AACC Better health through laboratory medicine.

PEARLS OF LABORATORY MEDICINE

Hypercortisolism

Qing H. Meng PhD, MD, DABCC, FCACB
Section Chief of Clinical Chemistry Laboratories
Professor
Department of Laboratory Medicine
The University of Texas MD Anderson Cancer Center

DOI:10.15428/CCTC.2017.284943

CCTC Clinical Chemistry Trainee Council

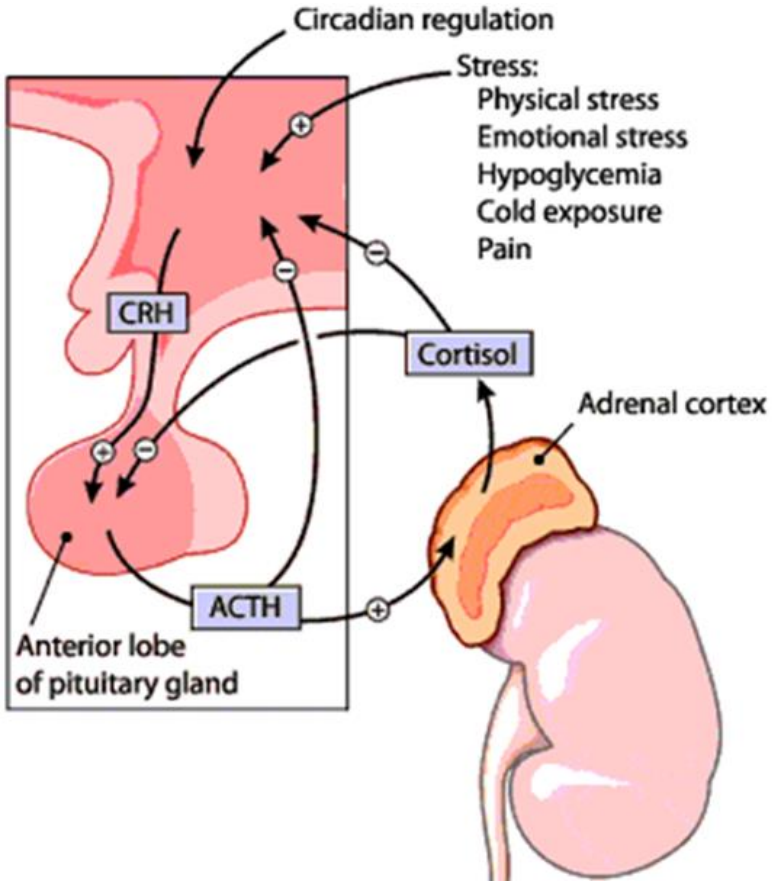
Learning Objectives

After participating in this presentation, you will be able to:

- Understand the different etiologies and pathophysiologies of hypercortisolism
- Discuss the screening tests for Cushing syndrome
- Establish diagnostic approach and differential diagnosis of Cushing syndrome

Regulation of Cortisol Secretion

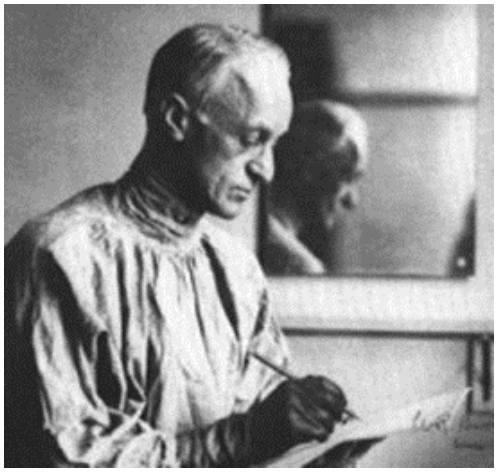
Hypothalamic-Pituitary-Adrenal Axis



- Pulsatile Secretion
- Circadian Rhythm

Kirk LF Jr et al. Am Fam Physician 2000;62:1119-27.

Hypercortisolism (Cushing Syndrome)



- A group of clinical abnormalities due to chronic exposure to excess of cortisol.
- The incidence of Cushing's syndrome is 10-15 per million and mostly occur between the ages of 20 and 50 years.
- First described by Harvey Cushing, an American neurosurgeon in 1912.

Causes of Cushing Syndrome

- **ACTH-dependent causes**
  - ACTH-secreting pituitary tumor (Cushing disease)(70% cases)
  - Ectopic ACTH-secreting tumors (non-pituitary)(15%)

- **ACTH-independent causes**
  - Adrenal adenoma: benign (5%)
  - Adrenal carcinoma: malignant (3%)
  - Nodular adrenal hyperplasia (9%)
  - Adrenal rest tumor (<1%)
  - Iatrogenic and factitious glucocorticoid administration(exogenous)

- **Pseudo-Cushing Syndrome**
  Associated in patients with alcoholism, depression, obesity, PCOS

Hypercortisolism

Cushing Disease vs. Cushing Syndrome

- Cushing disease and Cushing syndrome are caused by an oversecretion of the adrenal cortex.
- Cushing syndrome refers to the general state characterized by excessive production of cortisol leading to classic symptoms.
- Cushing disease is the pituitary-dependent form of Cushing syndrome caused by hypersecretion of ACTH by pituitary tumors primarily microadenoma.

Hypercortisolism

Common Causes of Ectopic ACTH Secretion

- Neuroendocrine tumors:
  - Carcinoid tumors of the lung (bronchi)
  - Carcinoid tumors of pancreas
  - Carcinoid tumors of thymus
  - Medullary thyroid cancer
- Small cell carcinoma of the lung
- Pheochromocytoma

Diagnosis of Hypercortisolism

- Clinical manifestations
- Lab findings
  - Serum cortisol
  - Plasma ACTH (not the 1st line test)
  - 24 hour urinary cortisol
  - Suppression or stimulation tests
- Imaging: CT, MRI

Laboratory Evaluations of Cushing Syndrome

- Serum cortisol levels elevated
- Plasma ACTH levels maybe elevated (ACTH-dependent)
- 24-hour urinary cortisol levels elevated
- Loss of diurnal variation in cortisol levels
- Dexamethasone suppression test

Screening Tests for Cushing Syndrome

Three screening tests are commonly applied:

- Measurement of the 24-hour urinary free cortisol (UFC)
- The overnight low-dose dexamethasone suppression test
- A midnight cortisol measurement (plasma or salivary cortisol)

Hypercortisolism is strongly suggested when any two out of three tests are abnormal.

Screening Tests for Cushing Syndrome

- **Measurement of the 24 hour urinary free cortisol (UFC)**

A 24 hour urinary free cortisol concentration <50 µg/day excludes the diagnosis of Cushing syndrome

A 24-hour urinary free cortisol concentration>120 µg/day suggests the diagnosis of Cushing syndrome.

Urine cortisol measurements do not establish the diagnosis and abnormal results need to be followed by further investigation or testing.

Screening Tests for Cushing Syndrome

- **The Overnight Low-Dose Dexamethasone Suppression Test**
  - 1.0 mg dexamethasone given orally at 2300h
  - Serum cortisol measured at 8:00am next day
  - Normal: Serum cortisol suppressed to <2µg/dL
  - Cushing Syndrome: Serum cortisol not suppressed. >10µg/dL suggestive of the diagnosis.

Screening Tests for Cushing Syndrome

- **Multiple Low-Dose Dexamethasone Suppression Test**
  - Urine is collected every 24h for 3 days for measurement of cortisol.
  - Dexamethasone, 0.5 mg q6h P.O on day 2 for 2 days
  - Urinary free cortisol decreased: Normal
  - Urinary free cortisol NOT decreased: Cushing Syndrome

Screening Tests for Cushing Syndrome

- **Midnight Serum Cortisol and Salivary Cortisol Measurements**
  - Serum (or salivary) cortisol measurement taken at 2400 hours
  - Cushing Syndrome
    - Elevated midnight cortisol levels
    - Loss of diurnal variation in cortisol levels (less helpful).

Diagnosis of Cushing Syndrome

Plasma ACTH

- Plasma ACTH concentrations are low in patients with adrenal tumor
- Plasma ACTH concentrations are normal or moderately elevated in patients with Cushing disease
- Plasma concentrations of ACTH are very often markedly elevated in patients with ectopic Cushing (ACTH) syndrome

High-Dose Dexamethasone Suppression Test

- High-dose dexamethasone suppression test can be used to differentiate Cushing syndrome from Cushing disease.
- Serum is collected at 0800 hours for the measurement of cortisol.
- In patients with adrenal tumor and in most of the patients with nonendocrine ACTH-secreting tumor, suppression does not occur after the high-dose 8 mg dexamethasone administration.

High-Dose Dexamethasone Suppression Test

- High-Dose Overnight Dexamethasone Suppression Test: DX 4mg, P.O at 2300 and 2400 hours

- Multiple High-Dose Overnight Dexamethasone Suppression Test: DX 2mg, P.O, q6h for 2 days.

- Serum or urinary free cortisol at 0800 hours reduced>50%: Cushing disease (Pituitary adenoma)
- Serum or urinary free cortisol NOT reduced>50%: Adrenal tumor, carcinoma, ectopic ACTH syndrome

CRH Stimulation Test

- Exogenous CRH, 1.0 μg/kg b.w, is given intravenously in bolus form at 0900 or 2000 hours.
- Serum cortisol and plasma ACTH are measured 15 min and immediately before and 5, 15, 30, 60, 120, and 180 min after CRH injection.

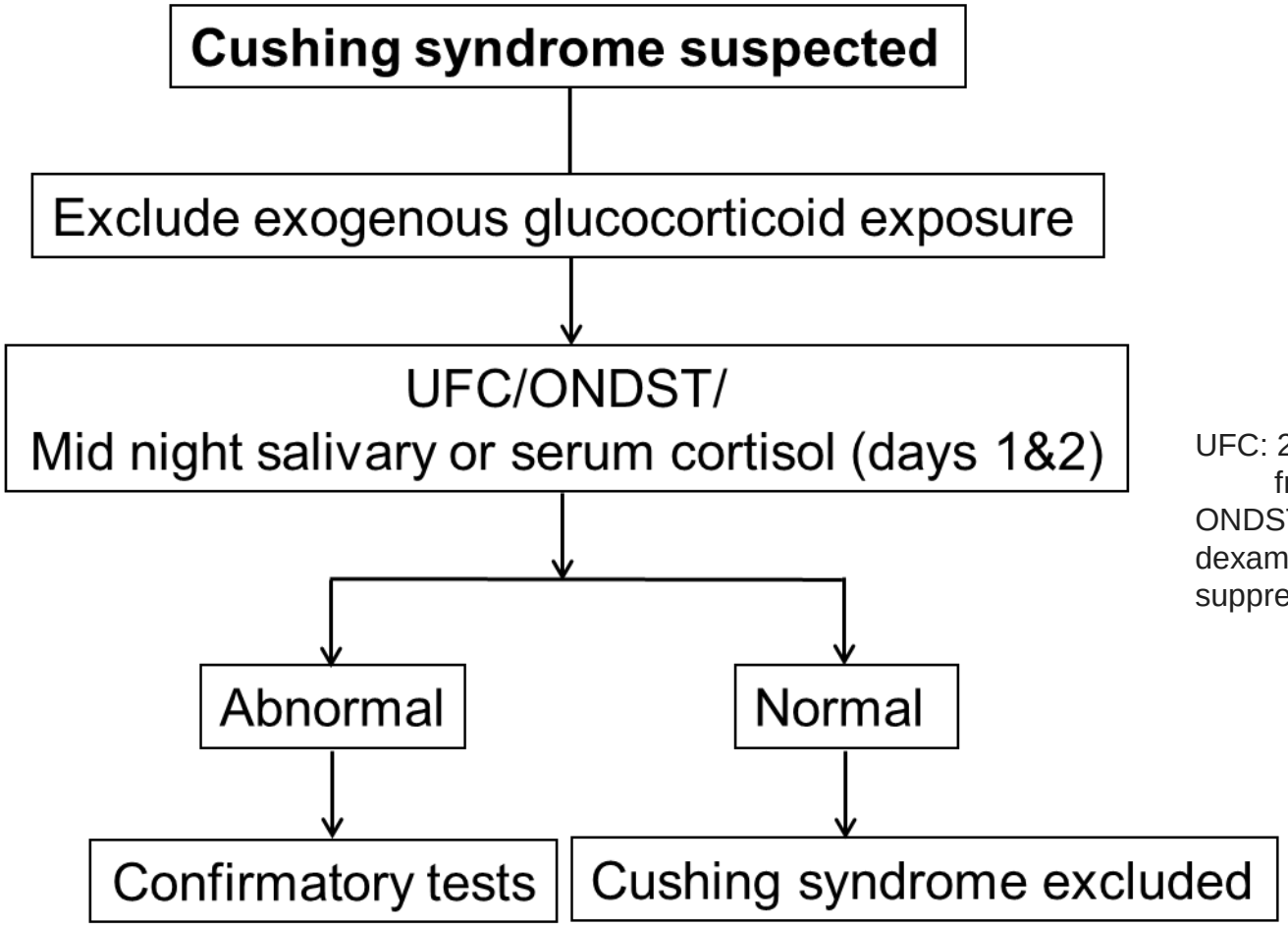
- Interpretation:
  - An increase of serum cortisol by ≥20% or ACTH by ≥ 50% above basal level is seen in patients with Cushing disease.
  - Poor responses occur in patients with adrenal tumor and in most patients with nonendocrine ACTH-secreting tumor

Tests for Localization of Cushing Syndrome

- Computed tomography (**CT**) and magnetic resonance imaging (**MRI**) are helpful in localizing the tumors

- Selective Inferior petrosal sinus sampling (**IPSS**) for ACTH measurements before and after CRH administration:
  - Blood samples are taken from each sinus vein and from a peripheral vein.
  - If the ACTH level in the inferior petrosal sinus vein is similar to the peripheral vein, this suggests a non-pituitary source of the ACTH (ectopic).
  - In Cushing disease, the ACTH level in the inferior petrosal sinus vein is much higher compared to the peripheral vein (>2:1).

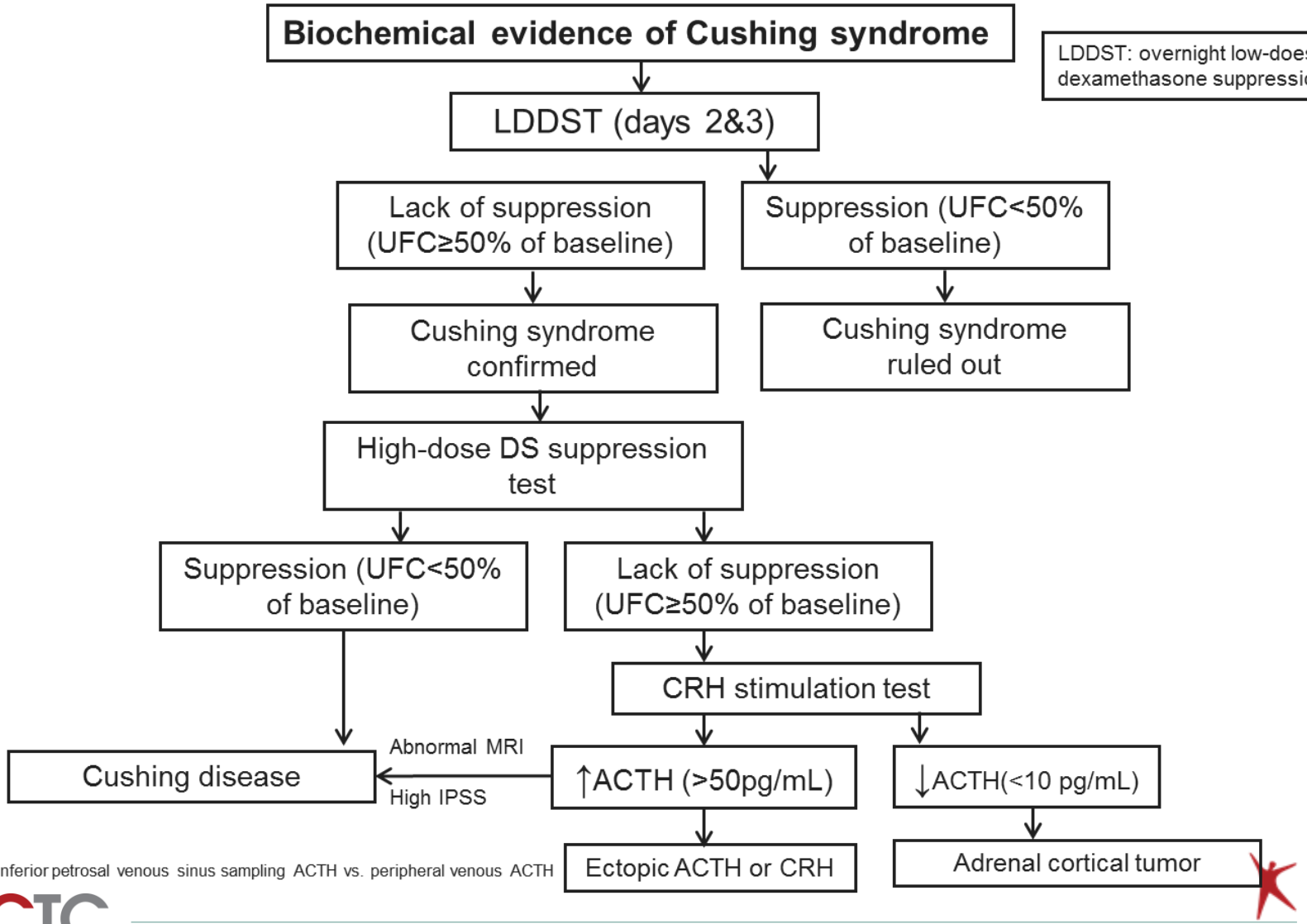
Laboratory Evaluation of Cushing Syndrome



UFC: 24-hour urinary free cortisol
ONDST: overnight 1mg dexamethasone suppression test

Nieman et al. J Clin Endocrinol Metab 2008;93:1526-40.
Tietz Text Book (5th edition)

Differential Diagnosis of Cushing Syndrome



Nieman et al. J Clin Endocrinol Metab 2008;93:1526-40.
Tietz Text Book (5th edition)

References

1. Kirk LF Jr, Hash RB, Katner HP, Jones T. Cushing's disease: clinical manifestations and diagnostic evaluation. Am Fam Physician 2000;62:1119-27.
2. Nieman LK, Biller BM, Findling JW, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2008;93:1526-40.
3. Burtis C, Ashwood E, and Bruns D. Tietz Text Book 2012, 5th edition

Disclosures/Potential Conflicts of Interest

Upon Pearl submission, the presenter completed the Clinical Chemistry disclosure form. Disclosures and/or potential conflicts of interest:

- **Employment or Leadership**:
- **Consultant or Advisory Role:**
- **Stock Ownership:**
- **Honoraria:**
- **Research Funding:**
- **Expert Testimony:**
- **Patents:**

*****This slide will be completed by CCJ Staff based on disclosure form completed electronically in the submission site.*****

Thank you for participating in this *Clinical Chemistry* Trainee Council Pearl of Laboratory Medicine.

Find our upcoming Pearls and other Trainee Council information at www.traineecouncil.org

Download the free *Clinical Chemistry* app on iTunes today for additional content!

Follow us: