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Enhanced cosyntropin stimulation test performance enabled by electronic medical record

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Abstract
Purpose To improve performance of the cosyntropin stimulation test (CST) used for diagnosis of adrenal-cortisol insufficiency by implementing an electronic medical record (EMR) system protocol.
Methods We implemented a SmartForm protocol of the validated CST in our EMR system (*CS-Link*^{TM}, EPIC) system and compared medical staff test performance before and after protocol implementation.
Results Correct performance of the CST improved significantly after EMR implementation. The number of correctly performed CSTs increased from 16.1 % before to 53.5 % after implementation ($p < 0.0001$) while those performed incorrectly and were uninterpretable decreased from 36.2 to 7.1 % ($p < 0.0001$). This performance improvement result in a calculated cost savings of $50,414 for every 100 tests performed.
Conclusions The EMR system is useful for guiding medical staff to accurately perform the CST, reduce the number of wasted tests, and maximize staff time and resources.

Keywords Adrenal cortisol insufficiency · Cosyntropin stimulation test · Electronic medical record · Performance improvement

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Introduction

The diagnosis of adrenal-cortisol insufficiency, due to either primary adrenal tissue loss or pituitary adrenocorticotrophin (ACTH) deficiency causing secondary adrenal atrophy, relies on the measurement of circulating cortisol levels [1]. Cosyntropin stimulation test (CST), widely used in patients suspected of cortisol deficiency, measures acute release of adrenal cortisol upon stimulation with the ACTH analogue cosyntropin (β^{1-24} corticotropin also known as synacthen). Cortisol levels measured 30 min after 250 μg cosyntropin injection tightly correlate with those obtained during the insulin-induced hypoglycemia test, which is the gold-standard test for the diagnosis of adrenal-cortisol insufficiency [2–4]. A 60-min post-stimulation cortisol level measurement is less well validated [5, 6]. Positive CST is determined when post-stimulation cortisol level are ≤18 μg/dL (500 nmol/L, in serum) [7] or ≤20 μg/dL (550 nmol/L, in plasma), supporting the diagnosis of adrenal-cortisol insufficiency.

While clinical signs and symptoms of cortisol deficiency in hospitalized patients are often vague, and routine blood tests are usually unhelpful for diagnosis [8], high clinical suspicion combined with a positive CST predicts true adrenal-cortisol insufficiency in almost 100 % of patients [9]. Importantly, falsely normal cortisol levels after stimulation may be seen immediately after acute damage to pituitary corticotroph cells or removal of an ACTH-secreting tumor [10], while falsely low cortisol level may be seen in cases of severe hypoalbuminemia, such as in patients with severe liver dysfunction, as measured cortisol represent both protein-bound and free cortisol levels [11, 12]. In addition, CST cannot reliably diagnose adrenal-cortisol insufficiency in critically ill patients [13, 14].

We previously analyzed clinical determinants associated with adrenal-cortisol insufficiency in hospitalized patients based on CST results [8]. To our surprise, many patients screened for that study did not meet study inclusion criteria due to incorrectly performed and uninterpretable tests. As adrenal-cortisol insufficiency is associated with increased morbidity and mortality [15, 16], inaccurately performed CSTs can erroneously guide treatment and are economically wasteful. We attempted to improve performance of the evidence-based CST protocol utilizing the electronic medical record (EMR) system at our tertiary medical center and conducted a test of change study to assess performance before and after protocol implementation.

Methods

In July 2014, we implemented a new CST protocol in our EMR system (*CS-Link*^{TM}, EPIC) for use in hospitalized patients at our institution. A SmartForm was created, which included the protocol steps and some tips for physicians (Table 1). The protocol comprises three steps: measurement of baseline cortisol level, immediately followed by a 250 μg cosyntropin IV/IM injection, and followed by cortisol measurement exactly 30 min later. In August 2015, after obtaining IRB approval, we identified 406 CSTs performed between January 2013 and May 2015, 279 before and 127 after EMR CST implementation.

CSTs were divided into three cohorts according to test performance. CSTs in Group 1 were performed according to the new EMR protocol. CSTs in Group 2 were not performed according to the new protocol, but results could still be interpreted, i.e., cortisol measures were made in serum samples taken up to 60 min from injection, only post-injection cortisol was recorded, and/or baseline cortisol was taken a few hours prior to cosyntropin injection but on the same day. CSTs in Group 3 were performed incorrectly per the new protocol and results could not be reliably interpreted. These included cortisol measurements in samples drawn more than 60 min after cosyntropin injection, no cortisol measured after documented cosyntropin injection, and/or high baseline cortisol level that did not increase after injection, suggesting blood level of hydrocortisone or prednisone treatment was measured and not endogenous cortisol.

Cortisol levels were measured using the Elecsys® Cortisol Immunoassay System (Roche Diagnostics, Indianapolis, IN). Cost was calculated based on our costs of $1718.00 per single vial of 250 μg cosyntropin and $7.21 per single serum cortisol measurement. Statistical analysis was done using SAS version 9.2 (SAS Institute, Cary, NC). Numerical variables were summarized by mean and standard deviation and compared between groups by the independent samples *t* test or the Wilcoxon rank sum test. Categorical variables were summarized by frequency and percent and compared across groups by the Fisher exact test. An unadjusted 0.05 significance level was used throughout.

Results and conclusions

Correct performance of the CST improved significantly after implementation of the new EMR protocol (Table 2). The number of CSTs classified as Group 1 increased from 16.1 % before to 53.5 % after implementation ($p < 0.0001$) while those classified as Group 3 decreased from 36.2 to 7.1 % ($p < 0.0001$). CSTs in Group 2 decreased from 47.7 to 39.4 %. A significant difference in between-group distribution was observed before and after implementation, with a significant shift to Group 1 after the intervention ($p < 0.0001$). The number of cortisol values measured in serum samples taken at 60 min also decreased, from 52 to 36.2 % ($p = 0.004$), while those measured in serum samples taken at times other than 30 and 60 min after cosyntropin injection decreased from 49.8 to 33.9 % ($p = 0.004$).

In calculating effects of improved performance on cost, we compared our per-CST actual cost with our effective cost, which accounts for loss due to incorrectly

Table 1 Cosyntropin stimulation test new EMR protocol

Cosyntropin stimulation test EMR protocol	1. Baseline serum cortisol should be drawn and exact activity time recorded
	2. Cosyntropin (250 μg) should be injected intravenously immediately after and exact activity time recorded
	3. Serum cortisol should be drawn exactly 30 min after injection and exact activity time recorded
Additional tips	1. Cosyntropin stimulation test can be performed at any time throughout the day, independent of food intake
	2. Some synthetic glucocorticoids can be detected by cortisol assays
	3. An additional measurement of blood cortisol 60 min after cosyntropin injection is not mandatory for the diagnosis of adrenal-cortisol insufficiency

This message appears in our EMR system when the nurse processes a CST. The performing staff is requested to document date and time for each of the three steps of the test

Table 2 CST performance before and after EMR CST protocol implementation

	Implementation of new EMR CST protocol		*p*
	Before	After	
Number of CSTs (N)	279	127	
Male, female (%)	50.2, 49.8	51.2, 48.8	0.91
CST performance [n (%)]			
Group 1: Correct	45 (16.1)	68 (53.5)	**<0.0001**
Group 2: Incorrect, interpretable	133 (47.7)	50 (39.4)	
Group 3: Incorrect, not interpretable	101 (36.2)	9 (7.1)	**<0.0001**
Cortisol taken at 60 min [n (%)]	145 (52.0)	46 (36.2)	**0.004**
Cortisol taken at times other than 30 or 60 min [n (%)]	139 (49.8)	43 (33.9)	**0.004**
GCt within the 24 h before CST [n (%)]	64 (22.9)	25 (19.7)	0.52
GCt after positive CST[a] in group 1 and group 2 [n (%)]	46/66 (69.7)	16/21 (76.2)	0.78
GCt after positive CST[a] in group 1 and group 2, without prior GCt exposure [n (%)]	19/36 (52.8)	10/13 (76.9)	0.19
Associated endocrinology consultation [n (%)]	102 (36.6)	44 (34.6)	0.74

Bold values are statistically significant *p* value

CST cosyntropin stimulation test, *GCt* glucocorticoid treatment

[a] Positive CST, serum cortisol ≤18 μg/dL after cosyntropin stimulation in Group 1 and Group 2, excluding Group 3, supporting adrenal-cortisol insufficiency

performed and uninterpretable tests (Group 3). Our actual per-CST cost is $1732.42 (1 cosyntropin vial and 2 cortisol assays). Prior to protocol implementation, accounting for our 36.2 % incorrect rate, our effective per-test cost was $2359.56; after protocol implementation, given our 7.1 % incorrect rate, our effective cost was $1855.42. For every 100 tests, performance improvement resulted in a cost savings of $50,414.00. Cost savings would be higher if we also account for nurse time and poor resource utilization.

The EMR protocol reminds clinicians that some synthetic glucocorticoids can be detected by cortisol assays (Table 1), as antibodies used to measure endogenous cortisol may cross-react with some synthetic glucocorticoids and therefore falsely increase cortisol level measured. Nevertheless, the profound improvement in CST performance following protocol implementation in our inpatient setting was not accompanied by a change in pre-CST synthetic glucocorticoid exposure (Table 2). The rate of glucocorticoid treatment in patients diagnosed with adrenal-cortisol insufficiency after a positive CST and the rate of endocrinology consultation in patients undergoing CST were also similar before and after EMR CST protocol implementation.

In conclusion, the EMR system is useful for guiding medical staff to accurately perform CSTs, reduce the number of wasted tests, and maximize staff time and resources. Additional interventions are required to improve pre- and post-diagnosis glucocorticoid treatment in patients with adrenal-cortisol insufficiency.

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Conflict of interest All authors (AB, JG, JM) declare that they have no conflict of interest.

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