

Risk of adrenal crisis in dental patients

Results of a systematic search of the literature

**Mohd W. Khalaf, BDS; Ruba Khader, BDS; Gregory Cobetto, DMD;
Juan Fernando Yepes, DDS, MD, MPH, DrPH; Dennis G. Karounos, MD;
Craig S. Miller, DMD, MS**

Adrenal insufficiency (AI) is an endocrine disorder characterized by inadequate production of adrenal androgens, mineralocorticoids and glucocorticoids by the adrenal cortex. The condition manifests as primary or secondary AI.¹⁻³ Primary AI, also known as Addison disease, is uncommon, occurring in approximately eight people per 1 million per year, with a prevalence of approximately 40 to 140 people per

Dr. Khalaf is an assistant professor, Division of Oral Diagnosis, Oral Medicine and Oral and Maxillofacial Radiology, Department of Oral Health Practice, College of Dentistry, University of Kentucky, Lexington.

Dr. Khader is an assistant professor, Division of Oral and Maxillofacial Surgery, Department of Oral Health Science, College of Dentistry, University of Kentucky, Lexington.

Dr. Cobetto is an assistant professor, Division of Oral and Maxillofacial Surgery, Department of Oral Health Science, College of Dentistry, University of Kentucky, Lexington.

Dr. Yepes is an associate professor, Division of Pediatric Dentistry, Department of Oral Health Science, College of Dentistry, University of Kentucky, Lexington.

Dr. Karounos is the chief, Endocrinology Section, and a staff physician, Lexington Veterans Administration Medical Center, Kentucky, and an associate professor, Department of Internal Medicine, Division of Endocrinology and Molecular Medicine, College of Medicine, University of Kentucky, Lexington.

Dr. Miller is a professor and a Provost Distinguished Service Professor, Division of Oral Diagnosis, Oral Medicine and Oral and Maxillofacial Radiology, Department of Oral Health Practice, College of Dentistry, University of Kentucky, 800 Rose St., MN 324, Lexington, Ky. 40536-0297, e-mail address cmiller@uky.edu. Address reprint requests to Dr. Miller.

ABSTRACT

Background. The authors performed a systematic search of the literature to identify the frequency of, risk of experiencing and factors associated with adrenal crises in dental patients.

Methods. The authors searched PubMed and Ovid MEDLINE (1947-June 20, 2012) and Embase (1974-2012) for English-language articles related to cases of adrenal crisis in dentistry and extracted and analyzed data from the articles. The six authors determined whether the cases identified met a consensus definition of adrenal crisis.

Results. Of 148 articles identified in the initial screening, 34 articles were included in the final review, from which six cases met the criteria of adrenal crisis. The authors categorized four cases as “suggestive of adrenal crisis” and two cases as “consistent with adrenal crisis.” Risk factors were significant adrenal insufficiency, pain, infection, having undergone an invasive procedure, having received a barbiturate general anesthetic, and poor health status and stability at the time of presentation. The authors estimated risk to be less than one in 650,000 in patients with adrenal insufficiency.

Conclusions. Adrenal crisis is rare in dental patients, with only six reports of it having been published in the past 66 years. Risk is associated with unrecognized adrenal insufficiency, poor health status and stability at the time of treatment, pain, infection, having undergone an invasive procedure and having received a barbiturate general anesthetic.

Clinical Implications. Risk of adrenal crisis is reduced through proper evaluation of the patient, identification of risk factors and following appropriate preventive measures.

Key Words. Adrenal crisis; adrenal insufficiency; dental infection; dental treatment.

JADA 2013;144(2):152-160.

1 million.³⁻⁶ It often is caused by a progressive destruction of the adrenal cortex, which usually is of idiopathic nature (most commonly autoimmune) but also can result from hemorrhage, sepsis, infectious diseases (such as tuberculosis, human immunodeficiency virus, cytomegalovirus and fungal infection), malignancy, adrenalectomy, amyloidosis, administration of certain drugs or congenital disorders.^{1,7} Clinical manifestations develop slowly and typically produce weakness, fatigue, loss of appetite, weight loss and patchy hyperpigmentation of the skin and oral mucosa. Clinical features generally are more prominent in cases of primary AI than in cases of secondary AI and, notably, can manifest as an acute crisis.

Secondary AI results from hypothalamic or pituitary disease or the treatment of these diseases or from the chronic administration of exogenous corticosteroids, which results in inhibition of the feedback loop between the pituitary and adrenal glands. As a result, the pituitary gland fails to produce enough adrenocorticotropin, a hormone that stimulates the adrenal glands to produce cortisol. Secondary AI selectively causes glucocorticoid deficiency; therefore, mineralocorticoid function is better maintained than in primary AI and the condition is less likely to cause acute adrenal crisis.⁷ Secondary AI is two to three times more common than primary AI.^{3,4} Because of the relationship between secondary AI and the medical administration of glucocorticoids, patients may exhibit cushingoid features (puffy round face, central obesity, growth of fat on back of neck, bruising); however, these clinical features are not always demonstrative, and an assessment of adrenal reserve requires measurement of serum cortisol levels and performance of cosyntropin/synacthen stimulation tests.^{8,9}

Adrenal crisis is a rare, potentially lethal event that is precipitated most often by stress (such as that associated with infection, trauma or surgery) in patients with chronic AI. Patients with primary AI are at higher risk of experiencing adrenal crisis than are those who have secondary AI.^{1,10,11} Adrenal crisis evolves because susceptible patients have diminished adrenal reserve and are unable to secrete sufficient amounts of the steroid the body requires during a stressful event.¹²⁻¹⁴ The clinical manifestations of an adrenal crisis are nonspecific and rather sudden in onset; they include fever, gastrointestinal complaints, hypotension, tachycardia and electrolyte disturbances. Without prompt recognition and treatment, hypovolemic shock and cardiovascular failure can ensue.

Adrenal crisis occurs at a rate of five to six events per 100 patient years among patients with primary AI.^{3,12,15} However, the frequency and risk of adrenal crisis in dental patients is less well known. Only a few reports of adrenal crisis associated with dental care exist,¹⁶⁻²¹ and systematic reviews of the subject are lacking. Because of the dearth of literature on this topic, it can be difficult to predict adrenal crisis and make evidence-based recommendations for prevention. Thus, we performed a systematic search of the literature with the intent to analyze the frequency of and factors associated with adrenal crisis in dental patients.

METHODS

Search strategy. We followed standard methodology for systematic reviews as described by Pawson and colleagues²² to conduct our analyses of the occurrence of adrenal crisis in dental patients. We searched PubMed and Ovid MEDLINE from 1947 through June 20, 2012, and with the assistance of librarians at the University of Kentucky Medical Center, Lexington, who specialized in health sciences database searches, we searched Embase from 1974 through June 20, 2012, for English-language articles.

Our search involved the following terms, which are both free text and from the National Library of Medicine's Medical Subject Headings: "adrenal gland diseases/etiology," "adrenal gland diseases/diagnosis," "adrenal insufficiency," "adrenal insufficiency/blood," "adrenal insufficiency/chemically induced," "adrenal insufficiency/drug therapy," "adrenal insufficiency/therapy," "adrenocortical hyperfunction," "oral surgery," "oral medicine," "orthognathic surgery," "oral surgical procedures/adverse effects," "oral surgical procedures/contraindications," "geriatric dentistry," "dental care," "dental care for the chronically ill," "dental care/adverse effects," "endodontics," "emergencies," "emergency medical services emergency treatment," "evidence-based dentistry metabolic diseases adolescent adult," "humans," "corticotropin-releasing hormone hydrocortisone/blood," "hydrocortisone/administration & dosage," "hydrocortisone/deficiency," "hypersensitivity/therapy," "hyperventilation/therapy," "hypoglycemia/therapy," "analgesia," "general anesthesia," "Addison disease/

ABBREVIATION KEY. **AI:** Adrenal insufficiency. **BP:** Blood pressure. **Const:** Constitutional. **CVD:** Cardiovascular disease. **GA:** General anesthesia. **GI:** Gastrointestinal disorder. **IV:** Intravenous. **Lab:** Laboratory test results.

TABLE 1

Criteria for diagnosis of adrenal crisis.*		
FEATURE INVOLVED	MAJOR CRITERIA	MINOR CRITERIA
Gastrointestinal	Abdominal pain, nausea, vomiting	Loss of appetite, weight loss, craving of salty food
Constitutional	Hyperthermia (fever) or hypothermia (loss of consciousness, toxic appearance)	Pale, fatigue, dizziness, unusual sweating, slow sluggish movement, confusion, headache
Cardiovascular	Hypotension, features of shock (such as loss of consciousness)	Rapid heart rate/pulse
Laboratory Test Abnormality	Hyponatremia, hyperkalemia, metabolic acidosis, low cortisol levels, low stimulation test results	Concurrent serum hypoglycemia
Other	None	Hyperpigmentation of skin or mucosa

* Each case was categorized according to the number and type (major or minor) of criteria met. The categories were as follows: consistent with adrenal crisis—two or more major criteria from separate categories that include at least one laboratory test abnormality; suggestive of adrenal crisis—at least one major criterion plus one or more minor criteria; unlikely adrenal crisis—no major criteria plus one or more minor criteria.

diagnosis,” “Addison disease/etiology,” “Addison disease/blood,” “Addison disease/drug therapy,” “glucocorticoids/administration & dosage,” “glucocorticoids/adverse effects,” “Cushing syndrome,” “oral pathology,” “periodontics,” “dentist’s practice patterns,” “stroke/therapy,” “Sjögren syndrome,” “/ complications,” “psychiatry and psychology,” “syncope/therapy,” “status epilepticus/therapy,” “polyendocrinopathies,” “autoimmune,” “pituitary disease,” “pituitary-adrenal system/physiopathology,” “pharmacological addictions,” “practice guidelines as topic,” “tooth diseases/surgery,” and “tooth diseases/complications.” In addition, we searched reference lists of all selected articles, previous systematic reviews, meta-analyses and other relevant articles regarding the need for supplemental corticosteroid use. This search resulted in the identification of 148 articles.

Selection criteria. We established inclusion and exclusion criteria and the review protocol before searching the literature. Included were case-control studies, case reports and case series that described an adrenal crisis in the context of a dental procedure or a planned dental procedure. Excluded were reviews, letters and studies not conducted in humans.

Study selection and data extraction. Two reviewers (M.W.K., C.S.M.) independently screened the titles and abstracts of the 148 articles. When the two reviewers considered an article relevant (that is, it contained mention of adrenal crisis with respect to dental treatment), they obtained and evaluated the full text of the

article. The data extracted involved the type of study design; the patients’ age, race, sex, medical history, medications and chief complaint; the physical findings; the dental procedures performed; the medications delivered; and the patient’s preoperative, operative and postoperative course.

Definition of adrenal crisis.

The two reviewers developed a consensus definition for the diagnosis of adrenal crisis on the basis of information from several references^{13,23,24} and consultation with a board-certified endocrinologist (D.G.K.). The definition was based on evidence of major and minor criteria associated with glucocorticoid and mineralocorticoid deficiency and a drop in extracellular fluid volume in an acute setting (Table 1). Cases were reviewed

independently by an endocrinologist (D.G.K.), three oral medicine practitioners (M.W.K., C.S.M., J.F.Y.) and two oral and maxillofacial surgeons (R.K., G.C.). Reviewers categorized each case as either “consistent with adrenal crisis,” “suggestive of adrenal crisis” or “unlikely adrenal crisis,” per the criteria listed in Table 1. They discussed any disagreements, and the final categorization was obtained by means of unanimous decision.

Statistical analysis. We estimated the probability of an occurrence of adrenal crisis in a dental setting among patients who have AI by dividing the number of cases reported in the literature by the estimated number of patients who visit the dentist per year.²⁵

RESULTS

Of 148 articles initially identified in this systematic search of the literature, 34 articles were included in the final review (Figure 1). From these, we identified six case reports (Table 2,¹⁶⁻²¹ page 156). Sufficient evidence was present such that the reviewers judged that an adrenal crisis was “likely” in all cases. Four cases¹⁶⁻¹⁹ met the criteria for “suggestive of adrenal crisis”; the remaining two^{20,21} were classified as “consistent with adrenal crisis.” Five patients were male and one was female. Most of the patients were adults, between the ages of 43 and 62 years. The youngest was a 6-year-old boy.

Three patients had primary AI. In two of these cases,^{20,21} primary AI was undiagnosed at the time the patient sought dental treatment.

Secondary AI was associated with asthma and use of 5 milligrams of prednisolone per day for five years in one patient,¹⁶ with rheumatoid arthritis and use of 5 to 15 mg prednisolone daily for four years in another patient¹⁸ and with acromegaly and lack of pituitary gland function that required daily use of hydrocortisone (25 mg each morning and 12.5 mg each evening for 13 years) in a third patient.¹⁹ Preoperative steroid coverage was provided in two cases involving patients with secondary AI.^{16,19} Steroid coverage was not provided at the time of the crisis in the two cases involving undiagnosed primary AI.^{20,21} In one case of secondary AI,¹⁸ the patient was advised to take additional steroid medication before the dental procedure; however, it is unclear whether he followed these orders.

Factors associated with adrenal crisis were the presence of illness, infection and cancer and the use of a barbiturate general anesthetic.

Infections were reported in two patients^{19,21} and likely were present in the other two patients who had multiple extractions.^{17,18} Cancer was present in two patients^{17,20} and a jaw fracture was present in one patient.¹⁶ Invasive procedures that caused bleeding were involved in five cases,¹⁶⁻²⁰ and pain was likely present in all cases. Extractions were the most common dental procedure. When extractions were involved, adrenal crisis developed within five hours after the dental procedure. Adrenal crisis occurred during the admission and evaluation process of the two patients who had undiagnosed primary AI.^{20,21}

Clinical presentation of the crisis involved cardiovascular features consistent with shock in all patients and included hypotension, tachycardia, profuse sweating, loss of consciousness or a combination of these. Gastrointestinal features occurred in three patients,^{16,17,21} and hyperpigmentation of skin or mucosa was evident in two cases of primary AI.^{20,21} Laboratory tests were performed in two cases in which patients had undiagnosed primary AI.^{20,21} The results of

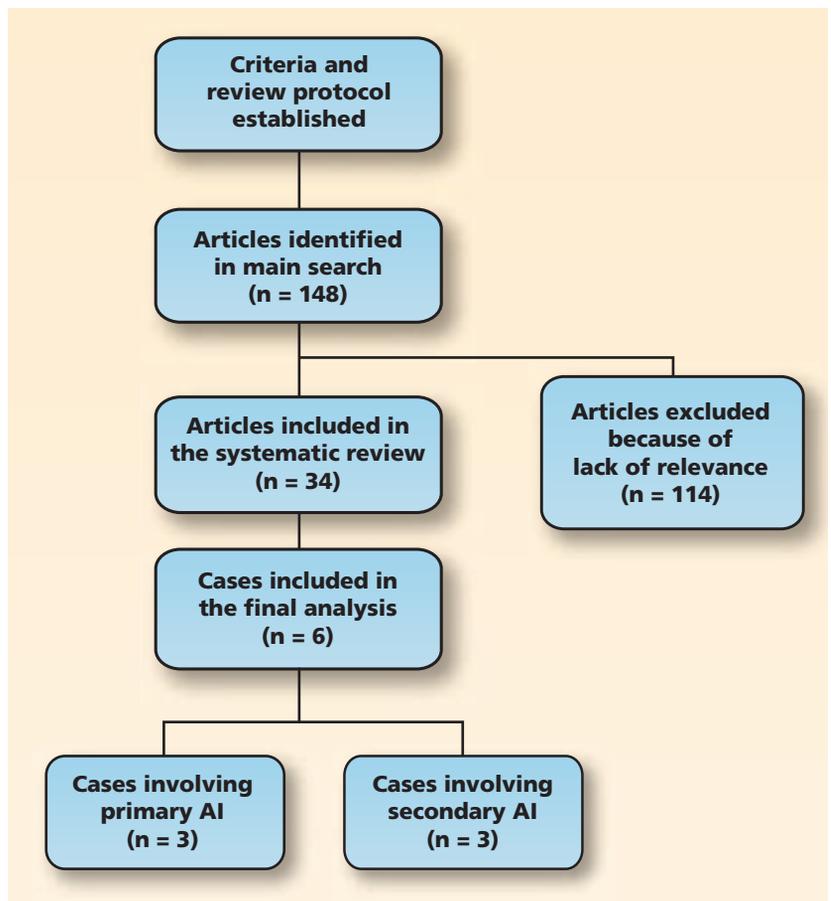


Figure 1. Search strategy. AI: Adrenal insufficiency.

the laboratory tests in both cases were consistent with the diagnosis of acute adrenal crisis. Emergency care for all the patients involved the administration of intravenous fluids, corticosteroids and medications to raise blood pressure. The patients' conditions improved within minutes to hours of medical treatment, and all patients survived the crises.

We estimated the probability of an adrenal crisis' occurring on the basis of three groups at risk of experiencing adrenal crisis (people receiving chronic steroid therapy, people with secondary AI and people with primary AI) and the current incidence of these conditions in the population^{25,26} (Table 3, page 157). The number of cases (n = 6) identified in this systematic search served as the numerator and the prevalence of patients in the population who sought dental care as the denominator. This analysis provided a crude estimate of the probability. It revealed that chronic steroid users were at lowest risk of experiencing adrenal crisis, with a potential occurrence of one in 74.3 million patient dental visits. Those with secondary AI

TABLE 2

Case reports of adrenal crisis in dental settings.

DENTAL CASES	AGE (YEARS), SEX	PREDISPOSING CONDITION	DENTAL CARE-RELATED FACTORS	MAJOR CRITERIA	MINOR CRITERIA	EVIDENCE SUPPORTING ADRENAL CRISIS	PROPHYLACTIC STEROID COVERAGE/SURVIVED
Parnell, 1964¹⁶	57, male	Secondary AI,* fractured mandible, delayed wound healing, prednisolone therapy for five years	Extraction resulting in jaw fracture requiring immobilization, fracture site debridement, general anesthesia (halothane and thiopentone)	GI †: Vomiting CV ‡: Low BP [§] Lab ¶: None	Const #: Patient collapsed CV : Rapid pulse	Suggestive	Yes/Yes
Broutsas and Seldin,¹⁷ 1972	53, female	Primary AI, disseminated cancer	Periodontal disease, extractions (n = 11), general anesthesia (IV** methohexital)	GI : Diarrhea, vomiting Const : Hypothermia CV : Low BP Lab : None	Const : Profuse sweating CV : Rapid pulse	Suggestive	Yes/Yes
Cawson and James,¹⁸ 1973	49, male	Secondary AI, prednisolone therapy for four years	Oral health status unknown, 15 extractions and significant bleeding, general anesthesia (IV methohexitone)	CV : Low BP, features of shock Lab : None	Const : Pale, sweating CV : Rapid pulse	Suggestive	Advised to double steroid dose morning of procedure/Yes
Scheitler and Colleagues,¹⁹ 1984	43, male	Secondary AI, acromegaly, irradiated pituitary gland, hydrocortisone therapy for an estimated 13 years	Periodontal abscess and endodontic abscess, oral pain likely, two extractions	Const : Fever CV : Low BP, features of shock Lab : None	Const : Dizziness, profuse sweating, chills, headache, malaise CV : Rapid pulse	Suggestive	Yes/Yes
Aono and Colleagues,²⁰ 1999	62, male	Undiagnosed primary AI, unknown bilateral adrenal calcification, history of tuberculosis with pleurisy and periostitis	Recurrent painful gingival carcinoma; admitted for lower maxillectomy and radical neck dissection; adrenal crisis occurred after gallium scan, during bleeding-time procedure as part of admission work-up (before dental procedure performed)	Const : Loss of consciousness CV : Low BP, features of shock Lab : Hyponatremia, low stimulation test results	Lab : Concurrent hypoglycemia Other : Hyperpigmentation on the hands and legs	Consistent	No/Yes
Milenkovic and Colleagues,²¹ 2010	6, male	Undiagnosed primary AI	Spreading painful odontogenic infection	GI : Nausea Const : Fever, toxic appearance CV : Low BP Lab : Hyponatremia, metabolic acidosis, low cortisol, low stimulation test results	GI : Underweight, decreased appetite, craving salty food Const : Fatigue, confusion CV : Rapid pulse Other : Skin hyperpigmentation	Consistent	No/Yes

* AI: Adrenal insufficiency.
 † GI: Gastrointestinal abnormalities.
 ‡ CV: Cardiovascular abnormalities.
 § BP: Blood pressure.
 ¶ Lab: Laboratory tests and results.
 # Const: Constitutional abnormalities.
 ** IV: Intravenous.

TABLE 3

Estimated risk of adrenal crisis in dental settings.*						
CONDITION	RATE	PREVALENCE IN POPULATION	VISITED A DENTIST IN PRECEDING 12 MONTHS†	NUMBER OF CASES OF ADRENAL CRISIS REPORTED IN THE LITERATURE	REPORTED RATE OF ADRENAL CRISES DURING PAST 66 YEARS	RISK OF OCCURRENCE OF ADRENAL CRISIS DURING DENTAL VISIT‡
Primary AI‡	140 people per 1 million	43,120	30,011	3	One event every 21.67 years	$21.67 \times 30,011 = 1$ in 650,338
Secondary AI	280 people per 1 million	86,240	60,023	3	One event every 21.67 years	$21.67 \times 60,023 = 1$ in 1.3 million
Potential Chronic Steroid Use	1.6 people per 100	4,928,000	3,429,888	3	One event every 21.67 years	$21.67 \times 3,429,888 = 1$ in 74.3 million

* Data derived by multiplying the average number of cases of adrenal crisis reported in the literature in the past 66 years (column 6) by the number of patients likely to have visited a dentist in the preceding year (column 4). Population figures based on a total U.S. population of 308 million people as of April 2010 (according to U.S. Census Bureau²⁶).

† Based on data from Centers for Disease Control and Prevention.²⁵

‡ AI: Adrenal insufficiency.

were at higher risk, with an estimated occurrence of one in 1.3 million patient dental visits, and those with primary AI were at highest risk, with an estimated occurrence of one in 650,338 patient dental visits.

DISCUSSION

Adrenal crisis is an unexpected and potentially lethal outcome of stressful procedures in patients with AI. To date, few cases have been reported during dental care, and a compilation of factors contributing to the event has been lacking. In this systematic search of the literature, we analyzed articles published during the past 66 years and identified six case reports. Our findings indicate the rarity of this event in dental practice and the need for several factors to come together for a crisis to evolve, as discussed below. However, we should note that although adrenal crisis is rare in dental patients, evidence indicates that between 5 and 8 percent of patients with primary AI require emergency glucocorticoid administration for treatment of adrenal crisis annually.^{3,10,12,15} Thus, dentists must be cognizant of the condition and astute as to the clinical features of this condition.

Recognition of an adrenal crisis in the clinical setting can be challenging because a crisis displays nonspecific features that can mimic those of surgical postoperative events, especially when adequate fluid replacement is not provided.²⁷ Furthermore, the diagnosis can be challenging because a strict definition of adrenal crisis is lacking in the literature. To this end, we developed a consensus definition for this study. The definition as shown in Table 1 is based on information from several sources,^{13,23,24} including consultation with a board-certified endocrinologist (D.G.K.). Six clinicians who had expertise in

the management of medically compromised patients used the criteria to assess each case independently, and they obtained a unanimous consensus. This strategy resulted in four cases' being designated "suggestive of adrenal crisis" and two cases' being designated "consistent with adrenal crisis." The patients with secondary AI showed features of shock, including hypotension, tachycardia, profuse sweating or a combination of these; however, all of these cases lacked laboratory confirmation of the crisis. The designations of "suggestive" seem accurate because the lack of laboratory findings makes it possible that other diagnoses (including low blood volume, hypoglycemia or both) could have contributed to the patient's condition. Also, because fluid replacement—either alone or in combination with glucose replacement—was not attempted before the administration of corticosteroid, it remains unclear whether the cases involving secondary AI were true adrenal crises.

The results of this systematic search of the literature provide some general insights into the risk factors associated with adrenal crisis related to dental treatment. We observed that factors occurred in two main categories: the health of the patient at the dental office and the procedures performed (Figure 2). With respect to the patient's health status, risk historically has been associated with acute destruction or absence of the adrenal gland, destruction of the pituitary gland or acute interruption of glucocorticoid therapy.²⁸ Our findings implicated two of these three factors; however, acute interruption of glucocorticoid therapy was not one of the factors identified by the authors. Instead, we found that long-term use of corticosteroids (that is, for more than four years) was a factor. This is similar to the findings of Omori and colleagues,¹³

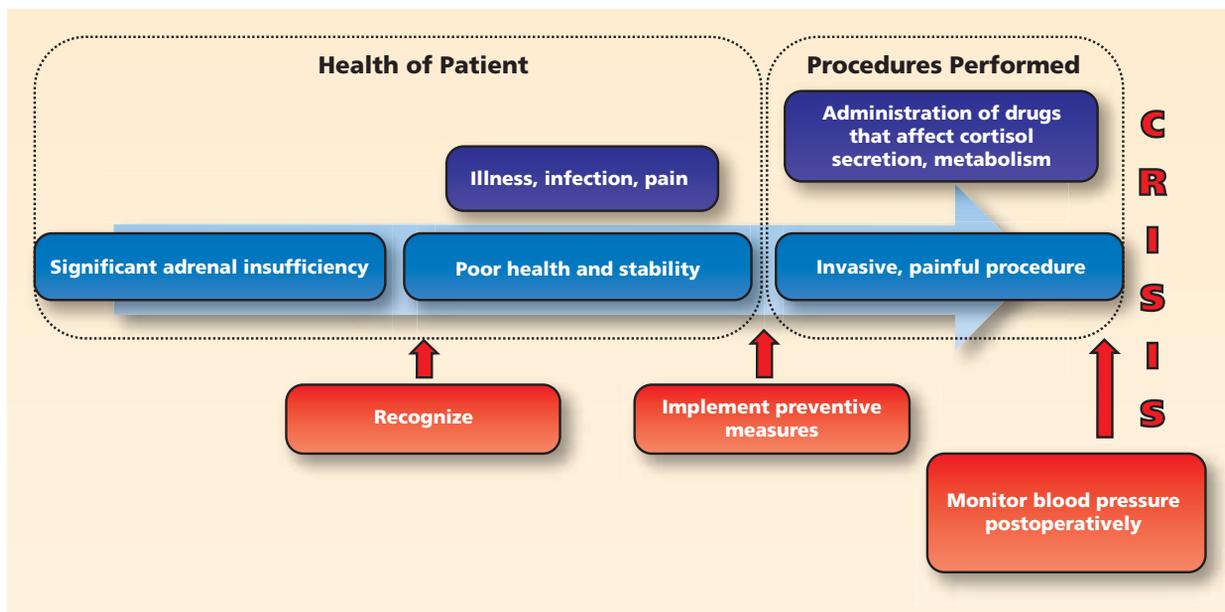


Figure 2. Major risk factors of adrenal crisis in dental setting. Boxes within the dashed rectangles indicate risk factors; boxes in red indicate preventive measures.

who observed that steroid replacement therapy of more than four years’ duration was a contributor to the appearance of an adrenal crisis.

Significant AI in the presence of poor health and disease instability were additional health risk factors. Undiagnosed AI occurred in two cases^{20,21}; gastrointestinal findings, patchy hyperpigmentation of the skin or mucosa, or both (in other words, diagnostic features of primary AI) were evident in four cases^{16,17,20,21}, and chronic oral illness that led to infection, pain or acute flare-ups appeared to occur in all cases. In five cases,^{16,17,19-21} patients had poorly controlled oral or systemic disease. These findings are consistent with those of Hahner and colleagues,¹² who reported that adrenal crisis often is triggered by infectious disease in patients who have chronic AI. The findings also emphasize the importance of a comprehensive patient evaluation during dental visits because routine diagnostic procedures can reveal important risk factors, including a history of an infectious disease that can contribute to decreased adrenal gland function, features of undiagnosed disease or predisposing health factors that increase the risk of experiencing adrenal crisis.

Undergoing a stressful invasive procedure is an additional factor. Invasive procedures that caused bleeding and discomfort were associated with five of six cases.¹⁶⁻²⁰ The stress of a surgery is known to increase cortisol secretion by two-fold to 10-fold between four and 10 hours after the start of an operation, depending on the

severity of the surgical trauma.²⁹⁻³¹ Pain also appears to be a contributing factor, because the timing of the crisis in these cases was coincident with the waning effects of local anesthetic and the onset of pain.

Drugs administered during the dental procedure also can be contributory.³² In this analysis, general anesthesia with a barbiturate was involved in three cases.¹⁶⁻¹⁸ Barbiturates are known to accelerate the metabolism of cortisol³³⁻³⁵ and can exacerbate AI in people who have limited pituitary or adrenal reserve or both. Phenytoin and rifampicin also can increase cortisol metabolism and should be used with caution in patients with AI.³⁶ Other drugs that can exacerbate AI by inhibiting cortisol biosynthesis include aminoglutethimide,³⁷ etomidate,³⁸ azole antifungals^{39,40} and metyrapone.⁴¹

In all cases identified, adrenal crisis was recognized within five hours of the dental procedure, and administration of fluids and corticosteroid resolved the crisis quickly. These medical procedures are well known and effective, if the diagnosis is made in a timely manner. However, clinicians should be aware that the clinical features of adrenal crisis (such as weakness, hypotension, tachycardia or confusion) can overlap with those of other conditions, including hypoglycemia. This can lead to delays in recognition of the crisis and delivery of emergency care. Therefore, the diagnosis of adrenal crisis should be considered in susceptible patients who become febrile, hypotensive or con-

fused after a surgical procedure. In this emergency situation, intravenous administration of a 100-mg hydrocortisone bolus is recommended.⁴²

Our data indicate that adrenal crisis in dental patients is a rare event. We identified only six such cases in the literature during the past 66 years. This is similar to the identification of only five case reports of adrenal crisis in the orthopedic joint surgery literature.^{27,43-46} Consistent with the scarcity of case reports in both of these data sets, the findings in Table 3 suggest that risk of dental patients' experiencing adrenal crisis is low. The cumulative data suggest that chronic users of steroids who may or may not have concurrent secondary AI are at lowest risk of experiencing adrenal crisis. Those with secondary AI are at slightly increased risk, and those with primary AI appear to have the highest risk. Because few of the at-risk patients would be expected also to have poor health status and undergo an invasive dental procedure, we estimate that the actual risk of experiencing adrenal crisis for a patient with primary AI is less than one in 650,338 per dental visit. Of course, readers are advised to use caution in applying these interpretations. This study was limited by the fact that we included only English-language reports; thus, some reports could have been omitted. In addition, the data we extrapolated were based on the original reports, which may have failed to include relevant information. Also, the consensus definition of adrenal crisis we used may not represent a universally accepted definition; interpretation of the findings could be different had a different definition been used. Finally, we are uncertain how many cases may have been prevented by prophylactic corticosteroid supplementation, which could have resulted in the underestimation of the risk we have reported here.

CONCLUSION

This systematic search of the literature and the use of evidence-based criteria for the diagnosis of adrenal crisis allowed us to identify risk factors associated with dental treatment and adrenal crisis. Precipitating risk factors are

- significant and unrecognized AI;
- poor health status and stability at the time of dental treatment (acute illness, fever);
- pain;
- infection;
- extractions or invasive procedures that caused bleeding and discomfort;
- use of general anesthetic containing a barbiturate.

Dentists should be aware of these factors and reduce risk by evaluating each patient properly and by following preventive measures that include pain control and steroid supplementation when indicated.⁴² If factors dictate (Figure 2), the target supplementation dose level for the day on which the patient is to undergo minor to moderate surgery is 25 to 75 mg hydrocortisone equivalent. Higher doses of 100 to 150 mg are recommended for the day of major surgery and the following day. Postoperatively, clinicians should consider appropriate patient monitoring that is based on the risk factors identified in Figure 2. ■

Disclosure. None of the authors reported any disclosures.

The authors thank Dr. Richard J. Kryscio for his advice in preparation of the manuscript of this article, as well as librarians Susan Foster-Harper, Rick A. Brewer and Mark A. Ingram for their help in the systematic review search.

1. Miller CS, Little JW, Falace DA. Supplemental corticosteroids for dental patients with adrenal insufficiency: reconsideration of the problem. *JADA* 2001;132(11):1570-1579.
2. Arlt W. Adrenal insufficiency. *Clin Med* 2008;8(2):211-215.
3. Arlt W, Allolio B. Adrenal insufficiency. *Lancet* 2003;361(9372):1881-1893.
4. Willis AC, Vince FP. The prevalence of Addison's disease in Coventry, UK. *Postgrad Med J* 1997;73(859):286-288.
5. Kong MF, Jeffcoate W. Eighty-six cases of Addison's disease. *Clin Endocrinol (Oxf)* 1994;41(6):757-761.
6. Nomura K, Demura H, Saruta T. Addison's disease in Japan: characteristics and changes revealed in a nationwide survey. *Intern Med* 1994;33(10):602-606.
7. Bouillon R. Acute adrenal insufficiency. *Endocrinol Metab Clin North Am* 2006;35(4):767-775.
8. Stewart PM, Corrie J, Seckl JR, Edwards CR, Padfield PL. A rational approach for assessing the hypothalamo-pituitary-adrenal axis. *Lancet* 1988;1(8596):1208-1210.
9. Clark PM, Neylon I, Raggatt PR, Sheppard MC, Stewart PM. Defining the normal cortisol response to the short Synacthen test: implications for the investigation of hypothalamic-pituitary disorders. *Clin Endocrinol (Oxf)* 1998;49(3):287-292.
10. White K, Arlt W. Adrenal crisis in treated Addison's disease: a predictable but under-managed event (published online ahead of print Sept. 23, 2009). *Eur J Endocrinol* 2010;162(1):115-120. doi:10.1530/EJE-09-0559.
11. Arlt W. The approach to the adult with newly diagnosed adrenal insufficiency. *J Clin Endocrinol Metab* 2009;94(4):1059-1067.
12. Hahner S, Loeffler M, Bleicken B, et al. Epidemiology of adrenal crisis in chronic adrenal insufficiency: the need for new prevention strategies (published online ahead of print Dec. 2, 2009). *Eur J Endocrinol* 2010;162(3):597-602. doi:10.1530/EJE-09-0884.
13. Omori K, Nomura K, Shimizu S, Omori N, Takano K. Risk factors for adrenal crisis in patients with adrenal insufficiency. *Endocr J* 2003;50(6):745-752.
14. Hahner S, Allolio B. Management of adrenal insufficiency in different clinical settings. *Expert Opin Pharmacother* 2005;6(14):2407-2417.
15. Reisch N, Willige M, Kohn D, et al. Frequency and causes of adrenal crises over lifetime in patients with 21-hydroxylase deficiency (published online ahead of print April 18, 2012). *Eur J Endocrinol* 2012;167(1):35-42. doi:10.1539/EJE-12-0161.
16. Parnell AG. Adrenal crisis and the dental surgeon. *Br Dent J* 1964;116:294-298.
17. Broutsas MG, Seldin R. Adrenal crisis after tooth extractions in an adrenalectomized patient: report of case. *J Oral Surg* 1972;30(4):301-302.
18. Cawson RA, James J. Adrenal crisis in a dental patient having systemic corticosteroids. *Br J Oral Surg* 1973;10(3):305-309.
19. Scheitler LE, Tucker WM, Christian DC. Adrenal insufficiency: report of case. *Spec Care Dentist* 1984;4(1):22-24.

20. Aono J, Mamiya K, Ueda W. Abrupt onset of adrenal crisis during routine preoperative examination in a patient with unknown Addison's disease. *Anesthesiology* 1999;90(1):313-314.
21. Milenkovic A, Markovic D, Zdravkovic D, Peric T, Milenkovic T, Vukovic R. Adrenal crisis provoked by dental infection: case report and review of the literature (published online ahead of print July 31, 2010). *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010; 110(3):325-329. doi:10.1016/j.tripleo.2010.04.025.
22. Pawson R, Greenhalgh T, Harvey G, Walshe K. Realist review: a new method of systematic review designed for complex policy interventions. *J Health Serv Res Policy* 2005;10(suppl 1):21-34.
23. Arlt W. Disorders of the adrenal cortex. In: Longo DL, ed. *Harrison's Principles of Internal Medicine*. 18th ed. New York City: McGraw Hill; 2012:2940-2961.
24. *Dorland's Illustrated Medical Dictionary*. 32nd ed. Philadelphia: Elsevier/Saunders; 2012:431.
25. Centers for Disease Control and Prevention; Office of Surveillance, Epidemiology, and Laboratory Services, Behavior Risk Factor Surveillance System. Prevalence and trends data: oral health—2010. <http://apps.nccd.cdc.gov/BRFSS/list.asp?cat=OH&yr=2010&qkey=6610&state=All>. Accessed Oct. 23, 2012.
26. U.S. Census Bureau. Population Estimates. www.census.gov/popest/data/national/totals/2012/index.html. Accessed Jan. 4, 2013.
27. Naka N, Takenaka S, Nanno K, et al. Acute adrenal crisis after orthopedic surgery for pathologic fracture. *World J Surg Oncol* 2007; 5:27.
28. Arafah BM. Hypothalamic pituitary adrenal function during critical illness: limitations of current assessment methods (published online ahead of print Aug. 1, 2006). *J Clin Endocrinol Metab* 2006; 91(10):3725-3745. doi:10.1210/jc.2006-0674.
29. Banks P. The adreno-cortical response to oral surgery. *Br J Oral Surg* 1970;8(1):32-44.
30. Thomasson B. Studies on the content of 17-hydroxycorticosteroids and its diurnal rhythm in the plasma of surgical patients. *Scand J Clin Lab Invest* 1959;11(suppl 42):1-180.
31. Nicholson G, Burrin JM, Hall GM. Peri-operative steroid supplementation. *Anaesthesia* 1998;53(11):1091-1104.
32. Thompson EB. Factors affecting adrenocortical hormone function. *Environ Health Perspect* 1981;38:99-103.
33. Oyama T, Takiguchi M, Aoki N, Kudo T. Adrenocortical function related to thiopental-nitrous oxide-oxygen anesthesia and surgery in man. *Anesth Analg* 1971;50(5):727-731.
34. Siker ES, Lipschitz E, Klein R. The effect of preanesthetic medications on the blood level of 17-hydroxycorticosteroids. *Ann Surg* 1956;143(1):88-91.
35. Stjernholm MR, Katz FH. Effects of diphenylhydantoin, phenobarbital, and diazepam on the metabolism of methylprednisolone and its sodium succinate. *J Clin Endocrinol Metab* 1975;41(5): 887-893.
36. Elias AN, Gwinup G. Effects of some clinically encountered drugs on steroid synthesis and degradation. *Metabolism* 1980;29(6): 582-595.
37. Fassnacht M, Beuschlein F, Vay S, Mora P, Allolio B, Reincke M. Aminoglutethimide suppresses adrenocorticotropin receptor expression in the NCI-h295 adrenocortical tumor cell line. *J Endocrinol* 1998;159(1):35-42.
38. Hildreth AN, Mejia VA, Maxwell RA, Smith PW, Dart BW, Barker DE. Adrenal suppression following a single dose of etomidate for rapid sequence induction: a prospective randomized study. *J Trauma* 2008;65(3):573-579.
39. Shibata S, Kami M, Kanda Y, et al. Acute adrenal failure associated with fluconazole after administration of high-dose cyclophosphamide. *Am J Hematol* 2001;66(4):303-305.
40. Michalakis K, Ilias I. Medical management of adrenal disease: a narrative review. *Endocr Regul* 2009;43(3):127-135.
41. Wright MC, Paine AJ, Skett P, Auld R. Induction of rat hepatic glucocorticoid-inducible cytochrome P450 3A by metyrapone. *J Steroid Biochem Mol Biol* 1994;48(2-3):271-276.
42. Little JW, Falace DA, Miller CS, Rhodus NL. *Little and Falace's Dental Management of the Medically Compromised Patient*. 8th ed. St. Louis: Mosby; 2012:240-250.
43. Ries MD, Guiney W Jr, Lynch F. Fatal massive adrenal hemorrhage after bilateral total knee arthroplasty. *J Arthroplasty* 1994; 9(5):559-562.
44. Cozzolino D, Peerzada J, Heaney JA. Adrenal insufficiency from bilateral adrenal hemorrhage after total knee replacement surgery. *Urology* 1997;50(1):125-127.
45. LaBan MM, Whitmore CE, Taylor RS. Bilateral adrenal hemorrhage after anticoagulation prophylaxis for bilateral knee arthroplasty. *Am J Phys Med Rehabil* 2003;82(5):418-420.
46. Schuchmann JA, Friedman PA. Bilateral adrenal hemorrhage: an unusual complication after bilateral total knee arthroplasty. *Am J Phys Med Rehabil* 2005;84(11):899-903.