CME/CE ARTICLE

Adrenal Insufficiency and Vasopressor-Resistant Hypotension in Critical Illness

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In the complex setting of critical illness, adrenal insufficiency is easily overlooked. This article illustrates how the presence of vasopressor-resistant hypotension can alert clinicians to this serious condition.

CONTINUING MEDICAL EDUCATION and CONTINUING EDUCATION

GOAL

To highlight the clinical features of acute adrenal insufficiency in the intensive care unit (ICU) and explore the link between this condition and vasopressor-resistant hypotension.

OBJECTIVES

After reading this article and taking the appropriate test (CME on page 67 or CE on page 69), all physicians and other health care professionals should be able to:

1. Recognize the signs, symptoms, and possible causes of adrenal insufficiency in patients with critical illness.
2. Describe the best methods for diagnosing adrenal insufficiency in such patients, and contrast these methods with those used in nonstressed patients.
3. Discuss the appropriate treatment of adrenal insufficiency in the ICU setting.

ACCREDITATION

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CME/CE PEER REVIEW

This article has been peer reviewed and approved for CME credit by Peter Dicpinigaitis, MD, professor of clinical medicine at Albert Einstein College of Medicine, Bronx, NY. Review date: February 2005. **Dr. Dicpinigaitis reports being a member of the consultant/advisory boards of Novartis, Schering-Plough, and Adams Respiratory Therapeutics and the speakers' bureau of Boehringer-Ingelheim.**

This article has been peer reviewed and approved for CE credit by Julie A. Hixson-Wallace, PharmD, BCPS, clinical associate professor and director of continuing education at Mercer University Southern School of Pharmacy, Atlanta, GA.

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CME test on page 67 CE test on page 69

Adrenal insufficiency impairs the body's ability to respond appropriately to the physical stress of illness. As such, it represents a serious threat to critically ill patients.[1] Although the overall incidence of adrenal insufficiency among patients in the intensive care unit (ICU) has been reported as low, many authors have suggested that the condition is underdiagnosed in this setting.[1–3] Furthermore, one study found that the incidence of adrenal insufficiency in a surgical ICU rose substantially (from 0.66% to 11%) when only patients over 55 years of age who had ICU stays of more than 14 days were considered.[2] This fact is particularly rele-

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vant to the VHA patient population, in which advanced age and multiple comorbidities are common.

One factor contributing to the difficulty of recognizing adrenal insufficiency in the ICU setting is the nonspecific nature of many of its characteristic symptoms. Weakness, weight loss, and anorexia,[1] for example, have a variety of possible etiologies and are so common in ICU patients as to render them unreliable markers of adrenal insufficiency.

Hypotension, another classic sign of adrenal insufficiency, also is commonly encountered in the ICU. Although few published reports have identified adrenal insufficiency as the cause of hypotension in this setting, three-year experience from the medical-surgical ICU of the VA Central California Health Care System, Fresno suggests that vasopressor-resistant hypotension, in combination with other telling features, should raise clinicians' suspicion for this serious disorder. This article details this experience and discusses a number of issues pertinent to the prompt diagnosis and treatment of adrenal insufficiency in the ICU setting.

THE CASES

The following five cases occurred in the 12-bed, medical-surgical ICU of the VA Central California Health Care System between 1998 and 2001. All of the patients developed hypotension that resisted standard treatment with vasopressors and IV fluids and were subsequently found to have adrenal insufficiency (defined here as a random or basal serum cortisol level of less than 15 µg/dL[2,4]). During this three-year period, the incidence of adrenal insufficiency in this ICU was determined to be 0.3%. Since not all hypotensive patients had cortisol values measured, however, the actual incidence may have been higher.

Patient 1

A 91-year-old patient developed respiratory failure due to pneumonia. He had a history of polymyalgia rheumatica and had been receiving daily doses of prednisolone varying from 1 to 7.5 mg for several years.

After several months in the ICU, the patient's prednisolone was inadvertently discontinued. He subsequently developed unexplained emesis and diarrhea and became hypotensive and somnolent. He required IV fluids and dopamine up to 20 µg/kg/min to maintain a systolic blood pressure (BP) greater than 90 mm Hg. His basal serum cortisol level was 6.6 µg/dL (Table 1).

Within 24 hours of initiating hydrocortisone 100 mg IV every eight hours, the patient's BP returned to normal. The dopamine was discontinued, the vomiting and diarrhea resolved, and his mental status improved. He was discharged with a regimen of prednisolone 7.5 mg/day.

Patient 2

A 51-year-old patient developed acute respiratory distress syndrome (ARDS) that persisted for two months following repair of a gastric perforation. During this time, he developed necrotizing fasciitis. Renal failure ensued, necessitating temporary hemodialysis. *Candida albicans* was cultured from the peritoneum.

After dialysis was completed, the patient began a regimen of fluconazole 400 mg IV every other day to treat his candidiasis. During this treatment, he developed hypotension and eosinophilia (15% eosinophils) (Table 2). His laboratory tests also revealed hyponatremia (serum sodium level, 129 mEq/L) and hyperkalemia (serum potassium level, 6.2 mEq/L). He required dopamine 12 µg/kg/min and IV fluids to keep his BP at 90/40 mm Hg. His central venous pressure (CVP) was elevated at 19 mm Hg and his basal serum cortisol level was 6.6 µg/dL.

The patient was given hydrocortisone 100 mg IV every eight hours, and within 24 hours, his BP nor-

Table 1. Cosyntropin stimulation test* results for five patients with vasopressor-resistant hypotension in the intensive care unit at the VA Central California Health Care System

Patient no.	Serum cortisol level (µg/dL)				
	Basal†	30 minutes	60 minutes	90 minutes	120 minutes
1	6.6	11.7	14.4	—	—
2	6.6	10.5	12.3	11.5	—
3	5.3	5.9	6.6	—	—
4	9.6	14.3	—	—	33.0
5	13.0	—	19.5	19.6	—

*Test consisted of administration of cosyntropin 250 µg IM and subsequent measurement of serum cortisol levels. (A normal test does not exclude adrenal insufficiency.)
†Random or basal serum cortisol level should be > 15 µg/dL in acute severe stress.[2,4]

malized, the dopamine was discontinued, and his renal function returned to baseline. Over the following weeks, the steroids were tapered and discontinued and the patient recovered completely from ARDS. A random serum cortisol measurement taken two months after discontinuation of fluconazole was normal at 16.6 µg/dL.

Patient 3

An 82-year-old patient with severe chronic obstructive pulmonary disease (COPD) underwent a hemicolectomy. He developed postoperative somnolence and respiratory failure and required reintubation and mechanical ventilation. After 16 days, he became hypotensive with BP measurements ranging between 70/40 and 120/60 mm Hg. His CVP was high at 10 mm Hg. He required dopamine up to 25 µg/kg/min and IV fluids to maintain even a suboptimal BP. He appeared apathetic, and his basal serum cortisol level was 5.3 µg/dL.

Within 24 hours of beginning treatment with hydrocortisone 100 mg IV every eight hours, his BP returned to normal, the dopamine was discontinued, and his mental status improved. It was later discovered that, for several years prior to the admission for colonic surgery, he had been receiving inhaled steroids (triamcinolone up to 1,600 µg/day) to treat his COPD, and this treatment had been discontinued erroneously around the time of his surgery. There was no evidence that the patient had received oral steroids over the previous six years. This patient died five months later from respiratory failure.

Patient 4

A 77-year-old patient with a history of COPD was seen in the emergency department because of a four-week history of shortness of breath and new-onset chest pain. He had a cardiac arrest immediately on arrival.

Following intubation and resuscitation, laboratory investigations revealed substantially elevated creatine phosphokinase and troponin I levels (653 U/L and 11.6 ng/mL, respectively). The patient remained hypotensive with a BP of 82/48 mm Hg and a heart rate of 96 beats/min. His CVP was elevated at 10 mm Hg. Initially, he was believed to be in cardiogenic

Table 2. Relevant laboratory and hemodynamic findings in five patients with adrenal insufficiency and hypotension in the intensive care unit at the VA Central California Health Care System

Parameter	Normal range	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Sodium (mEq/L)	135–145	Normal	129	132	Normal	Normal
Potassium (mEq/L)	3.5–5.3	Normal	6.2	Normal	Normal	Normal
% eosinophils	0–3	Normal	15	Normal	Normal	Normal
Creatine phosphokinase (U/L)	22–240	—	—	8	653	—
Troponin I (ng/mL)	0–0.5	—	—	—	11.6	—
CVP* (mm Hg)	2–6	—	19	10	10	11
Cardiac output (L/min)	4–8	—	—	—	—	10.9
SVR† (dyne-sec/m^2cm^5)	800–1,500	—	—	—	—	425

*CVP = central venous pressure. †SVR = systemic vascular resistance.

shock, but an echocardiogram taken at bedside upon admission showed good left ventricular function. He required norepinephrine 8 µg/min and dobutamine 10 µg/kg/min to maintain a systolic BP of 90 mm Hg.

The patient had been admitted for a COPD exacerbation three months previously, at which time his BP was 148/87 mm Hg. He had been given a 10-day course of prednisolone 40 mg/day with subsequent outpatient tapering.

During the present admission, a random serum cortisol test administered while the patient was hypotensive and receiving mechanical ventilation revealed a level of 9.6 µg/dL. (This level was used as the basal measurement for a cosyntropin test performed immediately afterward, which confirmed adrenal insufficiency.) Within 24 hours following initiation of hydrocortisone 100 mg IV every eight hours, the patient's BP improved to 126/65 mm Hg. At this point, norepinephrine and dobutamine were discontinued.

Subsequent thoracentesis revealed an adenocarcinoma of the lung with pleural metastases. With this new information, the patient was extubated. He died shortly afterward. At autopsy, his adrenal glands were found to be normal.

Patient 5

A 74-year-old patient was admitted to the surgical service with abdominal pain and was found to have an intestinal obstruction. His pulse was 117 beats/min and his BP was 130/52 mm Hg. At laparotomy, an impending ileocecal perforation with gangrenous changes in the bowel wall was observed. A hemicolectomy and ileostomy were performed.

Over the following five days he remained hypotensive on mechanical ventilation with a pulse of 86 beats/min and a BP of 75/42 mm Hg. He required dopamine 4 µg/kg/min and norepinephrine up to 4 µg/min to maintain a BP around 90/66 mm Hg. His CVP and cardiac output were elevated (11 mm Hg and 10.9 L/min, respectively), and his systemic vascular resistance (SVR) was low (425 dyne-sec/m^2cm^5). His wedge pressure was normal (11 mm Hg). A random serum cortisol measurement obtained on the fifth postoperative day was 13 µg/dL. (This measurement was used as a basal value for a cosyntropin test administered immediately afterward.)

Within 48 hours of starting hydrocortisone 100 mg IV every eight hours, the patient no longer required vasopressors. He was extubated seven days later. A subsequent cosyntropin test performed four days after hydrocortisone was discontinued revealed a basal serum cortisol level of 16.8 µg/dL that rose to 29.4 µg/dL one hour following administration of cosyntropin 250 µg. He recovered completely and was discharged.

CLUES TO ADRENAL INSUFFICIENCY

The patients described here had conditions and characteristics that are common in the patient population served by the VA health care system. All were male and four of the five (patients 1, 3, 4, and 5) were over 65 years of age. Three (patients 1, 2, and 3) had been hospitalized for several weeks prior to diagnosis, and three (patients 2, 3, and 5) were recovering from surgery.

The characteristic, nonspecific symptoms of adrenal insufficiency were largely absent in this group of patients—though two of them (patients 1 and 3) had lethargy and one (patient 1) experienced gastrointestinal disturbance. These patients also lacked some of the more specific features of adrenal insufficiency, such as salt craving and hyperpigmentation.

All of the patients, however, developed hypotension resistant to volume resuscitation and vasopressor therapy, which has been associated previously with adrenal insufficiency.[1,4,5] At the time the diagnosis of adrenal insufficiency was made, four of the five patients (patients 1, 2, 3, and 5) were receiving dopamine for their hypotension, one (patient 4) was receiving dobutamine, and two (patients 4 and 5) were receiving norepinephrine—all without a satisfactory response. In all cases, the hypotension resolved within 24 or 48 hours of hydrocortisone initiation.

Other clues to the possible existence of adrenal insufficiency include: failure to wean from a ventilator[2]; the presence of eosinophilia, hypoglycemia, hyponatremia, or hyperkalemia[1]; and unexpected high cardiac output with low SVR, in the absence of documented sepsis or other causes of elevated cardiac output.[1,6] All five of the patients described here were receiving mechanical ventilation at the time of diagnosis; one (patient 2) had eosinophilia, hyponatremia, and hyperkalemia; and one (patient 5) had an elevated cardiac output and low SVR.

MEASURING CORTISOL LEVELS

The traditional method used to detect primary adrenal insufficiency in patients who are not critically ill is to monitor the change in serum cortisol levels before and at 30 and 60 minutes after adrenal gland stimulation with cosyntropin 250 µg IV

or IM.[7,8] In these patients, the efficacy of intravenous and intramuscular methods of cosyntropin administration are equivalent.[9] In hypotensive patients, however, the intravenous route may be more effective since intramuscular doses may not be absorbed properly.

Following cosyntropin administration, a peak serum cortisol value of greater than 18 or 20 µg/dL has been used to identify normal adrenal function.[10] Of the five patients described here, four (patients 1, 2, 3, and 4) had a serum cortisol level below this threshold after 30 minutes, and three (patients 1, 2, and 3) were still under 18 µg/dL at the 60-minute measurement. A 30-minute measurement was not available for patient 5, and at the 60-minute point, his level was just over the minimum threshold at 19.5 µg/dL.

A normal response to cosyntropin, however, does not exclude adrenal insufficiency. Because the cosyntropin stimulation test assesses only the response of the adrenal gland to exogenous stimulation, it may not detect adrenal insufficiency that is due to hypothalamic-pituitary dysfunction. That, combined with use of a supraphysiologic dose of cosyntropin, gives the test a low negative predictive value.[1,11] And when a high cutoff value for adrenal insufficiency is used to increase the test's sensitivity, the chances of false-positives are increased.[11]

For patients outside the ICU setting, therefore, additional testing may be necessary to clarify the diagnosis—and to prevent both untreated disease and unnecessary lifelong corticosteroid replacement.[11] The insulin tolerance test and metyrapone test both assess the integrity of the entire hypothalamic-pituitary-adrenal (HPA) axis, and as such, may be useful adjuncts to the cosyntropin stimulation test. Situations in which the results of these tests have differed from the results of the cosyntropin test have been described,[12] and these serve to highlight the importance of hypothalamic-pituitary dysfunction as a possible source of adrenal insufficiency.

In the setting of critical illness and hypotension, however, these tests may not be practical. In fact, because the metyrapone test can reduce cortisol levels further in a hypotensive ICU patient, there is a potential that its use might worsen the adrenal crisis. In stressed ICU patients, the diurnal variation in cortisol is absent, so a random cortisol measurement presumably reflects maximum endogenous HPA activity.[1,4] For this reason, some authors suggest a random cortisol measurement alone is satisfactory to assess the entire HPA axis in a severely stressed, hypotensive patient, and that a random serum cortisol level of less than 25 µg/dL represents adrenal insufficiency.[1] Indeed, if we accept that the endogenous stress response is a more accurate picture of HPA function than is the response to exogenous stimulation with cosyntropin, the accuracy of a random cortisol value of less than 25 µg/dL in diagnosing adrenal insufficiency in stressed patients may be superior to that of the cosyntropin test alone in nonstressed patients.

Other studies have suggested lower thresholds for diagnosing adrenal insufficiency in patients with critical illness. In one review of the laboratory diagnosis of adrenal insufficiency, the authors state that random cortisol values greater than 18 µg/dL are considered normal, values between 13 and 18 µg/dL are indeterminate and require further testing, values less than 13 µg/dL mandate glucocorticoid therapy, and values below 5 µg/dL are considered adrenally insufficient.[10] Another review suggests a minimum satisfactory cortisol threshold of 15 µg/dL, below which adrenal insufficiency is likely, and a maximum cortisol value of 34 µg/dL, above which adrenal insufficiency is unlikely. According to this review, values between 15 and 34 µg/dL can be interpreted only in conjunction with cosyntropin stimulation.[4] In all five of the ICU cases presented here, adrenal insufficiency was confirmed by a basal serum cortisol value of less than 15 µg/dL.

Some authors suggest a random cortisol measurement alone is satisfactory to assess the entire HPA axis in a severely stressed, hypotensive patient.

UNDERSTANDING ADRENAL INSUFFICIENCY IN CRITICAL ILLNESS

Among the five cases described here, there were various factors

that may have contributed to the development of adrenal insufficiency. In the case of patient 1, the presence of pneumonia combined with the inadvertent discontinuation of his ongoing steroid therapy (for polymyalgia rheumatica) probably were to blame. Patient 2 was receiving fluconazole, which has been associated with adrenal insufficiency in a few case reports.[13,14] Moreover, adrenal insufficiency is a known adverse effect of a similar drug, ketoconazole[15]—indeed, ketoconazole has been used to treat Cushing's syndrome.[16,17] Patient 3, who had hypotension following abdominal surgery, had been receiving inhaled steroids preoperatively. Although the systemic steroid availability of inhaled triamcinolone is low due to its first-pass inactivation of the swallowed portion, inhaled steroids are known to cause adrenal insufficiency.[18,19] In the case of patient 4, critical cardiac illness (myocardial infarction) is believed to have precipitated the adrenal insufficiency. Patient 5 developed adrenal insufficiency following a surgical emergency, a situation that has been recognized previously.[3,20–23] In general, the more aggressive the surgery, the more likely it is that adrenal insufficiency will develop postoperatively.

Patients 2 and 5 experienced only transient adrenal dysfunction, which has been reported previously.[3,22,23] Although much has been written recently about sepsis-induced adrenal insufficiency, none of the patients described here had confirmed sepsis. It's possible, however, that patient 3 may have become septic due to his *C. albicans* infection.

All five patients were receiving mechanical ventilation at the time of diagnosis. Similarly, five of the six patients with adrenal insufficiency described by another author were on ventilators.[23] Four of the patients described here (patients 1, 2, 3, and 5) were successfully extubated following hydrocortisone treatment for adrenal insufficiency. Three (patients 1, 2, and 5) recovered completely and were discharged home, one (patient 4) died of disseminated carcinomatosis, and one (patient 3) died from respiratory failure.

"Relative adrenal insufficiency" is an entity in which a hypotensive patient has a cortisol value that falls into the normal—or normal to high—range but is inadequate to maintain a normal BP.[24] Patients with this condition often are in septic shock and may be receiving prolonged mechanical ventilation. Recent studies have demonstrated that treatment with "stress doses" of steroids can resolve hypotension and improve patients' general condition. In a prospective, randomized, double-blind study by Briegel and colleagues, patients with septic shock who received stress doses of hydrocortisone were able to cease vasopressor support in only two days, compared with seven days among those who received placebo.[25] This effect was mediated by an increase in the SVR attributed to the enhanced responsiveness of the vascular system to vasopressors.[25]

In both septic and nonseptic critically ill patients, the response of cyclic adenosine monophosphate to catecholamine is impaired. It is unclear whether this is due to a reduction in beta-receptor density or to a decreased affinity of receptors for agonists.[26]

Low dose dopamine increases BP by means of a positive inotropic effect on the heart and results in an increase in cardiac output. Higher dose dopamine stimulates the adrenergic receptors of the sympathetic nervous system. In contrast to dopamine's primarily inotropic effects on BP, steroids mainly enhance peripheral vasoconstriction.

Cortisol is necessary both to synthesize[27] and to facilitate the pressor action of catecholamines, including dopamine.[28] Chronic stress resulting in catecholamine elevation may downregulate adrenergic receptors. In the five stressed, hypotensive, ICU patients described here, treatment with hydrocortisone may have restored vascular responsiveness to catecholamines (including dopamine) by upregulating beta-receptors.[29]

RAISING AWARENESS

Considering the complex underlying diseases characteristic of many ICU patients, adrenal insufficiency is easily forgotten as a cause of vasopressor-resistant hypotension. The etiology of adrenal insufficiency in such patients is heterogeneous and different from that of patients with-out critical illness. Any history of steroid use (including inhaled steroids) or use of drugs that interfere with cortisol synthesis or metabolism should be noted. It is also important to be aware that adrenal insufficiency can be caused by suppression of any part of the HPA axis as a result of sepsis or a critical illness (for example, patient 4's acute myocardial infarction and patient 5's acute abdominal emergency).

In general, clinicians should keep a high index of suspicion for adrenal insufficiency in the vasopressor-dependent, hypotensive ICU patient, since even "normal" basal cortisol values in the range of 15 to 25 µg/dL may represent adre-

nal insufficiency.[1,2,4] Based on the data available and the experience described in this article, I would recommend that any ICU patient with vasopressor-resistant hypotension and a random or basal serum cortisol level less than 15 µg/dL receive physiologic doses of hydrocortisone (50 to 100 mg IV every eight hours). Larger doses could be detrimental. Recommendations regarding the dosing of steroids in the ICU setting have been published.[30]

In a 1996 article, Oelkers stated that "the treatment of adrenal crisis with full recovery of a dangerously ill patient within a few days is one of the greatest achievements of modern medicine."[5] Yet, there is still work to be done in improving recognition and management of adrenal insufficiency in the ICU. By staying aware of the condition and its various signs and by keeping abreast of the latest advances in diagnosis and treatment, we can help close the gap between the possible and the actual. ●

The author would like to thank Abdolkarim Sohrabi, MD, MPH and Gregory A. Wille, MD for permission to include their patients in this review.

The opinions expressed herein are those of the author and do not necessarily reflect those of the sponsors, Federal Practitioner, *Quadrant HealthCom Inc., the U.S. government, or any of its agencies. Please review complete prescribing information for specific drugs or drug combinations—including indications, contraindications, warnings, and adverse effects—before administering pharmacologic therapy to patients.*

REFERENCES

1. Marik PE, Zaloga GP. Adrenal insufficiency in the critically ill: A new look at an old problem. *Chest*. 2002;122:1784–1796.
2. Barquist E, Kirton O. Adrenal insufficiency in the surgical intensive care unit patient. *J Trauma*. 1997;42:27–31.
3. Merry WH, Caplan RH, Wickus GG, et al. Postoperative acute adrenal failure caused by transient corticotropin deficiency. *Surgery*. 1994;116: 1095–1100.
4. Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. *N Engl J Med*. 2003;348:727–734.
5. Oelkers W. Adrenal insufficiency. *N Engl J Med*. 1996;335:1206–1212.
6. Dorin RI, Kearns PJ. High output circulatory failure in acute adrenal insufficiency. *Crit Care Med*. 1988;16:296–297.
7. Wood JB, Frankland AW, James VH, Landon J. A rapid test of adrenocortical function. *Lancet*. 1965;191:243–245.
8. Streeten DH. What test for hypothalamic-pituitary-adrenocortical insufficiency? *Lancet*. 1999;354:179–180.
9. Hawkins JB Jr, Burch WM. Rapid tests of adrenocortical function. Intravenous versus intramuscular administration of synthetic ACTH. *N C Med J*. 1989;50:306–308.
10. Grinspoon SK, Biller BM. Clinical review 62: Laboratory assessment of adrenal insufficiency. *J Clin Endocrinol Metab*. 1994;79:923–931.
11. Dorin RI, Qualls CR, Crapo LM. Diagnosis of adrenal insufficiency. *Ann Intern Med*. 2003; 139:194–204.
12. Borst GC, Michenfelder HJ, O'Brian JT. Discordant cortisol response to exogenous ACTH and insulin-induced hypoglycemia in patients with pituitary disease. *N Engl J Med*. 1982;306: 1462–1464.
13. Gradon JD, Sepkowitz DV. Fluconazole-associated acute adrenal insufficiency. *Postgrad Med J*. 1991;67:1084–1085.
14. Albert SG, DeLeon MJ, Silverberg AB. Possible association between high-dose fluconazole and adrenal insufficiency in critically ill patients. *Crit Care Med*. 2001;29:668–670.
15. McCance DR, Kennedy L, Sheridan B, Atkinson BA. Ketoconazole as an inhibitor of steroid production [letter]. *N Eng J Med*. 1988;318:710–711.
16. Sonino N, Boscaro M, Paoletta A, Mantero F, Ziliotto D. Ketoconazole treatment in Cushing's syndrome: Experience in 34 patients. *Clin Endocrinol (Oxf)*. 1991;35:347–352.
17. Boscaro M, Barzon L, Fallo F, Sonino N. Cushing's syndrome. *Lancet*. 2001;357:783–791.
18. Wong J, Black P. Acute adrenal insufficiency associated with high dose inhaled steroids. *BMJ*. 1992;304:1415.
19. Zwaan CM, Odink RJ, Delemarre-van de Waal HA, Dankert-Roelse JE, Bokma JA. Acute adrenal insufficiency after discontinuation of inhaled corticosteroid therapy. *Lancet*. 1992;340: 1289–1290.
20. Steer M, Fromm D. Recognition of adrenal insufficiency in the postoperative patient. *Am J Surg*. 1980;139:443–446.
21. Baldwin WA, Allo M. Occult hypoadrenalism in critically ill patients. *Arch Surg*. 1993;128: 673–676.
22. Kidess AI, Caplan RH, Reynertson RH, Wickus GG, Goodnough DE. Transient corticotropin deficiency in critical illness. *Mayo Clin Proc*. 1993;68:435–441.
23. Mackenzie JS, Burrows L, Burchard KW. Transient hypoadrenalism during surgical critical illness. *Arch Surg*. 1998;133:199–204.
24. Lamberts SW, Bruining HA, de Jong FH. Corticosteroid therapy in severe illness. *N Engl J Med*. 1997;337:1285–1292.
25. Briegel J, Forst H, Haller M, et al. Stress doses of hydrocortisone reverse hyperdynamic septic shock: A prospective, randomized, double-blind, single-center study. *Crit Care Med*. 1999;27: 723–732.
26. Silverman HJ, Penaranda R, Orens JB, Lee NH. Impaired beta-adrenergic receptor stimulation of cyclic adenosine monophosphate in human septic shock: Association with myocardial hyporesponsiveness to catecholamines. *Crit Care Med*. 1993;21:31–39.
27. Bornstein SR, Breidert M, Ehrhart-Bornstein M, Kloos B, Scherbaum WA. Plasma catecholamines in patients with Addison's disease. *Clin Endocrinol (Oxf)*. 1995;42:215–218.
28. Zuckerman-Levin N, Tiosano D, Eisenhofer G, Bornstein S, Hochberg Z. The importance of adrenocortical glucocorticoids for adrenomedullary and physiological response to stress: A study in isolated glucocorticoid deficiency. *J Clin Endocrinol Metab*. 2001;86:5920–5924.
29. Saito T, Takanashi M, Gallagher E, et al. Corticosteroid effect on early beta-adrenergic down-regulation during circulatory shock: Hemodynamic study and beta-adrenergic receptor assay. *Intensive Care Med*. 1995;21:204–210.
30. Coursin DB, Wood KE. Corticosteroid supplementation for adrenal insufficiency. *JAMA*. 2002;287:236–240.

CORRECTION

A coauthor's name was inadvertently dropped from the article "Case in Point—Milk Alkali Syndrome" (*Federal Practitioner*, February 2005, page 12). The article was written by Samar Gupta, MD and Virginia G. Foshée, MD. Dr. Gupta's byline and biography appear on the first page of the article. Dr. Foshée, whose byline and biography did not appear, is a resident physician at the University of Wyoming's Family Practice Residency Program at Cheyenne.