Hypertension in End-Stage Renal Disease: Transplantation

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Abstract

Hypertension in children after renal transplantation is an important risk factor not only for graft loss but also for cardiovascular morbidity and mortality. The prevalence of posttransplant HTN ranges between 60% and 90%. The etiology of posttransplant HTN is multifactorial – chronic native kidney disease, immunosuppressive therapy, and chronic allograft dysfunction are the most common causes. Casual blood pressure (BP) should be measured at each outpatient visit; however, ambulatory blood pressure monitoring (ABPM) is the best method for BP evaluation in children after renal transplantation, as it often discloses especially nighttime HTN; given this, it should be regularly performed in each transplanted child. All classes of antihypertensive drugs are used in the treatment of posttransplant HTN because it has never been proven that one class would be better than another. The most commonly used antihypertensives are calcium channel blockers. The target BP for transplant children is still a matter of debate; it is recommended to target the same BP as for healthy children, i.e., <90th percentile. Control of HTN in transplanted children still remains poor – only 20–50% of treated children have normal BP. There is a great potential for improvement of antihypertensive treatment that could potentially result in improvement of both graft and patient survival in children after renal transplantation.

Keywords

Hypertension • Blood pressure • End-stage renal disease • Children • Kidney transplantation • Cardiovascular morbidity and mortality • Left ventricular hypertrophy

Contents

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J.T. Flynn et al. (eds.), *Pediatric Hypertension*,
https://doi.org/10.1007/978-3-319-31107-4_49

Introduction

Hypertension is a common and serious complication in patients after renal transplantation (Baluarte et al. 1994; Kramer et al. 2011; Sorof et al. 1999). It is an important risk factor for cardiovascular morbidity and mortality in transplanted patients (Tutone et al. 2005). Furthermore, it is a strong risk factor for impaired graft survival in adult and pediatric patients (Opelz et al. 1998; Mitsnefes et al. 2001). Cardiovascular events are the second most common cause of death in these patients. Therefore, the treatment of HTN is one of the most important strategies in transplanted children to improve their survival as well as survival of the transplanted grafts.

Measurement of Blood Pressure in Transplanted Children

Casual BP should be measured during every outpatient transplant follow-up visit. However, casual BP has its limitations, mainly that it can neither distinguish between true and white coat HTN nor measure BP during sleep or reveal masked HTN. It has been shown in several studies that ambulatory blood pressure monitoring (ABPM) is a better method for BP evaluation than CBP measurement in children after renal transplantation (Mitsnefes et al. 2003; Flynn 2012). The main reasons are the ability of ABPM to reveal white coat or masked HTN and to measure BP during nighttime (detection of isolated nocturnal hypertension). Furthermore, ABPM is superior to casual BP in regard to better correlation with target organ damage such as left ventricular hypertrophy (Mitsnefes and Portman 2003) in children after transplantation. Finally, the results of ABPM are more closely related to renal function in transplanted patients than the results of casual BP (Jacobi et al. 2000). Therefore, regular use of ABPM is recommended in all patients after renal transplantation regardless of the values of casual BP (Lurbe et al. 2009; Flynn 2012; Seeman 2012). ABPM should be performed at least once a year in every transplanted child and about 6 months after every change in antihypertensive therapy.

The predominant type of HTN in transplant children is nocturnal HTN, occurring in 50–70% of patients (Morgan et al. 2001; Seeman et al. 2006) (Table 1). This finding further stresses the importance of ABPM with its monitoring of BP values during the night. A reduced physiological decrease of BP during the night (blunted nocturnal dip, non-dipping) has been revealed in 30–72% of transplanted children (Morgan et al. 2001; Seeman et al. 2006). Adult transplant patients who are non-dippers have greater left ventricular mass than dippers (Lipkin et al. 1993). However, in a pediatric study, no significant difference in the left ventricular mass index between children with normal and attenuated nocturnal BP dip was found (Seeman et al. 2006). The reproducibility of dipping status in transplanted children is low (Krmar and Berg 2005); therefore, repeated ABPM studies might be needed to describe a transplanted child as a non-dipper. It may be more appropriate to rely on mean BP or BP load while asleep rather than dipping status to guide the treatment of HTN in transplanted children (Flynn et al. 2014).

Home BP measurement is also an important method for measurement of BP. It is increasingly used as a valuable supplement to casual BP and also ABPM in children with chronic renal failure or on renal replacement therapy (Bald et al. 2001; Hooper and Mitsnefes 2015; Wuhl et al. 2004). Bald et al. investigated home BP also in 21 transplanted children and found that it is an important method for control of blood pressure and a valuable supplement to ABPM also for transplanted children. It is especially recommended in children receiving antihypertensive medication to improve control of HTN and to support compliance with the medication; however, there are several problems with home BP such as lack of normative values in children and device validation.

Definition and Prevalence of Hypertension in Transplanted Children

The same definition is used for transplanted children as for otherwise healthy children. The prevalence of HTN in children after renal transplantation ranges considerably between 58% and 89% (Baluarte et al. 1994; Kramer et al. 2011; Morgan

Table 1 Prevalence of different forms of hypertension in children after renal transplantation using ambulatory blood pressure monitoring (ABPM)

Author	Definition of HT	Overall prevalence of HT (n)	Prevalence of nighttime HT (isolated nighttime HT) ((isolated daytime HT))	Prevalence of masked HT	Non-dipping (definition) systolic/ diastolic dip	Prevalence of untreated HT (among treated pts)	Prevalence of uncontrolled HT	Other findings
Morgan et al. 2001	daytime BP >95th centile for clinic BP or nighttime BP >95th centile for clinic BP minus 10% regardless of drugs	64% (n = 29/45)	64% (22%) ((0%))	n.d.	58% (<10% systolic or diastolic dip) 9%/14%	48%	82%	No significant relationship between ABPM data and LVM
Seeman et al. 2006	daytime or nighttime BP ≥95th centile or use of drugs	89% (n = 32/36)	60% (40%) ((0%))	n.d.	64% (<10% systolic or diastolic dip) 7%/13%	3%	45%	Better control of HT with ACEI and lower CyA/Tac dose/level
McGlothan et al. 2006	24-hr, daytime and nighttime mean BP >95th percentile or systolic load >35% and diastolic load >25% regardless of drugs	21/7% for daytime syst./diast. HT (n=6/2 of 29) 48/41% for nighttime syst./ diast. HT	51% (41%) ((n.d.))	n.d.	60% for systolic 37% for diastolic (<10% syst. or diast. dip) 40% for systolic 30% for diastolic (<5.5%) 8%/9%	n.d.	n.d.	Isolated nocturnal HT is more common than daytime HT, children on ACEI/ARB had lower systolic BP than on CCB
Seeman et al. 2007	daytime or nighttime BP ≥95th centile or use of drugs	97% at 2 years (n = 30/31)	n.d.	n.d.	45% at 2 years (<10% systolic or diastolic dip) 10%/14%	0% at 2 years	26%	Improved control of HT can be achieved and is associated with stabilization of graft function

(*continued*)

Table 1 (continued)

Author	Definition of HT	Overall prevalence of HT (n)	Prevalence of nighttime HT (isolated nighttime HT) ((isolated daytime HT))	Prevalence of masked HT	Non-dipping (definition) systolic/ diastolic dip	Prevalence of untreated HT (among treated pts)	Prevalence of uncontrolled HT	Other findings
Balzano et al. 2011	daytime or nighttime BP ≥95th centile or drugs	82% (n = 4/22) at 9 years follow-up	n.d.	n.d.	n.d.	5%	18% at 9 years follow-up	Very low prevalence of LVH (4%) and lack of progression of cIMT might reflect positive effect good BP control
Hamdani et al. 2016	a)daytime or nighttime BP ≥95th centile and daytime or nighttime BP load ≥25% b)24hr BP load ≥25%	a) 36% (n=80/221) b) 46% (n=102/221)	a) n.d. b) n.d.	a) 25% b) 32%	52% for systolic BP 28% for diastolic BP (<10% systolic or diastolic dip) 10%/15%	12%	49%	Very high prevalence of LVH (75%) among untreated sustained hypertensive pts. and prevalence of LVH in controlled HT (37%) similar to that in uncontrolled HT (44%)
Median values from all studies	n.a.	64%	60% (33%) ((0%))	29%	60% (for all definitions) 7%/13%	12%	45%	n.a.

HT hypertension, *BP* blood pressure, *ABPM* ambulatory blood pressure monitoring, *n.d.* not determined, *n.a.* not applicable, *LVM* left ventricular mass, *CyA* cyclosporine A, *Tac* tacrolimus, *Tx* transplantation, *ACEI* angiotensin converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *CCB* calcium channel blockers, *cIMT* carotic intima media thickness

et al. 2001; Seeman et al. 2006; Sinha et al. 2012; Sorof et al. 1999). The reason for the wide range in the prevalence of HTN is based mainly on the different methods of BP measurement and different definitions of HTN used in various trials. Studies using casual BP measurements alone always report lower prevalence of HTN than studies that used ABPM. This phenomenon clearly underlines the importance of ABPM since it also measures BP during the night when BP is often increased in transplanted patients (McGlothan et al. 2006).

Patients' BP status should be further classified based upon current antihypertensive drug treatment and measured BP level. Children on antihypertensive drugs with normal current BP should be regarded as having *controlled* HTN, and children on antihypertensive drugs with elevated current BP should be regarded as having *uncontrolled* HTN. The main reason for this differentiation is the fact that it has been shown in several trials that transplanted patients with controlled HTN have similar graft survival as spontaneously normotensive patients (i.e., normal BP without antihypertensive drugs). In contrast, patients with uncontrolled HTN have significantly worse graft survival (Mitsnefes et al. 2003; Vianello et al. 1993). Therefore, using only one category of HTN (regardless of the therapeutic control of HTN) or antihypertensive drugs as the only criterion for definition of HTN without knowing the current level of BP would lead to misinterpretation of the importance of the influence of BP on the overall prognosis of transplanted patients. The prevalence of hypertension can change also over the time after transplantation; it usually decreases but can also increase during long-term follow-up (Kaidar et al. 2014; Kramer et al. 2011; Sinha et al. 2012).

Etiology and Pathogenesis of Hypertension in Transplanted Children

The etiology of posttransplant HTN is multifactorial (Baluarte et al. 1994; Gordjani et al. 1990; Seeman 2009; Sorof et al. 1999). The main causes are summarized in Table 2.

Hypertension prior to transplantation caused mainly by the diseased native kidney is believed to be a significant risk factor for the presence of HTN after successful renal transplantation (Gordjani et al. 1990; Seeman 2012). Children receiving kidneys from deceased donors are more frequently hypertensive than children receiving grafts from living donors (Bald et al. 2001; Gordjani et al. 1990; Sorof et al. 1999). The lower prevalence of HTN among children after living donor transplantation could be one of the reasons for better graft survival of the living donor grafts. This hypothesis is supported by the results of a single-center study which shows that posttransplant HTN is, together with episodes of acute rejection, the only independent determinant of graft survival in children after living donor transplantation (El-Husseini et al. 2005).

Corticosteroids are a well-known risk factor for posttransplant HTN, with the major mechanisms likely being related to sodium retention or increase in cardiac output and renal vascular resistance. Elimination of steroids in stable patients showed reduction of BP in adult as well as in pediatric patients (Hocker et al. 2004; Kasiske and Ballantyne 2002), and children transplanted under a steroid avoidance immunosuppressive protocol showed improvement in HTN (Sarwal et al. 2012). In a cross-sectional study, the patients on alternate dose steroid treatment showed significantly lower prevalence of HTN than children on

Table 2 Causes of hypertension in transplanted children

Recipient´s native kidney
Immunosuppresive drugs (steroids, cyclosporine A, tacrolimus)
Graft dysfunction (acute rejection, chronic allograft dysfunction)
Kidney from cadaveric, borderline, or hypertensive donor
Renal graft artery stenosis
Overweight/excessive post-transplant weight gain
Genetic factors (primary hypertension, genes of RAAS)
Recurrent or de novo renal disease (e.g. IgA nephropathy, focal segmental glomerulosclerosis)
Others (e.g. polycythemia, pyelonephritis, ureteric obstruction, lymphocele)

RAAS renin-angiotensin-aldosterone system

daily steroid medication (Morgan et al. 2001), and another study showed that conversion from daily to alternate dose steroid therapy significantly reduces BP (Curtis et al. 1976). Therefore adoption of steroid sparing or steroid-free immunosuppression regimens can be considered a treatment strategy for improving control of BP in transplanted children.

With the introduction of the calcineurin inhibitor cyclosporine, there has been a dramatic increase in the prevalence of posttransplant HTN (Gordjani et al. 1990). Gordjani et al. showed in their large single-center study on 102 children that high trough levels of cyclosporine (>400 ng/ml) were associated with a significantly higher incidence of HTN in comparison to children with levels <400 ng/ml (91% vs. 57%). The newer calcineurin inhibitor tacrolimus also has hypertensinogenic effects similar to cyclosporine. In the only randomized controlled trial comparing cyclosporine- and tacrolimus-based immunosuppression in pediatric renal transplanted patients, there were no significant differences in the prevalence of HTN between children treated with cyclosporine and those with tacrolimus (Trompeter et al. 2002). Newer immunosuppressive agents such as mycophenolate mofetil, sirolimus, or everolimus do not have effects on BP, and therefore their use is a further option to improve control of HTN in transplanted children (Buscher et al. 2004).

Renal graft dysfunction is another risk factor for posttransplant HTN; however, there is a dual relationship between BP and graft dysfunction. On the one hand, graft dysfunction elevates BP, while on the other hand, elevated BP accelerates the decline of graft function. In adults, impaired graft function is associated with elevated BP and increased risk of HTN (Cheigh et al. 1989; Jacobi et al. 2000; Vianello et al. 1993). In a single-center study, Mitsnefes et al. did not find any difference in mean calculated glomerular filtration rate or acute rejection episodes between normotensive and hypertensive children (Mitsnefes et al. 2003). However, hypertensive children had reduced allograft function (glomerular filtration rate GFR <50 ml/min/1.73 m^2) more frequently than normotensive patients, whereas children with normal BP more frequently had normal graft function (GFR >75 ml/min/1.73 m^2).

Current body weight or change of body weight is a well-known and potent determinant of BP level in adults and children (Lurbe et al. 1998), and most children gain weight after renal transplantation (Hanevold et al. 2005). Therefore, control of body weight should be recommended in all children after renal transplantation to improve BP control (Wilson et al. 2010).

Stenosis of the graft artery has become a rare cause of HTN with current surgical technique using aortic patches (Fung et al. 1995). Doppler ultrasonography, magnetic resonance, and CT angiography are noninvasive techniques that can easily diagnose this cause of HTN. The treatment of choice is percutaneous transluminal angioplasty; surgery should be reserved for cases of angioplasty failure.

The development of recurrent or de novo glomerulonephritis (mainly IgA nephropathy or focal segmental glomerulosclerosis) may be associated with the occurrence of HTN, although these conditions are not common causes of significant posttransplant HTN (Ponticelli and Glassock 2010).

Complications of Hypertension in Transplanted Children

Hypertension is a strong predictor of graft loss. The most robust evidence comes from the results of the large multicenter Collaborative Transplant Study (CTS) published by Opelz et al. (1998) which showed that there is a linear negative relationship between casual BP and renal graft survival. This is true not only for adults but also for children <18 years. This relationship between BP and graft survival has been later confirmed by many other studies in adult and pediatric patients (Tutone et al. 2005; Mitsnefes et al. 2003). Hypertensive pediatric transplant recipients have the worse long-term graft survival than normotensive recipients (Fig. 1). The results from the NAPRTCS registry showed that the use of antihypertensive medication (the definition used for HTN in this retrospective analysis) was associated with higher rates of graft failure (Sorof et al. 1999). Increased BP is therefore clearly

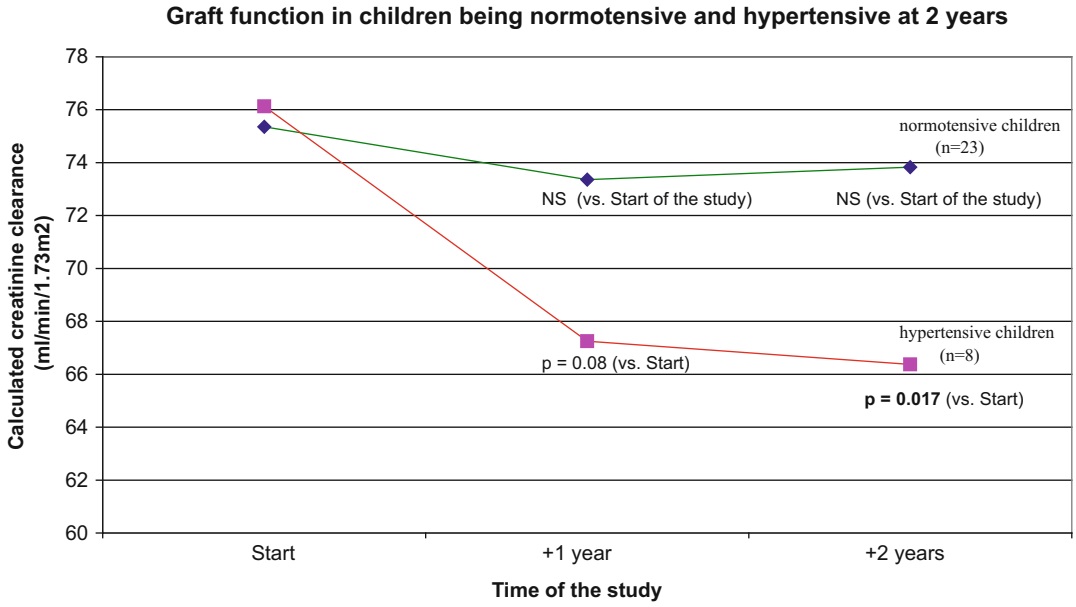

Fig. 1 Graft function in children being normotensive and hypertensive at 2 years

associated with decreased graft survival. Despite these clear findings, it is still a matter of debate whether posttransplant HTN is a real cause of chronic allograft dysfunction or only the result of renal dysfunction or both. Several findings from retrospective studies such as from the study done by Mitsnefes et al. (2003) showing that HTN is associated with allograft failure in children with normal graft function but not in children with severely impaired graft function suggests that HTN is not only a marker of graft dysfunction but also a direct cause of renal graft damage (Fig. 1).

Similar to the general population, HTN is also associated with increased cardiovascular morbidity in transplanted patients (Wilson and Mitsnefes 2009). Left ventricular hypertrophy (LVH) is a frequent type of cardiac end-organ damage in hypertensive children after renal transplantation, occurring in 50–82% children (Morgan et al. 2001; Seeman et al. 2006). Matteucci et al. (1999) found a correlation between left ventricular mass index (LVMI) and mean 24-h systolic BP, but Morgan et al. (2001) could not demonstrate any relationship between LVMI and ambulatory BP data. However, in another study of Kitzmueller et al., there was a correlation between LVMI and ABPM data at repeated measurement but not at baseline, suggesting that control of BP, i.e., change of BP level during longitudinal follow-up, is important for the maintenance of the myocardial architecture (Kitzmueller et al. 2004). Hypertensive transplanted children also have a greater prevalence of newer markers of cardiovascular damage such as increased cIMT, coronary calcifications, or increased pulse wave velocity (Kis et al. 2008; Mitsnefes et al. 2004; Litwin et al. 2005; Dvorakova et al. 2012).

Hypertension is also a risk factor for increased cardiovascular mortality seen in transplanted adult patients (Kasiske et al. 1996). Similar studies in children are rare. The Dutch Cohort Study has demonstrated that HTN is one of the most powerful risk factor for cardiovascular morbidity and mortality in children after renal transplantation (Groothoff et al. 2002). In this study cardiovascular events were the most common cause of death, and hypertensive children had a three times higher risk of overall mortality than normotensive children. Additional studies are needed for more information on the causal role of HTN in the high cardiovascular morbidity and mortality in transplanted children.

Evaluation of Hypertensive Children After Renal Transplantation

Casual BP should be measured during every outpatient visit, and regular use of ABPM is recommended in all patients after renal transplantation regardless of the values of casual BP because of high prevalence of nocturnal or masked HTN. This recommendation has been firstly used by the European Society of Hypertension (ESH) in its pediatric recommendations (Lurbe et al. 2009) and has been recommended also by other experts (Flynn 2012; Seeman 2012) and also by the most recent ESH Guidelines (Lurbe et al. 2016). ABPM should be performed at least once a year and about 6 months after change of antihypertensive medication to reassess control of HTN after modification of antihypertensive therapy.

The diagnostic evaluation of HTN in transplanted children should consider the multiple etiologies of posttransplant HTN (Table 2). Renal graft artery stenosis (Doppler renal ultrasonography, magnetic resonance, or CT angiography), high levels of immunosuppresive drugs (steroids, cyclosporine A, tacrolimus), chronic graft dysfunction (serum creatinine, event, graft biopsy), or ureteric obstruction (renal ultrasonography, renal scan) should be excluded in the differential diagnostics of HTN in a transplanted child. Echocardiography should be assessed at least once a year to determine the presence or absence of hypertensive target organ damage on the heart (Wilson and Mitsnefes 2009). Fundoscopy should be done in children with hypertensive crisis or posterior reversible encephalopathy syndrome (PRES). Moreover, acute graft dysfunction (serum creatinine, graft biopsy) or recurrent or de novo renal disease such as IgA nephropathy and focal segmental glomerulosclerosis (urinalysis, graft biopsy) should be excluded in the transplant patient who develops de novo HTN after being normotensive initially.

Newer methods for the detection of cardiovascular disease such as assessment of cIMT or PWV should also be considered research techniques in pediatric transplant patients.

Treatment of Hypertensive Children After Renal Transplantation

There is clear evidence from the observational studies on the correlations between BP and cardiovascular morbidity and mortality and graft function that posttransplant HTN must be treated. If an identified treatable cause of HTN is detected (such as renal graft artery stenosis, recurrence of primary disease, ureteric stenosis), the primary disease leading to BP elevation should be treated.

Many other issues on the treatment of HTN in children after renal HTN are less clear or even controversial. For example, there are no studies comparing different classes of antihypertensive drugs in children after renal transplantation; therefore, it is not known whether one class of drugs is better than another in transplanted patients.

Historically, calcium channel blockers (CCB) have been considered the drugs of choice for posttransplant HTN because they counteract the afferent arteriolar vasoconstriction caused by calcineurin inhibitors and reduce their nephrotoxicity (Curtis 1997; Silverstein et al. 1999).

There has been some concern that angiotensin converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARBs) may lead to deterioration of graft function in patients with undiagnosed graft artery stenosis or due to the preferential efferent arteriolar vasodilation and reduction of intraglomerular pressure. However, it has been demonstrated that ACE inhibitors are safe and effective drugs in adult as well as pediatric transplant patients (Stigant et al. 2000; Arbeiter et al. 2004). Moreover, they can reduce proteinuria which in addition to HTN is another treatable risk factor for impaired graft survival (Seeman et al. 2010). Furthermore, ACE inhibitors and ARBs can slow progression of chronic native kidney diseases mainly by long-term reduction of intraglomerular pressure and renal fibrosis (Simões et al. 2016; Sun et al. 2016). The ability of ACE inhibitors to slow progression of chronic allograft dysfunction, which is the most common cause of late graft loss, has never been proven in a prospective interventional trial in adult or pediatric patients. Some retrospective

studies have shown promising results, such as stabilization or even an improvement in patient survival and graft function in patients with chronic allograft dysfunction (Arbeiter et al. 2004; Heinze et al. 2006; Suszynski et al. 2013). However, the results from the CTS published recently did not show any improvement of patient or graft survival in patients treated with ACE inhibitors (Opelz et al. 2006). Therefore, this issue is still controversial and needs prospective interventional trials to resolve this controversy.

ARBs are less frequently used in adults and children after renal transplantation than ACE inhibitors (Calvino et al. 2000; Seeman et al. 2009); however, they seem to have similar risks and benefits as ACE inhibitors. Beta-blockers are also effective drugs in transplanted patients (Hausberg et al. 1999). However, beta-blockers are not able to reduce proteinuria as ACE inhibitors do. A further disadvantage of beta-blockers is their negative metabolic effects (increased lipid levels or impaired glucose tolerance), which may further contribute to the increased risk of cardiovascular disease in these patients.

Sodium retention is often present after renal transplantation, and therefore diuretics are important antihypertensive drugs in these patients as well. Thiazide diuretics should be preferred in patients with normal graft function, whereas loop diuretics should be given in patients with impaired graft function. Diuretics may also have detrimental metabolic effects such as hyperlipidaemia, hyperuricaemia, or hyperglycaemia. Potassium-sparing diuretics are used rarely due to their risk of hyperkalemia.

All five major classes of antihypertensive drugs can therefore be used in transplanted patients. Posttransplant HTN has a multifactorial etiology and is often severe; therefore, combination therapy is usually needed to control it. Which drug should be used as a first-line treatment remains the individual decision of the physician because it has not been consistently shown that one class is better than the other in renal transplant recipients (Curtis et al. 1976; Seeman 2009). In most pediatric renal transplantation centers, the most commonly used antihypertensive drugs are CCB, which are given to 38–65% of transplanted children (McGlothan et al. 2006; Morgan et al. 2001; Seeman et al. 2006). The second most commonly prescribed drugs are ACE inhibitors and beta-blockers. Diuretics and ARB are given less frequently to transplanted children.

Non-pharmacological lifestyle measures (reduction of increased body weight, reduction of salt intake, regular physical activity) should be encouraged even during antihypertensive drug therapy as they target the risk factors not only for HTN but also for cardiovascular morbidity and mortality of the patients (obesity, increased salt intake, physical inactivity) (Neale et al. 2016).

Minimizing hypertension-inducing immunosuppressive drugs, such as corticoids or calcineurin inhibitors, is another additional option on how to improve the efficacy of hypertension therapy (Hocker et al. 2004, 2010; Sarwal et al. 2012; Hooper and Mitsnefes 2015). However, great attention needs to be paid when manipulation with the immunosuppressive drugs happen due to the risk of acute rejection.

It is still a matter of debate what should be the target BP for patients after renal transplantation. The National Kidney Foundation Task Force on Cardiovascular Disease recommends a target BP level $<130/85$ for adult renal allograft recipients and $<125/75$ for proteinuric patients similar to guidelines for the management of HTN in patients with diabetic nephropathy (Task force report 1998). However, there are no prospective interventional trials showing that target BP lower than the conventional cutoff of 140/90 improves graft function or long-term graft survival. The same is true also for pediatric renal transplant recipients. The ESCAPE trial showed that reduction of ambulatory 24-h BP <50th percentile leads to significantly slower progression of CKD in children compared to BP between the 50th and 95th percentiles (Wuhl et al. 2009). However, it is not known whether these results can be extrapolated to transplanted children as no similar study has been published yet in kidney graft recipients. An ongoing study is investigating this issue (ESCORT trial – effects of strict control of blood pressure in pediatric renal transplant recipients).

The current recommendation of the European Society of Hypertension recommends target BP <75th percentile for children with CKDs without proteinuria and <50th percentile for children with proteinuria (Lurbe et al. 2016). While no such consensus recommendation has yet been made for the management of HTN after renal transplantation, we would recommend that the target BP for healthy children (<90th percentile) should be achieved in transplanted children (Flynn 2006; Seeman et al. 2007), pending publication of results of the ESCORT trial (see below).

The control of HTN in children after transplantation is still not adequate. Only a minority of children treated for HTN after kidney transplantation has BP at least below the target BP <95th percentile (Seeman 2012; Seeman et al. 2006; Sinha et al. 2012). The prevalence of persistent HTN despite antihypertensive treatment (i.e., prevalence of uncontrolled HTN) ranged between 27% and 37% in the recent pediatric studies using casual BP and as high as 45–82% in pediatric studies using ABPM (Morgan et al. 2001; Seeman 2012; Seeman et al. 2006) (Table 1). This means that only 18–55% of children after renal transplantation had ambulatory HTN controlled by drugs with BP at least <95th percentile. These data suggest that there is a high potential for improvement of antihypertensive therapy in children after renal transplantation.

The reasons for the insufficient antihypertensive therapy in transplanted patients have not been thoroughly investigated. Many factors, such as chronic allograft dysfunction, need for lifelong use of immunosuppressive drugs that increase BP (steroids, cyclosporine, tacrolimus), obesity, salt retention, renin secretion from diseased native kidneys, and the fear of ACE inhibitors or ARB in transplanted patients are often discussed as the major reasons for inadequate BP control in transplanted patients. Lastly, noncompliance (nonadherence) can play an important role in the control of HTN, particularly in adolescent patients. Therefore, compliance (adherence) not only to the recommended immunosuppressive medications but also to antihypertensive drugs should be reviewed during every outpatient visit. A system-based approach to managing hypertension in children following kidney transplantation has been described by Hooper and Mitsnefes that may improve the usually poorly controlled blood pressure in transplanted patients (Hooper and Mitsnefes 2015). This approach includes five essential elements: appropriate measurement of BP including ABPM, identification and classification of uncontrolled hypertension including nocturnal hypertension, antihypertensive therapy including assessment of response of therapy, appropriate minimization of medications that cause hypertension, and self-management report.

An important issue is whether the poor control of HTN can be improved and whether improved control of HTN can stabilize or even improve graft function or cardiac complications. Results from the CTS group showed that improved control of BP is associated with improved long-term graft and patient survival in adults (Opelz et al. 2005). However, a large retrospective observational study from the Midwest Pediatric Nephrology Consortium has demonstrated that transplanted children who required antihypertensives had worse graft dysfunction than those who did not require antihypertensive medication (i.e., had spontaneous normotension), even in those whose BP was within normal levels (i.e., had controlled hypertension) (Hamdani et al. 2016). This may reflect an effect of previously untreated or inadequately treated hypertension on worsening graft function and indicate the need for even more aggressive treatment of posttransplant hypertension.

Four recent prospective interventional studies have demonstrated promising result on this issue in children. In the first prospective interventional trial on intensified treatment of HTN, it was shown that the ambulatory BP could be significantly reduced after 2 years by increasing the number of antihypertensive drugs, especially ACE inhibitors and diuretics, and that children who remained hypertensive during a 2-year interventional trial on BP control lost significant graft function compared to children in whom BP was lowered to normotensive range despite similar graft function at the beginning of the trial (Fig. 1) (Seeman et al. 2007). Therefore, adequate

BP control is as essential as immunologic surveillance in the long-term care of transplanted children. In the second study, left ventricular mass index improved and the prevalence of LVH decreased from 54% to 8% in transplanted children in comparison to the same children being on dialysis, and these positive changes in cardiac structure were associated with decrease of systolic and diastolic BP index (Becker-Cohen et al. 2008). An even more impressive result was seen in an observational long-term study, where the regular annual use of ABPM over 9 years resulted in an improvement of the control of HTN to 82%, with a decrease of prevalence of LVH to 4% (Balzano et al. 2011). These recent encouraging data show that in transplanted children, the control of HTN and development of cardiac target organ damage can be improved in clinical practice. Furthermore, the results of the fourth, still ongoing ESCORT trial (3-year prospective randomized controlled study on the effects of strict BP control in pediatric renal transplant recipients) will show whether strict BP control (i.e., target 24 h BP $<$50th percentile similar to that used in the ESCAPE trial) can slow down the progression of chronic allograft dysfunction. The preliminary 2-year results have demonstrated that in the majority of transplanted children, the 24 h BP can be lower below the 50th percentile without any adverse effect (Seeman et al. 2015).

Conclusion

Hypertension is a common complication in children after renal transplantation; it affects 60–90% of transplanted patients. Blood pressure should be measured in a transplanted child as casual BP at each outpatient visit but also regularly by ABPM regardless of the values of casual BP due to the high prevalence of nocturnal and masked HTN. Hypertension is an important risk factor for cardiovascular morbidity, mortality, and graft survival. Treatment of hypertension should start always with pharmacologic agents; the target BP for transplanted children is still unknown; however, it should be at least similar to healthy children.

This is supported by the project CZ.1.05/2.1.00/03.0076 from European Regional Development Fund and by the project (Ministry of Health, Czech Republic) for conceptual development of research organization 00064203 (Motol University Hospital, Prague, Czech Republic).

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