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# Does secondary adrenal insufficiency require supplementation prior to oral surgery procedures? An update

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## Abstract

Adrenal insufficiency (AI) is linked to a rare medical emergency, acute AI, or adrenal crisis (AC), which can occur following stressful events, like infection or surgery. A commonly overlooked form of secondary AI occurs when individuals take exogenous glucocorticoids for extended periods of time, resulting in hypoactivity of the adrenal glands. Many patients take glucocorticoids to treat conditions like asthma, rheumatoid arthritis, Crohn's disease, ulcerative colitis, or dermatitis. These patients may be prone to secondary AI, which may go undetected, increasing their risk of facing a medical emergency.

Our aim is to review the literature on current guidelines for corticosteroid supplementation for patients at risk of AC; and assess the risk of developing AI in patients taking exogenous glucocorticoids and whether the current supplementation guidelines require modifications.

Current recommendations from the Addison's disease self-help group and Miller suggest steroid supplementation for dental procedures only for patients with primary AI. However, they do not recommend supplementation for patients with secondary or tertiary adrenal insufficiency.

The drawbacks of short-term supplementation of glucocorticoids in patients at risk of secondary AI, for stressful dental procedures is negligible. Adverse effects of glucocorticoid use are typically seen after prolonged usage. Thus, steroid supplementation before dental procedures should be considered, customized based on identified risk factors and the stress associated with the procedure, as a pragmatic and preemptive approach to reduce the risk of AC. Moreover, this review highlights the need for updated guidance on supplementing patients at risk of secondary AI

**Keywords:** Adrenal insufficiency; Adrenal crisis; Glucocorticoid; Steroid supplementation; Secondary adrenal insufficiency

## 1. Introduction

Adrenal insufficiency (AI) is a condition in which the adrenal glands fail to produce sufficient amounts of glucocorticoids, mineralocorticoids, and adrenal androgens due to dysfunction within the hypothalamic-pituitary-adrenal axis (HPA), requiring steroid supplementation to maintain normal bodily functions.(1,2) A rare but serious medical emergency linked with this condition is acute AI, also known as adrenal crisis (AC), which can occur following stressful events, like infection or surgery, in which the body is unable to produce enough corticosteroids to cope with the stress.(1)

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AI can be classified as primary, secondary and tertiary according to the underlying cause (see Figure 1) and the level of dysfunction within the adrenal-pituitary axis:

- Primary Adrenal Insufficiency: This condition is also referred to as Addison's diseases, where the cortisol production is limited by the autoimmune damage of the adrenal cortex.(1)
- Secondary Adrenal Insufficiency : Originates in the pituitary gland which produces adrenocorticotropic hormone (ACTH), responsible for stimulating the adrenal glands to produce cortisol. When the pituitary gland fails to produce sufficient ACTH, the result is decreased cortisol production by the adrenal glands. With prolonged insufficient stimulation, the adrenal glands may shrink and eventually cease functioning.(1)
- Tertiary Adrenal insufficiency : Stems from the hypothalamus, where corticotropin-releasing hormone (CRH) is produced. CRH signals the pituitary gland to produce adrenocorticotropic hormone (ACTH). When the hypothalamus fails to secrete sufficient CRH, it leads to inadequate production of ACTH by the pituitary gland. Consequently, the adrenal glands produce insufficient amounts of cortisol.(1)

A commonly overlooked form of secondary AI occurs when individuals take exogenous glucocorticoids for extended periods of time, resulting in hypoactivity of the adrenal glands.(1) Many patients may be taking glucocorticoids to treat conditions like asthma, rheumatoid arthritis, crohn's disease, ulcerative colitis, or dermatitis. These patients may be prone to secondary AI, which may go undetected, increasing their risk of facing a medical emergency.(1)

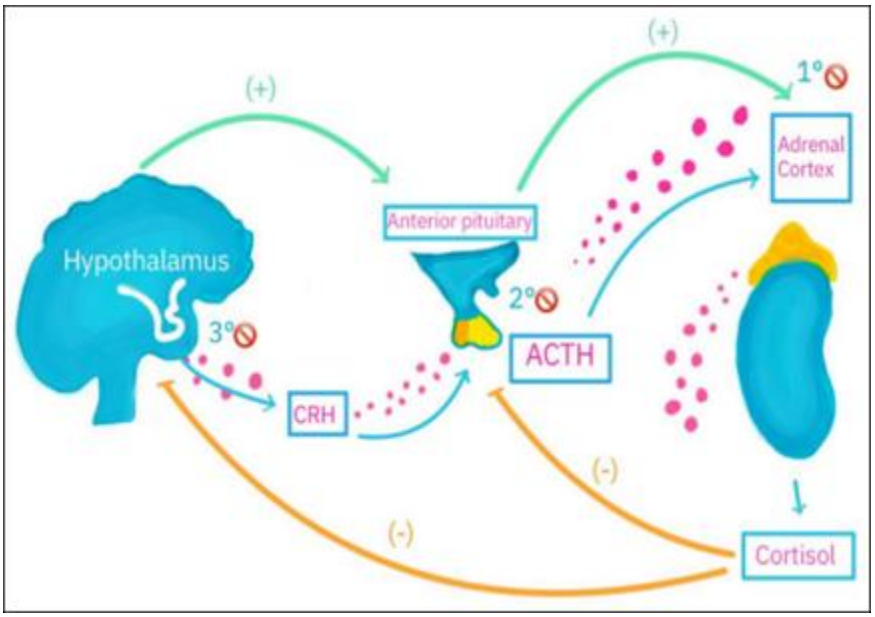


**Figure 1** Physiology of the hypothalamic-pituitary-adrenal axis

## 2. Epidemiology

Addison's disease has a prevalence of approximately 100 to 140 cases per million individuals, in North America and Europe.(3) Secondary AI is more prevalent, affecting an estimated 150 to 280 individuals per million people.(3)Tertiary AI is frequently grouped with secondary, making it difficult to estimate its prevalence.(4) Addison's disease is more common in women and typically manifests in individuals aged 30 to 50 but can occur at any stage of life, including childhood.(4)The frequency of adrenal crisis is roughly 8.3 cases per 100 patient years, with dental procedures accounting for approximately 4.6 to 9% of these events.(5)

Around 0.7% of the population are prescribed extended courses of glucocorticoids for various medical conditions like pemphigus, myasthenia gravis, lymphomas, leukemias, dermatitis, rheumatoid arthritis, and inflammatory bowel disease, among others.(6) However, long-term use, estimated at 1% to 3% globally, can lead to an increase in the mean body weight in the range of 4-8%.(1) Abrupt discontinuation of glucocorticoids can trigger acute AI, marked by symptoms like anorexia, vomiting, dyspnea, fever, arthralgia, myalgia and orthostatic hypotension.(1)

Various factors, such as dental infections, autoimmune adrenalitis, bodily infections, cancer metastasis, adrenal hemorrhage/infarction, or drug effects, can lead to adrenal crisis in patients with chronic AI. Pediatric endocrinologists and dentists should be aware of the potential risk posed by dental infections.(7) Additionally, certain stress-inducing situations can elevate ACTH secretion through specific neural pathways, causing cortisol levels to surge up to tenfold.(7) These stressors include infection, trauma, surgical stimulation, anesthesia, mental and emotional stress, hypothermia, hypoxemia, hypercarbia, and the administration of sympathomimetic agents like epinephrine or norepinephrine.(7) Therefore, dental practitioners should have sufficient knowledge to identify the signs and symptoms of AI and refer for medical evaluation when they present (see Figure 2).

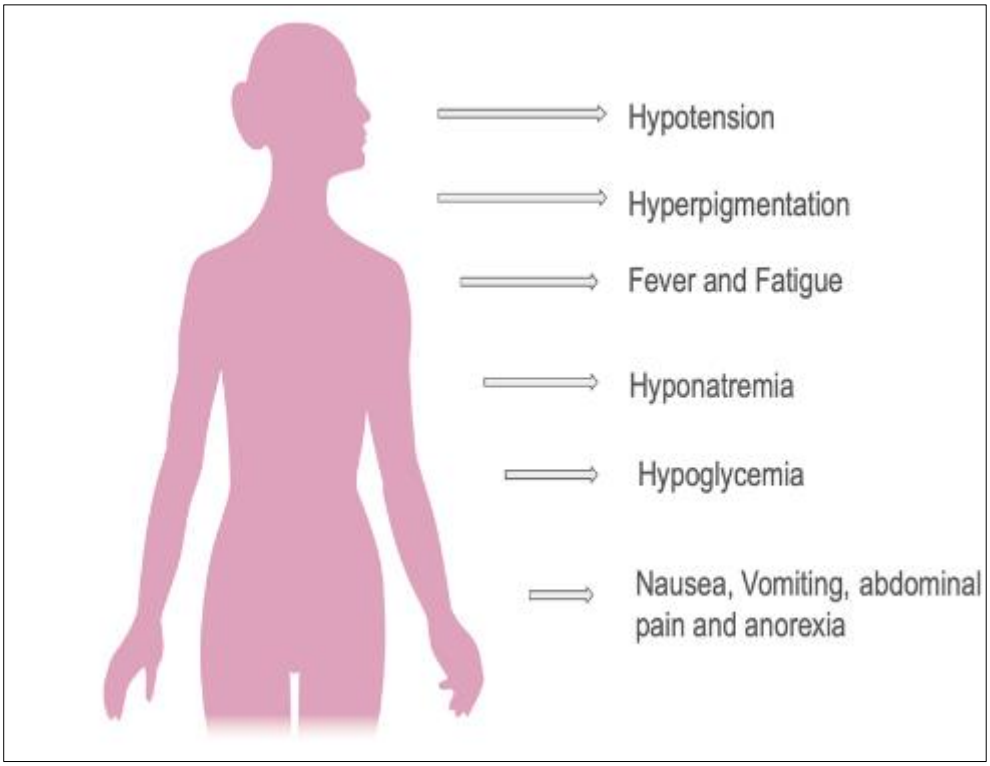


**Figure 2** Common signs and symptoms of adrenal insufficiency

## 3. Clinical Features

The most common symptoms of AI involve hyperpigmentation which is caused by the heightened activation of the melanocortin-1 receptor (MC1R) due to the elevated level of ACTH, which possesses inherent alpha-melanocytes stimulating hormone activity.(8) Other clinical findings include, fatigue, weight loss, and behavioral disturbances. A comprehensive list of signs and symptoms can be found in Table 1.(8)

**Table 1** Features of Adrenal Insufficiency

| Clinical findings | Laboratory findings |
|---|---|
| Fatigue | Hypocalcemia |
| Weight loss | Hyperkalemia |
| Gastrointestinal disturbances | Hyponatremia |
| Reproductive problems | Eosinophilia |
| Musculoskeletal problem | Electrolyte imbalance |
| Psychiatric problems | hypoglycemia |
| Auricular-cartilage thickening | |
| Hyperpigmentation | |
| Salt craving | |
| Postural hypotension | |
| Vitiligo | |

### 3.1. Aims and Methods

Our aim is to review the literature on current guidelines for corticosteroid supplementation for patients at risk of AC; and assess the risk of developing AI in patients taking exogenous glucocorticoids and whether the current supplementation guidelines require modifications.

We searched Embase and Medline from inception up to January 2024, using search terms "(adrenal insufficiency OR adrenal crisis) AND dent* AND glucocorticoid*". References of relevant papers were also manually searched.

## 4. Current Recommendations on Steroid Supplementation

Prolonged administration of corticosteroids such as prednisone, hydrocortisone, and dexamethasone for various systemic conditions disrupts adrenal gland function, resulting in reduced cortisol production within the body.(1) Consequently, unless supplemental steroids are prescribed, individuals at risk of secondary AI may struggle to generate adequate cortisol levels to manage the stress induced by dental procedures such as oral and maxillofacial surgeries, periodontal surgeries, and lengthy dental treatments, potentially resulting in AC within hours or days following the procedure.(1)

Current recommendations from the Addison's disease self-help group (ADSHG) and Miller et al. suggest steroid supplementation for dental procedures only for patients with primary AI (see table 2 and 3 for details). However, it does not recommend supplementation for patients with secondary or tertiary adrenal insufficiency.

**Table 2** Addison's disease self-help group: Supplementation guidelines for dental surgery for patients with primary adrenal insufficiency.(9)

| Type of Procedure | Pre-operative and operative needs | Post-operative needs |
|---|---|---|
| Major dental surgery | 100 mg hydrocortisone IM just before anesthesia | Double dose oral medication for 24 hours. Then return to normal dose |
| Dental surgery | Double oral dose (up to 20 mg hydrocortisone) one hour prior to surgery | Double dose oral medication for 24 hours. Then return to normal dose |
| Minor dental procedure | Not usually recommended | An extra dose where hypoadrenal symptoms occur afterwards. Then return to normal dose. |

Miller et al developed their recommended steroid supplementation schedule, for patients with primary AI, based on plasma cortisol levels.(10) They suggest that the level of secretion of cortisol during and after surgery is based on the magnitude of surgery and whether it was performed under general anesthesia.(10) They also state that the level of cortisol decreases after administration of analgesics postoperatively.(10) See table 3 for their recommended steroid supplementation schedule.

**Table 3** Miller et al: Supplementation guidelines for dental surgery for patients with primary adrenal insufficiency.(10)

| **Type of procedures** | **Regimen** |
|---|---|
| Non-Surgical dental procedure | No supplementation required. |
| Minor oral surgery(minor periodontal surgery, minor extractions) | 25mg of hydrocortisone or 5mg prednisone at the day of surgery. |
| Major oral surgery (multiple extractions, quadrant periodontal surgery,extraction of bony impaction, osseous surgery, cancer surgery and surgical procedure involving general anesthesia) | 50 to 100mg per day of hydrocortisone equivalent the day of surgery and for at least one postoperative day. |

## 5. Risk of Secondary Adrenal Insufficiency

Various studies reveal significant risk of secondary AI for patients taking glucocorticoids, based on corticosteroid dosage, administration route, and treatment duration.(11) Patients prescribed higher doses of corticosteroids, such as prednisone exceeding 20mg, face a 21.5 percent chance of AI (see Figure 3A).(11)

Notably, those receiving corticosteroids via intra-articular and oral routes exhibit approximately ten times higher risk of developing AI, compared to nasal and topical administration (see Figure 3B).(11)

Furthermore, patients taking corticosteroid for over 3 months confront a substantial increase in risk of AI, estimated at around 27.4%, contrasting with a lower risk of approximately 1.4 % for those taking them less than one month (see Figure 3C).(11)

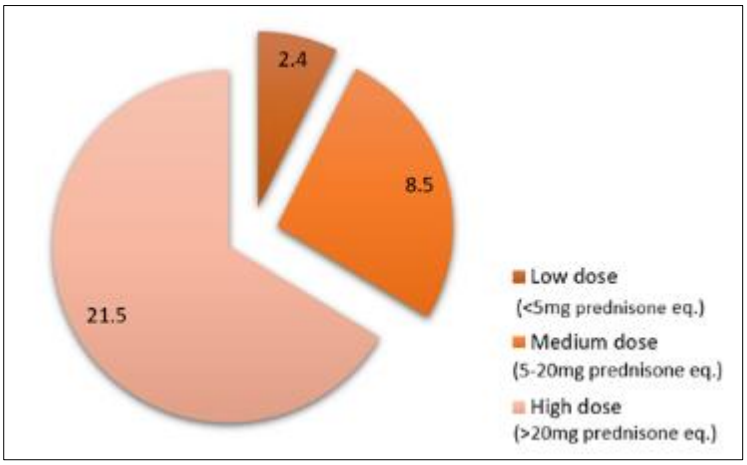


**Figure 3A** Risk of adrenal insufficiency (%) associated with dose of administration

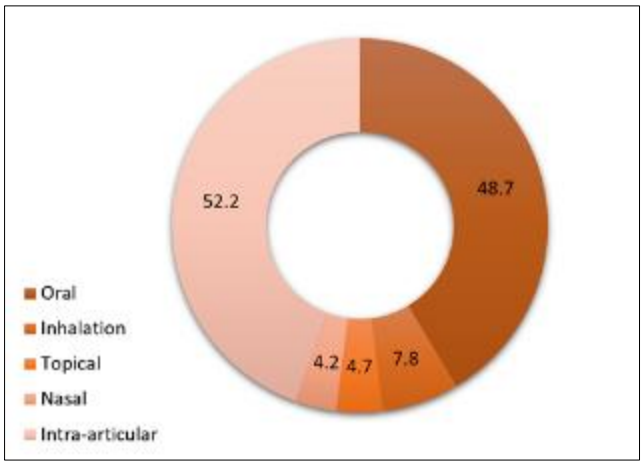


**Figure 3B** Risk of adrenal insufficiency (%) associated with route of administration

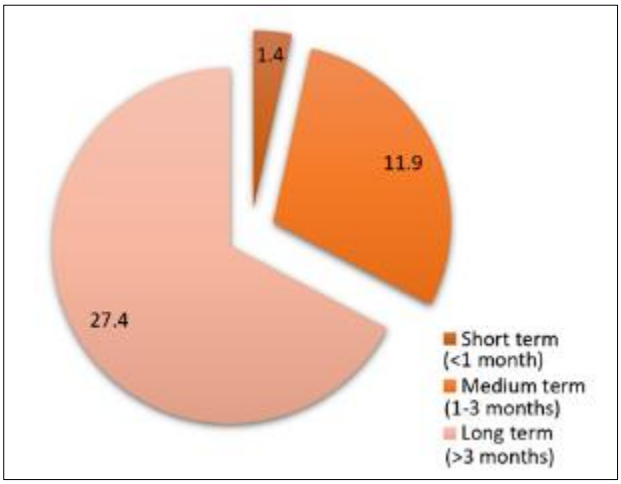


**Figure 3C** Risk of adrenal insufficiency (%) associated with treatment duration

When examining different corticosteroids, their potency is an important factor in the risk of developing secondary AI. Prednisone increases risk of AI when surpassing 20 mg doses, whereas dexamethasone increases risk of AI if administered at more than 3 mg doses (see table 4 for more details).(12)

**Table 4** Equivalent Doses of Common Corticosteroid Medications and their Medical Uses

| Steroid | Common medical use | Half-life (hours) | Eq <5mg Prednisone (Low dose) | Eq. 5-20mg Prednisone (Medium dose) | Eq. >20mg Prednisone (High dose) |
|---|---|---|---|---|---|
| Prednisone | Arthritis, COPD, Acute asthma, IBD, Gout, Cancer | 12-36 | <5 | 5-20 | >20 |
| Fluticasone | Asthma, Allergic rhinitis | 10-12 | <1 | 1-4 | >4 |
| Hydro-cortisone | IBD, skin disorders, asthma | 8-12 | <20 | 20-80 | >80 |
| Beta-methasone | Eczema, psoriasis | 36-54 | <0.6 | 0.6-3.2 | >3.2 |

| | | | | | |
|---|---|---|---|---|---|
| Dexa-methasone | Inflammatory disorder | 36-54 | <0.75 | 0.75-3 | >3 |


**Figure 4** Corticosteroid containing medications

The risk of AC also depends on the stress induced by the procedure. An analysis of salivary cortisol levels during various dental procedures indicates that oral prophylaxis and extraction result in major elevation in cortisol concentrations, exceeding 10 mg/ml (see Figure 5A for details).(12,13) Moreover, general anesthesia produces a markedly lower stress level during the time of surgery as compared to local anesthesia (see Figure 5B for details).(14)

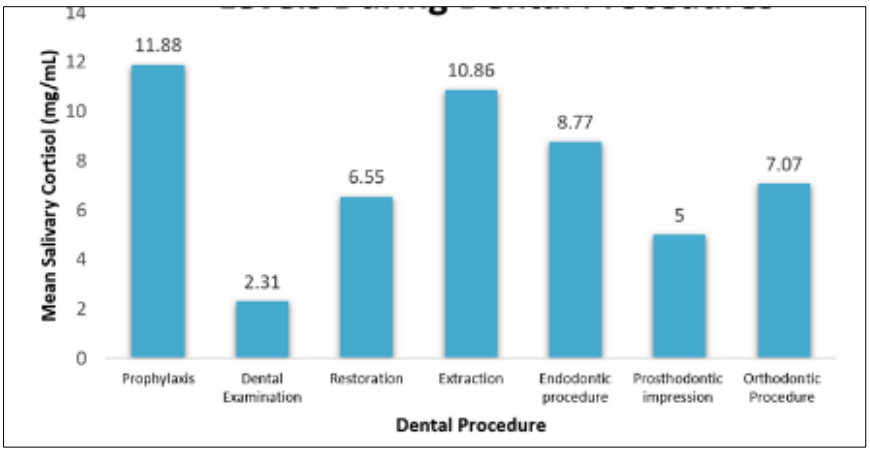


**Figure 5A** Mean salivary cortisol levels during dental procedures

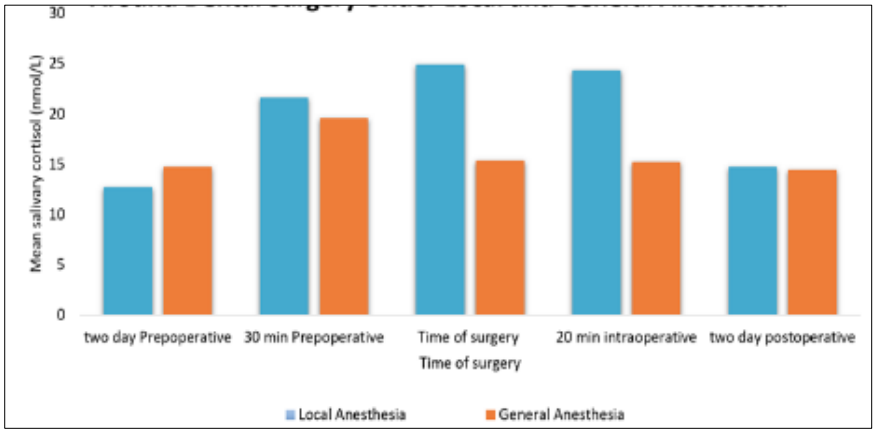


**Figure 5B** Mean salivary cortisol at various time points around dental surgery under local and general anesthesia

## 6. Discussion

Our review of the literature suggests that there is significant risk of secondary AI for patients taking glucocorticoids, which makes up 2-3% of the population.(15) The risk of developing AI varies widely for these patients, spanning from 1.4% to 60%.(11) Identifying mild to moderate symptoms of AI, like fatigue and abdominal discomfort, proves difficult due to their nonspecific nature, making it challenging to solely attribute them to AI.(11)

Our findings suggest that the risk of secondary AI is severely underestimated and since it is difficult to diagnose, the recommendations for steroid supplementation for these patients requires revision. Patients receiving corticosteroid therapy are inherently vulnerable to AI.(16) Therefore, it's crucial for clinicians to take proactive steps, such as educating patients about potential risk and symptoms and considering steroid supplementation when appropriate.

The drawbacks of short term supplementation of glucocorticoids in patients at risk of secondary AI, for stressful dental procedures is negligible.(17) Adverse effects of glucocorticoid use are typically seen after prolonged usage.(17) Thus, we advocate for the provision of steroid supplementation before dental procedures, customized based on identified risk factors and the stress associated with the procedure, as a pragmatic and preemptive approach to reduce the risk of AC. Moreover, this highlights the need for updated guidance on supplementing patients at risk of secondary AI.

Although secondary AI typically exhibits lower severity, with decreased glucocorticoid but normal mineralocorticoid secretion, and lower risk of AC compared to primary AI; all patients regularly taking exogenous glucocorticoids are at risk of AI and thereby AC.(16) This risk underscores the importance of taking comprehensive medical histories, being attentive in evaluating patients for risk elements, such as current dosage, duration, and method of glucocorticoid administration, to enhance patient safety and the standard of care provided.

## 7. Conclusion

The risk of secondary AI is greater than previously thought, which can lead to AC, however, these medical emergencies can be prevented by adequate steroid supplementation during stressful procedures, with minimal adverse effects.

Steroid supplementation guidelines for patients at risk of secondary AI requires revision. Moreover, our findings are constrained by a limited number of studies on the subject and are impacted by bias due to sample size. Further investigation into methods of measuring stress levels and optimal approaches to supplementation are warranted. General anesthesia was found to be associated with lower stress levels than local anesthesia during dental procedures. Hence dental practitioners should consider sedation during treatment, to reduce stress and enhance patient care and safety.

## Compliance with ethical standards

### *Disclosure of conflict of interest*

No conflict of interest to be disclosed.

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