

Drug-induced endocrine disorders in the intensive care unit

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The neuroendocrine response to critical illness is key to the maintenance of homeostasis. Many of the drugs administered routinely in the intensive care unit significantly impact the neuroendocrine system. These agents can disrupt the hypothalamic-pituitary-adrenal axis, cause thyroid abnormalities, and result in dysglycemia. Herein, we review major drug-induced endocrine disorders and highlight some of the controversies that remain in this area. We also discuss some of the more rare drug-induced syndromes that have been described in the intensive care unit. Drugs that may result in an intensive care unit admission secondary to an endocrine-related adverse event are also included.

Increasing emphasis is being placed on the avoidance of iatrogenic complications, particularly in the critically ill. A number of the medications that are commonly provided in the intensive care unit (ICU) have side effects that are important. In this review, we cover the major drug-induced endocrine effects and highlight some of the controversies that remain in this area. We also mention some of the more rare drug-induced syndromes that have been described in the ICU. In an effort to focus our review for the critical care clinician, we have deliberately overlooked some syndromes that are primarily seen in outpatients. In areas where definitive data are lacking, we have pro-

vided recommendations based on the best available evidence and our experience.

Drug-induced pituitary-adrenal axis dysfunction

Although pituitary disease is not frequently considered in the critically ill, a number of syndromes are common, involving the pituitary-adrenal axis. We have focused on etomidate and chronic glucocorticoid therapy as major issues. We also emphasize the importance of drugs that inhibit or induce adrenal enzyme activity, which can influence glucocorticoid metabolism.

Etomidate

The adrenal effects of etomidate were closely examined during the early 1980s in an attempt to investigate a disturbing increase in mortality noted among critically ill patients who received etomidate infusion for continuous sedation during mechanical ventilation. In one study (1), sedation with morphine with or without benzodiazepines was associated with a 28% mortality rate, compared with 77% in patients receiving morphine and etomidate ($p < .0005$). It was soon recognized that etomidate produced a concentration-dependent blockade of 11β -hydroxylase, the enzyme involved in the final conversion of cholesterol to cortisol (2).

Although adrenal dysfunction with single-dose etomidate had been documented as early as 1983 (3), the clinical relevance of this phenomenon was

Unfortunately, very few studies have systematically addressed drug-induced endocrine disorders in the critically ill. Timely identification and appropriate management of drug-induced endocrine adverse events may potentially improve outcomes in the critically ill. However, more research is needed to fully understand the impact of medications on endocrine function in the intensive care unit. (Crit Care Med 2010; 38[Suppl.]:S219–S230)

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thought to be minimal. This lack of concern is evidenced by the popularity of etomidate in rapid sequence intubation. For example, an observational study of 515 rapid sequence intubations reported etomidate use in 82.5% of cases (4). Emerging data suggest that, in the context of critical illness and specifically in septic shock, etomidate induces prolonged hypoadrenalism that increases the risk for morbidity and mortality.

Several studies (5–7) have noted that a single dose of etomidate significantly increases the likelihood that patients can have an abnormal response to a synthetic adrenocorticotropic hormone (ACTH) challenge. Lack of response to ACTH in septic patients is associated with refractory hypotension (8), higher levels of proinflammatory cytokines (9), and increased mortality (7, 10–14). *Post hoc* analysis of a randomized controlled trial (15) of corticosteroids for refractory septic shock suggested that treatment with hydrocortisone in patients exposed to etomidate attenuated the adverse effects of adrenal suppression. Despite the preliminary nature of these data, some experts (16) recommended that etomidate be abandoned, whereas others (17) suggested that etomidate use be continued and that steroids be prescribed to these patients.

Most recently, an *a priori* subgroup analysis (18) of the Corticosteroid Therapy of Septic Shock trial has provided valuable insight regarding etomidate-induced adrenal suppression in sepsis. Of

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the 499 patients enrolled in Corticosteroid Therapy of Septic Shock trial, 96 (19.2%) were administered etomidate. Etomidate exposure increased the ACTH nonresponder rate by 16.4% ($p = .004$) and the risk of death by 12.2% ($p = .02$, univariate analysis) compared with etomidate-naïve patients. Of note, patients receiving etomidate were older and had slightly higher Simplified Acute Physiology Scores II. Depending on the number of baseline characteristics included in the multivariate model, etomidate was either independently associated with ($p = .03$), or trended toward ($p = .06$) an increased risk of death. Unlike the previously mentioned trial, hydrocortisone administration did not influence the mortality of patients receiving etomidate. Based on these data, it would seem prudent to avoid the use of etomidate in septic patients.

Some continue to contend that etomidate use may simply be a marker of a sicker patient, not adequately captured by physiologic data. As such, more prospective randomized trials are needed to define the risk of etomidate. Recently, Jabre et al (19) published the first large-scale ($n = 469$) randomized trial of etomidate vs. ketamine for rapid sequence intubation. Ketamine was found to be a safe and effective alternative to etomidate and was associated with a lower risk of laboratory-diagnosed adrenal insufficiency (48% vs. 86%, $p < .0001$). Despite an increased rate of adrenal insufficiency with etomidate, clinical outcomes, such as 28-day mortality and length of stay, were not different. Importantly, <20% of these patients undergoing intubation were septic. Although controversial, multiple lines of evidence have linked adrenal insufficiency to poor outcomes in sepsis. In aggregate, the current data suggest a preferential role for ketamine in rapid sequence intubation for septic (or suspected septic) patients, but etomidate remains a reasonable choice in a nonseptic population. Additional discussion on etomidate-associated adrenal dysfunction can be found in this supplement's article titled "Adverse drug events associated with the use of analgesics, sedatives, and antipsychotics in the intensive care unit."

Chronic glucocorticoid therapy

ICU patients frequently arrive with a history of steroid therapy based on an indication, such as obstructive lung disease, organ transplantation, inflamma-

tory bowel disease, or collagen vascular diseases, among others. Such patients may be at risk of iatrogenic adrenocortical insufficiency. However, in our experience, iatrogenic adrenocortical insufficiency leading to distributive shock is quite rare. The dose or duration of prior steroid therapy does not seem to be a strong predictor of subsequent adrenal failure risk (20). Thus, some have advocated for more liberal use of "stress-dose steroids" among patients with a history of a requirement. However, some transplant programs have avoided stress dosing all together, with no apparent deleterious effects (21, 22). Such a strategy may help minimize bone loss and other chronic steroid complications and can likely be performed safely in patients who are being closely monitored. Thus, we recommend steroid repletion for patients in shock but careful observation for other patients who are not hemodynamically compromised.

Induction of cytochrome P-450 activity

Up-regulation of hepatic microsomal enzyme activity may increase cortisol metabolism possibly predisposing to adrenal insufficiency. Rifampin, phenytoin, and phenobarbital are inducers of the cytochrome P-450 (CYP-450) system and are commonly cited as agents causing drug-induced adrenal insufficiency (23, 24). In general, hepatic enzyme induction does not lead to clinically significant adrenal dysfunction, because normal individuals can synthesize more cortisol by increasing ACTH secretion. However, the effects of these drugs have not been examined during critical illness where multiple mechanisms are already at work that may impair pituitary-adrenal function and reserve. Given this uncertainty, it is important to examine the potential relevance of these agents.

Rifampin is a potent and rapid inducer of the CYP-450 system and is a useful adjunct for a variety of infectious diseases encountered in the ICU. Data from Ohnhaus et al (25) indicated that rifampin-related increases in cortisol metabolism occur with as few as two doses. After 7 days of rifampin treatment, a three-fold increase in the urinary excretion ratio of 6 β -hydroxycortisol:cortisol is seen. These data are indicative of enhanced cortisol breakdown; however, the implications of this finding in the critically ill have not been fully elucidated.

Dynamic assessment of the hypothalamic-pituitary-adrenal axis in rifampin-treated patients has largely been examined in the context of *Mycobacterium tuberculosis* infection. This represents a major confounder, because tuberculosis infection itself can result in acquired adrenal insufficiency. Additionally, comparisons across studies are difficult to make due to varying definitions of adrenal insufficiency. In a pilot trial (26), equivalent rates (20%) of adrenal dysfunction (defined as a cortisol increment of ≤ 9 $\mu\text{g/dL}$ in response to 250 μg of ACTH) were documented among patients treated with a rifampin-based tuberculosis regimen compared with a ciprofloxacin-based regimen. Using a peak cortisol of <20 $\mu\text{g/dL}$ in response to ACTH as diagnostic of adrenal insufficiency, Beadsworth et al (27) failed to identify any cases of adrenal insufficiency in 34 patients who were treated with a rifampin-based tuberculosis regimen. On the other hand, rifampin use was found to be associated with an increased risk of adrenal insufficiency in critically ill patients with human immunodeficiency virus (odds ratio, 11.39; 95% confidence interval, 2.15–60.34) (28). Based on these limited data, it is difficult to either support or refute a link between rifampin and clinically relevant adrenal insufficiency. Thus, clinicians should be aware of the potential need for steroid therapy in rifampin-treated patients.

Phenytoin induces 6 β -hydroxylase and also results in a rapid increase in the urinary excretion ratio of 6 β -hydroxycortisol:cortisol. Phenytoin has been shown to increase the urinary 6 β -hydroxycortisol:cortisol ratio by more than two-fold within 7 days of initiation (29). In patients with epilepsy, phenytoin has been shown to transiently decrease cortisol concentrations (30). Similar findings (25) have also been reported with phenobarbital. Phenytoin remains a first-line agent for the prevention of posttraumatic seizures in brain-injured patients (31). Interestingly, prospective studies (32, 33) have identified acute adrenal hyporesponsiveness in 15% to 53% of traumatic brain-injured patients. The contribution of phenytoin to this incidence is unknown. Preliminary data (34) with levetiracetam, an anticonvulsant that does not affect cortisol metabolism, suggested that it may be effective for seizure prophylaxis. Future studies comparing phenytoin and levetiracetam for seizure prophylaxis should also assess the integrity

of the hypothalamic-pituitary-adrenal axis.

Rifampin, phenytoin, and phenobarbital have all been shown to increase the metabolism of exogenously administered glucocorticoids. Several reports (35–37) exist in the literature of exacerbations of steroid-treated conditions when enzyme-inducing agents have been added to stable glucocorticoid regimens. Recommendations (35) exist to double or triple the dose of steroids empirically in the presence of certain inducers. Current guidelines (38) recommend fixed doses or weight-based doses of steroids for acute respiratory distress syndrome and septic shock. Although controversy persists regarding the role of steroids in these conditions, clinicians should be aware that these empirical regimens may be inadequate in the presence of inducing agents.

Inhibition of CYP-450: Azole antifungals

Azole antifungals have long been associated with adrenal suppressive effects due to their ability to inhibit CYP-450-dependent enzymes involved in steroidogenesis (39). These agents differ in their inhibitory potency and selectivity for the fungal P-450 system. Adrenal suppression is best documented with ketoconazole, and although *in vitro* data suggest that adrenal suppression is unlikely with triazole antifungals, e.g., fluconazole and itraconazole, several case reports (39–41) have documented reversible adrenal suppression in association with these agents. On the contrary, Magill et al (42) did not demonstrate an association between fluconazole use and adrenal insufficiency. This was a *post hoc* analysis of a randomized, placebo-controlled trial of fluconazole prophylaxis in surgical ICU patients. The impact of fluconazole on adrenal function was assessed by measuring cortisol concentrations in stored blood. The median cortisol concentration was 15.75 $\mu\text{g}/\text{dL}$ in patients randomized to fluconazole and 16.71 $\mu\text{g}/\text{dL}$ in patients randomized to placebo ($p = .52$). The proportion of patients with adrenal insufficiency, defined as a cortisol concentration of $<15 \mu\text{g}/\text{dL}$, did not differ between the fluconazole and placebo groups, 46.8% vs. 42.7%; $p = .6$. Conclusions from this study are limited by its nonrandomized *post hoc* design and use of stored blood. Overall, it seems that fluconazole-associated adrenal suppression in the critically ill is uncommon.

Azole antifungals are inhibitors of the CYP-450 system. As such, they theoretic-

ally increase the risk of the development of steroid-associated adverse effects, such as hyperglycemia, immune suppression, and hypothalamic-pituitary-adrenal suppression. The mechanism is thought to be related to increased concentrations of steroids due to reduced CYP-450-mediated metabolism. Limited reports (43–45) supported the clinical relevance of this interaction. Nonetheless, given the plausibility of this interaction, patients who receive azole antifungals or other CYP-450 inhibitors concomitantly with steroids should be closely monitored for adverse effects (46–48). Additional drugs that can affect adrenal function are discussed in Table 1 (49–67).

Drug-induced thyroid dysfunction

In discussing drugs that may affect thyroid function, we have focused on dopamine, lithium, and amiodarone.

Dopamine

The 2008 Surviving Sepsis Campaign (68) recommends dopamine as one of the first-line agents to correct sepsis-associated hypotension. Observational data from Europe and survey data from the United States (69, 70) indicated that dopamine is used in at least 25% of patients with septic shock. However, subgroup analysis from the Sepsis Occurrence in Acutely Ill Patients Study (69) found dopamine to be associated with an increased risk of hospital death compared with other catecholamines, 49.9% vs. 41.7% ($p = .01$). If these data are found to be reproducible by prospective randomized trials, then the possibility exists that dopamine effects on endocrine function may be a mediator of this potential risk.

Critical illness is associated with a variety of changes in thyroid function, including low serum thyroid-stimulating hormone, thyroxine, triiodothyronine, and increased reverse triiodothyronine (71, 72). Critical illness-associated thyroid dysfunction is commonly referred to as *euthyroid sick syndrome* or *nonthyroidal illness*. Although the degree of thyroid dysfunction has been linked to mortality in a variety of critically ill states (73–75), trials (76–78) of thyroid hormone supplementation in the ICU have not produced favorable results. The etiology of euthyroid sick syndrome is likely multifactorial; however, dopamine administration is known to further aggravate the thyroid abnormalities encountered in the critically ill (72). Dopamine infusion

reduces thyroid-stimulating hormone concentrations and thyroxine production rates (79). Changes in thyroid function occur within 24 hrs of dopamine initiation and the duration of infusion correlates with the severity of triiodothyronine suppression (71, 80). These thyroid abnormalities are nearly completely reversed within 24 hrs of dopamine discontinuation (80). In summary, these data reflect a causal link between dopamine administration and thyroid abnormalities in the critically ill. The full implications of these findings in the ICU are unclear, but many regard this dopamine-induced suppression of thyroid-stimulating hormone as “real” central hypothyroidism, rather than an artifact or euthyroid sick syndrome.

Lithium

Even though the calming effects of lithium were first discovered in 1949, it was not until almost two decades later when an association between lithium therapy and goiter was noted (81). Lithium is concentrated in the thyroid gland and is reported to inhibit thyroxine release and thyroid hormone synthesis (82, 83). The risk of hypothyroidism increases with the duration of treatment. In one study (84), hypothyroidism was found in 4% of patients treated with lithium for 1–5 yrs, compared with 21% in patients treated for >10 yrs. Lithium-associated hypothyroidism can range from subclinical hypothyroidism to life-threatening myxedema coma (85, 86). Although the latter is a very rare occurrence, critical care practitioners should be aware of this extreme presentation in order to initiate appropriate therapy in a timely manner. Of note, the thyroid suppressive effects of lithium make it a useful adjunct in managing the symptoms of thyrotoxicosis in patients who cannot tolerate or do not respond to thionamides (87, 88). Close monitoring of serum concentrations should be conducted when lithium is used therapeutically. The reader should also be aware that lithium is an uncommon cause of thyrotoxicosis (89). Although one review (90) suggested a higher prevalence of thyrotoxicosis in lithium-treated patients compared with the general population, others (91, 92) have found virtually no link between lithium and hyperthyroidism.

Amiodarone

Despite being approved by the Food and Drug Administration only for life-threatening recurrent ventricular arrhythmias (93),

Table 1. Drug-related adrenal dysfunction in the intensive care unit

Mechanism	Drugs	Comments
Hemorrhage	Heparins, warfarin, and other anticoagulants	In sepsis, adrenal failure may result from bilateral necrosis and hemorrhage of the adrenal glands (23). Anticoagulant therapy seems to increase the risk of hemorrhage (49). Additionally, unfractionated and low-molecular weight heparins can result in HIT. Numerous cases reports document an association between HIT and adrenal necrosis (50–54). It is recommended that acute adrenal insufficiency be considered in patients on heparin therapy who develop hypotension, abdominal pain, thrombocytopenia, and fever.
Induction of cortisol metabolism	Phenobarbital, phenytoin, rifampin	Induction of cortisol metabolism can occur rapidly with these agents but is usually transient and resolves on drug discontinuation. A high clinical suspicion for adrenal insufficiency should be present in patients with additional risk factors. These agents also increase the metabolism of exogenously administered glucocorticoids and can lead to clinical deterioration in patients on stable glucocorticoid regimens.
Inhibition of cortisol synthesis	Azole antifungals	Clinical relevance of short-term triazole fungal adrenal effects is questionable (42). However, these agents may contribute to the pathogenesis of adrenal insufficiency during states of increased glucocorticoid requirements, e.g., critical illness (24).
	Etomidate	In septic patients, etomidate increases the risk for laboratory-diagnosed adrenal insufficiency and possibly for mortality. Steroid administration does not protect against potential adverse outcomes. Previous data (55, 56) suggested a possible role for ascorbic acid for the treatment of etomidate-associated adrenal dysfunction, but this approach has not been validated. Ketamine has recently been shown to be a useful alternative to etomidate for rapid sequence intubation (19).
CRH and ACTH suppression	Glucocorticoid therapy	The threshold dosage and duration of steroid therapy associated with adrenal insufficiency are unknown and difficult to predict (20). Commonly cited thresholds include the equivalent of 20–30 mg per day of prednisone for >5 days (57) and prednisone maintenance doses of >5 mg per day (58). However, the predictive values of these thresholds are likely low.
	Opiates and benzodiazepines	Benzodiazepine administration results in a dose-dependent decrease in serum cortisol concentrations (59, 60). Opiates also result in decreased cortisol secretion (61). These drugs are thought to work in the hypothalamus (23). In addition, animal data (62) suggested that chronic exposure to opiates may increase cortisol-binding globulin, resulting in a decreased free fraction of cortisol. Reducing the dose of opiates may result in clinical improvement of adrenal insufficiency (63). These agents may contribute to the development of adrenal insufficiency in critical illness.
Decreased cortisol substrate	Statins	Cortisol is produced via a series of cytochrome-mediated enzymatic reactions from cholesterol. A recent study demonstrated a dose-dependent effect of statins on cortisol production. Intensive statin therapy (80 mg daily of atorvastatin) was associated with decreased cortisol concentrations, whereas atorvastatin 10 mg per day with ezetimibe 10 mg per day had no discernible effects on cortisol production (64).
Aldosterone suppression	Heparin	The exact mechanism of heparin-associated hypoaldosteronism is unknown but may be related to inhibition of 18-hydroxylase or impaired angiotensin II-induced stimulation of aldosterone synthesis (65, 66). Although life-threatening dysrhythmias have been reported (67), in general heparin-associated hyperkalemia is mild and resolves upon drug discontinuation (66). Marked hyperkalemia usually requires the presence of multiple risk factors, such as diabetes or renal insufficiency (65). Fludrocortisone can be used to treat heparin-associated hyperkalemia in situations where drug discontinuation is not feasible (66).

CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone; HIT, heparin-induced thrombocytopenia.

amiodarone is frequently used in the critically ill. Amiodarone use is also common in the community setting for the treatment of atrial fibrillation, particularly for the maintenance of sinus rhythm. Between January and September 2000, 1.8 million outpatient prescriptions for amiodarone were dispensed (94). Although controlled trial data

(95) supporting its efficacy in the critically ill are limited, amiodarone is considered to be a very effective antiarrhythmic (96) and is often included in the Advanced Cardiac Life Support protocols. However, both long- and short-term therapy can result in a variety of drug-related adverse effects, including thyroid abnormalities.

Amiodarone is a benzofuranic derivative whose structure is similar to that of thyroxine (97). Approximately 37% of amiodarone is comprised of iodine by weight. Standard therapeutic doses of amiodarone exceed the recommended daily requirements of iodine (150 µg) by 50- to 100-fold (97). This large iodine load can result in

amiodarone-induced thyrotoxicosis (AIT). AIT that is related to excessive synthesis and release of thyroid hormone secondary to iodine ingestion is referred to as *AIT-I*. AIT-I is most likely to occur in patients with preexisting thyroid disease, such as goiter. Amiodarone-induced thyrotoxicosis type I (AIT-II) is a destructive thyroiditis that causes the release of preformed thyroid hormone from the damaged thyroid gland (97–99). Amiodarone-induced thyrotoxicosis can occur at anytime during therapy, and because of its long half-life (50–100 days), AIT can occur long after drug discontinuation (100). Given the likely underlying cardiac comorbidities of patients prescribed amiodarone and the cardiovascular stress of thyrotoxicosis, it is not surprising that AIT increases by 2.7-fold the risk of cardiovascular mortality, stroke, myocardial infarction, and other major cardiac events (101).

These data suggest the importance of the appropriate recognition and timely treatment of AIT. Whereas AIT-I is treated with antithyroid drugs (methimazole or propylthiouracil), glucocorticoids are the mainstay of treatment for AIT-II (99). Unfortunately, the subtypes of AIT are not easy to distinguish based on clinical presentation, and mixed forms also occur. Although radioactive iodine uptake studies are often recommended, they are of limited utility in the United States and other iodine sufficient areas, because the uptake is generally low (97, 102, 103). In addition, radioactive iodine uptake studies may be impractical for ICU patients. Color flow Doppler sonography was first used to distinguish AIT subtypes in 1997 (104). In this study, all patients with AIT-II ($n = 16$) were found to have a color flow Doppler sonography pattern 0 (absent vascularity). This is in agreement with the proposed pathophysiology of AIT-II: direct thyroid damage. Color flow Doppler sonography patterns I to III are indicative of increased vascularity and are associated with AIT-I (98, 102).

Color flow Doppler sonography use is supported by other reports (105–107), but its diagnostic value is limited in mixed forms of AIT where both thyroid destruction and increased synthesis of thyroid hormone occur simultaneously (100). Emerging data (108) suggest that there is a potential role for technetium sestamibi scintigraphy in differentiating the AIT subtypes and that it may be superior in detecting mixed types of AIT. However, this test is not commonly employed in current ICU practice. Cardenas et al (102) proposed a scoring system to distinguish the different

AIT subtypes, but as noted by the authors, this system would require rigorous validation before it can be applied in clinical practice. These diagnostic challenges usually lead clinicians to start combination therapy for both AIT-I and AIT-II. The recommended daily doses for methimazole and propylthiouracil are 40–60 mg and 600–800 mg, respectively (97, 98). Although many reviews recommend potassium perchlorate (Perchloracaps) for AIT-I, this agent has been discontinued by the manufacturer and is no longer available. The starting dose of prednisone for AIT-II is usually 40 mg per day. The dose should be reduced to the lowest effective dose, and treatment is continued for 1–5 months (97, 98). Thyroidectomy should be considered in refractory cases and in those in whom amiodarone cannot be discontinued (97, 98). Early endocrinology involvement is recommended in cases of AIT. It is imperative that routine monitoring of thyroid function, as is advocated in practice guidelines, occur in amiodarone-prescribed patients to minimize the risks associated with therapy (109). Data (110, 111) from clinical practice indicated that current monitoring is suboptimal.

Amiodarone can also cause hypothyroidism (97). Risk factors for amiodarone-induced hypothyroidism include female sex and preexisting Hashimoto's thyroiditis (97). The pathogenesis of amiodarone-induced hypothyroidism is not completely understood but is thought to be related to a failure to recover (escape) from the Wolff-Chaikoff effect and/or defects in iodine organification and thyroid hormone synthesis (97, 112). In general, the hypothyroidism is mild and responds favorably to levothyroxine treatment or drug discontinuation. The reader should be aware that amiodarone has also been implicated as a rare cause of myxedema coma (113). Dronedarone is a new noniodinated benzofuran derivative structurally related to amiodarone (114). The omission of the iodine moiety should reduce the likelihood of thyroid-related adverse effects. Preliminary data (114) from a randomized controlled trial suggested that dronedarone may be associated with fewer laboratory-diagnosed thyroid abnormalities than amiodarone. Conclusions regarding the clinical relevance of this finding will be further elucidated upon full publication of the Efficacy and Safety of Dronedarone Versus Amiodarone for the Maintenance of Sinus Rhythm in Patients With Atrial Fibrillation (DIONYSOS) trial. Additional agents that

may result in drug-induced thyroid dysfunction are listed in Table 2 (115–137).

Pancreas

In discussing drugs that may affect pancreatic function, we have divided this section into the controversial topics of intensive insulin therapy and insulin-induced hypoglycemia, drug-induced dysglycemia, and glucose-insulin-potassium.

Intensive insulin therapy

Considerable controversy exists regarding the potential role of glucose control and insulin administration in critically ill patients. Initial enthusiasm for intensive insulin therapy (IIT) with a goal blood sugar level of 80–110 mg/dL developed following a landmark publication from Belgium (138). The authors observed a substantial improvement in mortality among a population of primarily cardiac surgery patients with the use of IIT compared with conventional therapy. Some critics questioned the generalizability of these findings based on the single-center, nonblinded study design, the frequent use of parenteral calories (a practice deviation from many ICUs), a relatively high control mortality for the apparent severity of illness, and a lack of statistical significance for 28-day mortality (139). Despite these potential concerns, IIT was widely embraced as standard of ICU care and was regarded by some as a benchmark for quality of care. Subsequent studies (140) were variable in their findings with several multicenter studies showing no important benefit to IIT. Several medical ICU-based studies (141) in fact showed harm from IIT, ostensibly related to insulin-induced hypoglycemia. Others (139, 142) concluded that some level of hyperglycemia may be adaptive, despite widespread acknowledgment that marked hyperglycemia is maladaptive.

Hypoglycemia has been defined as a threshold of <40 mg/dL in many randomized trials, but emerging evidence (143) is suggesting that values of <70 mg/dL or even 80 mg/dL may also be deleterious. Another debated issue is the mechanism whereby hypoglycemia leads to poor outcome (144). Some have suggested that hypoglycemia per se is harmful (due to neuroglycopenia and/or lack of metabolic substrate). Several studies (145) in animals and humans have shown

Table 2. Drug-related thyroid dysfunction in the intensive care unit

Mechanism	Drugs	Comments
Increased metabolism of thyroid hormone	Phenobarbital, phenytoin, rifampin, carbamazepine	These agents increase the nondeiodinative clearance of thyroxine via the induction of hepatic microsomal activity (115). Although there are limited reports of euthyroid patients developing overt hypothyroidism with rifampin, in general, these agents are well tolerated in patients with normal thyroid function (116, 117). In patients with preexisting disease, subclinical or overt hypothyroidism can occur, and monitoring of thyroid status is recommended. Higher levothyroxine doses may be required in patients receiving these drugs to achieve euthyroid status (83).
Increased thyroid hormone synthesis secondary to iodine administration	Amiodarone	In addition to providing a large iodine load, amiodarone also inhibits type I 5'-deiodinase resulting in increased thyroxine (98).
	Iodinated contrast dye	Contrast medium-induced thyrotoxicosis is rare. Patients at risk of developing thyrotoxicosis after contrast medium injection are patients with Graves' disease and patients with multinodular goiter with thyroid autonomy, especially if they are elderly patients and live in iodine-deficient areas (118).
Increased free fraction of thyroid hormone	Heparins	Heparin administration results in a transient increase of free concentrations of thyroxine (119). This occurs with even low-dose subcutaneous therapy (120). This is a result of displacement of thyroid hormone by the free fatty acids generated due to activation of lipoprotein lipase by heparin. Free thyroxine estimation should be taken at least 10 hrs after the last injection of low molecular weight heparin (80, 118).
TSH decrease	Dobutamine	One study using high-dose dobutamine (20–50 $\mu\text{g}/\text{kg}/\text{min}$) noted decreased TSH concentrations (122). Another study (123) in healthy volunteers, using more conventional doses (maximum of 20 $\mu\text{g}/\text{kg}/\text{min}$), reported no effect on TSH.
	Dopamine	Dopamine infusions have been shown to reduce TSH concentrations and T_4 production rates.
	Corticosteroids	Corticosteroids seem to blunt TSH release via a direct effect on the anterior pituitary (124). Low-dose hydrocortisone has been shown to reduce TSH secretion by 50% (125). Corticosteroids also inhibit the peripheral conversion of T_4 to T_3 , which makes them a useful adjunct in the management of thyrotoxicosis (126). Most studies have demonstrated an effect on TSH secretion within 24 hrs, others (127) suggested that only prolonged hypercortisolism is likely to inhibit TSH secretion. In general, corticosteroid administration does not result in hypothyroidism (128).
	Octreotide	Doses of 100 μg per day have been associated with decreases in TSH secretion; however, much like corticosteroids, octreotide is not thought to cause hypothyroidism due to negative feedback loop with the intact hypothalamic-pituitary-thyroid axis (128).
Displacement from protein-binding sites	Furosemide	At doses of >80 mg, the initial effect of furosemide on thyroid hormone results in a transient increase in serum free thyroxine concentrations and a decrease in total thyroxine level (128, 129). With continued administration, total T_4 levels may decrease while serum free T_4 normalizes. High-dose furosemide may be one factor that contributes to the development of euthyroid sick syndrome, specifically low thyroxine state (130).
Decreased thyroid hormone secretion	Lithium	Lithium-induced hypothyroidism can range from subclinical hypothyroidism to life-threatening myxedema coma. Lithium is concentrated in the thyroid gland and is reported to inhibit thyroxine release and thyroid hormone synthesis (82, 83).
Unknown	Atypical antipsychotics	Based on clinical trials, there is a dose-related decrease in both total and free T_4 levels with the effects being maximal in the first 2–4 wks (131–133). In addition, there are several case reports (134–136) of quetiapine-induced hypothyroidism. During the trials, patients either discontinued therapy or were initiated on levothyroxine. Recently, Kontaxakis et al (137) suggested that hypothyroidism may resolve spontaneously without having to stop quetiapine or initiating replacement therapy.

TSH, thyroid-stimulating hormone; T_3 , thyroxine; T_4 , triiodothyronine.

that autonomic function may be impaired (including impaired catecholamine secretion) by prior hypoglycemia. Others have argued that hypoglycemia is simply a marker for poor counterregulatory hormone response. As such, the development of insulin-induced hypoglycemia may be

simply a marker of poor physiologic reserve, similar to the poor prognosis associated with lack of adrenocortical function in ICU patients (11, 139). Spontaneous hypoglycemia seems to have a worse prognosis than insulin-induced hypoglycemia, although these data are still

evolving (146). Another issue, which has recently emerged, is the potential difference in outcome among surgical ICU patients receiving IIT vs. medical ICU patients (140). This observation is largely driven by one or two studies but is likely worthy of further research. Surgical pa-

Table 3. Drug-related hypoglycemia in the intensive care unit

Mechanism	Drugs	Comments
Increase in peripheral insulin sensitivity	ACE inhibitors	ACE inhibitors may be implicated in up to 14% of all hospital admissions for hypoglycemia among diabetics (148). A recent systematic review concluded that ACE inhibitors were associated with an increased risk of hypoglycemia (odds ratio, 3.0; 95% confidence interval, 1.7–5.3), but noted that this association was based on very low-quality evidence (149). Despite the limited evidence, clinicians should be aware of the potential risk for ACE inhibitors to cause hypoglycemia and subsequent hospitalization.
Possibly due to stimulation of pancreatic insulin secretion	Fluoroquinolones	Gatifloxacin was withdrawn from the market due to reports of hypoglycemia and hyperglycemia resulting in both hospitalizations and fatalities. The data regarding the other fluoroquinolones are mixed. Levofloxacin has been reported to cause fatal hypoglycemia (150, 151), and a large retrospective study (152) noted similar rates of dysglycemia with levofloxacin and gatifloxacin. However, a nested case control study (153) reported a higher rate of hypoglycemia with gatifloxacin compared with levofloxacin. Ciprofloxacin does not seem to cause significant hypoglycemia except when used concomitantly with glyburide (154, 155). Postmarketing studies (156) of moxifloxacin have not revealed an increased risk of hypoglycemia. Renal failure, sepsis syndrome, and concomitant hypoglycemic drug therapy seem to increase the risk of fluoroquinolone-related hypoglycemia (153).
Increase in insulin secretion through direct cytolytic effects to pancreatic β cells	Pentamidine	Pentamidine-induced hypoglycemia may result in death (157, 158). There is a higher incidence with intravenous or intramuscular formulations compared with the nebulized formulation. Oral diazoxide may be useful in treating pentamidine-induced hypoglycemia (159). Risk factors include long duration, increasing dosages, renal impairment, and repeat courses (158, 160).
Increase in pancreatic insulin secretion	Quinine	Risk factors include renal failure and poor nutrition (161). Quinine-induced hypoglycemia is more common after parenteral or rectal administration, although there are reports (162, 163) with large doses of oral quinine. Refractory hypoglycemia secondary to quinine may be treated with octreotide, a long-acting somatostatin analogue (164).
	Sulfonylurea toxicity	Due to their long duration of action, sulfonylurea-associated hypoglycemia may not be easily reversible. Numerous published cases (165) have demonstrated a beneficial role for octreotide in the treatment of refractory sulfonylurea-induced hypoglycemia. Concomitant use of glyburide and drugs that inhibit CYP2C9, such as co-trimoxazole, should be avoided due to increased hypoglycemia (166). Octreotide may also be useful in meglitinide overdose (167). Clinicians should consider octreotide as part of the standard regimen in patients presenting with sulfonylurea or meglitinide-induced hypoglycemia.
Increase in pancreatic insulin secretion, increase in peripheral glucose utilization, decrease in peripheral gluconeogenesis	Salicylates	Hypoglycemia, due to salicylate toxicity, is most commonly reported in children (161). In adults, salicylate toxicity is rare (168). Salicylate toxicity can occur regardless of the route of administration (169). Plasma glucose may not be a reliable indicator of cerebrospinal fluid glucose concentrations and hypoglycorrhachia may occur despite normal plasma glucose levels (170).

ACE, angiotensin-converting enzyme.

tients in general may have better nutritional status before ICU stay than medical patients. In addition, the use of parenteral nutrition may be more common in surgical ICUs compared with medical ICUs. Thus, ongoing research will be required to provide definitive recommendations regarding which patients, if any, should undergo IIT. A sensible glucose target threshold of 150–180 mg/dL has emerged from consensus (147), but further work will be required to provide any data-driven recommendations.

Drug-induced dysglycemia

In addition to insulin, Table 3 lists other drugs that should be considered in the differential diagnosis of hypoglycemia (148–170). Although many of these agents are not typically provided to the

critically ill, the critical care practitioner should be aware of these agents for cases of overdose, especially for very long-acting agents, such as sulfonylureas, which may induce metabolic derangements several days into ICU stay. Such abnormalities are frequently masked by the initial stress hyperglycemia that is commonly observed early in critical illness. In our experience, many of the causes listed in Table 3 are quite rare, mandating a high clinical index of suspicion to recognize these cases. Although many ICU patients are malnourished, hypoglycemia should not be attributed to underlying nutritional status alone.

Hyperglycemia

Despite the controversies about IIT, most agree that marked hyperglycemia is

problematic and should be both treated and, if possible, avoided in the ICU. Glucocorticoid therapy is a common cause of drug-induced hyperglycemia in the ICU. However, we have frequently observed ICU patients who receive pulse-dose steroids without adequate consideration for the resulting effects on glucose regulation. In addition, pressors including catecholamines are commonly associated with hyperglycemia. Other agents to consider are listed in Table 4 (171–184).

The role of total parenteral nutrition (TPN) in the critically ill has been controversial, due to a lack of supportive data. Some editorialists have suggested major harmful effects of TPN, whereas others have suggested that the lack of quality trials prevents any definitive conclusions (185, 186). In many prior ran-

Table 4. Drug-related hyperglycemia in the intensive care unit

Mechanism	Drugs	Comments
Increase in gluconeogenesis, increased insulin resistance, decrease in pancreatic insulin secretion	Glucocorticoids	Glucocorticoids can exacerbate preexisting hyperglycemia and may also result in new-onset diabetes (168, 171). Even low-dose hydrocortisone is associated with an increased rate of hyperglycemia (172). The impact of steroids on glycemic control can be minimized by administering the steroid as a continuous infusion instead of bolus dosing (173).
Indirect effects on pancreatic β -cells causes impaired insulin release	Pentamidine	Pentamidine seems to have a multiphasic effect on the β cell. Initially, hypoglycemia may occur (Table 3). With continued therapy, β cell destruction occurs, leading to hyperglycemia and even overt diabetic ketoacidosis (168).
Decreased insulin biosynthesis and release. Toxic concentrations have been shown to induce islet cell apoptosis	Calcineurin inhibitors (cyclosporine, tacrolimus)	Posttransplant diabetes can occur with calcineurin inhibitors. Controversy exists regarding the frequency of posttransplant diabetes between cyclosporine and tacrolimus (174, 175). If it occurs, posttransplant diabetes is likely to occur earlier with tacrolimus than cyclosporine (175). The combination of steroids and calcineurin inhibitors are major causes for the high rates of new diabetes among transplant patients (171).
Activation of glycogenolysis, increased hepatic gluconeogenesis, stimulation of glucagon and cortisol	Vasopressors	Vasopressors are a risk factor for poor glycemic control (176). Epinephrine causes more severe hyperglycemia than norepinephrine (177). The effects of catecholamines on glucose metabolism are mainly thought to be mediated by β_2 -adrenoceptors (178).
Multifactorial	Atypical antipsychotics	Glucose abnormalities can range from developing new-onset diabetes to life-threatening diabetic ketoacidosis (179, 180). This can occur even without a prior history of diabetes mellitus (181). The risk of diabetes is highest with clozapine and olanzapine (182). Most cases of olanzapine-induced diabetes or diabetic ketoacidosis typically occur within 3 mos, although the range is anywhere from 3 days to 17 mos (183, 184).

domized trials of TPN, glucose control was not adequately assessed (187). Therefore, some have concluded that the potentially deleterious effects of TPN may be mediated by iatrogenic hyperglycemia. Critics have argued that adequate glycemic control (not necessarily intensive insulin but minimizing marked hyperglycemia) may reduce such complications. For example, although TPN was classically blamed for cases of candidemia, evidence (142) suggested that hyperglycemia is a more robust predictor of this complication than TPN itself. In addition, observational data (188) suggested that the limit of 4 mg/kg/min of dextrose infusion helps minimize the occurrence of hyperglycemia. Furthermore, evolving studies (189) have suggested that the strategy of hypocaloric nutrition (i.e., providing enough calories to maintain nitrogen balance without necessarily meeting full caloric requirements) may be a safe and effective approach to feeding. One meta-analysis (186), focusing on studies using the intention to treat principle, has shown possible benefits to TPN in ICU patients. Although many consensus statements have advocated for early enteral nutrition, the existing data supporting this strategy remain sparse. The

National Institutes of Health Acute Respiratory Distress Syndrome Clinical Network is currently conducting a study to test the hypothesis that early enteral nutrition is beneficial (NCT00883948). Ibrahim et al (190) have observed complications, including aspiration from early bolus administration of enteral feeds in the ICU, leading some to question this practice. Van den Berghe is currently investigating the role of early parenteral nutrition in an ongoing trial (NCT00512122). Thus, further adequately designed randomized trials will be required to draw any definitive conclusions regarding optimal ICU nutrition.

Glucose-insulin-potassium has been advocated by many authors. The topic remains controversial, because various randomized trials have led to disparate conclusions. The Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study (191) created initial enthusiasm, as the authors observed marked improvements in short- and long-term outcome among myocardial infarction patients in whom insulin infusions were provided in hospital, and reasonable glycemic control was subsequently maintained. However, subsequent studies have been less

convincing. The largest randomized trial to date (Clinical Trial of Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation—Estudios Cardiológicos Latinoamerica, $n = >20,000$) showed no major improvement with a glucose-insulin-potassium-based strategy (192); however, critics emphasized that glucose levels were inadequately matched between the groups. As such, elevations in blood sugar in the glucose-insulin-potassium arm may have minimized potential benefits of this treatment approach. Thus, further research will be required regarding metabolic support of cardiac patients.

Conclusions

Considerable progress has been made in the care of critically ill patients. Advances in pharmacotherapy have been substantial but require an appreciation for the side effects of these medications. A number of medicines have important endocrine effects, which can have a major impact on ICU outcome. Endocrine diseases in the ICU are receiving increasing attention, although the influences of various medications on these entities require further study.

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