ENDOCRINE HYPERTENSION

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CLINICAL RECOGNITION

Hypertension is defined differently by various societies with a blood pressure exceeding 139/89 mm Hg for adults aged 18 years or older generally considered being elevated, based on the mean of 2 or more properly measured seated BP readings on each of 2 or more office visits. Hypertension affects approximately 31% of Americans when using the above cutoff level. Blood pressure control is suboptimal and is achieved in less than 1 in 3. For children, hypertension is defined as an average systolic BP and/or diastolic BP that is greater than the 95th percentile for age, gender, and height on more than 3 occasions. Normal BP in children is defined as a SBP and DBP less than the 90th percentile for age, gender, and height. Figure 1 provides an overview of classification of BP for adults 18 years and older.

SBP [mmHg]		DBP [mmHg]	ESH/ESC 2018	AHA/ACC 2017	Position of the DHL, 2017	NICE 2016
<120	and	<80	Optimal	Normal	Optimal	Normal
120–129	and	<80	Normal	Elevated	Normal	Normal
130–139	or	80–89	Upper range of normal	Grade I hypertension	Upper range of normal	Upper range of normal
140–159	or	90–99	Grade I hypertension	Grade II hypertension	Grade I hypertension	Grade I hypertension (≥ 135/85 mmHg)*
160–179	or	100–109	Grade II hypertension	Grade II hypertension	Grade II hypertension	Grade II hypertension (≥ 150/95 mmHg)*
≥ 180	or	≥ 110	Grade III hypertension	Grade II hypertension	Grade III hypertension	Severe hypertension

Figure 1. Classification of Hypertension. AHA, American Heart Association; ACC, American College of Cardiology; ESC, European Society of Cardiology; ESH, European Society of Hypertension; DHL, German Hypertension League; NICE, National Institute for Health and Care Excellence of the United Kingdom. DBP, diastolic blood pressure; SBP, systolic blood pressure. Modified from: Jordan J, Kurschat C, Reuter H. Arterial hypertension. Dtsch Arztebl Int. 2018 Aug 20;115(33-34):557-568

Less than 5% of hypertension is endocrine related, the vast majority being “essential”. Endocrine hypertension is suggested by finding physical or historical clues suggesting a specific endocrine

disease or patient's failure to respond to conventional therapy. The first step when evaluating a patient with suspected endocrine-related hypertension is to exclude other causes of secondary hypertension. A detailed medical history and review of systems should be obtained. The onset of hypertension and the response to previous anti-hypertensive treatment should be determined. A history of target organ damage (i.e. retinopathy, nephropathy, claudication, heart disease, abdominal or carotid artery disease) and the overall cardiovascular risk status should also be explored in detail. Moreover, a detailed family history may provide valuable insights into familial forms of endocrine hypertension.

A secondary cause of hypertension should be suspected with the following:

- Young age
- Resistant hypertension
- Need for more than 3 antihypertensives to control blood pressure
- Very high blood pressure >180/110 mm Hg
- Family history of kidney disease
- Hypokalemia
- Plethora with features of Cushing's syndrome
- Spells with variable blood pressure spikes
- Features of growth hormone excess
- Features of hypothyroidism, i.e. swollen eyes, dry skin
- Signs and symptoms of hyperthyroidism, i.e. palpitations, weight loss
- Retinal angiomas (?von Hippel Lindau disease)

Table 1 provides a specific description of the clinical presentation of endocrine conditions related to hypertension.

Table 1. Clinical Findings in Patients with Endocrine Hypertension

Condition	Clinical presentation
Primary hyperaldosteronism	Diastolic hypertension, headache, muscle weakness, hypokalemia, metabolic alkalosis
Cushing's syndrome	Fatigue, weight gain, round face, proximal myopathy, plethora, hirsutism, buffalo hump, central obesity
Pheochromocytoma	Headache, palpitation, sweating, pallor, paroxysmal BP
Hyperthyroidism	Tremor, tachycardia, atrial fibrillation, weight loss, goiter, ophthalmopathy, pretibial myxedema
Hypothyroidism	Fatigue, cold intolerance, weight gain, nonpitting edema, periorbital puffiness
CAH: 11beta-hydroxylase deficiency	Virilization, tall stature, hirsutism, advanced bone age, amenorrhea
CAH: 17alpha-hydroxylase deficiency	Pseudohermaphroditism (male), sexual infantilism (female), hypokalemia

Liddle syndrome	Severe hypertension, hypokalemia, and metabolic alkalosis
Apparent mineralocorticoid excess	Growth retardation/short stature, hypertension, hypokalemia, diabetes insipidus,
Pseudohypoaldosteronism type 2	Short stature, hyperkalemic metabolic acidosis, normal aldosterone
Glucocorticoid Resistance	Ambiguous genitalia, precocious puberty, hirsutism, oligo/anovulation
Hyperparathyroidism	Bones, stones, abdominal groans, and psychic moans
Acromegaly	Headache, jaw enlargement, macroglossia, amenorrhea, impotence, diabetes mellitus, hypertension, heart failure
Insulin Resistance	Hypertension, abdominal/visceral obesity, dyslipidemia, and insulin resistance

It is also important to identify correctly patients with hypertensive emergencies (increased BP and acute target-organ damage) and provide the necessary urgent treatment. A focused exam must be undertaken quickly with the purpose of rapid identification of the acute target-organ damage. Hypertensive urgency is defined as a SBP > 180 mm Hg or DBP >120 mm Hg with minimal or no target-organ damage. The following tables shows the common hypertensive emergencies and the possible types of acute end-organ injury. Approx. 1% of Americans with hypertension will present with a hypertensive emergency.

Table 2. Common Causes of Hypertensive Emergencies
Medication noncompliance
Renovascular and renoparenchymal disease
Pre-eclampsia/eclampsia
Malignant hypertension
Acute increase in sympathetic activity (Pheochromocytoma crisis)
Autonomic dysfunction (Guillain-Barré syndrome, post-spinal cord injury) and
Central nervous system disorders (head injury, cerebral infarction / hemorrhage)
Drugs

Sympathomimetics (cocaine, amphetamines incl. crystal meth, phencyclidine, etc)
MAO inhibitors and the ingestion of tyramine-containing foods
Withdrawal from clonidine and other central alpha2 adrenergic receptor agonists

Table 3. Hypertensive Emergency Acute End-Organ Injury
Cerebrovascular
Subarachnoid or intracerebral hemorrhage
Ischemic stroke
Encephalopathy
Renal damage
Acute renal failure, scleroderma renal crisis, microangiopathic hemolytic anemia
Cardiac
Heart failure
Acute coronary syndromes
Acute aortic dissection
Eye
Hemorrhage
Exudate
Papilledema

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Idiopathic (primary or essential) hypertension accounts for approximately 95% of diagnosed cases. It is estimated that approximately 5% of hypertensive patients have identifiable conditions that result in blood pressure elevation (secondary hypertension). Endocrine hypertension accounts for approximately 3% of the secondary forms of hypertension and is a term assigned to states in which hormonal derangements result in clinically significant hypertension. The major causes of secondary hypertension are summarized in table 4.

Table 4. Classification of Hypertension

Essential (95%)
Secondary causes (5%)
Endocrine Hypertension **Adults** Cushing's Syndrome Primary aldosteronism Pheochromocytoma Hyperthyroidism Hypothyroidism Hyperparathyroidism Acromegaly Insulin Resistance **Children** CAH: 11beta-hydroxylase deficiency CAH: 17alpha-hydroxylase deficiency Apparent mineralocorticoid excess Liddle syndrome Pseudohypoaldosteronism type 2 Glucocorticoid Resistance Insulin resistance Constitutive activation of the MR (Geller syndrome) **Non-Endocrine Hypertension** **Polycystic kidney disease** **Glomerular disease** Renovascular Atherosclerosis (older individuals) Fibromuscular dysplasia (women) Other: Scleroderma, vasculitis (PAN) Medications (Contraceptive drugs, NSAIDs, nasal decongestants with adrenergic effects, MAOIs, steroids, methamphetamine, cocaine) Obstructive sleep apnea Coarctation of aorta Pre-eclampsia, eclampsia Polycythemia vera

PATHOPHYSIOLOGY

Cushing's Syndrome

Hypercortisolemia is associated with hypertension in approximately 80% of adult cases and half of children. In Cushing's syndrome there is increased hepatic production of angiotensinogen and cardiac output, reduced production of prostaglandins via inhibition of phospholipase A, increased insulin resistance, and oversaturation of 11beta-Hydroxysteroid Dehydrogenase activity with increased mineralocorticoid effect through stimulation of the mineralocorticoid receptor.

Primary Aldosteronism (PA)

PA can be a sporadic or familial condition. Most cases of PA are caused by bilateral adrenal hyperplasia and less commonly by an aldosterone-producing adrenal adenoma. Very rarely, PA can be caused by an adrenal carcinoma or unilateral adrenal cortex hyperplasia (also called primary adrenal hyperplasia). Familial aldosteronism is estimated to affect at least 2% of all patients with primary hyperaldosteronism and is classified as type 1, 2, 3, and 4. In familial hyperaldosteronism type 1, an autosomal dominantly inherited chimeric gene defect in CYP11B1/CYPB2 (coding for 11beta-hydroxylase/aldosterone synthase) causes ectopic expression of aldosterone synthase activity in the cortisol-producing zona fasciculata, making mineralocorticoid production regulated by corticotropin. The hybrid gene has been identified on chromosome 8. Familial hyperaldosteronism type 2 is not glucocorticoid-remediable. During the last years, other forms of familial aldosteronism were identified with 18-oxoF 10-1,000 higher (in type 3) than seen in familial hyperaldosteronism type 1 and/or type 2. Familial hyperaldosteronism type 3 is caused by germline mutations in the potassium channel subunit *KCNJ5 and familial hyperaldosteronism* type 4 is caused by germline mutations in the *CACNA1H* gene, which encodes the alpha subunit of an L-type voltage-gated calcium channel (Cav3.2).

Pheochromocytoma

These rare neuroendocrine tumors are composed of chromaffin tissue containing neurosecretory granules. Adrenal pheochromocytomas and most paragangliomas located in the abdomen produce and secrete catecholamines which can cause paroxysmal or sustained hypertension with hypertensive crisis.

Hyperthyroidism

Hyperthyroidism increases systolic blood pressure by increasing heart rate, decreasing systemic vascular resistance, and raising cardiac output. In thyrotoxicosis, patients usually are tachycardic and have high cardiac output with an increased stroke volume and elevated systolic blood pressure.

Hypothyroidism

Hypothyroid patients have impaired endothelial function, increased systemic vascular resistance, extracellular volume expansion, and an increased diastolic blood pressure. Hypothyroid patients have higher mean 24-h systolic BP and BP variability on 24-h ambulatory BP monitoring.

Congenital Adrenal Hyperplasia: 11beta-hydroxylase deficiency (5% of CAH)

11beta-hydroxylase is responsible for the conversion of deoxycorticosterone (DOC) to corticosterone (precursor of aldosterone) and 11-deoxycortisol to cortisol. In approximately 2/3 of individuals affected by a deficiency of this enzyme, monogenic low renin hypertension with low aldosterone levels ensues

caused by accumulation of 11-deoxycortisol and DOC.

Congenital Adrenal Hyperplasia: 17alpha-hydroxylase deficiency

This enzyme deficiency is rare and leads to diminished production of cortisol and sex steroids. Chronic elevation of ACTH causes an increased production of DOC and corticosterone with subsequent hypertension, hypokalemia, low aldosterone concentrations with suppressed renin.

Apparent Mineralocorticoid Excess

Low-renin hypertension can present in various forms; one of them is apparent mineralocorticoid excess (AME), an autosomal recessive disorder caused by deficiency of the 11beta-hydroxysteroid dehydrogenase type 2 (11beta-HSD2) enzyme. This enzyme converts cortisol to the inactive cortisone in renal tubular cells. The lack of this enzyme results in high levels of cortisol in renal tubule cells, which activates the mineralocorticoid receptor.

Liddle Syndrome

Liddle described patients with severe hypertension, hypokalemia, and metabolic alkalosis, who had low plasma aldosterone levels and plasma renin activity. “Gain of function” mutations in the genes coding for the beta- or gamma-subunit of the renal epithelial sodium channel, located at chromosome 16p13, lead to constitutive activation of renal sodium resorption and subsequent volume expansion.

Pseudohypoaldosteronism Type 2

This condition is transmitted in an autosomal dominant fashion, and can cause low renin hypertension. Hypertension in these patients may develop as a consequence of increased renal salt reabsorption, and hyperkalemia ensues as a result of reduced renal K excretion despite normal glomerular filtration and aldosterone secretion. Abnormalities such as activating mutations in the amiloride-sensitive sodium channel of the distal renal tubule are responsible for the clinical phenotype.

Glucocorticoid Resistance or Chrousos Syndrome

This autosomal recessive or dominant inherited disorder is rare and caused by inactivating mutations of the glucocorticoid receptor gene. Permanent elevation of ACTH can lead to stimulation of adrenal compounds with mineralocorticoid activity (corticosterone, DOC), and elevation of cortisol may lead to stimulation of the mineralocorticoid receptor, resulting in hypertension. In women, hirsutism and oligomenorrhea may develop through stimulation of androgens.

Constitutive Activation of the Mineralocorticoid Receptor (MC receptor)

The MC receptor can be mutated leading to the onset of hypertension before age 20. “Gain of function” mutations in the MC gene on chromosome 4q31 were identified. The inheritance pattern is autosomal-dominant.

DIAGNOSTIC TESTS NEEDED AND SUGGESTED

The presence of clinical signs and symptoms suggestive of endocrine hypertension (see table 1) should lead to a general screening for the most common forms of endocrine hypertension (Table 5).

Table 5. Screening Tests for Endocrine Causes of Hypertension	
Cushing's Syndrome	24-hour urinary cortisol, overnight dexamethasone suppression test, midnight salivary cortisol
Primary Hyperaldosteronism	Plasma aldosterone: renin ratio
Pheochromocytoma	Urinary or plasma metanephrines, urinary catecholamines
Thyroid Dysfunction	TSH, FT4, T3

In patients with a positive screening test, subsequent confirmation by various testing modalities is necessary (Table 6). These steps may involve supplementary laboratory tests and localization imaging tests (CT, MRI).

Table 6. Tests for Diagnosing the Most Prevalent Forms of Endocrine Hypertension
Cushing's Syndrome ACTH-dependent (5-10%) (ACTH > 20 ng/L) High-dose Dexamethason suppression test or CRH test If positive, then pituitary MRI and/or bilateral inferior petrosal sinus sampling If negative, then chest/abdomen MRI and/or 68Ga-DOTATATE PET/CT scan or Octreoscan ACTH-independent (90-95%) (ACTH <10 ng/L) Adrenal CT or MRI
Hyperaldosteronism Salt suppression test positive if aldosterone excretion > 12 to 14 µg/d while urine Na > 200 mEq/day or *other* suppression tests: fludrocortisone suppression and captopril challenge Adrenal CT or MRI

Adrenal vein sampling
<u>Pheochromocytoma</u> Anatomic imaging (CT/MRI): abd/pelvis if negative then chest/head and neck Functional imaging [123/131] Iodine-Metaiodobenzylguanidine scan **specific PET ([18F] Fluorodopamine, [18F]Fluorodopa) scan** **non-specific PET ([18F] Fluorodeoxyglucose)** **Genetic testing**

If the above conditions have been ruled out but the suspicion of an endocrine cause of hypertension is still high, we should move to the next step and test for rare causes of hypertension. The diagnostic strategy is described in table 7.

Table 7. Testing for Rare Causes of Endocrine Hypertension
CAH: 11beta-hydroxylase deficiency ↑11-deoxycortisol, ↑DOC, ↑ 19-nor-DOC ↓renin, ↓↓ aldosterone, ↑urinary 100*THS/(THE+THF+5αTHF) and 100*THDOC/(THE+THF+5αTHF) ratios Genetic testing
CAH: 17alpha-hydroxylase deficiency ↑DOC, ↓11-deoxycortisol, ↓↓ aldosterone ↓renin, ↓plasma 17-hydroxyprogesterone, ↑urinary 100*THDOC/(THE+THF+5αTHF) and (THA+THB+5αTHB)/(THE+THF+5αTHF) ratios Genetic testing
Apparent mineralocorticoid excess ↓renin, ↓K, low aldosterone ↑ 24 h urinary free cortisol / cortisone ↑urinary (THF+5αTHF)/THE Genetic testing

Liddle Syndrome ↓renin, ↓ aldosterone, ↓urinary THALDO Genetic testing (ENaC gene)
Pseudohypoaldosteronism type 2 ↑K, hyperchloremic metabolic acidosis, ↓aldosterone, ↓renin, ↓serum HCO3, ↓urinary THALDO Genetic testing (ENaC gene)
Glucocorticoid Resistance Syndrome ↑cortisol, ↑ACTH, ↑androgens Genetic testing
Constitutive Activation of the Mineralocorticoid Receptor ↑K, ↓aldosterone, ↓renin ↓urinary THALDO Genetic testing

THE-tetrahydrocortisone; THF- tetrahydrocortisol; THA-tetrahydro 11-dehydro-corticosterone; THB-tetrahydrocorticosterone; DOC-deoxycorticosterone; THALDO-tetrahydro aldosterone

THERAPY

In the face of a hypertensive crisis, rapid action is important and the underlying disorder and the individual patient's comorbidities determine the treatment approach. Aortic dissection will require rapid lowering of blood pressure, whereas blood pressure in an ischemic cerebrovascular event should be lowered modestly considering the cerebral perfusion and intracranial pressures. Among 1000 participants with intracerebral hemorrhage and a mean systolic blood pressure of 201 mm Hg at baseline lowering the SBP to 110 to 139 mm Hg did not result in a lower rate of death or disability than standard reduction to a target of 140 to 179 mm Hg (Qureshi AI et al. NEJM 2016). For acute hypertension following stroke, labetalol, nicardipine, and nitroprusside are commonly administered with labetalol being considered first line therapy. For cocaine intoxication, phentolamine and nitroprusside are recommended. For an adrenergic crisis due to pheochromocytoma, phentolamine, nitroprusside and urapidil are preferred. For the management of a hypertensive emergency in pregnant and postpartal women, intravenous labetalol next to magnesium sulfate, ketanserine, hydralazine, and nicardipine are considered first line medications. Immediate release oral nifedipine can also be given, especially when no intravenous access is available.

In general, in the first hour of treatment the mean arterial blood pressure should be reduced by 15% to 20% from baseline and then another 10%-15% over the following 2 to 6 h with a further gradual reduction over the next 24 h to reach normal blood pressure levels.

The most common used intravenous drugs and their dose and duration of action are listed in the table 8.

Table 8. Commonly Used Intravenous Drugs

Agent	Dose	Onset/ duration of action
Vasodilators		
Nitroprusside	0.25-10 mcg/kg/min	0.5-1 min/ 1-10 minutes
Nitroglycerine	5-200 mcg/kg/min	1-2 min/ 3-5 minutes
Nicardipine	5-15 mg/h, increase every 15 min	5-10 min/ 1-4h
Fenoldopam	Initial dose:0.1 mg/kg/min followed by 0.05 to 0.1 mcg/kg/min q 15-20min till normal BP	10 min/ 30 minutes
Hydralazine	10-20 mg q 20-30min	10-20 min/3-8h
Beta-blockers		
Labetalol	20-80 mg as bolus every 10-20 min. or 0.5-2 mg/kg/min	5-10 min/2-6h
Esmolol	0.5-1 mg/kg bolus; 50-300 mcg/kg/min	1-2 min / 10-30 min
Alpha-blocker		
Phentolamine	1-5 mg bolus q 5-15min; 0.5-1 mg/h infusion	1-2 min/ 3-10 min
Urapidil	12.5-25 mg bolus; 5-40 mg/h infusion	3-5 min / 4-6 h
Antagonist of 5-HT2 (hydroxytryptamine) receptors		
Ketanserin	5 mg bolus, repeat; 2-6 mg/h infusion	1-2 min / 30-60 min

Once the diagnosis of a specific cause of endocrine hypertension has been established, treatment oriented toward the endocrine diseases should be instituted (see specific chapters in Endotext that discuss the treatment of these disorders in depth).

Table 9. Treatment for Endocrine Causes of Hypertension
Cushing's Syndrome **Adrenolytic Therapy** Metyrapone 250-6000 mg/day in 3-4 doses daily (oral)

Ketoconazole 200-1200 mg/day in up to 4 daily doses (oral) Mitotane up to 4-12 g/day (oral) Etomidate intravenously at 0.3 mg/kg/h based on the serum cortisol levels **Somatostatin analogues** Pasireotide 600-900 µg twice daily s.c. **Dopamine agonists** Cabergoline initially 0.5 mg/week, titrated to 4.5 mg/week (oral) **Alkylating drugs** Temozolomide (experimental, oral) **Glucocorticoid receptor antagonists** Mifepristone, CORT112716, 113083 (oral)
Primary aldosteronism **Mineralocorticoid receptor antagonist** Eplerenone 50 - 300 mg / day (oral) Spironolactone 50-225 mg/day (oral) **Glucocorticoids (GRA)** Dexamethasone (low dose i.e. 0.5 mg)
Pheochromocytoma **α-adrenoceptor blocker± B-blockers** Phenoxybenzamine at 10-20 mg (titrated up based on SBP) twice daily for 2 weeks before surgery Propranolol or other beta-blocker for reflex tachycardia **Hypertensive crisis** Phentolamine i.v. bolus of 2.5 mg-5 mg at 1 mg/min Sodium nitroprusside as an alternative at 0.25-10 mcg/kg/min
Hyperthyroidism **Thyroid storm** **Aggressive hydration** of up to 3-4 L/d of crystalloid **Antithyroid drugs** Methimazole 20-30 mg q 6-12h, then 5-40 mg/d Propylthiouracil (second line) 200 mg q 4-6hr initially then 100-150 mg/day BID **Dexamethasone** (up to 2 mg q6h) **β-blocker** Propranolol 40 mg q6h titrated to SBP **Iodide** i.e. Lugol's solution 1-2 drops
Hypothyroidism **Levothyroxine** (1.6 mcg/kg/day)-lower dose for patients at risk for ischemic heart disease **Myxedema coma** Loading dose 5-10 mcg/kg T4 iv then 50-100 mcg iv qd and steroid replacement (i.e.hydrocortisone 5-10 mg/hr) until normalization of adrenal function

GRA- Glucocorticoid-remediable aldosteronism

FOLLOW-UP

The long-term management of patients with the respective underlying endocrine disorder is discussed in depth in other sections of ENDOTEXT, for instance, the adrenal and pituitary sections.

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