



## Combined Liver Kidney Transplantation in Pediatrics: Indications, Special Considerations, and Outcomes

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### Abstract

Combined liver and kidney transplants (CLKTs) are not commonly performed in pediatric patients. Advancing the medical community's understanding of when these procedures may be the optimal choice for pediatric patients and when other options may be preferable is crucial. There are three main pediatric groups who may be considered candidates for CLKT: (1) those who suffer a disease that leads to irreversible liver and kidney damage—including autosomal recessive polycystic kidney disease; (2) those with end-stage renal disease caused by a liver-based metabolic disease—including primary hyperoxaluria types 1 and 2, methylmalonic acidemia, and atypical hemolytic uremic syndrome; and (3) those who present with concomitant liver and kidney failure—including patients with Boichis syndrome (nephronophthisis plus congenital hepatic fibrosis) or with liver tumor plus nephrotoxicity. We review here the indications and special considerations related to CLKT for patients in each of these groups and the outcomes seen to date in these pediatric patient groups. With the appropriate donor selection, family education, and medical team commitment CLKT has been shown to be and, we believe, will continue to be an outstanding option for medical management in this select group of patients. Continued advances pre-transplant, intra-operatively and post-transplant will be required to optimize success.

**Keywords:** Combined liver kidney transplantation; Simultaneous liver kidney transplantation; Autosomal recessive polycystic kidney disease; Primary hyperoxaluria, methylmalonic acidemia; Atypical hemolytic uremic syndrome; Boichis syndrome, Concomitant liver and kidney failure

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### Introduction

Since the first combined liver and kidney transplant (CLKT) was performed at Innsbruck University in 1983 [1], 7,255 such procedures have been performed in the U.S. through September 30, 2016 [2]. However, the vast majority of these (6,958) have been in adults, with only 297 CLKTs performed in pediatric recipients, 124 in children aged 11-17, 77 in those 6-10 years, 88 in those 1-5 years, and only eight in children < 1 year. Worldwide, only 10-30 pediatric CLKTs are performed annually [3]. Advancing the medical community's understanding of when these procedures may be the optimal choice for pediatric patients and when other options may be preferable is crucial.

There are three main groups of pediatric patients who may be considered candidates for CLKT: (1) those who suffer a disease that leads to irreversible liver and kidney damage—including autosomal recessive polycystic kidney disease (ARPKD); (2) those with end-stage renal disease (ESRD) caused by a liver-based metabolic disease—including primary hyperoxaluria type 1 (PH1) and type 2 (PH2), methylmalonic acidemia (MMA), and atypical hemolytic uremic syndrome (aHUS); and (3) those who present with concomitant liver and kidney failure—including patients with Boichis syndrome (nephronophthisis plus congenital hepatic fibrosis) or with liver tumor plus nephrotoxicity [3,4]. We review here the indications and special considerations related to CLKT for patients in each of these groups and the outcomes seen to date with CLKT in these pediatric patient groups.

### Autosomal Recessive Polycystic Kidney Disease

Occurring in an estimated one in 20,000 live births [5], ARPKD is rare but is the most common renal cystic/ciliopathy disease in childhood. In ARPKD there is a mutation in PKDHD1, a gene located on chromosome 6p12 that encodes fibrocystin (also known as polyductin), a signaling molecule in kidney tubuli and liver bile ducts that functions to maintain the 3-dimensional tubular architecture [6]. Because the fibrocystin signaling defect is variable, there are substantial variations in the manifestations of kidney and liver injury. Death occurs in 25-30% of neonates with the

most severe disease, most commonly from sepsis or respiratory failure from associated pulmonary hypoplasia. However, substantial improvements in survival rates are being seen with antihypertensive therapy and improved neonatal care [7,8]. Both kidney and liver disease are progressive in most patients, with nearly 50% progressing to ESRD in the first decade of life. Renal involvement ranges from a urinary concentration defect in apparently normal kidneys to fusiform dilatations of the renal collecting ducts leading to the formation of cysts and renal insufficiency [8-10]. Liver involvement includes defective remodeling of the ductal plate, abnormal portal veins and progressive fibrosis of the portal tract [8]. Although all ARPKD patients have congenital hepatic fibrosis (CHF), not all develop liver dysfunction. However, hepatic defects often become progressively more severe with age, with liver disease a major cause of morbidity and mortality. The histological changes in the liver can lead to severe portal hypertension, splenomegaly with hypersplenism, and esophageal varices resulting in bleeding complications [9].

The CHF commonly predisposes to recurrent cholangitis [9]. In approximately a third of ARPKD patients, Caroli syndrome develops, characterized by segmental non-obstructive cystic dilatation of the intrahepatic biliary ducts with conserved association with the intrahepatic biliary system [11]. In patients with Caroli syndrome, congenital hepatic fibrosis is always present; in the most advanced stage, there is hepatomegaly, portal hypertension, cholangitis and variceal bleeding [9]. Treatment strategies for ARPKD are challenging due to the fact that the kidney and liver disorders progress differently and the variability of organ involvement is not completely understood. In children with early presentation and a need for nephrectomy secondary to respiratory compromise, dialysis is started in the first days of life and isolated kidney transplant is done in the first years of life. Complications from liver disease (portal hypertension, cholangitis and hypersplenism) after isolated kidney transplant are common and would then require sequential liver transplant evaluation. In one study of 14 ARPKD patients who underwent kidney transplant, five patients died, four from complications of hepatic disease; of the nine patients who survived, CHF-related complications were present in 56% at a mean of 6.3 years post-transplant [12]. CLKT is indicated in older children with ESRD and evidence of CHF with hypersplenism and cholangitis [13]. Isolated liver transplant is indicated in older children with progressive complications of liver disease and stable kidney disease.

## Primary Hyperoxaluria Types 1 and 2

PH1 is a rare autosomal recessive metabolic disorder, with an estimated incidence of only one case in 120,000 live births [14], but is the most common indication for CLKT in children. The cause of PH1 is deficiency or mislocalization of the liver-specific peroxisomal enzyme alanine-glyoxylate aminotransferase (AGT) [11]. Because AGT is required to catalyze the conversion of glyoxylate to glycine, the enzyme deficiency results in the conversion of glyoxylate to oxalate which forms insoluble calcium salts which can collect in the kidney and other organs [15]. This can result in recurrent nephrocalcinosis (deposition of calcium oxalate in the renal parenchyma), nephrolithiasis (deposition of calcium oxalate in the renal pelvis/urinary tract), or ESRD with a history of renal stones or calcinosis [11-15]. There is substantial variation in the presentation of PH1, with the age at onset of symptoms ranging from birth to the sixth decade, with a median age of 5-6 years [16]. In the more severe, infantile form of PH1, 80% develop ESRD by the age of three

years [17]. Data from a 1990 German study had indicated that by age 15 approximately 50% of patients develop ESRD [18]. However, later surveys performed in Switzerland and France found that ESRD occurred in only 20% of patients by the age of 15 but in 50% of patients by the age of 25 [19-20]. When the glomerular filtration rate (GFR) drops below 40 mL/min/1.73m<sup>2</sup>, oxalate is deposited systemically into bone and soft tissue including the retina, the blood vessels, the nerves and the heart [13]. Because some infants are pyridoxine sensitive and will show improvement in renal function with high-dose vitamin B6 [14], responsiveness to pyridoxine should be evaluated prior to transplantation. The specific pathogenic variants p.Gly170Arg and p.Phe152Ile are associated with a positive response to pyridoxine supplementation, especially for homozygotes, so testing for these may have predictive value [14,21,22].

CLKT is the procedure of choice for PH1 patients [23-27] in order to protect the transplanted kidney from the same damage experienced by the native kidneys. Data from the United States Renal Data System shows patient survival above 80% at 5 years, with graft survival of 76% eight years post-transplant [28]. Data from the European PH1 Transplant Registry on 100 CLKT procedures performed from 1984 to 2004 has shown patient survival rates of 86%, 80%, and 69% at one, five, and ten years, respectively, with 13 kidney graft failures [29]. Small studies have pointed to important therapeutic considerations with patient and graft survival rates of 75% (at 5 years) in children with early CLKT in whom high hydration was maintained for 6 months to 5 years as long as oxaluria exceeded 0.5 mmol/day [30] and 100% (at 6.7 years) in infants with early diagnosis and early CLKT, aggressive pre-transplant dialysis, and avoidance of post-transplant renal dysfunction [31].

Because of the high risk of postoperative renal dysfunction due to mobilization of oxalate from other tissues, experts in the field suggest that sustained hyperhydration post-CLKT should be considered mandatory to protect the renal graft and vessels from oxalate deposition, with discontinuation only when the urinary oxalate/creatinine ratio has normalized [11,13]. Postoperative crystallization inhibitors are also recommended to prevent disease recurrence in the new kidney [11]. In addition, both intensive dialysis prior to transplantation and postoperative hemodialysis post-transplant until urine oxalate levels are normal are recommended to reduce the oxalate pool, preventing deposition of oxalate in the kidney graft [11]. Sequential transplantation beginning with the liver can be considered when a kidney is not available [27] and in PH1 patients with stage 5 chronic kidney disease (estimated GFR less than 15 ml per minute per 1.73 m<sup>2</sup>) [27] so that the new liver can allow aggressive dialysis to mobilize some of the systemic oxalate burden prior to the kidney transplantation, thus protecting the kidney graft [32-33]. DNA analysis should always be done to confirm the diagnosis of PH1 prior to consideration of CLKT [13]. With PH1, isolated kidney transplant is no longer recommended [13]. It cannot correct the primary metabolic defect since it is in the liver, and multiple studies have shown very poor renal graft survival due to the continuing high level of urinary oxalate excretion that results from both ongoing oxalate production by the native liver and oxalate deposits in tissues [13,33]. Only in developing countries where isolated renal transplant might provide a temporary solution until a child can be brought to a specialized center for CLKT is kidney transplant alone still considered [23].

Primary hyperoxaluria type 2 (PH2) is an autosomal recessive

metabolic disorder that is thought to be less common than PH1 but for which there is currently no prevalence data [34]. The cause of PH2 is deficiency of the enzyme glyoxylate reductase-hydroxypyruvate reductase (GRHPR), the lack of which results in substantial overproduction of oxalate and, thus, hyperoxaluria [11]. PH2 onset is most commonly in childhood with presenting symptoms typically those associated with renal stones, including renal colic, hematuria, and urinary tract obstruction [35-36]. In comparison to PH1, the clinical course of PH2 is generally more benign but there may be recurrent nephrolithiasis (deposition of calcium oxalate in the renal pelvis/urinary tract) and nephrocalcinosis (deposition of calcium oxalate in the renal parenchyma) [34], as well as ESRD in approximately 20% of cases [11]. In PH2 patients with ESRD, oxalosis (widespread tissue deposition of calcium oxalate) is common [34]. Although experience with organ transplantation in PH2 patients is limited, isolated kidney transplantation has been suggested as the possible procedure of choice [27,37]. However, the failure of this procedure in a pediatric PH2 patient because of disease recurrence has led others to question this and suggest that CLKT might be preferable [38]. Bacchetta et al. [13] suggest that responsiveness to pyridoxine should be assessed in PH2 patients prior to transplantation since it is possible that some may benefit from isolated kidney transplant if pyridoxine is maintained but note that only case reports and small series support such an approach.

### Atypical Hemolytic Uremic Syndrome

Atypical hemolytic uremic syndrome (aHUS) is a rare progressive disease most commonly the result of complement alternative pathway (AP) dysregulation, the cause of 60-70% of cases [39-42]. In aHUS there is impaired synthesis or function of factor H, a complement control protein that normally controls complement activation through the alternative pathway, resulting in deposition of complement, destruction of microvasculature, and severe renal and neurological involvement [43]. The disease is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and renal impairment [39]. CLKT is no longer commonly recommended for aHUS because eculizumab (Soliris, Alexion Pharmaceuticals, New Haven, Connecticut), a recombinant humanized monoclonal IgG2/4 antibody that binds to the terminal complement component 5 (C5), has been shown to be an effective treatment for most patients with aHUS, combined with isolated kidney transplant, if necessary. Studies to date have shown that eculizumab yields sustained inhibition of complement-mediated thrombotic microangiopathy (TMA) and allows improved or preserved renal function in the majority of patients with aHUS, including both children and adults [44-46]. However, certain gene mutations are associated with altered response to eculizumab. Mutations in multiple genes have been associated with increased aHUS susceptibility, including CFH, CFI, MCP, C3, CFB and THBD (thrombomodulin). In addition, mutations in DGKE have recently been shown to be associated with complement-independent forms of aHUS in which aHUS develops before age one and results in hypertension, hematuria and proteinuria (sometimes in the nephrotic range), with chronic kidney disease developing with age [47]. In patients with isolated DGKE mutation, no benefit was observed from eculizumab treatment [47]; in a patient with both DGKE mutations and an associated C3 variant, eculizumab treatment was associated with clinical improvement but persistent proteinuria [48]. In addition, a C5 variant that prevents eculizumab from binding to C5 has been identified in Asian-origin patients who were resistant to eculizumab [49].

Because the only other approach used in the past, plasma exchange/plasma infusion had limited efficacy with a high rate of complications [50] and considerable morbidity in children, isolated kidney transplant had been tried. However, post-transplant aHUS recurrence occurred in 60% of patients [39,51], with five-year graft survival of only 30% in patients with recurrence and 68% in patients without recurrence [51]. Prophylactic eculizumab has been successfully used to prevent post-transplant recurrence in patients in whom previous grafts had been lost due to recurrence or who had high-risk genetic abnormalities (CFH, C3, and CFB + CFI mutation) [52]. Patients treated with eculizumab after post-transplant recurrence have most often not reached full return of graft function [52]. In a 2016 international consensus statement by experts from Europe, Canada, Turkey, and the United States prophylactic eculizumab is recommended for patients at high risk of post-transplant recurrence; additional research will be required to determine when or if eculizumab withdrawal might be possible [52]. In the consensus statement these experts also note that liver transplantation or CLKT is the only way to cure aHUS in patients with severe aHUS and mutations of complement factors synthesized in the liver (CFH, CFB and C3) [52]. They recommend that CLKT should still be considered an option that should be discussed with patients and families, with full consideration of risks and benefits, and factoring in whether the cost of long-term eculizumab treatment after isolated kidney transplantation can be covered. There is currently substantial variation in eculizumab availability due to the extremely high cost of the drug; it is currently one of the most expensive drugs in the world. With any consideration of transplant, there should be meticulous pre-transplant multidisciplinary evaluation to assure that there is no metabolic crisis, infection or precipitating factor. Pre- and intra- operative plasma exchange can be used to inhibit unregulated complement deposition.

### Methylmalonic Acidemia

Methylmalonic acidemia (MMA) is an autosomal recessive disease of methylmalonic acid metabolism that results from either complete (*mut<sup>o</sup>*) or partial (*mut<sup>r</sup>*) congenital deficiency of the vitamin B12-dependent enzyme methylmalonyl-CoA mutase (*MUT*) or from defective adenosylcobalamin (cblA, cblB, cblD variant 2) metabolism [43]. Despite detection of MMA through newborn screening and the use of medical therapies, it causes significant morbidity and mortality in infancy and childhood and, for those who reach adulthood, significant debilitating end-organ damage [53], with substantial risk for metabolic decompensation and multiple long-term complications [54]. Although dietary management with medical foods has long been a major component of MMA therapy, it has been shown that even well-controlled MMA patients are at high risk for renal, cardiac, ophthalmological, growth, and neurological complications [53]. Patients commonly present with metabolic crisis, profound acidosis, seizures, neurological impairment and developmental delay [55-57].

With improved survival of MMA patients, chronic kidney disease due to tubule interstitial injury has become recognized as part of the disease, with some renal insufficiency present in 100% of MMA patients and progression to ESRD and need for transplant common [53,58,59]. In adolescents with MMA, it is estimated that the prevalence of ESRD is 20-60% [57]. In a study of long-term outcomes it was found that ESRD develops in 61% of MMA *mut<sup>o</sup>* patients and 66% of cblB patients [60]. The study found that patients with *mut<sup>o</sup>* and cblB defects had earlier symptom onset, as well as a higher frequency

of complications and deaths and more pronounced MMA urinary excretion compared to those with *mut* and *cblA* defects [60].

Isolated renal transplant can partially correct the metabolic defect of MMA since the kidney possesses approximately 18% of the methylmalonyl-CoA mutase activity present in the liver [43], and may contribute to stabilization of clinical conditions [61]. However, urinary excretion of methylmalonic acid remains elevated, potentially causing progressive injury to the renal allograft [43]. Isolated liver transplant replaces the missing enzyme and decreases hepatic production of methylmalonic acid [43] and has been shown to improve both metabolic stability and quality of life in MMA patients [53]. However, it only partially corrects the metabolic defect because abnormal methylmalonic acid metabolism continues in other tissues, including the muscles and skin [62], and injury to non regenerative tissues may not be mitigated [53]. In comparison to isolated transplant of either the kidney or liver, CLKT can improve the underlying enzymatic defect, increase the clearance of methylmalonic acid, and restore renal function [43].

In a Stanford University study we assessed biochemical, surgical, and long-term outcomes in children with severe, early-onset MMA who underwent either CLKT (n=8) or isolated liver transplantation (n=6) at mean age 8.2 years (range 0.8-20.7) [54]. For patients who received CLKT, the indication for transplantation was chronic kidney disease (stage III or IV). The indication for patients who received LT was a difficult clinical course with multiple admissions per year for hyperammonemia and metabolic acidosis. At the time of diagnosis, mean blood ammonia in the six patients for whom the level was available was  $611 \pm 404$   $\mu\text{mol/L}$  (range 197-1200). Pre-transplantation, all patients had multiple hospitalizations yearly as the result of hyperammonemia, metabolic acidosis, or both. Twelve patients received a whole liver graft and two a reduced-size graft. Postoperative survival was 100%; at mean follow-up of  $3.25 \pm 4.2$  years (range 0.25-14 years), patient, kidney graft, and liver graft survival were 100%, 100%, and 93%, respectively. In one case there was successful re-transplantation after losing the first liver graft because of hepatic artery thrombosis five days post-transplant. Mean serum MMA levels were 83% below pre-transplantation levels at four months post-transplant. Post-transplantation, there were no episodes of hyperammonemia or metabolic acidosis. At baseline, developmental delay had been present in 86% of patients; post-transplant, all patients either exhibited improvements in motor skills, learning abilities, and social functioning, or at least maintained neuro-developmental abilities.

Data from the United Network for Organ Sharing showed that in patients with urea cycle defects or organic acidemias who underwent liver transplant at < two years of age, the five-year overall survival was 88%, with 78% liver graft survival; in those who underwent liver transplant at > two years of age, there was 99% overall survival and 88% liver graft survival [63]. Quality of life has been shown to improve substantially post-CLKT in MMA patients, with improvements in energy, decreased hospitalizations, and the ability to return to school with discontinuation of dialysis [54,57,64]. Based on our outcomes to date at Stanford University, we recommend early CLKT for MMA patients with chronic kidney disease to prevent further neurological injury, avoid metabolic crisis, and provide the ability to liberalize nutritional support in order to enhance growth and development [54]. The complexity with these patients and the multispecialty team that is needed to manage their clinical care demands an experienced

group of subspecialists with vast experience in metabolic diseases and transplantation. With this, it is possible to accomplish excellent results with this complex group of children. Isolated liver transplant can be considered in patients with preserved renal function.

## Concomitant Liver and Kidney Failure

Pediatric patients with concomitant liver and kidney failure may also be candidates for CLKT. There are multiple conditions which may in some cases result in this combined organ failure. Included are the following: (1) nephronophthisis (NPHP) with congenital hepatic fibrosis (Boichis syndrome), (2) alpha-1-antitrypsin deficiency ( $\alpha$ 1-AT), (3) glycogen storage disease type Ia (GSDIa), (4) hepatorenal syndrome (HRS), and (6) liver tumor plus nephrotoxicity [3,4,13].

Nephronophthisis (NPHP) is an autosomal recessive cystic kidney disease that is the most common genetic cause of ESRD in children and young adults [65]. With NPHP there are mutations in NPHP genes that result in defects in signaling mechanisms that involve the non-canonical Wnt signaling pathway and the sonic hedgehog signaling pathway [65]. In NPHP there is commonly multiple organ involvement, which may include not only liver fibrosis, but also retinal degeneration, cerebellar hypoplasia, *situs inversus*, and intellectual disability [65]. There have been reports of successful CLKT for children with NPHP and hepatic fibrosis [66]. In one study, of three NPHP/hepatic fibrosis patients who underwent CLKT, there was no loss of liver graft but in one patient the kidney graft was lost 5 years after CLKT from chronic rejection that resulted from an over-reduction of immunosuppressive therapies (cyclosporine and azathioprine) due to an EBV infection [66]. This patient went back on hemodialysis and underwent a second renal transplant 4 years later but died from cardiovascular disease one year after the second renal transplant (10 years after the initial CLKT); at the time of death, both the second renal graft and the liver were functioning correctly.

The most common genetic cause of liver disease in children is alpha-1-antitrypsin deficiency ( $\alpha$ 1-AT) [67], an autosomal recessive disorder caused by mutations in the *SERPINA1* gene [3] which is the most common genetic disorder for which pediatric liver transplantation is performed [68]. In children with a homozygous Z mutation (Glu342L; PiZZ), the variant most commonly associated with liver disease, it is estimated that approximately 10% to 20% will develop cholestatic liver disease, with a minority progressing to cirrhosis and hepatic failure [3,67,69]. Mesangiocapillary (membranoproliferative) glomerulonephritis develops in some children with  $\alpha$ 1-AT, and may progress to ESRD [70]. There have been some reports of isolated liver transplantation in  $\alpha$ 1-AT patients achieving reversal of renal dysfunction. In patients who have already progressed to ESRD and advanced liver disease CLKT may be appropriate. There have been several reports of long-term survival post-CLKT in children [69,74,72].

Glycogen storage disease type I (GSDI) is an autosomal recessive disorder caused by the accumulation of glycogen in certain organs and tissues, especially the liver, kidneys, and small intestines. The overall incidence of GSDI is 1 in 100,000 individuals; GSDIa accounts for 80 percent of all GSDI cases. Glucose-6-phosphatase-alpha (G6PC) catalyzes the hydrolysis of glucose-6-phosphate to glucose and phosphate in the terminal step of gluconeogenesis and glycogenolysis [73]. The G6PC gene mutations that cause GSDIa prevent this, resulting in excessive conversion to glycogen and fat. The disease is characterized by hypoglycemia, hepatomegaly,

nephromegaly, hyperlipidemia, hyperuricemia, lactic acidemia, and growth retardation leading to short stature [74]. Proteinuria, hypertension, renal stones, nephrocalcinosis, and altered creatinine clearance occur in some younger GSDI patients; with progression, interstitial fibrosis becomes evident and some patients will progress to ESRD requiring kidney transplant [75-77]. Most GSDI patients will develop hepatic adenomas with the potential for intrahepatic hemorrhage by the second or third decade of life; there is also the potential for some adenomas to transform into hepatocellular carcinoma (HCC) [76,78-80]. The standard treatment is nutrition therapy aimed at preventing hypoglycemia and providing optimal nutrition for growth and development. Other therapies that may be used to address various disease manifestations include lipid-lowering medications, allopurinol to prevent gout, citrate supplementation to prevent nephrocalcinosis and urinary calculi development, and ACE inhibitors to treat microalbuminuria [81]. Full guidelines for management of GSDAa have been published by the American College of Medical Genetics and Genomics [82]. Isolated liver transplantation has been performed in GSDI patients with multiple unresectable adenomas, poor metabolic control, and progressive liver failure with resulting restoration of the liver gluco-regulatory function and normal metabolic balance, very significant catch-up growth and improved quality of life; however, post-transplant complications included focal segmental glomerulosclerosis with progressive renal insufficiency [83-84]. There have been reports of a small number of CLKTs that have been successfully performed in GSD1a patients [72,85-87]; physicians participating in these have recommended that CLKT be considered for patients with ESRD secondary to GSD1a [84,86,87].

In hepatorenal syndrome (HRS) renal failure develops in patients with advanced chronic liver disease and, in some cases, fulminant hepatitis, who have ascites and portal hypertension. Approximately 40% of patients with cirrhosis and ascites will eventually develop HRS. In most cases, HRS resolves with isolated liver transplantation [88]. However, in some patients with lengthy HRS there can be progression to irreversible renal failure. CLKT can be considered in such patients [3,89,90]. There are currently no guidelines for CLKT in pediatric HRS patients. CLKT is considered in adults with HRS who have been on dialysis > 6 weeks. Jalanko and Pakarinen propose that since the regenerative capacity of children's kidneys is not very different from that in adults, the recommendations for adults with HRS may be valid for children [3].

In children with hepatoblastoma, renal failure may develop because of the chemotherapy drugs used both before and after tumor resection. Since the 1990's most chemotherapy regimens for hepatoblastoma have included cisplatin, doxorubicin, or both agents [91,92]. Renal dysfunction develops in more than 70% of pediatric patients receiving cisplatin [93], typically beginning within only a few days of initiation of standard cisplatin treatment and shown by increased serum creatinine and blood urea nitrogen levels [94,95]. Despite the use of preventive measures, progressive renal failure can occur with successive cisplatin treatments, ultimately leading to ESRD [96]. Doxorubicin can also cause significant nephrotoxicity [97-100]. In some cases of hepatoblastoma, to meet the goal of complete tumor resection with negative margins, total hepatectomy with liver transplantation is required [101], particularly with large, solitary PRETEXT IV tumors, multifocal PRETEXT IV tumors, and unifocal centrally located tumors involving main hilar structures or main hepatic veins (as with some PRETEXT II or III V+/P+ tumors) [102]. For example, in the recent SIOPEL-4 study, total hepatectomy

with transplantation was required in 26% (16/62) of patients to achieve complete macroscopic resection of the primary tumor [102]. In patients who will require liver transplantation and have suffered kidney injury secondary to chemotherapy and/or intrinsic kidney disease, CLKT offers the best option for long term success for several reasons:

(1) The use of single donor for both organs offer immunological advantages; (2) Immunosuppression management is improved with the optimal renal function provided by the kidney transplant; (3) Post-op chemotherapy can be administered in therapeutic doses when renal function is improved.

### **CLKT Short and Long-Term Outcomes**

CLKT is a complex surgical procedure in which technical complications are not uncommon. In a retrospective analysis of 15 CLKTs performed in 14 pediatric patients between 1998 and 2009, it was shown that postoperative bleeding occurred in six patients (40%), three of whom required operative revision for intra-abdominal bleeding; postoperative hemodialysis was required in almost half of the infants (because of delayed kidney graft function or clearance of hyperoxaluria); two patients (13%) showed liver graft outflow complications; one patient developed renal artery thrombosis [103]. Despite these initial complications, the one- and five-year patient survival was 100%; one- and five-year graft survival was 80% for the liver and 93% for the kidney allograft. Because of small-sized anatomical structures and restricted space, CLKT in very young children presents technical challenges. However, in this study, subgroup analysis of the very small infants (age < 3 years and weight < 12 kg) showed both excellent short-term and long-term outcomes, with 100% survival of both grafts and patients at one and five years. Patient, liver graft and kidney graft survival rates have varied substantially in published pediatric CLKT series. Using the Scientific Registry of Transplant Recipients, Calinescu et al analyzed data to determine outcomes of 152 primary pediatric CLKTs performed from October 1987 to February 2011, the largest series to date [104]. Liver graft survival at one, five and ten years were 81.9%, 76.5%, and 72.6 %, and kidney graft survival was 83.4%, 76.5% and 66.8 %, respectively. Patient survival was 86.8% at one year, 82.1% at five years, and 78.9% at ten years, approximately equal to patient survival with isolated liver transplant at the same time points (86.7%, 81.2% and 77.4%) but inferior to survival with isolated kidney transplant at those points (98.2%, 95.4% and 90%). In PH1 patients, CLKT was associated with reduced patient, liver graft and kidney graft survival. However, liver graft survival improved after 2002.

### **Conclusion**

As our understanding of liver-derived metabolic disorders increases, our indications for CLKT are potentially expanding as children with these diagnoses are outliving their historic cohort. Interestingly, aside from patients with concomitant liver and kidney failure, the population that makes up the smallest percentage of CLKTs being performed in pediatrics, none of the indications for CLKT include liver failure. In that setting, the liver transplant must be technically perfect as does the lifelong transplant care. Technical complications will add significant comorbidities that would not have been factored into disease prognosis prior to transplant. Hemodynamic instability from a prolonged operation can lead to delayed kidney graft function or primary graft non-function in a setting where correction of renal failure is the major goal of the operation. Chronic rejection can lead to liver failure which is a new

entity in this patient population. Recent survival data suggest that we are tackling these issues but it remains imperative that these transplants be performed in experienced centers with full discussion and disclosure of potential risks and benefits to the patients and their families. With the appropriate donor selection, family education, and medical team commitment CLKT has been shown to be and, we believe, will continue to be an outstanding option for medical management in this select group of patients. Continued advances pre-transplant, intra-operatively and post-transplant will be required to optimize success.

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