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Perioperative Steroid Management

Approaches Based on Current Evidence

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CHRONIC steroid therapy is a cornerstone treatment for many common conditions, including inflammatory bowel disease, rheumatologic disease, reactive airway disease, and immunosuppression for transplant recipients. Patients on chronic steroid therapy may develop secondary adrenal insufficiency that can manifest as full-blown adrenal crisis in the perioperative period. When these patients present for surgery, the anesthesiologist must decide whether to administer perioperative stress-dose steroids to mitigate this rare but potentially fatal complication of chronic steroid use. In doing so, the patient's risk for adrenal crisis must be weighed against the risks of unnecessary steroid supplementation. Unfortunately, this decision is not always clear-cut, because even the recommendations found in major textbooks are confusing, inconsistent, and lacking in class A and B evidence (table 1). Despite the lack of standardization and the widespread use of perioperative stress-dose steroids observed in clinical practice, a recent search of the Anesthesia Closed Claims Project database containing 11,247 claim narratives using the terms "stress dose," "Cushing," "Addison," and "adrenal insufficiency" revealed that failure to administer stress steroids generated only two claims that resulted in liability payments, and both of these cases were complicated by other issues (written personal communication, Karen L. Posner, Ph.D., Department of Anesthesiology and Pain Medicine, University of Washington, Seattle, Washington, December 2015). It is unclear whether this paucity of claims is due to underdiagnosis of adrenal crisis or overtreatment of perioperative patients with steroids. We now review and evaluate the current data on the use of perioperative stress-dose steroids and propose approaches to administration and dosing.

Hypothalamic-Pituitary-Adrenal Axis Suppression

Acute physiologic or psychologic stress activates the hypothalamic-pituitary-adrenal axis (HPAA). The hypothalamus produces corticotropin-releasing hormone (CRH), which stimulates production of adrenocorticotrophic hormone (ACTH) in the anterior pituitary, which in turn signals cortisol production in the adrenal glands. Cortisol has a number of roles within the body, including stimulation of gluconeogenesis, catecholamine production, and activation of antistress and antiinflammatory pathways. Cortisol is also essential for maintenance of cardiac output and contractility and enhancement of vascular tone *via* modulation of β -receptor synthesis and function and increased sensitivity to catecholamines, respectively.^{1,2} Cortisol production is self-regulated *via* negative feedback loops that lead to decreased secretion of CRH and ACTH (fig. 1).³ Normally, the adrenal gland secretes approximately 8 to 10 mg of cortisol per day. Transient increases in cortisol secretion are seen in response to stress, such as illness or surgery. The rate varies between individuals but is usually up to 50 mg/day for minor procedures and up to 75 to 150 mg/day for more complex procedures, rarely exceeding 200 mg/day (table 2).⁴

Patients on chronic steroid therapy may experience HPAA suppression, resulting in low CRH and ACTH levels that lead to atrophy of the adrenal zona fasciculata and a decrease in cortisol production. This process is known as *secondary* adrenal insufficiency. Unlike in *primary* adrenal insufficiency, the renin-angiotension-aldosterone system remains intact, and there is no mineralocorticoid deficiency. Inadequate cortisol production may predispose to vasodilatation

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Table 1. Published Perioperative Steroid Dosing Recommendations

Publication	Recommendations	
Miller's anesthesia 8e ²⁴	Acknowledge "a precise amount required has not been established": IV 200 mg/day hydrocortisone phosphate per 70 kg of body weight or for minor procedure 100 mg/day hydrocortisone phosphate per 70 kg of body weight and then decreased at 25% per day until PO intake of maintenance dose can be resumed	
Clinical anesthesia 7e ³	Acknowledge both "an extensive review concluded that the best evidence was that patients should receive usual daily dose but no supplementation" and "many clinicians are unwilling to adopt the regimen until further trials have been undertaken in patients receiving physiologic steroid replacement" and ultimately give "popular regimen": 200–300 mg of hydrocortisone per 70 kg of body weight in divided dose on the day of surgery, with adjustment in dose based on extent and duration of surgery and patients are to take their daily dose of steroids	
Anesthesia and coexisting disease 6e ²	Surgery	Recommendations
	Superficial	Daily dose only
	Minor	Daily dose plus hydrocortisone (25 mg IV)
	Moderate	Daily dose plus hydrocortisone (50–75 mg, taper 1–2 days)
	Major	Daily dose plus hydrocortisone (100–150 mg, taper 1–2 days)
UpToDate: The Surgical Patient Taking Glucocorticoids ²²	Nonsuppressed (HPA) axis – defined as taking exogenous steroids for less than 3 weeks, or prednisone (<5 mg daily or its equivalent) for any duration, or less than 10 mg of prednisone or its equivalent every other day; we suggest continuing the same glucocorticoid regimen perioperatively (Grade 2C). These patients are unlikely to have a suppressed HPA axis, and neither preoperative evaluation of the HPA axis nor supraphysiologic doses of glucocorticoids are needed.	
	In suppressed patients (defined as equivalent to prednisone 20 mg/day for 3 weeks or more), recommendations are surgery specific	
	Surgery	Recommendations
	Minor	Morning dose only
	Moderate	Morning dose plus IV 50 mg of hydrocortisone before incision; then IV 25 mg every 8 h for 24 h and then maintenance
	Major	Morning dose plus IV 100 mg of hydrocortisone before induction; then IV 50 mg every 8 h for 24 h; Taper dose by half per day to maintenance level
Bornstein <i>et al.</i> : Diagnosis and treatment of primary adrenal insufficiency: An Endocrine Society Clinical Practice Guideline ⁶	Acknowledge the "proposed glucocorticoid regimen in the management of adrenal crisis places a higher value on the prevention of underdosage than on reducing potential negative effects of short-term overdosage" as "under-dosing of glucocorticoids in an adrenal crisis is potentially hazardous. . . . Harm from these doses has not been shown, and direct studies indicating that lower doses are safe do not exist."	
	Glucocorticoid dose adjustment based on severity of illness or magnitude of stressor, as follows:	
	Surgery	Recommendations
	Minor to moderate	Hydrocortisone, 25–75 mg/24 h (usually 1–2 days)
	Major surgery, trauma, delivery, disease that requires intensive care, suspected adrenal crisis	Hydrocortisone 100 mg IV followed by continuous IV infusion of hydrocortisone 200 mg/24 h (alternatively 50 mg every 6 h IV/IM)

HPA = hypothalamic-pituitary-adrenal; IM = intramuscular; IV = intravenous; PO = per os.

and hypotension.⁴ Thus, patients on chronic steroids are traditionally considered at risk for adrenal crisis during periods of stress due to their attenuated ability to mount a cortisol response.⁵ In the awake patient, signs and symptoms of adrenal crisis may include altered mental status, abdominal pain, nausea/vomiting, weakness, and hypotension.⁶ For the practicing anesthesiologist, however, perioperative adrenal crisis becomes a diagnosis of exclusion and requires a high index of suspicion because the signs and symptoms described above are largely absent in the anesthetized patient and nonspecific in the immediately postoperative patient. The clinical picture is one of severe, persistent hypotension that is poorly

responsive to fluid and vasopressor therapy. Perioperative adrenal crisis can be life-threatening and requires prompt recognition and treatment with stress-dose steroids in addition to supportive care with fluid and vasopressor administration.

There is no universally agreed-upon dose or duration of exogenous steroids required to cause HPAA dysfunction, though prednisone 20 mg/day or its equivalent for more than 3 weeks has been cited.¹ Indeed, based on biochemical testing, neither the dosage nor duration of exogenous glucocorticoid administration corresponds well with the level of HPAA suppression or its return to normality after discontinuation of therapy.⁷ The exact time course of recovery from HPAA

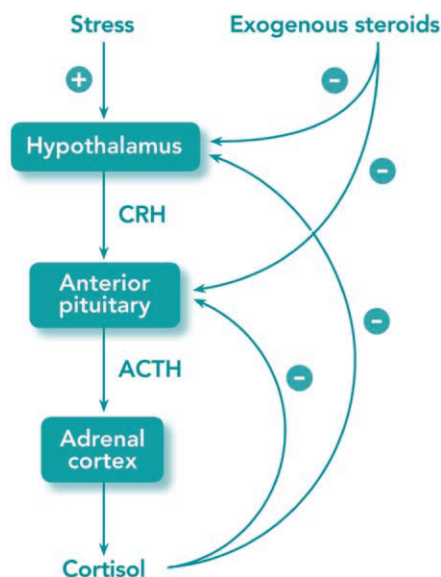


Fig. 1. Functional anatomy of hypothalamic-pituitary-adrenal axis. ACTH = adrenocorticotrophic hormone; CRH = corticotropin releasing hormone; – = negative feedback; + = positive feedback.

suppression differs between individuals and is difficult to predict. Nevertheless, most agree that HPA suppression does not continue beyond 1 yr after cessation of exogenous steroid therapy with the possible exception of patients receiving intraarticular glucocorticoid injections, for whom the time course of HPA suppression is variable, depending on the frequency and dose of injections, and not well studied.⁴

Historical Perspectives

In 1949, cortisone was first commercially produced for the treatment of primary adrenal insufficiency and shortly thereafter was being used as an antiinflammatory and immunosuppressant.⁵ The historical basis for giving perioperative stress-dose steroids lies in two case reports, each describing a single patient ($n = 1$), from the early 1950s in which cardiovascular collapse was attributed to secondary adrenal crisis based on autopsy findings.^{8,9} However, both case reports have subsequently been criticized for confounding factors such as the withholding of aggressive fluid resuscitation, vasopressors, antibiotics, and most importantly the lack of biochemical proof of adrenal insufficiency *via* measurement of serum cortisol levels.⁷ Indeed, Brown and Buie¹⁰ found that perioperative hypotension due to adrenal crisis is rare, with an estimated incidence of 1 to 2%, and this estimate was extrapolated mainly from a 1973 Kehlet and Binder prospective study¹¹ of patients on chronic steroids for whom steroids were withheld. Nevertheless, these two case reports form the basis for much of the current perioperative management of patients with suspected HPA suppression.

Current Evidence

Since these sentinel articles, there has been a growing body of literature and debate about the management of patients on chronic steroids who present for surgery. As a whole, the literature on administration of perioperative stress-dose steroids is devoid of class A or B levels of evidence and is complicated by

Table 2. Surgical Stress by Procedure and Recommended Steroid Dosing

Surgery Type	Endogenous Cortisol Secretion Rate	Examples	Recommended Steroid Dosing
Superficial	8–10 mg per day (baseline)	Dental surgery	Usual daily dose
Minor	50 mg per day	Biopsy Inguinal hernia repair Colonoscopy Uterine curettage Hand surgery	Usual daily dose <i>plus</i> Hydrocortisone 50 mg IV before incision Hydrocortisone 25 mg IV every 8 h \times 24 h Then usual daily dose
Moderate	75–150 mg per day	Lower extremity revascularization Total joint replacement Cholecystectomy Colon resection Abdominal hysterectomy	Usual daily dose <i>plus</i> Hydrocortisone 50 mg IV before incision Hydrocortisone 25 mg IV every 8 h \times 24 h Then usual daily dose
Major	75–150 mg per day	Esophagectomy Total proctocolectomy Major cardiac/vascular Hepaticojejunostomy Delivery Trauma	Usual daily dose <i>plus</i> Hydrocortisone 100 mg IV before incision Followed by continuous IV infusion of 200 mg of hydrocortisone more than 24 h <i>or</i> Hydrocortisone 50 mg IV every 8 h \times 24 h Taper dose by half per day until usual daily dose reached <i>plus</i> Continuous IV fluids with 5% dextrose and 0.2–0.45% NaCl (based on degree of hypoglycemia)

Data from Axelrod,⁴ Salem *et al.*,¹³ and Bornstein *et al.*⁶

IV = intravenous.

Table 3. Steroid Choices, Potency, Dosages, and Their Conversion Charts^{1,2}

Steroid	Glucocorticoid Activity	Mineralocorticoid Activity	Equivalent Dose (IV/PO)	Half-Life, h
Cortisol (hydrocortisone)	1	1	20	8–12
Cortisone	0.8	0.8	25	8–12
Prednisone	4	0.8	5	18–36
Prednisolone	4	0.8	5	12–36
Methylprednisolone	5	0.5	4	18–36
Dexamethasone	30–40	0	0.5–0.75	36–54

IV = intravenous; PO = per os.

a lack of consistency in patient selection, surgery and anesthesia type, clinical outcome, and steroid timing and dose. Randomized double-blinded, placebo-controlled trials addressing this topic are few in number and insufficiently powered (most involve 20 or fewer patients).¹⁰ This has made statistical analysis of the current steroid stress-dose literature close to impossible.

Kehlet and Binder¹¹ published perhaps the most robust data on stress-dose steroids. They looked at 73 patients on chronic steroid therapy ranging from 5 to 80 mg/day of prednisone or equivalent undergoing minor and major surgery for whom all steroids were withheld for 36 h preoperatively and not resumed until at least 24 h postoperatively. Plasma cortisol levels and vitals were followed. Unexplained hypotension (defined as systolic blood pressure less than 80 mmHg not due to sepsis, anaphylaxis, or bleeding) was found in 7 of 18 hypotensive patients. However, only 3 of the 7 patients with unexplained hypotension had low cortisol levels, defined in this study as less than 15 µg/100 ml, and these patients did not respond to treatment with rescue steroids. Additionally, patients who had low plasma cortisol levels before surgery were not significantly more likely to have hypotension. The authors concluded that preoperative plasma cortisol is “not the prime determinant of the level of blood pressure in the glucocorticoid-treated patients during and after surgery, and acute stress-induced adrenocortical insufficiency is rare even when steroids are withheld.”¹¹ It must be noted, though, that there is no agreed-upon definition of what constitutes a low cortisol level in physiologically stressed individuals, which makes these data difficult to interpret. Moreover, the method used to measure cortisol levels in this study is a fluorometric assay rarely used today, which further calls into question the applicability of these findings.

In 1997, Glowniak and Loriaux¹² studied 18 male patients taking prednisone for at least 2 months for various conditions with baseline secondary adrenal insufficiency as determined by cosyntropin study (also known as the short ACTH stimulation test). Cosyntropin, a synthetic analog of ACTH, is administered as a bolus of 250 µg IV or intramuscularly at least 24 h after the last dose of exogenous glucocorticoids. Plasma cortisol levels are then measured 30 to 60 min postadministration, with 18 µg/dl or higher, indicating a normal response.⁴ In this study,

patients underwent various surgical procedures using different anesthetic techniques, including local, neuraxial, and general. Patients were randomized to receive stress-dose steroid injections (100 mg of cortisol in normal saline based on the Salem *et al.* guidelines) versus control (normal saline).¹³ No significant perioperative differences in hemodynamic parameters were found between groups. The authors concluded that patients with secondary adrenal insufficiency as a result of chronic steroid therapy do not experience hypotension in the absence of stress-dose steroid administration and can be maintained on their usual daily dose of steroids in the perioperative period.¹² However, it should be noted that this study may not have been sufficiently powered (total n = 18) to detect statistical differences (*i.e.*, type II error).

Thomason *et al.*¹⁴ studied 20 organ transplant patients on chronic steroid therapy for immunosuppression presenting for gingival surgery under local anesthesia. Patients were randomized to receive stress-dose steroids versus placebo. Each patient required at least two operations and thus served as their own control. Serum ACTH levels were drawn pre- and postoperatively, and blood pressure was measured at set intervals throughout. No significant differences in blood pressure or ACTH measurements were found between groups. The authors concluded that patients on chronic steroids do not require stress-dose steroids before undergoing gingival surgery.¹⁴ Not only was this study underpowered, it is also unclear whether these conclusions would apply to major surgery performed under general anesthesia. Additionally, measurement of random plasma ACTH levels as an indicator of adrenal insufficiency is neither a standard nor valid method of assessing adrenocortical function and further decreases the applicability of the study findings.

Further complicating this muddled picture is the retraction of a Cochrane review in 2013¹⁶ that had concluded, largely based on the articles by Glowniak and Loriaux¹² and Thomason *et al.*,¹⁴ that there is “currently inadequate evidence to support the use of supplemental perioperative steroids in patients with adrenal insufficiency. It is likely that in the majority of adrenally suppressed patients undergoing surgery, administration of the patient’s daily maintenance dose of corticosteroid may be sufficient and that supplemental doses are not required.”¹⁵ This Cochrane review was

retracted after comments received “*via* direct correspondence which have challenged the eligibility criteria and interpretation of the evidence summarized in this review.”¹⁶

In contrast to the historical recommendations for perioperative stress-dose steroids, recent data suggest that the patient’s usual dose of steroids can be maintained preoperatively and taken the day of surgery, with vigilance to signs and symptoms (*e.g.*, hypotension) of adrenal insufficiency intraoperatively.^{5,10,17} Intraoperative hypotension that cannot be adequately managed by conservative means (*e.g.*, decreasing depth of anesthesia, fluid resuscitation, vasopressor administration, and managing metabolic abnormalities) should raise suspicion for adrenal crisis, and a rescue dose of 100 mg of hydrocortisone IV should be administered, followed by continued supplementation of 50 mg of hydrocortisone IV every 6 h.⁶

Chronic steroid therapy is well known to be associated with risk of immunosuppression, impaired wound healing, hyperglycemia, and psychologic disturbances in the postoperative period.¹⁸ Whether perioperative stress-dose steroids further increase these risks is debatable, especially as there are currently no randomized controlled trials that address their adverse effects. Elevated circulating levels of glucocorticoids are associated with a range of psychiatric symptoms including acute psychosis.¹⁹ One retrospective study on renal transplant patients undergoing lymphocele surgery showed that administration of stress-dose steroids resulted in elevated blood glucose, but there was otherwise no statistically significant difference between clinical outcome in patients treated with stress-dose steroids and those who were not. The authors concluded that stress-dose steroids increased the risk of hyperglycemia without apparent clinical benefit.²⁰

Our Approach

Recent data suggest that stress-dose steroids may not be necessary, even in patients with confirmed preoperative secondary HPAA suppression.¹² Instead, these patients may be maintained on their usual preoperative dose and treated with rescue dose steroids only if refractory hypotension presents in the perioperative period.^{5,10,17} Nonetheless, some authors advocate for the administration of stress-dose steroids for at-risk patients despite the lack of class A and B evidence given the rare, but possibly fatal, consequences of adrenal crisis.^{10,13} Indeed, the recent 2016 Endocrine Society Clinical Practice Guideline⁶ on primary adrenal insufficiency notes that harm has not been shown from recommended doses of perioperative stress-dose steroids and thus places a higher value on preventing adrenal crisis rather than reducing the potential adverse effects of short-term overtreatment.²¹

Marik and Varon¹⁷ suggest that most patients receiving chronic steroid therapy do not need preoperative evaluation of their adrenocortical function unless there is clinical reason to believe that it might affect perioperative

management, as this testing does not reliably predict which patients will develop adrenal crisis. For example, a patient experiencing complications of chronic steroid therapy (*e.g.*, gastrointestinal bleeding) who may otherwise benefit from rapid taper and cessation of steroid treatment may instead need to continue on glucocorticoids throughout the perioperative period if HPAA suppression is present.⁴ Patients on chronic steroids who are at low risk for HPAA suppression (*i.e.*, those taking any dose of glucocorticoid for less than 3 weeks, morning doses of prednisone 5 mg/day or less, or prednisone 10 mg/day or less every other day) need neither preoperative testing nor stress-dose steroid administration. Patients who are at high risk for HPAA suppression (*i.e.*, those with clinical Cushing syndrome due to exogenous glucocorticoid use or those taking more than 20 mg/day of prednisone for more than 3 weeks) require stress-dose steroid administration but also do not need preoperative testing. Preoperative evaluation may be helpful for patients on chronic steroid therapy who do not fall into either of the above categories, as stress-dose steroids can be safely withheld with proof of non-suppressed HPAA.²²

When preoperative evaluation is clinically warranted, the short ACTH stimulation test is the test of choice for assessing the integrity of the HPAA and its function. Patients with normal response to administration of cosyntropin do not require further evaluation or perioperative glucocorticoid treatment. Other diagnostic methods (*e.g.*, insulin-induced hypoglycemia, or low dose [1 µg] ACTH stress test) are neither practical nor validated and are not recommended.⁴ Nevertheless, the short ACTH stimulation test is not without its pitfalls, because it measures serum total cortisol levels rather than serum free cortisol levels. Free cortisol, not the protein-bound fraction, is responsible for the physiologic effects of cortisol. A recent study by Hamrahian *et al.*²³ on nutritionally deficient, critically ill patients with hypoproteinemia showed that these patients can have elevated serum free cortisol levels with concurrently lower-than-expected serum total cortisol levels. The diagnostic value of free cortisol levels, however, is not definitively proven, and the test itself is also not yet widely available.

An additional approach to management of the patient presenting for surgery on chronic steroids is to assess the anticipated surgical stress to determine the appropriate perioperative stress dose (table 2). If the estimated surgical stress requirement does not exceed the maintenance dose of exogenous steroids, stress-dose steroid administration is not warranted during the perioperative period unless the patient exhibits signs of adrenal suppression (*e.g.*, vasoplegia of unclear origin).

So the practical question remains: Which chronic steroid-treated patients require perioperative stress-dose steroids? Our approach involves categorizing patients into four groups based on the current available evidence:

1. Patients who have diagnosed secondary adrenal insufficiency as demonstrated by the short acting ACTH test. These patients will require perioperative stress-dose steroids with dosing based on surgical stress risk (table 2).
2. Patients at high risk of HPAA suppression, including patients who have been treated with a glucocorticoid in doses equivalent to at least 20 mg/day of prednisone for more than 3 weeks or who have clinical features of Cushing syndrome. Unless data confirming the integrity of the HPAA is available, these patients would benefit from perioperative stress-dose steroids with dosing based on surgical stress (table 2).
3. Patients at low risk of HPAA suppression, including patients who have been treated with any dose of glucocorticoid for less than 3 weeks, morning doses of prednisone 5 mg/day or less, or prednisone 10 mg/day every other day. Perioperative stress-dose steroids are not required unless they exhibit signs of HPAA suppression.
4. Patients at intermediate risk of HPAA suppression, including any patient on chronic steroid therapy who does not fall into one of the above categories. If time permits, consider referring these patients for preoperative testing to determine their HPAA integrity. If testing is unavailable, the anesthesiologist must exercise his/her clinical judgment as to whether to administer stress-dose steroids based on the patient's perioperative condition (*e.g.*, degree of hemodynamic stability) and surgical risk. It is reasonable, for example, to withhold glucocorticoids if the patient is otherwise healthy and stable preoperatively without signs or symptoms of Cushing disease, with a low threshold for administration of a rescue dose of steroids in the event of unexplained intra- or postoperative hypotension.

Hydrocortisone is the drug of choice for stress and rescue dose steroid coverage.^{2,4,13,22} When selecting a drug to use as a perioperative stress dose, it is important to remember that in secondary adrenal insufficiency, the problem is a glucocorticoid deficiency (as opposed to a mineralocorticoid deficiency); therefore, the relative glucocorticoid and mineralocorticoid activity of the chosen drug must be taken into consideration.^{2,5} Moreover, the mineralocorticoid properties of the drug may result in dose-dependent edema/fluid retention and hypokalemia. For example, if hydrocortisone dosages more than 100 mg are required, it is prudent to consider switching to methylprednisolone, because this drug has a higher glucocorticoid to mineralocorticoid activity ratio.^{2,4} Steroid equivalent dosages and their relative glucocorticoid and mineralocorticoid activities are outlined in table 3.

Conclusions

Patients on chronic steroid therapy should receive their usual preoperative dose of steroids on the day of surgery. However,

existing evidence on the necessity of administering perioperative stress-dose steroids for patients with suspected, or even confirmed, secondary adrenal insufficiency is inadequate to fully support or refute this practice. If HPAA suppression is a clinical concern, perioperative stress-dose steroid administration appears to carry minimal risk compared to the risk of adrenal crisis. However, the lack of class A and B evidence makes it controversial as to whether the administration of perioperative stress-dose steroids is the standard of care, even for patients with known HPAA suppression. The paucity of evidence highlighted by our examination of the available literature should serve as a call for more adequately powered studies comparing different strategies for perioperative steroid management that can generate robust, high-quality data. Until such time that class A and B evidence is available for determining an agreed-upon standard of care, we support this practical approach to the perioperative management of patients on chronic steroid therapy presenting for surgery based on our review of the currently available evidence.

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Competing Interests

The authors declare no competing interests.

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