

Resistant hypertension

Updates, issues and approach to management

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Successful management of poorly controlled hypertension requires careful distinction of true resistant hypertension from other causes such as poor adherence to hypertension medications, undiagnosed secondary hypertension and white-coat hypertension. An individualised approach that includes modifying lifestyle and diet and optimising pharmacotherapies is recommended for patients with suspected resistant hypertension.

Hypertension is the strongest contributor to the burden of disease worldwide according to the World Health Organization and, as such, is a leading cause of preventable and premature death.¹ Hypertension is highly prevalent in Australia, where at least 34% of adults are known to be

hypertensive, and is associated with reduced productivity and poorer quality of life.²⁻⁴ Globally, rates of hypertension are rising due to ageing populations and lifestyle risk factors including poor diet, obesity and physical inactivity.⁵ Despite the compelling benefits of reduced morbidity and mortality by treating

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hypertension, up to 23% of Australian adults have uncontrolled hypertension with blood pressure above currently recommended targets.⁴

People with hypertension that appears resistant to therapy are increasingly encountered in primary care. GPs play a crucial role in both delineating true resistant hypertension from other causes of poorly controlled hypertension and in improving blood pressure (BP) control



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in this important group with high cardiovascular risk. This article discusses an exemplary case (Box 1), summarises clinical issues and provides an approach to diagnosis and management of resistant hypertension.

Risk factors for resistant hypertension

Uncontrolled hypertension may have patient, clinician and environmental

factors contributing. Patient factors cross biopsychosocial domains and include lifestyle factors (high salt diet, alcohol consumption, physical inactivity, obesity, smoking), poor medication adherence and secondary causes of hypertension. Clinician factors such as therapeutic inertia are also important and have been implicated in high rates of uncontrolled hypertension, both locally and internationally.^{6,7}

KEY POINTS

- Resistant hypertension is present when blood pressure remains elevated despite adherence to three or more antihypertensive medications at optimally tolerated doses (including a diuretic) and lifestyle modification.
- White-coat hypertension and causes of secondary hypertension such as obstructive sleep apnoea and chronic kidney disease need to be excluded.
- Both 24-hour ambulatory and home blood pressure self-monitoring are important diagnostic and management tools in suspected resistant hypertension.
- Treatment of resistant hypertension comprises optimising lifestyle modifications such as lowering salt intake, weight loss and exercise, and using more aggressive pharmacotherapy with combinations of medications from different classes that also specifically include a diuretic. Specialist consultation may be required.
- Techniques to improve patient engagement such as app-based technologies and home blood pressure self-monitoring may improve adherence to medication and lifestyle modifications.

Resistant hypertension is distinct from uncontrolled hypertension and is defined by the International Society of Hypertension as an office BP above 140/90 mmHg in patients treated with three or more antihypertensive agents at maximally tolerated doses and including a diuretic.

The strongest risk factors for resistant hypertension are obesity and older age.⁸ Obesity is associated with sympathetic overactivity, sustained activation of the renin-angiotensin-aldosterone system and an increase in cardiac output and vascular stiffness, which all contribute to the development of resistant hypertension.⁹ Older individuals are more likely to have heavily calcified or atherosclerotic

1. A 57-YEAR-OLD MAN WITH RESISTANT HYPERTENSION

A 57-year-old male patient is diagnosed with hypertension by his GP after recording an average blood pressure (BP) of 170/110mmHg on three separate visits. He is a smoker and his body mass index is 35.6kg/m². End-organ damage is not evident, with normal fundoscopic examination and no microalbuminuria. The patient is started on ramipril and amlodipine, which are titrated to maximum doses; however, target BP is not achieved. At subsequent review hydrochlorothiazide is added to his antihypertensive regimen.

The patient returns three months later for follow up and his 24-hour ambulatory BP monitor profile shows an average daytime BP of 156/94mmHg and night-time BP of 146/92mmHg despite being adherent with his medications. He does not have features or a history of obstructive sleep apnoea, including sleep disturbance, daytime somnolence, heavy snoring or apnoea.

Nonpharmacological interventions are emphasised, including weight loss, dietary salt and caloric restriction, regular physical exercise, avoidance of excessive alcohol consumption and smoking cessation. Screening for secondary causes of hypertension is undertaken and is unremarkable. Additionally, the patient is assessed for overall cardiovascular risk, including diabetes and hypercholesterolaemia screening. Low-dose spironolactone is added with careful monitoring of serum electrolyte levels, particularly as it is used in combination with an ACE inhibitor. Should these measures fail, referral to a hypertension specialist should be considered.

arteries, contributing to this phenotype of resistant hypertension.

Secondary causes and pseudoresistance require exclusion

To diagnose resistant hypertension, clinicians must exclude pseudoresistance including white-coat hypertension (where

BP is artificially elevated when measured in healthcare settings but is normal in a patient’s home environment), non-adherence to medications or lifestyle interventions, or errors in blood pressure measurement technique.¹⁰ Twenty-four-hour ambulatory BP measurement or home BP self-monitoring can be useful tools for excluding these possibilities. A

thorough assessment of patient adherence to lifestyle modifications and medications is essential. Lack of adherence can account for up to 50% of cases of apparent resistant hypertension.¹¹ Addressing poor adherence due to intentional and nonintentional factors is vital to improving blood pressure control in apparent resistant hypertension. Improving poor adherence requires an individualised and patient-centred approach. Tools to improve patient engagement such as home BP self-monitoring and electronic resources that incorporate an array of behaviour change techniques have been shown to improve blood pressure control in various hypertensive patient populations and may be useful in certain individuals.¹²⁻¹⁴

A thorough investigation of secondary causes of hypertension is also required. Secondary causes include substance or drug-induced hypertension from medications and over-the-counter supplements (Table 1), chronic kidney disease (CKD), renal artery stenosis, obstructive sleep apnoea, hypothyroidism, primary hyperaldosteronism, Cushing’s syndrome and pheochromocytoma (Table 2). Secondary hypertension is more likely present in individuals who are younger (under 30 years of age), present with malignant hypertension, have features of end-organ damage, or have an acute rise in BP after previously stable readings.

Lifestyle modification and interventions require optimisation

Strong evidence supporting changes to diet and physical activity in the effective treatment of hypertension exists, and these are recommended in international guidelines.^{10,15-17} Specific lifestyle interventions proven to lower blood pressure in people with hypertension include:

- reducing dietary salt consumption (read food labels and target foods with sodium content less than 150 mg per 100 g, or consume a total of less than 4g of table salt per day)
- reducing alcohol intake (no more than one standard drink per day)

TABLE 1. CAUSES OF DRUG-INDUCED HYPERTENSION

Drug class	Examples
Angiogenesis inhibitors	Vascular endothelial growth factor inhibitors (bevacizumab, ramucirumab) Tyrosine kinase inhibitors (sorafenib, sunitinib)
Antidepressants	Venlafaxine, bupropion
Caffeine	
Calcineurin inhibitors	Tacrolimus, ciclosporin
Corticosteroids	Prednisolone
Decongestants	Pseudoephedrine, phenylephrine
Herbal preparations	Ginseng, ephedra, liquorice, St John’s Wort
Hormonal therapies	Oral contraceptive pill, testosterone
Illicit drugs	Amphetamines, cocaine
Nicotine replacement	Nicotine
Nonsteroidal anti-inflammatory drugs	Ibuprofen, celecoxib

TABLE 2. CAUSES OF SECONDARY HYPERTENSION AND INVESTIGATIONS

Cause	Possible clinical indicators	Initial investigations
Common		
Obstructive sleep apnoea	<ul style="list-style-type: none"> • Obesity • Apnoeic episodes during sleep or snoring 	<ul style="list-style-type: none"> • Sleep study (polysomnography)
Chronic kidney disease	<ul style="list-style-type: none"> • Elevated creatinine level/reduced glomerular filtration rate • Albuminuria/proteinuria • Abnormal renal imaging 	<ul style="list-style-type: none"> • Serum biochemistry • Urine microscopy and protein levels • Renal tract ultrasound
Renal artery stenosis	<ul style="list-style-type: none"> • Rise in creatinine level of >30% after starting ACE inhibitor/angiotensin II receptor blocker • Flash pulmonary oedema 	<ul style="list-style-type: none"> • CT renal angiogram
Primary hyperaldosteronism	<ul style="list-style-type: none"> • Hypokalaemia • Adrenal lesion 	<ul style="list-style-type: none"> • Serum aldosterone renin ratio
Less common		
Thyroid disease	<ul style="list-style-type: none"> • Bradycardia/tachycardia • Cold/heat intolerance • Constipation or diarrhoea • Irregular, heavy or absent menstrual flow 	<ul style="list-style-type: none"> • Serum thyroid stimulating hormone level
Phaeochromocytoma	<ul style="list-style-type: none"> • Flushing, palpitations, headaches, labile blood pressure 	<ul style="list-style-type: none"> • Serum and urine metanephrines and normetanephrines
Cushing's syndrome	<ul style="list-style-type: none"> • Central obesity and striae • Moon facies and buffalo hump 	<ul style="list-style-type: none"> • Midnight salivary cortisol • Dexamethasone suppression test
Coarctation of aorta	<ul style="list-style-type: none"> • Younger patients • Arm to leg systolic blood pressure difference • Delayed or absent femoral pulses 	<ul style="list-style-type: none"> • Transthoracic echocardiogram • MR or CT thoracic angiogram

- smoking cessation
- weight loss
- regular exercise (30 to 40 minutes, at least three times per week if possible).

Although specific targets and thresholds exist for optimal blood pressure management in most hypertension guidelines, there is also supportive evidence that any degree of dietary salt reduction, alcohol reduction or weight loss will likely be beneficial in lowering blood pressure.^{10,15-17}

Lifestyle factors are highly modifiable for most individuals; however, significant therapeutic nihilism and inertia exist. This

may be in part because modifying diet and physical activity are among the most difficult therapeutic interventions for patients to adopt with consistent and lasting effects. Significant investment of time and effort from both clinicians and patients is required, and clinically overt benefit may take weeks to months to occur, whereas medication effects are seen within days to weeks. Despite these challenges, persistence is rewarded not only by improved blood pressure control, but by additional improvement for the individual and their household in other important health outcomes such as risk

of developing type 2 diabetes and ischaemic heart disease.

Techniques to improve patient engagement and adherence to lifestyle interventions are numerous and require individualisation and effective use of available resources (Table 3). Electronic resources such as websites and smartphone apps have shown efficacy in promoting lasting positive diet and exercise changes in certain patient groups, particularly in relation to dietary salt restriction.^{18,19} These resources often focus on promoting behavioural change in patients through empowerment, increasing knowledge, increasing motivation and influence.²⁰ This is an exciting and rapidly evolving area; however, ongoing caution is needed as currently only a portion of smartphone apps have been scientifically validated with clinically significant outcomes.

Pharmacological treatment of resistant hypertension

Patients with resistant hypertension are already on three or more antihypertensive medications at the time of diagnosis. Ideally, these three agents should act through complementary mechanisms and typically include a combination of renin-angiotensin system (RAS) blockade with an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, a calcium-channel blocker and a thiazide-type diuretic. Medications should be titrated to maximally tolerated doses. However, in the presence of specific medical conditions such as concurrent heart disease, the initial therapeutic combination may be different and include medications such as beta-blockers.

Several therapeutic strategies should be considered before adding a fourth agent, including:

- combining all drugs into a single pill formulation to simplify the regimen and improve adherence
- modification of dose timing in order to include night-time dosing for at least one agent
- switching to a different type of diuretic.

TABLE 3. TECHNIQUES TO IMPROVE PATIENT ENGAGEMENT AND ADHERENCE TO MEDICATIONS AND LIFESTYLE MODIFICATION

Potential cause of poor adherence	Techniques to improve adherence
Poor understanding/health literacy	<ul style="list-style-type: none"> Improve education through use of electronic resources (internet, smartphone apps), written material and referral to dietician Educational and motivational interviewing
Cost	<ul style="list-style-type: none"> Prescribe generic medications or less-costly older/first generation antihypertensive agents
Complex medication regimen and polypharmacy	<ul style="list-style-type: none"> Use fixed-dose combination products Use medications with less frequent dosing intervals and longer half-life Use medication administration aids such as pharmacist-provided dosing boxes/packs
Poor patient recall and motivation	<ul style="list-style-type: none"> Prescribe medications with reminder packaging Engage electronic patient reminders for medications or lifestyle therapies such as smartphone apps Use drug administration aids such as pharmacist-provided dosing boxes Engage support from carers/family members Increase engagement and empowerment through long-term home blood pressure self-monitoring and medication self-titration in suitable individuals
Multiple medication intolerances	<ul style="list-style-type: none"> Consider using fourth- or fifth-line agents at maximally tolerated doses Refer for specialist consultation
Patient inertia with lifestyle modification	<ul style="list-style-type: none"> Individualise target lifestyle interventions to focus on one or two key relevant areas Simplify general dietary advice through adoption of a dietary pattern such as DASH (dietary approaches to stop hypertension) or the Mediterranean diet Engage support from carers/family members

2. APPROACH TO MANAGING PATIENTS WITH SUSPECTED RESISTANT HYPERTENSION

1. Confirm suspected poorly controlled blood pressure (BP) and exclude pseudoresistance (white-coat hypertension) with 24-hour ambulatory or home BP monitoring
2. Ensure adequate home BP measurement technique if used
3. Evaluate for possible nonadherence using compliance indicators
4. Screen for secondary causes of hypertension
 - common causes include obstructive sleep apnoea, chronic kidney disease, primary hyperaldosteronism and renal artery stenosis
 - less common causes include other endocrine disorders and drug-induced hypertension
5. Attempt aggressive lifestyle and diet modifications
6. Review and optimise antihypertensive therapy
 - ensure antihypertensive agents used are from different classes and at maximal tolerated doses
 - ensure a diuretic is used. Consider adding an aldosterone antagonist (e.g. spironolactone)
7. Incorporate techniques to improve patient engagement and adherence such as:
 - reduce tablet burden through using combination products and longer-acting medications which require once- or twice-daily dosing
 - home BP measurement
 - app-based technologies for mobile devices such as tablet reminders, home-monitoring and chronic disease management tools, diet and exercise reference guides and progress trackers
8. Refer to hypertension specialist if hypertension does not improve

Thiazide-type diuretics, such as hydrochlorothiazide, chlorthalidone or indapamide are equally considered as first-line diuretic choices in the management of hypertension. In patients with CKD with an estimated glomerular filtration rate (eGFR) of less than 30 mL/min/1.73m², thiazide-type diuretics may still be used; however, caution is needed, noting greater variability in efficacy and need for closer monitoring for adverse effects.^{21,22} Loop diuretics (furosemide, bumetanide) are generally preferred first-line diuretic drugs in this group.

Aldosterone excess associated with sympathetic nervous system activation, sodium retention and fluid excess has been described as a key mechanism in the pathophysiology of resistant hypertension.²³ The possibility of subclinical hypervolaemia should be considered in every patient with persistently elevated BP. In the case of uncontrolled resistant hypertension despite optimisation of triple therapy, low dose spironolactone (mineralocorticoid receptor antagonist [MRA]) is the preferred fourth-line treatment. This is strongly supported by a

recent randomised, double-blind, crossover trial – PATHWAY-2, which has been incorporated into the latest hypertension guidelines.²⁴

Limitations of spironolactone and use of alternative antihypertensives

Despite its effectiveness, a number of important considerations are required when prescribing spironolactone because of its potential adverse effects that may limit clinical use. Spironolactone needs to be used with caution in patients with an eGFR below 45 mL/min/1.73m²

and/or potassium level above 4.5 mmol/L, as it may lead to a decline in renal function and hyperkalaemia.^{10,21,22} Furthermore, hormonal adverse effects of spironolactone, such as gynaecomastia and erectile dysfunction in men and menstrual irregularities in women, are frequently encountered. The newer generation aldosterone antagonist eplerenone does not confer the same gender-specific adverse effects but it is not currently available through the PBS for management of hypertension. Amiloride is an alternative potassium-sparing diuretic that reduces systolic BP at a similar magnitude to spironolactone and has a lower propensity for causing hyperkalaemia. Amiloride has recently become unavailable in Australia, and it is unknown if this is temporary or permanent.

Novel potassium binders ... have been shown to normalise hyperkalaemia and maintain normokalaemia with an acceptable safety and tolerability profile

Alternative and fourth-line antihypertensive agents are often required for patients with CKD or chronic bradycardia, or for those who experience adverse effects including peripheral oedema. Unfortunately, evidence guiding optimal therapy in these patient groups is often lacking. As an example, patients with CKD have been excluded from most clinical studies to date, such as the PATHWAY-2 trial on the treatment of resistant hypertension. In such patients, a pragmatic approach should be taken when considering any other available antihypertensive class not already in use.¹⁰ These include:

- cardioselective beta-blockers (e.g. bisoprolol, metoprolol and atenolol)
- alpha-blockers (e.g. prazosin)
- alpha-2 receptor agonists

- (e.g. methyldopa and clonidine)
- imidazoline receptor antagonist (e.g. moxonidine)
- vasodilators (e.g. hydralazine or minoxidil).

Novel oral potassium binders

The occurrence or fear of inducing hyperkalaemia has often led to premature discontinuation or suboptimal dosing of RAS blockers or MRAs. More recently, novel potassium binders such as patiomer and sodium zirconium (the latter is not currently available in Australia) have been shown to normalise hyperkalaemia and maintain normokalaemia with an acceptable safety and tolerability profile, as opposed to sodium polystyrene sulfonate which can cause sodium overload and lead to fluid retention. Patiomer is a non-absorbed, sodium-free potassium binding polymer that exchanges calcium for potassium in the gastrointestinal tract, thereby facilitating potassium excretion and reducing serum potassium levels. The AMBER trial showed that, among patients with resistant hypertension and CKD (eGFR between 24 and 4 mL/min/1.73m²), patiomer enabled more persistent use of spironolactone and reduced the risk of hyperkalaemia by nearly 50% compared with placebo.²⁵ These agents represent an attractive future strategy to circumvent RAS blocker/MRA discontinuation or dose reduction due to hyperkalaemia, although novel potassium binders are currently neither recommended in guidelines nor available through the PBS in Australia.

Interventional treatments for resistant hypertension

The past decade has seen the emergence of interventional endovascular treatments as alternatives or as an adjunct to pharmacotherapy in the management of resistant hypertension. These include catheter-based renal sympathetic denervation, carotid baroreceptor stimulation and carotid body ablation. Current guidelines still exclude device-based therapies

for routine treatment of resistant hypertension. Device therapy for true resistant hypertension is an active field of clinical research and may emerge in the next few years as a therapeutic option for carefully selected patients.

Conclusion

Hypertension is a complex disorder with genetic, physiological and environmental factors at play in each individual. Resistant hypertension must be differentiated from poorly controlled hypertension, pseudo-resistance and medication nonadherence before consideration of escalating pharmacological treatment. Any secondary causes of hypertension should be identified and strict lifestyle strategies should be emphasised. An effective approach to the management of resistant hypertension is summarised in Box 2. **MT**

References

A list of references is included in the online version of this article (www.medicinetoday.com.au).

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