Hypertension in children with chronic kidney disease: pathophysiology and management

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Abstract Arterial hypertension is very common in children with all stages of chronic kidney disease (CKD). While fluid overload and activation of the renin–angiotensin system have long been recognized as crucial pathophysiological pathways, sympathetic hyperactivation, endothelial dysfunction and chronic hyperparathyroidism have more recently been identified as important factors contributing to CKD-associated hypertension. Moreover, several drugs commonly administered in CKD, such as erythropoietin, glucocorticoids and cyclosporine A, independently raise blood pressure in a dose-dependent fashion. Because of the deleterious consequences of hypertension on the progression of renal disease and cardiovascular outcomes, an active screening approach should be adapted in patients with all stages of CKD. Before one starts antihypertensive treatment, non-pharmacological options should be explored. In hemodialysis patients a low salt diet, low dialysate sodium and stricter dialysis towards dry weight can often achieve adequate blood pressure control. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers are first-line therapy for patients with proteinuria, due to their additional anti-proteinuric properties. Diuretics are a useful alternative for non-proteinuric patients or as an add-on to renin–angiotensin system blockade. Multiple drug therapy is often needed to maintain blood pressure below the 90th percentile target, but adequate blood pressure control is essential for better renal and cardiovascular long-term outcomes.

Keywords Hypertension · Children · Chronic kidney disease · Pathophysiology · Antihypertension therapy · Life-style changes

Introduction

Hypertension is one of the most common sequelae of chronic kidney disease (CKD) in children [1]. CKD-associated hypertension develops by a large variety of pathophysiological mechanisms. Blood pressure is one of the most critical determinants of the progression rate of renal failure in children [2, 3], and cardiovascular mortality in childhood onset renal failure [4]. Therefore, good antihypertensive management can substantially contribute to better renal and patient survival of adults with childhood-onset CKD.

As in many other complications of chronic renal failure, patients often do not report symptoms of hypertension, so an active screening approach is needed to prevent end-organ damage.

This article aims to give a short overview of the different pathophysiological pathways that lead to hypertension in CKD in order to explain how these can be targeted by different therapeutic approaches.

Pathophysiology of hypertension in CKD

Fundamentally, increased blood pressure is caused by an increase in cardiac output and/or of total peripheral resistance. Both can be altered by a plethora of different mechanisms in uremia and renal failure. Additionally, children with certain underlying diseases, e.g. glomerulopathies and polycystic kidney disease, are especially susceptible to hypertension [3,
Activation of the renin–angiotensin–aldosterone system plays a pivotal role in renal hypertension. While plasma renin activity is typically found to be markedly elevated only in patients with renal artery stenosis, many patients with CKD have ‘inappropriately normal’ renin levels (i.e. lower levels would be expected, considering their degree of hypertension and fluid overload [6, 7]). Hyper-reninemia occurs probably due to renin secretion in poorly perfused areas such as cysts and scars or after microangiopathic damage or tubulo-interstitial inflammation [8, 9] and leads to angiotensin II-mediated vasoconstriction as well as aldosterone-mediated salt retention, thus increasing both total peripheral resistance and blood volume. Additional delayed effects of a high angiotensin II tone include inflammation, cardiac hypertrophy and endothelial cell damage, mesangial cell proliferation and fibrosis [10], which contribute further to hypertension and end-organ damage.

Sodium retention and consequent fluid overload have long been recognized as causes of hypertension in CKD. Hypertensive children on dialysis have lower residual urine output than their normotensive peers have [5]. While interdialytic weight gain is correlated with the inter-dialytic increase in ambulatory blood pressure, the correlation is rather weak (in children r=0.41 [11]). This may be due to delayed effects [12] but also points to important volume-independent factors regulating blood pressure (BP) in patients on hemodialysis. This is also illustrated by the fact that nephrectomy in children on dialysis lowers mean blood pressure, despite causing anuria [13]. It has been proposed that fluid overload leads to hypertension only in those patients in whom peripheral resistance fails simultaneously to fall, i.e. when additional factors interfere with vascular autoregulation [14].

A growing body of evidence suggests that increased activity of the sympathetic nervous system (SNS) is an important volume-independent cause of hypertension. Campese et al. demonstrated that renal denervation improves both hypertension and increased sympathetic activity caused by phenol injection into rat kidneys [15]. Muscle sympathetic nerve activity is also elevated in hypertensive patients with chronic renal failure [16]. The underlying mechanisms of this phenomenon are, as yet, unclear and may include afferent signals from the failing kidney as well as dopaminergic abnormalities and the accumulation of leptin in CKD [17, 18]. Interestingly, not only beta blockade but also angiotensin-converting enzyme (ACE) inhibition can reduce the sympathetic hyperactivation of CKD [16, 19]. However, as sympathetic hyperactivity is also a feature of renovascular hypertension [20], essential hypertension and hypertensive patients with polycystic kidney disease [13], it appears that sympathetic activation also occurs independently of renal function. The most established cause for sympathetic over-activation is renal ischemia caused by renal artery stenosis [20, 21], but renal cysts might also cause local renal ischemia.

While children with end-stage renal disease (ESRD) usually have normal plasma noradrenaline and adrenaline concentrations, hemodialysis per se leads to substantial increase in both plasma renin activity and catecholamines, which can contribute to hypertension [22].

Recent experimental evidence suggests that renalase—an amine oxidase specifically expressed by the kidney—lowers blood pressure and heart rate. Its activity is markedly reduced in patients with ESRD [23]. However, whether the cardiovascular effects of this enzyme are really due to its catecholamine-metabolizing activity is still controversial [24].

There has been debate about the role of nitric oxide (NO) in mediating endothelial cell damage and hypertension in CKD. Newer studies have demonstrated that, in uremic patients, reduced NO stimulation leads to reduced agonist-induced endothelium-dependent vasodilation, whereas other vasodilatory pathways are not affected. Renal failure leads to the accumulation of endogenous NO synthase inhibitors such as asymmetric dimethyl-L-arginine (ADMA), which appears to be due to increased generation and decreased metabolism rather than decreased clearance [25]. ADMA independently predicts overall mortality and cardiovascular events in patients with ESRD [26], as well as progression of CKD [27]. While ADMA is related to blood pressure in animal models of CKD, clinical studies have not found differences in blood pressure [25].

Endothelial NO synthase is also suppressed by hyperparathyroidism in rats with CKD [28]. In contrast to ADMA levels, those of serum parathyroid hormone (PTH) correlate highly with blood pressure in patients with CKD [29]. Whereas acute infusion of PTH has a hypotensive effect, chronic hyperparathyroidism leads to accumulation
of calcium inside vascular smooth muscle cells, enhancing their sensitivity to calcium and norepinephrine [30, 31]. This effect can be blocked by calcium channel antagonists.

A number of drugs commonly administered in CKD can cause iatrogenic hypertension. For example, erythropoietin (EPO) causes blood pressure elevation over several weeks. This may be via arterial wall remodeling, causing increased vascular resistance [32]. Vaziri et al. have proposed that EPO acts directly on voltage-independent calcium channels in smooth muscle cells, leading to a decreased sensitivity to the vasodilatory action of nitric oxide [33]. The resulting possibility of calcium channel antagonists as ‘specific’ therapy for EPO-induced hypertension has been successfully tested in rats [34].

Glucocorticoids lead to fluid retention by their mineralocorticoid effect. Cyclosporine A causes vasoconstriction of glomerular afferent arterioles and hyperplasia of the juxtaglomerular apparatus, with subsequent increased release of renin and angiotensin II [35]. Increased circulating catecholamines and endothelin-1 precursors, and increased renal sodium absorption via the Na-K-2Cl co-transporter in the loop of Henle [36], have also been demonstrated after cyclosporine A treatment. Tacrolimus appears to be less pro-hypertensive than cyclosporine in children after renal transplantation [37], but, for other reasons, it is less commonly used prior to transplantation [38].

Treatment with growth hormone leads to water and sodium retention by the distal nephron [39], mediated by increased intra-renal insulin-like growth factor (IGF)-1. However, growth hormone (GH) does not appear to increase blood pressure in children with CKD or Turner syndrome, despite both groups being prone to hypertension [40, 41].

**Management**

Owing to the lack of acute symptoms and to the serious long-term consequences of hypertension, an active screening approach is necessary to detect elevated blood pressures early and to prevent end-organ damage [42]. In contrast to other complications of CKD, which become prevalent only in later stages of CKD, hypertension is already very common in CKD stage 1, with over 63% of children affected. In CKD stages 4 and 5 the incidence increases further to 80% [1]. More than 50% of children with ESRD have uncontrolled hypertension, despite widespread use of antihypertensive drugs [5, 43]. The frequency of blood pressure measurement during screening and during therapy should be appropriate to the patient’s risk of developing uncontrolled hypertension. A routine for this is suggested in the flow chart in Fig. 2. In general, we would consider all children with CKD to be at least at intermediate risk, and, therefore, we recommend 3-monthly clinic blood pressure (CBP) measurements; children with ESRD, multiple pro-hypertensive medications or confirmed hypertension should be considered as at high risk. In our experience 24 h ambulatory blood pressure measurement (ABPM) is a very valuable tool and should be performed annually in high-risk populations such as renal transplant recipients or those with rapidly progressive renal disease. ABPM is also useful to exclude white-coat hypertension, which is a problem even in children under long-term medical care [44]. While there are equivocal results about the long-term consequences of white-coat hypertension, end-organ damage could be clearly demonstrated in children with masked hypertension, i.e. elevated ABPM but normal CBP [45], underlining the usefulness of this method.

Whichever method is used, techniques should be in accordance with international consensus statements, and the appropriate pediatric reference ranges are very important. These are now available for clinic [46, 47], ambulatory [48] and home blood pressure measurements [49]. The diagnosis of hypertension should be based on at least three clinic blood pressure measurements above the 95th percentile [46]. As white-coat hypertension is very common, and the effects of thorough investigation and treatment can be far-reaching, we feel ABPM is advisable in nearly all newly diagnosed hypertensive children. In countries where health care providers do not cover the cost of ABPM, home blood pressure measurements may be helpful in confirming the diagnosis, but they do not pick up the nocturnal blood pressure dynamics [44].

Once hypertension has been confirmed, good management should not focus only on pharmacological therapy, but also on detection and treatment of end-organ damage and, where appropriate, improvement of the dialysis regime and consideration of therapeutic life-style changes.

Echocardiography and ophthalmological examination are the most important assessments of end-organ damage in hypertensive children. Left ventricular hypertrophy (LVH) is common in children with CKD, even during antihypertensive therapy [50]. LVH in patients with normal clinic blood pressure may indicate masked hypertension in untreated children [45] or insufficient efficacy of antihypertensive drug therapy in treated children (e.g. insufficient dose, non-compliance, or short duration of action of selected antihypertensive drugs). Echocardiography and ophthalmological evaluation should be repeated at regular intervals in children with initial signs of end-organ damage [46]. From personal experience we would also recommend follow-up examination in children with persistent hypertension or in those at high risk (e.g. ESRD). Additional assessments of end-organ damage include measurement of carotid intima media thickness and of pulse wave velocity, which reflect functional alterations of arterial wall properties caused
by hypertension and other factors such as hyperparathyroidism [51]. These investigations are still mainly used for research purposes, but clinical use has been facilitated by the recent provision of pediatric reference ranges [52].

In hypertensive patients who are undergoing renal replacement therapy, improvement of the dialysis prescription should be the primary therapeutic approach to hypertension, before pharmacological treatment is started. Extracellular volume overload can be efficiently reduced by adequately long dialysis times. Even though the reduction of fluid overload may take several weeks to translate into normalized blood pressure, drug-free control of hypertension is possible in many, if not most, hemodialysis patients [12]. A number of studies have shown improved BP control with short daily, long intermittent or nocturnal hemodialysis [53]. While conventional dialysis schedules can also improve control of hypertension by targeting dry weight more aggressively [54], this tends to be tolerated less well, with more intra-dialytic hypotensive episodes. Lower concentrations of dialysate sodium also produce a moderate fall in blood pressure on a population level, with best results in patients with previously high blood pressure [55].

In addition to intensified dialysis, dietary sodium restriction is a useful adjunct to intensified dialysis in avoiding sodium overload, and it reduces intra-dialytic hypotensive episodes. Indeed, some authors find dietary sodium restriction plus low sodium dialysate to be equally effective as time-intensified dialysis, and they maintain that with good dietary advice a low salt diet need not be unpalatable [56]. However, restriction of fluid and salt intake requires considerable patient motivation, which is often a problem in the adolescent population.

Therapeutic life-style changes can be effective in lowering blood pressure if obesity contributes to the patient’s hypertension. Obesity in children with CKD is uncommon and usually associated with steroid treatment; however, it is seen more commonly in populations with a higher background risk of obesity [3]. While weight loss can be effective in reducing blood pressure in overweight children with normal renal function [57], unfortunately, there are no controlled studies of life-style interventions in children with CKD. In our experience calorie-reduced diets are rarely effective in this population, probably due to the multifactorial etiology of hypertension in renal disease.
Also, the recommended intake of fresh fruit and vegetables may be hard to achieve if a potassium- and phosphate-reduced diet is also necessary. Interestingly, weight loss improves salt-induced increases in blood pressure in obese children [58]; therefore, combined calorie- and sodium-reduced diets may be particularly effective in obese CKD children who are salt retainers.

Pharmacological treatment remains the mainstay of antihypertensive management in all stages of CKD. In approximately 75% of children with CKD stages 2–4, blood pressure control below the 95th percentile can be achieved by antihypertensive monotherapy, but 50–60% of children need more than one drug if intensified BP control (<50th percentile) is targeted [Effect of Strict Blood Pressure Control and ACE Inhibition on Progression of CRF in Pediatric Patients (ESCAPE) trial, unpublished results]. In children with ESRD adequate control is much harder to achieve: a review of the North American Pediatric Renal Transplant Cooperative study (NAPRTCS) database also showed that over 50% of children on dialysis have uncontrolled hypertension [43], and a Polish nationwide survey found that in only 57% of children with ESRD was hypertension adequately controlled, despite the use of multiple drug therapy in 65% [5].

Even though multiple drug therapy is often required, it is advisable to start with a single drug at a low dose and to titrate upward until blood pressure is controlled [46]. Exceptions are hypertensive emergencies, such as hypertensive encephalopathy, when intravenous (i.v.) treatment should be started promptly.

ACE inhibitors and angiotensin II type 1 receptor blockers (ARBs) are the most useful drugs, as they are not only antihypertensive but also slow down the progression of renal failure more efficiently than do other antihypertensive treatments [59]. Surveys among pediatric nephrologists from both sides of the Atlantic show that ACE inhibitors are increasingly popular and are now the most commonly used drugs for pediatric hypertension [60, 61]. The renoprotective effect of renin–angiotensin system (RAS) blockade is due to a combination of reduced proteinuria, lower intra-glomerular pressure through selective dilatation of the glomerular efferent arteriole, and anti-inflammatory and anti-fibrotic effects [10]. Additionally, RAS inhibition reduces the sympathetic hyperactivity seen in CKD [16].

There is convincing evidence from studies of adults that all proteinuric patients should receive renin–angiotensin system blockade, even if they do not have hypertension [42]. Major side effects are a moderate increase of potassium and creatinine; these should be monitored more closely with declining renal function. Sexually active adolescent girls must use contraception. ACE inhibitor-induced cough appears to be less common in children than in adults [62]. There is no clear evidence suggesting clinical superiority of ARBs over ACE inhibitors [63], and a number of drugs in both classes are labeled for children. Food and Drug Administration (FDA) approval for children under 6 years old is expected soon for a number of ARBs.

Combination therapy with an ACE inhibitor and an ARB should be considered for patients who continue to show proteinuria while undergoing monotherapy, since it is effective in further reducing proteinuria (and progression of CKD) in adults [63, 64]. Experience in children is positive but very limited [65–68], and the increased risk of hyperkalemia and renal failure should be realized [69]. Therefore, for improved control of hypertension without proteinuria, the combination of single RAS blockade with a diuretic is preferable. The use of fixed-dose combinations of RAS antagonists with a thiazide diuretic may be an option in adolescents where compliance is an issue, but less so in younger children where frequent dose adjustments are required [46].

From trials in hypertensive patients without renal disease it appears that the blood pressure lowering effect, per se, is relevant for cardiovascular risk protection, without any class-specific benefits. Therefore, in essential hypertension, the choice of agents should be guided by the matching of the side effects profile of the individual drugs to the patientspecific risk factor profile [47]. In patients with CKD, meta-analyses of adult trials demonstrated superior renoprotection by ACE inhibitors, even after adjustment for blood pressure and urine protein excretion [70]. There is no conclusive evidence as to whether the inhibition of the renin–angiotensin system is superior to other antihypertensives in non-proteinuric CKD patients [59,71,72]. Recommendations for adults prefer to err on the side of caution and suggest a low threshold for considering CKD patients proteinuric (200 mg protein/g creatinine in spot urine) [42].

Diuretics are less commonly used in children with CKD than in adults with CKD, due to the preponderance of hypoplasplastic kidney disorders, which frequently present as salt-losing nephropathies. In patients with evidence of hypervolemia, thiazides and loop diuretics have proven most useful for controlling volume overload, and they have a very good side-effects profile. It should be remembered that, while thiazides are a popular first-line therapy in mild- to-moderate CKD, they are less effective when glomerular filtration rate (GFR) falls below 60 ml/min per 1.73 m$^2$ body surface area, and they are ineffective below 30 ml/min per 1.73 m$^2$. Therefore, furosemide should be preferred and used in adequate doses for CKD stages 4 and 5. Mineralocorticoid receptor antagonists (e.g. spironolactone) are theoretically attractive in CKD, due to their synergistic actions with RAS antagonists, and the new selective receptor blocker eplerenone is devoid of anti-androgenic side effects.
However, monotherapy (and, even more, combination therapy with RAS antagonists) is limited by the potentiated risk of hyperkalemia. During diuretic therapy, patients should be monitored for volume depletion and electrolyte disturbances. Long-acting formulations help to increase patient compliance [42].

Calcium channel blockers are very potent anti-hypertensive drugs and, therefore, useful as add-on therapy in children with resistant hypertension. Dihydropyridine (DHP) drugs (e.g. nifedipine, amlodipine) act mainly as vasodilators and do not have cardiac side effects. Amlodipine has pediatric labeling and is available as a suspension, and doses need not to be adjusted to renal function.

However, DHP-type calcium channel blockers (CCBs) increase intra-glomerular pressure and proteinuria, while non-DHP-type calcium channel blockers (e.g. verapamil and diltiazem) have an additional anti-proteinuric effect. In a long-term clinical trial of elderly patients with type II diabetic nephropathy, non-DHP calcium channel blockers showed as equally an effective slowing of CKD progression, reduction of proteinuria and antihypertensive efficacy as did the ACE inhibitor lisinopril (while both were superior to the beta blocker atenolol [73]). However, there are no published safety data on any of the non-DHPs in children with hypertension, so they should be used with caution due to their known prolongation of the PR interval in adults [74].

Intravenous administration of nicardipine is an option for controlling hypertensive crises, especially when the level of renal function is unclear or changing rapidly. It has been used safely, even in very small children with hypertension, despite reports of hypotension in normotensive newborns with asphyxias [74].

Beta blockers can be used as second-line therapy for renal hypertension in children. However, they are contraindicated in asthma and can cause fatigue. All beta blockers require dose reduction with progression of CKD. They should be used with caution in heart failure, and their adverse metabolic effects make them less suitable for diabetics. The largest clinical experience, especially for infants, is available for propranolol. A sustained-release form of this drug allows once daily administration in larger children. However, other agents, such as atenolol, which have the advantage of being both long acting and β1-selective, may be preferred in clinical practice.

Other drugs are used less commonly, mainly due to their more severe side-effects profiles. Alpha blockers (such as prazosin) can be used in patients who also require them for control of bladder emptying or Raynaud’s phenomenon. Centrally acting alpha agonists (such as clonidine) act via reduction of sympathetic nervous outflow. Rebound hypertension after discontinuation is a major problem of this drug. The vasodilators hydralazine and minoxidil are less suitable in CKD as they are less effective and cause salt and water retention.

The aim of antihypertensive management is the regression of end-organ damage (especially LVH) and the lowering of blood pressure below target values while minimizing drug side effects. The currently recommended treatment goal in hypertensive patients with CKD is a blood pressure of < 130/80 mmHg in adults [42, 47] and < 90th percentile in children [46]. However, a meta-analysis of 11 randomized trials in non-diabetic adults with CKD showed differing results for proteinuric and non-proteinuric patients: while there was no increase in adverse renal outcomes with higher blood pressure in non-proteinuric patients, ideal systolic blood pressure for proteinuric patients (> 1 g per day) was 110–129 mmHg. In proteinuric patients, renal survival decreased, with systolic blood pressures below 110 mmHg and above 130 mmHg. These data are hard to interpret conclusively, as persistent hypertension during treatment may also be a reflection of more severe underlying disease [70]. In children, the pending results of the ESCAPE trial may help us to elucidate optimal blood pressure targets.

Conclusion

Adequate management of hypertension in CKD requires an active screening approach in order to prevent the significant renal deterioration and cardiovascular morbidity and mortality associated with high blood pressure. Owing to the plethora of different pathophysiological mechanisms involved, a whole range of therapeutic options is available. Non-pharmacological options should not be disregarded for obese children or for children on hemodialysis. Inhibitors of the renin–angiotensin system should be preferred for proteinuric patients and, probably, also for non-proteinuric patients. Multiple drug therapy is often necessary to reach target blood pressure below the 90th percentile. For this, diuretics and calcium channel blockers are the most suitable options.

Questions

(Answers appear after the reference list)
Indicate the correct answer (only one).

1. Hypertension in CKD
   (a) is mainly a feature of the later stages of CKD.
   (b) is caused by volume overload with normal total peripheral resistance.
   (c) increases renal blood flow and, therefore, helps to maintain residual renal function.
(d) can be caused by fluid overload, sympathetic nervous system hyperactivity and/or activation of the renin–angiotensin system.

2. In patients on hemodialysis with hypertension:
   (a) serum sodium levels are not indicative of total body sodium load.
   (b) reduction of fluid overload by intensified dialysis will swiftly lower blood pressure.
   (c) low sodium dialysate causes intra-dialytic hypotensive symptoms and is therefore not advisable.

3. Adequate control of blood pressure
   (a) is hard to achieve with monotherapy. Therefore fixed-dose combination therapy should be started as first-line therapy.
   (b) is possible in a large number of hemodialysis patients on strict fluid management without anti-hypertensive drugs.
   (c) can be assumed once a patient has normal clinic blood pressure values.
   (d) makes screening for end-organ damage unnecessary.

4. Diuretics:
   (a) thiazides should always be preferred to loop diuretics due to their longer duration of action.
   (b) loop diuretics should always be preferred to thiazides due to their more potent diuretic action.
   (c) diuretics can be dosed sparingly in CKD due to greater sensitivity of the nephrons.
   (d) in a patient with a GFR of less than 30 ml/min per 1.73 m² body surface area, thiazides should be preferred to loop diuretics.
   (e) diuretics have additional antihypertensive efficacy if hypertension is still uncontrolled by renin–angiotensin system blockade.

5. ACE inhibitors:
   (a) retard progression of CKD only because they lower blood pressure.
   (b) retard progression of CKD only because they reduce proteinuria.
   (c) should not be used in proteinuric patients who already receive angiotensin receptor blockers.
   (d) may cause hyperkalemia, increased serum creatinine, hypotension and cough but are generally well tolerated.
   (e) should not be used in patients with polyuria, as they are mild diuretics.

6. Therapeutic life-style changes:
   (a) renal hypertension is usually so pronounced that pharmacological treatment is needed, and burdening patients with therapeutic life-style changes is therefore unnecessary.
   (b) low salt diet is not necessary in obese children.
   (c) there are no studies to show that weight loss, healthy diet, increased exercise or cessation of (passive) smoking are helpful in children with CKD.

7. Iatrogenic hypertension:
   (a) erythropoietin (EPO)-induced hypertension is mainly due to the increase in hematocrit.
   (b) calcium channel blockers may be a specific therapy for EPO-induced hypertension.
   (c) beta blockers may be a specific therapy for EPO-induced hypertension.
   (d) growth hormone causes salt and water retention with clinically relevant hypertension in children with ESRD.
   (e) cyclosporine A causes hypertension via constriction of the efferent glomerular arteriole.

8. The target blood pressure in pharmacological treatment is:
   (a) the 95th age- and height-dependent percentile in all children with CKD.
   (b) the 50th percentile in children with CKD stage 4 and above.
   (c) independent of co-morbid diseases.
   (d) still being debated but at least the 90th percentile in children with end-organ damage or CKD.

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