How to Manage Resistant Hypertension

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Definition

Resistant to *conventional* medical therapy

Definition of Resistant Hypertension

- Despite intake of three or more antihypertensive drugs
- Resistance is usually defined as

  BP > 140/90 mmHg (age < 60)

  BP > 160/90 mmHg (age ≥ 60)

Neusch et al. BMJ 2001

Definition ?

Resistant to *conventional* medical therapy

140/90 – 160/90 mmHg ?

How much doses / How many drugs ?

Definition ?

Resistant to *conventional* medical therapy

140/90 – 160/90 mmHg ?

How much doses / How many drugs ?

Prevalance : 1 -13 % ?

ESH / ESC Classification

Classification	SBP(mmHg)	DBP(mmHg)
Optimal	< 120	<80
Normal	120-129	80-84
High normal	130-139	85-89
Grade 1 hypertension (mild)	140-159	90-99
Grade 2 hypertension (moderate)	160-179	100-109
Grade 3 hypertension (severe)	≥ 180	≥ 110
Isolated systolic hypertension	≥ 140	< 90

ESH/ESC guidelines for the management of hypertension. J Hypertens, 2003

JNC-7 Classification

Classification	SBP(mmHg)	DBP(mmHg)
Normal	< 120	and <80
Prehypertension	120-139	or 80-89
Stage 1 hypertension	140-159	or 90-99
Stage 2 hypertension	≥ 160	or ≥ 100

The JNC 7 report. JAMA 2003

Definition

Resistant to *conventional* medical therapy

- √ JNC-7

  How much doses / How many drugs ?

Definition

Resistant to *conventional* medical therapy

√ JNC-7

How much doses / How many drugs ?

Triple-drug regimen to be tried before diagnosis of resistant hypertension

1. Oral diuretics

Equivalent to hydrochordthiazide 25 mg/d or

Equivalent to furosemide 320mg/d, or

metolazone 10 mg/d

(if serum creatinine > 2.5 mg/dL)

Triple-drug regimen to be tried before diagnosis of resistant hypertension

2. Sympathetic inhibitor

Atenolol 100 mg/d or

Clonidine 0.6 mg/d or

Prazocin 20 mg/d or

Methydopa 2 g/d

or

ACEI (captopril 200 mg/d) or

ARB (losartan 100 mg/d) or

CCB (nifedipine 120 mg/d)

Triple-drug regimen to be tried before diagnosis of resistant hypertension

3. Direct vasodilator

Hydralazine 100 mg/d

Minoxidil 20 mg/d

** In an alternative regimen, the direct vasodilator is omitted and a diuretics is used with two drugs from group 2(e.g. ACEI & CCB, or ARB & BB)*

Definition

Resistant to *conventional* medical therapy

- √ JNC-7
- √ Three or more antihypertensive regimen

Physician-Related Factor

- Adequate patient education
- Accurate clinical diagnosis
- Appropriate drug therapy

Patient-Related Factor

- Noncompliance with treatment schedules
- Use of drugs that interact with antihypertensive medications
- Obesity and diet

Etiology of Resistant hypertension

- Suboptimal therapy
- Extracellular volume expansion
- Poor compliance with medical or dietary therapy
- Secondary hypertension
- Office or "white coat" hypertension
- Pseudohypertension
- Ingestion of substances that can elevate the BP
- Side effects on many antihypertensive drugs

Yakovlevitch, et al. Arch Intern Med 1991

Suboptimal Therapy

- The most common and mostly correctable cause of resistant hypertennsion
- Adequate trial of maximally tolerated doses of at least three drugs; Sequential monotherapy with three drugs of different classes is not adequate
- Failure to prevent volume expansion with adequate diuretic therapy : one of which should be a diuretic; once the creatinine clearance falls to below 30 mL/min (sCr > 2.5 mg/dL), a loop diuretic should be substituted for a thiazide congener.

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Extracellular volume expansion

- Most patient has relative or absolute extracellular volume expansion
- Underlying conditions
  1) Renal insufficiency
  2) Sodium retention due to vasodilators
  3) Ingestion of a high salt diet
  4) Presence of clinically occult expansion
  5) Use of once-daily, short-acting loop diuretics
- Gradually removal of fluid for BP control

Taler et al. Hypertension 2002

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Poor Compliance

* Up to 80% are at least partially noncompliant

- Lack of knowledge about the disease and relative absence of symptoms
- Cost or side effects of medications
- Complex dosing schedules

Burnier et al. J Hypertension 2003

Poor Compliance – Check Points

- Patient education
- Rescheduling missed appointments
- Monitoring of drug-induced side effects
- Simplifying the drug regimen
- Monitoring of drug intake:
  - Pill counts
  - Physiologic changes after medication
    e.g. pulse rate for beta blockers

Life Style Modification

- Obesity
- Low salt diet
- Alcohol intake: limit intake to 1 oz of ethanol

  beer 24 oz/d, wine 8 oz/d, liquor 2 oz/d

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Secondary Hypertension

- Up to 11% of patients with refractory hypertension have an identifiable secondary cause.
- Most common are renal artery stenosis and chronic renal parenchymal disease.

Renovascular Hypertension

- When previously well-controlled hypertension has recently become resistant to therapy, patients older than 50 years of age with evidence of generalized vascular disease should be examined for renovascular disease.
- Captopril-induced renograms are useful for this purpose, unless the serum creatinine level is higher than 2 mg/dL.
- Doppler imaging of the renal arteries was recently shown to be sensitive in detecting radiologically confirmed renal arterial stenosis in patients with arteriosclerotic renal disease.

Primary Aldosteronism

- 5% of patients with refractory hypertension
- The aldosterone-renin ratio is useful when screening for primary aldosteronism
- Regardless of whether patients have an adrenal adenoma or idiopathic aldosteronism, they respond to aldosterone antagonists.

Pheochromocytoma

- Tests for urine metanephrines and/or catecholamines are used to screen for pheochromocytoma
- High-pressure liquid chromatography quantitation of metanephrines is used if there are any doubts about specificity.
- Endocrinologic evidence should be confirmed before proceeding to more expensive imaging techniques.

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Office or “White Coat” HT

- Most patients are anxious when visiting physician; Acute rise in BP; 20 to 30 % of patients
- Can be minimized by having a nurse or technician take the pressure rather than the physician
- Development of hypotensive symptoms (weakness, dizziness) on a variety of different antihypertensive medications

Pickering et al. JAMA 1988
Mancia et al. Hypertension 1987

Office or “White Coat” HT

- 24 hour ambulatory BP monitoring
  - Normal BP at work or home
  - Refractory office HT without end-organ damage (such as LVH on Echo)
  - Symptoms of hypoperfusion despite persistent hypertension

Redon et al. Hypertension 1998

24h BP Monitoring – Prognostic Value

- Refractory HT defined as

  Despite therapy with drugs ≥ 3

  Diastolic BP ≥ 100 mmHg on 24h BP

- Mean 24 h D-BP vs. CV events (median 49 months)

  1) < 88mmHg

  2) 88-97 mmHg

  3) > 97 mmHg ------- poor prognosis

Redon et al. Hypertension 1998

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Pseudohypertension

- Old patients - thickened, calcified arteries
- Compression of the brachial artery with a sphygmomanometer requires a cuff pressure greater than is present within the artery
- Pseudohypertension: S-BP & D-BP estimated from the sphygmomanometer may be considerably higher (> 10-15 mmHg) than the directly measured intraarterial pressure

Tsapatsaris, et al. Arch Intern Med 1991

Pseudohypertension

- Conditions suspicious of pseudohypertension:
  1) Marked cuff HT without end-organ damage
  2) HT medication induces hypotensive symptoms without excessive reduction in BP
  3) Pipestem calcification: brachial arteries on X-ray
  4) Brachial BP is higher than lower extremity BP
  5) Marked isolated systolic hypertension
- Pseudohypertension is diagnosed as high as 30 %

Zweifler, et al. J Hypertens 1993

Pseudohypertension

- Confirmative diagnosis of pseudohypertension by direct measurement of the intraarterial pressure
- Osler's maneuver
  - Palpating radial arterial wall after collapsing with inflation of sphygmomanometer
  - Poor reproducibility & interobserver variability

Tsapatsaris, et al. Arch Intern Med 1991

Cuff-Inflation Hypertension

- Neurogenic-mediated increase in BP as the sphygmomanometer cuff is being inflated
- It can be diagnosed only by comparing the directly measured intraarterial diastolic pressure
- Why it occurs in only a few patients is not known

Kugler, et al. J Hypertens 1994

Cuff-Inflation Hypertension

- Can also be induced by the muscular activity associated with inflating the cuff when the patient takes his or her own BP

Veerman, et al. Lancet 1990

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Yakovlevitch, et al. Arch Intern Med 1991

Ingestion of Vasoactive Substance

- Exogenous substances can raise the BP
- In some cases, reduce the response to HT drugs

Setaro, et al. N Engl J Med 1992

Commonly used medications and other substances that may interfere with blood pressure control

- Nonsteroidal anti-inflammatory drugs
- Over-the-counter nasal sprays, oral decongestants, and appetite suppressants containing vasoactive compounds
- Estrogen-containg oral contraceptives
- Cholestyramine: decreases absorption of diuretics
- Rifampin: increases clearance of propranolol
- Aspirin: increases clearance of captopril
- Tricyclic antidepressant

Commonly used medications and other substances that may interfere with blood pressure control

- Cyclosporin
- Erythropoietin
- Anabolic steroid, corticosteroid
- Recreational drugs or illicit substance
  - Amphetamines
  - Cocaine
  - Cigarettes: increases metabolism of propranolol
  - Alcohol: consumption of more than 1 oz of ethanol
    - has direct pressor effect that may lessen benefit of antihypertensive agent

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Yakovlevitch, et al. Arch Intern Med 1991

Compensatory physiologic mechanisms and other causes of poor response to various antihypertensive medications

Medication	Cause of poor response
Diuretics	Excessive salt intake Overdiuresis activating of RAA Failure to use loop diuretics when creatinine clearance < 30 mL/min

Compensatory physiologic mechanisms and other causes of poor response to various antihypertensive medications

Medication	Cause of poor response
Adrenergic Blocker	Salt and water retention Beta blocker causing unopposed alpha receptor activity and increased peripheral resistance Rebound hypertension with sudden discontinuation of alpha blocker

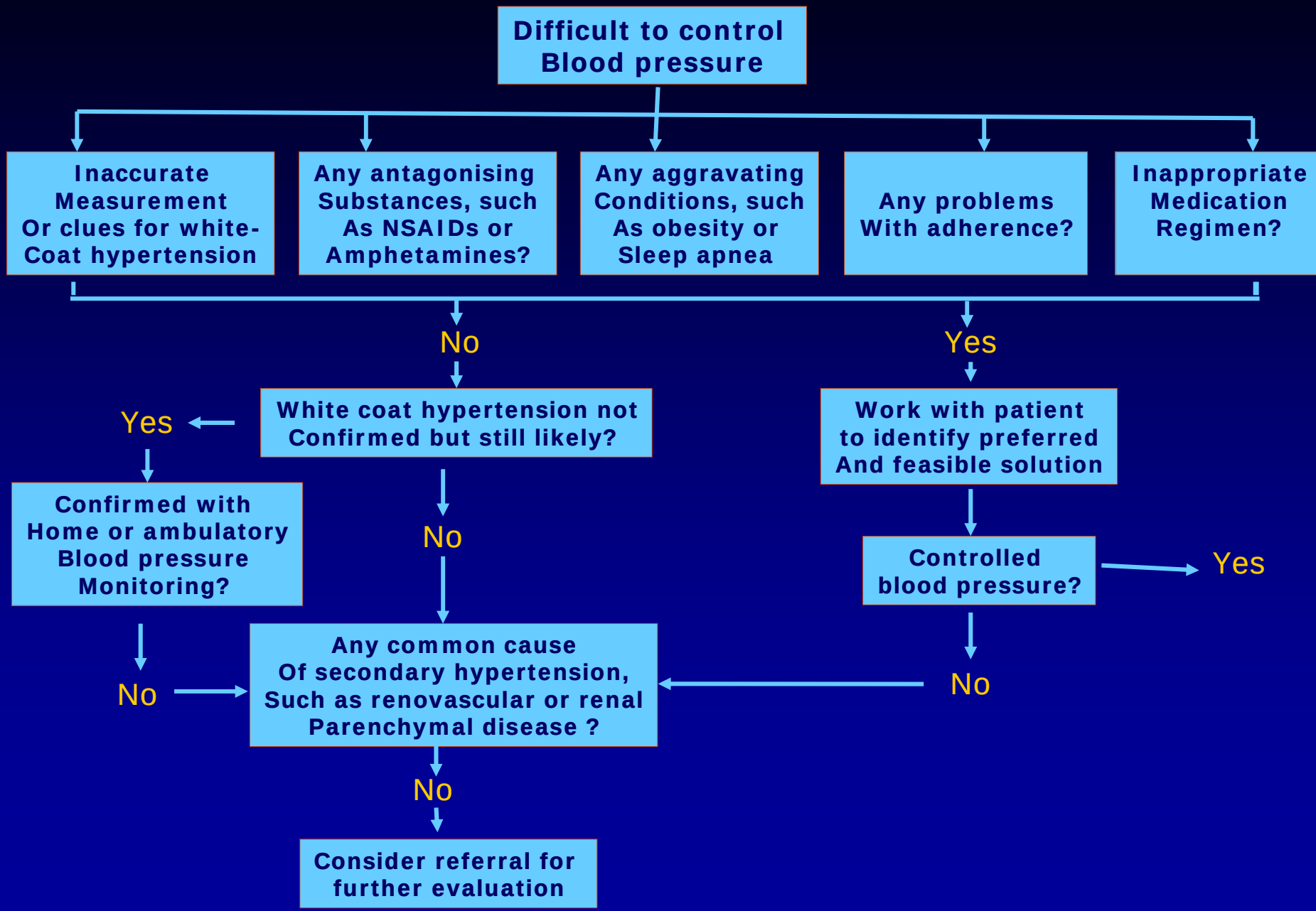
Compensatory physiologic mechanisms and other causes of poor response to various antihypertensive medications

Medication	Cause of poor response
ACEI	Salt and water retention Hyperreninemia leading to increased production of angiotensin I

Compensatory physiologic mechanisms and other causes of poor response to various antihypertensive medications

Medication	Cause of poor response
Direct Vasodilator	Salt and water retension Reflex sympathetic stimulation Hyperreninemia

Algorithm for resistant hypertension



Physicians should ask themselves ....

- Is the patient's blood pressure really elevated?
- Would home monitoring help?
- What is the extent of target-organ damage?
- Is the medical regimen appropriate?
- Have I added a diuretic?
- Is the patient adhering to the regimen?
- Can I help the patient be more compliant?
- What has happened to lifestyle modifications?
- What is the patient's sodium intake?
- Is there a secondary cause of hypertension that has not been excluded?

Summary

- With appropriate evaluation of both patient- and physician-related factors, many cases of resistant hypertension can be resolved.
- Patients often do not understand the implications of their disease and need specific information regarding the importance of compliance with medication schedules and dietary restrictions.
- Physicians should also consider the possibility of drug resistance or the presence of an identifiable secondary cause.


Thank
You for
Your Attention

Persistent Refractory HT

- Minoxidil (2.5 to 20 mg, twice daily) is often effective
- The diuretic dose usually must be increased to prevent fluid retention
- Sympathetic or ß-blocker also must be taken to minimize reflex sympathetic activation