

# World Journal of *Hepatology*

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Editorial board member of *World Journal of Hepatology*, Dr. Fernando Oscar Bessone is Professor of Gastroenterology and Chief of the Gastroenterology and Hepatology Department at the Hospital Provincial del Centenario, University of Rosario School of Medicine (Brazil). Dr. Bessone completed postgraduate training in Clinical Hepatology, Liver Pathology (Hospital de Clinicas, San Pablo, Brazil), Pediatric Hepatology (Hospital da Criança, San Pablo, Brazil), and Liver Transplantation and Clinical Hepatology (Hospital Clinic y Provincial de Barcelona, Spain). He has served as Principal Investigator or Co-Investigator in more than 50 clinical trials, and is currently the Coordinator of the Latin American Registry of Hepatotoxicity. He authored more than 70 articles, 30 book chapters, and more than 140 papers presented at scientific meetings. In addition, he serves as an editorial board member for several international hepatology-related journals. (L-Editor: Filipodia)

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## Combined liver-kidney transplantation for rare diseases

Mladen Knotek, Rafaela Novak, Alemka Jaklin-Kekez, Anna Mrzljak

**ORCID number:** Mladen Knotek 0000-0002-4989-9147; Rafaela Novak 0000-0001-9790-7298; Alemka Jaklin-Kekez 0000-0002-1836-8044; Anna Mrzljak 0000-0001-6270-2305.

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**Mladen Knotek**, Department of Medicine, Tree Top Hospital, Hulhumale 23000, Maldives

**Mladen Knotek, Anna Mrzljak**, Department of Medicine, Merkur University Hospital, Zagreb 10000, Croatia

**Mladen Knotek, Rafaela Novak, Anna Mrzljak**, School of Medicine, University of Zagreb, Zagreb 10000, Croatia

**Alemka Jaklin-Kekez**, Clinic for Pediatric Diseases Helena, Zagreb 10000, Croatia

**Corresponding author:** Anna Mrzljak, FEBG, MD, PhD, Associate Professor, Department of Medicine, Merkur University Hospital, Zajčeva 19, Zagreb 10000, Croatia. [anna.mrzljak@gmail.com](mailto:anna.mrzljak@gmail.com)

### Abstract

Combined liver and kidney transplantation (CLKT) is indicated in patients with failure of both organs, or for the treatment of end-stage chronic kidney disease (ESKD) caused by a genetic defect in the liver. The aim of the present review is to provide the most up-to-date overview of the rare conditions as indications for CLKT. They are major indications for CLKT in children. However, in some of them (*e.g.*, atypical hemolytic uremic syndrome or primary hyperoxaluria), CLKT may be required in adults as well. Primary hyperoxaluria is divided into three types, of which type 1 and 2 lead to ESKD. CLKT has been proven effective in renal function replacement, at the same time preventing recurrence of the disease. Nephronophthisis is associated with liver fibrosis in 5% of cases and these patients are candidates for CLKT. In alpha 1-antitrypsin deficiency, hereditary C3 deficiency, lecithin cholesterol acyltransferase deficiency and glycogen storage diseases, glomerular or tubulointerstitial disease can lead to chronic kidney disease. Liver transplantation as a part of CLKT corrects underlying genetic and consequent metabolic abnormality. In atypical hemolytic uremic syndrome caused by mutations in the genes for factor H, successful CLKT has been reported in a small number of patients. However, for this indication, CLKT has been largely replaced by eculizumab, an anti-C5 antibody. CLKT has been well established to provide immune protection of the transplanted kidney against donor-specific antibodies against class I HLA, facilitating transplantation in a highly sensitized recipient.

**Key Words:** Combined liver-kidney transplantation; Methylmalonic aciduria; Hereditary complement C3 deficiency; Glycogen storage diseases; Homozygous protein C deficiency; Primary hyperoxaluria; Atypical hemolytic uremic syndrome; Sensitization; Donor-

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specific antibodies

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**Core Tip:** Combined liver and kidney transplantation (CLKT) provides replacement of both liver and kidney function in both organ end-stage diseases, or in end-stage kidney disease with origin in the genetic defect in the liver. It has been proven as an invaluable treatment option in the range of rare diseases such as primary hyperoxalurias, atypical hemolytic uremic syndrome, lecithin cholesterol acyltransferase deficiency, alpha 1-antitrypsin deficiency, hereditary complement C3 deficiency, nephronophthisis glycogen storage diseases. In this review, we provide an overview of rare indications for CLKT.

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## INTRODUCTION

Combined liver and kidney transplantation (CLKT) is indicated for patients with failure of both organs, or for the replacement of genetic defect in the liver in the presence of advanced or end-stage chronic kidney disease. In the latter case, liver transplantation represents a form of gene therapy. CLKT is well established, although still presents a rare type of transplantation. In the United States, CLKT represented 8.6% of all adult and 2.9% of all pediatric liver transplants in 2018<sup>[1]</sup>. Only 3.1% of all adult kidney transplants and 2.2% of all pediatric kidney transplants consist of CLKT. The most frequent indications for liver transplantation in CLKT are cirrhosis caused by hepatitis C, cryptogenic cirrhosis, alcoholic cirrhosis, and polycystic liver disease, while most frequent renal indications are chronic glomerulonephritis, diabetic nephropathy, polycystic kidney disease, and hypertensive kidney disease<sup>[2]</sup>. In children, epidemiology is different, with rare diseases such as primary hyperoxaluria and congenital liver fibrosis/polycystic kidneys being the major indications for CLKT<sup>[3]</sup>. In this review, our goal is to provide the most up-to-date overview of the rare conditions as indications for CLKT (Table 1).

## PRIMARY HYPEROXALURIA AND CLKT

Primary hyperoxalurias (PHs) (reviewed in Cochat *et al*<sup>[4]</sup>) are autosomal recessive disorders that result in increased oxalate generation leading to hyperoxaluria, nephrocalcinosis, renal stone formation, urinary infections, chronic kidney disease (CKD) and finally to systemic oxalosis. Type 1 hyperoxaluria results from a deficiency of alanine-glyoxylate aminotransferase (AGT), which facilitates transamination of glyoxylate to glycine in the liver. Thus, AGT deficiency results in the accumulation of glyoxylate and overproduction of oxalate and glycolate. Type 2 PH is a consequence of deficiency of a primarily hepatic enzyme, glyoxylate reductase-hydroxypyruvate reductase (GRHPR). GRHPR deficiency results in the accumulation of oxalate and L-glycerate. PH type 3 is caused by a deficit of 4-hydroxy-2-oxoglutarate aldolase, resulting in the accumulation of oxalate. The most frequent among the PHs is type 1. The clinical course is also the most aggressive in PH1, while PH3 is the mildest form of the disease, without systemic oxalosis and with the uncommon occurrence of nephrocalcinosis, kidney stones, and renal failure. PHs are very rare diseases. It has been estimated that their combined prevalence by genetic analysis is approximately 17 per million population<sup>[5]</sup>.

Patients with PH1 and PH2 present with kidney stones or nephrocalcinosis early in life; median age at symptoms appearance was in recent studies 5.6 years in PH1 and 3.2 years in PH2. Mean age of patients at first liver/kidney transplant was 16.5 for PH1 and about 40 years in PH2<sup>[6,7]</sup>. Isolated kidney transplantation in patients with PH1 is

**Table 1 Rare indications for combined liver-kidney transplantation**

Disease	Indication(s) for CLKT
Monogenic diseases with primary hepatic expression without significant parenchymal damage	
Atypical hemolytic-uremic syndrome	Renal failure and alternative complement pathway activity
AIP	Renal failure and recurrent medically non-responsive AIP attacks
Primary hyperoxaluria	Renal failure and metabolic control of the disease
Homozygous protein C deficiency	Renal failure and coagulation control
Hereditary complement C3 deficiency	Renal failure and risk reduction of recurrent infections (?)
Monogenic diseases with primary hepatic expression with parenchymal damage	
Alpha-1-antitrypsin deficiency	Renal failure and liver failure (cirrhosis)
Glycogen storage disease	Renal failure with hepatocellular adenomatosis/carcinoma and metabolic control of the disease
Monogenic diseases with hepatic and extrahepatic manifestation	
Nephronophthisis associated with liver fibrosis	Renal failure and liver failure (cirrhosis)
Lecithin cholesterol acyl transferase deficiency	Renal failure and metabolic control of disease
Methylmalonic acidemia	Renal failure and metabolic decompensation
Other	
Antibody mediated rejection of the kidney	Renal failure and in the presence of positive CDC cross-match (?)

CLKT: Combined liver and kidney transplantation; AIP: Acute intermittent porphyria; CDC: Complement-dependent cytotoxicity.

associated with greatly decreased renal graft survival, because of the rapid recurrence of the disease<sup>[8,9]</sup>. Liver transplantation corrects genetic defects both in PH1 and PH2<sup>[10-12]</sup>. Although there are reports on preemptive liver transplantation in patients, who do not have advanced CKD, majority of patients receive CLKT<sup>[6,7,13,14]</sup>. CLKT (or sequential liver and kidney transplantation from a living donor<sup>[15]</sup>) has been consistently shown to provide better renal graft and patient survival, as compared to the isolated kidney transplantation. However, since a large amount of oxalate accumulates in the body over the years of disease, it is important to prevent rapid oxalate deposition in the renal graft. Namely, it can further lead to acute oxalate nephropathy and irreversible renal failure. This is achieved by high-intensity renal replacement therapy in the perioperative and early post-transplant period<sup>[16]</sup>, even in patients with good immediate renal function. Long-term in the post-transplant period, high urine output with urine alkalization (potassium citrate) and avoidance of dehydration should be maintained. Another option for PH1 patients may represent sequential liver and kidney transplantation, where liver is transplanted first and in the second procedure at least several months apart kidney is transplanted from the same living, or different deceased donor<sup>[17,18]</sup>. The rationale for sequential LKT is to decrease oxalate production prior to kidney transplantation.

A separate question is whether entire liver tissue replacement is required for patients with primary hyperoxalurias. Since genetic defect that results in oxalate hyperproduction resides in hepatocytes and there is no significant transport of oxalate into hepatocytes, common opinion has been that hepatectomy and orthotopic liver transplantation (whole, or a segment) are required<sup>[19]</sup>. However, we and others have reported that auxiliary partial orthotopic liver transplantation (as part of the CLKT) was sufficient to prevent recurrent kidney injury in patients with PH1<sup>[20-22]</sup>. This is important because auxiliary liver transplantation would be safer than native hepatectomy and liver transplantation, in the case of post-transplant liver graft failure. The effect of auxiliary CLKT *vs* total CLKT on systemic oxalosis is currently unknown.

## ATYPICAL HEMOLYTIC-UREMIC SYNDROME AND CLKT

Atypical hemolytic-uremic syndrome (aHUS) is a rare disease caused by enhanced activity of the alternative complement pathway. It is characterized by microangiopathic hemolytic anemia and thrombocytopenia, accompanied by acute kidney injury. aHUS results in death or end-stage kidney disease in up to 80% of patients within 3-10 years from the onset of the disease<sup>[23]</sup>. A recent systematic review reported prevalence in populations younger than 20 years old of 2.2-9.4 per million population (pmp), with an incidence in this population of 0.26-0.75 pmp. In all age groups, based on limited information, the prevalence was 4.9 and the incidence was 0.23-1.9 per million population<sup>[24]</sup>. Being constitutively active, the alternative complement pathway is controlled by several regulatory proteins, among which, some are synthesized in the liver<sup>[25]</sup>. A great majority of aHUS cases are caused by genetic abnormalities in complement proteins or their regulators, which results in uncontrolled activation of the alternative complement pathway. The most frequent cause of aHUS is factor H deficiency. In a great majority of patients, the deficiency is caused by mutations in factor H gene, with autoantibodies to factor H being responsible for up to 10% of cases<sup>[23]</sup>. Other causes may be mutations of factor I, B, and membrane cofactor protein (CD46), as well as mutations in C3. Factor H, together with factor I participates in the regulation of constitutive alternative pathway activity. They are both produced mainly by the liver. Mutations in factor H are responsible for about 30% of aHUS<sup>[26]</sup>.

Historically, recurrence of the disease following kidney transplantation was very frequent, which almost universally led to graft loss<sup>[27-31]</sup>. Liver transplantation can correct the genetic abnormality in patients with aHUS due to factor H deficiency. The first report of CLKT in aHUS in a 2-year-old child was published in 2002<sup>[32]</sup>. Subsequent results of CLKT, following a protocol of peritransplant plasma-exchange, were favorable<sup>[33-35]</sup>. Although CLKT appeared promising in patients with end-stage kidney disease due to aHUS, it was largely replaced by eculizumab, an anti-C5 antibody<sup>[36,37]</sup>. Eculizumab is currently the standard treatment of aHUS before and after kidney transplantation according to national and international guidelines<sup>[38-42]</sup>. However, high cost of eculizumab and uncertainty of the needed duration of eculizumab treatment, as well as relapse in rare patients following renal transplantation under eculizumab, leave doors for CLKT in select aHUS patients still open<sup>[43,44]</sup>.

## HEREDITARY COMPLEMENT C3 DEFICIENCY AND CLKT

Hereditary complement 3 deficiency is an extremely rare autosomal recessive disease, which is present in less than 1 per million people<sup>[45]</sup>. It is associated with recurrent bacterial infections and complement-mediated glomerulonephritis (C3 glomerulopathy) although end-stage renal disease (ESRD) is uncommon<sup>[46,47]</sup>. In the complement system, complement C3 is central to classical and alternative complement pathways, and it is predominantly synthesized in the liver<sup>[48]</sup>, but extra-hepatic synthesis such as monocyte- and kidney-derived is present as well<sup>[49,50]</sup>. Therefore, in case of kidney transplantation and inevitable immunosuppression post-transplant, the patient may be additionally compromised with the recurrence of bacterial infections.

Thus, the rationale behind the simultaneous liver-kidney transplantation lies in the long-term restoration of plasma C3 levels. So far only one case has been published of an adult with complete complement 3 deficiency due to homozygous mutation in C3, with a complete restoration of circulating C3 levels and good functioning both grafts 24 mo after simultaneous liver-kidney transplantation<sup>[51]</sup>.

## ALPHA-1-ANTITRYPSIN DEFICIENCY AND CLKT

Alpha-1-antitrypsin deficiency (A1AD) is a genetic condition caused by mutations in *SERPINA1* gene, resulting in synthesis and aggregation of misfolded alpha 1 antitrypsin (AAT) in the liver and its low serum level. Accumulation of abnormal protein leads to liver injury, while deficiency of protease inhibitor function disturbs antiprotease activity, primarily in the lungs. Some homozygous and compound heterozygous mutation patients typically develop liver disease in childhood and/or lung disease in adulthood, the later especially in smokers. Nowadays, A1AD with the prevalence of 24/100000 people<sup>[52]</sup>, is the most common genetic cause of pediatric LT,

and the third metabolic liver disease in adults which may also lead to cirrhosis and LT<sup>[53-55]</sup>.

In some A1AD patients, membranoproliferative glomerulonephritis (MPGN) develops as a rarely associated co-morbidity. The explanation for this pathology is not fully understood. It has been hypothesized that altered protein released from damaged hepatocytes becomes antigen for immunological reaction forming deposits in glomeruli. MPGN may progress to end-stage renal disease (ESRD) with a necessity for kidney transplantation. There have been literature reports of successful CLKT in A1AD patients with concomitant end-stage liver and advanced kidney disease<sup>[56,57]</sup>. Although, in A1AD cases with liver failure and MPGN, but without ESRD, an isolated LT may lead to the recovery of MPGN making renal transplantation unnecessary<sup>[58]</sup>. Therefore, for A1AT patients with end-stage liver disease and MPGN, careful evaluation of the kidney function and severity of damage should be done before deciding what would be the better option, isolated LT or CLKT<sup>[59]</sup>.

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## LECITHIN CHOLESTEROL ACYLTRANSFERASE DEFICIENCY AND CLKT

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Lecithin cholesterol acyltransferase (LCAT) deficiency is a rare autosomal recessive disorder, occurring in less than 1/million people<sup>[60]</sup> and it is caused by mutations in the *LCAT* gene (16q22.1), which encodes LCAT enzyme. It catalyzes the formation of cholesterol esters in lipoproteins. A deficiency of LCAT leads to increased plasmatic free cholesterol and lecithin with severe reduction of plasma HDL cholesterol, which in turn affects the metabolism of other lipoproteins and results in lipid-containing deposits in various tissues. Familial LCAT with the total loss of enzyme activity usually manifests in early adulthood with corneal opacifications, hemolytic anemia, and renal injury with proteinuria<sup>[61,62]</sup>. Enlargement of the liver, spleen, and lymph nodes may be found in addition to atherosclerosis<sup>[63]</sup>. Renal failure typically appears in the second or third decade and progresses to end-stage kidney disease, necessitating renal replacement therapies including kidney transplantation<sup>[62]</sup>. As kidney transplantation alone does not affect the levels of plasma LCAT nor the abnormal lipid profile, recurrence of the disease in the graft is to be expected within days after transplantation. However, long-term graft function is well-maintained despite the presence of deposits<sup>[61,64-66]</sup>.

Since LCAT is produced within the liver, CLKT provides a plausible treatment option. Though, so far only one report addressed the LCAT deficiency in a 29-year old man treated with kidney transplant combined with a year apart sequential auxiliary partial orthotopic liver transplant from the same living donor. The improvement in HDL and triglycerides was only present up to 1 year after transplantation, but the long-term follow-up showed no histological signs of LCAT nephropathy<sup>[67]</sup>.

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## GLYCOGEN STORAGE DISEASE AND CLKT

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Glycogen storage diseases (GSDs) are a group of inherited metabolic disorders of glycogen metabolism. GSDs affect liver and/or muscles. Subsequently, they are commonly divided into GSDs with the mainly hepatic presentation, which main features include hepatomegaly and hypoglycemia (0, I, III, IV, VI, IX, XI) and GSDs with the neuromuscular presentation, typically with muscle weakness and hypotonia (II, III, IV, V, VII, IXd)<sup>[68]</sup>.

Glycogen storage disease I, also known as Von Gierke's disease, is one of the most common types with the incidence of 1/million people<sup>[69]</sup>. GSD I is an autosomal recessive disease resulting in glucose-6-phosphatase (G6P) deficiency. Normally, G6P catalyzes the last step of glycogenolysis and it is expressed in the liver, kidney, and scarcely in intestines, resulting in glycogen deposits in the aforementioned organs<sup>[70]</sup>. Approximately 80% of patients have type Ia deficiency, with the G6P catalytic unit defect on the endoplasmic reticulum, while the rest have type Ib due to a G6P translocase defect<sup>[71,72]</sup>. Patients with GSDs usually present in infancy with poor tolerance to fasting, hepatomegaly, and growth retardation. Their characteristic laboratory findings include hypoglycemia, hyperlactacidemia, hyperlipidemia, and hyperuricemia<sup>[73]</sup>. GSD Ib patients additionally have frequent neutropenia, which creates common difficulties with recurrent infections<sup>[74]</sup>. Neutropenia in GSD Ib is possibly caused by abnormal neutrophil function since neutrophils energetically considerably depend on glycogenolysis<sup>[74]</sup>. The patients are usually diagnosed by molecular diagnostics<sup>[73]</sup> and prescribed with a strict diet regime (frequent meals, slow-

absorption carbohydrates) yielding in majority normoglycemia and good metabolic control<sup>[70]</sup>. The long-term course of GSD I is frequently complicated with hepatocellular adenomas (16%-75%), that appear in the second or third decade of life and progress in size and number<sup>[71]</sup>. The occurrence of hepatocellular carcinoma is also possible, and its incidence increases along with the increasing survival of the well-metabolically controlled patients<sup>[75]</sup>. Accordingly, hepatocellular adenomatosis and carcinoma are the main indications for LT in GSD I patients, which also provides good glucose homeostasis<sup>[71,76]</sup>.

However, several reports suggest that immunosuppression after LT may severely worsen renal function in these patients. Namely, pre-existent renal complications as focal segmental glomerulosclerosis, proximal and distal tubular dysfunction are also common GSDs trait<sup>[74,77]</sup>. Several authors thus report CLKT as a successful treatment for GSD I patients with hepatic adenomatosis and kidney failure<sup>[78-81]</sup>. As a treatment modality, CLKT provides GSD I patients correction of the metabolic defect, and consequently effective metabolic control. Hence, some investigators have even broadened the hepatic indications for CLKT, including poor metabolic control and severe growth retardation<sup>[82]</sup>. In the literature, there are also several reports of GSD I patients who underwent CLKT for terminal kidney failure, without hepatic adenomatosis being present, but with poor metabolic control<sup>[83-86]</sup>. As isolated kidney transplantation does not improve liver glucose metabolism and hence potentially presents a ground for reoccurring kidney failure, CLKT was recommended as a better option in those cases<sup>[83,85]</sup>. Patients who underwent CLKT so far, were all adults aged 19-42 years and they all have recovered well after transplantation<sup>[84,85]</sup>. CLKT meant great advance for two women with GSD I, who managed to conceive and successfully bear healthy children, despite the low fecundity and pre-transplantation metabolic disturbances<sup>[85,86]</sup>.

LT might provide a successful metabolic balance in poorly regulated GSD I patients, although CLKT might maintain that balance, particularly in severe cases with renal failure.

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## NEPHRONOPHTHISIS ASSOCIATED WITH LIVER FIBROSIS AND CLKT

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Nephronophthisis (NPHP) is a renal ciliopathy with the autosomal recessive inheritance of cystic kidney disease and with a prevalence of 1/100000 people<sup>[87]</sup>. It may progress to ESRD and is the most common genetic cause of renal failure in children and young adults<sup>[88]</sup>. In 10%-20% of NPHP there is an association with extra-renal manifestations; neurological, ocular, skeletal, hepatic, cardiac, and pulmonary, sometimes manifesting in specific clinical syndromes. Boichis syndrome is characterized by the simultaneous development of hepatic fibrosis, in up to 5% of patients with NPHP<sup>[89]</sup>. These patients are candidates for CLKT as injury of both organs may end in irreversible organ failures. One case report and case series of CLKT in patients with Boichis syndrome have been published so far. In all of the four reported patients, both liver and kidney functions recovered initially, but two died (one 2 wk after CLKT due to pneumonia and intracranial hemorrhage, and the second 10 years later due to cardiovascular disease)<sup>[18,90]</sup>. Sequential liver-kidney transplantation was also described in the literature. The liver transplantation was performed first, followed by kidney transplantation 4 mo later. Both grafts came from the same donor and retained good function after transplantation<sup>[91]</sup>.

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## HOMOZYGOUS PROTEIN C DEFICIENCY AND CLKT

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Homozygous protein C deficiency (HPCD) is a rare autosomal recessive disorder, which results in a hypercoagulable state due to very low levels of active protein C caused by a mutation in the *PROC* gene. Clinically significant HPCD occurs in 1/20000 people<sup>[92]</sup>. HPCD typically presents as neonatal *purpura fulminans* with thrombosis of major blood vessels that lead to ophthalmologic, neurological, and renal complications with high rates of mortality<sup>[93]</sup>. The condition is managed by substitution of protein C and anticoagulation therapy, although long-term survival without major co-morbidity is rarely reported<sup>[93]</sup>. Several reports demonstrate that liver transplantation, as it is the organ of protein C synthesis, provides a good therapeutic option. Namely, LT leads to the reconstitution of protein C activity, which in the long-term is both clinically effective and cost-effective<sup>[93-97]</sup>. To date, only one report has addressed CLKT in an 8-year-old patient with HPCD and bilateral renal vein thrombosis resulting in renal

failure. The patient underwent auxiliary liver with combined renal transplantation, which improved her quality of life and removed the need for protein C infusions and hemodialysis<sup>[95]</sup>.

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## ACUTE INTERMITTENT PORPHYRIA AND CLKT

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Acute intermittent porphyria (AIP) is an autosomal dominant disorder resulting in the deficiency of porphobilinogen deaminase (PBGD), an enzyme involved in heme synthesis<sup>[96]</sup>. AIP has a prevalence of 1/20000 people<sup>[99]</sup>. Only a minority of symptomatic patients with AIP (< 10%) develop potentially life-threatening recurrent acute attacks, which can be triggered by various metabolic and environmental factors as a consequence of accumulated phototoxic and neurotoxic heme precursors (PBG)<sup>[98,100,101]</sup>. Acute attacks are characterized by severe abdominal pain, nausea, vomiting, hypertension, and sometimes neurological manifestations (neuropathies, encephalopathy, convulsions, anxiety), while major chronic complications include chronic kidney disease and development of hepatocellular carcinoma<sup>[100,102]</sup>.

Current treatment for acute attacks consists of intravenous hemin and carbohydrate loading<sup>[101]</sup>, though repeated hemin therapy may complicate patients' conditions, causing vascular thromboses and restricting venous access<sup>[103]</sup>. Thus, liver transplantation (LT), as a major source of PBG production, should be considered for patients with AIP, who suffer from recurrent, medically non-responsive attacks that substantially impair the life quality<sup>[104]</sup>.

The outcome of the few LTs performed in AIP patients has been excellent so far, while the transplanted patients have not experienced further acute AIP attacks. Their biochemical PBG results markedly improved and the 5-year survival rate was nearly 80%<sup>[105]</sup>. However, a high incidence (40%) of hepatic artery thrombosis has been observed after LT and the patients with long-term neuropathies did not have significant neurological improvement<sup>[105]</sup>. Despite extrahepatic PBGD deficiency, there were no observed induced AIP attacks due to immunosuppressants<sup>[106]</sup>. A few successful renal transplantations have also been performed in patients with uncomplicated AIP and renal failure<sup>[107,108]</sup>. Even though, most recommendations for patients with frequent acute attacks, progressive neuropathies and deteriorating renal function suggest performing CLKT<sup>[101]</sup> yet only two published cases (aged 24 and 55 years) have undergone CLKT<sup>[109]</sup>. Wahlin *et al*<sup>[109]</sup> showed that their clinical and biochemical AIP markers significantly improved after CLKT, while one of them exhibited bile leakage as a post-transplant complication. Prior to CLKT, they had both presented with a diverse degree of neuropathies that subsequently completely resolved in the post-transplant period.

Although there were descriptions of unpredictable course of AIP and possible amelioration during the time<sup>[110]</sup>, current recommendations advise early LT as a cure, since recurrent attacks may prompt severe neurological deficits and end kidney failure. In advanced cases, CLKT may be a considerable treatment option if the patients are adequately clinically stable.

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## METHYLMALONIC ACIDURIA AND CLKT

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Methylmalonic aciduria (MMA) refers to a rare group of inherited disorders of the catabolic pathway of branched-chain amino acids and odd-chain fatty acids resulting in methylmalonic acid (MA) accumulation. The incidence of MMA varies from 1/50000 to 1/100000 of people<sup>[111]</sup>. MMA is inherited in autosomal recessive pattern, affecting MUT gene encoding methylmalonyl-CoA mutase or genes encoding key enzymes for the metabolism of the cofactor cobalamin<sup>[112]</sup>. MUT enzyme is normally expressed primarily in mitochondria of the liver, but also in kidneys, endocrine tissue, brain, and muscles<sup>[113]</sup>. Furthermore, the accumulation of MA provokes episodes of metabolic instability<sup>[114]</sup>.

The intensity of the clinical picture depends on the particular genetic mutation. In the most severe cases, shortly after birth patients experience recurrent episodes of metabolic acidosis and hyperammonemia, leading to neurologic, hematologic, renal, sometimes gastrointestinal, heart and vision impairment, followed with growth failure and developmental delay. In others, symptoms may not be so intense and its appearance may be postponed to even adulthood. Some triggers like fasting, infection, surgery, or any other stress may provoke sudden worsening and metabolic crisis<sup>[114-117]</sup>. Such episodes are also exacerbated by unrestricted protein intake, therefore high-

energy low-protein diet (low in propiogenic amino acid precursors) is crucial throughout life. Administration of L carnitine, vitamin B12, and symptoms-based treatment are also part of conventional therapy<sup>[118]</sup>. However, despite all measures, MMA may not be under sufficient control, therefore the organ injuries may also progress. In such patients, with frequent metabolic decompensation episodes, in spite of proper conservative management, better metabolic stability may only be accomplished with liver, kidney or CLKT. It is advisable to perform it before the appearance of irreversible neurologic damage<sup>[58,119]</sup>.

In the context of MMA, organ transplantation is not a curative option, but it can be a complementary therapeutic solution. Namely, liver transplantation reduces the systemic accumulation of MA, while kidney transplantation facilitates the clearance of MA<sup>[114]</sup>. Even more so, the amount of normal enzyme is higher in CLKT and in addition kidney rejection may be better controlled<sup>[59,120]</sup>.

After CLKT levels of MA decrease by 80%-97%<sup>[121,122]</sup> and are lower than after isolated LT with better metabolic outcomes and reduced number of hospitalizations<sup>[123-125]</sup>. The majority of reports show improvements in neuro-development (enhanced motor skills, learning abilities, social engagement) and improved quality of life after CLKT<sup>[18,114,118,121,123-128]</sup>. Yet, in most cases, MA levels after CLKT are still 1000x higher than normal<sup>[124,125]</sup>. Besides, neurologic and/or muscle impairments may continue despite normal graft function<sup>[59,117]</sup>. It is also of great importance to maintain close metabolic monitoring and dietary measures after the transplantation, as extrarenal and extrahepatic production of MMA continues to derive from skeletal muscles<sup>[117]</sup>. In some cases in the post-transplant period, a relaxed dietary protein diet may safely occur<sup>[128]</sup>.

To date, only several dozen CLKT cases performed in MMA have been described in the literature<sup>[129]</sup> with promising results. The age of MMA patients considered for CLKT ranged between 2 and 28 years<sup>[116,124,125,127]</sup>. Combined transplants were almost entirely performed in patients with mut0 type of MMA and their survival rates were excellent<sup>[114,116,118,121-128,130,131]</sup>. Two deaths after CLKT have been reported; one caused by a metabolic crisis after the transplant<sup>[132]</sup> and the other by early post-transplant complications<sup>[125]</sup>.

Preoperative treatment should be precisely planned to prevent catabolism afterward. Surgical complications are more frequent after an extensive procedure such as LKT and the procedure carries more risks<sup>[123-125]</sup>. Most of the immunosuppression regimens for CLKT in MMA patients consisted of calcineurin inhibitors (CNI) (tacrolimus and cyclosporine) steroids and mycophenolate-mofetil<sup>[116,124,125]</sup>. In addition, neurological complications such as seizures, tremor, ataxia, worsening vision, and altered mental status were common and occurred in 15%-40% of patients after CLKT. Early after the procedure, the patients with their pre-existent mitochondrial dysfunction are particularly prone to the development of CNI-neurotoxicity while later neurological symptoms are more probably metabolically induced<sup>[115,116,121,122]</sup>.

Though not curative, CLKT is generally a highly effective additional therapeutic option for MMA patients who cannot be stabilized only with regular dietary and pharmacological therapy, in spite of the higher risk for post-transplantation complications in this population. Decisions on whether or not CLKT will be performed should be individualized on a case by case basis balancing advantages and post-transplantation risks<sup>[115]</sup>.

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## ANTIBODY-MEDIATED REJECTION OF THE KIDNEY

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The long-term practice of many transplant centers was to proceed to CLKT even in the presence of positive complement-dependent cytotoxicity (CDC) crossmatch, as hyperacute kidney rejection in CLKT is extremely rare. Now, it has been well established that CLKT may confer partial kidney allograft protection against donor-specific antibody (DSA)-mediated rejection<sup>[133]</sup>. For example, in a recent retrospective study, CLKT patients with preformed DSA had lower rates of acute and chronic antibody-mediated rejection (AMR) as compared to isolated kidney transplant recipients<sup>[133]</sup>. In addition, recipients of CLKT had reduced the incidence of T-cell mediated rejection (TCMR) of kidney grafts as compared to kidney-transplant alone recipients<sup>[133]</sup>. This protection is predominantly related to anti-HLA class I DSA, as anti-HLA class II DSA has been associated with increased risk of graft loss and patient death in CLKT<sup>[134]</sup>. *De novo* DSAs following LT, that are in majority of cases directed against HLA class II, are associated with increased risk of antibody-mediated rejection, long-term graft failure and patient death, similar to their association with antibody-

mediated rejection and decreased long-term graft survival following kidney transplantation. However, some studies failed to demonstrate an increased risk for graft loss in liver transplant recipients with *de novo* DSA<sup>[135]</sup>. Currently, it is not well known whether patients with CLKT have a different incidence of *de novo* DSA and lower risk of AMR, as compared to kidney only transplant recipients.

Mechanisms providing immune protection of kidney grafts in CLKT are incompletely elucidated but may include HLA class I antigen shedding by the liver grafts, DSA absorption by the liver, and increased activation of tissue integrity/metabolism pathways in the kidney<sup>[133]</sup>.

To date, CLKT in highly sensitized recipients was performed only in patients with conventional indications for CLKT. Though, since acute AMR is associated with a high risk of renal graft loss and of progression into chronic AMR<sup>[136]</sup>, one could hypothesize that simultaneous auxiliary liver and kidney cross-match positive transplantation for an extremely sensitized patient in need of kidney only transplantation might improve short- and long-term kidney transplant outcomes. It is unknown whether the same degree of protection would be seen in the recipient of simultaneous auxiliary LKT, because of a smaller transplant liver tissue mass. That would be in line with the hypothesis, that the capacity of the liver graft providing immune protection for the kidney would be limited in the presence of too high levels of DSA<sup>[137]</sup>. Such auxiliary, partial, CLKT performed to facilitate HLA-incompatible kidney transplantation in a difficult to desensitize recipient remains to be reported.

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## CONTRAINDICATIONS FOR CLKT

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As in other forms of solid organ transplantation, absolute contraindications for CLKT include active infection, recent or active malignancy, severe irreversible heart or respiratory failure, severe non-adherence, and psychiatric disorder impairing consent or adherence<sup>[138]</sup>. In patients with liver cirrhosis, an additional contraindication is moderate or severe portopulmonary hypertension<sup>[139]</sup>. Timely referral for CLKT is essential, as long-standing chronic kidney disease may lead to the progression of cardiovascular disease. In addition, both long-standing chronic kidney disease and liver disease are associated with increased frailty, and consequently increased risk for poor transplant outcome<sup>[140]</sup>.

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## CONCLUSION

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Simultaneous liver and kidney transplantation has proven to be a life-saving procedure in the simultaneous failure of both organs. Though, besides the well-established indications for end-stage liver and kidney disease, it also represents a therapeutic option for numerous rare diseases. Namely, by replacing mutated genes, liver transplantation provides a cure for genetic diseases with origin in the liver. Although nowadays there are enzyme replacement therapies, in general, they are still too expensive and thus less cost-effective than LT. Furthermore, the indications for CLKT in rare metabolic disorders have even broadened, in order to achieve better metabolic control and improve the quality of life.

Advances in surgical technique, as well as improvement in immunosuppression, led to better long-term CLKT transplant outcomes. The risk of the procedure may be even lower in partial orthotopic auxiliary liver transplantation, which merits further evaluation in candidates for CLKT when a genetic disease with origin in the liver is present. Yet, meticulous estimation of risk is necessitated, including consideration of possible short- and long-term complications after transplant. Accordingly, it is also complex to decide on the time-point of CLKT. Despite the complexity of the procedure, CLKT has better outcomes in patients with metabolic diseases and renal failure than isolated LT, or isolated kidney transplantation, and in addition reduction of extrahepatic synthesis of metabolites may in some cases also be reduced. After the CLKT, careful monitoring for extrarenal and extrahepatic metabolic manifestations is necessary. As CLKT itself is not a frequent procedure, we believe that it should be performed only in high volume transplant centers. That is even more important in case of rare indications, where an experienced multidisciplinary team is a prerequisite.

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