Resistant hypertension

Introduction

Variably defined but usually a failure to reach target BP despite multiple antihypertensive agents, including a diuretic. It is most commonly a consequence of poorly controlled SBP.

Although thought to be relatively common—up to 20–30% of study populations in clinical trials—the experience, when recruiting to these studies, has been that true resistant hypertension is actually less common if drug therapy is optimized and contributing factors are rectified.

In the UK, resistant hypertension is considered to be BP not controlled to target with maximal recommended and tolerated doses of an ACE-I/ARB + CCB + thiazide. The 2011 BHS/NICE guideline recommends that such patients are managed with a further diuretic (consider spironolactone), an α-blocker, or a β-blocker (and that a referral for specialist input is considered).

Although evidence for treatment strategies are generally limited, more robust guidance will hopefully emerge in the next few years; for example, the BHS PATHWAY 2 study has been designed to evaluate whether resistant hypertension is due to excess sodium retention and whether further diuretic is the most effective treatment. The study also hopes to determine whether plasma renin can be a useful guide to further treatment in this circumstance. At present, some clinicians measure renin concentrations in resistant patients, add a β-blocker or additional ACE/ARB if high and an α-blocker if normal, and change the diuretic (usually to spironolactone) if low. (See Fig. 6.9 for management algorithm.)

Characteristics of patients with resistant hypertension

- Obese.
- Elderly.
- Black patients.
- CKD.
- DM.
- High starting BP.

Checklist

- Is it really resistant BP? Does it meet the definition given earlier? Are you confident about compliance? Does the patient understand the condition, the benefits of treatment. and the role of each tablet?
- Revisit dietary salt restriction (aim to restrict 24h uNa^+ to <100meq), alcohol consumption, and weight loss (diet and exercise).
- Exclude contributory drugs (e.g. NSAIDs, steroids, COC, ciclosporin, decongestants, ESAs).
- Reconsider secondary causes of ↑ BP, especially renal disease, sleep apnoea, and primary hyperaldosteronism (📖 p. 474).

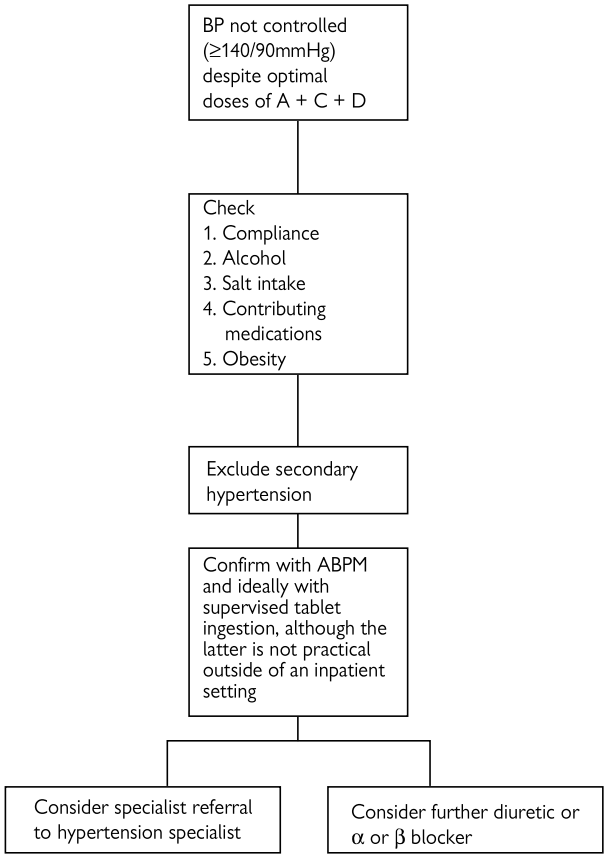

Fig. 6.9 Algorithm for the management of resistant hypertension.

Hypertensive urgencies and emergencies

Definitions

- ▶ Hypertensive crises are classified as *emergencies* or *urgencies*, based on the presence or absence of progressive target organ dysfunction.
  - *Emergencies:* severe ↑ BP complicated by evidence of acute or progressive organ dysfunction, such as cardiac ischaemia, encephalopathy, stroke, pulmonary oedema, or renal failure.
  - *Urgencies:* severe ↑ BP *without* evidence of acute or progressive target organ dysfunction.
- The term *malignant hypertension* was coined before antihypertensive therapy improved an appalling prognosis (1-year mortality ~90%). It is a syndrome of ↑ BP with progressive target organ damage and papilloedema. Pathologically, arteriolar fibrinoid necrosis is the characteristic lesion.
- *Accelerated hypertension* was applied to the scenario of retinal haemorrhages and exudates without papilloedema. The distinction from malignant hypertension is unhelpful, as both carry an identical prognosis.
- There is no threshold of BP above which malignant hypertension develops. DBP ranges from 100–180mmHg, SBP 150–290mmHg.
- ▶ Severity is not determined by BP alone—it is the clinical context and degree of target organ dysfunction.
- Affects <1% of the hypertensive population, but the hypertensive population is large. ♂>♀.
- Essential hypertension accounts for ~2–30% of episodes in Caucasians but ~80% in black patients (▶ therefore, usually avoidable).
- Renal disease (intrinsic and renovascular) accounts for the majority of the rest. Other previously unrecognized forms of secondary ↑ BP may also be responsible.
- The duration of hypertension prior to the development of malignant phase may range from days to years.

Pathophysiology

Vascular autoregulation

Autoregulation describes the ability of organs to maintain their perfusion, regardless of BP. ↑ BP causes distal arteriolar vasoconstriction, protecting end-organs from hypertensive mechanical stress. Hypertensive emergencies are associated with a failure of this process, resulting in transmission of ↑ BP to the microvasculature where mechanical trauma → endothelial injury →↑ vascular permeability → leakage → platelet and fibrin deposition → fibrinoid necrosis. Catecholamines and vasopressin release also contribute.

Endocrine and paracrine mediators, including RAS, are activated with ↑ A2, leading to further vasoconstriction and ischaemia. Volume depletion due to pressure natriuresis stimulates further renin release and worsens ↑ BP. A vicious cycle of vasoconstriction and worsening ↑ BP ensues.

Pathological changes

Vascular lesions are due to endothelial injury and consist of myointimal proliferation and fibrinoid necrosis, with subendothelial lipid deposition and hyaline thrombi. Vascular smooth muscle hypertrophy and collagen deposition contribute to medial thickening, which, with cellular intimal proliferation, results in the 'onion skin' appearance of small vessels, with luminal narrowing. Ischaemia or infarction of end-organs may occur. These changes are particularly well seen in the kidney, with proliferative endarteritis of the interlobular arteries, fibrinoid necrosis of the afferent arteriole, and glomerular ischaemia (± tubulointerstitial damage) (see Figs 6.10 and 6.11).

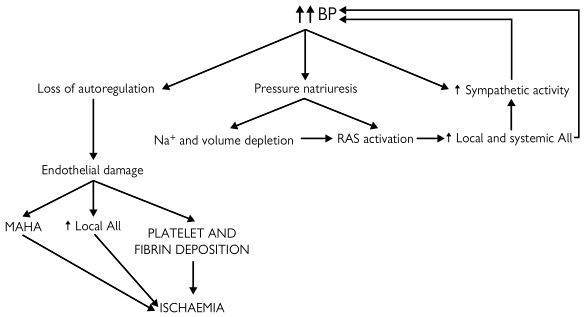

Fig. 6.10 The pathophysiology of malignant hypertension. Redrawn with permission from *Acute Renal Failure in Practice*, Imperial College Press. (MAHA: microangiopathic haemolytic anaemia.)

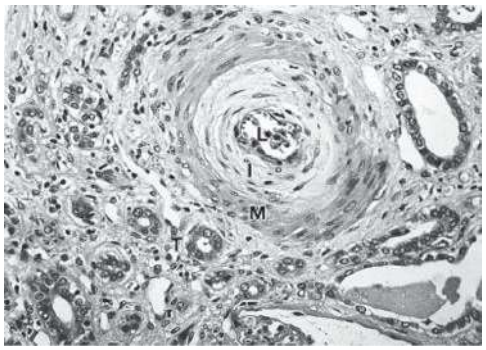

Fig. 6.11 Proliferative endarteritis of an interlobular artery in malignant hypertension. I, arterial intima showing gross proliferative change and 'onion skin' appearance; L, severely narrowed arterial lumen; M, arterial media; T, tubular atrophy and interstitial fibrosis. Reproduced with permission from Davison AMA, Cameron JS, Grunfeld J-P, *et al.* (eds) *Oxford Textbook of Clinical Nephrology*, 3rd edn. (2005) Oxford: Oxford University Press.

Assessing urgencies and emergencies

How does the BP compare to previous readings?

- 160/100 may be sufficiently high to cause acute TOD in a previously normotensive patient.
- A patient with long-standing hypertension may tolerate a higher BP without any evidence of acute TOD.

Clinical assessment

- ► Assess degree of target organ involvement.
- *Urgency* if ↑ BP without acute or progressive TOD.
- *Emergency* if ↑ BP with acute or progressive TOD.

Is there evidence of target organ damage?

Acute TOD

►► *Manage as an inpatient as an emergency:*

- Neurological symptoms: at risk for haemorrhagic or thrombotic stroke, encephalopathy (altered consciousness, fits, focal signs).
- LVF.
- Acute kidney injury failure (send U&E, dipstick urine).
- ⚠ Chest pain. Acute coronary syndrome → MI or aortic dissection. Perform ECG, and check pulses. If in doubt: CT aorta.
- Visual symptoms ± *either* grade III *or* IV hypertensive retinopathy.
- Pancreatitis due to haemorrhagic infarction (rare).

What medication has the patient been on until now?

- Continue current medication, adding in further treatment, as necessary.
- Check previous adherence to medication (recent non-compliance is very common in this situation). ⚠ Beware precipitating hypotension by restarting multiple antihypertensives in the previously non-adherent patient.
- ► Remember recreational drug use (cocaine, amphetamines).

Symptoms and signs

- *BP:* no pathognomonic values. Usually >220/140mmHg (range: DBP 100–180mmHg, SBP 150–290mmHg). Check BP in both arms; look for missing pulses, bruits, or an AAA.
- *Eyes:* visual disturbances (35–60%)—often present to ophthalmology.
- *Neurological:* headache (60%), dizziness (30%), neurological deficit, e.g. hemiparesis, cortical blindness (<10%). Posterior reversible encephalopathy syndrome (PRES), also known as reversible posterior leucoencephalopathy syndrome (RPLS), is increasingly recognized. PRES is characterized by headache, confusion, seizures, visual loss, and areas of cerebral oedema on MRI. The syndrome tends to resolve with treatment of BP, although visual defects may persist.
- *Renal:* AKI (30%).
- *Cardiovascular:* dyspnoea 2° to LVF (~10%), chest pain (~4%).

Hypertensive retinopathy

Grade 1: arterial narrowing (tortuosity, 'silver wiring' are subjective).
Grade 2: AV nipping.
Grade 3: haemorrhages and exudates.
Grade 4: papilloedema.

Investigations

- *Urinalysis:* proteinuria (can be nephrotic range—send uPCR, haematuria, cellular casts (red cell casts may indicate parenchymal renal disease).
- *U&E:*
  - *Serum creatinine, eGFR:* acute (or acute-on-chronic) kidney injury.
  - *Potassium:* ↓ K^+ (2° hyperaldosteronism → hypokalaemic alkalosis; renin and aldosterone are both raised in malignant hypertension), ↑ K^+ (2° to AKI) also possible.
- *FBC:* microangiopathic haemolytic anaemia—↓ Hb, ↓ platelets, red cell fragments, ↓ haptoglobins, ↑ ESR.
- *ECG (± echocardiogram):* LVH, ischaemia, MI.
- *CT brain*: if ↓ GCS or neurological signs.
- *MRI brain:* PRES/RPLS.
- *Renal biopsy:* a diagnostic or prognostic renal biopsy may be necessary. ⚠ Blood pressure must be controlled first (📖 p. 80).

Secondary hypertension?

Some conditions require specific management. Consider the list in Box 6.6.

Box 6.6 Causes of hypertensive emergencies

- Essential hypertension.
- Renal parenchymal disease:
  - Glomerulonephritis.
  - Tubulointerstitial disease.
- Systemic diseases:
  - Systemic sclerosis.
  - HUS/TTP.
  - SLE.
  - Antiphospholipid antibody syndrome.
  - Vasculitis.
- Renovascular disease:
  - Atheromatous.
  - Fibromuscular hyperplasia.
- Pre-eclampsia/eclampsia.
- Coarctation.
- Endocrine:
  - Conn's syndrome.
  - Phaeochromocytoma.
  - Cushing's syndrome.
- Drugs:
  - Cocaine.
  - Amphetamines.
  - Ecstasy.
  - MAOI interactions.
  - Erythropoietin.
  - Ciclosporin.
  - Tacrolimus.
- Tumour-related:
  - Renal cell carcinoma.
  - Lymphoma.

Management of urgencies and emergencies

Hypertensive emergency

Patients with severely raised or rapid rise in BP, with severe grade 3–4 hypertensive retinal changes. Often have evidence of concurrent TOD.

► ***Treatment when acute, life-threatening organ damage***

- Treat in a high dependency environment.
- Continuous BP monitoring.
- Volume depletion may be present—resuscitate with 0.9% NaCl.
- Initial aim of treatment is to ↓ DBP to ~110–115mmHg. Aim to achieve this in 2–6 hours.
- ⚠ A rapid fall may → clinical consequences with ↓ cerebral, spinal cord, and myocardial perfusion or acute kidney injury.
- Parenteral agents are often required.
- *Options:* see Table 6.11 for drugs used in emergencies.
  - Sodium nitroprusside. The parenteral drug of choice in many centres. Dose 0.25–1.5 micrograms/kg/min, with increase of 0.5 micrograms/kg/min every 5min until adequate response. ⚠ Associated with cyanide toxicity (prevent by protecting drug from light; risk increased at >2 micrograms/kg/min and in renal failure).
  - Labetalol (combined α- and β-blocker) particularly logical in IHD and aortic dissection. 20mg IV initially over 1min, followed by infusion 0.5–2mg/min. Safe in pregnancy.
  - Glyceryl trinitrate (GTN) 2–10mg/h. Useful with symptomatic coronary artery disease or acute LVF. ⚠ Care if volume-depleted. Tachyphylaxis occurs after 24–48h.
- Once BP within target range, transfer to oral agent, and wean IV infusion over 4–8h.

► ***Treatment when no life-threatening organ damage***

- May have features of malignant hypertension with TOD but not life-threatening.
- Aim ↓ diastolic BP to 110–115mmHg over 24–48h.
- Oral agents preferred.
- Low blood volume may manifest after treatment initiated (→ postural drop of >20mmHg suggests hypovolaemia in need of correction).
- Start with slow-release nifedipine, e.g. nifedipine retard/MR 10mg. Repeat the same dose at 2h intervals, with maintenance doses of 20mg 3× day. 1 Do not use capsules or LA preparations.
- Amlodipine is long-acting—it will reduce BP over days ∴ not suitable in urgent situations. Consider starting concurrently with nifedipine MR and then weaning off nifedipine after ~72 hours.
- Second-line therapy is a β-blocker. Particularly helpful with coexisting IHD or resting tachycardia.
- ⚠ ACE-I should be used with caution (→ abrupt ↓ BP, potential hypoperfusion/AKI).
- Diuretics should also be used with caution unless clear fluid overload.

Hypertensive urgency

► ***Severe uncontrolled hypertension (>130 DBP) with no evidence of acute TOD***

- If no acute TOD, does not necessarily require hospital admission.
- Repeat BP after 1–2h to confirm. If DBP still >130mmHg → treat.
- Use the same oral agents as in emergency. Start with a single agent. Aim for diastolic BP 100–110mmHg at first. Recheck BP after 24–48h.
- If still uncontrolled, increase dose, or add in second agent.

Recheck after every 2–3 days until BP at desired level. Treat according to BHS guidelines (📖 p. 488):

- Elderly or black patients → CCB.
- Then A + C.
- Then A + C + D.
- It is appropriate to start an ACE-I (e.g. ramipril) at full dose if normal renal function and unlikely significant RAS.

Prognosis

Without effective treatment: 1-year mortality ~90%, with effective treatment <10%. Many patients who develop renal insufficiency will recover renal function, even if initially dialysis-dependent, although this may take several months.

Table 6.11 Drugs used in hypertensive emergencies

Drug	Route and dose	Comment
Calcium channel blockers	Oral nifedipine MR 10mg 12h; max 40mg 12h (consider concomitant amlodipine 5–10mg; (see text on 📖 p. 522))	NEVER use rapid release formulations Nimodipine used post-subarachnoid haemorrhage
β-blockers	Oral Useful 2nd line (e.g. atenolol 50mg daily)	SE: bronchospasm
ACE inhibitors	Oral Start with low dose (e.g. ramipril 2.5mg or captopril 6.25mg), and titrate up	May cause rapid fall in BP Avoid in AKI Treatment of choice in scleroderma crisis
Diuretics	Oral/IV furosemide 40–120mg 12h	Beware volume depletion
α-blockers	Oral doxazosin MR 4mg 12h (up to 8mg 12h)	Useful because of titration range

(*Continued*)

Table 6.11 (Continued)

Drug	Route and dose	Comment
Labetalol	IV Up to 2mg/min as infusion or 20–80mg bolus every 10min	Safe in pregnancy. Used in pre-eclampsia Can be converted IV to PO SE: bronchospasm, LVF, heart block
Esmolol	IV25–200 micrograms/kg/min Initial bolus of 0.5–1.0mg/kg	Very short half-life SE: as for labetalol
Sodium nitroprusside	IV Start 0.25–1.5 micrograms/kg/min. (↑ 0.5 micrograms/kg/min every 5min until response). Range 0.25–10 micrograms/kg/min	Potent, rapid-acting, vasodilator Requires close monitoring (? arterial line) and light-resistant delivery equipment SE: nausea, vomiting, thiocyanate accumulation (esp. if renal impairment)
Nitrates (GTN)	IV 10–200 micrograms/min	Familiar SE: headache, tachycardia, tachyphylaxis, vomiting
Hydralazine	IV 5–10mg bolus, repeated after 1h. Infusion: start 200–300 micrograms/min, maintenance 50–150 micrograms/min	Arterial vasodilator used in eclampsia SE: Na^+ and water retention, headache, tachycardia, vomiting
Phentolamine	IV 1–5mg, repeated as necessary	Phaeochromocytoma SE: tachycardia, dizziness, flushing, nausea
Fenoldopam	IV 0.1–0.3 micrograms/kg/min	Dopamine-1 agonist and peripheral arterial vasodilator Also ↑ urine flow and both Na^+ and K^+ excretion attractive if ↓ GFR SE: headache, tachycardia, flushing