Pediatr Nephrol (2012) 27:741–751
DOI 10.1007/s00467-011-1964-0

EDUCATIONAL REVIEW

Hypertensive crisis in children

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Received: 7 December 2010 / Revised: 21 June 2011 / Accepted: 21 June 2011 / Published online: 20 July 2011

Abstract Hypertensive crisis is rare in children and is usually secondary to an underlying disease. There is strong evidence that the renin-angiotensin system plays an important role in the genesis of hypertensive crisis. An important principle in the management of children with hypertensive crisis is to determine if severe hypertension is chronic, acute, or acute-on-chronic. When it is associated with signs of end-organ damage such as encephalopathy, congestive cardiac failure or renal failure, there is an emergent need to lower blood pressures to 25-30% of the original value and then accomplish a gradual reduction in blood pressure. Precipitous drops in blood pressure can result in impairment of perfusion of vital organs. Medications commonly used to treat hypertensive crisis in children are nicardipine, labetalol and sodium nitroprusside. In this review, we discuss the pathophysiology, differential diagnosis and recent developments in management of hypertensive crisis in children.

Keywords Hypertension · Hypertension crisis · Hypertensive urgency · Children · Antihypertensive therapy

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Introduction

The prevalence of hypertension in children is on the rise, largely due to the epidemic of obesity and insulin resistance [1]. The definition of hypertension in children has evolved in recent years, and evidence-based normative data have been charted in children on the basis of age, gender, and height [2, 3]. These data have helped establish guidelines for the diagnosis, evaluation, and management of hypertension in children.

Hypertension is defined as average systolic (SBP) and diastolic blood pressure (DBP) >95th percentile for age, gender, and height. Stage one hypertension refers to systolic and diastolic blood pressures that range from >95th percentile to 5 mmHg above the 99th percentile. Stage 2 hypertension refers to systolic and diastolic blood pressures that are 5 mmHg above the 99th percentile for age, gender, and height [2, 3]. In general, secondary hypertension is more common in infancy and childhood and, as adolescence approaches, there is a higher incidence of primary or essential hypertension. Severe hypertension is usually secondary to an underlying disease in children and has not been clearly defined in this population. It is generally defined as 20 mmHg above the 95th percentile. Hypertensive crisis is defined as a sudden and abrupt elevation in blood pressure from baseline. The episode is considered to be a hypertensive emergency when there is an immediate threat to the integrity of the cardiovascular system, kidneys, or central nervous system. Hypertensive urgency is severe hypertension with no acute end-organ damage. Permanent neurological damage, blindness, and chronic renal failure are just a few of the long-term consequences of severe and persistent hypertension. Hypertensive crisis may occur in individuals previously not known to have hypertension or in those known to have chronic hypertension. In adults,

hypertensive crisis is generally characterized by blood pressures which are 50% above normal blood pressures or >180/120 mmHg [4].

Pathogenesis and pathology

The chain of events that lead to an abrupt elevation of blood pressure from its baseline has not yet been precisely elucidated. Experimental evidence on the pathogenesis of hypertensive crisis is based on animal models and adults. The rapidity, degree, and duration of the increase in blood pressure appear to be important factors that initiate hypertensive crisis. Fluid overload, sodium retention, and endothelial dysfunction contribute in varying degrees to the rise in blood pressure.

Blood pressure homeostasis is governed by the interaction of multiple forces involving the cardiovascular system and kidney, and modulated by neural and humoral mechanisms. Tissue perfusion in the kidney, brain, and heart are maintained over a wide spectrum of blood pressure fluctuations by humoral and myogenic mechanisms, resulting in the auto-regulation of blood flow in various organs. End-organ damage from severe hypertension occurs when blood pressure rises above the ranges of auto-regulation [5]. Hypertensive crisis is predominantly angiotensin dependent, with high vascular reactivity, elevated levels of norepinephrine and vasopressin, and decreased levels of vasodilating hormones, such as kininogens, kinins, and prostacyclins [6–13]. Severe hypertension has been demonstrated in adults to be associated with increased sympathetic activity which augments the vasoconstrictive action of angiotensin II. Drugs that reduce sympathetic outflow, such as clonidine, have been demonstrated to lower blood pressure [14, 15]. Angiotensin II facilitates nor-epinephrine release and inhibits reuptake, and potentiates vascular responsiveness to nor-epinephrine [16, 17]. Genetic models of severe hypertension in rats have shown that angiotensin II increases reactive oxygen species, such as the superoxide anion, activates T cells, and promotes vascular inflammation and endothelial dysfunction, thus playing an important role in the pathogenesis of severe hypertension. The effect of angiotensin II can be prevented by tissue angiotensin converting enzyme (ACE) inhibitors [18–21]. Severe hypertension in children with unilateral renovascular disease can manifest with hyponatremia, hypokalemia, and volume depletion as a consequence of pressure natriuresis and hyperaldosteronism [22]. This phenomenon has been observed in experimental animals and adults [13]

The central nervous system plays an important role in the regulation of blood pressure through sympathetic activation and modulation of neuron–humoral factors, such as angiotensin II and vasopressin. The antero–ventral third ventricle region is vital for cardiovascular and fluid homeostasis mediated by behavioral, neural, and humoral factors [23].

Severe hypertension induces changes in the renal arterioles that lead to endothelial damage, platelet and fibrin deposition, and thromboxane release. This cascades into vasoconstriction, ischemia, myointimal proliferation, and decompensation of auto-regulatory mechanisms, resulting in hypoperfusion to the heart, kidney, and brain. A microangiopathic hemolytic anemia and intravascular coagulation develop that mimicking thrombotic thrombocytopenic purpura. This sequence of events leads to proliferative endarteritis and fibrinoid necrosis of the arterial wall [13, 24].

Etiology and clinical features

Some cases of hypertensive emergency or urgency are preventable if stage 1 and 2 hypertension are appropriately treated, and the patient is adherent to treatment. However, there are many cases of unrecognized secondary hypertension due to renovascular hypertension (RVH) or pheochromocytoma or, rarely, hyperaldosteronism.

Neonate

Defining hypertension in the neonate should be based on published norms for gestational and post-natal age. Observations on SBP and DBP in neonates of varying gestational age and birth weight have been compiled [25, 26]. Continuous monitoring of blood pressure in the sick neonate by arterial or oscillometric measurement makes it easy to recognize hypertension when it is well beyond the norm. Hypertension in the neonate is almost always secondary. Renovascular hypertension, coarctation of the aorta, autosomal recessive polycystic kidney disease, and diffuse mesangial hyperplasia are some of the conditions causing severe hypertension in the neonate (Table 1). A complication of umbilical arterial lines in a sick neonate is the formation of renal or aortic thrombi, as well as emboli from aortic thrombi, resulting in renal ischemia and renovascular hypertension. Renal parenchymal disease, renal tumors, such as congenital mesoblastic nephroma, iatrogenic hypercalcemia, and drugs, such as phenylephrine eye drops and, rarely, theophylline, can cause severe hypertension [27, 28]. Acute inadvertent overdose of theophylline in children is associated with hypertension, and the incidence of this complication is 3% [28]. Theophylline toxicity has been associated with increased catecholamine activity, and this could account for hypertension in a small proportion of children. However,

Table 1 Etiology of hypertensive urgency and emergency

Age group	Etiology	History	Physical examination
Newborn	Renal artery and venous thrombosis Autosomal recessive polycystic kidney disease Coarctation of the aorta Congenital nephrotic syndrome (Diffuse mesangial sclerosis) Other renal parenchymal disease Renal artery stenosis Tumor Iatrogenic Mydriatics Theophylline overdose Caffeine overdose	Umbilical artery catheterization Oligohydramnios Prolonged mechanical ventilation Family history of renal disease Medications	Pulse volume and BP in 4 extremities Signs of congestive heart failure Abdominal mass and bruit Ambiguous genitalia
Infancy to 12 years	Renal parenchymal disease Polycystic kidney disease Renovascular disease Tumor Endocrine causes Coarctation of the aorta	Poor feeding Failure to gain weight History of UTI History of low birth weight Family history of renal disease Headache, palpitation, blurred vision Medications Accidental ingestion Excessive weight gain	Heart rate, BMI, Pulse volume and BP in 4 extremities Cardiovascular /pulmonary examination Abdominal mass and bruit Skin rash Peripheral edema Retinal examination Ambiguous genitalia
Adolescence	Essential hypertension Metabolic syndrome Renal parenchymal disease Iatrogenic Anabolic steroids Substance abuse Decongestants Renovascular disease Coarctation of the aorta Endocrine causes	History of fever and/or joint pain History of UTI History of low birth weight Family history of hypertension and renal disease Medications Drug overdose Headache, palpitation, blurred vision	Heart rate, BMI, pulse volume and BP in four extremities Cardiovascular pulmonary examination Thyroid examination Abdominal mass and bruit Skin rash Peripheral edema Retinal examination

BMI, Body mass index; BP, blood pressure; UTI, urinary tract infection

theophylline is a phospho-diesterase inhibitor and stimulates β adrenergic receptors, resulting in peripheral vasodilatation. Therefore, hypotension is a frequently recognized complication. Increased intracranial pressure should also be considered as a cause of severe hypertension.

Clinically an acute rise in blood pressure can manifest as congestive heart failure, hypertensive encephalopathy with seizures, intra-cranial hemorrhage, or renal failure.

When congestive heart failure sets in, blood pressure can be normal or low, thus obscuring the primary cause of congestive heart failure until cardiac function has improved [29]. Recognizing hypertension in a previously healthy infant can be a challenge. Initial symptoms, such as emesis and poor feeding, may be non-specific, and it is not uncommon for the presentation to be catastrophic with overt signs of end-organ damage, such as congestive heart failure or hypertensive encephalopathy with seizures.

Childhood

Hypertensive crisis in early and mid-childhood is rare. Renal artery stenosis, reflux nephropathy, hemolytic uremic syndrome, acute glomerulonephritis, renal parenchymal disease, chronic renal insufficiency, coarctation of the aorta, and neuro-endocrine tumors need to be considered. The child may have symptoms of hypertension, such as headache and blurred vision, and disease-specific symptoms, such as edema, pallor, and petechiae.

Adolescents

In adolescents, glomerular disease, collagen vascular disease, renal artery stenosis, reflux nephropathy, chronic renal insufficiency, coarctation of the aorta, and neuro-endocrine tumors can cause hypertensive crisis if hypertension has previously been undiagnosed or not adequately controlled. Substance abuse, specifically with cocaine, amphetamines, hallucinogens, and drug overdose with over-the-counter cold remedies containing pseudoephedrine, phenylpropanolamines, nonsteroidal anti-inflammatory drugs (NSAIDS), and monoamine oxidase inhibitors (MAOI) should be a strong consideration in adolescents [30–32]. Essential hypertension rarely causes hypertensive crisis.

Hypertension in patients on chronic dialysis

Hypertension is highly prevalent in children on chronic hemodialysis (HD) and is one of the etiological factors contributing to morbidity and mortality [33, 34]. Chronic hypertension leads to left ventricular hypertrophy and dysfunction and ultimately compromises cardiac function. The etiology is multifactorial, and hypertensive crisis can occur from a combination of factors. Extracellular volume expansion is one of the most important contributors to hypertension, which is further influenced by salt intake. There is an increase in cardiac output and peripheral resistance. The latter is triggered by inappropriately high angiotensin II levels. The primary disease may be mediating hypertension by activating the renin–angiotensin system. There is also evidence of sympathetic overactivity in patients on HD [35]. Secondary hyperparathyroidism, uremic toxins, such as homocysteine, and the use of erythropoietin are contributing factors to hypertension. Non-compliance with anti-hypertensive medications may play an important role in hypertensive crisis in patients with end-stage renal disease (ESRD). Endothelium-dependent vasodilatation is impaired in uremia, thus creating an imbalance between vasodilatory and vasoconstrictive forces in the vascular endothelium and resulting in increased peripheral resistance and vascular smooth muscle proliferation [34].

Hypertension in children with ESRD is very difficult to manage and consequently may result in hypertensive emergency or urgency.

Renovascular hypertension

Renovascular hypertension constitutes 5–10% of childhood hypertension [36, 37]. Fibromuscular dysplasia, neurofibromatosis type I, tuberous sclerosis, Takayasu's arteritis, middle aortic syndrome, and Williams syndrome are some of the primary conditions that result in renal arterial stenosis and renal ischemia [37, 38]. Recent technological advances have improved the diagnostic yield of non-invasive investigations of renal artery stenosis. Imaging studies include Doppler renal ultrasound, radio-isotope renograms with ACE inhibitors, high-resolution computed tomographic (CT) angiography, and magnetic resonance (MR) angiography [37, 38]. Non-invasive imaging studies, such as CT and MR angiography, have become more sensitive in detecting main renal artery stenosis and may be used as the investigative tool of choice when renovascular hypertension is highly suspected. However, they may not be sufficiently sensitive for assessing intra-parenchymal renal arteries [39]. The sensitivity and specificity of CT and MR angiography are not known in infants and young children in whom the renal arteries are small. Doppler renal ultrasound is less sensitive than CT or MR angiography in diagnosing renal artery stenosis [38]. Renal angiography is still the gold standard for definitive diagnosis. Digital subtraction angiography appears to be the most accurate diagnostic tool for assessing renovascular disease in children [37]. In children with renal insufficiency, the use of iodinated contrast can be minimized by CO_2 angiography. However, experience with this technique in children is limited [39].

Hypertension in the post-transplant period

Severe hypertension can be seen in the post-transplant period as a result of kinking of the renal artery or acute obstruction [40, 41]. Acute calcineurin inhibitor toxicity and thrombotic micro-angiopathy can cause renal vasoconstriction and should be considered when the onset of hypertension is acute [42]. Sirolimus potentiates the micro-angiopathy induced by calcineurin inhibitors [43]. High-dose steroids and fluid overload in the phase of a donor kidney recovering from ischemic insults are also major contributors. Severe rejection can result in microangiopathy and lead to hypertensive crisis [40, 41].

Hypertension and hypercalcemia

Hypercalcemia can cause severe hypertension [44]. Primary hyperparathyroidism, which is rare in children, can result in severe hypercalcemia and hypertension [45]. Although the mechanism is not clear, in patients with chronic kidney disease (CKD) and ESKD, tertiary hyperparathyroidism may contribute to severe hypertension. Iatrogenic causes of hypercalcemia from excessive use of vitamin D analogs should be considered [46].

Hypertension from endocrine causes

Pheochromocytoma

Severe hypertension, which can be paroxysmal or sustained, can be seen in pheochromocytoma. Associated symptoms are

headache, perspiration, and palpitation. Panic attacks, pallor, tremors, and weight loss can occur. Pre-operative and intra-operative management of blood pressure is important to minimize morbidity and mortality. Selective α_1 antagonists and, if necessary, followed with β blockers after an adequate α blockade has been achieved is the initial step in managing hypertension. Fluid and salt repletion is important when α blockers are used to prevent hypotension [47]. Calcium channel blockers have also been successfully used pre-operatively and intra-operatively to control blood pressure.

Severe and refractory hypertension can be a feature of monogenic hypertension, as seen in apparent mineralocorticoid excess (AME), Liddle's syndrome, and glucocorticoid remediable aldosteronism. Rare forms of congenital adrenal hyperplasia, such as 11β hydroxylase and 17α-hydroxylase deficiency, can cause severe hypertension [48].

Hypertension from neurological causes

Autonomic instability is a feature of Guillain–Barre syndrome and familial dysautonomia [49]. Intermittent severe hypertension and orthostatic hypotension characterize the clinical course of some of these patients. Severe hypertension with bradycardia is a feature of increased intracranial pressure. Hypertension in this context should be approached cautiously and should be primarily directed at decreasing the intracranial pressure. Hypertensive crisis can result in hypertensive encephalopathy from cerebral hyperperfusion, endothelial dysfunction, microvascular injury, and cerebral edema. This in turn can be manifested as posterior reversible encephalopathy (PRES) in imaging studies [50]. Changes are noted in the posterior cerebral cortex and can be considered to occur from vasogenic edema. Acute onset of hypertension is the most common cause of PRES and is often a trigger in other conditions, such as treatment with immunosuppressive drugs, vasculitidis, and renal insufficiency [51, 52]. Endothelial dysfunction and nitric oxide depletion are some of the proposed mechanisms for the development of PRES [52]. Clinical symptoms consist of altered mental status, headaches, and seizures.

Rebound hypertension can occur with the withdrawal of certain drugs, such as clonidine, β blockers, and ACE inhibitors [53, 54].

Diagnosis

The mercury sphygmomanometer was originally the gold standard for measuring blood pressure. In infants and pre-adolescent children, the first and fourth Korotkoff sounds (the fifth Korotkoff sound may not disappear until the pressure is very low) represent the SBP and DBP, respectively. Environmental and medical safety hazards of mercury have resulted in a decline in the use of mercury sphygmomanometers, leading to increased use of aneroid and oscillometric devices to measure blood pressure. Care should be taken to ensure that they are validated and periodically checked and calibrated for clinical accuracy. Aneroid sphygmomanometers in particular need frequent calibration. The Association for the Advancement of Medical Instrumentation (AAMI) requires that the average difference in blood pressure readings between two devices should not exceed 5 mmHg and the standard deviation should be less than 8 mmHg. An up-to-date list of validated blood pressure measuring devices is available on the DABL educational website (http://www.dableducational.org) [55]. Auscultatory devices for measuring blood pressure are inaccurate in infants and young children as the Korotkoff sounds are often difficult to hear. Non-invasive blood pressure measurements with validated oscillometric devices correlate well with arterial blood pressure measurements in infants [56].

Direct measurement of arterial blood pressure is useful when continuous monitoring of blood pressure is desirable, as in an acutely ill, hemodynamically unstable patient in the intensive care unit and for intra-operative monitoring. The transducer measuring the pressure should be calibrated to zero at the level of the heart. Improper zeroing of the transducer and the presence of a thrombus at the catheter tip or an air bubble will result in inaccurate measurements. Furthermore, the transducer has a natural frequency at which it oscillates, and signals of the same wavelength could be amplified, resulting in an exaggerated value [57]. The advantage of direct blood pressure measurements is the ability to have continuous readings. Aortic blood pressure measurements have been compared with the Dinamap non-invasive blood pressure measuring device (GE Healthcare, Waukesha, WI) in neonates and young children [58]. In this study, 94% of SBP and 97% of DBP readings by Dinamap were within 10 mmHg of aortic blood pressure measurements [58]. The disadvantage of the Dinamap is that vigorous respiratory activity and crying cause wide swings in arterial blood pressure. Inflation and deflation of automated devices every few minutes can decrease perfusion to the limb and impede venous return [58].

If blood pressure is measured non-invasively, it should be undertaken when the patient is calm and with the appropriately sized cuff. The reading should be verified several times before action is taken.

In all age groups, a thorough history is important to determine if there is an underlying acute or chronic illness. A determination should then be made if hypertension is acute, or acute upon chronic. Investigations should be tailored towards making a diagnosis and determining the extent of end-organ damage. The physical examination should be complete and should include examination of the

cardio-respiratory system, abdomen, genito-urinary system, thyroid, retina, and skin and four limb pulses and blood pressures (Table 1). Laboratory studies should include urine analysis, serum chemistries (sodium, potassium, chloride, serum total carbon dioxide, glucose, magnesium, calcium, phosphorous, total protein, albumin), plasma renin, aldosterone, and, if necessary, urine catecholamines. Other laboratory studies to be considered include serologic investigations for vasculitis, fasting lipid profile, and serum insulin depending on the history and clinical presentation. Urine analysis may reveal microscopic hematuria in the case of renovascular hypertension or proteinuria and casts in renal parenchymal disease. Electrolyte abnormalities include hypokalemic alkalosis in RVH or low renin hypertension, and evidence of renal dysfunction.

Renal ultrasound with Doppler of the renal arteries is a useful screening test to investigate hydronephrosis, renal blood flow and velocities, and renal parenchymal disease. The size of the kidneys could help establish the chronicity of kidney disease. After stabilization of the patient, objective evidence of end-organ damage should be sought and should include an echocardiogram and ophthalmologic examination.

Management

It is important to determine if hypertension is acute or chronic. However, this history may not be available and, therefore, the blood pressure should not be lowered too fast. Autoregulation of the blood flow may be altered and reset in vital organs in chronic hypertension, and rapid lowering of blood pressure can result in hypo-perfusion to vital organs, particularly the visual cortex and brain. The Food and Drug Modernization Act (FDAMA) of 1997 enabled clinical trials of anti-hypertensive agents in children. Although several oral anti-hypertensives have been tested, intravenous drugs used in hypertensive crisis are yet to be studied in clinical trials. As a result, most of the anti-hypertensives used in hypertensive crisis are off-label, with the exception of hydralazine [4, 59].

Management of hypertensive crisis

An intravenous drip is the preferred way to handle a hypertensive crisis as drug dosing can be titrated. Clinical experience suggests that the initial drop in blood pressure should not be more than 25–30% of the original value accomplished over a period of 6–8 h and followed by a gradual reduction within 24–48 h [3]. The choice of anti-hypertensive medication depends on the etiology of hypertension with an agent that has a rapid onset of action, has a short half life, and is safe and efficacious. In young children, quick placement of an intravenous (IV) access may not be immediately possible.

Table 2 lists the drugs used in hypertensive crisis, and Fig. 1 provides an algorithm for the treatment of hypertensive crisis (Fig. 1). Intravenous nicardipine is a dihydropyridine calcium channel blocker that reduces peripheral vascular resistance. It does not have a negative inotropic effect and can be used in the presence of bronchospasm and in patients with hepatic and renal failure. Its half life is 10–15 min, and the onset of action is within 15 min. It has been reported to be well-tolerated and efficacious [60, 61]. Tachycardia and flushing are side-effects of therapy. Nicardipine can be used for a longer period of time without the fear of cyanide toxicity and may be considered as the first line of therapy in children with hypertensive crisis.

Labetalol is an α and β sympathetic blocker which reduces peripheral vascular resistance. It has a relatively long half life (3–5 h), and this should be taken into account when titrating the dose of the drug. It should not be used in patients with bronchospastic disease or congestive cardiac failure as it has a negative inotropic effect. It should also be used with caution in children with diabetes. Caution should also be exercised in children with brain injury as they are more likely to develop hypotension [62, 63]. Labetalol has the potential to worsen hyperkalemia, and this has to be considered in children with impaired kidney function. This drug can be given as an intravenous bolus, which can be advantageous when an infusion cannot be started quickly.

Esmolol is used in hypertensive crisis and is particularly beneficial when there is associated tachycardia. β blockers reduce cardiac contractility and should not be used in acute decompensated heart failure, but they are used in adults with chronic stable heart failure [64]. No randomized clinical trials have yet studied theses drugs in acute heart failure.

Esmolol is a cardioselective β blocker that is rapidly acting and has a half life of 10 min. It is particularly useful after the repair of congenital heart disease. However, it can cause congestive heart failure, bradycardia, and bronchospasm. It should not be used when hypertensive crisis is caused by catecholamine excess as hypertension is perpetuated by persistent alpha stimulation [65].

Fenoldopam has a favorable safety profile and can be used in renal insufficiency [66]. It is a rapidly active vasodilator and is a selective dopamine$_1$ receptor agonist that binds with moderate affinity to α adrenoreceptors. The advantages of this drug are that it increases renal blood flow and urinary flow and induces natriuresis. The effective dose is significantly higher in children (0.8–1.2 mcg/kg/min) than in adults [67]. It is not associated with the accumulation of toxic metabolites.

IV hydralazine has been used in certain situations, particularly in neonates and pregnant teenagers, to control severe hypertension. In very sick and low-birth-weight neonates for whom enteral administration of medications is not possible, IV hydralazine is a good therapeutic option. It is a potent arterial vasodilator with an onset of action within 10 min, and its effect

Table 2 Management of hypertensive crisis

Drug used in therapy	Class	Route	Dose	Adverse effects
Hypertensive emergency				
Nicardipine	Ca^{++} channel blocker	IV	1–3 mcg/kg/min	Headache; increased intracranial pressure
Clevidipine	Ca^{++} channel blocker	IV	0.5–3.5 mcg/kg/min	Contraindicated in lipid disorders, egg, and soy allergy
Labetalol	α and β blocker	IV infusion bolus	0.25–1.5 mg/kg/hr 0.2–1 mg/kg/dose Maximum 20 mg/dose	Use with caution in hyperkalemia and CHF
Esmolol	β blocker	IV	Bolus 100–500 mcg over 1 min; 25–100 mcg/kg/min; can increase to 500 mcg/kg/min	Can cause CHF, bradycardia and brochospasm; contra-indicated in cocaine toxicity
Phentolamine	α blocker	IV	0.1–0.2 mg/kg/dose	Orthostatic hypotension, tachycardia, gastro-intestinal disturbances
Fenoldapam	Dopamine receptor agonist	IV	0.8–3.0mcg/kg/min	Tachycardia; increased intracranial pressure
Hydralazine	Vasodilator	IV	0.1–0.5 mg/kg/dose. every 4-6 h	Tachycardia, flushing, Lupus like syndrome
Sodium nitroprusside	Vasodilator	IV	0.5–0.8mcg/kg/min	Thiocyanate toxicity with decreased renal function
Enalaprilat	ACE inhibitor	IV	0.005–0.01 mg/kg/day	Acute renal failure and hyperkalemia
Hypertensive urgency				
Furosemide	Diuretic	IV/PO	1–2 mg/kg/dose	Electrolyte disturbances
Isradipine	Ca^{++} channel blocker	PO	0.05–0.1 mg/kg/dose up to 5 mg/dose	Tachycardia ; headache
Nifedipine	Ca^{++} channel blocker	Sub-lingual / PO	0.1–0.25 mg/kg/dose	Precipitous drop in blood pressure; tachycardia; headache
Clonidine	Central α agonist	PO	0.05–0.3 mg	Rebound hypertension; sedation
Minoxidil	Vasodilator	PO	0.1–2 mg/kg/dose	Pericardial effusion

IV, Intravenous, PO, orally; ACE, angiotensin-converting enzyme; CHF, congestive heart failure

lasts for 2–4 h. It can be administered intramuscularly when immediate IV access is not available. The side-effects of hydralazine are tachycardia and sodium retention [59].

Sodium nitroprusside has a rapid onset of action and reduces pre-load and after-load; consequently, it is beneficial in congestive heart failure induced by hypertensive crisis. This drug has been used for many years in the treatment of hypertensive crisis in children [68]. The dose can be titrated effectively and rapidly. It is an arterial and venous vasodilator and does not cause somnolence. Use of the drug for more than 24–48 h can lead to an accumulation of thiocyanate, especially in the presence of renal and hepatic insufficiency. Thiocyanate poisoning can cause methemoglobinemia, metabolic acidosis, altered mental status, and seizures. Sodium nitroprusside can increase intracranial pressure.

Enalaprilat is the only available IV ACE inhibitor that can be effective in renin-mediated hypertension. However, limited data are available on its use in children with hypertensive crisis [69, 70]. Its onset of action is 15 min, and its effect can last 12–24 h. It should not be used in the presence of renal insufficiency and hyperkalemia, and it should be avoided in neonates as it can result in renal failure [34, 69, 70]. It's use is contraindicated in pregnancy.

Clevidipine is an ultrashort-acting, third-generation IV dihydropyridine calcium channel blocker with a rapid onset. It produces arteriolar dilatation without having negative inotropic or chronotropic effects on the heart. There is no dose modification for liver or kidney failure. Its use in children has been reported in the peri-operative period. It is inactivated rapidly by tissue and blood esterases, making dose titration easy. Clevidipine can be used in situations where tight control of blood pressure is crucial. It is an oil emulsion and is water insoluble. It should not be used in children with egg and soy allergy and is contraindicated in patients with lipid disorders [71].

Phentolamine, phenoxybenzamine, prazosin, and doxazocin are α adrenergic blockers that are used in catecholamine-induced hypertension, as in pheochromocytoma [72]. Pre-operative management should include sodium and volume repletion to prevent hypotension. Once alpha blockade is achieved, β blockers may be used—if necessary—to counteract tachycardia. Calcium channel blockers have also been proven to be beneficial in the management of catecholamine-induced hypertension.

Severe hypertension from fluid overload in children with ESRD requires emergent ultrafiltration and dialysis. However,

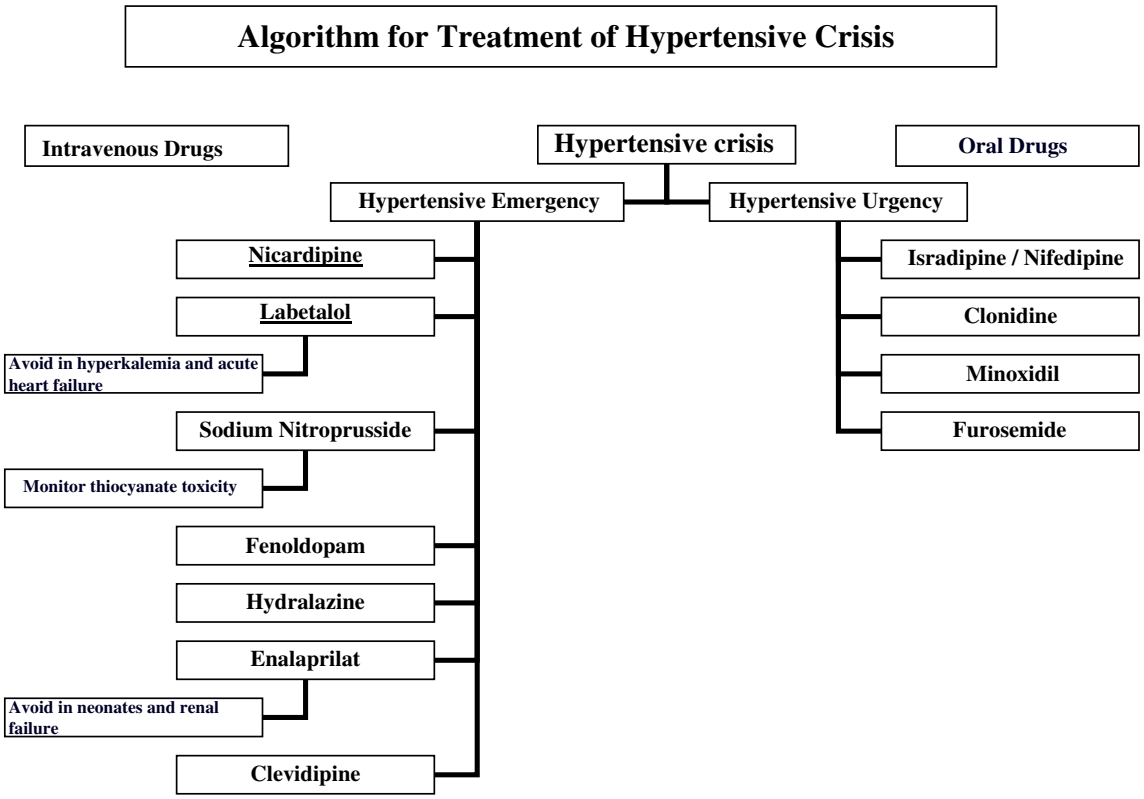

Fig. 1 Algorithm for treatment of hypertensive crisis

if the child is in congestive cardiac failure, inotropic agents with vasodilator properties will need to be used to stabilize the patient. Continuous venovenous hemofiltration would be a suitable option for fluid removal in a hemodynamically unstable patient. In patients who have residual urine output, high-dose furesomide can induce diuresis and alleviate hypertension. Diuretics can be effective in severe hypertension caused by acute glomerulonephritis.

IV or transdermal nitroglycerin is generally not used as the first line of therapy and has not been used in children. It is a venodilator and therefore reduces pre-load and cardiac output. It can cause methemoglobinemia, hypoxemia, reflex tachycardia, and tachyphylaxis. It is usually considered in adults as adjunctive therapy for acute coronary syndromes [73].

Long-acting oral medications should be introduced in a conscious child after the blood pressure has been reasonably controlled within 24–48 hours of commencement of the continuous infusion of the anti-hypertensive. The rate of IV infusion is then slowly decreased. Prolonged use of IV anti-hypertensive agents may result in sodium and water retention and tachyphylaxis.

Management of hypertensive urgency

In hypertensive urgencies, the patient is asymptomatic and does not have evidence of an immediate end-organ injury. Therefore, oral agents can be used to gradually lower the blood pressure. Oral Isradipine has also been used with good response in severe hypertension and can be used as a suspension in infants [74, 75]. It is a dihydropyridine calcium channel blocker that is efficacious and safe. Nifedipine is often used in children with severe hypertension because of its ease of administration and efficacy [76]. However, accurate dosing is a problem in young children, and the rate of drop in blood pressure is unpredictable. Serious adverse events, such as myocardial infarction and death, have been reported in some adults with precipitous drops in blood pressure. There are a few reports of adverse events in the pediatric population, such as cardiac arrhythmias [77]. If IV access cannot be obtained quickly, the judicious use of nifedipine with the lowest effective dose is recommended. In older children, clonidine and minoxidil can be given orally in a conscious child. Clonidine is a centrally acting α_2 adrenergic agonist that decreases cerebral sympathetic output. It has a fairly rapid onset of action in 15–30 minutes and can be used in renal failure, particularly in older children and adolescents [59, 78]. Excessive use can cause sedation and dry mouth. It has a narrow safety profile in young children. Minoxidil is also quite effective in severe hypertension [79]. Prolonged use can result in hirsutism and pericardial effusion [80].

Management of renovascular hypertension

Management of hypertension can be very challenging, especially in very young children and in those with involvement of intra-renal arteries. Due to the size of the involved vessels, endovascular or surgical intervention may not be possible. These children may need conservative medical management, and, in some cases, a carefully monitored therapeutic trial of an ACE inhibitor or angiotensin receptor blocker [37]. An ACE inhibitor may be used in the absence of bilateral renovascular disease or a solitary kidney [81]. However, ACE inhibitors should be avoided or used with extreme caution in neonates with renovascular hypertension due to the risk of renal failure [82]. Moreover, plasma creatinine may be normal, and subtle deterioration in the renal function of the uninvolved contralateral kidney may be evident only by renal scintigraphy [81]. Conventional renal angiography is indicated when an angioplastic or surgical intervention is planned and to diagnose branch renal artery stenosis. Renal arterial interventions should be performed by physicians with technical expertise in performing interventional procedures in children. Percutaneous trans-luminal renal angioplasty is preferred, and stenting is generally avoided in children unless dictated by circumstances [37, 39]. Arterial spasm and thrombosis may be complications of these procedures. Those patients with single vessel and mid-main renal arterial disease have the best outcome [39]. Surgical treatment such as revascularization and auto-transplantation may need to be considered in some cases. Nephrectomy may be indicated when the source of hypertension is a small, poorly functioning kidney [36]. Many children continue to need anti-hypertensive therapy even after interventional procedures [39, 78].

Conclusions

Hypertensive crisis is a medical emergency that results in acute end-organ damage and requires judicious management. It is important to determine the circumstances leading to an acute elevation in blood pressure so that an appropriate reduction in blood pressure can be achieved without compromising the perfusion of vital organs. Acute neurological complications, visual loss, and acute renal failure have been described with rapid reductions in blood pressure in children [83, 84]. In some situations, morbidity and mortality from hypertensive crisis can be avoided if chronic hypertension is well-managed. In hypertensive crisis, IV infusions of anti-hypertensives are preferred to manage the controlled decrease in blood pressure.

In children, nicardipine, labetalol, and sodium nitroprusside are the most frequently used IV drugs. The choice of anti-hypertensive agent should be geared toward the primary etiology of hypertension.

Questions (answers appear following the references)

A. The pathogenesis of hypertension in hypertensive crisis is all of the following except:

1. Increased activity of the renin angiotensin system
2. Increased nitric oxide activity
3. Increased sympathetic activity
4. Endothelial dysfunction
5. Decreased kininogen activity

B. A 45-day-old premature infant who weighed 700 g at birth is being weaned from oxygen to room air. An ophthalmologist performed an eye exam. The infant was noted to have an acute increase in blood pressure from a baseline of 70/40 mmHg to 130/70 mmHg with tachycardia. The most likely etiology is:

1. History of umbilical artery catheterization
2. Development of broncho-pulmonary dysplasia
3. Phenylephrine eye drops
4. Renal parenchymal disease
5. Coarctation of aorta

C. A 5-year-old female had a living donor kidney transplant. Seven days after the transplant she had a seizure. Her blood pressure was 170/120 mmHg, and her serum creatinine was 0.8 mg/dl. Calcineurin inhibitors were started on the third post-transplant day, and she was also started on mycophenolate mofetil. She is polyuric. What would you most likely expect to find upon investigation.

1. Posterior reversible encephalopathy
2. Acute vascular rejection
3. Fluid overload
4. Increased intracranial pressure
5. High mycophenolate mofetil levels

D. An 8-year-old male has ESRD and is on hemodialysis. He had severe hypertension which improved with aggressive fluid removal and re-adjustment of his dry weight. His hypertension was managed with β blockers, clonidine and a calcium channel blocker. Blood pressures are now generally 110/80 mmHg. Which of the following would you consider as the next step.

1. Wean clonidine
2. Stop calcium channel blocker
3. Increase β blocker
4. Increase dry weight
5. All of the above

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Answers:

A: 2
B: 3
C: 1
D: 1