2021

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Pediatric Nephrology (2021) 36:3595–3605
https://doi.org/10.1007/s00467-021-04949-5

EDUCATIONAL REVIEW

Kidney disease in children with heart or liver transplant

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Received: 17 June 2020 / Revised: 9 December 2020 / Accepted: 13 January 2021 / Published online: 18 February 2021

Abstract

Over the past few decades, there has been increasing recognition of kidney disease in children with non-kidney solid organ transplantation. The risk of kidney disease in children undergoing heart or liver transplantation is higher than the general population as the underlying disease and its associated management may directly impair kidney function. Both heart and liver failures contribute to hypoperfusion and kidney ischemia before patients reach the point of transplant. The transplant surgery itself can often be complicated by acute kidney injury (AKI), which may be further exacerbated by a complicated postoperative course. In the short- and long-term post-transplant period, these children are at risk of acute illness, exposed to nephrotoxic medications, and susceptible to rare but severe infections and immunologic insults that may contribute to AKI and chronic kidney disease (CKD). In some, CKD can progress to kidney failure with replacement therapy (KFRT). CKD and KFRT are associated with increased morbidity and mortality in this patient population. Therefore, it is critical to monitor for and recognize the risk factors for kidney injury in this population and mitigate these risks. In this paper, the authors provide an overview of kidney disease pertaining to heart and liver transplantation in children with guidance on monitoring, diagnosis, prevention, and management.

Keywords Children · Heart transplantation · Liver transplantation · Acute kidney injury · Chronic kidney disease · Kidney failure with replacement therapy · Risk factors

Introduction

In a 20-year national cohort study of pediatric solid organ transplant recipients, kidney failure with replacement therapy (KFRT – chronic dialysis or kidney transplantation) was found at a rate of 2.1 cases per 1000 person-years in liver transplant and 4.4 cases per 1000 person-years in heart transplant recipients [1]. The disease burden of earlier stages of chronic kidney disease (CKD) is much higher. CKD has been reported in 28–86% of long-term survivors of pediatric liver transplantation and 7–54% of heart transplant survivors [2]. Given the morbidity and mortality associated with CKD and KFRT, it is imperative for pediatric liver and heart transplant programs to anticipate, screen for, and mitigate modifiable risk factors for kidney injury in this high-risk population and provide nephroprotective measures to prevent progressive kidney damage. In the presence of kidney complications, it is advised to consult with pediatric nephrologists to guide further investigation and timely management.

Risk factors for kidney disease include patient factors, underlying disease process, and therapy provided in the pre-, peri-, and post-transplant periods.

Pre-transplant

Many patients awaiting heart or liver transplant may already have abnormal kidney function due to kidney involvement in a known multiorgan disease [3–5], or else secondary to prior acute kidney injury (AKI) related to decreased effective circulating volume from organ dysfunction or surgery [6], or exposure to nephrotoxic medications [7].

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Abnormal kidneys related to underlying disorder

Children requiring a heart transplant may have a higher incidence of low birth weight [8], and this in turn may be associated with low nephron number and decreased kidney functional reserve [9], increasing the risk of kidney complications heading into transplant.

In the liver transplant population, some underlying diseases may have kidney involvement contributing to acute and chronic kidney disease. Alagille syndrome often involves kidney anomalies, which can include defects in renovasculature, proximal tubules, and renal dysplasia with predisposition for kidney dysfunction [10]. Infections such as hepatitis C may result in chronic glomerulonephritis [11]. Metabolic diseases such as Wilson disease, methylmalonic acidemia, and tyrosinemia may cause chronic tubulopathy. Primary hyperoxaluria type 1 leads to KFRT, ultimately requiring kidney transplant, performed as part of a combined or else delayed procedure post-liver transplant [12]. Children with autosomal recessive polycystic kidney disease (ARPKD) who require liver transplantation for refractory portal hypertension and/or recurrent cholangitis [4] are generally co-followed by pediatric nephrologists for the ongoing management of CKD related to their underlying cystic kidney disease before liver transplantation [4].

AKI complicating the underlying disorder

AKI is defined as any of the following: an increase in serum creatinine by 26.5 umol/L (0.3 mg/dl) or more within 48 h, or by ≥1.5 times the baseline creatinine within 7 days, or by a urine volume of less than 0.5 mL/kg/h for 6 h [13]. Studies of the epidemiology of AKI in transplant recipients have historically been difficult to compare and pool, due to varied definitions of AKI. Much of the literature has come from retrospective cohort studies, although as awareness of the incidence and prognostic significance of AKI has increased, the literature in this area has expanded in recent years.

Kidney hypoperfusion

In children, the most common indication for heart transplant is cardiomyopathy (either dilated, hypertrophic, or, less commonly, restricted), although in infancy the most common indication is congenital heart disease [14]. Approximately half of pediatric heart transplant recipients are children under 5 years of age [14]. In these patients, chronic hypoxemia, reduced cardiac output, multiple cardiac surgical interventions, episodes of sepsis, and dehydration all contribute to increased risk of kidney damage and decreased kidney reserve heading into heart transplant [11, 15].

In the liver transplant population, the most common indication for transplant is biliary atresia and other cholestatic diseases [16]. There are many similar risk factors for kidney hypoperfusion including third spacing of the intravascular volume, sepsis, dehydration (e.g., related to acute illness, gastrointestinal bleeding, or aggressive paracentesis), and surgical intervention [11]. In addition, hepatorenal syndrome (HRS) can also contribute to kidney hypoperfusion in children with acute or chronic liver disease. HRS is a multifactorial process involving portal hypertension and resulting in splanchnic vasodilatation, causing a decreased effective circulating volume leading to kidney vasoconstriction [17]. It may present acutely and result in AKI or may have an indolent course and contribute to CKD [17].

Nephrotoxic medications

Pediatric data suggests that the majority of non-critically ill children in hospital receive at least one nephrotoxic medication [18]. Antimicrobials are one of the most common classes of medications prescribed and also among the most common causes of nephrotoxicity. Up to one third of children can develop medication-associated AKI after receiving intravenous aminoglycosides [19]. Furthermore, co-administration of certain nephrotoxic antibiotics, namely intravenous piperacillin/tazobactam together with vancomycin, has been shown to be associated with increased risk of AKI [7]. The AKI rate appears to double when children receive three or more nephrotoxic medications on a given day [18], and clinicians should exercise caution when prescribing multiple nephrotoxic medications. The addition of antifungals and antivirals may also contribute to nephrotoxicity via direct tubular injury and/or crystallization and tubular obstruction [20].

Pediatric cardiologists and hepatologists caring for patients with chronic heart and liver failure, respectively, should be cognizant of the potential risk of AKI when selecting antimicrobials and choose dosing/administration strategies that minimize toxicity to the kidneys [21]. Furthermore, clinicians should consider monitoring practices that can mitigate toxicity and include monitoring of kidney function, urine output, and hydration status in high-risk patients.

AKI and CKD continuum

Kidney Disease: Improving Global Outcomes (KDIGO) defines CKD as an abnormality of kidney structure or function, present for more than 3 months [22]. In a Canadian pediatric cohort study of patients undergoing non-kidney solid organ transplant between 2002 and 2011, 8% of all patients developed CKD within 4 years post-transplant, and multivariate analysis revealed that having one AKI episode was associated with a 2-fold greater risk of developing CKD at 3 months [23].

Peri-transplant

The time immediately before, during, and after the transplant surgery is a high-risk period for children, and the impact of kidney injury during this time may have considerable short- and long-term consequences on kidney survival.

AKI associated with transplant surgery

In a prospective study of 66 children in a Canadian pediatric heart transplant program, Macdonald et al. found a 73% incidence of AKI postoperatively, which was an independent predictor of prolonged ICU admission [24]. This is similar to the 67% incidence of perioperative AKI noted in 125 pediatric heart transplant patients by Williams et al. [23]. For pediatric liver transplant patients, studies have reported a 46 to 67% incidence of perioperative AKI [23, 25, 26]. These results highlight the need to anticipate this complication during transplant surgery and institute kidney protective measures whenever possible. Perioperative risk factors that can result in kidney injury are mainly those that result in decreased blood flow to the kidneys, such as hemodynamic instability, hypotension, prolonged cardiopulmonary bypass (CPB) time for heart transplant or prolonged cross-caval clamp time for liver transplant, and blood loss [27, 28].

The AKI-CKD continuum is highlighted in a recent retrospective study by Menon et al., who reported a cumulative incidence of 40.9% of CKD stage 3–5 at 60 months post-heart transplant and 10% in patients post-liver transplant with a history of AKI in the first week post-transplant, compared to 35.8% and 0% in heart and liver transplant recipients, respectively, who did not sustain an AKI in the first week post-transplant [29]. The pathophysiology of this long-term CKD is multifactorial but includes kidney ischemia-reperfusion injury, resulting in tubulointerstitial fibrosis and increased circulating angiotensin II [30]. The ensuing hypertension further exacerbates fibrosis and may contribute to proteinuria [30] and further progression of kidney damage.

Peri-transplant exposure to nephrotoxins

Calcineurin inhibitors (CNIs), namely tacrolimus and cyclosporin, may also contribute to kidney injury acutely in the peri-transplant period [31, 32]. MacDonald et al. noted that tacrolimus trough levels greater than 15 μg/L on postoperative day 3 were independently associated with more severe AKI in heart transplant patients [11]. Afferent arteriolar vasoconstriction results in a reversible reduction in glomerular filtration rate in the acute phase, a different mechanism than the chronic vasculopathy and tubulointerstitial fibrosis associated with long-term CNI use [33].

In pediatric liver transplant recipients, use of basiliximab induction as a kidney-sparing protocol for delayed CNI introduction has been shown to be safe and effective in preserving kidney function, with no significant increase in graft rejection [34].

The peri-transplant period is a high-risk time for AKI, which may contribute to poor long-term prognosis. Zhang et al. demonstrated a trend toward worse patient and graft survival in liver transplant recipients with peri-transplant AKI compared to those without AKI [26]. These data highlight the importance of kidney protective measures such as adequate hydration and limitation of nephrotoxins where possible, particularly in patients with a complicated surgical course.

Post-transplant

CKD in the context of previous AKI

Data from the 2018 International Society for Heart and Lung Transplantation (ISHLT) reported that severe CKD (serum creatinine greater than 221 umol/L, or need for kidney replacement therapy) was seen in fewer than 10% of patients at 10 years post-heart transplant; however, reduced estimated glomerular filtration rate (eGFR) was a significant risk factor for mortality [35]. In the heart transplant population, many of the same risk factors for AKI may also contribute to development of CKD [35, 36].

CKD was also reported in 17.6% of children 5 years post-liver transplant in the multicenter Studies of Pediatric Liver Transplantation (SPLIT) cohort [36]. Survival in those patients with CKD is significantly reduced compared to those with normal kidney function, and CNI exposure and peri-transplant kidney injury portends a higher risk of developing CKD [37]. The multifactorial etiology of post-transplant kidney disease is summarized in Table 1.

CKD from nephrotoxin exposure

Calcineurin inhibitor toxicity

Much like in the acute post-transplant period, CNIs may also be a primary causative agent, or a contributor to CKD in the solid organ transplant population [38]. In addition to their acute hemodynamic effects on kidney perfusion, CNIs can also cause chronic tubulointerstitial nephritis [38]. Arteriolar vasoconstriction may be a contributing factor to interstitial fibrosis and tubular atrophy, and CNIs may also have a direct effect on tubular epithelial cells [38]. Most patients with chronic CNI toxicity may be asymptomatic, with hypertension, mild-to-moderate proteinuria, or an abnormal serum creatinine being the only apparent manifestation [39]. The diagnosis of CNI toxicity can be confirmed by kidney biopsy, where the most common finding is interstitial fibrosis, though

Table 1 Risk factors for kidney disease

Pre-Transplant	Peri-Transplant	Post-Transplant
• AKI associated with surgery for primary disease • Decreased effective circulating volume • Nephrotoxins (e.g., antimicrobials) • AKI due to sepsis/shock • CKD secondary to repeated AKIs ± underlying kidney disease related to primary disease	• Decreased kidney perfusion during transplant surgery: hemodynamic instability, hypotension, prolonged CPB (heart) or cross-caval clamp time (liver), blood loss • Nephrotoxins (e.g., CNIs) • AKI due to sepsis/shock • Progression of CKD	• Decreased effective circulating volume • AKI due to sepsis/shock • Nephrotoxins • BK nephropathy • Thrombotic microangiopathy • CKD secondary to recurrent AKIs, underlying primary disease, CNI toxicity • Progression of CKD due to sustained hypertension ±proteinuria

AKI acute kidney injury, *CKD* chronic kidney disease, *CPB* cardiopulmonary bypass

"striped fibrosis" is pathognomonic [39]. In a multicenter pediatric heart transplant cohort, patients receiving either cyclosporin A or tacrolimus had similar creatinine clearances up to 7 years post-transplant [40]. Multiple trials in liver transplant patients have demonstrated improved long-term kidney function in patients on lower-dose CNI with co-administration of mycophenolate mofetil (MMF) for immunosuppression [41–43], highlighting the importance of CNI toxicity as a risk factor for CKD in these patients.

Mammalian target of rapamycin inhibitors

mTOR inhibitors have been explored as part of kidney-protective immunosuppression protocols, with mixed results when used as replacement for CNIs [44–48]. The risk of rejection reported appears to be similar in patients treated with either CNIs or mTOR inhibitors in these trials [44–48]. Of note, mTOR inhibitors may also have a deleterious effect on the kidney, as they have been implicated in development of proteinuria, even in the nephrotic range, related to direct glomerular injury [49, 50].

Hypertension

In addition to CNI toxicity, hypertension is another important modifiable risk factor for progression of CKD. The prevalence of hypertension in pediatric patients who underwent heart transplant from 1995 to 2017 was 14% according to the 2018 ISHLT report [35]. In a Canadian retrospective study of 24-h ambulatory blood pressure measurements (ABPM) in 51 pediatric patients 1-year post heart transplant, 49% were hypertensive [51]. In this study, hypertensive patients were receiving more immunosuppressive agents, had higher tacrolimus trough levels, and were more likely to be on maintenance prednisone therapy [51]. Similarly, post-liver transplant studies in children have shown a significant burden of hypertension and an association with CNI exposure and steroid therapy [52]. The role of CNIs and prednisone in hypertension has been well-established in solid organ transplantation [51, 53–55].

The pathophysiology of CNI-induced hypertension is still a subject of debate and is likely multifactorial [55]. CNIs may have a direct endothelin-mediated vasoconstrictive effect on the kidney vasculature and may also impair vasodilation [55]. The effect of CNIs on the renin-angiotensin system remains uncertain, with mixed evidence on the impact of these medications on plasma renin activity and angiotensin II levels [55]. Previous studies have also showed an association of CNI use with sympathetic activation [54]. A meta-analysis of 10 randomized trials in heart transplant patients found that tacrolimus appears superior to cyclosporine with regard to the risk of hypertension [56]. The reduced risk of hypertension with tacrolimus compared to cyclosporine has also been shown in liver transplant patients [57].

Studies in pediatric heart transplant recipients have shown that reduction in prednisone dose correlates with reduction in systemic blood pressure [51]. Given that steroids are a mainstay of induction immunosuppression and used chronically in approximately 50% of pediatric heart [58] and 60% of pediatric liver [59] transplant recipients, the burden of steroid-induced hypertension remains significant and provides further impetus for further refinement of steroid exposure in immunosuppression protocols.

Thrombotic microangiopathy

A rare but important cause of AKI and CKD following solid organ transplantation is thrombotic microangiopathy (TMA) [60]. Transplant-associated TMA results from endothelial injury, ultimately triggering a cascade of disseminated microthrombus formation, microangiopathic hemolytic anemia, and kidney dysfunction [60]. Though uncommon, the diagnosis should be considered in patients with new onset of thrombocytopenia and hemolysis with signs of nephritis (hematuria, proteinuria, increased creatinine, hypertension) [60]. The etiology of transplant-associated TMA is likely varied, and among them is exposure to immunosuppressive medications as both CNIs and mTOR inhibitors have been shown to predispose to endothelial injury and may impact complement

pathway regulation [60, 61]. Transplant surgery itself may predispose to TMA from ischemia-reperfusion injury [60].

In limited case reports of transplant-associated TMA in heart and liver transplant patients, prognosis is poor [60]. In the liver transplant population, the pathophysiology of TMA may also differ, as the liver is responsible for synthesis of ADAMTS13 and transplant patients may have a relative ADAMTS13 deficiency [60]. Early recognition of TMA in this population is important, and suspicion based on AKI in the setting of thrombocytopenia and anemia should prompt a hemolysis workup including a Coombs test and serum haptoglobin, bilirubin, LDH, and peripheral smear to confirm microangiopathic hemolytic anemia [60]. In the solid organ transplant population, it is also important to rule out invasive CMV disease, which may also cause thrombocytopenia and microangiopathic hemolytic anemia [60]. Upon confirming TMA, consideration can be given to changing immunosuppressive medications [60]. Supportive care has been the standard management option.

BK nephropathy

Among opportunistic infections known to affect solid organ transplant recipients, polyoma (BK) virus nephropathy is a rare, but important, cause of CKD in this population [62]. Much of the literature regarding BK nephropathy comes from the kidney transplant population and impact on the kidney allograft. The incidence of BK nephropathy appears to be lower in isolated heart or liver transplant recipients compared to kidney transplant patients [62]. However, the disease has been reported in native kidneys in pediatric patients undergoing heart transplant [63–67]. The literature in the liver transplant population is more sparse, with the first case of native BK nephropathy post-liver transplant reported in 2015 [68].

Primary BK viral infection typically occurs in childhood and the virus usually remains latent thereafter [66]. Nephropathy attributed to BK is less common in native than transplant kidneys [69]; however, patients receiving immunosuppressive medications for non-kidney solid organ transplant may still present with an elevated serum creatinine, often otherwise asymptomatic [63–67]. BK virus nephropathy may be underdiagnosed in non-kidney transplant patients, as many cases may be falsely attributed to CNI toxicity [63, 64, 66, 67, 69]. Urine and plasma may be sent for BK virus PCR; however, kidney biopsy is required for definitive diagnosis and is typically characterized by patchy interstitial nephritis, with immunohistochemical staining for SV40 (large T antigen) [66].

The mainstay of management for BK nephropathy is reduction of immunosuppression, but this needs to be balanced against the increased risk of rejection. In most cases of BK viremia in non-kidney solid organ transplant patients, this is sufficient for patients to clear the virus [62, 69].

Kidney hypoperfusion due to allograft dysfunction

In addition to the myriad of transplant-associated risk factors for CKD, patients undergoing heart and liver transplant may also develop CKD caused by complications of their primary graft function [2, 11]. In heart transplant patients, allograft dysfunction and chronic reduction of cardiac output may result in kidney hypoperfusion and increase the risk of CKD [11]. In the liver transplant population, hepatorenal syndrome may develop due to graft dysfunction, resulting in CKD [11].

In summary, CKD is common after non-kidney solid organ transplant and often related to previous episodes of AKI or CNI toxicity [11]. However, providers must maintain suspicion for rare but significant causes of CKD such as other nephrotoxin use, TMA, and BK nephropathy. In addition, function of the graft and the primary disease may also contribute to progression of CKD [11, 37, 70, 71].

Kidney failure with replacement therapy

As previously noted, the reported incidence of KFRT is relatively low (1–3%) in long-term survivors of pediatric heart and liver transplant [1, 72, 73]. The burden of earlier stages of CKD is much higher, and it is important to note the limitations of estimating GFR using routine biomarkers such as serum creatinine that may overestimate kidney function in many patients with chronic illness and low muscle mass [1]. Furthermore, historical data in transplant registries may not always include serial measurements of kidney function and data on proteinuria and/or hypertension as signs of kidney damage [1, 2, 72].

In a national retrospective study of patients transplanted between 1990 and 2010, the median time from transplant to KFRT was similar for heart (10.2 years) and liver (9.0 years) recipients [1]. Other 20-year retrospective cohorts of pediatric heart [73] and liver [72] transplant recipients have shown that in those patients reaching KFRT, 22% of heart and 29% of liver transplant patients received a preemptive kidney transplant, and the remaining 78% and 71%, respectively, required chronic dialysis [72, 73]. KFRT in heart and liver transplant recipients was an independent risk factor for mortality in both groups, particularly for those on chronic dialysis [72, 73].

While the reported incidence of KFRT is low, the burden of CKD in these patients is significant [2]. Given the limitations of kidney functional assessment and the impact of KFRT on long-term survival, it is important for heart and liver transplant recipients to be regularly screened and any modifiable risk factors for kidney injury addressed in their routine care. As overall survival continues to improve in solid organ transplant recipients, the burden of CKD progressing to KFRT may become more apparent, and consultation with the pediatric nephrology team will be critical to delay progression of kidney

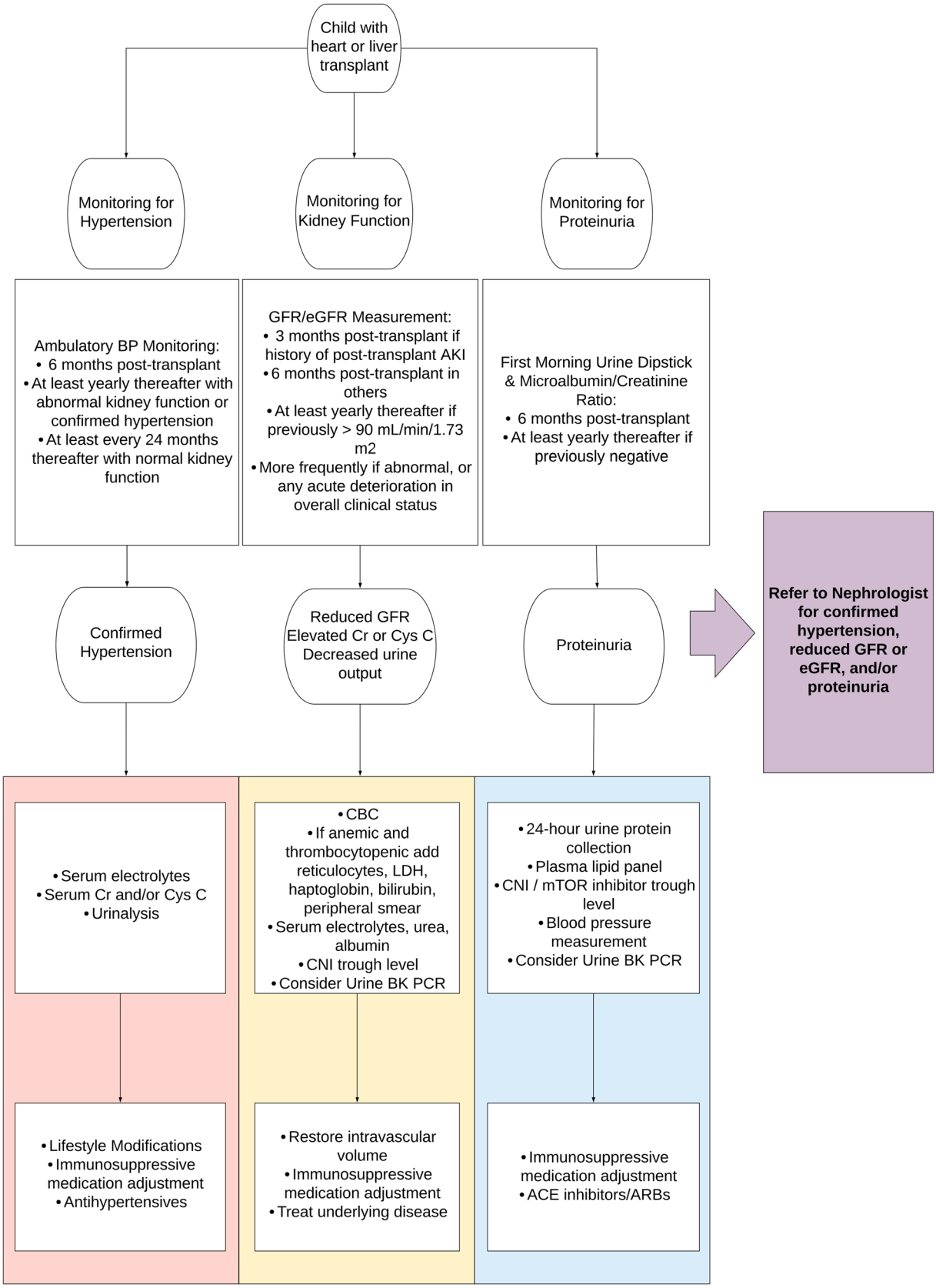

Fig. 1 Screening and diagnosis of kidney disease*. BP blood pressure, GFR glomerular filtration rate, Cr creatinine, Cys C cystatin C, CNI calcineurin inhibitor, mTOR mammalian target of rapamycin, ACE angiotensin-converting enzyme, ARB angiotensin receptor blocker. *Adapted from Practice Recommendations from Filler et al. (2016) [71] and local experience at the Hospital for Sick Children, Toronto, Canada

damage, monitor for complications of CKD, and prepare patients for kidney replacement therapy when necessary.

Guidance

Given the well-established continuum between AKI and CKD [23, 30], it is recommended that children who sustain an AKI should have routine monitoring of blood pressure, urine for protein, and kidney function during their hospital admission and following discharge. After discharge, providers should continue regular monitoring of these parameters, and the frequency of follow-up should be guided by the severity of kidney function impairment at discharge. Assessment of kidney function may be estimated using the Schwartz formula [74] or by nuclear medicine GFR [70, 75, 76]. With the high incidence of CKD in heart and liver transplant recipients, it would be appropriate for heart and liver transplant programs to perform regular assessment of GFR or estimated GFR (eGFR), serum electrolytes, urine protein, and blood pressure in all patients. Reassessment should be more frequent in patients having sustained previous AKI with any evidence of proteinuria, elevated blood pressure, and/or reduced GFR. As many of these patients may have low muscle mass, providers should be aware of the limitations of serum creatinine in calculating eGFR and consider the use of alternate biomarkers, such as cystatin C if available [71] or measure nuclear GFR.

There is considerable center-to-center variation in screening protocols for hypertension in these patients [77]. Given all the risk factors for hypertension, heart and liver transplant recipients should have routine monitoring of their blood pressure by their primary transplant team, with appropriate technique (manual office measurement and, when available, 24-h ABPM) and with reference to the most updated pediatric hypertension guidelines [78].

In addition to the above-mentioned kidney complications, providers should be aware of the potential for electrolyte abnormalities in these patients. Typically, such electrolyte abnormalities are related to medications (e.g., CNIs or diuretics). Electrolyte wasting may also be seen in children who have sustained AKI due to persistent tubular damage [79].

While many electrolyte abnormalities can be anticipated and mitigated, changes in clinical status, medication regimens, and diet can also impact serum chemistry. As such, it is important that transplant providers routinely monitor electrolytes, provide appropriate dietary counseling, and adjust medication and supplement dosing to meet the needs of each patient.

For all kidney complications, the most effective management centers around anticipation and prevention by the primary team. This includes awareness of patients' risk factors for AKI and subsequent CKD and kidney protective measures such as avoidance of nephrotoxic medications, maintenance of euvolemia, careful monitoring and management of blood pressure and proteinuria, and timely consultation with pediatric nephrology. Furthermore complications of CKD, including anemia, failure to thrive, and mineral-bone disorder, may contribute to significant morbidity and should be managed with local pediatric nephrology and allied health guidance.

The optimal strategy for mitigating chronic CNI nephrotoxicity remains to be determined, and providers must consider immunosuppression regimens for each patient on a case-by-case basis, balancing CNI toxicity with the risk of rejection and adverse effects from alternate agents and non-conventional regimens. Close monitoring of allograft and kidney function is critical with any change in immunosuppressive therapy.

Figure 1 presents a suggested approach to monitoring based on published practice recommendations [71] and our local experience. When there are persistent abnormalities noted in GFR, electrolytes, (first morning) urine protein, or blood pressure, involvement of a pediatric nephrologist may be warranted. Proteinuria as a modifiable risk factor may be controlled by blockade of the renin-angiotensin-aldosterone system with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). Educating families regarding the importance of hydration and careful monitoring of kidney function in patients receiving ACE inhibitors or ARBs are also advised due to increased risk of AKI particularly during episodes of dehydration or acute illness. Management of hypertension in these patients is best directed at addressing the underlying cause when possible, to guide optimal selection of antihypertensive agents as needed.

In many centers, heart or liver transplant teams may choose to manage dysregulated electrolytes, and in some centers, cardiologists may perform ABPM and manage hypertension. In all cases, given the high burden of reduced kidney function and kidney complications in the non-kidney solid organ transplant population, providers should consider creating a clinical pathway for monitoring kidney health, management, and timely referral to nephrologists for these issues at their transplant program.

Conclusion

Advances in medical and surgical management of children with heart and liver transplants have significantly improved their survival. Increased survival and longer follow-up have led to increased recognition and detection of kidney complications in this patient population. From initial diagnosis of organ failure to the time of transplant and long-term post-

transplant follow-up, providers caring for pediatric recipients of heart or liver transplants should be aware of their high risk for AKI and CKD and consider all measures of kidney protection such as minimizing exposure to nephrotoxic medications, avoiding episodes of dehydration, and monitoring and treating modifiable risk factors such as proteinuria and hypertension. Anticipation and prompt recognition of kidney impairment and early pediatric nephrology consultation are essential to improve long-term kidney outcomes for children with heart or liver transplants.

Key Summary Points

- Children with chronic cardiac or liver disease are at risk of kidney complications owing to systemic disease, acute illness, surgeries, and exposure to nephrotoxic medication(s).
- Acute kidney injury (AKI) is common in children with heart or liver transplant and AKI increases their risk for development of chronic kidney disease (CKD).
- CKD is often multifactorial and related to previous AKIs, ongoing nephrotoxin exposure, and chronic allograft dysfunction.
- Given the risk of acute and chronic kidney injury in both heart and liver transplant recipients, care providers should consider all measures of nephroprotection such as avoiding episodes of dehydration, minimizing exposure to nephrotoxic medications, monitoring and treating proteinuria, optimizing blood pressure control, and monitoring kidney function during follow-up.

Multiple choice questions (answers given following the reference list)

1. Which of the following is TRUE with regard to calcineurin inhibitor toxicity?

   a. The most common presentation is gross hematuria and edema.
   b. Interstitial "striped fibrosis" and tubular atrophy are considered pathognomonic histological findings.
   c. CNI nephrotoxicity decreases with duration of exposure.
   d. It is a clinical diagnosis.

2. Which of the following statements is TRUE regarding CKD in children with heart transplant?

   a. CNI exposure is the most common risk factor for CKD post-heart transplant.
   b. The risk of CKD decreases with increasing post-heart transplant survival.
   c. There is no relationship between AKI and the risk of developing CKD.
   d. BK nephropathy is a common cause of CKD in this population.

3. Which of the following statements is FALSE related to the risk of kidney injury in children undergoing liver transplantation?

   a. Cirrhosis pre-transplant may compromise kidney blood flow and result in kidney injury.
   b. Infections such as hepatitis C can cause kidney disease.
   c. Intraoperative basiliximab for induction immunosuppression is associated with kidney injury.
   d. Increased intraoperative bleeding can lead to AKI.

4. Which of these medications is LEAST likely to contribute to hypertension in a child with a solid organ transplant?

   a. Tacrolimus
   b. Cyclosporin A
   c. Prednisone
   d. Mycophenolate mofetil

5. All of the following statements are appropriate measures of nephroprotection in pediatric recipients of heart or liver transplant EXCEPT:

   a. Avoiding nonsteroidal anti-inflammatory drugs
   b. Avoiding episodes of dehydration
   c. Monitoring for and reducing proteinuria
   d. Avoiding the use of induction immunosuppression at the time of transplant surgery

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Answers 1. B; 2. A; 3. C; 4. D; 5. D

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