CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

# Clinical Factors Associated with Biochemical Adrenal-cortisol Insufficiency in Hospitalized Patients

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## ABSTRACT

**BACKGROUND:** Diagnosis of adrenal-cortisol insufficiency is often misleading in hospitalized patients, as clinical and biochemical features overlap with comorbidities. We analyzed clinical determinants associated with a biochemical diagnosis of adrenal-cortisol insufficiency in non-intensive care unit (ICU) hospitalized patients.

**METHODS:** In a retrospective cohort study we reviewed 4668 inpatients with random morning cortisol levels $\leq$15 μg/dL hospitalized in our center between 2003 and 2010. Using serum cortisol threshold level of 18 μg/dL 30 or 60 minutes after Cortrosyn (250 μg; Amphastar Pharmaceuticals, Inc., Rancho Cucamonga, Calif) injection to define biochemical adrenal-cortisol status, we characterized and compared insufficient (n = 108, serum cortisol $\leq$18 μg/dL) and sufficient (n = 394; serum cortisol >18 μg/dL) non-ICU hospitalized patients.

**RESULTS:** Commonly reported clinical and routine biochemical adrenal-cortisol insufficiency features were similar between insufficient and sufficient inpatients. Biochemical adrenal-cortisol insufficiency was associated with increased frequency of liver disease, specifically hepatitis C ($P = .01$) and prior orthotopic liver transplantation ($P < .001$), human immunodeficiency virus (HIV; $P = .005$), and reported pre-existing male hypogonadism ($P < .001$), as compared with the biochemical adrenal-cortisol sufficiency group. Forty percent of insufficient inpatients were not treated with glucocorticoids after diagnosis. Multivariable logistic analysis demonstrated that inpatients with higher cortisol levels ($P = .0001$) and higher diastolic blood pressure ($P = .05$), and females ($P = .009$) were more likely not to be treated, while those with previous short-term glucocorticoid treatment ($P = .002$), other coexisting endocrine diseases ($P = .005$), or who received an in-hospital endocrinology consultation ($P < .0001$), were more likely to be replaced with glucocorticoids.

**CONCLUSIONS:** Commonly reported adrenal-cortisol insufficiency features do not reliably identify hospitalized patients biochemically confirmed to have this disorder. Comorbidities including hepatitis C, prior orthotopic liver transplantation, HIV, and reported pre-existing male hypogonadism may help identify hospitalized non-ICU patients for more rigorous adrenal insufficiency assessment.

 • *The American Journal of Medicine (2014) 127, 754-762*

**KEYWORDS:** Adrenal insufficiency; Cortisol; Inpatient

As adrenal-cortisol insufficiency, that is, insufficient cortisol production to support cellular functions and stress responses, is associated with increased morbidity and potential mortality,[1-3] early diagnosis is crucial. Although endogenous adrenal-cortisol insufficiency is rare, glucocorticoid treatment-induced adrenal insufficiency may be more

**Funding:** Supported by the National Center for Advancing Translational Sciences through UCLA CTSI Grant UL1TR000124 and National Institutes of Health (NIH) grant CA75979. The content is solely the responsibility of the authors and does not represent the official views of the NIH.

**Conflict of Interest:** None.

**Authorship:** All authors had access to the primary data. AB, NL, and SM participated in study design, follow-up, interpretation, and manuscript writing; JM performed all statistical analysis; SMG, AKK, and RCS participated in data gathering; AB and SM wrote the paper.

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0002-9343/$ -see front matter 
http://dx.doi.org/10.1016/j.amjmed.2014.03.002

prevalent,[4] as 2.5% of UK elderly and 1.2% of the US population were reported to have received glucocorticoids at some time.[5,6] In-hospital incidence and prevalence of the disease are unknown.

Adrenal-cortisol insufficiency diagnosis is elusive and challenging, especially in hospitalized patients. Features including anorexia, fatigue, gastrointestinal abnormalities, weight loss, and low blood pressure[1] are nonspecific and overlap with other comorbidities. Electrolyte disturbances, azotemia, anemia, and eosinophilia[1] may be reflective of other comorbidities or are altered by in-hospital treatments.

Biochemical adrenal-cortisol insufficiency diagnosis relies on measurement of circulating cortisol levels.[1] Random plasma morning cortisol levels >14.5 μg/dL (400 nmol/L) suggest adrenal cortisol sufficiency.[1,7] However, as random morning cortisol levels are not diagnostic,[1,8] patients suspected of adrenal-cortisol insufficiency should undergo a Cortrosyn (Amphastar Pharmaceuticals, Inc., Rancho Cucamonga, Calif) stimulation test, which relies on the acute release of adrenal cortisol upon adrenocorticotropic hormone (ACTH) analog stimulation ($\beta^{1\text{-}24}$ corticotropin, cosyntropin, Cortrosyn, Synacthen [Novartis Pharmaceuticals Australia Pty Ltd, North Ryde, NSW, Australia]). This test requires measurement of total cortisol 30 minutes after 250 μg Cortrosyn injection[9-11] and rigorously correlates with levels obtained during the gold-standard insulin tolerance test (cortisol level following induced hypoglycemia of ≤2.2 mmol/L or 40 mg/dL) for adrenal-cortisol insufficiency diagnosis in outpatient.[11] Cortisol measurements 60 minutes after Cortrosyn injection[12-15] weakly correlate with insulin tolerance test results.[16] Cortisol level 30 minutes after Cortrosyn injection >18 μg/dL (500 nmol/L, in serum)[17] and >20 μg/dL (550 nmol/L, in plasma) are diagnostic for adrenal-cortisol insufficiency.[1,18] Cortrosyn stimulation test (250 μg) can be performed at any time and is not sex or age specific.[1,19] Low-dose (1 μg) Cortrosyn[20] elicits similar cortisol responses[19,21] with inconsistent reliability.[22] Importantly, as this test has not been rigorously validated in hospitalized acutely ill patients, often with multiple comorbidities, the accuracy by which this test validly diagnoses adrenal-cortisol insufficiency is unclear. We therefore chose to use the term biochemical adrenal-cortisol insufficiency or sufficiency in this study.

Relying on a serum cortisol threshold of 18 μg/dL during Cortrosyn stimulation test to segregate study subjects, we conducted a retrospective cohort study to distinguish between biochemically diagnosed adrenal-cortisol-insufficient and -sufficient hospitalized patients. The results highlight comorbidities more likely to coexist with the diagnosis of biochemical adrenal-cortisol insufficiency in non-intensive care unit (ICU) hospitalized patients with coexisting morbidities and may contribute to facilitating earlier diagnosis of adrenal insufficiency in the setting of an acute illness.

## CLINICAL SIGNIFICANCE

- Biochemical adrenal-cortisol insufficiency in hospitalized patients is associated with comorbidities including hepatitis C, prior liver transplantation, human immunodeficiency virus, and reported male hypogonadism.
- Almost half of inpatients with diagnosed biochemical adrenal-cortisol insufficiency were not replaced with corticosteroids while hospitalized. Random morning cortisol level, elevated blood pressure, sex, endocrinology consultation, coexisting endocrine diseases, and prior brief or low-dose glucocorticoid treatment were independent determinants of treatment decision.

## METHODS

### Hospitalized Patients

After institutional review board approval, we identified 4668 hospitalized patients in our electronic clinical data repository with reported serum random morning cortisol levels ≤15 μg/dL measured between 2003 and 2010. Exclusion criteria are detailed in Figure 1. Patients who received glucocorticoid treatment before Cortrosyn stimulation test were excluded (n = 904), except for inpatients (7.4% in insufficient and 9.1% in sufficient group) who received doses equivalent to ≤30 mg daily hydrocortisone for ≤2 weeks up to 24 hours before Cortrosyn injection, as these were not expected to have glucocorticoid-induced adrenal insufficiency.[1] Biochemical adrenal-cortisol insufficiency diagnosis in hospitalized patients was based on an abnormal Cortrosyn stimulation test. The final cohort included 502 inpatients: 108 were biochemically adrenal-cortisol insufficient and 394 were biochemically adrenal-cortisol sufficient.

Our real-time electronic repository system aggregates clinical data for efficient patient-centric queries and interactive access for front-end or user-facing applications. The inclusive system contains both electronically inserted data and scanned documents.

The 3 abstractors (SMG, AKK, RCS) were similarly trained by the first author, worked separately according to a predesigned template, were blinded to results and monitored by random data sampling. Statistical analysis was performed by a blinded statistician (JM).

### Cortisol Measurements

Utilizing serum random morning cortisol ≤15 μg/dL for screening allowed for inclusion of adrenal-cortisol insufficiency-suspected inpatients and exclusion of critically ill patients with high random morning cortisol level in whom Cortrosyn stimulation test is uninterpretable.[23] Baseline cortisol level is defined as total cortisol level taken immediately before Cortrosyn injection and separately from random morning cortisol measurement. While random