Chapter

29 NUTRITIONAL, GASTROINTESTINAL, AND ENDOCRINE DISEASE

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NUTRITIONAL DISORDERS

Morbid Obesity

Approximately 1.9 billion people worldwide are considered overweight, which is defined as a body mass index (BMI, weight in kg/height in m^2) between 25 to 30.[1] A desirable BMI is 18 to 25. The Centers for Disease Control and Prevention report that approximately 34% of U.S. adults older than 20 years of age are overweight and 35% are obese (BMI 30 to 40).[2] Morbid obesity is defined by a BMI of 40 or more. Superobesity (BMI ≥ 50) and super-superobesity (BMI ≥ 60) are an increasingly frequent health care challenge.[3]

The morbidity associated with obesity can affect virtually any part of the body and may account for 2.5 million deaths per year. Pulmonary manifestations of obesity include a reduced functional residual capacity (with rapidly decreasing oxygen saturations during apnea), restrictive lung disease, and obstructive sleep apnea. Hypertension, stroke, and right-sided heart failure are associated with morbid obesity, as are colon and breast cancer. Increased intra-abdominal pressure may predispose to hiatal hernias and gastroesophageal reflux. Skeletal diseases are also common, including back pain and osteoarthritis, particularly affecting the knees. Endocrine abnormalities may lead to reproductive hormonal imbalances and impaired fertility, and these patients may also be at increased risk for depression and other psychological illnesses.[4]

The combination of specific complications of obesity is called the *metabolic syndrome*. The metabolic syndrome has six components: abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance (glucose intolerance), a proinflammatory state, and a prothrombotic

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state. The metabolic syndrome is diagnosed by the presence of three of the five following factors: abdominal obesity, increased triglycerides, low high-density lipids, hypertension, and increased fasting blood glucose concentrations. The diagnosis and treatment are important because obesity alone predicts approximately 25% of all new-onset cardiovascular disease.[5]

The pathophysiology of morbid obesity is multifactorial and involves genetic, environmental, metabolic, and psychosocial factors. Caloric consumption is important, but the urge to eat (or overeat) can be modulated by hormones or inflammation. Treatment must be multifaceted; weight loss is not as easy as simply not eating because fasting releases several orexigenic (appetite-stimulating) hormones.[6,7]

Perioperative Considerations (Also See Chapter 13)

In the 1970s, fasted obese patients were asserted to have larger, more acidic gastric fluid volumes than nonobese patients and therefore at increased risk for pulmonary aspiration of injurious gastric contents.[8] Actually, just the opposite may be true. Nondiabetic obese patients may have a smaller volume of gastric contents with a higher pH than do lean nondiabetic patients.[9]

The care of obese patients presents several logistical issues because of their size and shape. These issues include intravenous (IV) access, noninvasive blood pressure monitoring, positioning, endotracheal intubation, and emergence techniques. Because of the amount of subcutaneous fat, insertion of a peripheral IV line may be difficult. As a result, central venous catheterization may be required for access, independent of the nature of the surgical procedure. Noninvasive blood pressure monitoring may be made difficult by the conical shape of the upper arm. Most arterial blood pressure cuffs are designed for a more cylindrical profile and may not remain in position or function correctly on a cone-shaped arm. Practical options in this situation include utilizing the forearm or inserting an arterial catheter for arterial blood pressure monitoring.

An obese patient may be wider than the horizontal surface of the operating table, and the table must be able to support the patient's weight and be able to move into positions required by the surgeon. If extreme angles of tilt are needed, the patient must be well secured and potential pressure points must be addressed.

Induction of anesthesia may be complicated by a rapid decrease of blood oxygen saturation because of a smaller functional residual capacity. Reverse Trendelenburg position (head up) can reduce atelectasis in dependent areas of the lung and may also move chest and breast tissue caudally, allowing easier access to the mouth for endotracheal intubation. Obesity may increase the risk of a difficult laryngeal intubation, especially in patients with a Mallampati airway classification score of III-IV, obstructive sleep apnea, reduced mobility of the cervical spine, and large neck circumference.[10,11]

No anesthetic drug has a distinct advantage in the obese patient, but emergence can be prolonged because elimination of some anesthetics from adipose tissues is slow. Obese patients are at risk of developing postoperative hypoxemia from atelectasis and hypercarbia due to airway obstruction. Noninvasive ventilator support in the recovery room may improve oxygenation.[12]

Bariatric Surgery

Surgical treatment of obesity was first described in 1954 with the creation of the jejunoileal bypass (JIB). The JIB was a malabsorptive operation that was used to treat many conditions ranging from hyperlipidemia and atherosclerosis to obesity. The JIB was abandoned by the 1980s because of unacceptable complications, including uveitis, kidney dysfunction, intestinal bacterial overgrowth, and liver damage.[13]

Subsequent operations were directed toward restriction of the intestinal tract with the goal of weight loss through decreased intake. Examples of commonly performed restrictive operations are the gastric bypass, gastric sleeve, and adjustable gastric band. Because of lower early postoperative morbidity and mortality rates, laparoscopic procedures are now preferred as compared to open bariatric procedures.[14] In the United States, the number of bariatric operations peaked in 2004 and has since plateaued. Use of the laparoscopic approach to bariatric surgery accounts for more than 90% of bariatric operations. In-hospital mortality rate is estimated at 0.1%.[15]

Most people who undergo bariatric procedures are morbidly obese (BMI ≥ 40), but surgical weight loss is more effective than conventional medical therapy if BMI is as low as 30.[16] Patients generally have improvements in their quality of life and a reduction in comorbid conditions and cardiovascular events (myocardial infarction and stroke).[17] Bariatric surgery improves several conditions such as hypertension, diabetes, and obstructive sleep apnea.

Appetite and insulin-regulating hormonal function may be changed by bariatric surgery, thus promoting weight loss. Ghrelin, an orexigenic hormone secreted by the gastric fundus and proximal small intestine, is increased in the face of nonsurgical weight loss, but ghrelin levels are either unchanged or decreased after bariatric procedures. Several other intestinal hormones that regulate appetite and glucose metabolism are affected more favorably by bariatric surgery than by fasting. These hormones include glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic peptide, and peptide YY, which are all secreted by the gastrointestinal tract in response to food.[18]

Malnutrition

Malnutrition occurs when caloric requirements exceed intake. Decreased intake, impaired absorption, or increased metabolic rate may cause profound malnutrition in a very

short time. Malnutrition may be present when weight loss of 10% to 20% occurs during a short period of time, when weight is less than 90% of ideal body weight, or when BMI is less than 18.5. Healthy patients may quickly become malnourished after an episode of trauma or acute illness.

Critically ill patients develop malnutrition if they are not properly fed. Feeding may take place enterally, through an enteric feeding tube, or parenterally, through an IV catheter. The preferred method of nutritional replacement usually is enteral nutrition because it maintains the absorptive villi of the gastrointestinal tract and reduces pathologic bacterial transfer across the gastrointestinal mucosa and into the bloodstream. Improved outcomes, including decreased infectious complications and fewer ventilator and intensive care unit days, have been demonstrated.[19] Long-term feeding usually requires a gastrostomy or jejunostomy tube. Postpyloric placement is frequently preferred because it is believed to reduce the potential for regurgitation and aspiration of gastric contents. However, the risk of vomiting and aspiration of gastric contents is not significantly different between postpyloric and gastric tube feeding.[20] In patients who have pancreatitis, jejunal placement helps avoid stimulation of pancreatic enzyme secretions.

IV feeding (total parenteral nutrition, or TPN) is required when the gastrointestinal tract is not functional. Peripheral parenteral nutrition may be used for brief periods, but long-term alimentation requires central venous access. TPN lacks the beneficial effects of enteral feeding on the gut and carries risks of catheter sepsis, thrombosis, hyperglycemia, iatrogenic hypoglycemia (from insulin added to the feeding solution in response to hyperglycemia), and the development of fatty liver.

Perioperative Considerations

Acute nutritional replacement in a malnourished patient may cause a refeeding syndrome, characterized by increased ATP (adenosine triphosphate) production and metabolic rate. Increased ATP production may cause a significant decrease in plasma phosphate, leading to respiratory and cardiac failure. An increased metabolic rate may cause a significant increase in CO_2 production, leading to respiratory acidosis. The refeeding syndrome can be avoided by slowly increasing the nutritional intake toward caloric goals.

In the perioperative setting malnourished patients may have muscular (including respiratory) weakness and may be immunocompromised. For severely malnourished patients, TPN or enteral feeding should be administered for 7 to 10 days prior to an elective surgical procedure as it takes several days to achieve goal-feeding levels.

An important clinical issue commonly arises for enterally fed critically ill patients (such as burn and trauma patients) who require a surgical procedure. A decision must be made regarding how long to fast such a patient prior to induction of anesthesia. The risk of pulmonary aspiration of gastric contents must be weighed against the benefit of continuing to keep the nutritional intake at the patient's goal level. Nutrition probably should be continued as long as possible. A short fast (45 minutes) from nutritional administration is reasonable when the feeding tube is located beyond the ligament of Treitz.[21] When TPN is in use, insulin is typically part of the infusion, and therefore blood glucose monitoring should be performed for procedures longer than 2 hours in duration.

GASTROINTESTINAL DISEASE

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) affects an estimated 1.4 million Americans and results from an aberrant response by the bowel mucosal immune system to normal luminal flora.[22] IBD is divided into two categories: ulcerative colitis (UC) and Crohn disease (CD). UC is restricted to the large intestine and manifests itself as inflammation and loss of colonic mucosa. CD can affect any part of the digestive tract and may cause transmural inflammation leading to abscesses or granulomatous disease. Although they are distinct entities, differentiation between the two diseases may be difficult when CD manifests itself by only affecting the colon.

The trigger for the activation of the immune system in IBD is multifactorial. Because of a genetic basis, there is an increased risk in close family members. Caucasian patients are more likely to develop IBD than other patients. Jewish patients have a more frequent risk for CD. In addition, several environmental factors including smoking, appendectomy, antibiotics, oral contraceptives, and nonsteroidal antiinflammatory drugs (NSAIDs) are associated with increased risk. Diagnosis may be suspected based on symptoms of chronic abdominal pain, fever, and diarrhea and is confirmed by endoscopy and biopsy.[23]

Although the primary mode of therapy is nonoperative, 60% to 70% of patients with IBD require surgical treatment at some point. Reasons include complications of the disease (fistulas, strictures, or toxic megacolon), complications of surgery (small bowel obstruction due to postoperative scarring), cancer prevention (colectomy in the case of UC), plus other reasons unrelated to the intestinal disease.[24]

Perioperative Considerations

CD and UC are chronic diseases that are typically managed by using up to six different classes of medications: antidiarrheal, antiinflammatory, immunosuppressant, antibiotic, anti-TNF (tumor necrosis factor), and other investigational

drugs. Patients who are taking steroids should continue to do so prior to surgery and may require supplementation in anticipation of adrenal insufficiency.

Specific anesthetics are neither preferred nor contraindicated for patients with IBD, but certain of their medications may have anesthetic implications. In general, potential interactions between anesthetic and antineoplastic drugs are not clear. Cyclosporine increases the minimum alveolar concentration (MAC) of volatile anesthetics.[25] Azathioprine has phosphodiesterase effects and may partially antagonize nondepolarizing neuromuscular blocking drugs. Cyclosporine and infliximab may enhance the potency of the nondepolarizing neuromuscular blocking drugs.[26] The clinical consequence of these interactions is minimal.

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) is defined as the retrograde movement of gastric contents through the lower esophageal sphincter (LES) into the esophagus. The pathophysiology of GERD involves impaired esophageal motility, LES, and gastric motility.[27] Retrograde movement of gastric contents past both the LES and the upper esophageal sphincter into the pharynx can lead to pulmonary aspiration of gastric acid and particulate matter.

GERD is an extremely common syndrome. The prevalence of GERD—defined as at least weekly heartburn or regurgitation, or both—in the United States is 18% to 28%.[28] Besides heartburn, the most common symptoms are noncardiac chest pain, dysphagia, pharyngitis, cough, asthma, hoarseness, laryngitis, sinusitis, and dental erosions.

Reflux occurs when the LES is incompetent or when LES pressure (LESP) is less than intra-abdominal (or intragastric) pressure. GERD can occur as a result of esophageal dysmotility or a hiatal hernia. In a patient with a hiatal hernia, the LES may be displaced cephalad into the thoracic cavity so that it loses the diaphragmatic contribution to LES function. The diaphragm can also obstruct the esophagus. GERD is associated with other conditions, including pregnancy, obesity, obstructive sleep apnea, gastric hypersecretion, gastric outlet obstruction, gastric neuropathy, and increased intra-abdominal pressure. The risk of pulmonary aspiration of gastric contents during induction of anesthesia in patients with GERD or the previously mentioned predisposing factors is not well established. In contrast, increased intra-abdominal (gastric) pressure and pregnancy are important risk factors. Significant GERD occurs with at least 30% to 50% of pregnant women. The mechanism is primarily a progesterone-mediated relaxation of LES tone, but there also may be contributions from delayed gastric emptying, impaired LES due to increased intra-abdominal pressure from the enlarging gravid uterus, and decreased bowel transit.[29]

Initial management of GERD usually consists of a combination of lifestyle modifications and drug therapy using medications that are moderately effective and have limited side effects. Lifestyle management includes elevating the head of the bed, eating food high in lean protein, and avoiding smoking, coffee, and foods and drugs known to relax the LES. Antacids and mucoprotective drugs may relieve symptoms. If not, further medical management includes drugs that are prokinetic and reduce gastric acid secretion.

Prokinetics minimize contact time of gastric contents with the esophagus by blocking dopamine or serotonin (5-HT [5-hydroxytryptamine]) receptors. Metoclopramide (a 5-HT receptor antagonist) can produce choreoathetosis and other extrapyramidal side effects. Histamine (H_2) receptor blockers decrease gastric acid secretion by gastric parietal cells; however, they may increase the production of gastrin and decrease LESP. In some patients, particularly the elderly (also see Chapter 35), H_2 receptor blocking drugs may cause adverse central nervous system side effects including confusion, agitation, and psychosis. Proton pump inhibitors (PPIs) are the most potent therapy for severe erosive esophagitis. Omeprazole may inhibit the metabolism and elimination of warfarin, digoxin, phenytoin, and benzodiazepines.[30]

Perioperative Considerations (Also See Chapter 13)

The customary approach to induction of general anesthesia in the patient at risk for pulmonary aspiration of gastric acid is the rapid-sequence induction (RSI) using cricoid pressure (CP) to obstruct any potential flow of gastric contents into the pharynx and trachea (also see Chapter 14). The putative benefits of the RSI and CP remain controversial. CP can be ineffective, especially if not properly applied, and can have undesired side effects including potentially increasing the risk of regurgitation and failed tracheal intubation. Furthermore, improperly performed CP sometimes might not effectively align the cricoid and esophagus with the solid cervical spine underneath. CP is not a benign procedure and can be associated

Table 29.1 Categories of Patients at Risk From Inappropriately Applied Cricoid Pressure

Patient Group at Risk	Reason
Elderly	Esophageal rupture, laryngeal obstruction
Children	Laryngeal obstruction
Parturient	May require more pressure
Laryngeal trauma	May require surgical repair after cricoid pressure
Cervical spine trauma	May displace an unstable cervical spine
Difficult airway	May worsen visualization

Modified from Brimacombe JR, Berry AM. Cricoid pressure. *Can J Anaesth*. 1997;44:414-425.

with several complications (Table 29.1). In addition, complications are more likely in the elderly, children, pregnant women, patients with cervical injury, and patients with a difficult airway and when there is difficulty palpating the cricoid cartilage.[31]

Surgical management of symptomatic reflux disease may be treated with an antireflux operation—most commonly the Nissen fundoplication in adults. This operation is typically performed laparoscopically. The Nissen fundoplication consists of reducing the herniated stomach, repairing the diaphragmatic defect, and performing a gastric wrap to prevent the stomach and LES from retracting into the thorax. Hypertension, bradycardia, high mean airway pressures, and desaturation are potential intraoperative complications and are a consequence of pneumoperitoneum and increased intra-abdominal pressure. Important postoperative events include discomfort from carbon dioxide gas accumulation under the diaphragm and postoperative nausea and vomiting. Subcutaneous air may also appear in the neck and chest. This is benign and self-limited because CO_2 gas is rapidly reabsorbed by the body. Nausea and vomiting are more serious complications associated with esophageal surgery because vomiting can lead to esophageal rupture.[32]

ENDOCRINE DISORDERS

Diabetes Mellitus

Between 1990 and 2010, the number of adults with a diagnosis of diabetes more than tripled from 6.5 million to 20.7 million. Diabetes mellitus, a disease that complicates most organ systems, is characterized by increased blood glucose concentrations due to a relative lack of endogenous insulin.[33] Previously, diabetes was classified in terms of insulin requirement (insulin-dependent versus non–insulin-dependent), but this system has proved less satisfactory because nearly all diabetics develop a need for insulin at some point. The current classification labels patients as having either type 1 (T1DM) or type 2 (T2DM) diabetes. T1DM is typically characterized by the absence of insulin production from the pancreas, whereas T2DM involves a relative lack of insulin plus resistance to endogenous insulin.

Blood glucose control is required in both types, but T1DM always requires insulin to prevent hyperglycemia, ketoacidosis, and other complications. Type 2 diabetics may require insulin, but often only require oral hypoglycemic drugs, weight loss, or dietary management. T1DM is commonly heralded at an early age by a dramatic episode of ketoacidosis. The onset of T2DM usually is more insidious. Type 2 diabetics constitute the majority and, unlike type 1 diabetics, are often overweight. Dietary control and weight loss are important in T2DM, but the cornerstone of management of both types is pharmacologic.[34]

Effectiveness of glucose control is monitored by measuring glycated hemoglobin (HbA_{1c}) levels. During hyperglycemia, glucose can permanently combine with hemoglobin in erythrocytes and form HbA_{1c}. Because erythrocytes normally have a 120-day life span, HbA_{1c} levels give an indication of how well the diabetes is being controlled over time. Normal HbA_{1c} levels are less than 6%, and risk of complications from diabetes increases with higher HbA_{1c} levels.[35]

Insulin is categorized as rapid, intermediate, or long acting. In the outpatient setting it is usually given by subcutaneous injection. For T1DM, intensive therapy consisting of three or more injections per day of basal and prandial insulin or continuous subcutaneous insulin infusion is imperative for improved glycemic control and prevention of ketoacidosis. Metformin is the preferred initial pharmacologic therapy for T2DM. Metformin reduces glucose load by decreasing hepatic production. If noninsulin monotherapy does not achieve target HbA_{1c}, the addition of a second oral agent, GLP-1 receptor agonist, or insulin is recommended.[34]

Complications are common in long-standing diabetes and result largely from microangiopathy and macroangiopathy. Diabetes is a well-recognized risk factor for large- and small-vessel coronary artery disease and was originally advanced as an indication for perioperative β-adrenergic blockade.[36] Diabetes in young and middle-aged adults is the leading cause of renal failure requiring hemodialysis. Diabetic retinopathy is characterized by a spectrum of lesions within the retina and is the leading cause of blindness among adults 20 to 74 years old. More than half of all individuals with diabetes eventually develop neuropathy, with a lifetime risk of one or more lower extremity amputations estimated to be 15%. Autonomic neuropathy occurs in 20% to 40% of patients with long-standing diabetes, particularly those with peripheral sensory neuropathy, renal failure, or systemic hypertension. Cardiac autonomic neuropathy may mask angina pectoris and obscure the presence of coronary artery disease. Gastroparesis, which may cause delayed gastric emptying, is a sign of autonomic neuropathy affecting the vagus nerves.[37]

Perioperative Considerations

A patient with well-controlled diabetes may not require special treatment before and during surgery, although reducing the morning dose of insulin by 30% to 50% in order to prevent hypoglycemia because of fasting is common and reasonable. Sulfonylurea drugs may be continued until the evening before surgery; however, these drugs may also produce hypoglycemia in the absence of morning caloric intake, so they should not be taken the morning of surgery.[38] (See Chapter 13, medications section for additional recommendations on perioperative insulin management.)

Recommendations regarding biguanides such as metformin have recently changed. The first biguanide

introduced, phenformin, was associated with lactic acidosis and was eventually replaced in clinical use by metformin. In the 1990s, a common recommendation was made for metformin to be discontinued 48 hours preoperatively to avoid risk of fatal lactic acidosis. This initial recommendation was based on individual case reports but was questioned by a subsequent meta-analysis.[39]

Perioperative hyperglycemia may result from many causes including stress-induced neuroendocrine changes, exogenous glucose administration, and a patient's underlying metabolic state. Preoperative measurement of blood glucose is usually performed prior to anesthesia; however, the desired intraoperative glucose level is not well established. Perioperative concerns include the risks of diabetic ketoacidosis, severe dehydration and coma related to the hyperosmolar hyperglycemic nonketotic state, the adverse effect of hyperglycemia on neurologic outcome after cerebral ischemia, and the increased risk of surgical wound infection. The optimal level of glucose control in the perioperative and critical care setting remains controversial. Attempts to maintain glucose levels of 81 to 108 mg/dL in critically ill patients resulted in higher rates of cardiovascular mortality and severe hypoglycemia compared to those patients in whom the level was controlled in the range below 180 mg/dL.[40-42]

Hyperthyroidism and Thyroid Storm

Hyperthyroidism, or thyrotoxicosis, is characterized by increasing circulating levels of unbound thyroid hormones triiodothyronine (T_3) and tetraiodothyronine (thyroxine, or T_4). The most common cause is Graves disease, an autoimmune condition in which thyrotropin receptor antibodies continuously mimic the effect of thyroid-stimulating hormone (TSH). However, it may also be caused by the following:[43]

- Toxic multinodular goiter
- Thyroiditis
- β-Human chorionic gonadotropin–mediated hyperthyroidism—gestational hyperthyroidism, choriocarcinoma, hydatidiform mole
- Struma ovarii, which is the presence of thyroid tissue in an ovarian teratoma
- The administration of iodinated contrast dye to a susceptible patient
- Drug-induced by amiodarone (which can lead to both hypo- and hyperthyroidism), lithium, interferon-α
- TSH secreting pituitary adenoma

The principal signs and symptoms of hyperthyroidism are cardiac, neurologic, and constitutional. Thyroid hormone increases cardiac sensitivity to catecholamines, resulting in hypertension and tachyarrhythmias. Other signs of severe hyperthyroidism include high-output congestive heart failure or angina, even in the absence of coronary plaques. Tremor, hyperreflexia, and irritability are common neurologic manifestations. Periodic paralysis, characterized by hypokalemia and proximal muscle weakness, may also occur. Fever and heat intolerance are common. Gastrointestinal symptoms include nausea, vomiting, and diarrhea as well as hepatic dysfunction and jaundice. Diagnosis is confirmed by demonstrating increased thyroid hormone levels in blood.[44]

Thyroid storm is characterized by worsening of the signs and symptoms of thyrotoxicosis, including severe cardiac dysfunction, hyperglycemia, hypercalcemia, hyperbilirubinemia, altered mental status, seizures, and coma. Thyroid storm may be triggered in a thyrotoxic patient by any of several stresses:[45]

- Infection
- Stroke
- Trauma, especially to the thyroid gland
- Thyroid and nonthyroid surgery
- Diabetic ketoacidosis
- Drugs: pseudoephedrine, aspirin, excess iodine intake, contrast dye, amiodarone
- Incorrect antithyroid drug discontinuation
- Metastatic thyroid cancer

The distinction between thyrotoxicosis and thyroid storm is one of degree, with thyroid storm being the most severe form of the disorder. All hyperthyroid patients are at risk to develop thyroid storm, which is a life-threatening emergent clinical syndrome that has approximately 30% mortality rate in spite of treatment. For this reason, the general rule regarding surgery in the setting of thyrotoxicosis or thyroid storm is to undertake only that which cannot be delayed until control of thyroid hormone secretion and effect has been accomplished, either with medical management or through ablation of the thyroid using radioiodine.

Perioperative Considerations

The initial medical treatment for hyperthyroidism is to reduce thyroid hormone synthesis. This is accomplished by administration of a thioamide such as propylthiouracil (PTU) or methimazole (MMI). PTU and MMI inhibit thyroid peroxidase (TPO), the enzyme that catalyzes the incorporation of iodide into thyroglobulin to produce T_3 and T_4. At least an hour after giving the thioamide, large doses of stable iodide may be given. This step takes advantage of a paradoxic effect, called the *Wolff-Chaikoff effect*. Rather than catalyze additional incorporation of iodide into thyroglobulin, as might be expected, large amounts of iodide suppress gene transcription of TPO, further reducing the gland's capacity to produce and release hormone. This benefit is temporary, lasting about a week.

In addition, especially in cases of thyroid storm, administration of β-adrenergic blockers reduces adrenergic symptoms. Propranolol is the β-blocker traditionally

selected because it also inhibits peripheral conversion of T_4 to the more potent hormone T_3; however, other β-adrenergic blockers such as atenolol, metoprolol, and esmolol have been used and are not contraindicated.[46] Corticosteroids can treat the relative adrenal insufficiency that results from accelerated metabolism in the context of thyroid storm. Cortisol levels tend to be in the normal range in these patients, but they should be higher to be appropriate to the level of stress. Plasmapheresis has been utilized as an adjunct method to reduce circulating thyroid hormone levels by removing T_3 and T_4 from the bloodstream.[47]

The goal of anesthesia is to avoid an increase in heart rate or sympathetic activation. Conversely, anesthetics and techniques that reduce or blunt sympathetic activity are usually favored. Ketamine would not be ideal to induce anesthesia or provide analgesia. Rather, fentanyl and its congeners would be favored for analgesia. Isoflurane, sevoflurane, and desflurane would all be useful for maintenance of general anesthesia, with the warning that high inspiratory concentrations of desflurane might not be advantageous. Regional anesthesia, when practical, might also be efficacious in avoiding sympathetic activation. Intraoperative thyroid storm may be difficult to distinguish from malignant hyperthermia. Dantrolene is beneficial in either situation and should be considered if there is suspicion of either condition.

Hypothyroidism

Hypothyroidism is characterized by decreased circulating levels of unbound thyroid hormones T_3 and T_4. Hypothyroidism may be congenital (cretinism) or acquired. The most common acquired cause in adults is Hashimoto thyroiditis, a chronic autoimmune disease characterized by progressive destruction of the thyroid gland. Medical or surgical treatment of hyperthyroidism may lead to iatrogenic hypothyroidism. Hypothyroidism after radioactive iodine treatment of hyperthyroidism occurs in at least 50% of patients within 10 years after treatment. Secondary hypothyroidism may occur as a consequence of hypothalamic or pituitary disease or after surgery on these structures. The absence of dietary iodine causes hypothyroidism and an enlarged gland ("endemic goiter").[48]

The onset of hypothyroidism usually is insidious, and the symptoms are often nonspecific. Adults may have easy fatigability, lethargy, weakness, and weight gain. The skin is usually dry and the hair brittle. In severe cases, myxedema develops and is characterized by a reduced cardiac output, attenuated deep tendon reflexes, and nonpitting pretibial edema. Untreated, hypothyroidism may progress to include electrolyte disturbance, hypoventilation, hypothermia, and coma.

Hypothyroidism may be either overt or subclinical. Overt hypothyroidism is diagnosed by measuring low T_3 and T_4 levels in blood. Primary hypothyroidism is characterized by low T_3 and T_4 levels but an elevated TSH. In secondary hypothyroidism, all thyroid-related hormones are reduced. Subclinical hypothyroidism, manifested by an increased serum concentration of TSH in combination with a normal free T_4, is present in about 5% to 8% of the American population, with a prevalence of more than 13% in otherwise healthy elderly patients, especially women.[49]

Hypothyroidism is treated with oral administration of synthetic levothyroxine, 75 to 150 μg/day. Thyroid replacement is initiated slowly because acute cardiac ischemia can develop in patients with coronary artery disease from the sudden increase in myocardial oxygen demand as the metabolism and cardiac output increase. Although IV thyroid replacement therapy is available, its use is limited to severe presentations such as myxedema coma.[48]

Perioperative Considerations

Asymptomatic mild to moderate hypothyroidism does not increase the risk of perioperative morbidity. Mildly hypothyroid patients do not possess unusual sensitivity to inhaled anesthetics, sedatives, or narcotics. Symptomatic or severe hypothyroidism in contrast should necessitate surgical delay for thyroid hormone replacement until the neurologic and cardiovascular abnormalities have resolved.

Thyroid Surgery

The most important perioperative considerations related to thyroid surgery involve physical or functional airway obstruction from tracheal compression or damage to the recurrent laryngeal nerves. Airway management is one of the primary challenges for providing safe anesthetic care to patients undergoing thyroidectomy. The potential issues are whether goiters predict difficult bag-mask ventilation, difficult laryngoscopy, and difficult endotracheal intubation. Tracheal compression may lead to the symptoms of dyspnea, wheezing, obstructive sleep apnea, or cough. Patients with thyroid enlargement should be evaluated prior to surgery for evidence of tracheal compression or deviation. Review of available computed tomography scans may reveal the size of the goiter and the resultant alteration of anatomy.[50]

There is a question as to whether tracheal compression or deviation has an impact on outcome. A prospective study reported the incidence of difficult endotracheal intubation in euthyroid patients undergoing a thyroidectomy as 5%; however, the cause of the airway difficulty was not related to the thyroid. Rather, the usual anatomic factors that predict a difficult airway in the general population were the predictors in this patient group. Independent risk factors of difficult intubation were cancerous goiter and Cormack grade III or IV view

at laryngoscopy.[51] In the presence of a cancerous goiter, tracheal invasion and tissue infiltration with associated fibrosis may reduce the mobility of laryngeal structures and impede the laryngoscopy view of the glottic opening. In patients with severe tracheal compression causing stridor, intubation of the trachea with the patient awake may be the method of choice to limit the risk of complete airway obstruction after spontaneous ventilation has been ablated. The surgical team should be prepared and ready to perform an emergent tracheotomy or rigid bronchoscopy if necessary.[52]

An important aspect of the anesthetic technique is directed at preventing coughing during emergence as a means of reducing the risk of postoperative hemorrhage. Various methods have been proposed as ways to minimize cough during emergence, including extubation during deep anesthesia and administration of the potent short-acting narcotic remifentanil, the α_2-agonist dexmedetomidine, or lidocaine. However, no single method has been proved superior.[53,54]

Postextubation airway compromise following thyroid surgery can result from an expanding wound hematoma, vocal cord dysfunction due to recurrent laryngeal nerve injury, or tracheomalacia. In the past, it was common practice to attempt to perform a direct laryngoscopy after extubation in order to confirm that both vocal cords moved normally. Many practitioners found it difficult to execute this maneuver at exactly the moment when the patient could tolerate laryngoscopy and demonstrate vocal cord mobility. This practice has not been validated as a predictor of postoperative vocal cord dysfunction and is not commonly recommended today.

Unilateral laryngeal nerve injuries from thyroid surgery produce voice impairment but are not a threat to airway function. Bilateral recurrent laryngeal nerve injury, in contrast, compromises the function of the posterior cricoarytenoid muscles, which are the muscles responsible for separating the cords during breathing. This can lead to life-threatening inspiratory airway obstruction that can only be relieved by intubation or tracheostomy. In such patients, the paralyzed vocal cords do not abduct during the respiratory cycle, and may appear apposed in the midline when seen during direct laryngoscopy.

Some surgeons request the use of a laryngeal nerve monitoring endotracheal tube during thyroid surgery as a putative safety measure to prevent inadvertent injury to the laryngeal nerves. These specialized endotracheal tubes have electrodes that are positioned in the immediate vicinity of the vocal cords and send an electromyographic signal to a receiver whenever the vocal cords contract. As a result, if the surgeon stimulates a laryngeal nerve either by retracting it or by using an electrocautery close to it, an audible signal provides a warning.[55]

Pheochromocytoma and Paraganglioma

Tumor overproduction of any of the adrenal medullary hormones dopamine, norepinephrine, and epinephrine results in hypertension and tachycardia plus cardiovascular hyperresponsiveness to noxious stimulation. The cells that produce these hormones are of neural crest origin. When the tumor arises in the adrenal medulla, it is called a *pheochromocytoma*; when it arises from ganglia of the sympathetic nervous system, it is called a *paraganglioma*. The biologic behavior is the same in either case. Life-threatening hypertensive crises and tachyarrhythmias may occur, especially during surgery on a previously undiagnosed patient. Pheochromocytoma often goes unrecognized because its symptoms (headache, palpitations, sweating) are nonspecific and as many as 8% are asymptomatic. These tumors are relatively rare (approximate prevalence is 1 in 2000 in the general population) and are diagnosed in less than 1% of patients with hypertension.[56]

Hypertension probably occurs because arteriolar smooth muscle has been exposed to norepinephrine, the neurotransmitter for sympathetic nervous system mediated vasoconstriction. According to this theory, tumor-secreted norepinephrine bathes the synapses directly. But if this were true, the production of norepinephrine by the sympathetic nerves should be suppressed and sympathetic nervous system activity should not be able to regulate arterial blood pressure; instead the circulating hormones would do so. This theory has prompted the practice of preoperative α-adrenergic blockade with phenoxybenzamine prior to tumor resection. It also may be the basis for the unproven beliefs that blood catecholamine levels correlate with arterial blood pressure values and that hypertension occurs when the surgeon manipulates the tumor because this manipulation squeezes hormones out of the tumor and into the bloodstream.

Other interpretations are likely. Catecholamine levels do not correlate with the time or magnitude of increases in arterial blood pressure value,[57] and clinical experience is that 2 weeks of preoperative treatment with nonselective α-adrenergic blockade is commonly ineffective for prevention of intraoperative hypertension. An alternative approach to preoperative preparation should be considered. Hypertension, if present, may be controlled prior to surgery with any of a variety of drugs, and once arterial blood pressure is under reasonable control, the tumor is resected. There is, however, no basis to expect that arterial blood pressure and heart rate lability during the surgery can be entirely prevented, no matter what pretreatment is administered.[58]

An alternate theory of why adrenergic receptor blockade is not fully effective is that chronic catecholamine exposure amplifies the sympathetic nervous system's responses to all forms of physical stimulation. These responses would include hypertension and tachycardia

from laryngoscopy and any surgical manipulations. Such hemodynamic responses may be seen in any patient, but the effect may be exaggerated under the influence of high catecholamine levels. Such a theory is supported by animal data suggesting that, despite chronic catecholamine excess, sympathetic nerves remain active and continue to release mediators that influence or even control blood pressure. The failure of competitive receptor blockade might be explained by the ability of the sympathetic nervous system to overwhelm the competitive blockade by releasing norepinephrine in quantities that are much greater than normal.[59]

Perioperative Considerations

In theory, the nonspecific α-blocking drug phenoxybenzamine should not be chosen because it has α_2-blocking properties. Because α_2-agonists generally produce bradycardia, sedation, and decreased arterial blood pressure, blocking the α_2-receptor should increase arterial blood pressure and heart rate, which would not be the intended therapeutic result. Nevertheless, phenoxybenzamine is often recommended. For the chronic treatment of patients with unresectable catecholamine-secreting tumors, its long pharmacologic half-life is desirable. However, phenoxybenzamine is very expensive, and many less costly alternatives exist for preoperative blood pressure control. The α_1-selective blockers (prazosin, doxazosin, terazosin), calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers, β-adrenergic blockers, and α_2-agonists all have been used with beneficial result prior to adrenalectomy. Intraoperative infusions of vasodilators and esmolol still may be required to treat hypertension or tachycardia. Infusions of magnesium and the α_2-agonist dexmedetomidine may be useful as well.[60]

Multiple Endocrine Neoplasia and Neuroendocrine Tumors

The two groups of multiple endocrine neoplasia (MEN) syndromes were originally called *Wermer syndrome* and *Sipple syndrome* but are now known as *MEN type 1* (MEN1) and *MEN type 2* (MEN2), respectively.

MEN1

This syndrome includes the triad of tumors of the pancreas, pituitary, and parathyroid glands and is inherited as an autosomal dominant trait. Parathyroid tumors, resulting in primary hyperparathyroidism, are the most common feature of MEN1 and occur in approximately 95% of MEN1 patients. All four parathyroid glands usually are removed surgically because all are involved by the disease.

Pancreatic tumors in MEN1 patients are usually adenomas that secrete an excess of a specific hormone. Gastrin secretion is most common, occurring in approximately 40%, but insulin, glucagon, vasoactive intestinal polypeptide, and pancreatic polypeptide secreting tumors are seen. Pituitary tumors most commonly secrete prolactin (60%) or growth hormone (25%). A small number secrete adrenocorticotropic hormone (ACTH), with the balance being nonfunctioning adenomas. Other tumors in MEN1 include adrenocortical adenomas, carcinoids and neuroendocrine tumors, lipomas, angiofibromas, and collagenomas.[61] There are no specific anesthetic implications of MEN1.

MEN2

Medullary (solid) thyroid carcinomas (MTCs) are a component of two endocrine syndromes, which are now called *MEN2A* and *MEN2B*. MEN2A accounts for 80% of hereditary MTC syndromes. In addition to MTC, up to 50% of patients with MEN2A develop pheochromocytomas and up to 30% develop hyperparathyroidism. MEN2B accounts for 5% of hereditary MTCs and includes mucosal neuromas, pheochromocytoma, and MTC. These patients may have a marfanoid habitus, ocular abnormalities (enlarged corneal nerves, conjunctivitis sicca, and the inability to cry tears), and musculoskeletal manifestations (bowing of the extremities and slipped capital femoral epiphysis). Unlike patients with MEN1, they do not develop parathyroid adenomas. A third subtype of MEN2 is characterized only by familial MTC. All the MEN2 subtypes are autosomal dominant conditions caused by germline activating mutations in the *RET* proto-oncogene on chromosome 10.[62] The anesthetic implications of MEN2 are related to its components and associated conditions. Von Hippel–Lindau disease, which may include cerebellar tumors, is associated with MEN2 and pheochromocytomas.[63] MTC, which accounts for only 5% of all thyroid tumors, is commonly malignant and is the most common cause of death in MEN2 patients. A patient of any age with MTC is therefore likely to undergo thyroidectomy and may be at risk to have an undiagnosed pheochromocytoma at the time of surgery.

Neuroendocrine Tumors

Carcinoid and neuroendocrine tumors arise from dispersed cells of neural crest embryologic origin. The normal function of these cells is to synthesize serotonin from the essential amino acid tryptophan. When these tumors arise in the midgut, they are called *carcinoid tumors*. When they arise elsewhere in the body, they are called *neuroendocrine tumors*.

The biochemical behavior of these tumors is to overproduce serotonin in preference to the normal products of tryptophan metabolism, including niacin (vitamin B_3). In rare instances, patients may therefore develop symptomatic niacin deficiency (pellagra), but this is rare. Most commonly, midgut carcinoid tumors are asymptomatic until they cause bowel obstruction or appendicitis because their venous drainage is via the portal vein to

the liver, which detoxifies the excess serotonin they produce. When the tumors arise outside the drainage field of the hepatic portal venous system, or when metastatic disease has replaced so much of the liver as to compromise hepatic synthetic function, systemic symptoms of serotonin excess occur. This is known as the *carcinoid syndrome* and is characterized by diarrhea, flushing, palpitations, and bronchoconstriction. Medical management with octreotide may help ameliorate these symptoms.[64]

Perioperative Considerations

The direct hemodynamic effects of serotonin usually are not problematic in the context of perioperative anesthetic care, and an escalation of hemodynamic monitoring is seldom required as a consequence of the endocrine activity of the tumor. However, certain medications can trigger mediator release resulting in labile arterial blood pressure. Drugs that trigger mediator release include opioids (particularly meperidine and morphine), neuromuscular blockers (atracurium, mivacurium, and d-tubocurarine), epinephrine, norepinephrine, and dopamine (also see Chapters 9 and 11).

Among those with carcinoid syndrome, approximately 50% develop carcinoid heart disease, which typically causes abnormalities of the right side of the heart. Echocardiography should be considered as a diagnostic tool. Right-sided heart failure, due to the sclerosing effect of serotonin on the tricuspid and pulmonary valves, ultimately may be the cause of death in 50% of patients with the carcinoid syndrome.[65]

Adrenal Insufficiency and Steroid Replacement

The principal hormones secreted by the adrenal cortex are cortisol and aldosterone. Cortisol production is stimulated by blood concentrations of pituitary ACTH, which is in turn secreted in response to hypothalamic corticotropin-releasing hormone (CRH). Stress stimulates the hypothalamus to release CRH, and blood cortisol levels exert negative feedback influence on the production of both CRH and ACTH. Chronic insufficient cortisol production and secretion, with or without aldosterone insufficiency, is referred to as *Addison syndrome*.[66]

The symptoms of chronic adrenal insufficiency are nonspecific. They include fatigue, malaise, lethargy, weight loss, anorexia, arthralgias, myalgias, nausea, vomiting, abdominal pain, diarrhea, and fever. In primary adrenocortical insufficiency, due to nonfunction of the adrenal glands, hyponatremia and hyperkalemia resulting from concomitant aldosterone deficiency may occur. In secondary or tertiary insufficiency, due to failure of the hypothalamus or pituitary to stimulate the adrenal glands, or when cortisol production is suppressed by exogenously administered steroid medications, aldosterone production is unimpaired. This is because the stimulus for aldosterone production is the renin-angiotensin system. In developed countries, 80% to 90% of cases of primary adrenal insufficiency are caused by autoimmune adrenalitis, which can be isolated (40%) or part of an autoimmune polyendocrinopathy syndrome (60%). Less common causes of primary chronic adrenal insufficiency are malignant (metastatic cancer, commonly from lung or breast) and infectious (such as tuberculosis).[67]

Cortisol maintains homeostasis of the cardiovascular system, especially in the presence of stress. It maintains vascular tone, endothelial integrity, and the distribution of total body water in the vascular compartment. It reduces vascular permeability and it potentiates the vasoconstrictor effects of catecholamines. When cortisol levels are deficient, systemic vascular resistance and myocardial contractility are decreased.

The term *acute adrenal failure*, or *Addisonian crisis*, refers to circulatory shock due to cortisol deficiency. It generally occurs in the presence of primary adrenal insufficiency with a superimposed acute stress such as trauma, surgery, or infection and is characterized by hypovolemic shock with myocardial and vascular unresponsiveness to catecholamines. Treatment usually requires the IV infusion of several liters of isotonic saline and corticosteroid administration. In an adult, 100 mg of IV cortisol (or the equivalent every 6 to 8 hours) usually reverses the pathophysiology within the first day of treatment. Orally administered drugs can be started in 1 to 4 days.[67] The equivalent doses of these drugs are expressed using hydrocortisone, the synthetic form of cortisol, with 100 mg as the standard for comparison (Table 29.2).[68]

Critical illness–related corticosteroid insufficiency (CIRCI) applies to clinical situations in which 100 to 300 mg/day of IV hydrocortisone eliminates a preexisting need for vasopressors.[69] The implication is that the patient may not meet traditional criteria for adrenocortical dysfunction, but the adrenal response to critical illness and other stresses is inadequate. Prior steroid treatment is a potential cause of this condition. Signs and symptoms may include unexplained vasopressor-dependent refractory hypotension, a discrepancy between the anticipated

Table 29.2 Relative Equivalent Potencies of Common Corticosteroid Drugs

Agent	Equivalent Dose (mg)	Relative Potency	Duration (h)
Hydrocortisone	100	1	8-12
Cortisone	125	0.8	8-12
Prednisone; prednisolone	25	4	12-36
Methylprednisolone	20	5	12-36
Dexamethasone	4	30	36-72

severity of the patient's disease and the present state of the patient, high fever without apparent cause or not responding to antibiotics, hypoglycemia, hyponatremia, hyperkalemia, neutropenia, and eosinophilia.

Perioperative Considerations

Etomidate (also see Chapter 8) is a relatively noncardiovascular depressant anesthetic that can suppress adrenocortical function. This is a significant but transient effect (<24 hours) even after a single dose of the drug. It can be clinically significant in the setting of CIRCI. Perhaps an anesthetic can be developed with the advantages of etomidate but without its adrenal suppressing effects.[70]

Steroid replacement for the patient who has received exogenous steroids and may have adrenal insufficiency should be adequate but not excessive. The proper dose of replacement steroids is based on surgical research in primates showing that 10 times the normal cortisol production rate was not superior to simply replacing the normal daily production of cortisol.

Stress dose steroid administration during the perioperative period remains controversial (also see Chapter 13). Steroid-induced adrenal suppression is highly variable, and its duration is unpredictable (days to perhaps years). Daily cortisol production rate is between 20 and 30 mg/day. In the past, the recommended approach had been to begin at the time of surgery with a dose between one and five times the daily production (no more than 100 to 150 mg of cortisol equivalent) per day and administer tapered replacement over 48 to 72 hours. However, a recent Cochrane review found only two randomized control trials assessing stress dose of steroids. These studies reported that endogenously produced steroid combined with exogenous steroid administration (i.e., daily dose) is adequate in the perioperative period. The authors concluded that the recommendations on the use of additional corticosteroids for surgical patients receiving preoperative steroids have not been adequately investigated.[66]

Pituitary Apoplexy

Acute pituitary hemorrhage, swelling, and infarction (pituitary apoplexy) is an exception to the general rule that adrenal crisis is not usually associated with secondary adrenal hypofunction. Pituitary apoplexy is a potentially life-threatening condition that can lead to sudden total loss of all anterior and posterior pituitary hormonal secretion and severe hypoglycemia, hypotension, central nervous system hemorrhage, cerebral edema, and loss of vision (often bitemporal hemianopia).

Two well-known causes of spontaneous pituitary apoplexy are infarction of a large pituitary adenoma and postpartum hypotensive pituitary necrosis (Sheehan syndrome). Other associations include diabetes, hypertension, sickle cell anemia, and acute shock. Acute pituitary hemorrhage into an unsuspected pituitary adenoma has also been reported following cardiopulmonary bypass.[71]

Signs and symptoms of pituitary apoplexy include severe headache, meningeal irritation, bitemporal hemianopia, ophthalmoplegia, cardiovascular collapse, and loss of consciousness. Computed tomography or magnetic resonance imaging most often confirms the diagnosis. Corticosteroid replacement is the first line of treatment, both for the resulting adrenal insufficiency and for brain swelling. If there is significant visual loss or mental status alteration, acute surgical decompression may be required.[72]

Cushing Syndrome

Cushing syndrome is characterized by elevated cortisol levels in the blood. Primary Cushing syndrome is independent of pituitary ACTH secretion, whereas secondary and tertiary disease is due to increased circulating levels of ACTH or an ACTH-like substance produced by a tumor. The primary condition is usually due to a hyperfunctioning adrenal gland or adenoma. The term *Cushing disease* usually refers to one specific form of secondary Cushing syndrome, that of adrenocortical hyperfunction due to excess production of ACTH by a pituitary adenoma, which accounts for 80% of Cushing syndrome patients. The remainder of the patients with secondary or tertiary Cushing syndrome have abnormal ACTH production from ectopic sources such as primary or metastatic cancers of the lung (usually small cell), thyroid, or prostate; tumors of the pancreas; or intrathoracic neuroendocrine tumors and have an increased ACTH as a result of hypothalamic oversecretion of CRH. Cushing syndrome may also be caused by exogenous administration of cortisol-like medications or synthetic ACTH.

Patients with Cushing syndrome are often recognizable by a physical appearance that consists of rounding of the face, truncal obesity and thin extremities, an upper thoracic fat pad or "buffalo hump," purple abdominal striae, and thinning of the skin. The physiologic effects of chronic elevated corticosteroid levels include weight gain, hypertension, hypercoagulability, muscular weakness, glucose intolerance, gonadal dysfunction, and osteoporosis. Biochemical diagnosis is made by measuring an elevated 24-hour urinary free cortisol.[73]

There is no definitive medical treatment for Cushing syndrome. Effective treatment requires removal of the source of the increased hormone production, followed by corticosteroid replacement therapy if necessary. Anesthetic management of patients with Cushing syndrome may have associated differences as compared to normal patients. For example, they may be more susceptible to the effects of neuromuscular blocking drugs and resultant unanticipated postoperative respiratory

failure (also see Chapter 11), even after laparoscopic surgery.[74]

QUESTIONS OF THE DAY

1. A morbidly obese patient presents for surgery. What logistical problems may be present during patient positioning and monitoring of vital signs? How can these potential problems be addressed?
2. In a patient at risk for aspiration of gastric contents, what is the potential benefit of cricoid pressure during rapid-sequence induction of anesthesia? What are the risks of inappropriately applied cricoid pressure?
3. A patient with type 2 diabetes mellitus presents on the day of surgery with a serum glucose level of 290 mg/dL. Is additional information needed? What are the risks of proceeding with surgery with this degree of hyperglycemia?
4. A patient develops respiratory distress in the postanesthesia care unit after thyroid surgery. What are the initial steps in management of the patient? What are the potential causes?
5. What are the options for preoperative arterial blood pressure control in a patient with a pheochromocytoma? What medications can be given intraoperatively to treat an episode of severe hypertension in a patient with a pheochromocytoma?
6. What is the rationale for perioperative intravenous steroid administration for a patient who may have adrenal insufficiency? What is the appropriate hydrocortisone dose in this setting?

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