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# Antihypertensive Management in Children: A Two-years Experience of Indonesia's National Referral Hospital

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## ABSTRACT

**Objectives:** The prevalence of hypertension (HT) in children has increased overtime. However, data related to antihypertensive options and outcomes are still limited in children, especially in Indonesia. This study aimed to describe pediatric HT cases and antihypertensive management in Cipto Mangunkusumo General Hospital (CMGH).

**Methods:** A retrospective cross-sectional study was conducted in CMGH from January 2016 to December 2017. Inclusion criteria were children age <18 years with primary and secondary HT visiting pediatric nephrology clinic. Patients were excluded if no blood pressure records were found. Clinical and antihypertensive treatments data were recorded from medical records. Diagnosis was based on the Fourth Report classification.

**Results:** This study included 176 children with HT. Secondary HT was found in 159 (90.3%) patients, and 82 (51.6%) of them had isolated kidney–urinary tract disease. Dual antihypertensive therapy was prescribed for 53 (30.1%) patients, whereas 55 (31.3%) patients was monotherapy. The most common antihypertensive used in monotherapy was angiotensin converting enzyme inhibitors (ACEI), received by 31 (56.3%) patients. The median duration of therapy until achievement of target blood pressure was 28.0 (1.0–365.0) days.

**Conclusion:** Pediatric HT is an often overlooked growing medical issue. Secondary HT was found more in children compare to primary HT. Secondary etiology was suspected if HT was found in children with kidney disease. The first-line antihypertensive drug used was ACEI, as single or combination therapy. The therapeutic effect of antihypertensive drugs was expected within 28 days of treatment.

**Keywords:** Antihypertensive agents, children, hypertension, essential hypertension



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## INTRODUCTION

Hypertension (HT) has been increasingly prevalent in the pediatric population, particularly in prepubertal age. Different from adults, in which the primary or essential HT is more prominent, the etiology of HT in children is predominated by secondary HT, especially in the younger age group. Primary HT may arise from genetic causes or an unhealthy lifestyle. By contrast, secondary HT develops from a specific disease entity or medication intake, including kidney parenchymal or renovascular diseases, high dose corticosteroid consumption, and heart or endocrine disorders. The majority of causes of secondary HT in children is kidney disease.<sup>[1,2]</sup> Despite the greater proportion of primary HT affecting adolescents, the trend has shifted toward younger age because of the emergence of pediatric obesity.<sup>[3]</sup>

Several factors, including unfavored perinatal events, nutritional status, and comorbidities are

evident to contribute to the development of HT in children. Edvardsson et al. showed that low birth weight was associated with elevated blood pressure (BP) in children.<sup>[4]</sup> A retrospective cohort study showed that the prevalence of HT is 7.3% among 3-year-old children who were born prematurely.<sup>[5]</sup> Overweight and obese children show a higher prevalence of HT with estimates of 4%–14% and 11%–23%, respectively.<sup>[6–9]</sup> The HT rate among children and adolescents with chronic kidney disease (CKD) is approximately 50%.<sup>[10–12]</sup> Furthermore, approximately 48%–79% of those with end-stage kidney disease, including those on dialysis and who underwent kidney transplant were hypertensive, with 20%–70% of them having uncontrolled HT. Approximately 20% of pediatric HT may be accountable to CKD.<sup>[13–16]</sup>

The cause and severity of HT determine the approach of treatment. Management ranges from dietary and lifestyle modification to multiple antihypertensive drugs. Because the evidence of the effectiveness of antihypertensive therapies in children is still limited, the first-line antihypertensive agent for primary HT is determined by preference of the treating physician. The most common agents prescribed are angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), or calcium channel blockers (CCB). Beta-blockers or diuretics are usually avoided for initial therapy due to concerns about the anticipated side effects. On contrary, treatment for secondary HT depends on the pathophysiologic mechanism of the underlying disease.<sup>[2]</sup> This study aimed to describe pediatric HT cases and antihypertensive management in Cipto Mangunkusumo General Hospital (CMGH).

## METHOD

This study was a retrospective descriptive study including all children with primary and secondary HT from birth to 18 years who visited the pediatric nephrology clinic at CMGH. Exclusion criteria were unavailable BP records of patients. Clinical and antihypertensive medication data were collected retrospectively from manual and electronic medical record. Clinical data recorded were gender, age, history of prematurity, family history of HT, history of high-dose corticosteroid exposure, nutritional status, type of kidney replacement therapy (KRT), type of HT, etiology of HT, history of hypertensive crisis, and HT related complications. Nutritional status was assessed by using World Health Organization z-score for children 0–5 years old and Centers for Disease Control and Prevention (CDC) percentile for children above 5 years old. Children age 0–5 years old with weight to length/height z-score < -2 SD were considered underweight, -2 SD to 2 SD was considered normal, >2 SD were considered overweight or obese. Children above 5 years old whose weight to length/height < 3<sup>rd</sup> percentile were

considered underweight, 3<sup>rd</sup>–95<sup>th</sup> percentile were considered normal, >95<sup>th</sup> percentile were considered overweight or obese. Overweight and obese children were measured for body mass index (BMI) and plotted to CDC BMI percentile. BMI >85<sup>th</sup> percentile and ≤95<sup>th</sup> percentile was considered overweight and BMI >95<sup>th</sup> percentile was considered obese.<sup>[17,18]</sup>

The type of HT was classified as primary, secondary, and postponed. Patients who remained under observation or had not completed an evaluation to determine the underlying diagnosis were classified as postponed HT diagnosis. Antihypertensive treatment data consisted of treatment duration, class of drug, choice of drug, combination of drugs, and time to reach target BP.

All patients who visited our clinic had their BP assessed. BP was measured thrice, and the mean was recorded. All BP measurements were initially performed by oscillatory devices, then confirmed by manual auscultation with a mercury sphygmomanometer by trained health staff using methodology recommended by the Fourth Report. HT in children was defined as a systolic and/or diastolic BP above the 95<sup>th</sup> percentile for age and gender on at least three separate measurements. Management of HT in children was started with lifestyle modification and administration of antihypertension drugs accordingly.<sup>[2]</sup>

All analyses were performed using SPSS version 20.0 (IBM Corp. Armonk, NY, IBM Corp). Continuous variables were expressed as median, minimum and maximum depending on the variable distribution. Categorical variables were expressed as frequency and percentage.

## RESULTS

The study included 176 children with HT. Based on the etiology, 11 (6.3%) children were diagnosed as having primary HT, 159 (90.3%) children were secondary HT and 6 (3.4%) children were postponed HT. The median age of first HT diagnosis was 8.8 (0.0–17.5) years. The highest case of HT was found in 6–12 years old group, with 71 (40.4%) children. Secondary HT caused by congenital adrenal hyperplasia (CAH), Castleman disease, congenital cystic adenomatoid malformation (CCAM), epilepsy, cerebral palsy, intracranial benign HT were respectively found in 1 (0.006%) child. Meanwhile, intracranial infection and obstructive sleep apnea was respectively found in 2 (0.013%) children with secondary HT.

This study found 21 (11.9%) obese, 5 (2.8%) overweight, 140 (79.6%) normal weight, and 10 (5.7%) underweight children. Approximately 135 (76.7%) of patients were administered high dose corticosteroid. Due to incomplete medical records, we were only able to obtain 122 (69.3%)

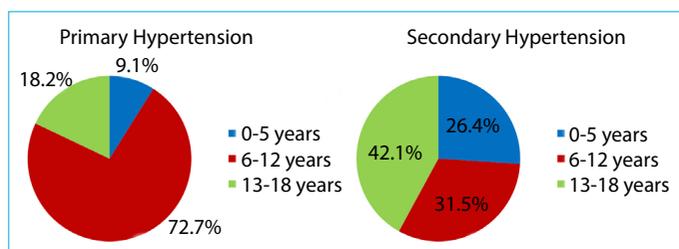
prenatal history and 115 (65.3%) family history of HT. In addition, 3 (2.5%) children were delivered preterm, and 7 (6.1%) children had a family history of HT. Six (22.2%) children died, and the cause of death was sepsis and respiratory failure. Among 162 (92.0%) of 176 patients recorded, 13 (8.0%) had experienced hypertensive crisis during study period. Complications following the course of HT were evident in 27 (15.3%) patients. The demographic and clinical characteristics of the patients are summarized in Table 1.

Primary HT was found in 8 (72.7%) children in the 13-18 age group, while secondary HT was found in 67 (42.1%) children in the 6-12 age group. The proportion of primary and secondary hypertension based on age groups are shown in Figure 1.

It was found that 24 (13.6%) patients with HT in our center had not received pharmacological HT therapy. The most common antihypertensive used in monotherapy was ACEI, which was administered to 31 (56.3%) patients. It was observed that ACEI and ARB combination was the most prescribed dual therapy in 26 (49.0%) patients. It was followed 84 (47.7%) patients from the first antihypertensive administration until achievement of normal BP. The median duration of antihypertensive therapy until achievement of target BP was 28.0 (1.0–365.0) days. Antihypertensive drugs used by patients are summarized in Table 2.

## DISCUSSION

Our hospital is the national tertiary referral hospital that served complete subspecialty services, including pediatric nephrology. In our pediatric nephrology clinic, primary, and secondary HT were diagnosed in 6.3% and 90.3% of children, respectively. Almost all patients were referred from other healthcare facilities, and they commonly had uncontrolled BP before their visit to CMGH. Therefore, their exact age at diagnosis and duration of therapy were difficult to record. Gupta-Malhotra et al. found that the mean age of children with primary and secondary HT was  $11.7 \pm 3.7$  years and  $8.7 \pm 6.1$  years, respectively.<sup>[1]</sup> This study showed the younger age of diagnosis in both groups due to slightly different research approach. Gupta-Malhotra combined the



**Figure 1.** The proportion of primary and secondary hypertension based on age groups.

**Table 1.** Demographic and clinical characteristics of the patients

	n (%)
Gender (n=176)	
Male	87 (49.4)
Female	89 (50.6)
Age of diagnosis (n=176)	
0-5 years	43 (24.4)
6-12 years	71 (40.4)
13-18 years	62 (35.2)
History of high dose systemic corticosteroid (n=176)	
No	41 (23.3)
Yes	135 (76.7)
Etiology of secondary HT (n=159)	
Autoimmune*	42 (26.4)
Isolated kidney disease <sup>†</sup>	82 (51.6)
Malignancy <sup>‡</sup>	17 (10.7)
Cardiac <sup>§</sup>	2 (1.3)
Part of syndrome <sup>  </sup>	1 (0.6)
Combination	5 (3.1)
Others <sup>¶</sup>	10 (6.3)
KRT modalities (n=12)	
Continuous ambulatory peritoneal dialysis	2 (16.7)
Hemodialysis	8 (66.6)
Combination	2 (16.7)
Complications (n=27)	
Hypertensive retinopathy	5 (18.5)
Stroke	1 (3.7)
Seizure	8 (29.7)
Hypertensive encephalopathy	6 (22.2)
Intracranial bleeding	1 (3.7)
Mortality	6 (22.2)

HT: Hypertension; KRT: Kidney replacement therapy.

\*Autoimmune disease: Systemic lupus erythematosus, Henoch-Schönlein purpura, Crohn's disease, transverse myelitis, juvenile idiopathic arthritis.

<sup>†</sup> Isolated kidney disease: Nephrotic syndrome, nephritic syndrome, acute post-streptococcal glomerulonephritis, congenital anomalies of the kidney and the urinary tract, renal tubular acidosis, tubulopathy, nephropathy.

<sup>‡</sup> Malignancy: Acute lymphoblastic leukemia, chronic myelogenous leukemia, central nervous system tumor, neuroblastoma, malignant lymphoma, osteosarcoma, hepatocellular carcinoma.

<sup>§</sup> Cardiac disease: Congestive heart failure, atrial septal defect.

<sup>||</sup> Syndrome: Mulvihill Smith syndrome.

<sup>¶</sup> Other causes: Congenital adrenal hyperplasia, Castleman disease, intracranial infection, congenital cystic adenomatoid malformation, epilepsy, cerebral palsy, benign intracranial hypertension, obstructive sleep apnea.

hospital-based and population-based population, so they also screened healthy children. Children with early course of HT might not show any clinical symptoms. In contrast, because our study was a hospital-based study only, pa-

**Table 2.** Antihypertensive drugs used by patients

	n (%)
Antihypertensive therapy (n=176)	
Not given	24 (13.6)
Monotherapy	55 (31.3)
Dual therapy	53 (30.1)
Triple and more therapy	44 (25.0)
Monotherapy: class of drug (n=55)	
ACEI	31 (56.3)
ARB	14 (25.5)
CCB	9 (16.4)
Other	1 (1.8)
Monotherapy: choice of drug (n=55)	
Captopril	22 (40.0)
Lisinopril	8 (14.5)
Losartan	5 (9.1)
Valsartan	10 (18.2)
Amlodipine	7 (12.7)
Others	3 (5.5)
Dual therapy: class of drug (n=53)	
ACEI + ARB	26 (49.0)
ACEI + CCB	8 (15.1)
ARB + CCB	6 (11.3)
Other combinations	13 (23.6)
Dual therapy: choice of drug (n=53)	
Lisinopril + valsartan	10 (18.9)
Lisinopril + losartan	9 (17.0)
Captopril + losartan	3 (5.7)
Captopril + valsartan	4 (7.5)
Captopril+ amlodipine	3 (5.7)
Lisinopril + amlodipine	3 (5.7)
Valsartan + amlodipine	4 (7.5)
Other combinations	17 (32.0)
Triple and more therapy: choice of drug (n=44)	
Lisinopril + valsartan + amlodipine	9 (20.5)
Captopril + nifedipine + furosemide	5 (11.4)
Lisinopril + valsartan + furosemide	3 (6.8)
Lisinopril + valsartan +amlodipine + bisoprolol	3 (6.8)
Other combinations	24 (54.5)
Duration of antihypertensive treatments (n=84)	
Up to 2 weeks	33 (39.3)
2-4 weeks	25 (29.8)
4-8 weeks	12 (14.3)
8-24 weeks	8 (9.5)
>24 weeks	6 (7.1)

ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blockers; CCB: Calcium channel blockers.

tients were likely to develop HT before their hospital visit. The diagnosis of HT was made by clinical BP measurement using an oscillometer and sphygmomanometer device in this study. Ambulatory BP monitoring was not performed because it may lead to higher prevalence of HT due to undetected white coat HT.

The most common cause of secondary HT was isolated kidney disease, followed by autoimmune disease in this study. Despite the small number of subjects, 18.2% of children aged 13-18 years had primary HT. The result was in consistent with the study by Wyszynska et al. involving 1025 children, wherein essential HT affected 27.8% children aged 15-18 years. The occurrence of secondary HT in children younger than 15 years were higher than that in the older age group. Kidney diseases were the most common cause of secondary HT in children younger than 15 years.<sup>[19]</sup> Our study also showed secondary HT occurring more in children younger than 13 years.

In a study by Goutham Rao, 275 children were diagnosed with HT.<sup>[20]</sup> Of these, 57% and 43% had an identifiable secondary and primary HT, respectively. Interestingly, 51% of teenagers had a secondary cause.<sup>[20]</sup> In another study, the leading cause of secondary HT was also kidney disease, followed by respiratory disease. The most common cause of HT in infants was respiratory disease.<sup>[1]</sup> In our study, only one patient had CCAM, as a respiratory diagnosis. One patient younger than 1 year with HT was diagnosed with CAH. In this study, 2.5% of patients had history of prematurity. Another study found that 20% of children with essential HT had a history of preterm birth at <37 weeks of gestation.<sup>[1]</sup>

Malignancy contributed as the third leading cause of secondary HT in our study. A study involving acute lymphoblastic leukemia (ALL) children reported that the risk factors for HT include high dose corticosteroids, hyperleukocytosis, tumor lysis syndrome, kidney leukemic infiltration, and sepsis.<sup>[21,22]</sup> This cross-sectional study showed that 14% of patients with ALL had HT.<sup>[23]</sup> Other studies reported a higher incidence of HT among children with ALL or lymphoma.<sup>[24,25]</sup> The mechanism is through electrolyte imbalance and hyperuricemia in tumor lysis syndrome, leading to renal injury and HT.<sup>[26]</sup>

Children with HT are commonly administered with prolonged moderate to high dose steroid.<sup>[27]</sup> The number of our patients administered with high dose steroid was high. Corticosteroid use leading to HT is related to sodium retention and increased antidiuretic hormone activity and plasma renin levels.<sup>[27]</sup>

Only 84 data were eligible regarding antihypertensive management. The median duration to achieve a normal BP

was 28 days. Most of the children were able to attain target BP within 2 weeks. This was due to most of the children followed up had monotherapy and dual therapy. However, this study was not designed to assess the effectiveness of each drug. The most preferred drug in monotherapy was ACE. Captopril and valsartan were prescribed in 40% and 18.2% of children. In a Cochrane study, ACE (enalapril) significantly lowered systolic BP compared with ARB (valsartan) in 12 weeks.<sup>[28]</sup> Both clonidine and hydrochlorothiazide reduced significant systolic BP significantly.<sup>[28]</sup> However, the study excluded HT associated with kidney transplant, nephrotic syndrome treated with calcineurin inhibitor or high dose steroid, and malignant HT.<sup>[28]</sup> In dual therapy, the most commonly used combination was ACEI and ARB. Unfortunately, no literature compared the most effective combination therapy in pediatric HT management. The dose among similar drugs was not compared because of the limited number of subjects. Antihypertensive treatment was decided not only based on the treating physician's decision, but also by the insurance coverage. Our national insurance only covers certain medications within the antihypertensive group.

The limitation of our study includes its retrospective, observational study design. Certain stratified analyses performed also had a limited power due to the small sample size in the stratified groups. White coat HT was also undetected because 24-h BP was not measured because of unavailability of the ambulatory BP machine.

## CONCLUSION

Pediatric HT is a growing medical issue that is often overlooked. Secondary HT was found more in children compare to primary HT. Secondary etiology was suspected if HT was found in children with kidney disease. The first-line antihypertension used was ACEI, as a single therapy or combination. The therapeutic effect of antihypertensive drugs was expected within 28 days of treatment.

## Disclosures

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**Ethics Committee Approval:** The Faculty of Medicine, Universitas Indonesia, Indonesia Ethics Committee approved this study (Approval date: Nov 28, 2016 and Approval number: 16-11-485).

**Authorship Contributions:** Concept – H.A.P.; Design – H.A.P.; Supervision – E.L.H.; Materials – H.A.P., N.T.I.; Data collection &/ or processing – H.A.P., N.T.I.; Analysis and/or interpretation – H.A.P., N.T.I.; Literature search – H.A.P., N.T.I.; Writing – H.A.P., N.T.I., E.L.H.; Critical review – H.A.P., E.L.H.

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