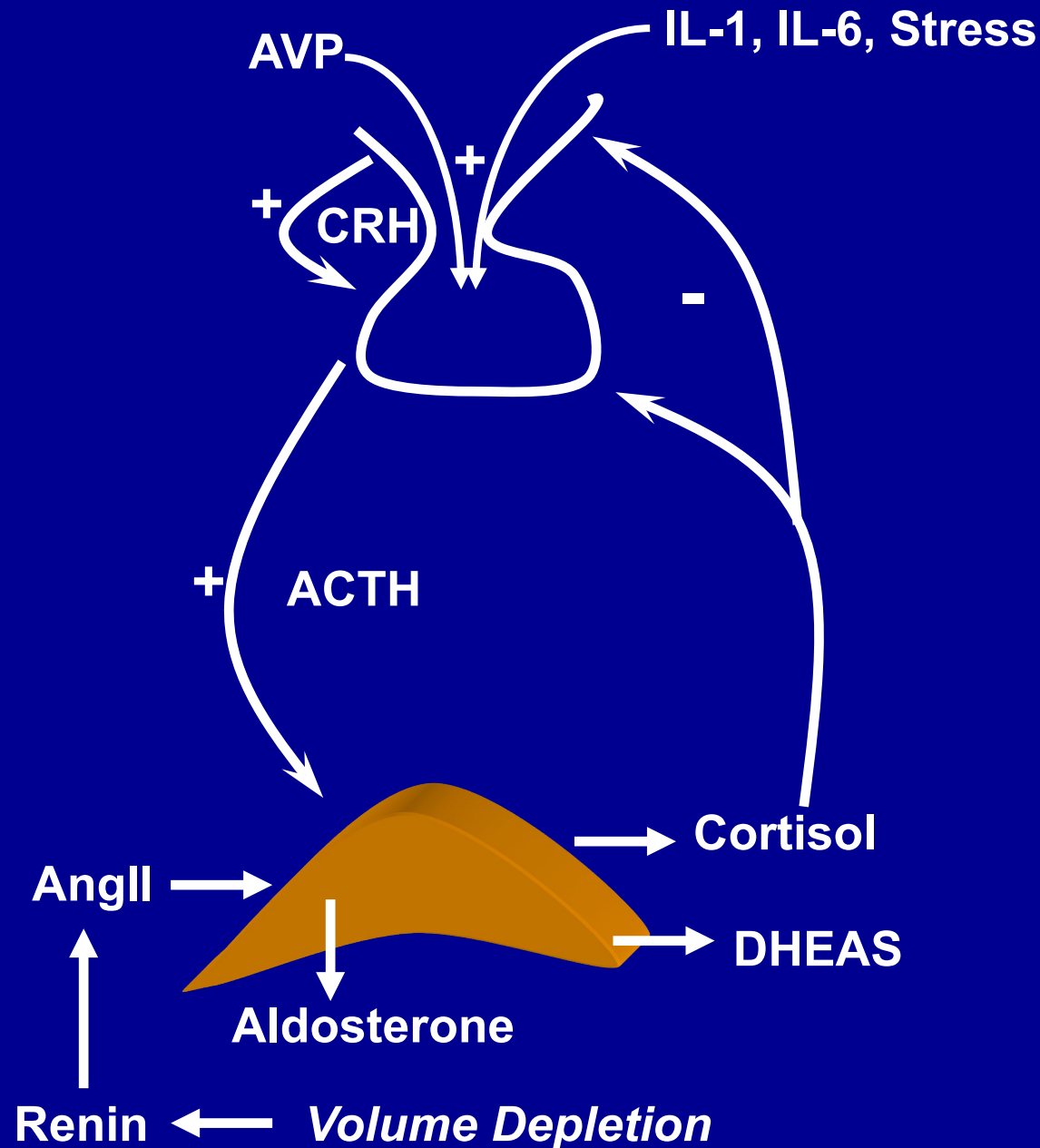


Primary Adrenal Insufficiency Practical Pointers

Richard J. Auchus, MD, PhD, FACE
**The James A. Shayman & Andrea S. Kevrick Professor
of Translational Medicine**
Division of Metabolism, Endocrinology & Diabetes
Departments of Internal Medicine & Pharmacology
University of Michigan & Ann Arbor VA Medical Center

Disclosures

- **Contracted Research**
 - Novartis Pharmaceuticals
 - Neurocrine Biosciences
 - Spruce Biosciences
 - Corcept Therapeutics
 - Diurnal, LTD
- **Consultant**
 - Quest Diagnostics
 - Corcept Therapeutics
 - Janssen Pharmaceuticals
 - Novartis Pharmaceuticals
 - Xeris Pharmaceuticals
 - Crinetix Pharmaceuticals
 - Adrenas Therapeutics
 - PhaseBio Pharmaceuticals
 - OMass Therapeutics
 - Recordati Rare Diseases
 - H Lundbeck A/S



HPA Axis

ACTH Controls
Cortisol & DHEAS
Synthesis;
Only Cortisol
Provides Feedback

Renin-Angiotensin-
Aldosterone Axis

Adrenal Insufficiency

Symptoms

• Weakness, fatigue	100%
• Anorexia	100%
• Nausea	86%
• Vomiting	75%
• Abdominal pain	31%
• Salt craving	16%
• Postural dizziness	12%
• Muscle or joint pain	6-13%

Adrenal Insufficiency

Signs

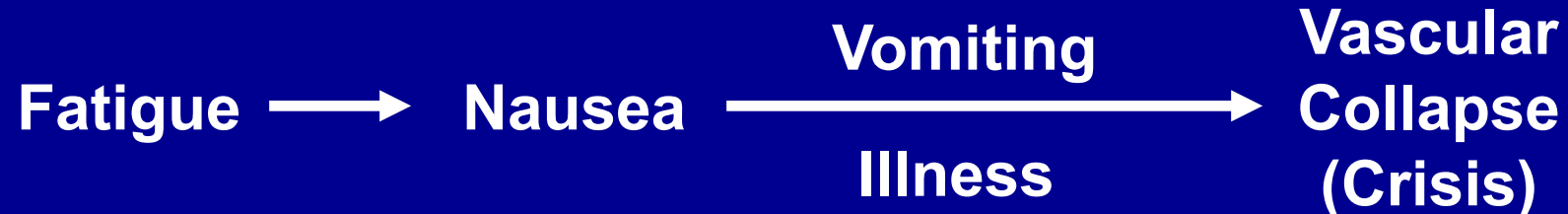
- **Weight loss** **100%**
- **Hyperpigmentation** **94%***
- **Hypotension** **88-94%**
- **Vitiligo** **10-20%**

***Primary Only**

Adrenal Insufficiency

Laboratory Abnormalities

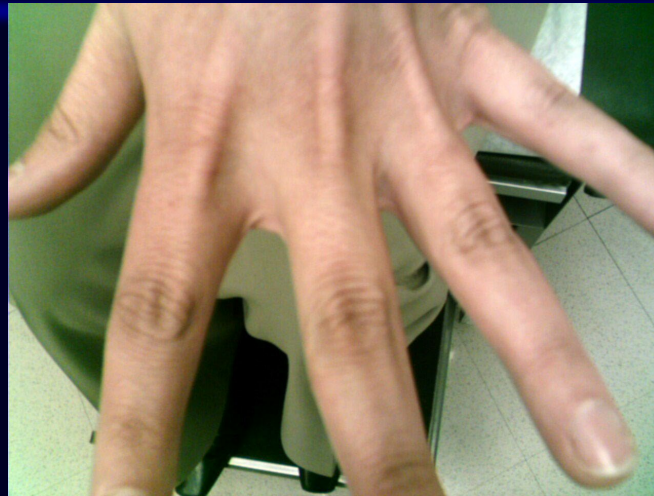
- Hyponatremia 88% (↓ Cortisol)
- Hyperkalemia 64% (↓ Aldosterone)
- Hypercalcemia 6%
- Azotemia 55%
- Mild Anemia 40%
- Eosinophilia 17% (Primary)



Hyperpigmentation in Primary Adrenal Insufficiency



Scars



Gums
Lips

Skin
Creases



Tongue

Which Knee Had Surgery First?



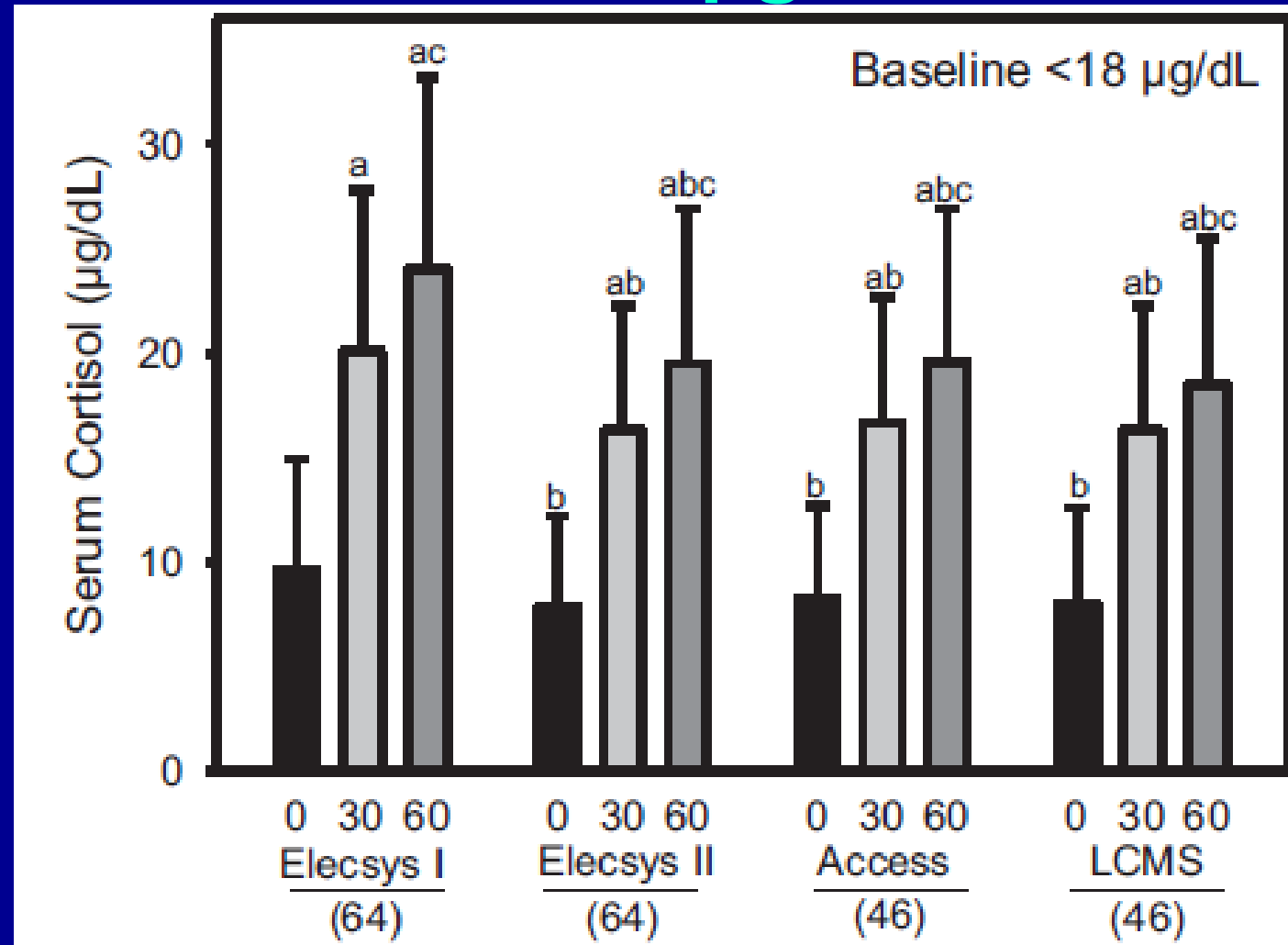
Adrenal Insufficiency

Diagnosis

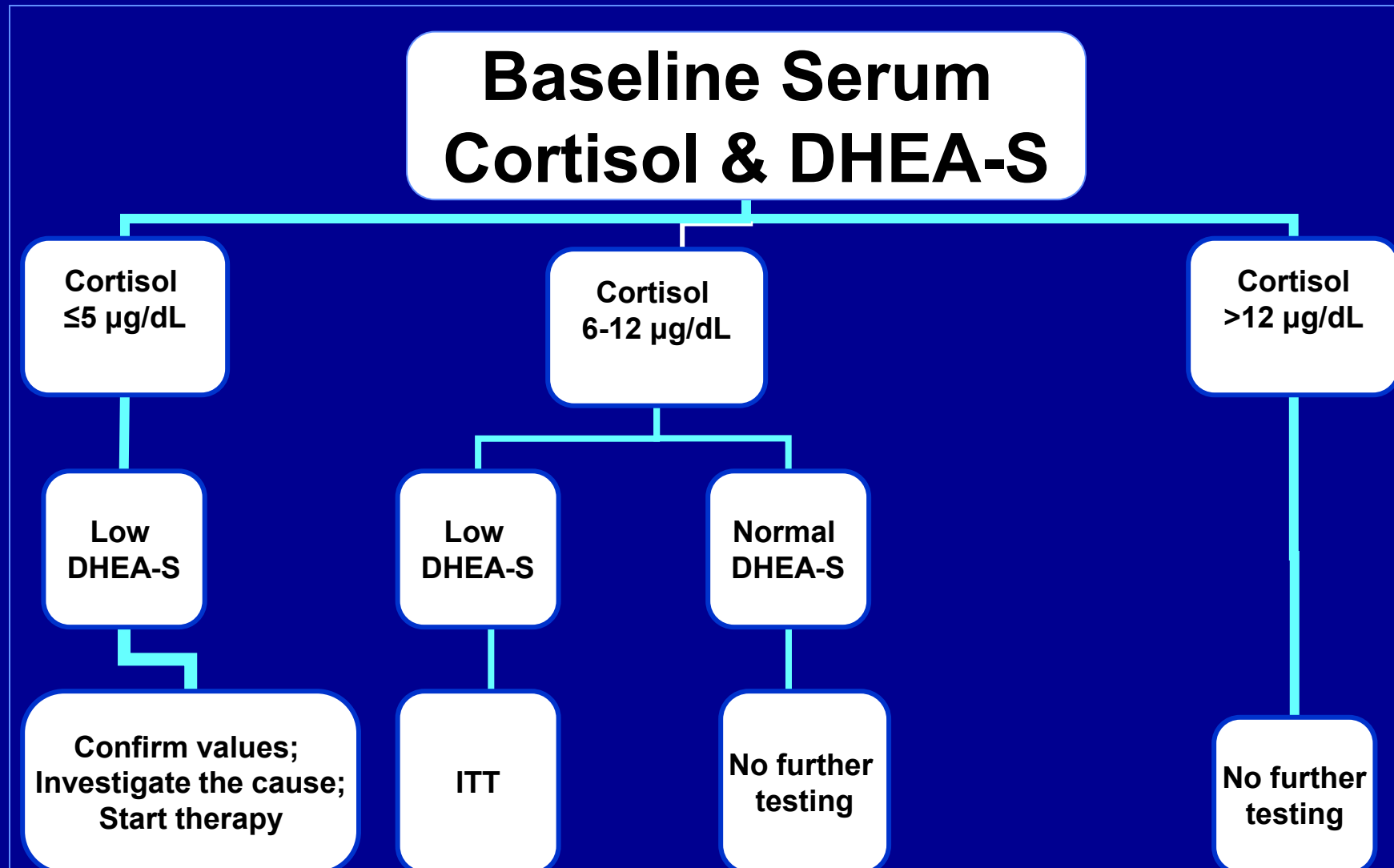
- **Basal (0800) Hormones Very Useful**
 - Cortisol: $<4 \mu\text{g/dL}$ (100 nmol/L) Low; >14 (400 nmol/L) Normal
 - DHEA-S: $>65 \mu\text{g/dL}$ ($>1700 \text{ nmol/L}$) Normal
 - ACTH: Low ($<10 \text{ pg/mL}$) or High ($>100 \text{ pg/mL}$)
 - Renin & Aldosterone
 - Primary AI: High Renin, Low Aldosterone
 - Secondary AI: Both Generally Normal & Track Together
- **Cosyntropin Stimulation Test**
 - $250 \mu\text{g ACTH}^{1-24}$ IM/IV
 - Cortisol@30-60 min: $>14 \mu\text{g/dL}$ ($>400 \text{ nmol/L}$)

Adrenal Insufficiency

Normal Cortisol $>14 \mu\text{g/dL} = 400 \text{ nmol/L}$



Diagnosis of Central AI: Ambulatory Setting



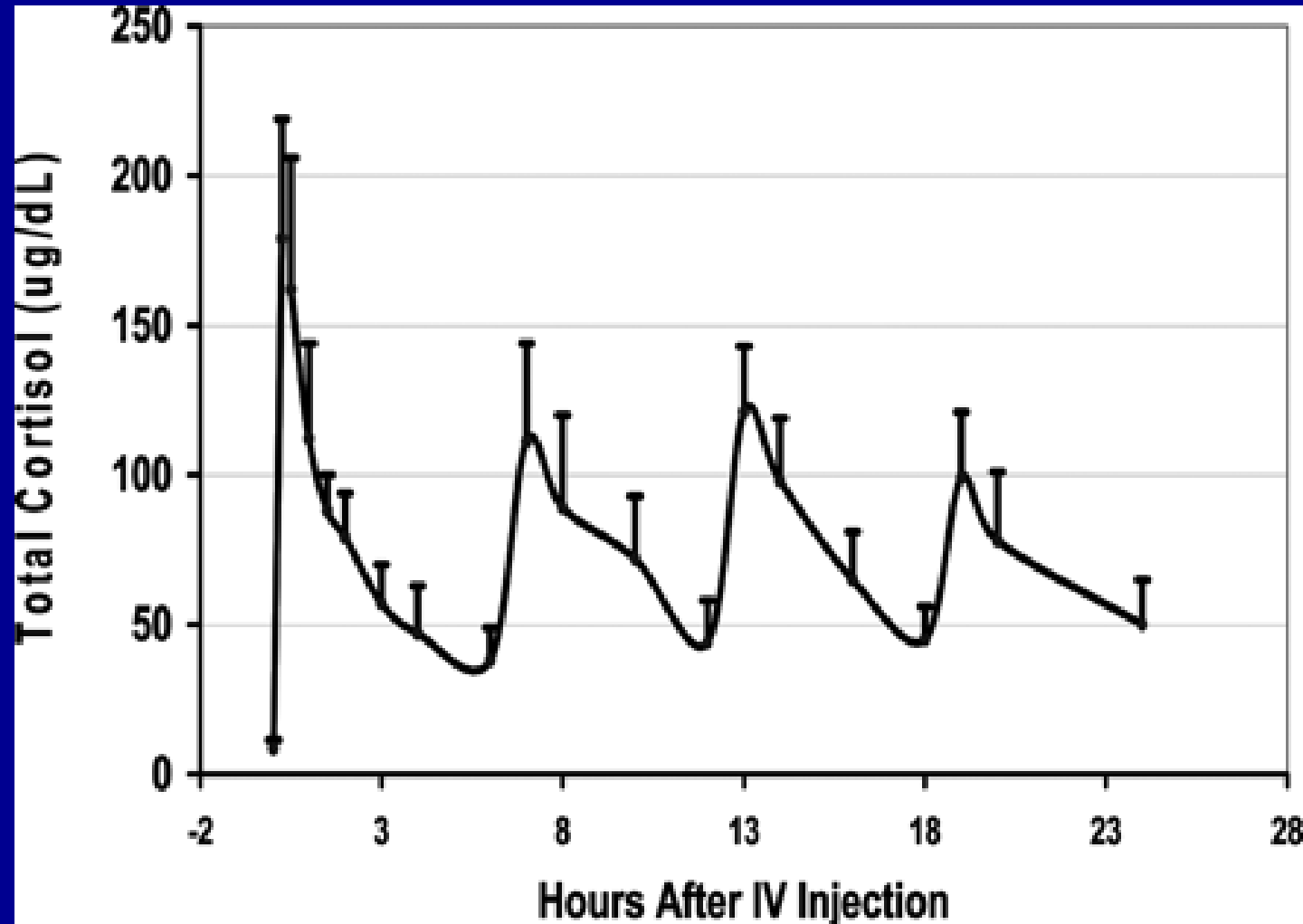
Adrenal Insufficiency

Treatment - Acute

- **Volume Repletion: Saline/Oral NaCl**
- **Glucocorticoids: Hydrocortisone Best**
 - No Need To Ever Give >100 mg/24h
 - 25 mg IV or IM or PO Q6h
 - Methylprednisolone 4 mg Q8h, Dex 1 mg Q24h
- **9 α -Fludrocortisone Acetate: If Hydrocortisone <30 mg/d**
- **Attention to Hyperkalemia**
- **Identify Etiology of Adrenal Dysfunction**

Hydrocortisone 50 mg Q6h

Serum Cortisol Values $>50 \mu\text{g/dL}$



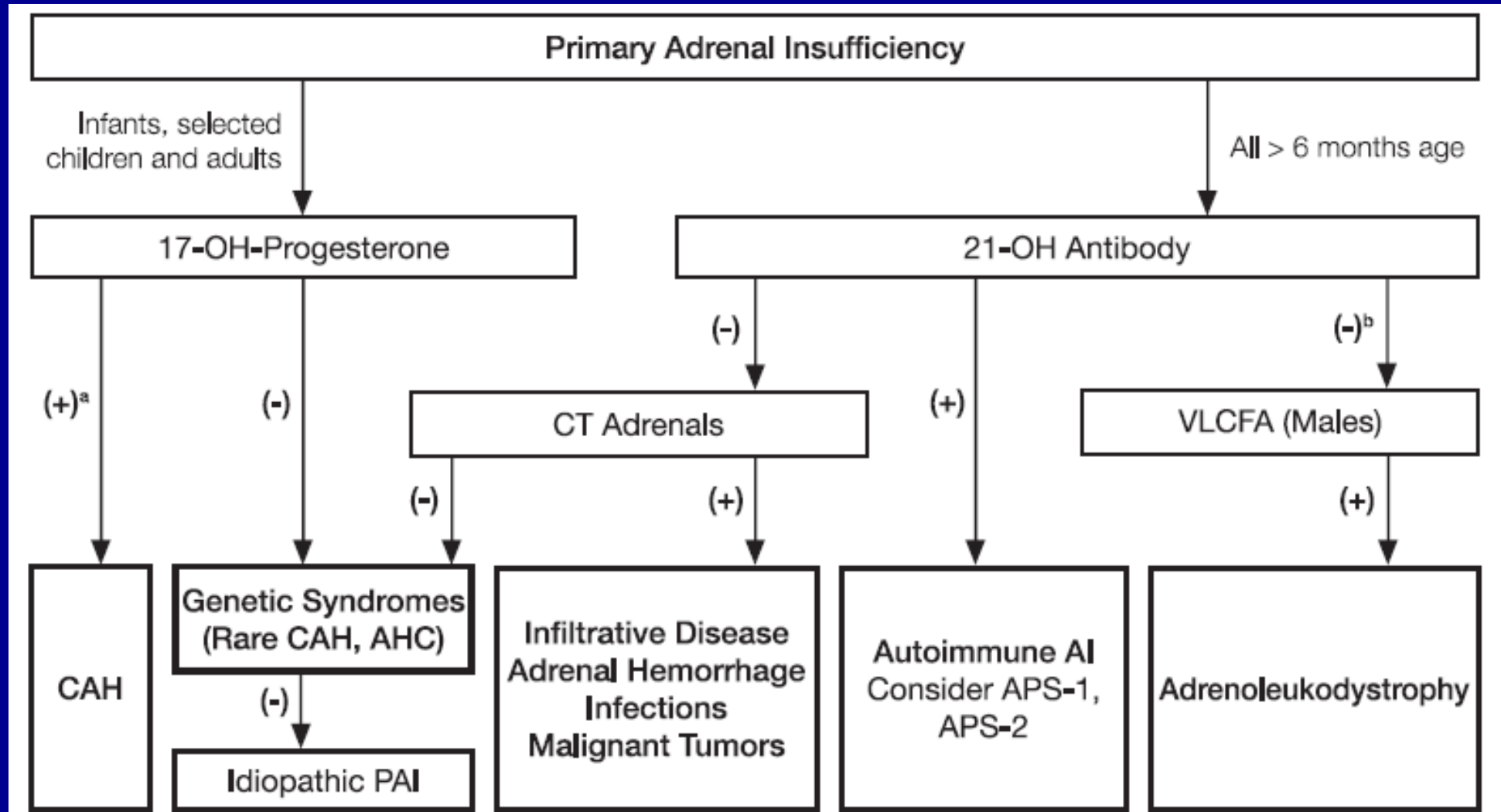
Primary Adrenal Insufficiency

Etiologies

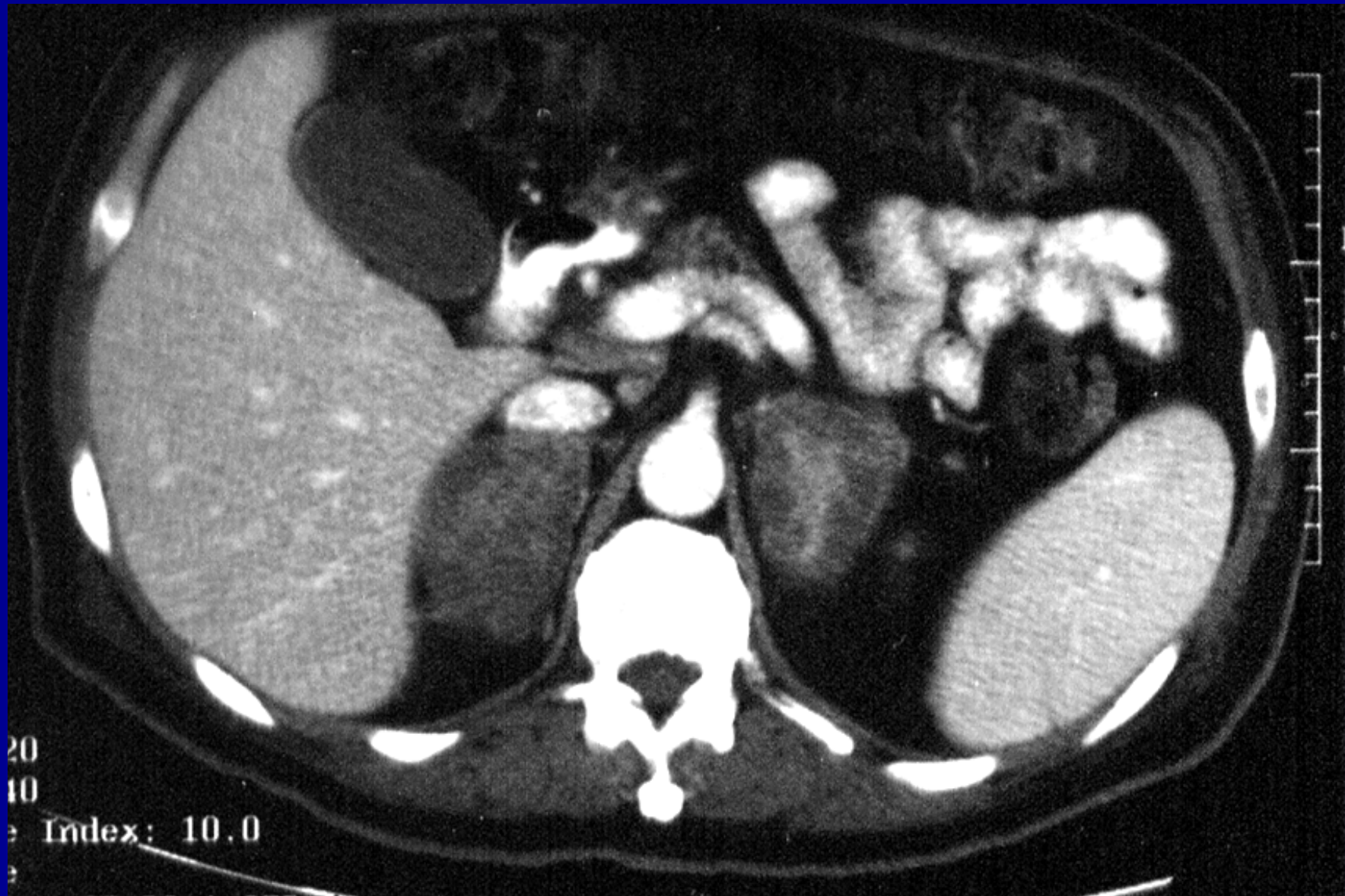
- **Autoimmune: Isolated or Polyglandular**
 - +21-Hydroxylase Antibodies
- **Infection: TB, CMV, Histoplasmosis/Fungal**
- **Infiltrative: Hemochromatosis, Amyloidosis**
- **Destruction: Surgical, Hemorrhage (Waterhouse-Friderichsen Syndrome), Cancer Rarely**
- **Developmental/Genetic**
 - X-Linked Adrenaleukodystrophy; Adrenal Hypoplasia Congenita
- **Enzyme Deficiencies: 21-Hydroxylase Deficiency (21OHD)**
 - Nonclassic 21OHD is not Adrenal Insufficiency

Primary Adrenal Insufficiency

Diagnostic Algorithm



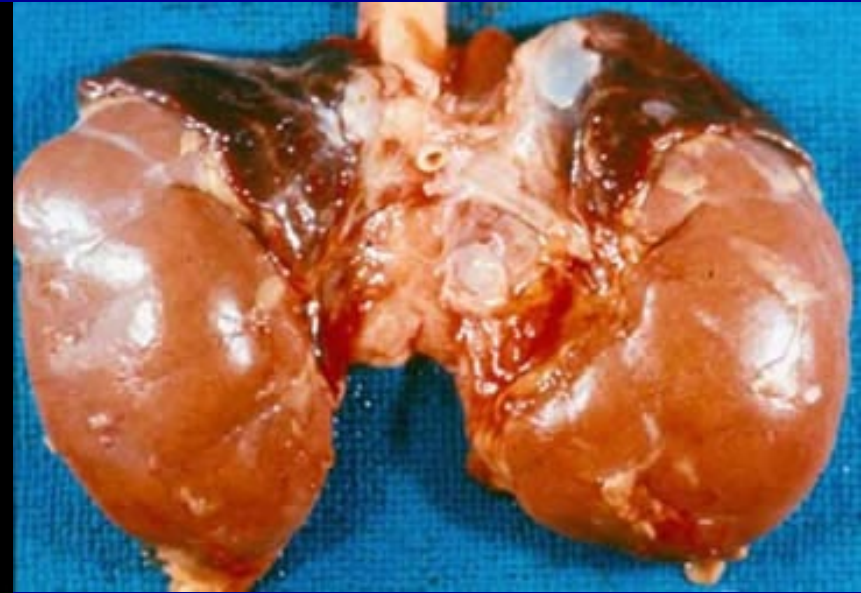
Adrenal CT: Histoplasmosis



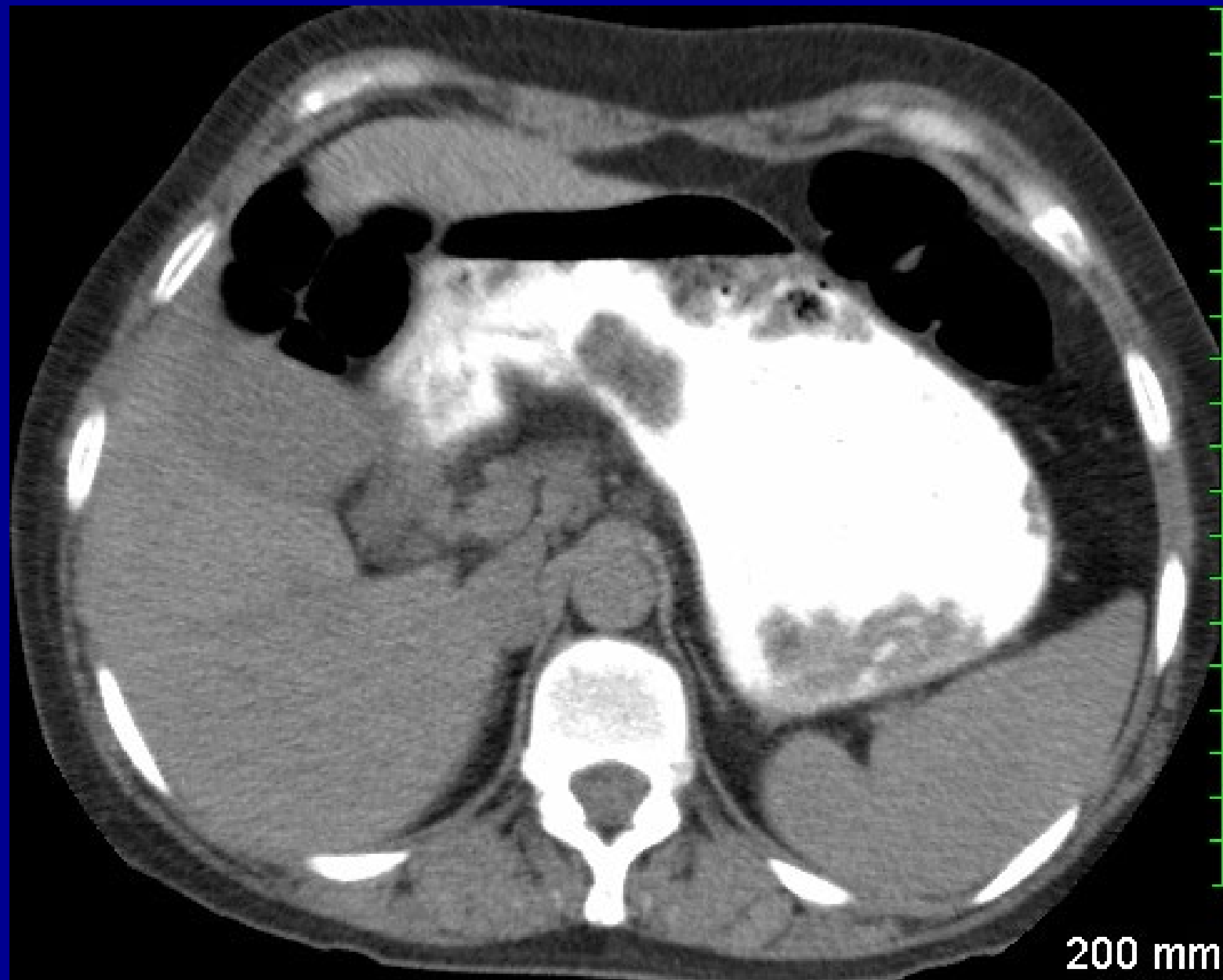
Adrenal CT: Hemorrhage



Adrenal Hemorrhage



Adrenal CT: Autoimmune AI

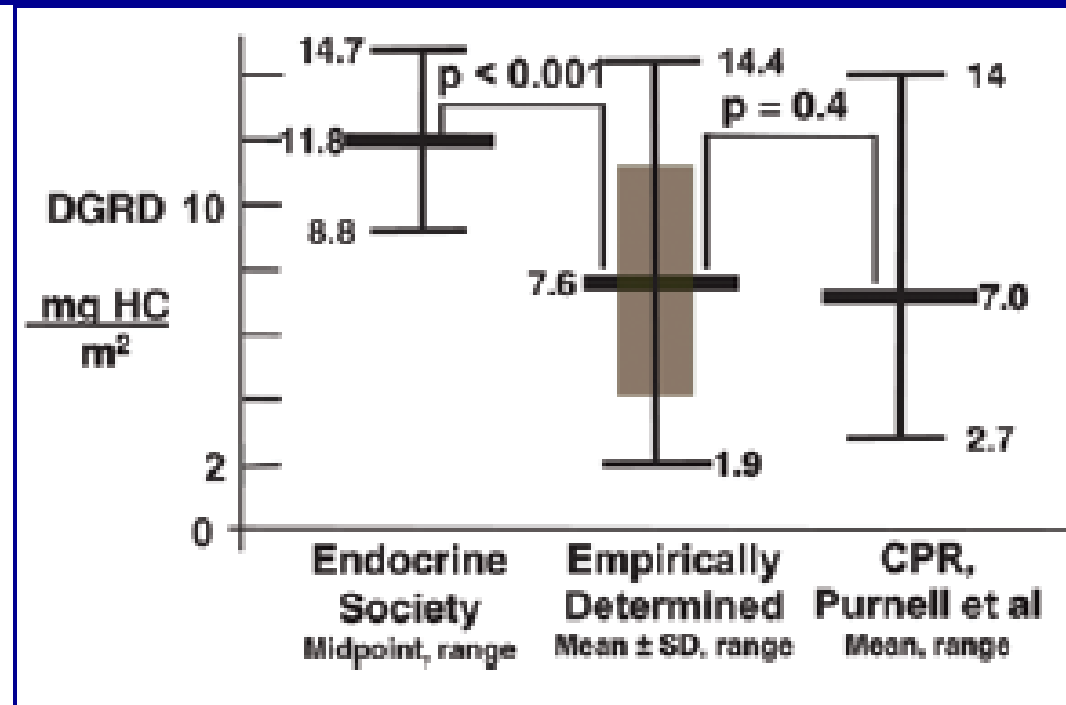


Adrenal Insufficiency

Optimal Hydrocortisone Dose

Table 1. Individual Patient Data

Subject	Age (y)	Sex	AI	Time Intervals (y)		HC Equivalence (mg)		Fludrocortisone (mg)		BMI (kg/m ²)		SBP (mm Hg)		DBP (mm Hg)		Serum [Na ⁺] (mmol/L)	
				Titration Time	Time on Lowest Dose	Initial	Final	Initial	Final	Initial	Final	Initial	Final	Initial	Final	Initial	Final
1	31	M	2°	0.7	10.8	20	16	0	0	35.7	35.5	120	104	85	76	141	140
2	62	M	2°	6.5	8.3	16	8	0	0	63.6	45.9	130	114	80	60	---	137
3	74	M	2°	10.3	3.1	20	15	0	0	32.4	30.8	120	140	62	60	138	137
4	64	M	2°	4.4*	1.3	12	12	---	0	---	23.9	---	134	---	82	---	139
5	70	F	2°	0.1	10.7	16	12	0	0	20.9	27.3	120	118	80	78	139	136
6	45	F	2°	6.8*	13.8	15	15	0	0	---	26.2	---	136	---	91	---	137
7	37	F	1°	2.4	2.9	40	4	0.1	0.1	34.4	35	128	120	80	80	139	138
8	67	F	1°	4.9*	14.8	20	20	0.1	0.1	24.1	23.4	110	148	75	100	140	145
9	53	F	1°	13.8	0.5	15	10	0.1	0.1	27.4	28.4	118	105	80	70	---	141
10	62	F	1°	9.4*	8.3	20	20	0.2	0.1	---	19.9	---	130	---	80	---	138
11	49	F	1°	4.1	8.8	40	5	0.1	0.1	29.9	24.7	110	116	70	80	143	133
12	29	F	1°	4.3	0.5	40	8	0.1	0.2	40.6	32.1	120	118	82	58	138	137
13	88	F	1°	19.6*	7.8	20	20	0.05	0.1	---	32.7	---	120	---	50	---	136
14	78	F	1°	2.3	5.2	40	12	0.1	0.1	37.3	22	122	150	70	70	139	135
15	28	F	1°	1.8	0.5	40	8	0.1	0.1	41.4	34.4	110	107	75	71	141	139
16	38	M	1°	1.5	0.8	80	16	0.1	0.1	36.8	31	130	110	85	80	136	140
17	54	F	1°	12.3	2.3	10	7.2	0.2	0.2	25.5	26.2	100	90	70	66	138	139
18	61	F	1°	16.4*	14.4	20	20	0.2	0.2	---	24.2	---	110	---	68	---	134
19	59	M	1°	0.7	1.5	40	20	0.1	0.1	24.6	23.7	130	114	80	78	137	136
20	32	F	1°	1.8	10.5	20	10	0.2	0.1	33.8	39.6	145	98	110	62	---	138
21	71	F	1°	1.5	2.8	40	12	0.1	0.1	26.7	28.7	128	132	74	88	134	141
22	64	F	1°	10.3*	7.4	20	20	0.2	0.2	---	26.5	---	124	---	84	---	140
23	66	M	1°	9.8*	15.1	15	15	0.1	0.1	---	24.5	---	126	---	76	---	137
24	49	M	1°	6.4	5.3	40	12	0.1	0.2	27.6	27.6	120	150	85	88	135	134
25	60	M	1°	0.9	5.2	35	30	0.1	0.1	25.2	23.7	150	142	80	82	141	141



Adrenal Insufficiency

Treatment – Chronic Titration

- **Glucocorticoid**
 - Cushingoid Features: Bruising, Striae, Skin Thinning, Fat Pads
 - Underdosing: Weight Loss, Anorexia, Afternoon Fatigue
 - Dose Distribution: Trial & Error, Symptoms Improve Post-Dose
 - Exposure: Measure Cortisol 1-2 h Post-Dose (Peak)/Pre-Dose
- **Mineralocorticoid**
 - Standing BP Most Important
 - Serum K Not High
 - Plasma Renin Not High

Precipitants for Adrenal Crisis

- Infection
- Other Intercurrent Illness (MI, PE, etc)
- Surgery
- Trauma
- Environmental Volume Depletion
- Drugs (Rifampin, Phenytoin)

Sick Days & Adrenal Crises

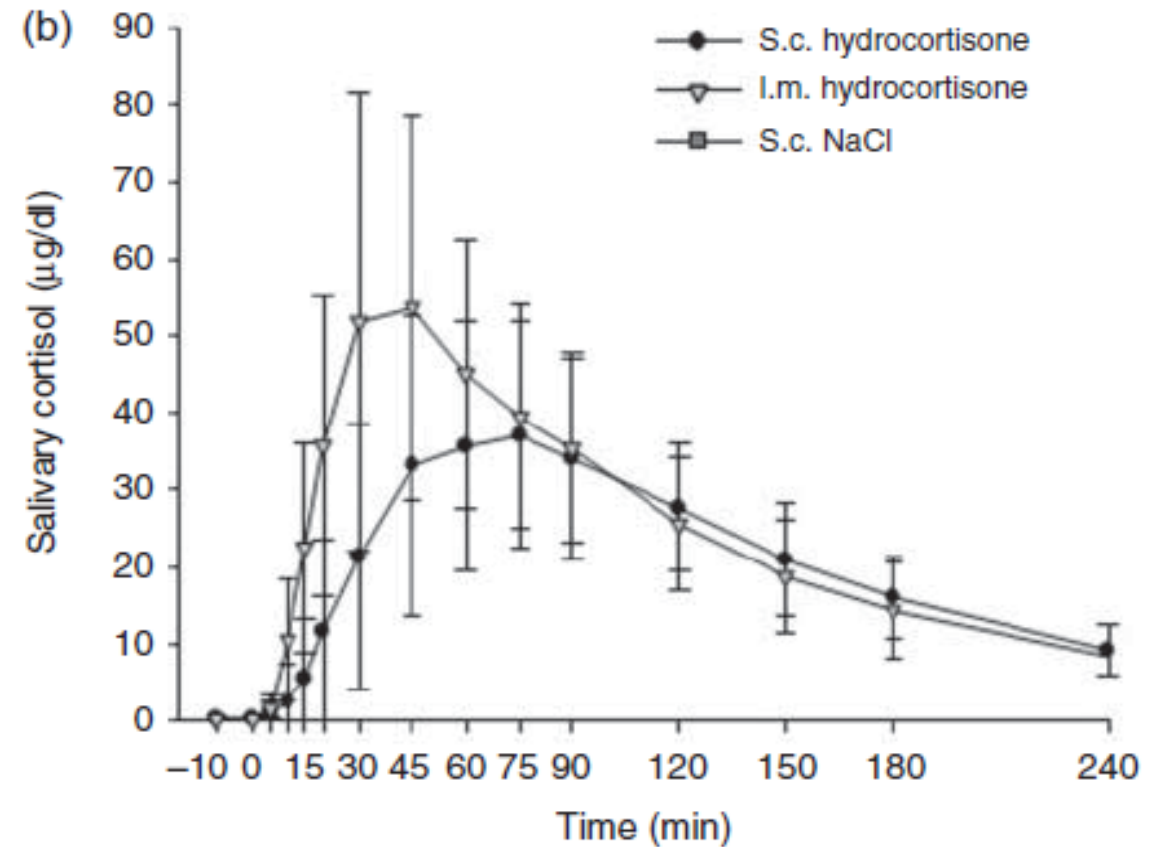
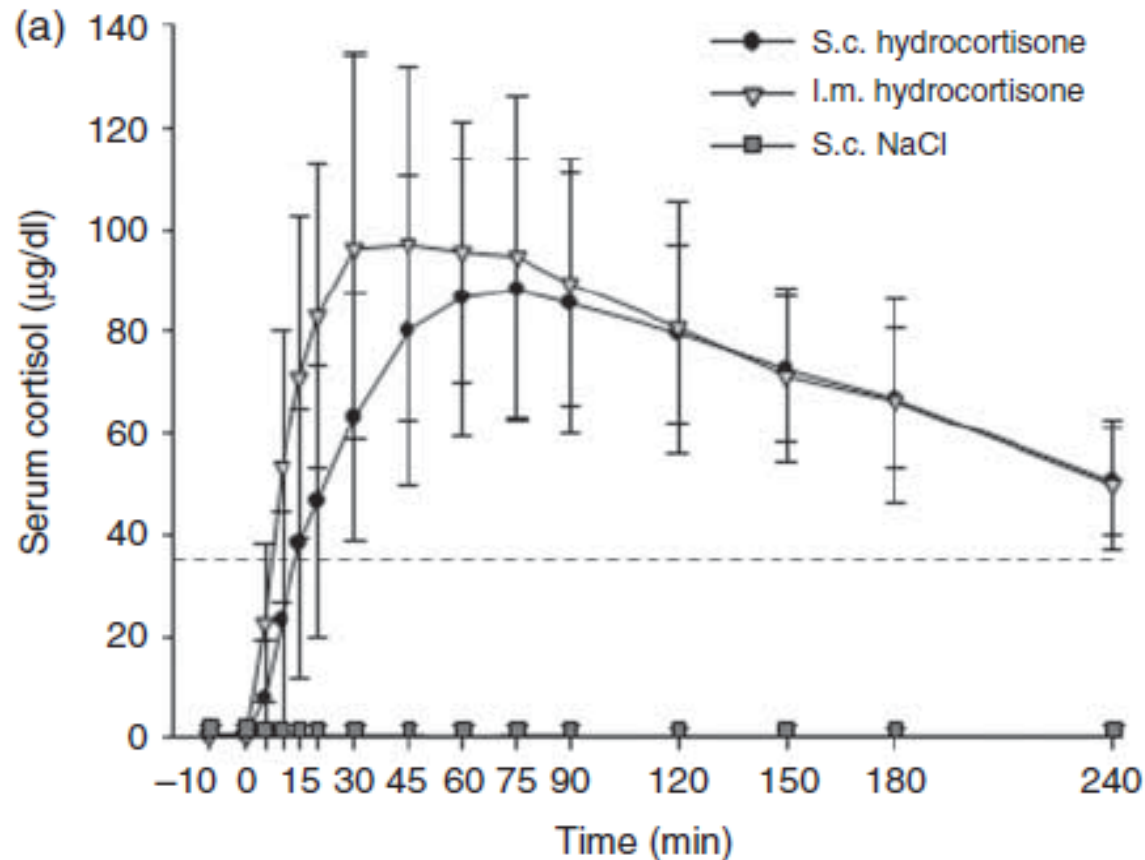
- **Double Dose for Fluid Loss>Intake**
 - Vomiting, Diarrhea, High Fever, Environmental
 - Not for Mental Stress, Head Cold, Bad Days
- **Rescue Injection if Not Able To Take Pills**
 - 100 mg Hydrocortisone IM/SC x 1
 - Then Call 911/Go To Emergency Room!
- **Continue Double Dose Until Well For 1 Day**
- **Identify Reason For Sick Day**

Surgery & Adrenal Insufficiency

- **Major Surgery Entering Abdomen/Chest + NPO**
 - Hydrocortisone 25 mg Q6h
 - Methylprednisolone 4-6 mg Q8h
 - Most Patients Get 4 mg Dexamethasone Anyway!!!
- **Minor Surgery or Procedure**
 - Hydrocortisone 25 mg x 1 or Double Usual AM Dose
 - Double Dose 1 Day, Resume Usual Dose If Well
 - Ex: C-Section, Carpal Tunnel, Colonoscopy

Adrenal Insufficiency

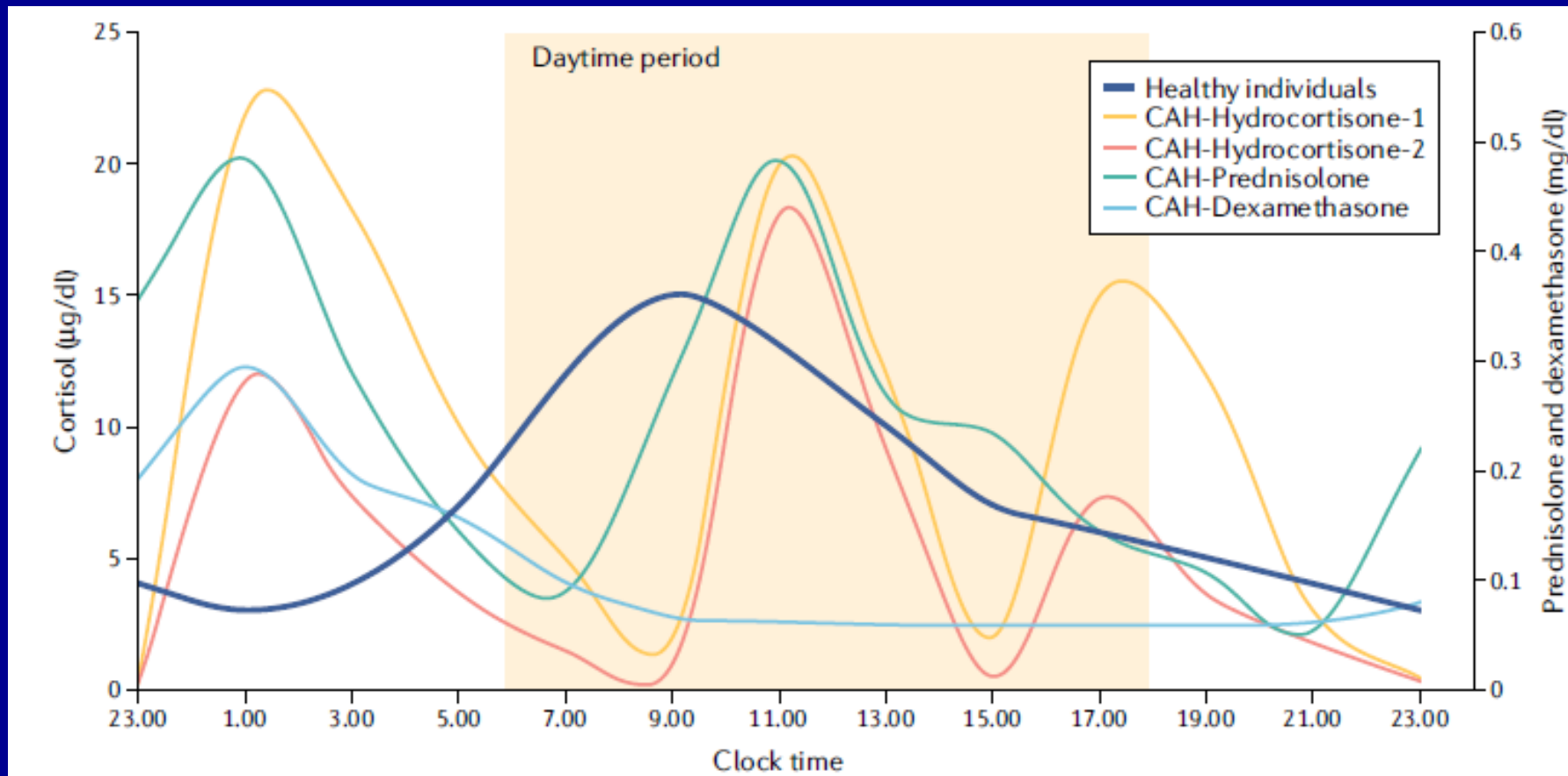
IM vs SC Hydrocortisone



Adrenal Insufficiency

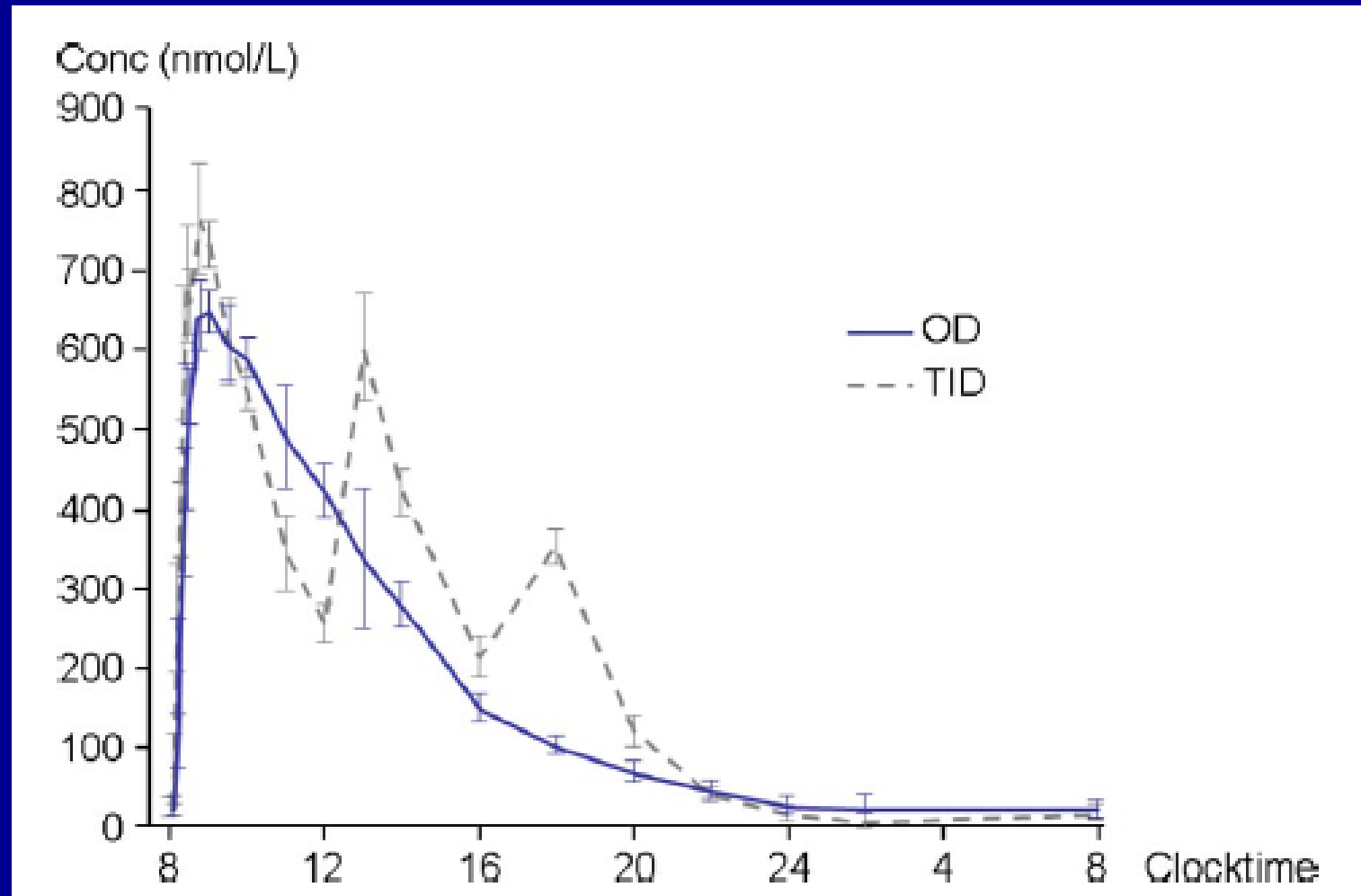
Alternate Treatments

- Modified-Release Hydrocortisone
- Continuous Subcutaneous Infusion



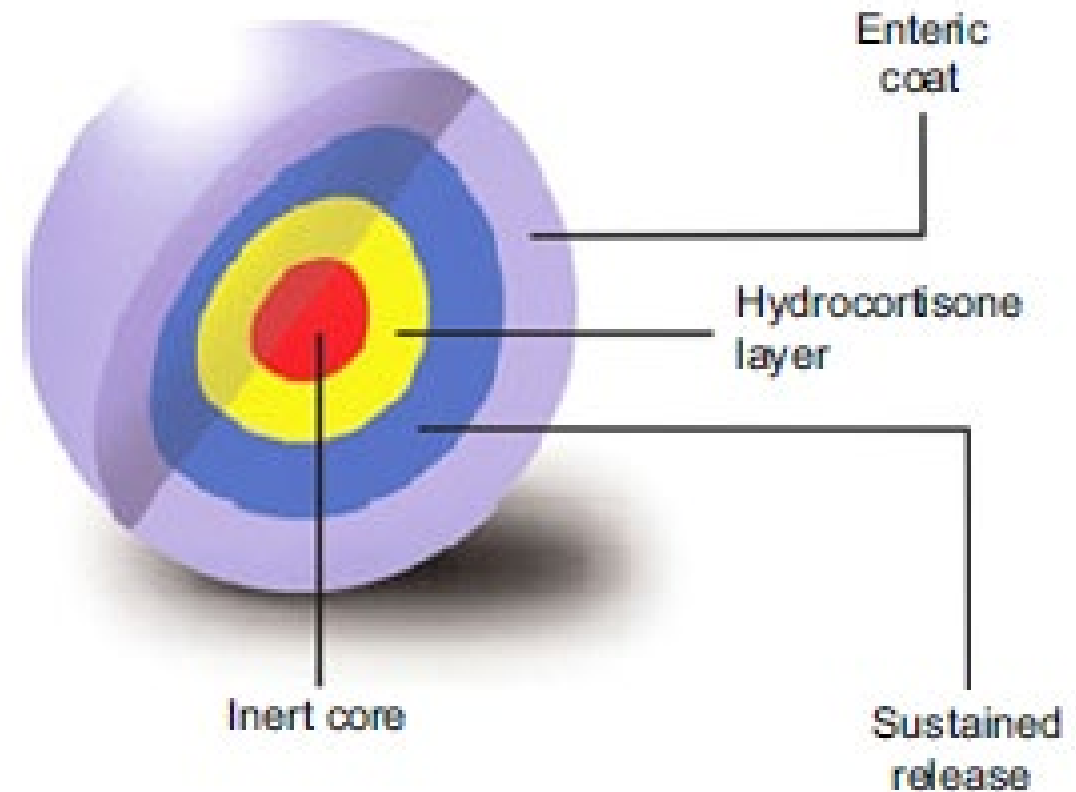
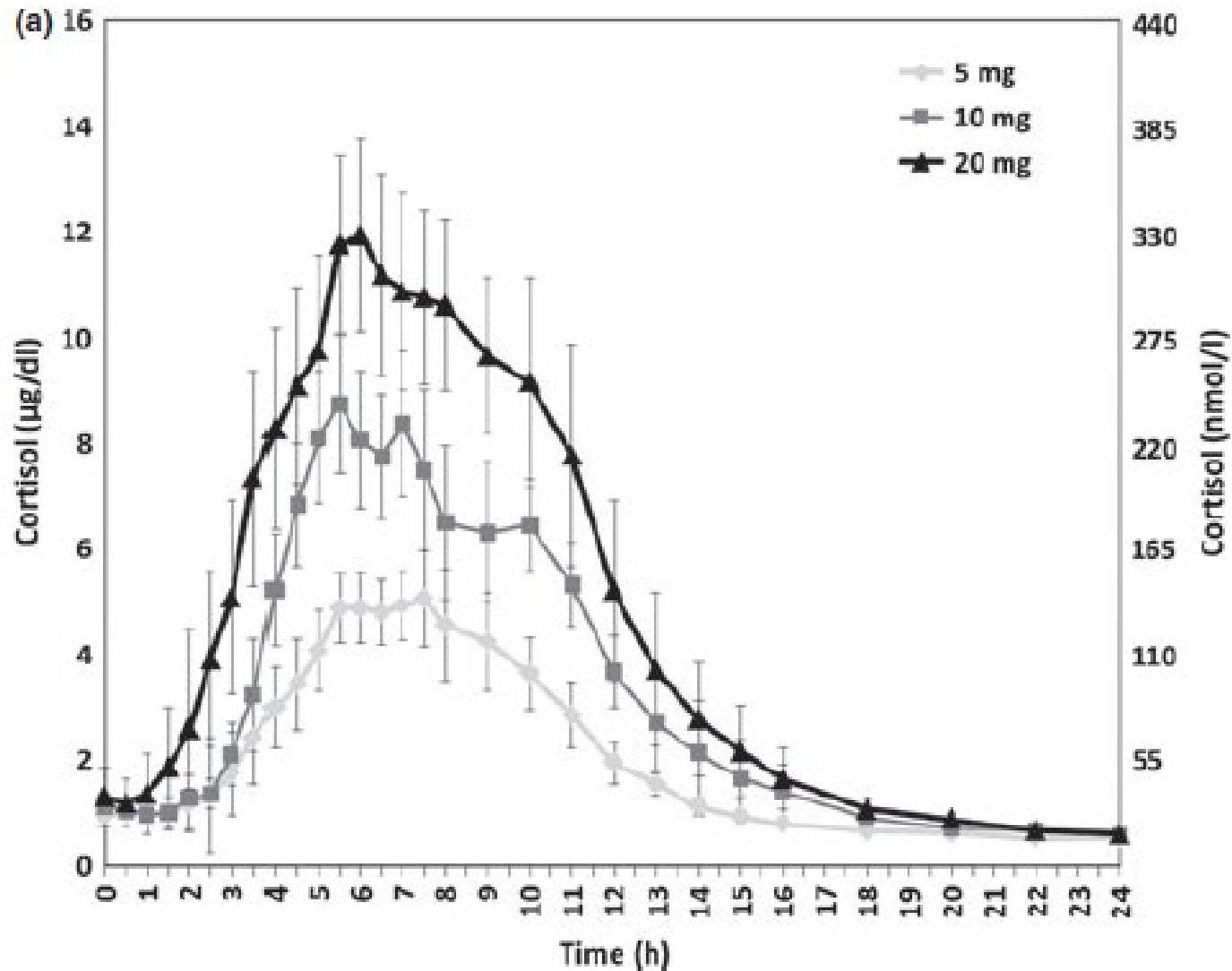
Adrenal Insufficiency

Modified-Release Hydrocortisone (Plenadren)



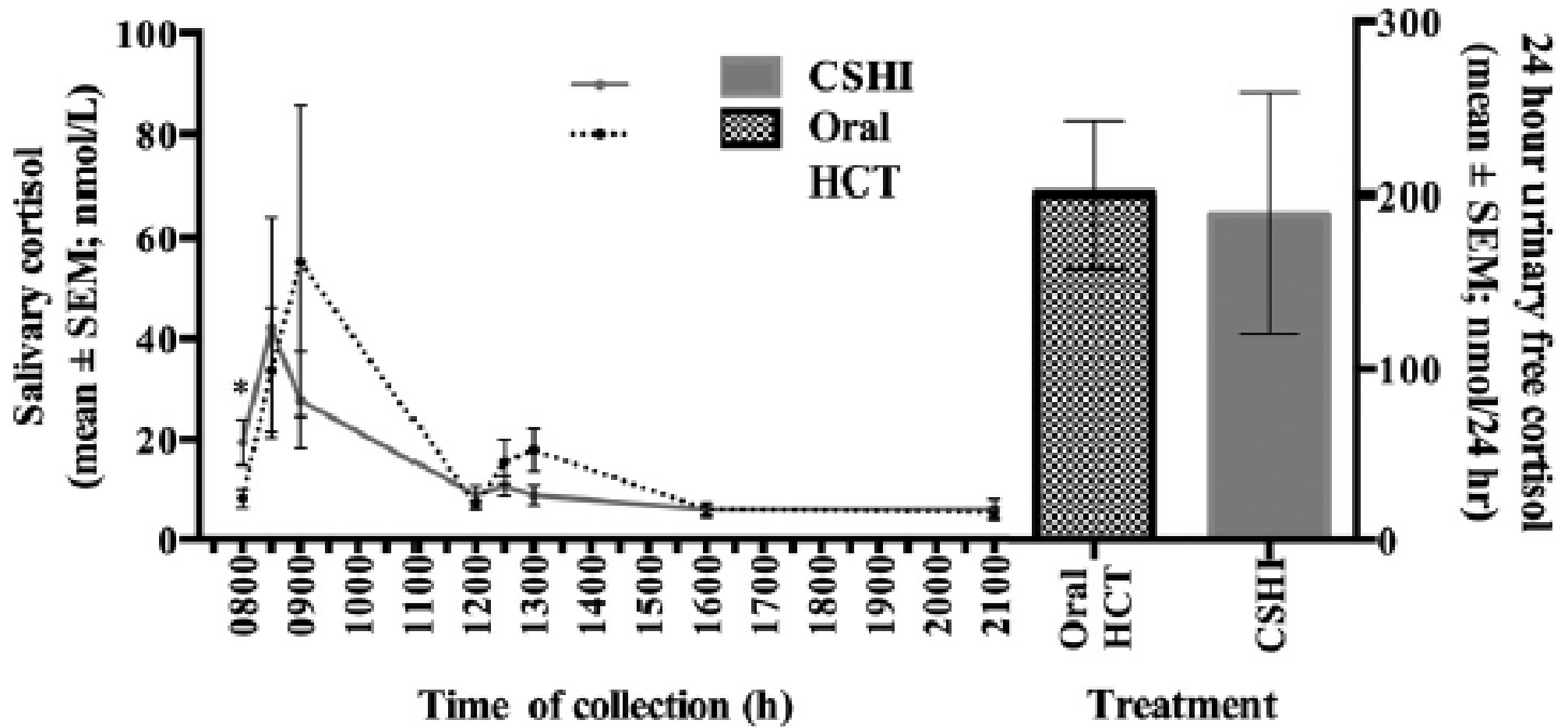
Adrenal Insufficiency

Modified-Release Hydrocortisone (Chronocort)



Adrenal Insufficiency

Continuous SC Hydrocortisone



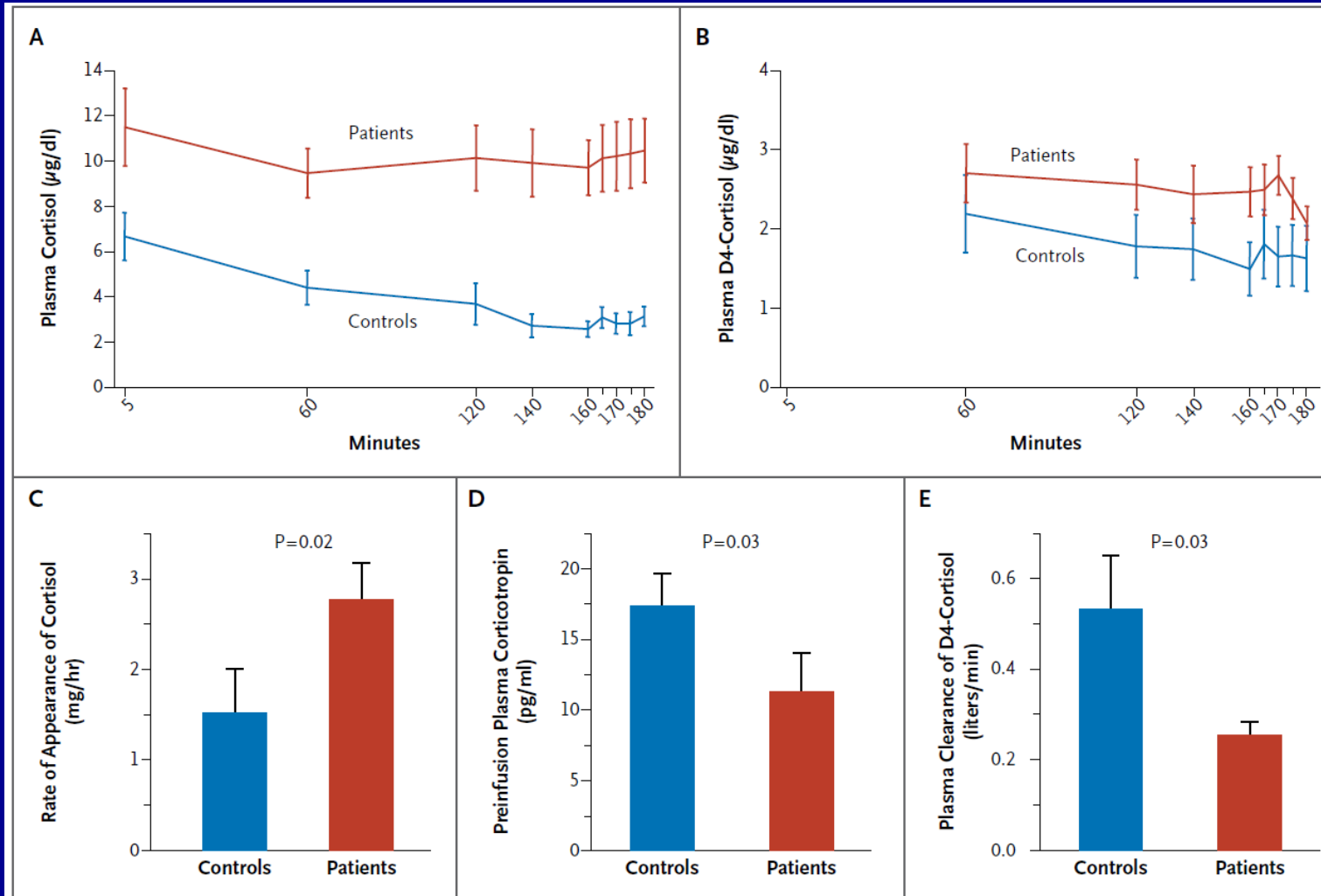
Adrenal in Critical Illness

Alterations

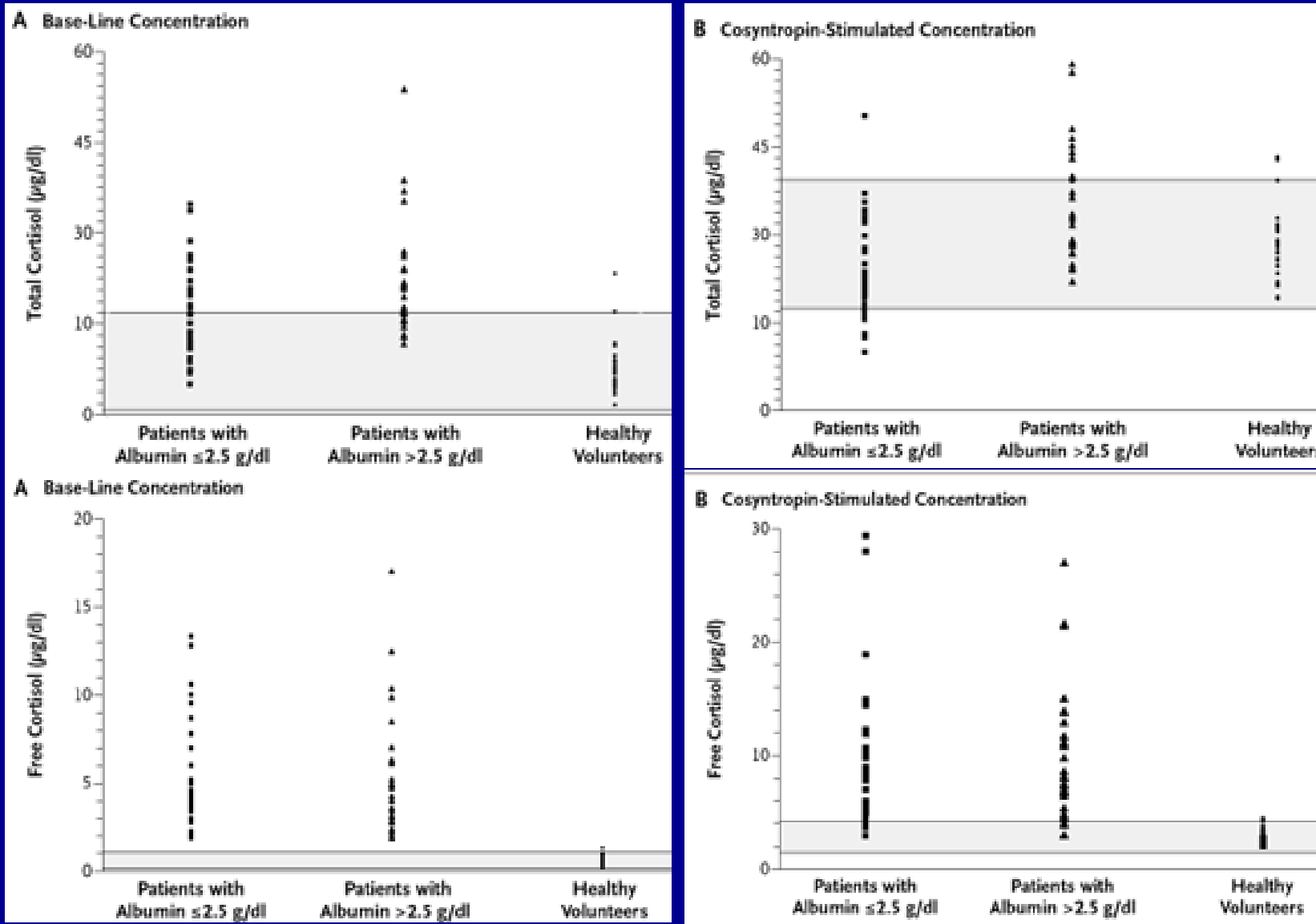
- **Activation of HPA Axis**
 - **Profound But Transient**
 - **Hypersensitive to Stimuli**
 - **Loss of Diurnal Rhythm**
 - **ACTH Falls After Several Days**
- **Resistance to Suppression**
- **Altered Cortisol Metabolism**
- **Altered Protein Binding**

Cortisol in Critical Illness

Production vs Metabolism



Total vs. Free Cortisol in ICU



Salivary Cortisone

- How Best Monitor Adrenal Replacement?
- F/E Ratio in Serum 4:1 in Saliva 1:6
- Normal Volunteers
- AI Patients IV or PO Hydrocortisone
- Sal Cortisone Correlates Best With Serum Cortisol

Salivary Cortisone

Table 3 Correlation Matrix Period 2 After Oral HC With ρ ($P \leq .001$) (n = 14)

ρ (95% CI)	Serum F	Serum E	FCI	Salivary F ^a	Salivary E
Serum F	1.0	0.51 (0.40–0.60)	0.97 (0.96–0.97)	0.30 (0.16–0.43)	0.84 (0.79–0.87)
Serum E		1.0	0.53 (0.43–0.62)	NS	0.61 (0.52–0.68)
FCI			1.0	0.30 (0.16–0.43)	0.88 (0.84–0.90)
Salivary F ^a				1.0	NS
Salivary E					1.0

Table 4 Correlation Matrix Period 3 After iv HC With ρ ($P \leq .001$) (n = 14)

ρ (95% CI)	Serum F	Serum E	FCI	Salivary F ^a	Salivary E
Serum F	1.0	0.68 (0.6–0.75)	0.97 (0.97–0.98)	0.89 (0.85–0.91)	0.94 (0.92–0.95)
Serum E		1.0	0.68 (0.60–0.74)	0.33 (0.20–0.46)	0.66 (0.58–0.73)
FCI			1.0	0.87 (0.84–0.91)	0.96 (0.95–0.97)
Salivary F ^a				1.0	0.87 (0.83–0.90)
Salivary E					1.0

Non-Invasive Adrenal Testing

- **Intranasal Cosyntropin Poorly Absorbed**
- **Chitosan Enhances Absorption/Exposure**
 - Cationic Polymer from Shellfish Exoskeleton
 - Nasacthin003 0.5 mg Gives 14% Exposure
 - Peaks at 10 Min, More Sustained Than IV
- **Measure Saliva Cortisone or Cortisol**
 - LC-MS/MS, Cortisone > Cortisol in Saliva
 - 24 Children Studied Plus Adults

Noninvasive Adrenal Testing

Intranasal Cosyntropin + Saliva Cortisone

Figure 3a

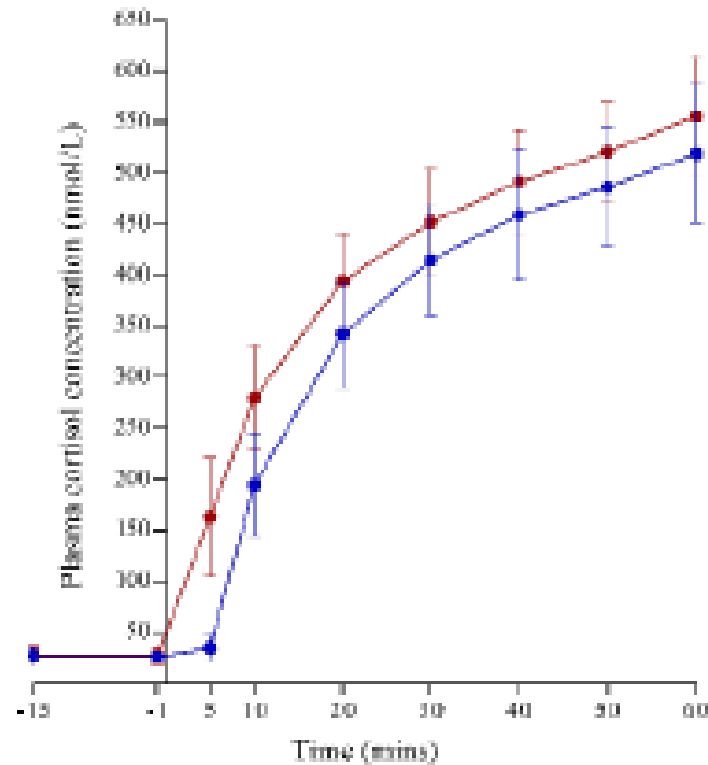


Figure 3b

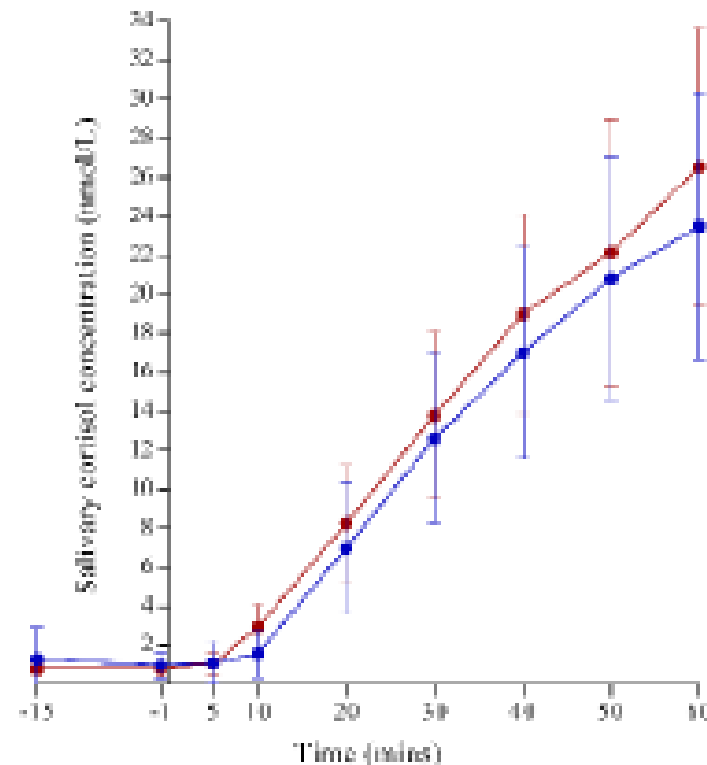
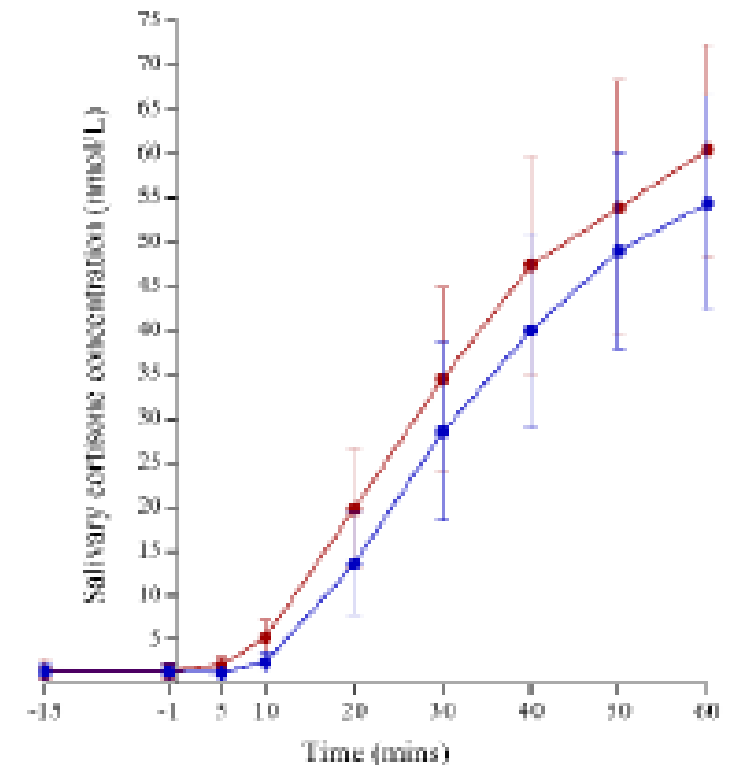


Figure 3c



■ Nasacthin003 (500 µg)
■ Intravenous cosyntropin (145 µg/m²)

**Adrenals Are Life;
The Rest is Just Details**