Combined liver and kidney transplantation in children

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Received: 7 February 2013 / Revised: 25 March 2013 / Accepted: 8 April 2013 / Published online: 4 May 2013
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Abstract Simultaneous combined liver–kidney transplantation (CLKT) is a rare operation in pediatric patients so that annually only 10–30 operations are performed worldwide. The main indications for CLKT are primary hyperoxaluria type 1 and autosomal recessive polycystic kidney disease. In addition, CLKT is indicated in individual patients with metabolic or cirrhotic liver diseases and end-stage kidney disease. The surgery and immediate post-operative management of CLKT remain challenging in infants and small children. The patients should be operated on before they become severely ill or develop major systemic manifestations of their metabolic disorder. The liver allograft is immunologically protective of the kidney graft in simultaneous CLKT, often resulting in well-preserved kidney function. The long-term outcome after CLKT is nowadays comparable to that of isolated liver and kidney transplantations.

Keywords Liver transplantation · Kidney transplantation · Children · Primary hyperoxaluria · Autosomal recessive polycystic kidney disease · Atypical hemolytic uremic syndrome

Introduction

Combined liver–kidney transplantation (CLKT) is a two-step procedure, in which whole or partial liver and kidney

from a donor are transplanted to a recipient in the same operation. The first successful CLKT was performed at Innsbruck University in 1983, and since then CLKT has become an established treatment modality for both adults and children with severe liver and kidney disorders [1, 2]. The recent introduction of the MELD (model for end-stage liver disease) scoring system for prioritization of adult liver transplantation, which is strongly influenced by renal dysfunction, has increased the number of CLKT in the USA [3], and currently over 400 CLKT are performed annually in Europe and USA. The great majority of the recipients are adults, and CLKT is still a rare operation in children and adolescents, with only 10–30 pediatric CLKT performed annually worldwide. CLKT accounts for 1–2 % of all pediatric liver transplantations, with one-third of recipients being 0–5 years of age and two-thirds being between 6 and 17 years old [1].

Combined liver–kidney transplantation is indicated in pediatric patients for three reasons: (1) the patient has a disease leading to both irreversible liver and kidney failure, such as autosomal recessive polycystic kidney disease (ARPKD); (2) the patient has an end-stage kidney disorder (ESRD) caused by a liver-based metabolic disease, such as primary hyperoxaluria type 1 (PH1) or atypical hemolytic uremic syndrome (aHUS), in which case liver is transplanted to correct the underlying defect; (3) the patient has a severe liver disease and poorly functioning kidneys (drug toxicity, vascular complications), in which case concurrent kidney transplantation (KT) is performed to ensure sufficient renal function after liver transplantation (LT). The last indication is common in adults but not in children (Table 1).

Surgical aspects

Combined liver–kidney transplantation combines the technical aspects of both isolated LT and KT. After hepatectomy,

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Table 1 Indications for pediatric combined liver–kidney transplantation

Major indications

- Primary hyperoxaluria type 1 (PH1)
- Autosomal recessive polycystic kidney disease (ARPKD)

Minor indications

- Liver disease with an occasional kidney failure
 - Alpha-1-antitrypsin deficiency
 - Glycogen storage disease, type 1
 - Alagille syndrome
 - Biliary atresia
 - Hyperalimentation-induced liver disease
 - Primary sclerosing cholangitis
- Liver disorder with a previous kidney transplant (allograft nephropathy)
- Liver tumor with drug nephrotoxicity
- Metabolic disease with a controversial experience (see the text)
- Atypical hemolytic uremic syndrome (aHUS)
- Methylmalonic acidemia (MMA)

the recipient's liver can be replaced by a full size, a reduced size, or a split liver graft (donor liver divided between two recipients) depending on the donor/recipient size match (Fig. 1) [4]. The organs usually come from a deceased adult donor, but living donor CLKT using a left-lateral liver graft and kidney from the same donor (a parent) has also been performed [5]. To ensure enough functional tissue, the

weight of the reduced size or split liver should exceed 2 % of the recipient body weight.

The vascular anastomoses are critical in liver graft implanting. Reconstruction of the arterial and portal veins and of liver vein outflow depend on the type of the graft and possible vascular variants of the donor liver. End-to-end anastomoses of the blood vessels are mostly used, but the hepatic artery (from the graft) can also be anastomosed directly to the aorta in small children with narrow vessels. For the biliary reconstruction, end-to-end anastomosis of donor and recipient bile ducts can be performed when a whole liver or a right extended graft is used. A biliodigestive anastomosis with the Roux-en-Y jejunal limb is used with left lateral grafts or when the primary disease affects the biliary tract, such as polycystic diseases and biliary atresia.

After implantation of the liver, a solitary kidney from the same donor is placed extraperitoneally into the right or left iliac fossa, as is the case in isolated KT. When there is a lack of space, the kidney can also be placed into the abdominal cavity. To create enough space for the organs, unilateral or bilateral nephrectomy is often performed in ARPKD patients before CLKT. If organs from a very young donor are used, both kidneys can be transplanted en bloc into the same recipient [6].

Surgical complications after CLKT are not uncommon. Bleeding from the resected liver into the abdominal cavity may require operative revision. Gastrointestinal hemorrhage

Fig. 1 Combined liver–kidney transplantation includes an orthotopic transplantation of a whole, reduced size, or split liver depending on the donor/recipient size match as well as isolated kidney transplantation from the same donor. The kidney graft is implanted in the right or left iliac fossa or intraperitoneally

can occur, especially if hemodialysis (requiring anticoagulation) is performed after the operation. Vascular complications include hepatic artery and portal vein thromboses as well as hepatic outflow obstruction. Frequent post-operative Doppler flow measurement (two times a day) during the first few days is important for early detection of circulatory problems. Early thrombectomy or an operative revision of the vascular anastomosis may be needed. A persisting poor blood flow can lead to graft loss and subsequent retransplantation. Also, leak or strictures of the biliary anastomosis may require operative intervention, although a significant proportion of these can be treated with a combination of drainage and stenting. Stents are placed either percutaneously or endoscopically [7]. Little published data are available on surgical problems after CLKT, but after isolated pediatric LT the frequency of bleeding, thrombotic, and biliary complications varies between 5 and 18 %, 3 and 20 %, and 3 and 35 %, respectively [8, 9]. Surgical complications of the renal graft are less common and include lymphocele and leakage or stenosis of the vesical implantation site or the ureter. Vascular complications may appear, especially if the space for the kidney graft is limited.

After the operation, primary non-function of the liver graft is rare. Delayed function of the kidney graft (DGF) is more common, and patients with PH1 especially have a risk for poor early kidney function, and hemodialysis or continuous hemofiltration may be required. Ventilation is usually needed for 1–2 days only, and the stay in intensive care typically lasts for a few days [10]. Intensive care, however, may last several weeks for patients with multiple problems. As is the case in isolated LT, post-operative ascites formation and intra-abdominal bacterial and yeast infections can require drainage and long-lasting antimicrobial therapy [11].

Immunological aspects

The immunosuppressive medication of CLKT patients is center-dependent. Induction with anti-interleukin-2-receptor antibodies (basiliximab) or anti-thymocyte globulin (ATG) is used in some, but not all, centers. The use of induction and the slow introduction of calcineurin inhibitor (CNI) have been advocated to reduce post-transplant kidney injury, especially in PH1 patients. Triple immunosuppression with a CNI (cyclosporine A or tacrolimus), antimetabolite (azathioprine or mycophenolate), and glucocorticoid (prednisone or methylprednisolone) is widely used as a maintenance therapy. The immunosuppressive medication of a patient is individualized according to the rejection episodes and drug toxicity. Glucocorticoid is weaned off in some centers.

ABO blood group compatibility of the donor and recipient is usually required in CLKT. On the other hand, human

leukocyte antigen (HLA)-matching and negative T-cell or B-cell cross-match have not been regarded important, as is the case in isolated LT [12]. Retrospective analyses and clinical experience indicate that patients with a positive cross-match do not easily develop hyperacute or acute antibody-mediated rejection (AMR) in either graft [13]. The preformed antibodies are possibly trapped by the liver (Kupffer cells) without affecting the function of either graft. Thus, the liver offers immunologic protection against AMR of the kidney graft. Recent studies, however, suggest that the liver may not be completely protective [14]. Preformed donor-specific antibodies have been reported to promote AMR, and in a large analysis of over 2,484 CLKT recipients, pre-sensitization had a negative impact on survival of both the patient and the kidney graft [12].

Acute rejection (AR) episodes may appear after the operation in either or both grafts and usually resolve following treatment with high doses of glucocorticoid. Several studies on adult patients; however, have shown that recipients of simultaneous CKLT have a lower incidence of kidney rejection and allograft loss than patients with isolated KT or sequential transplantation [15]. According to the United Network for Organ Sharing (UNOS) database, 21 % of adult CLKT patients had AR episodes as compared to 30 % of patients with isolated KT [16]. The lower rejection rate was more pronounced in sensitized patients and those receiving HLA-mismatched organs. Data on the liver's protective effect are limited in pediatric patients. In a report from the University of California, Los Angeles, there was only one AR episode in ten CLKT patients, as compared to 16 episodes in 100 KT children [17]. In another pediatric study of 12 patients, a lower AR rate was seen following simultaneous CLKT as compared to sequential transplantation [18]. The lower incidence of rejection is also reflected in the long-term kidney graft function and survival, as recently shown by pediatric and adult data from the UNOS database [17, 19]. In our center the measured long-term glomerular filtration rate (GFR) is on average 23 % better in CLKT patients than in KT children.

The mechanism by which a liver simultaneously transplanted with a kidney would protect the kidney graft from AR episodes, and prolong renal allograft survival, is not known. It has been suggested that CLKT results in microchimerism and donor-specific hyporesponsiveness. Soluble class I HLA-antigens from the liver could neutralize cytotoxic T-lymphocytes and anti-HLA antibodies. Similarly, regulatory HLA-G antigens produced by the liver might inhibit T-cell cytotoxicity [20]. Secretion by the liver of immunomodulatory cytokines has also been suggested. In a recent study of combined auxiliary liver–kidney transplantation, liver grafts strongly up-regulated CCL20 lymphokine, which can recruit dendritic cells and regulatory T-cells and thus prevent rejection [21].

CLKT in different indications

Primary hyperoxaluria type 1

Primary hyperoxaluria type 1 is an autosomal recessive disorder caused by mutations in the *AGXT* gene encoding vitamin B6-dependent liver-specific peroxisomal enzyme alanine-glyoxalate aminotransferase. This deficiency leads to elevated levels of oxalate and glycolate. Oxalate is excreted in the urine, where it forms crystals with calcium, leading to oxalate stones, nephrocalcinosis, tubular epithelial damage, and renal failure. General oxalosis develops when the GFR declines to $<40\text{--}50\text{ ml/min/1.73 m}^2$, leading to oxalate accumulation in bones, skin, blood vessels, myocardium, nerves, joints, and retina, but not in the liver. The mean age of onset of symptoms is 4–6 years, and ESRD is reached at the median age of 24–35 years. Early and aggressive conservative management, including high fluid intake, oxalate crystallization inhibitors, and pyridoxine, may preserve renal function and delay the development of ESRD [22]. Infantile PH1, which nowadays represents almost half of the cases, however, often progresses rapidly, and ESRD is reached before the age of 2–3 years [23]. The most recent recommendations for the diagnostics and management of PH1 were published in 2012 by the OxalEurope Study Group (Table 2) [24].

For over two decades the predominant strategy for management of PH1 in Europe has been to directly pursue CLKT for patients with kidney failure [25, 26]. According to a recent report of the International Primary Hyperoxaluria Registry (IPHR), the use of CLKT as the primary therapy has also increased in non-European centers such that, since 2000, 24 of the 29 transplanted PH1 patients underwent CLKT [27]. CLKT is the method of choice in patients with severe forms of PH1 but not in those who clearly benefit from vitamin B6 therapy and/or have favorable mutations,

such as the homozygous c.508G>A mutation [28]. CLKT restores the renal function and corrects the metabolic defect. The new liver, however, does not eliminate the oxalate that has already been deposited in tissues although it does prevent its further overproduction. Oxalate is mobilized from the tissues to plasma and urine so that the oxalate levels remain elevated for up to 3–4 years. Recurrent nephrocalcinosis is still a risk in these patients and may lead to reduced kidney graft function. High fluid intake and crystallization inhibitors are necessary post-transplantation. The aim of the therapy is to reach plasma oxalate levels of $<30\text{ }\mu\text{mol/l}$ and to reduce urinary oxalate excretion ($<0.5\text{ mmol/1.73 m}^2/\text{day}$) as well as calcium excretion (0.1 mmol/kg/day) in order to minimize kidney graft damage. PH1 patients often show a delayed recovery of renal function after CLKT [29], and the use of induction therapy with ATG or basiliximab has been recommended [1], which allows slow and careful introduction of CNIs during the first 1–2 weeks post-transplantation. The benefit of post-transplantation hemodialysis is not clear, but it is often used in patients with significant systemic involvement and high plasma oxalate levels as well as in those with DGF or acute kidney injury [24].

The outcome of PH1 patients after CLKT is quite good. The 5- and 10-year patient survival rates were 80 and 69 %, respectively, in a European cohort of 117 PH1 patients transplanted before 2005 [25]. In this cohort, 13 renal grafts failed, of which seven were lost due to oxalate deposition. Better survival following CLKT for PH1 has been attributed to early diagnosis, short time on dialysis, and good condition of the patient (less complications of oxalosis) before the operation. In two recent registry reports, kidney graft survival rates in PH1 patients were 79 and 84 %, respectively, at 3 years [23, 27].

Transplantation strategies for PH1 have included isolated KT, isolated LT followed by KT (metabolic defect corrected first), or preemptive LT (the patient has stable renal function). Isolated KT, especially using a living donor, has been advocated in solitary patients, such as those who show partial response to pyridoxine therapy. Early reports from the USA suggested equally good outcomes with isolated KT and CLKT [30]. However, more recent data from Europe and USA indicate significantly better outcomes after CLKT [27, 29]. In the European database, only one of 38 PH1 children (3 %) transplanted after 2000 received isolated KT. Successful isolated LT has also been performed in PH1 patients with a good renal function ($\text{GFR}>60\text{ ml/min/1.73 m}^2$) [31]. An early LT would theoretically be the best cure, but because of the delay in diagnosis and questionable long-term results the strategy is rarely used.

Atypical hemolytic uremic syndrome

One-third of the patients with aHUS have mutations in genes encoding complement factors H, I, and C3, which

Table 2 Suggested transplant strategy in primary hyperoxaluria type 1 according to the stage of the chronic kidney disease of the patient^a

1. CKD stage III ($\text{GFR } 30\text{--}60\text{ ml/min/1.73 m}^2$)
Careful monitoring of the GFR decline
Planning of the transplant strategy
2. CKD stage IV ($\text{GFR } 15\text{--}30\text{ ml/min/1.73 m}^2$)
Simultaneous liver–kidney transplantation
Sequential liver–kidney transplantation is an option
3. CKD stage V ($\text{GFR } <15\text{ ml/min/1.73 m}^2$)
Simultaneous or sequential live–kidney transplantation
4. Infantile form
Simultaneous or sequential liver–kidney transplantation

CKD, Chronic kidney disease; GFR, glomerular filtration rate

^a Modified from the recommendations of the OxalEurope Study Group [24]

are synthesized and secreted by the liver. The genetic defects lead to uncontrolled complement activation, which in turn causes kidney capillary damage, deterioration of kidney function, thrombocytopenia, and hemolytic anemia. Isolated KT may correct the renal failure, but due to a very high recurrence rate (>80 %) it is not a viable treatment modality alone (see below). In contrast to isolated KT, CLKT not only restores kidney function, but also corrects the underlying biochemical defect of the liver.

The early experience on performing CLKT in aHUS patients was disappointing. Severe thromboses appeared perioperatively in the liver, leading to graft loss. Recent studies suggest that this was due to heavy complement activation during the operation [32]. In 2006, a successful CLKT was performed on a 5-year old boy with complement factor H (CFH) mutations [33]. Before the operation, extensive plasma exchange (PE) was performed to remove the defective CFH. Since then, about 14 aHUS patients have undergone CLKT, of whom 12 are still alive [34]. Guidelines for CLKT in aHUS patients were published in 2009 [35]. These define the patients in whom CLKT is possibly indicated, as well as give instructions for perioperative management, including PE, plasma infusion, and early anticoagulation.

Since the publication of the guidelines for CLKT, interesting data on the use of anti-C5 (anti-C5; eculizumab) in aHUS patients with genetic defects in complement components (CFH, CFH, C3) have been published. This antibody prevents the formation of C5b and the C5b–C9 complex (membrane attack complex), and the recent findings indicate that anti-C5 is effective in treating aHUS patients. Moreover, recent data suggest that eculizumab is effective in preventing and treating post-transplant recurrences of aHUS after isolated KT [36]. The first two doses can be given just before and after KT followed by maintenance infusions at 2-week intervals. It remains to be seen whether anti-C5 therapy can substitute for CLKT in the management of aHUS. The risk for life-threatening complications is much higher after CLKT than after KT, which strongly speaks for the use of isolated KT and anti-C5 therapy. On the other hand, after a successful CLKT the risk for aHUS recurrence is practically nonexistent, and patients do not need regular and expensive infusions, which further weaken their immunological defenses.

Methylmalonic acidemia

Methylmalonic acidemia (MMA) is an autosomal recessive disorder caused by complete or partial deficiency of methylmalonyl-CoA-mutase (MCM) or by defects in the synthesis of adenosylcobalamin (cb1A, cb1B). MCM is a mitochondrial enzyme involved in the catabolic pathways of branched amino acids, odd chain fatty acids, and cholesterol. The enzyme defect leads to the accumulation of toxic

methylmalonic acid in body fluids and tissues, leading to metabolic acidosis, metabolic stroke, neurological impairment, poor feeding and cardiomyopathy, and pancreatitis, as well as kidney tubular damage and renal failure. The conservative treatment includes a protein-restricted diet, amino acid substitution, L-carnitine, and metronidazole to restrict gut bacterial flora.

MMA is a rare disease (1:80,000) and to date the criteria for transplantation are not well-established [37]. A literature survey in 2008 identified 27 MMA patients who had undergone transplantation, including six KT, 15 LT, and six CLKT [38]. All diagnoses were made within the first 4 months of life, and the average age at transplantation was 9.2 years. Five deaths occurred post-transplantation—four from infection and one due to metabolic decompensation. All patients with CLKT were alive at the time of the literature survey [38]. Common post-operative sequelae included infection, acute rejection, CNI toxicity, and continued neurologic deterioration. Since this report appeared, only a few cases of MMA with isolated living donor LT or isolated KT have been reported [39, 40].

It is clear that none of the transplant modalities are curative for MMA. CLKT or LT decreases the methylmalonic acid levels in urine and plasma but it does not normalize them [37]. Liver and kidney contain only part of the body's MCM activity, and the production of methylmalonic acid from the central nervous system and skeletal muscle continues post-transplant. Neurologic deterioration and metabolic stroke have been documented in several MMA patients post-transplant, and the continuation of protein restriction has been advocated [41]. However, the frequency of metabolic decompensation has decreased significantly in individuals undergoing LT or CLKT despite persistent metabolic abnormalities. LT has been reported to provide a satisfactory quality of life, allowing the mitigation of protein restriction and cessation of tube feeding. Also, LT has been shown to eradicate lethargy and cognitive deficit, which are major symptoms of patients with MMA. It has been proposed that in this clinical context isolated KT might be a safer alternative to CLKT. The transplanted kidney may be sufficient to ensure the partial correction of metabolism and prevent the onset of episodes of metabolic compensation in some patients [40, 42]. At our center, a 10-year old girl with MMA received CLKT 2 years ago; suffered from severe pancreatitis soon after the operation but is now doing clinically well. Her methylmalonic acid levels in plasma and cerebrospinal fluid decreased after CLKT, but remained over 100-fold higher than normal. In general, the genotype of the MMA patient most probably affects the outcome, and since the number of individuals who have undergone CLKT is still small, the detailed effects of transplantation on the underlying metabolic disorder and the overall outcome have yet to be determined.

Other metabolic diseases

Alpha-1-antitrypsin deficiency (α 1-AT) is the most common genetic disease requiring isolated LT in children. It is an autosomal recessive disorder caused by mutations in the *SERPINA1* gene. About 10 % of infants and children with a homozygous Z mutation (Glu342L;PiZZ) develop cholestatic liver disease, and a minority of these progress to cirrhosis and terminal liver failure. Membranoproliferative glomerulonephritis, which in some cases may progress to severe renal failure, is an unusual, associated problem in children and young adults with severe α 1-AT. Reversal of renal dysfunction has been reported in patients with isolated LT. However, CLKT has been a successful procedure in the rare patients with ESRD [43]. Thus, kidney biopsy and evaluation of kidney function have been suggested for all α 1-AT patients referred for LT.

Type 1a glycogen storage disease (GSD1a), or von Gierke disease, is a rare, autosomal recessive disease caused by a deficiency of glucose-6-phosphatase, which leads to glycogen accumulation in the liver, kidneys, and intestinal mucosa. Clinical manifestations include hypoglycemia, growth retardation, hepatomegaly, lactic acidemia, hyperlipidemia, and hyperuricemia. Long-term complications include renal disease (mostly focal segmental glomerulosclerosis), osteoporosis, pulmonary hypertension, gout, short stature, and hepatocellular adenomas, all of which may undergo malignant transformation. Isolated LT has been successfully performed in patients with multiple adenomas or with poor metabolic control of the disease, and a small number of GSD1a patients with ESRD have undergone a successful CLKT [44]. Recently, preemptive CLKT has also been performed in a GSD1a patient showing rapid normalization of glucose and lipid metabolism [45]. According to the authors of this study, uremic GSD1a patients with or without adenomas should be considered for early CLKT.

Autosomal recessive polycystic kidney disease

Autosomal recessive polycystic kidney disease is the most common cystic disease of kidney and liver in childhood with an incidence of one in 20,000 live births. ARPKD is caused by mutations in the fibrocystin gene (*PKHD1*). Fibrocystin is a signaling molecule in kidney tubuli and liver bile ducts, and its genetic defects lead to variable kidney and liver manifestations. In many patients large and non-functioning kidneys require nephrectomy and dialysis in the neonatal period and early kidney transplantation. In others, the kidneys are moderately enlarged, and renal failure develops slowly so that ESRD is reached later in childhood or adolescence (30 % have ESRD at the age of 10 years). In the ARPKD liver, defective remodeling of

the ductal plate, portal fibrosis, and bile duct dilatations cause enlargement of the liver, portal hypertension (gastrointestinal varices, hypersplenism, ascites), and cholangitis episodes. Typically, liver function remains satisfactory for a long time.

Since kidney and liver manifestations progress differently in ARPKD, an individualized management is required. Most often isolated KT is performed first, followed by LT or CLKT later in childhood or adulthood. However, some patients with polycystic disease liver problems proceed quite fast, and LT or CLKT should be regarded as the first option. In a recent literature survey of 116 transplanted ARPKD patients, 56 % had undergone isolated KT, 34 % had LT, and 9 % had CLKT [46].

The decision of the right type of transplantation may be challenging. Although the patients have large liver and portal hypertension, the liver function often remains satisfactory for a long time, and the indications for LT or CLKT are not clear. When isolated KT is performed, hepatic disease can worsen the outcome, especially by increasing the risk for cholangitis and sepsis [47, 48]. In a retrospective analysis of 203 patients with polycystic kidney disease and isolated KT, nine patients (4.4 %) died from sepsis post-transplant, which is a high frequency among KT patients. Also, after an isolated KT the quality of life of children with ARPKD often remains impaired due to the large size of the liver and spleen as well as the infectious and bleeding complications. Placement of a portosystemic shunt may help but carries a risk for hepatic encephalopathy, especially in uremic patients. Also, the shunt may need revision because of thrombosis or growth of the child [46, 47, 49].

No general guidelines for the use of CLKT in ARPKD patients have been published. The morbidity and mortality after CLKT are still higher than in isolated KT, which favors the use of isolated KT as the first option. On the other hand, refractory complications of portal hypertension and recurrent cholangitis suggest CLKT as the first option (Table 3). Severe pathological findings of the liver (cirrhosis, large and infected biliary dilatations) and genotype (truncating mutations) also affect the treatment strategy [50]. Many of the children need KT later on, and simultaneous CLKT from the same donor probably provides better long-term kidney function than a sequential transplantation.

Patients with liver failure and kidney dysfunction

A child with a severe liver disease may occasionally have renal failure not caused by the primary disease. The concomitant dysfunction may be the result of renal vascular thrombosis, urinary tract malformation, glomerulonephritis, or drug toxicity (CNIs used in a previous transplantation; cytostatic drugs used because of liver tumors). In these patients the decision of isolated LT versus CLKT may be

Table 3 Indications for combined liver and kidney transplantation or isolated liver transplantation in patients with autosomal recessive polycystic kidney disease

1. Complications of portal hypertension
 - Bleeding episodes from esophageal varices or ventricle
 - Very large spleen (and liver)
 - Hypersplenism (thrombopenia, leukopenia, anemia)
 - Refractory ascites
2. Complications of biliary tract dilatation
 - Repeated episodes of cholangitis
 - Chronic cholangitis
 - Large biliary dilatations ('biliary lakes')
3. Impaired liver function
 - Low synthetic capacity of the liver
(factor V, VII, pre-albumin, albumin)
 - Low cholesterol level
 - Hyperammonemia
4. Severe liver cirrhosis in biopsy
5. 'Severe' PKD1 mutations
 - Truncating mutations

PKD, Polycystic kidney disease

difficult, as the prognosis of kidney function is not clear-cut. While no general recommendations for pediatric patients have been published, the indications in adult patients were addressed by a consensus conference in 2006 [51]. According to these guidelines patients with advanced kidney disease [chronic kidney disease (CKD) stages IV/V; GFR <30 ml/min/1.76 m²] or significant glomerulosclerosis (>35 %) or with tubulointerstitial fibrosis (>30 %) on renal biopsy are better served with CLKT. With this approach one can avoid the complications of renal failure in the post-operative period as well as the need for dialysis and KT after LT. This has been clearly demonstrated in adult patients, but data on children are scarce [52].

Patients who develop hepatorenal syndrome (HRS) due to the failing liver, however, often show recovery of the renal function and need only a liver graft. In adults, only a small percentage of LT patients with short-lasting HRS subsequently develop ERSD [51]. On the other hand, those adult patients who need dialysis for over 6 weeks prior to transplantation have a significant risk for persistent renal failure and should be considered for CLKT.

Since the regenerative capacity of the kidneys in children is not very different from that in adults, the published recommendations for adult patients with HRS or other renal problems seem quite valid also for children. However, the strategy must be chosen individually. In cases with structural problems and severe fibrosis in kidney biopsy, the decision is easier than in the rare children with functional problems such as HRS.

Long-term outcome

The outcome of CLKT is dependent on the primary cause of hepatic and kidney dysfunction as well on as the clinical condition of the patient. While children with a metabolic disease and an early transplantation usually have a good prognosis, patients with multi-organ failure are likely to experience poorer outcome. In adults and adolescents, liver and kidney allograft survival following CLKT is comparable with that seen following isolated LT and KT, respectively. On the other hand, implantation of a reduced size or a split liver with an adult kidney into an infant still presents a technical challenge. In the long term, liver function is usually very stable without evidence of chronic rejection (vanishing bile duct syndrome). However, a slow decrease of kidney function caused by chronic allograft nephropathy is often unavoidable.

Due to the small number of operations in children the outcome data for CLKT are still sparse. Analysis of the 1995–2005 UNOS database revealed that 20.1 % of the 111 pediatric patients with CLKT lost their kidney graft within the first 6 months after transplantation as compared to 5.9 % of patients receiving only kidney graft. However, death-censored 5-year kidney graft survival (>6 months) was significantly better in patients with CLKT as compared to the KT alone group (88 vs. 72 %) [17]. Outcome data for CLKT in patients with ARPKD are limited. Among 78 patients in the USA, the 1-, 3-, and 5-year survival rates were 79.5, 75.5, and 75.5 %, respectively [1]. Similar percentages have been reported in single-center reports [50]. In our center, four of the 14 transplanted ARPKD patients had CLKT as the first operation, and five first underwent KT followed by CLKT at a later date. Seven of the nine patients are alive (follow-up of 2–14 years), and their quality of life is good.

Transplantation outcome in PH1 patients has improved over the past decades. Of the 26 PH1 patients in the IPHR, 67 % were alive 7 years after CLKT. Among patients who were transplanted since 2000, 84 % of the 29 first kidney grafts (24 CLKT) were functioning in 2010 [27]. In the large European registry, the kidney graft survival rate in PH1 patients was 82, 79, and 76 % at 1, 3, and 5 years, respectively, for CLKT. These percentages are still about 10 % lower than those observed in patients with isolated KT for reasons other than PH1 [23]. Due to the oxalate load, the recovery of renal function is often delayed in PH1 patients [29]. Aggressive pre- and post-operative medical management is crucial in PH1.

Conclusions

Combined liver–kidney transplantation has become an accepted treatment modality for patients with severe liver and

kidney disorder. While CLKT is still technically challenging in infants and small children, it is the only curative treatment for several types of congenital disorders, especially PH1 and ARPKD. The early mortality after CLKT is mostly associated with infections and surgical complications of the liver graft. On the other hand, chronic problems with liver graft are quite rare, and the liver most probably protects the kidney allograft from rejection, which results in improved late kidney function and survival.

Key summary points

The major indications for combined liver–kidney transplantation (CLKT) in children are primary hyperoxaluria (PH1) and autosomal recessive polycystic kidney disease (ARPKD).

Patients should be listed for CLKT before the development of major systemic manifestations of the original disease.

The outcome of CLKT has improved during recent years and is comparable to that of isolated liver or kidney transplantation.

Multiple choice questions (answers are provided following the reference list)

1. The main indications for combined liver–kidney transplantation (CLKT) in children are:
 - a. Primary hyperoxaluria type 1 (PH1) and autosomal recessive polycystic kidney disease (ARPKD)
 - b. PH1 and atypical hemolytic uremic syndrome (aHUS)
 - c. aHUS and methylmalonic academia (MMA)
 - d. aHUS and PH1
2. The major life-threatening surgical complication after CLKT is:
 - a. Ureteral stricture of the kidney graft
 - b. Thrombosis of liver artery
 - c. Thrombosis of the kidney artery
 - d. Biliary stricture
3. The major immunological problem after CLKT is:
 - a. Acute antibody-mediated rejection of the liver graft
 - b. Chronic rejection of the liver graft (vanishing bile duct syndrome)
 - c. Chronic rejection of the kidney graft
 - d. Acute cellular rejection of the liver
4. CLKT is performed:
 - a. More often in children than in adults
 - b. Often in patients with liver failure and hepatorenal syndrome (HRS)
 - c. More often than isolated kidney transplantation in PH1 patients
 - d. Usually as the first transplantation in ARPKD patients
5. The outcome of CLKT is:
 - a. Better in infants than in older children and adolescents
 - b. Better in ARPKD as compared to PH1
 - c. Better in MMA than in PH1
 - d. Better in MMA than in ARPKD

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Answers

1. a
2. b
3. c
4. c
5. b