PITFALLS IN DIAGNOSIS AND TREATMENT OF CUSHING'S SYNDROME

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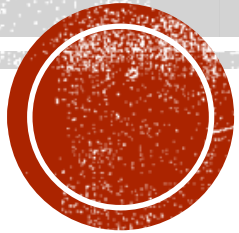
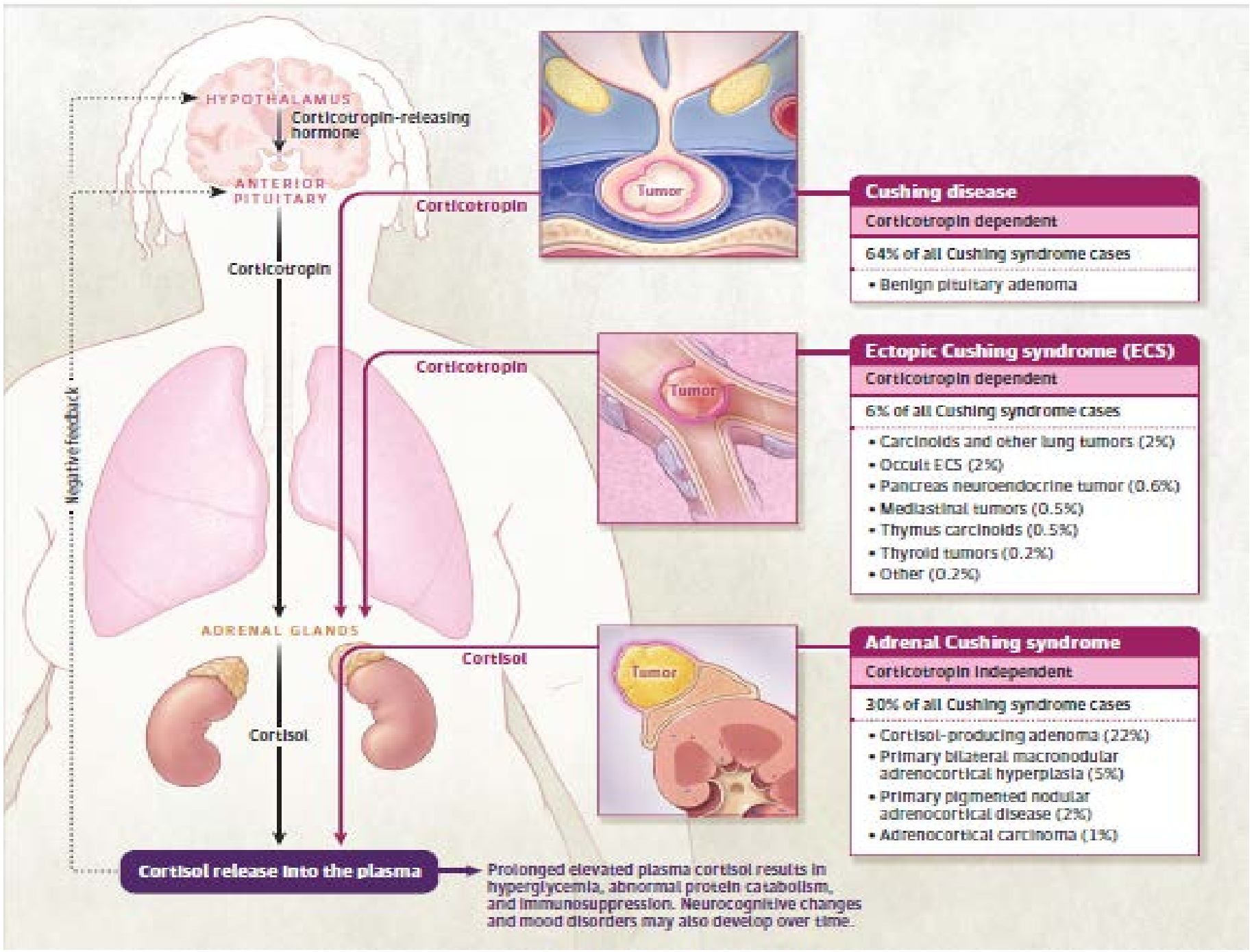


AGENDA:

- Introduction
- Challenges in Diagnosis
  - Clinical symptomatology
  - Laboratory assessment
- Cushing VS Pseudo-Cushing
- Cushing's Subtype (Localization)
  - Intrapituitary vs Extrapituitary
- Treatment
- Complications of Cushing's syndrome
- Glucocorticoid withdrawal syndrome (GWS)

INTRODUCTION

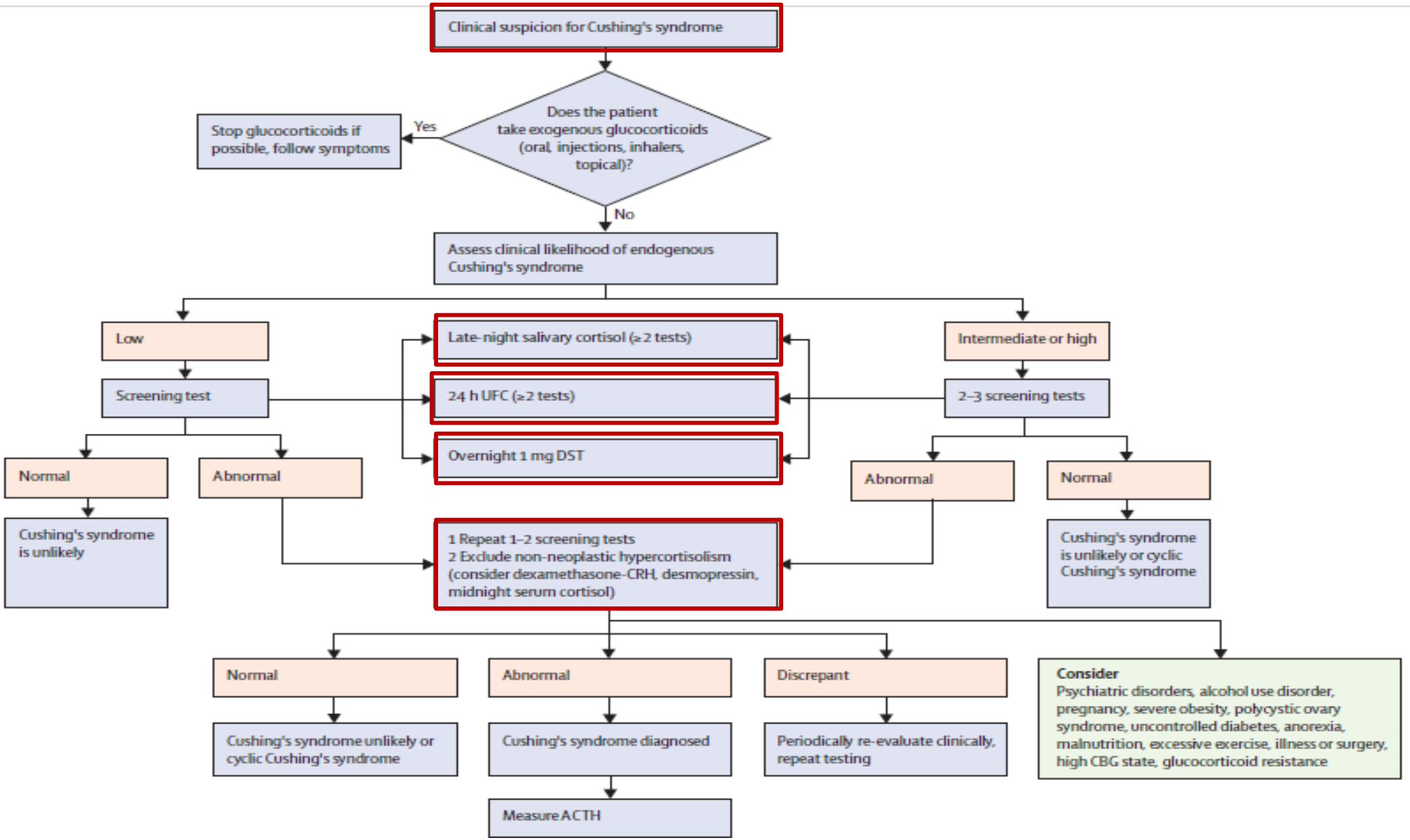
- Cushing syndrome (CS) - is one of the most challenging diagnostic and management problems in clinical endocrinology
- The estimated incidence ranges from about 2 to 3 per million people to 8 per million people annually.
- ACTH-dependent hypercortisolism
  - Intra-pituitary corticotrope tumor (Cushing disease, CD)- 64%
  - non-pituitary (ectopic) tumor secreting ACTH- 6%
- ACTH-independent hypercortisolism (Adrenal CS)- 30%
  - unilateral
  - bilateral adrenal nodular disease


HYPOTHALAMUS
Corticotropin-releasing hormone
ANTERIOR PITUITARY
Corticotropin
Corticotropin
Corticotropin
Tumor
Tumor
Tumor
Negative feedback
ADRENAL GLANDS
Cortisol
Cortisol
Cortisol release into the plasma
Prolonged elevated plasma cortisol results in hyperglycemia, abnormal protein catabolism, and immunosuppression. Neurocognitive changes and mood disorders may also develop over time.
Cushing disease
Corticotropin dependent
64% of all Cushing syndrome cases
• Benign pituitary adenoma
Ectopic Cushing syndrome (ECS)
Corticotropin dependent
6% of all Cushing syndrome cases
• Carcinoids and other lung tumors (2%)
• Occult ECS (2%)
• Pancreas neuroendocrine tumor (0.6%)
• Mediastinal tumors (0.5%)
• Thymus carcinoids (0.5%)
• Thyroid tumors (0.2%)
• Other (0.2%)
Adrenal Cushing syndrome
Corticotropin independent
30% of all Cushing syndrome cases
• Cortisol-producing adenoma (22%)
• Primary bilateral macronodular adrenocortical hyperplasia (5%)
• Primary pigmented nodular adrenocortical disease (2%)
• Adrenocortical carcinoma (1%)

QUESTIONS IN SUSPECTED CS

- There are two stages in the investigation of suspected Cushing's syndrome
- 1: "Does This Patient Have CS?"
- 2: "What is the Cause of CS in this Patient?"

➢ It is essential to answer question "1" before moving to question "2."


Clinical suspicion for Cushing's syndrome
Does the patient take exogenous glucocorticoids (oral, injections, inhalers, topical)?
Yes
Stop glucocorticoids if possible, follow symptoms
No
Assess clinical likelihood of endogenous Cushing's syndrome
Low
Screening test
Normal
Cushing's syndrome is unlikely
Abnormal
Late-night salivary cortisol (≥2 tests)
24 h UFC (≥2 tests)
Overnight 1 mg DST
Intermediate or high
2–3 screening tests
Abnormal
Normal
Cushing's syndrome is unlikely or cyclic Cushing's syndrome
1 Repeat 1–2 screening tests
2 Exclude non-neoplastic hypercortisolism (consider dexamethasone-CRH, desmopressin, midnight serum cortisol)
Normal
Cushing's syndrome unlikely or cyclic Cushing's syndrome
Abnormal
Cushing's syndrome diagnosed
Measure ACTH
Discrepant
Periodically re-evaluate clinically, repeat testing
Consider
Psychiatric disorders, alcohol use disorder, pregnancy, severe obesity, polycystic ovary syndrome, uncontrolled diabetes, anorexia, malnutrition, excessive exercise, illness or surgery, high CBG state, glucocorticoid resistance

WHOM TO SCREEN FOR CUSHING'S SYNDROME

An Endocrine Society Clinical Practice Guideline emphasize testing

1. Only in those with clinical features more specific for CS, especially if progressive
2. also suggests that "Patients with unusual features for age (e.g., osteoporosis, hypertension)..."

- To avoid widespread in-discriminant testing in large "at-risk" populations such as those with T2DM or hypertension.

CHALLENGES IN CLINICAL PRESENTATION (1)

1) In some patients, one symptom may predominate, and this causes delay in diagnosis, for months to years, with symptoms ascribed to rheumatologic, cardiologic, or psychiatric disease

   - Mild forms may be mistaken for all sorts of ill-defined conditions, such as PCOS, idiopathic hirsutism, idiopathic cyclic edema, and essential hypertension.

2) In mild forms of CD, the diagnosis is often less apparent in men than in women. It has been suggested that some persistent testicular androgens offer better protection against the protein-wasting effect of cortisol.

CHALLENGES IN CLINICAL PRESENTATION (2)

3) Most patients with CD exhibit some fluctuation of cortisol secretion, others display a truly cyclic pattern. Episodes of active hypercortisolism are separated by periods of normal pituitary-adrenal activity of varying lengths.
4) CD may present with symptoms so severe (including profound myopathy and hypokalemia) that presentation will resemble the ectopic ACTH syndrome (EAS).

CHALLENGES IN CLINICAL PRESENTATION (3)

5) In rare instances, the first presenting symptoms will be those of a pituitary tumor. Careful evaluation of a macroadenoma might clearly indicate a state of ACTH hypersecretion in a patient who had no evident feature of chronic hypercortisolism (Clinically silent CD).
6) Unusually, CD may be recognized in the systematic evaluation of a patient with MEN 1 or during family screening of familial isolated pituitary adenoma due to AIP mutation

“FIRST-LINE” TESTS

- First-line tests: (In severe hypercortisolism) These are expected to be:
  - highly sensitive
  - simple to perform
  - feasible in outpatients
  - not costly.

I. Late-night salivary cortisol (LNSC)
II. 24 hours urine cortisol (UFC)
III. 1 mg and 2 mg 48 hours dexamethasone suppression tests (1 mg ODST, LDDST)

LATE NIGHT SALIVARY CORTISOL (LNSC)

- LNSC is based on the assumption that patients with CS lose the normal circadian nadir of cortisol secretion;
  - at least 2-3 LNSC tests are recommended.
- Sampling saliva at usual bedtime rather than at midnight could decrease false positive results, as cortisol nadir is tightly entrained to sleep onset.
- False positive: older men (mean age 61 year , co-morbidities of DM and/or HTN
- LNSC should not be done in nightshift workers.

OVERNIGHT 1-MG DST

- **False positive results**
  - Increased CBG concentrations caused by:
    oral estrogens, pregnancy, or chronic active hepatitis, which can increase total cortisol concentrations.
  - Concomitant treatment with CYP3A4 inducers (eg, phenobarbital, carbamazepine, St John's wort);
  - Rapid absorption or malabsorption of dexamethasone due to increased gut transit time, chronic diarrhea, or coeliac disease;

  - Measuring dexamethasone concomitantly with cortisol, using laboratory specific ranges of expected values, can reduce the risk for false positive results.

  -

OVERNIGHT 1-MG DST

- **False negative results** are less common,
  - Decreased CBG and albumin concentrations, which can be noted in patients with concurrent nephrotic syndrome,
  - Inhibition of dexamethasone metabolism by concomitant medications such as fluoxetine, cimetidine, or diltiazem, leading to a higher biologically available dose.

➢ DST might be the preferred test for shift workers and patients with disrupted circadian rhythm due to uneven sleep schedules,

URINE FREE CORTISOL (UFC)

- Random variability can be as high as 50%.
- As with LNSC, UFC relies on accurate collection by the patient.
- At least 2-3 24h urine collections are advised to measure UFC to account for intra-patient variability.

  - Glycyrrhetinic acid: causes apparent mineralocorticoid excess by inhibition of the enzyme 11-β-hydroxysteroid dehydrogenase. UFC is falsely elevated in subjects taking excess quantities of licorice.

TABLE 17.4 Hypercortisolemic States Without Cushing's Syndrome

Some clinical features of Cushing's syndrome may be present

Pregnancy
Depression and other psychiatric conditions
Alcohol dependence
Glucocorticoid resistance
Morbid obesity
Poorly controlled diabetes mellitus

Unlikely to have any clinical features of Cushing's syndrome

Physical stress (hospitalization, surgery, pain)
Malnutrition, anorexia nervosa
Intense chronic exercise
Hypothalamic amenorrhea
Cortisol binding globulin excess (increased serum but not urine cortisol)

HYPERCORTISOLEMIC STATES WITHOUT CUSHING'S SYNDROME "PSEUDO-CUSHING"- (NON-NEOPLASTIC HYPERCORTISOLISM)

I. Usually Mild
II. Transient
III. Regresses with its cause.

- UFC is almost always within 3 fold of normal concentrations.

➢ Useful test for differentiation Between ACTH dependent Cushing's syndrome and pseudo-Cushing's syndrome- Second line tests:

1. The combined LDDT–corticotrophin releasing hormone (CRH; DexCRH) test,
2. LDDT
3. Desmopressin Stimulation test (DST)
4. Midnight serum cortisol

DEPRESSION

- Patients with severe endogenous depression frequently have biochemical hypercortisolism (clinically and biologically mild)
  - Plasma cortisol and UFC are increased (**UFC < 3 Times**)
  - are not suppressed normally on LDDST.
  - ACTH: NL or Slightly high
- CRH test (Or DST):
  - ACTH response is blunted (sensitive to negative feedback of increased cortisol levels)
  - Cortisol response is NL
- The circadian pattern of plasma cortisol levels is less disrupted
  - LNSC-LNSeC

ALCOHOL

- **chronic alcohol dependence** may present with clinical and biochemical features of glucocorticoid excess with HPA axis activation.
- General fatigue, diminished muscle strength, plethoric facies, truncal obesity, and abdominal striae may be present
  - With increased serum cortisol and UFC
  - lack of normal response to LDDST.
  - a disrupted circadian rhythm

➢ The most effective way to avoid a false diagnosis is to assess after a period of abstinence.

PREGNANCY

- In the first months of pregnancy, increased estrogens induce a 2-3 fold rise in plasma CBG that reaches a maximum at about 3 months and plateaus thereafter.
- In the third trimester
  - 30% of women have UFC > the upper limit of normal (nonpregnant women)
  - Mean unbound and salivary cortisol and UFC show a 2-3 fold increase.
  - Most have an abnormal response to the classic L

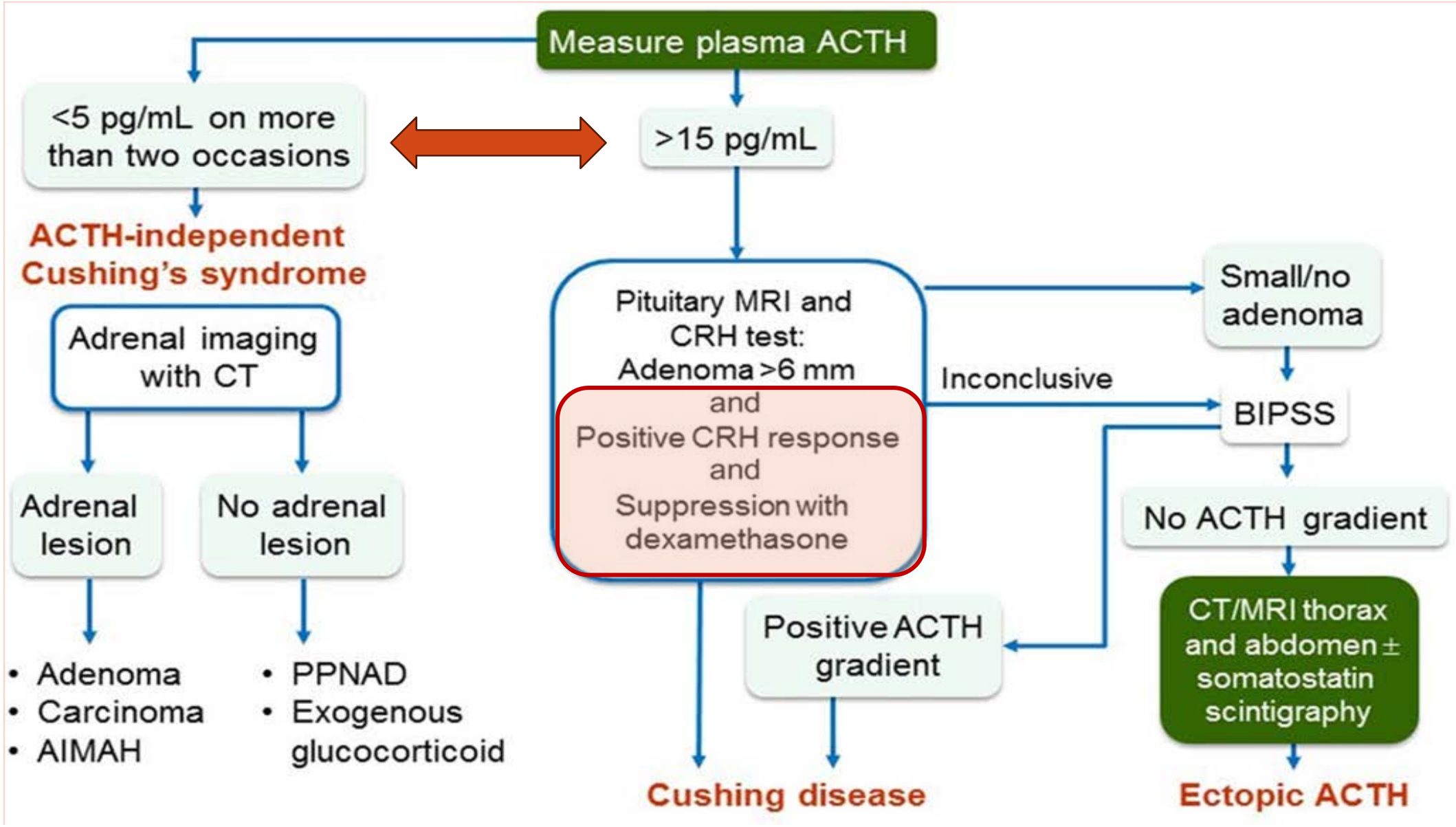
STRESS

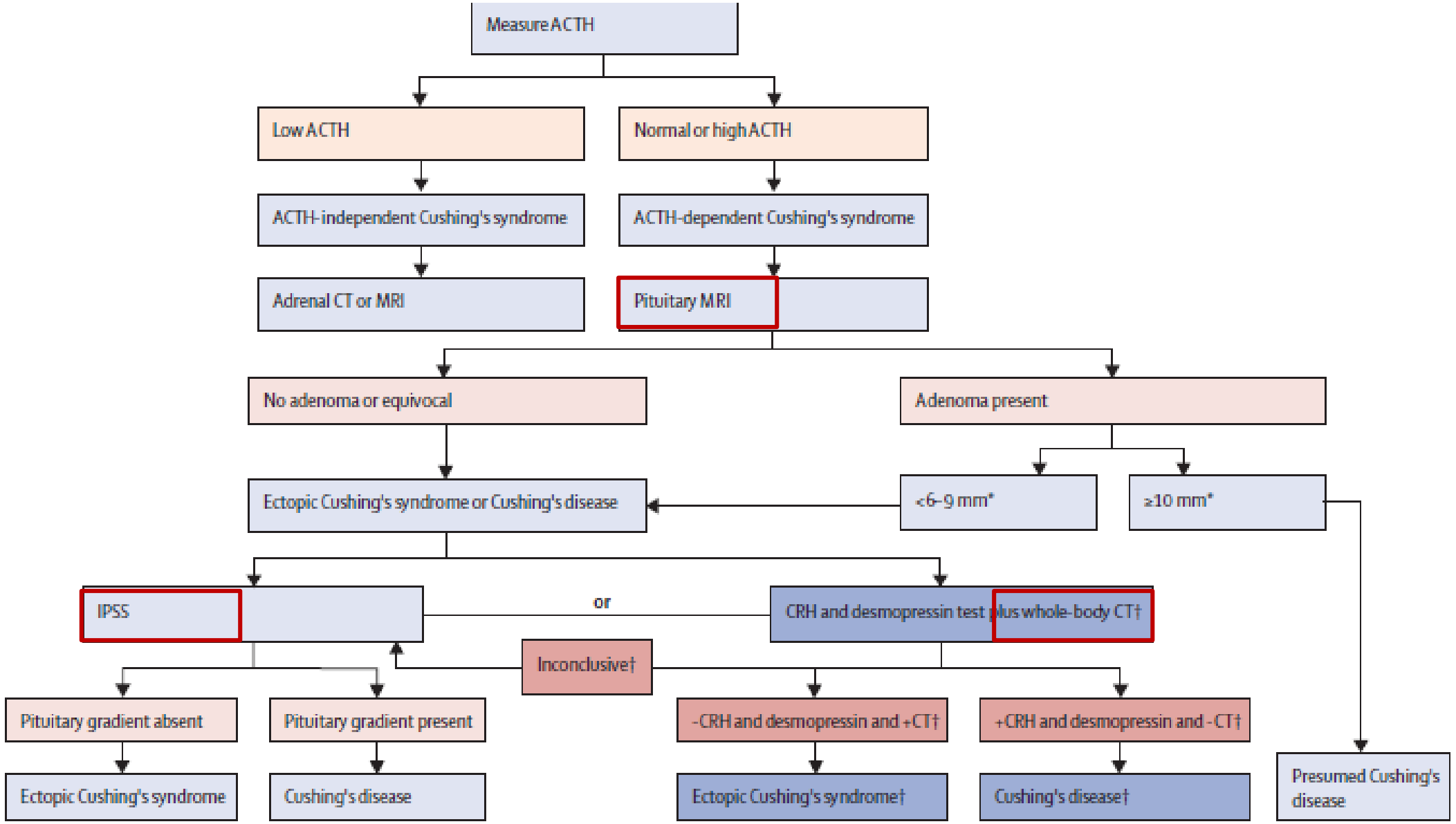
- Including surgery, test-taking, various acute and chronic illnesses, terminal illnesses, extended burns, and DM.

- The absolute need to await the resolution of stressful intercurrent conditions before initiating a proper diagnostic evaluation.

PITFALLS IN DIFFERENTIAL DIAGNOSIS

1. Cushing Disease Mimicking an Autonomous Adrenocortical Tumor
2. Severe Cushing Disease Mimicking Classic Ectopic ACTH Syndrome
3. Mild Ectopic ACTH Syndrome Mimicking Classic Cushing Disease


Measure plasma ACTH
<5 pg/mL on more than two occasions
>15 pg/mL
ACTH-independent Cushing's syndrome
Adrenal imaging with CT
Adrenal lesion
No adrenal lesion
• Adenoma
• Carcinoma
• AIMAH
• PPNAD
• Exogenous glucocorticoid
Pituitary MRI and CRH test:
Adenoma >6 mm
and
Positive CRH response
and
Suppression with dexamethasone
Inconclusive
Small/no adenoma
BIPSS
No ACTH gradient
Positive ACTH gradient
CT/MRI thorax and abdomen ± somatostatin scintigraphy
Cushing disease
Ectopic ACTH


Measure ACTH
Low ACTH
Normal or high ACTH
ACTH-independent Cushing's syndrome
ACTH-dependent Cushing's syndrome
Adrenal CT or MRI
Pituitary MRI
No adenoma or equivocal
Adenoma present
<6–9 mm*
≥10 mm*
Ectopic Cushing's syndrome or Cushing's disease
IPSS
or
CRH and desmopressin test plus whole-body CT†
Inconclusive†
Pituitary gradient absent
Pituitary gradient present
-CRH and desmopressin and +CT†
+CRH and desmopressin and -CT†
Presumed Cushing's disease
Ectopic Cushing's syndrome
Cushing's disease
Ectopic Cushing's syndrome†
Cushing's disease†

NEGATIVE MRI IN CD

- use of standard 1.5 T MRI only approximately 50% of microadenomas are clearly depicted.
  - Technical refinements, including spoiled gradient recalled (SPGR) acquisition echo with 1 mm slice intervals,
  - Fluid attenuation inversion recovery,
  - and constructive interference in the steady state, might enhance detection,
  - variants of T1 weighted turbo spin echo sequences
  - use of ultra high field 3 T and 7 T magnets allows improved localization of microadenomas (can increase the risk of detecting incidentalomas potentially unrelated to the disorder).
- Nevertheless, approximately a third of scans in patients with Cushing's disease still remain negative


SIEMENS

BILATERAL INFERIOR PETROSAL SINUS SAMPLING (BIPSS):

- Although BIPSS is still the most accurate method to distinguish between CD and EAS,
- False-negative results (3–19%):
  1. abnormal venous anatomy and drainage
  2. and insufficient expertise.
  3. pituitary corticotroph adenomas that do not respond to exogenous CRH
  4. when adenomas are being sampled during a low secretory phase

➢ Venous angiography, collecting, analyzing, and processing samples appropriately

➢ a reference hormone could be used (Prolactin)

BILATERAL INFERIOR PETROSAL SINUS SAMPLING (BIPSS):

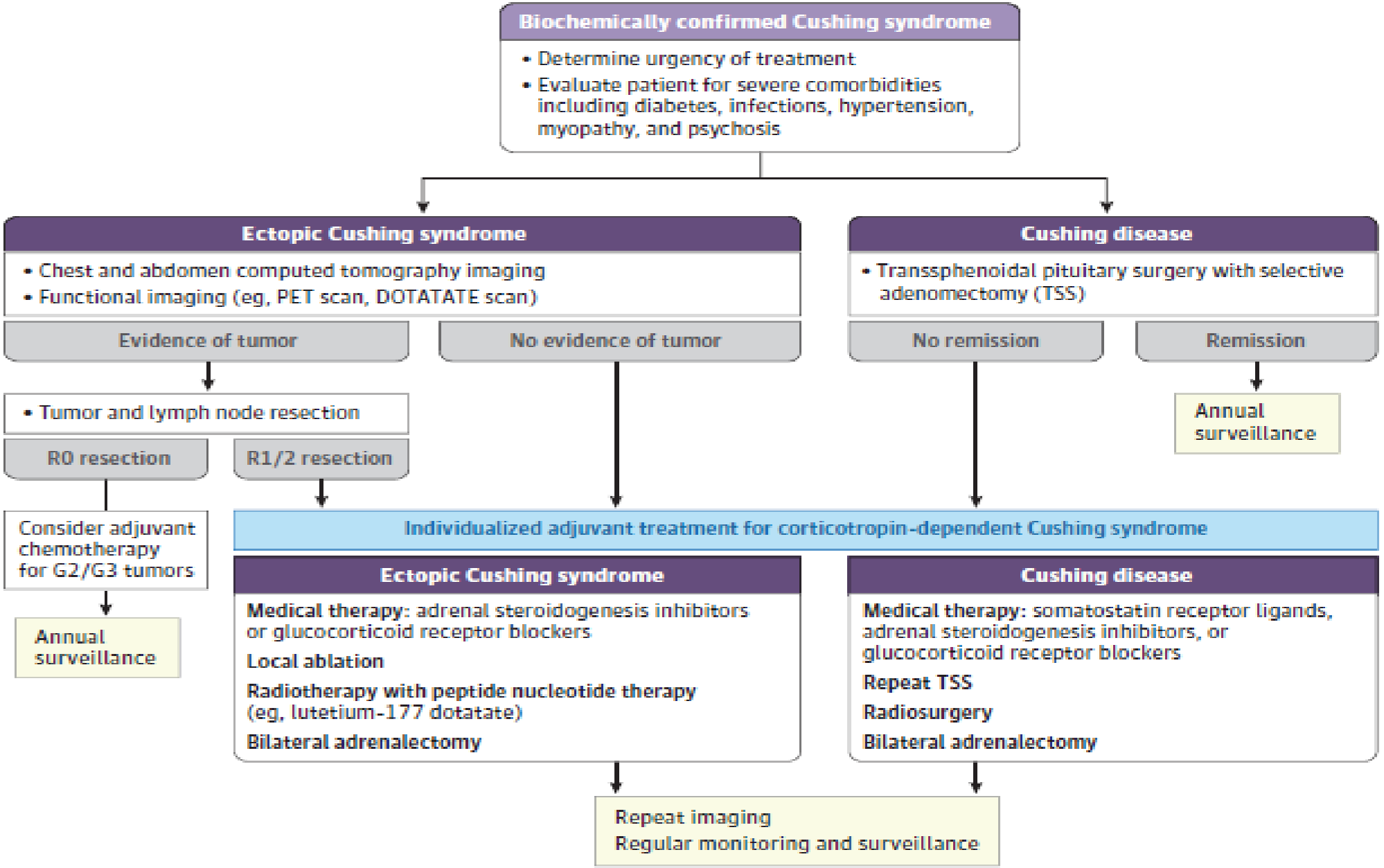
- False- positive results
  1. Previous cortisol-lowering medication
  2. Cyclical EAS
  3. CRH alone or in combination with ACTH is secreted

- In classical cyclic Cushing's disease or in patients with unpredictable fluctuating cortisol concentrations, dynamic testing and localization testing, including IPSS, should be preceded by
  - a confirmatory Serum cortisol (> 10 µg/dl), LNSC or UFC to document that the patients are in the active phase.

TREATMENT

- The goals of treatment are to
  1. ablate or destroy the primary tumoral lesion,
  2. preserve anterior pituitary function (possibly restoring a normal pituitary-adrenal axis), and
  3. correct adrenocortical oversecretion,
  4. eventually reverse the peripheral manifestations of steroid excess.

➢ These ideal goals cannot always be achieved


Biochemically confirmed Cushing syndrome
• Determine urgency of treatment
• Evaluate patient for severe comorbidities including diabetes, infections, hypertension, myopathy, and psychosis
Ectopic Cushing syndrome
• Chest and abdomen computed tomography imaging
• Functional imaging (eg, PET scan, DOTATATE scan)
Evidence of tumor
No evidence of tumor
• Tumor and lymph node resection
R0 resection
R1/2 resection
Consider adjuvant chemotherapy for G2/G3 tumors
Annual surveillance
Cushing disease
• Transsphenoidal pituitary surgery with selective adenomectomy (TSS)
No remission
Remission
Annual surveillance
Individualized adjuvant treatment for corticotropin-dependent Cushing syndrome
Ectopic Cushing syndrome
Medical therapy: adrenal steroidogenesis inhibitors or glucocorticoid receptor blockers
Local ablation
Radiotherapy with peptide nucleotide therapy (eg, lutetium-177 dotatate)
Bilateral adrenalectomy
Cushing disease
Medical therapy: somatostatin receptor ligands, adrenal steroidogenesis inhibitors, or glucocorticoid receptor blockers
Repeat TSS
Radiosurgery
Bilateral adrenalectomy
Repeat imaging
Regular monitoring and surveillance

CHALLENGES AFTER TREATMENT

- Glucocorticoid withdrawal syndrome (GWS)
- Complications of Cushing's syndrome
  - Hypercoagulability
  - Cardiovascular disease
  - Bone disease
  - GH deficiency
- Myopathy and neurocognitive dysfunction can be chronic complications of CS that do not completely recover.

CHALLENGES AFTER TREATMENT

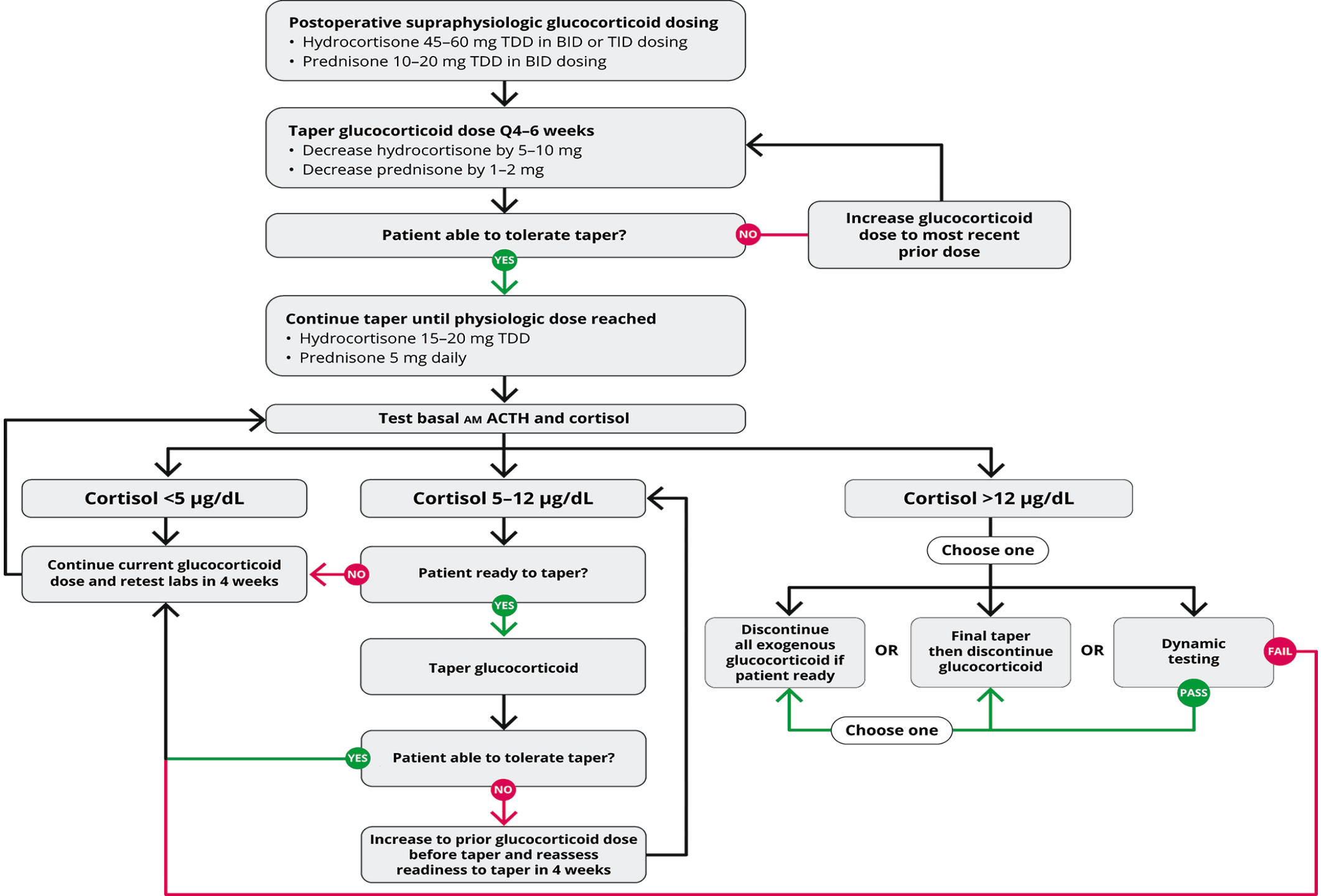
- Return of the HPA axis function to normal after curative surgery varies according to the etiology of the disorder
  - Ectopic Cushing syndrome: Median of 0.6 years
  - Cushing disease: median of 1.4 years
  - adrenal Cushing syndrome: median of 2.5 years

HYPERCOAGULABILITY

- Hypercoagulability is not immediately reversible with cortisol normalisation.
- At 30 days after adrenalectomy, VTE risk was 3·4–4·75%,
- and the OR for thromboembolic events after bilateral adrenalectomy in a longer term study was 3.74.
- Thromboprophylaxis can decrease the incidence of postoperative VTE, particularly when extended to 30 days.
- Strategies to identify patients most likely to benefit from thromboprophylaxis are still being developed

GLUCOCORTICOID WITHDRAWAL SYNDROME (GWS)

- GWS occurs following withdrawal of supraphysiologic exposure to either exogenous or endogenous glucocorticoids of at least several months duration
- Difficult to differentiate from adrenal insufficiency and CS recurrence,
- GWS also occurs during medical management of CS,
- Gradual dose titration based primarily on symptoms is essential to maintain adherence and to eventually achieve disease control.


Postoperative supraphysiologic glucocorticoid dosing
• Hydrocortisone 45–60 mg TDD in BID or TID dosing
• Prednisone 10–20 mg TDD in BID dosing
Taper glucocorticoid dose Q4–6 weeks
• Decrease hydrocortisone by 5–10 mg
• Decrease prednisone by 1–2 mg
Patient able to tolerate taper?
NO
Increase glucocorticoid dose to most recent prior dose
YES
Continue taper until physiologic dose reached
• Hydrocortisone 15–20 mg TDD
• Prednisone 5 mg daily
Test basal AM ACTH and cortisol
Cortisol <5 µg/dL
Continue current glucocorticoid dose and retest labs in 4 weeks
Cortisol 5–12 µg/dL
NO
Patient ready to taper?
YES
Taper glucocorticoid
YES
Patient able to tolerate taper?
NO
Increase to prior glucocorticoid dose before taper and reassess readiness to taper in 4 weeks
Cortisol >12 µg/dL
Choose one
Discontinue all exogenous glucocorticoid if patient ready
OR
Final taper then discontinue glucocorticoid
OR
Dynamic testing
FAIL
PASS
Choose one

TAKE HOME MESSAGE

- CS - is the most challenging diagnostic and management problems in clinical endocrinology
- Many Challenges are observed
  - In clinical symptomatology
  - In first and second-line lab tests
  - In subtypes determination even with gold standard test (IPSS)
  - For treatment especially in persistent and recurrent cases
  - and for management of cortisol-related comorbidities such as VTE
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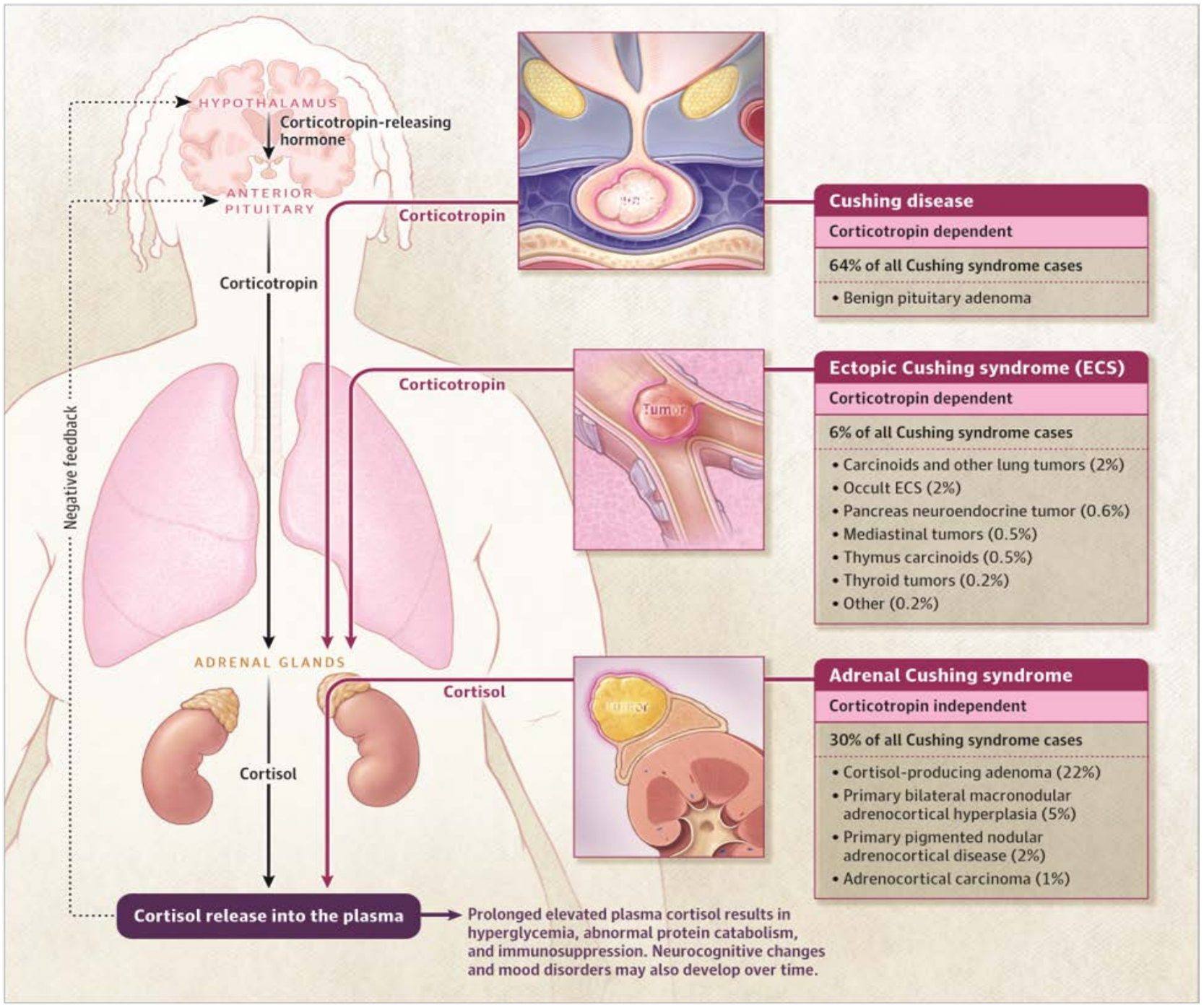
THANK YOU FOR YOUR ATTENTION

Figure 1. Prevalence of Endogenous Cushing Syndrome



CHALLENGES IN DIAGNOSIS (1)

- 1. In some patients, one symptom may predominate, and this causes delay in diagnosis, for months or even years, with symptoms ascribed to rheumatologic, cardiologic, or psychiatric disease before it is realized that Cushing's syndrome is responsible for the symptomatology.
- Mild forms may be mistaken for all sorts of ill-defined conditions, such as polycystic ovary syndrome, idiopathic hirsutism, idiopathic cyclic edema, and essential hypertension.
- The reported prevalence of Cushing's syndrome is
  - between 1% and 9.5% in screening studies of patients with type II diabetes
  - between 0.5% and 1% in patients with hypertension,
  - and as high as 10.8% in patients with osteoporosis.
- All of these are likely to be significant overestimates.

- Cushing disease in children
- Cushing disease in pregnant women
-

WHEN TO SCREEN FOR CUSHING'S SYNDROME

- In patients with severe stressful conditions or pathological situations known to be accompanied by functional hypercortisolism (acute illness, anorexia nervosa, alcoholism), investigation should be withheld until resolution of the primary disorder.
- A patient with authentic Cushing's syndrome may have such severe complications of disease that some tests which could further compromise the condition may be contraindicated.
- Thus, the diagnostic approach may need to be modified by some clinical presentations.
- There may be cases where it is important to delay testing, and others where it is urgent to treat and bypass tests.
- In most cases, however, a defined and coordinated approach should be followed.

A STEPWISE STRATEGY

- A two-step diagnostic approach should
  - first establish the hypercortisolemic state and
  - subsequently its cause.

INTERCURRENT ILLNESS

- Any severe intercurrent illness will cause appropriately increased cortisol secretion, driven by ACTH.

ANOREXIA NERVOSA

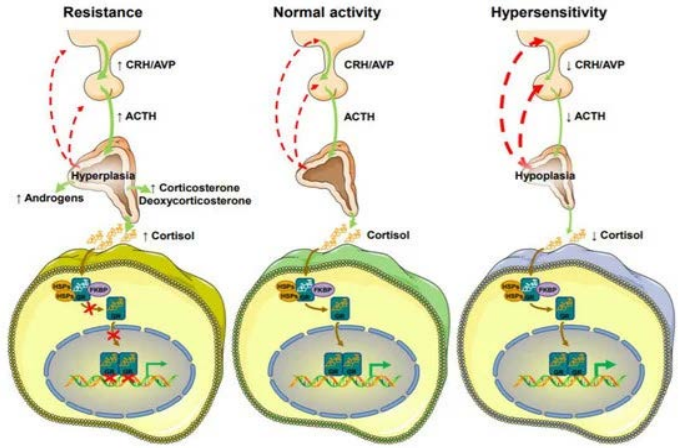
- Evaluation of ACTH and cortisol response to CRH in underweight patients with anorexia nervosa reveals patterns very similar to those observed in depressed patients.
- There is generally no clinical confusion for the diagnosis.
- Abnormal corticotroph dynamics are corrected with calorie replenishment and weight restoration

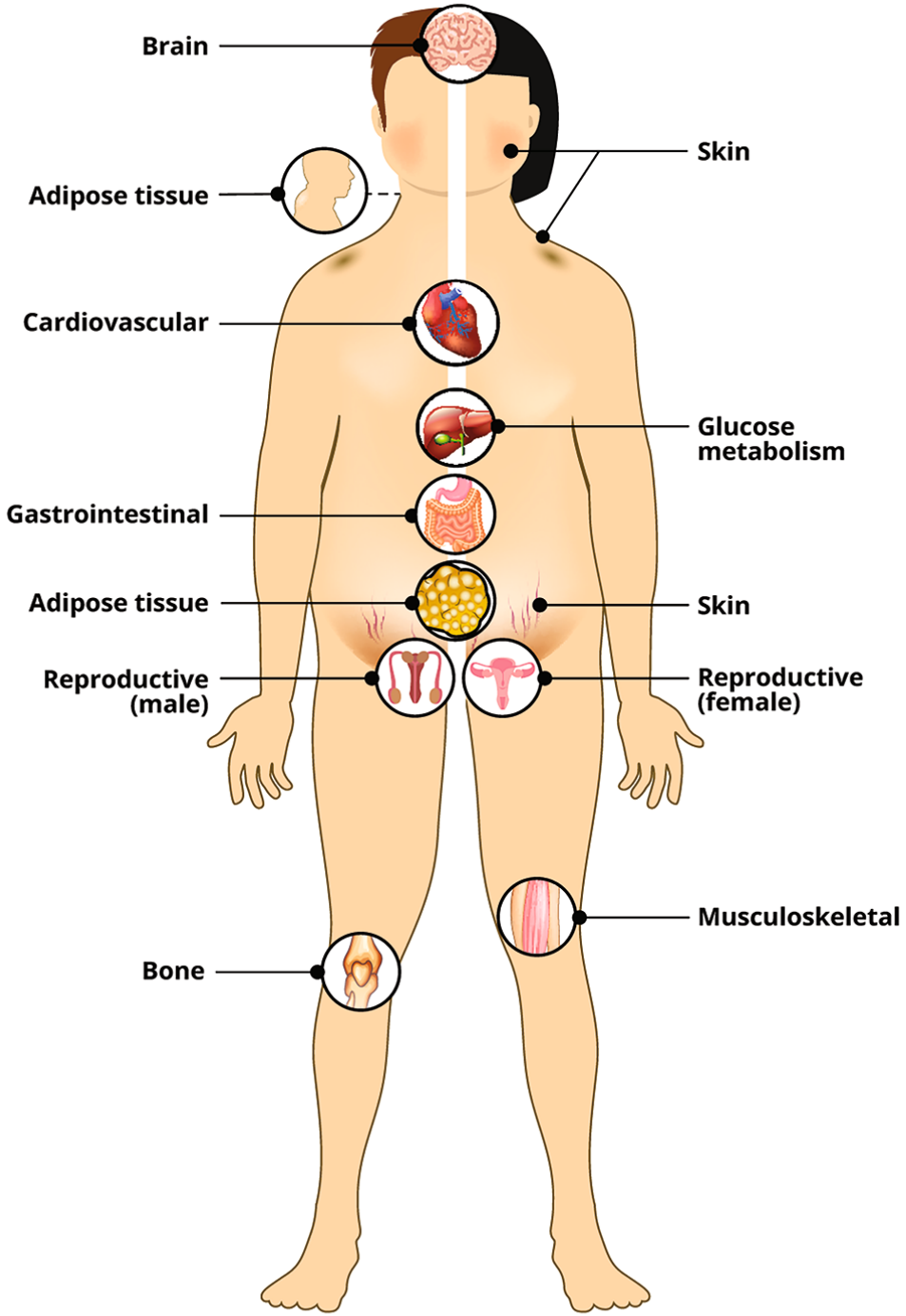
STRENUOUS EXERCISE

- Moderate elevation in baseline plasma cortisol
- Blunted ACTH and cortisol response to CRH were observed in normal men running more than 45 miles (72 Km)/ week

FAMILIAL RESISTANCE TO GLUCOCORTICOIDS

- Hypertension and hypokalemia are explained by increased mineralocorticoid activity due to excess DOC and cortisol acting on the normally sensitive mineralocorticoid receptor.
- Suppression of plasma cortisol by increasing doses of dexamethasone is abnormal with a shift to the right of the dose-response curve.
- There is a normal circadian rhythm of plasma cortisol and an absence of clinical features of hypercortisolism





			CS	GWS	AI
	Brain	Mood and cognitive disturbance	●	●	○
		Insomnia	●	○	○
		Hypersomnia	○	●	○
	Cardiovascular	Hypertension	●	○	○
		Hypercoagulability	●	○	○
		Hypotension	○	○	●
	Glucose metabolism	Hyperglycemia	●	○	○
		Hypoglycemia	○	○	●
	Gastrointestinal	Anorexia	○	●	●
		Vomiting	○	○	●
		Hyperphagia	●	○	○
	Adipose tissue	Central obesity	●	○	○
		Supraclavicular and dorsocervical fullness	●	○	○
		Weight loss	○	●	●
	Reproductive	Gonadal hypofunction	●	○	○
		Infertility/Subfertility	●	○	○
	Skin	Facial plethora	●	○	○
		Violaceous striae	●	○	○
		Skin atrophy and bruising	●	○	○
	Bone	Osteopenia	●	○	○
		Osteoporosis	●	○	○
	Musculoskeletal	Physical deconditioning	●	●	○
		Musculoskeletal discomfort	●	●	●
		Fatigue	●	●	●

WHEN TO SCREEN FOR CUSHING'S SYNDROME

- In patients with severe stressful conditions or pathological situations known to be accompanied by functional hypercortisolism (acute illness, anorexia nervosa, alcoholism), investigation should be withheld until resolution of the primary disorder.

TESTS TO DISTINGUISH BETWEEN "PSEUDO-CUSHING" AND CUSHING'S SYNDROME (IN MILD HYPERCORTISOLISM)

"Second-line" tests

I. Dex-CRH test: The plasma cortisol value 15 minutes after CRH is expected to be greater than 38 nmol/L (or 1.4 μg/dL or 14 ng/mL) in patients with Cushing's syndrome, but to remain suppressed in normal subjects and in patients with pseudo-Cushing's syndrome.

II. The CRH test.

III. The desmopressin Stimulation test.

IV. Midnight serum cortisol, (serum and salivary cortisol cycle)

CUSHING DISEASE MIMICKING AN AUTONOMOUS ADRENOCORTICAL TUMOR

- Basal ACTH is low or undetectable and adrenal imaging reveals a unilateral adrenal mass.
- When unilateral adrenalectomy is performed, although transiently ameliorated, hypercortisolism inevitably recurs, allowing a correct and a posteriori diagnosis of Cushing disease in its macronodular hyperplastic form.
-

SEVERE CUSHING DISEASE MIMICKING CLASSIC ECTOPIC ACTH SYNDROME

- Mimic the classic form of ectopic ACTH syndrome,
  - with rapid onset, profound myopathy, severe hypokalemia, and definite hyperpigmentation
- Pituitary imaging will point to the source of ACTH often showing a large macroadenoma on CT scan or MRI.
- In the absence of an imaging abnormality bilateral IPSS becomes even more important.
-

MILD ECTOPIC ACTH SYNDROME MIMICKING CLASSIC CUSHING DISEASE

- In a minority of such cases, a positive response to the CRH test is another pitfall for diagnosis.
- Because most of these patients have had small and rather indolent bronchial carcinoid tumors that escaped the usual means of detection by standard imaging, many have undergone inappropriate and unsuccessful pituitary surgery.
- Bilateral IPSS provides the best means to distinguish between the two conditions.

CAUSES OF THE HYPERCORTISOLEMIC STATE

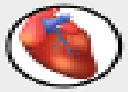
I. ACTH: two separate occasions
   I. If there is any doubt, it is advisable to carry out (ACTH Between 5-15 Pg/ml) a CRH (DST) test or / a HDDST and a CT scan of the adrenal glands
II. Dynamic tests (HDDST; CRH; for some teams, desmopressin stimulation test),
III. Tumor markers, pituitary MRI, thoraco-abdominopelvic CT scan (if necessary, somatostatin receptor scintigraphy),
IV. Bilateral IPSS for ACTH

- Those patients with a negative gradient in whom axial imaging fails to reveal a potential source of ectopic ACTH production are classed "ACTH-source unknown," even though many will ultimately turn out to have Cushing disease.

NONINVASIVE APPROACH TO DISTINGUISH BETWEEN PITUITARY AND ECTOPIC ACTH SECRETING TUMOURS

- Combination of laboratory and imaging testing
  - CRH and
  - desmopressin stimulation plus
  - MRI,
  - followed by whole body CT if diagnosis is equivocal

  - ^{68}Ga DOTATATE localises about 65% of these tumours, including those not seen or not definitively identified on crosssectional imaging

			CS	GWS	AI
	**Brain**	Mood and cognitive disturbance	●	●	○
		Insomnia	●	○	○
		Hypersomnia	○	●	○
	**Cardiovascular**	Hypertension	●	○	○
		Hypercoagulability	●	○	○
		Hypotension	○	○	●
	**Glucose metabolism**	Hyperglycemia	●	○	○
		Hypoglycemia	○	○	●
	**Gastrointestinal**	Anorexia	○	●	●
		Vomiting	○	○	●
		Hyperphagia	●	○	○
	**Adipose tissue**	Central obesity	●	○	○
		Supraclavicular and dorsocervical fullness	●	○	○
		Weight loss	○	●	●
	**Reproductive**	Gonadal hypofunction	●	○	○
		Infertility/Subfertility	●	○	○
	**Skin**	Facial plethora	●	○	○
		Violaceous striae	●	○	○
		Skin atrophy and bruising	●	○	○
	**Bone**	Osteopenia	●	○	○
		Osteoporosis	●	○	○
	**Musculoskeletal**	Physical deconditioning	●	●	○
		Musculoskeletal discomfort	●	●	●
		Fatigue	●	●	●

STRATEGY FOR DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

- Overall, the fewest number of tests should be performed that enable a reliable diagnosis with minimum risk and discomfort for the patient at the maximum cost-benefit ratio.
- Testing should always be guided by specific clinical features and proceed in a stepwise fashion.

PITFALLS IN DIAGNOSIS (LAB TESTS)

- **Drug Interactions**
- Inducers of High CBG Plasma Levels: High estrogen states, as encountered in pregnancy

and in oral contraceptive treatment → CBG effect – Mitotane (Estrogen-like action)

  - Solution: **LNSC-UFC**
- Liver Enzyme Inducers: Several drugs (e.g., rifampicin, phenytoin, and barbiturates) induce the liver enzyme CYP3A4 that accelerates metabolism of endogenous and/or exogenous steroids and of some pharmacological agents
  - Solution: **Salivary Cortisol, Plasma dexamethasone measurement**