CORE CURRICULUM IN NEPHROLOGY

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

1. Chobanian AV, Bakris GL, Black HR, et al: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 42:1206-1252, 2003

2. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R: Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 360:1903-1913, 2002

3. Vasan RS, Larson MG, Leip EP, et al: Impact of high-normal blood pressure on the risk of cardiovascular disease. N Engl J Med 345:1291-1297, 2001

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

From the Nephrology Research and Training Center, and Division of Nephrology, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL; and the Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN.

Address reprint requests to David G. Warnock, MD, Room 647 THT, 1530 3rd Avenue South, UAB Station, University of Alabama at Birmingham, Birmingham, AL 35213. E-mail: dwarnock@uab.edu

0272-6386/04/4402-0031$30.00/0

doi:10.1053/j.ajkd.2004.06.002

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

2. Lifton RP, Gharavi AG, Geller DS: Molecular mechanisms of human hypertension. Cell 104:545-556, 2001

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 osteal, 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

1. Chobanian AV, Bakris GL, Black HR, et al: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 42:1206-1252, 2003

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

3. National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Am J Kidney Dis 39:S1-S266, 2002 (suppl 1)

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

- Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension (full document regarding therapy[1])
  - 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[2]

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 (Antihypertensive 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]
- β-Blocker therapy/α-β blockade: Recent studies confirm benefits with previous coronary disease, however, argue that ARBs may offer greater protection (LIFE trial[8]).
- Calcium channel blocker (CCB) therapy: Included in JNC recommendations on basis of placebo-controlled efficacy data (Sys-Eur[9]). Effective antihypertensives, but multiple trials argue that proteinuria may increase with dihydropyridine CCBs, as compared with therapy with ACE inhibitors.[5,10] 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/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 disease[15]
  - 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 $<$60 mL/min/1.73 m^2 or the presence of albuminuria ($>$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 methyldihydroxyphenylalanine.

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[17]

- Epidemiology and prevalence: Recognition of widespread disease
- Recognition of potential for progression[18]
- Inclusion in medical management of cardiovascular/atherosclerotic disease
- Incidental disease/need for caution[19]
- 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[20,21]
- Evolution of surgical methods/recognition of nephrectomy value in selected cases

Adrenal Disorders: Primary Aldosterone Excess[22]

- Recognition of epidemiology/predilection for missing this diagnosis: Impact of aldosterone/renin ratio: Benefits and risks[23]
- Prevalence in resistant hypertension series[24]
- Options for specific therapy:
  - Spironolactone
  - Eplerenone[13]
  - Amiloride
- Surgical intervention/laparoscopic methods
- Recognition and distinction between other hypokalemic syndromes including monogenic hypertension: Liddle syndrome

Pheochromocytoma

- Recognition as confounder/paroxysmal hypertension[25]
- Current considerations regarding diagnosis: Use of metanephrines[26]
- 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[27]

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

Hypertensive Urgencies/Emergencies[28]

- 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

1. Chobanian AV, Bakris GL, Black HR, et al: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (Complete Version). Hypertension 42:1206-1252, 2003

2. Abosaif NY, Arije A, Atray NK, et al: K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis 43:S1-S290, 2004 (suppl 1)

3. ALLHAT officers: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 288:2981-2997, 2002

4. Mann JFE, Gerstein HC, Pogue J, Bosch J, Yusuf S and the HOPE investigators: Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: The HOPE randomized trial. Ann Intern Med 134:629-636, 2001

5. Agodoa LY, Appel L, Bakris GL, et al: Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis. JAMA 285:2719-2728, 2001

6. Brenner BM, Cooper ME, de Zeeuw D, et al for the RENAAL Study investigators: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 345:861-869, 2001

7. Lewis EJ, Hunsicker LG, Clarke WR, et al: Renopro-

tective effect of the angiotensin-receptor antagonist irbesartan in patient with nephropathy due to type 2 diabetes. N Engl J Med 345:851-860, 2001

8. Dahlof L, Devereux R, Kjeldsen SE, et al: Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): A randomized trial against atenolol. Lancet 359:995-1003, 2002

9. Neal B, MacMahon S, Chapman NF: Effects of ACE inhibitors, calcium antagonists, and other blood pressure lowering drugs: Results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists Collaboration. Lancet 356:1955-1964, 2000

10. Maki DD, Ma JZ, Louis TA, Kasiske BL: Long-term effects of antihypertensive agents on proteinuria and renal function. Arch Intern Med 155:1073-1080, 1995

11. Fogari R, Preti P, Zoppi A, et al: Effects of amlodipine fosinopril combination on microalbuminuria in hypertensive type 2 diabetic patients. Am J Hypertens 15:1042-1049, 2002

12. ALLHAT: Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone. JAMA 283:1967-1975, 2000

13. Pitt B, Remme W, Zamad F, et al: Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 348:1309-1321, 2003

14. Lim PO, Jung RT, MacDonald TM: Is aldosterone the missing link in refractory hypertension? Aldosterone-to-renin ratio as a marker of inappropriate aldosterone activity. J Hum Hypertens 16:153-158, 2002

15. Ruggenenti P, Perna A, Gherardi G, et al: Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. Lancet 354:359-364, 1999

16. Wright JT, Bakris G, Greene T, et al: Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease. JAMA 288:2421-2431, 2002

17. Textor SC, McKusick M: Renovascular hypertension and ischemic nephropathy: Angioplasty and stenting, in Brady HR, Wilcox CS (eds): Therapy in Nephrology and Hypertension (ed 2). Philadelphia, PA, Saunders, 2003, pp 599-609

18. Textor SC: Renovascular hypertension, in Johnson RJ, Feehally J (eds): Comprehensive Clinical Nephrology. London, UK, Mosby, 2000, pp 41.1-41.12

19. Chabova V, Schirger A, Stanson AW, McKusick M, Textor SC: Outcomes of atherosclerotic renal artery stenosis managed without revascularization. Mayo Clin Proc 75:437-444, 2000

20. Isles CG, Robertson S, Hill D: Management of renovascular disease: A review of renal artery stenting in ten studies. Q J Med 92:159-167, 1999

21. Dorros G, Jaff M, Mathiak L, He T: Multicenter Palmaz stent renal artery stenosis revascularization registry report: Four-year follow-up of 1,058 successful patients. Multicenter Registry Participants. Catheter and Cardiovasc Interv 55:182-188, 2002

22. Young WF Jr: Primary aldosteronism: A common and curable form of hypertension. Cardiol Rev 7:207-214, 1999

23. Calhoun DA, Nishizaka MK, Zaman MA, Thakkar RB, Weissmann P: Hyperaldosteronism among black and white subjects with resistant hypertension. Hypertension 40:892-896, 2002

24. Mosso L, Carvajal C, Gonzalez A, et al: Primary aldosteronism and hypertensive disease. Hypertension 42: 161-165, 2003

25. Young WF Jr: Pheochromocytoma and primary aldosteronism: Diagnostic approaches. Endocrinol Metab Clin North Am 26:801-827, 1997

26. Lenders JWM, Pacak K, Walther MM, et al: Biochemical diagnosis of pheochromocytoma: Which test is best? JAMA 287:1427-1434, 2002

27. Taler SJ, Textor SC, Augustine JE: Resistant hypertension: Comparing hemodynamic management to specialist care. Hypertension 39:982-988, 2002

28. Elliott WJ: Hypertensive urgencies, in Bakris GL (ed): The Kidney and Hypertension. London, UK, Martin Dunitz, 2004, pp 139-154