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The Crux

BIMONTHLY FORUM FOR THE LABORATARIANS

CONTENTS

Editorial

The Tulip group and the ever increasing family wishes you a very happy new year. We pray that problems never prey on you - not now, not ever. Diagnostic and related interpretational problems are the fields where we can definitely assist you. Remember, we have almost everything under one roof. Your single window contact for all laboratory related aspects. No more a toddler, we have completed eight years of this selfless service to our professional brethrens. WE assure this and our other corporate social responsibilities shall continue with a greater force and zeal.

ENJOY THIS EXTENDED VERSION OF YOUR OWN The Crux

This issue touches an extremely important disease segment that afflicts millions or perhaps (with the current population levels) billions? What comes to your mind? Hypertension ? Yes, this is discussed in ample detail under the "DISEASE DIAGNOSIS" segment. Hypertension (HTN) or **high blood pressure** is a cardiac chronic medical condition in which the systemic arterial blood pressure is elevated. What that means is that the heart is having to work harder than it should to pump the blood around the body. Blood pressure involves two measurements, systolic and diastolic. Normal blood pressure is at or below 120/80 mmHg. The first figure is the systolic blood pressure, the pressure in the arteries when your heart is contracting. The second, or lower figure, is the diastolic blood pressure, which is the pressure in your arteries between heart beats. High blood pressure is anything above 140/90 mmHg. Hypertension is the opposite of hypotension. Hypertension is classified as either primary (essential) hypertension or secondary hypertension; about 90–95% of cases are categorized as "primary hypertension," which means high blood pressure with no obvious medical cause. The remaining 5–10% of cases (Secondary hypertension) are caused by other conditions that affect the kidneys, arteries, heart or endocrine system.

Persistent hypertension is one of the risk factors for stroke, myocardial infarction, heart failure and arterial aneurysm, and is a leading cause of chronic kidney failure. Moderate elevation of arterial blood pressure leads to shortened life expectancy. Dietary and lifestyle changes can improve blood pressure control and decrease the risk of associated health complications, although drug treatment may prove necessary in patients for whom lifestyle changes prove ineffective or insufficient. All related clinico-diagnostic aspects are given within the covers of this communique.

"INTERPRETATION" lays LIPOREPROTEINS threadbare for you. What are they and what is their utility in relation to coronary arterial disease is presented in a nicely and easily assimilable format.

What if? Yes, what if a Laboratarian is exposed to blood or potentially infectious body fluids while at work place. Answers to this question are given inside, just flip a few pages and look for **"TROUBLE SHOOTING".**

Did I forget anything? No I haven't! **"BOUQUET"** is flying around within. Take a peep!

TÜV MANAGEMENT SERVICE ISO 9001

Tulip Group

DISEASE DIAGNOSIS

HYPERTENSION

INTRODUCTION

Hypertension is one of the most common worldwide diseases afflicting humans. Because of the associated morbidity and mortality and the cost to society, hypertension is an important public health challenge. Over the past several decades, extensive research, widespread patient education, and a concerted effort on the part of health care professionals have led to decreased mortality and morbidity rates from the multiple organ damage arising from years of untreated hypertension. Approximately 30% of adults are still unaware of their hypertension; up to 40% of people with hypertension are not receiving treatment; and, of those treated, up to 67% do not have their blood pressure (BP) controlled to less than 140/90 mm Hg. Hypertension is the most important modifiable risk factor for coronary heart disease (the leading cause of death internaionally), stroke, congestive heart failure, end-stage renal disease, and peripheral vascular disease. Therefore, health care professionals must not only identify and treat patients with hypertension but also promote a healthy lifestyle and preventive strategies to decrease the prevalence of hypertension in the general population.

Definition and classification: Defining abnormally high blood pressure is extremely difficult and arbitrary. Furthermore, the relationship between systemic arterial pressure and morbidity appears to be quantitative rather than qualitative. A level for high BP must be agreed upon in clinical practice for screening patients with hypertension and for instituting diagnostic evaluation and initiating therapy. Because the risk to an individual patient may correlate with the severity of hypertension, a classification system is essential for making decisions about aggressiveness of treatment or therapeutic interventions. (See Clinical Presentation.) The classification of BP (expressed in mm Hg) for adults aged 18 years or older is as follows: Normal - Systolic lower than 120, diastolic lower than 80; Prehypertension - Systolic 120-139, diastolic 80-90; Stage 1 - Systolic 140-159, diastolic 90-99; Stage 2 - Systolic equal to or more than 160, diastolic equal to or more than 100. The classification above is based on the average of 2 or more readings taken at each of 2 or more visits after initial screening. Normal BP with respect to cardiovascular risk is less than 120/80 mm Hg. However, unusually low readings should be evaluated for clinical significance. Prehypertension, a new category designated in the international fora report, emphasizes that patients with prehypertension are at risk for progression to hypertension and that lifestyle modifications are important preventive strategies. From another perspective, hypertension may be categorized as either essential or secondary. Essential hypertension is diagnosed in the absence of an identifiable secondary cause. Approximately 95% of the adults with hypertension have essential hypertension, while secondary hypertension accounts for fewer than 5% of the cases. However, secondary forms of hypertension, such as primary hyperaldosteronism, account for 20% of resistant hypertension (hypertension that requires 4 or more medications to control). Especially severe cases of hypertension may be further categorized. Severe hypertension is defined by a blood pressure above 180/110 without symptoms. Hypertensive urgency is defined as a BP above 180/110 with mild end organ effects, such as headache and dyspnea. Hypertensive emergency is a BP of 220/140 or greater with life-threatening end-organ dysfunction. Hypertensive emergencies encompass a spectrum of clinical presentations in which uncontrolled BPs lead to progressive or impending end-organ dysfunction; in these conditions, the BP should be lowered aggressively over minutes to hours. Acute end-organ damage in the setting of a hypertensive emergency may include the following : Neurologic - Hypertensive encephalopathy, cerebral vascular accident/cerebral infarction. subarachnoid hemorrhage, intracranial hemorrhage, Cardiovascular - Myocardial ischemia/infarction, acute left ventricular dysfunction, acute pulmonary edema, aortic dissection, Other - Acute renal failure/insufficiency, retinopathy, eclampsia, microangiopathic hemolytic anemia.

Pathophysiology: The pathogenesis of essential hypertension is multifactorial and highly complex. Multiple factors modulate the blood pressure (BP) for adequate tissue perfusion and include humoral mediators, vascular reactivity, circulating blood volume, vascular caliber, blood viscosity, cardiac output, blood vessel elasticity, and neural stimulation. A possible pathogenesis of essential hypertension has been proposed in which multiple factors, including genetic predisposition, excess dietary salt intake, and adrenergic tone, may interact to produce hypertension. Although genetics appears to contribute to essential hypertension, the exact mechanism has not been established. The natural history of essential hypertension evolves from occasional to established hypertension. After a long invariable asymptomatic period, persistent hypertension develops into complicated hypertension, in which target organ damage to the aorta and small arteries, heart, kidneys, retina, and central nervous system is evident. The progression begins with prehypertension in persons aged 10-30 years (by increased cardiac output) to early hypertension in persons aged 20-40 years (in which increased peripheral resistance is prominent) to established hypertension in persons aged 30-50 years, and, finally, to complicated hypertension in persons aged 40-60 years. One mechanism of hypertension has been described as high-output hypertension. High-output hypertension results from decreased peripheral vascular resistance and concomitant cardiac stimulation by adrenergic hyperactivity and altered calcium homeostasis. A second mechanism manifests with normal or reduced cardiac output and elevated systemic vascular resistance due to increased vasoreactivity. Another (and overlapping) mechanism is increased salt and water reabsorption (salt sensitivity) by the kidney, which increases circulating blood volume.

Etiology: Hypertension may be primary, which may develop as a result of environmental or genetic causes, or secondary, which has multiple etiologies, including renal, vascular, and endocrine causes. Hypertensive emergencies are most often precipitated by inadequate medication or poor compliance.

Environmental and genetic causes: Hypertension develops secondary to environmental factors, as well as to multiple genes, whose inheritance appears to be complex. Very rare secondary causes are related to single genes and include Liddle syndrome, glucocorticoid-remediable hyperaldosteronism, 11 beta-hydroxylase and 17 alpha-hydroxylase deficiencies, the syndrome of apparent mineralocorticoid excess, and pseudohypoaldosteronism type II. Primary or essential hypertension accounts for 90-95% of adult cases, and a small percentage of patients (2-10%) have a secondary cause.

Causes of secondary hypertension:

Renal causes (2.5-6%) include the renal parenchymal diseases and renal vascular diseases, as follows: Polycystic kidney disease, Chronic kidney disease, Urinary tract obstruction, Renin-producing tumor, Liddle syndrome. Renovascular hypertension (RVHT) causes 0.2-4% of cases. Since Goldblatt's seminal experiment in 1934, RVHT has become increasingly recognized as an important cause of clinically atypical hypertension and chronic kidney disease, the latter by virtue of renal ischemia. The coexistence of renal arterial vascular (ie, renovascular) disease and hypertension roughly defines this type of nonessential hypertension. More specific diagnoses are made retrospectively when hypertension is improved after intravascular intervention.

Vascular causes include the following: Coarctation of aorta, Vasculitis, Collagen-vascular disease.

Endocrine causes account for 1-2% and include exogenous or endogenous hormonal imbalances. Exogenous causes include administration of steroids. The most common form of secondary hypertension is an endocrine cause: oral contraceptive use. Activation of the renin-angiotensin-aldosterone system is the likely mechanism because hepatic synthesis of angiotensinogen is induced by the estrogen component of oral contraceptives. Approximately 5% of women prescribed oral contraceptives may develop hypertension, which abates within 6 months of discontinuation. The risk factors for oral contraceptive–associated hypertension include mild renal disease, familial history of essential hypertension, age older than 35 years, and obesity. Exogenous administration of the other steroids used for therapeutic purposes also increases blood pressure, especially in susceptible individuals, mainly by volume expansion. Nonsteroidal anti-inflammatory drugs (NSAIDs) may also have adverse effects on blood pressure. NSAIDs block both cyclooxygenase-1 (COX-1) and COX-2 enzymes. The inhibition of COX-2 can inhibit its natriuretic effect, which, in turn, increases sodium retention. NSAIDs also inhibit the vasodilating effects of prostaglandins and the production of vasoconstricting factors, namely endothelin-1. These effects can contribute to the induction of hypertension in a

normotensive and/or controlled hypertensive patient.

Endogenous hormonal causes include the following: Primary hyperaldosteronism, Cushing syndrome, Pheochromocytoma, Congenital adrenal hyperplasia.

Neurogenic causes include the following: Brain tumor, Bulbar poliomyelitis, Intracranial hypertension.

Drugs and toxins that cause hypertension include the following: Alcohol, Cocaine, Cyclosporine tacrolimus, NSAIDs, Erythropoietin, Adrenergic medications, Decongestants containing ephedrine, Herbal remedies containing licorice or ephedrine.

Other causes include the following: Hyperthyroidism and hypothyroidism, Hypercalcemia, Hyperparathyroidism, Acromegaly, Obstructive sleep apnea, Pregnancy-induced hypertension.

Causes of hypertensive emergencies: The most common hypertensive emergency is a rapid unexplained rise in BP in a patient with chronic essential hypertension. Most patients who develop hypertensive emergencies have a history of inadequate hypertensive treatment or an abrupt discontinuation of their medications. Other causes of hypertensive emergencies include the use of recreational drugs, abrupt clonidine withdrawal, post pheochromocytoma removal, and systemic sclerosis. Other causes include the following: Renal parenchymal disease - Chronic pyelonephritis, primary glomerulonephritis, tubulointerstitial nephritis (accounts for 80% of all secondary causes). Systemic disorders with renal involvement - Systemic lupus erythematosus, systemic sclerosis, vasculitides. Renovascular disease - Atherosclerotic disease, fibromuscular dysplasia, polyarteritis nodosa. Endocrine disease - Pheochromocytoma, Cushing syndrome, primary hyperaldosteronism. Drugs - Cocaine, amphetamines, cyclosporine, clonidine withdrawal, phencyclidine, diet pills, oral contraceptive pills. Drug interactions - Monoamine oxidase inhibitors with tricyclic antidepressants, antihistamines, or tyramine-containing food. Central nervous system (CNS) factors - CNS trauma or spinal cord disorders, such as Guillain-Barré syndrome, Coarctation of the aorta, Preeclampsia/eclampsia, Postoperative hypertension.

Epidemiology: Hypertension is a worldwide epidemic; accordingly, its epidemiology has been well studied. In many countries, 50% of the population older than 60 years has hypertension. Overall, approximately 20% of the world's adults are estimated to have hypertension. The 20% prevalence is for hypertension defined as BP in excess of 140/90 mm Hg. The prevalence dramatically increases in patients older than 60 years.

Prognosis: Most individuals diagnosed with hypertension will have increasing BP as they age. Untreated hypertension is notorious for increasing the risk of mortality and is often described as a silent killer. Mild-to-moderate hypertension, if left untreated, is associated with a risk of atherosclerotic disease in 30% of people and organ damage in 50% of people after only 8-10 years of onset. Death from both ischemic heart disease and stroke increase progressively as BP increases. For every 20 mm Hg systolic or 10 mm Hg diastolic increase in BP above 115/75 mm Hg, the mortality rate for both ischemic heart disease and stroke doubles. The morbidity and mortality of hypertensive emergencies depend on the extent of end-organ dysfunction on presentation and the degree to which BP is controlled subsequently. With BP control and medication compliance, the 10-year survival rate of patients with hypertensive crises approaches 70%. Nephrosclerosis is one of the possible complications of long-standing hypertension. The risk of hypertension-induced end-stage renal disease is higher in black patients, even when blood pressure is under good control. Furthermore, patients with diabetic nephropathy who are hypertensive are also at high risk for developing end-stage renal disease.

Patient Education: Hypertension is a lifelong disorder. For optimal control, a long-term commitment to lifestyle modifications and pharmacological therapy is required. Therefore, repeated in-depth patient education and counseling not only improve compliance with medical therapy but also reduce cardiovascular risk factors. Various strategies to decrease cardiovascular disease risk include the following: Prevention and treatment of obesity, Appropriate amounts of aerobic physical activity, Diets low in salt, total fat, and cholesterol, Adequate dietary intakes of potassium, calcium, and magnesium, Limited alcohol consumption, Avoidance of cigarette smoking, Avoidance of the use of illicit drugs, such as cocaine.

CLINICAL

History: Following the documentation of hypertension, which is confirmed after an elevated blood pressure (BP) on at least 3 separate occasions (based on the average of 2 or more readings taken at each of 2 or more visits after initial screening), a detailed history should extract the following information: Extent of target organ damage, Assessment of patients' cardiovascular risk status, Exclusion of secondary causes of hypertension, Patients may have undiagnosed hypertension for years without having had their BP checked. Therefore, a careful history of end organ damage should be obtained. A history of cardiovascular risk factors includes hypercholesterolemia, diabetes mellitus, and tobacco use (including chewing tobacco). Obtain a history of the patient's use of over-the-counter medications; herbal medicines such as herbal tea containing licorice; ephedrine; current and previous unsuccessful antihypertensive medication trials; oral contraceptives; ethanol; and illicit drugs such as cocaine. The historical and physical findings that suggest the possibility of secondary hypertension are a history of known renal disease, abdominal masses, anemia, and urochrome pigmentation. A history of sweating, labile hypertension, and palpitations suggests the diagnosis of pheochromocytoma. A history of cold or heat tolerance, sweating, lack of energy, and bradycardia or tachycardia may indicate hypothyroidism or hyperthyroidism. A history of obstructive sleep apnea may be noted. A history of weakness suggests hyperaldosteronism. Kidney stones raise the possibility of hyperparathyroidism.

Physical Examination: An accurate measurement of blood pressure is the key to diagnosis. Several determinations should be made over a period of several weeks. At any given visit, an average of 3 blood pressure readings taken 2 minutes apart using a mercury manometer is preferable. On the first visit, blood pressure should be checked in both arms and in one leg to avoid missing the diagnosis of coarctation of aorta or subclavian artery stenosis. The patient should rest quietly for at least 5 minutes before the measurement. Blood pressure should be measured in both the supine and sitting positions, auscultating with the bell of the stethoscope. As the improper cuff size may influence blood pressure measurement, a wider cuff is preferable, particularly if the patient's arm circumference exceeds 30 cm. Although somewhat controversial, the common practice is to document phase V (a disappearance of all sounds) of Korotkoff sounds as the diastolic pressure. Ambulatory or home blood pressure monitoring provides a more accurate prediction of cardiovascular risk than do office blood pressure readings. "Non-dipping" is the loss of the usual physiologic nocturnal drop in blood pressure and is associated with an increased cardiovascular risk. A funduscopic evaluation of the eyes should be performed to detect any evidence of early or late, chronic or acute hypertensive retinopathy, including AV nicking or changes in the vessel wall (eg, copper wiring, silver wiring, sot, hard exudates, flame-shaped hemorrhages, papilledema). Ocular changes can be the initial finding in an asymptomatic patient necessitating a primary care referral. Both acute and chronic changes may manifest in the eyes. On the other side, a symptomatic patient may be referred to the ophthalmologist for visual changes due to hypertensive changes. Palpation of all peripheral pulses should be performed. Absent, weak, or delayed femoral pulses suggests coarctation of the aorta or severe peripheral vascular disease. Listen for renal artery bruit over the upper abdomen; the presence of a bruit with both a systolic and diastolic component suggests renal artery stenosis. A careful cardiac examination is performed to evaluate signs of LVH. These include displacement of apex, a sustained and enlarged apical impulse, and the presence of an S_4. Occasionally, a tambour S_2 is heard with aortic root dilatation.

Hypertension and Cerebrovascular Disease: Long-standing hypertension may manifest as hemorrhagic and atheroembolic stroke or encephalopathy. Both the high systolic and diastolic pressures are harmful; a diastolic pressure of more than 100 mm Hg and a systolic pressure of more than 160 mm Hg have led to a significant incidence of strokes. Other cerebrovascular manifestations of complicated hypertension include hypertensive hemorrhage, hypertensive encephalopathy, lacunar-type infarctions, and dementia. Hypertensive encephalopathy is one of the clinical manifestations of cerebral edema and microhemorrhages seen with dysfunction of cerebral autoregulation and is characterized by hypertension, altered mentation, and papilledema.

Hypertensive Emergencies: The history and physical examination determine the nature, severity, and management of the hypertensive event. The history should focus on the presence of end-organ dysfunction, the circumstances surrounding the hypertension, and any identifiable etiology. The physical examination should assess whether end-organ dysfunction is present. BP should be measured in both the supine position and the standing position (assess volume depletion). BP should also be measured in both arms (a significant difference may suggest aortic dissection). The most common clinical presentations of hypertensive emergencies are cerebral infarction (24.5%), pulmonary edema (22.5%), hypertensive encephalopathy (16.3%), and congestive heart failure (12%). Other clinical presentations associated with hypertensive emergencies include intracranial hemorrhage, aortic dissection, and eclampsia, as well as acute myocardial infarction.

Hypertensive Heart Disease: Uncontrolled and prolonged BP elevation can lead to a variety of changes in the myocardial structure, coronary vasculature, and conduction system of the heart. These changes in turn can lead to the development of left ventricular hypertrophy (LVH), coronary artery disease, various conduction system diseases, and systolic and diastolic dysfunction of the myocardium, which manifest clinically as angina or myocardial infarction, cardiac arrhythmias (especially atrial fibrillation), and congestive heart failure (CHF). Thus, hypertensive heart disease is a term applied generally to heart diseases—such as LVH, coronary artery disease, cardiac arrhythmias, and CHF—that are caused by direct or indirect effects of elevated BP. Although these diseases generally develop in response to chronically elevated BP, marked and acute elevation of BP can also lead to accentuation of an underlying predisposition to any of the symptoms traditionally associated with chronic hypertension.

Hypertension in Pediatric Patients: Recent advances in the ability to identify, evaluate, and care for infants with hypertension, coupled with advances in the practice of neonatology in general, have led to an increased awareness of hypertension in modern neonatal ICUs (NICUs) since its first description in the 1970s. The true incidence of hypertension in the pediatric population is not known. Hypertension is now commonly discovered in children. The long-term health risks to these children with hypertension may be substantial. Systemic hypertension is less common in children than in adults, but the incidence of hypertension in children is approximately 1-5%. The presence of hypertension in younger children is usually indicative of an underlying disease process (secondary hypertension). In children, approximately 5-25% of secondary hypertension is attributed to renovascular disease.

Hypertension in Pregnancy: Hypertension is the most common medical problem encountered during pregnancy, complicating 2-3% of pregnancies. Hypertensive disorders during pregnancy are classified into the 4 following categories: Chronic hypertension, Preeclampsia-eclampsia, Preeclampsia superimposed on chronic hypertension, Gestational hypertension (transient hypertension of pregnancy or chronic hypertension identified in the latter half of pregnancy); this terminology is preferred over the older but widely used term pregnancy-induced hypertension (PIH) because it is more precise.

Primary Aldosteronism: Mineralocorticoid excess secondary to primary hyperaldosteronism is infrequently observed and is characterized by excessive production of aldosterone. Renal sodium retention, kaliuresis, hypokalemia, and hypochloremic metabolic alkalosis are the common manifestations. These patients develop increased intravascular volume, resulting in hypertension. The BP increase may vary from mild hypertension to marked elevation in primary hyperaldosteronism. Patients may have underlying adenoma or hyperplasia of the adrenal gland and rarely have an extra-adrenal source for aldosterone.

Diagnostic Considerations: Problems to be considered include the following: Steroid use, Use of over-the-counter or recreational sympathomimetic drugs, Pheochromocytoma, Acute vasculitis, Serotonin syndrome, Other CNS pathology, Coarctation of the aorta.

Differential Diagnosis: Anxiety Disorders, Apnea, Sleep, Cardiomyopathy Cocaine, Cardiomyopathy Hypertrophic, Congestive Heart Failure and Pulmonary Edema, Hyperaldosteronism, Primary, Hyperthyroidism, Thyroid Storm, and Graves Disease, Myocardial Infarction, Stroke Hemorrhagic, Stroke Ischemic, Toxicity Amphetamine, Toxicity Phencyclidine.

WORKUP

Approach Considerations: Digital subtraction angiography with arterial injection of radiocontrast dye is the criterion standard, but it carries the risk of dye nephropathy and atheroemboli in patients with diabetes or chronic kidney disease.

Routine Laboratory Studies: Unless a secondary cause for hypertension is suspected, only the following routine laboratory studies should be performed: Complete blood count (CBC), serum electrolytes, serum creatinine, serum glucose, uric acid, and urinalysis, Lipid profile (total cholesterol, low-density lipoprotein [LDL], high-density lipoprotein [HDL], and triglycerides).

Laboratory Studies in Hypertensive Emergencies: Electrolytes, blood urea nitrogen (BUN), and creatinine levels to are used to evaluate for renal impairment. CBC count and smear help to exclude microangiopathic anemia. Dipstick urinalysis can be used to detect hematuria or proteinuria (renal impairment), and microscopic urinalysis can be used to detect red blood cells (RBCs) or RBC casts (renal impairment). Optional studies include toxicology screen, pregnancy test, and endocrine testing.

Laboratory Studies for Assessment of Suspected Secondary Causes: Microalbuminuria is an early indication of diabetic nephropathy and is also a marker for a higher risk of cardiovascular morbidity and mortality. Present recommendations suggest that individuals with type I diabetes should be screened for microalbuminuria. Usefulness of this screening in hypertensive patients without diabetes has not been established. Measurement of the aldosterone/plasma renin activity ratio is performed to detect evidence of primary hyperaldosteronism. A ratio of more than 20-30 is suggestive of this condition. Hypokalemia and metabolic alkalosis are relatively late manifestations of this disorder. A 24-hour urine specimen should be collected for sodium and potassium measurement. If the urine sodium level is more than 100 mmol/L and urine potassium is less than 30 mmol/L, hyperaldosteronism is unlikely. If urinary potassium exceeds 30 mmol/L, the patient should have plasma renin activity (PRA) measured. If the PRA is high, the likely causes are estrogen therapy, renovascular hypertension, malignant hypertension, or salt-wasting renal disease. In the presence of low PRA, the serum aldosterone level can be measured. A low aldosterone level indicates licorice ingestion or other mineralocorticoid ingestions. A high aldosterone level indicates primary hyperaldosteronism. A CT scan may identify the presence of an adenoma. In the absence of CT scan findings, differentiating hyperplastic hyperaldosteronism from adenoma is often difficult. Determination of a sensitive thyroid-stimulating hormone (TSH) level excludes hypothyroidism or hyperthyroidism as a cause of hypertension. If pheochromocytoma is suspected, urinary catecholamines and fractionated metanephrines are the tests of choice. Plasma fractionated metanephrines have specificity, but their sensitivity is too low for screening purposes. Urinary vanillylmandelic acid (VMA) is no longer recommended because of its poor sensitivity and specificity.

Other Diagnostic Modalities include Echocardiography: The limited echocardiography study, rather than the complete examination, may detect left atrial dilatation, left ventricular hypertrophy (LVH), and diastolic or systolic left ventricular dysfunction more frequently than electrocardiography. The main indication for limited echocardiography is evaluation for end organ damage in a patient with borderline high BP. Therefore, the presence of LVH despite normal or borderline high BP measurements requires antihypertensive therapy. In addition, a stress echocardiogram can provide prognostic information in patients with hypertension and CAD.

Ultrasonography/ Nuclear Imaging/ Imaging Studies for Renovascular Stenosis and Ambulatory Blood Pressure Monitoring: Indications for ambulatory blood pressure monitoring include labile BP, a discrepancy between blood pressure measurements inside the physician's office and those outside it, and poor BP control. Ambulatory monitoring also identifies patients who have the distinct syndrome called white coat hypertension.

TREATMENT

Approach Considerations: Consider lifestyle modifications. As the cardiovascular disease risk factors are assessed in individuals with hypertension, pay attention to the lifestyles that favorably affect blood pressure (BP) level and reduce overall cardiovascular disease risk. A relatively small reduction in BP may affect the incidence of cardiovascular disease on a

standard, two or more antihypertensive drugs at maximal doses should be used to achieve optimal blood pressure targets in patients with diabetes and hypertension. Either an ACE inhibitor or an ARB is usually required in patients with diabetes and hypertension. If the patient cannot tolerate one class of drugs, the other should be tried. If needed to achieve blood pressure goals, a thiazide diuretic is indicated for those patients with an estimated GFR (eGFR) ≥30 mL/min/1.73 m2 and a loop diuretic for those with an eGFR < 30 mL/min/1.73 m2. Regardless of which antihypertensive drugs are used, kidney function and serum potassium levels should be monitored.

Surgical Treatment of Hypertension: Aortorenal bypass using a saphenous vein graft or a hypogastric artery is a revascularization technique for renovascular hypertension that has become much less common since the advent of renal artery angioplasty with stenting. Surgical resection is the treatment of choice for pheochromocytoma, because hypertension is cured by tumor resection. In patients with fibromuscular renal disease, angioplasty has a 60-80% success rate for improvement or cure of hypertension.

Management of Hypertensive Emergencies: The primary goal of the emergency physician is to determine which patients with acute hypertension are exhibiting symptoms of end-organ damage and require immediate intravenous (IV) parenteral therapy. The fundamental principle in determining the necessary emergency department (ED) care of the hypertensive patient is the presence or absence of end-organ dysfunction. Approximately 3-45% of adult ED patients have at least one increased BP during their stay in the ED. Many patients present to the ED with elevated BPs; however, only a small proportion of patients will require emergency treatment. In contrast, patients presenting with acutely elevated BPs (systolic BP >200 mm Hg or diastolic BP >120 mm Hg) without symptoms that are sustained throughout the ED stay and stay significantly elevated to this level on discharge should have initiation of medical therapy and close follow-up in the outpatient setting.

Treatment of Hypertension in Pediatric Patients: Usually, continuous IV infusions are the most appropriate initial therapy, especially in acutely ill infants with severe hypertension. The advantages of IV infusions are numerous, most importantly including the ability to quickly increase or decrease the rate of infusion to achieve the desired BP. As in patients of any age with malignant hypertension, take care to avoid too rapid a reduction in BP in order to avoid cerebral ischemia and hemorrhage; premature infants in particular are already at an increased risk because of the immaturity of their periventricular circulation. Because of the paucity of available data regarding the use of these agents in newborns, the choice of agent depends on the individual clinician's experience.

Treatment of Hypertension in Pregnancy: In normal pregnancy, women's MAP drops 10-15 mm Hg over the first half of pregnancy. Most women with mild chronic hypertension (ie, systolic BP 140-160 mm Hg, diastolic BP 90-100 mm Hg) have a similar decrease in BPs and may not require any medication during this period. Conversely, diastolic BP greater than 110 mm Hg has been associated with an increased risk of placental abruption and intrauterine growth restriction, and systolic BP greater than 160 mm Hg increases the risk of maternal intracerebral hemorrhage. Therefore, pregnant patients should be started on antihypertensive therapy if the systolic BP is greater than 160 mm Hg or the diastolic BP is greater than 100-105 mm Hg. The goal of pharmacologic treatment should be a diastolic BP of less than 100-105 mm Hg and a systolic BP less than 160 mm Hg. Women with preexisting end-organ damage from chronic hypertension should have a lower threshold for starting antihypertensive medication (ie, >139/89) and a lower target BP (< 140/90). Although the primary risk of chronic hypertension in pregnancy is development of superimposed preeclampsia, no evidence suggests that pharmacological treatment of mild hypertension reduces the incidence of preeclampsia in this population.

Treatment of Hypertension in the Elderly: The systolic pressure continues to rise progressively throughout life, reaching the highest levels in later stages of life. Isolated systolic hypertension may be present in 10% of the population aged 70 years and in 24% of those aged 80 years. Furthermore, severe arteriosclerosis may lead to pseudohypertension. Isolated hypertension results in low cardiac output because of the decreased stroke volume and high peripheral resistance. This may reduce glomerular filtration further, which is why low activity of renal angiotensin aldosterone cascade is encountered in elderly individuals who are hypertensive. Despite low PRA, blood pressure responds well to ACE inhibitor and ARB therapy. Low doses of diuretics may also be effective. Calcium antagonists are quite useful because of their strong antihypertensive effects. Often, combining 2 drugs at a lower dose may be preferable to using a single drug at a high dose that has the potential for adverse effects. The 2011 internationally acceptable document recommends starting the evaluation of the elderly patient with known or suspected hypertension with 3 measurements of blood pressure, to obtain an accurate BP value. If BP is elevated, the cause should be isolated. Any organ damage should be assessed. Other CVD risk factors or comorbid conditions should be identified, along with any potential barriers to treatment adherence. The 2011 collective clinical consensus advises against the routine use of laboratory testing in elderly patients. Instead, it recommends a more deliberative, focused approach. This would include a urinalysis for signs of renal damage (albuminuria/ microalbuminuria); blood chemistries (especially potassium and creatinine with eGFR); total cholesterol, LDL, HDL, and triglycerides; fasting blood sugar (A1c if diabetes mellitus is suspected; and an ECG. Also lifestyle modifications may be all that is necessary to treat milder forms of hypertension in elderly patients. However, drug treatment for elderly patients with hypertension is generally recommended and should be started at the lowest dose possible, with gradual increases depending on response.

Treatment of Ocular Hypertension: In the presence of hypertensive optic neuropathy, a rapid reduction of BP may pose a risk of worsening ischemic damage to the optic nerve. The optic nerve demonstrates autoregulation, so there is an adjustment in perfusion based on the elevated blood pressure. A precipitous reduction in BP will reduce perfusion to the optic nerve and central nervous system as a result of their autoregulatory changes, resulting in infarction of the optic nerve head and, potentially, acute ischemic neurologic lesions of the CNS.

Treatment of Renovascular Hypertension: The goals of therapy for renovascular hypertension (RVHT) are maintenance of normal BP and prevention of end-stage renal disease. The therapeutic options include medical therapy, percutaneous transluminal renal angioplasty (PTRA) and stenting, and surgical revascularization. These options must be individualized, because no randomized studies document the superiority of one option over the other. In a study focusing on patients with atherosclerotic renal artery stenosis, data suggested that revascularization therapy should be confined to patients who have renal ischemia with viable underlying renal function because they will experience the greatest clinical benefit. The indications for surgery or angioplasty include an inability to control BP while on a medical regimen, the need to preserve renal function, and intolerable effects of medical therapy. With the advent of noninvasive techniques, aortal renal bypass using a saphenous vein or hypogastric artery is not commonly employed for revascularization. PTRA can be an effective treatment for hypertension and the preservation of renal function in a subset of patients that is difficult to identify. PTRA may be the initial choice in younger patients with fibromuscular lesions amenable to balloon angioplasty. Renal artery stenting of osteal lesions has been associated with improved long-term patency. PTRA may also be used for arthrosclerotic renal artery stenosis; the outcome may be comparable to that of surgical revascularization. Medical therapy is required in the preoperative phase of interventional therapy. Medical therapy is also indicated for high-risk individuals and for older patients who have easily controlled hypertension. The specific population that will benefit from these techniques has yet to be clearly defined. ACE inhibitors are quite effective in patients with unilateral renal artery stenosis; however, avoid ACE inhibitors in patients with bilateral renal artery stenosis or stenosis of a solitary kidney. A diuretic can be combined with an ACE inhibitor. Because of their glomerular vasodilatory effect, calcium antagonists are effective in renal artery stenosis and do not compromise renal function. For most patients with RVHT, with the exception of persons with fibromuscular dysplasia, it is unclear whether revascularization will be beneficial. Fibromuscular dysplasia responds well to angioplasty. The causes of renovascular hypertension include atherosclerosis, fibromuscular dysplasia, coarctation of the aorta, embolic renal artery occlusion, aneurysm of the renal artery, and diffuse arteritis. Additionally, causes of diffuse bilateral renal ischemia, such as accelerated hypertension, vasculitis, hepatitis B, and IV drug abuse, may also lead to hypertension.

Treatment of Resistant Hypertension: Some patients may have a persistent

standard, two or more antihypertensive drugs at maximal doses should be used to achieve optimal blood pressure targets in patients with diabetes and hypertension. Either an ACE inhibitor or an ARB is usually required in patients with diabetes and hypertension. If the patient cannot tolerate one class of drugs, the other should be tried. If needed to achieve blood pressure goals, a thiazide diuretic is indicated for those patients with an estimated GFR (eGFR) ≥30 mL/min/1.73 m2 and a loop diuretic for those with an eGFR < 30 mL/min/1.73 m2. Regardless of which antihypertensive drugs are used, kidney function and serum potassium levels should be monitored.

Surgical Treatment of Hypertension: Aortorenal bypass using a saphenous vein graft or a hypogastric artery is a revascularization technique for renovascular hypertension that has become much less common since the advent of renal artery angioplasty with stenting. Surgical resection is the treatment of choice for pheochromocytoma, because hypertension is cured by tumor resection. In patients with fibromuscular renal disease, angioplasty has a 60-80% success rate for improvement or cure of hypertension.

Management of Hypertensive Emergencies: The primary goal of the emergency physician is to determine which patients with acute hypertension are exhibiting symptoms of end-organ damage and require immediate intravenous (IV) parenteral therapy. The fundamental principle in determining the necessary emergency department (ED) care of the hypertensive patient is the presence or absence of end-organ dysfunction. Approximately 3-45% of adult ED patients have at least one increased BP during their stay in the ED. Many patients present to the ED with elevated BPs; however, only a small proportion of patients will require emergency treatment. In contrast, patients presenting with acutely elevated BPs (systolic BP >200 mm Hg or diastolic BP >120 mm Hg) without symptoms that are sustained throughout the ED stay and stay significantly elevated to this level on discharge should have initiation of medical therapy and close follow-up in the outpatient setting.

Treatment of Hypertension in Pediatric Patients: Usually, continuous IV infusions are the most appropriate initial therapy, especially in acutely ill infants with severe hypertension. The advantages of IV infusions are numerous, most importantly including the ability to quickly increase or decrease the rate of infusion to achieve the desired BP. As in patients of any age with malignant hypertension, take care to avoid too rapid a reduction in BP in order to avoid cerebral ischemia and hemorrhage; premature infants in particular are already at an increased risk because of the immaturity of their periventricular circulation. Because of the paucity of available data regarding the use of these agents in newborns, the choice of agent depends on the individual clinician's experience.

Treatment of Hypertension in Pregnancy: In normal pregnancy, women's MAP drops 10-15 mm Hg over the first half of pregnancy. Most women with mild chronic hypertension (ie, systolic BP 140-160 mm Hg, diastolic BP 90-100 mm Hg) have a similar decrease in BPs and may not require any medication during this period. Conversely, diastolic BP greater than 110 mm Hg has been associated with an increased risk of placental abruption and intrauterine growth restriction, and systolic BP greater than 160 mm Hg increases the risk of maternal intracerebral hemorrhage. Therefore, pregnant patients should be started on antihypertensive therapy if the systolic BP is greater than 160 mm Hg or the diastolic BP is greater than 100-105 mm Hg. The goal of pharmacologic treatment should be a diastolic BP of less than 100-105 mm Hg and a systolic BP less than 160 mm Hg. Women with preexisting end-organ damage from chronic hypertension should have a lower threshold for starting antihypertensive medication (ie, >139/89) and a lower target BP (< 140/90). Although the primary risk of chronic hypertension in pregnancy is development of superimposed preeclampsia, no evidence suggests that pharmacological treatment of mild hypertension reduces the incidence of preeclampsia in this population.

Treatment of Hypertension in the Elderly: The systolic pressure continues to rise progressively throughout life, reaching the highest levels in later stages of life. Isolated systolic hypertension may be present in 10% of the population aged 70 years and in 24% of those aged 80 years. Furthermore, severe arteriosclerosis may lead to pseudohypertension. Isolated hypertension results in low cardiac output because of the decreased stroke volume and high peripheral resistance. This may reduce glomerular filtration further, which is why low activity of renal angiotensin aldosterone cascade is encountered in elderly individuals who are hypertensive. Despite low PRA, blood pressure responds well to ACE inhibitor and ARB therapy. Low doses of diuretics may also be effective. Calcium antagonists are quite useful because of their strong antihypertensive effects. Often, combining 2 drugs at a lower dose may be preferable to using a single drug at a high dose that has the potential for adverse effects. The 2011 internationally acceptable document recommends starting the evaluation of the elderly patient with known or suspected hypertension with 3 measurements of blood pressure, to obtain an accurate BP value. If BP is elevated, the cause should be isolated. Any organ damage should be assessed. Other CVD risk factors or comorbid conditions should be identified, along with any potential barriers to treatment adherence. The 2011 collective clinical consensus advises against the routine use of laboratory testing in elderly patients. Instead, it recommends a more deliberative, focused approach. This would include a urinalysis for signs of renal damage (albuminuria/ microalbuminuria); blood chemistries (especially potassium and creatinine with eGFR); total cholesterol, LDL, HDL, and triglycerides; fasting blood sugar (A1c if diabetes mellitus is suspected; and an ECG. Also lifestyle modifications may be all that is necessary to treat milder forms of hypertension in elderly patients. However, drug treatment for elderly patients with hypertension is generally recommended and should be started at the lowest dose possible, with gradual increases depending on response.

Treatment of Ocular Hypertension: In the presence of hypertensive optic neuropathy, a rapid reduction of BP may pose a risk of worsening ischemic damage to the optic nerve. The optic nerve demonstrates autoregulation, so there is an adjustment in perfusion based on the elevated blood pressure. A precipitous reduction in BP will reduce perfusion to the optic nerve and central nervous system as a result of their autoregulatory changes, resulting in infarction of the optic nerve head and, potentially, acute ischemic neurologic lesions of the CNS.

Treatment of Renovascular Hypertension: The goals of therapy for renovascular hypertension (RVHT) are maintenance of normal BP and prevention of end-stage renal disease. The therapeutic options include medical therapy, percutaneous transluminal renal angioplasty (PTRA) and stenting, and surgical revascularization. These options must be individualized, because no randomized studies document the superiority of one option over the other. In a study focusing on patients with atherosclerotic renal artery stenosis, data suggested that revascularization therapy should be confined to patients who have renal ischemia with viable underlying renal function because they will experience the greatest clinical benefit. The indications for surgery or angioplasty include an inability to control BP while on a medical regimen, the need to preserve renal function, and intolerable effects of medical therapy. With the advent of noninvasive techniques, aortal renal bypass using a saphenous vein or hypogastric artery is not commonly employed for revascularization. PTRA can be an effective treatment for hypertension and the preservation of renal function in a subset of patients that is difficult to identify. PTRA may be the initial choice in younger patients with fibromuscular lesions amenable to balloon angioplasty. Renal artery stenting of osteal lesions has been associated with improved long-term patency. PTRA may also be used for arthrosclerotic renal artery stenosis; the outcome may be comparable to that of surgical revascularization. Medical therapy is required in the preoperative phase of interventional therapy. Medical therapy is also indicated for high-risk individuals and for older patients who have easily controlled hypertension. The specific population that will benefit from these techniques has yet to be clearly defined. ACE inhibitors are quite effective in patients with unilateral renal artery stenosis; however, avoid ACE inhibitors in patients with bilateral renal artery stenosis or stenosis of a solitary kidney. A diuretic can be combined with an ACE inhibitor. Because of their glomerular vasodilatory effect, calcium antagonists are effective in renal artery stenosis and do not compromise renal function. For most patients with RVHT, with the exception of persons with fibromuscular dysplasia, it is unclear whether revascularization will be beneficial. Fibromuscular dysplasia responds well to angioplasty. The causes of renovascular hypertension include atherosclerosis, fibromuscular dysplasia, coarctation of the aorta, embolic renal artery occlusion, aneurysm of the renal artery, and diffuse arteritis. Additionally, causes of diffuse bilateral renal ischemia, such as accelerated hypertension, vasculitis, hepatitis B, and IV drug abuse, may also lead to hypertension.

Treatment of Resistant Hypertension: Some patients may have a persistent

diastolic BP above 100 mm Hg despite the use of 3 or more different classes of antihypertensive medications. Although among more than one third of patients with resistant hypertension, ambulatory BP is normal; this stresses the importance of monitoring patients to achieve correct diagnosis and management. Patients who require 4 or more medications to control their BP should be considered resistant to treatment. A study has shown that the addition of low-dose spironolactone provides significant additive BP reduction in African-American and white patients who have resistant hypertension with or without primary hyperaldosteronism. Catheter-based renal sympathetic denervation also lowers BP for an extended period of up to 2 years. In addition, data suggest baroreceptor activation treatment (BAT) by an implantable stimulator can potentially safely reduce systolic blood pressure (SBP) over the long term in patients with resistant hypertension.

Inadequate treatment: Inadequate treatment was described as the most common cause of resistant hypertension in several published series. Patients may not be on an effective drug, or concomitant volume expansion may occur as a side effect of the drug.

Extracellular volume expansion: Extracellular volume expansion may contribute to the inability to lower systemic BP. The volume expansion may occur because of renal insufficiency, sodium retention due to treatment with vasodilators, high-salt diet, or insufficient dosing of diuretic. This situation can be treated with more aggressive diuretic therapy until clinical signs of extracellular volume depletion (eg, orthostatic hypotension) develop.

Noncompliance: Noncompliance with medical therapy or dietary modifications (eg, salt restriction) may play a role in causing resistant hypertension. Address noncompliance with extensive patient education, simplification of the drug regimen, use of fixed-dose combinations, and use of drugs with the fewest adverse effects. Limited data suggests better compliance with ACE inhibitors and ARBs than some other antihypertensive medications.

Vasoactive substances: Resistant hypertension may be encountered in patients who are ingesting vasoactive substances despite taking antihypertensive drugs regularly. Use of salt and alcohol are the common examples; others include use of cocaine, amphetamines, anabolic steroids, oral contraceptives, cyclosporine, antidepressants, and nonsteroidal anti-inflammatory drugs.

Excluding secondary causes: Whenever confronted with resistant hypertension, try to exclude any secondary causes of hypertension. A reevaluation of the patient's history, physical examination, and laboratory results may provide clues to secondary hypertension (eg, renal artery stenosis, primary hyperaldosteronism, obstructive sleep apnea). Primary hyperaldosteronism has a prevalence of 20% in this population. Obstructive sleep apnea is also associated with resistant hypertension, with 85% of patients with resistant hypertension having an elevated apnea/hypopnea index. Blood pressure rise secondary to anxiety may be observed in 20-30% of patients. This may be avoided by having patients rest prior to measurement, having a nurse check the blood pressure, or arranging to have the blood pressure monitored at home. Development of hypotensive symptoms on medications is an indication of so-called white-coat hypertension. White-coat hypertension can also be evaluated by the use of a 24-hour ambulatory monitor.

Treatment of Pseudohypertension: Pseudohypertension may be observed in elderly individuals who have thickened, calcified arteries. Much higher cuff pressure may be required to occlude a thickened brachial artery, and diastolic BP may also be overestimated. Consider pseudohypertension in situations in which no organ damage occurs despite marked hypertension, when patients develop hypotensive symptoms on medications, and when calcification of the brachial artery is observed on radiologic examination. Direct measurement of intra-arterial pressure may be required in this setting.

Treatment of Pheochromocytoma: Following suspicion of pheochromocytoma, the presence of a tumor should be confirmed biochemically by measuring urine and plasma concentrations of catecholamine or their metabolites. In most situations, computed tomography (CT) or magnetic resonance imaging (MRI) may be used to localize the tumor in the abdomen. In the absence of abdominal imaging, nuclear scan with metaiodobenzylguanidine (MIBG) may further help with the localization. Surgical resection is the treatment of choice because hypertension is cured by tumor resection. In the preoperative phase, combined alpha- and beta-adrenergic blockade is recommended for hypertension control. Alpha-adrenergic blockade is initiated with phenoxybenzamine or prazosin, and, following adequate alpha-adrenergic blockade, beta-adrenergic blockade is initiated. These patients are often volume contracted and require saline or sodium tablets. Catecholamines can be reduced further by metyrosine. For adrenal pheochromocytoma, laparoscopic adrenalectomy is becoming the procedure of choice in suitable patients. Follow-up 24-hour urinary excretion studies of catecholamines should be performed 2 weeks following surgery (and periodically thereafter) to detect recurrence, metastases, or development of second primary lesion.

Treatment of Primary Hyperaldosteronism: The prevalence of primary hyperaldosteronism increases with the severity of hypertension, being 2% in stage 1 and 20% in resistant hypertension. Hypokalemia and metabolic alkalosis are important clues to the presence of primary hyperaldosteronism. However, these are relatively late manifestations, and in a large subset of patients, the serum potassium concentration and bicarbonate are within the reference range. Measurement of the plasma aldosterone/renin activity ratio is the best initial screening test for primary hyperaldosteronism. A ratio of over 20-30 suggests that primary hyperaldosteronism may be present. Some labs require a minimum plasma aldosterone level of 12 ng/dL. The diagnosis of primary hyperaldosteronism can be confirmed by the determination of the aldosterone excretion rate in a 24-hour urine following IV or oral salt loading. If the urinary aldosterone excretion rate is greater than 12-14 µg/24 h, with urine sodium of at least than 200 mEq/24 h, this confirms the diagnosis of primary hyperaldosteronism. The appropriate therapy depends on the cause of excessive aldosterone production. A CT scan may help localize an adrenal mass, indicating adrenal adenoma. If the results of the CT scan are inconclusive, adrenal venous sampling for aldosterone and cortisol levels should be performed. Medical therapy is indicated in patients with adrenal hyperplasia, patients with adenoma who are poor surgical risks, and patients with bilateral adenomas. These patients are best treated with sustained salt and water depletion. Hydrochlorothiazide or furosemide in combination with either spironolactone or amiloride corrects hypokalemia and normalizes the blood pressure. Some patients may require the addition of a vasodilator or a beta blocker for better control of hypertension. Adrenal adenomas may be resected via a laparoscopic procedure. Surgical resection often leads to the control of blood pressure and the reversal of biochemical abnormalities. These patients may develop hypoaldosteronism during the postoperative follow-up period and require supplementation with fludrocortisone.

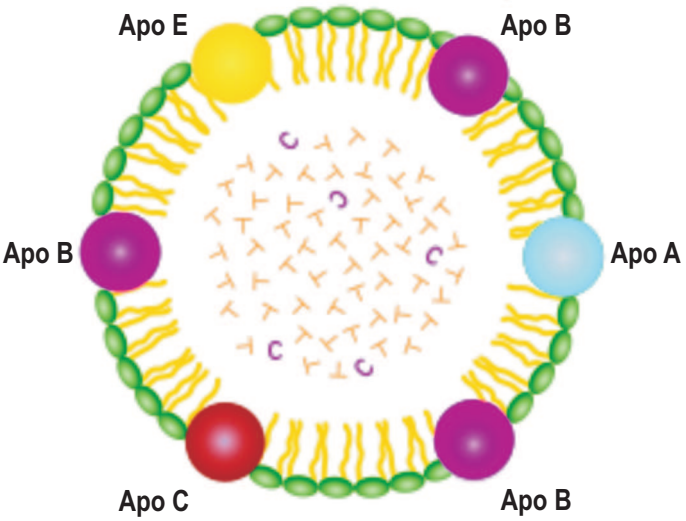
Continuing Care: Various interventions can be implemented to improve BP control in patients with hypertension or to treat uncontrolled hypertension. These interventions include the following: Self-monitoring, Educational interventions directed to the patient, Educational interventions directed to the health professional, Health professional (nurse or pharmacist)–led care, Organizational interventions that aim to improve the delivery of care, Appointment reminder systems.

Deterrence and Prevention: A comprehensive strategy for reduction in mortality and morbidity from hypertension must include prevention strategies, earlier detection, and adequate treatment. Ideally, a population strategy should be used in order to lower BP in the community. More intensive efforts are required to lower blood pressure in high-risk population groups, which include individuals with a family history of hypertension, black ancestry, obesity, excessive sodium consumption, physical inactivity, and/or alcohol consumption. Even a small reduction in BP confers significant health benefits. A 2-mm Hg reduction in diastolic BP is estimated to decrease the risk of stroke by 15% and the risk of coronary heart disease by 6%. Prevention of hypertension may be achieved by the following interventions: Weight control, Increased physical activity, Moderated sodium and alcohol intake, Increased potassium intake, A dietary pattern rich in fruits and vegetables and low-fat meat, fish, and dairy products (see Lifestyle Modifications).

Medication Summary: The goals of pharmacotherapy are to reduce morbidity and to prevent complications. Medications include diuretics, alpha- and beta-adrenergic blockers, antihypertensives, calcium channel blockers, ACE inhibitors, and vasodilators.

INTERPRETATION

LIPOPROTEINS



Lipoprotein structure (chylomicron)

ApoA, ApoB, ApoC, ApoE (apolipoproteins); T (triacylglycerol); C (cholesterol); green (phospholipids).

A lipoprotein is a biochemical assembly that contains both proteins and lipids water-bound to the proteins. Many enzymes, transporters, structural proteins, antigens, adhesins and toxins are lipoproteins. Examples include the high density (HDL) and low density (LDL) lipoproteins which enable fats to be carried in the blood stream, the transmembrane proteins of the mitochondrion and the chloroplast, and bacterial lipoproteins.

Function

The function of lipoprotein particles is to transport lipids (fats) (such as triacylglycerol) around the body in the blood.

All cells use and rely on fats and cholesterol as building blocks to create the multiple membranes which cells use to both control internal water content, internal water soluble elements and to organize their internal structure and protein enzymatic systems.

The lipoprotein particles have hydrophilic groups of phospholipids, cholesterol and apoproteins directed outward. Such characteristics makes them soluble in the salt water-based blood pool. Triglyceride-fats and cholesterol esters are carried internally, shielded from the water by the phospholipid monolayer and the apoproteins.

The interaction of the proteins forming the surface of the particles with (a) enzymes in the blood, (b) with each other, and (c) with specific proteins on the surfaces of cells determine whether triglycerides and cholesterol will be added to or removed from the lipoprotein transport particles.

Regarding atheroma development and progression as opposed to regression, the key issue has always been cholesterol transport patterns, not cholesterol concentration itself.

Transmembrane lipoproteins

The lipids are often an essential part of the complex, even if they seem to have no catalytic activity by themselves. To isolate transmembrane lipoproteins from their associated membranes, detergents are often needed.

Classification

By density

Lipoproteins may be classified as follows, listed from larger and less dense to smaller and denser. Lipoproteins are larger and less dense, if they consist of more fat than of protein. They are classified on the basis of electrophoresis and ultracentrifugation.

- Chylomicrons carry triglycerides (fat) from the intestines to the liver, skeleta muscle, and to adipose tissue.
- Very low density lipoproteins (VLDL) carry (newly synthesised) triacylglycerol from the liver to adipose tissue.
- Intermediate density lipoproteins (IDL) are intermediate between VLDL and LDL. They are not usually detectable in the blood.
- Low density lipoproteins (LDL) carry cholesterol from the liver to cells of the body. LDLs are sometimes referred to as the "bad cholesterol" lipoprotein.
- High density lipoproteins (HDL) collect cholesterol from the body's tissues, and bring it back to the liver. HDLs are sometimes referred to as the "good cholesterol" lipoprotein.

Alpha and beta

It is also possible to classify lipoproteins as "alpha" and "beta", according to the classification of proteins in serum protein electrophoresis. This terminology is sometimes used in describing lipid disorders such as Abetalipoproteinemia.

Lipoprotein Normal Values

Lipoprotein(a) – Lp(a), Cardiology diagnostic tests
< 30 mg/dL : Normal

Lipoprotein A1 – 105-205 mg/dL : Normal

Lipoprotein B – 55-140 mg/dL : Normal

How to lower: aerobic exercise, niacin, aspirin, guggulipid.

Metabolism

The handling of lipoproteins in the body is referred to as "lipoprotein

Density (g/mL)	Class	Diameter (nm)	% Protein	% Cholesterol	% Phospholipid	% Triacylglycerol
>1.063	HDL	5–15	33	30	29	4
1.019–1.063	LDL	18–28	25	50	21	8
1.006–1.019	IDL	25–50	18	29	22	31
0.95–1.006	VLDL	30–80	10	22	18	50
<0.95	Chylomicrons	100-1000	<2	8	7	84

metabolism'. It is divided into two pathways, exogenous and endogenous, depending in large part on whether the lipoproteins in question are composed chiefly of dietary (exogenous) lipids or whether they originated in the liver (endogenous).

Exogenous pathway

Epithelial cells lining the small intestine readily absorb lipids from nutritive substances. These lipids, including triglycerides, phospholipids, and cholesterol, are assembled with apolipoprotein B-48 into chylomicrons. These nascent chylomicrons are secreted from the intestinal epithelial cells into the lymphatic circulation in a process that depends heavily on apolipoprotein B-48. As they circulate through the lymphatic vessels, nascent chylomicrons bypass the liver circulation and are drained via the thoracic duct into the bloodstream.

In the bloodstream, HDL particles donate apolipoprotein C-II and apolipoprotein E to the nascent chylomicron; the chylomicron is now considered mature. Via apolipoprotein C-II, mature chylomicrons activate lipoprotein lipase (LPL), an enzyme on endothelial cells lining the blood vessels. LPL catalyzes the hydrolysis of triacylglycerol (i.e. glycerol covalently joined to three fatty acids) that ultimately releases glycerol and fatty acids from the chylomicrons. Glycerol and fatty acids can then be absorbed in peripheral tissues, especially adipose and muscle, for energy and storage.

The hydrolyzed chylomicrons are now considered chylomicron remnants. The chylomicron remnants continue circulating until they interact via apolipoprotein E with chylomicron remnant receptors, found chiefly in the liver. This interaction causes the endocytosis of the chylomicron remnants, which are subsequently hydrolyzed within lysosomes. Lysosomal hydrolysis releases glycerol and fatty acids into the cell, which can be used for energy or stored for later use.

Endogenous pathway

The liver is another important source of lipoproteins, principally VLDL. Triacylglycerol and cholesterol are assembled with apolipoprotein B-100 to form VLDL particles. Nascent VLDL particles are released into the bloodstream via a process that depends upon apolipoprotein B-100.

As in chylomicron metabolism, the apolipoprotein C-II and apolipoprotein E of VLDL particles are acquired from HDL particles. Once loaded with apolipoproteins C-II and E, the nascent VLDL particle is considered mature.

Again like chylomicrons, VLDL particles circulate and encounter LPL expressed on endothelial cells. Apolipoprotein C-II activates LPL, causing hydrolysis of the VLDL particle and the release of glycerol and fatty acids. These products can be absorbed from the blood by peripheral tissues, principally adipose and muscle. The hydrolyzed VLDL particles are now called VLDL remnants or intermediate density lipoproteins (IDLs). VLDL remnants can circulate and, via an interaction between apolipoprotein E and the remnant receptor, be absorbed by the liver, or they can be further hydrolyzed by hepatic lipase.

Hydrolysis by hepatic lipase releases glycerol and fatty acids, leaving behind IDL remnants, called low density lipoproteins (LDL), which contain a relatively high cholesterol content. LDL circulates and is absorbed by the liver and peripheral cells. Binding of LDL to its target tissue occurs through an interaction between the LDL receptor and apolipoprotein B-100 or E on the LDL particle. Absorption occurs through endocytosis, and the internalized LDL particles are hydrolyzed within lysosomes, releasing lipids, chiefly cholesterol.

Diagnostic Relevance of Apo A1 and Apo B Measurement:

- **Apolipoproteins A1** is the major protein of HDL and **Apolipoprotein B** is the main part of LDL, but also present on VLDL and Intermediate Density Lipoproteins (IDL). Each of the three particle classes LDL, IDL and VLDL carries exactly one molecule of **Apo B** per particle, the latter is a measure for the total number of LDL, IDL and VLDL.
- The liver secretes a Triglyceride rich lipoprotein, VLDL, which by the removal of the most of its Triglycerides is converted to a smaller Cholesterol rich Lipoprotein, LDL. The biological Half Life of an LDL particle is at least 9 times longer than that of a VLDL particle and, therefore, there are always 9 times more LDL particles than VLDL particles. Because each VLDL and LDL particles contains one molecule of **Apo B**, measuring plasma **Apo B** measures exactly the total number of VLDL and LDL particles, that is 90% of which is LDL.
- As LDL particles differ substantially from one another in the amount of cholesterol they contain, Total and LDL cholesterol are imprecise measure the number of **Apo B** particles. Therefore measuring **Apo B**, provides a direct estimate of the total number of atherogenic particles.
- **Apo B** measurement can be performed on non-fasting samples.
- Elevated **Apo B** levels were associated with an increased risk, independent of the LDL particle size as per the study conducted by Dr. Benoit Lamarche, Dr.Ande Tchernof and Dr. Bernard Cantin on 2103 men initially free of IHD, among whom 114 developed IHD during a 5 years follow up period. These 114 case patients were matched with health control subjects for age, body mass index, smoking habits and alcohol intake. The study found that individuals having both elevated **Apo B** levels and Small LDL particles showed the increase in IHD risk by 6 folds. The study found that among lipids, lipoproteins and apolipoprotein variables, **Apo B** individually and **Apo B:Apo A1** ratio is the best and only significant predictor of IHD. Normal ratio is from 0.3 to 0.9. A higher value signifies elevated health risk.
- The Quebec Cardiovascular study found that **Apo B** concentration was the best metabolic predictor of IHD risk.
- The study suggests that prevention and treatment of IHD should only be focused on reducing the number of LDL+VLDL+IDL particles, that is **Apo B** concentration rather than altering the size of the particles.
- The study by Dr. Judith F Lynch and Dr. Michella D Marshell in Australian children, of 6992 (3501 boys and 3491 girls) aged 5-13 years, between 1991-1995 showed that Indian children had the highest levels of **Apo B** and **Apo B:Apo A1** ratio. This suggests that, when the food habits and life style is altered or changes the **Apo B** gets elevated and Indians are prone to retain additional Cholesterol in their body.
- As per another study, **Apo A1** and **Apo B** ratio has emerged as a better predictor of angiographically assessed coronary artery disease. In 17.3% of cardiac population, the levels of HDL cholesterol and LDL cholesterol were considered to be normal, the **Apo B:ApoA1** ratio was increased.

Suggestions:

1. Why should one not measure **Apo A1** and **Apo B** in routine practice if it improves the prediction of risk and the outcome?

2. If statin therapy is chosen, the evidence described, suggests that only **Apo B** need to be measured in follow up. That is, care would be simpler for the patient, in that, fasting is not necessary and simpler for the physician in that only one result, and not all the 5, need to be considered and tested on. Simpler care would translate into more cost effective care.
3. Please note, it is emphasized that **modification, not abolition**, of the present system is advocated. **Apo A1** and **Apo B** should not be the only parameter measured in the initial assessment of the risk of disease due too lipids.

Conclusion:

Given the importance that has been assigned to Cholesterol, change will not be easy in the initial periods. But however, one should have the regular Cholesterol testing for a period of time with **Apo A1** and **Apo B** in the lipid profile. Change is the price of progress.

Given the potential for benefit to the patients and the society, it is hoped that **Apo A1** and **Apo B** testing will prove the case.

BOUQUET

In Lighter Vein

A panda walked into a bar. He went up to the bar and said "I'd like a steak and kidney pie and a Coke please" so the barman took his order and the panda went to sit down. Soon a waiter brought over his meal. The panda ate it up, thanked and tipped the waiter and paid the bill.
All this seemed pretty normal until the panda pulled out a gun from the depths of his fur, pulled the trigger and BANG! shot the waiter.
The barman came over and said "Wha.. wh.. You just shot my friend!!!" the panda calmly replied "Do you know what I am?" "Why yes," the barman answered. "Your a panda." "Good," the panda nodded "Now go home and look up 'panda' in the dictionary." And with that, the panda walked out of the bar.
The barman was a little unsure, however he was very eager to be enlighted on the subject of his friend's murder, so he went home to find his dictionary.
After a while, he found 'panda' and quickly read the definition: PANDA:1. A black and white bear native to China. Eats shoots and leaves.

A man walked into a cafe, went to the bar and ordered a beer.
"Certainly, Sir , that'll be one cent."
One Cent?" the man exclaimed.
He glanced at the menu and asked: "How much for a nice juicy steak and a bottle of wine?"
"A nickel," the barman replied.
"A nickel?" exclaimed the man.
"Where's the guy who owns this place?"
The bartender replied: "Upstairs, with my wife."
The man asked: "What's he doing upstairs with your wife?"
The bartender replied: "The same thing I'm doing to his business down here."

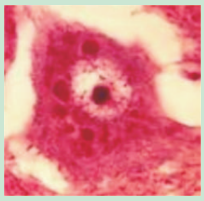
A man is sitting at the bar in his local tavern, furiously imbibing shots of whiskey. One of his friends happens to come into the bar and sees him.
"Lou," says the shocked friend, "what are you doing? I've known you for over fifteen years, and I've never seen you take a drink before. What's going on?"
Without even taking his eyes off his newly filled shot glass, the man replies, "My wife just ran off with my best friend."
He then throws back another shot of whisky in one gulp.
"But," says the other man, "I'm your best friend!"
The man turns to his friend, looks at him through bloodshot eyes, smiles, and then slurs, "Not anymore! He is!"

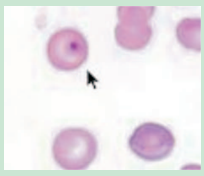
Wisdom Whispers

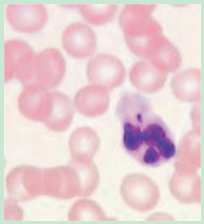
- If you love something let it go free. If it doesn't come back, you never had it. If it comes back, love it forever."
- If you don't know where you are going, any road will get you there."
- Never allow someone to be your priority while allowing yourself to be their option".
- Courage is the discovery that you may not win, and trying when you know you can lose."
- Excellence is not a singular act, but a habit. You are what you repeatedly do."
- Limitations live only in our minds. But if we use our imaginations, our possibilities become limitless."
- We're so busy watching out for what's just ahead of us that we don't take time to enjoy where we are."
- Being happy doesn't mean that everything is perfect. It means that you've decided to look beyond the imperfections."

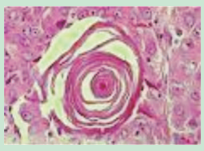
Brain Teasers

Match the following bodies:

1. 
A. Howell Jolly body

2. 
B. Negri body

3. 
C. Psammoma body

4. 
D. Barr body

Answers : 1-B, 2-A, 3-D, 4-C.

TROUBLESHOOTING

PROTOCOL FOR MANAGING EXPOSURE TO BLOOD OR POTENTIALLY INFECTIOUS BODY FLUIDS IN THE LABORATORY.

Parenteral (needlestick) exposure to HIV infection is 0.3% risk of transmission of HIV. This is because of the low concentration of virus in the blood of infected patients. The risk in the case of HBV infected specimen in similar situations is 5-30 %.

Immediate care

For needle- stick injury: Briefly induce bleeding from wound. Wash for 10 minutes with soap and water, or a disinfectant. For non- intact skin exposure: Wash with soap and water or antiseptic. For mucosal exposure (e.g. Splash into eyes): Irrigate copiously by running a pint of normal saline over 10 minutes, the eye being held open the another person.

Reporting

All sharps injury (break of skin with any sharp instrument such as hypodermic needle previously used on a patient) and mucosal exposure (blood or body fluids coming into contact with eyes, mouth etc.) should be reported to the Consultant Pathologist/ Microbiologist and then to the Consultant Physician. All blood and body fluids with visible blood are considered infectious. Other body fluids may be potentially infectious and must be evaluated on case - to - case basis.

Management

Assessing the risk of transmission of HBV/ or HIV infection: For All exposure the following investigations need to be done: Index patient should be checked for the following: HIV antibody, HbsAg, HCV antibody. Health care worker: After obtaining consent, blood of the health care worker is checked for: HbsAg, HIV, Anti HBs antibodies. The blood samples for the investigations listed above are sent for rapid testing.

If the index case is HbsAg positive:

HCW	ACTION
HbsAg	
Antibodies >100 MIU	Reassure
Antibodies negative or <10 MIU	First of HBV vaccine and HBV immuno- globulin(0.6ml/kg-IM)
Antibody between 10- 100 MIU	Booster dose of vaccine
HbsAg Positive	Counselling

Follow up: Staff asked to come back for HbsAg testing at 3& 6 months and for completion of vaccination.

If the index case is HbsAg negative:

HCW	ACTION
HbsAg negative	
Antibodies >100 MIU	Reassure
Antibody negative or <100MIU	Vaccination (full or booster as required)
HbsAg positive	Counselling

If the index case is HIV negative or the index case is unknown:

Do not start chemoprophylaxis; consult the HICC chairman. The HCW is offered HIV antibody testing 0,1,3,6,12 months.

If the index case is HIV positive and HCW is HIV negative, the protocol given below is followed.

- For Indian setting all HIV positive index patients are to be considered as highly infectious.
- Chemoprophylaxis is best when started within 1-2 hours following exposure. The cut off period for chemoprophylaxis is 72 hours following exposure.
- The following investigations are to be done while starting chemoprophylaxis. Do not delay starting chemoprophylaxis for the sake of these investigations.
- Hemoglobin estimation, Platelet count, Reticulocyte count, WBC-total & differential counts, Serum creatinine, Liver function test, Random blood sugar.

Categorization of exposures with recommended prophylaxis

Use three drugs (Zidovudine+ Lamuvudine + Indinavir) for All percutaneous injuries with contaminated sharps, Mucous membrane/ non-intact skin exposure with large volumes of body fluid for long duration.

Use 2 drugs (zidovudine + Lamuvidine) for mucous membrane/ non-intact skin exposure with small volume body fluid for short duration.

If in doubt, start on 3 drug immediately and consult a senior person as early as possible.

Drug Regimen

3 drugs – Azidothymidine (Zidovudine) 200 mg thrice daily, Lamuvidine 150 mg twice daily and Indinavir 800 mg every 8 hours. If Indinavir is not available, Nelfinavir 750 mg three times is to be used.

2 drugs – Zidovudine and Lamuvidine.

Total duration 4 weeks for both.

If the index patient is already on anti-retroviral treatment with 1 drug, add 2 new drugs for the staff. The pharmacy will stock all 3 drugs used in chemoprophylaxis at all times.

Follow up of HCW

The HCW should be tested for HIV antibodies after 6 weeks, 3 months and 6 months following the exposure, irrespective of the HIV status of the index patient.

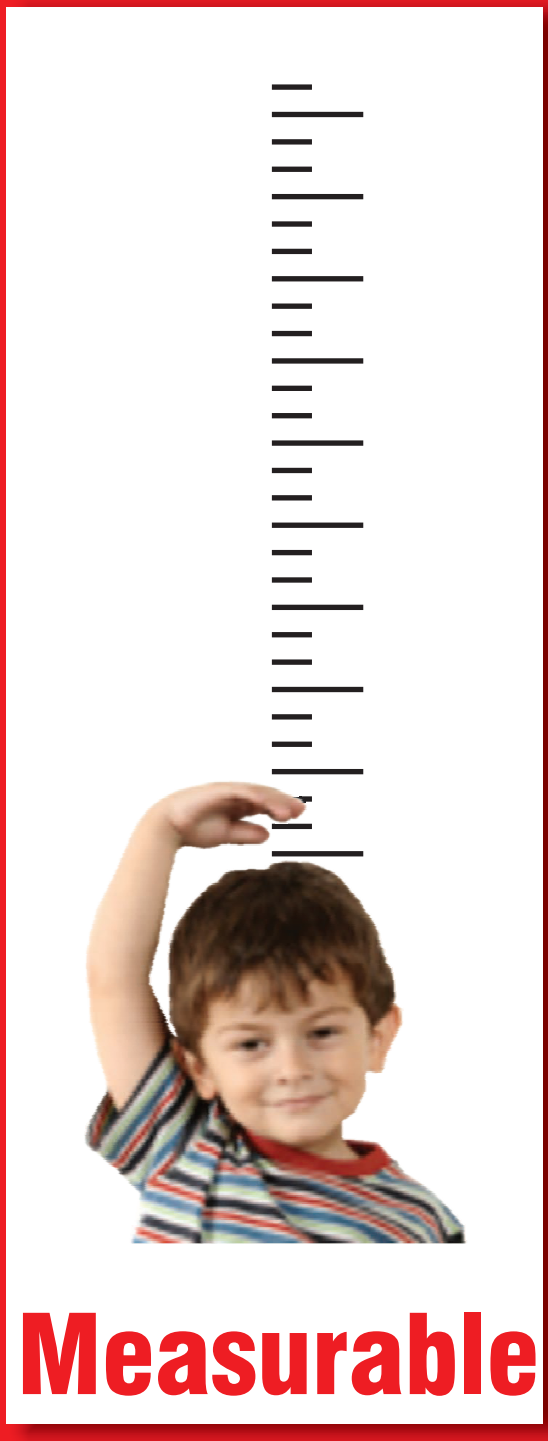
Counselling

Counselling of the HCW is performed when necessary.

How to handle a bloodspill?

- Wear gloves.
- Cover the spill with cotton cloth or newspaper or any other absorbent material.
- Pour 1% sodium hypochlorite solution over the spill.
- Wipe spilled area after 30 minutes.
- Discard soiled material in yellow colour waste bag.
- Clean / mop the area with detergent.
- Discard gloves into red colour waste bag.
- Wash hands with soap and water.

TULIP NEWS



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