juices, soft drinks, candy, or food. An initial dose of 20 g carbohydrate is recommended. The carbohydrate must be swallowed: Glucose applied to the buccal mucosa is not absorbed [6]. This dose of carbohydrate should be repeated if the plasma glucose is not increased 15–20 min after administration.

(c) If the patient cannot take oral carbohydrate: A subcutaneous or intramuscular injection of 1 mg glucagon is very effective [7]. Because glucagon works by stimulating insulin secretion and glycogenolysis, it will be less effective in type 2 compared to type 1 diabetes and will be ineffective in glycogen-depleted individuals such as the aftermath of an alcoholic binge, or in patients with end stage liver disease.

After successful treatment of an episode of hypoglycemia, measures that will prevent its recurrence are required. An understanding of the pathogenesis of the initial hypoglycemic episode and a rational approach to its treatment are essential components of successful management.

Frequency and Impact of Hypoglycemia

Hypoglycemia is the limiting factor in the glycemic management of diabetes [1]. Iatrogenic hypoglycemia—triggered by treatment with a sulfonylurea, a glinide, or insulin—causes recurrent morbidity in most people with type 1 diabetes and many with advanced type 2 diabetes and is sometimes fatal. Indeed, while early studies indicated that 2–4 % of people with type 1 diabetes die from hypoglycemia [10–12], more recent data indicate hypoglycemic mortality rates of 6 % [13], 7 % [14], and 10 % [15] in type 1 diabetes. Hypoglycemic deaths occur in type 2 diabetes, but the mortality rate is as yet unknown [16, 17]. In addition, hypoglycemia generally precludes maintenance of euglycemia over a lifetime of diabetes and, therefore, full realization of the vascular benefits of glycemic control [18–22]. Lastly, hypoglycemia impairs defenses against subsequent falling plasma glucose concentrations and thus causes a vicious cycle of recurrent hypoglycemia [1].

Most people with type 2 diabetes ultimately require treatment with insulin. The incidence of iatrogenic hypoglycemia in insulin-treated type 2 diabetes is about one third of that in type 1 diabetes [23] but the frequency increases over time [24]. Because type 2 diabetes is about 20-fold more prevalent than type 1 diabetes, most episodes of hypoglycemia, including those of severe hypoglycemia, occur in people with type 2 diabetes.

In contrast, hypoglycemia is an uncommon clinical event in individuals without diabetes [2]. Nonetheless, there is a differential diagnosis of Whipple's triad documented hypoglycemia (Table 3.1). The leading cause of hypoglycemia in such individuals is drugs other than those used to treat diabetes [3, 4]. The latter include alcohol and several drugs that are used commonly and are occasionally associated

Table 3.1 Differential diagnosis of hypoglycemia

Ill or mediated individual
1. Drugs
• Sulfonylurea, glinide, or insulin to treat diabetes
• Alcohol
• Many others [3, 4]
2. Critical Illness
• Renal, hepatic, or cardiac failure
• Sepsis
• Inanition
3. Hormone Deficiency
• Cortisol deficiency
• Growth hormone deficiency
• Glucagon and epinephrine deficiency in insulin-deficient diabetes
4. Nonislet cell tumor
Seemingly Well Individual
5. Endogenous hyperinsulinism
• Insulinoma
• Noninsulinoma pancreatogenous hypoglycemia including post-gastric bypass hypoglycemia
• Autoimmune hypoglycemias—antibody to insulin, antibody to insulin receptor
• Insulin secretagogue
• Others
6. Accidental, surreptitious, or malicious hypoglycemia

Source: From ref [2].

with hypoglycemia. Those include angiotensin converting enzyme inhibitors and angiotensin receptor antagonists, β-adrenergic antagonists, selective serotonin reuptake inhibitors, some anti-arrhythmics (e.g., disopyramide), some quinolone antibiotics, sulfonamides, quinine, and analgesics including salicylates, acetaminophen, and indomethacin among many other drugs [3, 4]. Clearly, intentional, accidental, surreptitious, and even malicious drug use should be considered when the mechanism of hypoglycemic episodes is obscure.

Physiologic and Behavioral Defenses Against Hypoglycemia

The physiologic defenses that normally prevent, or rapidly correct, hypoglycemia are (1) a decrease in pancreatic islet β-cell insulin secretion, (2) an increase in pancreatic islet α-cell glucagon secretion, and absent the latter, (3) an increase in adrenomedullary epinephrine secretion [25] (Fig. 3.1). The behavioral defense is carbohydrate ingestion, prompted by symptoms and the resulting recognition of hypoglycemia [25] (Fig. 3.1).
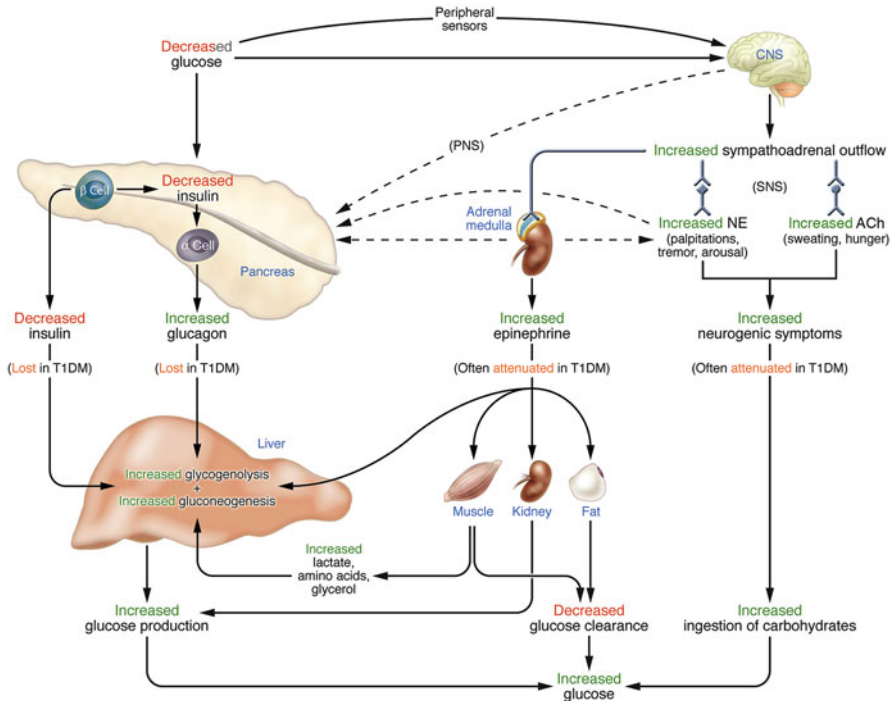
Fig. 3.1 The mechanisms of defense against falling plasma glucose concentrations. *Source*: From Cryer PE. Mechanisms of sympathoadrenal failure and hypoglycemia in diabetes. J Clin Invest 116:1470–1473, 2006 with permission of the American Society for Clinical Investigation

Pathophysiology of Hypoglycemia

Hypoglycemia in diabetes is fundamentally iatrogenic, started by sulfonylurea, glinide, or insulin induced increments in circulating insulin that are independent of the corresponding plasma glucose concentration. However, because of the effectiveness of the normal defenses against falling glucose levels, hypoglycemia rarely results from hyperinsulinemia per se. Rather, hypoglycemia in diabetes is typically the result of the interplay of therapeutic hyperinsulinemia and compromised physiological and behavioral defenses against falling plasma glucose concentrations [1] (Figs. 3.1 and 3.2). In type 1 diabetes, as glucose levels fall, those compromised defenses include (1) loss of the decrease in insulin, the result of β-cell failure, (2) loss of the increase in glucagon, which is also likely the result of β-cell failure since a decrease in β-cell insulin normally signals an increase in glucagon secretion during hypoglycemia [26], and (3) an attenuated increase in sympathoadrenal activity. These abnormalities cause the clinical syndrome of defective glucose counterregulation which is associated with a 25-fold [27] or perhaps greater increased risk of severe

Fig. 3.2 Hypoglycemia-associated autonomic failure in diabetes. *Source*: Modified from Cryer PE. The barrier of hypoglycemia in diabetes. Diabetes 57:3169–3176, 2008 with permission of the American Diabetes Association

hypoglycemia during aggressive therapy of type 1 diabetes [28]. The attenuated sympathoadrenal response, particularly the attenuated sympathetic neural response [29, 30], causes the clinical syndrome of hypoglycemia unawareness (or impaired awareness of hypoglycemia) which is associated with a sixfold [31] or greater [32] increased risk of severe hypoglycemia during aggressive glycemic therapy of diabetes.

The concept of hypoglycemia-associated autonomic failure (HAAF) in diabetes posits that recent antecedent hypoglycemia, as well as sleep and prior exercise, causes both defective glucose counterregulation (by attenuating the epinephrine response to subsequent hypoglycemia in the setting of absent insulin and glucagon responses) and hypoglycemia unawareness (by attenuating the sympathoadrenal, sympathetic neural response to subsequent hypoglycemia). This can lead to a vicious cycle of recurrent hypoglycemia [1, 33]. Perhaps the most compelling support for the clinical relevance of HAAF is the finding, originally in three independent laboratories, that hypoglycemia unawareness, and to some extent the reduced epinephrine component of defective glucose counterregulation, is reversible in most affected patients [34–37].

The pathophysiology of glucose counterregulation is the same in type 2 diabetes and type 1 diabetes except that it develops more slowly as absolute β-cell failure develops more slowly in type 2 diabetes [1, 33, 38]. That explains why iatrogenic hypoglycemia becomes a major problem early in type 1 diabetes but only later in type 2 diabetes.

The pathophysiology leading to hypoglycemia in people without diabetes is as diverse as the differential diagnosis (Table 3.1). The various mechanisms have been reviewed [39].

Risk Factors for Hypoglycemia and Risk Factor Reduction in Diabetes

The conventional risk factors for hypoglycemia (Table 3.2) are based on the premise that relative or absolute insulin excess is the sole determinant of risk [1]. While this is important, aside from insulin or insulin secretagogue doses that are excessive, ill-timed, or of the wrong type, they explain only a minority of episodes of hypoglycemia [40]. The risk factors suggestive of HAAF (Table 3.2) are also relevant.

An approach to hypoglycemia risk factors reduction in diabetes [1, 41] is outlined in Table 3.3.

Table 3.2 Risk factors for hypoglycemia in people with diabetes

Relative or absolute insulin excess (the conventional risk factors):
1. Insulin or insulin secretagogue doses are excessive, ill-timed, or of the wrong type
2. Exogenous glucose delivery is decreased (e.g., after missed meals and during the overnight fast)
3. Endogenous glucose production is decreased (e.g., after alcohol ingestion)
4. Glucose utilization is increased (e.g., during and shortly after exercise)
5. Sensitivity to insulin is increased (e.g., after weight loss or improved glycemic control and in the middle of the night)
6. Insulin clearance is decreased (e.g., with renal failure)

Hypoglycemia-associated autonomic failure:
1. Absolute endogenous insulin deficiency
2. A history of severe hypoglycemia, hypoglycemia unawareness, or both as well as a relationship to recent antecedent hypoglycemia, prior exercise, or sleep.
3. Aggressive glycemic therapy per se (lower A1C levels, lower glycemic goals)

Source: From ref [1].

Table 3.3 Hypoglycemia risk factor reduction in diabetes

Acknowledge the problem

Apply the principles of aggressive glycemic therapy
1. Patient education and empowerment
2. Frequent self-plasma glucose monitoring (or continuous glucose monitoring)
3. Flexible and appropriate insulin (and other drug) regimens
4. Individualized glycemic goals
5. Ongoing professional guidance and support

Consider the conventional risk factors

Consider the risk factors indicative of hypoglycemic-associated autonomic failure

Source: From ref [1].

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Chapter 4
Necrotizing Soft Tissue Infections

J. Stone Doggett and Brian Wong

Précis

Necrotizing soft tissue infections

1. Clinical setting: Up to half of the patients that develop necrotizing soft tissue infections have diabetes mellitus. Diabetics are more likely to present without the usual overt symptoms of necrotizing soft tissue disease.
2. Diagnosis:

    (a) History: Clinical findings include cellulitis that fails to respond to antibiotic treatment, pain out of proportion to the size of the lesion, the appearance of local anesthesia, bullous lesions, crepitus, and inflammation edema beyond the margin of the skin findings. Fever and leucocytosis are almost always present.
    (b) Imaging: Radiologic studies lack the necessary specificity in this disease to be very useful. That said, the preferred test is a non-contrast CT because it can be performed quickly. CT findings include vessel thrombosis, fluid tracking, perifacial air, skin thickening, lymphadenopathy, muscle edema, and fat stranding.
    (c) Management: Once the diagnosis is clear, aggressive surgical debridement and broad spectrum antibiotics must be initiated. Delayed "time to surgery" is consistently associated with increased morbidity and mortality. Without surgery, mortality approaches 100 %. Multiple debridements are usually required.

Empiric antibiotic therapy should cover gram positive, gram negative, and anaerobic bacteria. Empiric antibiotic therapy should include clindamycin with either piperacillin-tazobactam or an antipseudomonal carbapenem. If MRSA is suspected, vancomycin or other antiMRSA antibiotic should be added.

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Necrotizing Soft Tissue Infection

Necrotizing soft tissue infections have been divided into different clinical entities based on the microbiology, location, and degree of tissue involvement. Despite different classifications, all necrotizing soft tissue infections are medical emergencies that require early diagnosis, parenteral antibiotics, and aggressive surgical debridement to achieve optimal outcomes.

The incidence of necrotizing soft tissue infection is estimated to be 0.04 cases per 1,000 person-years in the US. [1]. Diabetics are more susceptible to skin and soft tissue infections in general, and in current studies, up to half of patients who develop necrotizing soft tissue infection have diabetes [2, 3]. Diabetics are also more likely to present without overt symptoms indicative of a necrotizing infection. Because of this, physicians should consider necrotizing soft tissue infection in diabetics who present with skin infection and systemic signs of illness or progressive infection despite antibiotics.

Necrotizing soft tissue infections are comprised of necrotizing cellulitis and necrotizing fasciitis. Necrotizing cellulitis is characterized by gas formation in the skin, sparing the fascia and muscle. Necrotizing fasciitis spreads along the fascial plane and overlying skin involvement may not be apparent. These infections may be mono-microbial or poly-microbial. Mono-microbial infections are most commonly due to *Streptococcus pyogenes* and *Clostridium* species, but *Staphylococcus aureus, Vibrio vulnificus*, anaerobic *Streptococci,* and *Aeromonas* species have been reported with some frequency. Up to half of the patients with poly-microbial necrotizing soft tissue infections have diabetes, whereas there is no clear association with diabetes and mono-microbial infections. An exception to this principle is infection caused by methicillin-resistant *Staphylococcus aureus* (MRSA), where up to one fifth of patients have diabetes.

Necrotizing cellulitis and fasciitis are usually distinguished from one another by surgical exploration. Necrotizing infection may spread from a site of skin injury such as surgical wound, IV drug use, abscess, or in 20 % of cases, no apparent lesion. Specific necrotizing soft tissue infection syndromes are denoted by the anatomic location. These include Fournier's gangrene, which is a necrotizing infection of the perineum, and cervical necrotizing fasciitis, which is located in the cervical area and typically follows odontogenic infection.

Clinical Presentation

Necrotizing fasciitis may be difficult to diagnose in its early stages when there is overlying cellulitis or a lack of distinguishing characteristics. Clinical features that suggest necrotizing fasciitis are failure to respond to antibiotics, pain out of proportion to appearance or anesthesia, signs of systemic illness, or altered mental status. Skin findings include bullous lesions, crepitus, necrosis, ecchymosis, or firm edema beyond the margin of skin findings. Patients typically have lab abnormalities consistent with systemic inflammation.

Diagnosis

Clinical prediction tools using laboratory data or CT findings have been proposed to distinguish between necrotizing and non-necrotizing soft tissue infections. The "laboratory risk indicator for necrotizing fasciitis score" created by Wong et al. assigns points for elevated c-reactive protein, leukocytosis, elevated creatinine, hyperglycemia, hyponatremia, and anemia [4]. Based on this score, patients are divided into low, intermediate, and high risk. In the retrospective validation cohort, 92.9 % of patients with necrotizing fasciitis had an intermediate or high risk score. 91.6 % of patients without necrotizing fasciitis had low risk scores. The authors recommend that patients with soft tissue infections who have intermediate or high risk scores undergo urgent evaluation for necrotizing fasciitis. However, this scoring system has had variable performance in subsequent studies and needs further prospective validation to fully determine its role [5–8].

Radiographic studies lack the sensitivity required to detect necrotizing infection and surgical evaluation should not be delayed for imaging. Of the imaging modalities, non-contrast CT is the most practical when it can be performed quickly. CT findings consist of vessel thrombosis, fluid tracking, perifascial air, skin thickening, lymphadenopathy, abscess, muscle edema, and fat stranding [9].

When evaluating diabetic patients with cellulitis, the signs and symptoms mentioned above should lead to surgical evaluation. If these clinical features are absent, suspicion for necrotizing infection should remain until the patient responds adequately to medical therapy. Currently, definitive diagnosis of necrotizing soft tissue infection requires surgical exploration. Surgical findings include necrotic tissue, lack of bleeding, vascular thrombosis, "dishwater" pus, non-contracting muscle, and a lack of resistance to blunt dissection of the fascial plane (Fig. 4.1) [10]. Tissue gram stain and cultures should be obtained during surgery to distinguish mono-microbial from poly-microbial infection and to detect drug-resistant organisms.

Treatment

Once the diagnosis of a necrotizing soft tissue infection is made, aggressive surgical debridement and broad spectrum antibiotics must be initiated. Delayed time to surgery is consistently associated with increased morbidity and mortality. Mortality approaches 100 % without surgery. After the initial debridement, patients should return to the operating room for further evaluation and may require multiple debridements. There are no clinical studies that have established a superior antibiotic regimen and empiric coverage should be based on the patient's risk for drug-resistant infection and local bacterial drug-resistance patterns. That being said, empiric antibiotic therapy should cover gram positive, gram negative, and anaerobic bacteria. Suggested initial parenteral antibiotics include a beta-lactam antibiotic with a

Fig. 4.1 A diagnostic incision was performed at the bedside in the left flank of a patient with necrotizing fasciitis. Necrotic fat is seen in the incision. The darkened discoloration of the skin is indicative of the loss of blood supply to the skin due to infection causing the thrombosis of blood vessels

beta-lactamase inhibitor such as piperacillin-tazobactam or a carbapenem. The treatment of Fournier's gangrene should always include coverage of *Pseudomonas*. Clindamycin is often added based on in vitro studies that have demonstrated bacterial toxin suppression and mouse-models of *Streptococcus pyogenes* myositis in which clindamycin had greater efficacy than penicillin [11, 12]. The efficacy of clindamycin is also supported by two small retrospective clinical studies that showed improved clinical responses with clindamycin in deep infection and in group A streptococcal necrotizing fasciitis [13, 14]. If MRSA infection is suspected, treatment should include vancomycin or another antiMRSA antibiotic. Once a microbiological diagnosis is made, antibiotics may be tailored for mono-microbial infections, but antibiotic coverage should remain broad for poly-microbial infection because all of the pathogens may not grow in culture. Group A streptococcal infection should be treated with intravenous penicillin G and clindamycin [15]. The great majority of necrotizing infections in diabetics are poly-microbial and require continued broad spectrum antibiotics. Intravenous immunoglobulin and hyperbaric oxygen have been studied as adjunctive therapy but there is no sufficient evidence to support their use.

Summary

Necrotizing soft tissue infections are one of the more common infectious emergencies in diabetics. While there are many distinct forms of necrotizing soft tissue infections, the management is the same. Patients typically present with acute, severe illness, and prominent skin findings. However, a percentage of patients will present with subtle findings that may be difficult to delineate from cellulitis. Laboratory and radiographic scoring systems have been proposed to aid in the diagnosis of necrotizing soft tissue infections, but the role of these systems is evolving. Surgical evaluation remains the definitive means of diagnosis and patients who are suspected of having necrotizing infection should be rapidly evaluated. Aggressive surgical debridement is essential to reduce morbidity and mortality and should be coupled with broad empiric antibiotic therapy. Empiric therapy against MRSA and the addition of clindamycin should be considered. Recent studies have shown improvements in overall mortality to 12 % or less [2, 3, 16]. When diabetics present with soft tissue infection, physicians should consider the possibility of underlying necrotizing infection and pursue surgical evaluation if there are signs of systemic illness, characteristic skin findings, failure to respond to antibiotics, or characteristic radiographic findings.

- Necrotizing soft tissue infection in diabetics is typically poly-microbial.
- Diagnosis of necrotizing soft tissue infection requires a high degree of clinical suspicion and is definitively diagnosed by surgical exploration.
- Necrotizing soft tissue infection should be treated empirically with broad spectrum antibiotics and emergent surgical debridement.

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Chapter 5
Malignant (Necrotizing) Otitis Externa

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Précis

Malignant (Necrotizing) Otitis Externa

1. Clinical Setting: A patient with diabetes mellitus who has ear pain, often severe, and drainage from the external ear canal, often associated with headache or pain in the temperomandibular joint.
2. Diagnosis:

    (a) History: Almost all patients with malignant otitis externa are diabetics. Ear pain and otorrhea occur in 90 % of patients. Systemic signs of infection such as fever and altered mental other state are uncommon. The facial nerve is the most commonly affected, but cranial nerves may be involved as well.
    (b) Imaging: Both CT and MRI are recommended. CT is better at detecting early cortical bone erosion, and MRI is better at detecting medullary changes in bone, and thickening of the Dura.
    (c) Biopsy: Biopsy is required to differentiate infection from malignancy in some cases.

3. Management: After biopsy has been taken, empiric therapy is started with an antibiotic that has anti-pseudomonal and anti-staphylococcal activity. Candidates include cefepime, piperacillin-tazobactam, or an anti-pseudomonal carbapenem. Antibiotics can be narrowed in scope as specific organisms are identified.

Surgical debridement is now reserved for cases in which there are abscesses or bony sequestration. Early surgical consultation for biopsy and to assess the need for debridement is mandatory.

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Malignant (Necrotizing) Otitis Externa

Malignant or necrotizing otitis externa is a rare, invasive infection that begins in the external ear canal and spreads to adjacent tissue. Severe infection may extend to the base of the skull or intra-cranially. Medical knowledge of malignant otitis externa is primarily derived from retrospective case series. The majority of reported patients are elderly diabetics infected with *Pseudomonas aeruginosa*. Patients typically present with otalgia and otorrhea with little evidence of systemic illness. Diagnosis is based on clinical presentation, radiographic imaging with CT or MRI, and tissue histology and culture. Treatment requires prolonged systemic antibiotics and surgery is not required for cure in most cases. Mortality for malignant otitis externa has improved since the disease was first characterized, but a significant number of patients have recurrent disease and require multiple courses of antibiotics. Clinicians should suspect malignant otitis externa in diabetic patients who present with symptoms of otitis externa.

Diabetic Susceptibility

Chandler coined the term "malignant external otitis" in 1968 when he described a series of 13 patients with severe invasive *Pseudomonal* infection originating from the external ear canal [1]. Chandler's series, as well as a review of 262 cases 20 years later, found that 86–100 % of patients had diabetes [2]. However, recent series have described greater variation in rates of diabetes (51–100 %) as the number of malignant otitis externa patients with other immunosuppressive disorders, such as chronic prednisone use, AIDS, and hematologic malignancy, has increased [2–5]. The majority of patients with diabetes are typically close to 70 years old, and poor glycemic control does not appear to be associated with malignant otitis externa [2]. This has led to speculation that increased susceptibility to invasive infection in diabetics is primarily due to diabetic microvascular disease.

Pathogenesis

Trauma and increased moisture in the external ear canal are thought to contribute to infection. Hearing aids and irrigation for cerumen disimpaction have been proposed as sources of trauma or increased moisture [6]. Moist conditions provide a favorable environment for *Pseudomonas*, a gram negative aerobic bacterium that can colonize moist surfaces. Once infection crosses the epithelial surface of the ear canal, it may spread through various paths. Infection typically begins at the osseous-cartilaginous junction and spreads anteriorly inferiorly through the fissures of

Santorini to the mastoid and toward the parotid gland. It may also spread anteriorly to the temporomandibular joint, or medially to the petrous apex of the temporal bone and the jugular foramen [7]. The tympanic membrane and middle ear are typically spared until late in advanced infection. As infection spreads, it may compromise cranial nerves. The facial nerve is the first and most common nerve affected, followed by the vagus and the glossopharyngeal nerves. Rarely, infection may spread intra-cranially causing meningitis or abscess.

P. aeruginosa is the most common pathogen and in early series made up close to 100 % of cases [1, 2]. In recent series, *Pseudomonas* remains the most common pathogen, but makes up a smaller percentage of cultures (27–69 %) [3, 4, 7–10]. *Klebsiella* sp. and *Staphylococcus aureus* have been found in up to 20 % of cultures in several recent studies. *Aspergillus* sp. and *Candida* sp. occur less frequently but a small percentage have been seen in diabetics across multiple studies. A significant percentage of patients have received antibiotics prior to diagnosis and have negative culture results.

Clinical Presentation

Malignant otitis externa is typically a subacute progressive infection and patients often present after several weeks of symptoms, though prodromes of several days are reported. Malignant otitis externa may be difficult to differentiate from otitis externa or otitis media, but the pain is often severe in malignant otitis externa. The most common symptoms, otalgia and otorrhoea, are present in approximately 90 and 75 % of cases, respectively. Pain is often worse at night and severe pain should raise suspicion for deep infection. Pain may include headache or temporomandibular joint pain with palpation or mastication. Erythema or swelling of the external ear and canal may be present. However, many patients present after receiving empiric oral antibiotics for external otitis or otitis media and may not have visible signs of infection. Conductive hearing loss is often present secondary to soft tissue blocking the external canal.

Systemic signs of infection such as fever or altered mentation are uncommon. Granulation tissue on the floor of the external ear canal at the osseo-cartilaginous junction is found in over half of patients. The tympanic membrane and middle ear is typically spared. Twenty to forty percent of patients have cranial nerve palsies. The facial nerve is most frequently involved due to its proximity to the ear canal, but the glossopharyngeal, vagus, and spinal accessory nerve may be affected if infection spreads to the jugular foramen, causing dysphagia, dysphonia, or diminished shoulder elevation. Rarely, the trigeminal, and abducens nerve may be affected when infection spreads to the petrous apex of the temporal bone. Laboratory values are frequently normal with the exception of elevations in erythrocyte sedimentation rate or c-reactive protein [3, 5].

Diagnosis

The diagnosis of malignant otitis externa should be suspected in older diabetic patients who present with otalgia. Diagnostic imaging with CT or MRI should be obtained if there is severe pain, granulation tissue, cranial nerve palsy, or failure to respond to therapy for otitis externa (Fig. 5.1). The diagnosis of malignant external otitis is based on imaging and tissue pathology and culture. Carcinoma of the ear canal can have similar clinical and radiologic findings, and biopsy is required to distinguish infection from malignancy [5]. Various nuclear medicine studies have been used previously, but are problematic for initial diagnosis because they lack sensitivity, specificity, and resolution, compared to CT and MRI. CT or MRI both have advantages as initial radiologic studies. CT is better than MRI at detecting early cortical bone erosion. However, MRI is better at detecting dural enhancement and changes in the medullary space of bones [7]. Overall, MRI is superior in fully defining the extent of infection in difficult cases [11]. As is the case with all forms
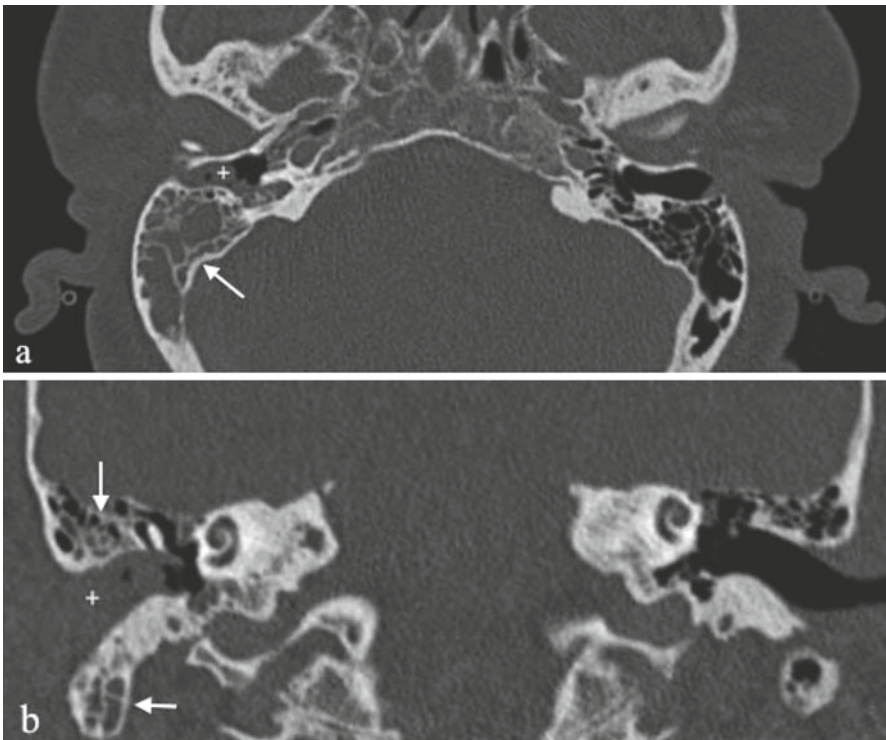
Fig. 5.1 Maxillofacial CT bone images of right-sided malignant otitis externa. Axial (**a**) and coronal (**b**) images show opacification of the right mastoid air cells (*arrows*) and occlusion of the right external auditory canal (+) with minimal involvement of the middle ear

of osteomyelitis, CT and MRI do not provide a reliable means for determining cure of infection and duration of treatment. However, response to therapy is supported by normalization of soft tissue and lack of further spread [6].

Treatment

Malignant otitis externa is best treated with antimicrobial therapy based on tissue culture results. Prior series have demonstrated successful therapy with ciprofloxacin in treating *Pseudomonas* infection and in some instances ciprofloxacin has been used empirically. However, it is important to consider the diversity of pathogens in recent series and the emergence of fluoroquinolone-resistant *Pseudomonas* [4]. These factors make tissue biopsy of greater importance and the choice of empiric antibiotic therapy more complex. After biopsy is obtained, or if the patient presents with severe infection, empiric therapy should be initiated with an agent that has anti-pseudomonal and anti-staphylococcal activity such as cefepime, piperacillin-tazobactam, or a carbapenem. When attempts to culture the pathogen are unsuccessful, empiric antibiotics should be continued and the patient's response to therapy should be followed closely. If a pathogen is cultured then antibiotics should be chosen according to the antimicrobial susceptibilities. In cases of ciprofloxacin-sensitive *Pseudomonas*, oral ciprofloxacin may be used for the full course of therapy. The optimal duration of therapy is unknown, but given the high relapse rate when short courses of antibiotics have been used, the majority of patients should receive at least 6 weeks of culture-guided antibiotics. Topical antibiotics provide no benefit. In the case of *Aspergillus*, the majority of clinical experience in malignant otitis externa is with amphotericin B. However, voriconazole is a newer, orally available drug that is a promising alternative to amphotericin B. Voriconazole has been shown to be superior to amphotericin B in invasive pulmonary aspergillosis, is orally available, and has been used successfully in *Aspergillus* osteomyelitis and malignant otitis externa [12, 13].

Surgical debridement was once standard in all cases but is now reserved for cases in which there are abscesses or there is a need for debridement of granulation tissue or bony sequestration [1, 3]. Response to therapy should be monitored based on normalization of ESR or CRP and resolution of symptoms, appreciating that pain and cranial nerve palsies may resolve slowly. In many cases, cranial nerve palsies may not resolve or only recover partially [4].

Opinions regarding the use of imaging to evaluate response to therapy and resolution vary. Some authors suggest using nuclear medicine scans for diagnosis and monitoring response to therapy while others use CT or MRI. Some authors use gallium 67 isotope scans to determine cure of infection, but cases of recurrence after normal gallium 67 scans have been reported [4, 6, 14]. The other approach commonly used is to follow clinical response combined with ESR or CRP to determine response to treatment. CT or MRI is then repeated several weeks after completion of 4–6 weeks of antibiotics as a baseline study, in case there are later concerns for

recurrence [3, 6, 11, 15]. None of these approaches have been validated in controlled studies of malignant otitis externa, but the latter approach is similar to the general management of osteomyelitis. In cases where the pathogen is not identified and the patient is receiving empiric therapy, imaging should be repeated during antimicrobial therapy to evaluate the initial response with the understanding that bony changes may not show improvement but soft tissue findings should be stable if not improved [11]. Tissue biopsy should be repeated if infection progresses despite treatment.

Prognosis

The mortality from malignant otitis externa has improved from 46 % in Chandler's series in 1968 to 0–24 % in more recent series [2, 3, 5, 8]. Improvements in mortality are likely related to better diagnostic imaging that allows earlier detection and improved anti-pseudomonal antibiotics, particularly ciprofloxacin. Despite improvements in treatment, recurrent infection remains an active concern in managing malignant otitis externa, with 15–20 % of patients developing recurrent infection after completing antibiotics [3]. With this in mind, patients should be monitored after completion of therapy for recurrent symptoms.

Summary

Malignant otitis externa is a potentially devastating infection. Timely diagnosis requires a high degree of clinical suspicion when assessing diabetic patients with otalgia or with symptoms of persistent otitis. Diagnostic imaging with CT or MRI is required to detect invasive infection and to determine the extent of infection. Tissue biopsy for diagnosis and to guide therapy is imperative. Prolonged courses of antibiotics are required to cure infection. There are varying approaches to following response to therapy with imaging, but measuring ESR during therapy and monitoring patients after the completion of antibiotics are key elements of management. Outcomes of malignant otitis externa have improved, but the increasing frequency of drug-resistant bacteria could compromise successful treatment.

- Malignant otitis externa is an invasive infection of soft tissue and bone that begins in the external ear canal.
- Diagnosis is made by CT or magnetic resonance imaging (MRI).
- Treatment of malignant otitis externa consists of prolonged antibiotics that are based on tissue culture. In the case of negative culture, empiric antibiotics should include agents active against *Pseudomonas*.

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Chapter 6
Mucormycosis

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Précis

Mucormycosis

1. Clinical Setting: The patient is usually diabetic with a history of moderate to poor control. A recent history of ketoacidosis is often present. The patient usually complains of rhinorrhea, headache, facial swelling, and pain.

2. Diagnosis: Diabetic patients presenting with the complaint of sinusitus associated with facial swelling, decreased vision, opthalmoplegia, and other cranial nerve palsies associated with signs of infection that include necrosis and/or a black eschar in the nasal cavity or on the palate should prompt an urgent evaluation for mucormycosis.

    (a) Laboratory tests: The diagnosis of mucormycosis depends upon the demonstration of fungal elements in tissues. If the disease is suspected, urgent endoscopic sinus examination and biopsy are mandatory.
    (b) Imaging: The extent of disease should be determined by CT or MRI.

3. Treatment: Prompt and aggressive surgical debridement is essential. This should be in conjunction associated with the administration of Amphotericin B. The lipid formulations are currently preferred because they are less nephrotoxic. The standard initial dose is 5 mg/kg/day given intravenously over a 2 h infusion at 2.5 mg/kg/h. The dose and form of the Amphotericin should be adjusted to optimize treatment as culture results become available.

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Mucormycosis

Most severe infections that disproportionately affect diabetics are caused by common bacterial pathogens. The fungal species in the order Mucorales that cause invasive mucormycosis are an exception. Mucormycosis is a rare infection that often starts in the sinuses of diabetics and may invade the orbit or cerebral structures leading to disfiguring or fatal outcomes. Early diagnosis and treatment are the primary means to limit the morbidity and mortality caused by mucormycosis.

Diabetic Susceptibility

Since the initial description of mucormycosis in 1885, diabetics have made up the largest percentage of patients described in reported cases and case series, but this distribution may be changing. In an extensive literature review of 929 cases, diabetes was the underlying condition in 36 % of patients [1]. Alternatively, mucormycosis also occurs in patients with immunosupression due to bone marrow transplant, solid organ transplant, or hematologic malignancy. A recent prospective study of 230 European cases found that hematologic malignancy was the underlying condition in 41 % of mucomycosis cases and diabetes was present in 9 % [2]. Mucormycosis also occurs in patients who receive iron chelation with desferoxamine, injection drug users, and in patients without an identifiable underlying condition.

Sinus-related infection that may involve the orbit or cerebral structures comprises two thirds of reported cases in diabetics [1]. Rarely, diabetics may develop pulmonary or cutaneous infection. This differs from individuals with hematologic malignancy or transplant, who are more likely to have pulmonary infection, or immunocompetent patients, who most often develop cutaneous infection. In nondiabetic patients, mucormycosis may primarily involve the kidneys or gastrointestinal tract. Mucormycosis occurs in type 1 and type 2 diabetics. Diabetic ketoacidosis and poor glycemic control are frequently documented [3]. However, mucormycosis may also be the initial presentation of diabetes. Unlike other susceptible populations, it is very uncommon for diabetics to develop disseminated mucormycosis. Mucormycosis may present at any age, but average ages of 57 and 39 years have been described in an analysis of incidence based on hospital diagnostic codes and from literature review, respectively [1, 4].

Increased susceptibility to mucormycosis in diabetics is thought to be due to microvascular disease, impaired neutrophil function, and the increased availability of iron. The fungi that cause mucormycosis rely on iron chelators and iron permeases to obtain iron from the host. Diabetic ketoacidosis decreases the capacity of transferrin to bind iron, which increases the amount of iron that is available to fungi. Experiments have shown that *Rhizopus oryzae* growth is enhanced in the sera of patients with diabetic ketoacidosis. Similarly, growth is enhanced in nondiabetic sera when it is supplemented with iron and the pH is less than 7.4 [5]. The importance of

iron is also supported by experiments that show reductions in expression of the *R. oryzae* high affinity iron permease gene led to reduction in the virulence of *R. oryzae* in mice with diabetic ketoacidosis [6].

Pathogenesis and Microbiology

There are multiple pathogenic genera of the order Mucorales that cause mucormycosis. The most commonly reported are *Rhizopus, Mucor, Cunninghamella, Apophysomyces,* and *Absidia* [1]. *Rhizopus* species are the most frequent causes of sinus-related disease, whereas *Cunninghamella* is more often found in pulmonary disease [1]. These organisms are readily found in the soil and on decaying plant matter. Spores may be inhaled or introduced through skin trauma. Humans are frequently exposed to these fungi, but very rarely develop infection. Calculations of incidence have varied from 0.43 to 1.7 cases per 1,000,000 people [4]. Although a significant percentage of cases have been reported in patients with no underlying condition, the majority of these reports were of cutaneous infection due to trauma. In diabetics, ketoacidosis contributes to susceptibility to infection by altering cellular immunity [7]. Once infection begins in the nasal turbinates or in alveoli, fungal hyphae invade vasculature causing thrombosis and tissue infarction. Invasive sinus infection then may spread to the face, to the orbit, or to the cerebrum. Intracranial extension may cause cavernous or sagittal sinus thrombosis, epidural, and subdural abscesses, but meningitis is very rare.

Clinical Presentation

After mucormycosis develops in the nasal passages or sinuses, it usually progresses rapidly and often is advanced before infection is detected. Patients may present with rhinosinusitis, facial swelling or erythema, or with orbital or cerebral involvement (Figs. 6.1 and 6.2). Despite the severity of disease, patients may have minimal evidence of infection. In a literature review of 114 patients with sinus-related mucormycosis, there were few consistent overt clinical findings within the first 72 h of presentation: fever (44 %), nasal ulceration or necrosis (38 %), periorbital or facial swelling (34 %), decreased vision (30 %), ophthalmoplegia (29 %), sinusitis (26 %), headache (25 %), facial pain (22 %), decreased mental status (22 %), and increased white blood cell count (19 %) [8]. Evidence of invasive disease includes necrosis or eschar of the nasal cavity, face or palate, trigeminal or facial nerve palsies, diplopia, ophthalmoplegia, periorbital edema, proptosis, loss of vision, or decreased level of consciousness. These findings in a diabetic patient with poor glycemic control should prompt an urgent evaluation for mucormycosis.

Fig. 6.1 A 49-year-old man with diabetic ketoacidosis had rhino-orbital-cerebral mucormycosis, which was characterized by left-sided facial swelling and erythema, left-sided opthalmoplegia, and left-sided facial numbness

Fig. 6.2 Axial T1 MRI images of the patient in figure (**a**) show low signal edema in the premaxillary soft tissues, extending laterally (*arrow*) and near complete opacification of the left maxillary sinus (+), and (**b**) left periorbital soft tissue thickening (*arrow*) as well as left orbital proptosis
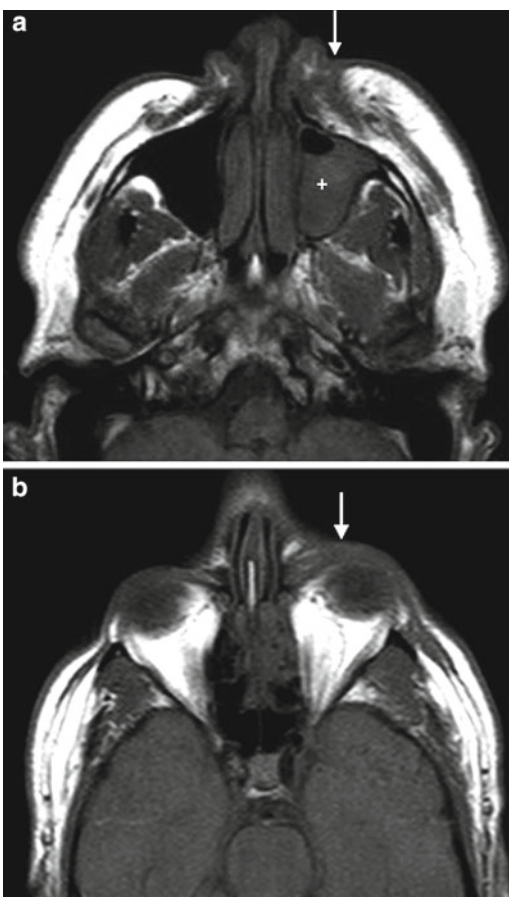
Diagnosis

Diagnosing mucormycosis before extensive tissue destruction occurs requires a high degree of suspicion. Physicians should consider this diagnosis in patients with diabetic ketoacidosis and the above-mentioned features. However, it is noteworthy that mucormycosis occurs in diabetics without acidosis. The diagnosis of sinus-related mucormycosis relies on identification of fungal elements in the tissue. Early identification may be achieved by performing a potassium hydroxide preparation and microscopy on tissue scrapings of mucosal ulcers. If mucormycosis is suspected, the diagnosis should be pursued through urgent endoscopic sinus examination and tissue biopsy. The characteristic histologic appearance of mucormycosis is broad hyphae that do not have septae and branch at right angles (Fig. 6.3). Tissue should be cultured for definitive identification, but culture may not be successful and the diagnosis may rely on histology. The extent of disease should be determined with CT or MRI.

Treatment

The treatment of mucormycosis requires prompt aggressive surgical debridement and treatment with amphotericin B deoxycholate or with a lipid formulation of amphotericin B [8, 9]. Although there are few studies that compare amphotericin B deoxycholate to lipid preparations of amphotericin B, the majority of practitioners with access to lipid preparations prefer to use them out of concern for renal toxicity. Posaconazole is an oral antifungal agent that has been shown to be clinically effective in a retrospective study of salvage therapy and may be used in patients who do not tolerate amphotericin B and as step-down therapy [10]. Echinocandins are sometimes used in combination with lipid preparations of amphotericin B based on
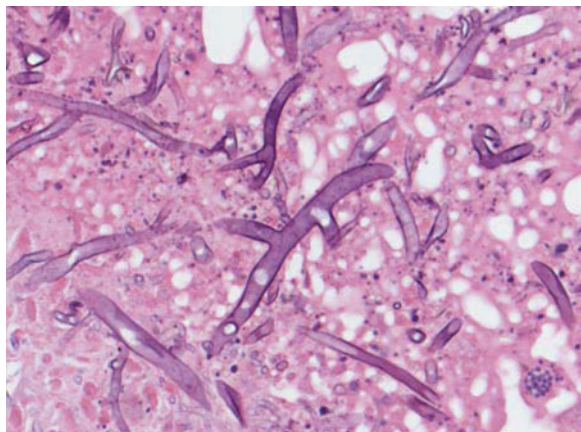
Fig. 6.3 Periodic acid-Schiff stain of mucormycosis at 400× that shows broad nonseptate hyphae that branch at wide angles

improved outcomes in a retrospective study that compared six patients who received caspofungin in addition to amphotericin B lipid complex (5/6) or liposomal amphotericin B (1/6) to 31 patients who received amphotericin B or lipid formulations of amphotericin B alone [11]. Further studies are necessary to demonstrate the utility of adjunctive echinocandin therapy before its use can be routinely recommended. Timely intervention is essential and has been shown to decrease mortality and morbidity [8, 9, 12]. Acidosis, hyperglycemia, and immunosuppression should be corrected. Surgery is often disfiguring and multiple surgeries may be required.

Mortality

Despite improvements in the diagnosis and management of mucormycosis, overall mortality remains high at 47 % [1, 2]. Although still high, mortality in diabetics is closer to 23 % [8]. This is likely due to less severe immunosuppression conferred by diabetes and the greater percentage of sinus-related mucormycosis among diabetics.

Summary

Mucormycosis is a devastating infection in diabetics that has high mortality and requires prolonged treatment with amphotericin B and surgery. The majority of mucormycosis in diabetics is sinus-related disease that may spread to contiguous structures including the face, orbit, and cerebrum. Early diagnosis of mucormycosis is challenging because patients often present with subtle findings. Clinicians should have a high degree of suspicion in patients who present with diabetic ketoacidosis or poorly controlled diabetes and have findings suggestive of disease that involves the sinus, eyes, face, cranial nerves, or altered mental status. Diagnosis is made from tissue scrapings of lesions, tissue biopsy, endoscopic examination, fungal culture, and characteristic tissue histology. Tissue culture is definitive, but often does not grow. Urgent intervention with antibiotics and surgery improves clinical outcomes, but despite appropriate therapy a significant number of patients will die or be disfigured.

- Mucormycosis, in diabetics, typically involves the sinuses and may spread to the orbit or brain.
- Diagnosis is made by demonstrating fungal elements of one of the Mucorales fungi on tissue scraping or tissue biopsy.
- Treatment of mucormycosis consists of aggressive surgical debridement and amphotericin B.

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Chapter 7
Emphysematous Cholecystitis

J. Stone Doggett and Brian Wong

Précis

Emphysematous cholecystitis

1. Clinical setting: The clinical picture of cholecystitis in a diabetic patient, usually a male, usually over 50 years of age. Two thirds of the patients have gallstones compared to 90 % in typical cholecystitis: crepitus of the abdominal wall over the gallbladder can occur. The most common symptoms are right upper quadrant pain, nausea, and vomiting. Fever is the rule.
2. Diagnosis: All diabetic patients with a problematic or confirmed diagnosis of choleocystitis must be suspected of having emphysematous disease.

    (a) History: The severity of the diabetes, history of control, presence or absence of diabetic complications do not influence the probability of this condition in a diabetic patient.
    (b) Imaging: The diagnosis of emphysematous cholecystitis is made radiographically or at the time of surgery. Gas in the gallbladder wall, lumen, or pericholecystic space can be seen on plain film and ulstrasonography. CT, however, is the test of choice in this setting.

3. Management: The recommended approach is parenteral antibiotics with surgical intervention within 48–72 h.

   Empiric antibiotic therapy should be initiated with ampicillin-sulbactam or piperacillin-tazobactam.

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Emphysematous Cholecystitis

Emphysematous cholecystitis is a rare, severe form of acute cholecystitis in which infection leads to gas formation in the gallbladder wall or pericholecystic space. The risk of gallbladder perforation in emphysematous cholecystitis is up to five times that of ordinary acute cholecystitis [1]. Timely recognition and treatment are crucial, and clinicians should be aware that ultrasound may fail to detect gas formation. Patients who develop emphysematous cholecystitis differ from typical cholecystitis patients as well: 38–50 % are diabetics, males outnumber females 2:1, and the majority are 50–70 years old [2, 3]. It is thought that these patients have vascular disease and that the distinct characteristics of emphysematous cholecystitis result from vascular occlusion and ischemia.

Pathogenesis and Microbiology

The bacterial pathogens and gallbladder pathology found in emphysematous cholecystitis differs from typical cholecystitis. Gallstones are found in 40–70 % of patients with emphysematous cholecystitis, as opposed to 90 % of typical cholecystitis cases, and the anaerobic bacterium *Clostridium perfringens* is the most frequently reported pathogen [1–4]. In a review of 109 cases, *Clostridium* species made up 46 % of positive cultures and *E. coli* was present in 33 %, often with *Clostridia. Klebsiella, Bacteroides, Staphylococcus, Streptococcus, Pseudomonas,* and *Salmonella* have also been reported [1–4]. Examinations of gallbladder pathology frequently reveal occlusion of the cystic artery or pericholecystic abscess [1, 5].

Clinical Presentation

The clinical presentation of emphysematous cholecystitis is very similar to typical acute cholecystitis. However, crepitus in the abdominal wall over the gall bladder may rarely be detected and should raise suspicion for emphysematous infection. Otherwise, patients typically complain of right upper quadrant pain and fever. Close to half of patients report nausea and vomiting.

Diagnosis

The diagnosis of emphysematous cholecystitis is made radiographically or at the time of surgery. The first preoperative diagnosis of emphysematous cholecystitis, made in 1931 by Hegner, led to recognition of emphysematous cholecystitis as a distinct clinical entity [2]. Gas in the gallbladder lumen, wall, or pericholecystic space may be seen on plain films, ultrasound, or CT (Figs. 7.1 and 7.2). CT is the most sensitive and specific imaging modality. Ultrasonography may demonstrate

Fig. 7.1 Non-contrast axial CT image demonstrating a thick-walled gallbladder prolapsing into a large abdominal wall hernia. There is pericholecystic inflammation and three small locules of gas in the wall

Fig. 7.2 Abdominal radiograph demonstrating mottled gas outlining the wall of the gallbladder as well as lucency within the gallbladder lumen also representing gas
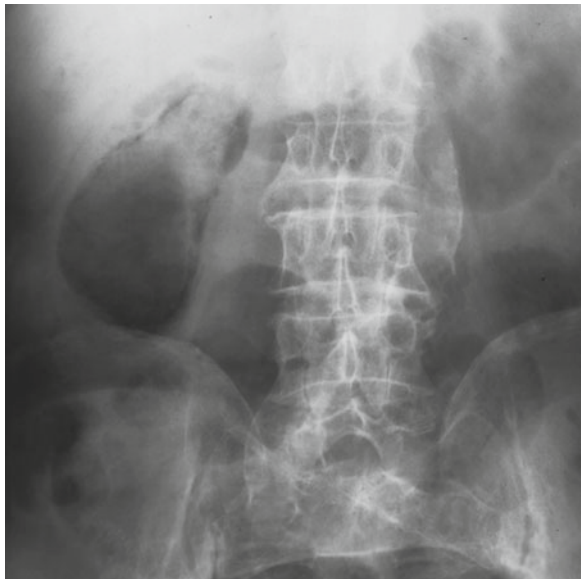
highly echogenic reflections with posterior shadowing and reverberation artifact from the gallbladder wall or lumen. The champagne sign or effervescent gallbladder is a more specific finding in which bubbles rise up from the dependent portions of the gallbladder lumen, like bubbles in a flute of champagne [6]. Given that ultrasound is a frequently used modality to evaluate patients for cholecystits, it is important to note that it misses a significant number of cases of emphysematous

cholecystitis and may be misinterpreted due to bowel gas [7, 8]. In fact, inability to visualize the gallbladder with ultrasound may be due to emphysematous infection. When the gallbladder is not seen or poorly visualized and there is suspicion for cholecystitis, CT is indicated.

Treatment

Traditionally, the recommended approach has been parenteral antibiotics and surgical intervention within 48–72 h. Emphysematous cholecystitis may progress rapidly, as illustrated in a report of a patient who developed radiographic findings of emphysematous cholecystitis within 24 h after a normal CT [9]. This is consistent with older reports of patients with gangrene and perforation who presented with fewer than 72 h of symptoms [1]. In contrast, some authors have argued that the use of CT has led to increased detection of a milder spectrum of disease. These authors report several patients who did well after delaying surgical intervention for 2–4 weeks, suggesting that delayed surgical intervention has a role in the management of emphysematous cholecystitis [7]. While there may be a subset of patients that do not require urgent surgery, the majority of the literature supports cholecystectomy within 48–72 h. When surgery is contraindicated, percutaneous drainage with cholecystostomy tubes can be used. There is limited literature to determine whether open or laparoscopic cholecystectomy is superior. However, a recent small series has shown equivalent results with laparoscopic cholecystectomy [10].

Prognosis

Heightened awareness and timely diagnosis of emphysematous cholecystitis are important because of the need for urgent surgical evaluation. The mortality of emphysematous cholecystitis was 15 % compared to 4 % of acute cholecystits in a large series in 1975 [1]. A more recent series in 1999 found a mortality rate of 25 % in emphysematous cholecystitis [4]. Increased mortality is related to higher rates of perforation or complicated infection. In a review of 20 patients with emphysematous cholecystitis, seven patients had gallbladder perforation, nine had pericholecystic abscess, and three had bile peritonitis [4].

Summary

Emphysematous cholecystitis is a distinct form of cholecystitis that should be considered in diabetics who present with symptoms of typical cholecystitis. Emphysematous cholecystitis carries a greater risk of complication. The increased

rates of complications are thought to be related to vascular occlusion and gallbladder ischemia. Treatment consists of parenteral antibiotics and cholecystectomy within 48–72 h.

- Emphysematous cholecystitis may progress more quickly than typical cholecystitis and has higher rates of complication.
- CT is the preferred diagnostic test for emphysematous cholecystitis.
- Treatment of emphysematous cholecystitis consists of parenteral antibiotics and cholecystectomy within 48–72 h.

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Chapter 8
Emphysematous Pyelonephritis

Brian Wong and J. Stone Doggett

Précis

Emphysematous Pyelonephritis

1. Clinical setting: The picture of pyelonephritis in a diabetic patient. The typical picture is fever, flank or abdominal pain, nausea, and vomiting. The commonest pathogens are *E. coli* (67 %) and *Klebsiella* sp. (20 %).
2. Diagnosis: All diabetic patients with the probable or confirmed diagnosis of pyelonephritis must be suspected of having emphysematous disease.

    (a) History—The severity of diabetes complications, the degree of control, and the duration of diabetes do not exclude the possibility of emphysematous disease.
    (b) Imaging—Emphysematous pyelonephritis is diagnosed by abdominal CT or MR scan. Abdominal CT is the test of choice. Detection of gas in the parenchyma, collecting system, or perirenal space confirms the diagnosis.

3. Management: Initial management consists of prompt antibiotic treatment that will cover the multitude of organisms that are associated with emphysematous pyelonephritis. Second, a surgical consultation is essential. Some patients recover without surgical drainage or nephrectomy, but most do not. Surgical intervention is very likely, and it should be early rather than late.

    A typical antibiotic regimen for the disorder is:
    Empiric antibiotic therapy should be initiated with ampicillin-sulbactam or piperacillin-tazobactam, but the choice of antibiotic should ultimately be guided by

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local patterns of antimicrobial resistance and the patients' previous antibiotic exposure. Antibiotic therapy subsequently should be modified based on urine and blood cultures. Drainage should be assessed with imaging and multiple drainage procedures may be required. Patients who fail to respond should undergo nephrectomy.

Infectious Emergencies in Diabetics

Emphysematous Pyelonephritis

Emphysematous pyelonephritis is a rare form of pyelonephritis that occurs more commonly in diabetics than in nondiabetics and requires urgent surgical intervention with percutaneous drainage or nephrectomy. This severe infection occurs predominately in diabetics and other individuals with urinary obstruction due to strictures, calculi, or neoplasm. The underlying pathology that puts diabetic patients at increased risk for emphysematous infection is not known.

Diabetic women have an increased prevalence of bacteriuria and urinary tract infections compared to nondiabetic women. The prevalence of bacteriuria in diabetic women is 9–27 % and increases with duration of diabetes. It is not related to glycemic control [1]. Although diabetic women with asymptomatic bacteriuria are not more likely to progress to urinary tract infection than those without bacteriuria, diabetic patients are diagnosed with urinary tract infections more frequently than nondiabetic patients [2]. Two large studies found that diabetics had increased rates of urinary tract infections. In a prospective cohort of 7,417 patients with type 1 and type 2 diabetes, the adjusted odds ratio for infection was 1.96 and 1.24, respectively [3]. Similarly, a retrospective cohort study of 513,749 diabetics found that risk ratios for hospitalization for cystitis and pyelonephritis were 1.39 and 1.95, respectively, for diabetic patients compared to nondiabetic patients [3].

The incidence of bacteriuria is directly related to the duration of diabetes. Since cellular immune defects have not been demonstrated in diabetics with urinary tract infections, it is thought that the increased prevalence of bacteriuria is related to autonomic neuropathy and urinary stasis [4]. This, as well as the increased incidence of urinary tract infections among diabetics, likely contributes to diabetic susceptibility to emphysematous pyelonephritis.

Diabetic Susceptibility

More than 90 % of patients with emphysematous pyelonephritis and 70 % of patients with emphysematous cystitis have diabetes [5, 6]. The majority of diabetics with emphysematous pyelonephritis have poorly controlled diabetes. In one study, 76 % of patients had hemoglobin A1c values greater than 7 %, and in a separate study, 72 % of patients had hemoglobin A1c values greater than 8 % [6, 7]. While these two series indicate the importance of glycemic control, they also demonstrate that

diabetics with well-controlled diabetes can develop emphysematous infection. The majority of nondiabetic patients have urinary obstruction. Women outnumber men 4:1, and the majority of patients are over 60 years old with a range of 24–83 [5].

Clinical Presentation

The clinical presentation of emphysematous disease is indistinguishable from severe pyelonephritis; fever (79 %), flank pain or abdominal pain (71 %), and nausea and vomiting (17 %) [6]. Symptoms are usually acute, but can develop over several weeks. The two most common pathogens are *Escherichia coli* (67 %) or *Klebsiella* (20 %) [5]. Other microbial species that have been reported infrequently are *Proteus*, *Pseudomonas*, *Enterobacter*, *Enterococcus, Staphylococcus, Clostridium, Pneumocystis, Candida,* and *Cryptococcus* [8, 9]. Bacteremia occurs in 26–54 % of patients [6, 7]. The severity of the illness does not distinguish emphysematous pyelonephritis from typical pyelonephritis. A recent case series describes a frequency of signs of severe illness in emphysematous pyelonephritis that is consistent with older studies: hypotension (systolic blood pressure less than 90 mmHg) 28 %, altered mental status 18 %, leukocytosis (more than 14,000/μL) 46 %, thrombocytopenia (less than 40,000/μL) 31 %, and serum creatinine more than 2.5 mg/dL 46 % [6, 7].

Diagnosis

The evidence regarding the importance of diagnosing emphysematous infection is limited to retrospective case series and is not definitive. However, emphysematous pyelonephritis should be considered in diabetic patients who present with symptoms of pyelonephritis. Suspicion should be heightened if there is not a response to medical therapy within the first 24 h. Diagnosis of emphysematous pyelonephritis requires the demonstration of gas on abdominal imaging. Abdominal ultrasound, X-ray, or CT can detect gas in the renal or perirenal tissue, but CT is the preferred initial imaging study (Fig. 8.1) [10]. In a systematic review of 210 cases, ultrasound and plain radiography were diagnostic in only 69 and 65 % of cases, respectively, compared to CT [5]. Beyond the detection of gas, CT can sometimes identify the site of obstruction, the extent of infection, and prognostic findings.

Radiographic Classification

Several radiologic classification systems have been proposed for the prognosis and management of emphysematous pyelonephritis [6, 11, 12]. The two that are currently used are based on CT findings and have been retrospectively evaluated in subsequent studies. The classification system proposed by Wan et al. divides radiographic findings into two types. Images that show parenchymal destruction with
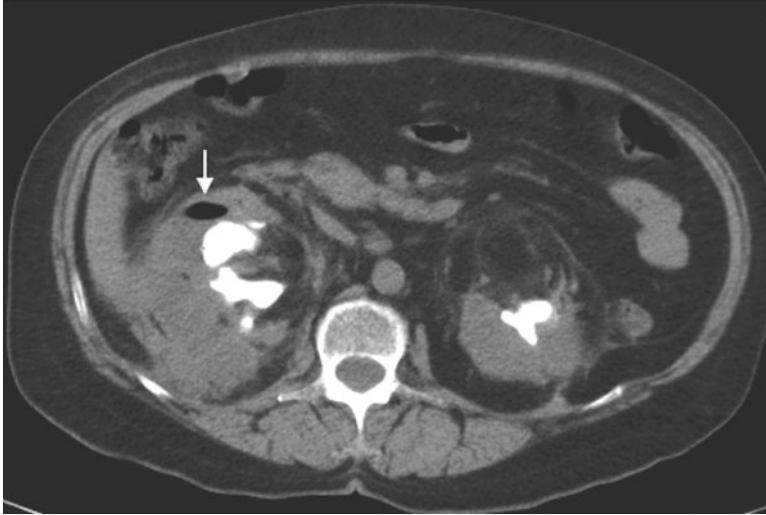
Fig. 8.1 Non-contrast axial CT image demonstrating gas in the right renal parenchyma (*arrow*), bilateral staghorn calculi, and perinephric inflammation

either the absence of fluid collection or the presence of streaky or mottled gas are classified as Type I. Type II is characterized by renal or perirenal fluid collections with bubbly or loculated gas, or gas in the collecting system. Type I is associated with necrosis or hemorrhagic infarction and greater mortality [11, 13]. The system developed by Huang and Tseng divides images into five categories based on the involvement of gas in the collecting system (class 1), renal parenchyma (class 2), extension of gas or abscess into the perinephric space (class 3a), extension beyond the perinephric space (class 3b) or involvement of both kidneys, or a solitary kidney (class 4). Despite inconsistencies between the original study and a subsequent study that evaluated this method of classification retrospectively, it can be concluded that patients with class 1 findings do well with antibiotics and percutaneous drainage and rarely require nephrectomy. Patients with findings of classes 2, 3, or 4 are more likely to fail management with percutaneous drainage and antibiotics and are more likely to undergo nephrectomy. They have a higher mortality. Mortality and progression to nephrectomy in these classes is increased when there is more than one risk factor present (i.e., altered mental status, hypotension, thrombocytopenia, acute kidney injury) or parenchymal destruction of greater than 50 % [6, 7].

Treatment

The optimal management of emphysematous pyelonephritis requires early recognition, parenteral antibiotics, and prompt surgical intervention based on the extent of infection or the presence of obstruction. Studies have suggested that patients treated

with antibiotics alone or urgent nephrectomy have higher mortality [5]. However, these studies are limited in that they are retrospective and do not account for severity of illness. The current literature supports a management strategy of supportive care, antibiotic therapy, early percutaneous drainage, and correction of any underlying urinary obstruction. Empiric antibiotic therapy should be initiated with ampicillin-sulbactam or piperacillin-tazobactam, but the choice of antibiotic should ultimately be guided by local patterns of antimicrobial resistance and the patient's previous antibiotic exposure. Antibiotic therapy should subsequently be modified based on urine and blood cultures. Drainage should be assessed with imaging and multiple drainage procedures may be required. Patients who fail to improve significantly should undergo nephrectomy [7, 9].

Prognosis

Mortality rates of up to 78 % were reported until the late 1970s [9]. In contrast, a recent series of 39 patients found a mortality rate of 13 % with a kidney salvage rate of 67 % [7]. Changes in reported mortality are likely due to increased detection of less severe infection with CT and earlier diagnosis and intervention. The preferred approach has shifted from urgent nephrectomy to that of percutaneous drainage, reserving nephrectomy for patients who do not improve clinically. Signs of poor prognosis that have been seen in multiple studies include the pattern or degree of gas formation on CT, infection of both kidneys, altered mental status, thrombocytopenia, acute kidney injury, and hypotension [6, 11–13]. Poorly controlled diabetes, age, and bacteremia were not associated with mortality [13].

Summary

Emphysematous pyelonephritis is a severe form of pyelonephritis that is found more frequently in diabetics and individuals with urinary tract obstruction. The majority of patients have poorly controlled diabetes, but a significant percentage of patients have well-controlled diabetes. The clinical presentation is similar to typical pyelonephritis and abdominal imaging is required to diagnose emphysematous infection. CT scan is the preferred diagnostic imaging modality due to its capacity to detect gas and urinary obstruction. CT may also provide prognostic information by itself or in conjunction with clinical signs of severe illness. Treatment for emphysematous pyelonephritis consists of prompt antibiotics, correction of obstruction if present, and percutaneous drainage. In some cases of extensive infection, nephrectomy is necessary.

- Emphysematous pyelonephritis is clinically similar to typical pyelonephritis and should be suspected in diabetics who do not respond quickly to therapy.

- Computerized tomography (CT) is the preferred diagnostic test for emphysematous pyelonephritis.
- Successful treatment often requires percutaneous drainage or nephrectomy in addition to parenteral antibiotics.

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Chapter 9
Thyrotoxic Crisis: Thyroid Storm

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Pathogenesis

The pathogenesis of thyroid storm is still not fully understood as there is usually no difference in thyroid hormone levels between patients with "uncomplicated" thyrotoxicosis and those undergoing a thyrotoxic crisis [1, 2].

One hypothesis that may explain the pathogenesis of thyroid storm is a possible increase in target cell β (beta)-adrenergic receptor density or post-receptor modifications in signaling pathways [3–5] leading to an increased sensitivity to catecholamines.

Another theory to explain the cause of thyroid storm is an increase in the amount of free thyroid hormones. In one study comparing six subjects with thyroid storm to fifteen subjects with more typical thyrotoxicosis, Brooks and colleagues [6] found that the mean free thyroxine (FT4) concentration was higher in subjects with thyroid storm, whereas the total thyroxine (TT4) concentration was similar in both groups.

Etiology (See Table 9.1)

Graves' disease remains the most common cause of thyrotoxic crisis/thyroid storm. Graves' disease is mediated by the thyrotropin (TSH) receptor antibodies that stimulate excess and uncontrolled synthesis and secretion of thyroid hormones (thyroxine

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Table 9.1 Etiology of thyrotoxicosis

Thyrotoxicosis with a normal or high radioiodine uptake[a]
Autoimmune thyroid disease (AITD)
Graves' disease (GD)
Hashitoxicosis
Autonomous thyroid tissue
Toxic adenoma (TA)
Toxic multinodular goiter (TMNG)
TSH-mediated
TSH producing pituitary adenoma
Non-neoplastic TSH-mediated hyperthyroidism
Human chorionic gonadotropin-mediated
Hyperemesis gravidarum
Trophoblastic disease
Resistance to thyroid hormone (T3 receptor mutation)[b]
Thyrotoxicosis with a decreased or near-absent radioiodine uptake
Thyroiditis
Painless (silent, lymphocytic) thyroiditis
Subacute (de Quervain's, granulomatous) thyroiditis
Acute thyroiditis
Amiodarone-induced thyroiditis
Radiation thyroiditis
Palpation thyroiditis
Exogenous thyroid hormone intake
Iatrogenic thyrotoxicosis
Factitious ingestion of thyroid hormone
Intentional suppressive therapy
Ectopic hyperthyroidism
Struma ovarii
Extensive metastasis from follicular thyroid carcinoma

[a]Uptake may be low if recent iodine load caused iodine-induced thyrotoxicosis

[b]Patients may not be hyperthyroid

Source: Adapted from: Bahn R, Burch H, Cooper D, et al. Hyperthyroidism and Other Causes of Thyrotoxicosis: Management Guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Thyroid 2011; 21(6): 593–646 [73]

(T4) or triiodothyronine (T3)). It is more frequent in young women, but can occur in both genders and any age group.

Thyroid storm can also occur with a solitary toxic adenoma or toxic multinodular goiter. Rare causes of thyrotoxicosis that can lead to thyroid storm include: hypersecretory thyroid carcinoma (specially follicular thyroid carcinoma), thyrotropin-secreting pituitary adenoma, struma ovarii/teratoma, and human chorionic gonadotropin–secreting hydatidiform mole. It is very rare for ingestion of excess exogenous T4 and/or T3 to be associated with thyroid storm.

Other causes include certain medications: Interferon α(alpha) (IFN-α) and interleukin-2 (IL-2) can cause thyrotoxicosis (via destructive thyroiditis) during treatment for viral hepatitis and HIV infection [7–10]. Of relevance is hyperthyroidism aggravated by iodine exposure, which can occur following the intravenous administration of radiocontrast dye, or during or after amiodarone administration. Amiodarone contains 70–75 mg iodine per 200 mg tablet, and about 10 % of it (7–7.5 mg) is released as free iodide during amiodarone metabolism (about a 35 to 50-fold increase when compared with the recommended optimal intake of 0.15–0.20 mg) [11].

A precipitating event usually causes the transition from thyrotoxicosis to thyroid storm. Triggering events include systemic insults such as surgery, trauma, myocardial infarction, pulmonary thromboembolism, diabetic ketoacidosis, parturition, or severe infection [7]. Thyroid storm has also been reported to be precipitated by the discontinuation of antithyroid drugs, excessive ingestion or intravenous administration of iodine (e.g., amiodarone, radiocontrast dyes), radioiodine therapy, and even pseudoephedrine and salicylate use (salicylates may increase free thyroid hormone levels disproportionately) [12].

The most common precipitating cause of thyroid storm currently seems to be infection, although it is difficult to know if published reports mirror actual frequencies [13]. In our experience, discontinuation of antithyroidal medications is a common denominator in patients with severe thyrotoxicosis and thyroid storm.

Clinical Presentation

Thyroid storm is part of a continuum that begins with the development of decompensated thyrotoxicosis. The point at which thyrotoxicosis transforms to thyroid storm is not clear and is relatively subjective. In an effort to standardize and objectify thyroid storm, as compared with severe thyrotoxicosis, Burch and Wartofsky [3] have delineated a point system assessing degrees of dysfunction in various organ systems (see Table 9.2). Although this classification is helpful clinically, it is prudent, in most circumstances, to assume that someone with severe thyrotoxicosis has impending thyroid storm, and to treat them aggressively, rather than focus on specific definitions.

Table 9.3 summarizes the clinical manifestations of thyrotoxicosis.

Older individuals may not manifest the typical symptoms of thyrotoxicosis. They may present with "apathetic" thyrotoxicosis, with symptoms including weight loss, palpitations, weakness, dizziness, syncope, or memory loss, and physical findings of sinus tachycardia or atrial fibrillation [14].

Diagnosis

The distinction between severe thyrotoxicosis and life-threatening thyrotoxicosis or thyroid storm is a matter of clinical judgment. Objective means such as the point scale by Burch and Wartofsky (Table 9.2) can, and perhaps should, be used.

Table 9.2 Point scale criteria for the diagnosis of thyroid storm

Criteria	Points
Thermoregulatory dysfunction	
Temperature (°F)/(°C)	
99.0–99.9/37.2–37.7	5
100.0–100.9/37.8–38.2	10
101.0–101.9/38.3–38.8	15
102.0–102.9/38.9–39.4	20
103.0–103.9/39.5–39.9	25
≥104.0/≥40.0	30
Cardiovascular	
Tachycardia (beats/min)	
100–109	5
110–119	10
120–129	15
130–139	20
≥140	25
Atrial fibrillation	
Absent	0
Present	10
Congestive heart failure	
Absent	0
Mild (pedal edema)	5
Moderate (bibasilar rales)	10
Severe (pulmonary edema)	20
Gastrointestinal-hepatic dysfunction	
Absent	0
Moderate (diarrhea, abdominal pain, nausea/vomit)	10
Severe (unexplained jaundice)	20
Central nervous system disturbance	
Absent	0
Mild (agitation)	10
Moderate (delirium, psychosis, extreme lethargy)	20
Severe (seizure, coma)	30
Precipitating history	
Absent	0
Present	10

Total score: ≥45: thyroid storm, 25–44: impending thyroid storm, <25: unlikely thyroid storm

Source: Adapted from: Burch HB, Wartofsky L. Life-threatening thyrotoxicosis. Thyroid storm. Endocrinol Metab Clin North Am 1993;22:263–77 [3]

However, it is most prudent to treat a patient suspected of having thyroid storm aggressively for his/her hyperthyroidism/thyrotoxicosis, rather than excessively investigate whether this case really meets the criteria for thyroid storm. These patients require close clinical monitoring usually in an intensive care unit.

There is no arbitrary serum T4 or T3 cutoff that discriminates severe thyrotoxicosis from thyroid storm. Brooks et al. found no significant difference in the levels

Table 9.3 Clinical manifestations of thyrotoxicosis

Constitutional [14]

Weight loss, despite having the same or greater caloric intake: Due to the hypermetabolic state that results in an imbalance between energy production and use, resulting in increased heat production and elimination

The thermogenesis leads to increased perspiration and heat intolerance

Generalized weakness and fatigue

Neuropsychiatric [14, 16]

Emotional lability, restlessness, anxiety, agitation, confusion, psychosis, and even coma

Behavioral studies reveal poor performance in memory and concentration testing proportional to the degree of thyrotoxicosis

Muscle wasting, hyperreflexia, fine tremor, periodic paralysis

Gastrointestinal

Hyperdefecation due to increased peristalsis in the small bowel

Hepatitic injury [69, 70]

Increase in the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) was reported in 27 % and 37 % of patients, respectively. The majority of these patients showed no other clinical or biochemical features of liver impairment

The mechanism of injury appears to be relative hypoxia in the perivenular regions, due to an increase in hepatic oxygen demand without an appropriate increase in hepatic blood flow generally associated with the onset of heart failure (often precipitated by arrhythmias)

The clinical presentation of this type of injury is usually that of a self-limiting hepatitis; however, there are a few case reports of thyrotoxic patients presenting with fulminant hepatic failure

Cholestatic injury [71, 72]

Elevated serum alkaline phosphatase (bone or liver origin) is seen in 64 % of patients with thyrotoxicosis

Elevations in gamma-glutamyl transpeptidase (17 %) and bilirubin (5 %) as an indicators of cholestasis

Jaundice is uncommon but when it occurs, complications of thyrotoxicosis (heart failure/sepsis) or intrinsic liver disease need to be excluded

In the vast majority of cases, the hepatic abnormalities associated with hyperthyroidism are reversible, following the early recognition and treatment of the disorder

Reproductive symptoms [14]

Irregular menstrual cycle: oligomenorrhea and anovulation

In men: decreased libido, gynecomastia, and development of spider angiomas, perhaps related to an increase in sex hormone-binding globulin and a subsequent increase in estrogen activity

Cardiorespiratory [14]

Palpitations/tachycardia, hyperdynamic precordium, increased pulse pressure, and a strong apical impulse

Pleuropericardial rub may be heard

Congestive heart failure

Dyspnea on exertion. The dyspnea can be multifactorial in origin because of decreased lung compliance, engorged pulmonary capillary bed, or left ventricular failure

Chest pain similar to angina pectoris, owing to increased myocardial oxygen demand and coronary artery spasm. Coronary artery disease should be excluded as appropriate

Thyroid [14, 15]

In Graves' disease, diffuse enlargement of the gland, and possibly a bruit, can be appreciated, due to increased vascularity and blood flow

With a toxic multinodular goiter, physical findings of the thyroid gland may include one or more nodules

With subacute thyroiditis, a tender thyroid gland could be found

Table 9.3 (continued)

Dermatologic
Hair loss
Pretibial myxedema, palmar erythema, warm and moist skin
Ophthalmologic
Diplopia, eye irritation
Exophthalmos, ophthalmoplegia, conjunctival injection

of serum triiodothyronine among patients with thyroid storm vs. uncomplicated thyrotoxicosis [2]. Also, systemically ill patients have decreased ability to convert T4 to T3. Therefore, a minimally elevated T3 or even a "normal" T3 may be considered inappropriately elevated in this context.

In thyroid storm, the pattern of elevated free T4 and free T3 with a depressed thyrotropin (TSH) (less than 0.05 mU/mL (in third generation TSH assays)) can be comparable to the levels seen in "uncomplicated" thyrotoxicosis (the TSH is always undetectable).

The thyroid gland secretes all of the circulating T4. Approximately 80 % of circulating T3 is derived from monodeiodination of T4 in peripheral tissues by Types I (D1) and II (D2) deiodinases, whereas only about 20 % comes from direct thyroidal secretion. Secreted T4 and T3 are bound to serum proteins: thyroxine-binding globulin (TBG), transthyretin, and albumin. Only a small fraction of the hormones, 0.025 % of T4 and 0.35 % of T3, are free and unbound [14, 15] and thus are available to the tissues to effect biologic action. Laboratory measurement of total T3 and total T4, but not free levels, may be affected by conditions that affect protein binding. Conditions that increase TBG (and as a result total T4 and T3) include infectious hepatitis, pregnancy, estrogens, and opiates. In addition, many drugs interfere with protein binding, including heparin, furosemide, phenytoin, carbamazepine, diazepam, salicylates, and nonsteroidal anti-inflammatory drugs. Therefore, free hormone concentrations are preferable in the diagnosis of thyrotoxicosis [12]. Serum total and free T3 concentrations are elevated in most patients who have thyrotoxicosis because of increased thyroidal T3 production and more enhanced extrathyroidal conversion of T4 to T3. In less than 5 % of patients who have thyrotoxicosis there can be an increase in serum-free T3 while having a "normal" free T4 ("T3 toxicosis") [14, 15]. The T3/T4 ratio may be helpful in distinguishing the etiology of thyrotoxicosis. With Graves' disease and toxic nodular goiter, as there tends to be a higher proportion of T3, the T3/T4 ratio is usually greater than twenty. With thyrotoxicosis caused by thyroiditis, iodine exposure, or exogenous levothyroxine intake, there is generally a greater proportion of T4, with a T3/T4 ratio of less than fifteen [15].

Other laboratory findings that may be associated with thyrotoxicosis include hyperglycemia (due to catecholamine-induced inhibition of insulin release, and increased glycogenolysis), mild hypercalcemia (due to enhanced thyroid hormone–stimulated bone resorption), mildly elevated alkaline phosphatase (both form liver and bone origin), leukocytosis, and elevated liver enzymes (ALT, AST) [4, 12, 16, 17].

Adrenocortical function may also be affected by thyrotoxicosis. Thyrotoxicosis accelerates the metabolism of endogenous or exogenous cortisol by stimulating the rate-limiting step in the degradation of glucocorticoids (accomplished by the hepatic enzymes, D4,5 steroid reductases). Therefore, steroids, including cortisol, corticosterone, deoxycorticosterone, and aldosterone, are metabolized at an accelerated rate [18]. However, in thyrotoxicosis, both degradation and production of cortisol are accelerated, resulting in a normal to increased circulating cortisol level. Given the stressful condition of thyroid storm, a normal cortisol level may be interpreted as a relative adrenal insufficiency. Serum cortisol response to a corticotrophin (ACTH) stimulation test should be normal. However, in long-standing, severe thyrotoxicosis, adrenocortical reserve can be diminished [18]. Tsatsoulis and colleagues [19] assessed adrenocortical reserve in ten subjects with severe, long-standing (4–6 months) thyrotoxicosis with a low-dose corticotrophin (ACTH) stimulation test (0.1 µg/kg of ACTH given as IV bolus) and found that the cortisol response decreased significantly when subjects were thyrotoxic, compared with the cortisol response in the euthyroid state.

Cross-sectional Imaging studies are not required to make the diagnosis of thyrotoxicosis or thyroid storm. However, in the evaluation of thyroid storm, a chest X-Ray (or chest CT *without* contrast when appropriate) would be helpful to determine a possible infectious source as a precipitant. The IV radiocontrast contains significant iodine and may aggravate the hyperthyroidism, especially in unblocked patients. Nuclear medicine imaging (radioioactive iodine uptake and scan) is usually not performed initially given the urgency and clinical context. However, it can be helpful in determining the etiology of thyrotoxicosis [4] (see Table 9.1). A noninvasive readily available test is a thyroid ultrasound with Doppler flow to assess thyroid gland size, vascularity, and the presence of nodules. Typically, a thyroid gland secreting excessive hormones would be enlarged and have enhanced Doppler flow. On the other hand, in the setting of subacute, postpartum, or silent thyroiditis, or exogenous causes of hyperthyroidism, the thyroid gland would be expected to be small, with decreased Doppler flow.

Electrocardiogram manifestations of thyrotoxicosis include sinus tachycardia (40 %) and atrial fibrillation (10–20 %), occurring more commonly in patients older than 60, who are more likely to have underlying structural heart disease or coronary artery disease [19].

Management

Medical treatment of thyroid storm is based on three principles: (1) inhibition of thyroid hormone synthesis and release; (2) counteracting the peripheral, biologic effects of thyroid hormones; and (3) treatment of systemic complications. These measures should bring about clinical improvement within 12–24 h [1].

Management of thyroid storm is outlined in Table 9.4.

With regard to the use of thionamide therapy and iodine therapy, the order of therapy is important: Inhibition of thyroid gland synthesis of new thyroid hormone with

Table 9.4 Management of thyroid storm

1. Inhibition of thyroid hormone synthesis[a,c]		
Methimazole	20–30 mg PO q6 h	
Propylthiouracil	200–400 mg PO q6–8 h	Decrease peripheral T4 → T3 conversion
2. Inhibition of thyroid hormone release from the thyroid gland[b,c]		
SSKI	5 drops PO q6 h or	SSKI 1 g/mL contains 76.4 % iodine.
	5–10 drops per rectum q6–8 h or	20 drops/mL = 764 mg iodine
	8 drops sublingual q8 h	
Lugol's solution	4–8 drops PO q6–8 h or	125 mg/mL of total iodine. 100 mL = 5 g
	5–10 drops per rectum q6–8 h or	of iodine and 10 g potassium iodide
	5–10 drops IV[d] q6–8 h	
3. Counteraction of peripheral effects of thyroid hormone		
Beta-blockers[c]		
Propranolol	60–80 mg PO q4 h or	At doses of >160 mg/day can have
	80–120 mg PO q6 h or	minimal effect on decreasing
	0.5–1 mg IV over 10–15 min every few hours as needed	peripheral T4 → T3 conversion
Atenolol	50–200 mg PO qday (or divided bid)	
Metoprolol	100–200 mg PO qday (or divided bid)	
Nadolol	40–80 mg PO qday	
Esmolol	Loading dose of 250–500 µg/kg IV, then 50–100 µg/kg/min IV	
Steroids[c]		
Hydrocortisone	100 mg IV q8 h	Minimal on decreasing peripheral T_4 → T_3 conversion
Dexamethasone	2 mg IV q6 h	
Betamethasone	0.5 mg IV or IM q6 h	
4. Supportive therapy		
Steroids	As above	Helps in vasomotor stability
Acetaminophen	325–650 mg PO/PR q4–6 h prn	Avoid salicylates (due to displacement of T4 from binding globulin, increasing free T4). Can be given as enema
Thiamine	IV as clinically indicated	To prevent Wernicke's encephalopathy
4. Fluids D5%NS or D10%NS		
5. Treatment of systemic complications and precipitant factor		
Management of underlying disease/condition		
6. Alternative therapies		
Lithium Carbonate	300 mg PO q8 h	Adjust to achieve serum levels of 0.6–1.0 mEq/L
Cholestyramine	4 g PO qday	

(continued)

Table 9.4 (continued)

Potassium perchlorate	1 g P qday	Warning: aplastic anemia, nephrotic syndrome
Reserpine	2.5–5 mg IM q4 h	Anti-adrenergic
Guanethidine	30–40 mg PO q6 h	Anti-adrenergic

[a] For non-oral formulations, please refer to Table 9.5
[b] Administer at least 1 h after thionamide
[c] Use one agent of each group as clinically indicated
[d] Routine pharmacologic sterility needed as indicated per local regulations
Source: Adapted from: Nayak B, Burman K. Thyrotoxicosis and Thyroid Storm. Endocrinol Metab Clin N Am 35 (2006): 663–686 [13].; Alfandhli E, Gianoukakis A. Management of Severe Thyrotoxicosis When the Gastrointestinal Tract is Compromised. Thyroid 2011; 21(3): 215–220 [27]

a thionamide should be initiated *before* iodine therapy, to prevent the stimulation of new thyroid hormone synthesis that can occur when iodine is given initially [3, 7, 16]. The time delay between antithyroid medications and iodine administration is controversial. It can be only 30–60 min (although this may not be enough time for the thionamides to start working), depending on the clinical urgency.

Antithyroid Medications (Thionamides)

The two specific antithyroid agent classes are thiouracils and imidazoles. Propylthiouracil (PTU) is a thiouracil, whereas methimazole (MMI) and carbimazole are imidazoles. Carbimazole is not available in the United States and is more commonly used in Europe. Carbimazole is metabolized rapidly to MMI [20, 21].

Thionamides interfere with the thyroperoxidase-catalyzed coupling process by which iodotyrosine residues are combined to form T4 and T3. Thionamides may also have an inhibitory effect on thyroid follicular cell function and growth [20]. PTU, but not MMI, also inhibits the peripheral conversion of T4 to T3. Thionamides may also have clinically relevant immunosuppressive effects, including decreasing antithyrotropin-receptor antibodiy titers over time and decreasing levels and activities of other immunologically important molecules, such as intracellular adhesion molecule 1 and soluble interleukin-2 (IL-2). Antithyroid drugs may also induce apoptosis of intrathyroidal lymphocytes and decrease HLA antigen class II expression [22].

MMI circulates free or unbound in the serum, whereas 80–90 % of propylthiouracil is bound to albumin [20, 22]. Both agents are concentrated within the thyroid gland where they exert their major actions. It is believed that MMI has a longer duration of action as compared to PTU. The dosing of PTU in thyroid storm is 800 to 1,200 mg daily in divided doses of 200 or 300 mg every 6 h. The dosing for MMI is 80 to 120 mg daily in divided doses of 20–30 mg every 6 h (once the patient is stable, the frequency of dosing can be decreased to once or twice daily and the dose of these agents can be decreased) [16]. Typically, administration has been orally;

however, both MMI and propylthiouracil can be administered rectally [23–27]. The rectal administration is most relevant to patients with severe GI issues in which they cannot take mediation orally or if they have severe malabsorption.

MMI has shown to have similar pharmacokinetics for both oral and intravenous use in normal subjects and in subjects with hyperthyroidism [28]. Although there are no commercially available parenteral formulations of the thionamides, there are case reports of MMI being administered intravenously when the oral and rectal routes could not be used [29, 30].

The rectal formulations of the antithyroid drugs have been prepared either as enemas or suppositories (Table 9.5).

Jongjaroenprasert et al. demonstrated that the enema form of PTU provided better bioavailability than the suppository form. However, both preparations proved to have comparable therapeutic effect [26].

Possible adverse effects of MMI and PTU include abnormal sense of taste, pruritus, urticaria, fever, and arthralgias. More rare but serious adverse effects include agranulocytosis, hepatotoxicity, and vasculitis.

A serious side effect is agranulocytosis. 0.37 % of subjects receiving propylthiouracil and 0.35 % of subjects receiving MMI develop severe agranulocytosis (<500/mm^3) in one study [31]. Most cases of agranulocytosis occur in the first 3 months of treatment, but can occur at anytime. When MMI is the culprit, agranulocytosis tends to be dose-related, especially at doses more than 40 mg daily. However, agranulocytosis does not appear to be dose related with propylthiouracil use [21, 22]. Nonetheless, agranulocytosis can occur at any time with either MMI or PTU, and close monitoring is mandatory. The use of granulocyte colony-stimulating factor (G-CSF) for treatment of agranulocytosis induced by antithyroid medications seems to be effective in shortening the recovery time if the granulocyte count was above 0.1×10^9/L [32, 33]. Another study, however, did not demonstrate this beneficial effect [34]. Therefore, the use of G-CSF can be recommended for treatment of antithyroid drug-induced agranulocytosis, with consideration of the individual context [22].

Hepatotoxicity can occur in 0.1–0.2 % of patients using antithyroid drugs. PTU-induced hepatotoxicity tends to be an allergic hepatitis with evidence of hepatocellular injury, whereas MMI-induced hepatotoxicity tends to result in a cholestatic process [22].

Vasculitis is associated more commonly with propylthiouracil than with MMI. And it is associated with some serologic markers: perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) and anti-myeloperoxidase (anti-MPO) antibodies. Anti-neutrophil cytoplasmic antibody (ANCA) positivity is associated with acute renal failure, arthritis, skin ulcerations, vasculitic rash, and possibly sinusitis or hemoptysis [22].

Since 1996 MMI has become the most frequently prescribed thionamide. As described above, the side effect profile favors MMI. Although agranulocytosis is a potential adverse effect of both thionamides, it is dose-related for MMI and less so for PTU. PTU is the cause of rare but potentially life-threatening hepatotoxicity, whereas severe hepatotoxic reactions related to MMI are extraordinarily rare. PTU is a far more common cause of ANCA-positive vasculitis than is MMI. Also, the more

Table 9.5 Non-oral formulations of antithyroid medications

Antithyroid medication	Quantity for formulation	Vehicle	Route	Dosage	Reference
Methimazole	1,200 mg	12 mL Water with 2 drops of polysorbate (Span) 80, mixed with 52 mL of cocoa butter	Suppository	20–40 mg every 6–8 h	Nabil et al [23]
Methimazole	500 mg powder	0.9 % NaCl total volume of 50 mL (Methimazole 10 mg/mL)	IV filtered through a 0.22 μm filter over 2 min, followed by saline flush[a]	20–40 mg every 6–8 h	Hodak et al. [29]
Propylthiouracil	600 mg	90 mL Sterile water	Enema[b]	400–600 mg every 6 h	Yeung et al. [24]
Propylthiouracil	400 mg	60 mL Fleet's mineral oil OR 60 mL of Fleet's phospho soda	Enema[b]	400–600 mg every 6 h	Walter et al. [25]
Propylthiouracil	400 mg	90 mL Sterile water	Enema[b]	400–600 mg every 6 h	Jongjaroenprasert et al. [30]
Propylthiouracil	200 mg	Polyethylene glycol	Suppository	400–600 mg every 6 h	Jongjaroenprasert et al. [26]

[a]Routine pharmacologic sterility needed as indicated per local regulations
[b]For enema preparation, deliver by Foley catheter inserted into rectum and inflate balloon to prevent leakage

convenient dosing of MMI, translated into enhanced adherence, makes it preferable to PTU. And finally, MMI is more effective than PTU in controlling severe hyperthyroidism [35]. However PTU is the preferred treatment for hyperthyroidism in the first trimester of pregnancy. It is recommended that patients on MMI be switched to PTU if pregnancy is confirmed in the first trimester. Following the first trimester, consideration should be given to switching to MMI [36].

Iodine Therapy

Iodine therapy complements the effects of thionamide therapy by blocking the release of pre-stored hormone and decreasing iodide transport and oxidation in follicular cells. This decrease in organification due to increasing doses of inorganic iodide is known as the "Wolff-Chaikoff" effect. Over the short term of approximately 1–4 weeks, small increments in available iodide cause increased thyroid hormone synthesis; however, large amounts of exogenous iodide actually inhibit synthesis of thyroid hormone. However, despite maintenance of high doses of iodide, the thyroid gland eventually (perhaps over 1–4 weeks) escapes this inhibition, starting approximately after 48–72 h, as the iodide transport system adapts to the higher concentration of iodide by modulating the activity of the sodium-iodide symporter [37] (This effect is termed "Release from the Wolff-Chaikoff effect). Although iodide is rapid and effective in reducing serum thyroid hormone levels, usually within 1–2 weeks, most patients escape the inhibition, returning to hyperthyroidism within 2–3 weeks, unless thionamide treatment have been implemented. This increase in T4 and T3 synthesis and secretion can occur at variable time intervals and can also occur in patients being treated with PTU or MMI. As a result, the long-term use of exogenous iodine is discouraged and all patients taking PTU, MMI, and/or iodine must be counseled and monitored frequently.

Administering iodine before thionamide therapy may influence treatment options for thyrotoxicosis in the short and longer-term. In the acute setting, iodine therapy can stimulate new hormone synthesis if given prior to thionamide treatment. After the acute phase, when planning definitive therapy for thyrotoxicosis, the prior use of exogenous iodine can predispose a patient to increased surgical risk because of the enrichment of thyroid hormone stores. It can also cause postponement of radioiodine ablation until an adequate clearance of the iodine load occurs [3].

Initial blockade of iodine organification begins within 1 h of treatment with thionamide therapy [7], although the initial effect is minor. Therefore, it is recommended that iodine therapy should be administered no sooner than 30–60 min after thionamide therapy.

Oral formulations of inorganic iodine include Lugol's solution and saturated solution of potassium iodide (SSKI). The dosing for these preparations in thyroid storm is 0.2–2 g daily, with 4–8 drops of Lugol's solution (assuming 20 drops/mL, and 6–8 mg iodine/drop) every 6–8 h, and 5 drops of SSKI (with 20 drops/mL, and 38 mg iodide/drop) every 6 h [3, 38].

β-Blockade

Propranolol is probably the most common β-blocker prescribed for management of thyroid storm. It is dosed usually at 60–80 mg orally every 4 h, with a maximum of 120 mg every 4 h. Large doses can be required in the setting of thyrotoxicosis because of the faster metabolism of the drug, and possibly because of a greater quantity of cardiac β-adrenergic receptors [39]. The onset of action after oral dosing is approximately 1 h. Propranolol in large doses (greater than 160 mg daily) can decrease T3 levels by as much as 30 % via the inhibition of 5′monodeiodinase, which is mediated slowly over 7–10 days.

Other oral β-blockers used alternatively in the management of thyroid storm include: atenolol at 50–200 mg daily (divided once or twice daily) [21], metoprolol at 100–200 mg daily (divided once or twice daily), and nadolol at 40–80 mg daily [20]. Clinical response and titration must be done as appropriate.

β-blockers can also be administered intravenously: Propranolol at a initial bolus of 0.5–1 mg over 10 min followed by 1–3 mg over 10 min, every few hours [4, 40]. Esmolol at 50–100 mg/kg/min (after an initial loading dose of 250–500 μg/kg) [20]. See Table 9.4. Intravenous administration of β-blockers should be performed in a monitored setting.

Moderate to severe congestive heart failure can be exacerbated in the acute setting by the administration of β-blockers. However, if the cause of the heart failure was considered to be underlying tachycardia, then β-blockade might be particularly useful. In situations in which the cause of the heart failure cannot be ascertained easily, β-Blockade should only be administered with a short-acting drug, under close hemodynamic monitoring [39].

In patients with reactive or obstructive airway disease, the use of cardio-selective β-blockers (metoprolol, atenolol) can be considered carefully [21].

Atrial fibrillation which occurs in 10–35 % of thyroid storm cases [41] must be managed according to current guidelines.

Steroids

Glucocorticoids, mainly hydrocortisone and dexamethasone, have been used as adjuvant therapy in the treatment of thyroid storm, as they each have an inhibitory effect on peripheral conversion of T4 to T3, although the clinical relevance of this relatively minor effect is unknown. An added benefit for the use of steroids in thyroid storm is to treat possible relative adrenal insufficiency. Some studies have found improved survival in patients treated with glucocorticoids, as patients with thyroid storm may have inappropriately normal levels of serum cortisol [3, 42]. Therefore, treatment with glucocorticoids has become standard practice in patients with thyroid storm because of the possibility of relative adrenal insufficiency or undiagnosed adrenal insufficiency [18]. Hydrocortisone is generally utilized at a

dose of 100 mg intravenously every 8 h or Dexamethasone at 2 mg intravenously every 6 h, with tapering and discontinuation as the patient improves clinically. When appropriate, relevant biochemical tests can be performed to assess underlying adrenal insufficiency.

Alternative Therapies (See Table 9.4)

Alternative or supplemental therapeutic options can be considered in the management of thyrotoxicosis crisis or thyroid storm when first-line therapies (thionamides, iodide, β-blockers, and glucocorticoids) are less effective than desired or cannot be used due to toxicity, allergy, or intolerance.

Lithium

Lithium appears to be actively concentrated in the thyroid follicular cell [43] and inhibits thyroid hormone release [44]. It can be used in combination with PTU or MMI [45]. Lithium decreases directly thyroid hormone secretion, thereby increasing intrathyroidal iodine content and inhibiting coupling of iodotyrosine residues that form iodothyronines (T4 and T3) [46–48]. Boehm et al. compared the relative therapeutic efficacy of iodine (I) and lithium (Li) in thyrotoxicosis and demonstrated that I and Li together displayed additive inhibition of thyroidal release only if I is administered initially, but the combination, if Li is used first, does not appear to be more effective than Li alone [45].

In thyroid storm, lithium can be used at a dose of 300 mg every 8 h [20]. Lithium levels should be monitored regularly (daily at first) to maintain a concentration of 0.6–1.0 mEq/L [16, 20]. As the patient becomes euthyroid, the lithium concentration may change.

Potassium Perchlorate

The perchlorate anion, ClO_4^-, is a competitive inhibitor of iodide transport [20]. However, historically due to possible side effects of aplastic anemia [49–51] and nephrotic syndrome, its use fell out of favor. The regimen of potassium perchlorate (1 g daily) and MMI (30–50 mg daily) has been found to normalize thyroid hormone levels successfully, with an average duration of treatment of 4 weeks. At this dose and duration aplastic anemia and nephrotic syndrome did not occur in several more recent studies [52–54].

Anti-adrenergic Agents

Reserpine is an alkaloid agent that depletes catecholamine stores in sympathetic nerve terminals and the central nervous system. Guanethidine also inhibits the release of catecholamines. Side effects of these medications include hypotension and diarrhea. Reserpine can also have central nervous system depressant effects. Guanethidine can be used in thyroid storm at 30–40 mg orally every 6 h, and reserpine at 2.5–5 mg intramuscularly every 4 h [16]. These agents are used extremely rarely given the advent of the utility of β-blockers.

Cholestyramine

In states of thyrotoxicosis, there is increased enterohepatic circulation of thyroid hormones. Cholestyramine, an anion exchange resin, has also been used in the treatment of thyrotoxicosis, by decreasing the reabsorption of thyroid hormone from the enterohepatic circulation [55]. In several trials, cholestyramine therapy, in combination with MMI or propylthiouracil, caused a more rapid decline in thyroid hormone levels than standard therapy with thionamides alone. Solomon et al. evaluated fifteen thyrotoxic patients in a double blind placebo-controlled cross-over study and found that the cholestyramine-treated group had a more rapid decline in all thyroid hormone levels ($P < 0.01$) than the placebo group [55]. Cholestyramine has been dosed at 4 g orally every 6 h [55–58]. The effect of cholestyramine is generally minimal or moderate and it should not be administered at the same time as other medications because it may inhibit their absorption. On the other hand, cholestyramine is generally not associated with significant adverse effects.

Plasmapheresis, Charcoal, and Resin Hemoperfusion

Removal of thyroid hormone from circulation must be considered when there is progressive clinical deterioration despite aggressive medical management. Plasmapheresis, charcoal hemoperfusion, resin hemoperfusion, and plasma exchange have been effective in rapidly reducing thyroid hormone levels in thyroid storm [59–62].

Plasmapheresis possibly works by removing thyroxine-binding globulin with bound thyroid hormones. The availability of unbound thyroxine-binding globulin can explain the lowering of free and bound hormone levels after plasmapheresis. In addition, removal of circulating autoantibodies against the thyroid gland could be a possible mechanism for decreased thyrotoxicosis. Plasmapheresis and hemoperfusion

have been successfully used to diminish thyrotoxicosis due to thyroid medication overdose [63], iodinated radiocontrast-induced hyperthyroidism, amiodarone-induced hyperthyroidism, and thyrotoxicosis induced by molar pregnancy, as well as in cases of hepatotoxicity and coma induced by antithyroid drugs and in the preoperative and postoperative management of thyroid hormone in patients with severe thyrotoxicosis. Plasmapheresis has also been shown to yield rapid improvement of Graves ophthalmopathy and pretibial myxedema, perhaps by removing circulating antibodies and immune complexes. It is important to realize, however, that the effect of plasmapheresis on thyrotoxicosis is transient and lasts for approximately 24–48 h. Hence, repeat therapy may be necessary until definitive therapy such as surgical intervention is performed [61].

Burman et al. [59] evaluated the ability of an extracorporeal hemoperfusion system employing neutral Amberlite^R resin to bind thyroid hormone and to decrease circulating levels in dogs made thyrotoxic by the intramuscular administration of thyroid hormone. The mean serum T3, T4, and FT4 decreased during 2 h of resin hemoperfusion by 39 %, 35 %, and 46 %, respectively.

Supportive Care/Treatment of Precipitating Cause

Hyperpyrexia is very common in patients with severe thyrotoxicosis. Antipyretics are indicated in this setting, and acetaminophen is the agent of choice. Salicylates should be avoided as they can decrease thyroid protein binding, causing an increase in free thyroid hormone levels [16, 40]. External cooling measures, such as alcohol sponging, ice packs, or a cooling blanket, can also be implemented as appropriate.

Fluid and electrolyte imbalance are also common in severe thyrotoxicosis. The fluid depletion can be secondary from the combination of fever, diaphoresis, vomiting, and diarrhea. Intravenous fluids with dextrose (isotonic saline with 5 or 10 % dextrose) are the preferred solution to replenish glycogen stores [40].

Thiamine should be administered to prevent Wernicke's encephalopathy, which could result from the administration of intravenous dextrose in the presence of thiamine deficiency [64].

A fundamental tenet in the management of thyroid storm is assessment for and treatment of a precipitating cause. Given that the most common precipitant is thought to be infection, if a precipitating factor is not apparent, a search for an infectious source would be warranted in the febrile thyrotoxic patient (blood, urine, and sputum cultures, and chest radiograph or *noncontrast* CT). However, empiric antibiotics are not recommended without an identified source of infection. Other possible precipitants include diabetic ketoacidosis, myocardial infarction, and pulmonary embolism. In those cases, appropriate management of the specific underlying condition must be started along with the treatment of thyrotoxicosis [3].

Perioperative Management

Preoperative management of the thyrotoxic patient can be divided into two categories: preparation for elective/nonurgent procedures and preparation for emergent procedures.

Elective/Nonurgent Procedures

The standard course of therapy in this setting would be to achieve euthyroidism before surgery. Thionamide therapy would be recommended and would generally achieve euthyroidism within several weeks [21]. The use of iodine as a method of decreasing thyroid vascularity and friability before thyroid surgery has been debated. Several studies have shown some evidence that iodine treatment decreases blood flow to the thyroid gland [65, 66]. However, one retrospective study that compared surgical outcomes in 42 hyperthyroid patients who underwent subtotal thyroidectomy with propranolol treatment alone, or propranolol and iodine treatment, revealed no benefit in terms of intra-operative blood loss [67]. Therefore, it seems reasonable to recommend that in the nonemergent setting, iodine use may be indicated only if thionamides cannot be tolerated.

Emergent Procedures

In this situation, rapid lowering of thyroid hormone levels, control of thyroid hormone release, and control of peripheral manifestations of thyroid hormone are needed. Table 9.6 outlines the management of rapid preparation of thyrotoxic patients for emergent surgery. In this context, emergency surgery could be for a thyroidectomy or for a non-thyroid cause.

In one study, thyroidectomy was performed on the sixth day after preoperative use of betamethasone, iopanoic acid (no longer available), and propranolol. Rapid lowering of thyroid hormone levels occurred with good surgical outcomes [68].

Following thyroidectomy in thyrotoxic patients, treatment with β-blockers may still be required for a short period of time because the half-life of T4 is 7–8 days. However, thionamide therapy usually can be stopped postoperatively, assuming that there is little thyroid tissue remaining.

Preoperative management of thyrotoxic patients aims to achieve a euthyroid status before surgery, hence decreasing significantly morbidity and mortality due to thyroid or non-thyroid surgery [21].

Table 9.6 Rapid preparation of thyrotoxic patient for emergent surgery

Medication	Dosage	Postoperatively
Thionamide[a]		
Methimazole	20–30 mg PO q4 h	Stop after total or near total thyroidectomy.
Propylthiouracil	200–400 mg PO q4 h	Continue after non-thyroidal surgery
Beta-blocker[a]		
Propranolol	60–80 mg PO q4 h or 80–120 mg PO q6 h	Continue
Esmolol	50–100 µg/kg/min IV	Change to oral agent
Steroids[a]		
Hydrocortisone	100 mg IV q8 h	Taper over 72 h or as clinically indicated
Dexamethasone	2 mg IV q6 h	
Betamethasone	0.5 mg PO, IM or IV q6 h	
Iodine[a]		
SSKI	5 drops PO q6 h	Stop
Lugol's solution	4–8 drops PO q6–8 h	

[a]Use one agent of each group as clinically indicated
Source: Adapted from: Langley RW, Burch HB. Perioperative management of the thyrotoxic patient. Endocrinol Metab Clin North Am 2003;32:519–34 [21]

Definitive Therapy

Once the life-threatening aspects of thyroid storm are treated, an evaluation for definitive therapy of thyrotoxicosis must be considered. Thionamide therapy, at gradually decreasing doses, usually is required for weeks to months after thyroid storm, to attain euthyroidism. β-Adrenergic receptor blockade is also needed while the patient is still thyrotoxic. However, as the patient shows clinical improvement, some of the treatment modalities may be tapered and discontinued, as appropriate.

Radioactive iodine ablation may not be able to be used for weeks or months following treatment with iodine for thyroid storm. Thyroidectomy can be performed once the patient is euthyroid; it is preferable to allow the patient to be euthyroid for several weeks prior to surgery to decrease tissue stores of thyroid hormones. The goal of definitive therapy is to prevent a future recurrence of severe thyrotoxicosis/thyroid storm [3]. Usually radioactive iodine and thyroidectomy result in permanent hypothyroidism and the patient will be placed on exogenous levothyroxine and have periodic monitoring.

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Chapter 10
Myxedema Coma

Ines Donangelo and Glenn D. Braunstein

Précis

1. Clinical setting: A patient with long-standing undiagnosed/untreated hypothyroidism who develops lethargy and hypothermia following a precipitating factor (intercurrent illness, surgery, use of sedatives or narcotics, or exposure to cold).
2. Diagnosis:

    (a) History: Important clues include history of hypothyroidism, thyroid surgery, and radioactive iodine treatment. A precipitating factor is often identified.
    (b) Physical exam: The presence of a thyroidectomy scar on examination. Features of severe hypothyroidism may be present (dry skin, scaly elbows and knees, yellowness of skin without scleral icterus, coarse hair, puffiness of face and hands, thinning of the lateral aspects of the eyebrows, macroglossia, hoarseness, delayed relaxation phase of deep tendon reflexes, and bradycardia), in a patient with decreased mental status and hypothermia (core body temperature <35 °C).
    (c) Laboratory values: Elevated TSH and low free T4 in primary hypothyroidism, while in central hypothyroidism TSH is low-normal to low. Cortisol levels should be obtained at baseline, ideally following Cortrosyn stimulation.

3. Management: Treatment of myxedema coma is based on thyroid hormone replacement, glucocorticoids, supportive care, and management of coexisting illness such as infection. Thyroid hormone should be given as a venous loading dose followed by a daily maintenance dose of levothyroxine (200–500 µg IV

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loading, followed by 50–75 IV daily) or liothyronine (10–20 μg IV loading, followed by 10 μg IV or by nasogastric tube every 4–6 h), or a combination of both (levothyroxine 200–250 μg IV followed by 100 μg 24 h later and 50 μg daily afterwards; liothyroinine 10 μg IV and then 10 μg every 8–12 h until patient is alert, at which time a switch to levothyroixine only should be made). There are no prospective studies comparing outcome with these different replacement regimens. Stress doses of hydrocortisone (50 mg IV every 6–8 h) should be given pending results of the Cortrosyn stimulation test due the possibility of concomitant adrenal insufficiency, which occurs in 5–10 % of cases. Supportive measures include early mechanical ventilation when indicated, passive rewarming for hypothermia, vasopressor agents for hemodynamic instability, and standard intensive care unit measures.

Introduction

For the last few months my mother has been slowing down and today she stopped. (Son of an elderly woman presenting with myxedema coma as related to Dr. Braunstein.)

Myxedema coma is defined by severe and prolonged depletion of thyroid hormone leading to altered mental status, typically associated with hypothermia and other symptoms related to widespread organ system dysfunction. Although myxedema coma is currently a rare presentation of hypothyroidism given the widespread measurement of thyroid function with thyrotropin secreting hormone (TSH) assays, its early recognition and treatment are crucial because of the high mortality associated with delays in the treatment of this medical emergency. The clinical presentation often follows prolonged symptoms of thyroid dysfunction, followed by a decrease in mental status related to an identifiable precipitating event. There may be a history of radioactive iodine treatment or prior thyroid surgery, or a thyroidectomy scar may be noted on physical exam. Initiation of treatment should be based on clinical suspicion and not delayed until the results of laboratory tests are available.

Historical Remarks

Adult patients with symptoms suggestive of severe hypothyroidism were not recognized until the nineteenth century, with the first reports of women who, though adults, looked like cretinous children. Dr. William M. Ord (1834–1902) described autopsy findings on such patients: "the skin in particular retained its oedematous condition even when cut up into small fragments, whereas the skin of dropsical patients collapses when so treated" and that it contained an excess of mucin as assessed by a crude gravimetric test. He gave it a specific name, myxedema ("mucinous edema"). He did find the thyroid follicules "mostly annihilated" but thought this—as everything else—was due to excess mucin. In 1888, the Committee to

Investigate the Subject of Myxoedema presented their report at the Clinical Society of London. It included an analysis of clinical information on 109 patients with myxoedema and the results on experimental animal models of thyroidectomy and concluded that: "While [myxoedema and endemic cretinism]…depend on, or… are associated with destruction or loss of the function of the thyroid gland, the ultimate cause of such destruction or loss is at present not evident." They noted that patients had "expressionless, apathetic, large-featured" physiognomy, intellectual slowness, "subnormal" body temperature, and often exhibited "watery dropsy." Worsening of symptoms culminating in death occurred in a subset of patients due to "pneumonia, exhaustion, coma, collapse, suffocation or increasing slowness of mind." At that time, there was no inkling of any treatment involving transplants or injection of thyroid tissue or thyroid extracts. Warmth, jaborandi (a plant containing alkaloids including pilocarpine), purified pilocarpine, and nitroglycerine were favored as treatment options.

Myxoedema (spelled myxedema after a while) is now recognized as a manifestation of hypothyroidism rather than being a specific separate disease. Much of the abnormal physical appearance of patients with myxedema is due to the excessive production of glycosaminoglycans, the present-day equivalent of "mucin," in the absence of adequate quantities of thyroid hormone. The term myxedema coma has remained to indicate extreme presentation of untreated hypothyroidism [1].

Pathogenesis

Myxedema coma can result from the usual causes of hypothyroidism such as chronic autoimmune thyroiditis and post-ablative hypothyroidism (Table 10.1 [2–5]). The progression from long-standing untreated hypothyroidism to myxedema coma can be precipitated by an acute insult such as infection, surgery, myocardial infarction, or the use of sedative drugs (Table 10.2 [2, 3, 6, 7]).

The decrease in serum thyroxine (T4) results in lowering of serum and intracellular triiodothyronine (T3). This decrease in intracellular T3 can cause (a) decrease in thermogenesis resulting in hypothermia; (b) decrease sensitivity to adrenergic stimuli, with resulting decreased cardiac inotropism (decreased cardiac output), chronotropism (bradycardia), and vasoconstriction that may culminate in hypotension and shock [8]; (c) increase free water retention due to decrease in renal perfusion, excessive antidiuretic hormone secretion, and increase in vascular permeability, resulting in hyponatremia and effusions; (d) decrease in central nervous system sensitivity to hypercapnia and hypoxia and respiratory muscle weakness resulting in respiratory insufficiency [9]; and (e) slowing of central nervous system function leading to altered mental status. In myxedema coma, decreased mental status is multifactorial and related to the combination of the direct effect of low thyroid hormone action in the central nervous system, cerebral anoxia and hypercapnia from respiratory insufficiency, hemodynamic instability resulting in reduced brain perfusion, and electrolyte abnormalities [10].

Table 10.1 Disorders that can result in hypothyroidism and myxedema coma

Chronic autoimmune (or Hashimoto's) thyroiditis
Postsurgical hypothyroidism
Post-ablative (^{131}I) hypothyroidism
Neck irradiation
Central hypothyroidism due to hypothalamic or pituitary disorder
Drug-induced hypothyroidism
• Lithium
• Amiodarone
• Sunitinib
Excessive consumption of goitrogenic foods, such as raw Chinese white cabbage (bokchoy)
Information from references [2–5]

Table 10.2 Common precipitating factors of myxedema coma

Infection
Surgery
Cerebrovascular accident
Myocardial infarction
Congestive heart failure
Gastrointestinal hemorrhage
Acute trauma
Exposure to cold
Drugs
• Sedatives (narcotics, tranquilizers, anesthetics)
• Cardiac medications (amiodarone, beta blockers)
• Diuretics
• Lithium
• Phenytoin
Rifampin
Information from references [2, 3, 6, 7]

Clinical Presentation

The classic presentation of myxedema coma is that of an elderly female with long-standing hypothyroidism who develops an intercurrent illness, is given sedatives or narcotics or exposed to cold weather, and develops lethargy and hypothermia. It is important to keep a high degree of clinical suspicion, as myxedema coma can occur in males and younger patients, and may be related due to some of the less common causal agents listed in Table 10.1. The features of severe hypothyroidism can be present, including dry skin, scaly elbows and knees, yellowness of skin without scleral icterus, coarse hair, puffiness of face and hands, thinning of the lateral

Table 10.3 Clinical finding in myxedema coma

Hypothermia
- Core body temperature (<35 °C or 95 °F)
- Infection with the absence of fever

Decreased mental status
- Confusion, lethargy, obtundation, or coma

Cardiovascular abnormalities
- Bradycardia
- Decreased myocardial contractility
- Low cardiac output
- Hypotension, or shock

Respiratory abnormalities
- Central depression of ventilator drive
- Respiratory muscle weakness
- Mechanical obstruction by large tongue

Laboratory abnormalities
- Respiratory acidosis due to hypoventilation
- Hypoglycemia, directly due to hypothyroidism or due to associated adrenal insufficiency
- Hyponatremia, due to impaired free water excretion
- Anemia, typically normocytic normochromic from decreased erythropoiesis
- Elevation in muscle-derived creatinine phosphokinase, due to increased muscle permeability

aspects of the eyebrows, macroglossia, hoarseness, delayed relaxation phase of deep tendon reflexes, and bradycardia. Patients with severe hypothyroidism can develop effusions (pericardial and pleural) that do not cause organ compromise because of their slow rate of formation. Decreased mental status and hypothermia are characteristic of myxedema coma. The term myxedema coma, however, is a misnomer as most patients do not present with frank coma but only signs of cognitive deterioration, such as lethargy, confusion, or disorientation. Diastolic hypertension can be present, but hypotension that may progress to shock can occur due to sepsis or other causes of decreased cardiac output [8]. Hyponatremia is a common electrolyte abnormality in the severe hypothyroid state and results from decreased free water clearance due to increased release of antidiuretic hormone and decreased renal blood flow from hypotension or decreased cardiac output. Hypoglycemia results from decreased gluconeogenesis and reduced insulin clearance. Hypoglycemia also can be a sign of adrenal insufficiency which can be present in a small subset of patients with myxedema coma, especially those with hypopituitarism as the etiology of hypothyroidism or in patients with the polyglandular autoimmune failure syndrome. Hypoventilation with respiratory acidosis also can be encountered in myxedema coma. Late-onset epilepsy that resolves with thyroid hormone replacement is described in severe hypothyroidism [11], and myxedema coma presenting in status epileticus is reported [12, 13]. Clinical features of myxedema coma are listed in Table 10.3. A more active presentation of hypothyroidism that includes psychotic manifestations (delusions, visual hallucinations, auditory hallucinations, perseveration, loose associations, and paranoia) can occur—a

condition known as "myxedema madness." There is no clear correlation between degree of thyroid dysfunction and development of psychiatric symptoms [14]. The precipitating insult should be sought, if not already clinically evident (Table 10.2). Infections can present without fever in patients with myxedema coma.

Diagnosis

The diagnosis should be considered in patients with altered mental status who have hypothermia and other features of severe hypothyroidism. Other causes of decreased mental status could lead or contribute to a similar presentation and should be sought on history and through investigation, including drugs (ethanol, toxins), infections of the central nervous system, severe sepsis, metabolic disorders (diabetes, uremia), or traumatic brain injury. The history obtained from family members can reveal a diagnosis of hypothyroidism or past radioactive iodine treatment. Evidence of a thyroidectomy by a surgical scar on examination is an important clue.

Essential laboratory tests include TSH, free T4, and cortisol. If possible, the cortisol axis should be investigated in more detail with Cosyntropin (ACTH) stimulation test (serum cortisol before, and 30 min, and 60 min after Cosyntropin 250 µg as an intravenous bolus). Therapy can be started empirically if clinically indicated pending laboratory results, although laboratories in large clinical centers currently can provide a TSH result in 1–2 h.

In most patients, the etiology of myxedema coma is primary hypothyroidism, and the laboratory results will show elevated TSH and low free T4. TSH may not be as elevated as expected for the low level of free T4. This is usually due to intercurrent illness, or the use of dopamine and/or glucocorticoids. On the other hand, a normal-to-low or low TSH coupled with a low free T4 value indicates central hypothyroidism, especially if associated with adrenal insufficiency and other clues such as inappropriately normal gonadotropins in postmenopausal women, or a history of pituitary surgery. It can be difficult to differentiate patients with myxedema coma due to central hypothyroidism from ill patients with the nonthyroidal illness ("euthyroid sick") syndrome associated with decreased mental status. The latter can present with a low TSH and a low total T3 due to critical illness and the drugs used to treat the patient in the intensive care unit setting. In the "nonthyroid illness syndrome," free T4 measured by immunoassays can reveal a low value due to interference with abnormally high levels of thyroid hormone binding globulin. Free T4 measured by dialysis, however, is normal.

Management

Myxedema coma is associated with a high mortality and should be treated aggressively. Several factors on presentation may serve as indicators of a worse prognosis. One prospective study from India evaluated prognostic factors in 23 patients treated

Table 10.4 Proposed methods of replacement with thyroid hormone in patients with myxedema coma

Method	Thyroid hormone	Loading dose[a]	Daily maintenance dose
1	Levothyroxine	200–500 µg IV	50–75 µg IV or
			100–150 µg (1.6 µg/kg) PO/NGT
2	Liothyronine	10–20 µg IV	10 µg IV/PO/NGT every 4–6 h
3[b]	Levothyroxine	200–250 µg IV	100 µg IV 24 h after loading dose, followed by 50 µg IV/PO daily
	Liothyronine	10 µg IV	10 µg IV every 8–12 h, until patient can take PO, then switch to LT4 PO regimen only

IV intravenous, *PO* oral administration, *NGT* nasogastric tube administration

[a]Thyroid hormone loading dose should be titrated to lower end of recommended dose in elderly and patients with ischemic heart disease

[b]Replacement method suggested in [22]

for myxedema coma. They noted that hypotension and bradycardia at presentation, hypothermia unresponsive to treatment, sepsis, the need for mechanical ventilation, sedative drugs, a poor score on models that estimate outcome (Glasgow Coma Scale, Acute Physiology, Age, Chronic Health Evaluation (APACHEII) and Sequential Organ Failure Assessment (SOFA) scores) all were associated with increased mortality [15]. A Spanish study prospectively evaluated 11 patients treated for myxedema coma and found that, in addition lower Glasgow Coma Scale and APACHEII scores, lower level of consciousness on presentation was significantly associated with mortality [16]. A review of 87 cases of myxedema coma (8 new and 79 reported in the medical literature) revealed that increasing age and increasing frequency of cardiac abnormalities correlate with fatal outcome [17]. Advanced age was also associated with increased mortality [18].

Treatment of myxedema coma is based on thyroid hormone replacement, glucocorticoids, supportive care, and management of coexisting illness such as infection. Addressing all these components of care in a prompt and intense manner led to a considerable decrease in mortality from myxedema coma. Mortality dropped from close to 100 % to the current rates of 30–50 % [15–17].

There is no consensus on the optimal mode of thyroid hormone replacement in patients with myxedema coma, largely because the condition is so rare that there are no clinical trials comparing different treatment regimens. Therefore, most recommendations are based on expert opinion. The preferred route of administration of thyroid hormone is intravenous, as oral medications may be poorly absorbed due to gastric atony or ileus. Although oral absorption of levothyroxine (LT4) is variable, the clinical response occurs promptly [16], and in one small observational study the route of administration (oral or intravenous) did not affect mortality [15], suggesting that if intravenous thyroid hormone is not readily available, oral LT4 is a reasonable alternative.

Data on mortality and outcome comparing LT4 or liothyronine (LT3) only with combined LT4/LT3 regimens are lacking, again due to the rarity of the condition. We have chosen to describe all three methods of replacement (Table 10.4). The first approach is to replace with LT4 only. The average size of the extrathyroidal T4 pool

is 500 µg per 1.73 m^2 in a normal person and may be reduced to lower than 250 µg per 1.73 m^2 in hypothyroidism [19]. Therefore, to restore this pool, the initial LT4 dose should be 200–500 µg IV given intravenously. Given that T4 has a volume of distribution of about 10 L, this dose will raise total serum T4 by 2–5 µg/dL. Thyroxine levels should be within the reference range in the first 48 h after starting replacement. The normal turnover rate of thyroid hormone is 10 % or about 50 µg per day [20]. In one study, the daily production of thyroxine was estimated to range between 80 and 100 µg [21]. This is thought to be a little high by most authorities. Therefore, after the loading dose, the maintenance replacement dose of LT4 should be about 50–75 µg IV daily, or 100–150 µg oral daily doses (intravenous LT4 is about twice as bioavailable as oral LT4).

The second approach is to treat with LT3 only. In hypothyroid patients without major intercurrent illness LT4 alone may suffice to increase serum T3 levels to normal in 2–3 days due to normal activity of the 5′-deiodinase enzyme that converts T4 into T3. However, critically ill patients with multiple organ dysfunction may have reduced 5′-deiodinase activity. The patients, therefore, may benefit from supplemental LT3 replacement. Moreover, T3 works more rapidly than T4 [21]. The proportion of T4:T3 produced by the normal thyroid gland is approximately 80:20, with the normal daily production of triiodothyronine between 30 and 40 µg [21]. A dose of LT3 of 10–20 µg intravenously can be given initially, followed by 10 µg intravenously or per nasogastric tube every 4–6 h, depending on the patient's age and coexistent cardiac risk factors. This is followed by oral LT3 or LT4 therapy once there is improvement.

Finally, some authorities prefer to treat with a combination of LT4 and LT3. Wartofsky recommends intravenous LT4 at a dose of 4 µg/kg lean body weight (~200–250 µg) initially and then 100 µg 24 h later, followed by 50 µg daily. LT3 is given initially as 10 µg intravenously and repeated every 8–12 h until the patient is alert enough to take maintenance oral doses of LT4 [22].

Elderly patients and those with ischemic heart disease may need smaller doses of thyroid hormone, and all patients should have the heart rhythm continuously monitored during the early phases of replacement. High daily doses of thyroid hormone replacement (LT4 ≥500 µg or LT3 ≥75 µg daily) are associated with increased mortality, especially in the elderly [17].

The incidence of decreased adrenal function in patients with myxedema coma is about 5–10 %. Thus, intravenous cortisol is indicated before initiating thyroid hormone therapy and should be continued until adrenal function is known to be normal. Patients with myxedema coma could have associated hypopituitarism and secondary adrenal insufficiency or primary adrenal insufficiency due to concomitant autoimmune gland dysfunction. Patients should be treated with stress dose steroids, i.e., hydrocortisone 50 mg IV every 6–8 h. In critically ill patients, if serum cortisol is greater than 20–30 µg/dL then steroid support is probably unnecessary. If serum cortisol is lower than 20 µg/dL, stress dose steroid should be continued for the first 48 h, and then the dose may be tapered over the next few days in parallel with clinical improvement, unless a diagnosis of adrenal insufficiency is made from the Cortrosyn testing. In the latter situation, plans should be made to convert the patient over to oral glucocorticoids for the ongoing treatment of adrenal insufficiency.

Supportive measures are an important component of care for patients with myxedema coma. Early intubation and mechanical ventilation is life saving for patients with hypoventilation and profound decrease in mental status. Posterior pharyngeal edema complicating endotracheal intubation is described in myxedema coma [23]. Passive rewarming is indicated for hypothermia, but active rewarming should be avoided since it can promote vasodilatation and hypotension. Vasopressor agents are indicated for hemodynamic instability. Free water restriction may be needed to help correct hyponatremia. Fluid overload should be avoided. If necessary, small amounts of hypertonic saline can be used to treat severe hyponatremia (serum sodium <120 mEq/L). Sedative medications should be restricted when possible as their blood levels may accumulate due to decreased metabolism.

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Chapter 11
Acute Suppurative Thyroiditis

J. Stone Doggett and Brian Wong

Précis

1. Clinical setting: Fever, leucocytosis, and neck pain, often associated with asymmetrical thyroid enlargement.
2. Diagnosis:

   (a) History—Thyroid infection is rare and an underlying alteration in host susceptibility is usually present. These include congenital fistula from the pyriform sinus to the thyroid gland, persistent thyroglossal duct, thyroid nodules, and immunocompromise for any reason.
   (b) Physical examination: Pain on palpating the thyroid gland is the primary finding. Most patients are euthyroid. Most patients will have fever (92 %), dysphagia (91 %), dermal erythema (82 %), and dysphonia (82 %).
   (c) Laboratory values: Most patients have a leucocytosis of greater than 10,000 cells/mm^3, with a left shift. Thyroid function tests are usually in the normal range.

Imaging: CT scan is the preferred first modality. Usually, an abscess is revealed if present. When possible, an ultrasound-guided fine needle aspiration of the abscess should be done. White cells and microbes revealed by gram stains strongly suggest

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a suppurative thyroiditis. Giant cells and granulomas point toward a painful non-suppurative acute thyroiditis.

Treatment: The initial antibiotic therapy should cover gram positive, gram negative, and anaerobic organisms. If the patient is not allergic to penicillin, ampicillin-sulbactam plus vancomycin should be administered intravenously. Penicillin-allergic patients should be treated with ceftriaxone plus vancomycin. If an attempt to aspirate for abscess contents is anticipated, it should precede the administration of antibiotics of any kind.

Acute Suppurative Thyroiditis

Of the multiple types of thyroiditis, acute and chronic suppurative thyroiditis are the two types in which there is ongoing infection of the thyroid gland. Although there is a presumed relationship between viral infections and painful subacute thyroiditis, painful subacute thyroiditis is typically self-limited and treatment is aimed at decreasing inflammation and addressing fluctuations in thyroid hormone [1]. Chronic and acute suppurative thyroiditis can be caused by bacteria, mycobacteria, fungi, or parasites. Acute suppurative thyroiditis is most often caused by bacteria, can progress rapidly, and can be fatal if not treated emergently. Clinical knowledge of acute suppurative thyroiditis is based primarily on retrospective case reports and case series. Despite the paucity of clinical studies, recent attempts have been made to construct a treatment algorithm for acute suppurative thyroiditis [2, 3].

Predisposing Factors

Thyroid infection is rare, and an underlying host susceptibility is present in most cases. Frequently, immunocompetent patients with acute suppurative thyroiditis have a congenital fistula from the pyriform sinus that extends to the thyroid capsule. This defect provides a tract for pathogens to establish infection in or around the thyroid gland and is the most common predisposing factor in children [4]. Otherwise, in an immunocompetent host, the thyroid gland can become infected through a persistent thyroglossal duct, or by direct spread from an adjacent tissue infection or from trauma. In individuals who are immunocompromised or have preexisting thyroid disease, such as thyroid nodules or thyroid malignancy, infection can develop through hematogenous or lymphatic spread. Case reports describe a wide range of nonbacterial pathogens that cause suppurative thyroiditis in immunocompromised patients. Patients with AIDS, as an example, are reported to develop suppurative thyroiditis due to the opportunistic fungal pathogen *Pneumocystis jirovecii* [5]. Preexisting thyroid disease has been observed in 61 % of reported patients with suppurative thyroiditis [6].

Suppurative thyroiditis can occur within the first year of life or in the elderly. The average age of patients with acute suppurative thyroiditis in a literature review of 153 cases reported from 1900 to 1980 was 30 years for men and 35 years for women [6]. Twenty two of these cases occurred in children under ten years of age.

Microbiology

The majority of acute suppurative thyroiditis cases are caused by *Staphylococcus aureus* and *Streptococcus* species [6]. However, a broad range of pathogens are reported and infections may be due to gram negative, anaerobic, or polymicrobial infection [3]. Drug-resistant pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA), have been reported as well [7].

Clinical Presentation

An acute suppurative thyroiditis can be difficult to distinguish from painful subacute thyroiditis or from head and neck infections such as parapharyngeal abscesses. Acute suppurative thyroiditis differs from Hashimoto's thyroiditis and other painless forms of thyroiditis in that pain is typically a prominent aspect of the patient's presentation. The majority of patients with acute suppurative thyroiditis are euthyroid, but hyperthyroidism may result from inflammation or hypothyroidism may occur due to tissue destruction. In contrast, thyroid hormone abnormalities are common in painful subacute thyroiditis [9]. When there is thyrotoxicosis, both painful subacute thyroiditis and suppurative thyroiditis have low radioactive iodine uptake. Moreover, patients with acute suppurative thyroiditis tend to be acutely ill, and infection can occur after a respiratory tract infection or with concurrent pharyngitis.

Based on case reports, the most common features are anterior cervical pain (100 %), fever (92 %), dysphagia (91 %), dermal erythema (82 %), and dysphonia (82 %) [6]. Leukocytosis of greater than 10,000 cells/mm^3 is present in 73 % of patients. The left lobe is the most frequently involved area of the thyroid. The above features may be present in subacute thyroiditis, but they are much less common and should raise suspicion for acute suppurative thyroiditis [8].

Diagnosis

Initial imaging can be performed with ultrasound or CT. When there is concern for extensive infection outside of the thyroid, CT with intravenous contrast may be needed to define the extent of thyroid infection and the involvement of adjacent

tissue. However, it should be noted that intravenous-iodinated contrast will interfere with radioactive iodine thyroid uptake scans for several weeks. Typically, thyroid imaging in acute suppurative thyroiditis shows an abscess, whereas in painful subacute thyroiditis the thyroid appears diffusely heterogeneous. If suppurative thyroiditis is suspected, and the patient is stable, evaluation with ultrasound-guided needle aspiration should be pursued to identify the pathogen. Fine needle aspiration can also be used to distinguish painful subacute thyroiditis from acute suppurative thyroiditis by demonstrating giant cells and granulomas as opposed to abscess formation with microorganisms. If there is airway compromise, cultures should be obtained during aggressive drainage of infection with surgery or percutaneous drainage. The identification of a pyriform fistula is often not possible during the acute inflammatory period, but can be seen on imaging studies or endoscopically once the inflammation is decreased. Radiographic evaluation for a pyriform fistula can be done with a barium swallow or a CT scan with trumpet maneuver in which the patient inflates a syringe during the scan [2].

Treatment

The management of acute suppurative thyroiditis has been debated recently [2, 3]. While there are differing approaches to abscess drainage and the duration of antibiotic therapy, there is agreement that initial therapy includes broad antibacterial coverage. Empiric therapy should include coverage for gram positive, gram negative, and anaerobic bacteria and should be based on local antibiotic susceptibility patterns. Coverage for drug-resistant bacteria, particularly MRSA, should be considered. Once culture results are available, antibiotics can be tailored to the pathogen. Drainage of infection is indicated when there is airway obstruction or an abscess. In cases of extensive infection, or when there is no improvement with drainage and antibiotics, thyroidectomy may be required. Infection in the setting of preexisting thyroid disease is often more difficult to treat [2].

A pyriform fistula is more easily detected once acute inflammation resolves [10]. Endoscopic obliteration of the fistula can be performed with chemical or electrical cauterization during the infected period. It is more often done with a surgical fistulectomy after infection has resolved. The total duration of antibiotics should be determined on a case by case basis and guided by clinical response.

Summary

Acute suppurative thyroiditis is a medical emergency that usually presents with anterior neck pain, fever, and dysphagia and can lead to airway obstruction. Differentiating acute suppurative thyroiditis from painful subacute thyroiditis or invasive head and neck infections usually requires diagnostic imaging with CT or

ultrasound. In certain instances, tissue histology obtained by fine needle aspiration may be required to definitively diagnose acute suppurative thyroiditis. Obtaining cultures by aspiration, surgery, or percutaneous drainage is required to guide antibiotic therapy. Acute suppurative thyroiditis should be treated urgently with antibiotics and abscess drainage. Consultation with a surgeon and an infectious diseases specialist should be done when possible. The majority of immunocompetent patients will have a pyriform sinus fistula that can be detected endoscopically, by a barium swallow study or by a CT scan with the trumpet maneuver. Anatomic defects, such as a pyriform sinus fistula, should be corrected, to prevent recurrent infection.

- Acute suppurative thyroiditis is typically a bacterial infection of the thyroid that occurs in patients who have a congenital pyriform fistula, but may occur in patients who are immunocompromised or have underlying thyroid disease.
- CT or ultrasound is the preferred initial diagnostic test.
- Acute suppurative thyroiditis should be treated emergently with parenteral antibiotics and abscess drainage.

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Chapter 12
Hyponatremia: SIADH

David H. Ellison

Précis

1. Clinical setting—hyponatremia in the ambulatory or hospital setting.
2. Diagnosis:

   (a) History: the presence of cancer, especially of lung or brain; infections of lung or central nervous system; use of drugs known to predispose to SIADH; recent use of "Ecstasy" (3,4-methylenedioxymethamphetamine, MDMA); other systemic infectious or malignant processes. Nonspecific symptoms, especially weakness, unsteadiness, confusion, fatigue. A sensation of thirst may be prominent.

   (b) Physical examination: neurological impairment, typically non-focal, including confusion, somnolence, or lethargy; neurological dysfunction may progress to grand mal seizures, in severe cases, and to death from uncal herniation. Most of the physical exam is notable for what is not present. Signs of depletion or expansion of the extracellular fluid (ECF) volume make a diagnosis of SIADH less likely. Thus, peripheral edema, ascites, pulmonary crackles, and jugular venous distension suggest that hyponatremia is the consequence of depletion of the "effective" arterial blood volume. This typically results from heart failure or cirrhosis of the liver. Conversely, postural hypotension, tachycardia, dry axillae, or mucus membranes raise the possibility that arginine vasopressin secretion is, in fact, an appropriate response to true ECF volume depletion.

   (c) Laboratory values: hyponatremia is required to make a diagnosis and is typically the most prominent feature. A low serum uric acid supports that diagnosis; conversely, hyperuricemia suggest that depletion of the ECF

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volume may be responsible. Also the blood urea nitrogen concentration usually is low. A urine Na concentration less than 30 mmol/L argues strongly that ECF volume depletion is present and typically compels a trial of volume replacement. Conversely, a urine Na concentration ≥40 mmol/L is consistent with SIADH. Notably, measurement of plasma AVP is usually not a part of the diagnostic evaluation.

(d) Imaging: An MR or CT scan of the brain can be useful in distinguishing acute symptomatic hyponatremia from chronic hyponatremia. This is an important distinction since the approach to treatment depends on the acuity.

3. Treatment—treatment of SIADH depends on its acuity, the associated symptoms and signs, and the cause. The initial decisions with respect to treatment involve a decision about treatment urgency. If the hyponatremia is symptomatic and deemed to be acute (typically defined as less than 48 h in duration), then rapid correction is safe and effective in preventing or correcting neurological sequelae. In this case, treatment with hypertonic saline (3 % NaCl) is recommended at rates designed to increase serum Na concentration by 1–2 mmol/h for a total correction of 4–8 mmol/L during the first day (rates and approaches remain controversial and are discussed in detail, below).

When hyponatremia is chronic and asymptomatic, then a more conservative approach is recommended. This typically includes restriction of water intake. It may also include the use of pharmaceuticals to block vasopressin receptors in the kidney. Traditionally, demeclocycline has been employed. More recently, oral tolvaptan has become available.

Syndrome of Inappropriate Antidiuretic Hormone

The antidiuretic hormone (ADH) secretion was characterized by Schwartz, Bartter, and colleagues in 1957, when they described two patients with renal sodium loss and hyponatremia, associated with lung cancers, without apparent ECF volume depletion.

> These two patients with mediastinal tumors presented a syndrome in which the cardinal feature was hyponatremia. Renal and adrenal cortical function was normal. As hyponatremia and hypotonicity of the ECF developed, the urine was persistently hypertonic compared to the plasma. Since hypertonicity of the urine, in the presence of a normal glomerular filtration rate, constitutes prima facie evidence for the presence of ADH, it was postulated that there was sustained, inappropriate secretion of ADH in these subjects, and that this was responsible for the disorder of sodium metabolism [1].

They were aware that exogenous administration of vasopressin (Pitressin) to normal subjects who were allowed to drink water as they desired led to a similar syndrome of hyponatremia and salt wasting. Although measurement of serum arginine vasopressin was not possible at the time, the authors inferred correctly that the peptide hormone was being produced inappropriately. Later analysis indicated that

tumors themselves were usually the source of the antidiuretic hormone [2]. Subsequently, many other causes of the syndrome have been reported (see Table 12.1). Many of these involved disease of the lungs or the brain and included both malignant and infectious processes. It became clear that certain commonly administered drugs could lead to a similar syndrome, which was reversible on their discontinuation. Finally, other situations in which excessive ADH secretion occurs, such as the perioperative period, and during pain, further expanded the list of causes.

Antidiuretic Hormone Secretion

The human antidiuretic hormone is arginine vasopressin. This nonapeptide hormone (Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-Gly-NH_2, see Fig. 12.1) is produced by the hypothalamus and trafficked to the posterior pituitary, where it is stored (Fig. 12.2). In response to small increases in plasma tonicity (Fig. 12.3), AVP is secreted into the bloodstream, where its half-life is short (15–20 min). Secretion is also stimulated by effective arterial blood volume (EABV) depletion, although this response only occurs when ECF volume depletion amounts to approximately 10 %. Thus, day to day control of AVP secretion is regulated primarily by the serum sodium concentration.

AVP binds to two classes of receptor, vascular receptors (V1R), which lead to vasoconstriction, and renal tubular receptors (V2R) on the basolateral membrane of principal cells in the collecting duct. Engagement with V2R leads to insertion of preformed water channels (aquaporin-2) into the apical plasma membrane, which increases transcellular water permeability (see Fig. 12.4). As the interstitium of the kidney is hypertonic, owing to countercurrent exchange, water is reabsorbed from the collecting duct and urine becomes concentrated. Via the action of this system, the urine osmolality can rise to 1,200 mOsm/kg H_2O, although any value greater than 100 mOsm/kg H_2O is believed to reflect some AVP action (as urinary osmolality in the absence of AVP is as low as 50 mOsm/kg H_2O).

The AVP system typically acts in concert with thirst to regulate the serum Na concentration and, therefore, the effective osmolality of ECF. In contrast, ECF volume is regulated largely by the renin/angiotensin/aldosterone system, which modulates NaCl balance. Thus, *disorders of Na concentration* are analyzed as disorders of *water balance* (rather than salt balance) and typically result from disordered AVP secretion or action.

Presentation and Diagnosis

The patient with SIADH can be asymptomatic or suffer from severe neurological symptoms. The difference is determined largely by the acuity of the process. Severe hyponatremia ([Na]$_s$ less than 125 mmol/L), especially when developing rapidly

Table 12.1 Causes of the syndrome of inappropriate antidiuretic hormone secretion

Malignancies	Pulmonary disorders	Central nervous system disorders	Drugs	Miscellaneous
Carcinomas	Infections	Infections	Drugs that stimulate AVP release or enhance its actions	Inherited (Gain of function V2R mutations)
Pulmonary	Bacterial pneumonia	Encephalitis	Chlorpropramide	Idiopathic
Small cell	Viral pneumonia	Meningitis	SSRIs	Transient
Mesothelioma	Pulmonary abscess	Brain abscess	Tricyclic	Endurance exercise
Oropharynx	Tuberculosis	Rocky Mountain Spotted Fever	Antidepressants	Surgery anesthesia
GI tract	Aspergillosis	AIDS	Clofibrate	Nausea
Stomach	Asthma	Bleeds and masses	Carbamazepine	Pain
Duodenum	Cystic fibrosis	Subdural hematoma	Vincristine	Stress
Pancreas	Positive-pressure breathing	Subarachnoid hemorrhage	Nicotine	
GU tract		Cerebrovascular accident	Narcotics	
Ureter		Brain tumors	Antipsychotics	
Bladder		Head trauma	Ifosfamide	
Prostate		Hydrocephalus	Cyclophosphamide	
Endometrial		Cavernous sinus thrombosis	Nonsteroidal anti-inflammatory drugs	
			MDMA (ecstasy)	
Endocrine		Miscellaneous	AVP analogs	
Thymoma		Multiple sclerosis	Desmopressin (dDAVP)	
Lymphomas		Guillain-Barré syndrome		
			Oxytocin	
Sarcomas		Shy-Drager syndrome	Vasopressin	
Ewing sarcoma		Delerium tremens		
		Acute intermittent porphyria		

SSRI selective serotonin reuptake inhibitors, *MDMA* 3,4-methylenedioxymethamphetamine, *AVP* arginine vasopressin
Source: from [21], with permission
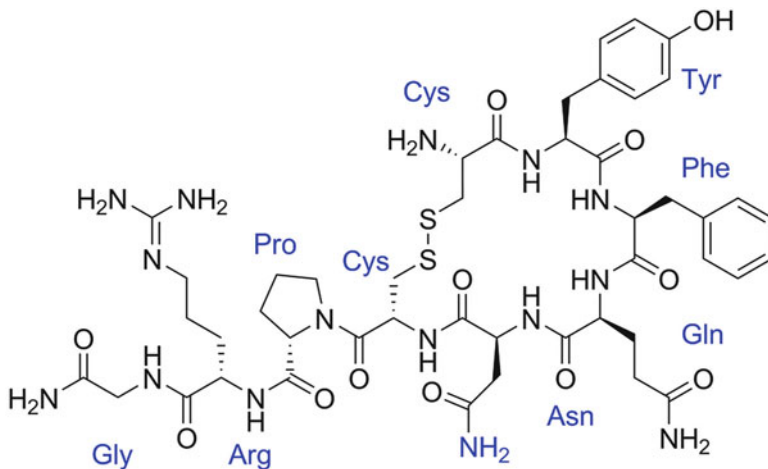
Fig. 12.1 Chemical structure of arginine vasopressin. Chemical structure of arginine vasopressin
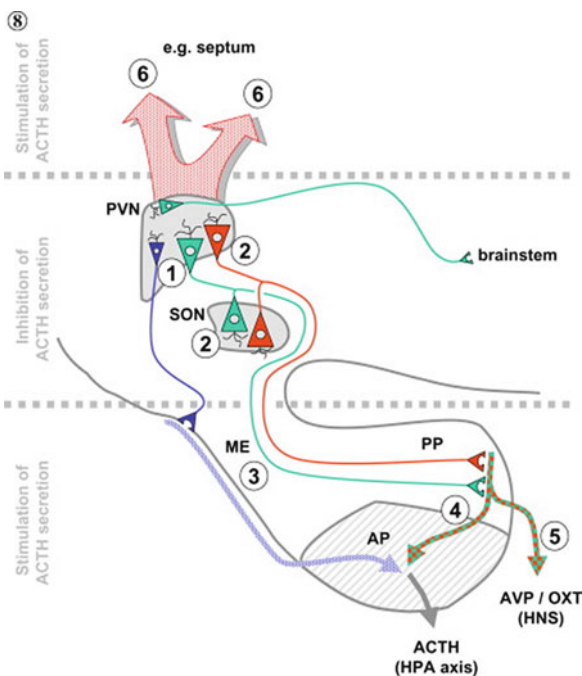
Fig. 12.2 Hypothalamic pituitary axis. Diagram shows parvocellular neurons of the paraventricular nucleus (PVN) mediate release of corticotropin-releasing hormone (*labeled 1*). Magnocellular neurons of the PVN (*labeled 2*) mediate AVP (*red*) and oxytoxin: (*green*) production. They traverse the median eminence (ME) to be stored in axonal terminals in the posterior pituitary (PP), but also innervate the supraoptic nucleus (SON). AVP is released from the PP upon signals discussed in the text (the hypothalamic neurohypophyseal system (HNS) to have effects, both systemic (4) and local (5). Some work suggests that locally produced AVP may affect other central sites (6)). From [31]
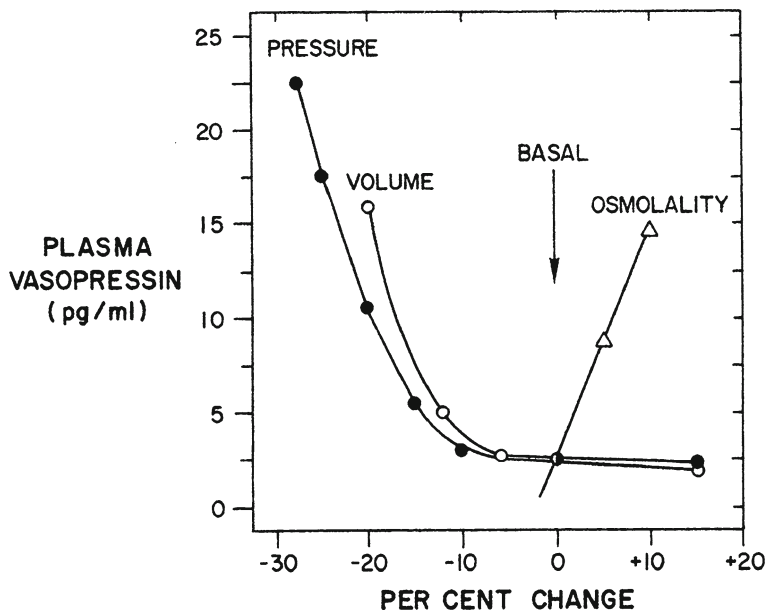
Fig. 12.3 Plasma vasopressin levels versus osmolality, volume, and pressure. Graph shows steep effects of percentage changes in plasma vasopressin with osmolality. Small percentage changes in extracellular fluid volume (*open circles*) and arterial pressure (*filled circles*) have little effect until the change exceeds 10 %. Graph from [32], with permission

(duration less than 48 h), can lead to confusion, hallucinations, seizures, coma, decerebrate posturing, respiratory arrest, and death. Milder symptoms include headache, difficulty concentrating, impaired memory, muscle cramps, and weakness. Women are more prone to develop neurological symptoms and signs than are men.

Diagnostic criteria for SIADH are summarized in Table 12.2 [3]. It is important to measure serum osmolality to exclude pseudohyponatremia, a laboratory artifact that occurs when serum lipids or proteins are elevated and $[Na]_s$ is measured using common indirect techniques [4]. Hypertonic hyponatremia occurs when osmotically active solutes (typically glucose or mannitol) draw water from cells. A correction factor (serum sodium concentration declines by 1.6–2.4 mmol/L for each 100 mg/dL increase in plasma glucose) can be used to determine whether the elevation of plasma glucose accounts for the decline in serum Na. Alternatively, the *effective* osmolality (sometimes called "tonicity") can be estimated as the *measured osmolality—blood urea nitrogen/2.8* (where BUN is measured in mg/dL). As the effective osmolality depends on properties of biological membranes, it cannot be measured in the laboratory [5]. To diagnose hypotonic hyponatremia, the *estimated* effective osmolality must be less than 275 mOsm/L (Table 12.2).

A second diagnostic criterion for SIADH is that the urine osmolality must exceed 100 mOsm/kg H_2O, when the plasma effective osmolality is low (Table 12.2). Although the urine may be highly concentrated, AVP secretion in SIADH is not
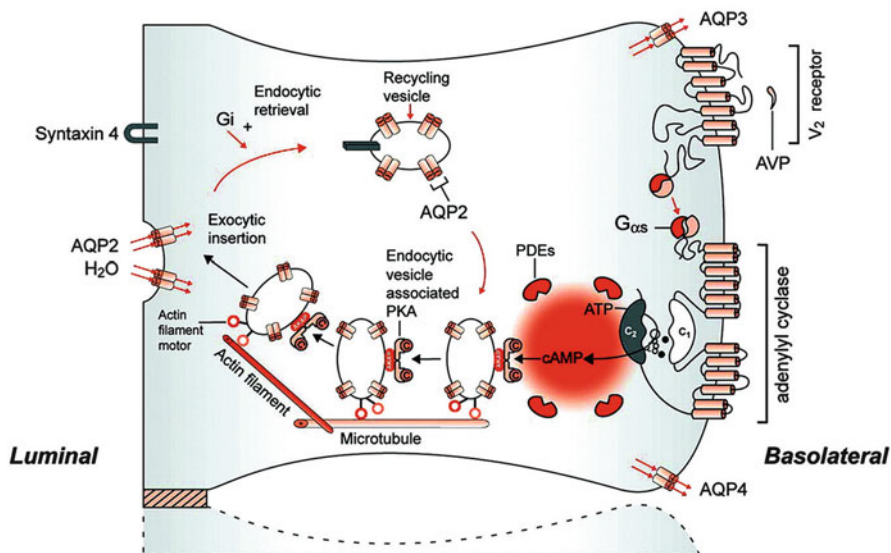
Fig. 12.4 Mechanism of vasopressin effects on water. Cartoon shows a principal cell with V2 G protein-coupled V2 receptors on the basolateral cell surface. Agonist binding activates adenylyl cyclase, increases intracellular cyclic AMP, activates protein kinase A (PKA), and stimulates exocytic insertion of preformed aquaporin-2 (AQP2) molecules into the apical membrane. Other aquaporins (AQP3 and AQP4) permit constitutive water movement across the basolateral membrane (from [33], with permission)

necessarily continuous and at a high level (see Fig. 12.5). *Clinical euvolemia* is also considered essential, because EABV depletion also stimulates AVP secretion (Fig. 12.2). If AVP secretion is the result of an edematous disorder (such as heart failure or cirrhosis of the liver), then edema is typically easily detected, as hyponatremia only occurs in the setting of severe disease. In contrast, it can be difficult to discern ECF volume depletion as the cause of hyponatremia, because the sensitivity of clinical assessment is limited [6]. Laboratory tests can often provide additional guidance. A low serum uric acid or blood urea nitrogen, or a urinary Na concentration greater than 40 mmol/L in hyponatremic patients suggest SIADH [7]; for example, a serum uric acid concentration lower than 4 mg/dL (when hyponatremia is present) has a positive predictive value for SIADH between 73 and 100 %, whereas a urine [Na] <30 mmol/L has a predictive value of 71–100 % that 0.9 % saline infusion will effectively increase the serum [Na] [6, 8].

When diagnostic uncertainty remains and the patient's symptoms are mild, it is usually safe to infuse 2 L of 0.9 % saline during 24 h. Even though 0.9 % saline is not the preferred treatment for SIADH, correction of the hyponatremia suggests that ECF volume depletion was contributing to the hyponatremia. Although there is concern that 0.9 % saline may worsen hyponatremia in patients with severe SIADH, owing to

Table 12.2 Diagnosis of the syndrome of inappropriate antidiuresis

Essential
  Decreased effective osmolality ($P_{eff} < 275$ mOsm/kg H_2O)
  Urine osmolality >100 mOsm/kg H_2O during hypotonicity
  Clinical euvolemia
No clinical signs of ECF volume depletion
No orthostasis, tachycardia, decreased skin turgor, or dry mucous membranes
No signs of ECF volume excess
No edema or ascites
  Urine [Na] >40 mmol/L, on a normal NaCl intake
  Normal thyroid and adrenal function
  No recent diuretic use
Supplemental
  Plasma uric acid less than 4 mg/dL
  Blood urea nitrogen less than 10 mg/dL
  Fractional Na excretion >1 %; Fractional urea excretion >55 %
  Failure to correct hyponatremia after 0.9 % saline infusion
  Correction of hyponatremia with fluid restriction
  Abnormal water load test (excretion of <80 % of 20 mL/kg body wt water during 4 h, or failure to dilute urine to <100 mOsm/kg H_2O)
  Elevated plasma AVP levels, despite hypotonicity and clinical euvolemia

Source: Adapted from [1, 20]. Water load tests and AVP measurement are rarely recommended
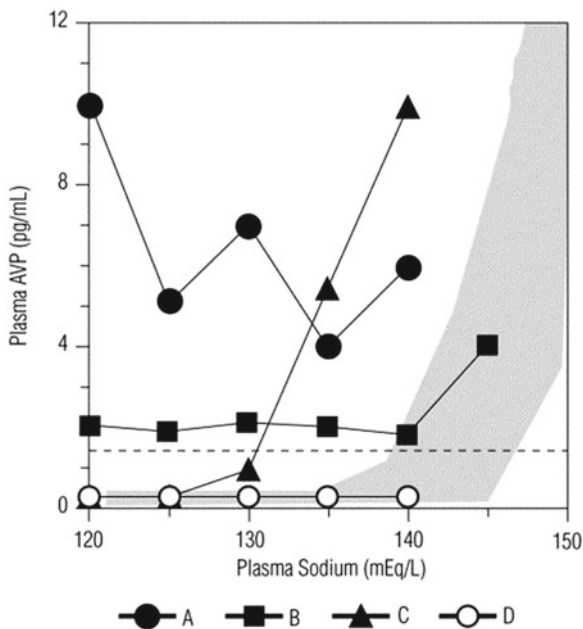
Fig. 12.5 Patterns of AVP secretion in SIADH. Patterns of plasma AVP (ADH) versus plasma sodium observed in patients with SIADH. Type A: unregulated secretion; Type B: Elevated basal secretion, despite normal regulation by osmolality; Type C: Reset osmostat; Type D: undetectable AVP. From [34], with permission

the phenomenon of desalination [9], this maneuver is usually safe when baseline urinary osmolality is less than 500 mOsm/kg H_2O [8, 10, 11]. Measurement of the serum AVP level is not recommended routinely as part of the diagnostic evaluation.

Treatment of Symptomatic SIADH

The most important factors dictating the management of SIADH are its severity, duration, and the presence of symptoms [12–14]. Decisions about the best therapeutic approach always involve balancing competing risks; *undertreatment* may permit progressive neurological deterioration, possibly leading to death, whereas rapid, or too extreme, treatment may lead to osmotic demyelination, another dreaded and morbid complication.

For symptomatic patients with severe hyponatremia of less than 48 h duration, clinical experience suggests that treatment is safe and effective. The goal is to raise the $[Na]_s$ enough to prevent neurological deterioration, while avoiding complications. The target values for correction have changed during the past 20 years, and they remain highly controversial. Some experts advocate restricting the total correction to 6 mmol/L during the first 24 h of treatment, and 12 mmol/L during 48 h, even when the hyponatremia is acute. An expert panel suggested that correction be limited to 10 mmol/L during the first 24 h, and 18 mmol/L during 48 h and yet this group noted that some patients are at high risk for complications from treatment and should be treated more cautiously [15]. Others, however, continue to emphasize the danger in treating too conservatively and suggest that more aggressive treatment is warranted [16]. Although it has been suggested that one should emphasize the absolute change in [Na] during the first 12 or 24 h, rather than the rate of rise [15], many authorities recommend increasing the [Na] by 1 mmol/L/h initially by infusing 3 % saline; this approach is guided only by case series, in the absence of data from randomized trials, but it is widely accepted. Some authorities have recommended concomitant furosemide [17], but most recommend avoiding it [18] or reserving it for patients who become ECF volume expanded [19, 20].

Several formulas are available to estimate the rate at which saline should be infused. While the Adrogué-Madias formula [21] is commonly used and has been validated in some situations [22], it is a two-step procedure that is relatively complicated, making it subject to error. A simpler approach, advocated by Jancic and Verbalis [20], gives quite similar results [21]. Three percent saline is administered at a rate in mL/h that is equal to the body weight in kilograms. This is expected to raise the [Na] by 1 mmol/L per hour, as desired. Thus, if the goal is to raise [Na] by 6 mmol/L in a 6 h period and the patient weighs 70 kg, 3 % saline can be infused at 70 mL/h for 6 h. The simplicity of this approach is advantageous.

Others continue to advocate more aggressive treatment. One approach is to administer 250 mL of 3 % NaCl, giving 50 mL by intravenous push (which should raise the plasma sodium concentration by 1–2 mmol/L), and letting the remaining 200 mL drip for the next 4–6 h. This is said to raise the [Na] by 8–10 mmol/L and

avoid the acute neurologic dangers of hyponatremia. In this case, the recommendation is to keep the [Na] below 120 mmol/L during the first 24 h of treatment and then correcting the remaining deficit gradually [16].

The management of hyponatremia of unclear duration with nonspecific symptoms or signs (e.g., headache or lethargy) is particularly challenging. Some reports suggest that patients risk adverse outcomes if not treated aggressively [23], whereas others suggest that such patients are at higher risk from rapid correction [24], and that the reported morbidity results from the underlying disease [25]. It does seem clear that a longer duration of hyponatremia increases the risk of osmotic demyelination (OD). This syndrome, which includes both central pontine and extrapontine myelinolysis, often begins following an initial symptomatic improvement and presents with lethargy and affective changes, followed by mutism or dysarthria, spastic quadriparesis, and pseudobulbar palsy [26]. Case series and experimental data indicate that this complication can result from rapid or too extreme correction of chronic hyponatremia [26]. Some authorities recommend initial evaluation with a CT scan or MRI of the brain to determine whether cerebral edema is present as a measure of the urgency of correction. It is not clear that this improves outcomes [27]. Many authorities recommend correcting such patients at 0.5-1 mmol/L/h using a lower rate of hypertonic saline infusion (half of that noted above). As above, many limit correction to 6–8 mmol/L in 24 h and 12–18 mmol/L in 48 h. Perhaps the one area in which all authorities agree is that close monitoring of [Na] (every 2–4 h) is imperative and can help prevent complications.

One recent variant on the approach described above has been to re-lower [Na] by administering water and desmopressin (dDAVP; a synthetic analog of AVP that activates V2R selectively) in patients who have exceeded recommended correction rates [28]. Some patients, especially those with reversible causes of SIADH, will develop a spontaneous water diuresis upon admission to the hospital. This can lead to rapid and potentially harmful correction rates. When this has occurred, desmopressin, given as 1–2 µg doses intravenously or subcutaneously, can be administered to slow the water losses and dextrose in water can be administered as needed to achieve the [Na] target level [29]. An even more aggressive approach is to start both desmopressin and 3 % saline simultaneously, to prevent sudden water diuresis and excessive correction [30]. While this approach may be considered in selected individuals, it should be used cautiously, since experience with it is very limited.

A more recent option for treating SIADH is VR antagonists. For acute use, conivaptan is available. In a double-blind, randomized trial, $[Na]_s$ increased by 6 mmol/L more in groups assigned to conivaptan than placebo for 4 days. Other studies have suggested that the drug effectively raises [Na]. Yet, there are concerns about its use. In a single center trial, conivaptan led to correction more rapidly than desired in approximately 50 % of treatments, and hypotension (presumably because conivaptan blocks both types of VR) and phlebitis were noted. Thus, the appropriate role for conivaptan in the treatment of symptomatic hyponatremia remains to be determined.

Chronic treatment of SIADH is beyond the scope of this chapter, but, in addition to eradication of the underlying disorder, involves restricting fluid intake, demeclocycline, and perhaps oral vaptans. The interested reader is referred to reviews, for more information [21].

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Chapter 13
Diabetes Insipidus

David H. Ellison

Précis

1. Clinical setting—Urine output greater than 3 L daily (in an adult) or >2 L/M^2 in a child (polyuria).
2. Diagnosis—Exclude primary polydipsia, and then determine whether the process reflects (a) central diabetes insipidus (CDI; owing to a lack of antidiuretic hormone) (ADH, also known as *arginine vasopressin*, AVP) production or (b) nephrogenic diabetes insipidus (NDI; owing to the failure of the kidney to respond to AVP).

   (a) History: The most prominent symptom or sign is polyuria, typically including nocturia. In most affected individuals, this is accompanied by polydipsia, which is a secondary phenomenon. There may be a history of a central nervous system event (with CDI), the ingestion of a drug known to damage the urinary concentrating capacity (such as lithium, for NDI), or a family history (for inherited disease). When thirst is impaired or when fluid intake is impossible (such as during acute hospitalization or anesthesia), hypernatremia will develop unless water losses are replaced. In this case, lethargy, confusion, weakness, and irritability, sometimes progressing to twitching, seizures, and coma, can occur.
   (b) Physical examination: Often, the physical exam is relatively normal. Signs of depletion or expansion of the extracellular fluid (ECF) volume are typically absent. Thus, peripheral edema, ascites, pulmonary crackles, or jugular venous distension suggest that other processes have supervened. Neurological impairment, which occurs during frank hypernatremia, is typically non-focal unless the result of a specific neurological insult (such as a stroke).
   (c) Laboratory values: Most laboratory tests are normal, including serum Na concentration and osmolality. Hypernatremia is only observed when there is

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a defect in thirst or in the ability to drink; thus hypernatremia is typically observed only in the very young (who cannot access fluids by themselves), the very old (who tend to experience a mild to moderate loss of thirst as they age), or the very ill (who are unable to gain access to, or indicate the need for, fluids). The urine is typically dilute, with an osmolality <250 mOsm/kg water. A low serum Na⁺ concentration suggests primary polydipsia. A water deprivation test (see below) may be necessary to distinguish between polydipsia and DI, but this is not necessary if the basal plasma Na⁺ concentration exceeds 145. In this case, desmopressin (dDAVP) can be used to distinguish CDI from NDI. Measurement of plasma AVP can be used during dehydration to help confirm the nature of the underlying process.

(d) Imaging: Imaging is not typically employed to make a diagnosis of diabetes insipidus; it is, however, important to determine whether processes within the central nervous system are contributing to any observed defects in urinary concentration.

3. Treatment—The two goals of therapy are to replace the free water deficit and to stop the ongoing inappropriate loss of free water. The free water deficit can be calculated by the formula.

$$\text{Water deficit} = \frac{\left(\text{Plasma Na}^+ - 140\right)}{140} \times \text{Total body water.}$$

Total body water is about 60 % of body weight in men and 50 % of body weight in women. That deficit, typically between 2.5 and 5 L, should be corrected slowly over 48–72 h. The serum sodium should be lowered no faster than 0.5 mmol/L/h or 12 mmol/L/day. Saline, 0.5 N, is the usual choice for rehydration.

Ongoing water loss will be corrected by dDAVP (desmopressin) in most cases of NDI. The usual adult dose is 50 μg by mouth twice a day or 1–2 μg IV twice a day.

NDI will not respond to dDAVP, but can often be helped by a low sodium diet and a thiazide diuretic.

Diabetes Insipidus

Diabetes insipidus means the excessive production of dilute urine; the term *diabetes* indicates excessive urine production (Greek: διαβετεσ = siphon), and the term *insipidus* implies "tasteless," in contrast to the taste of urine from patients with diabetes mellitus. A syndrome in which copious amounts of dilute urine are produced has been recognized since at least the mid eighteenth century, when Cullen stressed that the urine in "diabetes" might be sweet or not. He stated, "I myself, indeed, think I have met with one instance of diabetes in which the urine was perfectly insipid; and it would seem that a like observation had occurred to Dr. Martin Lister. I am persuaded, however, that such instances are very rare; and that the other is much more common and perhaps the almost universal occurrence. I judge therefore, that the presence of such a saccharine matter may be considered as the principal circumstance in idiopathic diabetes" [1].

Over the ensuing years, it gradually became clear that there is a circulating factor (hormone) responsible for concentrating the urine, and that the circulating factor is produced by hypothalamic neurons and secreted from the posterior lobe of the pituitary. The chemical structure of this factor, AVP, was finally determined by du Vigneaud, which led, together with his work on oxytocin, to the Nobel Prize in 1955. The kidney receptor for vasopressin (the type 2 vasopressin receptor, V2R) was cloned in 1992 by Birnbaumer, Rosenthal, and colleagues [2]. Water channels were identified first in 1992 by Peter Agre [3], a discovery also leading to the Nobel Prize. In the collecting duct apical membrane, aquaporin 2 (AQP2) mediates vasopressin-sensitive water reabsorption.

Although primary polydipsia (psychogenic polydipsia) also leads to copious amounts of dilute urine, this disorder, which affects individuals with serious psychiatric disease, with anxiety disorders, and occasionally with infiltrative diseases of the brain, is not typically considered to be a cause of diabetes insipidus. Instead, the diagnosis of diabetes insipidus is given only to individuals in whom the elaboration of copious amounts of highly dilute urine results from defective urinary concentrating *ability* (the dilute urine is, therefore, inappropriate).

Antidiuretic Hormone Secretion

The human ADH is AVP. This nonapeptide hormone (Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-Gly-NH$_2$, see Fig. 12.1) is produced by the hypothalamus, and trafficked to the posterior pituitary, where it is stored (see Fig. 12.2). In response to small increases in plasma tonicity (see Fig. 12.3), AVP is secreted into the bloodstream, where its half-life is short (15–20 min). Secretion is also stimulated by depletion of the effective arterial blood volume (EABV), although this response only occurs when ECF volume depletion amounts to approximately 10 % (see Fig. 12.3); thus day to day control of AVP secretion is regulated primarily by plasma osmolality.

AVP binds to two classes of receptor, vascular receptors (V1R), which lead to vasoconstriction, and renal tubular receptors (V2R) on the basolateral membrane of principal cells in the collecting duct. Engagement with V2R leads to insertion of preformed water channels (AQP2) into the apical plasma membrane, which increases transcellular water permeability (see Fig. 12.4). As the interstitium of the kidney is hypertonic, owing to countercurrent exchange, water is reabsorbed from the collecting duct and urine becomes concentrated. Via the action of this system, the urine osmolality can rise to 1,200 mOsm/kg H$_2$O; conversely, in the presence of copious water intake, the urinary osmolality can be as low as 50 mOsm/kg H$_2$O.

The AVP system typically acts in concert with thirst to regulate the serum osmolality (usually reflected by the serum Na$^+$ concentration). In contrast, ECF volume is regulated largely by the renin/angiotensin/aldosterone system, which modulates NaCl balance. Thus, *disorders of Na concentration* are typically analyzed as disorders of *water balance* (rather than salt balance) and result from disordered AVP secretion or action or water intake or excretion.

Causes and Classification of Diabetes Insipidus

Diabetes insipidus is classified as *central* (CDI), resulting from deficient AVP secretion, and *nephrogenic* (NDI), resulting from renal resistance to AVP (see Table 13.1). Although some patients are completely unable to concentrate their urine, others can increase urine osmolality moderately, in response to increases in plasma osmolality (see Fig. 13.1). Such individuals have been labeled as suffering from "partial" DI, to reflect this. It is believed that their disease can become complete in some cases.

Although there are hereditary causes of both CDI and NDI, most cases are acquired, especially in adults. A urinary concentrating defect can be observed

Table 13.1 Causes of polydipsia and hypotonic polyuria

Central DI
Congenital
Inherited neurohypophyseal DI (autosomal dominant, OMIM 125700)
Acquired
Trauma (neurosurgery, deceleration injury)
Vascular incident (cerebral hemorrhage or infarction)
Infectious (meningitis, encephalitis)
Inflammatory (lymphocytic infundibuloneurohypophysitis)
Drug-/toxin-induced
Ethanol
Phenytoin
Snake venom
Nephrogenic DI
Congenital
X-linked recessive ($AVPR_2$ mutations; OMIM 304800)
Autosomal recessive (AQP2 mutations; OMIM 2222000)
Dominant (AQP2 mutations; OMIM 125800)
Acquired
Infiltrating lesions (sarcoidosis, amyloidosis)
Vascular (sickle cell)
Drug-/toxin-induced
Lithium, cisplatin, methoxyflurane, demeclocycline, vaptans
Metabolic
Hypercalcemia
Hypokalemia
AVP-metabolism
Pregnancy (vasopressinase)
Primary polydipsia
Psychogenic (schizophrenia)
Dipsogenic (resetting of the thirst threshold; same causes as central DI)
Osmoreceptor Dysfunction (essential hypernatremia; both thirst and concentration defects)
Granulomatous
Neoplastic
Vascular
Other
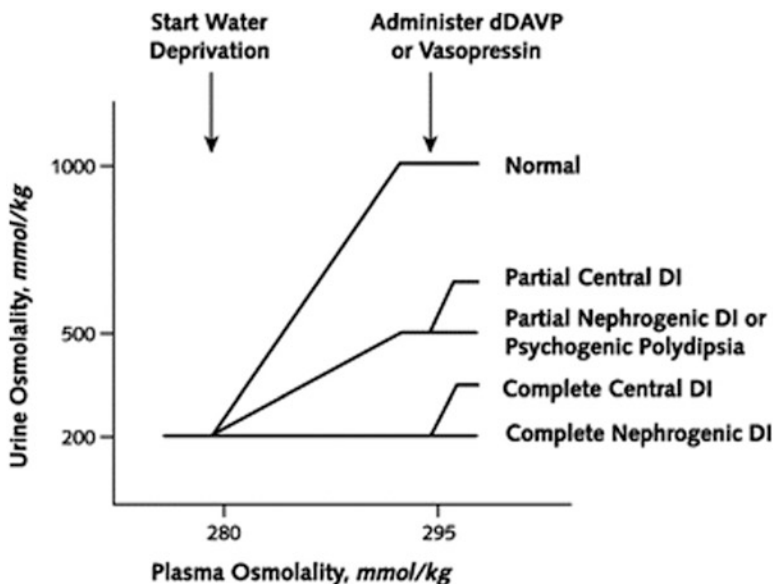
Fig. 13.1 Effect of plasma osmolality on urine osmolality in complete and partial diabetes insipidus. Typical response to water deprivation in healthy individuals and patients with complete or partial DI. The 200 mOsm/kg H_2O line is for schematic representation, because patients with the full phenotypes have urine osmolalities less than 100 mOsm/kg H_2O. From [6], with permission

during pregnancy when the placenta elaborates vasopressinase, resulting in a deficiency of circulating AVP, but not from inadequate secretion (thus, this is neither CDI nor NDI). Finally, a distinct disorder results when hypothalamic lesions impair both AVP secretion and thirst simultaneously. Here, the natural compensatory process of increased fluid intake is absent, and affected individuals invariably present with the symptoms of hypernatremia. This syndrome has been called *essential hypernatremia* because of this presentation.

There are hereditary causes of both CDI and NDI (see Table 13.1) [4]. These are rare, accounting for less than 10 % of cases, but their diagnosis is important, when they occur. Individuals with *autosomal dominant neurohypophyseal diabetes insipidus* typically retain some capacity for AVP secretion, so that symptoms usually appear after the first year. In contrast, individuals with *X-linked NDI* as a result of AVPR2 mutations present with severe failure-to-thrive after birth that can lead to physical and mental retardation because of the recurrent episodes of dehydration. A similar presentation can be seen with mutations of AQP2, but this variant is observed in both boys and girls, as it is autosomal.

Acquired processes are much more common causes of polyuric syndromes, especially in adults. These include multiple central processes, such as traumatic, neoplastic, infectious, or surgical events (Table 13.1). NDI can be caused by kidney disease, but the most common cause is therapeutic drugs. Lithium treatment of bipolar disease is the most frequent cause of drug-induced NDI. Between 20 and 50 % of patients taking lithium develop this complication [5].

Presentation and Diagnosis

The patient typically presents with polyuria. A sudden increase in urine output suggests CDI, whereas a more gradual onset suggests NDI. Presentation during infancy clearly suggests an inherited cause. Historical features are crucial in distinguishing CDI from NDI. The history of a neurological event points toward CDI, whereas the use of offending drugs points toward NDI. Conversely, a history of psychiatric disease suggests that the disorder may be primary polydipsia, rather than DI. Oftentimes, progressive nocturia in the absence of prostatic hypertrophy can be a clue to the development of a concentrating defect. A family history of polyuria suggests the possibility of an inherited defect.

Although hypernatremia and hyperosmolality are not the most common presenting features (owing to compensatory fluid intake), they are the most common emergent complications. This is most often observed, as noted, in situations where fluid intake is difficult. In adults, it is most common in the elderly, or in those who require intensive care. Signs and symptoms of hypertonic dehydration include prerenal azotemia, hypotension and, sometimes, shock. In a person with a urinary concentrating defect, rapidly developing hypernatremia can occur when the underlying process is not recognized. When this occurs, symptoms resulting from neurological dysfunction are common. These include lethargy, confusion, weakness, irritability, twitching, seizures, and coma. The severity of symptoms resulting from a given rise in serum Na^+ concentration is dependent upon the time period over which the change occurs. A rapid rise will cause confusion, weakness, or extreme thirst. In contrast, chronic hypernatremia is often asymptomatic because of the adaptive processes of neurons which accumulate electrolyte and nonelectrolyte ("idiogenic") osmoles to balance the hypertonicity of the plasma (see below).

To make the diagnosis of DI in the setting of polyuria (or hypernatremia), the urine concentration must be less than 250 mOsm/kg H_2O, despite a stimulus for AVP secretion (typically, plasma hypertonicity). Although these criteria appear straightforward, their application is not always so easy. Although low serum Na^+ concentration in the presence of polyuria suggests the presence of primary polydipsia, a formal water deprivation test (see Table 13.2) is often recommended to differentiate primary polydipsia from DI. In contrast, if the serum Na^+ concentration exceeds 145 mmol/L *at baseline*, and the urine osmolality is less than the plasma osmolality, *the diagnosis of DI has been established*; the diagnostic workup only involves determining whether the DI is central or nephrogenic (see below).

Although water deprivation can sometimes be necessary to confirm a diagnosis, it does present risk, and is not always recommended. Caution is required when evaluating newborns and young children and individuals at risk for a thirst defect. Patients with a history of lithium ingestion and dilute urine also may not need a formal water deprivation test. Some authorities do not recommend overnight fluid restriction for patients with substantial polyuria, as this can prove hazardous [6]. Others suggest that overnight deprivation can be tried in routine cases [7]. A protocol for water deprivation is presented in Table 13.2, along with guidelines to interpret the test. In general, to make a diagnosis of CDI, the urine osmolality should rise

Table 13.2 Water deprivation test

Before the test
Ask the patient to cease fluid consumption 2 h before coming to the office or clinic
On arrival
Measure the body weight and plasma Na and osmolality at baseline
Ask the patient to void
Record each urine void, record its volume, and determine the specific gravity and osmolality
Obtain weight and vital signs every 2 h for the first 4 h and then hourly
Measure plasma Na and osmolality at 4 h and then every other hour
A testing threshold is reached when the
1. Urine specific gravity ≥1.020
2. Serum Na >145 mmol/L
3. Plasma osmolality ≥300 mOsm/kg H_2O
4. Urine osmolality reaches a plateau (<10 % change over 3 periods)
For safety reasons, stop the test when any of the following occur
1. There is a weight loss ≥3 % or patient exhibits signs of volume depletion
2. A preselected time point is reached: this may be 6 h if <6 months old, 8 h is <2 years, and 12 h for children older than 2
At the end of the test, measure weight, vital signs, plasma sodium, and plasma and urine osmolality and urine-specific gravity
Measure plasma AVP
Then administer 1 μg desmopressin subcutaneously and follow the urine osmolality for 2 h more
Interpretation
CDI is diagnosed if the urine osmolality rises by >50 % following desmopressin
NDI is diagnosed if the urine osmolality rises <10 %
Intermediate cases (urine osmolality rise 10–50 %) can be assessed by examining the plasma AVP

by at least 50 % following AVP or desmopressin administration. On the other hand, a less robust response can be observed in patients with partial DI. Both AVP and desmopressin can be used to assess diabetes insipidus. Some authorities prefer desmopressin because it is selective for the V2 receptor and does not have the vasoconstrictive properties of AVP (Pitressin).

Treatment of Hypernatremia

Hypernatremia is the most dreaded complication of diabetes insipidus. In diabetes insipidus, the hypernatremia is generally driven by the loss of water only, meaning that repletion with water (as opposed to hypotonic saline) is generally recommended. A key determinant of the rate at which hypernatremia should be corrected is its duration. When hypernatremia has been present for a short period of time (<12 h), then correcting it promptly is important to prevent neurological consequences. In contrast, when the hypernatremia is chronic, rapid correction is hazardous owing to the appearance of organic osmolytes (previously called idiogenic osmoles) within cells of the central nervous system. These organic osmolytes help
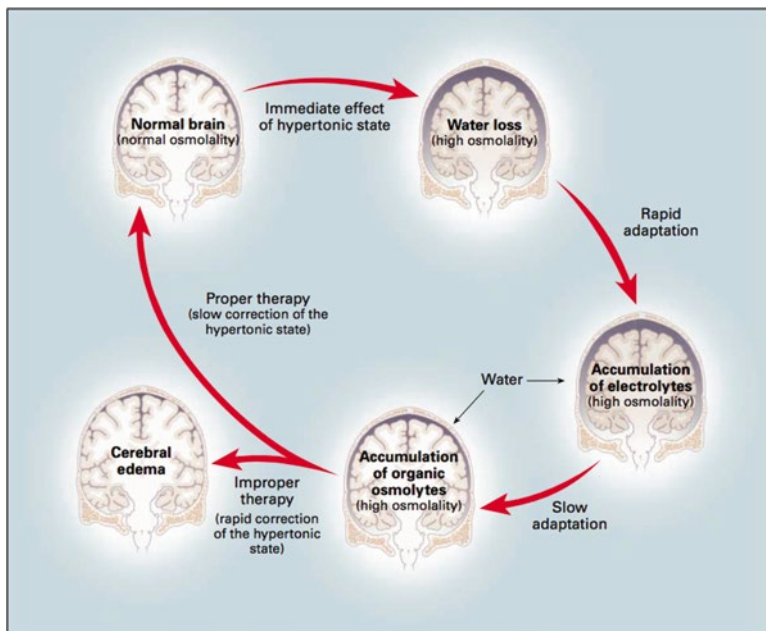
Fig. 13.2 Effects of hypernatremia on brain water. During acute hypertonicity, the brain loses water. Volume regulatory processes rapidly lead to some accumulation of electrolytes within brain cells, attenuating the shrinkage that would otherwise occur. Over time, these electrolytes are replaced by organic osmolytes, which help to equalize the intracellular osmolality without cellular toxicity, leading to brain re-expansion. If aggressive sodium lowering occurs at this time, brain edema can result. Used, with permission, from [8]

to maintain the intracellular osmolality in the face of high extracellular osmolality, permitting the brain to re-expand (see Fig. 13.2). If overly rapid correction is begun once these adaptations have occurred, cerebral edema can result. When hypernatremia is demonstrably acute (<12 h) the serum Na concentration can be corrected at a rate of 1 mmol/h to reduce the risk of neurological complications [8]. In contrast, when the hypernatremia is of unknown or longer duration, such rapid correction can lead to cerebral edema. In this case, a slower rate of correction is typically recommended, often 0.5 mmol/h [8]. In either case, it is recommended to restrict the total correction to 10 mmol during the first 24 h.

Correcting the Water Deficit

It is important to assess the magnitude of existing water deficit to guide the rate at which hypotonic fluids should be administered. Two approaches are commonly recommended. The first involves estimating the water deficit.

Method #1 (the *Water Deficit Method*) [9]:

$$\text{Water Deficit} = \text{Total Body Water} \times \left(\frac{[Na]}{[140]} - 1 \right),$$

where *Total Body Water* is estimated as the current weight×0.6 (for men) or 0.5 (for women). [Na] is the current serum Na^+ concentration [10].

For example, in a 70 kg man with a Na^+ concentration of 165 mmol/L, the TBW = 42 L. The water deficit is estimated as 42×0.179 = 7.5 L. As this is the amount of water required to correct the deficit by 25 mmol, and the goal is to correct by 10 mmol/L per day, then $7.5 \times \frac{10}{25} = 3L$ of D5W is required to reduce the serum Na^+ by 10 mmol/L. To correct at a rate of 1 mmol/L/h (one tenth of the daily correction per hour), the total fluid volume (3 L) should be administered over a 10 h period giving an infusion rate of approximately 300 mL/h. To correct more slowly, for the patient with chronic hypernatremia, the infusion rate can be 125 mL/h during 24 h (which gives the same daily correction, but a slower infusion rate).

Method #2 (the *Rate Calculation Method*) [8]:

First, estimate the effect of infusing 1 L of fluid on the serum Na^+ concentration. For an infusate that contains only water and Na^+, the

$$\text{Change in Serum Na} = \frac{infusate\,Na^+ - serum\,Na^+}{Total\,Body\,Water + 1},$$

where the total body water is estimated as above.

For an infusate that contains K^+, as well as Na^+, then the formula is

$$\text{Change in Serum Na} = \frac{\left(infusate\,Na^+ + infusate\,K^+\right) - serum\,Na^+}{Total\,Body\,Water + 1}.$$

For the same example as above, where D5W is infused (infusate Na^+ is 0), 1 L will reduce Na^+ by −165/43 = 3.8 mmol/L. To reduce Na^+ by 10 mmol/L, the second formula recommends infusing 2.63 L (=10 mmol/3.8 mmol/L) [8].

Thus, the two formulas give similar, but not identical, recommended infusion rates. The first approach has the benefit of greater simplicity. The second approach can be used when infusion rate for fluids contain both Na^+ and K^+.

Ongoing Losses

The predicted infusion rates for hypotonic fluid often underestimate water needs. This is most commonly because insensible losses (typically 0.5 L per day) and ongoing urinary losses have not been fully accounted for. To estimate urinary losses,

especially in the setting of NDI, where urinary water losses may be relatively fixed, it is generally recommended to calculate the electrolyte-free water excretion [11].

$$CH_2O^e = V \times \left(1 - \frac{\left(U_{Na} + U_k\right)}{P_{Na}}\right).$$

Thus, if the individual above is making 4 L per day of urine, with a urine [Na+]=41 and a K+=41, then the electrolyte-free water clearance will be approximately 2 L per day. This amount should be added to the infusion rate, calculated from the deficit, using the formulas above.

The greatest importance of these formulas and approaches is to provide an initial estimate of water infusion rates. These are only estimates, and rates of ongoing water loss can increase or decrease unexpectedly. As the goal of treatment is to achieve a measured reduction in serum Na+, the physician must remain vigilant during treatment, monitoring the serum electrolytes frequently (every 4 h initially) and adjusting infusion rates appropriately. If dextrose containing infusion solutions are employed, the patient should also be monitored for the possible development of hyperglycemia.

Treating the Underlying Disorder

Once a plan for correction of any water deficit has been devised, attention turns to the underlying disorder, and to the major symptoms associated with DI, namely polyuria. In the case of CDI with an urgent need to treat (such as a patient going to surgery), parenteral desmopressin is typically preferred. This drug has the advantage of high specificity for V2R, over V1R, therefore avoiding the side effects associated with AVP. For the urgent situation, desmopressin should be administered parenterally, intravenously, intramuscularly, or subcutaneously, in doses of 1–2 μg every 8–12 h.

For longer-term treatment of CDI, especially when complete, desmopressin represents the best approach. In the absence of thirst defects, the treatment of CDI is directed toward amelioration of bothersome symptoms, especially nocturia. Complete correction of the water excretory defect runs a risk of water retention and is not generally recommended. Dose finding is empiric. One approach is to start 0.05–0.2 mg orally or 5–10 μg intranasally at bedtime [9]. If this dose controls nocturia, and polyuria does not return until afternoon, then it may be sufficient. The patient should be instructed to detect inadvertent hyponatremia, and report these symptoms immediately. Once a stable dose is reached, twice yearly monitoring may be sufficient. Patients should be monitored for a potential return of concentrating capacity during the annual visits. For partial DI, simply restricting solute intake may be sufficient to reduce polyuria to an acceptable level.

The efficacy of endogenous AVP in partial CDI can be enhanced using pharmacological agents, including chlorpropramide (250–500 mg/day), clofibrate (500 mg 3–4 times daily), or carbamazepine (400–600 mg daily) [9]. Alone, these agents are typically only marginally effective, but when combined with AVP treatment and oral solute restriction, they may be useful. Unfortunately, as all are used primarily for other conditions, such as diabetes or seizures, side effects are common.

The treatment of NDI is more difficult, as no specific agents are available. For patients with acquired disease, it is always best to eradicate the underlying cause. Factors such as hypokalemia, hypercalcemia, or the use of drugs such as demeclocycline, glyburide, or colchicine should be removed, if possible. Many times, however, lithium is found to be essential for control of bipolar disease. Amiloride (5 mg/day), which apparently competes for lithium for uptake into distal cells [12], can improve polyuria in such patients [13]. For other patients with NDI, thiazides are well-known to reduce urine flow, probably by inducing mild volume depletion and by increasing water reabsorption along the collecting duct [14, 15].

Finally, for gestational diabetes insipidus resulting from the placental secretion of vasopressinase, desmopressin is recommended. The secreted vasopressinase does not metabolize the synthetic drug, and the drug has a good safety record in pregnant individuals [16].

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Chapter 14
Pheochromocytoma Hypertensive Crisis

Vitaly Kantorovich and Karel Pacak

Précis

1. Clinical setting: Severe, often episodic, arterial hypertension resistant to the usual therapeutic interventions, or any acute hypertensive event in an otherwise non-hypertensive person. There can be an associated family history of pheochromocytoma, von Hippel–Lindau syndrome, multiple endocrine neoplasia type 2, neurofibromatosis type 1, or one of the hereditary paraganglioma (extra-adrenal pheochromocytoma) syndromes. There is a growing association with the incidentally discovered adrenal.

2. Diagnosis

    (a) History: The classic "paroxysmal attack" begins abruptly and can last for minutes to hours. The frequency of attacks varies between several attacks per day, to a single attack every few months. Patients usually complain of palpitations, diaphoresis, and headache. Some patients complain of lightheadedness on rising from a lying or sitting position. Other symptoms include anxiety, tremulousness, chest and abdominal pain, weakness, and weight loss.

    (b) Physical examination: Sustained or episodic hypertension with or without orthostatic hypotension is usually the initial finding. Tachycardia and pallor are often present. Physical findings suggesting a hereditary pheochromocy-

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toma syndrome include renal tumor, retinal angioma, thyroid nodule, mucosal neuroma, and neurofibroma.

(c) Laboratory evaluation: Plasma or urinary metanephrines should be measured. If the plasma or urinary metanephrine values are equivocal (usually less than 4 times above the upper reference limit) and no interfering medication effect can be shown, a clonidine suppression test should be considered.

(d) Imaging studies: CT of the adrenal glands is the preferred imaging modality. MRI is also useful, especially in where radiation exposure must be minimized. "Brightening" of the tumor with T_2 weighted images is highly suggestive of pheochromocytoma. Functional imaging—^{123}I-MIBG scintigraphy and Octreoscan—can improve diagnostic accuracy. Most tumors are intra-adrenal (80 %), unilateral (90 %), and benign (80 %).

3. Initial treatment: Treatment of the hypertensive crisis should be carried out in an intensive care unit when possible. Nitroprusside is the first line of therapy with an initial intravenous dose of 0.3 µg/kg/min. This dose can be increased by increments of 0.1–0.3 µg/kg/min at 3–5 min intervals until the hypertension is controlled. The maximum recommended dose is 10 µg/kg/min.

Phentolamine, a nonselective α-adrenoceptor antagonist, can and should be used outside the ICU. The usual dose for adults is 5 mg intravenously which can be repeated every several minutes until the blood pressure is controlled.

Patients who present with tachyarrhythmia should receive a β-adrenoceptor antagonist. Labetalol is recommended at an initial dose of 20 mg administered intravenously over a 2-min period. Additional doses of 40 mg, up to 80 mg, can be administered at 10-min intervals until the tachycardia is controlled. The total dose should not exceed 300 mg in a 24 h period. Metoprolol can be given IV at an initial dose of 2.5–5.0 mg every 6–12 h and titrated as needed up to 15 mg every 3 h. Alternatively, atenolol is very effective, especially outside the ICU.

Once satisfactory control of the hypertensive crisis is achieved, treatment is transitioned to oral phenoxybenzamine, an α-adrenoceptor antagonist, 10 mg twice daily, adjusted upward in 10 mg increments every 2 or 3 days, to a maximum of 50–100 mg 3 times daily. Intravenous β-adrenoceptor blockade can be transitioned to oral atenolol 25–50 mg every 8–12 h. β-adrenoceptor blockade should never be introduced before α adrenoceptor blockade is at a satisfactory therapeutic level.

Pheochromocytoma

Fränkel and colleagues reported the first case of pheochromocytoma in 1886. The patient was a previously healthy 18-year-old woman from Wittenweier, Germany, who presented to the University Hospital of Freiburg in 1884 and died 10 days after admission. Her medical history included recurrent attacks of sudden-onset palpitations, anxiety, dizziness, headache, vomiting, and constipation. Weakness appeared and progressed during the year before her death. She was found to be malnourished

and pale with an "agitated heart action and strong pulse." She had hypertension, retinopathy, proteinuria, and microhematuria. She had paroxysmal tachycardia (up to 180 beats per minute), sweating attacks, headaches, vomiting, visual deterioration, epistaxis, anxiety and, in the end, severe chest pain [1]. Her autopsy showed all the signs of acute and chronic hypertension. She had two adrenal tumors. A retrospective family history points to the diagnosis of MEN-2 with bilateral adrenal pheochromocytomas [1].

Pheochromocytoma is a rare disease. It is hard to estimate the exact prevalence because of its variable clinical features. It is estimated that the overall prevalence of pheochromocytoma is between 1:1,700 and 1:4,500, with an annual incidence of 3–8 cases per one million per year [2]. It occurs at any age, most often in the fourth and fifth decades. It has an equal gender distribution. Most of the tumors (80 %) are in the adrenal gland. The rest are extra-adrenal paragangliomas. Paragangliomas can be found anywhere from the head and neck to the urinary bladder and pelvis where they are usually in and around the organ of Zuckerkandl. About 10–20 % of pheochromocytomas are malignant [3], but there are "patient subgroups" in which a much higher prevalence of malignancy is reported [4]. Recently, there has been a significant shift in the patient population undergoing the "work-up" for pheochromocytoma—most of the patients are now referred because of an incidentally discovered adrenal mass, and less often because of poorly controlled hypertension.

Clinical signs and symptoms of pheochromocytoma relate to catecholamine action through adrenergic and dopaminergic receptors. The net effect of α-adrenergic stimulation is an increase in systemic vasoconstriction, peripheral pressure, and a decrease in target organ (myocardial, cerebral, renal, GI) perfusion. Activation of β-adrenoceptors induces pronounced myocardial inotropic and chronotropic effects, as well as the release of renin (Table 14.1). The "classic" symptoms and signs of a pheochromocytoma are headache, palpitations, and sweating. Hypertension, often the only sign of the disease, occurs in 90 % of patients. Other symptoms and signs include tachycardia, anxiety, pallor, and orthostatic hypotension [5]. Sustained hypertension occurs in 50 % of patients. Episodic or paroxysmal hypertension occurs in 45 %. Five percent of patients are normotensive [3]. Sustained hypertension strongly correlates with high levels of plasma norepinephrine. Paroxysmal hypertension is seen more frequently with epinephrine-secreting tumors and is typical of MEN-2-related pheochromocytoma [6]. The frequency of hypertensive spells can vary from "rare" to daily, but most occur at 7- to 10-day intervals. The length of each attack varies from minutes to an hour. The longer lasting ones often evolve into a hypertensive crisis [7, 8]. A hypertensive crisis refers to markedly increased arterial blood pressure that is resistant to the usual antihypertensive indications. Because of potentially devastating consequences that include acute myocardial infarction, congestive heart failure, renal failure, acute cerebrovascular accident, retinal detachment, and aortic dissection, crises are usually treated in the ICU. These spells are related to a sudden release of catecholamines from the tumor induced by factors such as physical activity, smoking, abdominal pressure, postural changes, and anxiety [6, 9]. Foods or beverages with a high tyramine content (cheese, beer, and wine) and certain medications (histamine, phenothiazine, and tricyclic antidepressants)

Table 14.1 Pathogenesis and organ-specific clinical features of pheochromocytoma

Organ	Syndrome	Mechanism	Receptor	Receptor action
Heart	Angina	Coronary spasm	Coronary α_1, β_2	Constriction
	Heart attack	Positive inotropy	Conducting system β_1, β_2	Increased conduction, automaticity, and contractility
	Cardiomyopathies	Positive chronotropy	Conducting system β_1, β_2	
	Myocarditis	Unmatched O_2 demand	Cardiomyocyte β_1, β_2	
	Acute failure	Hypoperfusion		
	Arrhythmias			
Brain	Stroke	Vasoconstriction	Cerebral arterioles α_1	Mild constriction
	Encephalopathy	Unmatched O_2 demand		Most of effect related to systemic hypertension
		Hypoperfusion		
Vascular	Shock	Vasoconstriction	Skeletal muscle α_1, α_2, β_2	Arteriolar constriction
	Postural hypotension	Unmatched O_2 demand		Venous dilation
	Aortic dissection	Hypoperfusion		
	Organ ischemia			
	Limb ischemia			
Kidneys	ARF	Vasoconstriction	Vascular α_1, α_2, β_1, β_2	Dilation > constriction
	Hematuria	Unmatched O_2 demand		
		Hypoperfusion		
Lungs	Pulmonary edema	Cardiac decompensation	Vascular α_1, β_2	Dilation > constriction
	ARDS	Increased permeability	Smooth muscle β_2	bronchodilation
	Fibrosis			
	Pulmonary HTN			
GI	Intestinal ischemia (necrosis, peritonitis)	Vasoconstriction	Visceral arterioles α_1, β_2	Constriction
		Unmatched O_2 demand		
		Hypoperfusion		
Ocular	Acute blindness	Vasoconstriction		
	Retinopathy			
AMF	All of the above			(acute multiorgan failure)

can precipitate a hypertensive paroxysm in patients with pheochromocytoma [10]. Metoclopramide is often used to treated nausea. When the treatment is given to a patient who has a pheochromocytoma, it can precipitate a severe life-threatening hypertensive crisis [11]. Glucocorticoids used to treat many inflammatory diseases also can cause a pheochromocytoma crisis [12]. Pheochromocytomas that secrete predominantly dopamine usually present with normotension. These tumors are

often extra-adrenal, and are diagnosed biochemically by increased plasma levels of free methoxytyramine, a metabolite of dopamine [13].

The complications associated with catecholamines excess are shown in Table 14.1. Catecholamines, mainly norepinephrine, induce peripheral vasoconstriction and elevated blood pressure, leading to increased arterial stiffness [14]. Hypercatecholaminemia can lead to hypoxic myocardial damage, aseptic myocarditis, and cardiomyopathy [8]. In most of these events, the coronary arteries are patent. The pathophysiology of asymmetric myocardial ballooning in tako-tsubo cardiomyopathy is poorly understood, but we suggest that it is related to the differential expression of adrenergic receptors in endocardium and myocardium, with an increased concentration in the region of the pacemaker. Increased myocardial oxygen demand shortens diastolic relaxation, resulting in worsening of myocardial damage. Peripheral vascular disease can be the result of intense vasoconstriction and result in limb ischemia, necrosis, gangrene, and aortic dissection. Pheochromocytoma can cause neurologic complications, including hypertensive encephalopathy with headache, papilledema, altered mental status, and stroke. Paroxysmal hypertension usually causes hemorrhagic stroke while postural hypotension is associated with ischemic stroke. The renal effects of pheochromocytoma include hypertensive nephropathy, renovascular hypertension, renal artery stenosis and, eventually, renal failure. Rarely, severe peripheral vasoconstriction can cause rhabdomyolysis due to muscular ischemia and acute tubular necrosis caused by myoglobinuria. Renal artery stenosis can coexist with extra-adrenal pheochromocytoma, making both diagnosis and treatment more complicated [15]. Acute intestinal ischemia is one of the most feared complications of pheochromocytoma. It presents with severe abdominal pain due to a spasm of the visceral arteries [16]. Paralytic ileus with pseudo-obstruction can be associated with pheochromocytoma and may respond to high dose phentolamine and metyrosine (see below) [17]. Eye disease associated with pheochromocytoma includes hypertensive retinopathy, secondary retinal arteriosclerosis, and retinal microaneurysms, hemorrhages, cotton-wool spots, and venous hemorrhage. Pheochromocytoma in pregnancy is associated with increased maternal and fetal morbidity and mortality [18]. Pheochromocytoma should be suspected with resistant hypertension and hypertensive crisis.

Diagnosis: The diagnostic approach is based on the assessment of either plasma or urine metanephrines [19]. Catecholamines should not be used in the biochemical diagnosis of pheochromocytoma since they often are secreted episodically and elevated levels can be missed with a single plasma sample (Fig. 14.1). Metanephrines are produced continuously and independently of catecholamine release. Therefore, metanephrines are more reliable in the detection of patients with pheochromocytoma (Figs. 14.2 and 14.3). Metanephrine levels correlate well with tumor size. Failure to suppress plasma normetanephrine with clonidine is very supportive of the diagnosis of pheochromocytoma (97 % sensitivity, 100 % specificity). Imaging studies are used to localize the tumor (Fig. 14.4). CT and MRI provide high resolution images that allow for the assessment of size, consistency, contrast washout rate, and lipid content. Functional images allow the detection of specific transporters/receptors associated with pheochromocytoma and include PET scans, ^{123}I-MIBG scintigraphy, and Octreoscan.
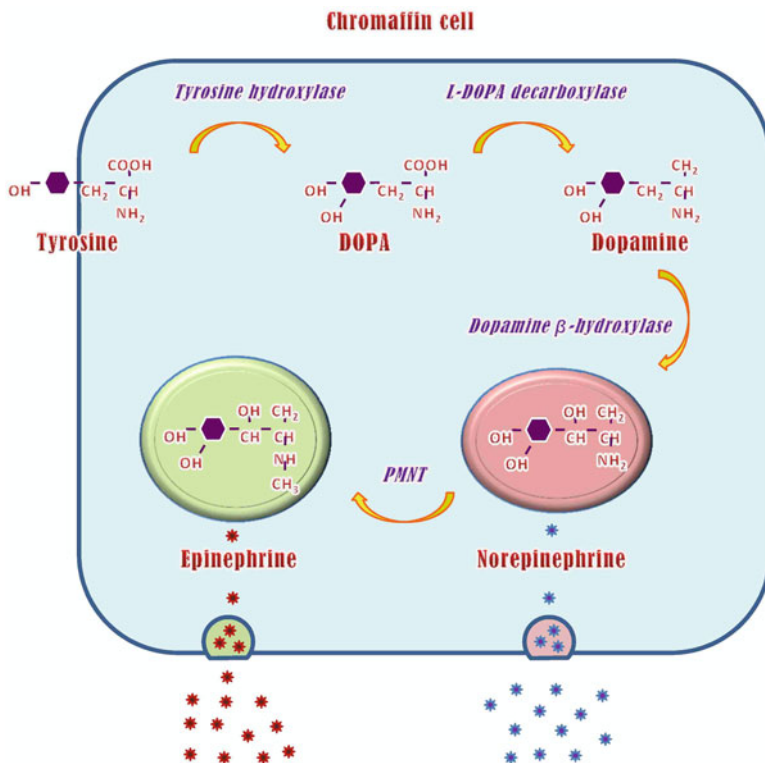
Fig. 14.1 Catecholamine synthesis

Treatment rests on two main principles: (a) medical treatment in preparation for surgery and (b) surgery for the definitive treatment of pheochromocytoma. The mainstay of medical therapy is the use of a noncompetitive α_1- or α_2-adrenoceptor antagonist. Phenoxybenzamine is the drug of choice. The usual dose is 10–30 mg twice a day. Postoperative hypotension is sometimes a complication of phenoxybenzamine treatment. Selective α_1-adrenoceptor blockade with prazosin, terazosin, or doxazosin can prevent the tachycardia associated with phenoxybenzamine and all of them have a shorter duration of action. These competitive α-adrenoceptor antagonists can lead to markedly increased plasma levels of catecholamines. When treatment with α-adrenoceptor antagonists leads to tachycardia, β-adrenoceptor blockade can be very helpful. An alpha-methyl-L-tyrosine (metyrosine, Demser) is the only medication that causes an actual decrease in catecholamine production. It blocks tyrosine hydroxylase and is effective in preoperative preparation and in the treatment of patients with metastatic disease [20]. Intravenous nitroprusside or phentolamine is used to control hypertensive crisis.
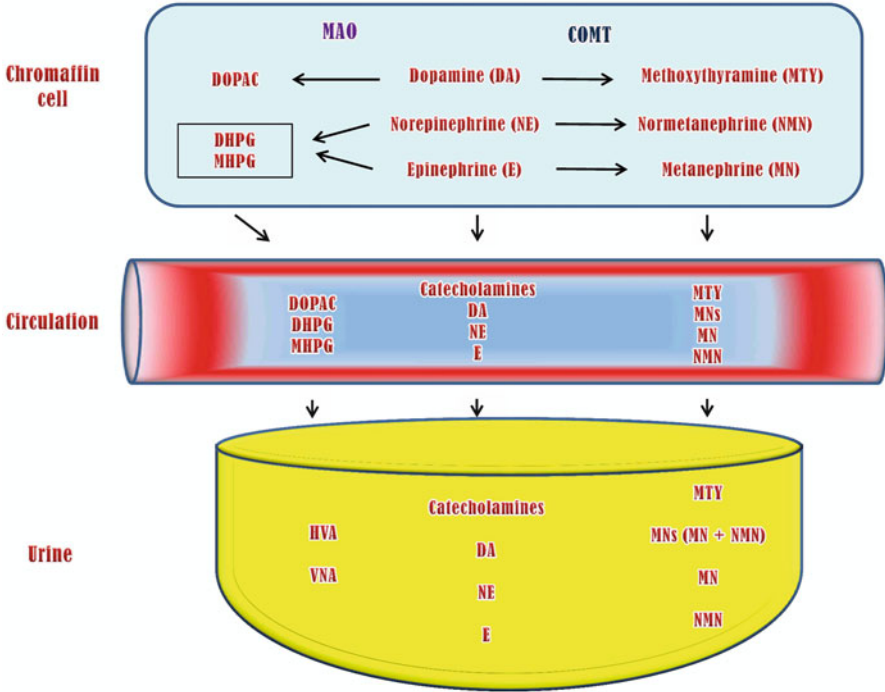
Fig. 14.2 Catecholamine metabolism
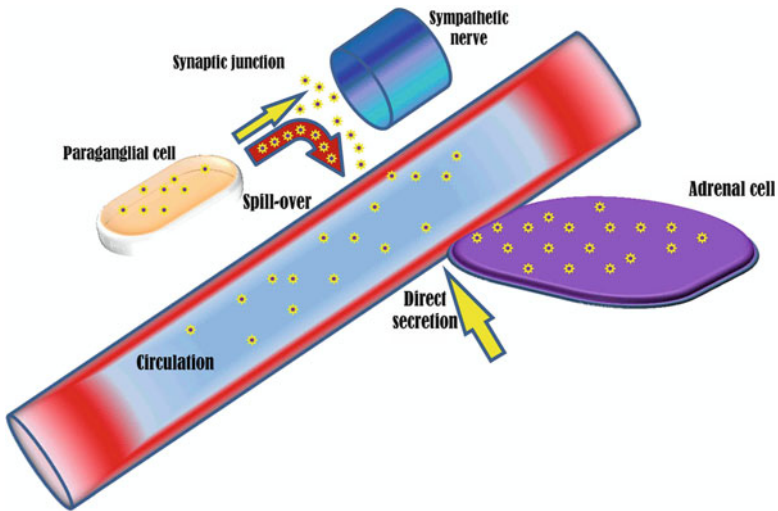
Fig. 14.3 Catecholamine secretion from adrenal medulla and paraganglia

Fig. 14.4 Biochemical diagnosis of pheochromocytoma

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Chapter 15
Hypocalcemia

Robert Klein

Précis

1. Clinical setting—Hypocalcemia, defined as an ionized calcium level of less than 1.1 mmol/L, is a common electrolyte disturbance complicating nearly one-quarter of hospital admissions. It is found in the majority of patients admitted to an intensive care unit (ICU).
2. Diagnosis—The potential causes of hypocalcemia are diverse and numerous. In general terms, hypocalcemia can result from inadequate parathyroid hormone (PTH) or vitamin D production, resistance to the actions of PTH or vitamin D, and the consequence of an underlying medical condition in which multiple factors (e.g., sepsis, critical illness) are contributing. Correct management depends on an accurate diagnosis. If the patient has severe symptoms, therapy should be initiated immediately, and the diagnosis pursued after the patient's condition is stabilized.

    (a) The initial evaluation of a patient with hypocalcemia should include a detailed family history (searching for a genetic cause) and a relevant medical history (e.g., inadequate nutrition, prior neck surgery, infiltrative disorders, autoimmune disease, intestinal or renal dysfunction, and medications that interfere with calcium homeostasis).
    (b) Physical examination—The clinical presentation of hypocalcemia depends on the chronicity and severity of the disturbance and ranges from few if any symptoms with longstanding minor hypocalcemia, to severe life-threatening symptoms if an acute and dramatic decline has taken place. Circumoral anesthesia, cataracts, papilledema, and laryngeal stridor can be observed in hypocalcemic patients. The bedside Trousseau sign (indicative of latent tetany) is a sensitive and specific indicator for hypocalcemia.

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(c) Laboratory evaluation—It is important to verify with the repeat measurement of ionized calcium or total serum calcium corrected for albumin to confirm a true decrease in the serum calcium concentration. Additional laboratory testing should include measurements of phosphorus, magnesium, vitamin D metabolites, alkaline phosphatase, and intact PTH levels. An electrocardiogram can reveal a prolonged QT interval and alert the treating physician to the increased likelihood of ventricular arrhythmias.

3. Treatment—Hypocalcemia with neurological, muscular, or cardiac dysfunction is associated with significant morbidity and mortality and should be handled as a medical emergency. Parenteral infusions of calcium are indicated when a rapid correction of the serum calcium level is required. Emergency treatment should be initiated with 2 g calcium gluconate (180 mg elemental calcium) in 100 mL of normal saline given intravenously over a 10 min period. This should be followed by an infusion of 6 g calcium gluconate in 500 mL normal saline over 4–6 h. Serum calcium should be measured at 4 h intervals, and the infusion rate adjusted to maintain the serum calcium between 8 and 9 mg/mL. If the albumin is less than 3 mg/dL, the calcium infusion rate should be between 120 and 130 mL/h.

Introduction

Calcium is the single most abundant mineral in the human body and it serves as a critical ion for many physiological processes including blood coagulation, platelet adhesion, neuromuscular activity, endocrine and exocrine secretory functions, and bone metabolism. The adult human body contains approximately 1 kg of calcium [1]. Most of this calcium (99 %) is stably incorporated into bone as hydroxyapatite, with less than 1 % in the serum [1]. Plasma normally contains 8.9–10.1 mg/dL of calcium. Approximately 40–50 % of calcium in the blood is bound to plasma proteins, primarily albumin. An equivalent amount is ionized or "free," and the remainder is complexed to phosphate, citrate, bicarbonate, and other ions. Only the free calcium is physiologically active. Ionized serum calcium is closely regulated by the endocrine system and, as such, is a better indicator of the functional status of calcium metabolism than total calcium levels [2]. The normal range for ionized serum calcium concentration is 1.20–1.30 mmol/L.

The regulation of ionized calcium concentration is primarily accomplished by the coordinated actions of PTH and calcitriol (the activated form of vitamin D or 1,25-dihydroxyvitamin D) at the three main sites of calcium transport (intestine, bone, kidney) [3]. Calcium-sensing receptors on the surface of parathyroid cells constantly sense the extracellular ionized calcium concentration, and, when the concentration falls, direct the synthesis and release of PTH [4]. PTH exerts effects in several target organs, including the skeleton, where it increases osteoclast-mediated bone resorption, leading to the release of calcium and phosphorus, and the kidney, where PTH increases reabsorption of calcium into the extracellular space from the

distal convoluted tubules and decreases the reabsorption of phosphorus from the proximal convoluted tubules. Additionally, PTH increases renal 1α(alpha)-hydroxylase activity, which increases the conversion of 25-hydroxyvitamin D to its hormonally active form 1,25-dihydroxyvitamin D (calcitriol). Calcitriol, in turn, binds to nuclear receptors in the intestine where it directs the expression of calcium transport proteins to enhance calcium uptake, augments the actions of PTH on distal convoluted tubules in the kidney, and stimulates the mobilization of calcium and phosphorus from the skeleton into the circulation.

In the short-term serum proteins, chiefly albumin, can serve to stabilize the ionized calcium concentration by acting as a calcium buffer. A transient drop in the ionized calcium concentration is compensated for by a concomitant release of calcium from some of the 30 calcium-binding sites on an albumin molecule. The albumin–calcium buffer is highly sensitive to pH. Changes in pH alter the fraction of charged amino acid residues in albumin, and, thus, the number of calcium ions bound. This results in a change in the fraction of total calcium that is free. Increases in pH, such as respiratory alkalosis caused by hyperventilation, will cause the ionized calcium to fall, while decreases in pH will cause ionized calcium to rise [2].

Although an ionized calcium determination is the most physiologically relevant measure of calcium homeostasis, it is neither the easiest nor the cheapest to measure. In comparison, the laboratory costs for total serum calcium and albumin assays (part of most large automated chemistry analyzers) are much lower than those associated with an ionized calcium analysis. The total serum calcium concentration is a reliable indicator of the serum ionized calcium concentration under most, but not all, circumstances. One important situation in which total serum calcium poorly reflects the ionized calcium concentration is when serum albumin levels are abnormal. As the primary calcium-binding site in serum is albumin, and because albumin molecules bind a relatively predictable quantity of calcium at a given pH, it is possible to estimate ionized calcium levels from protein and total calcium measurements [5]. The adjustment is accomplished by adding or subtracting 0.8 mg/dL to the measured total serum calcium for every 1 g/dL of albumin below or above 4 g/dL albumin, respectively. The "albumin-adjusted" total calcium value is then compared to a standard (non-adjusted) total calcium reference range. Total calcium or albumin-corrected calcium measures, however, can still misclassify a significant proportion of patients due to alterations in blood pH, drugs or fatty acids bound to albumin, the presence of calcium-binding immunoglobulins, gadolinium-containing agents that interfere with the colorimetric detection of total calcium, etc. [6–9]. Consequently, in critically ill patients the direct measurement of ionized calcium concentration is strongly recommended [2].

Etiology

A low circulating ionized calcium level can be the consequence of decreased entry of calcium into the vascular space, accelerated removal of calcium from the vascular space, or by sequestration of ionized calcium. Clinical disorders associated

Table 15.1 Causes of hypocalcemia

Reduced PTH action	Reduced vitamin D action	Calcium deposition/complexation
Hypoparathyroidism	*Vitamin D deficiency*	*Hyperphosphatemia*
Surgical	Dietary lack or limited sunlight exposure	Rhabdomyolysis
Idiopathic	Malabsorption	Renal insufficiency
Autoimmune		Tumor lysis syndrome
Infiltrative (Fe, Cu, tumor)	*Abnormal vitamin D metabolism*	Phosphate administration
Postradiation	Liver or kidney disease	
Genetic (DiGeorge; activating CaSR mutation, etc.)	Abnormal enterohepatic circulation	*Acute pancreatitis*
Hypomagnesemia (functional)	Anticonvulsants	
	Nephrotic syndrome	*Blood transfusions*
PTH resistance	*Vitamin D resistance*	*Excessive skeletal mineralization*
Pseudohypoparathyroidism	Vitamin D-dependent rickets	Hungry bone syndrome
Renal insufficiency		Osteoblastic metastases

with hypocalcemia are listed in Table 15.1. The most common cause of acute hypocalcemia is postoperative hypoparathyroidism in the context of neck surgery during which damage or unintentional removal of most or all functioning parathyroid tissue has taken place [11, 12]. Damage to the parathyroid glands may also be caused by immune-mediated destruction of the parathyroid glands [13], iron (hemochromatosis) or copper (Wilson's disease) accumulation in the parathyroid glands [14–16] or, in rare cases, by iodine-131 therapy for thyroid diseases [17], or metastatic infiltration of the parathyroid glands by tumor [18]. Hypoparathyroidism causes hypocalcemia because PTH secretion is inadequate to mobilize calcium from bone, reabsorb calcium from the urine, or stimulate renal 1α(alpha)-hydroxylase activity. As a result, insufficient 1,25-dihydroxyvitamin D is produced for optimal intestinal absorption of calcium [12]. Parathyroid secretory reserve is sizeable, so considerable damage must take place for hypocalcemia to develop. It is estimated that one normal gland is sufficient for maintaining PTH and calcium homeostasis [12]. A number of genetic disorders have been identified in patients with inherited hypoparathyroidism (e.g., DiGeorge, or velocardiofacial, syndrome, activating mutations in the extracellular calcium-sensing receptor, pseudohypoparathyroidism) and should be considered a possible cause of hypocalcemia in the appropriate clinical setting [19, 20].

Magnesium is essential for PTH secretion and receptor activation [21]. Thus, magnesium depletion can cause hypocalcemia by inducing a functional hypoparathyroid state. Hypomagnesemia as the underlying cause for hypocalcemia should be considered in a variety of clinical situations (malnutrition, pancreatitis, chronic alcohol abuse, diarrhea) or as a consequence of certain therapies (diuretics, antibiotics, and chemotherapeutic agents such as cisplatin derivatives).

Vitamin D deficiency (resulting from dietary insufficiency, sunlight deprivation, or hepatic or renal impairment) or reduced vitamin D-mediated signaling can be a primary cause of hypocalcemia or aggravate the hypocalcemia initiated by other processes [22, 23]. Excessive remineralization of bone can occur after successful parathyroid surgery for hyperparathyroidism ("hungry bone" syndrome) [24] and in the setting of osteoblastic bone metastases (e.g., breast or prostate cancer) [25, 26]. Hyperphosphatemia, commonly seen in renal impairment, tumor lysis syndrome, and rhabdomyolysis, causes hypocalcemia by complexing with circulating free calcium ions. Acute pancreatitis is associated with the formation of calcium complexes within the abdominal cavity. Calcium chelation can occur iatrogenically with citrate-containing blood transfusions but is rare if renal and hepatic functions are normal. Acute and critical illness, often in the ICU setting, is frequently accompanied by low ionized calcium values. This entity is typically multifactorial with poor nutrition, vitamin D insufficiency, renal dysfunction, acid–base disturbances, release of inflammatory cytokines, magnesium abnormalities, frequent transfusions, and other factors all likely contributing to some degree. Finally, a number of medications are associated with symptomatic hypocalcemia (e.g., foscarnet, calcitonin, bisphosphonates, denosumab, phenobarbital, and phenytoin) especially in the setting of unrecognized calcium and/or vitamin D deficiency [27].

Clinical Signs and Features

The clinical manifestations of hypocalcemia depend on the degree of hypocalcemia (ionized calcium level) and the rate of its development. An acute decrease in blood calcium level enhances neuron excitability, but chronic hypocalcemia can be asymptomatic even at quite low levels of serum calcium. Conversely, severe or acute hypocalcemia is usually associated with predictable signs (Table 15.2). Patients with acute hypocalcemia will present with neurologic complaints ranging from circumoral tingling and distal parasthesias to severe central nervous system symptoms such as confusion, delirium, and/or seizure. Laryngospasm and bronchospasm, which could lead to respiratory compromise, also can indicate hypocalcemia. Cardiovascular manifestations of hypocalcemia can include depressed myocardial contractility, congestive heart failure, and arrhythmias due to prolonged QT intervals. Tetany is typically seen when the ionized calcium drops below 1.0 mmol/L, but chronic hypocalcemia can be asymptomatic even with these low serum calcium levels. In this situation, the clinician can attempt to draw out latent tetany due to hypocalcemia by demonstrating Trousseau's sign. A sphygmomanometer cuff is inflated 20 mmHg above systolic pressure for 3 min to occlude the brachial artery. Flexion of the wrist and metacarpophalangeal joints, hyperextension of the fingers, and flexion of the thumb result. This response to anoxia is known as the "main d'accoucheur" (*French* for "hand of the obstetrician") (Fig. 15.1). Chvostek's sign, an abnormal contraction of the ipsilateral facial muscles in response to tapping the facial nerve 2 cm in front of the tragus of the ear, is also indicative of hypocalcemic

Table 15.2 Clinical manifestations of hypocalcemia

Acute neuromuscular features
Paresthesias
Perioral numbness
Muscle cramps and weakness
Confusion, delirium
Carpopedal spasm
Tetany
Seizure
Laryngospasm and bronchospasm
Congestive heart failure
Arrhythmia, prolonged QT interval
Other features more common with chronic hypocalcemia
Subcapsular cataracts
Dry skin and hair
Papilledema
Pseudotumor cerebri
Basal ganglia calcification
Depression
Dementia

neural irritability. However, perioral twitching occurs in up to 25 % of normal individuals, and the Chvostek sign is negative in approximately 30 % of those with hypocalcemia [28]. By contrast, the Trousseau sign is considerably more sensitive (94 %) and specific for hypocalcemia [28]. Other manifestations of chronic hypocalcemia include premature cataracts, alopecia, depression, dementia, pseudotumor cerebri, calcification of the basal ganglia, and seizures.

The etiology of hypocalcemia may be obvious from the clinical history. A family history of hypocalcemia suggests a genetic cause (e.g., activating mutation of the calcium-sensing receptor, pseudohypoparathyroidism). In contrast, acquired hypoparathyroidism is most often the result of postsurgical or autoimmune damage to the parathyroid glands. A history of head and neck surgery or the presence of a neck scar suggests postsurgical hypoparathyroidism, while the presence of chronic mucocutaneous candidiasis, diabetes mellitus type 1, and adrenal insufficiency suggests a polyglandular autoimmune syndrome. Other causes of hypocalcemia include acute or chronic kidney disease, acute pancreatitis, metastatic disease, and malnutrition.

Laboratory Evaluation

Based upon the patient's history and physical examination, there are several laboratory measurements that can confirm the underlying etiology of the hypocalcemia. Serum intact PTH is the most important. It only can be interpreted correctly only when serum calcium is measured simultaneously. The most potent stimulus of PTH secretion is a reduced ionized calcium level. A low or normal serum PTH concentration in a patient
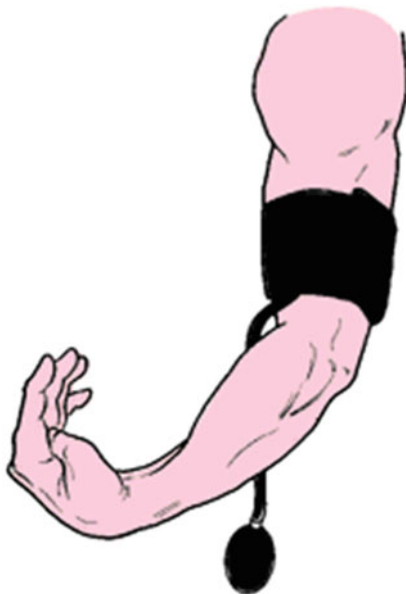
Fig. 15.1 Trousseau's sign of latent tetany. Trousseau sign of latent tetany can be observed in patients with low calcium. To elicit the sign, a blood pressure cuff is placed around the upper arm and inflated to a pressure greater than the systolic blood pressure and held in place for 3 min. In the absence of brachial artery blood flow, the patient's hypocalcemia and resultant neuromuscular irritability will induce spasm of the muscles of the hand and forearm. The wrist and metacarpophalangeal joints flex, the DIP and PIP joints extend, and the fingers adduct. The sign is also known as main d'accoucheur (*French* for "hand of the obstetrician") because of its resemblance to the position of an obstetrician's hand in delivering a baby. Importantly, this sign may become positive before other gross manifestations of hypocalcemia such as hyperreflexia and tetany are manifest (reproduced from TheFreeDictionary.com)

with hypocalcemia is strong proof of hypoparathyroidism. In contrast, patients with hypocalcemia as a result of vitamin D deficiency or pseudohypoparathyroidism (PTH resistance) will have elevated levels of PTH (secondary hyperparathyroidism). Hypomagnesemia (serum magnesium concentration below 1 mg/dL or 0.4 mmol/L) can cause a functional (but reversible) form of hypoparathyroidism. Serum magnesium should be measured in any patient with hypocalcemia in whom the PTH concentration is low but the cause is not obvious. In states of PTH deficiency or resistance, elevated serum phosphate levels will occur due to a loss of the stimulatory effect of PTH on urinary phosphate excretion. Conversely, the presence of a low serum phosphate concentration in the context of hypocalcemia indicates either secondary hyperparathyroidism or poor nutrition with limited dietary phosphate intake. Thus, the serum phosphate level can serve as an important discriminating factor when evaluating hypocalcemic patients.

When vitamin D deficiency is suspected, serum 25-hydroxyvitamin D should be assessed first rather than serum 1,25-dihydroxyvitamin D (calcitriol). The diminished intestinal calcium absorption seen in vitamin D deficiency results in a state of secondary hyperparathyroidism. As increased circulating PTH levels and hypophosphatemia

are both potent stimulators of renal 1,25-dihydroxyvitamin D production, individuals with vitamin D deficiency will typically exhibit normal or high serum 1,25-dihydroxyvitamin D levels. In contrast, patients with hypoparathyroidism can have normal serum 25-hydroxyvitamin D but generally low 1,25-dihydroxyvitamin D concentrations (in that clinical setting the hyperphosphatemia and reduced PTH levels attenuate, to some degree, renal 1,25-dihydroxyvitamin D production). The determination of 1,25-dihydroxyvitamin D concentrations should be reserved for hypocalcemic patients with underlying renal insufficiency or when a state of vitamin D resistance is suspected. An elevated alkaline phosphatase is common in severe vitamin D deficiency but can also occur with osteoblastic bone metastases, which can cause hypocalcemia due to rapid deposition of calcium in bone metastases.

Treatment

The treatment of hypocalcemia should vary with its severity and the underlying cause (Table 15.3). For example, asymptomatic hypocalcemia due to hypoalbuminemia requires no therapy, while severe hypocalcemia (total serum calcium concentration of less than 7.5 mg/dL or ionized calcium concentration below 0.9 mmol/L) or acute symptomatic hypocalcemia requires urgent medical attention. It is important for the treating physician to recognize that patients with acute hypocalcemia can be quite symptomatic (e.g., tetany, seizures, laryngospasm, or cardiac dysfunction) at serum calcium values that would not usually cause symptoms in patients with chronic hypocalcemia. Clinical manifestations can also vary with other factors such as acid–base status and underlying illness.

Parenteral infusions of either calcium gluconate or calcium chloride are indicated when rapid correction of serum calcium levels is required. Although calcium chloride provides nearly 4 times more elemental calcium than an equivalent amount of calcium gluconate, calcium gluconate is the preferred salt for peripheral venous administration as calcium chloride can cause tissue necrosis in the event of local extravasation. Initially, 1 g of calcium chloride (272 mg of calcium) or up to 3 g of calcium gluconate (276 mg of calcium) can be delivered over 30–90 min to control symptoms (Table 15.3). However, a single intravenous injection of calcium is usually only effective for a few hours [29]. A continuous infusion of calcium gluconate will be required to fully control symptoms and achieve a safe and stable ionized calcium level, usually above 1.0 mmol/L. In patients receiving parenteral calcium replacement, the serum ionized calcium level should be measured every 1–2 h until the patient's condition has stabilized, and then every 4–6 h in order to monitor therapy. The recurrence of hypocalcemic symptoms can necessitate an increase in the infusion rate but should always be correlated with a simultaneous ionized calcium value. The infusion rate should not exceed 1–2 mg/min because of the potential risk for cardiac arrhythmias associated with rapid calcium infusion. Oral calcium and vitamin D therapy should be started as soon as possible and the intravenous calcium infusion tapered slowly (over a period of 24–48 h or longer) while oral therapy is adjusted.

Table 15.3 Therapeutic options for hypocalcemia

Agent	Dosing information	Notes
Acute management		
Parenteral calcium infusion		
Calcium chloride	10 mL ampule (272 mg elemental calcium) diluted in 200 mL of 5 % dextrose in water given intravenously over 30–90 min	CaCl$_2$ solutions can be irritating to surrounding tissues if extravasated, so this agent should be administered by a central venous catheter, if possible
Calcium gluconate	10 mL ampules (92 mg elemental calcium); 1–3 ampules diluted in 200 mL of 5 % dextrose or normal saline given intravenously over 30–90 min	Therapy should be individualized and guided by frequent serum ionized calcium determinations
Calcium gluconate infusion	10 ampules (920 mg elemental calcium) diluted in 1 L 5 % dextrose in water	Infusion rate should be 1–3 mg/kg/h to maintain serum calcium levels within the targeted range
Long-term management		
Calcium supplements		
Calcium carbonate	40 % elemental calcium by weight	Best absorbed in small, multiple doses with meals and with acid present in the stomach
Calcium citrate	21 % elemental calcium by weight	Preferred option for patients with achlorhydria
Vitamin D preparations		
D$_2$ (ergocalciferol) D$_3$ (cholecalciferol)	2,000–100,000 IU once daily; onset of action 10–14 days; offset of action 14–75 days	Wide dose range reflects the various disorders these agents are used. Careful attention to serum levels of calcium, phosphorus, and creatinine is necessary for safe use
25-Hydroxyvitamin D$_3$ (calcifediol)	20–200 µg daily; onset of action 5–10 days; offset of action 14–75 days	Used in hepatic failure when renal function is intact to insure 1-alpha hydroxylation available to activate this metabolite
Dihydrotachysterol	0.2–1 mg once daily; onset of action 4–7 days; offset of action 7–21 days	Active D metabolite that does not require renal conversion
1α(Alpha)-hydroxyvitamin D$_3$ (alfacalcidiol)	0.5–3 µg daily; onset of action 1–2 days; offset of action 5–7 days	Rapidly converted to active 1,25-dihdroxyvitamin D$_3$ in vivo
1,25-Dihydroxyvitamin D$_3$ (calcitriol)	0.25–1 µg once or twice daily; onset of action 1–2 days; offset of action 2–3 days	Active D metabolite that does not require renal conversion
Thiazide diuretic		
Hydrochlorothiazide Chlorthalidone	25–100 mg daily	Used in concert with a low-sodium diet (80–100 mmol per day) to promote renal calcium retention; hypokalemia and hyponatremia are adverse events

Table adapted from Table 3 in Shoback D. Hypoparathyroidism. N Engl J Med 359:391–403, 2008.

When magnesium depletion is present, hypocalcemia is frequently difficult to correct without first normalizing the serum magnesium concentration. If the serum magnesium concentration is low, 2 g of magnesium sulfate in 20 mL of DSW should be infused over 10–20 min, followed by 1 g in 100 mL DSW per hour as long as the serum magnesium concentration remains less than 1 mg/dL. As intracellular magnesium deficits are generally large and inadequately mirrored by the serum magnesium level, continued supplementation with oral magnesium salts over an extended period of time may be necessary. Careful monitoring is required in patients with impaired renal function who are at greater risk of developing hypermagnesemia.

The chronic management of hypocalcemia should be tailored to the underlying etiology and will almost always rely on oral calcium supplements, vitamin D metabolites and, sometimes, thiazide diuretics (Table 15.3). Although calcium supplements of all types can be used for hypocalcemia, the most efficient means of supplementation is in the form of either carbonate or citrate salts. The former contains 40 % calcium by weight and the latter 21 %. A reasonable starting dose is 0.5–1 g of elemental calcium 2 or 3 times each day. Subsequent dosing can then be adjusted based on patient compliance, side effects, and clinical objectives.

In addition to calcium, patients with vitamin D deficiency will require vitamin D supplementation [22]. For vitamin D-deficient subjects with intact renal function, either ergocalciferol (vitamin D_2) or cholecalciferol (vitamin D_3) can be used. Patients who choose to avoid the ingestion of animal products should be aware that cholecalciferol is of animal origin. Although the recommended regimen to reach a 25-hydroxyvitamin D concentration of 25–30 ng/mL is 50,000 international units (IU) of vitamin D weekly for 8–12 weeks, a daily 50,000 IU dose of ergocalciferol can be safely administered for 5 days at the beginning of therapy in patients with severe vitamin D deficiency. Because of their long-term storage in fat, these forms of vitamin D have an extended tissue half-life (up to months) and toxicity may be difficult to anticipate and/or correct quickly. Hypercalcemia, should it occur, can persist for weeks after the vitamin D supplement is stopped. For this reason calcitriol, despite its increased expense compared to vitamin D, is preferred by many clinicians because of its rapid onset and offset of action. Calcitriol is most useful in diseases in which the activity of renal 1α(alpha)-hydroxylase is impaired, such as renal failure or hypoparathyroidism. Although hypercalcemic events are more common with calcitriol than with vitamin D, halting treatment is followed by resolution of hypercalcemia in a few days rather than a few weeks. Calcifediol (25-hydroxyvitamin D) does not require hepatic 25-hydroxylation, and therefore can be useful in patients with liver disease. The pharmacokinetics of calcifediol are intermediary—more rapid and not as prolonged as that of vitamin D, but slower in onset and more prolonged than that of calcitriol.

Serum calcium, phosphorus, and creatinine along with a measure of urinary calcium excretion should be monitored regularly to avoid toxicity from calcium and vitamin D therapy. In patients who develop hypercalciuria (urinary calcium excretion greater than 300 mg/day) thiazide diuretics (along with a low-salt diet) can be employed to promote urinary calcium retention [30]. Effective doses of hydrochlorothiazide are generally between 50 and 100 mg/d. Patients should be monitored for

alterations in serum potassium, sodium, and magnesium. Soft-tissue calcification and nephrocalcinosis can be prevented by keeping the serum calcium-phosphate product below 55 [31]. Hyperphosphatemia can be managed by reducing the patient's dietary intake of phosphate-rich foodstuffs (e.g., meats, eggs, and dairy products) and, if necessary, with oral phosphate binders.

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Chapter 16
Hypercalcemia

Robert Klein

Précis

1. Clinical Setting—Hypercalcemia (serum calcium >10.5 mg/dL or ionized calcium level >1.3 mmol/L) is a disorder commonly encountered by primary care physicians and is usually well tolerated if calcium levels remain below 12 mg/dL (ionized calcium level of 1.5 mmol/L). Calcium levels above this threshold are associated with increasingly severe volume contraction, neurological, cardiac, and gastrointestinal dysfunction, and require urgent treatment to prevent life-threatening consequences.

2. Diagnosis—The differential of hypercalcemia is broad and can be categorized based on parathyroid hormone (PTH) levels. The principal challenges in the management of hypercalcemia are distinguishing primary hyperparathyroidism (PHPT) from conditions that will not respond to parathyroidectomy (e.g., cancer, granulomatous disorders, vitamin D intoxications). Correct management depends on an accurate diagnosis. However, in the setting of hypercalcemic crisis, therapy should be initiated immediately, and the diagnosis pursued after the patient's condition has been stabilized.

   (a) History—Important complaints include polyuria and altered mental status which together can contribute to volume contraction and worsening hypercalcemia. Calcium levels elevated to the extent that overt symptoms are present nearly always indicates PHPT or malignancy. The most frequent presentation of PHPT is that of relatively "asymptomatic" disease. Constitutional symptoms (fevers, night sweats, weight loss) raise concern for a malignant or infectious etiology. A careful family history should provide

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clues as to whether the patient has a familial form of hyperparathyroidism or familial hypocalciuric hypercalcemia (FHH). Calcium and vitamin D supplement use or ongoing treatment with a thiazide or lithium represents other obvious causes.

(b) Physical Examination—Just as with hypocalcemia, the clinical presentation of hypercalcemia depends on the chronicity and severity of the disturbance—ranging from few if any symptoms with longstanding mild hypercalcemia to severe life-threatening symptoms if an acute and dramatic change has taken place. The term hypercalcemic crisis describes a severely debilitated patient with profound volume depletion, cardiac decompensation, and altered neurocognitive function. This can present as obtundation and even coma.

(c) Laboratory Evaluation—Hypercalcemia is defined as a serum calcium >10.5 mg/dL or ionized calcium level >1.3 mmol/L. Once the diagnosis is considered, a repeat measurement (ionized calcium or total serum calcium corrected for albumin) should be obtained to confirm a true increase in the serum calcium concentration. The first step in evaluating hypercalcemia is to establish whether the process is PTH-dependent. Additional laboratory testing should include measurements of serum creatinine, phosphorus, vitamin D metabolites, thyroid function, serum electrophoresis, and renal calcium excretion. The QT interval on the electrocardiogram can be shortened by hypercalcemia due to the increased rate of cardiac repolarization.

3. Treatment—Severe hypercalcemia is an endocrine emergency that requires prompt action to prevent severe neurological, cardiac, and renal consequences. The diagnosis should be considered in any patient with known parathyroid disease or malignancy who presents with acute clinical decline, especially in the event of neurological deterioration. The emergent treatment of hypercalcemia must focus on restoring intravascular volume and increasing renal calcium excretion. In most situations, 500–1,000 mL 0.9 % saline should be infused over the first hour, and an additional 2–5 L over the next 24 h. The goal is to achieve a urine output of 200 mL/h. This can be continued for several days and will usually lower serum calcium by 1–3 mg/dL. If this degree of hydration leads to pulmonary edema or pitting edema, loop diuretics should be added. In this case, potassium and magnesium levels must be closely monitored. If hypophosphotemia occurs, it should be replaced with enteral phosphate to achieve a plasma level of phosphate of 2.5–3.0 mg/dL. For patients with congestive heart failure and end-stage renal disease, hemodialysis or peritoneal dialysis, with a low-calcium dialysate, can be very helpful.

The most important element of treatment is swift volume resuscitation, followed by the administration of specific therapies tailored to the underlying pathophysiologic process (e.g., calcitonin and bisphosphonates to slow bone resorption; glucocorticoids to limit 1,25-dihyroxyvitamin D synthesis). It is essential that physicians know how to evaluate and optimally manage patients with hypercalcemia, because treatment and prognosis vary according to the underlying disorder. Surgery remains

the only effective therapy for PHPT and all patients whose course has been complicated by severe hypercalcemia should be referred for parathyroidectomy. Despite encouraging developments in pharmacologic management, the prognostic implications related to malignancy-associated hypercalcemia (MAH) remain relatively bleak. Only patients for whom effective antineoplastic therapy is available can be expected to experience a longer survival.

Etiology

Hypercalcemia is defined as a serum calcium more than two standard deviations above the laboratory's population mean, commonly 10.5 mg/dL for total serum calcium and 1.30 mmol/L for ionized serum calcium. Under normal conditions, the flux of ionized calcium between the vascular space and the skeleton, the intestine, and the kidney is very tightly regulated [1]. Consequently, for hypercalcemia to develop one or more of the following disturbances must be in play: (a) increased intestinal calcium absorption; (b) increased bone resorption; or (c) decreased renal calcium excretion. Approaching hypercalcemia from this physiological perspective can serve as a very practical means to establish the correct diagnosis and devise an effective treatment strategy.

The main function of PTH is to maintain the serum calcium concentration by promoting the release of calcium from bone, stimulating renal calcium conservation by the kidney, and augmenting intestinal calcium absorption by increasing renal 1,25-dihydroxyvitamin D synthesis. Accordingly, in the event of hypocalcemia, PTH release into the blood stream should be enhanced while hypercalcemia should prompt a decrease in circulating PTH concentrations. It is for this reason that the underlying causes of hypercalcemia can be conveniently divided into those associated with an elevated or inappropriately normal PTH level, and those where PTH levels are appropriately suppressed (Table 16.1).

PHPT is a relatively common endocrine disease, with an incidence as high as 1 in 500 to 1 in 1,000 [2]. As such, PHPT accounts for the vast majority of hypercalcemia (>90 %) detected in the outpatient clinic setting [3]. PHPT occurs at all ages but is most frequent in those over the age of 50 with women affected nearly 3 times more often than men [2]. Most cases of the disease (~80 %) are caused by a benign, solitary adenoma. Parathyroid adenomas are most commonly sporadic but can be part of an endocrine neoplastic syndrome such as multiple endocrine neoplasia (MEN)-1 or MEN-2a, especially if multiple or discovered in the young patient [2]. Less commonly (~15–20 % of cases), the disease is caused by hyperplasia of all four parathyroid glands. Rarely, hyperparathyroidism can result from a parathyroid carcinoma. In adenomas, the parathyroid cell loses its normal sensitivity to calcium (altered "set-point"), whereas in hyperplasia of the parathyroid glands, the overall increase in the number of parathyroid cells is responsible for the hypercalcemia.

Other causes of hypercalcemia in the setting of parathyroid hyperplasia and inappropriately normal or high PTH secretion are tertiary hyperparathyroidism, FHH,

Table 16.1 Causes of hypercalcemia

Parathyroid hormone-dependent etiologies
Primary hyperparathyroidism
Adenoma
Hyperplasia
Sporadic
Familial
Multiple endocrine neoplasia, type 1 and type 2a
Carcinoma
Familial hypocalciuric hypercalcemia
Lithium therapy
Tertiary (severe secondary) hyperparathyroidism
Ectopic PTH production by non-parathyroid tumor (extremely rare)
Parathyroid hormone-independent etiologies
Malignancy
Humoral hypercalcemia of malignancy
Local osteolytic hypercalcemia
1,25-dihyroxyvitamin D-mediated
Vitamin D-related
Vitamin D intoxication
Granulomatous disorder (excessive 1,25-dihyroxyvitamin D production)
Milk-alkali syndrome
Immobilization
Hyperthyroidism
Pheochromocytoma
VIP-oma syndrome
Vitamin A intoxication

and lithium therapy [4]. Physiologically appropriate (or secondary) hyperparathyroidism that accompanies longstanding calcium insufficiency or renal insufficiency can sometimes lead to parathyroid autonomy that persists even after resolution of the stimulus (calcium and vitamin D repletion; renal replacement therapy). When hypercalcemia develops under these circumstances, the condition is referred to as tertiary hyperparathyroidism and 4-gland hyperplasia is the rule. FHH is an autosomal-dominant genetic disorder resulting from an inactivating mutation in the calcium-sensing receptor (CaSR) [5]. The diminished ability of renal tissue to detect calcium results in enhanced renal tubular reabsorption of calcium and mild hypercalcemia. Similarly, parathyroid tissue in FHH inadequately senses circulating calcium so that parathyroid hyperplasia occurs and inappropriately normal PTH levels are maintained despite the chronic mild hypercalcemia. Lithium therapy produces a physiologic picture that mimics FHH as the calcium "set-point" for suppression of PTH release is raised above normal [6].

In contrast to PHPT, MAH accounts for up to 90 % of the hypercalcemia encountered among hospitalized patients and hypercalcemia complicates 10–30 % of malignancies [7–10]. The most common form of MAH is humoral hypercalcemia

of malignancy (HHM), which derives from tumor-associated PTH-related protein (PTHrP), a peptide with significant homology to PTH [11]. Based on its structural similarity to PTH, PTHrP can activate skeletal and renal PTH receptors. As a result, enormous amounts of calcium (up to 1 g/d) are delivered into the circulation and, combined with the anticalciuric effects of PTHrP to restrict renal calcium clearance, marked hypercalcemia ensues. In contrast to PHPT, HHM is associated with suppressed PTH levels and normal or low calcitriol levels. Many solid tumors are associated with HHM and include squamous cell carcinomas of the lung, skin, cervix, head, neck and esophagus, renal cell carcinoma, and breast carcinoma. Humoral-mediated bone resorption accounts for the majority of hypercalcemia in these malignancies even when osteolytic metastases are present.

A second form of MAH is local osteolytic hypercalcemia (LOH) that occurs in cancer subjects with widespread skeletal involvement [12]. The tumors most commonly associated with LOH are breast cancer and hematological neoplasms such as leukemia, lymphoma, and myeloma. Locally produced, tumor-derived osteoclast-activating cytokines (including interleukins-1 and -6, PTHrP, and macrophage inflammatory protein-1α(alpha)) are thought to be responsible for most instances of LOH. As such, LOH is primarily a resorptive (skeletally derived) form of hypercalcemia in which massive removal of skeletal calcium overwhelms the ability of the kidney to eliminate calcium.

In a third form of MAH, certain lymphomas and ovarian dysgerminomas can cause 1,25-dihydroxyvitamin D-mediated hypercalcemia. Malignant cells (or perhaps adjacent normal cells) overexpress 1α(alpha)-hydroxylase that converts normal levels of circulating 25-dihydroxyvitamin D into elevated concentrations of 1,25-dihydroxyvitamin D [13]. Because 1,25-dihydroxyvitamin D activates intestinal calcium absorption, this syndrome is principally considered an absorptive form of hypercalcemia. Finally, rare cases in which production of authentic PTH, and not PTHrP, by tumors has been shown to cause MAH [14–16].

Together, PHPT and malignancy account for the vast majority (>90 %) of hypercalcemia cases. Among the remaining miscellaneous etiologies are granulomatous disorders, a few endocrine disorders, immobilization and a number of medications. Just as is the case with certain lymphomas and dysgerminomas, granulomas possess 1α(alpha)-hydroxylase activity that can result in absorptive hypercalcemia due to increased circulating levels of 1,25-dihydroxyvitamin D [17]. Hypercalcemia has been described in virtually every disease associated with granuloma formation and the mineral disturbance resolves with elimination of the granulomas. The accelerated bone resorption that accompanies hyperthyroidism can cause mild hypercalcemia [18]. Hypercalcemia has been associated with pheochromocytoma and the VIP-oma (vasoactive intestinal polypeptide) syndrome though the mechanisms are not well understood [19, 20]. Immobilization can also cause hypercalcemia through accelerated osteoclastic bone resorption [21]. A number of medications may result in hypercalcemia [22]. Thiazide diuretics are well-recognized for the ability to cause mild hypercalcemia due to stimulation of renal calcium reabsorption [23]. Consumption of large amounts of calcium carbonate (daily doses in excess of 4,000 mg/d taken for esophageal reflux of peptic ulcer symptoms) can lead to a

disorder termed milk-alkali syndrome that is characterized by hypercalcemia, alkalosis, and renal insufficiency [24]. Similarly, vitamin D intoxication from over-the-counter supplements or prescribed forms of ergocalciferol and calcitriol may also cause hypercalcemia due to a combination of increased intestinal calcium absorption and reduced renal calcium clearance. Vitamin A intoxication has also been associated with hypercalcemia and the effect appears to be mediated through increased bone resorption [25].

Clinical Signs and Features

Just as is the case with hypocalcemia, the clinical manifestations of hypercalcemia depend on the degree of hypercalcemia (ionized calcium level) and the rapidity of its onset (Table 16.2). In general, however, overt symptoms are rare in patients with serum calcium concentrations below 12 mg/dL (ionized calcium below 1.5 mmol/L), but at concentrations above 14 mg/dL (ionized calcium of 1.75 mmol/L) most patients are symptomatic [26]. Neuromuscular function depends upon a normal extracellular calcium concentration. So it is not surprising that, as with hypocalcemia, a spectrum of neurologic symptoms can accompany hypercalcemia, ranging from slight cognitive difficulties, mild fatigue, lethargy, and depression to confusion, agitation, obtundation, and even coma. The effect of hypercalcemia to raise the depolarization threshold of skeletal and smooth muscle

Table 16.2 Clinical manifestations of hypercalcemia

Neuromuscular
Muscle weakness
Lethargy, fatigue
Poor recent memory
Impaired cognition
Confusion, stupor, coma
Renal
Polyuria
Dehydration
Nephrolithiasis
Nephrocalcinosis
Gastrointestinal
Nausea, vomiting
Anorexia
Abdominal pain
Constipation
Skeleton
Bone pain, fracture
Cardiovascular
Arrhythmia
Cardiovascular calcification
Band keratopathy

cells results in a skeletal myopathy and diffuse gastrointestinal complaints (e.g., constipation, abdominal pain, nausea, vomiting, and anorexia). In a similar fashion, bradyarrhythmias, cardiac conduction defects, and digitalis sensitivity are associated with increased ionized calcium levels. Beyond its neuromuscular impact, hypercalcemia also exerts clinically important renal effects. The increased delivery of calcium to the nephron impairs normal renal tubular reabsorption of water, leading to polyuria and increased thirst. Aquaporin-2 water channels are decreased by hypercalcemia and tubulointerstitial injury can result from direct calcium deposition [27]. When fluid intake fails to match the obligatory renal fluid losses, volume contraction and prerenal azotemia develop, which in turn limit renal clearance of calcium and further worsen the hypercalcemia. Longstanding hypercalcemia can cause precipitation of calcium salts in the renal interstitium (nephrocalcinosis), urinary tract (nephrolithiasis), cornea ("band keratopathy"), vasculature, myocardium, and cardiac valves as well as accelerated bone loss and a predisposition to fragility fractures.

As the clinical presentation of hypercalcemia is, for the most part, the same regardless of the underlying etiology, the history and physical examination of the hypercalcemic patient should focus on signs and symptoms relevant to the causal disorder. In the acute setting, hypercalcemia is most commonly seen in the context of parathyroid dysfunction and malignancy. MAH is generally a late development in the course of disease, and thus tumors causing hypercalcemia are rarely occult. Palpable neck masses are extremely unusual in PHPT unless the patient has a parathyroid carcinoma. In contrast, osteoporosis of cortical bone is frequently observed [28]. A careful family history should provide clues as to whether the patient has FHH or another variant of familial hyperparathyroidism. Hyperthyroidism should be suspected from physical examination findings, as should a history of recent ingestion of any medication known to cause hypercalcemia.

Laboratory Evaluation

After taking a careful history and physical examination, laboratory testing should be designed to assess the extent of the alteration in calcium homeostasis and to ascertain the underlying etiology. A single raised serum calcium value should be repeated (along with an ionized calcium, if available) to confirm that the disorder is clinically genuine and not the consequence of a lab artifact. Hypercalcemia without a concomitant elevation in ionized calcium can occur in the setting of hyperalbuminemia, severe dehydration, thrombocythemia, or in multiple myeloma with a calcium-binding M-paraprotein [29]. If accessible, previous values for serum calcium should also be reviewed. Evidence of longstanding asymptomatic hypercalcemia would suggest PHPT or FHH as likely explanations. The degree of hypercalcemia also can be useful. Serum calcium concentrations above 13 mg/dL (1.6 mmol/L) are infrequent in PHPT and, in the absence of another apparent cause, are more commonly the result of malignancy.

Fig. 16.1 Immunora-diometric assay for intact parathyroid hormone. Intact PTH measured by two-site immunoradiometric assay in sera from 72 normal individuals, 37 patients with surgically proven primary hyperparathyroidism and 24 patients with malignancy-associated hypercalcemia. The normal reference range is 12–65 pg/mL. (Reproduced from Nussbaum SR, Zahradnik RJ, Lavigne JR, Brennan GL, Nozawa-Ung K, Kim LY, Keutmann HT, Wang CA, Potts JT, Jr., Segre GV 1987 Highly sensitive two-site immunoradiometric assay of parathyrin, and its clinical utility in evaluating patients with hypercalcemia. Clin Chem **33**(8):1364–7.)
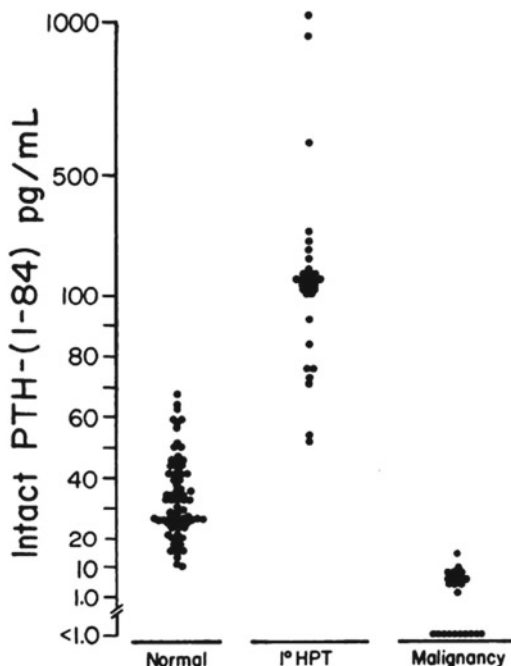
Once confirmed the next step in the laboratory evaluation of hypercalcemia is to establish whether or not the process is PTH-dependent (Fig. 16.1). Two-site immunoradiometric assays for the intact PTH molecule are now performed routinely and have eliminated most of the problems related to circulating biologically inactive fragments (present in patients with impaired renal function) [30]. The finding of an elevated or at least incompletely suppressed PTH level in the setting of hypercalcemia is virtually diagnostic of PHPT. Cancer patients appear to have a higher incidence of PHPT than the general population [31]. Thus, the intact PTH assay is an important component of the routine evaluation for all hypercalcemic patients, even those with a known malignancy.

A low or low-normal serum PTH level (below 20 pg/mL) points to the presence of a PTH-independent cause of hypercalcemia. In this clinical situation, malignancy should be regarded as the most likely cause, especially if the hypercalcemia is of relatively recent onset. An elevated serum concentration of PTHrP, the primary mediator of HHM, would confirm the diagnosis [32]. However, this assay is often superfluous. In most such patients, the malignancy is readily apparent. In the rare situation where the circulating PTHrP value indicates the presence of an occult malignancy, further evaluation should focus on localizing the primary site and determining the extent of spread of the neoplasm. MAH generally develops in patients with advanced disease and its appearance has grave prognostic significance. Consequently, if the patient has a low serum PTH but longstanding hypercalcemia, a PTH-independent disorder, apart from malignancy, should be pursued.

A disturbance in the serum levels of vitamin D metabolites should be considered if there is no obvious malignancy and neither PTH nor PTHrP levels are elevated. An elevated serum concentration of 25-hydroxyvitamin D is indicative of vitamin D intoxication due to the ingestion of over-the-counter supplements or prescribed forms of vitamin D (D_2, ergocalciferol or D_3, cholecalciferol). Assessment of 1,25-dihydroxyvitamin D is only required if the patient is taking calcitriol, or has a confirmed or suspected diagnosis of a granulomatous disease or lymphoproliferative disorder. Additional testing for specific clinical disorders based on findings from the history and physical examination could include a TSH determination if signs of thyrotoxicosis are present, a serum retinol level if hypervitaminosis A is possible, serum and urine protein electrophoresis if multiple myeloma is suspected, or a 24 h urine collection for calcium if the family history suggests FHH.

Treatment

Optimal management of hypercalcemia requires aggressively dealing with the underlying pathophysiologic process. Although there are dozens of clinical entities that can cause hypercalcemia, PHPT and malignancy account for 80–90 % of cases. Hypercalcemia is generally a late feature of malignancy and thus it is rare for an underlying malignancy not to be clinically evident when hypercalcemia is first noted. Consequently, hypercalcemia in otherwise healthy outpatients is usually the result of PHPT while malignancy is more often responsible for hypercalcemia in hospitalized patients. If the patient's serum calcium concentration is less than 12 mg/dL (1.5 mmol/L), treatment should primarily be directed towards the underlying disorder. For example, discontinuing or reducing the dose of an offending medication such as vitamin D or lithium, removal of a parathyroid adenoma, or elimination of a tumor responsible for HHM with chemotherapy or surgery if possible. When the patient has symptoms and signs of acute hypercalcemic crisis (azotemia, somnolence, and/or coma) and the serum calcium is greater than 12 mg/dL (1.5 mmol/L), a series of urgent calcium-specific measures should be instituted (Table 16.3).

The emergent treatment of hypercalcemia must first focus on correcting dehydration, restoring intravascular volume, and enhancing renal calcium excretion. As delineated above, hypercalcemia induces a severe extracellular fluid deficit due to nausea, vomiting, and polyuria. Within the kidney, calcium is actively reabsorbed via PTH action in the distal tubule and passively reabsorbed because of the favorable electrochemical gradient created by reabsorption of sodium and chloride ions in the proximal tubule and in the thick ascending limb of the loop of Henle. Restoration of intravascular volume will thus enhance urinary calcium excretion by increasing glomerular filtration of calcium and decreasing proximal tubular and loop sodium reabsorption. Although a necessity in the management of a hypercalcemic crisis, parenteral fluid resuscitation must be administered cautiously in patients with compromised cardiovascular or renal function. Appropriate fluid

Table 16.3 Therapeutic options for hypercalcemia

Agent	Dosing information	Mechanism of action	Notes
Normal saline	2–5 L daily	Corrects volume depletion and enhances calciuria	May be poorly tolerated by patients with cardiac or renal failure
Loop diuretic (furosemide, ethacrynic acid)	Furosemide 10–20 mg Ethacrynic acid 50 mg	Inhibits distal tubular calcium reasborption	Can worsen hypercalcemia by reducing intravascular volume
Calcitonin	4–8 IU/kg intramuscularly or subcutaneously every 6 h	Inhibits osteoclastic bone resorption	Efficacy declines after 6–8 doses
Bisphosphonate	Pamidronate 60–90 mg intravenously over 4 h Zoledronic acid 4 mg intravenously over 15 min	Inhibits osteoclastic bone resorption	Potent inhibition of bone resorption can result in hypophosphatemia. Effects can last weeks
Glucocorticoids	Hydrocortisone 100–200 mg intravenously daily Prednisone 60 mg orally daily	Inhibits vitamin D conversion to active calcitriol	Side effects include hyperglycemia, immune suppression, and myopathy

administration depends on the patient's volume status, but in most situations of 500–1,000 mL of 0.9 % saline should be infused over the first hour, and then an additional 2–5 L over the first 24 h. The goal is to achieve a urine output of 200 mL per hour. This regimen can be continued for several days and usually succeeds in lowering calcium levels by 1–3 mg/dL. The addition of loop diuretics (e.g., furosemide, ethacrynic acid) to ongoing saline infusion has been advocated to enhance calciuria, but if administered before adequate hydration has taken place, the diuretic-induced volume contraction can instead worsen the hypercalcemia [33]. Therefore, loop diuretics are best reserved for those patients where vigorous fluid resuscitation may provoke cardiogenic fluid overload. Central venous access with hemodynamic monitoring should be considered in patients who do not tolerate initial attempts at fluid administration. With aggressive hydration and diuretic-induced diuresis, potassium and magnesium levels should be carefully monitored and appropriately replaced, as required. Hypophosphatemia also can occur and should be repleted enterally to a level of 2.5–3 mg/dL. Parenteral administration of phosphate is contraindicated as it can cause severe hypocalcemia and renal failure [34]. For patients with renal insufficiency or congestive heart failure in whom isotonic saline infusion is not feasible, hemodialysis or peritoneal dialysis with low calcium levels in the dialysate can be an effective strategy for removing calcium from the circulation [35].

In severe hypercalcemia, increased mobilization of skeletal calcium is often an important contributor. A parenteral bisphosphonate is the treatment of choice for inhibition of bone resorption in this situation [36]. Bisphosphonates (e.g., pamidronate, zoledronic acid) target and adhere to actively remodeling bone surfaces where they interfere with the ability of osteoclasts to resorb bone. Pamidronate 60–90 mg is administered intravenously in 500 mL of 0.9 % saline over 4 h and zoledronic acid 4 mg is administered intravenously in 5 mL of 0.9 % saline over 15–30 min. These agents can cause transient fever, flu-like symptoms or myalgias for a day or two. The effect of a parenteral bisphosphonate to lower serum calcium is apparent within 3–4 days, with maximal effect within 7–10 days after commencing treatment. The effect can persist for 7–30 days. Transient hypophosphatemia can occur, especially in malnourished patients. Due to the prolonged period of activity of bisphosphonates, it is crucial to first ascertain the etiology of the underlying disorder and correct reversible causes of hypercalcemia before administering one of these agents. Bisphosphonates are contraindicated if parathyroid surgery is imminent as their use can lead to profound postoperative hypocalcemia. Calcitonin is another therapeutic option to inhibit osteoclastic resorption. It has a rapid onset of action, causing serum calcium levels to fall by as much as 2 mg/dL within 2–6 h of administration. Consequently it may be used in conjunction with a bisphosphonate to more rapidly reduce the serum calcium level [37]. It is usually given intramuscularly or subcutaneously at a dose of 4–8 IU/kg. However, the efficacy of parenteral calcitonin is transient (lasting 24–48 h) due to rapidly acquired resistance. Immobilization suppresses osteoblastic bone formation and markedly increases osteoclastic bone resorption, for this reason early ambulation should always be encouraged, if possible.

To optimally address severe hypercalcemia, multiple therapies should be started as soon as possible. For example, aggressive parenteral rehydration and calcitonin along with a potent bisphosphonate can all be used in the first few days. Any drugs that inhibit urinary calcium excretion, decrease renal blood flow, or augment PTH action as well as supplements that contain calcium, vitamin D, vitamin A, or other retinoids should be discontinued as soon as possible. Immobilization promotes osteoclastic bone resorption, hence early ambulation should be encouraged. Though the gut has an important role in normal calcium homeostasis, intestinal absorption is usually diminished in the setting of hypercalcemia, making dietary calcium restriction unnecessary.

Once the acute episode of hypercalcemia has been successfully addressed and the patient is stable, clinical efforts should then be directed towards the underlying hypercalcemic disorder per se. Ultimately, definitive therapy directed at the underlying disorder is necessary to prevent the redevelopment of hypercalcemia. Parathyroidectomy should be considered at the earliest safe opportunity in all patients with hypercalcemic crises as a result of underlying parathyroid disease (e.g., parathyroid adenoma, hyperplasia, or carcinoma). Definitive cytoreductive therapies (surgery, radiation, or chemotherapy) for cancer patients with HHM can prevent further hypercalcemic events while, for other patients with LOH, improvement may come with radiation therapy directed at the lesion(s). Treatment of granulomatous disorders with standard regimens including glucocorticoids and/or immunosuppressants can usually succeed in reducing circulating 1,25-dihydroxyvitamin D levels. Substituting an alternative psychotropic agent effective in bipolar disease can be an effective approach in those patients with lithium-induced hypercalcemia.

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Chapter 17
Pituitary Apoplexy

Pouyan Famini and Shlomo Melmed

Précis

1. Clinical setting—acute development of neurological symptoms and signs often accompanied by resistant shock and other symptoms of hypopituitarism.
2. Diagnosis

    (a) History: Most common presenting symptoms include sudden severe headache, double vision, visual loss including field deficits, nausea, and vomiting. Altered mental status may present. Complaints of hypopituitarism, such as loss of libido and sexual function, may precede or accompany the development of neurological complaints. History of a pituitary adenoma and precipitating factors that may result in pituitary apoplexy include acute hypotension, hypertension, diabetes mellitus, coagulopathy, pregnancy, head trauma, and major surgical procedures. Medications that increase bleeding risk including anticoagulants, antiplatelets, and thrombolytics as well as medications that act directly on pituitary function such as dopamine agonists may all increase risk.

    (b) Physical examination: Fever, orthostatic hypotension, ophthalmoplegia, decrease or loss of visual acuity, visual field loss, and meningismus are commonly seen. Rarely encountered physical findings include hemiplegia, Horner's syndrome, trigeminal neuralgia, photophobia, proptosis, eyelid edema, rhinorrhea, and epistaxis.

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    (c) Laboratory values: Hyponatremia, hypoglycemia, and elevated leukocyte count are often observed. Most patients also present with partial or complete hypopituitarism at presentation including hypocortisolism. Prolactin may be elevated or often below normal.

    (d) Imaging: Computerized tomography (CT) and magnetic resonance imaging (MRI) findings are consistent with intrasellar hemorrhage and/or necrosis of a pituitary and or adenoma.

3. Treatment—High-dose corticosteroids in addition to intravenous fluids and vasopressors are the mainstay of treatment in the acute period. Surgical decompression, preferably through the transsphenoidal route, can restore neuro-ophthalmic and pituitary function. Patients with altered mental status, severe reduced visual acuity, and/or severe or deteriorating visual field deficits should be managed with timely surgery. A conservative approach may be undertaken in patients with milder symptoms such as ophthalmoplegia or headache. Assessment of normal adrenal function, defined as elicited cortisol levels >20 µg/dl, should be urgently determined upon presentation. High-dose corticosteroid therapy should be titrated with improvement of clinical status and serial adrenal evaluations to prevent side effects of over-therapy. Assessments of other hypothalamic–pituitary function may be determined weeks after initial presentation with replacement of hormone therapy initiated at that time. Long-term endocrine reassessments are essential as anterior pituitary function may fully or partially recover from initial presentation. Follow-up radiological imaging is also essential since recurrent apoplexy may occur.

Introduction

Pituitary apoplexy is a life-threatening, acute clinical syndrome of pituitary infarction, hemorrhage, and/or necrosis presenting as abrupt onset headache, nausea and vomiting, fever, meningismus, visual disturbances, and altered sensorium [1]. Varying degrees of transient or persistent hypopituitarism accompany the syndrome [2–5]. Bailey first described hemorrhage into a pituitary adenoma in 1898 in a male with acromegaly presenting with sudden onset headache, nausea, vomiting, fever, visual loss, and oculomotor palsies [6]. Autopsy demonstrated hemorrhage in an intrasellar adenoma with endarteritis of the adenohypophyseal vasculature [6]. However, the clinical syndrome [7–11] was not fully recognized until 1950 when Brougham et al. coined the phrase "pituitary apoplexy" [1].

Apoplexy describes hemorrhagic and necrotic changes, usually of vascular origin. Derived from the Greek word *apoplēssein*, which means to strike down and incapacitate, the ancient Greeks believed that those suffering from cerebrovascular accidents had been struck down by the gods. Historically, failure to diagnose this condition until autopsy resulted in significant neurological morbidity and death, sometimes hours within presentation [1, 9, 12]. In contrast, diagnosis and surgical

removal of hemorrhagic and necrotic tumor resulted in prompt neurological recovery as early as the 1920s [13, 14]. Physicians also became aware of the valuable effects of hormone replacement by the early 1950s, although corticosteroids could not yet be synthesized and administered. Early attempts included implantation of adrenal cortex extract [15] and fresh calf pituitaries [16]. By the end of the 1950s, preoperative cortisone administration was advocated [17]. Following such improvements in therapy, the mortality reviewed in the literature became exceedingly rare [12].

Significant advances have been made in both diagnostics and surgical techniques. MRI is now the radiological modality of choice due to its ability to demonstrate hemorrhage and infarction, as well as disease impact on neighboring perisellar structures [18–20]. Transsphenoidal decompression and immediate institution of high-dose intravenous corticosteroid replacement therapy are generally considered the standard of care [2, 21–24]. However, there is also considerable literature advocating conservative management in a carefully selected group of patients [25–27]. Yet, pituitary apoplexy remains a frequently misdiagnosed and poorly understood condition with often vision-threatening and sometimes life-threatening consequences [4, 22].

Pathogenesis of Pituitary Apoplexy and Clinical Manifestations

Pituitary apoplexy results from hemorrhage, infarction, or a combination of hemorrhagic infarction of a pituitary adenoma and normal pituitary gland [28]. However, the exact pathogenesis is not completely understood nor well delineated. The unusual pituitary blood supply likely contributes to this process (Fig. 17.1). Presentation of pituitary apoplexy varies from relatively benign events to clinical catastrophes involving severe neurological deficits, endocrine dysfunction, and even death [2, 21, 24, 29]. The clinical spectrum may be explained by three mechanisms (see Table 17.1) [30]. (1) Destruction or compression of the pituitary gland causing hypopituitarism. (2) Sudden development of pressure and compression of neighboring parasellar neurovascular structures due to upward or lateral enlargement of hemorrhagic and/or necrotic pituitary gland. (3) Subarachnoid leakage of blood or necrotic tissue within the basal cisterns leading to inflammatory responses similar to subarachnoid hemorrhage or aseptic meningitis.

Pituitary Anatomy

The pituitary gland lies within the sella turcica (see Fig. 17.2), surrounded by the anterior and posterior clinoid processes, and is composed of three sections. The tuberculum sella is an olive-shaped swelling on the anterior slope between the chiasmal sulcus and the sella turcica. The hypophyseal fossa, which contains
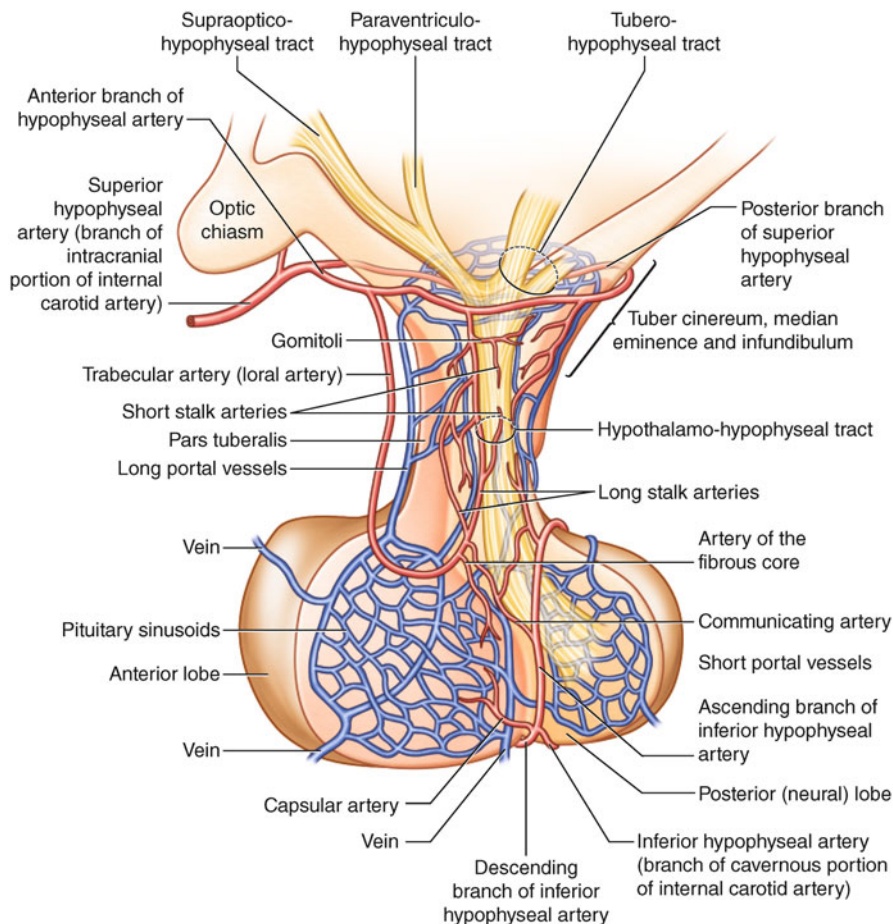
Fig. 17.1 Pituitary blood supply

the pituitary gland, lies immediately posterior to the tuberculum sellae. The dorsum sella forms the posterior aspect of the sella turcica and terminates at the posterior clinoid process.

Anterior and posterior pituitary lobes are separated by a section of avascular tissue called the pars intermedius, or intermediate lobe. The pituitary gland is connected via the pituitary stalk to the hypothalamus at the median eminence, a thin plate of tissue making up the floor of the anterior part of the third ventricle. The optic chiasm is located superiorly in a cerebrospinal fluid filled space and the lateral walls of the pituitary fossa are formed by the cavernous sinuses, which contain the internal carotid arteries, branches of sympathetic chain, and cranial nerves III, IV, V (first and second divisions), and VI. The blood drainage of the orbit also traverses the cavernous sinus.

Table 17.1 Pituitary apoplexy pathophysiology and correlating clinical manifestations

Pathophysiology	Clinical manifestations
Leakage of blood or necrotic tissue into	
Subarachnoid space and/or basal cisterns	Features of subarachnoid hemorrhage or meningitis including hyperpyrexia, headache, nausea and/or vomiting, nuchal rigidity, altered consciousness
Surrounding brain parenchyma	Altered consciousness, seizures
Pituitary damage	Hypopituitarism, resolution of preexisting hyper-functioning endocrinopathy
Pressure or compression on	
Cavernous sinus	Chemosis, proptosis
Cranial nerve III	Ptosis, mydriasis, dipoplia due to medial rectus, superior rectus, and inferior oblique palsies
Cranial nerve IV	Head-tilt or dipoplia due to superior oblique palsy
Cranial nerve V (first and second divisions)	Facial paresthesia, loss of corneal reflex
Cranial nerve VI	Diplopia due to lateral rectus palsy
Internal carotid and its branches	Hemiplegia, unilateral focal hemispheric signs, altered consciousness, seizures
Hypothalamus	Hyperpyrexia, altered consciousness, impaired water balance, sympathetic dysregulation
Optic tracts and/or chiasm	Impaired visual acuity, visual field defects
Sympathetic chain	Horner's syndrome: ptosis, miosis, anhidrosis, loss of ciliospinal reflex, conjunctival erythema
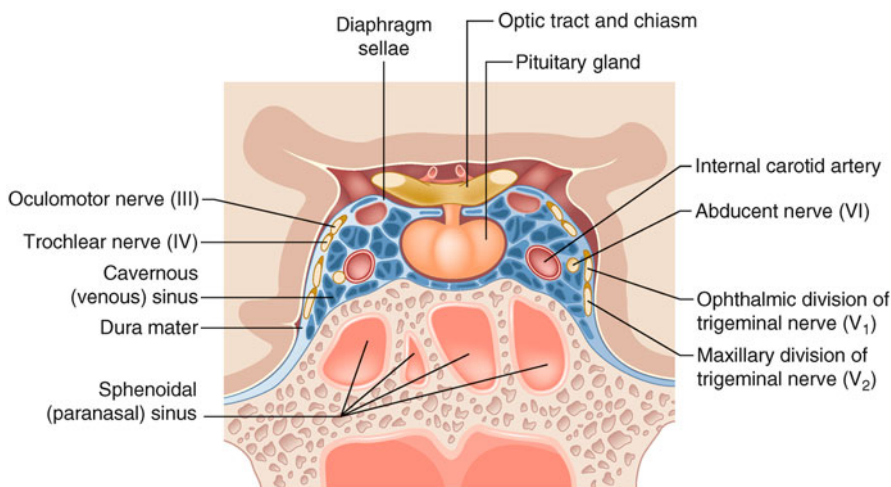
Fig. 17.2 Pituitary anatomy

Pituitary Blood Supply

The pituitary blood supply is derived through branches of the internal carotid arteries, the superior hypophyseal artery, a branch distal to the cavernous sinus, and the inferior hypophyseal artery, a branch at the cavernous sinus level. The neurohypophysis receives direct arterial blood from the inferior hypophyseal artery via an anastomotic arterial circle. In contrast, the adenohypophysis receives little to no direct systemic arterial blood supply from the internal carotid artery, mainly via trabecular (loral) arteries, a branch of the superior hypophyseal artery that descends alongside the pituitary stalk [31, 32].

The pars distalis blood supply is delivered by long portal veins that connect a primary capillary plexus at the base of the hypothalamus, the median eminence, to a secondary capillary plexus of the pars distalis. These long portal veins descend along the ventral aspect of the pituitary stalk. The primary portal capillary plexus at the median eminence in turn receives arterial blood from the superior hypophyseal artery. The pars distalis also receives venous blood draining directly from the posterior pituitary through short portal vessels. Thus, the anterior pituitary receives most of its blood supply through the hypothalamus and posterior pituitary [33].

Pathogenesis

Pituitary apoplexy may occur in the setting of a rapidly growing pituitary tumor that outstrips its blood supply resulting in ischemic necrosis and hemorrhage [1, 15, 17]. Pituitary tumor growth may be responsible for disrupted tissue organization and vascularization at the parenchymal–pericapillary interface [34]. Furthermore, pituitary adenomas have a greater dependence on direct arterial blood than the normal gland [31, 35]. Despite the greater presence of direct arterial supply within adenomas, these small "twig" end arteries have little total effect on anterior pituitary perfusion as does the portal venous system [32]. Therefore, pituitary apoplexy occurs due to the compromised vascular supply of a suddenly expanding large tumor, leading to ischemia, hemorrhage, and ultimately necrosis. However, this is unlikely to explain all cases of pituitary apoplexy [24], as the incidence of pituitary hemorrhage does not correlate with tumor size [29, 36].

Another potential mechanism is based on observations that increased intrasellar pressure due to coughing and sneezing has been associated with pituitary apoplexy in five patients [37]. As adenomas extend laterally, the cavernous sinus may gradually become occluded. Venous back pressure rises with repeated coughing and/or sneezing as a direct result of further increased tension in the cavernous sinus, leading to compromised adenoma arterial circulation. Subsequently, adenoma infarction and/or hemorrhage develop.

Ischemia, necrosis, and hemorrhage may also ensue within pituitary adenomas when an expanding pituitary neoplasm extends upward and compresses the

infundibular and superior hypophyseal vessels against the diaphragmatic notch [38]. As a pituitary neoplasm grows, it compresses the normal gland, leading to expansion of the pituitary fossa, stretching of the diaphragma sella, and as space becomes limited the pituitary neoplasm must squeeze itself into the narrow channel that houses the hypophyseal stalk; ultimately resulting in distortion and impairment of infundibular circulation [38]. Concomitant hyperprolactinemia due to stalk compression, observed at high frequency with pituitary apoplexy supports this theory [39–42]. However, angiography has demonstrated that vessels supplying adenomas often originate from the inferior hypophyseal artery [43]. Consequently, disruption of superior hypophyseal artery flow should not necessarily affect blood circulation to the enlarging adenoma. Ischemia and hemorrhage may also originate within the normal pituitary gland, either due to compression by the growing adenoma [24] or from disruption of superior hypophyseal artery flow that supplying the adenohypophysis [21].

Potential vascular risk factors for pituitary apoplexy in adenomas include decreased overall vascular density [44], newly formed immature blood vessels [45], and microscopic vascular injury with endothelial cell blebbing, modifications of the basal laminae, and changes in capillary permeability [34]. Difference in pituitary tumor immunological targets may also explain why some adenomas have a predilection toward apoplexy. Mou et al. analyzed 426 pituitary adenomas, 83 of which had undergone apoplexy [46]. Proliferating cell nuclear antigen (PCNA) expression was higher in patients with pituitary apoplexy for all hormonal subtypes except prolactin-secreting tumors, and growth-hormone secreting and multi-hormonal adenomas with apoplexy had increased matrix metallopeptidase 9 (MMP-9) expression [46]. Differences in expression of angiogenesis factors may underlie distinctive mechanisms resulting in apoplexy in different hormonal subtypes.

Pathophysiology of the Clinical Manifestations

The typical presentation of pituitary apoplexy is characterized by sudden onset headache, followed within hours to days by nausea, vomiting, ocular palsies, decreased visual acuity or blindness, visual field defects, signs of meningeal irritation, and/or progressive alterations of consciousness [1, 21, 38, 47, 48]. Acute adrenal insufficiency is a major cause of mortality in these patients. Sudden headache is invariably the predominant and initial symptom, usually precedes visual symptoms [21], and is likely due to increased intrasellar pressure, mass effect, compression of neighboring structures and nerves within the cavernous sinus, and/or subarachnoid hemorrhage [29, 36, 49]. Likely mechanisms include referred pain due to stretching of dura and meningeal irritation secondary to subarachnoid hemorrhage [21, 50, 51]. Pituitary apoplexy also commonly presents with pyrexia induced by adrenal insufficiency, chemical meningitis, or hypothalamic dysregulation [1, 47]. Nausea and vomiting may be secondary to hypoadrenalism, hypothalamic injury or irritation, increased intracranial pressure, or meningeal irritation [47].

Altered mental status may present as mild stupor to coma, from insidious to abrupt, due to several possible pathophysiologic mechanisms. Although acute adrenal insufficiency may cause electrolyte abnormalities including hyponatremia and hypoglycemia, some patients continue to display alterations in mental status despite correction of electrolyte abnormalities and corticosteroid treatment. Dorsal tumor extension and hemorrhage with pressure on the hypothalamus or midbrain may also contribute [1, 21, 30, 38, 47]. Other mechanisms include obstructive hydrocephalus due to infiltration or displacement of the third ventricle by necrotic tissue or hemorrhage [36, 50], extensive brain edema with herniation of cerebellar tonsils [36, 52], or impaired cerebral circulation due to internal carotid artery vasospasm in the setting of subarachnoid hemorrhage or compression within the cavernous sinus [50, 53, 54].

Suprasellar extension and upward enlargement of the adenoma and hemorrhage may compress the optic pathways, diencephalon, and mesencephalon. Suprachiasmatic elevation with distention of optic nerves and chiasm leads to decreased visual acuity and visual field defects, including classical bitemporal hemianopsia. Hypothalamic involvement may lead to dysregulation of vital functions including hypotension, dysrhythmias, and disordered breathing, disturbances of temperature regulation, diabetes insipidus, or syndrome of inappropriate antidiuretic hormone [21, 30, 47]. Midbrain involvement may cause muscle tone changes, abnormal responses to visual and/or auditory stimuli, hiccups, and retraction nystagmus [21, 48, 55]. Pressure on nearby olfactory tracts may rarely cause anosmia [17].

Lateral tumor extension with pressure upon the cavernous sinus may cause variable symptoms consistent with the cavernous sinus syndrome [21, 30]. Involvement of cranial nerves III, IV, and VI may produce variable degrees and combination of ocular palsies. Cranial nerve III palsy may be accompanied by ptosis and mydriasis depending on severity of nerve damage. Horner's syndrome with unilateral ptosis, miosis, and anhidrosis may present following damage to sympathetic fibers within the cavernous sinus [30], and compromise of the cavernous sinus venous plexus can lead to proptosis and chemosis [37, 56]. Compression of the first or second divisions of the trigeminal nerve may produce facial pain, altered facial sensation, and/or loss or decreased corneal reflex [1, 20, 38]. Hemispheric signs with possible addition of aphasia mimicking a cerebrovascular accident may also be induced by internal carotid artery compression, occlusion, or vasospasm [1, 15, 38, 47, 52, 57]. Venous stasis can also produce rhinorrhea or eyelid edema [21]. Extensive hemorrhage may extend into the subarachnoid space, surrounding brain parenchyma, and/or ventricles, with fever, photophobia, nausea, vomiting, meningeal signs, and altered mental status [3, 21, 36]. Hemorrhage into brain parenchyma and subsequent cortical irritation may induce seizures [47].

The acuity of pituitary apoplexy and degree of hemorrhage and edema within the sellar and parasellar region determine the nature and extent of presenting neurological symptoms. Generally, patients with pituitary tumors develop symptoms of mass compression after significant tumor growth due to adaptation of adjacent neurological structures to gradual tumor growth [58]. Alternatively, symptoms of pituitary apoplexy develop acutely due to rapid expansion of hemorrhage and/or infarction.

While patients with histological evidence of hemorrhage have similar clinical presentations and hypopituitarism to those patients who exhibit infarction without hemorrhage, the severity of presenting clinical symptoms is greater and neuro-ophthalmic clinical outcomes are less favorable in the former group [59]. These observed differences are likely due to slower rate of increase and overall decreased intrasellar pressure in lone-infarction pituitary apoplexy than in those with a hemorrhagic component [59]. This is in accordance with findings that microadenomas present less commonly with overt clinical features of pituitary apoplexy than macroadenomas, likely due their smaller size and relatively less extent of hemorrhage [60].

Pathophysiology of Hypopituitarism

Development of hypopituitarism may be due to preexisting deficiencies prior to apoplexy from a macroadenoma [2, 39] or occur rapidly from rapid increase of intrasellar pressure [61]. Most patients with pituitary apoplexy present with variable decreases in pituitary hormone function ranging from single hormone involvement to panhypopituitarism, while diabetes insipidus is relatively uncommon [2, 4, 5, 21, 24, 61, 62]. Differences in anterior and posterior pituitary blood supply may explain why transient or persistent anterior pituitary dysfunction is common, while there is relative sparing of antidiuretic hormone secretion [5]. While destruction of the adenohypophysis may lead to multiple pituitary hormone deficiencies, significant pituitary tissue loss is required prior to development of life-threatening endocrine abnormalities as survival has been estimated to occur with as little as 10 % residual functional tissue [63].

Alterations of portal vessel blood flow can potentially disturb hypothalamic regulation of the anterior pituitary, and hypopituitarism may be due to impaired hypothalamic regulation of pituitary axis hormones, rather than a direct insult to the adenohypophysis [5]. Impaired delivery of hypothalamic releasing factors via the neurohypophyseal vasculature is a likely cause, as direct damage to the hypothalamus or median eminence derangements is rarely observed with pituitary apoplexy [5]. Given that adenomectomy may resolve macroadenoma-associated hypopituitarism, gradual compression of pituitary stalk and portal vessels by a growing macroadenoma may underlie pituitary failure [39]. Furthermore, urgent surgical decompression after pituitary apoplexy has been associated with rapid reversal of pituitary dysfunction [61]. The underlying mechanism of abrupt onset pituitary dysfunction may therefore likely be due to rapid increase in intrasellar contents causing compression of portal vessel circulation and pituitary stalk pituitary dysfunction during apoplexy, rather than adenohypophyseal destruction [61].

Increased intrasellar content and pressure may also cause progression of potentially reversible hypopituitarism during pituitary apoplexy [42, 64]. As intrasellar pressure increases, increased portal venous pressure may disrupt hypothalamic control of the anterior pituitary [42]. For example, valsalva maneuver with a positive

airway pressure of only 30 mm H_2O has caused complete arrest of portal blood flow from the hypothalamus in Rhesus monkeys [65]. Intraoperative increases in intrasellar pressure of patients harboring pituitary tumors has been demonstrated to disrupt and even cause complete arrest of pituitary blood flow [66]. This theory is further supported by observations of higher recorded intrasellar pressures in patients who harbor macroadenomas and have hypopituitarism than patients with macroadenomas and normal pituitary function [41]. Furthermore, higher elevated intrasellar pressures have been recorded with pituitary apoplexy [64] than with non-apoplectic macroadenomas [41]. Therefore, pituitary apoplexy results in greater, sudden increases of intrasellar pressure due to rapid increase in intrasellar contents with more abrupt cessation of portal vessel blood flow [64]. Hypopituitarism subsequently develops due to sudden decreased delivery of hypothalamic hormones and anterior pituitary perfusion [64].

Measurements of prolactin (PRL) levels may be used as a prognostic marker of pituitary function following pituitary apoplexy. Normally PRL may mildly increase in patients harboring non-PRL-secreting sellar masses due to a stalk effect, through disruption of the negative tonic hypothalamic control via dopamine. In contrast, low or suppressed serum PRL levels may indicate irreversible ischemic anterior pituitary necrosis due to loss of viable hormone producing cells [64]. Patients presenting with PRL levels less than 2.5 μg/L were less likely to recover or maintain pituitary function following surgical decompression than patients with PRL levels greater than 3.5 μg/L [64]. Therefore, hypopituitarism may be reversible due to ischemia from decreased portal vessel blood flow [61], or irreversible with fulminate necrosis of the pituitary gland [64].

Epidemiology

Classical pituitary apoplexy is rare, with an incidence of approximately 1.2 per million per year [67]. Pituitary tumors account for 15 % of all intracranial masses [68], with up to 90 % due to adenomas [69–71]. Pituitary apoplexy develops in 9.5 % of patients harboring asymptomatic non-functioning pituitary adenomas [72]. Hemorrhagic and necrotic changes have been reported in 9.5–28 % of all surgically treated pituitary adenomas [19, 29, 36, 49, 73]. However, symptomatic pituitary apoplexy occurs in only 0.6–9.1 % of patients harboring pituitary tumors [24, 29, 36, 50, 74–76].

Pituitary apoplexy most commonly occurs in middle-aged males in the fifth decade of life [2, 4, 24, 26, 50, 62, 75, 77], but has been reported in a young 6-year-old child [78] to 90-year-old male [79]. The frequency of pituitary apoplexy among different histological types is similar to the distribution of pituitary tumor types in the population [21, 30]. However, there is often a low yield of tumor type identification by immunohistochemical staining due to extensive necrosis of most pathological specimens [2, 24, 26].

Recognition

Clinical History

Pituitary apoplexy is a clinical syndrome of sudden neurological, ophthalmologic, and endocrinological derangements that occur due to sudden tumor expansion and hemorrhage [1, 21, 30], normally evolving within hours to 2 days [48, 57]. Symptom manifestation is largely dependent on compression of neighboring neurovascular structures, extravasation of blood into the subarachnoid space of the basal cisterns, and/or partial to complete pituitary destruction. Pituitary apoplexy occurs in a small percentage of patients harboring pituitary tumors [24, 29, 36], and may be first indication of the presence of a pituitary tumor [4, 24, 25, 62, 75, 79]. Severe attacks manifest with altered consciousness, hemiparesis, meningism, visual disturbances including loss of vision and visual field defects, and ocular palsies. Minor events are characterized by headache, nausea, vomiting, and vertigo. Major and minor symptoms are not exclusive, and usually overlap. Most common presenting symptoms are listed in Table 17.2. Occasionally patients present with sudden unexpected death [2, 12, 18, 29, 38, 57, 79, 80].

Headache is the most commonly observed symptom and is usually described as retro-orbital, frontal, or diffuse [2, 21, 24, 38, 75, 81]. Fever may be present in up to 20 % of patients [24]. Blindness presents in up to 42 % of patients [27]. Ocular palsy may be unilateral or bilateral, and involve any combination of the oculomotor nerves [2, 24, 82]. The oculomotor nerve is most commonly affected, followed by the abducens nerve [2, 25, 27, 57].

Table 17.2 Most common presenting symptoms and signs of pituitary apoplexy in 509 patients[a]

Symptom	Mean percentage (%)	Number of patients
Headache	87	509[b]
Ophthalmoplegia	61	370
Visual acuity deficit	57	469
Nausea and/or vomiting	54	436
Visual field defect	51	367
Photophobia	32	117
Meningismus	19	85
Hyperthermia	16	155
Altered mental status	15	470
Trigeminal neuralgia (V1 or V2)	7	76
Hemiparesis	4	84
Seizure	4	24

[a]The data presented in this table were generated from 16 published series [2, 4, 18, 24–27, 29, 50, 62, 75–77, 79, 149, 150]

[b]The following symptoms were not reported among all patients and/or among all series, except for headache

Patients with apoplexy may also rarely present with other neurological deficits including seizures [47] and Horner's syndrome [21, 30]. Unilateral facial pain or altered facial sensation with loss or decreased corneal reflex due to trigeminal nerve involvement occurs infrequently [1, 2, 20, 38]. Other nonspecific symptoms and signs include hiccups, anosmia, photophobia, eyelid edema, proptosis, abnormal papillary reactions, retraction nystagmus, rhinorrhea, and epistaxis [21].

Symptoms and evidence of hypopituitarism are present prior to the apoplectic event in 20–62 % of patients [2, 24, 29, 75]. The degree of hypopituitarism does not necessarily correlate with preoperative visual impairments [61]. Since pituitary apoplexy occurs most frequently with macroadenomas [36, 38, 57, 75], preexisting partial or complete hypopituitarism is an expected occurrence [39]. Menstrual disturbances and decreased libido due to decreased gonadal hormone secretion are often the most common clinical features suggesting preexisting hypopituitarism [2, 24, 27, 76]. Occasionally, pituitary apoplexy may result in regression of hyperfunctioning anterior pituitary states [3, 83, 84]. Hypocortisolism is of concern and can present with weakness, light headedness, nausea, vomiting, and abdominal pain. Signs of hypocortisolism include fever, tachycardia, hypovolemia, orthostatic vital signs, and hypotension refractory to intravenous fluids.

Initial Laboratory Assessment

Alterations of both electrolytes and pituitary function can occur. Hyponatremia, occurring in 12–44 % of patients, may be due to the syndrome of inappropriate antidiuretic hormone secretion, hypocortisolism, and/or hypothyroidism [4, 18, 24, 62, 75, 85]. Hypoglycemia may occur in the setting of hypocortisolism. Elevated leukocyte count may also be present, especially during the acute phase in up to 18 % of patients [47, 62].

Up to 80 % of patients have laboratory evidence of partial or complete hypopituitarism at presentation [4, 18, 25, 50, 61, 62, 77], including attenuated thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and/or growth hormone (GH). Following pituitary apoplexy, 88 % of patients have been deficient in GH, 76 % in LH, 66 % in ACTH, 58 % in FSH, and 42 % in thyroid function [5]. PRL levels may also be either elevated or suppressed due to stalk effect or anterior pituitary destruction, respectively [64]. In contrast, diabetes insipidus is an uncommon finding of pituitary apoplexy only occurring in 2–4 % of patients [5]. Inappropriate secretion of antidiuretic hormone is very rarely observed [5, 86].

High opening CSF pressure, elevated protein, increased red blood cell count, and/or xanthochromia [2, 38, 87, 88] may increase suspicion for alternative diagnoses, particularly subarachnoid hemorrhage and infectious meningitis. Pleocytosis may also be present, with either mixed [88] or neutrophilic predominance [89]. However, sterile CSF cultures are the norm [89–91], and serologic studies for infectious etiologies are negative [89].

Fig. 17.3 Axial non-contrast-enhanced computed tomography imaging of the head demonstrates high density in the sella consistent with hemorrhage in a large pituitary macroadenoma due to apoplexy

Imaging Evaluation

Radiological evidence of pituitary apoplexy on computerized tomography (CT) or MRI includes sellar and/or suprasellar abnormalities consistent with hemorrhage and/or necrosis (see Fig. 17.3). CT findings suggesting hemorrhage evolve from a well-defined high-density mass with minimal to no enhancement at 1–2 weeks of presentation to intra-tumor low density areas with possible ring enhancement at greater than 2 weeks following pituitary apoplexy [21, 29, 88]. CT offers good reliability in detection of acute hemorrhage [88]. However, as blood density changes with hemoglobin degeneration, it can become difficult to distinguish subacute and chronic hematomas on CT scans from cystic degeneration, abscesses, and bland infarction [88]. Similarly, CT cannot readily distinguish pituitary infarction due to apoplexy from cysts or pituitary adenomas that have rim enhancement but have not undergone apoplexy [19, 88]. CT scan detection rates of 93 % and 21 % for pituitary tumor and hemorrhage/necrosis, respectively, were observed in 35 patients [24]. An apparently normal sella may be present in up to 14 % of patients [2, 24, 26].

MRI is superior to CT and tumor and hemorrhage/infarction detection rates of 100 % and 88 % have been observed in symptomatic cases of pituitary apoplexy, respectively [24]. Furthermore, MRI if often able to detect hemorrhage not initially detected by CT [18]. Increased detection rate of hemorrhage by MRI (84 %) vs. CT (71 %) was reported within apoplectic pituitary macroadenomas [75].

Pituitary apoplexy may present with hemorrhagic and non-hemorrhagic changes on T1-weighted images [20]. Intraparenchymal hemorrhage is typically hyperintense on T1-weighted images and hypointense on T2-weighted during acute phase, days 1–2, of pituitary apoplexy [20, 92, 93]. However, MRI may fail to demonstrate hemorrhage during the acute phase of pituitary apoplexy [94]. By days 3–15, during the subacute phase of hemorrhage, signal intensity changes occur due to degeneration of hemoglobin into methemoglobin, and both T1 and T2-weighted signals appear bright [92, 95]. After day 15, a fluid–fluid level may be observed in the mass due to sedimentation of blood products [20, 94]. Pituitary infarction without hemorrhage is described as low signal intensity with associated rim enhancement on T1 and T2-weighted MRI sequences [19, 88].

Etiologies

"Pituitary apoplexy" [1] applies to cases of pituitary hemorrhage and/or necrosis associated with symptoms and signs of compression of parasellar structures or meningeal irritation [21]. Therefore cases of pituitary hemorrhage and/or infarction which do not present with classical acute neuro-ophthalmic clinical features of pituitary apoplexy, as with obstetrical hemorrhage [96] or asymptomatic hemorrhage, are considered separate entities. "Pituitary apoplexy" is a clinical rather than a radiological or pathological diagnosis and should be reserved for symptomatic cases. Symptomatic pituitary apoplexy has been most frequently associated with preexisting macroadenomas [21, 38, 57, 75]. Only a few cases of symptomatic pituitary apoplexy associated with microadenomas [97, 98], Rathke cleft cysts [18, 99, 100], craniopharyngiomas [55], lymphocytic hypophysitis [101, 102], and other non-adenomatous pituitary glands [20, 82, 103], have been reported.

Subclinical or asymptomatic pituitary apoplexy, defined as histopathological findings consistent with pituitary apoplexy without classical neuro-ophthalmic features, has been described in both macro- and microadenomas [29, 36, 49, 60, 104]. In 664 patients with pituitary adenomas, 9.5 % of surgically treated adenomas had pathological evidence of hemorrhagic and/or necrotic degeneration while only 0.6 % of patients had symptoms of classical pituitary apoplexy [36]. In 560 surgically resected adenomas, pituitary hemorrhage was present in 16.6 % of cases, with clinical symptoms present in only 9.1 % [29].

Asymptomatic pituitary hemorrhage and/or necrosis may present as a new headache or new onset endocrinopathy without other overt neurological or visual symptoms and diagnosed incidentally on imaging or pathology [98, 104]. Due to lack of headache specificity, it is difficult to attribute episodes of headache to hemorrhagic foci discovered in pituitary adenomas of patients with previous hemorrhage. Occasionally, changes in anterior pituitary function may develop following infarction or hemorrhagic infarction, and may be the only sign of this event. Due to microadenomas smaller relative size, infarction or hemorrhage of microadenomas will

less commonly produce the classical clinical features of pituitary apoplexy, except for hypopituitarism [60]. Regardless, due to improved imaging techniques, asymptomatic or subclinical pituitary hemorrhage and/or infarction are likely being diagnosed earlier in presentation and with increasing frequency.

Precipitating Factors

Although pituitary apoplexy is most often a spontaneous vascular event [21, 105], it has been associated with numerous pathological conditions, medications, and dynamic pituitary testing (see Table 17.3). Although pituitary apoplexy presents similarly whether there is an associated risk factor present or not, patients with associated risk factors may present more frequently with altered mental status and worse visual prognosis, as well as more difficult disease to diagnosis [79]. Since up to 80 % of cases of pituitary apoplexy occur spontaneously without a prior history of pituitary tumor [4, 51, 105], many of these associated conditions are usually regarded as precipitating factors retrospectively, after the catastrophic event has already occurred. Furthermore, the role of these potential risk factors in pituitary

Table 17.3 Precipitating factors in pituitary apoplexy	*Pathologic conditions*
	Acute hypotension
	Hypertension
	Diabetes mellitus
	Coagulopathy
	Pregnancy
	Head trauma
	Major surgical procedures (e.g., CABG)
	Transient changes in intracranial pressure
	Angiography
	Coughing and/or sneezing
	Lumbar puncture
	Pneumoencephalography
	Positive pressure ventilation
	Medications
	Anticoagulant
	Antiplatelet
	Clomiphene
	Dopamine agonist, initiation, or withdrawal
	Dynamic pituitary function tests
	Estrogen therapy
	Gonadotropin-releasing hormone agonist
	Isosorbide dinitrate
	Pituitary irradiation
	Thrombolytics

apoplexy in regard to pathophysiology, prognosis, and management is not completely understood [79].

Conditions that have been associated with pituitary apoplexy include sudden head trauma [2, 18, 75, 76, 106, 107], arterial hypertension [20, 24, 25, 50, 62, 108], diabetes mellitus [27, 108, 109], acute hypotension due to any cause including sepsis [81], coagulopathies including thrombocytopenia [36, 50], and high estrogen states including pregnancy [2, 18, 24]. Pituitary apoplexy has also been described after various surgical procedures [79, 110–112], most commonly coronary artery bypass [26, 79, 113–117]. Transient changes in intracranial pressure due to coughing or sneezing [37, 76], positive pressure ventilation [118], angiography [52, 57, 119], and pneumoencephalography [80, 120] have also been considered potential precipitating events.

Medical treatments have also been reported to precipitate pituitary apoplexy and increase the risk of such events. These include anticoagulants [2, 36, 50, 75, 121], antiplatelet medications [24, 122], thrombolytics [79, 122], clomiphene [123], gonadotropin-releasing hormone (GnRH) agonists [124–126], initiation or discontinuation of dopamine agonists [27, 29, 76, 127, 128], and pituitary radiation therapy [1, 17, 36, 48, 129, 130]. Development of pituitary apoplexy occurring soon after dynamic pituitary testing with GnRH, thyrotropin-releasing hormone, corticotropin-releasing hormone, chlorpromazine, and triple bolus test has also been reported [131–137].

Differential Diagnosis

Pituitary apoplexy is often misdiagnosed due to nonspecific symptoms and signs that mimic other common medical emergencies. Patients may present to different clinical specialties causing delays in diagnosis and appropriate treatment, unless the condition is recognized early. Diagnosis can be difficult since the apoplectic event is often the first indication of the presence of a pituitary tumor [4, 21, 24, 62, 75, 79], despite symptoms consistent with previously undiagnosed pituitary hormone dysfunction prior to the catastrophic event [29]. Therefore, heightened clinical acumen and suspicion is critical to early diagnosis and treatment to prevent significant morbidity and rarely mortality.

The differential diagnosis of pituitary apoplexy includes several intracranial and systemic pathologic entities (see Table 17.4). Most commonly, subarachnoid hemorrhage due to a ruptured intracranial aneurysm or meningitis are initially considered diagnoses [21, 51]. Headache, photophobia, stiff neck, and oculomotor palsy may mimic subarachnoid hemorrhage from a ruptured intracranial aneurysm [1, 29, 37, 57]. Alternatively fever, lethargy, photophobia, and meningismus may indicate bacterial or viral/meningoencephalitis [37, 55, 57, 76, 87, 89]. Findings of a pituitary mass on brain imaging and CSF findings of neutrophilic pleocytosis with signs consistent with infectious meningitis have also been misinterpreted for a coexisting pituitary abscess [89]. Cavernous sinus thrombosis may be mistakenly diagnosed due to

Table 17.4 Differential diagnosis of pituitary apoplexy

Brain stem infarction
Carotid-cavernous fistula
Cavernous sinus thrombosis
Cerebral metastasis
Cerebrovascular accident
Cluster headache
Diabetic oculomotor palsy
Encephalitis
Hypertensive encephalopathy
Intracerebral hematoma/hemorrhage
Meningitis
Migraine
Optic neuritis
Subarachnoid hemorrhage from aneurysmal rupture
Temporal arteritis
Transtentorial herniation
Vertebrobasilar insufficiency
Viral gastritis

ocular palsies and periorbital edema caused by compression of cranial nerves and venous plexus, respectively, within the cavernous sinus [37, 56]. Pituitary apoplexy presenting with hemiplegia mimicking a cerebrovascular accident may also confound the diagnosis [37, 52, 76]. Headache and third cranial nerve palsy has also been incorrectly attributed to a primary or metastatic brain tumor [76, 81]. Occasionally headache can be insidious and may mimic migraine or other forms of chronic headache [76, 138, 139]. Systemic shock with circulatory collapse secondary to sudden arrest of pituitary ACTH secretion or hypothalamic damage has also been observed [1, 37]. Due to the wide spectrum of symptomatology and presentations, it can be quite challenging to properly diagnose pituitary apoplexy during the acute presentation. However, with the advent of more reliable and detailed MR imaging, time to proper diagnosis has decreased and even asymptomatic cases are now likely being diagnosed with increasing frequency.

Management and Outcomes

Initial Assessment

Pituitary apoplexy is often misdiagnosed on early presentation and varies widely in duration and severity. Significant morbidity and mortality are often due to failure to recognize the condition and initiate appropriate interventions. Treatment is aimed at decreasing local compression that compromises adjacent neurologic and vascular structures. Once a suspicion of pituitary apoplexy is made, even prior to imaging

confirmation, acute medical management of pituitary apoplexy with intravenous corticosteroids is critical to obtaining favorable clinical outcomes [21].

Acute management of pituitary apoplexy includes close observation and early endocrine, neurosurgical, and ophthalmologic consultations. Detailed history and physical examination should be undertaken, with focus on symptoms and signs of neuro-ophthalmologic derangements and hypopituitarism. Bedside visual acuity and field testing should be performed, followed by formal tests by an ophthalmologist. Baseline Snellen chart test and Goldmann perimetry or Humphrey visual field analyzer examinations may help guide clinical decision making for either a surgical or conservative approach and document clinical responsiveness to treatment with repeat follow-up assessments throughout the hospitalization.

Baseline laboratory assessments include urgent analysis of electrolytes, renal function, liver function including clotting screen, and complete blood cell count. Electrolyte abnormalities, including hyponatremia and hypoglycemia, should be assessed and corrected. Fluid balance should be monitored closely as diabetes insipidus and inappropriate secretion of antidiuretic hormone may become apparent following corticosteroid treatment.

Endocrine Assessment

Endocrinological laboratory evaluation, with emphasis on adrenal function, should be performed to determine baseline hypothalamic–pituitary axis in hemodynamically stable patients with serum ACTH and 9 A.M. serum cortisol evaluation. Initially corticosteroid replacement with intravenous dexamethasone is preferable as it will not interfere with the serum cortisol assay, although hydrocortisone may be preferred afterward due to its favorable physiological properties. Hemodynamically unstable patients should have immediate initiation of intravenous hydrocortisone after baseline assessment of serum cortisol and ACTH regardless of time of day. There is limited utility in performing a Cosyntropin stimulation test in the setting of acute secondary adrenal insufficiency.

Baseline hypothalamic–pituitary axes should also be screened, including PRL, TSH, free T4 (FT4), insulin-like growth factor 1 (IGF-1), GH, LH, FSH, and testosterone in men or estradiol measurements in women. Intact gonadal function may be assumed by the presence of normal menses in premenopausal females. Although it is important to assess for thyrotropin deficiency, initiation of thyroid hormone replacement is not mandatory prior to contemplated surgery, and baseline GH function is also not critical for survival as replacement therapy is not acutely indicated. Monitoring PRL is important as patients with prolactin-secreting adenomas and clinically stable presentations may be successfully treated with conservatively with intravenous fluids, corticosteroids, and dopamine agonist therapy, without the need for surgery [24, 75, 77, 140]. A single patient was reported with complete resolution of visual field deficit and ocular nerve palsy with administration of bromocriptine in

treatment of an apoplectic macroprolactinoma, with follow-up MRI demonstrating decreased tumor burden [140]. Assessment of PRL levels may also help determine prognosis and responsiveness to decompressive surgery, as patients with elevated PRL, not due to PRL-secreting tumors are more likely to have reversible hypopituitarism [64].

Radiological Assessment

When pituitary apoplexy is suspected, patients should have urgent brain MRI performed, preferably with a focused pituitary MRI. The use of preferred neuroimaging studies used to verify the diagnosis of pituitary apoplexy has evolved over the past several decades [77]. Even with high-quality CT scans a diagnosis of pituitary apoplexy may be missed in up to 60 % of patients unless physicians are aware of other CT findings, besides hemorrhage, that indicate pituitary apoplexy [88]. MRI is the diagnostic modality of choice in evaluation of pituitary apoplexy [18, 24, 25, 51, 62]. In recent retrospective series, up to 60 % of patients have MRI as the primary neuroimaging investigation, without CT to aid in diagnosis [4, 77]. With greater accessibility of MRI scans, and improvements in imaging resolution, the dependence on prior radiological studies and CSF analysis as a means to diagnosis has decreased. In fact, CSF findings often complicate reaching a proper diagnosis. Incidental findings of pituitary pathology may be discovered on CT or MRI during evaluation of nonspecific symptoms such as headache [70, 141], raising suspicion for pituitary apoplexy while potentially decreasing time to diagnosis and initiation of proper treatment. However, with diagnostic MRI improvements incidental findings of subclinical or asymptomatic pituitary hemorrhage is also likely increasing in frequency.

MR imaging exhibits its multiplanar capability to characterize the extent of pituitary hemorrhage and necrosis in fine detail and evaluate effects of expanding pituitary mass on neighboring neurovascular structures [20, 24]. As MR imaging features of blood components evolve over time, hemorrhage age may be better estimated [20, 94], and cystic or degenerative changes from previous hemorrhage are better differentiated [92, 141]. Furthermore, MRI has demonstrated good ability to correlate images with surgical findings [94].

Although MR has been unable to predict the severity of visual symptoms based on imaging findings of mass size or optic tract/chiasm involvement [20, 25], there is evidence that the presence of sphenoid sinus thickening may indicate less favorable neurological and endocrinological outcomes [77]. Furthermore, the ability to correlate MR image findings with pathological findings of pituitary apoplexy has profound effects on determining prognosis [28]. In a retrospective study, 22 patients with confirmed ischemic necrosis without hemorrhage on pathological examination had a more benign course with less severe visual symptoms and neurologic deficits than 37 patients with the presence of hemorrhage on pathology [59]. A follow-up study demonstrated MRI findings correlated with histopathological diagnosis in

approximately 80 % of 26 subjects [28]. Therefore, in most cases MR imaging can predict the nature of pituitary apoplexy and possibly guide the type and timing of therapy [28]. Furthermore, baseline MRI prior to any neurosurgical procedure will often guide the neurosurgical approach during surgical decompression.

Despite limitations of CT scanning to clearly delineate hemorrhage during sub-acute and chronic stages, it is still the most commonly used imaging modality used in emergency situations in the evaluation of acute neurological deficits. Emergency rooms rarely begin evaluation of neurological changes with MRI scans. CT can be valuable during the acute period in demonstration of hemorrhage, during the first 24–48 h of symptoms [19]. Furthermore, the presentation of a patient with signs and symptoms consistent with pituitary apoplexy and discovery of any pituitary pathology on head CT, including evidence of a cyst, should alert a suspecting physician of this diagnosis [81]. Clinicians should still suspect pituitary apoplexy when patients present with sudden onset headache, visual alterations, ocular palsies, and altered mental status despite a normal head CT scan [51]. Although MRI is preferred, when it is not available or contraindicated, head CT scans may be acceptable as the initial diagnostic imaging examination.

Treatment and Outcomes

Steroid Therapy

Recognition of acute secondary adrenal insufficiency, if present, is critical, and prompt life-saving empiric intravenous corticosteroid therapy should be initiated to avert adrenal crisis and may also serve to improve visual outcomes [21]. Patients with hemodynamic instability or other symptoms or signs consistent with acute hypocortisolemia should be treated with corticosteroids prior to confirmatory laboratory tests. Other indications for steroid therapy include altered level of consciousness, reduced visual acuity, or severely restricted visual fields. Patients with suboptimal 9 A.M. cortisol levels, less than 18–20 µg/dl, should also be considered for corticosteroid therapy. Since some patients may not develop signs of adrenal insufficiency until surgery or during stress [55], empiric corticosteroids are indicated during the acute time period especially if surgery is being considered.

Many patients with pituitary apoplexy are unable to tolerate oral medications due to altered mental status, nausea, and/or vomiting intravenous hydrocortisone is preferred. A recommended hydrocortisone formulation during the acute phase is 100–200 mg of hydrocortisone bolus followed by 2–4 mg per hour by continuous infusion or 50–100 mg injections every 6 h [142]. Once the patient is stabilized and can tolerate oral medication, hydrocortisone should be quickly tapered and standard oral maintenance doses of 15–30 mg per day may be initiated.

Surgical Versus Conservative Management

Traditionally, emergent surgical treatment within hours to several days of presentation has been advocated [47, 61, 74, 143]. Surgery provides an opportunity for direct and immediate sellar decompression with reversal of neurological, visual, and endocrine abnormalities and can potentially decrease the chance of continued neoplastic viability. Transsphenoidal surgery is the preferred route with low associated morbidity and mortality, favorable neuro-ophthalmic results [2, 18, 21, 57], and occasional restoration of normal pituitary function [61]. Transsphenoidal decompression can improve visual acuity in 88 %, visual field defects in 95 %, and ocular paresis in 100 % of patients presenting with pituitary apoplexy [2].

Craniotomy carries higher morbidity rates than transsphenoidal surgery, but an intracranial approach may be necessary in cases of severe suprasellar extension of hemorrhage, small sella with a large suprasellar mass, or poorly aerated sphenoid sinus [18, 21, 144], or when transsphenoidal surgery is unsuccessful in improving symptoms or removing significant amounts of hemorrhagic and/or necrotic tissue [50]. Currently, there is general consensus that emergent decompressive surgery under steroid cover is the definitive treatment of pituitary apoplexy in patients with sudden, severe diminishing level of consciousness, hypothalamic dysfunction, and/or visual acuity/field defects [2, 4, 12, 18, 21, 24, 27, 30, 51, 76]. Rapid diagnosis based on clinical grounds and imaging, steroid replacement, and transsphenoidal decompression offers excellent results [57]. While it is evident that complete blindness at presentation has a poor prognosis [4, 18, 26], it is difficult to decipher from the literature how severe or rapid symptoms should be to mandate surgical intervention.

Retrospective studies have demonstrated similar outcomes in visual and endocrine function in patients managed conservatively or by timely surgical intervention [25, 26, 62]. Patients with visual acuity loss, visual field cuts, and/or ophthalmoplegia without complete blindness have been observed to have similar visual outcomes with either medical or surgical management [26]. There is evidence that rapid initiation of high-dose corticosteroids without surgical intervention can improve symptoms of pituitary apoplexy, sometimes within a few days [37, 76, 80, 113]. Therefore, there is a divergence of views regarding the role of surgery vs. conservative management since it is unclear which management option offers the best outcome for patients, especially those with less severe presentations.

Perioperative and postoperative surgical complications should be considered in management decisions when considering morbidity and mortality of pituitary apoplexy. These include cerebrospinal leaks, meningitis, cardiac arrest, cerebrovascular accidents, and postoperative pain [25, 76]. Visual acuity may also worsen following surgery [2], possibly due to residual tumor bleeding [85], and surgical reintervention should be considered. The risk of worsening hypopituitarism that may develop following surgical removal of anterior pituitary tissue should also be considered [3, 5]. Diabetes insipidus occurs more commonly postoperatively, and is transient in up to 50 % of patients and permanent in 6–30 % of patients [5, 24–26, 61, 75].

Timing of Surgery

The timing of surgery is important for obtaining favorable outcomes. Emergent surgery is critical in patients with deteriorating clinical status and/or severe hypothalamic dysfunction given such high mortality despite even optimal treatment [38]. Several retrospective studies have demonstrated that the optimal time period to decompressive surgery for patients who present with either unilateral or bilateral blindness is within 1 week of development of symptoms [2, 24, 85, 104, 145]. Optic nerves appear to be able to withstand ischemia due to compression for up to 5–7 days, even if patients present with unilateral or even bilateral visual blindness [145].

A retrospective analysis of 37 patients demonstrated that surgery within 7 days of pituitary apoplexy onset resulted in significant improvement of visual acuity deficits, while further delay of surgery had less favorable results [2]. A significant difference was not observed for visual field deficit or ocular palsy improvement among the different surgical timeframes [2]. Surgery within 8 days led to higher rates of improvements of visual acuity deficits (88 %), visual field deficits (95 %), and ocular paresis (100 %) than surgery performed after this time frame [24]. Visual acuity improved within 24 h of transsphenoidal surgery in four of five patients, and in 50 % of total eyes, who initially presented with near or complete visual loss when transsphenoidal surgery was performed within 7 days [145]. Alternatively, three patients who presented with complete bilateral blindness remained without observable improvement on Snellen's test when surgery was performed after 10 days [145].

Deferral of surgical intervention for longer than 1 week in patients with neurological and visual deterioration is not advocated, unless comorbidities are the cause of delay [2, 24, 75, 85]. In one study, conservative medical management in seven patients with deferral of surgery to 8.7 days from onset of apoplectic symptoms due to associated medical conditions and/or coagulopathies resulted in less favorable visual outcomes and greater need for hormone replacement than six patients without associated medical illnesses, who underwent surgery within 3.5 days [85]. Patients with complicated medical histories may still benefit from timely surgery, although it is likely that higher age, associated comorbidities, and coagulation disorders contribute to less favorable clinical outcomes [85].

However, several retrospective studies have not observed differences in outcomes of surgically managed patients if surgery is performed within 1 week or later [25, 62, 76]. Nevertheless, if surgery has been delayed and more than a week has passed, surgery may still be considered as there are cases of significant visual improvement after delayed surgical decompression from 2 weeks to several months after the initial event [2, 3, 24]. Ultimately, visual outcomes are more affected by optic disc appearance rather than severity of initial visual acuity deficit or length of visual history [76].

Outcomes of Visual Function

Routine early transsphenoidal decompression has demonstrated improved visual acuity and visual field deficits in 41 of 46 and 60 of 65 patients, respectively, reviewed from multiple retrospective studies [2, 18, 24, 25, 61, 62, 145]. Although such studies demonstrate high success with surgical management, other retrospective reviews report similar results with conservative management (see Table 17.5).

The need for emergent surgery in patients with mild symptoms is also challenged by evidence of spontaneous resolution of neurological and visual symptoms following pituitary apoplexy [3]. Generally, conservative management may be considered in carefully selected cases. Several earlier retrospective studies demonstrated successful outcomes with conservative medical management in patients with stable or nonprogressive neuro-ophthalmic deficits [3, 55, 97, 130]. More recent retrospective studies have reconfirmed such findings in patients presenting with absent, stable or resolving neuro-ophthalmic symptoms and signs [25, 26, 62].

One non-randomized prospective trial of 12 patients reported the importance of carefully selecting patients prior to decision for conservative management [27]. Resolution or improvement of neuro-ophthalmic symptoms was observed in seven patients managed conservatively with intravenous dexamethasone, only two of which had mild visual blurring [27]. Surgery was performed on five patients who either did not improve within 1 week of conservative management or symptoms worsened with tapering of dexamethasone [27]. Four of five patients who required surgery had either unilateral or bilateral blindness upon initial presentation, and one developed unilateral blindness due to tumor recurrence whom required another surgical intervention [27]. Recovery of visual function was minimal in two, partial in one, and complete in only two patients, one of which had a recurrent tumor [27].

Conservative management of 18 of 33 patients with pituitary apoplexy and observed resolution of visual field defects in all six patients [25]. In a retrospective analysis of 30 patients, 10 surgically and 20 conservatively managed patients had similar visual outcomes when complete blindness was not a presenting symptom [26]. While these studies demonstrate that conservative management may be undertaken successfully, such favorable outcomes usually occur in patients with mild visual acuity loss, who do not have unilateral or bilateral blindness at presentation, or who do not experience acute visual deterioration. Generally, decompressive surgery is more effective than conservative management for decreased visual acuity caused by pituitary apoplexy. Patients managed by conservative therapy should be monitored diligently for signs of clinical deterioration and for indications that would require a surgical approach, including worsening visual deficits, decreasing level of consciousness, and development of hemiparesis [25, 26].

Table 17.5 Selected retrospective studies showing neuro-ophthalmic outcomes after surgery or conservative management of pituitary apoplexy

| Studies | Number of patients | | Key findings |
	Total	Surgically treated	
Arafah et al. [61]	8	8	Complete or partial VF recovery in 7/7 and complete OP resolution in 4/4 patients
Onesti et al. [18]	16	16	Ophthalmic improvement in 13/16 patients; blindness had poor prognosis
McFadzean et al. [76]	15	9	Similar VA improvement in patients treated surgically and conservatively; similar VA outcome in patients undergoing surgery within 7 days of onset, or later
Bonicki et al. [149]	39	19	Full ophthalmic recovery in 14/19 surgically treated patients; clinical improvement in 16 conservatively managed patients without severe ophthalmic signs at presentation
Bills et al. [2]	37	36	Better VA (but not VF or OP) outcome in patients undergoing surgery within 7 days of symptom onset
Maccagnan et al. [27]	12	5	Favorable ophthalmic recovery in most conservatively managed patients but five patients with severe VA at presentation and deferred surgical management had less favorable VA outcomes
Da Motta et al. [22]	16	10	Higher rates of ophthalmic improvement in surgically treated patients; higher rate of mortality in conservatively managed patients
Randeva et al. [24]	35	31	Better VA and VF (but not OP) outcomes in patients undergoing surgery within 8 days of onset of symptoms
Biousse et al. [79]	30	27	Less favorable VA and VF outcomes in patients with associated precipitating factors compared to those without precipitating factors despite similar time lag for diagnoses and surgery
Ayuk et al. [25]	33	15	No observed difference in visual recovery with surgery performed within or after 8 days
Sibal et al. [62]	45	27	VA, VF, and OP improvement in both surgical and conservative-treated groups; no difference in visual outcomes in patients undergoing surgery within 7 days or after 7 days
Agrawal et al. [145]	8	8	Greater resolution of complete blindness with surgery within 7 days than after 10 days
Lubina et al. [75]	40	34	VF and OP recovery in 81 % and 71 % of patients, respectively
Semple et al. [4]	62	58	Improved VA and VF in 76 % and 79 % of patients, respectively; blindness at presentation had poor prognosis
Chuang et al. [85]	13	13	Surgery in patients without comorbidities resulted in more favorable visual and endocrine function than patients with associated comorbidities
Gruber et al. [26]	30	10	Similar ophthalmic outcomes in surgical and conservatively managed patients; complete blindness had poor prognosis
Liu et al. [77]	28	25	Improvement of visual function in 9/9 and OP in 8/8 surgically managed patients

VA visual acuity, *VF* visual fields, *OP* ocular palsy
Table adapted with permission from Table 7 Sibal et al. [62]

Outcomes of Ocular Palsies

There is controversy whether surgical decompression affects outcomes of ocular paresis. Ocular paresis is more likely to resolve from apoplexy than any other visual symptoms [21]. Some authors advocate surgical decompression in patients with ocular paresis, even if decreased level of consciousness or other visual defects are not present [24]. Higher rates (74 %) of complete resolution of ocular paresis were observed in patients undergoing surgery within 8 days than patients who underwent surgery after 8 days (42 %), although these results were not significant [24].

Most studies demonstrate that ocular paresis without significant visual compromise does not appear to be an absolute indication for surgery [2, 25–27]. Timing of surgery did not affect improvement of ocular paresis in 36 patients managed with transsphenoidal decompression, with even significant increase in eye movements noted in two patients who had surgery delayed by 3 months [2]. In a study of 33 patients, 100 % of 18 conservatively managed and 63 % of 15 surgically managed patients had full recovery of ocular palsies [25]. Similarly, in patients who presented with visual defects, but without complete blindness, ocular paresis resolved completely in 83 % and partially resolved in 17 % of 12 conservatively managed patients [26]. In a prospective study, conservative management with intravenous dexamethasone resulted in significant improvement of ophthalmoplegia even with the presence of mild visual blurring upon initial evaluation [27].

Bromocriptine may decrease tumor mass effects and rapidly restore function of compressed vessels in patients harboring prolactin-secreting adenomas with apoplexy. Several documented cases of apoplectic macroprolactinomas presented with headache and oculomotor nerve palsy with resolution of symptoms within 48 h of initiation of bromocriptine [77, 140]. Given such favorable rapid results, prompt initiation of bromocriptine in addition to intravenous corticosteroids may be administered at time of diagnosis, prior to obtaining results of PRL levels [140].

Outcomes of Hypopituitarism

Hypopituitarism, whether partial or complete, is a prominent feature of apoplexy and likely contributes to the morbidity and mortality of this disease [3, 5, 21, 38, 47, 61]. Hypopituitarism may be transient or permanent following pituitary apoplexy with return of function occurring from weeks to months after the initial event [3, 4, 57, 61]. More than 50 % of patients ultimately require hormone replacement [2, 3, 5, 24, 50, 61, 146]. Postoperative hypopituitarism occurred in 86 % of patients, with at least one hormone dysfunction, in 33 patients who underwent transsphenoidal surgery within 3 days of admission [75]. Similarly 83 % of 62 patients required hormone replacement [4].

However, there is no clear consensus on whether surgical treatment improves pituitary function outcomes. An increased incidence of hormonal deficiencies was

reported with conservative management [27]. Emergent surgical surgery within 3 days after onset of symptoms restored endocrine function, by return of ACTH secretion, in 11 of 15 patients within 3 days of surgery [51]. Transsphenoidal decompressive surgery resulted in resolution of hypopituitarism with return of normal adrenal, thyroidal, and gonadal function in the immediate postoperative period in 86 %, 67 %, and 50 % of 8 patients, respectively [61], although findings have not been repeated in larger studies [25]. Earlier surgery has also been suggested to decrease the occurrence of long-term hormone replacement therapy as those undergoing surgery within 6 days of admission had lower hormone replacement requirements [24] than others when surgery was performed within 7.7 of admission [2].

Advocates of conservative management maintain no difference in long-term hypopituitarism rates between surgically managed and carefully selected conservatively managed patients exists [25, 62]. Eighteen conservatively managed patients presenting with absent or improving visual deficits had similar rates of hypocortisolism, hypothyroidism, and hypogonadism than 15 surgically managed patients who underwent transsphenoidal surgery with a median time of 4 days, without significant deleterious effects on visual function [25]. Indications for surgery included worsening visual deficits, decreased level of consciousness, or development of hemiparesis [25]. Similar long-term hormone replacement rates were observed, with requirements of corticosteroid therapy in 60 % and 68 %, testosterone in 86 % and 82 % of males, and thyroxine in 70 % and 68 % of 10 surgically and 20 medically managed patients, respectively [26]. Although advocates of timely surgical treatment argue that conservatively managed patients may have decreased rates of pituitary dysfunction had they been treated surgically, given their less severe initial presentation, this approach has not been substantiated since the degree of hypopituitarism and visual impairments at presentation and postoperatively do not necessarily correlate [61]. Diabetes insipidus is a relatively rare consequence of pituitary apoplexy with an incidence of 4 % for transient and 2 % for persistent diabetes insipidus [5]. However, diabetes insipidus occurs commonly after surgery, with permanent dysfunction present in as many as 11–30 % of patients [2, 25, 26].

Postoperative Care

Patients managed surgically should be monitored carefully for any of the aforementioned surgical complications. Hourly fluid intake and output should be carefully followed and if diabetes insipidus is suspected, hourly sodium, serum creatinine, and plasma and serum osmolalities should be monitored. Daily laboratory assessments of complete cell count, electrolytes, and renal function should also be followed during the immediate postoperative period. Visual acuity, visual fields, and extraocular eye movements should be assessed within 48 h of surgery, followed by formal tests prior to discharge. Development of worsening visual symptoms should prompt an urgent MRI and neurosurgical reevaluation.

Since many patients may not have undergone preoperative endocrine function assessments, evaluation of steroid reserve and thyroid functions are essential prior to hospital discharge. Measurements of 9 A.M. serum cortisol should be undertaken on postoperative days 2 and 3. If the patient is already receiving hydrocortisone, the cortisol measurement should be performed at least 12 h after the last dose of corticosteroid dose by omitting the evening dose. Results of 9 A.M. cortisol levels will determine postoperative hydrocortisone requirements. TSH and FT4 should be assessed prior to discharge and thyroid replacement hormone should be initiated if deficient, although TSH and FT4 may be falsely normal during acute pituitary damage. Euthyroid sick syndrome may also confound obtaining a proper diagnosis.

Long-Term Management

Long-term endocrine reassessments are essential since anterior pituitary function may fully or partially recover [3, 5, 104]. Decreased requirement for endocrine replacement therapy was observed in 78 % at 3-month follow-up, and in 26 % at 2-year follow-up in 22 patients who presented with acute classical pituitary apoplexy [104]. Each case should be individualized, and timing of follow-up interval assessments is based on symptoms and clinical signs.

Patients should be monitored for intact ACTH secretion, as inadequate treatment of secondary adrenal insufficiency can lead to significant morbidity, including fatigue, weight loss, muscle weakness, nausea, vomiting, and abdominal pain. Measurements of 9 A.M. serum cortisol should be made, at least 12 h after last dose of exogenous glucocorticoid. Patients with chronic secondary adrenal insufficiency should be continued on maintenance hydrocortisone therapy of 15–30 mg per day and during times of illness, such as pneumonia, they should be treated with stress dose corticosteroid treatment. Such patients should also have emergency wrist bracelets indicating their disease.

Hypothyroidism should be monitored by measurements of FT4 4 to 8 weeks following pituitary apoplexy. There is little utility in monitoring TSH in patients with secondary hypothyroidism. Maintenance of regular menses in premenopausal women implies an intact pituitary–gonadal axis, otherwise LH, FH, and estradiol may be measured. Men should be screened for secondary hypogonadism with evaluation of FSH, LH, and total testosterone levels, especially if decreased libido or erectile dysfunction is present. PRL levels should also be monitored, especially if pituitary apoplexy occurs in a PRL-secreting adenoma, as supra-physiologic prolactin levels can cause hypogonadism. GH function may also be monitored with IGF-1 levels, although rarely replaced. Annual laboratory endocrine function tests should be performed to regularly assess for return or further loss of pituitary function.

Follow-up radiological imaging is essential since recurrent apoplexy has been reported in both medically [25, 48, 82], and surgically managed patients [2, 24, 25, 27, 147]. Residual tumor tissue may be observed in up to 37 % of operated cases [75].

Therefore, it is prudent to follow patients with serial MRI scans over several years for evidence of tumor reoccurrence after transsphenoidal surgery, especially since late tumor occurrence up to 3 years after the apoplectic episode has been reported [3, 24–26]. Prophylactic radiotherapy is not recommended prior to adenoma recurrence, as it may precipitate further unnecessary hemorrhagic necrosis [17, 47, 48].

Mortality

Significant morbidity and mortality occur due to delay of medical and surgical interventions or failure to diagnose pituitary apoplexy [1, 17]. Historically, mortality was attributed to lack of medical treatment of hypopituitarism, specifically corticosteroid replacement therapy [12, 17]. Fatalities in the modern medical era typically occur due to massive subarachnoid hemorrhage [50, 148], extensive hypothalamic involvement [5, 12, 50], or from secondary systemic complications, such as myocardial infarction or respiratory distress [47, 52].

Death, although now rare [12], still remains a concern despite early diagnosis in both surgically [50, 75] and conservatively managed patients [22, 26]. Patients with severe or declining clinical status on presentation, including progression to coma, have high mortality rates regardless of surgical and medical treatments [38]. Higher mortality rate have also been reported in nonsurgically treated patients [22]. However, there is some controversy as conservative management with highdose intravenous dexamethasone has been adequate in over 50 % of patients, and patient mortality was not increased by delaying surgery by 1 week from initial presentation [27]. Patients with non-functioning pituitary adenomas have similar survival rates whether pituitary apoplexy is present or not [67]. Nevertheless, with early diagnosis and rapid initiation of endocrinological management and modern neurosurgical techniques, mortality has decreased from a rate of 61 % in 1950s [17] to 6.7 % more recently [21].

Conclusion

Pituitary apoplexy commonly presents as a neurosurgical emergency with sudden onset, severe headache accompanied by nausea, vomiting, fever, loss of visual acuity or blindness, visual field defects, ophthalmoplegia, meningismus, alterations of mental status, hypopituitarism, and sometimes bizarre neurological deficits. Symptoms develop from hemorrhage and/or infarction of the pituitary with surrounding mass compression of parasellar structures. Diagnosis is confirmed by radiological imaging, with MR as diagnostic modality of choice.

Important initial investigations include assessments of intact neurological status and visual field acuity and fields. Acute pituitary insufficiency should be assumed
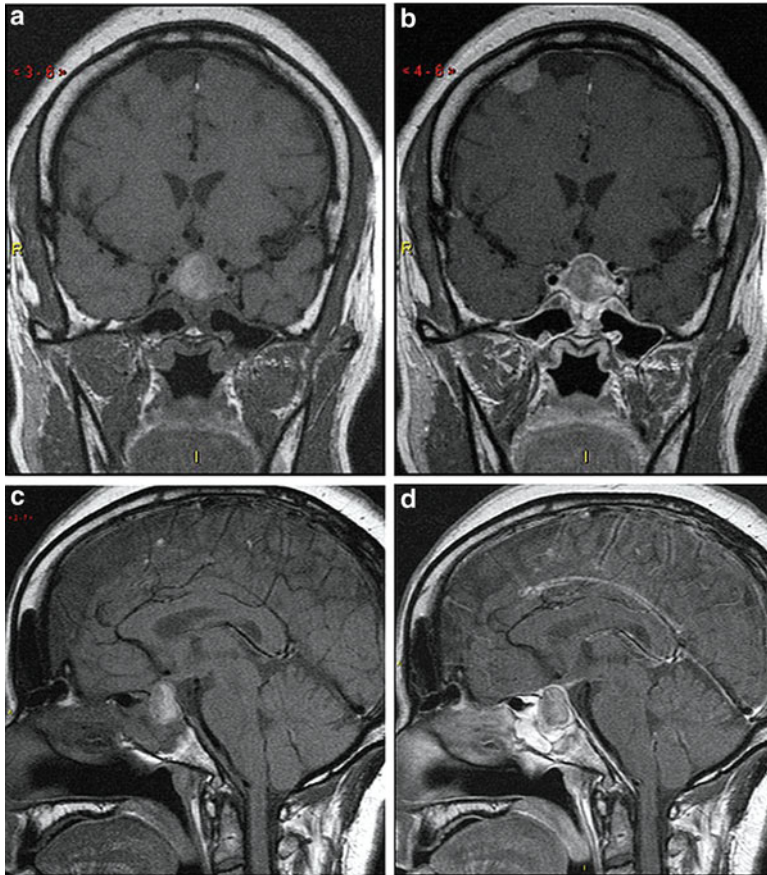
Fig. 17.4 Magnetic resonance imaging T1-weighted sequences in the coronal (**a**) and sagittal (**b**) planes demonstrate acute infarction of a pituitary macroadenoma with expansion of the sella. High T1 signal intensity is consistent with hemorrhage. Post-contrast coronal (**c**) and sagittal (**d**) T1-weighted sequences demonstrate heterogeneous enhancement with clival epidural hematoma

until excluded by endocrinological laboratory tests and empiric corticosteroid replacement therapy is vital to outcomes of mortality and morbidity. Although rare cases of spontaneous recovery have been reported, pituitary apoplexy may potentially follow a fatal course if not diagnosed early and treated promptly with medical and/or surgical treatment. Definitive management is transsphenoidal decompression and pituitary tumor removal under corticosteroid cover, although conservative management, with corticosteroids and dopamine agonists, may be successful in selected group of patients.

Ultimately, decisions for emergent surgery or conservative management should be addressed by a multi-disciplinary team, including specialists in neurosurgery, ophthalmology, and endocrinology (see Fig. 17.4). Patients presenting with
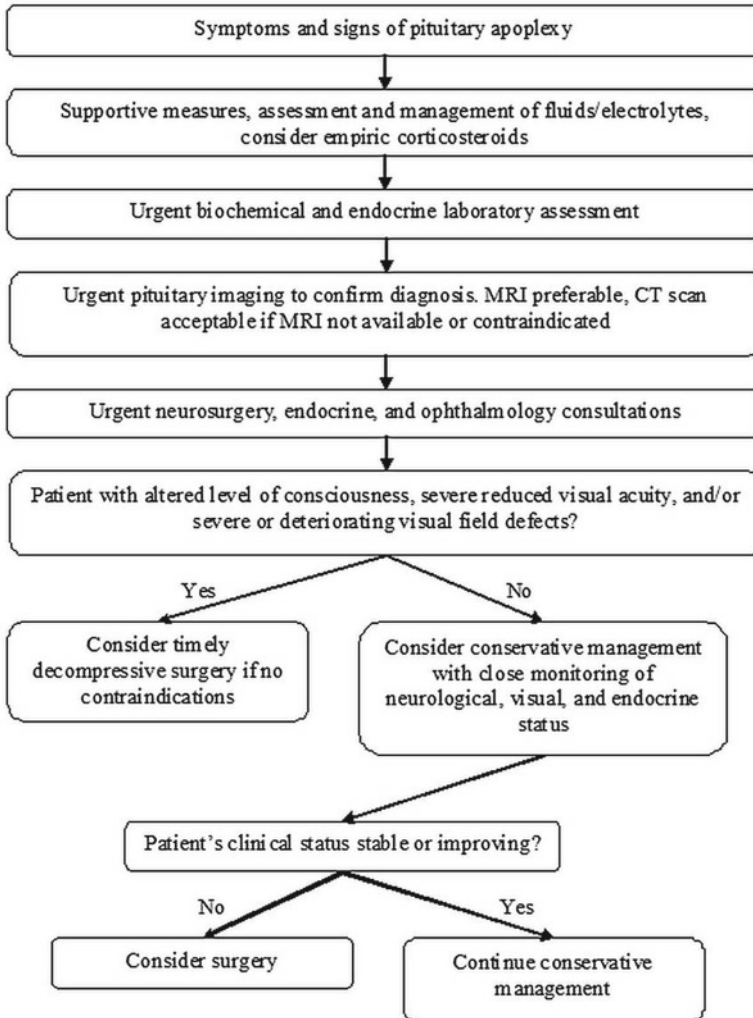
Fig. 17.5 Algorithm for the management of pituitary apoplexy

severe alterations of consciousness and visual acuity including blindness should be managed by timely surgery, preferably by transsphenoidal decompression, within 1 week of development of symptoms. Equally, patients with sudden, worsening, severe neurological and visual deterioration should have expedited surgery. Alternatively, patients with absent, stable, or improving visual symptoms and normal mental status may be successfully managed conservatively, despite the presence of ophthalmoplegia (Fig. 17.5).

Visual improvement and resolution of ocular palsies usually appear following either surgery or medical intervention and long-term anterior pituitary function is

usually poor regardless of therapy and multiple hormone deficits persist in most patients [2, 24, 75]. Due to the unpredictable clinical course of pituitary apoplexy prompt surgical decompression may be considered even though results suggest favorable outcomes with conservative management [51, 75]. Especially in conditions of visual acuity and field compromise, waiting for absorption of hemorrhagic areas and spontaneous resolution of these signs is potentially risky. It may not be possible to predict which physical conditions will remain stable or which continue to deteriorate [51]. Furthermore, clinicians should be aware of the preselection bias in data supporting conservative management. Most patients treated with conservative management in such studies often lack altered mental and visual deficits were absent, stable, or improving [25, 27, 75].

Overall, treatment strategies should be individualized and determined by the severity of clinical presentation and disease course. Long-term management should include reevaluations of hypothalamic–pituitary axis function, visual acuity and fields, and serial MRI studies to prevent long-term neurological or endocrinological deficits, and to screen for tumor recurrence.

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Chapter 18
Ovarian Hyperstimulation Syndrome (OHSS)

Robert L. Barbieri

Précis

1. Clinical Setting: abdominal bloating and distention, intravascular volume depletion, ascites, hemoconcentration, and oliguria following a fertility intervention involving the administration of exogenous FSH.
2. Diagnosis:

    (a) History: Abdominal bloating, distention, abdominal and/or pelvic pain, acute weight gain, and shortness of breath. A recent fertility intervention involving the administration of exogenous FSH. Young age, polycystic ovary syndrome or low body mass. A previous history of OHSS.
    (b) Physical examination: Abdominal distention, weight gain, evidence for ascites (flank dullness), or pleural effusion (dullness to percussion, decreased breath sounds).
    (c) Laboratory values: Hemoconcentration (Hct >50 %), elevated BUN and creatinine, elevated liver function tests.
    (d) Imaging: bilateral ovarian enlargement, peritoneal fluid or ascites on ultrasound, pleural effusions on ultrasound.
    (e) Prevention: Use of lower doses of FSH to produce fewer large follicles. Use of a GnRH agonist to stimulate endogenous LH secretion to trigger ovarian follicle luteinization in order to reduce ovarian production of VEGF. Cessation of FSH stimulation (coasting), in order to reduce the ovarian production of VEGF. Freezing all embryos and cancelling embryo transfer to avoid a late case of OHSS caused by pregnancy. Administration of a dopamine agonist such as cabergoline to reduce ovarian production of VEGF.

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Administration of albumin or hydroxyethyl starch at the time of oocyte retrieval to improve intravascular volume and enhance renal function.

(f) Treatment: Close monitoring of hemodynamic status and renal function. Paracentesis to resolve the abdominal compartment syndrome. Administration of albumin or hydroxyethyl starch to improve renal function and urine output. Treatment with cabergoline to reduce ovarian VEGF production. Thrombosis prophylaxis to reduce the risk of thromboembolism.

The most dangerous complications of OHSS are renal failure, hypovolemic shock, thrombosis, stroke, acute respiratory distress, ovarian torsion, ovarian rupture and rarely, death.

Ovarian hyperstimulation syndrome (OHSS) is the presence of the combination of *ovarian enlargement* due to hormone-secreting *luteinized ovarian cysts* and an associated vascular dysfunction manifested by *increased capillary permeability*, resulting in the accumulation of fluid in the peritoneal and pleural cavity, and hemoconcentration. OHSS may be associated with renal failure, hypovolemic shock, thrombosis, stroke, acute respiratory distress, ovarian torsion, ovarian rupture and rarely, death.

Definition and Staging of OHSS

There is no established uniform definition of OHSS [1]. One staging system for OHSS is presented in Table 18.1 [2]. Most staging systems regard *mild* OHSS, which includes abdominal discomfort and distention, along with variably enlarged ovaries, as a normal physiological consequence of ovarian hyperstimulation regimens that stimulate the growth of multiple ovarian follicles. *Severe* OHSS is a serious problem characterized by marked fluid shifts into the extravascular compartment and renal dysfunction. Mathur and colleagues have championed the division of OHSS into early and late cases. Early cases of OHSS present 3–7 days after

Table 18.1 Ovarian Hyperstimulation Syndrome staging system

Category	Description
MILD	
Grade 1	Abdominal distention and discomfort, abdominal pain
Grade 2	Features of grade 1 PLUS Nausea, vomiting, and diarrhea
	Ovaries are 5–12 cm in diameter
MODERATE	
Grade 3	Features of MILD OHSS PLUS sonographic evidence of ascites
SEVERE	
Grade 4	Features of MODERATE OHSS PLUS clinical evidence of ascites or hydrothorax or breathing difficulties
Grade 5	All of the above PLUS hemoconcentration or diminished renal perfusion and function or coagulation abnormalities

Adapted from Ovarian Hyperstimulation Syndrome Staging (Golan A, Ron-el R, Herman A, Soffer Y, Weinraub Z, Caspi E. Ovarian hyperstimulation syndrome: an update review. Obstetrical and Gynecological Survey 1989; 44: 430–440 [2])

follicle luteinization [3]. Late cases of OHSS present 12–17 days after luteinization. Early cases of OHSS are associated with excessive ovarian stimulation and the events surround luteinization. Late cases of OHSS are associated with singleton and multiple gestations with continuing stimulation of the ovary by rising levels of hCG from the trophoblast tissue. Late cases of OHSS are more severe and difficult to anticipate based on events during the follicular phase of the stimulated cycle [3].

Pathophysiology

In most cases of OHSS the inciting cause is fertility treatment involving the sequential administration of exogenous FSH to stimulate multiple follicle growth followed by administration of a hormone to induce luteinization of the large follicles. Occasionally, OHSS may occur following clomiphene ovulation induction, during the agonist phase of GnRH agonist monotherapy [4, 5] or following monotherapy with an anti-estrogen such as tamoxifen [6]. Rarely a spontaneous pregnancy may cause OHSS [7].

A goal of many fertility treatments, such as in vitro fertilization (IVF) and FSH-intrauterine insemination (FSH-IUI) is to stimulate the growth and luteinization (IVF) or ovulation (FSH-IUI) of *multiple* follicles. In a typical IVF cycle, exogenous FSH is administered at a dose sufficient to stimulate the development of approximately ten or more large follicles. When the follicles are sufficiently mature a luteinizing hormone is administered to cause luteinization of the granulosa and theca cells in the follicles. Hormones that can be used to trigger luteinization of mature follicles include recombinant human LH (rLH), human chorionic gonadotropin (hCG), or a GnRH agonist which triggers the release of endogenous LH from the pituitary gland. These hormones trigger luteinization of the follicle, shifting the granulosa cells from estradiol production to progesterone, and estradiol synthesis. They also stimulate the oocyte to resume meiotic division in order to prepare it for fertilization. The sequential ovarian stimulation regimen of FSH followed by a luteinization trigger is termed a controlled ovarian hyperstimulation (COH) or controlled ovarian stimulation (COS) cycle. In COH and COS cycles hCG is the most commonly used hormone to trigger luteinization of the follicles.

Luteinized granulosa cells, *stimulated by hCG or LH*, *secrete vascular endothelial growth factor* (*VEGF*). *In turn*, *VEGF increases endothelial permeability* [8–10]. In model systems of ovarian hyperstimulation, increased capillary permeability caused by excessive VEGF secretion from luteinized follicles can be blocked by the administration of an inhibitor of VEGF, such as Flt-1 Fc [11].

In a COH cycle the multiple luteinized cysts secrete large quantities of VEGF which cause a marked increase in capillary permeability resulting in fluid shift from the intravascular to extravascular space. Circulating concentrations of VEGF are positively correlated with the risk of developing OHSS and the severity of the syndrome. Other proteins which may play an auxillary role in the development of OHSS include interleukin-6, the renin-angiotensin system, the kinin-kallikrein system, selectins, IGF-1, epidermal growth factor, transforming growth factors alpha and beta, basic fibroblast growth factor, platelet-derived growth factor, and interleukin-1 beta.

During fertility treatment OHSS most often occurs after luteinization triggered by hCG (early cases occur 3–7 days after the administration of the luteinization trigger). Compared to endogenous or recombinant LH, hCG has a much longer half-life (>24 h for hCG versus <20 min for LH). Compared to LH, hCG has a higher affinity for the LH receptor and a longer duration of intracellular effect [12]. Interestingly, GnRH agonist stimulation of ovulatory events, by causing the endogenous pituitary release of LH, is associated with lower ovarian production of VEGF. In contrast, hCG administration is associated with greater ovarian production of VEGF [13]. As noted below one approach to reducing the risk of developing OHSS following the use of FSH to stimulate multiple follicle growth, is to trigger ovulation with a GnRH agonist or rLH rather than hCG.

Among women there is great variability in the magnitude of ovarian follicle response to a fixed dose of FSH. The size of the woman's ovarian follicle pool is an important predictor of response to FSH. Women with large numbers of responsive antral follicles, such as young women and women with polycystic ovary syndrome (PCOS), respond more vigorously to a given dose of FSH than women with a small number of antral follicles, such as women >40 years of age and those with premature loss of ovarian follicles due to alkylating chemotherapy or multiple ovarian surgeries. Genetic mutations in proteins that regulate ovarian follicle growth may modulate the risk of developing OHSS by sensitizing the ovary to the stimulatory effects of FSH. Bone morphogenetic protein 15 (BMP15) is an important regulator of ovarian follicle development in sheep and mice. Certain alleles of BMP15 appear to be associated with increased ovarian response to FSH and an increased risk of OHSS [14, 15].

The ovary contains high concentrations of dopamine and the theca-lutein cells of the corpus luteum contain dopamine receptors [16]. In human granulosa cells, cabergoline, a dopamine agonist, inhibits VEGF production. Women with PCOS are at increased risk for developing OHSS when treated with the sequential combination of FSH and a luteinizing hormone. Follicles from women with PCOS appear to have reduced ovarian dopamine concentration and decreased concentration of dopamine receptors suggesting that reduced dopamine tone permits increased VEGF secretion in these women [17]. As noted below cabergoline treatment appears to have a beneficial effect on women with OHSS.

Rare causes of OHSS include an FSH secreting pituitary tumor or genetic mutations in the FSH receptor [18]. The most common FSH receptor mutation associated with OHSS (FSHR D567N) results in the expression of a permissive FSH receptor that binds not only FSH but also LH, hCG, and TSH. Women with FSH receptor mutations typically develop OHSS when they become pregnant due to excessive ovarian stimulation of the FSH receptor by placental hCG.

OHSS is associated with the accumulation of large amounts of fluid in the peritoneal cavity and occasionally in the pleural space. In women with OHSS, intra-abdominal pressure is often elevated, creating an *abdominal compartment syndrome*. In patients with mild and severe OHSS, the intra-abdominal pressure has been reported to be 13 and 40 mmHg respectively [19]. Intra-abdominal pressure greater than 16 mmHg can cause reduced renal blood flow, decreased urine output, decreased cardiac output,

increase systemic vascular resistance, and a coagulopathy. Paracentesis performed early and often in the course of OHSS can reduce intra-abdominal pressure and prevent the complications associated with the abdominal compartment syndrome.

Epidemiology

Moderate and severe forms of OHSS have been reported to occur in approximately 4 % and 0.5 % respectively of women undergoing ovarian stimulation for IVF [20]. In a consecutive case series of 214,219 US women undergoing assisted reproductive treatment (ART), moderate and severe OHSS developed in 0.7 % and 0.3 % of the women respectively, but under-reporting may have occurred [21]. Mild forms of OHSS occur in about 30 % of ART cycles.

The most important pretreatment risk factors for developing OHSS include: (1) a previous history of OHSS, (2) age <30 years, and (3) diagnosis of polycystic ovary syndrome. The most important risk factors identified during an ovarian stimulation cycle include: (1) elevated circulating estradiol, >3,500 pg/mL, (2) rapidly rising estradiol, (3) large number of follicles, for example >20 follicles, and (4) use of hCG to stimulate luteinization [22]. On a positive note, OHSS is more likely to occur in women who become pregnant during their fertility treatment, likely because of the continued stimulation of ovarian VEGF secretion by hCG secreted from trophoblast cells. Women who become pregnant with multiple gestations, which are associated with higher levels of circulating hCG, are also more likely to develop OHSS.

Clinical Presentation

Most cases of OHSS occur following ovarian stimulation with fertility medications. Women with mild OHSS typically present with lower abdominal pain, discomfort and distention, bloating, mild nausea and occasionally vomiting. Women with moderate and severe forms of OHSS present with rapid weight gain, shortness of breath and tachypnea, reduced urine output, orthostatic hypotension and tachycardia should alert the clinician to that the patient. The differential diagnosis includes ovarian hemorrhage, ovarian torsion, pelvic infection, intra-abdominal hemorrhage, ectopic pregnancy, and appendicitis.

Clinical examination should include sequential measurement of body weight, abdominal circumference, and pelvic ultrasound to measure ovarian size and check for the presence of ascites. Laboratory tests that are useful include hemoglobin/hematocrit concentration, creatinine, electrolytes, and liver function tests. Follow-up evaluation every 2–3 days is adequate to assess the progress of the condition. If a woman reports increasing and severe pain, abdominal distention, shortness of breath, and reduced urine output, immediate clinical reevaluation is warranted. Early cases of OHSS (3–7 days after administration of a luteinizing agent) tend to

resolve within 1–2 weeks if pregnancy does not occur. Late cases of OHSS (presenting 12–17 days after administration of LH or hCG) are often associated with an ongoing pregnancy and may persist for weeks.

Women with severe OHSS should be considered for hospitalization. Specific conditions that may require intensive unit care include adult respiratory distress syndrome, renal failure, or thromboembolism. Severe OHSS is associated with a hematocrit >50 % and hyponatremia in about 50 % of cases. Oliguria is present in about 30 % of women with severe OHSS. Abnormal liver function tests are present in about 30 % of women with OHSS. Severe OHSS may occasionally be associated with pulmonary dysfunction including pneumonia, respiratory distress syndrome, and pulmonary embolism [23]. Chest X-ray is indicated to assess women for pleural effusion and coincident pulmonary infection.

Severe OHSS is associated with increased plasma levels of D-dimer, increased thrombin-antithrombin III complex, and decreased protein S activity [24]. Rarely, severe OHSS may cause arterial and venous thrombosis [25]. When the CNS is involved in the thrombotic process the results can be devastating [26, 27]. Thrombosis can also occur in arteries supplying the limbs, rarely requiring amputation [28].

Prevention of OHSS

Selection of Stimulation Regimens Based on Risk Stratification

Prior to the initiation of a cycle of ovarian stimulation, higher circulating levels of antimullerian hormone (AMH) and a higher basal ovarian antral follicle count are associated with an increased risk of developing OHSS [29]. Therefore it is possible to stratify women into high and low risk groups for the development of OHSS. It is known that certain ovarian stimulation protocols are associated with a higher risk of OHSS and other protocols with a lower risk of OHSS. For example, the risk of developing OHSS is lower with an ovarian stimulation protocol that uses FSH injections, GnRH antagonist to suppress a premature LH surge and a GnRH agonist analogue to trigger luteinization by stimulating the pituitary to release endogenous LH [30, 31]. In contrast the risk of developing OHSS is greater with an ovarian stimulation protocol that uses a long downregulation regimen with GnRH agonist analogue started in the luteal phase of the cycle preceding the treatment cycle (to suppress a premature LH surge), FSH injections, and hCG to trigger luteinization. Using this information, it has been proposed that women with high AMH (>29 pM) who are at higher risk of OHSS, receive the ovarian stimulation protocol that is associated with a lower risk of OHSS (FSH, GnRH antagonist, GnRH agonist) and women with normal AMH (16–29 pM), who are at a lower risk of developing OHSS receive a standard protocol (long-cycle downregulation GnRH agonist analogue, FSH injections, hCG) [32].

Why not treat all women with the protocol associated with the lowest risk of OHSS? Many clinicians believe that the protocol with the lowest risk of OHSS which utilizes a GnRH antagonist plus a GnRH agonist to trigger luteinization is associated with lower pregnancy rates than the standard long downregulation protocol

with a GnRH agonist or protocols that use a GnRH antagonist plus hCG to trigger luteinization [33]. Experienced clinicians are concerned that the stimulation protocols associated with a low risk of developing OHSS increase the risk of the "empty follicle syndrome," where no oocytes can be retrieved at the time of oocyte harvest. Therefore the use of the GnRH antagonist plus a GnRH agonist to trigger luteinization might best be limited to those women at the highest risk of OHSS and women who have experienced OHSS in a previous cycle.

Another option for reducing the risk of OHSS is to stratify women into high and low risk groups for OHSS and then give the women at high risk for OHSS, lower doses of FSH [34]. In a similar manner, if the treatment cycle appears to have resulted in excessive stimulation, the luteinization trigger can be switched from a standard dose of hCG to a low dose of hCG [35] or to switch, mid-cycle, to a GnRH antagonist plus GnRH agonist for luteinization protocol [36].

Coasting

A very elevated level of estradiol (>3,000 pg/mL) and/or the presence of a marked excess of growing antral follicles (>20 follicles >12 mm in diameter) are risk factors for developing OHSS. It is likely that the presence of a very elevated level of estradiol is a predictor for excessive ovarian production of VEGF following luteinization. Since estradiol levels are somewhat predictive of the risk of developing OHSS, one approach to prevention is to stop administering daily FSH when estradiol exceeds some predetermined threshold, such as 3,000 pg/mL. Without continuing FSH stimulation, granulosa production of estradiol will decrease during the following days. When circulating estradiol reaches a lower level, such as 2,000 pg/mL, a luteinizing stimulus is administered, and the cycle proceeds. A major advantage of coasting is that the treatment cycle is not abandoned, and for IVF cycles, in contrast to cryopreservation of all embryos, it allows the transfer of fresh embryos [37]. Coasting for more than 3 days may reduce oocyte quality and pregnancy rates. Some experts recommend that after 3 days coasting should be abandoned and the cycle should proceed with cryopreservation of all the embryos [38]. In a systematic review of four randomized trials, there was no evidence that coasting reduced the risk of moderate or severe OHSS. However, in the review, coasting was associated with the retrieval of fewer oocytes [39].

Colloid Infusion at the Time of Oocyte Retrieval

Women with an estradiol >3,000 pg/mL on the day of triggering luteinization are at increased risk for OHSS. In one trial, women with an estradiol >3,000 pg/mL, or >20 follicles on the day of hCG administration were randomized to receive 500 mL of 6 % hydroxyethyl starch or 50 mL of 20 % human albumin or 500 mL of 0.9 % NaCl at the time of oocyte retrieval [40]. The rate of moderate or severe OHSS was 19 %, 10 %, and 6 % in the groups receiving saline, albumin, or hydroxyethyl starch respectively.

Cryopreserving all Embryos and Delaying Embryo Transfer to Another Cycle

The goal of fertility treatments is to achieve a pregnancy. In programs involving the administration of FSH to stimulate multiple follicle development followed by the administration of an agent to trigger ovulation, the pregnancy rate is positively correlated with the magnitude of the ovarian response. Within a corridor of safety, the greater the number of follicles stimulated, the greater the pregnancy rate. Clinicians who are highly focused on achieving a pregnancy recognize the increased risk of OHSS but want to achieve the highest pregnancy rate possible. Sometimes FSH stimulation results in the development of a great excess of mature ovarian follicles, thereby putting the patient at a risk of OHSS. One option to prevent OHSS in these cases is to retrieve the oocytes, fertilize the oocytes with sperm, and then freeze all the oocytes at an early embryonic stage [41], or after the embryos have developed for a few days in vitro. The embryo transfer is then cancelled for the stimulation cycle complicated by a high risk of OHSS.

The "freeze all" approach reduces the risk of severe and late onset OHSS, but mild or moderate early onset OHSS may still occur. In one study, women with circulating estradiol >3,500 pg/mL had all their embryos cryopreserved after oocyte retrieval and fertilization. The outcomes in this experimental group were compared with a group of historical controls with a similar estradiol concentration, but who had their embryos transferred to the uterus. In this study, 60 % of the historical controls with an estradiol >3,500 pg/mL who had embryos transferred and became pregnant had OHSS, compared to 6 % of the women who had all their embryos cryopreserved [42]. Following a "freeze all" cycle, the patient is prepared for a cryopreserved embryo transfer in a subsequent cycle. In large IVF programs this approach is used in about 2 % of all initiated cycles [43]. In the "freeze all" cycle following oocyte retrieval the patient may be treated with agents to reduce VEGF and estradiol production by the ovary (GnRH antagonist, dopamine agonist and/or aromatase inhibitor) in order to further reduce the risk of OHSS [44].

Cabergoline

As noted above, excess ovarian production of VEGF causes increased vascular permeability and plays a central role in the development of OHSS. Ovarian theca-lutein cells contain dopamine receptors and the dopamine agonist, cabergoline appears to reduce VEGF production from these cells [16]. Clinical trials report that cabergoline, initiated at the time of hCG administration, in women at high risk reduces the severity of OHSS. For example, in one trial women with >20 growing follicles >12 mm in diameter were randomized to receive

cabergoline 0.5 mg daily or a placebo daily for 8 days starting on the day of hCG administration. Hemoconcentration and ascites were significantly reduced by cabergoline compared to placebo. MRI scanning documented reduced vascular permeability in the women receiving cabergoline [45]. A meta-analysis reported that women at risk treated with cabergoline had a reduced the incidence of OHSS (OR 0.41, 95 % CI 0.25–0.66), and a trend to a reduced severity of OHSS. Cabergoline treatment did not reduce clinical pregnancy rate [46]. A standard prevention dose of cabergoline is to administer 0.5 mg daily for 8 days beginning on the day of hCG administration.

The dopamine agonist quinagolide, when administered at doses of 50, 100, or 200 µg daily for 17–21 days starting on the day of hCG administration reduced the incidence and severity of OHSS in women at high risk of OHSS ($\geq$20 follicles $\geq$l10 mm in diameter) [47].

Treatment of OHSS

Women with mild OHSS and many women with moderate OHSS can be managed as ambulatory patients. Pain can be managed with narcotics. Nonsteroidal anti-inflammatory drugs should not be used to treat pain in women with OHSS because they can reduce renal function [48]. Nausea may be treated with agents consistent with the possibility of a developing pregnancy, such as prochlorperazine, metoclopramide, or cyclizine. Strenous exercise and sexual intercourse should be avoided by women with OHSS because of the risk of torsion or ovarian rupture and hemorrhage. hCG injections to support the luteal phase should not be given to women with established OHSS.

Women with severe OHSS should be considered for hospitalization. Specific conditions that may require intensive unit care include adult respiratory distress syndrome, renal failure, or thromboembolism. Increasing abdominal pain, oliguria, weight gain, increased abdominal circumference, and shortness of breath suggest worsening OHSS. In the hospital, hydration and cardiopulmonary function should be assessed frequently. Abdominal examination should include an assessment for peritoneal signs, presence of ascites (flank dullness), and paralytic ileus. Diuretics should not be used in women with OHSS because they may further deplete intravascular volume unless hemodynamic monitoring is instituted. Women with hemoconcentration and oliguria may benefit from the administration of 6 % hydroxyethylstarch or albumin (see below). Paracentesis (see below) may help reduce symptoms, reduce intra-abdominal pressure, and increase renal perfusion.

Thromboprophylaxis should be administered to all hospitalized women with OHSS. Compression stockings and prophylactic heparin (5,000 unit sc twice daily) are commonly used because they permit the patient to ambulate. If the patient is at bed rest, an intermittent pneumatic compression device may be used.

Paracentesis

As noted above, leaky vessels and the accumulation of fluid in the peritoneal cavity can result in an *abdominal compartment syndrome* causing decreased cardiac output, reduced renal blood flow, and decreased urine output. In non-randomized case series, aggressive and early paracentesis has been reported to be successful in the outpatient management of OHSS [49]. Based on modeling the cost effectiveness of outpatient paracentesis versus in-patient management of OHSS, early aggressive outpatient paracentesis was reported to result in lower costs [50].

Paracentesis can be initiated for symptom control in patients with moderate or severe OHSS. Paracentesis can be performed either through a transvaginal route or through a standard lateral abdominal wall approach historically used to treat ascites caused by liver disease. In both cases paracentesis is performed under ultrasound guidance. Gravity drainage or controlled vacuum suction can be used to remove the fluid. In most patients, 500–4,500 mL of fluid is removed during a paracentesis over the course of 30–60 min. When massive pleural effusion occurs, pleurocentesis may be performed, or a chest tube inserted [51].

Anticoagulation

Some experts recommend full anticoagulation when the hematocrit rises above 50 %. Heparin or enoxaparin administered through subcutaneous injection have both been utilized. If the patient is hospitalized, and not mobile, the use of an intermittent pneumatic compression device is recommended. If the patient is mobile compression stockings may be preferred.

Colloid Infusion

Colloid infusion may improve hemodynamic function in women with OHSS. In a systematic review of three trials, hydroxyethyl starch infusion was reported to be more effective in reducing the risk of developing severe OHSS than no treatment (OR 0.12, 95 % CI 0.04–0.40) [52]. In a systematic review of eight trials, albumin infusion was reported to be modestly more effective than no treatment in reducing the risk of developing severe OHSS (OR 0.67, 95 % CI 0.45–0.99) [52]. Building on these findings, investigators have reported that in cases of OHSS, hydroxyethyl starch 6 % infusion is modestly more effective than albumin for increasing urine output, reducing the need for paracentesis, and reducing the length of hospitalization [53]. However, hydroxyethyl starch infusions have been reported to be associated with renal dysfunction and coagulopathy [54], causing some experts to prefer albumin infusions for the treatment of OHSS.

Recombinant Tissue Plasminogen Activator to Treat Thrombosis

Major arterial thrombosis is a devastating consequence of severe OHSS. In one case of OHSS causing thrombosis of the middle cerebral artery, intra-arterial infusion of recombinant tissue plasminogen activator was used to lyse the clot and facilitate neurological recovery [55].

Pregnancy Outcome

IVF pregnancy complicated by moderate or severe OHSS has an increased risk of spontaneous abortion, venous thrombosis, gestational diabetes, pregnancy-induced hypertension, placental abruption, premature delivery, and low birthweight compared to IVF pregnancy not associated with OHSS [56, 57]. A pregnancy occurring following an IVF cycle complicated by OHSS is a high-risk pregnancy and should be monitored closely during the antepartum period.

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Chapter 19
Ambiguous Genitalia in the Newborn

Walter L. Miller and Selma F. Witchel

Précis

1. Clinical Setting: Development of the external genitalia is atypical and examination does not allow for accurate determination as to whether the infant is a girl or a boy.
2. Diagnosis:

   (a) History: Family history of genetic disorders, infertility, infant deaths, and disorders of puberty should be obtained. Virilization of mother during pregnancy or exposures to androgens or anti-androgens should be queried.
   (b) Physical Examination: The external genitalia should be inspected for symmetry and palpable gonads. The urethral meatus should be located. Length and diameter of the phallus should be determined. The distances from the base of the phallus to the posterior forchette should be determined. Careful physical examination to assess for other anomalies should be performed.
   (c) Laboratory Evaluation: Karyotype with Y-specific probes should be obtained. An ACTH test with measurement of 17-hydroxyprogesterone, 11-deoxycortisol and cortisol, and basal LH, FSH, testosterone, dihydrotestosterone, anti-mullerian hormone, and inhibin B should be considered depending on the physical findings. Serum electrolytes may not be helpful in the first days of life. A microarray may be beneficial.
   (d) Imaging Studies: Pelvic sonography should be performed to assess uterine development. Gonads may or may be visualized on ultrasound.

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3. Initial Assessment and Treatment: Specific medical management depends on the underlying disorder. The multi-disciplinary team should meet with the parents to discuss that their infant has a disorder affecting the complex system that directs genital development. Sex assignment and naming of the infant should be deferred until adequate information is available.

The Problem

The birth of a child with genital ambiguity, now more appropriately termed "disordered sexual development" or "DSD" is not a medical emergency. Such infants are perfectly healthy, at least initially, with normal cardiopulmonary function, normal electrolytes, and normal glucose concentrations. Even among infants with adrenal failure, the signs of mineralocorticoid deficiency (hyperkalemia, hyponatremia, acidosis) are not typically seen until 5–10 days of age, and hypoglycemia is quite rare. Instead, the emergency is social. The standard birth announcement declares "It's a boy!" or "It's a girl!" rather than the more appropriate "We had a healthy baby!", and reflects society's intransigently dichotomous, Manichean obsession with defining people by their sex. Thus, following the physical exam and review of the pregnancy history, the first step in the evaluation of the child with DSD is to speak to the family, congratulate them on the birth, and reassure them about all the good news about the baby. It is critical not to offer guesses or presumptive diagnoses; instead, tell the parents that, as embryos, boys and girls start out looking the same, that the processes of genital development are complex, and that a definitive diagnosis will be available within a few days to a week (depending on the available laboratory infrastructure). Parents are typically quite gratified when the doctor says, "We don't know if your baby is a boy or a girl, but we know how to find out, we know how to deal with the various potential problems, and everything is going to be OK." The next step is to call the best pediatric endocrinologist available.

DSD may be suspected prenatally, based on fetal ultrasound findings. In some instances, the fetal karyotype is discordant from the appearance of the fetal genitalia. When the appearance of the external genitalia makes determining the sex not readily obvious and/or differs from expectations based on results of prenatal testing, consultation with a multidisciplinary team should be obtained immediately. Members of this team include pediatric endocrinologists, pediatric urologists/surgeons, geneticists, neonatologists, radiologists, behavioral health providers, and pediatric endocrine nurse educators. Some pediatric hospitals have ongoing committees to help with the decision-making and management of children with DSDs.

A Word About "Sex" and "Gender"

Although sex pervades our popular culture, music, literature, and advertising, much of the contemporary American public is surprisingly squeamish about the word "sex." Instead, applications for drivers' licenses, airline reservations, and meeting registrations typically ask one to check a genteel box labeled "Gender" as "M" or "F."

"Sex" is a biological concept that can be defined at various levels: genetic (presence/absence of TDF gene), karyotypic, gonadal, hormonal, and anatomic. By contrast, "gender" is a psychological concept defined by the individual's self-perception. Thus both rats and humans have sex, but only humans have gender. In most individuals, the various components of biological sex are concordant and those are also concordant with the perception of self. Thus this chapter is about "sex" and not about "gender."

Embryology

DSD, in which external genital development differs from normal male or female appearance, encompasses a broad range of congenital conditions with diverse pathogeneses in which genetic, chromosomal, gonadal, hormonal, or anatomic sex is atypical. Consensus conferences have refined the terminology and categorization of DSDs to provide descriptive names reflecting the genetic etiology [1, 2]. In some instances such as bladder exstrophy, external genital development can be altered due to non-endocrine malformation syndromes.

Normal sexual development entails two sequential processes: *sex determination* and *sexual differentiation*. Sex determination entails the regulated expression and interaction of specific genes and gene products that ultimately determine gonadal structure and function. This process reflects the consequences of a binary switch that directs the embryonic gonads to become either testes or ovaries [3]. By contrast, sexual differentiation describes the processes by which the hormonal products of the gonads (or their absence) mediate the differentiation of embryonic structures into the more familiar structures seen postnatally.

Understanding the mechanisms of sex determination and differentiation are essential in the evaluation of infants with DSD, and drive the choice of initial laboratory studies. In the male zygote, the SRY gene on the Y chromosome encodes the testis-determining factor, which is the initial switch in sexual development. While there are rare cases of 46,XX males in which a portion of the Y chromosome carrying TDF is transferred to another chromosome, the *karyotype* is a rapid, reliable surrogate assay for the presence of SRY. In the presence of SRY, the embryonic bipotential gonad differentiates into a testis; whereas ovarian development requires the absence of SRY plus the action of a number of other genes [3, 4]. The gonads, internal genital ducts, and external genital structures develop from bipotential embryologic tissues. By 4–6 weeks of gestation, the urogenital ridges have developed as outgrowths of coelomic epithelium. Subsequently, urogenital ridges develop into the gonads, adrenal cortex, kidneys, and reproductive tracts. Testicular hormones are required for male sexual differentiation; by contrast, the fetal ovary is hormonally quiescent, and ovarian hormones are not needed for the development of female reproductive structures as evidenced by the normal female reproductive anatomy in 45,X females with Turner Syndrome who lack functional ovaries. Thus, much of the discussion of DSD centers on the testis and its products.

The early human embryo has transient structures (Wolffian and Müllerian ducts, urogenital sinus, genital tubercle, urethral folds, and labioscrotal swellings) that are

precursors (anlage) of adult reproductive organs. The Wolffian (male) ducts originate as the excretory duct of the mesonephros; testosterone secreted by the fetal testes stabilizes the Wolffian ducts so that they develop into the epididymis, vas deferens, ejaculatory ducts, and seminal vesicles. In the absence of testosterone, the Wolffian ducts regress, as in the normal female fetus. The Müllerian ducts are the precursors of female reproductive structures (Fallopian tubes, uterus, cervix, and upper 1/3 of the vagina). In the male fetus, testicular Sertoli cells secrete anti-Müllerian hormone (AMH), also known as Müllerian inhibitory hormone, which acts through specific receptors in Müllerian duct cells to stimulate their apoptosis. Thus, males lack Müllerian structures, but the absence of AMH in the female fetus permits the Müllerian structures to differentiate.

The genital tubercle, urethral folds, and labioscrotal swellings give rise to the external genital structures. In the absence of androgens, as in a normal 46,XX female, the genital tubercle becomes the clitoris, the urethral folds become the labia minora and the labioscrotal swellings become the labia majora. In male development between 7 and 13 weeks, both dihydrotestosterone produced in the fetal testis by a novel, alternative pathway [5] and dihydrotestosterone produced in the genital skin from circulating testosterone act on these target tissues. Dihydrotestosterone induces the urethral folds to fuse and form the corpus spongiosum and penile urethra, the genital tubercle to form the corpora cavernosa of the penis, and the labioscrotal folds to fuse and form the scrotum in the male fetus [6]. These fetal structures are sensitive to androgens at different times in development, but these structures are androgen-sensitive regardless of the sex of the fetus or the source of the androgen. The androgen-induced labioscrotal fusion is unidirectional, from posterior to anterior, providing a "bio-assay" of first trimester fetal androgen action. Thus early (first trimester) exposure of a female fetus to androgen can cause varying degrees of labioscrotal fusion, whereas late exposure (after 20 weeks) may result in isolated clitoromegaly. As virtually all DSD is genetic and occurs in the first trimester, the physical exam of the DSD infant should emphasize the degree of labioscrotal fusion. INSL3 is required for transabdominal testicular descent. Testicular descent into the scrotum, which requires the action of androgens, is a late event that may not be complete until 32 weeks.

Both the adrenal and testis express the enzymes needed for androgen biosynthesis, so that either gland can be the source of androgenizing hormones. However, although the fetal adrenal makes very little cortisol throughout most of gestation, it transiently produces cortisol between 8 and 12 weeks post-conception, thus suppressing ACTH and consequently suppressing the production of adrenal androgenic steroids, permitting female fetuses to develop normally [7].

Pathophysiology of DSD

The recently developed classification of DSD discarded older terminology (female pseudohermaphrodite, male pseudohermaphrodite, and true hermaphrodite) and substituted descriptive terminology, e.g., 46,XX DSD; 46,XY DSD; ovotesticular DSD, 46,XX testicular DSD; and 46,XY complete gonadal dysgenesis (Table 19.1) [1, 2].

Table 19.1 Classification of disorders of sex development associated with ambiguous genitalia

I. Disorders of sex determination (gonadal differentiation)
  A. 46,XY Gonadal dysgenesis
  B. 45,X/46,XY Gonadal dysgenesis
  C. 46,XX (+SRY) Male
  D. 46,XX (-SRY) Male (overexpression of SOX3)
  E. Ovotesticular DSD

II. 46,XX DSD
  A. Androgen-Induced
    1. Feto-placental disorders
      a. Congenital adrenal hyperplasia (CYP21A2, CYP11B1, POR)
      b. Glucocorticoid receptor mutation
      c. Aromatase deficiency (CYP19A1)
    2. Maternal source
      a. Ingestion
      b. Virilizing ovarian or adrenal tumor
      c. Virilizing luteoma of pregnancy
  B. Genetic
    1. RSPO1 mutation

III. 46,XY DSD
  A. Testicular unresponsiveness to hCG and LH (Leydig cell agenesis or hypoplasia)
  B. Defects in steroidogenesis
    1. Enzyme deficits affecting both adrenal and gonadal steroids
      a. StAR deficiency (congenital lipoid adrenal hyperplasia):
      b. Cholesterol side chain cleavage (P450scc) deficiency
      c. 3-Hydroxysteroid dehydrogenase-2 deficiency
      d. P450c17 (17-hydroxylase/17,20 lyase) deficiency
      e. P450 oxidoreductase deficiency
      f. 7-dehydrocholesterol reductase deficiency (Smith-Lemli-Opitz syndrome)
    2. Enzyme defects confined to androgen biosynthesis
      a. 17-Hydroxysteroid dehydrogenase-3 deficiency
      b. 5-Reductase-2 deficiency
  C. Defects in androgen action (androgen receptor defects)
  D. Dysgenetic 46,XY DSD
    1. Denys-Drash and Frasier syndromes (WT-1 mutation)
    2. WAGR syndrome (WT-1 deletion)
    3. Campomelic dysplasia (SOX9 mutation)
    4. SF1 mutation
    5. WNT-4 duplication
    6. DHH (mutation)
    7. ATRX syndrome (XH2 mutation)
    8. ARX mutations
    9. Testicular regression syndrome
    10. CBX2
    11. MAP3K1

(continued)

Table 19.1 (continued)

E. Defects in synthesis, secretion, or response to AMH
1. Persistent Müllerian duct syndrome (in otherwise normal men;)
F. Environmental chemicals (endocrine disrupters)
IV. Unclassified forms of disorders of sexual development
A. In males
1. Hypospadias
2. Ambiguous external genitalia in 46,XY males with multiple congenital anomalies (VATER, CHARGE, IMAGE Syndromes)
3. Intrauterine growth retardation with incomplete masculinization of external genitalia
V. Disorders of genital-urinary tract development
1. Cloacal/Bladder exstrophy

In general, two broad categories can be considered: (1) abnormalities in sex determination, such as sex chromosome anomalies and gene mutations that interrupt or disrupt normal gonadogenesis, and (2) abnormalities of sex differentiation, resulting in abnormal development of the somatic sex structures (genital ducts, urogenital sinus, and external genitalia) (for a detailed description of these disorders see [8]). Genital ambiguity is common, affecting about 1 in 4,500 newborns [9], and cryptorchidism affects approximately 3 % of newborn males.

46,XX DSD

Patients with 46,XX DSD have disorders of sexual differentiation; disorders of female sex determination, such as 45,X Turner Syndrome, do not result in a DSD phenotype because a functional ovary is not needed for female fetal sexual differentiation. Thus patients with 46,XX DSD are genetic females with ovaries and female ducts who have experienced various degrees of masculinization of the urogenital sinus and external genitalia secondary to intrauterine exposure to androgens. While such exposure is rarely caused by maternal androgen ingestion or a virilizing tumor (luteoma of pregnancy) the overwhelming majority of 46,XX DSD is caused by one of the congenital adrenal hyperplasias (CAH), which are genetic disorders of adrenal steroidogenesis that result in inappropriate adrenal synthesis of androgens [10]. The virilizing CAHs account for about half of all cases of ambiguous external genitalia. These autosomal recessive disorders involve mutations in genes needed for cortisol production; low cortisol results in increased ACTH secretion and consequent overproduction of androgens or steroids that are peripherally converted to androgens.

21-Hydroxylase deficiency (21OHD) accounts for over 90 % of cases of 46,XX DSD, with an incidence of about 1:15,000 births. This form of CAH is due to mutations in the *CYP21A2* gene on chromosome 6p21-p23, within the histocompatibility locus. The genetics, pathophysiology, and management of 21OHD are well understood [11]. Depending on the severity of the *CYP21A2* mutations, patients may have

severe salt-wasting 21OHD, in which aldosterone synthesis is deficient, or simple virilizing 21OHD, both of which cause 46,XX DSD. The mild, non-classic form of 21OHD does not cause DSD. The hyponatremia, hyperkalemia, and acidosis of salt-wasting CAH are typically not seen until 5–10 days of age, so that normal electrolyte values before this time are not informative.

Other disorders of steroidogenesis associated with 46,XX DSD include 11β-hydroxylase deficiency (*CYP11B1* gene), P450 oxidoreductase (POR) deficiency and, very rarely, aromatase deficiency [10]. 11-Hydroxylase deficiency, which is the second-most common form of CAH in the United States and Europe, can cause hypertension in older children, but, paradoxically, can be associated with salt loss in the newborn. POR deficiency can cause both 46,XX and 46,XY DSD, but is not associated with adrenal insufficiency in the newborn [12, 13].

Because 21OHD is common and salt loss can be fatal, all 50 states and all Western European countries have instituted newborn screening programs for CAH based on measuring the high levels of 17-hydroxyprogesterone (17OHP, the substrate for the 21-hydroxylase enzyme) in newborn blood. These values can be spuriously elevated if obtained before 24 h of age, in any premature infant, or in the presence of severe illness. 17OHP can also be elevated in patients with 11β-hydroxylase deficiency, POR deficiency, and 3β-hydroxysteroid dehydrogenase (3βHSD) deficiency, so that a careful ACTH stimulation test with measurement of all relevant steroid precursors (not just cortisol and 17OHP) is needed [11].

46,XY DSD

Patients with 46,XY DSD may have disordered sex determination (abnormal gonadal differentiation), or disordered sexual differentiation, in which case the testis has developed but there are errors in testicular hormone synthesis or action, leading to undervirilization [14]. Disordered sex determination causing 46,XY DSD include chromosomal aberrations and mutations in genes involved in testicular development. Anomalies of testis-determining SRY gene, sex chromosome abnormalities (e.g., 45,X/46,XY mosaicism), structural abnormalities of the Y chromosome, or translocation of the SRY gene to an X chromosome or autosome, can cause 46,XY DSD. Mutations in the *WT1* gene can be associated with Wilms tumor (Denys-Drash syndrome) or with an increased risk for gonadoblastoma (Frasier syndrome). Duplications of the *DAX1* (NR0B1) gene are associated with male to female sex reversal. Heterozygous mutations in the *SOX9* gene are associated with camptomelic dysplasia, and 46,XY DSD.

Defects in androgen synthesis or androgen action result in disordered sexual differentiation causing 46,XY DSD. These infants typically have normal Sertoli cell function, AMH secretion, and AMH action, but have undervirilized external genitalia (i.e., perineoscrotal hypospadias, and a short vaginal pouch without a uterus). Defects in androgen synthesis include mutations in the steroidogenic acute regulatory protein (StAR), the cholesterol side-chain cleavage enzyme (P450scc, *CYP11A1* gene), 17α-hydroxylase/17,20-lyase (P450c17, *CYP17A1* gene), the type 3

(testicular) 17β-hydroxysteroid dehydrogenase (*HSD17B3* gene), 5α-reductase, type 2 (*SRD5A2* gene), and 3α-hydroxysteroid dehydrogenase (*AKR1C2/4* genes). Mutations in the gene for 7-dehydrocholestrol (*DHCR7*) cause Smith-Lemli-Opitz syndrome, characterized by multiple congenital anomalies including genital anomalies. Mutations in the LH receptor (*LHR*) are a rare cause of defective testicular steroidogenesis. Mutations in the androgen receptor (*AR*) gene cause varying degrees of androgen insensitivity; testosterone production is normal or increased, but target tissues cannot respond to androgens. The spectrum of androgen insensitivity ranges from complete, in which affected infants have normal female external genitalia, labial masses, and absence of a uterus to partial, with 46,XY DSD, to phenotypically normal males with decreased fertility [15].

Other Forms of DSD

Ovotesticular DSD is characterized by presence of both ovarian follicles and seminiferous tubules in the gonad. Development of internal and external genital structures depends on the extent to which these elements of the gonad function are active. *Malformation syndromes* such as Aarskog-Scott, CHARGE, IMAGE, and VATER syndromes are also associated with disordered genital development. *Bladder exstrophy* is associated with abnormal genito-urinary tract development, but is not due to an abnormality in sex development. Males with bladder exstrophy may have bifid penis and scrotum with a testis located on each side.

Diagnosis

Clinical Setting

Because prenatal ultrasound examinations are common, parents have often been told the (presumed) sex of their child and may have already selected a sex-specific name. The birth of a newborn with genital ambiguity is disconcerting and disrupts the family's plans. Infants with ambiguous genitalia are usually recognized in the delivery room or at the time of their initial examination. The approach to the infant with ambiguous genitalia needs to be systematic and involve a multidisciplinary team. The diagnostic evaluation focuses on etiology, appropriate sex assignment, and ascertainment of associated, potentially life-threatening conditions such as mineralocorticoid deficiency. The infant should be referred to as "your baby." avoiding terms conveying a sex assignment. The parents need to be involved in the infant's evaluation and informed that the child's sex of rearing will be determined as rapidly as possible. The parents' level of understanding, cultural background, and religious views must be considered to enable them to participate in this process, have full disclosure, and to provide true "informed consent."

History

Information should be obtained concerning maternal exposures to androgens or androgen-modifying drugs (e.g., finasteride); maternal virilization during pregnancy may suggest a luteoma, aromatase deficiency, or POR deficiency. The family history may provide information about genetic disorders; information should be obtained concerning relatives with infertility or abnormal pubertal development, and about other infants with genital ambiguity or neonatal deaths.

Physical Examination

A careful, knowledgeable physical examination of the genitalia is essential. Palpable gonads must be sought, and may be "hiding" in the inguinal canal. The urethral meatus must be located, and the length and width of the phallus must be measured (both a clitoris and a penis are phalluses). Mean stretched penile length is 3.5 ± 0.4 cm for full-term infant boys and 2.5 ± 0.4 cm for males at 30 weeks gestation. The pigmentation and rugation of the labioscrotal structures must be described. The potential presence of posterior labial fusion must be quantitated by measurement of the ano-genital ratio (in normal girls, the distance from base of the phallus to the posterior forchette should be 2/3 of the distance from the base of phallus to anus) [16]. The presence of other physical anomalies may suggest specific syndromes.

One specific form of gonadal dysgenesis is characterized by asymmetric external genital development; the karyotype is often 45,X/46,XY and features of Turner syndrome can be present. Gonadal asymmetry also can occur in the ovotesticular disorder. The physical exam for infants with complete androgen insensitivity often reveals female external genitalia with labial masses. The presence of midline defects, renal anomalies, and syndactyly of the second and third toe prompts the consideration of Smith-Lemli-Opitz syndrome.

Laboratory Evaluation

Several diagnostic algorithms have been published, but no single evaluation protocol covers all circumstances. Each infant benefits from an individualized approach to the selection of diagnostic studies, guided by the history and physical examination. The karyotype should be ordered immediately, preferably supplemented with Y-specific probes, since it usually requires several days to get the results. Infants with CAH have normal electrolytes for several days after birth, typically developing hyperkalemia, hyponatremia, and elevated plasma renin activity after 7–10 days. Initial bloodwork should include LH, FSH, AMH, and possibly inhibin B if male sex is suspected but testes are not palpable. Testosterone will be high in androgen resistance syndromes, but simultaneous measurements of testosterone and

dihydrotestosterone are needed to diagnose 5α-reductase deficiency. To assess CAH, stimulation testing with ACTH must be done with measurement of all steroids in the glucocorticoid and androgen pathways. This should be done after 24 h of age to permit clearance of fetal steroids. Samples should be sent to a reference laboratory equipped for small assay volumes and utilizing HPLC/tandem mass spectrometric methods for steroid hormone determinations. Fetal adrenal steroids can cross-react in the clinical radioimmunoassay making this kind of analysis unreliable. Rare defects in testicular steroidogenesis (e.g., 17β-HSD3 deficiency) will require an hCG test. The physiologic mini-puberty of infancy permits assessment of the newborn HPG axis in the second month of life [17]. Molecular genetic analyses are commercially available for some disorders (http://www.genetests.org).

Imaging Studies

Sonographic studies to assess the presence of a uterus can be helpful, remembering that the uterus may not be seen in some normal newborn females, and a uterus may be seen in males with dysgenetic testes. Normal gonads can escape detection by ultrasound or MRI. The inability to detect gonads radiologically does not ensure that they are absent. Sonography and MR imaging of the pelvis and perineum may identify the urogenital sinus when separate urethral and vaginal orifices cannot be seen. A renal sonogram is of value for detecting anomalies of the urinary tract. Adrenal glands may or may not be enlarged in infants with CAH.

Treatment

Approach to the family

The first interview with the parents should set a positive and optimistic tone to promote parental bonding with their infant. The emotional tone of this initial interaction is usually more meaningful than the factual information provided and is recalled by parents for many years. Initially, the parents need to hear that there has been a problem in the complex system that directs genital development, which makes it impossible to tell the sex of their child simply by examining the external genitalia. It is important to acknowledge that such development is not a consequence of anything that they, as parents, did or did not do. Respect for the parents, extended family, and their cultural viewpoints together with a willingness to repeat or defer detailed explanations are crucial. Sex assignment and naming of the infant should be deferred until the diagnostic evaluation has been completed. During this initial evaluation, a patient information publication of the Endocrine Society might be helpful for parents (http://jcem.endojournals.org/content/96/3/33A.long).

During the diagnostic evaluation, information needs to be obtained that can assist the parents and healthcare professionals in determining the most appropriate sex of rearing. Usually this can be accomplished within a few days. In more complex instances, the diagnostic process may take longer. In situations in which it is impossible to identify the specific etiology, the general DSD category provides a basis for decision-making. These considerations include the extent of external and internal reproductive system development, evidence of gonadal function (potential hormone secretion and fertility), and hormone responsiveness. In some instances, these factors are more relevant than the karyotype. Involvement of the multidisciplinary team comprised of pediatric endocrinologists, neonatalogists, geneticists, pediatric urologists/surgeons, radiologists, and behavioral health professionals is essential. When consensus has been reached regarding a diagnostic category, available outcome information for that diagnosis should be reviewed. It is best to present the results of all tests at one time, with a clear conclusion, rather than informing the family of each result incrementally, which can add to confusion. Knowledge of the specific etiology including the details of the diagnosis enables planning therapeutic interventions and genetic counseling for future pregnancies. A written resource that might be helpful for parents is "Consortium on Disorders of Sex Development. Handbook for Parents" (http://dsdguidelines.org).

Medical Management

Specific medical management depends on the underlying disorder. All children with genital ambiguity require long-term care by pediatric endocrinology, pediatric urology/surgery, behavioral health, and their primary care provider.

Children with CAH or other forms of adrenal insufficiency require glucocorticoid, and often mineralocorticoid replacement therapy. The typical initial glucocorticoid dose for newborn infants is approximately 25 mg/m^2/day hydrocortisone (Cortef™) divided into three daily doses, but may be reduced later [11]. Infants require higher mineralocorticoid doses than older children or adults; 9α-fludrocortisone (Florinef) at 0.1–0.3 mg daily is generally sufficient; newborns with salt-losing CAH need sodium supplementation. Both hydrocortisone and 9α-fludrocortisone are available only as tablets, which may be crushed and administered orally; hydrocortisone suspensions are unstable leading to variable dosing and should be avoided.

Surgical Management

Surgical treatment is rarely needed in the immediate newborn period. In rare instances, diagnostic laparoscopy and gonadal biopsy may be necessary to evaluate internal genital structures and obtain tissue for histological examination. Extremely

virilized infants with female sex of rearing, i.e., infant girl with CAH, may benefit from feminizing genitoplasty and repair of the common urogenital sinus. This surgery should only be performed by a highly skilled and experienced pediatric urologist or surgeon, with appropriate attention to anatomic structures to preserve erectile function and clitoral innervation. Contemporary reports favor repair before age 1 year as the neonatal exposure to placental estrogens reduces scarring [11, 18]. Hypospadias repair is often performed in stages and involves surgical urethral reconstruction and repair of associated chordee. For children with dysgenetic gonads, gonadectomy may be necessary at some future time because of the risk for malignant degeneration. In all cases, a skilled and experienced pediatric surgeon or urologist is needed.

Complications

Infants with unrecognized classical salt-losing CAH can die due to mineralocorticoid and glucocorticoid deficiencies. Extremely virilized 46,XX infants with CAH can resemble male infants with bilateral undescended testes and have been assigned to male sex at birth. The availability and use of newborn screening for 21OHD has greatly decreased the occurrence of these complications [11].

Prognosis

The goal for a child with genital ambiguity is thorough and accurate diagnosis followed by appropriate medical and surgical management. The overall goal is that the child experiences normal growth and development and is a productive member of society. Long-term outcome concerns include internal and external genital anatomy, pubertal development, fertility, gender identity, psychosexual adjustment, mental health, healthy relationships, and risk for gonadal malignancy arising in dysgenetic gonads. Available data are inconsistent regarding long-term outcome for children with DSDs.

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Chapter 20
Porphyrias: Acute Manifestations

Karl E. Anderson

Précis

1. Clinical setting: An acute illness characterized by abdominal pain, mental symptoms and lower motor neuronal paresis and paralysis that can progress to respiratory and bulbar paralysis.
2. Diagnosis:

    (a) History: A family history is uncommon. Although three of the four porphyrias that lead to the acute porphyric syndrome are autosomal dominant, penetrance is so variable that it confounds the simple pedigree. The "acute porphyrias" are more common in women and rare in prepubertal individuals. Mental abnormalities include insomnia, anxiety, agitation, depression, disorientation and, hallucinations and delusions. The abdominal pain can be constant or colicky in nature, often associated with ileus. The pain can be accompanied by nausea, vomiting, and constipation or diarrhea.

    The primary neurological abnormality is a peripheral motor neuropathy. Weakness occurs more frequently in the upper extremities, can be asymmetrical, and can progress to respiratory paralysis or bulbar palsy. Cranial nerve defects may occur. Sudden death can occur and is usually attributed to a cardiac arrhythmia.

    (b) Physical examination: Tachycardia and hypertension are common. A mental status examination may reveal confusion, delirium, and disorientation. Examination of the abdomen will not reveal a cause for the steady, sometimes colicky, abdominal pain. Bowel sounds can vary from absent to high

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      pitched and continuous. Neurological examination will reveal findings comparable with a peripheral motor neuropathy: selective weakness, areflexia in advanced cases, fasciculations, and flaccidity.

(c) Laboratory studies: These patients often have hyponatremia and abnormal liver function tests. A key laboratory finding, however, is a marked increase in urinary porphobilinogen (PBG). This abnormality is present in the three most common acute porphyrias. Demonstration of a substantial elevation in urinary PBG establishes the diagnosis of acute porphyria and allows treatment to be started as soon as possible. This measurement can be made with a rapid screening test using random spot urine. An excretion rate of greater than 6 mg/day ensures the diagnosis of acute porphyria.

(d) Treatment: The treatment for an acute porphyric crisis is Hemin (lyophilized hematin) 3–4 mg/kg body weight, as an intravenous infusion once a day for 4 days.

      Carbohydrate loading can be used for less severe attacks, usually in a patient with a known history of acute porphyria. The usual approach is an intravenous infusion of 300 g of glucose daily in the form of D-10, 3 L a day. This treatment is contraindicated in patients with hyponatremia due to the inappropriate secretion of antidiuretic hormone. When in doubt, use Hemin. Side effects of Hemin include phlebitis at the infusion site, fever, malaise and, rarely, hemolysis and anaphylaxis.

Porphyrias result from altered activity of enzymes of the heme biosynthetic pathway. These disorders may be latent, but when clinically expressed, are associated with accumulation of heme pathway intermediates. The genes encoding all eight enzymes in the heme biosynthetic pathway have been sequenced and multiple mutations have been found in each of the porphyrias. Because these disorders are heterogeneous at the molecular level, different mutations are to be expected in unrelated families [1, 2]. As shown in Fig. 20.1, a type of porphyria has been associated with each of the eight enzymatic steps in the heme biosynthetic pathway [1]. With one exception, these diseases are due to heritable mutations affecting a specific enzyme. Porphyria cutanea tarda is due to an acquired tissue-specific inhibition of the fifth enzyme in the pathway, but the majority of patients do not have mutations of this enzyme [3, 4].

As shown in Table 20.1, porphyrias are classified as erythropoietic or hepatic, depending on whether overproduction of heme pathway intermediates occurs primarily in the bone marrow or in the liver. In addition, they are classified based on clinical features. The acute porphyrias are characterized by neuropathic manifestations and the cutaneous porphyrias by skin photosensitivity resulting from activation of porphyrins by light with generation of activated oxygen species that damage the skin. The major clinical features, factors that can contribute to disease expression, including hormonal influences, and effective treatments differ greatly among the different types of porphyria, as summarized in Table 20.2 [1].

Although heme is required in all tissues for many vital hemoproteins, the marrow and liver are most active in heme synthesis. As a result, one of these tissues is the
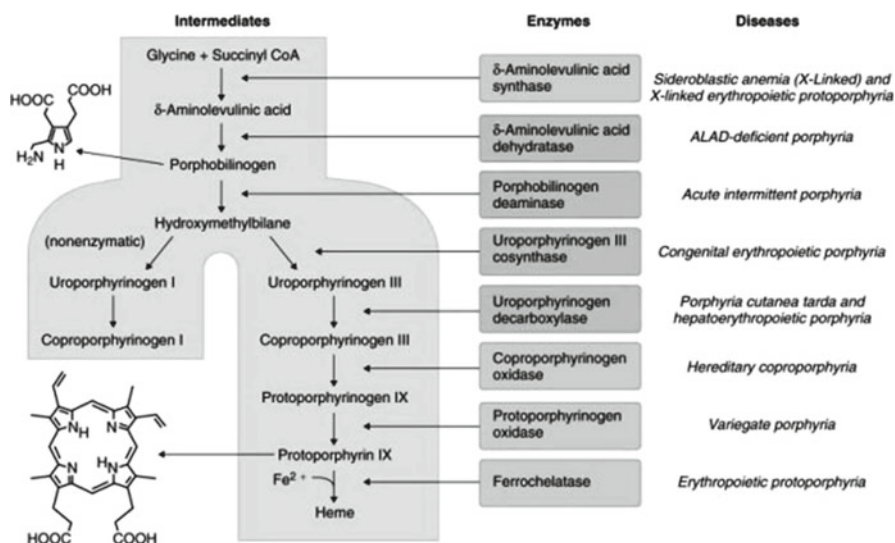
Fig. 20.1 Intermediates and enzymes of the heme biosynthetic pathway and the major diseases of porphyrin metabolism that have been associated with altered activity of specific enzymes. The initial and last three enzymes are mitochondrial and the other four are cytosolic. Heme is synthesized from glycine and succinyl coenzyme A. Intermediates in the pathway include **δ**-aminolevulinic acid (an amino acid used exclusively for heme synthesis), porphobilinogen (a pyrrole), and hydroxymethylbilane (a linear tetrapyrrole). Uroporphyrinogen III cosynthase catalyzes closure of hydroxymethylbilane, with inversion of one of the pyrroles, to form a porphyrin macrocycle, uroporphyrinogen III. (Nonenzymatic closure occurs without inversion of this pyrrole, forming uroporphyrinogen I, which is not metabolized beyond coproporphyrinogen I.) The next two enzymes result in decarboxylation of six of the eight side chains of uroporphyrinogen III, with sequential formation of heptacarboxyl porphyrinogen, hexacarboxyl porphyrinogen, pentacarboxyl porphyrinogen, tetracarboxyl porphyrinogen (coproporphyrinogen III), tricarboxyl porphyrinogen (harderoporphyrinogen), and dicarboxyl porphyrinogen (protoporphyrinogen IX). The final two enzymes catalyze oxidation of protoporphyrinogen IX to protoporphyrin IX and insertion of ferrous iron into the porphyrin macrocycle to form heme (iron protoporphyrin IX). With the exception of protoporphyrin IX, all porphyrin intermediates are in their reduced forms (hexahydroporphyrins or porphyrinogens). Chemical structures of two intermediates are shown. ALAD, **δ**-aminolevulinic acid dehydratase. (From [1], with permission)

major site of overproduction of pathway intermediates in all of the various types of porphyria. Heme is used in the marrow primarily for hemoglobin and in the liver for synthesis of cytochrome P-450 enzymes (CYPs). Hepatic heme biosynthesis is regulated primarily by activity of the ubiquitous form of δ-aminolevulinic acid (ALA) synthase (ALAS1), which is the initial and rate limiting enzyme, and is under sensitive feedback control by a regulatory "free" heme pool in hepatocytes. Hepatic ALAS1 is induced by many of the same drugs and steroids that induce CYPs. Regulation of additional pathway enzymes and the cellular uptake of iron are important in controlling heme synthesis in erythroid cells [2].

Table 20.1 Diseases caused by altered activities of enzymes in the heme biosynthetic pathway with common abbreviations, chromosome location of the affected genes, inheritance, and classifications

Disease (abbreviation)	Altered enzyme (abbreviation)	Gene location	Inheritance	Classifications
X-linked protoporphyria (XLP)	ALA synthase—erythroid (ALAS2)[a]	Xp11.21	X-linked	Erythropoietic/cutaneous
ALA dehydratase porphyria (ADP)	ALA dehydratase (ALAD)	9q34	Autosomal recessive	Hepatic?/Acute
Acute intermittent porphyria (AIP)	Porphobilinogen deaminase (PBGD)[b]	11q24.1 q24.2	Autosomal dominant	Hepatic/Acute
Congenital erythropoietic porphyria (CEP)	Uroporphyrinogen III (co)synthase (UROS)	10q25.2 q26.3	Autosomal recessive	Erythropoietic/Cutaneous
Porphyria cutanea tarda(PCT)	Uroporphyrinogen decarboxylase (UROD)[c]	1p34	Autosomal dominant	Hepatic/Cutaneous
Hepatoerythropoietic porphyria (HEP)			Autosomal recessive	Hepatic and Erythropoietic/Cutaneous
Hereditary coproporphyria (HCP)	Coproporphyrinogen	3q12	Autosomal dominant	Hepatic/Acute and Cutaneous
Variegate porphyria (VP)	Protoporphyrinogen oxidase	1q22 or 23	Autosomal dominant	Hepatic/Acute and Cutaneous
Erythropoietic protoporphyria (EPP)	Ferrochelatase oxidase	18q21.3 or 22	Autosomal recessive[d]	Erythropoietic/Cutaneous

[a]The X-linked variant of EPP is due to gain of function mutations of ALAS2. Loss of function mutations affecting this enzyme are found in X-linked sideroblastic anemia. Disease-causing mutations of ALAS1, the ubiquitous form of ALAS, which is encoded by a gene on chromoxome 3p21, have not been described

[b]This enzyme is also known as hydroxymethylbilane synthase and formerly as uroporphyrinogen I synthase

[c]PCT results from an acquired inhibition of UROD to <20% of normal in the liver in the presence of multiple susceptibility factors. In ~80% of cases (type 1) there are no UROD mutations; ~20% are heterozygous for UROD mutations (type 2). HEP is the homozygous (or compound heterozygous) form of type 2 PCT

[d]>90% of EPP cases are due to FECH mutations. Inheritance was previously classified as autosomal dominant with variable penetrance but is now recognized as recessive at the molecular level, with inherited mutations affecting both FECH alleles. Most patients have a null mutation trans to a hypomorphic mutation, IVS3-48T>C, that is common in the population but does not itself cause disease

ALA δ-aminolevulinic acid

Table 20.2 Clinical features including contributing factors and treatment of the three most common human porphyrias

	Presenting symptoms	Exacerbating factors	Screening tests	Treatment
Porphyria cutanea tarda[a]	Blistering skin lesions (chronic)	Iron, alcohol, estrogens, hepatitis C virus, halogenated hydrocarbons	Plasma (or urine) porphyrins	Phlebotomy, low-dose hydroxy-chloroquine
Acute intermittent porphyria[b]	Neurovisceral (acute)	Drugs (mostly P-450 inducers) Progesterone Dietary restriction	Porphobilinogen (urine)	Heme, glucose
Erythropoietic protopor-phyria	Painful skin and swelling(mostly acute)		Total erythrocyte protoporphyrin	β-Carotene

[a]Porphyria cutanea tarda, the most common porphyria, is not discussed here because its manifestations are chronic and rarely emergent or life threatening

[b]The same considerations pertain to the other three acute porphyrias except that hereditary coproporphyria and variegate porphyria can also cause skin lesions identical to those in porphyria cutanea tarda, and δ-aminolevulinic acid dehydratase porphyria does not significantly elevate porphobilinogen

This chapter will discuss the four acute porphyrias and EPP, with emphasis on diagnosis and management of their acute, life-threatening features. PCT, the most common porphyria, and congenital erythropoietic porphyria (CEP), which is very rare, cause chronic blistering skin manifestations that are rarely emergent and will not be discussed.

Acute Porphyrias

The four acute porphyrias present with identical attacks of neurological symptoms, and all are due to deficiencies of different enzymes in the heme pathway (Table 20.1). Acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP) are autosomal dominant genetic disorders due to deficiencies of the third, sixth, and seventh enzymes in the pathway, respectively. They are manifest most commonly in adult females. AIP is the most common acute porphyria, and the second most common porphyria. Porphyria due to an inherited deficiency of ALA dehydratase (ALAD), the second enzyme in this pathway, is very rare, with only six documented cases in the literature. Features of ALAD porphyria (ADP) that differ from the other acute porphyrias include autosomal recessive inheritance and occurrence in males in the cases reported to date [5]. VP, and less commonly

HCP, can also cause blistering skin lesions, either with or apart from the neurological manifestations. Although these are identical to the skin findings in PCT, they do not respond to the same treatments. Acquired deficiencies of ALAD occur in lead poisoning and hereditary tyrosinemia type 1 and can be associated with symptoms such as abdominal pain, ileus, and motor neuropathy that are strikingly similar to those of the acute porphyrias. Lead potently inhibits ALAD by displacing zinc from the enzyme. In tyrosinemia type 1 the inherited deficiency of fumarylacetoacetase leads to accumulation of succinylacetone (2,3-dioxoheptanoic acid), which is a structural analogue of ALA and a potent inhibitor of ALAD [1, 2].

Clinical Presentation

AIP and the other acute porphyrias usually present after puberty as acute attacks, lasting for several days or longer and, with the exception of ADP, more commonly in women than men. These disorders are almost never symptomatic before puberty, except in very rare homozygous cases of AIP, HCP, and VP. Symptoms are highly variable and nonspecific, and the history and physical examination may not immediately suggest the diagnosis [6].

Pertinent History

A family history of porphyria can suggest the diagnosis of acute porphyria. Usually there is no such history because most relatives who have inherited mutations for AIP, HCP, or VP never have symptoms. These mutations occur in all populations, so race and country of origin are of little importance in suspecting the diagnosis. Founder effects may increase prevalence in some populations. Most notable is a high prevalence of VP in South Africans of Dutch ancestry. Patients with symptoms may or may not have a history of similar manifestations in the past [6].

A porphyric attack can begin with insomnia and anxiety and progress, over hours or days, to abdominal pain (the most common symptom), nausea, vomiting, constipation and, less commonly, diarrhea, pain in the extremities, head, neck, or chest, muscle weakness, dysuria, and other symptoms of bladder dysfunction. Paresis can develop, especially with severe and prolonged attacks, and is caused by a peripheral motor neuropathy. The muscle weakness is often accompanied by pain in the extremities, back, and chest. Motor weakness typically affects the proximal muscles, most commonly in the upper extremities. It can progress to respiratory and bulbar paralysis. Paresis is usually symmetrical but can be asymmetrical and focal, and cranial nerves can be affected. Sudden death can occur, presumably from elevated catecholamines and cardiac arrhythmia. Anxiety and insomnia can be accompanied by other central nervous system manifestations such as agitation, depression, disorientation, hallucinations, and paranoia. Hyponatremia is common in severe attacks and can be

due to inappropriate antidiuretic hormone secretion or a combination of causes such as vomiting, diarrhea, poor intake, and excess renal sodium loss [7–9]. Seizures can be caused by hyponatremia or can be a neurological manifestation of porphyria itself [6]. Symptoms of acute porphyria could be caused by the neurotoxic effects of one or more heme pathway intermediates, such as ALA, but this has not been proven. Recurrent attacks tend to be similar in a given patient, but can vary depending on exacerbating factors. Some patients develop frequent recurring attacks and chronic symptoms including pain and depression [6].

A history of exposure to certain drugs known to cause attacks should suggest the diagnosis and prompt diagnostic testing. Many such drugs are inducers of hepatic CYPs. ALAS1 and CYP genes share upstream enhancer elements that respond to inducing drugs and chemicals that interact with PXR [10]. Therefore, half-normal activity of an enzyme in the heme biosynthetic pathway resulting from a mutation inherited from one parent can become limiting in the liver when there is exposure to drugs or hormones that induce ALAS1 and CYPs.

Attacks are also provoked by reduced calorie intake (as in crash dieting to lose weight), infections, and major surgery [11]. Induction of ALAS1 by fasting is mediated by the peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α), now recognized as an important link between nutritional status and the acute porphyrias [12]. Onset after puberty and more frequent clinical expression in women suggest that endogenous hormones are important. Luteal phase attacks are probably due to progesterone and its metabolites, which are potent inducers of hepatic ALAS1. Estrogens are not. Attacks may occur from administration of progestins, although the risk may be lower with newer low-dose progestin-estrogen oral contraceptives. Although pregnancy is usually well tolerated despite high progesterone levels, some women experience attacks during pregnancy, and hyperemesis gravidarum, reduced calorie intake and harmful drugs (e.g., metoclopramide) may contribute [6].

Some drugs known to be unsafe and safe drugs are listed in Table 20.3, but it is important to access online interactive websites maintained by the American Porphyria Foundation (www.porphyriafoundation.com/) or the European Porphyria Initiative (www.porphyria-europe.com/) for more complete and updated information when questions arise. Cigarette smoke contains chemicals that can induce ALAS1 and may predispose to attacks [13]. These and other unknown exacerbating factors are additive, which can explain why harmful drugs do not always cause attacks. For example, barbiturate anesthetics were observed to exacerbate porphyria more often if symptoms were present before anesthetic exposure [14].

Pertinent Physical Findings

Patients are typically acutely ill with severe pain and other neurovisceral signs and symptoms. Common findings include tachycardia, hypertension, restlessness, fine tremors, and excess sweating attributed to sympathetic overactivity.

Table 20.3 Selected drugs considered unsafe and safe in the acute porphyrias

Unsafe	Safe
Alcohol	Acetaminophen
Barbiturates[a]	Acetazolamide
Calcium-channel blockers	Allopurinol
Carbamazepine[a]	Amiloride
Carisoprodol[a]	Angiotensin-converting enzyme inhibitors[b]
Clonazepam	Angiotensin receptor antagonists[b]
Danazol[a]	Aspirin
Diclofenac and possibly other nonsteroidal anti-inflammatory drugs[a]	Atropine
Ergots	Beta-adrenergic antagonists[b]
Glutethimide[a]	Bromides
Methyprylon	Cimetidine
Ethchlorvynol[a]	Erythropoietin[a,c]
Griseofulvin[a]	Estrogens[a,d]
Mephenytoin	Gabapentin
Meprobamate[a] (also mebutamate,1 tybutamate[a])	Gentamicin
	Glucocorticoids
Metoclopramide[a]	Insulin
Phenytoin[a]	Narcotic analgesics
Primidone[a]	Ofloxacin
Progesterone and synthetic progestins[a]	Penicillin and derivatives
	Phenothiazines
Pyrazinamide[a]	Ranitidine[a,c]
Pyrazolones (aminopyrine, antipyrine)	Streptomycin
	Tetracycline
Rifampin[a]	Vagabatrin
Succinimides (ethosuximide, methsuximide)	
Sulfonamide antibiotics[a]	
Valproic acid[a]	

[a]Porphyria is listed as a contraindication, warning, precaution, or adverse effect in US labeling for these drugs. For drugs listed here as unsafe, absence of such cautionary statements in US labeling does not imply lower risk
[b]Some drugs in these classes may be safer than others: see websites of the American Porphyria Foundation (www.porphyriafoundation.com/) and the European Porphyria Initiative (www.porphyria-europe.com/)
[c]Although porphyria is listed as a precaution in US labeling, these drugs are regarded as safe by other sources
[d]There is little evidence that estrogens alone are harmful in acute porphyrias. They have been implicated as harmful mostly on the basis of experience with estrogen-progestin combinations and because they can exacerbate porphyria cutanea tarda

Fever is absent or mild. The abdomen may be distended. Usually, the bowel sounds are decreased and there is little or no tenderness. On occasion, the bowel sounds are increased. In the early stages of an attack, deep tendon reflexes may be normal or hyperactive, even with clonus. Sensory loss is variable [6].

Pertinent Laboratory Data

It is important to understand the properties and routes of excretion of the heme pathway intermediates that accumulate in these diseases, since their measurement is essential for diagnosis. Normally these intermediates are excreted only in small amounts. Urinary excretion of ALA and PBG is usually reported in mg/24 h and normally exceeds urinary excretion of porphyrins. The porphyrin precursors ALA and PBG and the porphyrinogens are colorless and nonfluorescent. However, porphyrinogens undergo auto-oxidation outside cells and are excreted primarily as the corresponding porphyrins, which are reddish and fluoresce on exposure to long-wave ultraviolet light. ALA and PBG are mostly excreted in urine, as are the highly carboxylated porphyrins, namely uroporphyrin (octacarboxylporphyrin), heptacarboxylporphyrin, hexacarboxylporphyrin, and pentacarboxylporphyrin. Coproporphyrin (tetracarboxylporphyrin) is excreted in both urine and bile. Harderoporphyrin and protoporphyrin, which are tricarboxyl and dicarboxyl porphyrins, are excreted in bile and feces. Measurement of PBG is especially important for initial diagnosis of acute porphyrias, as discussed below [2, 6].

Anemia is absent, since the marrow is not affected significantly in these hepatic porphyrias. Leukocytosis is absent or mild, since there is little inflammation. Hyponatremia and other electrolyte abnormalities may be present. Chronic hepatic abnormalities including low-grade transaminase elevations are common. It is not known whether underlying liver disease is significant and can progress to cirrhosis. However, risk of hepatocellular carcinoma is increased [15]. When associated with acute porphyria, these tumors are not associated with α-fetoprotein elevated levels and require imaging for early detection. AIP can predispose to chronic hypertension and significant renal impairment that can require chronic hemodialysis or renal transplantation [6].

Diagnosis: Key Tests

Acute porphyria should be suspected in any patient with abdominal pain or other nonspecific symptoms of these diseases if an initial workup for more common conditions does not provide a diagnosis. A marked increase in urinary PBG excretion, which is characteristic of AIP, HCP, and VP, does not occur in other medical conditions, and is therefore a highly specific and diagnostic finding. During attacks of AIP, PBG excretion is generally in the range of approximately 50–200 mg/day (reference range, 0–4 mg/day) and ALA excretion is approximately 20–100 mg/day (reference range, 0–7 mg/day) but may be somewhat lower and decrease more rapidly in HCP and VP. In ADP excretion of ALA is markedly increased and PBG is normal or only slightly increased. Urinary porphyrins are increased on all four acute porphyrias, but this is a nonspecific finding that also occurs in other medical conditions, and especially those affecting the liver or bone marrow.

Inexpensive, sensitive, and specific tests should be available for early diagnosis of acute porphyrias, rather than delaying such testing until the end of a lengthy and
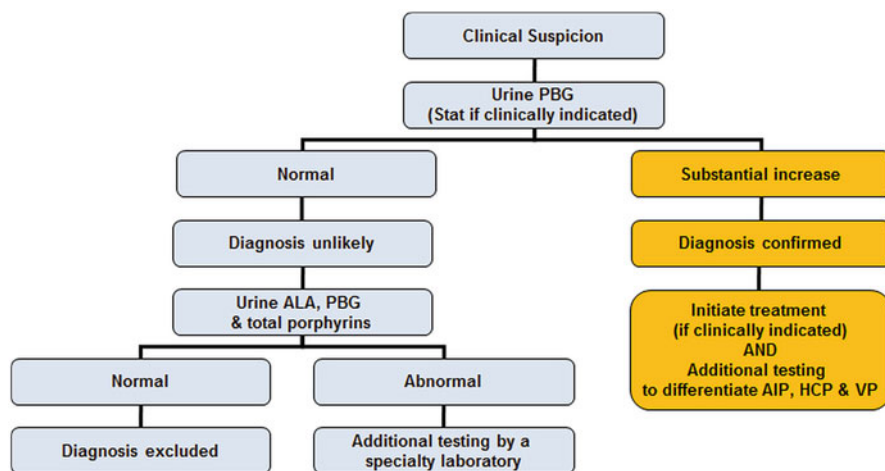
Fig. 20.2 Approach to the diagnosis of acute porphyria in patients with current symptoms that suggest these disorders. A rapid test for elevated urine porphobilinogen will almost always establish or exclude this diagnosis in the acutely ill patient. If a marked porphobilinogen elevation is found, further testing is initiated to establish the type of acute porphyria, but treatment can begin before the laboratory reports those results

expensive diagnostic workup. This is important because treatment is most effective if implemented early. A diagnostic flow chart for use when acute porphyria is suspected is presented in Fig. 20.2. When acute porphyria is suspected, a spot urine should be obtained for rapid screening for elevated PBG. It is recommended that a kit be available in all medical centers for rapid detection of elevated PBG using a random urine sample [6, 16].

Demonstration of a substantial elevation in PBG is a specific finding that establishes a diagnosis of acute porphyria. Treatment can be started promptly, but after saving the original random urine sample and collecting a blood sample and a random fecal sample for additional testing to differentiate HCP and VP from AIP. The urine sample is processed to confirm the elevated PBG by a quantitative method, and to measure ALA and porphyrins. The blood sample is used to measure plasma porphyrins (elevated in VP with a distinctive fluorescence peak at neutral pH) [17, 18] and erythrocyte PBG deaminase (usually decreased in AIP). The fecal sample is used to measure porphyrins (elevated in HCP and VP). Samples collected after treatment is started are less useful because levels of ALA, PBG, and porphyrins may decrease, especially after treatment with hemin [6].

In ADP, urinary coproporphyrin III and ALA are markedly elevated, and plasma and fecal porphyrins are mildly elevated [5]. Erythrocyte zinc protoporphyrin is markedly increased in ADP, as in other homozygous recessive porphyrias, and normal or slightly and nonspecifically increased in active cases of AIP, HCP, and VP.

Urinary PBG and porphyrin levels can decrease after an attack; they often remain elevated between attacks of AIP. Although some have proposed that acute attacks

must be proven by documenting a particular level of increase in PBG [19], this is not practical, and the diagnosis of a recurrent attack is based on evaluation of clinical findings and exclusion of other potential causes of abdominal pain or other presenting symptoms [6].

PBG deaminase deficiency, most conveniently demonstrated by measuring the cytosolic enzyme activity in erythrocytes, helps confirm a diagnosis of AIP. However, erythrocyte PBG deaminase activity is normal in some AIP patients because a) some PBG deaminase mutations reduce the ubiquitous enzyme found in the liver, but not the erythroid form of the enzyme, b) erythrocyte PBG deaminase has a wide normal range (up to threefold) that overlaps the AIP range, and c) the enzyme may be increased in erythrocytes by inapparent concurrent conditions that stimulate erythropoiesis. The assay is useful for analysis of pedigrees of known AIP patients if it is established that an index case has a low value. However, DNA studies are more dependable, although more expensive. It is now recommended that the specific PBG deaminase mutation be identified for a family so relatives can be tested reliably for latent AIP. Mutations in CPO and PPO can also be identified in HCP and VP, respectively; enzyme assays for these mitochondrial enzymes are difficult and not generally available. Diagnosis of acute porphyrias in utero is possible but seldom indicated in view of the favorable outlook for most subjects who inherit these mutations [6].

Importantly, DNA studies and the measurement of erythrocyte PBG deaminase are not useful in acutely ill patients because an abnormal finding does not distinguish between active and latent stages of acute porphyria. Therefore it remains important to document the diagnosis in active cases of acute porphyrias by measuring PBG, ALA, and total porphyrins in urine. These can be measured in serum in patients with renal insufficiency [6, 20].

Treatment

Attacks may resolve spontaneously. For example, attacks during the luteal phase of the menstrual cycle usually resolve with onset of menses. However, most attacks should be treated with hemin [6, 21, 22]. Effective treatment requires an accurate diagnosis, and in a patient not previously known to have porphyria, the prompt demonstration of a substantial elevation of PBG. Severe attacks can become life threatening with progression to quadriplegia and respiratory impairment without treatment with hemin. Complete recovery of axonal degeneration can occur even with advanced motor weakness, but may require 1–2 years. Residual weakness sometimes affects distal extremities.

Hospitalization is usually required for the intravenous administration of glucose and hemin. Precipitating factors, which are often multiple, should be identified and excluded whenever possible.

Effective symptomatic therapy is essential. Narcotic analgesics are usually required for pain, and small or moderate doses of a phenothiazine for nausea, vomiting,

anxiety, and restlessness. Continued treatment after recovery with a phenothiazine is seldom indicated. Short-acting benzodiazepines in low doses can be safe for insomnia and as minor tranquilizers. Bladder distention may require catheterization [6].

Hemin therapy and carbohydrate loading are considered specific therapies because they repress hepatic ALAS1. Hemin 3–4 mg/kg body weight is infused intravenously once daily for 4 days. A longer course of treatment is seldom necessary if treatment is started soon after onset of symptoms. Efficacy is reduced and recovery less rapid when treatment is delayed and neuronal damage becomes more advanced. Hemin is an approved product in the United States, is available as lyophilized hematin (hydroxyheme, Panhematin™, Recordati) and should be reconstituted with human albumin [6, 23]. Hemin is available as heme arginate (Normosang™, Orphan Europe) in Europe and South Africa. Availability in other countries is less dependable. Hemin has been administered safely during pregnancy [6, 21, 22, 24, 25].

Carbohydrate loading can suffice for mild attacks (e.g., pain not requiring narcotics, and without paresis, seizures, or hyponatremia) and can be given orally as sucrose, glucose polymers, or carbohydrate-rich foods. If oral intake is poorly tolerated or contraindicated by distention and ileus, intravenous administration of glucose (at least 300 g daily) is usually indicated, although larger amounts may be more effective. However, this may entail administration of a large volume of fluids and increase the risk of hyponatremia. A central venous line facilitates more complete parenteral nutrition support and avoids excess fluid volumes [6]. The effect of glucose is mediated in part by elevation of insulin, which reduces expression of PGC-1a in the liver [12].

Treatment of seizures is difficult because almost all antiseizure drugs can exacerbate AIP. Bromides, gabapentin, and vigabatrin can be given safely. β-Adrenergic blocking agents can control tachycardia and hypertension in acute attacks of porphyria, but they can be hazardous in patients with hypovolemia, in whom increased catecholamine secretion may be an important compensatory mechanism. Cimetidine is reported to be beneficial, but controlled studies are lacking, and it should not be used in place of hemin. Numerous other therapies have been tried in this disease but have not been consistently useful [1, 2, 6].

Frequent cyclic attacks can be prevented by treatment with a GnRH analogue [26]. Oophorectomy is not an acceptable option for preventing cyclic attacks, unless there are additional indications for such surgery. Hemin infusions can also prevent recurrent attacks, although experience is limited. Liver transplantation can be curative for patients with repeated disabling attacks that are refractory to hemin therapy. This experience is strong evidence that the liver is responsible for the neuropathic manifestations of the acute porphyrias [27].

Complications of Therapy

Hemin has few adverse effects. However, hematin is unstable when reconstituted with sterile water, and when infused degradation products adhere to endothelial cells, platelets, and coagulation factors, causing a transient anticoagulant effect and

frequently a phlebitis at the site of infusion. Reconstitution with human albumin enhances the stability of hematin and prevents these side effects [6, 28]. Uncommon side effects include fever, aching, malaise, hemolysis, anaphylaxis, and circulatory collapse [29, 30].

Family members should be screened, preferably by DNA methods, to detect latent cases. Potentially harmful drugs and "crash diets" for weight loss should be avoided. Suicide is a risk in patients with chronic symptoms and depression, and such symptoms require active management [31].

Erythropoietic Protoporphyria "Crisis"

Erythropoietic protoporphyria (EPP) is a genetic disease that typically causes lifelong photosensitivity due to high levels of protoporphyrin, initially in marrow reticulocytes and then in plasma and circulating erythrocytes [1, 32, 33]. Protoporphyrin is excited by light, generating free radicals and singlet oxygen, leading to skin damage [34]. Factors that increase circulating levels of the hormone erythropoietin and stimulate erythropoiesis can increase protoporphyrin production in the marrow and worsen the disease. However, steroid hormones and drugs that are important in hepatic porphyrias have little effect in erythropoietic porphyrias. Protoporphyrin is water insoluble and is excreted only by the liver into bile and may form gallstones.

Protoporphyrin is hepatotoxic and can cause significant liver disease in less than 5% of cases. Liver disease complicating EPP is referred to as protoporphyric hepatopathy. It is also termed EPP crisis when it presents with jaundice, rapidly progressive liver decompensation and severe right upper quadrant pain [35, 36].

Clinical Presentation

EPP is the most common porphyria in children and the third most common in adults, with a reported prevalence of 5–15 cases per million individuals [37–39]. Photocutaneous symptoms usually begin in childhood and are generally much more prominent than are physical findings. Burning, itching, erythema, and swelling can occur within minutes of sun exposure, and the diffuse edema of sun-exposed areas can resemble angioneurotic edema. Chronic skin changes are subtle, with little or no blisters, crusting, or scarring. Mild anemia with hypochromia, microcytosis, and low serum ferritin is common, and is poorly understood. High protoporphyrin levels may in some manner decrease iron absorption [40].

Protoporphyric hepatopathy can be the cause of previously unexplained abnormalities in liver function tests, particularly elevated serum transaminases, in a patient with longstanding photosensitivity. Some patients present with severe liver disease before they are recognized to have EPP. Acute porphyrias, which do not cause photosensitivity, and porphyria cutanea tarda, which is associated with

chronic, blistering cutaneous manifestations can also have persistent liver function abnormalities. CEP is associated with severe blistering photosensitivity caused by marked accumulation of water soluble porphyrins that do not damage the liver and are excreted primarily in urine.

Pertinent History

There is often no family history of EPP or photosensitivity. In most families, EPP is an autosomal recessive disease due to an inherited deficiency of ferrochelatase (FECH), the final enzyme in the heme biosynthetic pathway [32, 41]. The enzyme activity is less than about 30% of normal in affected individuals, which is explained by the presence of a severe *FECH* mutation inherited from one parent and a hypomorphic low-expression *FECH* allele from the other parent [42]. This hypomorphic allele, identified as IVS 3-48T→C, is found in about 10% of Caucasians, and by itself has no phenotype even when homozygous. Multiple different *FECH* mutations have been identified in different families [43]. An individual who inherits a severe *FECH* mutation and a normal allele does not develop EPP, but if his or her spouse happens to carry the IVS 3-48T→C allele, their offspring are at risk for having the disease [44]. EPP occurs in all races, but the frequency of the hypomorphic *FECH* allele in different populations determines the differences in prevalence of EPP. The hypomorphic allele and EPP are rare in Africa and more common in China, Japan, Europe, and North America. Rarely, a severe *FECH* mutation is inherited from each parent. In these cases the hypomorphic allele is absent and at least one of the severe mutations expresses some FECH enzyme [43]. Interesting features in some of these cases have included seasonal palmar keratoderma, neurological symptoms, less than expected increases in erythrocyte protoporphyrin and the absence of liver dysfunction [45]. EPP also can develop late in life in the setting of a myeloproliferative or myelodysplastic disorder due to expansion of a clone of hematopoietic cells with a *FECH* mutation [46–48].

A variant form of EPP without FECH mutations and a sex-linked inheritance pattern was recently found to be due to gain of function mutations of ALAS2 (the only heme pathway enzyme found on the X chromosome) [49]. Early studies of this condition, which is termed X-linked protoporphyria (XLP), suggest that it is responsible for about 5% of EPP cases. The clinical phenotype is the same as in cases with *FECH* mutations, but it has been suggested that XLP patients may be at greater risk for iron deficiency and liver disease.

A long history of nonblistering photosensitivity in a patient presenting with acute or chronic liver disease strongly suggests protoporphyric hepatopathy. Patients who present with acutely decompensated liver disease usually have underlying cirrhosis. Rapid progression of liver disease often ensues due to an increasing level of protoporphyrin in plasma, which results from impaired hepatobiliary excretion [35, 36]. Gallstones are commonly present, and acute cholecystitis and common bile duct obstruction must be excluded by imaging. Hepatopathy is sometimes precipitated

by another cause of liver dysfunction such as viral or alcoholic hepatitis, which impairs hepatic uptake of protoporphyrin and causes plasma porphyrins to increase further and cause hepatotoxicity [50]. Protoporphyrin is cholestatic, and can form crystalline structures in hepatocytes and impair mitochondrial function, leading to decreased hepatic bile formation and flow [35, 51].

Pertinent Physical Findings

Chronic skin changes such as blistering, milia, scarring, and hypertrichosis, as seen in other cutaneous porphyrias, are not common in EPP. Findings such as lichenification, leathery pseudovesicles, labial grooving, and nail changes are difficult to recognize. There is no fluorescence of the teeth and neuropathic manifestations occur only with advance liver disease [52].

Patients who present acutely with protoporphyric hepatopathy are often jaundiced and have right upper quadrant tenderness that may suggest cholecystitis or biliary obstruction. They may develop a severe motor neuropathy similar to that seen in the acute porphyrias, and manifest initially by proximal muscle weakness that is difficult to detect by physical examination in its early stages, and may involve the respiratory muscles [53].

Pertinent Laboratory Data

EPP is associated with marked elevation of protoporphyrin in erythrocytes. Plasma porphyrins are less elevated than in other cutaneous porphyrias and may be normal in mild cases. Fecal porphyrins are normal or modestly elevated and consist mostly or protoporphyrin. Urine porphyrins are normal in uncomplicated EPP, since protoporphyrin is not excreted in urine. Liver function test elevations in protoporphyric hepatopathy may be marked but are not specific. Urine porphyrins are increased in protoporphyric hepatopathy, as in other liver diseases, and consist mostly of coproporphyrin.

Diagnosis: Key Tests

Diagnosis of this porphyria may be delayed longer than with any other type of porphyria, in part because skin changes are not prominent on physical examination and urine porphyrins are not elevated. The diagnosis requires measurement of erythrocyte porphyrins. However, there is considerable confusion regarding measurement and reporting of erythrocyte porphyrins, which are increased in many other medical conditions [1].

The markedly increased erythrocyte porphyrins in most cases of CEP are predominantly uroporphyrin I and coproporphyrin I. However, protoporphyrin predominates in EPP and many other medical conditions such as homozygous porphyrias (including mild cases of CEP), iron deficiency, lead poisoning, anemia of chronic disease [54], hemolytic conditions, and many other erythrocyte disorders [55]. Erythrocyte protoporphyrin is usually chelated with zinc in normal erythrocytes as well as all these circumstances, with the exception of EPP. Formation of zinc protoporphyrin in the marrow from protoporphyrin not utilized for heme formation is catalyzed by FECH, which can use metals other than ferrous iron.

A unique finding in EPP is increased erythrocyte protoporphyrin that is predominantly metal-free rather than complexed with zinc. This occurs because FECH is deficient and formation of zinc protoporphyrin as well as heme is impaired. Because FECH is not deficient in XLP, erythrocytes in this disorder contain increased amounts of both zinc and free protoporphyrin, although the latter still predominates.

The diagnosis of EPP (as well as XLP) requires the demonstration of an increase in total erythrocyte protoporphyrin with a predominance of free protoporphyrin rather than zinc protoporphyrin. Relative amounts of free and zinc-chelated protoporphyrin can be measured by an ethanol extraction or HPLC. Unfortunately, some methods for measuring what in the past was termed "free erythrocyte protoporphyrin" (especially in screening for lead poisoning) in fact measured zinc protoporphyrin. Continued use of this methodology and terminology by some major laboratories results in considerable confusion in testing for EPP. It is best initially to measure *total* erythrocyte porphyrins (or total protoporphyrin) and avoid laboratories that measure only zinc protoporphyrin. Thereafter, if the total is increased, the relative amounts of free and zinc protoporphyrin are estimated by ethanol extraction and fluorescence scanning. In EPP due to FECH deficiency, more than 85% of total will be metal-free protoporphyrin and less than ~15% zinc protoporphyrin. In XLP, in which FECH is not deficient, zinc protoporphyrin may comprise 15–50% of the total. Zinc protoporphrin predominates in other erythrocytic disorders, and this finding effectively excludes EPP.

The plasma porphyrin concentration is almost always increased in EPP, but often less than in other cutaneous porphyrias, and may be normal in mild cases. Plasma porphyrins in EPP are particularly subject to photodegradation from light exposure during sample processing [56]. Therefore, measurement of erythrocyte rather than plasma porphyrins should be the primary screening test for EPP. Fecal porphyrins are often increased, and consist mostly of protoporphyrin. Urine porphyrins are normal, except after hepatopathy develops, which causes increases in urinary coproporphyrin, as in other liver diseases.

The diagnosis of protoporphyric hepatopathy is best documented by liver biopsy, which will demonstrate accumulated protoporphyrin that appears as brown pigment in hepatocytes, Kupffer cells, and biliary canaliculi and are doubly refractive with a Maltese cross appearance under polarizing microscopy [57]. Histological evidence of other contributing causes of liver damage is important to recognize and may alter treatment.

Treatment

Avoidance of sunlight is essential to prevent painful photosensitivity in all patients with EPP. This often requires restrictions in lifestyle and employment, and significantly impairs quality of life [39]. Topical sunscreens that absorb UV-A and occlusive sunblocks may be helpful. β-carotene may afford some protection after 1–3 months of therapy, but results are variable. Originally approved as a drug for treating EPP, β-carotene is now available without a prescription as Lumitene™ (Tishcon) a high quality nutritional product that may prevent photosensitivity by quenching activated oxygen radicals [58, 59]. A daily dose of 120–180 mg or higher is recommended to achieve a serum β-carotene level of 600–800 μg/dL [60]. Oral cysteine may also quench excited oxygen species and increase sunlight tolerance in EPP [61]. Other treatments that aim to either increase skin pigmentation or scavenge activated oxygen species have been reviewed [59, 62]. An α-melanocyte-stimulating hormone analogue that increases skin melanin is in clinical trials as a treatment for EPP [63]. Because patients limit their exposure to sunlight, vitamin D supplementation is recommended. Unfortunately, it is not possible to identify patients at risk for development of protoporphyric hepatopathy. But it is advisable to avoid alcohol and hepatotoxic drugs, agents that impair hepatic excretory function, iron deficiency as assessed by serum ferritin, and severe caloric restriction. Hepatitis A and B vaccination and yearly monitoring of liver function tests and erythrocyte and plasma porphyrin levels are also recommended [36, 64, 65].

Protoporphyric hepatopathy may resolve if another reversible cause of liver dysfunction, such as viral hepatitis or alcohol, is contributing [50, 66]. Medical treatment can bridge patients to liver transplantation and sometimes leads to resolution of an acute episode. Plasmapheresis and hemin can lower plasma porphyrin levels [67], and red blood cell transfusions are used to correct anemia [68], and reduce marrow protoporphyrin production. Cholestyramine [35, 69, 70], ursodeoxycholic acid [71], and vitamin E are also recommended [36]. Acute motor neuropathy may develop before or after liver transplantation, and is potentially reversible [53, 72, 73].

Liver transplantation is as successful in protoporphyric hepatopathy as in other liver diseases, even though the disease may recur in the new liver [74–76]. Because impaired liver function further elevates plasma protoporphyrin levels, these patients are subject to severe phototoxic damage to the exposed skin and visceral surfaces from operating room lights, which can be ameliorated with special filter membranes [77].

Bone marrow transplantation can achieve remission in human EPP [78, 79] as well in murine models of protoporphyria [80]. But it is not yet possible to predict which patients would benefit from marrow transplantation to prevent hepatopathy. Sequential liver and bone marrow transplantation can prevent recurrence of liver disease [81]. If hepatopathy responds adequately to medical treatment, marrow transplantation to prevent recurrence can be considered [82]. Studies in mice suggest a future role for gene therapy in human EPP [23, 83].

Complications of Therapy

As noted above, avoidance of sunlight to prevent photosensitivity can lead to vitamin D deficiency. Therapeutic doses of β-carotene typically cause yellowish skin discoloration, which can be embarrassing especially for younger patients. Patients should be monitored yearly by a specialist regarding liver function, iron status, and levels of porphyrins in erythrocytes and plasma.

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Chapter 21
Acute Pancreatitis due to Hyperchylomicronemia

P. Barton Duell

Précis

1. Clinical setting: severe abdominal pain, nausea, and emesis
2. Diagnosis:

   a. History: Usually recent onset of severe abdominal pain, often after a period of increased intake of dietary fat and/or alcohol, or uncontrolled diabetes. Episodes also can be provoked by the recent addition of triglyceride-raising medications such as oral estrogen therapy, beta-adrenergic blockers, or corticosteroids in patients with baseline hypertriglyceridemia. Some patients may have a history of recurrent bouts of abdominal pain and/or transient outbreaks of small pimple-like lesions (i.e., eruptive xanthomas) on their trunk and extremities.

   b. Physical Examination: Abdominal tenderness often with peritoneal signs, eruptive xanthomas (sometimes present only on the buttocks), lipemia retinalis. Blood may appear lipemic ex vivo. Fever, diaphoresis, hypotension may be present depending on the severity of illness.

   c. Laboratory values: Plasma triglyceride concentrations >2,500–3,000 mg/dL are usually required to cause acute pancreatitis, but the triglyceride concentration can drop by more than 1,000 mg/dL per day if the patient is NPO with nausea and emesis for 1–2 days prior to presentation. Whole blood will appear lipemic like tomato soup; plasma or serum will have the appearance of whole milk or cream depending on the severity of hypertriglyceridemia. Pseudohyponataremia, pseudohemogloginemia, pseudohypoxemia, pseudohyperbilirubinemia, falsely normal amylase concentrations, and thyroid hormone abnormalities may be found during chylomicronemia. Clarification of

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plasma or serum by ultracentrifugation will correct most of these abnormalities. Hyperglycemia and hypothyroidism need to be identified and treated. Other laboratory abnormalities related to complications of pancreatitis are often seen (e.g., hypocalcemia, hypoalbuminemia, anemia).

d. Imaging: Abdominal CT imaging is useful for diagnosis and staging of pancreatitis regardless of the etiology.

3. Treatment—The primary treatment for chylomicronemia-induced pancreatitis involves making the patient NPO, giving fluid resuscitation and analgesia as needed, and waiting for plasma chylomicrons to be cleared by zero order kinetics. Plasmapheresis is sometimes considered, but the benefit is unproven. Intravenous fat emulsions should be avoided. If hyperglycemia is present, an insulin drip is indicated to reduce free fatty acid release from tissues, decrease the glucose substrate for hepatic triglyceride synthesis, and restore lipoprotein lipase (LPL) activity. Patients with hypothryoidism need to receive thyroid hormone replacement. Non-fat or very low fat foods should be provided when the patient begins oral nutrient intake. Lipid-lowering medications normally do not serve a role in the acute management of pancreatitis and may have increased toxicity in acutely ill patients, but are often required in the long-term management of this condition. Treatment of complications of pancreatitis, such as pancreatic hemorrhage or pseudocyst formation, is the same as in other forms of pancreatitis.

Acute Pancreatitis due to Hyperchylomicronemia

Pancreatitis is a life-threatening complication of severe hypertriglyceridemia, usually associated with plasma triglyceride concentrations >2,000–3,000 mg/dL. Hypertriglyceridemia is the third most common cause of pancreatitis, following gallstones and alcohol [1, 2], but alcohol intake is often a contributor to hypertriglyceridemia and may precipitate pancreatitis through direct toxicity and indirectly through aggravation of hypertriglyceridemia. Rapid diagnosis and treatment of triglyceride-induced pancreatitis is important to improve patient survival and avoid complications.

Most patients who develop triglyceride-induced pancreatitis have an underlying genetic disorder of triglyceride metabolism that is aggravated by other factors, resulting in severe hypertriglyceridemia. Under optimal conditions, the genetically susceptible patient may have fasting triglyceride concentrations as low as 150–500 mg/dL, which are insufficient to cause pancreatitis. When additional aggravating factors are superimposed on the platform of baseline hypertriglyceridemia, the ensuing progressive accumulation of chylomicrons in plasma can lead to triglyceride concentrations sufficient to cause pancreatitis. In contrast, an individual with normal triglyceride metabolism may experience modest hypertriglyceridemia in response to the superimposition of factors that aggravate hypertriglyceridemia, but very rarely will achieve plasma triglyceride concentrations >600–800 mg/dL.

Accordingly, the identification of triglyceride-induced pancreatitis is usually a marker for an underlying genetic predisposition for hypertriglyceridemia in combination with one or more aggravating factors responsible for secondary hypertriglyceridemia. It is important for the clinician to carefully scrutinize the patient history so they can identify and treat all of the precipitating factors that may be operative in patients with triglyceride-induced pancreatitis.

Triglyceride Metabolism

Triglycerides consist of a glycerol backbone covalently bound to three triglyceride molecules. They are an important form of energy storage as well as a source of fatty acids for synthetic function and energy production. Being insoluble in aqueous solutions, triglycerides are packaged with phospholipids, cholesteryl esters, cholesterol, and apoproteins in lipoprotein particles for transport in plasma. Chylomicrons and very low density lipoproteins (VLDL) carry the majority of triglycerides in plasma. Chylomicrons are produced from dietary fat and cholesterol via the exogenous pathway and VLDL are secreted by the liver via the endogenous pathway. Both deliver fatty acids to peripheral tissues as well as transporting other cargo such as some fat-soluble vitamins and other lipid and apoprotein moieties.

Although all of us undergo transient periods of chylomicronemia after ingestion of dietary fat, the term chylomicronemia usually refers to the presence of chylomicrons in plasma or serum after fasting for more than 10–12 h. Hyperchylomicronemia may be a more precise term for pathological chylomicronemia, but the term chylomicronemia is often sufficient because chylomicrons are normally absent from plasma after fasting overnight. The half-life of chylomicrons in plasma is normally minutes, but the slow intestinal uptake of dietary triglycerides and secretion of chylomicrons into the circulation via the thoracic duct produces peak postprandial triglyceride concentrations after 3–4 h in normal individuals with a return to baseline after 6–8 h (Fig. 21.1). The amount of fat ingested is an important determinant of postprandial excursions in plasma triglyceride concentrations (Fig. 21.1), as is the fasting plasma triglyceride concentration. Among patients with disorders of triglyceride clearance, the peak in postprandial plasma triglyceride concentrations may be delayed to 6–8 h and baseline levels may not be reached for 8–12 h or longer, as shown in Fig. 21.2. These individuals also experience a more dramatic rise in peak postprandial triglyceride levels and larger area under the curve in response to a high fat load (Fig. 21.2), which emphasizes the need for restriction of dietary fat intake in these individuals. Chylomicrons are almost always present in plasma when the fasting plasma triglyceride concentration is >1,000 mg/dL, and usually absent when the fasting triglyceride concentration is below this concentration [3].

Chylomicrons are large triglyceride-rich lipoprotein particles that have a diameter of 80–500 nm, a composition that is about 85 % triglycerides, a single molecule of apo B-48 (the truncated form of apo B containing 48 % of the sequence of apo B-100), and variable amounts of apo A-I, apo A-II, apo A-IV, apo C-I, apo C-II, apo

Postprandial Changes in Plasma Triglycerides After
Dietary Fat Ingestion in Normal Individual
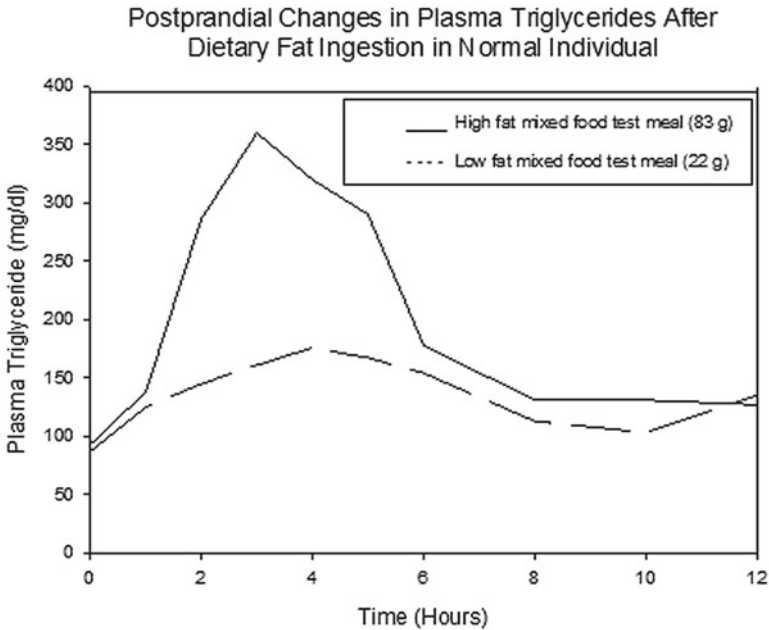
Fig. 21.1 Postprandial changes in plasma triglycerides in a normal individual. The high fat test meal providing 83 g of fat caused a tripling in the plasma triglyceride concentration at 3 h, whereas the low fat meal providing only 22 g of fat caused a minimal excursion in the plasma triglyceride concentration. This demonstrates the significant impact of dietary fat ingestion on plasma triglyceride concentrations

C-III, apo E, and other apoproteins [4]. During dietary fat absorption, triglycerides are hydrolyzed in the intestinal lumen to facilitate uptake of fatty acids by enterocytes. The enterocyte subsequently re-esterifies the intracellular fatty acids to form triglycerides, which are packaged with apo B-48, phospholipids, cholesteryl esters, and cholesterol to form chylomicrons. Chylomicrons are slowly released into circulation via the thoracic duct, making them available for utilization by various tissues. After secretion into the blood, chylomicrons acquire apo C-II primarily from high-density lipoprotein (HDL) particles. The acquired apo C-II is a cofactor for LPL, a key triglyceride hydrolyzing enzyme that is present on the luminal plasma membrane of vascular endothelial cells and is essential for triglyceride clearance. LPL interacts with chylomicrons and VLDL particles on the surface of endothelial cells through interactions with proteoglycans and glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1), thereby catalyzing release of fatty acids for uptake by adjacent cells [5]. The resulting chylomicron and VLDL remnants that remain after partial triglyceride depletion are cleared by the liver, but a proportion of chylomicron and VLDL remnants can be deposited in the artery wall, leading to atherosclerotic plaque formation. Accumulation of elevated concentrations of remnant lipoproteins in plasma is a risk factor for atherosclerotic vascular disease.
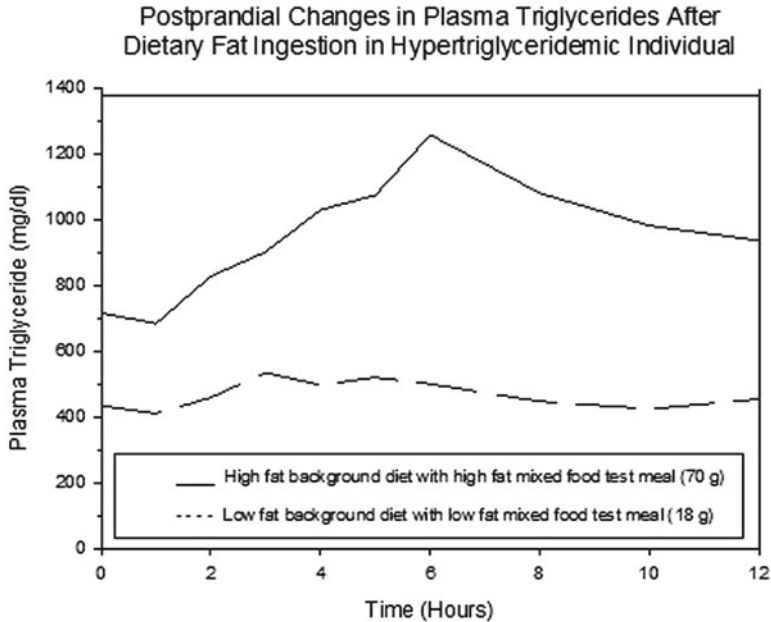
Fig. 21.2 Postprandial changes in plasma triglycerides in a typical hypertriglyceridemic individual. In contrast to the data shown in Fig. 21.1, hypertriglyceridemic individuals have higher fasting plasma triglyceride concentrations, a greater postprandial increase in the plasma triglyceride concentration, a delay in reaching the postprandial peak, and prolongation of the time to return to baseline levels. The incremental area under the curve for the high fat meal is about fourfold higher than the area under the curve shown in Fig. 21.1. Consumption of the low fat background diet for 7 weeks was associated with a 40 % reduction in the fasting plasma triglyceride concentration as a consequence of decreased input of chylomicrons. The low fat test meal caused a minimal excursion in the plasma triglyceride concentration. This demonstrates the benefit of chronic restriction of dietary fat intake in patients with marked hypertriglyceridemia

Genetic or primary causes of hypertriglyceridemia are shown in Table 21.1. Familial combined hyperlipidemia is one of the more common primary causes of hypertriglyceridemia, occurring in about 1 in 100 individuals and typically being associated with overproduction of apo B and VLDL [4, 6]. Familial hypertriglyceridemia is also relatively common. Type III hyperlipidemia, also known as dysbetalipoproteinemia, is seen in only 1 in 5,000–10,000 individuals and is usually associated with homozygosity for apo E2, a ligand that has reduced receptor affinity, resulting in accumulation of remnant lipoproteins in plasma. Apo E2 homozygosity alone does not cause hyperlipidemia, but the addition of a disorder of VLDL and triglyceride overproduction causes the dyslipidemia to be manifested. LPL deficiency is a rare condition occurring in about 1 in 10^6 individuals that is often associated with pancreatitis, typically presenting in childhood. This condition in the context of normal or increased dietary fat intake is sufficient to produce severe hypertriglyceridemia and pancreatitis. Restriction of dietary fat intake is the

Table 21.1 Genetic causes of hypertriglyceridemia

Disorder	Estimated Prevalence	Inheritance
Familial combined hyperlipidemia	1:100–200	Dominant
Familial hypertriglyceridemia	1:200–500	Dominant
Type III hyperlipidemia	1:5,000–10,000	Usually recessive
Lipoprotein lipase deficiency	$1:10^6$	Recessive
Apo CII deficiency	Rare	Recessive
Apo A-V deficiency	Rare	Recessive
Glycosylphosphatidylinositol-anchored High-density lipoprotein-binding Protein 1 (GPI-HBP-1) deficiency	Rare	Recessive

primary and essential intervention because the central defect is an inability to clear triglycerides from plasma due to LPL deficiency.

Chylomicronemia is a highly dynamic process that can change in severity over hours to days in response to external or internal aggravating factors superimposed on a genetic or acquired susceptibility to hypertriglyceridemia. These aggravating factors are causes of secondary hypertriglyceridemia (Table 21.2) that influence the production of triglycerides and triglyceride-rich lipoproteins, the catabolism of lipoproteins and clearance of triglycerides, or both production and clearance of triglycerides. As noted above, one or more aggravating factors often are required in addition to underlying genetic susceptibility to produce severe hypertriglyceridemia and chylomicronemia. Conditions such as diabetes or hypothyroidism tend to cause more chronic increases in plasma triglyceride concentrations, but other factors such as acute increases in intake of dietary fat and/or alcohol can lead to severe hypertriglyceridemia and precipitation of pancreatitis over a period of days. Similarly, acute decompensation of glycemic control can produce severe hypertriglyceridemia during a relatively short time span. The addition of triglyceride-raising medications such as prednisone or oral estrogen can potentially precipitate severe hypertriglyceridemia and pancreatitis over a period of days to weeks. The most common aggravating factors are increases in intake of alcohol and fat, particularly in combination with hyperglycemia.

Uncontrolled diabetes causes hypertriglyceridemia through several mechanisms that are relevant to the therapeutic interventions required for treatment of triglyceride-induced pancreatitis [7]. First, glucose is a substrate for triglyceride synthesis in the liver, so hyperglycemia drives hepatic triglyceride overproduction. Second, deficient insulin action in the adipocyte allows excess lipolysis of stored triglycerides, resulting in increased flux of free fatty acids to the liver and stimulation of hepatic triglyceride overproduction. Third, insulin is needed for maintenance of full LPL activity on the endothelial surface, so absolute or relative insulin deficiency is associated with a reduction in LPL activity, thereby diminishing the capacity for triglyceride clearance. The combination of these factors results in overproduction and decreased clearance of triglycerides, but these adverse conditions can be ameliorated by insulin administration and correction of hyperglycemia. Alcohol intake also drives triglyceride overproduction and impairs triglyceride catabolism.

Table 21.2 Causes of secondary hypertriglyceridemia

Category	Condition
Dietary	Excess calories
	Excess dietary fat in individuals with disorders of triglyceride overproduction and clearance (Excess carbohydrate can modestly elevate triglyceride levels in normotriglyceridemia individuals)
Endocrine	Insulin deficiency (relative or absolute)
	Hyperglycemia (diabetes and impaired glucose tolerance)
	Hypothyroidism
	Obesity (can be more severe during weight gain)
	Lipodystrophy
	Cushing syndrome
	Acromegaly
	Some glycogen storage diseases
Drugs	Alcohol
	Glucocorticoids
	Oral estrogen and estrogen analogues/SERMs
	Older beta-adrenergic blockers
	Thiazides
	Retinoic acid derivatives
	Newer antipsychotic medications (e.g., risperidol)
	Protease inhibitors and HAART regimens for HIV
	Immunosuppressants (e.g., sirolimus)
	Bile acid sequestrants
Other	Renal insufficiency/failure
	Proteinuria/nephrotic syndrome
	Pregnancy
	Dysglobulinemia (e.g., in lupus and multiple myeloma)
	Acquired apo C-III excess (blocks hepatic uptake of remnants and may impair LPL activity)

Mechanism of Chylomicron-Induced Pancreatitis

The mechanism by which chylomicronemia causes pancreatitis is unclear, but it is believed to be related to pancreatic cytotoxicity mediated by free fatty acids and lysolecithin that are produced by pancreatic lipases from excess amounts of chylomicrons in pancreatic capillaries [8]. Hyperviscosity due to hyperchylomicronemia has also been proposed. Surprisingly, not all patients with severe hypertriglyceridemia develop pancreatitis, with some patients remaining completely asymptomatic despite plasma triglyceride concentrations as high as 9,000–10,000 mg/dL. This suggests that there are genetic factors or other variables that influence the susceptibility to chylomicron-induced pancreatitis. Several genetic factors have been identified that increase the risk of pancreatitis in patients without hypertriglyceridemia, such as polymorphisms in the cationic trypsinogen gene, cystic fibrosis transmembrane regulator (CFTR) gene, and pancreatic secretory trypsin inhibitor gene (PST1) [9],

but these factors may also synergistically influence the susceptibility of patients to triglyceride-induced pancreatitis. Miniature Schnauzer dogs are an animal model that is predisposed to develop hypertriglyceridemia and pancreatitis, which may be related to an increased prevalence of homozygosity for mutations in pancreatic secretory trypsin inhibitor gene (referred to as SPINK1 in dogs) [10]. In a Chinese population, a mutation in the gene for CFTR and polymorphisms in the tumor necrosis factor (TNF) promoter were both associated with the risk of triglyceride-induced pancreatitis [11].

Clinical Presentation

Patients with triglyceride-induced pancreatitis often present with the same symptoms and signs as patients with other etiologies of pancreatitis [2], but there may be additional history and physical findings that suggest the diagnosis of chylomicronemia. Symptoms of pancreatitis typically involve an acute onset of sharp abdominal pain with possible radiation to the back, nausea, and emesis. Some patients may have indolent symptoms with recurrent episodes of abdominal pain and nausea over months prior to presenting with acute illness. Since the nausea and abdominal pain can lead to decreased oral intake of calories and fat, the change in dietary habits can be sufficient to temporarily reduce the severity of hypertriglyceridemia and result in resolution of symptoms, averting the development of overt pancreatitis. Specific questioning may yield a history of increased intake of fatty foods and alcohol during the days prior to presentation. An example of this that may be seen during Summer months is a high intake of hot dogs, hamburgers, potato chips, and potato salad (all high in fat) in combination with excess beer at weekend picnics. Patients also need to be questioned about all medications with a focus on agents that may aggravate hypertriglyceridemia. Some patients may forget to mention, for example, a recent prescription for a short course of prednisone. Diabetic patients may report a recent exacerbation of hyperglycemia, possibly related to infection, changes in dietary habits, or changes in diabetes medications. Uncontrolled diabetes and alcohol intake may account for 50–75 % of cases of triglyceride-induced pancreatitis [12]. Patients with chylomicronemia may also have symptoms of dyspnea, paresthesias of the hands, peripheral neuropathy, and reversible memory impairment and cognitive dysfunction.

Physical findings in patients with all etiologies of pancreatitis who seek emergency care typically include tachycardia, possible hypotension, and abdominal pain with rebound tenderness. Lipemia retinalis, the presence of retinal blood vessels with the coloration of creamy tomato soup instead of the usual dark red appearance (Fig. 21.3), is definitive evidence of chylomicronemia, but the retina is often not examined in acutely ill patients. This physical finding is often identified retrospectively after the diagnosis of chylomicronemia has been made. An alternative assessment is a visual inspection of the patients' plasma after centrifugation or sitting for 20–60 min. Because of their large size, chylomicrons in plasma cause light

Baseline Plasma Triglyceride   Post-Treatment Plasma Triglyceride
Concentration > 5000 mg/dl   Concentration < 200 mg/dl
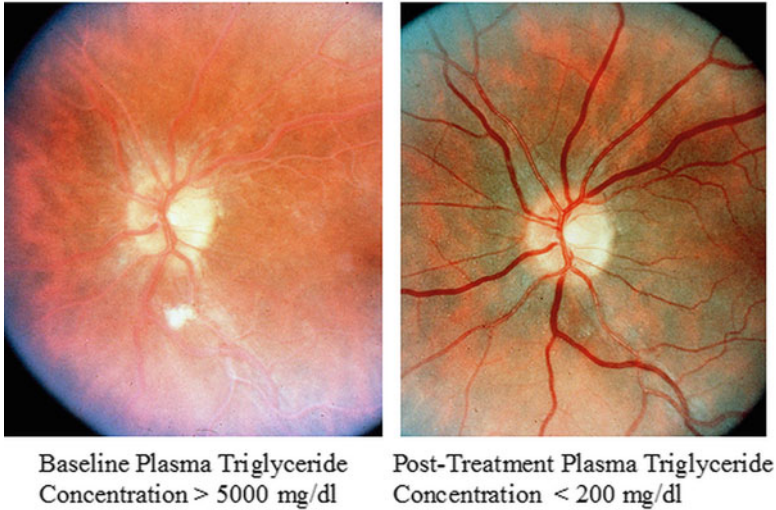
Fig. 21.3 Lipemia Retinalis before and after treatment of chylomicronemia (photo provided by the late Edwin L. Bierman)

scattering producing the appearance of turbidity. Plasma with a triglyceride concentration of 500 mg/dL will usually appear turbid and plasma with a triglyceride concentration of 1,000 mg/dL will have an appearance similar to skim milk. At a triglyceride concentration of 2,000 mg/dL, the plasma will appear more latescent, and at levels >4,000–5,000 mg/d the plasma will appear creamy (Fig. 21.4). Accordingly, the visual identification of creamy plasma or serum is sufficient to make the diagnosis of severe hypertriglyceridemia prior to the availability laboratory results. With experience, the plasma triglyceride concentration can be estimated on the basis of the severity of latescence of plasma (Fig. 21.5).

Patients with chylomicronemia may have additional physical findings of eruptive xanthomas (Fig. 21.6), hepatomegaly resulting from hepatic steatosis, and possible splenomegaly or splenic firmness. Eruptive xanthomas are cutaneous accumulations of triglyceride-laden macrophages and extracellular lipid that have the appearance of small painless raised pimples, sometimes with an erythematous base. They occur most commonly on the back and buttocks, and sometimes on the neck and other extensor surfaces, but rarely on the palms, soles, or face. Patients with type III hyperlipidemia may have palmar xanthomas, which consist of a yellowish waxy coloration of the palmar creases (Fig. 21.7), and tuberoeruptive xanthomas, which occur on the elbows and extensor surfaces and consist of bulbous tuberous xanthomas surrounded by eruptive xanthomas (Fig. 21.8) [13].

Routine diagnostic testing in the setting of pancreatitis includes a chemistry battery, amylase and or lipase, and complete blood count. Abdominal ultrasonography or CT imaging also may be performed, as well as an ECG. Laboratory testing specifically related to the chylomicronemia should include measurements of plasma triglycerides and cholesterol, plasma glucose, HgbA1c, TSH, free T4, and

Fig. 21.4 Appearance of
normal and chylomicronemic
plasma after blood standing
for 60 min without
centrifugation. The plasma on
the left has a normal
triglyceride concentration
<150 mg/dL and the plasma
on the right has a triglyceride
concentration of 5,600 mg/dL

| 150 | 500 | 1000 | 1500 | 2000 | 3000 | 4000 | 5000 | 10,000 | 14,000 |

Plasma Triglyceride Concentration (mg/dl)
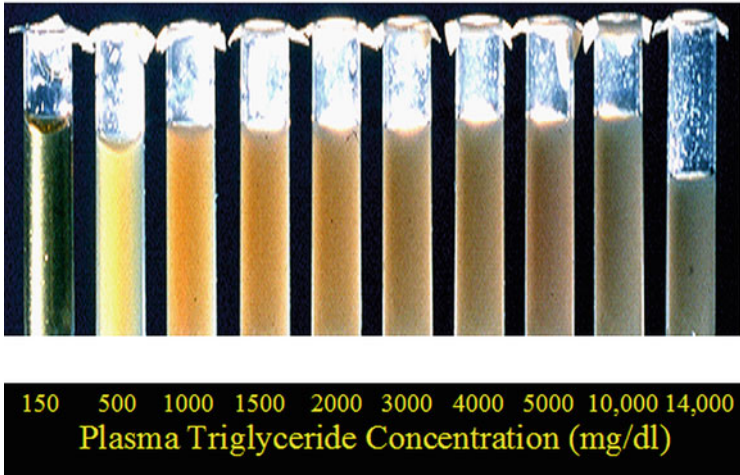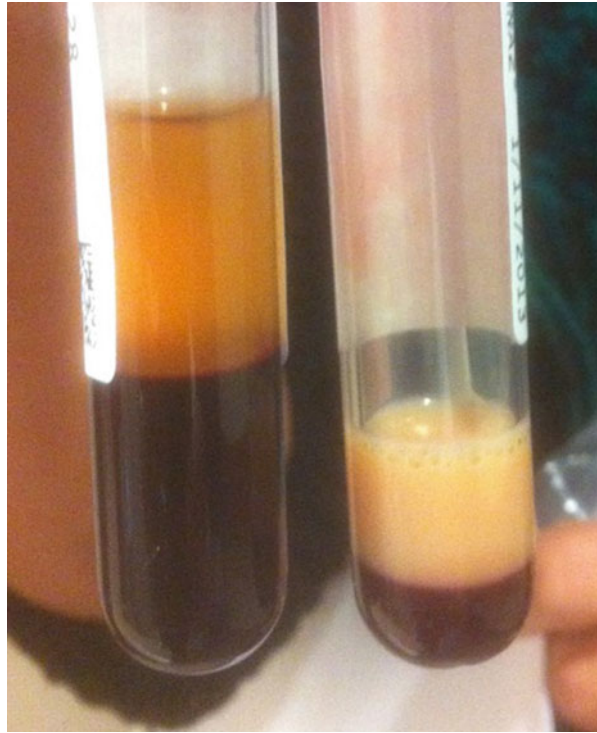
Fig. 21.5 Visual assessment of plasma triglyceride concentrations. The presence of mild turbidity
is indicative of plasma triglyceride concentrations >500 mg/dL, as shown in the second tube from
the left. The third tube has an appearance of skim milk and contains 1 % fat. The last two tubes
have the appearance of whipping cream and contain 10 % and 14 % fat, respectively
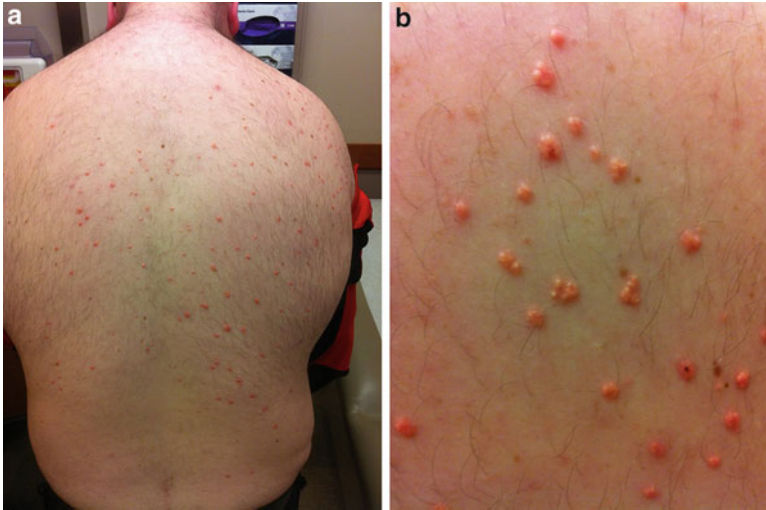
Fig. 21.6 (**a**) Eruptive xanthomas on back of a patient. (**b**) Close-up view of eruptive xanthomas

Fig. 21.7 Palmar Xanthomas

urinalysis for detection of proteinuria. Measurements of low density lipoprotein (LDL) cholesterol are unimportant in the acute setting and typically are very low because of the derangement of lipid metabolism. Pseudohyponataremia, pseudohemogloginemia, pseudohypoxemia, pseudohyperbilirubinemia, falsely normal amylase concentrations, and spurious thyroid hormone abnormalities may be found in association with chylomicronemia, but clarification of plasma or serum by ultracentrifugation will alleviate most of these abnormalities. The sodium concentration in non-clarified plasma may artifactually drop by 2–4 mEq/L for each 1,000 mg/dL

Fig. 21.8 Tuberoeruptive Xanthomas on the Elbows

increase in the plasma triglyceride concentration because of the volume of plasma displaced by chylomicrons [14].

Occasionally, patients with pancreatitis will have plasma triglyceride concentrations less than the 2,000 mg/dL threshold that is generally thought to be required to precipitate pancreatitis. In some of these cases, the self-imposed starvation and cessation of dietary fat intake resulting from nausea and emesis may have been sufficient to reduce the plasma triglyceride concentration from higher levels to <2,000 mg/dL. Under these conditions, the plasma triglyceride concentration can sometimes decrease by ≥1,000 mg/dL daily.

Treatment

In the acute phase, most aspects of treatment are the same as for other forms of pancreatitis. Acutely ill patients are typically admitted to the intensive care unit for close monitoring for complications. Patients are made NPO, IV hydration is provided, appropriate analgesia is administered, and precipitating factors are identified and corrected. Imaging of the abdomen, commonly by computed tomography, is indicated for evaluation of possible hemorrhagic pancreatitis and/or pseudocyst formation.

Additional measures are required for patients with chylomicronemia-induced pancreatitis. If hyperglycemia is present, initiation of an insulin drip is indicated to help restore euglycemia, suppress lipolysis in adipocytes, and facilitate restoration of LPL activity. The effects of insulin on lipolysis take longer than the

Fig. 21.9 Time course of resolution of hypertriglyceridemia. Representative time course of changes in plasma triglycerides over time showing rapid resolution of hypertriglyceridemia in response to zero fat intake and treatment of hyperglycemia with insulin in a patient with chylomicronemia-induced pancreatitis and uncontrolled diabetes

glucose-lowering effects of insulin, so coadministration of a glucose infusion can be initiated to allow continuation of the insulin drip after glucose levels approach normal. The improvement in LPL activity can take weeks to accrue in response to long-term insulin therapy. Administration of insulin probably has minimal benefit in patients who do not have hyperglycemia or insulin insufficiency.

The cessation of fat intake during the acute phase of treatment also needs to include avoidance of intravenous fat emulsions because these preparations are cleared from plasma similarly to chylomicrons. Triglyceride-lowering medications are often initiated during the acute illness, but these drugs are often unnecessary because the plasma triglyceride concentration can decrease by 1,000–2,000 mg/dL daily in response to being NPO with no fat intake in combination with insulin treatment in hyperglycemic individuals (Fig. 21.9). Since triglyceride clearance pathways are saturated in the setting of chylomicronemia, and triglyceride-lowering medications suppress triglyceride production more than they increase triglyceride clearance [15], administration of triglyceride-lowering medications may not significantly accelerate the resolution of chylomicronemia. Moreover, medications such as fibrates and niacin can cause hepatotoxicity and muscle toxicity, effects that are more frequent in the acutely ill patient, so we prefer to delay initiating these medications until after the acute illness resolves.

It has been proposed that plasmapheresis may be helpful in the management of chylomicron-induced pancreatitis [2]. This is a logical consideration because plasmapheresis can rapidly clear chylomicrons from plasma, thereby reducing the mass of pancreatitis-causing chylomicrons, but the results of clinical trial data have not demonstrated clear benefit of this intervention. The primary support comes from case reports and uncontrolled case series, which are insufficient to demonstrate benefit from plasmapheresis. The results of one large case series compared the outcomes of hypertriglyceridemic pancreatitis in 34 patients treated prior to the availability of plasmapheresis at their hospital versus 20 patients treated after plasmapheresis became available [16]. The results showed no differences in complications or mortality between the two groups, suggesting that plasmapheresis did not provide clinical benefit [16]. The requirement for dual venous access and an extracorporal blood volume of several hundred milliliters can add risk in an acutely ill patient. At this time it is unclear whether plasmapheresis actually improves patient outcomes.

Although heparin was recognized long ago as a plasma clearing factor in hypertriglyceridemic patients [17], the administration of heparin during acute pancreatitis may not appreciably increase LPL activity and it can significantly increase the risk of hemorrhagic complications. Therefore, heparin is not indicated in the acute treatment of triglyceride-induced pancreatitis.

The chronic phase of treatment requires major lifestyle modifications by the patient. As the patient begins to recover and food intake is initiated, dietary fat intake should be restricted to <10 % of energy intake, which is easy to regulate in the hospital. As the patient prepares for discharge, it may be possible to liberalize the dietary fat intake, but the goal of <10–20 % of energy should be emphasized. Although the low fat diet may initially be unpleasant or difficult for the patient, many acclimate well to low fat eating over time, particularly when they understand the importance of this intervention in avoiding recurrent pancreatitis. Alcohol intake also needs to be restricted or eliminated. Regular exercise is an important component of the outpatient treatment regimen, which helps reduce hyperglycemia, improves insulin sensitivity, lowers plasma triglycerides, and facilitates weight loss. Efforts to achieve sustainable weight loss are indicated in overweight and obese patients, but weight regain needs to be avoided because it can cause rebound hypertriglyceridemia. Lifestyle modification is the cornerstone for weight loss, but pharmacologic treatment can be considered for patients with BMI >27–30 kg/m^2 and bariatric surgery is a consideration for patients with BMI >35–40 kg/m^2. Evaluation and counseling by a dietitian is invaluable in this endeavor. Patients are usually highly motivated to make changes immediately after hospitalization for acute pancreatitis, so the opportunity should be seized to maximize patient education and implementation of essential lifestyle changes. Unfortunately, motivation and compliance tend to wane during the months after discharge, so close follow-up of the patient with reinforcement of positive lifestyle habits helps the patient to persevere in the difficult task of maintaining healthy lifestyle attributes.

Pharmacologic treatment of the hypertriglyceridemia and associated conditions is often also needed in addition to lifestyle modification [6]. An exception to this is the rare condition of LPL deficiency (and related conditions with loss of LPL activity) in

Table 21.3 Medications for treatment of hypertriglyceridemia

Fibrates	Gemfibrozil
	Fenofibrate
	Fenofibric acid
Niacin	OTC nicotinic acid
	OTC slow or intermediate release nicotinic acid
	Prescription intermediate release nicotinic acid (Niaspan)
Fish oil	OTC fish oil
	Prescription concentrated distilled ethyl esters of EPA + DHA (Lovaza)
	Prescription purified EPA (Vascepa)

Statins (only modestly effective for triglyceride lowering)

which avoidance of dietary fat is the key intervention and triglyceride-lowering medications provide only minimal efficacy [18]. In response to lifestyle changes the fasting plasma triglyceride concentration may decrease to 200–800 mg/dL. Rarely, patients may achieve a normal triglyceride concentration <150 mg/dL, but persistent hypertriglyceridemia is the norm. Identification and correction of secondary hyperlipidemia is an important first step (Table 21.2). Attention should include a focus on control of hyperglycemia in diabetic patients and titration of thyroid hormone replacement in hypothyroid patients.

Several medications are helpful in the treatment of hypertriglyceridemia [18] (Table 21.3). Fibrates are PPAR-alpha agonists that reduce triglyceride synthesis and can help increase LPL activity. Gemfibrozil is the oldest fibrate that is currently available and has been shown to prevent CHD events in the Helsinki Heart Study [19] and the VA-HIT study [20]. Fenofibrate is a newer fibrate that showed a reduction in CHD events in the FIELD trial, but only after adjusting for the important confounding effect of statin use in the placebo arm [21]. Both drugs are useful for treatment of hypertriglycerideamia, but fenofibrate has fewer drug–drug interactions, particularly in combination with statins [15]. Fenofibric acid has effects that appear to be comparable to fenofibrate, since fenofibrate is rapidly converted to fenofibric acid after ingestion, but the brand name Trilipix is FDA-approved for use in combination with statins. Niacin is the best all-around lipid-altering medication, but side-effects such as flushing and aggravation of hyperglycemia or gout can be limiting factors. Niacin is the best agent for raising HDL cholesterol levels, the only agent for lowering lipoprotein(a), and a moderately effective agent for lowering triglycerides and LDL. Despite the results of recent studies that have been misinterpreted as showing that niacin has no cardiovascular benefit, niacin unequivocally reduced the risk of myocardial infarction in the Coronary Drug Project, one of the first tests of the cholesterol hypothesis [22]. Fish oil in its various forms can be useful in the treatment of hypertriglyceridemia and is often underutilized. Eicosapentanoic acid (EPA) and docosahexanoic acid (DHA) are the active ingredients responsible for triglyceride lowering. A minimum triglyceride-lowering dose of EPA and DHA is about 2 g daily. Proper dosing is confounded by variability in the EPA and DHA content of various OTC preparations, but 6 g of typical

OTC fish oil containing 30 % EPA + DHA will provide 1.8 g of EPA + DHA, which is a starting dose. Lovaza is a prescription preparation of distilled, purified, and concentrated ethyl esters of EPA and DHA that comprise 84 % of the mass of the product. The FDA-approved dose is 4 g daily, which provides about 3.4 g of EPA + DHA. The FDA recently approved Vascepa, a fish oil preparation containing EPA without DHA, which may have the advantage of avoiding the modest increases in LDL cholesterol that may occur during treatment with the combination of EPA + DHA. Statins are second-line drugs for the treatment of hypertriglyceridemia because they may lower the triglyceride concentration by only 25–35 %, which is less than the 30–50 % reduction that can be achieved with the other medications. Combination therapy with two or more drugs may be required for patients who have severe residual hypertriglyceridemia.

Summary

In summary, chylomicronemia-induced pancreatitis is a potentially life-threatening condition that warrants emergency treatment. Most patients with this problem have an underlying genetic disorder of triglyceride metabolism on which is superimposed one or more forms of secondary hypertriglyceridemia, commonly related to uncontrolled diabetes, alcohol intake, and excess dietary fat intake. Patients with chylomicronemia-induced pancreatitis present with symptoms and signs that are similar to other patients with pancreatitis, but they also can have hepatosplenomegaly related to hepatic steatosis and eruptive xanthomas or tuberoeruptive xanthomas. Lipemic plasma is the hallmark of chylomicronemia that can be visualized as lipemia retinalis or ex vivo in plasma or serum. Treatment of chylomicronemia-induced pancreatitis is focused on correction of the chylomicronemia as well as reversal of the factors that may be aggravating hypertriglyceridemia. Long-term therapy requires extensive lifestyle changes, often with the addition of triglyceride-lowering drugs. A very low fat diet, avoidance of alcohol, regular exercise, and sustainable weight loss are important components of the intervention. Patients who are compliant with their treatment regimen can often avoid a recurrence of pancreatitis, but recurrent pancreatitis occurs in many patients.

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