Hypertension
David G. Warnock, MD, and Stephen C. Textor, MD

EPIDEMIOLOGY

Definition

Stages of blood pressure in adults
- Normal: Systolic blood pressure (BP) <120 mm Hg, diastolic BP <80 mm Hg
- Prehypertension: Systolic BP 120 to 139 mm Hg, diastolic BP 80 to 89 mm Hg
  Patients with “prehypertension” are at risk of progression to overt hypertension; those in the range of 130 to 139/80 to 89 mm Hg have twice the risk of developing hypertension and cardiovascular disease (CVD) than those with lower BP
- Stage I: Systolic BP 140 to 159 mm Hg or diastolic BP 90 to 99 mm Hg
- Stage II: Systolic BP >160 mm Hg or diastolic BP >100 mm Hg

Population-Based Risk Issues
- Race
- Regional variations in incidence and complications
- Sex
- Target organ assessment
  - CVD
  - Cerebrovascular disease
  - Kidney disease

Other Risk Issues
- Systolic BP >140 mm Hg is a more important risk factor for CVD than diastolic BP in persons older than 50 years:
  - Risk of CVD beginning at 115/75 mm Hg doubles with each increment of 20/10 mm Hg
  - Risk of CVD is continuous, consistent, and independent of other risk factors
  - Normotensive individuals at age 55 have a 90% lifetime risk for developing hypertension

ADDITIONAL READINGS

PATHOGENESIS

Essential Hypertension Is a Multifactorial Disease
- Population-based risk factors for developing hypertension:
  - Diet
  - Salt intake
  - Stress
  - Race
  - Obesity
  - Smoking
- Sympathetic nervous system:
  - Sympathetic outflow and tone
  - Diurnal variations
  - Peripheral vascular tone
- Increased peripheral resistance is the final common pathway
- Cardiac output may be increased early in
process, with changes in peripheral vascular tone a secondary event

- Primary vascular processes may directly affect peripheral vascular tone
- Balance between vasodilating and vasoconstricting modulators:
  - Vascular endothelium may play primary role, but remodeling of endothelium, smooth muscle, and interstitium contribute to final state
  - Short-term pressor effects distinguished from longer-term effects of cytokines and growth factors
- Local autocrine loops, especially for the renin, angiotensin, and aldosterone system, may be of major importance

Other Systemic Diseases Contribute to Process

- Atherosclerosis
  - Central arteries versus peripheral vessels
  - Endothelial vasoreactive factors
  - Lipidation and oxidative stress
  - Homocysteine
- Diabetes
  - Microvascular disease
  - Metabolic syndrome
- Vasculitides

Renal Artery Stenosis

- Fibromuscular hyperplasia
- Atherosclerosis
  - Osteal lesions and arterial lesions
  - Segmental lesions
- Vasopressor release as a consequence of local ischemia

Low Renin Hypertension

- Plasma renin activity as a reflection of effective volume status
- Prevalence varies by race and perhaps region

Primary Aldosteronism

- Adrenal adenoma versus hyperplasia
- Surgical versus medical treatment
- May recur or transition
  - Hyperplasia to adenoma
  - Bilateral disease
  - Some cases are familial

Genetic Forms of Hypertension

- Major advances in recent years
- All defined forms present as low renin hypertension
- Family history an important clue
- Single gene defects have been identified:
  - Epithelial sodium channel (Liddle)
  - Glucocorticoid-remedial aldosteronism
  - Apparent mineralocorticoid excess (11 beta OH SDH, type II)
  - Mineralocorticoid receptor defects (S829L)

ADDITIONAL READINGS
1. Izzo JL Jr, Black HR: Hypertension Primer (ed 3). Dallas, TX, Council on High Blood Pressure, American Heart Association, 2003

WORKUP: BASIC EVALUATION AND EXPANDED EVALUATION FOR SECONDARY CAUSES

Establish Diagnosis

- Repeated measurements:
  - Routine office measurements
  - Random zero and automated devices
  - Ambulatory 24-hour monitoring

Assess Concomitant Systemic Diseases

- Atherosclerosis, lipid profiling
- Diabetes
- Kidney function:
  - Estimated glomerular filtration rate (GFR)
  - Proteinuria
  - 24-Hour urine sodium as reflection of dietary intake

Assess Target Organ Effects

- Cardiovascular
  - Electrocardiography
  - 2-Dimensional echocardiography
- Cerebrovascular
- Eyes
- Kidney function
  - Estimated GFR
  - Proteinuria: microalbuminuria
Renin Profiling in High-Risk Groups

- Distinguish between primary ("essential") and other forms of hypertension
- Elevated plasma renin on adequate salt intake suggests some form of local ischemia:
  - Renal artery stenosis
  - Vasculitides
  - Primary kidney disease like glomerulonephritis
- Suppressed plasma renin on adequate salt intake:
  - Low renin hypertension
  - Monogenic forms of hypertension
  - Kidney diseases accompanied by volume excess

Renal Artery Stenosis

- Intermediate test of moderate sensitivity and specificity
- Magnetic resonance angiography
- Ultrasonography for kidney size and echogenicity
- Color Doppler assessment of resistive indices
- Captoril renal scans
- Selective renal arteriography remains the gold standard
- Assessment of pressure drop across the lesion
- Evaluation of ostial, main stem, and branch lesions
- Percutaneous transluminal angioplasty with or without stenting
- Vascular reconstruction and repair

Monogenic Forms of Hypertension

- Family history important clue
- Plasma renin profile and aldosterone may be helpful
- Profoundly suppressed aldosterone in Liddle syndrome
- Suppressed renin in other forms of monogenic hypertension
- Special testing from reference laboratories for unusual steroid metabolites
- Mutational analysis in targeted pedigrees

ADDITIONAL READINGS

TREATMENT (ESSENTIAL AND SECONDARY)

Goals of Treatment

- Reduction of cardiovascular morbidity and mortality related to untreated hypertension
- Delayed progression of proteinuric renal disease

JNC-7

- Prehypertension: Nonpharmacologic changes, sodium restriction, lifestyle
- Target of drug therapy: <140/90 mm Hg
- High-risk individuals: Diabetes, proteinuric renal failure (lower goals: <130/80 mm Hg)

NKF/K-DOQI

- National Kidney Foundation–Kidney Disease Outcomes Quality Initiative
- Guidelines regarding management of hypertension in renal disease published May 2004

Essential Hypertension

- Nonpharmacologic therapy:
  - Recommended for all individuals
  - Reduction of sodium intake, body weight, increased potassium intake, withholding smoking
- Interaction with body weight, activity, glucose intolerance: Metabolic syndrome
- Pharmacologic therapy:
  - Specific drug classes:
    - Diuretics: JNC-7 argues that trial data support unbeaten efficacy and safety for uncomplicated hypertension (Anti-hypertensive and Lipid-Lowering
Treatment to Prevent Heart Attack Trial [ALLHAT]3).

- Angiotensin-converting enzyme (ACE) inhibitor therapy: Major additional role for reducing BP and cardiovascular risk in numerous groups (previous CVD: myocardial infarction, congestive heart failure) and proteinuric renal disease, particularly in diabetics (HOPE trial regarding reduction of cardiovascular risk in mild chronic kidney disease [CKD]4).
- NOTE: Multiple trials argue that ACE inhibition is more likely to reduce proteinuria and delay progression of renal disease, including in African Americans.5
- Angiotensin receptor blocker (ARB) therapy: Most data support similar arguments as above; some favor as primary class in type II diabetes mellitus.6,7
- Blocker therapy/α-β blockade: Recent studies confirm benefits with previous coronary disease, however, argue that ARBs may offer greater protection (LIFE trial8).
- Calcium channel blocker (CCB) therapy: Included in JNC recommendations on basis of placebo-controlled efficacy data (Sys-Eur9). Effective antihypertensives, but multiple trials argue that proteinuria may increase with dihydropyridine CCBs, as compared with therapy with ACE inhibitors.3,10
- Data from Europe argue that combinations with ACE inhibitors allow both better BP control and reduced proteinuria.11 Non-dihydropyridine agents are less potent as antihypertensives, but are not associated with proteinuria.
- Peripheral α antagonists: Effective antihypertensive agents, but associated with excessive congestive heart failure admissions when used as primary agents in ALLHAT.12
- Centrally acting sympatholytic agents
- Peripheral vasodilating agents: Minoxidil, hydralazine
- Aldosterone antagonists: Spironolactone/spironolactone/eplerenone: Effective and safe for hypertension, but caution for hyperkalemia, particularly in diabetics with impaired renal function who are taking ACE inhibitors.13,14

Proven Benefits of Therapy
- Prevention of progression of hypertension: Stabilization of BP
- Reduction in stroke risk: Isolated, elderly, role of age
- Reduction in cardiovascular risk: Congestive heart failure, myocardial infarction
- Less consistent outcomes: Progression of renal disease15
- Established benefits in proteinuric renal disease: Modification of diet in renal disease (MDRD), ramipril efficacy in nephropathy (REIN), diabetes
- Questionable efficacy in slowing progression in nonproteinuric renal disease: MDRD, African American Study of Kidney Disease and Hypertension (AASK),16 ALLHAT

Special Situations in Therapy

Compelling indications
- Specific drug classes are indicated for identified complications of hypertension, based on outcome data from clinical trials:
  - Ischemic heart disease complicated by hypertension
    - Most common form of target organ damage from hypertension
    - Stable angina is benefited by β blockers and long-acting calcium CCBs.
    - Unstable angina and acute coronary syndromes are best treated with β blockers and ACE inhibitors.
    - Following myocardial infarction, secondary prevention results have been demonstrated with β blockers, ACE inhibitors, and aldosterone antagonists.
  - Heart failure complicated by hypertension
    - Asymptomatic patients can be treated with β blockers and ACE inhibitors.
    - Symptomatic patients are best treated with ACE inhibitors, ARBs, aldosterone antagonists, and diuretics; hyperkalemia is a frequent complication of this approach.
Hypertension in the setting of diastolic dysfunction may respond best to rate control with β blockers and the nonhydropyridine forms of CCBs.

Diabetes: More than a single drug needed to reach the target goal of 130/80 mm Hg
- Thiazide diuretics, β blockers, ACE inhibitors, ARBs, and CCBs have been shown to reduce the incidence of stroke and CVD in diabetics.
- ACE inhibitors and/or ARBs are the first-choice therapy for diabetics who have albuminuria or overt nephropathy; ARBs have been shown to slow the progression of microalbuminuria overt nephropathy.

Hypertension in the setting of CKD
- In patients with GFR <60 mL/min/1.73 m² or the presence of albuminuria (>300 mg/d, or >200 mg/g creatinine), goal is to slow progression of CKD and prevent CVD.
- Three or more drugs, including diuretics, may be needed to reach BP target of 130/80 mm Hg.
- ACE inhibitors and/or ARBs have been shown to slow the progression of CKD and are first-line therapies.
- Dietary salt restriction is an important component of BP control in CKD.

Cerebrovascular disease
- Primary and secondary prevention of stroke has been demonstrated with thiazides and ACE inhibitors.
- Management of acute strokes should not be overaggressive due to deranged autoregulation; BP target of 160/100 mm Hg appears to be adequate.

Special populations
- Minority populations
  - Access to health care and social-economic issue may impact success of BP control.
  - African Americans have increased prevalence, severity, and target organ events due to hypertension; angioedema caused by ACE inhibitors is 2 to 4 more times frequent than in other populations.
  - Monotherapy may well be unsuccessful; even in multiple drug therapy studies, the outcome event rates may be less favorable in minority populations.
- Obesity and metabolic syndrome reflect lifestyle issues
- Left ventricular hypertrophy
  - Independent risk factor for CVD
  - Regression of left ventricular hypertrophy can occur with aggressive BP control, weight loss, and salt restriction.
- Hypertension in the elderly
  - Systolic hypertension is a frequent occurrence:
    - May reflect reduced arterial vascular compliance
    - Responds to thiazide diuretics and CCBs, often at lower initial doses
- Hypertension in women
  - Risk of hypertension increases with duration of oral contraceptive use
  - Some classes of antihypertensive agents must be avoided in pregnancy and if pregnancy is being considered (eg, ACE inhibitors and ARBs); preferred agents include β blockers, CCBs, and methyl-dihydroxyphenylalanine.

SECONDARY HYPERTENSION

Hypertension in CKD
- Role in cardiovascular risk and mortality
  - Left ventricular hypertrophy, congestive heart failure in advanced CKD
  - Diabetic nephropathy

Renovascular Disease and Renovascular Hypertension
- Epidemiology and prevalence: Recognition of widespread disease
- Recognition of potential for progression
- Inclusion in medical management of cardiovascular/atherosclerotic disease
- Incidental disease/need for caution
- Clinical syndromes encountered:
  - Accelerated hypertension
  - Deteriorating kidney function during antihypertensive therapy
  - Fluid retention/refractory or “flash” pulmonary edema
  - Advanced renal failure with bilateral disease/solitary functioning kidney
Realistic expectations from renal revascularization: Improved BP, possible stabilization of renal function/distinction between fibromuscular disease and atherosclerosis

Evolution of endovascular stent therapy: Recognition of complications and benefits

Evolution of surgical methods/recognition of nephrectomy value in selected cases

Adrenal Disorders: Primary Aldosterone Excess

- Recognition of epidemiology/predilection for missing this diagnosis: Impact of aldosterone/renin ratio: Benefits and risks
- Prevalence in resistant hypertension series
- Options for specific therapy:
  - Spironolactone
  - Eplerenone
  - Amiloride
- Surgical intervention/laparoscopic methods
- Recognition and distinction between other hypokalemic syndromes including monogenic hypertension: Liddle syndrome

Pheochromocytoma

- Recognition as confounder/paroxysmal hypertension
- Current considerations regarding diagnosis: Use of metanephrines
- Surgical intervention

Other Secondary Hypertension

- Ureteral obstruction syndromes
- Coarctation of the aorta: Important consideration in young adults
- Oral contraceptives
- Drugs: Cocaine/over-the-counter supplements
- Pregnancy
- Hypertension after transplantation
- Role of nonsteroidal anti-inflammatory drugs/erythropoietin/calcineurin inhibitors/steroids regarding BP control
- Role of chemotherapeutic agents: Leuprolide acetate/tamoxifen
- Diabetic nephropathy/interactions with metabolic syndrome
- Sleep apnea syndromes: Role of intervention

Treatment-Resistant Hypertension

- Mechanisms of treatment failure resistance
- Volume assessment/hemodynamic measurement
- BP/target dissociation
- Compliance issues in therapy

Hypertensive Urgencies/Emergencies

- Definition: based on time-to-intervention requirement:
  - Emergencies: BP reduction in minutes:
    - Neurologic, including subarachnoid hemorrhage, hypertensive encephalopathy, head trauma
    - Cardiac: Acute coronary syndromes, pulmonary edema
    - Vascular: Aortic dissection, recent vascular surgery
- Treatment:
  - Oral agents: Difficult to control: Nifedipine, nicardipine, clonidine, labetalol, hydralazine
  - Intravenous agents: Nitroprusside, labetalol, enalapril, nicardipine, fenoldopam, nitroglycerin
- Situations not considered emergencies: Thrombotic stroke, asymptomatic hypertension, CKD

REFERENCES