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REVIEW ARTICLE

The Growing Epidemic of Hypertension Among Children and Adolescents: A Challenging Road Ahead

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Abstract Currently, it is clear that primary hypertension begins in childhood and that it contributes to the early development of chronic kidney disease (CKD). Hypertension also increases the risk of cardiovascular morbidity and mortality, and that risk rises as blood pressure levels escalate. As among adult patients, overweight and obesity rates are on the rise among children and adolescents with primary hypertension and can develop target organ damage including left ventricular hypertrophy. An elevated level of C-reactive protein (CRP) and microalbuminuria are early manifestations of cardiovascular disease and CKD in hypertensive patients. Lifestyle interventions are recommended for all children with hypertension. Pharmacologic therapy should be added for symptomatic children, those with stage 2 hypertension, and children with prehypertension and stage 1 hypertension who exhibit an insufficient response to lifestyle modifications. Although the recommendations for choice of drugs generally are similar for children and adults, dosages for children should be lower, based on weight, and adjusted very carefully. Medications that are effective and safe for children and adolescents include thiazide diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and calcium channel-blockers. Hypertension is not being detected early enough for initiation of a treatment regimen to reduce death and disability. Initiatives should be undertaken to make health care providers and the general population more aware of the seriousness of hypertension in children and adolescents. This review focuses on the principles underlying the importance of a team approach for hypertension control, especially one that incorporates increased data sharing using enhanced health information technology for early detection and intervention.

Keywords Cardiovascular events · Children and adolescents · Chronic kidney disease · Epidemic · Hypertension · Team approach

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Hypertension (HTN) is one of the most important risk factors for the development of cardiovascular disease (CVD), stroke, and chronic kidney disease (CKD) [8, 23]. The estimated prevalence of HTN in the pediatric age group is 1–5 %, and its prevalence continues to rise [20]. Childhood risk factors for high adult blood pressure (BP) include obesity, metabolic syndrome, premature infants, and low-birth-weight infants, and low birth weight is inversely associated with the presence of CVD and HTN [10, 11].

Currently, it is clear that HTN begins in childhood and adolescence and that it contributes to early development of CVD and CKD [10]. As among adults, children and adolescents with established HTN can experience target organ damage and early markers of CVD including left ventricular hypertrophy, increased intima-media thickness, reduced arterial compliance, atherosclerosis, and diastolic dysfunction [16, 33]. Also, based on a recent study of nearly 27,000 teenagers, the hazard ratio of HTN in adulthood increased gradually across BP groups within the normotensive range at the age of 17 years without a discernible threshold effect [24].

Hypertension is not being detected early enough for initiation of a treatment regimen to reduce death and disability.

Many published reports over the last decade have addressed ways to achieve better BP control. However, experts agree that far more needs to be done toward early identification of hypertensive children at risk for CKD and CVD.

The road to improvement of patient outcomes is to focus on public awareness and screening programs as well as initiatives to educate both patients and primary health professionals. Nephrologists have an ambitious long-term goal worldwide, to make every patient, particularly those with metabolic syndrome and diabetes, aware that prompt treatment is necessary once his or her BP values are no longer in the normal range. Additionally, nephrologists should strongly encourage public health authorities to support efforts to raise public awareness of HTN and promote initiatives to reduce the incidence of HTN, CKD, and CVD mortality and morbidity.

This article reviews the quality improvement strategies for HTN control by focusing on a team approach, especially one that incorporates increased data sharing using enhanced health information technology for early detection and intervention, and highlights the role of primary physicians, nurses, social workers, and dietitians, which holds great promise for improving patient outcomes if applied globally.

Defining Hypertension

One complicating factor is the difficulty involved in determining what constitutes HTN in young people compared with adults. Hypertension in this population is defined as either systolic or diastolic BP in the 95th percentile or higher as measured on three or more separate occasions. BP tables for children and adolescents are available from the National Heart, Lung, and Blood Institute [23]. However, most primary health care providers rarely use these references when their patients undergo BP monitoring during well-child care visits. Therefore, it is not surprising that although approximately 1 million children in the United States may have high BP, it is diagnosed in only about 1 in 4 cases [17].

Because normal BP in children is a function of age, sex, and height percentiles, clinicians probably are not able to memorize the charts so they can instantly recognize normal BP for the wide range of children they treat in their practices. As an example, the 95th BP percentile for a 15-year-old girl in the 75th percentile for height is 129/84 mmHg, but the 95th BP percentile for an 8-year-old boy in the 10th percentile for height is 112/76 mmHg.

The updated tables currently include the 50th, 90th, 95th, and 99th percentiles for BP by sex, age, and height. The 50th percentile has been added to the tables to provide clinicians with the BP level at the midpoint of the normal range. Normal BP is defined as systolic and diastolic BP below the 90th percentile. Patients are considered prehypertensive if their BP is above normal (BP $\geq$90th percentile but <95th percentile) or if their BP exceeds 120/80 mmHg even if the BP is below the 90th percentile. Stage 1 HTN is defined as systolic or diastolic BP at the 95th percentile plus 5 mmHg, and stage 2 HTN is defined as systolic or diastolic BP 5 mmHg above the 99th percentile (Table 1).

The new guidelines describe HTN and pre-HTN as significant health issues in the young due to the marked increase in the prevalence of overweight children [23, 24]. Prehypertensive individuals are at high risk for HTN development later in life, so both patients and clinicians are alerted to this risk and encouraged to intervene and prevent or delay the disease from developing [19].

Overweight and HTN are components of the insulin resistance syndrome, a combination of multiple risk factors for CVD and type 2 diabetes. The guidelines call for a comprehensive assessment of cardiovascular risk factors. The new guidelines, also noting the association of high BP and overweight with sleep apnea, additionally suggest that a history of sleeping patterns should be obtained for a child with HTN [23].

Causes

Primary HTN

Primary HTN is associated with being overweight, a positive family history of HTN, or both. As among adult patients, overweight and obesity rates are on the rise among

Table 1 Classification of blood pressure in children and adolescents

Blood pressure classification	SBP	DBP
Normal	<90th percentile	<95th percentile
Prehypertension	90th to <95th percentile or >120 mmHg	$\geq$90th but <95th percentile or >80 mmHg
Stage 1 hypertension	95–99th percentile plus 5 mmHg	95–99th percentile plus 5 mmHg
Stage 2 hypertension	>99th percentile plus 5 mmHg	>99th percentile plus 5 mmHg

For gender, age, and height percentile measured on at least three separate occasions [23]

SBP systolic blood pressure, *DBP* diastolic blood pressure

children and teens, accompanied by a variety of diseases and conditions historically seen almost exclusively among adults [24, 30]. An analysis of 2007–2008 National Health and Nutrition Examination Survey (NHANES) data (released June 2010) showed that since 1976–1980, obesity has increased from 5.0 to 10.4 % among preschool children 2–5 years of age, from 6.5 to 19.6 % among children 6–11 years of age, and from 5.0 to 18.1 % among adolescents 12–19 years of age [30]. As with adults, being overweight increases the risk for HTN among this population, leaving many children and adolescents at risk for high BP and subsequent target organ damage [24].

Secondary HTN

Whereas primary chronic HTN is increasingly common in adolescence, secondary forms of hypertension are more common among children. Disorders that may cause secondary HTN include

1. Renal parenchyma or structural kidney disorders (glomerulonephritis, cystic dysplastic kidney disease, and hydronephrosis)
2. Renin-mediated HTN (renal vascular HTN and coarctation of the aorta)
3. Mineralocorticoid-induced HTN (hyperaldosteronism and Liddle syndrome)
4. Catecholamine-induced HTN (pheochromocytoma and postsurgical HTN).

Besides disorders that might cause HTN, many drugs can increase an individual's BP including the use of over-the-counter, prescription, or illicit drugs. Equally important is the use of nutritional supplements, especially preparations intended to enhance athletic performance, the so-called "energy drinks," many of which are powered by caffeine, as well as coffee and soft drinks.

Pathogenesis

For many patients with HTN, overactivity of the renin-angiotensin system (RAS) is the main cause of their elevated BP [8, 23]. The effects of RAS are seen in the heart, the kidneys, the central nervous system, and the vasculature. Overactivity of RAS results in water and salt retention, which can lead to myocardial hypertrophy. Within the kidney, increased angiotensin 2 (AT2) production can lead to glomerular capillary HTN and proteinuria, largely because of AT2-mediated efferent glomerular arterial vasoconstriction. In the blood vessel, increased formation of AT2 causes not only vasoconstriction but also fibrous thickening of the vessel wall, which leads to additional complications related to stroke and ischemic heart disease. The overactivity of RAS in hypertensive people explains why patients with chronic kidney disease and HTN are twice as likely to have major CVD, strokes, and renal failure. In general, each increase of 20 mmHg in systolic BP or 10 mmHg in diastolic BP doubles cardiovascular mortality rates.

Diagnostic Approach

An important initial setup for the management of HTN in children is to distinguish between essential and secondary HTN. The likelihood of arriving at a diagnosis is directly related to the degree of HTN and is inversely related to the age of the child. Prepubertal children usually have some form of secondary HTN, whereas adolescents and postpubertal children usually (75 %) have essential HTN [23]. For example, renal artery thrombosis, renal artery stenosis, congenital renal malformation, coarctation of the aorta, and bronchopulmonary dysplasia are the most common causes of HTN in newborn infants. By contrast, essential HTN is cause of 60–80 % of HTN in adolescents.

Essential HTN, characterized by mild HTN or stage 1 HTN, is associated with both a family history of HTN and obesity, whereas stage 2 HTN usually is associated with secondary HTN. Primary HTN should be considered when HTN is associated with obesity, a strong family history of essential hypertension, normal renal function, and normal renal structure [23].

Initial diagnostic tests may include urinalysis, complete blood count (CBC), serum electrolytes, blood urea nitrogen (BUN) and creatinine (Cr) levels, lipid profile, renal ultrasound, and echocardiogram (Fig. 1). If HTN is associated with proteinuria, hematuria, or renal dysfunction, measurement of serum complement profile (C3, C4), antinuclear antibody (ANA) and anti–double-stranded DNA antibody titers is recommended. If hydornephrosis is detected, a diuretic-enhanced diethylenetriamine pentaacetic acid (DTPA) renal scan and a voiding cystoureterogram (VCUG) should be considered. If HTN is associated with metabolic alkalosis and hypokalemia, then serum aldosterone and plasma renin activity (PRA) should be measured. If HTN is severe and PRA is not elevated, blood and urinary catecholamine levels and adrenal magnetic resonance imaging (MRI), metaiodobenzylguanidine (MIBG) scan, or both should be considered.

For patients with severe HTN and elevated PRA and aldosterone levels, an intraarterial digital subtraction angiogram is indicated when the history is highly suggestive of renal vascular HTN. Spiral computed tomography (CT) scanning or gadolinium-enhanced MR angiography also provide a minimally invasive and, in most cases, equally accurate alternative to angiography (Fig. 1).

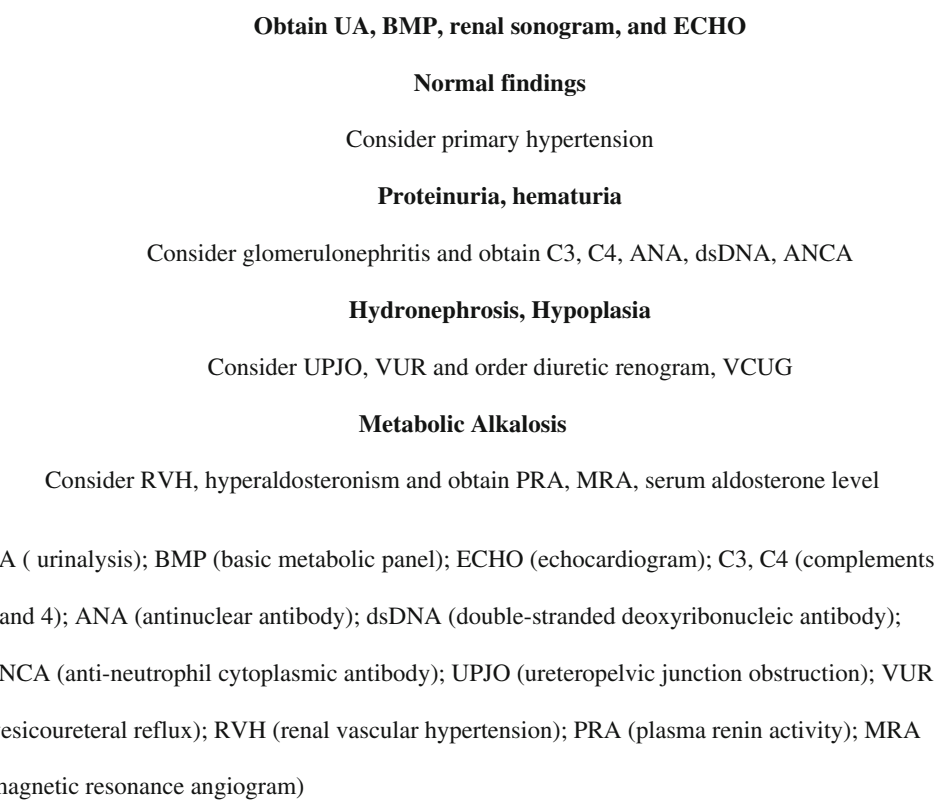

Fig. 1 Evaluation algorithm

UA (urinalysis); BMP (basic metabolic panel); ECHO (echocardiogram); C3, C4 (complements 3 and 4); ANA (antinuclear antibody); dsDNA (double-stranded deoxyribonucleic antibody); ANCA (anti-neutrophil cytoplasmic antibody); UPJO (ureteropelvic junction obstruction); VUR (vesicoureteral reflux); RVH (renal vascular hypertension); PRA (plasma renin activity); MRA (magnetic resonance angiogram)

One of the most important measures in the management of HTN is the assessment of cardiovascular risk. As the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP (The JNC 7) clearly states, "the relationship between BP and risk of cardiovascular events is continuous, consistent, and independent of other risk factors." [8]. "The higher is the BP, the greater is the chance of heart attack, heart failure, stroke, and kidney diseases" [16].

An elevated level of CRP (>3.0 mg/dL) is a marker of cardiovascular risk for both hypertensive patients and the general population [5]. The presence of microalbuminuria (MA/Cr ratio >30) also is an early manifestation of nephropathy in essential HTN and may be associated with an increased incidence of CVD [3, 6].

Use of Ambulatory BP Monitoring

Children, like adults, with ambulatory HTN or white-coat HTN are at increased risk for target organ damage, and CVD is present at the time of diagnosis for a significant number of children referred for ambulatory HTN [21]. Target organ damage has been noted in up to 30 % of children with white-coat HTN, comparable with the percentage found in HTN patients despite similar body mass index, significantly lower average BP, and a well-preserved BP dipping pattern [21].

When necessary, ambulatory BP monitoring (ABPM) can offer critical information about BP levels during daily activities and sleep, and may be a better tool than clinic readings. Monitoring BP over 24 h will provide a more complete picture of a patient's BP values, taking into account the body's normal profile of higher BP levels when awake and active as well as lower levels at rest and sleep, plus early morning increases [15].

Findings have shown ABPM to be a better predictor of CVD than office BP measurement. This is because of a greater reliability due to the multiple BP measurements under standardized conditions. In addition, ABPM can identify the nocturnal dipping status of children at high risk for CVD. Normal dipping generally is defined as at least a 10 % decline in mean systolic and diastolic BP levels from day to night as follows. Blunted nocturnal dipping has been associated with nephropathy and cardiovascular risk. Patients with sleep disorders often fail to demonstrate the nocturnal physiologic dip in BP [25, 29]. Clinical situations in which ABPM may help to predict CVD include suspected white-coat hypertension in patients with HTN and no target organ damage, apparent drug resistance (office resistance), hypertensive symptoms with antihypertensive medication, episodic HTN, and autonomic dysfunction.

Recent data suggest that lowering systolic BP in adult patients with CVD below the target goal may increase the risk for heart attack or stroke [2]. Recent studies also recommend that BP should be measured in both arms. A

difference in systolic BP of 10–15 mmHg or more between arms could identify patients at high risk for symptomatic peripheral vascular disease and mortality who might benefit from further assessment [1, 13].

Treatment

Lifestyle interventions are recommended for all children with HTN. These interventions include weight reduction for overweight children, a regular aerobic exercise regimen, salt restriction, and limits to alcohol consumption and smoking or preferably their avoidance [22].

The American Academy of Pediatrics recently examined the issue of athletic participation by adolescents with HTN. They recommended that the presence of persistent HTN without target organ damage or concomitant heart disease should not limit the eligibility of these adolescents to participate in competitive athletics. Athletes with persistent HTN should have their BP measured regularly (every 2 months at the physician's office) to monitor the impact of exercise on their BP levels [22].

Therefore, primary care providers should help young athletes with HTN, regardless of the degree of disease severity, by strongly encouraging them to adopt healthy lifestyle behaviors including the avoidance of exogenous androgens, growth hormone, drugs of abuse (especially cocaine), alcohol, tobacco use (by all routes), and high sodium intake . In addition, they should advise their young athletes with HTN that the use of diuretics and beta-blockers has been prohibited by some athletic governing bodies. In these instances, other types of medications may need to be considered.

Pharmacologic therapy should be added for symptomatic children, those with stage 2 HTN, and children with pre-HTN and stage 1 HTN who exhibit an insufficient response to lifestyle modifications after 4–6 months. Multiple clinical studies have shown that antihypertensive therapy reduces cardiovascular morbidity and mortality [4, 31, 34]. A recent prospective study showed that for every 2-mmHg decrease in mean systolic BP, there was a 10 % reduction in stroke mortality and a 7 % reduction in coronary heart disease mortality [36]. Despite increasing awareness and treatment, it is clear that about two-thirds of patients are still uncontrolled [23].

Although the recommendations for choice of drugs are generally similar in children and adults, dosages for children should be lower, based on weight, and adjusted very carefully. Medications that are effective and safe for children and adolescents include thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, and calcium channel blockers (CCBs) (Fig. 2) [12, 18, 28, 32].

As for adults, guidelines suggest that physicians select an appropriate therapy for children and adolescents with HTN based on the presence of comorbidities (Fig. 2) [23]. For example, thiazide diuretics should be used as an initial therapy for most children with essential HTN. An ACE inhibitor or ARB therapy would be best for children with diabetes or renal disease, whereas beta-blockers or CCBs are recommended for children with migraine headaches. If a patient is pregnant, ACE inhibitors should not be used, and they should be used with extreme caution for sexually active women because of known adverse effects on the fetus if taken before or after the first trimester and then only after counseling and effective pregnancy precautions have been established. Beta-blockers, ACE inhibitors and ARBs, and diuretics including aldosterone antagonists are widely used among patients with left ventricular dysfunction and heart failure (Fig. 2).

In prescribing antihypertensive medication for children and adolescents, a stepped-care approach often is used. Treatment is started with a recommended initial dose and then titrated higher until BP control is achieved or the maximum dose of the monotherapy is reached [23]. If BP still is not controlled, a second agent is added. If BP control is not achieved with dual therapy, a third agent may be added, or consultation with an HTN specialist may be considered (Fig. 2).

Resistant Hypertension

Resistant HTN is defined as persistent elevation of BP above the goal despite concurrent use of three antihypertensive agents, each of a unique class, including a diuretic, with all drugs at maximally tolerated doses. Hypertension controlled with the use of four or more medications also is considered resistant to treatment.

Evaluation for secondary cases should be done for patients with resistant HTN, and a high suspicion of primary aldosteronism should be entertained for patients with the following clinical history: spontaneous or unprovoked hypokalemia with renal potassium wasting, severe diuretic-induced hypokalemia that does not normalize after discontinuation of diuretics for at least 4 weeks and is unresponsive to angiotensin blockers, HTN with adrenal adenoma, and a family history of primary hyperaldosteronism [7, 14, 27].

Primary aldosteronism, or hyperaldosteronism, currently is recognized as the most common secondary cause of resistant HTN [14, 27]. It is present in $\sim$20 % of patients with resistant HTN [7]. Adding a mineralocorticoid receptor antagonist has been shown to reduce resistant HTN for patients with primary aldosteronism. Experts recommend screening patients with resistant HTN for plasma aldosterone and 24-h urinary aldosterone levels and for PRA even if the serum potassium level is normal [27]. Studies suggest that serum potassium levels often are within the normal

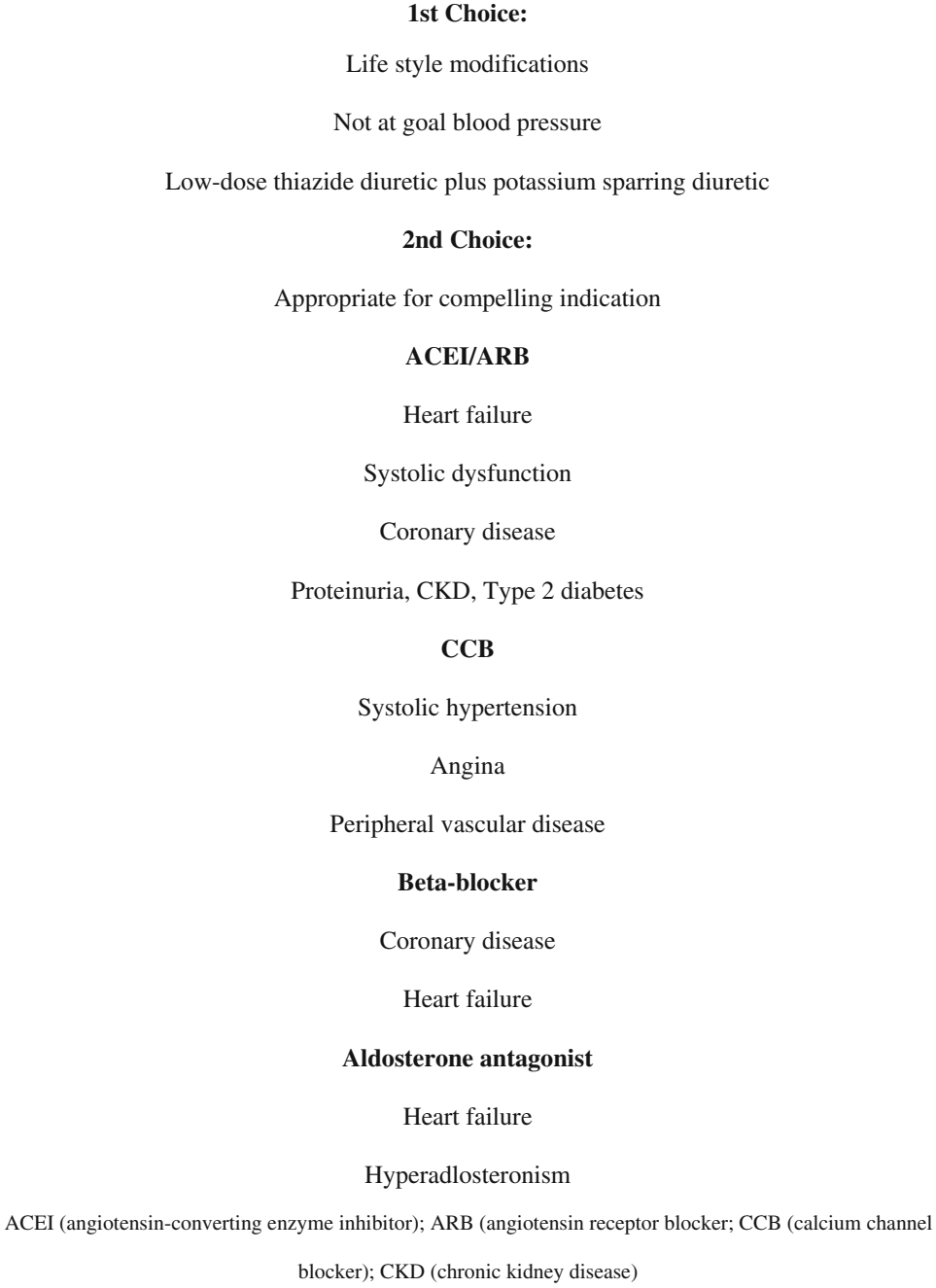

Fig. 2 Treatment algorithm

range in patients with confirmed primary aldosteronism [7]. In addition, patients with resistant HTN should be evaluated for renal artery stenosis, and if the results all are negative, it is reasonable to begin an evaluation for pheochromocytoma if patients have suggestive manifestations such as episodic hypertension, palpitations and/or diaphoresis, or tremor.

Team Approach

The use of a team approach, especially one that incorporates increased data sharing using enhanced health information technology (e.g., electronic records and electronic data transmission), is an effective method for improving BP control [9]. According to an analysis of controlled clinical trials, the only quality improvement strategy that has significantly improved BP control is interdisciplinary team-based care [35]. Quality improvement strategies for hypertension management include a systematic review [26].

Improvements in BP control seen with a team approach can be attributed to numerous factors, but one of the most important is greater patient adherence to medication regimens [26]. Primary physicians remain the cornerstone of diagnosis and treatment as well as general team direction.

With a team model, nurses or nurse practitioners may assume the supervisory role of direct patient care, provide educational support, and perform or supervise follow-up activities.

Because diet is such an important lifestyle modification for patients with hypertension, dietitians often become team members. Dietitians can help patients design general or individualized heart-healthy meal plans and can be particularly helpful for patients who struggle to eat right and lose weight. This is particularly important for patients who also have the metabolic syndrome or diabetes.

Use of proper home monitoring, especially a unit that allows transmission of data electronically to permit team member review and intervention as appropriate, decreases both the frequency of clinic visits and BP levels. The team approach allows more effective use of home monitoring.

Patients educated to improve their health are more likely to understand and follow through on medical recommendations and therapies. Patients are ultimately in charge of their own adherence.

Conclusion

Pediatric HTN is a public health problem worldwide. Its diagnosis and therapy are inadequately applied. Children with HTN are at risk for CVD. They should be evaluated and treated according to the established criteria. Pediatricians and other primary care providers are the first line of defense against HTN. They can play a significant role in early diagnosis, treatment, and patient education. Antihypertensive therapies with ACE inhibitors or ARBs are proven to lessen progression of CVD. BP control, a regular aerobic exercise regimen, salt restriction, and avoidance of alcohol consumption and smoking also help to lessen the CVD progression. Hypertensive children at increased risk for CKD should be tested for serum CRP and urine MACR ratio at the time of a health evaluation.

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