UNIT NO. 3

MANAGEMENT OF HYPERTENSION

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Diagnosis and evaluation

Management of hypertension begins with a careful evaluation of the patient. The following questions need to be asked:

1. Is there true hypertension? Is there a white-coat element?
2. What is the severity of blood pressure elevation?
3. Is there a possibility of secondary hypertension?
4. Presence or absence of target organ damage (TOD)
5. Presence of coronary artery disease (CAD) and CAD risk factors
6. Presence of other co-morbidities and conditions e.g. diabetes.

A complete history and physical examination is essential. Baseline laboratory tests such as urine examination, blood biochemistry and ECG should be performed. Further tests (renal assessment, urinary catecholamines, renin and aldosterone) are indicated if a secondary cause is suspected.

"White-coat" or isolated office hypertension, should be suspected in any patient with marked hypertension in the absence of end-organ damage or with normal ambulatory blood pressures taken at work or at home. Other clues include unusual variability of blood pressure readings, symptoms suggesting episodes of hypotension and apparent resistant hypertension. Ambulatory or home blood pressure readings will be especially useful here.

A number of clues suggest the need to exclude renovascular hypertension:

1. Severe or refractory hypertension, including retinal hemorrhages or papilledema; bilateral renovascular disease may be present in those patients who also have a plasma creatinine above 1.5 mg/dL (132 µmol/L)[4].
2. An acute rise in blood pressure over a previously stable baseline – this includes renovascular disease superimposed upon underlying and often well-controlled essential hypertension.
3. Proven age of onset is below 20 (especially if before puberty) or above 50 years of age.
4. An acute elevation in the plasma creatinine concentration that is either unexplained or occurs after the institution of therapy with an angiotensin converting enzyme inhibitor (in the absence of an excessive reduction in blood pressure).
5. Moderate to severe hypertension in a patient with diffuse atherosclerosis or an incidentally discovered asymmetry in renal disease (e.g. a unilateral small kidney).
6. A systolic-diastolic abdominal bruit that lateralizes to one side.
7. Negative family history for hypertension.
8. Moderate to severe hypertension in patients with recurrent episodes of acute (flash) pulmonary edema or otherwise unexplained heart failure.

The decision to begin treatment will depend on the overall risk to the patient. In general, there is clear evidence of likely benefit for diastolic pressure $\geq$ 90 mmHg, systolic $\geq$ 140 mmHg. Both systolic and diastolic pressures are predictive of events and should be considered for treatment.

Based upon the average of two or more readings at each of two or more visits after an initial screen, the following classification is recommended (JNC 6):

1. Optimal blood pressure: systolic <120 mmHg and diastolic <80
2. Normal blood pressure: systolic 120-129 and diastolic 80-84
3. High-normal blood pressure: systolic 130-139 or diastolic 85-89
4. Hypertension:
   Stage 1: systolic 140-159 or diastolic 90-99
   Stage 2: systolic 160-179 or diastolic 100-109
   Stage 3: systolic $\geq$ 180 or diastolic $\geq$ 110.

In the absence of end-organ damage, a patient should not be labelled as having hypertension unless the blood pressure is persistently elevated after three to six visits over a several-month period. Many patients who appear to have mild hypertension initially are actually normotensive.

It is important to consider the overall risk of the patient in the light of other risk factors apart from hypertension. The decision to treat should depend on the overall risk rather than the blood pressure alone.

Major risk factors are: Smoking, hyperlipidemia, diabetes, age over 60 years, gender: men and postmenopausal women, a family history of cardiovascular disease in men < 55 and women < 65.

Target organ damage and clinical cardiovascular disease are: left ventricular hypertrophy, angina or prior infarct, prior revascularisation therapy, heart failure, stroke or TIA, nephropathy, peripheral arterial disease and retinopathy.

Risk stratification is then performed as follows:

1. Risk group A – no risk factors, no target organ damage (TOD) and no clinical cardiovascular disease (CCD).
2. Risk group B – at least one risk factor (excluding diabetes), but no TOD or CCD.
3. Risk group C – TOD and/or CCD and/or Diabetes

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The risk group and blood pressure stage would then be used as a guide to treatment initiation.

Blood pressure stage	Risk group A	Risk group B	Risk group C
High normal: 130-139/85-89	Lifestyle modification	Lifestyle modification	Drug treatment if heart failure, DM or renal insufficiency, LM
Stage 1: 140-159/90-99	Lifestyle modification for up to 12 months	Lifestyle modification for up to 3-6 months, consider drugs as part of initial treatment if multiple risk factors	Drug therapy and lifestyle modification
Stage 2 and 3 >160/>100	Drug therapy and lifestyle modification	Drug therapy and lifestyle modification	Drug therapy and lifestyle modification

Non-pharmacologic treatment should be instituted initially in all but severe cases and consists of the following (JNC6):

1. Lose weight if overweight.
2. Limit alcohol intake (< 1 oz/30 ml ethanol = 24 oz beer, 10 oz wine), less in women and lighter men.
3. Aerobic exercise 30-35 minutes most days of the week
4. Reduce sodium intake to not more than 100 mEq/day (2.4 g of sodium, 6 g salt)
5. Maintain potassium intake (90 mq/day)
6. No smoking
7. Reduce dietary intake of saturated fat and cholesterol

It is important to remember that drug treatment should be considered for patients with blood pressure below 140/90 mmHg if they have heart failure, diabetes or renal insufficiency.

Pharmacologic agents

Antihypertensives can be classified as follows:

1. Diuretics
2. Potassium-sparing agents
3. Adrenergic inhibitors
   a. Peripheral
   b. Central alpha agonists
   c. Alpha-blockers
   d. Beta-blockers
   e. Combined alpha & beta-blockers
4. Direct vasodilators
5. Calcium channel blockers
6. Angiotensin converting enzyme inhibitors
7. Angiotensin receptor blockers.

Thiazide diuretics are among the cheapest and most widely used antihypertensive drugs with a strong evidence base demonstrating benefit for treatment in patients with moderate and severe hypertension. However, there are adverse metabolic effects such as hypokalemia, hyperuricemia, mild elevations in lipids and glucose especially at high dose; hence they may be better used at low dose (12.5 to 25 mg) or in low-dose combination with ACE inhibitor or beta-blocker.

In patients suitable for ACE inhibitors but with side effects such as cough, an angiotensin II receptor blocker (ARB) is an alternative. In the LIFE study, hypertensive patients with LVH had better outcomes with losartan than atenolol. They should also not be given to pregnant women.

Beta-blockers are the other widely used, low-cost antihypertensive that was used in many of the initial studies of hypertension treatment. They are preferred in patients with prior ischaemic heart disease, angina pectoris but are contraindicated in patients with bronchospasm, peripheral vascular disease and heart block.

ACE inhibitors are of particular value in many high-risk patients with diabetic nephropathy, heart failure, and post-myocardial infarction. In addition, there is evidence from the HOPE study of improved survival in patients at high risk of cardiovascular disease, independent of blood pressure lowering. Limitations to use include the development of a dry cough in up to 15%-20% of patients, especially women. Pregnancy is a contraindication to use.

Calcium antagonists are another widely used class of antihypertensives, including the dihydropyridines (nifedipine, nicardipine, amlodipine), verapamil and diltiazem which have differing side effects. The long acting dihydropyridines such as amlodipine are powerful vasodilators and effective agents. Side effects of their vasodilator action include flushing and peripheral oedema. The short-acting agents have been linked to increased cardiovascular risk in observational studies, thus nifedipine should be avoided in its short acting form.

Choice of antihypertensive

All antihypertensive drugs can be effective but there is considerable individual and ethnic variability in responsiveness to drug effects. Thus attempts have been made to predict efficacy in a given individual.

For instance, in younger whites, atenolol is more effective than hydrochlorothiazide, whereas in older blacks, it is the reverse. The other major consideration and controversy is whether the choice of drug (independent of its efficacy in lowering blood pressure) has an impact on long-term morbidity

and mortality. A number of trials such as the MRC study, the CAPP study and the STOP-2 study suggest that the benefit of newer and older antihypertensive drugs is generally comparable. Although there are a wide variety of drugs available, the strongest evidence of benefit rests with the diuretics and beta-blockers, with increasing data for angiotensin converting enzyme inhibitors.

In clinical practice, the individual response to therapy will vary significantly and can be difficult to predict. The choice of drug will often depend on the patient's other medical conditions and his response to therapy.

A diuretic or a beta-blocker is often a reasonable choice in a patient with no contraindications and no specific reasons that favour a particular drug. The evidence indicating benefit from these drugs is strong and their cost and side-effect profile is well-established.

In patients with specific conditions, there may be a compelling reason to favour a particular drug. For instance, diabetic nephropathy and heart failure favours the use of an ACE inhibitor, while coronary artery disease or prior myocardial infarction should support the use of beta-blocker.

The following is a standard guide to the choice of drug:

Indication	Drug choice
Compelling indications	
Diabetes with proteinuria	ACE Inhibitor esp. type 1 DM
Non-diabetic renal failure with proteinuria	ACE Inhibitor
Congestive heart failure	ACE Inhibitor, diuretic
Isolated systolic hypertension	Diuretic (preferred), Long-acting calcium blocker
Myocardial infarction	Beta-blocker (no ISA), ACE Inhibitor if systolic dysfunction
May have favourable effect on co-morbid conditions	
Angina pectoris	Beta-blocker, calcium blocker
Atrial fibrillation, tachycardia	Beta-blocker, calcium blocker
Diabetes with proteinuria	Calcium blocker (non-DHP)
Dyslipidemia	Alpha blocker
Congestive heart failure	Carvedilol, losartan
Osteoporosis	Thiazide diuretic
Contraindications	
Bronchospastic disease	Beta-blocker
Depression	Reserpine
Liver disease	Methyldopa
Pregnancy	ACE Inhibitor, AII blocker
Second or third degree heart block	Beta-blocker, Calcium blocker (non-DHP)
May have adverse effect on comorbid condition	
Depression	Beta-blocker, central alpha agonist
Diabetes mellitus	Beta-blocker, high dose diuretic
Gout	Diuretic
Liver disease	Labetalol
Renovascular disease	ACE Inhibitor, AII blocker

(Adapted from the Sixth Report of the Joint National Committee on detection, Evaluation and Diagnosis of High Blood Pressure (JNC VI). Arch Intern Med 1997; 157:2413.)

Monitoring and dose adjustment

In general, one should always start with a low dose, slowly titrating upward depending on the patient's responses and any side effects.

Long-acting formulations that provide total 24-hour coverage with one dose per day improve compliance.

If the patient is not at target BP with the initial drug and if there is no response or if troublesome side effects have occurred, consider substituting with another drug from a different class.

If the patient is not at target BP with the initial drug but there has been some response and the drug is well-tolerated, consider adding a second drug from a different class (usually a diuretic if not already used); use low-dose combinations to increase efficacy and reduce dose-dependent side-effects.

Drug combinations which are effective include the following: beta-blocker with diuretic, diuretic with ACE inhibitor or ARB, diuretic with calcium blocker.

If target blood pressure is still not achieved, continue adding drugs from other classes and consider referral to a hypertension specialist.

For monitoring of therapy, the blood pressure should be measured before antihypertensive medications are taken to estimate the trough or nadir effect. If the blood pressure is taken soon after drug ingestion, the blood pressure may be normal or even below normal and will gradually increase to potentially hypertensive levels until the next dose is taken.

Based on studies such as the HOT study which evaluates the optimal treatment target, the goal of antihypertensive therapy in patients with combined systolic and diastolic hypertension is a blood pressure of less than 140/90 mmHg for elderly patients. The greatest benefit is derived from lowering the diastolic pressure to approximately 85 mmHg. For diabetics, there appears to be optimal benefit in aiming for a target of BP below 130/85 mmHg.

All hypertensive patients require regular follow-up, not only to assess the adequacy of blood pressure control, but also control of other risk factors and evaluation of side-effects, target organ damage and other co-morbidities. Thus, weight, blood electrolytes, lipids, sugar, exercise and diet need to be evaluated.

Treatment of hypertension should be seen as part of an overall goal in reducing cardiovascular risk. Treatment of other risk factors such as hyperlipidemia, diabetes and smoking should not be overlooked.

Patient education is often overlooked in the management of hypertension, yet it is often critical to its success. Treatment is life-long for a condition which is usually asymptomatic and side-effects are not uncommon. Hence, it is well worth the time and effort to ensure that the patient understands the goals and rationale of treatment. The benefits of treatment need to be explained to the patient.

Overall, with every 10-14 mmHg reduction in systolic blood pressure and 5-6 mmHg reduction in diastolic pressure, there appears to be a 40% reduction in stroke risk and a 14% reduction in coronary artery disease risk, although this risk will vary with the overall risk profile of the patient.

Take Home Messages

- Hypertension is an extremely common medical problem. There is strong evidence of treatment benefit in large clinical trials. However, blood pressure readings are subject to many variables and the possibility of a white-coat effect must always be considered. There is no substitute for repeated measurements taken when the patient is fully at rest.
- A wide spectrum of drugs is available. Careful evaluation and treatment specifically tailored to the patient's overall risk and profile are the keys to successful control of hypertension. Treatment should not be limited to blood pressure but also to other risk factors. Patient education is essential to ensure compliance.

RECOMMENDED READINGS

1. The Sixth Report of the Joint National Committee on detection, Evaluation and Diagnosis of High Blood Pressure (JNC VI). Arch Intern Med 1997;157:2413.)

2. Clinical Practice Guidelines for Hypertension. Ministry of Health, Singapore. Available at:http://www.gov.sg/moh/newmoh/pdf/abo/clinic2000/hypertension.pdf. This is an excellent guide to the management of hypertension.