Polish Society of Hypertension

2019 Guidelines for the Management of Hypertension

Part 8–9

Recommendations of the Polish Society of Hypertension

Guideline editors: Andrzej Tykarski, Krzysztof J. Filipiak, Andrzej Januszewicz, Mieczysław Litwin, Krzysztof Narkiewicz, Aleksander Prejbisz, Danuta Ostalska-Nowicka, Krystyna Widecka, Katarzyna Kostka-Jeziorny

Experts: Marcin Adamczak, Marta Buraczewska, Ludwina Szczepaniak-Chicheł, Marzena Chrostowska, Danuta Czarnecka, Piotr Dobrowolski, Grzegorz Dzida, Zbigniew Gaciong, Jerzy Gąsowski, Tomasz Grodzicki, Dagmara Hering, Beata Wożakowska-Kapłon, Przemysław Kosiński, Beata Begier-Krasińska, Jan Krekora, Jacek Manitius, Małgorzata Myśliwiec, Anna Niemirska, Arkadiusz Niklas, Łukasz Obrycki, Agnieszka Olszanecka, Sylwester Prokurat, Grażyna Brzezińska-Rajszys, Marek Rajzer, Katarzyna Stolarz-Skrzypek, Agnieszka Szadkowska, Filip M. Szymański, Anna Szyndler, Andrzej Więcek, Barbara Wizner, Jacek Wolf, Tomasz Zdrojewski

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8. Secondary hypertension

8.1. Introduction

Secondary hypertension is present in 5–10% of all hypertensive patients. Appropriate investigations followed by therapy directed at the cause of secondary hypertension may lead to elimination of the underlying cause, resulting in improved control or normalization of BP values with cardiovascular risk reduction.

Clues to the presence of secondary hypertension include:

- severe BP elevation (including paroxysmal hypertension and hypertensive crisis);
- rapidly progressing development of hypertension or worsening of BP control;
- resistant hypertension;
- development of malignant hypertension;
- poor response to antihypertensive drugs;
- presence of target organ damage that is disproportionate to the duration or severity of hypertension.

Suggestive signs and symptoms and diagnostic procedures to investigate for specific forms of secondary hypertension are summarized in Table XXXVII.

8.2. Obstructive sleep apnoea

8.2.1. Prevalence

Obstructive sleep apnoea (OSA) is present in a relatively large proportion of hypertensive patients, particularly among those with resistant hypertension (about 80%). Studies indicate that moderate to severe OSA that requires appropriate therapeutic management may be present in as many as 40–50% of patients with resistant hypertension. Of note, OSA is also associated with a 70% relative increase in the cardiovascular morbidity and mortality risk.

Due to frequent coexistence, common pathogenetic mechanisms with hypertension, and a limited effect of specific OSA treatment on BP values, some European experts have postulated to consider it a concomitant condition and not a secondary form of hypertension. However, American guidelines (JNC7) have listed OSA as an important and reversible cause of secondary hypertension.

8.2.2. History, physical examination, and routine and additional laboratory test abnormalities

The most common symptoms of OSA are habitual snoring, episodes of apnoea, and excessive daytime somnolence. Other manifestations of OSA include the following nocturnal symptoms: nycturia, increased motor activity and sweating during the night, awakenings, dyspnoea and/or choking during sleep, difficulties with falling asleep, insomnia, palpitations, mouth and throat dryness, and symptoms of gastroesophageal reflux. In addition to excessive daytime somnolence, other symptoms during the day include morning tiredness, morning headaches, impaired memory and concentration, decreased libido and impotence, psychoemotional problems, and an increased rate of traffic and workplace accidents. Studies also indicate that in some hypertensive patients, daytime symptoms of even severe OSA may be modest.

Obesity is the most common finding on physical examination, in particular abdominal obesity. The corrected neck circumference above 48 cm (measured neck circumference in centimetres plus 4 cm in hypertensives plus 3 cm if habitual snoring, and plus 3 cm if nocturnal choking/dyspnoea) is associated with a significantly increased risk of OSA.

Major underlying causes may include anatomical abnormalities of the upper airways, such as tongue hypertrophy, elongation of the soft palate, tonsil hypertrophy, and impaired nasal patency. Less frequent abnormalities include an abnormal anatomy of the splanchnocranium, for example mandibular hypoplasia and/or retraction.

Most commonly, OSA coexists with metabolic syndrome and thus abnormal glucose and lipid metabolism is often indicated by basic laboratory tests in these patients.

In patients with OSA, ABPM may reveal a reduced nocturnal BP fall, non-dipping BP pattern, or even BP elevation during the night. The presence of OSA may also be indicated by increased morning BP values as detected by HBPM. Holter monitoring in patients with OSA may show intermittent periods of brady- and tachycardia. Echocardiography may show left ventricular hypertrophy (usually of the concentric pattern), left atrial enlargement, diastolic dysfunction, and other abnormalities.

8.2.3. Investigations

Investigations for OSA should be considered in hypertensive patients with:

- clinical symptoms suggesting OSA;
- resistant hypertension;
- abdominal obesity and metabolic disturbances (particularly diabetes);
- concomitant coronary artery disease;
- a history of stroke/TIA;
- non-dipping BP pattern;
- nocturnal arrhythmia and/or conduction disturbances.

Available questionnaires, such as the Epworth Sleepiness Scale and the Berlin Questionnaire, lack specificity to allow excluding OSA. However, they

Table XXXVII. Suggestive symptoms, signs and laboratory test results, and specific investigations for secondary forms of hypertension

Cause of hypertension	Symptoms, signs, and routine and additional laboratory test results suggesting a secondary form of hypertension				Investigations	
	History	Physical examination	Routine tests	Additional tests	First choice (screening) tests	Confirmatory tests
Obstructive sleep apnoea	Characteristic daytime and nocturnal symptoms* Symptom evaluation using questionnaires*	Abdominal obesity Increased neck circumference* Abnormalities of the splanchnocranium	Elevated glucose level Dyslipidaemia	Reduced or absent nocturnal BP fall in ABPM Elevated morning BP values in HBPM Arrhythmia and/or conduction disturbances in Holter ECG monitoring becoming worse during sleep	Evaluation using questionnaires and nocturnal study using a type IV device*	Nocturnal study using a type I–III device*
Parenchymal renal disease	History or urinary tract infection or abnormal anatomy Haematuria Overuse of analgesics Family history of kidney disease	Palpable enlarged kidneys (in cystic kidney disease)	Presence of protein, erythrocytes, or leukocytes in urine Reduced GFR	Albuminuria/proteinuria of varying severity	Renal ultrasound	Detailed investigations for kidney disease
Primary hyperaldosteronism	Muscle weakness Family history, particularly of severe hypertension or early onset hypokalaemia and cerebrovascular events at < 40 years of age	Cardiac arrhythmia	Hypokalaemia (spontaneous or diuretic-induced)	Incidentally found adrenal lesion Severe target organ damage Reduced or absent nocturnal BP fall in ABPM	Aldosterone-renin ratio*	Confirmatory hormonal testing* Adrenal CT/MRI Adrenal venous sampling
Atherosclerotic renal artery stenosis	Hypertension: • sudden onset • increasing severity • worsening of BP control • resistant or malignant hypertension Recurrent flash pulmonary oedema	Vascular bruit in mid-abdomen	Rapid worsening of renal function (spontaneous or during treatment with RAAS inhibitors) Hypokalaemia	Renal ultrasound: kidney length difference > 1.5 cm, small kidney	Doppler renal ultrasound	CTA MRA Invasive angiography
Renal artery stenosis due to fibromuscular dysplasia	Age < 30 years Women of reproductive age Hypertension: • sudden onset • increasing severity • worsening of BP control • resistant or malignant hypertension History of fibromuscular dysplasia	Vascular bruit in mid-abdomen	Rapid worsening of renal function (spontaneous or during treatment with RAAS inhibitors) Hypokalaemia	Renal ultrasound: kidney length difference > 1.5 cm, small kidney	CTA MRA Doppler renal ultrasound (in experienced centres)	CTA MRA Invasive angiography
Catecholamine-secreting tumour	Paroxysmal BP elevations Headaches Increased sweating Palpitations, pallor Family history of phaeochromocytoma	Skin lesions typical for neurofibromatosis (*café au lait* spots, neurofibromas)	Hyperglycaemia	Incidentally found adrenal (or sometimes extra-adrenal) lesion	Plasma free metanephrines or urinary fractionated metanephrines	CT or MRI of the abdomen and pelvis ^{123}I-MIBG scintigraphy Screening genetic testing for pathogenetic mutations
Cushing syndrome	Rapid increase in body weight Polyuria Polydipsia Mood disturbances	Typical body physique (central obesity, moon face, buffalo hump) Red striae Hirsutism Easy bruising	Hyperglycaemia	Incidentally found adrenal lesion	24-hour urinary free cortisol excretion Low-dose (1 mg) dexamethasone suppression test	Dexamethasone suppression tests

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Table XXXVII. Suggestive symptoms, signs and laboratory test results, and specific investigations for secondary forms of hypertension

Cause of hypertension	Symptoms, signs, and routine and additional laboratory test results suggesting a secondary form of hypertension				Investigations	
	History	Physical examination	Routine tests	Additional tests	First choice (screening) tests	Confirmatory tests
Coarctation of the aorta	Intermittent claudication Headaches Syncope Epistaxis	Murmur heard in the precordial or interscapular area Diminished and delayed femoral artery pulse and decreased blood pressure in the femoral artery compared to simultaneous arm measurement Blood pressure difference between the left and right arm	Reverse E sign and rib notching on chest X-ray	Abnormalities on echocardiography	Echocardiography	CTA MRA
Renin-secreting tumour	Severe/resistant hypertension Polydipsia Polyuria	Cardiac arrhythmia (in severe hypokalaemia)	Hypokalaemia	Incidentally discovered kidney lesion	Renin level or plasma renin activity and aldosterone level	Kidney CT or MRI

*details see text; ABPM — ambulatory blood pressure monitoring; BP — blood pressure; CT — computed tomography; CTA — computed tomography angiography; ECG — electrocardiographic; HBPM — home blood pressure monitoring; GFR — glomerular filtration rate; MIBG — metaiodobenzylguanidine; MRA — magnetic resonance angiography; MRI — magnetic resonance imaging; RAAS — renin–angiotensin–aldosterone system

may be helpful in identifying patients at an increased risk of OSA and should be included in the basic evaluation of a hypertensive patient.

Investigations for OSA include 4 types of diagnostic devices and systems:

I. Complete polysomnography performed in a sleep laboratory.
II. Portable (unsupervised) polysomnography, recording a minimum of 7 channels, including all that are necessary to evaluate the sleep structure and the breathing pattern.
III. Respiratory polygraphy, or a limited recording of at 4 least parameters, including respiratory movements of the chest and abdomen, air flow through the upper airway, and arterial oxyhaemoglobin saturation, without evaluation of the sleep structure.
IV. Recording of maximum 2 parameters, e.g., nocturnal pulse oximetry.

Use of different diagnostic devices and the diagnostic algorithm in cases of suspected OSA are summarized in Figure 9.

8.2.4. Diagnostic criteria[1]

For the diagnosis of OSA, the criteria A, B, and D, or C and D must be met.

A. At least one of the following:
- inadvertent falling asleep, excessive daytime somnolence, ineffective sleep, tiredness, or insomnia;
- awakenings with the feeling of breathing cessation, dyspnoea or choking;
- habitual snoring or episodes of apnoea noted by the partner of the patient.

B. Polysomnography findings:
- at least 5 disordered breathing events per hour of sleep (AHI ≥ 5);
- respiratory muscle activity noted during these episodes;

C. Polysomnography findings:
- at least 15 disordered breathing events per hour of sleep (AHI ≥ 15);
- respiratory muscle activity noted during these episodes;

D. The above findings are not related to other sleep disturbances, conditions (including neurological disease), or use of medications or other substances.

Classification of the severity of OSA:
- mild OSA (AHI ≥ 5 and ≤ 15);
- moderate OSA (AHI > 15 and ≤ 30);
- severe OSA (AHI > 30).

[1]Modified American Academy of Sleep Medicine (AASM) criteria. In the original document, the diagnosis is based on the respiratory disturbance index (RDI) which includes apnoeas, hypopnoeas, and respiratory effort related arousals (RERA). However, many authors use the apnoea-hypopnoea index (AHI) for the diagnosis and evaluation of the severity of OSA, particularly in studies on the prevalence of OSA among hypertensives. Clinically, the difference between RDI and AHI is usually not significant, and reliable evaluation of RERA episodes requires oesophageal pressure measurement during sleep, and the latter is not routinely recorded during polysomnography. If RERA episodes cannot be evaluated, than AHI = RDI

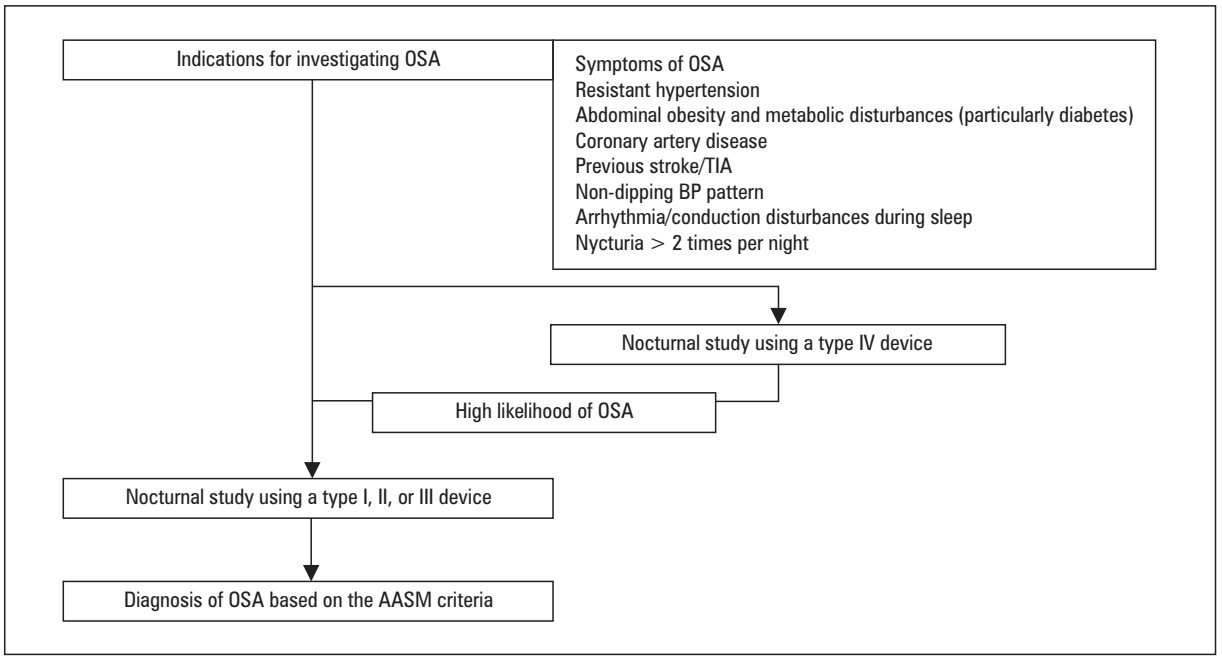

Figure 9. Diagnostic algorithm for obstructive sleep apnoea. AASM — American Academy of Sleep Medicine; BP — blood pressure; OSA — obstructive sleep apnoea; TIA — transient ischemic attack

8.2.5. Management of obstructive sleep apnoea

The management of OSA includes the following:

- body weight reduction (in all patients);
- avoidance of a supine position during sleep (in patients with confirmed positional OSA) or sleeping in a semi-sitting position (in patients with mild or moderate OSA without severe obesity);
- avoidance of alcohol intake (in all patients);
- smoking cessation (in all patients);
- avoidance of sedative-hypnotics and narcotic analgesics (in all patients);
- mandibular advancement devices (simple snoring and mild OSA not responsive to behavioural treatment);
- continuous positive airway pressure (CPAP) therapy [all patients with AHI > 30; patients with AHI > 15 and excessive daytime somnolence (Epworth Sleepiness Scale score > 10) or cardiovascular disease; in some cases CPAP may be considered in patients with AHI 5–15];
- surgical upper airway procedures (indications set on an individual basis, particularly in non-obese patients).

Studies indicate that regular use of CPAP for an appropriately long period of time during the night may be associated with BP lowering, particularly in patients with resistant hypertension, and may have a beneficial effect on the reduction of cardiovascular event risk.

8.2.6. Treatment of hypertension in patients with obstructive sleep apnoea

Limited data are available to develop recommendations regarding antihypertensive therapy in patients with OSA. Some evidence suggests benefits of diuretics, in particular aldosterone antagonists, in terms of not only improvement of BP control but also reduction of the severity of OSA. However, these studies were performed in small groups of patients and further studies are required. Further research is also necessary to determine potential benefits of renal denervation in these patients.

8.2.7. Care for patients with hypertension and concomitant obstructive sleep apnoea

The following issues should be evaluated during each visit related to the treatment of hypertension:

- in patients with previously undiagnosed OSA:
— symptoms suggestive for, and the risk of OSA,
— indications for investigations to diagnose OSA;
- in patients with established OSA without previous indications for CPAP therapy:
— compliance regarding behavioural therapy for OSA,
— indications for reassessment of the severity of OSA;
- in patients with established OSA and indications for CPAP therapy:
— compliance regarding behavioural therapy for OSA,
— compliance regarding CPAP therapy, and factors associated with noncompliance,

— frequency and duration of CPAP use during the night (based on data retrieved from the device memory).

8.3. Atherosclerotic renal artery stenosis

8.3.1. Definition

Hypertension due to renal artery stenosis, also known as renovascular hypertension, is a secondary form of hypertension caused by excessive renin production in the ischemic kidney. Significant renal artery stenosis does not only produce hypertension but also impairs excretory, endocrine, and homeostatic renal function and results in ischemic nephropathy. In some patients, renal artery stenosis is a cause of end-stage renal disease and the need for renal replacement therapy. Most commonly, renal artery stenosis is of atherosclerotic origin. The second most common cause of renal artery stenosis is fibromuscular dysplasia, which is discussed in a separate section of the present document.

8.3.2. Clinical presentation of atherosclerotic renal artery stenosis

Investigations for atherosclerotic renal artery stenosis should be considered particularly in patients with:

- hypertension that is:
— severe,
— resistant to treatment,
— malignant (accelerated);
- episodes of unexplained flash pulmonary oedema (Pickering syndrome) and/or unexplained congestive heart failure;
- unexplained renal failure (including patients in whom renal replacement therapy is initiated);
- new-onset azotaemia or worsening of renal function following administration of a RAS inhibitor;
- hypokalaemia, particularly in patients treated with diuretics;
- an abdominal bruit;
- difference in kidney length > 1.5 cm or a small kidney of unknown cause.

Atherosclerotic renal artery stenosis should also be suspected in hypertensive patients with atherosclerosis in other vascular beds, including coronary arteries. The rates of atherosclerotic renal artery stenosis correlate with the severity of atherosclerosis in other vascular beds.

Symptoms and signs and laboratory test findings suggestive of atherosclerotic renal artery stenosis are summarized in Table XXXVII.

8.3.3. Screening and confirmatory diagnostic methods for atherosclerotic renal artery stenosis

8.3.3.1. Doppler renal ultrasonography

Doppler renal ultrasonography is recommended as the first-line noninvasive diagnostic test in patients with suspected renal artery stenosis. It allows evaluation of the extra- and intrarenal arteries and localization of the stenosis. Assessment of the resistive index (RI) may be helpful for evaluating significance of a stenosis (difference versus the contralateral kidney ≥ 0.05) or predicting procedural outcomes.

In case of normal Doppler renal ultrasonography findings in patients with a significant clinical suspicion of renal artery stenosis, computed tomography angiography (CTA) or magnetic resonance angiography (MRA) of the renal arteries should be performed.

Doppler renal ultrasonography allows long-term follow-up of patients after correction of renal artery stenosis (to exclude recurrent stenosis) and evaluation of disease progression in medically treated patients. Follow-up examinations in revascularized patients should be performed immediately after the revascularization procedure and 6–12 months afterwards. Follow-up examinations to evaluate progression of borderline lesions treated medically should be performed annually. In these patient groups, urgent Doppler renal ultrasound reevaluation should be performed in case of acute worsening of BP control and/or renal function.

8.3.3.2. Computed tomography angiography

Computed tomography angiography is indicated to confirm the diagnosis of renal artery stenosis (in patients with eGFR > 30 mL/min/1.73 m^2). Normal CTA findings exclude a hemodynamically significant stenosis of the main renal artery.

8.3.3.3. Magnetic resonance angiography

Magnetic resonance angiography is indicated to confirm the diagnosis of renal artery stenosis (recommendation class I, level of evidence B). The most effective imaging sequence is three-dimensional gradient echo (3D GRE) following intravenous administration of a contrast agent. Contrast-enhanced MRA allows excluding a hemodynamically significant stenosis of the main renal artery. Paramagnetic contrast agents in doses used for magnetic resonance imaging (MRI) are not nephrotoxic. However, a possibility of nephrogenic systemic fibrosis in patients with renal dysfunction should be borne in mind. Gadodiamide, gadopentetate dimeglumine and gadoversetamide are contraindicated in patients with eGFR below 30 mL/min/1.73 m^2, including those on dialysis therapy and patients with acute kidney injury. In patients with eGFR 30–60 30 mL/min/1.73 m^2, these contrast agents may be used provided that a 7-day interval between subsequent studies is maintained. Other paramagnetic contrast agents not listed above

may be used in patients with eGFR below 30 mL/min/1.73 m^2 provided that a 7-day interval between subsequent studies is maintained, and they may be used without these restrictions in patients with eGFR 30–60 30 mL/min/1.73 m^2.

8.3.3.4. Invasive renal angiography

Invasive renal angiography is performed to image the renal artery and its branches. It involves introduction of a pigtail catheter to the aorta at the level of renal arteries and injecting an iodine contrast agent. This method allows very good visualization of both the main renal artery and accessory renal arteries, and particularly their origin from the aorta. Selective renal angiography using catheters with appropriately curved tips is also recommended. Invasive renal angiography may be considered to confirm the diagnosis of renal artery stenosis in patients with a clinical suspicion of renal artery stenosis and equivocal non-invasive imaging findings.

8.3.4. Management of atherosclerotic renal artery stenosis

Until now, no randomized study showed a significant effect of interventional treatment on the course of hypertension, renal function, and cardiovascular event rate. The decision to implant a stent into a renal artery with an atherosclerotic stenosis should be based on multiple additional clinical factors and laboratory parameters, including the degree of BP control, presence and/or progression of renal dysfunction, and occurrence of the Pickering syndrome (unexplained flash pulmonary oedema). Decisions to proceed with invasive treatment and performance of revascularization procedures should be left to appropriately experienced hypertension units.

The 2017 ESC guidelines do not recommend routine revascularization of atherosclerotic renal artery stenosis. According to these guidelines, balloon angioplasty with or without stenting may only be considered in patients with atherosclerotic renal artery stenosis and recurrent unexplained congestive heart failure or flash pulmonary oedema, and in patients with bilateral renal artery stenosis and acute oligo- or anuric renal failure without renal atrophy.

In patients with unilateral renal artery stenosis, ACEI and ARB are effective in the treatment of hypertension and may decrease progression of nephropathy. Even in unilateral renal artery stenosis, however, treatment with ACEI or ARB requires caution and monitoring of renal function parameters. ACEI and ARB are contraindicated in bilateral renal artery stenosis and renal artery stenosis in the single kidney. It is difficult to accept the opinion voiced in the 2017 ESC guidelines that these drugs may also be used in the latter patient groups provided that they are tolerated (no adverse effect on the renal function) and the treatment is strictly monitored.

Diuretics, calcium antagonists, and β-blocker-blockers are also effective in lowering BP to target values in patients with renal artery stenosis (with some reports indicating an adverse effect manifested by eGFR reduction in patients with bilateral renal artery stenosis).

All patients with atherosclerotic renal artery stenosis should be treated in accordance with the guidelines on secondary cardiovascular disease prevention. This includes use of antiplatelet and lipid-lowering therapies.

8.4. Renal artery stenosis due to fibromuscular dysplasia

The present section of the guidelines was developed based on the most recent First International Consensus on the diagnosis and management of fibromuscular dysplasia (FMD), published in *Journal of Hypertension* and *Vascular Medicine* in early 2019.

8.4.1. Definition of fibromuscular dysplasia

Fibromuscular dysplasia is an idiopathic, segmental, non-atherosclerotic, and non-inflammatory vascular disease that leads to the development of stenoses in small- and medium-sized arteries. In addition to atherosclerosis, FMD is the second most common cause of renal artery stenosis, responsible for about 10% of cases. The diagnosis and confirmation of FMD requires that the following conditions are excluded:

- renal artery spasm or artifacts during CTA imaging;
- atherosclerotic origin of arterial lesions;
- inflammatory arterial disease;
- monogenic arterial disease (e.g., neurofibromatosis type I).

8.4.2. Clinical presentation

Fibromuscular dysplasia most commonly involves renal arteries and leads to the development of hypertension. Cervicocephalic (carotid, vertebral and intracranial) arteries are the second most common location of FMD. However, FMD may be present in virtually all vascular beds, and is often concomitantly present in several areas in the vascular system. The arterial wall affected by FMD is prone to dissection and the development of aneurysms.

Renal artery dissection may have serious clinical consequences, leading to an acute development of severe hypertension, loss of kidney function, and renal infarction. In patients with FMD, dissection

may also involve other arteries, including carotid arteries (which may lead to stroke or TIA) and coronary arteries (which may result in an acute coronary syndrome).

Based on radiological findings, arterial wall lesions typical for FMD are categorized as unifocal or multifocal.

The diagnosis of FMD requires that at least one unifocal or multifocal lesion is identified in the arterial wall.

If uni- or multifocal FMD lesions are present in one vascular bed, the presence of an aneurysm, dissection or tortuosity within another artery suggests a multivessel involvement. In contrast, an isolated presence of an arterial aneurysm, dissection or tortuosity is not sufficient for the diagnosis of FMD.

Indications for investigating a possibility of renal artery stenosis due to FMD in hypertensive patients include:

- age below 30 years, particularly in women;
- grade 3 hypertension (≥ 180/110 mm Hg), accelerated or malignant hypertension;
- resistant hypertension (BP above target values despite use of 3 antihypertensive medications in optimal doses, including a diuretic);
- unilateral small kidney without a previous history of uropathy;
- abdominal bruit without evidence of atherosclerosis or its risk factors;
- established FMD in at least one other vascular bed.

Of note, no specific genetic testing for FMD is available, and genetic testing is not justified in asymptomatic relatives of patients with FMD.

While awaiting further advances in genetic testing targeted at FMD, relatives of patients with FMD should currently undergo clinical evaluation and imaging to evaluate potentially involved vascular beds, particularly as suggested by clinical symptoms.

Symptoms and signs and laboratory test findings suggestive of renal artery stenosis due to FMD are summarized in Table XXXVII.

8.4.3. Investigations for renal artery stenosis due to fibromuscular dysplasia — screening and confirmatory tests

Doppler renal ultrasonography should be performed as a screening test for renal artery stenosis due to FMD in all hypertensive women of reproductive age, particularly those planning pregnancy.

While duplex ultrasound to evaluate renal arteries is used as a screening method in women of reproductive age (particularly those planning pregnancy), in patients with a suspicion of renal artery stenosis due to FMD (with indications for testing as outlined above) it remains a first-line imaging test only in tertiary care units with extensive experience with the use of this modality for the evaluation of the vascular system.

In patients with a suspicion of renal artery FMD, CTA remains the imaging test of choice, and MRA is the alternative imaging modality if CTA is contraindicated.

Imaging to identify FMD within renal, carotid, vertebral, and intracranial arteries should be considered if typical symptoms of FMD are present.

Invasive digital subtraction angiography of the renal arteries is recommended in patients with FMD confirmed by CTA or MRA if revascularization is clinically indicated. It may also be considered in patients with a high degree of suspicion of renal artery stenosis due to FMD if the diagnosis is uncertain based on non-invasive studies.

A separate issue is the choice of imaging modality in patients with suspected FMD in carotid, vertebral and intracranial arteries, as currently there is no evidence that would clearly favour any single modality. In most centres investigating for FMD, CTA or MRA remains the first-line imaging test.

In experienced centres, duplex ultrasound may be used for the initial evaluation of FMD in carotid arteries but it does not allow adequate assessment of distal segments of the internal carotid arteries, vertebral arteries, and intracranial arteries.

In patients with FMD, regardless of the presence and location of FMD lesions in various vascular beds, evaluation for intracranial aneurysms using CTA or MRA should be performed at least once.

It is also recommended that regardless of the location of initially identified FMD lesions, patients with FMD undergo, at least once, imaging of the vascular system from the brain to the pelvis to identify FMD in other vascular beds and screen for asymptomatic aneurysms or dissections.

8.4.4. Management of renal artery stenosis due to fibromuscular dysplasia

Antiplatelet therapy (acetylsalicylic acid 75–100 mg), if not contraindicated, is reasonable to prevent thrombotic and thromboembolic complications in patients with FMD.

Renal angioplasty is the treatment of choice for significant renal artery stenosis due to FMD (defined as translesional pressure gradient of 10% of the mean aortic pressure, i.e., Pd/Pa < 0.90). Stenting is not recommended, except for periprocedural dissection, primary renal artery dissection, or as a part of interventional treatment for renal artery aneurysm.

Surgical treatment of significant renal artery stenosis due to FMD should be considered in patients with:

- stenosis associated with a complex aneurysm;
- recurrent stenosis after two unsuccessful angioplasty procedures;
- a lesion involving renal artery bifurcation and its branches.

In hypertensive patients with renal artery stenosis due to FMD in whom revascularization is not indicated, appropriate follow-up is recommended:

- patients with FMD should undergo annual clinical follow-up on an outpatient basis;
- long-term clinical follow-up in patients with FMD should include clinical evaluation, renal function testing (in patients with FMD within renal arteries), and imaging studies (with insufficient data to suggest a specific algorithm for imaging during long-term clinical follow-up in patients with FMD);
- it seems reasonable to suggest that the extent of imaging — taking into account local availability of imaging modalities — should be determined individually based on the severity of FMD, the need to monitor progression of FMD complications (aneurysm or dissection), and previous revascularization procedures;
- in patients after spontaneous coronary artery dissection, imaging of the whole arterial system from the brain to the pelvis using CTA or MRA should be performed at least once to evaluate the presence of FMD and its complications in non-coronary arteries.

8.5. Primary hyperaldosteronism

8.5.1. Definition and prevalence

Primary hyperaldosteronism (PHA) is defined as a hormonally mediated form of hypertension caused by autonomous aldosterone production. Using this definition, PHA is diagnosed by showing that aldosterone level is unaffected by factors that affect its production in physiological conditions.

Primary hyperaldosteronism is not a pathogenetically uniform condition, and several forms of PHA are distinguished depending on the hormonal profile and the management approach:

- bilateral adrenal hyperplasia;
- adrenal cortex adenoma;
- familial hyperaldosteronism type I, II, III or IV;
- aldosterone-producing adrenal carcinoma;
- ectopic aldosterone production (by neoplastic tissue).

The prevalence of PHA in hypertensive patients depends on BP values. In the general hypertensive population, PHA is present in up to 7% of patients (depending on the definition of PHA), while the prevalence of PHA in patients with resistant hypertension has been estimated at 6–23%.

8.5.2. Clinical presentation

Compared to patients with primary hypertension, patients with PHA have been found to have more frequent target organ damage such as left ventricular hypertrophy, increased carotid artery intima-media thickness, reduces arterial compliance, and microalbuminuria.

An adverse effect of aldosterone excess on the cardiovascular system has been highlighted, resulting primarily in myocardial, vascular, and renal damage. Myocardial hypertrophy and fibrosis lead to diastolic dysfunction, which may result in overt heart failure and is a substrate for arrhythmia (such as atrial fibrillation provoked by concomitant hypokalaemia).

In patients with PHA, the cardiovascular risk is significantly increased. Multiple studies showed a largely increased risk of coronary artery disease, myocardial infarction, heart failure, atrial fibrillation, and stroke in this population compared to matched patients with primary hypertension.

Symptoms and signs and laboratory test findings suggestive of PHA are summarized in Table XXXVII.

According to the Endocrine Society guidelines, investigations for PHA should be considered in patients:

- with BP values above 150/100 mm Hg in each of three measurements during separate visits (according to the 2019 PTNT guidelines expert panel, investigations for PHA should be considered in patients with grade 2–3 hypertension);
- with resistant hypertension;
- with spontaneous or diuretic-induced hypokalaemia;
- with hypertension and incidentally discovered adrenal tumour;
- with hypertension and OSA;
- with hypertension and a family history of early onset hypertension or a cerebrovascular event at a young age (< 40 years);
- in all hypertensive first-degree relatives of patients with established PHA.

In addition, investigations for PHA should be considered if the severity of target organ damage is disproportionate to the severity of hypertension.

8.5.3. Screening for primary hyperaldosteronism

The primary screening test for PHA is evaluation of the aldosterone-to-renin ratio (ARR). When evaluat-

ing and interpreting ARR, the following should be taken into consideration:

- in patients with hypokalaemia, potassium level should be brought to normal values by adequate supplementation, and dietary sodium intake should also be controlled (normal sodium diet);
- antihypertensive drug therapy should be appropriately modified:
  - drugs that significantly affect ARR should be withdrawn 4 weeks before testing, including spironolactone, eplerenone, triamterene, amiloride, thiazide/thiazide-like diuretics, and loop diuretics,
  - if ARR is nondiagnostic and hypertension may be adequately controlled using drugs that do not affect ARR (see below), the following medications should be withdrawn 2 weeks before testing: β-blockers, central α2-agonists (clonidine, methyldopa), nonsteroidal anti-inflammatory drugs (false-positive ARR), and ACEI, ARB, renin inhibitors, and dihydropyridine calcium antagonists (false-negative ARR),
  - drugs that have the least effect on ARR should be used to control hypertension, including verapamil, hydralazine, doxazosin, prazosin, and terazosin; however, some authors do not recommend using verapamil due to a potential effect on ARR in patients with adrenal adenoma and a somatic *KCJN5* gene mutation;
  - in some situations, due to high BP values and concomitant conditions, appropriate modification of antihypertensive drug therapy is not possible and may be even associated with an increased cardiovascular risk; in these circumstances, the effect of drug therapy used in the patient should be taken into account;
- blood sampling for ARR should be performed in a sitting position between 9 and 10 AM, with the patient remaining upright (sitting, standing, walking) for 2–4 hours before blood collection, and the collected blood samples should be handled appropriately as agreed with the laboratory;
- due to the fact that interpretation of ARR is based on values considered abnormal in previous research studies and not the reference ranges for the assays used in the laboratories, ARR should be determined in laboratories in which the assays for aldosterone and plasma renin activity or renin level have been validated against the laboratories that have appropriate experience in the diagnosis of PHA;
- most commonly, the ARR value suggesting PHA is defined as:
  - above 30 (aldosterone level in ng/dL and plasma renin activity in ng/mL/h); or
  - above 750 (aldosterone level in pmol/L and plasma renin activity in ng/mL/h),
  - for an elevated ARR to suggest PHA, plasma aldosterone level must be at least moderately increased [e.g., >15 ng/dL (150 pg/mL or 416 pmol/L)],
  - ARR is also much affected by the lower limit of detection of plasma renin activity by a given assay, which may be different for different assays and laboratories (plasma renin activity value used for calculating ARR should not be lower than 0.2 ng/mL/min),
  - in the recent years, commercial assays for plasma renin level (direct renin concentration) have been introduced; ARR conversion coefficient for renin level should be determined separately for each assay;
- other factors that may affect ARR value interpretation should also be taken into account, including age (low-renin essential hypertension in the elderly), creatinine level, concomitant conditions, difficult blood sampling, and use of hormonal drugs (e.g., oestrogen-containing preparations are associated with false-positive ARR values).

8.5.4. Confirmatory tests

The diagnosis of PHA is confirmed by establishing no effect of factors that normally decrease plasma aldosterone level or 24-hour urinary aldosterone excretion. In clinical practice, the two most commonly used tests are captopril suppression test and saline suppression test (with intravenous infusion of 2 litres of normal saline).

8.5.5. Differentiation between various forms of primary hyperaldosteronism

After the diagnosis of PHA has been established based on clinical symptoms and biochemical test findings, it is necessary to assess the nature and location of adrenal lesions. Various forms of PHA, in particular bilateral adrenal hyperplasia and adrenal adenoma, should also be differentiated.

Computed tomography (CT) is currently the standard method to evaluate adrenal lesions. Its sensitivity for detecting adrenal tumours exceeds 90%. CT allows assessment of the morphology of detected adrenal tumours.

Adrenal venous sampling is the method of choice for differentiating between various forms of PHA. It is indicated in all patients in whom adrenalectomy is considered. Exceptions include young patients (< 35–40 years of age) with a typical adenoma

on CT/MRI and normal contralateral adrenal gland who may be referred for surgery based on imaging only. However, many centres perform adrenal venous sampling also in such patients.

8.5.6. Management of primary hyperaldosteronism

In documented unilateral PHA due to an aldosterone-producing adenoma or unilateral adrenal hyperplasia, the treatment of choice is unilateral laparoscopic adrenalectomy, while patients with bilateral adrenal disease (idiopathic adrenal hyperplasia or bilateral adenomas) should be treated with aldosterone antagonists. Glucocorticoid-remediable aldosteronism should be treated with low doses of a long-acting glucocorticosteroid, e.g., dexamethasone.

In patients with bilateral adrenal disease and those with unilateral PHA who did not undergo adrenalectomy for various reasons, aldosterone antagonists are indicated. The initial spironolactone dose should be 12.5–25 mg once daily. The lowest effective dose should be determined by a gradual dose increase to 100 mg per day or more. To avoid high spironolactone doses, which may result in adverse effects, a thiazide diuretic, amiloride, or triamterene may be added. Eplerenone is a newer, selective mineralocorticoid receptor antagonist characterized by a weaker antiandrogenic effect and a weaker agonist effect on the progesterone receptor, and thus it is associated with a lower rate of adverse effects. The strength of its mineralocorticoid receptor antagonist effect has been estimated at 60% of that of spironolactone. Due to a shorter duration of action, this drug should be administered more frequently than once daily (initially 25 mg twice daily). However, eplerenone has not been licensed to treat PHA in the European Community.

8.6. Catecholamine-producing tumours

8.6.1. Definition

Adrenal catecholamine-producing tumours are known as phaeochromocytomas, and the remaining extra-adrenal chromaffin cell tumours, which may also be hormonally active, are known as paragangliomas. Collectively, these are called phaeochromocytomas-paragangliomas (PPGL).

8.6.2. Clinical presentation

The most common symptoms, usually paroxysmal in nature, include:

- paroxysmal BP surges (with typically large BP variation) which may last from several minutes to several hours;
- chronic hypertension;
- headache;
- excessive sweating;
- palpitation;
- pallor;
- tremor;
- anxiety;
- orthostatic hypotension.

Elevated glucose level may be found on biochemical testing. ABPM may show large BP variation and a decreased nocturnal BP fall, or even a non-dipping BP pattern and BP elevation during the night.

The provoking factors include exercise, abdominal pressure, large meals, some medications [ephedrine, phenylephrine, adrenocorticotropic hormone (ACTH), phenothiazines, amphetamine, metoclopramide, tricyclic antidepressants, some anaesthesia drugs], stress, and alcohol intake. Catecholamine release by the tumour may also be induced by glucocorticosteroid administration. Phaeochromocytomas may also remain asymptomatic (including with normal BP values).

8.6.3. Investigations for catecholamine-producing tumours

Indications for investigations for PPGL include:

- symptoms suggestive of PPGL, particularly if episodic in nature;
- medication-induced PPGL symptoms;
- an incidentally detected adrenal tumour (with or without hypertension);
- a gene mutation predisposing to PPGL or clinical evidence of a hereditary PPGL syndrome;
- a history of PPGL.

The major diagnostic criterion for a hormonally active PPGL is the finding of an elevated catecholamine metabolite serum level or urinary excretion, followed by tumour localization by imaging studies. The final diagnosis is based on histopathologic assessment of the resected tumour.

Plasma free metanephrines and urinary fractionated metanephrines are considered the most useful (i.e., most sensitive) biochemical tests. The highest sensitivity was reported for plasma free metanephrines (sensitivity 97–99%, specificity 82%). Urinary adrenaline and noradrenaline excretion is characterized by lower sensitivity and specificity, and the least diagnostic utility was shown for measurements of urinary vanillylmandelic acid and dopamine and plasma catecholamines. In rare cases, the clonidine suppression test may be performed.

Anatomical imaging studies in patients with PPGL should be performed after excessive catechol-

amine and/or their metabolite levels have been identified in plasma or urine. Localization studies for PPGL are also performed in PPGL gene mutation carriers. Useful imaging methods for PPGL include CT and MRI.

8.6.4. Management of catecholamine-producing tumours

Paroxysmal BP surges caused by catecholamine-producing PPGL may be best managed by administering phentolamine intravenously, usually at the dose of 2–5 mg repeated as needed.

Surgical removal of catecholamine-producing PPGL is the treatment of choice.

Appropriate preoperative patient preparation is important to reduce BP values, lower the heart rate, and control paroxysmal BP surges and other symptoms related to the excess of circulating catecholamines. For this purpose, α-blockers are administered orally for 2–3 weeks, including phenoxybenzamine (in increasing doses starting from 10 mg twice daily up to 1 mg/kg/day in 2–3 divided doses) or doxazosin (in gradually increasing doses starting from 2 mg up to 32 mg/day in 1–2 divided doses). If α-adrenergic receptor blockade is unsuccessful at controlling BP, a calcium antagonist (nifedipine or amlodipine) may be added as the second antihypertensive medication. In patients with significant tachycardia, addition of a cardioselective β-blocker is desirable but only after α-adrenergic receptors have been blocked. Catecholamines released by PPGL act on both α- and β-adrenergic receptors. Administering a β-blocker without previous α receptor blockade is contraindicated as it may lead to excessive α receptor activation and a significant BP rise. Combined α- and β-adrenergic receptor blockers (labetalol and carvedilol) should not be used. Correcting hypovolemia by adequate sodium and fluid intake to avoid orthostatic hypotension is also important during preoperative patient preparation.

8.6.5. Long-term care of patients with catecholamine-producing tumours

Following surgical PPGL removal, long-term patient follow-up is necessary that should include monitoring of BP values and plasma or urinary metanephrines. The initial postoperative evaluation to allow early identification of a possible tumour recurrence or development of hormonally active metastases should be undertaken depending on the overall clinical picture (genetic predisposition, tumour size, multiple tumours) at 6–12 months and then repeated annually.

8.6.6. Genetic testing in patients with catecholamine-producing tumours

The proportion of genetic forms of PPGL is currently estimated at 30–40%. Genetic testing for known mutations associated with PPGL is recommended in all PPGL patients. Modern genetic assay technologies allow testing for several PPGL-associated genes in a single sample.

8.7. Other rarer forms of secondary hypertension

Other rare forms of secondary hypertension, such as renin-secreting tumours, coarctation of the aorta, and Cushing syndrome, are summarized in Table XXXVII.

9. Recommendations on the diagnostic and therapeutic management of hypertension in children and adolescents

Hypertension is a major potentially modifiable cardiovascular risk factor. It is also a major clinical problem in adult medicine, and one of the most common chronic conditions in adolescents. In addition to the primary form, hypertension is also an important complication of other chronic conditions such as diabetes type 1 and 2, chronic kidney disease, coarctation of the aorta, congenital adrenal hyperplasia, and others. Although diabetes type 2 is relatively uncommon in Caucasian children and adolescents, children with overweight and obesity, and particularly those with carbohydrate intolerance and insulin resistance should be considered a potential risk group for hypertension. Another important problem is hypertension in children and adults born prematurely, particularly before 33 weeks of gestation, or as small for gestational age newborns.

The current guidelines are expanded and updated 2015 PTNT paediatric recommendations, previously presented in an expanded version in 2016 as The Children's Memorial Health Institute (IP-CZD) recommendations. The current edition of the PTNT paediatric recommendations has been developed based on the previously published fourth report of the National High Blood Pressure Education Program Working Group on Children and Adolescents (hereafter referred to as the Fourth Report), 2009 and 2016 paediatric ESH guidelines, ESC guidelines, AHA guidelines, 2017 American Academy of Paediatrics (AAP) guidelines, literature review, and expert opinion. Detailed recommendations were also based on the current recommendations of the respective society working groups.

Compared to the 2015 paediatric PTNT recommendations, the present edition includes extended epidemiological data on the prevalence and incidence of hypertension, extended or modified sections on the evaluation of target organ damage, hypertension in children with diabetes or chronic kidney disease, and a section on diagnostic and therapeutic challenges. A section has also been added on the approach to early diagnosis of hypertension during postdischarge care for children born below 33 weeks of gestation, as recommended in 2018 by the Polish Neonatal Society. Another important novelty is the current classification of hypertension, presented earlier in the 2016 ESH guidelines and 2016 IP-CZD guidelines.

Problems with defining target BP values have been discussed in a new subsection. The chapter on BP measurement principles includes new recommendations regarding BP measurements in newborns, neonates, and infants. References have been updated and expanded.

9.1. Epidemiology of hypertension in children and adolescents

Data from representative population studies indicate that hypertension is present in 3–5% of children and adolescents aged 0–18 years. In the OLAF and OLA studies, conducted in representative population samples, BP values above the 95th percentile for age and gender, calculated as the mean of the second and third BP measurement during a single visit, were noted in 6.9% of children aged 3 years, 7.7% of children aged 6–10 years, and 6.2% of youths aged 10–20 years.

The prevalence of hypertension among adolescents 14–18 years of age, defined in 18-year-olds using the adult definition, i.e., BP ≥ 140/90 mm Hg, is 10–13%, similarly to that among young adults. Starting from puberty, hypertension is 3–4 times more prevalent in boys compared to girls. This gender difference is maintained until the fifth decade of life and is associated with a physiological BP rise during puberty in boys. In risk groups, such as obesity, chronic kidney disease, and diabetes type 1 and 2, the prevalence of hypertension is much higher ranging from 5–25% (diabetes type 1) to 30–40% (diabetes type 2). Prematurity and low birth weight are associated with a particular risk of developing hypertension. It has been estimated that at 3 years of age, hypertension in present 7.3% of children born prematurely. The risk of developing hypertension increases with younger gestational age at birth and is particularly high in persons born below 33 weeks of gestation.

Secondary hypertension is the major cause of hypertension in younger children. The higher rates of obesity in children and adolescents, the more common is primary hypertension which accounts for 50% of all hypertension cases in this age group.

9.2. Recommendations regarding screening for hypertension

According to the 2009 and 2016 ESH guidelines and the Fourth Report, BP should be measured in children above 3 years of age at least once a year during routine health supervision visits and visits related to health problems. In children below 3 years of age, BP measurement is recommended in selected cases in children with identified health problems (Tab. XXXVIII). Screening for hypertension in children below 24 months of age is not supported by society guidelines and epidemiological study findings, as BP measurements in younger children are at a high risk of failure due to lack of patient cooperation: the proportion of unreliable BP measurements is 41% in children at one year of age, 20% in children aged 3 years, and 9% of children aged 3–6 years.

9.3. Diagnosis of hypertension

9.3.1. Definitions and classification of hypertension in children and adolescents

According to the generally accepted definition of hypertension in children, this diagnosis requires BP readings ≥ 95th percentile for age, gender, and height during three independent measurements. A term "elevated blood pressure" has also been used in the literature to denote children with single BP values above 95th percentile, which is not sufficient for the diagnosis of hypertension. However, the meaning of the term "elevated blood pressure" changed when the 2017 AAP guidelines used this term to denote BP values previously categorized as prehypertension.

Classification of hypertension in children and adolescents depends on the method of BP measurement. **Due to diverging opinions on interpreting BP values in adolescents (see below), use of the adult BP classification is recommended in adolescents ≥ 16 years of age.** Based on office measurements (using the auscultatory or oscillometric method), the following categories are distinguished (Tab. XXXIX):

- **normal BP** — BP values below the 90th percentile for age, gender, and height; in adolescents ≥ 16 years of age, normal BP is < 130/85 mm Hg;
- **high normal BP (Europe) or elevated BP (United States)** — SBP and/or DBP between the 90th and 95th percentile, and BP 130–139/85–89 mm Hg in adolescents ≥16 years of age (note: in

Table XXXVIII. Blood pressure measurements in children and adolescents — indications and technique

BP should be measured in all children aged ≥ 3 years at least once a year and during any routine physician examination
- BP measurement is more reliable if the child has not eaten a meal within 30 minutes before the measurement, has not received medications that might affect BP, and has been resting in a sitting position with its back supported in a quiet environment for 5–10 minutes before the measurement
- During the initial consultation, BP should be measured on all four limbs. During the first year of life and until the child assumes the upright position, BP readings in the lower limbs are lower than in the upper limbs. During the second year of life in a child who stands/walks, BP readings in the lower limbs are higher by about 20 mm Hg, and at a later age they are higher by about 30–40 mm Hg
- Subsequent measurements should be performed on the right arm that is fully exposed, abducted and supported at the level of the heart
- The cuff should encircle the full circumference of the arm and cover at least two thirds of its length. The inflatable bladder should encircle at least 80% of the arm circumference, including the whole medial aspect of the arm. BP may be overestimated by as much as 30% if the cuff is too narrow, and underestimated if the cuff is too wide
- In infants, the body position has no significant effect on BP values. During sleep, SBP values in infants are lower by 5–7 mm Hg
- As readings obtained during the first measurement are usually overestimated, BP should be measured 2–3 times during a single examination
- BP readings above the 90th percentile by the oscillometric method require verification by the auscultatory method
- If the BP difference between the upper limbs is ≥ 5 mm Hg, this fact should be noted in the medical record

In younger children (< 3 years), BP should be measured in specific situations including:
- perinatal morbidity: prematurity, low birth weight, intensive therapy in the perinatal period
- congenital anomalies
- recurrent urinary tract infections, kidney and/or urinary tract disease
- malignancy
- solid organ or bone marrow transplantation
- use of drugs affecting BP
- symptoms and conditions associated with hypertension (neurofibromatosis, tuberous sclerosis, others), intracranial pressure rise

BP — blood pressure; SBP — systolic blood pressure

Table XXXIX. Blood pressure classification in children and adolescents based on office blood pressure measurements

	0–16 years of age	≥ 16 years of age
BP category	**SBP and/or DBP percentiles**	**SBP and/or DBP values**
Normal BP	< 90th percentile	< 130/85 mm Hg
High normal BP/prehypertension	≥ 90th and < 95th percentile	130–139/85–89 mm Hg
Hypertension	≥ 95th percentile	≥ 140/90 mm Hg
Grade 1 hypertension	95th to 99th percentile + 5 mm Hg	140–159/90–99 mm Hg
Grade 2 hypertension	> 99th percentile + 5 mm Hg	160–179/100–109 mm Hg
Grade 3 hypertension		≥ 180/110 mm Hg
Isolated systolic hypertension	SBP ≥ 95th percentile and DBP < 90th percentile	SBP ≥ 140 and DBP < 90 mm Hg

BP — blood pressure; DBP — diastolic blood pressure; SBP — systolic blood pressure

the AAP classification, elevated BP is defined as values up to 129/80 mm Hg);
- **hypertension** — mean SBP and/or DBP values ≥ 95th percentile for age, gender, and height based on at least three independent measurements; in adolescents ≥ 16 years of age, the threshold for the diagnosis of hypertension is the same as in adults, i.e., ≥140/90 mm Hg;
- **white coat hypertension** — office BP measurements above the 95th percentile, or ≥ 140/90 mm Hg in adolescents ≥ 16 years of age but home BP or ABPM values within normal limits;
- **grade 1 hypertension** — BP values between the 95th percentile and 5 mm Hg above the 99th percentile for age, gender, and height, or 140–159/90–99 mm Hg in adolescents ≥ 16 years of age;
- **grade 2 hypertension** — BP values more than 5 mm Hg above the 99th percentile for age, gender, and height, or 160–179/100–109 mm Hg in adolescents ≥ 16 years of age; as use of the adult BP classification is recommended in the latter group, BP ≥ 180/110 mm Hg is categorized as **grade 3 hypertension** in adolescents ≥ 16 years of age;
- **isolated systolic hypertension** — SBP values ≥ 95th percentile but DBP values < 90th percentile, or SBP ≥ 140 mm Hg but DBP < 90 mm Hg in adolescents ≥ 16 years of age.

Categories of severe hypertension and hypertensive urgencies and emergencies have not been defined

Table XL. Blood pressure classification in children based on ambulatory blood pressure monitoring*

Category	Office BP	Mean SBP and/or DBP by ABPM	SBP and/or DBP load
Normal BP	< 90th percentile	< 95th percentile	< 25%
White coat hypertension	≥ 95th percentile	< 95th percentile	< 25%
Masked hypertension	< 95th percentile	≥ 95th percentile	< 25%
High normal BP	≥ 90th percentile and/or 120/80 mm Hg	< 95th percentile	25–50%
Ambulatory hypertension	≥ 95th percentile	≥ 95th percentile	25–50%
Severe ambulatory hypertension	≥ 95th percentile	≥ 95th percentile	> 50%

*In patients ≥ 16 years of age, it is recommended to use adult cut-off values, i.e., 130/80 mm Hg for the 24-hour mean BP, 135/85 mm Hg for the daytime period and 120/70 mm Hg for the night-time period; ABPM — ambulatory blood pressure monitoring; BP — blood pressure; DBP — diastolic blood pressure; SBP — systolic blood pressure

in the classifications of hypertension in children that were adopted in European and U.S. guidelines. However, the following definitions of these conditions are used for practical reasons:

- **severe hypertension** — BP values more than 30 mm Hg above the 99th percentile for age, gender, and height;
- **hypertensive urgencies** — impending organ failure related to hypertension, requiring rapid intervention, usually with concomitant unspecific symptoms such as headache and vomiting;
- **hypertensive emergencies** — established or acute organ damage related to hypertension, mostly with organ failure, symptoms of encephalopathy, and Keith-Wagener-Barker grade 3 and/or grade 4 retinopathy on fundoscopy.
- **malignant hypertension** — in the past, this term was used to describe sudden BP increase with grade 3 and/or grade 4 retinopathy on fundoscopy, consistent with a hypertensive emergency in the present classification. According to the nomenclature in the 2016 paediatric ESC guidelines, malignant hypertension is defined as sudden BP increase with evidence of damage to at least three organs, or with concomitant microangiopathy. In practice, this definition is met by hypertension accompanying acute haemolytic-uraemic syndrome;
- **resistant hypertension** — hypertension that is not controlled despite treatment with three antihypertensive drugs including a diuretic.

The classification of hypertension based on ABPM also includes the category of masked hypertension, defined as abnormal BP values in ABPM and normal BP values in office measurements (Tab. XL). As similarly to office BP measurements, 95th percentile BP values by ABPM may exceed values considered normal in adults, the 2016 ESH guidelines recommend using 95th percentile-based threshold values in children and adolescents as long as they do not exceed the upper limit of normal values in adults. If 95th percentile BP values exceed normal values in adults, it is recommended to use adult thresholds, i.e. 130/80 mm Hg for the 24-hour mean, 135/85 mm Hg for the daytime mean, and 120/70 mm Hg for the night-time mean.

9.3.2. Reference blood pressure values

9.3.2.1. Reference values for office measurements

It is recommended to use reference BP values for a given age, gender and height developed for specific BP measurement methods (auscultatory, oscillometric). For BP measurements using the auscultatory method, the most commonly used are reference values for children aged 0–18 years, developed for the population of the United States, Canada, Mexico, and Great Britain and published in the Fourth Report. For oscillometric (automated) BP measurements, reference values developed for the Polish population of children aged 3–18 years are recommended. As automated measurements are most commonly performed in everyday paediatric practice, these norms have been included in the new Polish child's health record book (2016).

9.3.2.2. Home blood pressure measurements

In children with the diagnosis of hypertension, home BP measurements using a validated oscillometric device are recommended (https://nadcisnienietetnicze.pl/dla_lekarzy/zalecenia_i_standardy/zalecenia_ptnt). Use of the reference values developed by

Table XLI. Reference home blood pressure values in boys and girls (95th percentile)

Height [cm]	Girls	Boys
120–129	119/74	119/76
130–139	120/76	121/77
140–149	122/77	125/77
150–159	123/77	126/78
160–169	124/78	128/78
170–179	125/79	132/78
180–189	128/80	134/79

Stergiou et al. for children and adolescents aged 6–18 years is recommended (Tab. XLI). No reference BP values were developed for HBPM in younger children. Evaluation based on BP measurements twice daily during at least 3 days, at equal intervals and before administration of antihypertensive medications, is considered reliable. It is recommended to perform 2–3 measurements at short intervals and record the last measurement. The optimal approach involves morning and evening BP measurements performed during 7 subsequent days. Adequate home BP measurements are considered a reliable indicator of the effectiveness of antihypertensive therapy.

9.3.2.3. Ambulatory blood pressure measurement

Ambulatory BP measurement using a validated oscillometric device is recommended in all children above 5 years of age in whom hypertension was diagnosed based on office BP measurements. Use of the reference BP values for ABPM developed by Wühl et al. and adopted in the 2014 AHA guidelines is recommended, and references values for adults should be used in adolescents ≥ 16 years of age. Routine repeated ABPM is recommended to evaluate treatment effects.

9.3.3. Principles of blood pressure measurement

The technique of BP measurements is summarized in Table XXXVIII. Both automated (oscillometric) and auscultatory method may be used for routine measurements, and auscultatory method is used for confirming hypertension identified by automated measurements. Different principles apply to neonates and infants in whom auscultatory measurements are technically difficult and associated with a more pronounced white coat effect compared to automated (oscillometric) measurements. In this age group (up to 3–4 years of age), repeated automated measurements at short intervals are recommended. In addition, when BP measurements are indicated in newborns and neonates, they should follow the protocol described in the section *Neonatal hypertension*.

9.3.3.1. Interpretation issues

When interpreting BP measurements, age, gender, and height of the patient should be taken into consideration. Significant issues have been raised for neonates (see "Neonatal hypertension" below), children in the first year of life, and adolescents, as well as interpretation of oscillometric measurements including ABPM. In neonates and children in the first year of life in whom BP has been measured, evaluation of SBP only is recommended.

Of note, the 95th percentile SBP values for girls aged 13–18 years are much lower compared to those for boys, and at the age of 18 years, the 95th percentile values for both SBP and DBP in girls are 5–10 mm Hg lower than 140/90 mm Hg. The latter values correspond to 99th percentile in girls aged 18 years. Another phenomenon in adolescents is isolated systolic hypertension, seen particularly in boys without significant additional risk factors, frequently participating in sports. In these cases, spurious hypertension should be considered, with elevated SBP only in peripheral arteries, such as brachial artery, but normal central BP. No evidence of target organ damage is seen in these patients. For this reason, exposure to cardiovascular risk factors (intermediate phenotype) and the presence of subclinical target organ damage should also be considered when interpreting BP values (see below).

As most currently used ABPM devices are based on the oscillometric method, it should be emphasized that with this method, the mean arterial pressure (MAP) is directly evaluated, and SBP and DBP values are calculated using appropriate algorithms. In addition, results of some controlled paediatric studies (e.g., the ESCAPE study) and therapeutic recommendations (see below) are based on the analysis of MAP values. Another interpretation issue related to ABPM is the fact that using this method, higher BP values compared to office measurements are obtained in children below 10 years of age and those with the height below 120 cm. Due to lacking reference values and the above mentioned interpretation issues, routine use of ABPM is not recommended in children below 5 years of age.

In turn, 95th percentile values in tall children and adolescents may exceed BP considered normal in adults. These problems led to a change in the definition and classification of hypertension in adolescents ≥ 16 years of age (see: *Diagnosis of hypertension*).

9.3.3.2. Problems with defining target blood pressure values in children receiving antihypertensive treatment

The hypertension literature, including the ESH guidelines, the Fourth Report, the AAP guidelines, and expert opinions, defines threshold BP values for the diagnosis of hypertension and target BP values during treatment. These values differ, i.e., while the diagnosis of hypertension is defined as BP ≥ 95th percentile, it is also recommended to lower BP below the 90th percentile in patients without concomitant conditions. However, setting these target BP values during treatment should also be associated with a change in the definition of hypertension by setting a lower threshold for the diagnosis, i.e., the 90th

percentile. This also necessitates defining the management in subjects with BP values in the 90–95th percentile range.

The current approach generates interpretation issues as it implies initiating treatment in children with BP values in the 90–95th percentile range. While non-drug therapy is not a problem, drug therapy should also be considered in those with BP values persistently in the high normal range despite non-drug therapy. Thus, a change in the definition of hypertension would be logical.

Indirect evidence in favour of setting target BP threshold at the 90th percentile in children with primary hypertension without concomitant conditions has been provided by studies in adult hypertensives, in particular the SPRINT trial and a 2016 meta-analysis that evaluated the efficacy of antihypertensive treatment in risk groups such as chronic kidney disease and diabetes. Arguments in favour of setting both the definition of hypertension in children and the target BP threshold at the 90th percentile have also been provided by the Cardiovascular Risk in Young Finns Study results. In this study, significantly higher BP values and higher arterial stiffness, as evaluated by the pulse wave velocity, were noted in adults who had high normal BP (i.e., 90–95th percentile range) in childhood and adolescence compared to those who had BP < 90th percentile in childhood and adolescence. In the 2017 AAP guidelines, new definitions of hypertension were recommended based on the SPRINT trial results. Lower target BP values (< 90th percentile or < 130/80 mm Hg) were also recommended in children with essential hypertension, with an argument that lowering BP below these thresholds leads to a further reduction in the rate of left ventricular hypertrophy. It should be noted, however, that the mean age in the SPRINT study was 67 years, and the participants were subjects with concomitant conditions who already received antihypertensive treatment. In addition, the method of BP measurements differed from those used in routine clinical practice. Furthermore, the studies cited in the AAP guidelines do not support further reduction in left ventricular mass (LVM) in children in whom BP was lowered below the 90th percentile. It should also be noted that in children and adolescents with primary hypertension, the strongest predictor of a reduction of LVM and the rate of left ventricular hypertrophy is not BP lowering but a reduction in visceral fat, as assessed by a reduction in waist circumference and normalization of metabolic disturbances. For this reason, target BP < 95th percentile (or < 140/90 mm Hg) has been recommended in the present guidelines in children and adolescents with primary hypertension without concomitant conditions.

At the same time, the present guidelines recommend intensive non-drug treatment as the primary management strategy in essential hypertension.

Similar issues arise regarding the threshold for the diagnosis of hypertension and recommended target BP values in children with chronic kidney disease and diabetes. In paediatric patients with chronic kidney disease, drug treatment is recommended with BP values above the 90th percentile, and the target BP values depend on the presence of proteinuria. The current recommendations are based on the ESCAPE study results which showed that in children with proteinuria > 0.5 g/d, reducing MAP by ABPM below the 50th percentile is beneficial. Such benefits were not shown, however, in children with less severe proteinuria or without proteinuria. Despite this, the ESH guidelines and other expert opinions (presented in review articles) suggest target BP values below the 75th percentile in such cases. However, even studies cited in these documents do not offer any support for such a threshold.

9.4. Methods to evaluate target organ damage

Basic modalities to evaluate the severity of hypertensive target organ damage in children include evaluation of LVM, systolic function, and diastolic function by echocardiography, ECG, fundoscopy, and evaluation of renal function.

9.4.1. Evaluation of left ventricular mass

Left ventricular mass is a major criterion of target organ damage in hypertension. Echocardiography is the standard method to diagnose left ventricular hypertrophy, and ECG is only an additional diagnostic tool due to its low specificity and the need for age-specific interpretation (however, ECG also allows diagnosing arrhythmia and myocardial ischaemia, which is of practical importance as exercise/sport-based non-drug therapy is the mainstay of the management of primary hypertension). The most commonly used approach to evaluate LVM is based on the recommendations of the American Society of Echocardiography and uses the Deveraux formula. As LVM depends on height, it is recommended to calculate LVM indexed for height in meters to the power of 2.7 according to the formula suggested by DeSimone. Published reference values and percentiles of the LVM index calculated using this formula allow using this parameter in children over 1 year of age. A limitation of indexing LVM for height is the possibility to overdiagnose left ventricular hypertrophy in obese children

in comparison to indexing for fat-free body weight. Nevertheless, it is currently the most commonly used and recommended (2009 and 2016 ESH guidelines, Fourth Report, AAP) approach to evaluate LVM in children and adolescents that allows not only comparisons of echocardiographic findings in children of varying age but also comparing paediatric data with the results obtained in adults. However, as a hypertension classification consistent with the adult definitions has been introduced for adolescents ≥ 16 years of age, it is recommended to evaluate left ventricular hypertrophy in this age group using the adult approach (see below).

The principles of evaluating left ventricular systolic and diastolic function are the same as in adults. When evaluating diastolic function, a higher early (E) to atrial (A) inflow velocity ratio (E/A) in younger children should be taken into account. Tissue Doppler imaging is increasingly commonly used for the evaluation of left ventricular diastolic function, and respective paediatric reference values have been published. Findings using this method may be an additional parameter in the evaluation of target organ damage.

Definitions:

- left ventricular hypertrophy — LVM ≥ 95th percentile for age and gender;
- severe ventricular hypertrophy — LVM index ≥ 51 g/m$^{2.7}$*.

In adolescents ≥ 16 years of age, left ventricular hypertrophy is diagnosed when LVM is ≥ 115 g/m^2 of body surface area in boys and ≥ 95 g/m^2 of body surface area in girls.

It is recommended to evaluate the relative left ventricular wall thickness (threshold value 0.42) and assess left ventricular geometry (normal geometry, concentric remodelling, concentric hypertrophy, eccentric hypertrophy).

*In adult studies, it has been shown that LVM above 51 g/m$^{2.7}$ is associated with a 4-fold higher risk of a cardiovascular event during 5 years of follow-up. LVM of 51 g/m$^{2.7}$ is approximately consistent with the 99th percentile of LVM in children and adolescents.

9.4.2. Fundoscopy

The principles of fundoscopic examination in children do not differ from those in adults. The Keith-Wagener-Barker classification is commonly used in clinical practice. A simplified classification includes 2 types of changes, benign and malignant. Benign changes are Keith-Wagener-Barker grade 1 and/or grade 2 lesions, and malignant changes are grade 3 and/or grade 4 lesions. The simplified classification allows initial patient selection for more or less intensive treatment. Computer-assisted analysis of the width of retinal arteries and veins is increasingly used for the assessment of cardiovascular event risk, including that of stroke in adult hypertensives but this method has not been yet widely adopted in children with hypertension.

Although initial fundus evaluation is relatively simple, few paediatric hypertension specialists perform it in routine clinical practice. For this reason, this test is recommended as optional in the evaluation of children and adolescents with asymptomatic hypertension. However, it is recommended in symptomatic hypertension and hypertensive emergencies and urgencies.

9.4.3. Evaluation of renal damage

Routine methods to evaluate renal function include glomerular filtration rate (GFR) estimation using the Schwartz formula and/or serum cystatine C level measurements. Albuminuria is an indicator of hyperfiltration and/or microvascular damage. There are no commonly accepted reference values for albuminuria in children, and adult cut-off values are used in practice, with albuminuria above 30 mg/24 h corresponding to the 95th percentile values.

Hyperuricaemia is considered an abnormality specific for hypertension. However, it is not clear whether an increased uric acid level is a primary phenomenon or occurs secondarily to subclinical renal damage. Clinical and population studies indicate that in adolescents 12–17 years of age, uric acid level above 5.5 mg/dL is associated with a 2-fold increased risk of hypertension.

Non-obligatory additional tests to evaluate the extent of target organ damage in children and adolescents:

These include:

- evaluation of large artery damage [measurement of the intima-media thickness (IMT)];
- measurement of the pulse wave velocity (PWV).

During the last decade, multiple reports have been published that support using IMT and PWV measurements to evaluate target organ damage, and reference IMT and PWV values for children and adolescents aged 6–20 years have been reported (Tab. XLII and XLIII). These tests are already recommended (ESH 2016) as additional tools to evaluate target organ damage in children with hypertension. In clinical practice, however, carotid IMT and PWV measurements are still performed only in selected centres. For this reason, they are recommended as non-obligatory additional tests pending their wide introduction to clinical practice.

Table XLII. Referential values of common carotid artery intima-media thickness (50th and 95th percentile) in millimetres

Age (years)	50th percentile [mm]		95th percentile [mm]	
	Boys	Girls	Boys	Girls
6	0.37	0.36	0.44	0.43
7	0.37	0.37	0.44	0.43
8	0.37	0.37	0.44	0.44
9	0.37	0.37	0.45	0.44
10	0.38	0.37	0.45	0.44
11	0.38	0.38	0.45	0.44
12	0.38	0.38	0.46	0.44
13	0.38	0.38	0.46	0.45
14	0.39	0.38	0.47	0.46
15	0.39	0.38	0.47	0.46
16	0.40	0.39	0.48	0.46
17	0.40	0.39	0.48	0.46
18	0.40	0.39	0.48	0.47

Table XLIII. Referential values of pulse wave velocity (95th and 97th percentile) evaluated by tonometry (PulsePen; based on Reusz et al., Hypertension 2010) and the oscillometric method (Vicorder)

Age (years)	PulsePen (tonometry)		Vicorder (oscillometric method)	
	Boys 95th percentile [m/s]	Girls 95th percentile [m/s]	Boys 97th percentile [m/s]	Girls 97th percentile [m/s]
7	5.4	5.2	4.8	4.8
8	5.5	5.4	5.0	5.0
9	5.5	5.5	5.1	5.1
10	5.6	5.6	5.2	5.3
11	5.8	5.8	5.4	5.4
12	5.9	5.9	5.5	5.5
13	6.1	6.0	5.7	5.6
14	6.3	6.0	5.8	5.7
15	6.5	6.2	6.0	5.7
16	6.7	6.3	6.2	5.7
17	6.9	6.5	6.3	5.6
18	7.1	6.7		
19	7.3	6.9		

9.5. Principles of the differential diagnosis of hypertension in children and adolescents

Differential diagnosis of hypertension in children includes three steps (Tab. XLIV). The extent of diagnostic investigations depends on the severity of hypertension, patient's age, and concomitant conditions. Indications for more extensive investigations that include diagnostic steps 1 and 2 include younger patient's age (before puberty; an arbitrarily chosen age threshold in girls and boys in Poland is 12 years), grade 2 hypertension, and presence of target organ damage or concomitant chronic conditions. Diagnostic step 1 includes confirmation of the diagnosis of hypertension, exclusion of white coat hypertension, grading the severity of hypertension, evaluation of target organ damage, and basic laboratory tests to exclude secondary hypertension. Diagnostic step 2 includes tests that require hospital admission and is generally appropriate in children with grade 2 hypertension and younger children with hypertension. Diagnostic step 3 includes highly specialized tests reserved for patients in whom the diagnosis has not been established despite completed step 1 and 2 investigations or hypertension is resistant to treatment.

Table XLIV. Diagnostic steps in children and adolescents with hypertension

	Investigations	Comments
Step 1	• Complete blood count, creatinine, sodium, potassium, chloride, calcium, bicarbonate, total cholesterol, triglycerides, HDL and LDL cholesterol, uric acid, glucose • Urinalysis with culture • Daily albumin excretion or albumin/creatinine ratio in a spot urine sample • Kidney and renal artery Doppler ultrasound • ECG • Echocardiography with evaluation of LVM and the aortic arch • cIMT measurement • Transcranial ultrasound in neonates and infants • ABPM in children > 5 years of age	Step 1 investigations should be performed in all patients with the diagnosis of hypertension cIMT measurement is optional ABPM is currently widely available; evaluation in children < 6 years of age has not been validated
Step 2	• Fasting blood glucose, oral glucose tolerance test, insulinaemia in patients with BMI > 85th percentile • Urinary catecholamines in younger children and all patients with grade 2 hypertension • Plasma renin activity/renin level and aldosterone level in younger children and all patients with grade 2 hypertension • Urinary steroid profile or urinary 17-keto- and 17-hydroxysteroids in younger children and all patients with grade 2 hypertension • Thyroid hormones, vitamin D3 metabolites • Renal scintigraphy (captopril test) in younger children and all patients with grade 2 hypertension	Oral glucose tolerance test is recommended as mandatory in patients with BMI > 85th percentile. Fasting insulin allows calculation of HOMA-IR, and insulin in the fasting conditions and at 120 minutes after glucose administration allows evaluation of the insulin sensitivity index. Multiple measurements during a 240-minute test allow calculation of areas under the glucose and insulin curves and are optional Urinary steroid profile is currently recommended over previously used urinary 17-keto- and 17-hydroxysteroids Measurements of thyroid hormones and vitamin D3 metabolites are recommended in patients with a suspicion of specific pathologies Dynamic scintigraphy is recommended to evaluate renal perfusion, urine excretion, relative renal function, and to estimate scarring (static DMSA scintigraphy is more sensitive in detecting scarring but does not allow evaluation of renal perfusion)
Step 3	• Non-invasive and invasive renal artery imaging (CTA, MRA, invasive angiography) • Imaging to detect adrenal lesions/paraganglioma • Non-invasive imaging of other vascular beds (visceral arteries, intracranial arteries) • Molecular testing	Step 3 investigations are performed in patients in whom the diagnosis has not been established despite completed step 1 and 2 investigations and/or treatment is unsuccessful

ABPM — ambulatory blood pressure monitoring; BMI — body mass index; cIMT — common carotid artery intima-media thickness; CTA — computed tomography angiography; DMSA — dimercaptosuccinic acid; ECG — electrocardiogram; HDL — high-density lipoprotein; HOMA-IR — homeostatic model assessment-insulin resistance; LDL — low-density lipoprotein; LVM — left ventricular mass; MRA — magnetic resonance angiography

The diagnosis of hypertension in children and adolescents should by confirmed by ABPM. Due to lack of reference values for younger children and the possibility of false positive diagnoses, only children above 5 years of age and/or above 120 cm in height should be routinely referred for ABPM. In younger children, the diagnosis of hypertension is based on office measurements, and ABPM is performed in individually selected cases.

In most children with hypertension, an immediate institution of antihypertensive therapy is not necessary, which usually allows complete diagnostic investigations before the treatment is started. Indications for initiating antihypertensive therapy before completion of the differential diagnosis include high BP values (grade 2 hypertension with clinical symptoms) and/or advanced target organ damage and/or symptomatic hypertension. Except for hypertensive urgencies and emergencies, if drug treatment is necessary before completion of the diagnostic tests, long-acting dihydropyridine calcium antagonists are preferred as this drug class has the least effect on laboratory test findings.

9.6. General approach to the treatment of hypertension

General approach to and indications for the treatment of hypertension in children and adolescents are based on evaluation of the severity of hypertension, its nature (primary versus secondary), target organ

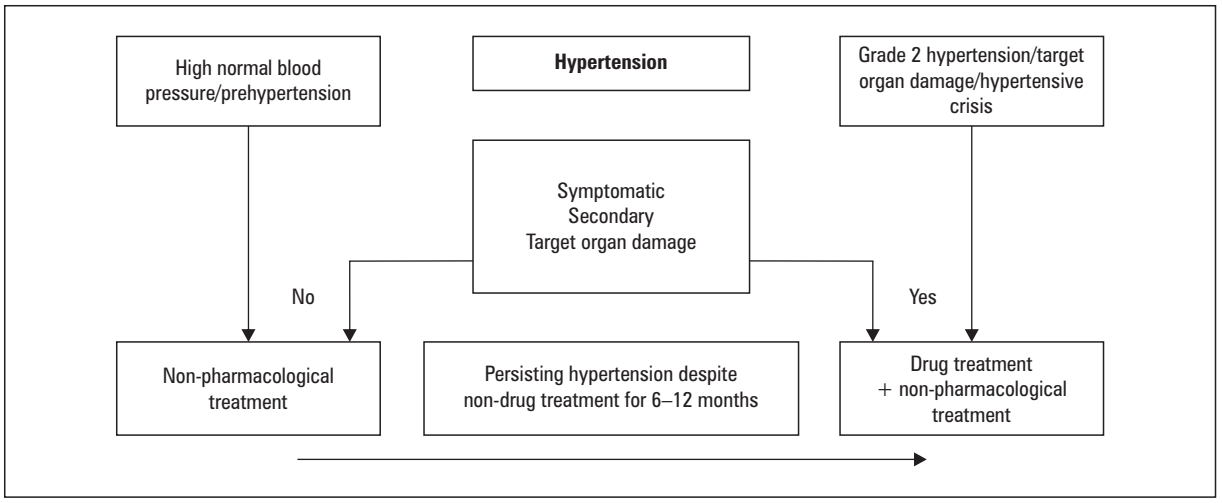

Figure 10. Treatment of hypertension in adolescents

damage, and concomitant conditions. Treatment monitoring and modifications based on ABPM are recommended (Fig. 10). Antihypertensive drug treatment and its success rates depend on the aetiology of hypertension.

9.7. Hypertension in chronic kidney disease

Hypertension secondary to chronic kidney disease is the major cause of hypertension in younger children, and the major cause of severe hypertension with target organ damage at all ages. Hypertension is present in more than 54% of children with chronic kidney disease, the more common, the lower GFR values. Hypertension is more common in children with chronic kidney disease due to glomerulopathy and occurs virtually in all in whom chronic kidney disease is due to haemolytic-uraemic syndrome. Among dialyzed children (chronic kidney disease stage 5), hypertension is present in up to 80% of patients. The pathogenesis of hypertension in chronic kidney disease includes both the renin and the volaemic mechanism. With decreasing GFR, sodium and water retention plays an increasingly important role in the pathogenesis of hypertension in patients with chronic kidney disease. Poorly controlled hypertension is a major cause of cardiovascular deaths during renal replacement therapy. In addition to proteinuria, hypertension is also the major risk factor for progression of chronic kidney disease. Goals of hypertension treatment in children with chronic kidney disease include both reduction of the risk of future cardiovascular events and delaying chronic kidney disease progression. According to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, the BP threshold for initiating antihypertensive therapy is the 90th percentile for gender and age. In contrast, the ESH guidelines (2009 and 2016) do not offer a clear threshold for therapy initiation. Based on prospective randomised studies, clinical observations, expert opinions, and the results of recently published metaanalyses of adult studies, antihypertensive therapy should be initiated in children with chronic kidney disease and BP values above the 90th percentile. It is recommended to monitor antihypertensive treatment by ABPM, and treatment effectiveness should be evaluated based on the mean 24-hour MAP. Target BP values depend on the severity of proteinuria. Reduction of the mean 24-hour MAP below the 90th percentile (50–90th percentile range) is recommended in children with chronic kidney disease without proteinuria or with proteinuria below 0.5 g per day, and below the 50th percentile in children with proteinuria above 0.5 g per day. Of note, the 2009 and 2016 ESH guidelines suggested (based on the expert opinion) reducing BP below the 75th percentile in children with chronic kidney disease without proteinuria. In our opinion, this recommendation is not justified by the ESCAPE study results which are cited by ESH. In addition, with such target BP values, the threshold for initiating antihypertensive therapy in chronic kidney disease should be automatically reduced from the 90th to the 75th percentile.

First-line antihypertensive drug classes in children with chronic kidney disease are RAAS inhibitors: ACEI and ARB. This is based on the pathomechanism of hypertension in chronic kidney disease and the published results of clinical trials and observational studies in children. Prospective multicentre studies showed the efficacy and safety of ACEI as

antihypertensive and renoprotective drugs (ramipril, enalapril), and similar data were obtained for ARB (losartan) in single-centre studies. In addition, observational studies showed better BP control in children treated with RAAS inhibitors compared to other antihypertensive drug classes. These drugs are not recommended in patients with a very low GFR (< 15–20 mL/min/1.73 m^2) due to a risk of significant renal function worsening and/or hyperkalaemia. Dual therapy with ACEI and ARB may result in an additional BP-lowering effect and a reduction of proteinuria. However, such treatment is currently not recommended if additional indications are not present (antiproteinuric effect) due to concerns regarding the safety of such combined treatment. Renin inhibitors were tested in clinical studies in children but their renoprotective effect was not evaluated and these drugs continue to be not licensed for use in children.

Achieving target BP in patients with chronic kidney disease usually requires multiple antihypertensive drugs. Individualization of further drug treatment depending on the clinical scenario is recommended in children. Beta-blockers are the recommended second-line drugs in children with chronic kidney disease due to their additional effect on the RAAS, antiadrenergic effect, and a reduction of proteinuria. Diuretics are recommended for fluid retention which is usually seen in children with GFR below 40 mL/min/1.73 m^2. In children with large proteinuria or low GFR, often the diuretic dose has to be increased for an adequate therapeutic effect. Thiazide/thiazide-like diuretics retain their effectiveness only in patients with GFR above 30–40 mL/min/1.73 m^2. Dihydropyridine calcium antagonists, previously used as first-line drugs in children with chronic kidney disease, are currently used as further choice drugs due to the fact that they increase hyperfiltration and proteinuria. However, this negative effect is absent or reduced in combination with RAAS inhibitors.

9.7.1. Hypertension in patients undergoing dialysis therapy

Hypertension is found in 55–79% of children with chronic kidney disease who require renal replacement therapy, including 56–79% treated with haemodialysis, 54–75% treated with peritoneal dialysis (in Poland 56% and 54%, respectively), and approximately 66% of patients after kidney transplantation. Of note, about 20% of these patients with hypertension remain untreated, and among those treated, hypertension is not controlled in nearly 75% of children. As BP measurements performed in dialysis units (before and after haemodialysis) show less correlation with left ventricular hypertrophy compared to 24-hour ABPM in the interdialytic period, the diagnosis of hypertension in children on chronic dialysis treatment should be based on ABPM in the interdialytic period. The main risk factors for hypertension in children on chronic dialysis treatment are hypervolaemia and excessive salt intake. Other risk factors include young age (< 6 years), black race, female gender, acquired underlying kidney disease, anaemia in patients treated with haemodialysis, and duration of dialysis therapy, with a lower proportion of hypertension among patients undergoing dialysis therapy for a longer time. The most important element in the prevention and treatment of hypertension in children undergoing dialysis therapy is proper assessment of the volume status and achieving so called dry mass. It is believed that safe increase in body weight between dialysis sessions in children should not exceed 3% of the body dry mass. In paediatric patients undergoing peritoneal dialysis, the main cause of hypervolaemia is occult overhydration associated with uraemic cachexia. In these patients, residual diuresis plays a major role, as the higher is the latter, the lower BP increase related to hypervolaemia.

According to the 2005 National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guidelines, BP values below the 95th percentile for gender, age, and height should be aimed for in children requiring chronic renal replacement therapy. Normal body dry mass should be achieved by intensification of dialysis therapy, with session duration increased to 5–8 hours, performing 4–6 procedures per week, and periodic use of haemodiafiltration and/or nocturnal dialysis. In patients undergoing peritoneal dialysis, increased ultrafiltration can be achieved by using higher osmolality dialysis fluids or icodextrin-containing fluids. Dihydropirydine calcium antagonists, ACEI, and ARB are used for drug therapy. There are no clear guidelines regarding drug choice but attention should be paid to hyperkalaemia that accompanies use of the two latter drug classes.

9.8. Renovascular hypertension

Renovascular hypertension is among the major causes of severe hypertension in children and adolescents. The most common cause of renovascular hypertension in this age group is FMD but in 20–40% of cases, renovascular hypertension is a complication of other conditions (syndromic renovascular hypertension), including neurofibromatosis type 1 (> 15%). Renovascular hypertension may also be caused by a congenital or acquired (e.g., transplant

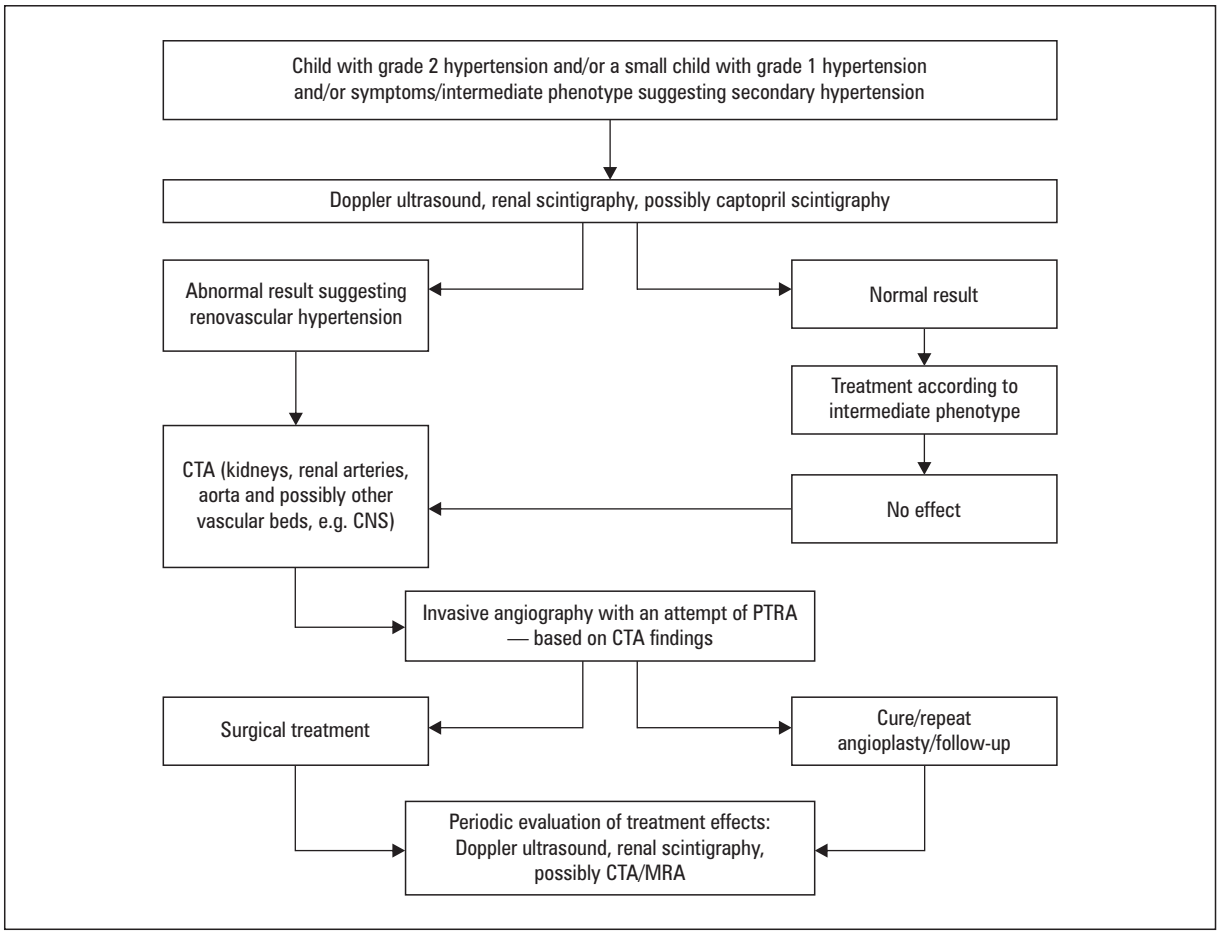

Figure 11. Diagnosis and treatment in children with renovascular hypertension. CNS — central nervous system; CTA — computed tomography angiography; MRA — magnetic resonance angiography; PTRA — percutaneous transluminal renal angioplasty

renal artery stenosis) stenosis of the main renal artery or additional renal arteries and/or segmental branches.

9.8.1. Investigations for and the diagnosis of renovascular hypertension

The diagnosis of renovascular hypertension is based on a finding of a haemodynamically significant stenosis of one or both renal arteries (Fig. 11). Invasive angiography, often with selective renal artery catheterization, is still considered a reference method but should be performed only directly prior to intervention and during the same procedure if percutaneous treatment is planned based on the results of non-invasive imaging. Of note, the sensitivity and specificity of non-invasive imaging studies in children and adolescents with renovascular hypertension, such as Doppler ultrasonography (73% and 83%, respectively), MRA (80% and 62%) and CTA (93% and 81%), are significantly lower than those of conventional invasive angiography used to confirm the diagnosis.

Routine evaluation of renal vein renin activity or level is not recommended. This test may be performed in case of diagnostic uncertainties.

In the diagnostic algorithm for renovascular hypertension, scintigraphy is not recommended neither in the AAP guidelines nor in the adult guidelines, including the PTNT guidelines. A similar opinion is shared by the authors of the present guidelines but it should be noted (an expert opinion) that assessment of kidney excretory function may help guide a decision regarding surgical treatment in difficult cases (small children, percutaneous intervention not feasible), and after invasive treatment (percutaneous intervention/surgery) it allows evaluation of the treatment outcomes and is an additional criterion for the diagnosis of hypertensive nephropathy in a kidney with normal renal artery exposed to high BP values before treatment.

9.8.2. Treatment of renovascular hypertension

The ultimate and causative therapy of renovascular hypertension is an interventional treatment that

Table XLV. Drug treatment of renovascular hypertension.

Unilateral renal artery stenosis	Bilateral renal artery stenosis
ACEI/ARB (use in caution; usually in cases of lack of effect of other drugs) Dihydropyridine calcium antagonists β-blockers α-blockers Centrally acting imidazoline agonists	Diuretics Dihydropyridine calcium antagonists β-blockers α-blockers Centrally acting imidazoline agonists

ACEI — angiotensin-converting enzyme inhibitors; ARB — angiotensin receptor blockers

eliminates the underlying cause of hypertension. Although drug treatment allows at least partial BP control, it does not cure the patient. In patients with Takayasu disease, immunosuppressive treatment should be considered causative therapy, and antihypertensive treatment, including invasive procedures, is targeted at the disease complications.

Drug treatment of renovascular hypertension depends on whether unilateral or bilateral renal artery stenosis is present (Tab. XLV).

9.8.2.1. Interventional treatment of renovascular hypertension

Interventional treatment of renovascular hypertension includes percutaneous transluminal renal angioplasty (PTRA) and surgical revascularization. PTRA may be successfully undertaken by balloon angioplasty with or without stenting. PTRA is the initial step of the interventional treatment and it should it be attempted during invasive renal angiography. Complications of PTRA include mechanical vessel wall damage with formation of a pseudoaneurysm, thrombosis, arterial spasm, arterial wall laceration with bleeding, and entrapment of a balloon catheter within the vessel lumen. Some complications may require immediate surgical treatment, and thus both invasive renal angiography and PTRA should be performed in experienced paediatric centres with vascular surgical team backup. Local administration of an arterial smooth muscle relaxant should be always possible throughout the PTRA procedure. Drugs administered locally to relieve arterial spasm during PTRA include nifedipine, nitroglycerin, and sodium nitroprusside. According to experts' recommendations, prophylactic doses of low-molecular-weight heparin should be given for 1–7 days after the procedure in all cases of renal artery catheterization with PTRA, followed by administration of ASA at 1 mg/kg/day for 3–6 months.

Experience with stenting in renovascular hypertension in children and adolescents is relatively limited. Due to ongoing growth, stents mounted on balloon catheters that can be redilated later are recommended. If it is possible to implant a stent with a diameter corresponding to the size of the renal artery in an adult person, implantation of a self-expandable stent is an alternative option.

Surgical treatment (revascularization or nephrectomy) is the ultimate approach to the treatment of renovascular hypertension. Surgical revascularization is indicated if drug therapy and PTRA were unsuccessful, and nephrectomy is indicated for unilateral renal artery stenosis with severely impaired function of the ischemic kidney. Nephrectomy is considered appropriate if the ischemic kidney is reduced in size and its relative function has decreased to below 10–15%. In children and adolescents in whom renovascular hypertension is associated with an involvement of visceral vessels and/or midaortic syndrome, the therapeutic approach must be planned individually and mostly commonly involves staged procedures, taking into consideration their possible extent, type and sequence, including renal revascularization.

Major surgical techniques used for renal revascularization in adolescents include repair using a prosthetic or autologous patch, and kidney autotransplantation following excision of the stenosed arterial segment.

9.9. Hypertension in children after surgical treatment of coarctation of the aorta

Hypertension is an invariable and major symptom of congenital coarctation of the aorta. Following interventional treatment that resulted in a correction of the anatomical stenosis, hypertension persists or develops after a period of normotension in about 32.5% (25–68%) of patients. In a large proportion of patients, exercise-induced hypertension may be diagnosed based on an exercise test.

9.9.1. Treatment of hypertension in children after surgical treatment of coarctation of the aorta

Paediatric studies showed efficacy of ACEI (ramipril), ARB (candesartan), and β-blockers (metoprolol). AHA recommends ARB or ACEI and β-blockers as first-line drugs. In patients with coarctation of the aorta, routine annual ABPM and an exercise test every 2 years are recommended by the experts. Abnormal results of these tests are an indication for drug therapy and possible diagnostic investigations for recoarctation. According to both AHA and ESC guidelines, assessment of postprocedural aortic anatomy, including that of the aortic arch, as factors affecting development of recoarctation and severity of hypertension, requires repeated imaging studies (echocardiography, CTA, or MRA depending on the

patient's age), usually every several years. In patients with coarctation of the aorta and concomitant bicuspid aortic valve, this surveillance must also include the anatomy and (dys)function of aortic valve, and the degree of ascending aortic dilatation. In these patients, treatment of hypertension should be particularly aggressive.

9.10. Monogenic hypertension

The diagnosis of monogenic hypertension is based on the finding of a typical intermediate phenotype, which is often possible already during step 1 and 2 investigations. In some cases, a family history of hypertension associated with a typical phenotype or resistance to treatment may be ascertained (Tab. XLVI). The diagnosis of a specific form usually allows treatment directed at major abnormalities leading to hypertension. The evaluation and treatment of these forms of hypertension should be undertaken in tertiary care centres where the molecular diagnosis is available.

9.11. Primary hypertension

Primary hypertension is the major cause of hypertension in children above 12 years of age, accounting for about 50% of all cases of hypertension in the developmental period. Recently, it has been increasingly diagnosed also in younger children, including those below 6 years of age, and is associated with obesity. The predominant intermediate phenotype of primary hypertension is abnormal body composition with visceral obesity, abnormal muscle-to-adipose tissue proportion, and metabolic disturbances typical for metabolic syndrome (Tab. XLVII). In addition, a trend for higher uric acid level is typical for essential hypertension. The risk of target organ damage is related to the degree of metabolic abnormalities and the amount of visceral fat as evaluated by waist circumference.

9.11.1. Management of primary hypertension

Non-drug therapy including both dietary modifications and physical activity (moderate- to high-intensity exercise for 60 to 90 minutes daily) is of major importance in the management of primary hypertension. There are no contraindications to participate in specific types of sport/exercise. The dietary management is the same as for the prevention and treatment of obesity. In addition to limitations regarding the size, composition, and energy value of meals, a significant reduction in salt intake is also important. In practice, this calls for elimination of adding salt to foods.

Drug therapy should be considered in children with grade 1 essential hypertension in whom BP was not adequately lowered despite 6–12 months of non-drug therapy. Drug therapy is indicated in children with grade 2 hypertension and/or target organ damage. Due to concomitant metabolic disturbances and the mechanism of action (increase in peripheral vascular resistance), β-blockers and diuretics are not recommended as first- and second-line drugs, and the preferred drug classes are ACEI, ARB, and dihydropyridine calcium antagonists. In post-pubertal women who do not use contraception, new generation β-blockers with vasodilatatory properties may be recommended, as these drugs do not induce adverse metabolic effects and do not increase peripheral vascular resistance, as well as dihydropyridine calcium antagonists. Due to the fact that the risk of target organ damage is associated with metabolic disturbances and visceral obesity, it is recommended to include regular anthropometric measurements (body weight, waist circumference) in addition to evaluation of BP values and target organ damage when monitoring treatment effects.

9.12. Hypertension in children with diabetes

Diabetes type 1 is currently present in about 205,000 individuals in Poland, including about 20,000 children and adolescents. A four-fold increase in the incidence of diabetes type 1 has been noted over the last 25 years. With increasing rates of overweight and obesity in the Polish population, the number of children with diabetes type 2 also increases.

Based on few studies that used the generally accepted paediatric definition for the diagnosis, the prevalence of hypertension among children with diabetes type 1 has been estimated at 4–7%, while hypertension is present in as many as 23–40% of young patients with diabetes type 2. Consistent with the pathogenesis of diabetes type 2, a higher severity of metabolic disturbances and the metabolic syndrome is also seen in this patient group. Although hypertension is usually seen in patients with diabetes type 2, its occurrence in children and adolescents with diabetes type 1 is an increasingly common clinical problem. Hypertension is associated with an increased risk of micro- and macrovascular complications, cardiovascular disease and diabetic nephropathy which are major causes of morbidity and mortality among patients with diabetes type 1 and 2.

9.12.1. Pathogenesis of hypertension in children with diabetes

The pathogenesis of hypertension in children with diabetes type 1 is not been entirely clear. Comparison of the clinical presentation in children with essential hypertension and those with diabetes type 1 and hy-

Table XLVI. Monogenic hypertension syndromes — intermediate phenotypes, mode of inheritance, and treatment.

Syndrome	Gene	Mode of inheritance	Clinical phenotype	Serum K^+	Serum HCO_3^-	PRA	Serum aldosterone	Other biochemical abnormalities	Treatment
Liddle syndrome	*SCNN1A* *SCNN1B* *SCNN1G*	AD	Hypertension at varying age	↓ –	↑	↓	↓		Amiloride, triamterene
Apparent mineralocorticoid excess	*HSD11B2*	AR	More frequently low birth, nephrocalcinosis, hypertension at varying age 4 variants of disease	↓ –	↑	↓	↓	Excess of cortisol metabolites relative to cortisone metabolites	Distal nephron-acting diuretics (amiloride, triamterene), spironolactone/eplerenone, low doses of dexamethasone
Pseudohypoaldosteronism type II	*WNK1* *WNK4* *KLHL3* *CUL3*	AD/AR	More frequently after puberty, clinical course and severity of biochemical abnormalities depend on the mutated gene	↑	↓	↓	↓ –	Hypercalciuria, normal GFR	Thazide diuretics
MR receptor mutation	*NR3C2*	AD	In women hypertension may appear or exaggerate in the second trimester pf pregnancy; may occur also in men; spironolactone may cause rise of blood pressure	↓ –	↑	↓	↓		Amiloride, triamterene, thiazide diuretics, non-steroid MR antagonists
Familial hyperaldosteronism type I (FH I)	*CYP11B2*	AD	Hypertension in childhood	↓	↑	↓	↑	Hybrid steroids in urine Positive dexamethasone suppression test	Dexamethasone/eplerenone/spironolactone
Familial hyperaldosteronism type II (FH II)	*CLCN2*	AD	Hypertension may develop in childhood but usually manifests in the 2nd or 3rd decade of life	↓	↑	↓	↑	Uni- or bilateral adrenal hyperplasia	Spironolactone/eplerenone, adrenalectomy
Familial hyperaldosteronism type III (FH III)	*KCNJ5*	AD	Varying clinical expression, severe hypertension may develop already in the first years of life Type A — severe clinical course, may require bilateral adrenalectomy; Type B — milder clinical course; drug treatment may be effective and sufficient	↓	↑	↓	↑	Hybrid steroids may be present in urine; bilateral adrenal hyperplasia may develop	Spironolactone/eplerenone, adrenalectomy

→

Table XLVI. Monogenic hypertension syndromes — intermediate phenotypes, mode of inheritance, and treatment.

Syndrome	Gene	Mode of inheritance	Clinical phenotype	Serum K^+	Serum HCO_3^-	PRA	Serum aldosterone	Other biochemical abnormalities	Treatment
Familial hyperaldosteronism type IV (FH IV)	*CACNA1H*	AD	Varying clinical expression; severe hypertension may develop already in preschool age	↓	↑	↓	↑	Normal adrenals	Spironolactone/eplerenone, ARB as additional drugs Calcium antagonists probably effective as additional drugs
Familial hyperaldosteronism type V (FH V) (primary aldosteronism with seizures and neurological abnormalities, PASNA)	*CACNA1D*		Severe impairment of psychoneurological development. No family history — patients are not able to procreate due to severe disability	↓	↑	↓	↑	Normal adrenals	Spironolactone/eplerenone, calcium antagonists ARB as additional drugs
11α-hydroxylase deficiency	*CYP11B*	AR	Hypertension in childhood or infancy; precocious puberty	↓ –	↑ –	↓ –	↓	Excess urinary excretion of deoxycorticortone and testosterone metabolites	Spironolactone, hydrocortisone
17α-hydroxylase deficiency	*CYP17A1*	AR	Hypertension in childhood; delayed puberty	↓ –	↑ –	↓ –	↓	Sex hormone deficiency	Spironolactone
Familial glucocorticoid resistance	?	AR/AD	Hypercortisolaemia without features of Cushing syndrome	↓ –	↑ –	↓ –	↓	Hypercortisolaemia without features of Cushing syndrome	Spironolactone
Brachydactylia with hypertension	*PDE3A*	AD	Short stature, brachydactylia type E	–	–	– ↑	– ↑	Neurovascular conflict — posterior inferior cerebellar artery impingement on the medulla oblongata, possible arterial anomalies in other vascular beds	Combined treatment including ARB, β-blockers, calcium antagonists

AD — autosomal dominant; AR — autosomal recessive; ARB — angiotensin receptor blockers; GFR — glomerular filtration rate; PRA — plasma renin activity

Table XLVII. Definitions of metabolic syndrome in children according to the International Diabetes Federation, 2007

Age	Criteria
< 10 years	Metabolic syndrome should not be diagnosed. Extended diagnostic investigations are indicated in risk groups
10–15 years (< 16 years)	Waist circumference ≥ 90th percentile or ≥ cut-off point for adult patients + 2 or more from the following criteria: — serum triglycerides ≥ 150 mg/dL — serum HDL cholesterol < 40 mg/dL — SBP > 90th percentile — fasting blood glucose ≥ 100 mg/dL or type 2 diabetes
> 16 years	Criteria as in adults: Waist circumference ≥ 94 cm in boys and 80 cm in girls + 2 or more from the following criteria: — serum triglycerides ≥ 150 mg/dL — serum HDL cholesterol < 40 mg/dL in boys and < 50 mg/dL in girls — SBP ≥ 130 mm Hg and/or DBP ≥ 85 mm Hg or antihypertensive drug treatment — fasting blood glucose ≥ 100 mg/dL or type 2 diabetes

DBP — diastolic blood pressure; HDL — high-density lipoprotein; SBP — systolic blood pressure

pertension suggests a role of common pathogenetic mechanisms, such as overweight and obesity, abnormal distribution of fat tissue, and related insulin resistance. Other factors are worse diabetes control and use of higher insulin doses. Similarly to the general population, a significant increase in the rate of hypertension since puberty is seen among children with diabetes type 1. Patients with diabetes type 1 are also characterized by an abnormal diurnal BP pattern, including non-dipping and rapid and significant morning BP surge. An association between elevated BP and an abnormal diurnal BP pattern with early markers of kidney damage suggests a role of both renal mechanisms and central BP regulation. Metabolic disturbances due to chronic hyperglycaemia, leading to arteriosclerosis and increased arterial stiffness, also contribute to the development of abnormal BP control in diabetic patients.

Although renal failure due to diabetic nephropathy usually develops only after many years of disease, early stages of diabetic nephropathy, characterized by increased urinary albumin excretion, are seen also in the paediatric population. Kidney damage due to diabetes type 1 in adolescents is directly associated with elevated BP values, and effective BP-lowering treatment reduces progression of this complication.

Among children and adolescents with diabetes type 2, hypertension is present at the time of diabetes diagnosis in 12–25% of patients and is associated with disturbances related to insulin resistance and associated abdominal obesity. In addition, patients with diabetes type 2 present more commonly with atherogenic dyslipidaemia leading to early increased arterial stiffness, and patients with severe obesity develop renal dysfunction already prior to the development of overt diabetes type 2. In some patients, elevated urinary albumin excretion is present at the time of diabetes diagnosis. Concomitant presence of hypertension and other features of metabolic syndrome predisposes to more frequent and earlier development of cardiovascular disease and nephropathy compared to diabetes type 1. For this reason, patients with diabetes type 2 require comprehensive treatment of all disturbances related to metabolic syndrome.

9.12.2. Evaluation of hypertension in children with diabetes

In children and adolescents with diabetes, BP measurements should be performed at each visit, and at least twice a year in children below 7 years of age. In adolescents above 12 years of age with diabetes type, abnormal BP is defined as values above the 95th percentile or > 130/80 mm Hg regardless of the 95th percentile value. Performance of a 24-hour ABPM is recommended to confirm hypertension.

Due to an increased risk of cardiovascular disease in diabetic children, it is recommended to lower BP at least to the 90th percentile for age, gender, and height, or to ≤ 120/80 mm Hg regardless of age.

Blood pressure lowering leads to regression of target organ damage but too intensive treatment with DBP reduction below 60 mm Hg may impair coronary flow.

Investigations for secondary hypertension should be performed using the approach discussed above.

9.12.3. Management of hypertension in patients with diabetes

The management of hypertension in young patients with diabetes should include lifestyle modifications, good metabolic control of diabetes, and drug therapy. A major role is played by non-drug therapy which included normalization of body weight (BMI below the 90th percentile for gender and age), regular physical activity (moderate- to high-intensity exercise for > 1 hour daily), and low-sodium diet (Tab. XLVIII).

For drug therapy, the recommended antihypertensive drug classes in children and adolescents with hypertension and diabetes are ACEI, or ARB in case of ACEI intolerance. Antihypertensive therapy in children with diabetes is also a nephroprotective

Table XLVIII. Treatment of hypertension in children with diabetes

Threshold values	Treatment
BP > 90th percentile for age, gender, and height	Lifestyle changes*
BP > 90th percentile for age, gender, and height despite lifestyle changes	+ ACEI/ARB
BP > 95th percentile for age, gender, and height	Lifestyle changes* + ACEI/ARB

*Body weight reduction to normal values (body mass index < 90th percentile) and physical activity > 1 hour per day. It is recommended to monitor treatment effects using home blood pressure measurements and ambulatory blood pressure monitoring, including evaluation of nocturnal blood pressure fall (dipping). ACEI — angiotensin-converting enzyme inhibitors; ARB — angiotensin receptor blockers; BP — blood pressure

treatment and is based on similar principles. Effective drug therapy in patients with diabetic nephropathy delays development of end-stage renal failure. ACEI treatment in adolescents is continued for many years, which may lead to multiple adverse effects, such as cough, hyperkalaemia, headaches, impotence, and a risk of pseudoallergic reactions. Possible severe foetal complications should be also borne in mind, which is a potential problem when treating adolescent girls.

In one third of patients with diabetes type 2, monotherapy using ACEI or ARB is ineffective. These patients required combined drug therapy, and the second-line drugs are dihydropyridine calcium antagonists followed by vasodilating β-blockers and possible thiazide-type diuretics.

9.13. Hypertension with emergent and urgent indications for treatment

In the developmental period, hypertensive emergencies are virtually always caused by secondary hypertension, including due to acute kidney disease (acute glomerulonephritis, haemolytic-uraemic syndrome). Hypertensive urgencies related to an acute BP increase are also seen in children with primary hypertension. The management of hypertensive emergencies and urgencies has been evaluated in case reports and case series but not in controlled clinical studies, and recommendations presented in the guidelines (ESH 2009 and 2016, Fourth Report, AAP 2017) are based on expert opinions (Fig. 12). It is recommended to treat hypertensive emergencies in an intensive care unit, with intravenous line access and ECG, BP, respiratory function (pulse oximetry), and fluid balance monitoring. BP should be measured every 15 minutes until it is reduced by 30% compared to the baseline. Biochemical blood testing including renal function, electrolytes, and venous blood gases is recommended in all patients with hypertensive urgencies and emergencies, and if the aetiology of hypertension is not known, an initial differential diagnosis should also be performed including renal ultrasound with Doppler evaluation of the renal arteries and echocardiography to evaluate LVM. During subsequent hours of treatment, BP may be measured every 30–60 minutes depending on the clinical condition of the patient. The general ap-

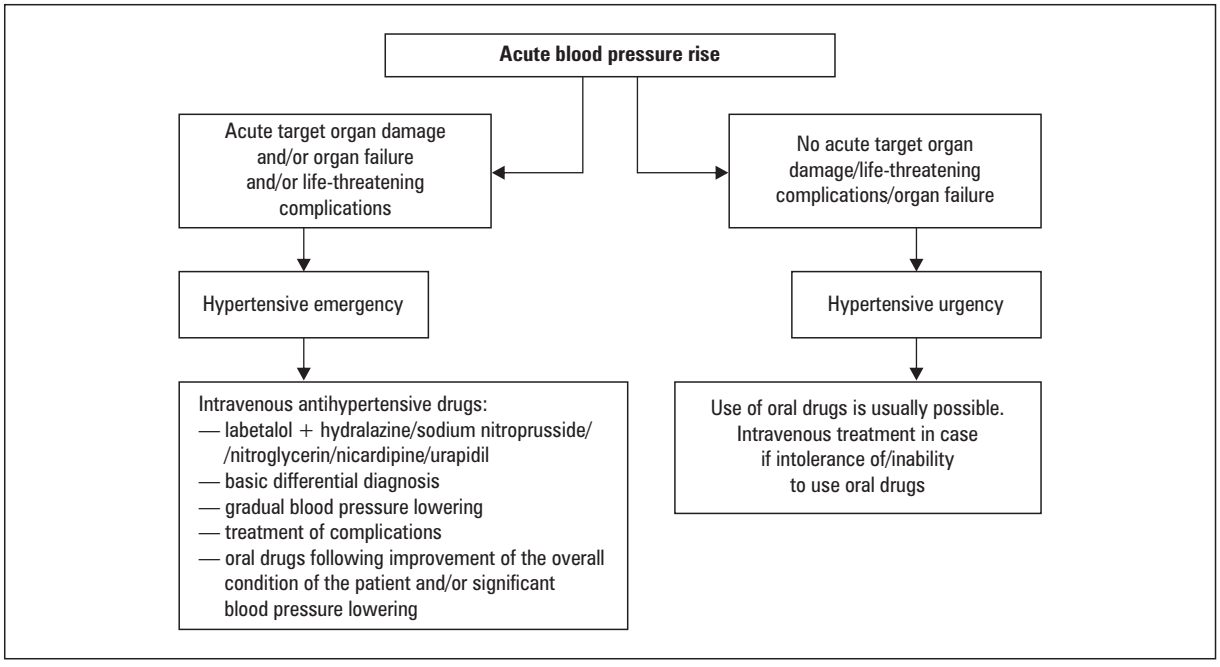

Figure 12. Management of an acute blood pressure rise in children and adolescents

Table XLIX. Antihypertensive drugs used in hypertensive emergencies

Antihypertensive drug	Dosage	Comments
Labetalol	**Bolus:** 0.2–1 μg/kg per dose, maximum 40 mg/kg per dose Infusion: 0.25–3 μg/kg/hour	**Contraindications:** asthma, heart failure, diabetes May result in hyperkalaemia and hypoglycaemia Does not induce reflex tachycardia **Onset of action:** 5–10 minutes
Phentolamine	**Bolus:** 0.05–0.1 mg/kg per dose, maximum 5 mg per dose	May result in tachycardia Drug of choice in an adrenergic crisis **Onset of action:** 1–2 minutes
Furosemide	**Bolus:** 0.5–5 mg/kg per dose	Need to monitor potassium level (may cause hypokalaemia), useful in hypertension due to hypervolaemia **Onset of action:** 5–10 minutes
Hydralazine	**Bolus:** 0.2–0.6 μg/kg, maximum 20 mg per dose IV or IM	Often reflex tachycardia, fluid retention, headaches. Intravenous boluses should be given every 4 hours. Need for concurrent furosemide administration **Onset of action:** 10–20 minutes
Sodium nitroprusside	Infusion: 0.5–8 μg/kg/min	Risk of cyanide poisoning if long-term use or concomitant renal or hepatic failure Need to monitor cyanide levels during long-term use (> 48 hours) **Onset of action:** 1–2 minutes
Nitroglycerin	Infusion: 0.1–2 μg/kg/min	May result in methaemoglobinaemia; vasodilating effect mainly in the venous bed — effective in heart failure, limited effectiveness in children **Onset of action:** 2–5 minutes
Esmolol	Infusion: 100–500 μg/kg/min, maximum 1000 μg/kg/min	May result in bradycardia Contraindications: asthma, heart failure Very short duration of action **Onset of action:** 1–2 minutes
Nicardipine	**Bolus:** 30 μg/kg, maximum 2 mg per dose Infusion: 0.5–4 μg/kg/min	May induce reflex tachycardia **Onset of action:** 5–10 minutes
Enalaprilat	**Bolus:** 5–10 μg/kg per dose, maximum 1.2 mg per dose	May result in long-lasting hypotension, hyperkalaemia or acute renal failure Limited indications **Onset of action:** 15–30 minutes

IM — intramuscular; IV — intravenous

proach to the treatment of a hypertensive emergency in children and adolescents is based on gradual, controlled BP reduction. It is recommended to lower BP by 25–30% of the overall target BP reduction within 6–8 hours and by another 30% within the next 24–36 hours. Normal BP values (< 90^{th} to 95^{th} percentile) should be reached within 72–96 hours. Intravenous medications are used for the treatment of hypertensive emergencies, with the choice of the drug based on the aetiology of hypertension. In hypertensive emergencies, administration of an intravenous β-blocker (labetalol, esmolol) and a peripheral vasodilating agent (hydralazine, sodium nitroprusside, or nitroglycerin) is recommended. Due to fluid retention caused by peripheral vasodilation during prolonged therapy, an addition of a diuretic is also recommended. Oral treatment is initiated upon improvement of the general clinical condition of the patient. In hypertensive crisis due to acute or chronic kidney disease (patients on dialysis therapy), volume control and removal of excess fluid by dialysis, or using diuretics in patients with preserved glomerular filtration, is of major importance. Addition of a RAAS inhibitor is recommended in hypertensive emergencies due to microangiopathy.

In hypertensive urgencies, oral treatment is usually possible. BP should be lowered by 30% within the first 6 hours, and target BP values should be gradually reached during the next 36–48 hours. The approach to the management of an acute BP increase is shown in Figure 12, and dosing of the drugs used in hypertensive emergencies and urgencies, along with their adverse effects and contraindications, is summarized in Tables XLIX and L. In children with hypertensive urgencies and those with an acute BP increase who may be treated with oral medications, rapidly acting drugs are recommended, followed by institution of long-term antihypertensive therapy (Tab. LI).

Other selected forms of hypertension are listed in Table LII.

9.14. Neonatal hypertension

The incidence of hypertension in neonates is about 0.2–0.3%. However, it is much higher (0.81–9%)

Table L. Oral antihypertensive drugs used in hypertensive urgencies

Antihypertensive drug	Dosage	Comments
Captopril	0.1–0.2 mg/kg per dose, maximum 6 mg/kg/day	Need to monitor potassium and creatinine level **Onset of action:** 10–20 minutes
Clonidine	2–5 μg/kg per dose, maximum 10 μg/kg per dose	**Adverse effects:** dry mouth, sedation **Onset of action:** 30–60 minutes
Amlodipine	0.06–0.3 mg/kg per dose, maximum 5–10 mg per dose	**Adverse effects:** dizziness, reflex tachycardia **Onset of action:** 1–2 hours
Doxazosin*	1 mg per dose, maximum 4 mg/day	**Adverse effects:** dizziness, orthostatic hypotension **Onset of action:** 1–2 hours
Prazosin*	0.05–1 mg/kg/day in 3 doses, maximum 0.5 mg/kg/day	**Adverse effects:** dizziness, nausea, orthostatic hypotension **Onset of action:** 1–2 hours
Propranolol*	1 mg/kg/day in 2–3 doses, maximum 4 mg/kg/day up to 640 mg/day	Contraindications: asthma, bradycardia, cardiac arrhythmia, diabetes **Adverse effects:** bradycardia, bronchospasm, hypotension, Raynaud phenomenon **Onset of action:** 1–2 hours

*Drugs recommended in adrenergic hypertension (phaeochromocytoma/paraganglioma/neuroblastoma). In such cases, blood pressure should be first reduced using α-blockers (doxazosin, prazosin), followed by initiation of a β-blocker (propranolol)

Table LI. Recommended doses of oral antihypertensive drugs in children

Drug class	Drug	Initial dose	Number of daily doses	Maximum dose
Aldosterone antagonists	Eplerenone	25–50 mg/day	1–2	100 mg/day
	Spironolactone	1 mg/kg/day	1–2	3.3 mg/kg/day up to 100 mg/day
Angiotensin-converting enzyme inhibitors	Benazepril	0.2 mg/kg/day up to 10 mg/day	1	0.6 mg/kg/day up to 40 mg/day
	Captopril	0.3–0.5 mg/kg per dose	2–3	6 mg/kg/day up to 450 mg/day
	Enalapril	0.08–0.6 mg/kg/day	1–2	40 mg/day
	Fosinopril	0.1–0.6 mg/kg/day or 5–10 mg/day	1	40 mg/day
	Lisinopril	0.08–0.6 mg/kg/day up to 5 mg/day	1	0.6 mg/kg/day up to 40 mg/day
	Quinapril	5–10 mg/day	1	80 mg/day
	Ramipril	2.5–6.0 mg/day (6 mg/m^2/day)	1	20 mg/day
Angiotensin receptor blockers	Candesartan	0.16–0.5 mg/kg/day up to 4 mg/day	1	32 mg/day
	Irbesartan	75–150 mg/day	1	300 mg/day
	Losartan	0.75 mg/kg/day up to 50 mg/day	1	1.4 mg/kg/day up to 100 mg/day
	Valsartan	0.4 mg/kg/day	1	40–80 mg/day
	Olmesartan	2.5 mg/day	1	40 mg/day
Renin inhibitors	Aliskiren	2 mg/kg/day	1	6 mg/kg/day up to 600 mg/day
α- and β-blockers	Labetalol	1–3 mg/kg/day	2	10–12 mg/kg/day up to 1.2 g/day
	Carvedilol	0.1 mg/kg/ per dose up to 12.5 mg per dose	2	0.5 mg/kg per dose up to 50 mg/day
β-blockers	Atenolol	0.5–1 mg/kg/day	1–2	2 mg/kg/day up to 100 mg/day
	Bisoprolol/ /hydrochlorothiazide	0.04 mg/kg/day up to 2.5/6.25 mg/day	1	10/6.25 mg/day

→

Table LI. Recommended doses of oral antihypertensive drugs in children

Drug class	Drug	Initial dose	Number of daily doses	Maximum dose
β-blockers	Metoprolol	0.5–1.0 mg/kg/day	1–2	2 mg/kg/day
	Propranolol	1 mg/kg/day	2–3	4 mg/kg/day up to 640 mg/day
Calcium antagonists	Amlodipine	0.06–0.3 mg/kg/day	1	5–10 mg/day
	Felodipine	2.5 mg/day	1	10 mg/day
	Isradipine	0.05–0.15 mg/kg per dose	3–4	0.8 mg/kg/day up to 20 mg/day
	Nifedipine (slow release)	0.25–0.5 mg/kg/day	1–2	3 mg/kg/day up to 120 mg/day
Central α-agonists	Clonidine	2–5 μg/kg per dose	2	10 μg/kg/day
	Methyldopa	5 mg/kg/day	2–3	40 mg/kg/day up to 3 g/day
Diuretics	Amiloride	0.4–0.6 mg/kg/day	1	20 mg/day
	Chlorthalidone	0.3 mg/kg/day	1	2 mg/kg/day up to 50 mg/day
	Furosemide	0.5–2.0 mg/kg per dose	1–2	6 mg/kg/day
	Hydrochlothiazide	0.5–1 mg/kg/day	1	3 mg/kg/day
	Triamterene	1–2 mg/kg/day	2	3–4 mg/kg/day up to 300 mg/day
α-blockers	Doxazosin	1 mg/day	1	4 mg/day
	Prazosin	0.05–0.1 mg/kg/day	3	0.5 mg/kg/day
	Terazosin	1 mg/day	1	20 mg/day
Vasodilators	Hydralazine	0.75 mg/kg per dose	4	7.5 mg/kg/day up to 200 mg/day
	Minoxidil	0.2 mg/kg per dose	1–3	50–100 mg/day

among prematurely born infants and with the presence of additional risk factors (umbilical vessel catheterization, patent ductus arteriosus, intraventricular haemorrhage) and concomitant conditions (40% in neonates and infants with chronic bronchopulmonary disease). Neonatal hypertension is generally of a secondary nature, related mainly to renal pathology, most commonly renovascular disease, but iatrogenic factors are also of major importance.

Despite multiple data on normal BP values in neonates depending on specific measurement techniques, the definition of hypertension is still based on the percentile values reported in the 1987 Report of the Second Task Force on Blood Pressure Control in Children and derived from BP measurements using a mercury sphygmomanometer (Tab. LIII). According to the 1987 Report of the Second Task Force, hypertension may be diagnosed in neonates when SBP values above the 95th percentile for chronological age are found on three occasions. Despite numerous methodological limitations and the fact that BP is currently nearly always measured by the oscillometric method, reference BP values given in the 1987 Report of the Second Task Force are practical and easy to use. Table LIV shows a compilation of previous reference BP values that summarizes the 95th and 99th SBP, DBP, and MAP percentiles in 2-week-old neonates in relation to gestational age at birth.

Due to high rates of unreliable findings, including false positive results (up to 41% in children below 12 months of age), and resulting exposure to unnecessary investigations and treatment, BP measurement in healthy neonates is not recommended. BP measurements and investigations for hypertension are indicated in neonates born prematurely, those with concomitant congenital disease or other conditions associated with hypertension, and in neonates who require hospital admission. It is recommended to perform BP measurements in appropriate conditions and using the technique described in Table LV. Auscultatory technique should not be used in newborns, neonates and small children due to technical difficulties and more common white coat effect compared to automatic, oscillometric measurements. Automatic BP measurements using the oscillometric method are prone to an erroneous finding of elevated BP values at the first measurement. If BP measurements are

Table LII. Selected causes of secondary hypertension

Kidney disease	Glomerulonephritis Interstitial nephritis Kidney cystic disease Urinary tract defects Hydronephrosis Radiation nephropathy Renovascular (including vasculitis) Renin-producing tumours Obstructive lesions (renal stones, tumours, subpelvic stenosis) Diabetic nephropathy Hypertension after kidney transplantation
Endocrine disease	Primary hyperaldosteronism Mineralocorticoid metabolism disturbances Congenital adrenal hyperplasia Cushing syndrome Phaeochromocytoma Hyperparathyroidism Acromegaly Hyperthyroidism Hypothyroidism Carcinoid syndrome
Cardiovascular disease	Coarctation of the aorta Aortic regurgitation Abdominal aortic syndrome
Haematologic disease	Anaemia Polycytaemia
Neurologic disease	Porphyrias Vegetative neuropathy Increased intracranial pressure Subcapsular hematoma Tetraplegia Guillain-Barré syndrome Brain trauma Brain tumour
Malignancies	Wilms' tumour Mesoblastic nephroma Neuroblastoma CNS malignancies
Acute stress	Burns Hypoglycaemia Hypoxia Perioperative period Psychogenic hyperventilation Abstinence in alcohol- and psychoactive substance-addicted individuals
Gestational hypertension	Preeclampsia Eclampsia
Reduced vascular resistance	Arteriovenous fistula Paget disease Beriberi
Related to medications, substances, and electrolyte disturbances	mTOR inhibitors (ciclosporin, tacrolimus) Erythropoietin Oral contraceptives (oestrogen, progestin) Glucocorticosteroids Mineralocorticoids Sympathomimetics MAO inhibitors Antidepressant drugs (SSRI, tricyclic antidepressants) Buspirone Modafinil Carbamazepine Methylphenidate Non-steroidal anti-inflammatory drugs Vitamin D overdose Hypercalcaemia Teophilline Amphetamine and derivatives (ephedrine, pseudoephedrine) Cocaine Heroin Ginseng Heavy metals Oncological drugs (anti-VEGF agents, cisplatine, carboplatine, paclitaxel, docetaxel, 5-fluorouracil)
Hypervolaemia	Renal failure Heart failure SIADH
Obstructive sleep apnoea	Obesity Adenotonsillar hypertrophy Anatomical defects of the splanchnocranium
Syndromic hypertension	Turner syndrome Marfan syndrome Klinefelter syndrome Down syndrome Klippel-Trenaunay-Weber syndrome Feuerstein-Mims syndrome von Hippel-Lindau disease von Recklinghausen disease Klippel-Feil syndrome Alagille syndrome Tuberous sclerosis Ehlers-Danlos syndrome
Monogenic hypertension	Liddle syndrome Apparent mineralocorticoid excess Pseudohypoaldosteronism type II MR receptor mutation Familial hyperaldosteronism type I–IV 17-α-hydroxylase deficiency Familial glucocorticoid resistance Brachydactylia with hypertension

CNS — central nervous system; MAO — monoaminooxidase; mTOR — mammalian target of rapamycin; SSRI — selective serotonin reuptake inhibitor; VGEF — vascular endothelial growth factor; SIADH — syndrome of inappropriate antidiuretic hormone

indicated in these age groups and the result of the initial measurement is abnormal, it is recommended to perform multiple repeated automated measurements at short intervals.

The approach to the differential diagnosis of hypertension and evaluation of target organ damage in neonates does not differ from that in older age groups (Tab. LVI).

Table LIII. Reference systolic blood pressure values (95th percentile) in neonates and infants

Age	95th percentile SBP during the first year of life [mm Hg]	
	Boys	Girls
≤ 7 days	96	96
8–30 days	104	104
1 month	104	104
2 months	109	106
3 months	110	108
4 months	110	109
5 months	110	112
6–12 months	110	113

Table LV. Technique of blood pressure measurements in neonates

1. Measurement using an oscillometric device
2. 1.5 hours after feeding or a medical intervention
3. Child supine or prone
4. Selection of an appropriately sized cuff
5. BP measurement on the right arm
6. Earlier placement of the cuff and BP measurement after 15 minutes of a quiet rest
7. BP measurement during sleep or in a quiet awake state
8. 3 properly performed BP measurements 2 minutes apart

BP — blood pressure

Table LIV. Blood pressure values (95th and 99th percentile) at 2 weeks of life in neonates born between 26 and 44 weeks of gestation

Postconceptional age	95th percentile	99th percentile
44 weeks of gestations		
SBP	105	110
DBP	68	73
MAP	**80**	**85**
42 weeks of gestation		
SBP	98	102
DBP	65	70
MAP	**76**	**81**
40 weeks of gestation		
SBP	95	100
DBP	65	70
MAP	**75**	**80**
38 weeks of gestation		
SBP	92	97
DBP	65	70
MAP	**74**	**79**
36 weeks of gestation		
SBP	87	92
DBP	65	70
MAP	**72**	**71**
34 weeks of gestation		
SBP	85	90
DBP	55	60
MAP	**65**	**70**
32 weeks of gestation		
SBP	83	88
DBP	55	60
MAP	**62**	**69**
30 weeks of gestation		
SBP	80	85
DBP	55	60
MAP	**65**	**68**
28 weeks of gestation		
SBP	75	80
DBP	50	54
MAP	**58**	**63**
26 weeks of gestation		
SBP	72	77
DBP	50	56
MAP	**57**	**63**

DBP — diastolic blood pressure; MAP — mean arterial pressure; SBP — systolic blood pressure

9.14.1. Management of neonatal hypertension

Given the lack of long-term randomized studies to evaluate outcomes of antihypertensive therapy in neonates, most recommendations are expert opinions based on clinical experience. It is not recommended to initiate treatment in asymptomatic neonates with BP values between the 95th and 99th percentile. Initiation of drug treatment is justified when BP values are above the 99th percentile, or target organ damage is present with BP values above the 95th percentile. The general rule of drug treatment in newborns and infants is to choose medications depending on the potential aetiology of hypertension and the presence of concomitant abnormalities, and the treatment should be started with as low doses as possible. The safest approach is to use short-acting intravenous drugs (Tab. LVII). Oral antihypertensive therapy is reserved for neonates in a good overall clinical condition (Tab. LVIII).

Table LVI. Criteria for the diagnosis of target organ damage in neonates

Target organ damage	Diagnostic criteria
Eye fundus	Keith-Wagener-Barker grade 3/4 retinopathy
Albuminuria	No reference values
cIMT	No reference values, technically difficult to evaluate
Features of hypertensive cardiomyopathy and aortopathy: • Systolic dysfunction without left ventricular enlargement	• Ejection fraction < 60% • Shortening fraction < 29%
• Left ventricular hypertrophy • Indirect evidence of left ventricular diastolic dysfunction — left atrial enlargement	• Left ventricular mass index > 47.4 ± 6.2 g/m^2 • Left atrial dimension > 1.89 ± 0.27 cm
• Enlargement of the ascending aorta	• Ascending aortic dimension > 1.04 ± 0.2 cm

cIMT — common carotid artery intima-media thickness

Table LVII. Intravenous antihypertensive drugs used in neonates

Antihypertensive drugs	Dosage	Comments
Diazoxide	2–5 mg/kg per dose Rapid intravenous infusion	Slow infusion is ineffective, may cause acute hypotension Currently not routinely used for the treatment of hypertension
Enalaprilat	15 ± 5 μg/kg per dose Repeat q 8–24 hours Injections every 5–10 minutes	May result in long-term hypotension or acute kidney failure Use limited due to these adverse effects
Esmolol	Infusion: 100–300 μg/kg/min	Short-acting drug, continuous intravenous infusion necessary
Hydralazine	Infusion: 0.75–5.0 μg/kg/min Bolus: 0.15–0.6 μg/kg per dose	Frequent tachycardia; boluses given every 4 hours
Labetalol	Infusion: 0.25–3.0 μg/kg/hour Bolus: 0.2–1.0 μg/kg per dose	Contraindications: heart failure, bronchopulmonary dysplasia
Nicardipine	Infusion: 1–3 μg/kg/min	May result in reflex tachycardia
Sodium nitroprusside	Infusion: 0.15–10 μg/kg/min	Risk of cyanide poisoning if long-term use or renal failure

Table LVIII. Oral antihypertensive drugs used in neonates

Antihypertensive drug	Dosage	Dosing interval	Comments
Captopril	< 6 months: 0.01–0.5 mg/kg per dose, maximum 6 mg/kg/day	3 × day	Drug of choice in most neonates. Need to monitor potassium and creatinine level
Clonidine	5–10 μg/kg/day, maximum 25 μg/kg/day	2–3 × day	Side effects: dry mouth, somnolence, and constipation Rebound hypertension if stopped abruptly
Hydralazine	0.25–1.0 mg/kg per dose, maximum 7.5 mg/kg/day	3–4 × day	Tachycardia and fluid retention are frequent adverse effects
Isradipine	0.05–0.15 mg/kg per dose, maximum 0.8 mg/kg/day	4 × day	Effective in acute and chronic hypertension
Amlodipine	0.1–0.3 mg/kg per dose, maximum 0.6 mg/kg/day	2 × day	Hypotension less frequent than with isradipine
Minoxidil	0.1–0.2 mg/kg per dose	2–3 × day	Most potent oral vasodilator. Effective in resistant hypertension

Table LVIII. Oral antihypertensive drugs used in neonates (continued)

Antihypertensive drug	Dosage	Dosing interval	Comments
Propranolol	0.5–1.0 mg/kg per dose	3 × day	Maximum dose depends on heart rate If bradycardia is not present, the dose may be increased to 8–10 mg/kg/day Contraindicated in bronchopulmonary dysplasia
Labetalol	1.0 mg/kg/dose, maximum 10 mg/kg/day	2–3 × day	Contraindicated in bronchopulmonary dysplasia Need to monitor heart rate
Spironolactone	0.5–1.5 mg/kg per dose	2 × day	Results in potassium retention — need to monitor electrolytes Full effect seen after several days
Hydrochlorothiazide	1–3 mg/kg per dose	4 × day	Need to monitor electrolytes
Chlorothiazide	5–15 mg/kg/dose	2 × day	Need to monitor electrolytes

9.14.2. Early diagnosis of hypertension during postdischarge care for children born below 34 weeks of gestation

Prematurity and low birth weight are risk factors for the development of hypertension. It has been estimated that at 3 years of age, hypertension is diagnosed in 7.3% of children born prematurely. The risk of hypertension increases with age and is particularly high in children born at ≤ 33 weeks of gestation.

During specialist postdischarge care for children born prematurely in whom BP is measured, the approach presented above should be followed, using respective BP reference values (see: Neonatal hypertension).

9.14.2.1. Screening for hypertension during postdischarge care for children born prematurely (at ≤ 33 weeks of gestation)

The present guidelines have adopted the approach to postdischarge care for children born prematurely recommended by the Polish Neonatal Society in 2018 and by the Low Birth Weight and Nephron Number Working Group in 2017.

Children with the diagnosis of hypertension before discharge from a neonatal unit should be consulted and enlisted for specialist care in a paediatric hypertension unit already before hospital discharge. Further diagnostic and therapeutic management should be based on the current paediatric PTNT, IP-CZD and ESC recommendations.

Children with accompanying kidney and urinary tract pathology should be enlisted for specialist care in a paediatric nephrology, hypertension, and urology unit. This will allow early planning of both the treatment of the urinary tract pathology and nephroprotective treatment.

In children in whom elevated BP values have not been identified before discharge from the neonatal unit should have BP measured at each visit. In patients below 3 years of age, automatic measurements on the right arm are recommended as the primary BP measurement method. If elevated BP values are identified, this should be confirmed by the auscultatory method. The diagnosis of hypertension is an indication for referral to a paediatric hypertension unit.

10. References

Suplementary file to this article available on-line on Arterial Hypertension website.