Chapter 6: Blood pressure management in children with CKD ND

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INTRODUCTION

This chapter addresses the management of BP in children (defined as 18 years or younger, although chronological age does not necessarily parallel biological or social development). Children with non-dialysis-dependent CKD (CKD ND) differ from adults in the etiologies of CKD, definition of hypertension, and CKD associated co-morbidities. As cardiovascular end points such as myocardial infarction, stroke, or cardiovascular death are rare, effects of high BP and its treatment on kidney outcomes (e.g., lowering of GFR, initiation of dialysis, or transplantation) and target-organ damage are relevant end points in studies of children with CKD, although in the longer-term, CVD has a more important role.

Elevated BP and high BP are common in children with CKD, but RCTs of various treatment agents or targets are scarce. Observational studies and registry data[311–315] demonstrate that more than half of children with CKD have high BP based upon a casual BP reading. Observational data also suggest that hypertensive children with CKD progress to kidney failure significantly faster than normotensive children with CKD.[313] In studies of young adults with kidney failure whose kidney disease began in childhood, the risk of cardiovascular death is extremely high.[316,317] Sudden cardiac death is the main cause of cardiac death in these individuals.[318]

In light of the high prevalence and substantial morbidity associated with elevated BP in children with CKD, we systematically reviewed the existing literature and previously published guideline statements regarding the management of elevated BP in this vulnerable population. As RCTs are considered to provide the strongest evidence for CPGs, we reviewed RCTs with kidney and cardiovascular outcomes in which children with CKD was the study population. We supplemented this limited RCT evidence with information obtained from case series, cohort studies, and previous guideline statements on BP in healthy children and children with CKD. We further described the evidence base in detail in the narrative following each recommendation statement.

The strict evidence-based approach of formulating recommendations may have resulted in statements that do not include some commonly accepted treatment practices in children. The rationale for this approach is that we do not wish to provide guideline recommendations and discourage research in areas where evidence is weak. The research recommendations listed at the end of the chapter illustrate areas where more evidence is needed.

BACKGROUND

Definitions. For this Guideline, the age range for children is defined as from birth through 18 years. The preferred method of BP measurement in children is auscultation, and reference tables for BP percentiles for age, sex, and height can be accessed at the National Heart, Lung, and Blood Institute's *Fourth Report on the Diagnosis, Evaluation, and Treatment of High BP in Children and Adolescents* at http://www.nhlbi.nih.gov/health/prof/heart/hbp/hbp_ped.pdf.[319]

Throughout this guideline when we refer to thresholds or targets for BP therapy, we are referring to manual, auscultatory measurements of both systolic and diastolic BP unless otherwise specified. Correct BP measurement requires a cuff that is appropriate to the size of the child's upper arm and elevated BP must be confirmed on repeated visits. In deciding on treatment, unless severe hypertension is present, an individual's BP level should be determined as an average of multiple BP measurements taken over weeks to months.[319] Current recommendations suggest that measurements obtained by oscillometric devices that exceed the 90th percentile for age, sex, and height should be repeated by auscultation.[319] Detailed descriptions of appropriate BP measurement techniques in children and the strengths and limitations of various BP measurement methods in children with CKD have been detailed previously in the *KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease*, Guideline 13: Special Considerations in Children.[1]

Although there is insufficient trial evidence to recommend the use of ABPM in this Guideline, by virtue of frequent measurement and recording, ABPM allows the practitioner to compute the mean BP during the day, night, and over 24 hours, as well as to assess the time in which BP exceeds the upper limit of the normal range (i.e., the BP load). A number of reviews and guidelines suggest that in children with CKD, ABPM is a particularly useful tool to assess BP patterns.[320–322] In children, ABPM can be particularly useful, as a significant number of patients have masked hypertension and would not be recognized as having hypertension based on the outpatient measurements only. A few studies using ABPM in patients with CKD suggest that it may give a better measure of overall BP and better indicate risk for kidney disease progression than office BP measurement.[12,77,323] In fact, the only large RCT of BP control in children with CKD used ABPM as the method for BP assessment.[14] Further research may elucidate

that future guidelines for therapy should be based on ABPM, rather than office based measures that are commonly used today. We have not recommended ABPM targets in this Guideline as ABPM is currently expensive and not readily available as routine clinical care in many settings.

6.1: We recommend that in children with CKD ND, BP-lowering treatment is started when BP is consistently above the 90th percentile for age, sex, and height. ***(1C)***

RATIONALE

CVD has long been recognized as a substantial cause of late morbidity and mortality in individuals with onset of CKD during childhood.[324] The majority of children with CKD are hypertensive,[312] and a substantial proportion show evidence of target-organ damage associated with both masked and confirmed hypertension in a dose–dependent fashion.[325] However, few RCTs directly comparing thresholds for initiation of BP treatment (vs. no treatment) or targets of BP treatment to prevent or reverse target-organ damage have ever been performed in children with CKD.

Observational studies of healthy children suggest that persistent elevations in BP are associated with significant late sequelae. In cross-sectional studies, elevated BP is associated with evidence of target-organ damage, including left ventricular hypertrophy and increased carotid intimal–medial thickness.[326] In longitudinal analysis from the Bogalusa Heart Study, high systolic or diastolic BP was associated with an increased risk of developing kidney failure during long-term follow-up,[327] and high childhood BP was an independent predictor of increased ankle–brachial pulse wave velocity in young adults.[328] Persistently elevated BP in the young has been associated with decreased measures of carotid artery elasticity.[329]

In healthy children, in the absence of long-term data linking specific BP levels with adverse cardiovascular or kidney events, hypertension is defined on the basis of a population-based distribution. Specifically, hypertension is defined as average systolic BP or diastolic BP that is greater than or equal to the 95th percentile for sex, age, and height on three or more occasions.[319] In healthy children, the goal of anti-hypertensive treatment is reduction of the BP to below the 95th percentile, unless concurrent conditions are present. CKD is considered such a concurrent condition. In children with CKD, according to the *Fourth Report on the Diagnosis, Evaluation, and Treatment of High BP in Children and Adolescents*, the BP should be lowered to below the 90th percentile (http://www.nhlbi.nih.gov/health/prof/heart/hbp/hbp_ped.pdf).[319] The rationale for this approach is similar to the recommended treatment of hypertension in adults with additional cardiovascular risk factors or co-morbid conditions.

A number of expert panels have reviewed the existing literature and made similar recommendations. The National High Blood Pressure Education Program Working Group on High BP in Children and Adolescents has recommended initiating pharmacologic therapy for BP above the 90th percentile if a compelling indication such as CKD is present.[319] In 2004, the NKF *KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease*[1] recommended that the target BP in children with CKD should be lower than the 90th percentile for normal values adjusted for age, sex, and height or $<130/80$ mm Hg, whichever is lower. Similarly, the Cardiovascular Risk Reduction in High-Risk Pediatric Patients report[330] listed children with CKD or kidney failure as a pediatric population at high risk for CVD, for which a target BP below the 90th percentile for age, sex, and height is suggested. According to that consensus statement, CKD is considered a coronary heart disease equivalent for which the treatment recommendations are similar to those in secondary prevention guidelines for adults with established coronary disease.

Among children with CKD, observational data have shown that those with hypertension (i.e., BP above the 95th percentile) have a more rapid decline in estimated GFR than those without hypertension.[313,331] In a study by the European Study Group of Nutritional Treatment of Chronic Renal Failure in Childhood, children with a systolic BP >120 mm Hg had a significantly faster decline in GFR.[332] In children who have received a kidney transplant, hypertension is a strong predictor of accelerated GFR decline[333] and graft loss.[334,335] Preliminary data from the ongoing observational Chronic Kidney Disease in Children (CKiD) study show that, among 425 children with repeated measures of GFR, having systolic BP above the 90th percentile for age, sex, and height is associated with faster progression of CKD as compared with lower BP.[336] In this cohort, the annualized percent change in GFR among those with systolic BP above the 90th percentile was -7.5 ml/min/1.73 m^2 (95% CI -16.6–0.1), compared to -3.8 (95% CI -11.8–3.8) in those with systolic BP between the 50th and 90th percentiles and -2.5 (95% CI -8.9–3.9) in those with systolic BP below the 50th percentile. In the ESCAPE trial (described in detail in the next section), the kidney survival rate was 66% during follow-up among those with systolic BP below the 90th percentile but only 41% among those with systolic BP above the 90th percentile ($P=0.0002$). In ESCAPE, a diastolic BP below the 90th percentile was associated with a kidney survival rate of 67%, compared to 28% among those with diastolic BP above the 90th percentile ($P<0.0001$) (F. Schaefer and E. Wuhl, personal communication). On the basis of the RCT evidence, observational data, and other guidelines, the Work Group graded this recommendation as 1C. The quality of evidence was graded as C because the RCT evidence is limited to inferred evidence from one trial.

6.2: We suggest that in children with CKD ND (particularly those with proteinuria), BP is lowered to consistently achieve systolic and diastolic readings less than or equal to the 50th percentile for age, sex, and height, unless achieving these targets is limited by signs or symptoms of hypotension. ***(2D)***

RATIONALE

The evidence for this recommendation comes largely from the ESCAPE trial,[14] which showed a benefit in slowing CKD progression by targeting 24-hour MAP by ABPM to less than the 50th percentile for age, height and sex. Secondary analysis of the data suggested the effect was stronger in proteinuric children with CKD. (See Supplementary Tables 63–64 online). Based largely on the ESCAPE results, the European Society of Hypertension guidelines recently recommended that in children with CKD, BP targets should be below the 50th percentile in the presence of proteinuria and below the 75th percentile in the absence of proteinuria.[337] In the European Society of Hypertension guidelines, the rationale for choosing the 75th percentile as a threshold in children with CKD without proteinuria is based on a re-analysis of ESCAPE results, examining kidney outcomes according to achieved 24-hour mean BP level. Since the 75th percentile was not an original targeted intervention in the ESCAPE trial, and the trial was not powered to detect differences by levels of proteinuria in recruited subjects, we have not made a separate specific recommendation distinguishing between the presence and absence of proteinuria for target BP levels for children with CKD, but this is an important area for future study.

Our guideline includes a statement of caution in aggressively pursuing low BP targets in children with CKD. We recognize that children are particularly susceptible to intercurrent illnesses, gastroenteritis and dehydration, and aggressive use of BP lowering medications in polyuric and dehydrated patients can lead to hypotension and alterations in renal perfusion. Clinicians who prescribe anti-hypertensive medications, particularly ACE-Is and ARBs in children need to be aware of the risk of drug toxicity in children susceptible to intravascular dehydration. Clinicians should consider discontinuing the drugs in the presence of acute diarrhea.[338] Additionally we recognize that reaching a target of less than the 50th percentile BP may be quite difficult in some children with CKD. The risks of polypharmacy have to be weighed against the potential benefits of achieving lowered BP.

In the ESCAPE trial,[14] 468 hypertensive children with a 24-hour MAP above the 95th percentile for age, sex, and height, and a GFR (based on the Schwartz formula) of 15–80 ml/min/1.73 m^2, received ramipril at a fixed dose of 6 mg/m^2/day and were randomized to target a 24-hour MAP, measured by means of ABPM, of either between the 50th and 90th percentile or below the 50th percentile. Additional anti-hypertensive agents, except for other antagonists of the RAAS, were added at the discretion of the local provider to achieve the target BP.

In this study—the largest prospective RCT of BP therapy in children with CKD to date—fixed-dose ramipril and a lower therapeutic BP target (MAP below the 50th percentile for age, sex, and height by ABPM delayed the progression to kidney failure. There were no differences in the frequency or types of adverse events between the intensified and conventional BP target arms in the trial. In subsequent stratified analyses, the effects were more pronounced in children with glomerulopathy and kidney hypodysplasia or dysplasia. There was no evidence of improved outcomes in individuals with hereditary nephropathies or other congenital causes of kidney disease other than aplasia or dysplasia, although there were relatively few individuals in these subgroups. Additionally, in stratified analyses, the efficacy of the intensified BP control intervention was most marked in children with a urine PCR of >150 mg/g (>15 mg/mmol) (see supplement of Wuhl *et al.*[14]).

Data presented at the American Society of Nephrology 2010 annual meeting from the observational CKiD study[336] also shows slower progression of decline in kidney function in individuals with auscultatory manual BP below the 50th percentile for age, sex, and height as compared to individuals with BP between the 50th and 90th percentile and those with BP above the 90th percentile. BP in this study is measured according to a standard protocol at annual study visits with an aneroid device.

BP targets in children with CKD should be individualized on the basis of susceptibility to hypotension. Many causes of childhood CKD include diagnoses associated with salt and water losses in the urine. As such, the risk of hypotension associated with aggressive BP control should temper the ramping-up of BP-lowering medication to reach a low BP target.

6.3: We suggest that an ARB or ACE-I be used in children with CKD ND in whom treatment with BP-lowering drugs is indicated, irrespective of the level of proteinuria. *(2D)*

RATIONALE

This recommendation is based on published experience with these agents in children with hypertension, showing the drugs to be safe and effective in lowering BP and to confer a benefit for slowing CKD and reducing urine protein levels in adults with CKD. However in teenage girls, pregnancy testing and the use of birth control prior to and during ACE-I/ARB therapy need to be considered. Additionally, as mentioned above, discontinuing these agents during episodes of diarrheal illness and dehydration should be considered.[338]

ACE-Is or ARBs should be the preferred choice in treating proteinuric CKD (see Chapters 3 and 4). Multiple studies in adults with CKD have shown renoprotection with the use of ACE-Is or ARBs. RAAS antagonists preserve kidney function not only by lowering BP but also by means of anti-proteinuric, anti-fibrotic, and anti-inflammatory properties. In the ESCAPE trial described above, on the basis of previous research in adults, the children in both arms of the intervention received a fixed, maximum dose of the ACE-I ramipril.[323] Further BP lowering was achieved through the addition of other medications at the discretion of the local provider.

Others have recommended ACE-Is or ARBs as first-line agents in treating children with CKD and high BP,[339] particularly in those with proteinuria.[340] The recently released European Society of Hypertension guidelines[337] assert that 'it is reasonable to recommend agents blocking

the renin–angiotensin system as first choice in proteinuric, and also in non-proteinuric patients with CKD.' However, limited direct evidence from clinical trials is available with which to assess the efficacy of RAAS in children with CKD. In healthy children with hypertension, a number of clinical trials have examined the safety and efficacy of ACE-Is.[341–345] Small, uncontrolled studies have shown stable kidney function in children with CKD treated with ACE-Is or ARBs.[346–348] Kidney dysfunction that is hemodynamic in origin has been more commonly associated with the use of ACE-Is and ARBs than with other anti-hypertensive agents. Additionally, since elevations in serum potassium levels have also been observed, counselling about potassium intake and addition of thiazide or loop diuretics are sometimes advised.[339]

Although analysis of registry data from the ItalKid Project database failed to show clear evidence of ACE-I efficacy in slowing the progression of CKD,[311] other observational evidence shows that ACE-Is are associated with lower urine protein levels[349] and that BP control in childhood CKD is superior with anti-hypertensive regimens containing an ACE-I or ARB.[312] In a small trial, an ARB was more effective at lowering urine protein levels than a calcium-channel blocker.[350] The only study to date that has compared ACE-Is and ARBs in children found that urine protein levels were similarly reduced with the ACE-I enalapril and the ARB losartan.[351]

As in adults, ARBs may be more tolerable than ACE-Is in children, with fewer adverse events such as cough, angioneurotic edema, and hyperkalemia—but this has not been systematically studied in large trials. Combination therapy with ACE-Is and ARBs may be used for additive anti-proteinuric and renoprotective effects, but this approach has rarely been studied in children. Small randomized trials of combinations of ACE-Is and ARBs in children with CKD demonstrate significant reductions in urine protein levels as compared to the use of only one of the drug classes.[335,352] However, further study of long-term outcomes and safety data are necessary.

Use of ACE-Is and ARBs should be individualized on the basis of susceptibility to hypotension and of the risk of pregnancy in young women of child-bearing age. ACE-Is and ARBs are labelled by the US FDA as pregnancy category C for the first 3 months of pregnancy and category D for the last 6 months (the second and third trimesters). Pregnancy category C means that a risk may exist but its magnitude is unknown because of a lack of trustworthy studies in pregnant women, and animal studies either have shown risk in pregnancy or have not been performed. Pregnancy category D means that there have been studies in pregnant women showing that the drug is associated with some risk for the fetus, but the benefit of the drug may still outweigh that risk for some patients.[84,85]

Monitoring for hyperkalemia may be considered in high-risk children as kidney function declines. In the ESCAPE trial,[14] individuals with CKD receiving a high-dose ACE-I had an increase in mean (± standard deviation [SD]) serum potassium levels from 4.31 ± 0.52 mmol/l to 4.71 ± 0.57 mmol/l. The upper limit of the normal range for children (5.6 mmol/l) was exceeded in 3.3% of tests. In all but 5 patients, medical management through adjustment of diet, addition of a diuretic, or prescription of potassium-exchange resins resulted in persistent normalization of serum potassium levels while the child remained on ACE-I therapy.

ACE-Is and ARBs have similar hemodynamic effects in the kidney which leads to decrease in GFR. It has been stated that increases of the SCr level by up to 30% should be expected and tolerated after initiating therapy with ACE-Is or ARBs in adults with chronic kidney failure, but children have not been prospectively studied in this regard.[88]

Few direct comparisons of classes of anti-hypertensive agents have been performed in children with CKD. Extensive reviews of different drugs and classes of anti-hypertensive agents in children with CKD have recently been published.[337,339] There is no clear evidence that one second-line BP agent is superior to the another in children. In the ESCAPE trial,[14] calcium-channel blockers were used as first-choice anti-hypertensive co-medication (in 38% of patients), followed by diuretics (in 36%) and beta-blockers (in 26%), without differences between the randomization groups. Other guidelines suggest diuretics or calcium-channel blockers as the most suitable second-line agents.[353]

LIMITATIONS

In children with CKD, there is a dearth of RCTs; in fact, the recommendations in this chapter are largely based on a single trial, ESCAPE, which limits the quality of the evidence and the strength of the recommendations. The ESCAPE trial was performed in a predominantly Caucasian population. Therefore, the generalization of these findings to other populations is uncertain.

RESEARCH RECOMMENDATIONS

- Further RCTs are needed to replicate the findings from ESCAPE and to examine the safety and efficacy of intensified BP control on slowing CKD progression and incidence of CVD in children with CKD.
- Studies addressing BP targets and comparing home BP monitoring via oscillometric devices, ABPM, and clinic-based BP monitoring are needed, as are robust ABPM reference measures in populations of various races and ethnicities.
- Long-term observational studies of the onset of target-organ damage in children with CKD are necessary to obtain evidence on which to base thresholds for BP treatment and targets rather than relying on population-based percentiles. Large, long-term randomized trials addressing targets and comparing various agents to prevent target-organ damage are also necessary to improve knowledge of the advantages and disadvantages of specific doses and classes of anti-hypertensive agents in this population.

SUPPLEMENTARY MATERIAL

Supplementary Table 63. RCTs examining the effect of intensified vs. conventional BP control on children with CKD without DM [categorical outcome].

Supplementary Table 64. RCTs examining the effect of intensified vs. conventional BP control on children with CKD without DM [continuous outcome].

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/bp.php