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Novelties in the management of arterial hypertension in children and adolescents in accordance with US (2017) and European guidelines (2016)

Novosti pri obravnavi arterijske hipertenzije pri otrocih in mladostnikih glede na ameriške (2017) in evropske (2016) smernice

Rina R. Rus,[1] Nataša Marčun Varda[2]

[1] Department of Nephrology, University Childrens Hospital, University Clinical Centre Ljubljana, Ljubljana, Slovenia
[2] Department of Nephrology, Division of Paediatrics, University Medical Centre Maribor, Maribor, Slovenija

Correspondence/ Korespondenca:
Rina R. Rus, e: rina.rus@guest.arnes.si

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Abstract

Arterial hypertension is less common in children than in adults, however, it has been found to be an important risk factor for early cardiovascular disease in adulthood. The purpose of this paper is to present the latest American and European guidelines for the management and treatment of arterial hypertension in children and implement them for Slovenian paediatric patients.

Izvleček

Arterijska hipertenzija se pri otrocih redkeje pojavlja kot pri odraslih, vendar pa je pomemben dejavnik tveganja za zgodnejši pojav srčno-žilnih bolezni v odrasli dobi. Namen prispevka je predstaviti zadnje ameriške in evropske smernice za obravnavo in zdravljenje arterijske hipertenzije pri otrocih in jih smiselno prenesti na slovenska tla.

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1 Introduction

Arterial hypertension (AH) is known to be less common in children and adolescents than in adults. Nevertheless, there is growing evidence that AH in adults can be traced all the way back to childhood, which theoretically increases the likelihood of developing cardiovascular disease in adulthood.

Before 1977, when the first guidelines for treating children with AH (First Task Force Report) were published (1), not much was known about AH in children. Blood pressure (BP) in children had not been routinely measured until then, and

no reference values for BP were available. Several guidelines were later published by the American Academy of Pediatrics and, in recent years, the European Society of Hypertension. Percentile curves, which showed the normal distribution of BP in infants and children according to age with correction for weight and height, were first published by the U.S. Second Task Force Report in 1987 (2). The U.S. guidelines, published in 1996 (Third Task Force Report), described primary prevention and specified the diagnosis and treatment of AH in children (3). In 2004, the fourth guidelines for the treatment of AH in children and adolescents were published, with published reference values of BP in children by age, height, and sex. The data was based on growth curves of children from Centers for Disease Control and Prevention. Normal BP value in children, defined as BP below the 90th percentile curve with respect to age, sex, and height, was defined. The notion of prehypertension, which we speak of when systolic and diastolic CT values are equal to or higher than the 90th percentile and lower than the 95th percentile, also first appeared. An adolescent with BP above 120/80 mm Hg (4) was also diagnosed with prehypertension. The first European guidelines defining the diagnosis and treatment of AH were published in 2009 (5). The definition of AH was taken from the 2004 U.S. guidelines.

The latest U.S. guidelines for the management and treatment of AH in children and adolescents were published in 2017, and the European guidelines in 2016 (6,7). Both guidelines are consistent in the way BP is detected and measured and treated, but there are some differences that do not significantly affect management and the treatments themselves. In Slovenia, guidelines for the management of paediatric patients were published in 2005 and 2013. We still basically take them into account in routine clinical work today, but we sensibly include new knowledge and revised guidelines (8,9).

2 Classification of AH

In adults, the limit of BP at which we talk about AH is set in regard to the increase in morbidity and mortality due to cardiovascular disease. According to the latest U.S. guidelines for adults, published in 2017 (10), the limit defining AH has been lowered to 130/80 mm Hg, regardless of age. In contrast, the 2018 European guidelines do not change the limit for AH, which remains at 140/90 mm Hg, with AH stages being further defined by cardiovascular risk assessment if AH is significantly elevated with concomitant chronic kidney disease, diabetes or failure of target organs (11).

In children, the diagnostic criterion for AH is based on normal distribution of BP in healthy children. BP height is defined by the age, sex, and body height of a child. The 2016 European guidelines use the BP tables taken from the 2004 U.S. guidelines (4) to assess BP in children and adolescents, while the 2017 U.S. guidelines use the new BP Tables that have excluded BP measurements in obese and overweight children (6).

The classification of AH in children and adolescents differs between the guidelines and is shown in Table 1. There is also a difference in the age of an adolescent, at which the AH criteria for adults come into force.

The 2016 European guidelines also address isolated systolic AH (Table 1), which is most common in adolescents (7). They mention the possible clinical significance of central BP measurement, which is not yet performed in clinical practice, while paediatric studies on the correlation of this parameter with changes in target organs are also required (7).

Table 1: Classification of arterial hypertension in children and adolescents according to European (2016) (7) and U.S. guidelines (2017) (6).

Category	EUROPEAN GUIDELINES		US GUIDELINES	
	0–15 years SBP and / or DBP	≥ 16 years SBP and / or DBP (mm Hg)	0–13 years SBP and / or DBP	≥ 13 years SBP and / or DBP (mm Hg)
Normal BP	< 90 percentile	< 130/85	< 90 percentile	< 120/80
Normal, on the high side (EG)	≥ 90 to < 95 percentile	130–139/85–89		
Elevated BP (AG)			≥ 90 to <95 percentile or 120/80 to 95. percentile	120/80 to 129/80
stage 1 AH	95–99 percentile + 5 mm Hg	140–159/90–99	≥ 95. to < 95 percentile + 12 mm Hg or 130/80–139/89 mm Hg	130/80 to 139/89
stage 2 AH	> 99 percentile + 5 mm Hg	160–179/100–109	≥ 95 percentile + 12 mm Hg or above 140/90 mm Hg	≥ 140/90
ISAH	SBP ≥ 95 and DBP < 90 percentile	≥ 140/< 90		

Legend: SBP - systolic blood pressure; DBP - diastolic blood pressure; AH - arterial hypertension; EG - European guidelines; AG - American guidelines; ISAH - isolated systolic arterial hypertension.

We recommend the classification of AH according to European guidelines.

3 Measuring BP

The guidelines are uniform regarding the methods of measuring BP (6,7), which we also recommend for Slovenia:

- BP should be measured in a quiet environment; the child should be relaxed before the measurement, rest for 3 to 5 minutes, and the measurement should be taken with the child leaning back and with their feet on the floor.
- BP is measured on the right arm with a suitably large cuff, the width of which should be 40% of the upper arm circumference, and the inflatable part of the cuff should cover 80 to 100% of the upper arm circumference.
- If the first BP measurement is above the 90th percentile, 2 more BP measurements need to be taken at 3-minute intervals; then, the average of the last 2 measurements is calculated.
- The first BT measurement can be performed with an oscillometric device, if properly calibrated, or by the auscultation method, which is particularly desirable when measuring elevated BP with an oscillometric device.
- Routine BT measurement is recommended once a year in children 3 years of age or older, and in younger people, if there is an increased likelihood of AH (children who required intensive care and treatment during the neonatal period; with congenital heart and kidney disease; with treatment with drugs that may cause an increase in BP; and with signs of increased intracranial pressure). At

each doctor's examination, BT should be measured in obese children, those with diabetes, and children who have the aforementioned diseases and are receiving the aforementioned medications.
- The European guidelines recommend that BP is to be measured on both hands on the first visit in order to determine any difference in BP, and then the measurements are to be performed on the limb where BP is higher.
- According to auscultation method, the bell of the stethoscope should be placed above the brachial artery in the antecubital fossa; the lower end of the cuff should be 2 to 3 cm above it. The cuff should be inflated for 20 to 30 mm Hg above the point when the radial pulse disappears. Excessive inflation of the cuff should be avoided. The first Korotkoff sound is systolic BP and the fifth is diastolic BP.
- U.S. guidelines recommend that in newborns and children who do not yet take part in the measurements, BP be measured with oscillometric devices on the right arm and in a supine position.
- European guidelines recommend BP measurements in the home environment for both diagnosis and treatment of patients, with normative values.

Recommendations for 24-hour ambulatory BP monitoring with an automatic device (6,7):

To set a diagnosis:
- confirmation that it is AH before the start of treatment in order to avoid treating the so-called white coat AH;
  - according to U.S. guidelines, the measurement is needed to confirm the diagnosis if BP was in the AH area for three consecutive check-ups or if BP has been in elevated BP range for 1 year;
  - to exclude the so-called masked AH;
  - with type 1 and type 2 diabetes;
  - with chronic kidney disease;
  - with kidney, liver or heart transplants;
  - with severe obesity, with or without sleep apnoea;
  - with a hypertensive response to a stress test;
  - with a significant difference between BP measured at home and in the outpatient setting.
- During AH treatment:
  - assessment of possible resistance to treatment;
  - assessment of BP in children with target organ injury present.
- In clinical trials.

Recommended BP values in 24-hour ambulatory BP monitoring in children are published in the European guidelines 2016 (7). The measurement is performed for 24 to 48 hours. A longer-lasting measurement may be even slightly more reliable than a shorter one, especially in the second 24 hours, because the child is already slightly relaxed and the BP values are lower (12).

Measuring BP at home has an advantage mainly in the large number of repetitions, but it cannot replace all-day BP monitoring with an automatic meter. At home, BP should be measured by all patients receiving antihypertensive drugs, those with suspected white coat AH, high-risk patients, and in the case of clinical trials. Each time, BP should be measured twice, with an interval of 1-2 minutes, and the average of the measurements should be recorded. Before the examination, they should measure BP for seven days in a row, in the morning and in the evening. The average of the measurements is calculated, excluding the measurement of the first day (7).

Table 2: Monitoring and treatment of children and adolescents according to the level of measured BP, summarized according to U.S. guidelines (6).

BP	Monitoring	Lifestyle change counseling	BP assessment on upper and lower limbs	AMBP	Diagnosis	Method of treatment	Referral to a specialist
Normal BP	yearly	X	-	-	-	-	-
Elevated BP	**First** measurement	X	-	-	-	-	-
	Second measurement after 6 months	X	X	-	-	-	-
	Third measurement after 6 months	X	-	X	X	-	X
Stage 1 AH	**Initial** measurement	X	-	-	-	-	-
	Second measurement after 1–2 weeks	X	X	-	-	-	-
	Third measurement after 3 months	X	-	X	X	X	X
Stage 2 AH	**Initial** measurement	X	X	-	-	-	-
	Second measurement: repeat + refer to a specialist within 1 week	X	-	X	X	X	X

Legend: BP - blood pressure; AH - arterial hypertension; AMBP - all-day blood pressure monitoring with an automatic meter.

For Slovenia, we recommend compliance with all the above criteria.

The 2017 U.S. guidelines recommend (6) how a child should be treated according to the height of the measured BP (Table 2). Given that in Europe and in Slovenia, we follow the reference values of European guidelines, we suggest that when monitoring children and adolescents and when a referral to a specialist is made, we follow U.S. guidelines, taking into account the reference values of European guidelines. In any case, in the event of a clear suspicion that a secondary AH is present, or, in the event of symptomatic AH, a referral to a specialist in the shortest time possible is necessary.

4 Diagnostics

Treatment of a child with AH includes a good medical history, clinical examination, laboratory and imaging examinations 4-9), which is defined in the guidelines similarly to diagnostics in Slovenia. We also implement and recommend all this on a step-by-step basis.

4.1 Medical history

Family history includes important data on chronic diseases in the family such as AH, diabetes, cardiovascular disease, dyslipidaemia, hereditary kidney disease, e.g., Alport syndrome, endocrinological diseases, monogenic syndromes with AH, and syndromes with concom-

itant AH, e.g., neurofibromatosis (6,7).

Secondary AH should be considered (6,7):

- if there is a history of oligohydramnios, anoxia and if an umbilical catheter was inserted in the first days of life due to the possibility of arterial and/or venous thrombosis;
- in the case of chronic or other diseases such as kidney disease, trauma, recurrent urinary tract infections, oedema, weight loss, lack of weight gain, thirst, polyuria, nocturia, haematuria, heart disease, endocrine and neurological diseases, cold limbs, intermittent claudication, palpitations, sweating, fever, paleness, redness, sweating, muscle weakness, virilization, primary amenorrhea, male pseudohermaphroditism, skin abnormalities, systemic diseases (systemic lupus erythematosus);
- if the child or adolescent is receiving medicines or other substances that can cause AH: steroids, calcineurin inhibitors, decongestants, oral contraceptives, amphetamines, cocaine…

We are interested in anamnestic data on possible symptoms due to target organ failure, such as headaches, epistaxis, dizziness, visual disturbances, convulsions, stroke, sudden learning difficulties, dyspnoea, chest pain, palpitations and syncope (6,7).

We always assess risk factors for AH, such as diabetes, dyslipidaemia, obesity, lack of exercise and poor eating habits, smoking and alcohol, body weight and gestational age, snoring, and a history of sleep apnoea (6,7).

Psychosocial history is also important. They found that anxiety and depression in childhood are significantly associated with the development of AH in adulthood. Obese children are more often exposed to ridicule and various forms of violence because of their appearance, so they have more difficulty accepting their body, which in turn leads to anxiety and depression (13).

Anamnestic data on the age at which the child first had elevated BP, previous BP measurements, whether the child is already being treated for AH, what the treatment participation is, and whether there are any side effects of treatment, are also important (7).

4.2 Clinical examination

All children should be measured and weighed during the examination to determine percentile curves. Delayed growth can also be a sign of chronic disease. The examination focuses on the search for possible secondary causes of AH and damage to target organs (6,7). When elevated BP or stage 1 AH is measured at the second visit to the doctor, or stage 2 AH is diagnosed at the first visit, BP has to be measured on both arms and legs (Table 2). Usually, BP measured on the legs is 10 to 20 mm Hg higher. If BP on the legs is lower than on the arms or if there are weak or absent femoral pulses, aortic coarctation should be considered.

We perform a **general examination**. At the same time, we evaluate swelling, obesity, delayed growth, cushingoid features, dysmorphic signs characteristic of various syndromes, such as e.g., Turner syndrome and Klippel-Trenaunay syndrome.

When assessing t**he skin**, we look for rashes, vasculitic changes, butterfly rash on the face (systemic lupus erythematosus), white coffee spots (neurofibromatosis), acanthosis nigricans, paleness, redness, acne, hirsutism, stretch marks (Cushing's syndrome, anabolic abuse) as well as tuberous sclerosis (adenoma sebaceum).

Examination of **the eyes** assesses cataracts (corticosteroids), proptosis (hy-

perthyroidism), changes in the retina (severe hypertensive changes, usually associated with secondary hypertension).

We look for possible masses in **the abdomen** (Wilms tumour, neuroblastoma, pheochromocytoma, polycystic kidney disease, multicystic dysplastic kidney, obstructive uropathy) and murmur above the renal arteries (stenosis).

During the examination of **the heart**, we listen for murmurs (coarctation, aortic stenosis), murmur between the shoulder blades (coarctation of the aorta, mid-aortic syndrome), feel the femoral pulses and assess possible tachycardia (hyperthyroidism, pheochromocytoma).

We assess **the genitourinary area**, where the phenomenon of virilization (congenital adrenal hyperplasia) is observed.

When examining **the limbs**, we pay attention to a possible swelling of the joints (systemic lupus erythematosus).

During **the neurological examination**, we examine the cerebral nerves (paralysis of the third and sixth cranial nerves) and assesses muscle weakness (hyperaldosteronism, Liddle syndrome, hypokalaemia).

4.3 Laboratory tests

Basic laboratory tests are required for all children with AH. Basic laboratory tests include creatinine, urea, electrolytes, urate, fasting blood sugar, lipidogram, blood gas analysis, native urine test (erythrocyte plugs - glomerular disease and leukocyturia - interstitial disease), assessment of albuminuria and proteinuria, and urine culture test (6,7). Ultrasound examination (US) of the urinary system must also be performed in all children and is performed regularly in Slovenia (7). According to U.S. guidelines, urinary tract ultrasound should only be performed in children under 6 years of age and in those with urinary tract infection and impaired renal function (6).

In the obese (body mass index above the 95th percentile), an assessment of glycosylated haemoglobin and liver tests (fatty infiltration of the liver) are recommended.

Other tests are decided on the basis of anamnesis and clinical examination. These include thyroid hormones (thyrotoxicosis), drug tests, sleep studies (daytime sleepiness, snoring), plasma renin activity (PRA) and aldosterone (renovascular AH - high PRA, primary hyperaldosteronism - low PRA, hypokalaemia), catecholamines and metanephrines in urine and plasma (pheochromocytoma, tumours outside the adrenal gland that form catecholamines), free cortisol in urine (Cushing's syndrome), plasma cortisol, adenocorticotropic hormone, cortisol in 24-hour urine sample, molecular genetic testing with suspected Liddle syndrome, aldosteronism recovered after glucocorticoid therapy, hypertensive form of congenital adrenal hyperplasia, appropriate hormonal tests in case of suspected congenital adrenal hyperplasia or familial hyperaldosteronism (6,7). If renal vascular involvement is suspected, renal ultrasound with Doppler ultrasound of the renal arteries should be performed. Magnetic resonance (MR) angiography or computed tomography (CT) angiography are also recommended. The gold standard for definitive diagnosis is renal vascular and aortic angiography. Scintigraphic renography, however, is no longer recommended (6,7).

Assessment of target organ damage is performed in all patients after confirmation of the diagnosis. The ECG is highly specific but poorly sensitive in the identification of children with left ventricular hypertrophy (LV), which means that its prognostic value for hypertrophy is low (14). **Ultrasound of the heart**

is most important in the assessment of target organs. In patients with AH, measurements of structure (diameter of the interventricular septum, posterior wall, and diameter of the LV in diastole by mass calculation) and systolic LV function are important. Because the size of the heart depends on the size of the body, the LV mass index is important in childhood, which is especially important with infants and small children. We also know that physical activity increases LV mass in a healthy sense and that appropriate antihypertensive treatment reduces LV hypertrophy. The guidelines define this parameter differently. We recommend following European guidelines that recommend the use of percentile curves of LV wall mass and thickness as well as consideration of child height and inclusion of children under 8 years of age (6,15-19). Regarding the performance of cardiac ultrasound, we recommend following the U.S. guidelines on ultrasound monitoring every 6 to 12 months in order to assess the deterioration or improvement of the condition. Indications, however, are persistent AH despite treatment, concentric LV hypertrophy, and reduction of the ejection fraction. In patients who do not have visible target organ damage on initial cardiac ultrasound but have stage 2 AH, secondary AH, or persistent stage 1 AH that does not respond to treatment (non-response to treatment or drug ineffectiveness), cardiac ultrasound is repeated every 12 months.

The assessment of target organ damage also includes **the assessment of albuminuria** (> 30 mg albumins/g of creatinine) and proteinuria. Albuminuria is a nonspecific finding and may also be present in obese and diabetic patients, in insulin-resistant patients, and in those who have recently participated in strenuous sports activities. Due to all the above, the U.S. guidelines do not recommend routine detection of microalbuminuria in children with primary AH, but in Slovenia, it has been routinely detected recent years (8).

Glomerular filtration test and abdominal ultrasound are also recommended to assess possible renal impairment.

According to European guidelines, the possible presence of **hypertensive retinopathy** should also be assessed (examination of the back of the eye is recommended), especially in children with symptoms of hypertensive encephalopathy (7).

In the case of very high BP and with concomitant symptoms of **nerve damage** (convulsions, stroke, blurred vision, changes in the back of the eye), imaging examinations (CT and/or MRI) are necessary.

The guidelines also mention pulse wave measurement and thickness of intima-media of the carotid artery. As there are currently no clear reference values for children, these tests are not routinely carried out according to the guidelines.

5 Treatment

The goal of treating AH in children is to achieve the BP that reduces the risk of target organ damage while reducing the likelihood of developing AH in adulthood, thereby indirectly reducing the incidence of cardiovascular disease in adulthood.

Some longitudinal studies of BP in childhood and later in adulthood have indirectly assessed cardiovascular injuries. The results of the measurements showed that the number of cardiovascular diseases increases if BP in childhood is above 120/80 mm Hg. There is some evidence that a decrease in BP below the 90th percentile leads to a reduction in the LV mass index and thus reduces the incidence of LV hypertrophy (6). The

2017 U.S. guidelines recommend that by using non-pharmacological and pharmacological treatments, systolic and diastolic BP is lowered below the 90th percentile, or below 130/80 mm Hg in adolescents who are 13 years of age or older (6).

In patients with chronic kidney disease, European guidelines recommend lowering BP below the 75th percentile if they do not have proteinuria, and below the 50th percentile if they have it, which is also recommended for Slovenian patients. U.S. guidelines recommend that desirable BP in patients with chronic kidney disease is below the 50th percentile, regardless of the presence of proteinuria, although there is no evidence that lower BP in patients with chronic kidney disease without proteinuria has a significant effect on improving renal function (6).

5.1 Non-pharmacological treatment (6,7)

The first steps in the treatment of elevated BP are lifestyle changes, which include:

- Regular moderate to intense **physical activity**. According to U.S. guidelines, children and adolescents should exercise at least 30-60 minutes three to five times a week, and European guidelines recommend that children between the ages of 5 and 17 exercise regularly for at least 60 minutes once a day. Most of the daily activity is supposed to be aerobic, including muscle strengthening activities and resistance training at least three times a week. It is also desirable that sitting in one piece is limited to a maximum of 2 hours per day. Participation in competitive sports is limited only when there is an uncontrolled stage 2 AH.
- Eating a **healthy diet**, rich in fruits, vegetables, olive oil, poultry, red meat, low-fat dairy products, nuts, whole grain breads and fish. At the same time, it is important to limit salt, saturated fats and sugars.
- **Maintaining a normal body weight.** It means that the body mass index should be below the 85th percentile. If the latter is above the 95th percentile in a child, a gradual monthly weight loss of a maximum of 1 to 2 kg per month is recommended.
- Encouraging expectant mothers to quit smoking and providing adequate support in doing so.
- Impact on stress reduction.
- Setting realistic goals and developing a reward system while promoting a healthy lifestyle.

5.2 Pharmacological treatment (6,7)

Children in whom AH persists despite lifestyle changes have symptomatic AH, stage 2 AH without a factor that could be directly affected (e.g., obesity), target organ damage AH, or any stage AH with associated diabetes or chronic kidney disease, we begin treatment with drugs (Table 3). We usually start with one drug - monotherapy. The starting dose should be low, then gradually (every 2 to 4 weeks) increased to the desired BP value, which should not exceed the 90th percentile. At home, such a child should regularly monitor their BP. Control all-day BP measurements should also be considered to assess the effectiveness of treatment, which is especially important in patients with chronic kidney disease.

A child treated with an antihypertensive drug should be monitored every 4 to 6 weeks until BP returns to normal. After normalization of BP, the patient is initially monitored every 3 to 4 months. If with the first drug, despite the maximum dose, BT cannot be adequately reduced, the second drug (combination

therapy) is added and titrated in the same way as the first. According to U.S. guidelines, a thiazide diuretic is often most preferred as the next medication in the treatment of AH.

Angiotensin converting enzyme inhibitors or angiotensin-receptor blockers are the most suitable antihypertensive drugs to be introduced in children, except in the case of absolute contraindi-

Table 3: Antihypertensive drugs for the treatment of arterial hypertension in children and adolescents (6,7).

Drug category	Healthy adults	Initial oral dose (per day)	Maximum oral dose (per day)	Dosage interval	Age
ACE inhibitor	benazepril	0.2 mg/kg max:10 mg	0.6 mg/kg max: 40mg	1 x per d	≥ 6 years
	captopril*	0.05 mg/kg/ dose (max: 40 mg) 0.5 mg/kg/ dose	6 mg/kg 6 mg/kg	4 x na d 3 x per d	infants children
	enalapril*	0.08 mg/kg up to max: 5mg	0.6 mg/kg	1–2x per d	≥ 1 month
	fosinopril*	0.1–0.6 mg/kg max: 5 mg	40 mg	1x per d	≥ 6 years
	lisinopril	0.07 mg/kg up to 5 mg	0.6 mg/kg max: 40 mg/d	1x per d	≥ 6 years
	ramipril*	1.6 mg/m2	6 mg/m2	1x per d	-
ARBs	candesartan*	0.16–0.5 mg/kg	<50 kg – 16 mg >50 kg – 32 mg	1x per d	>1 year
	irbesartan*	75 mg 150 mg	150 mg 300 mg	1x per d	6-12 years >13 years
	losartan*	0.7 mg/kg to 50 mg	1.4 mg/kg max:100 mg	1x per d	≥ 6 years
	olmesartan	<35 kg – 10 mg >35 kg – 20 mg	20 mg 40 mg	1x per d	≥ 6 years
	valsartan*	0.4 mg/kg	40–80mg	1x per d	≥ 6 years
β-blockers	atenolol*	0.5–1 mg/kg	2 mg/kg max: 100mg	1–2x per d	
	metoprolol*	0.5–1 mg/kg	2 mg/kg	1–2x per d	
	propranolol*	1 mg/kg	4 mg/kg max :640mg	2–3x per d	
Thiazide diuretics	chlorthalidone*	0.3 mg/kg	2 mg/kg max: 50mg	1x per d	child
	chlorothiazide	10 mg/kg/d	20 mg/kg max: 375mg	1–2x per d	child
	hydrochlorothiazide**	1 mg/kg/d	2 mg/kg max: 37.5mg	1–2x per d	child

Drug category	Healthy adults	Initial oral dose (per day)	Maximum oral dose (per day)	Dosage interval	Age
Other diuretics	amiloride**	0.4–0.6 mg/kg	20 mg	1x per d	
	spironolactone*	1 mg/kg	3.3 mg max: 100mg	1–2x per d	
	furosemide*	0.5–2 mg/kg	6 mg/kg	1–2x per d	
	eplerenone*	25 mg	100 mg	1–2x per d	
	triamterene	1–2 mg/kg	3–4 mg/kg		
Ca channel blockers	amlodipine*	0.1 mg/kg 0.3 mg/kg	5 mg 10 mg	1x per d	1-5 years ≥6 years
	felodipine	2.5 mg	10 mg	1x per d	≥6 years
	isradipine	0.05–0.1 mg/kg	0.6 mg/kg max:10mg	2–3x per d	child
	nifedipine*	0.25–0.5 mg/kg	3 mg/kg max:120 mg	1–2x per d	
α- and β-blockers	labetalol*	1–3 mg/kg	10–12 mg/kg max: 1200mg	1x per d	
Central agonists α	clonidine*	0.2 mg/kg	2.4 mg	2x per d	
Peripheral α-blockers	doxazosin*	1 mg	4 mg	1x per d	
	prazosin	0.05–0.1 mg/kg	0.5 mg/kg	3x per d	
Vasodilators	hydralazine*	0.75 mg/kg	7.5 mg/kg max: 200mg	4x per d	
	minoxidil*	0.2 mg/kg	50–100 mg	1–3x per d	

The drug that patients can get in Slovenia is marked with *; a drug that is in combination with another drug in Slovenia is marked with **; ARBs - angiotensin receptor blockers; d - day; Ca - calcium; ACE - Angiotensin-converting enzyme.

cations (allergy, hyperkalaemia…). It is necessary to warn adolescents about the possible side effects of this drug on the foetus in case of pregnancy. If pregnancy occurs, the drug should be replaced by a calcium channel blocker or beta-blocker.

Beta-blockers are not recommended as initial treatment for AH according to U.S. guidelines. Drugs such as peripheral alpha receptor blockers, beta-blockers, centrally acting drugs, potassium-sparing diuretics, and direct vasodilators are prescribed if treatment with two or more drugs fails.

5.3 Treatment of resistant AH

Resistant AH is persistently elevated BP despite treatment with three or more antihypertensive drugs of different types at maximum doses. One of these medications should be a diuretic. Patients with resistant AH are further treated with salt restriction and substances known to increase BP are eliminated. In adult patients, spironolactone is usually added to the therapy, which reduces the volume of fluid in the body and at the same time cures hyperaldosteronism, which is common in adults.

5.4 Treatment of patients with chronic kidney disease

AH is an important risk factor that causes the progression of chronic kidney disease in children and adults. U.S. guidelines recommend (6) that BT in these children be measured at each doctor's visit. As for adults, it is recommended that children who concurrently suffer from chronic kidney disease and AH have their mean blood pressure, as measured by full-day BP monitoring, below the 50th percentile. This examination is recommended for patients at least once a year.

We recommend following all recommendations.

5.5 Treatment of patients with diabetes

In patients with type 1 and 2 diabetes, early atherosclerotic changes have been known to be found, so it is advisable to measure their BP at each visit to the doctor. It is also desirable that their BP is below the 90th percentile or below 130/80 mm Hg (6,7), which is also taken into account in Slovenia.

6 Treatment of hypertensive emergencies

Severe AH can damage target organs such as the heart, kidneys, and brain. The causes are usually secondary. Very common symptoms are dizziness, headache, nausea, vomiting, confusion, convulsions, visual disturbances and facial nerve paresis (6,7). In the event of severe AH, an ophthalmic examination is required to assess for possible exudate and bleeding, neurological evaluation and CT (exclusion of bleeding) or MRI (exclusion of white matter in the parieto-occipital region - posterior reversible encephalopathy syndrome (PRES). These patients should be treated in the intensive care unit for better monitoring. Renal function should also be assessed, and an ECG performed.

Severe AH is usually treated with short-acting antihypertensive drugs intravenously. We start administering medicines orally only when the child is able to take them in this manner. BP can be reduced by 25% in the first 6 to 8 hours, and then over the next 24 to 48 hours, BP should gradually normalize.

Children with extremely urgent hypertensive conditions should receive antihypertensive drugs intravenously in a continuous infusion. Drugs used in children to treat extremely urgent hypertensive conditions are listed in Table 4.

7 AH in the neonatal and infant periods

A special chapter of paediatric hypertension is AH in the neonatal period and the infant period. The U.S. guidelines put much emphasis on this. They emphasize the issue of normative values in this period and recommend the use of values published a few years ago for newborns of gestational age from 26 to 44 weeks, including the 95th and 99th percentiles (6,20). As normative values for infants up to the first year of age, in the absence of more recent data, they recommend values published in 1987 (2), which are also used in Slovenia. Using these tables, the authors recommend the same approach to identifying patients with AH as in older children (20). Direct intra-arterial BP measurement or indirect measurement by oscillometric technique can be used to measure BP in hospitalized neonates. The latter is also recommended for outpatient measurement, which should be performed on the right arm in a supine position using appropriate cuffs and with validated gauges (6).

In neonates and infants, we usually

Table 4: Doses of antihypertensive drugs for the treatment of hypertensive emergencies, summarized according to U.S. guidelines (6).

Healthy adults	Type of drug	Dose	Commentary
Drugs to treat AH in a child with a life-threatening condition			
esmolol*	β-blocker	100–500 µg/kg/min IV infusion	bradycardia
hydralazine*	direct vasodilator	0.1–0.2 mg/kg/ dose, to 0.4 mg/kg/ dose iv, im	tachycardia, every 4 hours in iv boluses
labetalol*	α- and β- blocker	0.2–1 mg/kg/ IV dose, max: 40mg per dose in IV boluses, 0.25–3 mg/kg/h IV infusion	asthma and heart failure are relative contraindications
nicardipine*	Ca channel blocker	30 µg/kg up to 2 mg per dose IV bolus dose, 0.5–4 µg/kg/min IV infusion	reflex tachycardia, elevated levels of cyclosporine and tacrolimus
Sodium nitroprusside*	direct vasodilator	0,5–3 µg/kg/min to max: 10µg/kg/ min IV	infusion, monitor cyanide levels when used over 72 h, especially at CKD, add Na thiosulfate
Drugs to treat AH in a child with less pronounced symptoms			
clonidine*	central α agonist	2–5 mg/kg per dose to 10 mg/kg/ dose per 6 to 8 hours, orally	dry mouth, drowsiness
fenoldopam	dopamine-receptor agonist	0.2–0.5 mg/kg/min to 0.8 mg/kg/min continuous IV infusion	higher doses exacerbate tachycardia without a significant decrease in BP
hydralazine*	direct vasodilator	0.25 mg/kg/ dose to 25 mg/ dose per 6–8 hours, orally	
isradipine	Ca channel blocker	0.05–0.1 mg/kg/ dose max: 5 mg/ dose per 6–8 hours, orally	significant drop in BP in patients receiving antifungal therapy
minoxidil*	direct vasodilator	0.1–0.2 mg/kg/dose max: 10 mg/ dose per 8–12 hours, orally	long-acting, potent

The drug that patients can get in Slovenia is marked with *; AH - arterial hypertension; BP - blood pressure; IV - intravenous.

identify the cause or risk factors for AH, which then guide the treatment of patients (20,21). The guidelines draw attention to the importance of perinatal history, including data on complications in the delivery room and neonatal intensive care unit and the placement of catheters in the umbilical cord (6). In the neonatal period, common causes of AH are renal artery thrombosis, renal artery stenosis, renal vein thrombosis, congenital renal abnormalities, aortic coarctation, bronchopulmonary dysplasia, patent ductus Botalli, ventricular haemorrhage, which must be identified by diagnosis (8).

They may develop severe AH. It is an urgent condition often manifested by congestive heart failure or other life-threatening complications (22). In severe AH, short-acting intravenous drugs for controlled reduction of BP are preferred (22). Esmolol, nicardipine,

labetalol, nitroprusside and hydralazine are recommended in particular (20). There is but little data on the effectiveness of antihypertensive drugs in this specific population, but there is also no consensus yet on treatment recommendations among experts. The treatment of patients is mostly based on the experience of individual centres and on the recommendations of individual experts, which causes a lot of heterogeneity between different neonatal units (23). Antihypertensive drugs from most groups are used in treatment, but caution should be exercised when using angiotensin converting enzyme inhibitors up to 44 weeks of corrected gestational age, when using nifedipine, due to unpredictability, and when using beta-adrenergic receptor blockers in patients with chronic lung disease (20).

8 Comparison of treatment of adult and paediatric patients with AH

Good international recommendations are available for both paediatric and adult patients with AH, which are revised following periods in which new knowledge is acquired and must be meaningfully transferred to practice in Slovenia. In both cases, these are comprehensive documents covering a structured approach to treating patients - definition, classification and epidemiology of AH, methods of measuring CT, approach to diagnosis, including genetic testing and examination of hypertensive target organs, approach to treatment, presentation of AH in specific clinical circumstances, patient monitoring and the need for new research. In Slovenia, for adult patients in clinical practice, the European recommendations from 2018 have been adapted to our patients and are used for treatment in reference clinics, family doctor clinics and also at the subspecialist level as Slovenian guidelines for the treatment of patients with AH (24). Slovenian paediatricians also use European guidelines adapted to Slovenian conditions, which in some items are upgraded with U.S. guidelines, especially in areas that are not covered by European guidelines, such as the transition of a patient with AH from paediatric care to internists caring for adults. Traditionally, all paediatric AH is treated by a paediatric nephrologist, mainly due to the frequency of secondary AH - renoparenchymal and renovascular - in childhood. The younger the patient, the more likely secondary AH is (8). Adult patients with AH, who have a high proportion of essential AH, are managed by family physicians with clear instructions regarding referral to a specialist level, in part due to the frequency of pathology (24).

The definition of AH in adults is related to numerical values, and in paediatrics to percentile curves, except for adolescents after the age of 16, when the values are the same as for adults. However, adult patients also have third-degree AH, and adolescents only first- and second-degree AH (6,7,11). The latter is very important for the transition of patients to adult health care. The guidelines for children and adults are also fundamentally comparable in terms of the principles of measuring BP and the approach to treatment. All patients with AH need basic diagnostic tests to determine cardiovascular risk, to determine the condition of hypertensive target organs, co-morbidity and total cardiovascular risk, and to introduce non-pharmacological treatments. Additional diagnostics in the direction of searching for secondary causes are performed according to the clinical picture, the level of BP and the response to treatment (6,7,11). The basic principles of treatment and mon-

itoring of patients are the same. Certain forms of treatment, such as renal denervation, not used in the paediatric population, rarely use fixed combinations of antihypertensive drugs. Compared to adult patients, there is not as much research on the efficacy and safety of drugs in children as there is no prospective research on the impact of therapy on morbidity and mortality (6,7,25). Given the many parallels, in our opinion, it would be worth considering the inclusion of paediatric recommendations in a single document of the Slovenian guidelines for the treatment of patients with AH. This would be particularly important for adolescents with AH who are transitioning to family physician treatment and for those with secondary AH to the management of subspecialists. Most adolescents belong to the group of patients with mildly elevated BP, who are mostly asymptomatic, with no changes present in hypertensive target organs, but with possible cardiovascular complications later in life. These are adolescents with essential AH or AH-related obesity. We also sometimes set a a clinical suspicion on one of the secondary forms of AH, especially with adolescents who have had a normal diet, but have symptoms and a significantly elevated BP and no family history of cardiovascular disease (8). In this case, the most common causes are the use of certain dietary supplements and drugs, iatrogenic causes, kidney parenchymal disease, renal vascular disease, endocrinological causes, and aortic coarctation (8). Guidelines for adults include the area of secondary AH and the treatment of AH in young adults (11). They list patient characteristics that indicate the possibility of secondary AH, possible causes by age, and diagnostic investigations, which is essentially in line with paediatric guidelines. The guidelines also highlight the issue of the need to treat young adults with stage 1 AH without other changes (11).

9 Transition of patients with AH

Recommendations for the transition of adolescents with AH from a paediatric nephrologist to an internist nephrologist are meagre. The U.S. recommendations already mention the importance of the transition and emphasize that it should be completed by the age of 22, while for individuals, especially those with special needs, it can be completed later (6). The recommendation is labelled as a strong recommendation and relates primarily to the aetiology of AH, previous disease occurrences, and complications. As a basis for the recommendation, they cite the general recommendations of the American Academy of Pediatrics on the importance of transition for chronic paediatric patients (26). We believe that we need to pay special attention to the transition process, preferably within a special transition clinic of chronic nephrology patients.

10 Conclusion

Since 1977, several guidelines for the management and treatment of AH in children and adolescents have been published. In 2016, the latest European and in 2017, the U.S. guidelines were published, which differ significantly from one another, especially in the definition of AH and in the assessment of LV hypertrophy. The limit for AH has been lowered, according to U.S. guidelines, at the expense of excluding overweight and obese people. The guidelines are consistent that elevated BP should be actively sought in patients with chronic kidney disease and diabetes, in whom AH is also intensively treated. The most important marker for assessing target organ involvement is LV hypertrophy,

which is always sought in children with elevated BP. We recommend monitoring and treatment of children and adolescents who have elevated BP. It is very important that we teach these children and adolescents and their parents about the importance of a healthy diet and maintaining a normal body weight and encourage them to engage in regular daily physical activity.

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