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EDUCATIONAL REVIEW

Hypertensive crisis in children and adolescents

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Abstract

Hypertensive crisis is a relatively rare condition in children. However, if not treated, it might be life-threatening and lead to irreversible damage of vital organs. Clinical presentation of patients with hypertensive crisis can vary from very mild (hypertensive urgency) to severe symptoms (hypertensive emergency) despite similarly high blood pressure (BP). Individualized assessment of patients presenting with high BP with emphasis on the evaluation of end-organ damage rather than on the specific BP number is a key in guiding physician's initial management of a hypertensive crisis. The main aim of the treatment of hypertensive crisis is the prevention or treatment of life-threatening complications of hypertension-induced organ dysfunction, including neurologic, ophthalmologic, renal, and cardiac complications. While the treatment strategy must be directed toward the immediate reduction of BP to reduce the hypertensive damage to these organs, it should not be at a too fast rate to cause hypoperfusion of vital organs by an excessively rapid reduction of BP. Thus, intravenous continuous infusions rather than intravenous boluses of antihypertensive medications should be the preferable mode of initial treatment of children with hypertensive emergency.

Keywords Hypertensive crisis · Children · Severe hypertension · Hypertensive emergency · Hypertensive urgency · End-organ damage

Abbreviations

BP	Blood pressure
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
LVH	Left ventricular hypertrophy
HTN	Hypertension

Terminology and definitions

One of the most commonly used terms to define severe hypertension is *hypertensive crisis*: a sudden and abrupt severe elevation in blood pressure (BP) from baseline, with life-threatening potential to cause rapid end-organ damage. Two other terms describing hypertensive crisis are *hypertensive emergency* and *hypertensive urgency*. In the case of *hypertensive emergency*, BP elevation is accompanied by evidence of severe symptoms and end-organ damage, while minor or no symptoms are present in the case of *hypertensive urgency* [1]. The distinction between emergency and urgency is not absolute and depends frequently on clinical judgment [2]. Moreover, hypertensive urgency might worsen and lead to hypertensive emergency. The recent 2017 Clinical Practice Guidelines (CPG) for Screening and Management of High BP in Children and Adolescents [3], instead of "urgency" or "emergency," used the term *acute severe hypertension* in reference to any acute *symptomatic* presentation of severe hypertension.

In adults, severe hypertension is commonly defined as BP *above 180/120 mmHg*, which is equal to *50% above* "*normal BP*" *of 120/80 mmHg* [4]. However, there is no clear definition of severe hypertension in children and adolescents. Before the 2017 CPG report, several definitions had been used in the literature including "BP well above the 99th percentile," stage 2 hypertension [1, 2], or "20 mmHg above the 95th percentile" [5]. The 2016 European Society of Hypertension

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guidelines for the management of high BP in children and adolescents also suggested to use a cutoff of *20% above the stage 2 hypertension* limit, which, using the Fourth Report on BP, corresponded with a systolic BP (SBP) of 178 mmHg in a 17-year-old boy [6]. The 2017 CPG states that "patients who present with acute severe hypertension will have BP elevation *well above the stage 2 hypertension threshold*" and that "clinicians should be concerned about the development of these complications when child's BP increases *30 mmHg or more above the 95th percentile*". This corresponds to a SBP of above 160 mmHg in children 13 years and older or above 135 mmHg in a 1-year-old child. This definition also results in relatively higher cutoff values for hypertensive crisis in younger children. For example, it will be about 29% above limits in average height 1-year-old child but only 21% above limits in adolescents.

It is important to emphasize that while different patients can present with a similarly high BP and will be diagnosed with severe hypertension based on a BP number, their clinical presentation can vary from no to severe symptoms. Alternatively, there are some specific circumstances in which lower levels of BP (not meeting the definition of severe hypertension) may be associated with significant end-organ damage and, therefore, require acute intervention. Such cases include perioperative hypertension [7], patients who are at higher risk of bleeding (e.g., oncologic and bone marrow transplant patients), and patients at higher risk for neurological complications [8]. In summary, rather than the use of a strict numeric cutoff definition of severe hypertension, a more individualized approach should be taken in the assessment of the patient's BP status, with emphasis on the evaluation of specific risk associated with the development of end-organ damage.

Epidemiology

The prevalence of hypertensive emergencies in the pediatric population is difficult to estimate given the lack of a uniform definition and/or methodological approach as can be illustrated in the following examples. In a single study from London, among 454 children admitted for hypertension, 24% had severely raised BP, defined as BP > 99th percentile [9]. In a cross-sectional analysis of secondary school students in Houston between 2003 and 2005, the prevalence of stage 2 hypertension (based on the Fourth Report) was 0.6% (19% of hypertensives) [10]. In a retrospective study from Taiwan, 0.021% of total visits to pediatric emergency departments between 1995 and 2010, and 54% of those presenting with hypertension, had a first-attack hypertensive crisis, though this study excluded patients after kidney or bone marrow transplants and drug-induced hypertension. In this particular study, among those with hypertensive crisis, 84% had hypertensive urgency, while only 16% had hypertensive emergency [11]. However, in another recent study, 61% of pediatric patients with hypertensive crisis had hypertensive emergency [12].

Based on limited data [9, 11], 12–14% of patients with hypertensive crisis present before 1 year of age. According to the study from Taiwan [11], 78% of patients diagnosed with hypertensive crisis were older than 7 years of age, and 44% were older than 13 years. The same study indicated that there was a significant male predominance of 5:1, a finding that was not confirmed by other studies. In older patients with hypertensive crisis, there is a reported association with increased body mass index [10, 13]. There are some limited data from adult studies indicating a seasonal variation in the frequency of hypertensive crisis, with a higher frequency of cases in the winter [14, 15]. There are no data regarding this issue in the pediatric population.

Etiology

Hypertensive crisis may be associated with any known cause of hypertension (Table 1). In adults, the majority of cases of hypertensive crises are due to nonadherence to prescribed medication, drug overdose, or sudden withdrawal of antihypertensive medications [16, 17]. Traditionally, hypertensive crisis in the pediatric population has been mostly attributed to secondary causes of hypertension, specifically to renal causes [2, 3]. In earlier reports from England, only 2–5% of children with severe hypertension were diagnosed with primary/essential hypertension, while 76–82% were found to have underlying renal conditions [9, 18, 19]. However, as the prevalence of primary hypertension increases in the pediatric population, the number of children with severe hypertension associated with primary hypertension may increase as well. In a more recent report from Taiwan [11], 48% of patients who presented to the emergency department with hypertensive crisis had primary hypertension, though this study, as indicated above, excluded patients with a history of kidney and bone marrow transplantation, as well as those with drug-induced hypertension.

Conditions like coarctation of aorta, renal vein or artery thrombosis, and polycystic kidney disease predominate in *neonates* [5]. Other potential etiologies more specific for this age group include congenital mesoblastic nephroma, iatrogenic hypercalcemia, and drugs, such as phenylephrine eye drops and, rarely, theophyline [20, 21]. There is also a report of prenatal exposure to methyldopa leading to a withdrawal effect, hypertensive crisis, and cardiac failure postnatally [22].

Primary hypertension, renal parenchymal disease, endocrine conditions, autoimmune diseases, and medications, on the other hand, are important etiologies in *older children and adolescents*. In adolescents, substance abuse, specifically with cocaine, amphetamines, hallucinogens, and drug overdose with over-the-counter cold remedies containing pseudoephedrine, phenylpropanolamines, nonsteroidal anti-inflammatory

Table 1 Etiologies of hypertensive emergencies

Secondary	
Renal (renoparenchymal and renovascular)	Glomerulonephritis, reflux nephropathy, obstructive uropathy, polycystic kidney disease (especially autosomal recessive), thrombotic microangiopathy (especially hemolytic uremic syndrome), lupus nephritis, renal artery stenosis, acute kidney injury, end-stage renal failure (especially oligo-anuric with volume overload), s/p kidney transplantation
Cardiovascular	Aortic coarctation (thoracic, abdominal), systemic vasculitides
Malignancies	Pheochromocytoma, Wilms tumor, neuroblastoma, s/p bone marrow transplantation
Endocrine	Cushing syndrome, thyrotoxicosis, rare forms of congenital adrenal hyperplasia
Neurologic	Dysautonomia (familial, Guillain-Barre, other), increased intracranial pressure
Immunologic	Systemic lupus erythematodes, Takayasu's arteritis, polyarteritis nodosa
Medications/toxins related	Antihypertensive medication noncompliance, illicit drugs (cocaine, MDMA), over the counter treatment (OTC) cold remedies, amphetamines, Nonsteroidal anti-inflammatory drugs (NSAIDS), anabolic steroids, corticosteroids, calcineurin inhibitors (cyclosporine/tacrolimus), erythropoetin, rapid withdrawal of antihypertensives (clonidine, beta-adrenergic blockers)
Monogenic HTN	Liddle syndrome, Gordon syndrome, apparent mineralocorticoid excess, glucocorticoid remediable aldosteronism
Primary	Especially in combination with obesity or high-renin HTN

HTN, hypertension

drugs (NSAIDS), and monoamine oxidase inhibitors (MAOI) should be strongly considered as cause of severe hypertension [23–25]. There is increasing evidence that consumption of energy drinks is associated with a risk for severe hypertension in adolescents and young adults.

Hypertensive crisis may be more common in end-stage renal disease (ESRD) patients and is frequently secondary to significant extracellular volume expansion. Other potential contributors to hypertension in these patients include secondary hyperparathyroidism, uremic toxins, such as homocysteine, and the use of erythropoietin. Severe hypertension can be seen in the posttransplant period as a result of kinking of the renal artery or acute obstruction [26, 27]. Acute calcineurin inhibitor toxicity and thrombotic microangiopathy can cause renal vasoconstriction and should be considered when the onset of hypertension is acute [28]. Sirolimus increases the risk for microangiopathy secondary to calcineurin inhibitors [29]. High-dose steroids and fluid overload in the phase of a graft recovery from peritransplant ischemic insults may also contribute to severe acute hypertension. Transplant rejection can result in microangiopathy and lead to hypertensive crisis [26, 27].

Pathophysiology

As majority of cases of hypertensive crisis in the pediatric population are attributed to secondary hypertension, the mechanism of severe hypertension is directly related to the nature of the underlying condition (e.g., pheochromocytoma, thyrotoxicosis, fluid overload in ESRD patients, etc). However, regardless of the cause, there are some common pathways that may relate to the severity of hypertension itself and to the processes leading to symptoms and end-organ damage.

The pathogenesis of hypertensive crisis involves several systems. According to one theory [30], an initial stimulus to cause elevation in BP may then lead to activation of the renin-angiotensin system, oxidative stress, and endothelial dysfunction resulting in protein fragmentation and formation of neoantigens. These neoantigens promote activation of T cells, which enter the kidney and vasculature. T-cell-derived signals promote the entry of other inflammatory cells and the release of cytokines causing more vasoconstriction, sodium and water retention, and thus, more severe hypertension. In addition, the vasoconstriction and pressure natriuresis resulting from this BP elevation may lead to volume depletion and positive feedback to the renin-angiotensin system leading to further increase in BP and end-organ damage [31–47]. The end result of this cascade is a vicious cycle of increased vasoconstriction, oxidative stress, and inflammation leading to progressive cytotoxic effects on the vascular wall, worsening endothelial damage, and eventually, tissue ischemia [48–56].

Clinical presentation

Patients with hypertensive crisis may present with a wide spectrum of symptoms, from no/mild symptoms, such as headache, nausea, vomiting, blurred vision, or an anxiety

attack in the case of hypertensive urgency to severe life-threatening symptoms and conditions in case of hypertensive emergency. These may include hypertensive encephalopathy, cerebral infarction, cerebral hemorrhage, bilateral retinal hemorrhage, papilledema, facial nerve palsy, acute kidney injury, acute heart failure, and pulmonary edema. As for other differences between hypertensive urgency and emergency, according to one study, symptomatic patients with hypertensive emergency generally have higher BP compared to those with hypertensive urgency [11]. While one adult study suggested that tachycardia is a sign of hypertensive emergency [57], another study suggested that signal peptide-CUB-EGF (complement C1r/C1s Uegf Bmp1-Epidermal Growth Factor) domain-containing protein1 (SCUBE1), an indicator of platelet activation, might be a diagnostic marker for hypertensive emergency and end-organ damage [58].

The most common clinical manifestations of hypertensive crisis in children are neurologic. In recent studies [11, 12], 55% of patients with hypertensive crisis in the emergency department presented with headaches, 46% with dizziness, 36% with nausea/vomiting, 16% with altered consciousness, and 11–20% with seizures. An older report from England reported that 25% of patients with hypertensive emergencies (including asymptomatic patients) had hypertensive encephalopathy [9], 12% were reported to have facial nerve palsy (a symptom that is associated with hypertension mainly in children [59]), 25% with seizures, and 9% with hemiplegia. According to a recent report on pediatric hypertensive encephalopathy patients, those with a renal etiology of hypertension had higher frequency of seizures and a more severe clinical course [60].

Hypertensive encephalopathy can manifest in imaging studies as posterior reversible encephalopathy syndrome (PRES) [8, 61], which has been reported to predominantly affect the occipitoparietal area, but in many cases, other affected areas have been reported [62]. PRES is often seen in conditions such as postchemotherapy, posttransplant, autoimmune diseases, immunosuppressive drugs, and ESRD [8, 63–65]. Therefore, these conditions might require tighter BP control, as "hypertensive crisis" might present at a lower BP threshold. Clinical features of PRES can vary and may present with mild symptoms (headache, nausea, and vomiting) or severe manifestations characterized by altered mental status, seizures, cortical blindness, and/or focal neurological deficits. Classical features of PRES on magnetic resonance imaging (MRI) are bilateral, symmetrical changes of white matter in the occipitoparietal regions. While PRES is by definition a reversible condition, there are some rare case reports of long-term neurological sequelae [66–68]. There are reports of hypertension-induced cerebellar encephalopathy and hydrocephalus manifesting with cerebellar tonsillar herniation requiring ventriculostomy. Initial imaging studies of these children were suspicious of intracerebral masses, but these findings resolved following improvement in BP control [69, 70]. The differential diagnosis of hypertensive encephalopathy includes intracranial hemorrhage, cerebral thrombosis and infarction, uremia with encephalopathy, brain tumors, encephalitis, pseudotumor cerebri, and anxiety of hysterical states.

Cardiovascular manifestations of hypertensive crisis may include congestive heart failure (dyspnea on exertion, peripheral or pulmonary edema, and a gallop rhythm on auscultation), as well as chest pain and/or tenderness, which according to the recent report from Taiwan, was present in 29% of pediatric patients with hypertensive crisis [11]. According to other reports, 13–26% of patients with hypertensive emergencies had left ventricular hypertrophy (LVH) [9, 12], while in another study, all patients with severe hypertension had cardiomegaly and 9% had cardiac failure [19].

Visual abnormalities may include retinal infarcts, hemorrhages, optic disk edema, cortical blindness, acute ischemic optic neuropathy, and visual disturbances with increased intracranial pressure. Acute visual changes are frequently associated with hypertensive encephalopathy and PRES [71]. One report found that in adults, patients with hypertensive retinopathy were significantly younger compared to those without retinopathy [72]. In children, Williams et al. [73] examined patients undergoing workup for severe renovascular hypertension and found that 18% had hypertensive retinopathy. These children had higher BP than those without retinopathy. In an earlier report, 27% of pediatric patients with hypertensive emergencies had retinopathy, while 9% had visual symptoms [9]. In another study, 36% of children with severe hypertension had papilledema [19].

Renal manifestations of hypertensive crisis may include acute kidney injury (AKI), hematuria, and/or proteinuria. In a recent report in adults, those with hypertensive emergency had higher serum creatinine and higher urine NGAL (neutrophil gelatinase-associated lipocalin), a marker of early kidney injury [56] as compared to controls. Patients with unilateral renal artery stenosis might develop a hyponatremic hypertensive syndrome (HHS). The mechanism involves hyperfiltration, pressure diuresis, and natriuresis on the contralateral kidney. These changes are secondary to activation of the renin-angiotensin-aldosterone system in the affected kidney. Patients may present with polyuria, polydipsia, and headaches as well as other neurological symptoms. Laboratory findings usually include hyponatremia, hypokalemia, hypochloremic alkalosis, and proteinuria, which can sometimes be in the nephrotic range [74, 75].

Of note, in neonates and infants, common manifestations of hypertensive crisis are irritability, feeding problems, failure to thrive, tachypnea, apnea, cyanosis, congestive heart failure, lethargy, and seizures [76, 77]. Some infants with severe hypertension may present with secondary hypotension and

cardiogenic shock [78, 79]. In these cases, hypertension will be unmasked after improvement of heart function.

Evaluation

The major goal of initial evaluation of a child presenting with acute severe hypertension is to recognize the difference between urgency and emergency. This step is extremely important since it will guide the physician's decision on initial management. More than two decades ago, Deal et al. [9] noted that "the assessment of the need for urgent treatment depends upon a clinical assessment of the degree and rate of rise of BP and the potential for end organ damage or loss of life in each individual patient."

Initial evaluation should be done within minutes and include brief history (if possible) and physical exam to explore the possible clinically evident cause of hypertension (Table 2). Laboratory and radiological evaluation might include different tests based on initial history and physical exam (Table 3). While the results of the tests might inform the physician about the cause and mechanisms of acute severe hypertension and eventually will guide specific treatment options, immediate treatment, especially in case of hypertensive emergency, should be started before the results are available.

Treatment

The main aim of the treatment of hypertensive crisis is prevention or treatment of life-threatening complications of hypertension-induced organ dysfunction, mainly neurologic, ophthalmologic, renal, and cardiac [80]. Children with hypertensive crisis necessitate immediate intervention to effectively but safely lower the BP and should be treated in an intensive care unit (ICU) to ensure

1. Intravenous access for application of intravenous (IV) drugs, especially prompt delivery and titration of antihypertensive medications
2. Intra-arterial access for invasive BP monitoring
3. Monitoring of the vital organs including neurological (e.g., Glasgow coma scale, GCS), cardiac (ECG, cardiac telemetry), and renal status (urinary output, kidney function)
4. Supportive therapy for possible life-threatening complications (e.g., anticonvulsives and cardiotropics)

Several decisions will need to be made before starting treatment of a child with hypertensive crisis: Which route of administration should be the antihypertensive drug given? Which drug should be used? How fast should the BP be lowered? What should be treatment BP target?

Route of administration

Children with hypertensive *emergency* initially must always be treated with intravenous drugs, preferably, if available, by intravenous continuous infusion. The treatment strategy must be directed toward the immediate reduction of BP to reduce the end-organ damage, but not at a rate to likely cause hypoperfusion of vital organs by an excessively rapid reduction of BP (mainly cerebral hypoperfusion with neurological or visual sequelae such as seizures, unconsciousness, visual loss, or renal hypoperfusion with acute kidney injury). This is particularly true in children with long-standing hypertension where autoregulatory compensation has occurred (Fig. 1). In a retrospective British study, Deal et al. showed that complications induced by antihypertensive therapy were much more likely in children who received intravenous bolus drugs with rapid and extensive BP reduction (23%) than in children with gradual BP decrease with continuous intravenous drug infusions (4%) [9]. Specifically, they reported rapid and extensive BP reduction induced by bolus delivery (up to 195 mmHg over the first 24 h in some cases!) was associated with transient or even permanent visual loss, transient acute renal failure, or transverse ischemic myelopathy. However, one of the patients experienced permanent damage also by much smaller BP reduction of 40 mmHg only. This might be much more representative in clinical practice for the immanent risk of rapid BP lowering than the very uncommon extreme reduction of BP > 100 mmHg.

Hypertensive *urgencies* can be treated by oral drugs if the children are able to tolerate them. Otherwise, bolus intravenous drugs can also be given. Again, the decision should be made based on individual case presentation.

Choosing the drug

There are no comparative studies investigating what is the best class of antihypertensive medications to use in case of hypertensive crisis in children. Selection of an initial medication is often based on physician preference and experience as well as drug availability in the hospital rather than a physiologic advantage of medication in question. The drugs are also chosen based on their rapidity of action, safety, and ease of use. However, in specific situations when the cause of acute hypertension is known (e.g., renal disease, coarctation of aorta, etc), after initial BP reduction, physician should try to maximize the antihypertensive potential by choosing a drug that targets the proposed pathophysiologic process of BP elevation (see below under "Management of hypertensive crisis in specific settings").

Table 2 Clinical symptoms of a patient presenting with hypertensive crisis and the possible etiologies of hypertension

Clinical symptoms of hypertensive crisis	Possible etiology of hypertension
Palpitations, sweating, flushing	Catecholamines producing tumors
Exophthalmos, tachycardia, diarrhea, weight loss	Hyperthyroidism
Abdominal palpable mass	Neuroblastoma, Wilms tumor, autosomal recessive polycystic kidney disease, multicystic kidney dysplasia, obstructive uropathy
Fluid overload	End-stage renal disease, acute glomerulonephritis
Abdominal bruit	Renal artery stenosis
Moon face, truncal obesity, striae, hirsutism	Cushing syndrome
Weak peripheral pulses and low BP in the lower extremity	Aortic coarctation
Bradycardia, irregular breathing/apnea*	Brain injury/trauma

*Should be identified before instituting antihypertensive treatment as the primary goal is to maintain cerebral perfusion and dropping their blood pressure (BP) could result in devastating cerebral consequences

Rate of BP lowering and goal of BP

There is no experimental or clinical evidence upon which to base recommendations on the optimal rate of BP reduction in hypertensive emergencies. From the clinical experience, in the first phase, the commonly practiced recommendation is to lower BP by no more than 25% (one quarter) of the planned BP reduction over the first 6 h (one quarter of a day). It could be described by a "principle of quarters"—reduce the BP only by one quarter of the planned BP reduction during the first quarter of the day.

This initial first phase should be followed by a second phase with a further gradual reduction of BP over the next 24–48 h to BP values around the 95th percentile [2, 5, 81, 82]. Faster normalization of severe hypertension must be strictly avoided as it can cause more harm (treatment-

Table 3 Initial laboratory and radiological evaluation

Blood: complete blood count
Electrolytes, BUN, creatinine, thyroid function tests
Plasma renin activity, cortisol, fractionated plasma metanephrines
Pregnancy test in adolescent girls
Urine: urinalysis, event culture
Urine toxicology screen
Radiological: renal ultrasound with Doppler
Echocardiogram
Head CT or MRI if signs of encephalopathy
Chest X-ray in pulmonary symptoms
CTA/MRA in suspicion of renal artery stenosis
Ophthalmoscopic (fundoscopic) examination

BUN, blood, urine, nitrogen; *CT*, computed tomography; *MRI*, magnetic resonance imaging; *MRA*, magnetic resonance angiogram; *CTA*, computed tomographic angiography

induced complications as we discussed above) than severe hypertension itself. Some authors suggest that in patients with new onset of acute hypertension, the treatment can be more aggressive than in children with chronic long-lasting hypertension. This strategy is based on the fact that the patients with new onset of severe hypertension, as compared to those with chronic hypertension (Fig. 1), have minimal cerebral perfusion autoregulation and, therefore, are at a lower risk of cerebral hypoperfusion [83].

In the management of hypertensive crisis, it is important and practical for the management to set the target BP in absolute numbers for the first 6–48 h. For example, in a 15-year-old boy presented with a systolic BP of 190 mmHg, the overall goal is to reduce BP by 60 to about 130 mmHg over next

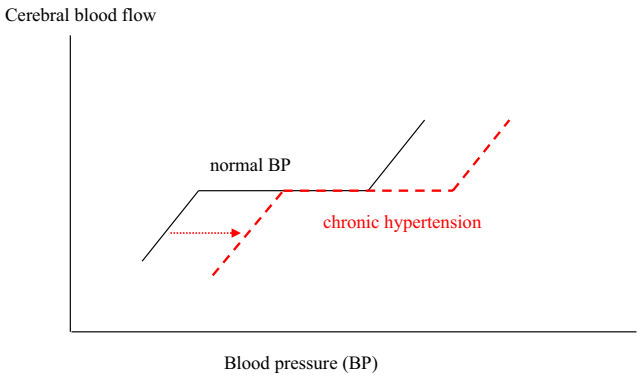

Fig. 1 Autoregulatory "pressure flow" curve in chronic hypertension. During chronic hypertension, the autoregulatory "pressure flow" curve that enables stable blood flow (especially to the brain) within a wide range of BP is shifted to the right (red arrow) to enable stable blood flow within higher BP values in comparison to normotension (black curve). Immediate reduction of BP in patients with severe chronic hypertension would cause decrease flow (hypoperfusion) to the brain by an excessively rapid reduction of BP before restoration of normotensive "pressure flow" occur (reshift to the left)

24–48 h. In this case, ideally, over the first 6 h, BP should be reduced by 15 mmHg (25% of planned 60 mmHg). In the next 24–48 h, the BP should be gradually reduced from 175 to about 130 mmHg.

In case of BP lower than the target BP or appearance of symptoms of vital organ hypoperfusion (e.g., changes in neurological status, seizures, or oliguria), rapid IV infusion of normal saline or inotropes to increase BP toward target BP should be immediately introduced. A treatment algorithm for a child with hypertensive crisis is given in Fig. 2.

Antihypertensive drugs

The dosages, onsets of action, and common adverse effects of the most commonly used antihypertensive drugs in children are summarized in Table 4.

Intravenous agents

Vasodilators

Nitroprusside is one of the most commonly used drugs for hypertensive crisis in children. However, it is no longer available in some countries. It is favorable due to its antihypertensive efficacy, rapid onset of action, and rapidity of withdrawal of action in case of relative hypotension. As a direct arterial and venous vasodilator, it reduces preload and afterload and is therefore also beneficial in patients with congestive heart failure [84]. Its main side effect is accumulation of thiocyanate that can occur if used for longer than 24–48 h, which can cause methemoglobinemia, metabolic acidosis, or seizures.

Hydralazine is a direct arteriolar vasodilator that decreases BP by decreasing systemic vascular resistance [85]. Because this occurs in the absence of opposing negative inotropic effects on the heart, hydralazine often causes side effects such as reflex tachycardia, activation of the renin-angiotensin-aldosterone system, and sodium retention. Hydralazine can be used also orally. There are no pediatric studies on hydralazine in the treatment of hypertensive crisis.

Diazoxide is a direct vasodilator that increases the permeability of the vascular smooth muscle membrane to potassium. It has a quick hypotensive effect without significant adverse effects in small dosages in children [86]; however, currently, it is unavailable in many countries.

Nitroglycerine (glyceryl trinitrate) is a nitric oxide donor and a potent vasodilator which reduces preload and cardiac output that is usually not used as first-line treatment; however, it is commonly used as adjunctive treatment in adults with acute coronary syndromes [87].

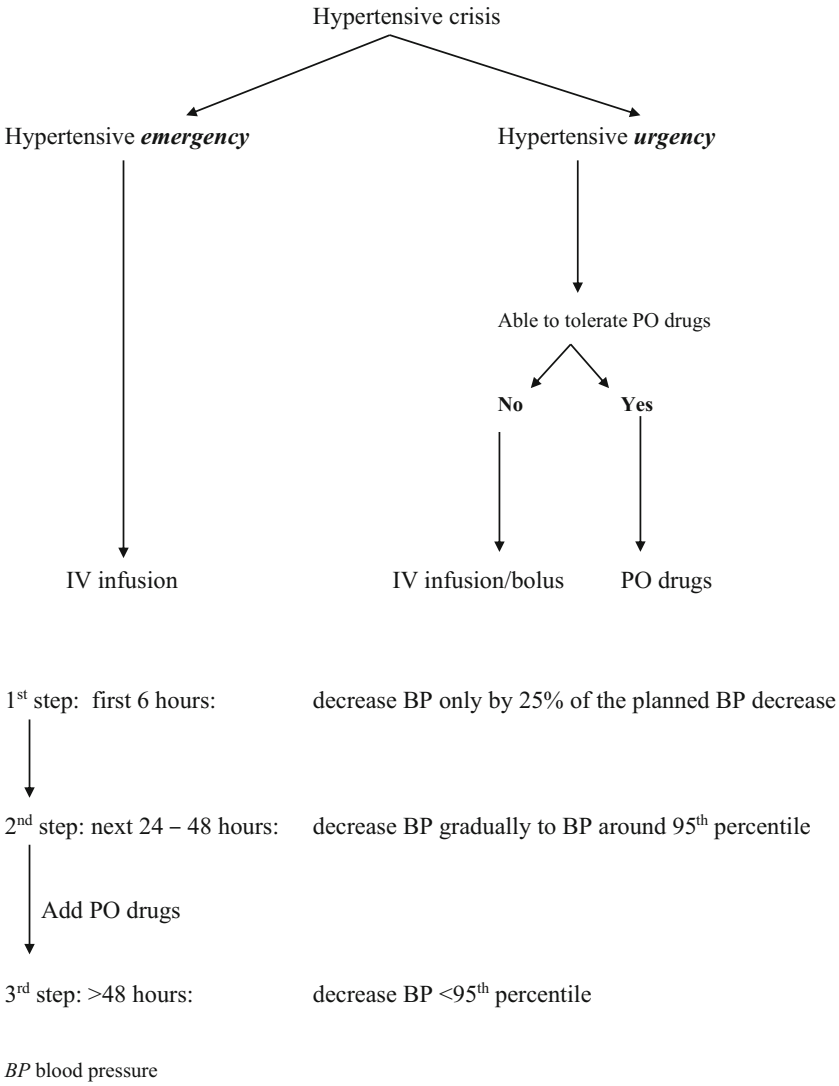

Fig. 2 Decision-making tree for treatment of hypertensive crisis in children

Calcium channel blockers

Nicardipine is a second-generation dihydropyridine calcium channel blocker (CCB) which induces vascular smooth muscle cell relaxation and peripheral vasodilation. There is a large experience with nicardipine in treating severe hypertension in children [88, 89]. The main adverse effects are due to its vasodilation effects consisting of tachycardia, flushing, and palpitation.

Adrenergic blockers and agonists

Labetalol is a combined α_1- and β-adrenergic blocker causing BP reduction by reduction of peripheral vascular resistance with little effect on cardiac output. Its disadvantage is the same as in all β-blockers, namely its negative inotropic effect and bronchoconstriction, and therefore, it should not be used in children with asthma or with decompensated or unstable congestive heart failure. It has been used in infants and small children and has produced a significant reduction in BP within the first 6 h of therapy [90].

Urapidil is a combined peripheral α_1 postsynaptic adrenergic receptor antagonist and central 5-hydroxtryptamine 1A receptor agonist. Its advantage is that the vasodilatory action is not accompanied by reflex tachycardia or any modification of the renin-angiotensin-aldosterone system. Urapidil decreases both cardiac preload and afterload and is capable to induce renal vasodilatation. It has very few side effects and its only single contraindication is aortic stenosis. There are only few reports on urapidil in children with severe hypertension [91, 92].

Esmolol is an ultra-short-acting cardioselective β_1-adrenergic blocker. It is one of the few antihypertensive drugs for which randomized double-blind trials in pediatrics exist [93]. Tabbutt et al. showed that esmolol was able to significantly reduce systolic BP within the first 6 h of administration in 116 children undergoing surgery for coarctation of aorta repair without a dose dependency. Common side effects were

Table 4 Antihypertensive drugs for hypertensive emergencies and urgencies

Drug class	Drug	Route	Dose	Onset of action	Side effects, comments
Direct vasodilator	Diazoxide	Intravenous bolus	1–3 mg/kg every 5–15 min	Within minutes	Risk of hypotension in large doses
	Hydralazine	Intravenous bolus	0.2–0.6 mg/kg	5–20 min	Reflex tachycardia, headache, fluid retention
	Minoxidil	Orally	0.1–0.2 mg/kg per dose	5–10 min	Fluid retention
	Nitroglycerine	Intravenous infusion	0.1–2 μg/kg per min	1–2 min	Methemoglobinemia, vasodilating effect primarily on the venous side—efficient in heart failure, limited efficacy in children
	Nitroprusside	Intravenous infusion	0.5–8 μg/kg per min	Within seconds	Thiocyanate toxicity, inactivated by light
α-Blocker	Phentolamine	Intravenous bolus	0.1–5 mg/kg	1–2 min	Tachycardia. Used only in pheochromocytoma
	Phenoxybenzamine	Orally	0.2–1.2 mg/kg, daily	Several hours	Tachycardia. Used only in pheochromocytoma
	Doxazosin	Orally	1–2 mg per dose, daily	2–6 h	Orthostatic hypotension, dizziness
	Prazosin	Orally	0.02–0.04 mg/kg, three times daily	30–90 min	Dizziness, headache
β-Blocker	Esmolol	Intravenous infusion	100–500 μg/kg per min	Within seconds	Contraindication in asthma, may cause bradycardia
α- and β-blockers	Labetalol	Intravenous infusion	0.25–3 mg/kg per hour	5–10 min	Contraindication in asthma, heart failure, bradycardia
Peripheral α-blocker and central agonist of 5-HT_{1A} receptors	Urapidil	Intravenous infusion	Initial dose 0.5–4.0 mg/kg per hour Maintenance dose 0.2–2.0 mg/kg per hour	1–5 min	May cause sedation, palpitation, nausea
Central α agonist	Clonidine	Intravenous bolus	2–6 μg/kg per dose	Within 10 min	Dry mouth, sedation, rebound hypertension
		Orally	2–10 μg/kg per dose every 6–8 h	2–4 h	Dry mouth, sedation, rebound hypertension
Angiotensin-converting enzyme inhibitors (ACEIs)	Enalaprilat	Intravenous bolus	0.005–0.01 mg/kg per dose	15 min	Contraindication in suspected bilateral renal artery stenosis
	Captopril	Orally	0.1–0.2 mg/kg per dose 0.01–0.1 in neonates	10–20 min	Contraindication in suspected bilateral renal artery stenosis
Calcium channel blocker (CCB)	Clevidipine	Intravenous infusion	1–7 μg/kg per min	Within 5 min	Reflex tachycardia
	Isradipine (L-type of CCB)	Orally	0.05–0.1 mg/kg per dose	1 h	Higher doses may cause BP drop of > 25%
	Nicardipine	Intravenous infusion	1–3 μg/kg per min	Within minutes	Reflex tachycardia
	Nifedipine	Orally or sublingually	0.25 mg/kg per dose	20–30 min	May cause unpredictable hypotension, reflex tachycardia
Diuretic (loop)	Furosemide	Intravenous bolus	0.5–5 mg/kg per dose	Within minutes	Hypokalemia. Useful in volume hypertension
Dopamine receptor agonist	Fenoldopam	Intravenous infusion	0.2–0.8 μg/kg per min	Within 5 min	Tachycardia, flushing, headache

Disclaimer: Not all antihypertensive drugs listed above have been licensed for use in children. All dosing information is given to the best of knowledge

bradycardia, hypotension, and wheezing. At higher doses, its β_1 cardioselectivity is lost and also peripheral β_2 receptors are activated in bronchioles and may induce bronchoconstriction. It should not be used in acute decompensated heart failure.

Clonidine is a centrally acting α_2-adrenergic agonist that reduces BP by reducing central sympathetic output with vasodilation. It is only minimally excreted by urine and minimally removed by hemodialysis; therefore, it is very popular in children with chronic renal failure treated by hemodialysis. There are several pediatric experiences with clonidine showing its efficacy and safety also in children [94]. The most common side effects are due to its inhibition of central sympathetic tone—dry mouth and sedation. It can be administered intravenously as well as orally.

Fenoldopam is a selective dopamine D_1 receptor agonist that binds to α_2 adrenoreceptors and induces artery vasodilation. In one large pediatric study in infants and children, fenoldopam was used to produce controlled hypotension during surgery with significant decrease of BP. Its side effects are tachycardia and flushing [2, 95].

Angiotensin-converting enzyme inhibitors (ACE inhibitors)

Enalaprilat is the only intravenous angiotensin-converting enzyme inhibitor on the market. Due to its mechanism of action, it is very effective in high-renin hypertension, either in children with renoparenchymal, renovascular, or high-renin primary hypertension. It is often used in adults; however, the published pediatric experience is very limited [96, 97]. Its main adverse effects are due to the anti-renin properties and range from hyperkalemia to functional acute kidney injury. Enalaprilat is contraindicated in children with bilateral renal artery stenosis or stenosis of a solitary kidney; therefore, renal Doppler ultrasound should be performed before starting enalaprilat therapy. It should also be used with caution in children with volume depletion and neonates and young infants as these pediatric categories have physiological high-renin status and an ACEI can cause hypotension.

Diuretics

Furosemide is a loop diuretic that is effective in children with volume-dependent hypertension, e.g., with oliguric acute kidney injury, glomerulonephritis, or congestive heart failure [85]. It initiates diuresis and natriuresis thereby decreasing blood pressure. Its repeated use can cause hypokalemia or volume depletion; therefore, serum potassium levels and hydration status should be regularly checked.

Oral agents

Calcium channel blockers

Nifedipine is historically the most commonly used short-acting CCB. It has a very potent blood pressure-lowering effect in nearly all forms of pediatric hypertension [98]. Its disadvantage is the risk of sudden unpredictable severe reduction of BP that can cause change in neurological status including cerebral ischemia or ventricular arrhythmia. It should be initially used with low dose (such as 0.25 mg/kg per dose) to maximally avoid these adverse effects. The short-acting nifedipine is contraindicated in adults with hypertensive crisis because of its risk of severe drop of BP and neurological or cardiac sequelae.

Isradipine is a second-generation L-type dihydropyridine CCB that is currently the more commonly recommended CCB than nifedipine because of its similar antihypertensive potency with a lower risk of the unpredictable severe BP reduction. It causes vasodilation without an effect on myocardial function. There is a large experience with isradipine in pediatric patients showing efficacy of the drug in children from infants to adolescents [99]. The children who suffered from hypotension were concurrently taking azole antifungals, which inhibit the degradation of isradipine producing high serum levels of the drug and toxicity.

ACE inhibitors

Captopril is a first-line short-acting ACE inhibitor that is used more than 30 years for the treatment of hypertension (HTN); however, due to its short half-time of only 6–8 h, it is currently obsolete for chronic treatment of HT. It can be used with similar indications and contraindications as intravenous enalaprilat, and it is especially effective in high-renin HT and neonates who have physiologically high-renin status and, therefore, require lower doses [100].

Adrenergic blockers and agonists

Doxazosin and prazosin are α-adrenergic blockers that are used mainly in catecholamine-induced hypertension as in pheochromocytoma [101]. They are used in the preoperative management before surgical resection of the tumor to prevent complications not only from HTN but also from catecholamine release.

For clonidine and urapidil, see section on IV agents and Table 4.

Vasodilators

Minoxidil is a potent direct arterial vasodilator. It has originally been invented as a drug to treat ulcers; however, in trials, the

compound did not cure ulcers but proved to be a powerful vasodilator. It opens potassium channels in vascular smooth muscle cells, thus leading to relaxation and vasodilation. It is possibly the most potent oral drug as it has a very potent BP-lowering effect in all forms of hypertension even in those that are refractory to other antihypertensives including volume hypertension in hyperhydrated dialyzed children [102, 103]. Its main adverse effect is hirsutism, although this is not a problem in the short-term treatment of acute hypertensive crisis. Minoxidil is therefore today used more for treatment of hair loss than for hypertension. Other side effects are fluid retention including pericardial effusion.

Management of hypertensive crisis in specific settings

As we emphasized above, the initial treatment should be initiated immediately even if the specific cause of severe hypertension is unknown. From our experience, the safest choice of antihypertensive medications during initial phase is IV infusion of vasodilators or CCB. When the cause is established, treatment should be maximized based on pathophysiological mechanism.

Glomerulonephritis

Children with acute glomerulonephritis experience acute increase of BP from normotensive levels and are at high risk of PRES as they have only little time for resetting the cerebral perfusion autoregulation. These children therefore require faster lowering of high BP and are at minimal risk of organ (cerebral) hypoperfusion. They suffer from sodium and water retention and therefore benefit from diuretics. ACE inhibitors are not recommended as they have low efficacy due to sodium and water retention and have a risk of hyperkalemia or acute kidney injury.

Acute kidney injury

In children with oliguric AKI, loop diuretics should be used. Again, ACE inhibitors are not recommended due to similar risks. In cases of severe volume hypertension in children with oligoanuric AKI when diuretics are ineffective, dialysis with ultrafiltration may be indicated to treat usually drug-resistant volume hypertension.

Renovascular hypertension

In children with bilateral renal artery stenosis or stenosis of a solitary kidney, ACE inhibitors are absolutely contraindicated due to their risk of functional AKI. However, in children with unilateral hemodynamically not important renal artery stenosis causing high-renin hypertension, ACE inhibitors are very potent antihypertensives. They should be used with caution in neonates with renovascular hypertension due to the risk of AKI as the neonates have physiologically high-renin levels that are blocked by ACE inhibitors. Beta-blockers are preferred second-line therapy due to their ability to reduce renin release from the kidneys.

Pheochromocytoma

Alpha-adrenergic antagonists (e.g., phentolamine) are the drug of choice in children with pheochromocytoma [101]. Once α blockade is achieved and children experience tachycardia, β-blocker may be used in combination. Beta-blockers should not be used as first-line therapy without α-blockers as this can lead to unopposed α-adrenergic stimulation and a further increase in BP. Second- or third-line therapy drugs in children with pheochromocytoma are calcium channel blockers.

Aortic coarctation

Beta-adrenergic drug esmolol is frequently used in infants and children with aortic coarctation. In an American study, it effectively reduced BP in 19 of 20 hypertensive children aged 1 month to 12 years without adverse effects [104]. BP reduction in these patients should be especially gentle, since significant reduction of BP in these children could lead to hypoperfusion of many vital organs.

Hypertensive crisis in newborns

The majority of antihypertensive medications are not approved for use in neonates, although they are commonly used as 1–2% of infants in the neonatal ICU suffer from hypertension [76]. Neonates with hypertensive crisis should be treated exclusively with intravenous infusions or short-acting antihypertensives. The drugs with published experience in neonates are nitroprusside, labetalol, esmolol, nicardipine, isradipine, clonidine, and hydralazine. ACE inhibitors (e.g., captopril) have also been used, although they can produce a severe decline in BP due to higher physiological plasma renin activity in neonates. This can be unresponsive to fluids and inotropes and can occur with subsequent symptoms of kidney or cerebral hypoperfusion, ischemia, hemorrhage, or even death [105]. Therefore, ACEI must be used with great caution in neonates.

Prognosis of children with hypertensive crisis

The prognosis of hypertensive crisis depends on its duration, extent of end-organ dysfunction at the time of presentation,

inappropriate therapy leading to acute reduction of BP (iatrogenic consequences), and the degree to which BP is controlled chronically after managing hypertensive crisis.

The consequences of hypertensive crisis can involve all types of hypertensive target organ damage: cardiac changes (left ventricular hypertrophy, congestive heart failure, hypertensive cardiomyopathy) [106], neurological sequelae (seizures, facial palsy, hemorrhage, papilledema, PRES, altered consciousness), renal (hypertensive nephropathy manifesting by AKI, or proteinuria and chronic kidney disease, CKD), or visual disturbances including blindness and retinal bleeds [5]. There have been early reports of fatal outcomes in children with renal artery stenosis [107, 108] or autosomal-recessive polycystic kidney disease (personal experience in a newborn with BP up to 210/120 mmHg).

Furthermore, the prognosis of children with hypertensive crisis depends also on appropriate acute therapy. In case of inappropriately rapid BP lowering resulting in hypoperfusion of vital organs, complications such acute kidney injury, seizures, transverse ischemic myelopathy, transient or even permanent visual loss, or death can occur [9, 76].

Finally, the long-term prognosis of children after hypertensive crisis depends also on the long-term BP control. With good chronic BP control and medication adherence, even severe hypertensive target organ damages such as severe left ventricular hypertrophy of retinal angiopathy are usually reversible. In general, the prognosis is good if severe hypertension is not long-standing, acute therapy is appropriate, and the underlying disease is effectively treated.

Conclusions

Hypertensive crisis is a life-threatening event that merits immediate treatment. The causes are usually secondary in children, who should be treated in the pediatric ICU. The main treatment strategy principle is to reduce BP safely to prevent hypoperfusion of vital organs.

Questions (answers are provided following the reference list)

1. A 17-year-old previously healthy boy presents in the emergency department with a few hours of pounding headache, chest pain, and anxiety. Initial evaluation showed heart rate of 110 beats per minute and BP 165/64. Physical examination is otherwise unremarkable. Which one of the following tests is likely to determine the cause of elevated BP in this patient?

   a) Thyroid stimulating hormone
   b) Plasma renin activity
   c) Urine drug screen
   d) Plasma metanephrine

2. Match the following symptoms of hypertensive crisis with the most possible etiology of hypertension:

   a) Tachycardia
   b) Striae
   c) Abdominal mass
   d) Sweating, flushing

   1. Autosomal recessive polycystic kidney disease
   2. Hyperthyroidism
   3. Catecholamine producing tumors
   4. Cushing syndrome

3. Which route of administration should be preferentially used in children with hypertensive emergency:

   a) Oral
   b) Intravenous bolus drugs
   c) Intramuscular injection
   d) Continuous intravenous infusion

4. How fast should be the BP lowered in the first 6 h in children with hypertensive crisis?

   a) As fast as possible
   b) Approximately 25% of the planned BP reduction
   c) Approximately 25% of the actual BP level
   d) To the BP level of the 95th percentile

5. Which drugs should be used in neonates with great caution:

   a) Alpha-blocker
   b) Beta-blockers
   c) ACE inhibitors
   d) Calcium channel blockers

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Answers

1. c; **2**. a-2, b-4, c-1, d-3; **3**. d; **4**. b; **5**. c