World Journal of Hepatology

Submit a Manuscript: https://www.f6publishing.com

World J Hepatol 2020 October 27; 12(10): 722-737

DOI: 10.4254/wjh.v12.i10.722

ISSN 1948-5182 (online)

REVIEW

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.

Author contributions: Knotek M and Mrzljak A contributed to the study design and wrote the manuscript; Novak R and Jaklin-Kekez A contributed to the data acquisition and wrote the manuscript; All authors read and approved the final manuscript.

Conflict-of-interest statement: The authors declare no conflicts of interest.

Manuscript source: Invited manuscript

Received: May 12, 2020
Peer-review started: May 12, 2020

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

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-

First decision: July 29, 2020
Revised: July 30, 2020
Accepted: September 18, 2020
Article in press: September 18, 2020
Published online: October 27, 2020

P-Reviewer: Guo JS, Pan GD
S-Editor: Ma YJ
L-Editor: Filipodia
P-Editor: Wang LL

specific antibodies

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.

Citation: Knotek M, Novak R, Jaklin-Kelez A, Mrzljak A. Combined liver-kidney transplantation for rare diseases. *World J Hepatol* 2020; 12(10): 722-737
URL: https://www.wjgnet.com/1948-5182/full/v12/i10/722.htm
DOI: https://dx.doi.org/10.4254/wjh.v12.i10.722

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[1]. 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[2]. In children, epidemiology is different, with rare diseases such as primary hyperoxaluria and congenital liver fibrosis/polycystic kidneys being the major indications for CLKT[3]. 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*[4]) 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[5].

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[6,7]. 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[8,9]. Liver transplantation corrects genetic defects both in PH1 and PH2[10-12]. Although there are reports on preemptive liver transplantation in patients, who do not have advanced CKD, majority of patients receive CLKT[6,7,13,14]. CLKT (or sequential liver and kidney transplantation from a living donor[15]) 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[16], 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[17,18]. 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[19]. 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[20-22]. 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[23]. 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[24]. Being constitutively active, the alternative complement pathway is controlled by several regulatory proteins, among which, some are synthesized in the liver[25]. 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[23]. 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[26].

Historically, recurrence of the disease following kidney transplantation was very frequent, which almost universally led to graft loss[27-31]. 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[32]. Subsequent results of CLKT, following a protocol of peritransplant plasma-exchange, were favorable[33-35]. Although CLKT appeared promising in patients with end-stage kidney disease due to aHUS, it was largely replaced by eculizumab, an anti-C5 antibody[36,37]. Eculizumab is currently the standard treatment of aHUS before and after kidney transplantation according to national and international guidelines[38-42]. 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[43,44].

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[45]. It is associated with recurrent bacterial infections and complement-mediated glomerulonephritis (C3 glomerulopathy) although end-stage renal disease (ESRD) is uncommon[46,47]. In the complement system, complement C3 is central to classical and alternative complement pathways, and it is predominantly synthesized in the liver[48], but extra-hepatic synthesis such as monocyte- and kidney-derived is present as well[49,50]. 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[51].

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[52], 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[53-55].

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[56,57]. 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[58]. 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[59].

LECITHIN CHOLESTEROL ACYLTRANSFERASE DEFICIENCY AND CLKT

Lecithin cholesterol acyltransferase (LCAT) deficiency is a rare autosomal recessive disorder, occurring in less than 1/million people[60] 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[61,62]. Enlargement of the liver, spleen, and lymph nodes may be found in addition to atherosclerosis[63]. Renal failure typically appears in the second or third decade and progresses to end-stage kidney disease, necessitating renal replacement therapies including kidney transplantation[62]. 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[61,64-66].

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[67].

GLYCOGEN STORAGE DISEASE AND CLKT

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)[68].

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[69]. 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[70]. 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[71,72]. 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[73]. GSD Ib patients additionally have frequent neutropenia, which creates common difficulties with recurrent infections[74]. Neutropenia in GSD Ib is possibly caused by abnormal neutrophil function since neutrophils energetically considerably depend on glycogenolysis[74]. The patients are usually diagnosed by molecular diagnostics[73] and prescribed with a strict diet regime (frequent meals, slow-

absorption carbohydrates) yielding in majority normoglycemia and good metabolic control[70]. 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[71]. The occurrence of hepatocellular carcinoma is also possible, and its incidence increases along with the increasing survival of the well-metabolically controlled patients[75]. Accordingly, hepatocellular adenomatosis and carcinoma are the main indications for LT in GSD I patients, which also provides good glucose homeostasis[71,76].

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[71,77]. Several authors thus report CLKT as a successful treatment for GSD I patients with hepatic adenomatosis and kidney failure[78-81]. 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[82]. 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[83-86]. 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[83,85] Patients who underwent CLKT so far, were all adults aged 19-42 years and they all have recovered well after transplantation[84,85]. 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[85,86].

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.

NEPHRONOPHTHISIS ASSOCIATED WITH LIVER FIBROSIS AND CLKT

Nephronophthisis (NPHP) is a renal ciliopathy with the autosomal recessive inheritance of cystic kidney disease and with a prevalence of 1/100000 people[87]. It may progress to ESRD and is the most common genetic cause of renal failure in children and young adults[88]. 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[89]. 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)[18,90]. 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[91].

HOMOZYGOUS PROTEIN C DEFICIENCY AND CLKT

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[92]. 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[93]. The condition is managed by substitution of protein C and anticoagulation therapy, although long-term survival without major co-morbidity is rarely reported[93]. 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[93-97]. 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[95].

ACUTE INTERMITTENT PORPHYRIA AND CLKT

Acute intermittent porphyria (AIP) is an autosomal dominant disorder resulting in the deficiency of porphobilinogen deaminase (PBGD), an enzyme involved in heme synthesis[98]. AIP has a prevalence of 1/20000 people[99]. 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)[98,100,101]. 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[100,102].

Current treatment for acute attacks consists of intravenous hemin and carbohydrate loading[101], though repeated hemin therapy may complicate patients' conditions, causing vascular thromboses and restricting venous access[103]. 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[104].

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%[105]. 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[105]. Despite extrahepatic PBGD deficiency, there were no observed induced AIP attacks due to immunosuppressants[106]. A few successful renal transplantations have also been performed in patients with uncomplicated AIP and renal failure[107,108]. Even though, most recommendations for patients with frequent acute attacks, progressive neuropathies and deteriorating renal function suggest performing CLKT[101] yet only two published cases (aged 24 and 55 years) have undergone CLKT[109]. Wahlin *et al*[109] 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[110], 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.

METHYLMALONIC ACIDURIA AND CLKT

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[111]. 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[112]. MUT enzyme is normally expressed primarily in mitochondria of the liver, but also in kidneys, endocrine tissue, brain, and muscles[113]. Furthermore, the accumulation of MA provokes episodes of metabolic instability[114].

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[114-117]. 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[118]. 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[58,119].

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[114]. Even more so, the amount of normal enzyme is higher in CLKT and in addition kidney rejection may be better controlled[59,120].

After CLKT levels of MA decrease by 80%-97%[121,122] and are lower than after isolated LT with better metabolic outcomes and reduced number of hospitalizations[123-125]. The majority of reports show improvements in neuro-development (enhanced motor skills, learning abilities, social engagement) and improved quality of life after CLKT[18,114,118,121,123-128]. Yet, in most cases, MA levels after CLKT are still 1000x higher than normal[124,125]. Besides, neurologic and/or muscle impairments may continue despite normal graft function[59,117]. 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[117]. In some cases in the post-transplant period, a relaxed dietary protein diet may safely occur[128].

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

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[123-125]. Most of the immunosuppression regimens for CLKT in MMA patients consisted of calcineurin inhibitors (CNI) (tacrolimus and cyclosporine) steroids and mycophenolate-mofetil[116,124,125]. 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 CLKD. 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[115,116,121,122].

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[115].

ANTIBODY-MEDIATED REJECTION OF THE KIDNEY

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[133]. 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[133]. 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[133]. 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[134]. *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[135]. 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[133].

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[136], 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[137]. Such auxiliary, partial, CLKT performed to facilitate HLA-incompatible kidney transplantation in a difficult to desensitize recipient remains to be reported.

CONTRAINDICATIONS FOR CLKT

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[138]. In patients with liver cirrhosis, an additional contraindication is moderate or severe portopulmonary hypertension[139]. 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[140].

CONCLUSION

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.

REFERENCES

1 **U.S. Department of Health & Human Services**. OPTN/SRTR 2018 Annual Data Report: Liver. [Cited May 10, 2020] Available from: https://srtr.transplant.hrsa.gov/annual_reports/2018/Liver.aspx#LI_10_char_adult_tx_tx

2 **Ruiz R**, Jennings LW, Kim P, Tomiyama K, Chinnakotla S, Fischbach BV, Goldstein RM, Levy MF, McKenna GJ, Melton LB, Onaca N, Randall HB, Sanchez EQ, Susskind BM, Klintmalm GB. Indications for combined liver and kidney transplantation: propositions after a 23-yr experience. *Clin Transplant* 2010; **24**: 807-811 [PMID: 20002463 DOI: 10.1111/j.1399-0012.2009.01180.x]

3 **Calinescu AM**, Wildhaber BE, Poncet A, Toso C, McLin VA. Outcomes of combined liver-kidney transplantation in children: analysis of the scientific registry of transplant recipients. *Am J Transplant* 2014; **14**: 2861-2868 [PMID: 25274400 DOI: 10.1111/ajt.12935]

4 **Cochat P**, Rumsby G. Primary hyperoxaluria. *N Engl J Med* 2013; **369**: 649-658 [PMID: 23944302 DOI: 10.1056/NEJMra1301564]

5 **Hopp K**, Cogal AG, Bergstralh EJ, Seide BM, Olson JB, Meek AM, Lieske JC, Milliner DS, Harris PC; Rare Kidney Stone Consortium. Phenotype-Genotype Correlations and Estimated Carrier Frequencies of Primary Hyperoxaluria. *J Am Soc Nephrol* 2015; **26**: 2559-2570 [PMID: 25644115 DOI: 10.1681/ASN.2014070698]

6 **Garrelfs SF**, Rumsby G, Peters-Sengers H, Erger F, Groothoff JW, Beck BB, Oosterveld MJS, Pelle A, Neuhaus T, Adams B, Cochat P, Salido E, Lipkin GW, Hoppe B, Hulton SA; OxalEurope Consortium. Patients with primary hyperoxaluria type 2 have significant morbidity and require careful follow-up. *Kidney Int* 2019; **96**: 1389-1399 [PMID: 31685312 DOI: 10.1016/j.kint.2019.08.018]

7 **Jamieson NV**; European PHI Transplantation Study Group. A 20-year experience of combined liver/kidney transplantation for primary hyperoxaluria (PH1): the European PH1 transplant registry experience 1984-2004. *Am J Nephrol* 2005; **25**: 282-289 [PMID: 15961948 DOI: 10.1159/000086359]

8 **Harambat J**, van Stralen KJ, Espinosa L, Groothoff JW, Hulton SA, Cerkauskiene R, Schaefer F, Verrina E, Jager KJ, Cochat P; European Society for Pediatric Nephrology/European Renal Association-European Dialysis and Transplant Association (ESPN/ERA-EDTA) Registry. Characteristics and outcomes of children with primary oxalosis requiring renal replacement therapy. *Clin J Am Soc Nephrol* 2012; **7**: 458-465 [PMID: 22223608 DOI: 10.2215/CJN.07430711]

9 **Cibrik DM**, Kaplan B, Arndorfer JA, Meier-Kriesche HU. Renal allograft survival in patients with oxalosis. *Transplantation* 2002; **74**: 707-710 [PMID: 12352890 DOI: 10.1097/00007890-200209150-00020]

10 **Dhondup T**, Lorenz EC, Milliner DS, Lieske JC. Combined Liver-Kidney Transplantation for Primary Hyperoxaluria Type 2: A Case Report. *Am J Transplant* 2018; **18**: 253-257 [PMID: 28681512 DOI: 10.1111/ajt.14418]

11 **Bergstralh EJ**, Monico CG, Lieske JC, Herges RM, Langman CB, Hoppe B, Milliner DS; IPHR Investigators. Transplantation outcomes in primary hyperoxaluria. *Am J Transplant* 2010; **10**: 2493-2501 [PMID: 20849551 DOI: 10.1111/j.1600-6143.2010.03271.x]

12 **Fagiuoli S**, Daina E, D'Antiga L, Colledan M, Remuzzi G. Monogenic diseases that can be cured by liver transplantation. *J Hepatol* 2013; **59**: 595-612 [PMID: 23578885 DOI: 10.1016/j.jhep.2013.04.004]

13 **Kotb MA**, Hamza AF, Abd El Kader H, El Monayeri M, Mosallam DS, Ali N, Basanti CWS, Bazaraa H, Abdelrahman H, Nabhan MM, Abd El Baky H, El Sorogy STM, Kamel IEM, Ismail H, Ramadan Y, Abd El Rahman SM, Soliman NA. Combined liver-kidney transplantation for primary hyperoxaluria type I in children: Single Center Experience. *Pediatr Transplant* 2019; **23**: e13313 [PMID: 30475440 DOI: 10.1111/petr.13313]

14 **Martínez Caballero J**, Marcacuzco Quinto A, Justo Alonso I, Nutu OA, Manrique Municio A, Calvo Pulido J, Cambra Molero F, Caso Maestro Ó, Jiménez Romero C. Liver-kidney simultaneous transplantation in adult patients with primary hyperoxaluria. *Rev Esp Enferm Dig* 2018; **110**: 82-87 [PMID: 29106285 DOI: 10.17235/reed.2017.5016/2017]

15 **Mor E**, Nesher E, Ben-Ari Z, Weissman I, Shaharabani E, Eizner S, Solomonov E, Rahamimov R, Braun M. Sequential liver and kidney transplantation from a single living donor in two young adults with primary hyperoxaluria type 1. *Liver Transpl* 2013; **19**: 646-648 [PMID: 23526660 DOI: 10.1002/Lt.23642]

16 **Franssen CF**, Kema IP, Eleveld DJ, Porte RJ, Homan van der Heide JJ. Intra-operative continuous renal replacement therapy during combined liver-kidney transplantation in two patients with primary hyperoxaluria type 1. *NDT Plus* 2011; **4**: 113-116 [PMID: 25984128 DOI: 10.1093/ndtplus/sfq216]

17 **Alkhunaizi AM**, Al-Sannaa NA, Raslan WF. Hyperoxaluria and rapid development of renal failure following a combined liver and kidney transplantation: emphasis on sequential transplantation. *JIMD Rep* 2012; **3**: 91-95 [PMID: 23430879 DOI: 10.1007/8904_2011_67]

18 **Duclaux-Loras R**, Bacchetta J, Berthiller J, Rivet C, Demède D, Javouhey E, Dubois R, Dijoud F, Lachaux A, Badet L, Boillot O, Cochat P. Pediatric combined liver-kidney transplantation: a single-center experience of 18 cases. *Pediatr Nephrol* 2016; **31**: 1517-1529 [PMID: 27060059 DOI: 10.1007/s00467-016-3324-6]

19 **Trotter JF**, Milliner D. Auxiliary liver transplant is an ineffective treatment of primary hyperoxaluria. *Am J Transplant* 2014; **14**: 241 [PMID: 24330139 DOI: 10.1111/ajt.12535]

20 **Onaca N**, Sanchez EQ, Melton LB, Netto GJ, Glastad KA, Martin PA, Ueno T, Levy MF, Goldstein RM, Klintmalm GB. Cadaveric orthotopic auxiliary split liver transplantation and kidney transplantation: an alternative for type 1 primary hyperoxaluria. *Transplantation* 2005; **80**: 421-424 [PMID: 16082341 DOI: 10.1097/01.tp.0000168147.88707.80]

21 **Elias N**, Kawai T, Ko DS, Saidi R, Tolkoff-Rubin N, Wicky S, Cosimi AB, Hertl M. Native portal vein embolization for persistent hyperoxaluria following kidney and auxiliary partial liver transplantation. *Am J Transplant* 2013; **13**: 2739-2742 [PMID: 23915277 DOI: 10.1111/ajt.12381]

22 **Knotek M**, Maksimović B, Gunjača M, Mihovilović K, Ljubanović DG, Kocman B. Combined auxiliary split liver and kidney transplantation for type I primary hyperoxaluria and end-stage kidney disease.

Nephrology (Carlton) 2014; **19**: 814-815 [PMID: 25403990 DOI: 10.1111/nep.12325]
23 **Jokiranta TS**. HUS and atypical HUS. *Blood* 2017; **129**: 2847-2856 [PMID: 28416508 DOI: 10.1182/blood-2016-11-709865]
24 **Yan K**, Desai K, Gullapalli L, Druyts E, Balijepalli C. Epidemiology of Atypical Hemolytic Uremic Syndrome: A Systematic Literature Review. *Clin Epidemiol* 2020; **12**: 295-305 [PMID: 32210633 DOI: 10.2147/CLEP.S245642]
25 **Liszewski MK**, Java A, Schramm EC, Atkinson JP. Complement Dysregulation and Disease: Insights from Contemporary Genetics. *Annu Rev Pathol* 2017; **12**: 25-52 [PMID: 27959629 DOI: 10.1146/annurev-pathol-012615-044145]
26 **Bowen EE**, Coward RJ. Advances in our understanding of the pathogenesis of hemolytic uremic syndromes. *Am J Physiol Renal Physiol* 2018; **314**: F454-F461 [PMID: 29167171 DOI: 10.1152/ajprenal.00376.2017]
27 **Quan A**, Sullivan EK, Alexander SR. Recurrence of hemolytic uremic syndrome after renal transplantation in children: a report of the North American Pediatric Renal Transplant Cooperative Study. *Transplantation* 2001; **72**: 742-745 [PMID: 11544443 DOI: 10.1097/00007890-200108270-00033]
28 **Davin JC**, Gruppen M, Bouts AH, Groothoff JW, van Amstel SP, Surachno J, ten Berge IJ, Weening JJ. Relapse of atypical haemolytic uraemic syndrome after kidney transplantation: role of ATG and failure of mycophenolate mofetil as rescue therapy. *Nephrol Dial Transplant* 1999; **14**: 984-987 [PMID: 10328487 DOI: 10.1093/ndt/14.4.984]
29 **Müller T**, Sikora P, Offner G, Hoyer PF, Brodehl J. Recurrence of renal disease after kidney transplantation in children: 24 years of experience in a single center. *Clin Nephrol* 1998; **49**: 82-90 [PMID: 9524777 DOI: 10.1097/SLA.0b013e3181b16e24]
30 **Miller RB**, Burke BA, Schmidt WJ, Gillingham KJ, Matas AJ, Mauer M, Kashtan CE. Recurrence of haemolytic-uraemic syndrome in renal transplants: a single-centre report. *Nephrol Dial Transplant* 1997; **12**: 1425-1430 [PMID: 9249780 DOI: 10.1093/ndt/12.7.1425]
31 **Bresin E**, Daina E, Noris M, Castelletti F, Stefanov R, Hill P, Goodship TH, Remuzzi G; International Registry of Recurrent and Familial HUS/TTP. Outcome of renal transplantation in patients with non-Shiga toxin-associated hemolytic uremic syndrome: prognostic significance of genetic background. *Clin J Am Soc Nephrol* 2006; **1**: 88-99 [PMID: 17699195 DOI: 10.2215/CJN.00050505]
32 **Remuzzi G**, Ruggenenti P, Codazzi D, Noris M, Caprioli J, Locatelli G, Gridelli B. Combined kidney and liver transplantation for familial haemolytic uraemic syndrome. *Lancet* 2002; **359**: 1671-1672 [PMID: 12020532 DOI: 10.1016/S0140-6736(02)08560-4]
33 **Jalanko H**, Peltonen S, Koskinen A, Puntila J, Isoniemi H, Holmberg C, Pinomäki A, Armstrong E, Koivusalo A, Tukiainen E, Mäkisalo H, Saland J, Remuzzi G, de Cordoba S, Lassila R, Meri S, Jokiranta TS. Successful liver-kidney transplantation in two children with aHUS caused by a mutation in complement factor H. *Am J Transplant* 2008; **8**: 216-221 [PMID: 17973958 DOI: 10.1111/j.1600-6143.2007.02029.x]
34 **Saland JM**, Emre SH, Shneider BL, Benchimol C, Ames S, Bromberg JS, Remuzzi G, Strain L, Goodship TH. Favorable long-term outcome after liver-kidney transplant for recurrent hemolytic uremic syndrome associated with a factor H mutation. *Am J Transplant* 2006; **6**: 1948-1952 [PMID: 16889549 DOI: 10.1111/j.1600-6143.2006.01375.x]
35 **Saland JM**, Shneider BL, Bromberg JS, Shi PA, Ward SC, Magid MS, Benchimol C, Seikaly MG, Emre SH, Bresin E, Remuzzi G. Successful split liver-kidney transplant for factor H associated hemolytic uremic syndrome. *Clin J Am Soc Nephrol* 2009; **4**: 201-206 [PMID: 19005013 DOI: 10.2215/CJN.02170508]
36 **Legendre CM**, Licht C, Muus P, Greenbaum LA, Babu S, Bedrosian C, Bingham C, Cohen DJ, Delmas Y, Douglas K, Eitner F, Feldkamp T, Fouque D, Furman RR, Gaber O, Herthelius M, Hourmant M, Karpman D, Lebranchu Y, Mariat C, Menne J, Moulin B, Nürnberger J, Ogawa M, Remuzzi G, Richard T, Sberro-Soussan R, Severino B, Sheerin NS, Trivelli A, Zimmerhackl LB, Goodship T, Loirat C. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. *N Engl J Med* 2013; **368**: 2169-2181 [PMID: 23738544 DOI: 10.1056/NEJMoa1208981]
37 **Licht C**, Greenbaum LA, Muus P, Babu S, Bedrosian CL, Cohen DJ, Delmas Y, Douglas K, Furman RR, Gaber OA, Goodship T, Herthelius M, Hourmant M, Legendre CM, Remuzzi G, Sheerin N, Trivelli A, Loirat C. Efficacy and safety of eculizumab in atypical hemolytic uremic syndrome from 2-year extensions of phase 2 studies. *Kidney Int* 2015; **87**: 1061-1073 [PMID: 25651368 DOI: 10.1038/ki.2014.423]
38 **Legendre CM**, Campistol JM, Feldkamp T, Remuzzi G, Kincaid JF, Lommelé Å, Wang J, Weekers LE, Sheerin NS. Outcomes of patients with atypical haemolytic uraemic syndrome with native and transplanted kidneys treated with eculizumab: a pooled post hoc analysis. *Transpl Int* 2017; **30**: 1275-1283 [PMID: 28801959 DOI: 10.1111/tri.13022]
39 **Kato H**, Nangaku M, Hataya H, Sawai T, Ashida A, Fujimaru R, Hidaka Y, Kaname S, Maruyama S, Yasuda T, Yoshida Y, Ito S, Hattori M, Miyakawa Y, Fujimura Y, Okada H, Kagami S; Joint Committee for the Revision of Clinical Guides of Atypical Hemolytic Uremic Syndrome in Japan. Clinical guides for atypical hemolytic uremic syndrome in Japan. *Pediatr Int* 2016; **58**: 549-555 [PMID: 27460397 DOI: 10.1111/ped.13044]
40 **Claes KJ**, Massart A, Collard L, Weekers L, Goffin E, Pochet JM, Dahan K, Morelle J, Adams B, Broeders N, Stordeur P, Abramowicz D, Bosmans JL, Van Hoeck K, Janssens P, Pipeleers L, Peeters P, Van Laecke S, Levtchenko E, Sprangers B, van den Heuvel L, Godefroid N, Van de Walle J. Belgian consensus statement on the diagnosis and management of patients with atypical hemolytic uremic syndrome. *Acta Clin Belg* 2018; **73**: 80-89 [PMID: 29058539 DOI: 10.1080/17843286.2017.1345185]
41 **Lee H**, Kang E, Kang HG, Kim YH, Kim JS, Kim HJ, Moon KC, Ban TH, Oh SW, Jo SK, Cho H, Choi BS, Hong J, Cheong HI, Oh D. Consensus regarding diagnosis and management of atypical hemolytic uremic syndrome. *Korean J Intern Med* 2020; **35**: 25-40 [PMID: 31935318 DOI: 10.3904/kjim.2019.388]
42 **Campistol JM**, Arias M, Ariceta G, Blasco M, Espinosa L, Espinosa M, Grinyó JM, Macía M, Mendizábal S, Praga M, Román E, Torra R, Valdés F, Vilalta R, Rodríguez de Córdoba S. An update for atypical haemolytic uraemic syndrome: diagnosis and treatment. *Nefrologia* 2015; **35**: 421-447 [PMID: 26456110 DOI: 10.1016/j.nefro.2015.07.005]

43 **Coppo R**, Bonaudo R, Peruzzi RL, Amore A, Brunati A, Romagnoli R, Salizzoni M, Galbusera M, Gotti E, Daina E, Noris M, Remuzzi G. Liver transplantation for aHUS: still needed in the eculizumab era? *Pediatr Nephrol* 2016; **31**: 759-768 [PMID: 26604087 DOI: 10.1007/s00467-015-3278-0]

44 **Cho H**, Lee Y. Favorable long-term outcomes of isolated liver transplantation in a child with atypical hemolytic uremic syndrome caused by a novel complement factor H mutation. *Clin Nephrol* 2017; **88**: 52-56 [PMID: 28502324 DOI: 10.5414/CN109138]

45 **Orphanet**. Complement component 3 deficiency. Orphanet encyclopedia, May 2020. [Cited May 5, 2020] Available from: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=en&Expert=280133

46 **Goodship TH**, Cook HT, Fakhouri F, Fervenza FC, Frémeaux-Bacchi V, Kavanagh D, Nester CM, Noris M, Pickering MC, Rodríguez de Córdoba S, Roumenina LT, Sethi S, Smith RJ; Conference Participants. Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. *Kidney Int* 2017; **91**: 539-551 [PMID: 27989322 DOI: 10.1016/j.kint.2016.10.005]

47 **Botto M**, Kirschfink M, Macor P, Pickering MC, Würzner R, Tedesco F. Complement in human diseases: Lessons from complement deficiencies. *Mol Immunol* 2009; **46**: 2774-2783 [PMID: 19481265 DOI: 10.1016/j.molimm.2009.04.029]

48 **Alper CA**, Johnson AM, Birtch AG, Moore FD. Human C'3: evidence for the liver as the primary site of synthesis. *Science* 1969; **163**: 286-288 [PMID: 4883617 DOI: 10.1126/science.163.3864.286]

49 **Naughton MA**, Botto M, Carter MJ, Alexander GJ, Goldman JM, Walport MJ. Extrahepatic secreted complement C3 contributes to circulating C3 Levels in humans. *J Immunol* 1996; **156**: 3051-3056 [PMID: 8609428]

50 **Tang S**, Zhou W, Sheerin NS, Vaughan RW, Sacks SH. Contribution of renal secreted complement C3 to the circulating pool in humans. *J Immunol* 1999; **162**: 4336-4341 [PMID: 10201966]

51 **Nayagam JS**, McGrath S, Montasser M, Delaney M, Cairns TD, Marchbank KJ, Denton H, Yang Y, Sacks SH, Cook HT, Shah S, Heaton N, Pickering MC, Suddle A. Successful simultaneous liver-kidney transplantation for renal failure associated with hereditary complement C3 deficiency. *Am J Transplant* 2020; **20**: 2260-2263 [PMID: 31970896 DOI: 10.1111/ajt.15785]

52 **Greulich T**, Nell C, Hohmann D, Grebe M, Janciauskiene S, Koczulla AR, Vogelmeier CF. The prevalence of diagnosed α1-antitrypsin deficiency and its comorbidities: results from a large population-based database. *Eur Respir J* 2017; **49** [PMID: 27824593 DOI: 10.1183/13993003.00154-2016]

53 **Patel D**, Teckman JH. Alpha-1-Antitrypsin Deficiency Liver Disease. *Clin Liver Dis* 2018; **22**: 643-655 [PMID: 30266154 DOI: 10.1016/j.cld.2018.06.010]

54 **Kalfopoulos M**, Wetmore K, ElMallah MK. Pathophysiology of Alpha-1 Antitrypsin Lung Disease. *Methods Mol Biol* 2017; **1639**: 9-19 [PMID: 28752442 DOI: 10.1007/978-1-4939-7163-3_2]

55 **Graziadei I**, Zoller H, Fickert P, Schneeberger S, Finkenstedt A, Peck-Radosavljevic M, Müller H, Kohl C, Sperner-Unterweger B, Eschertzhuber S, Hofer H, Öfner D, Tilg H, Vogel W, Trauner M, Berlakovich G. Indications for liver transplantation in adults : Recommendations of the Austrian Society for Gastroenterology and Hepatology (ÖGGH) in cooperation with the Austrian Society for Transplantation, Transfusion and Genetics (ATX). *Wien Klin Wochenschr* 2016; **128**: 679-690 [PMID: 27590261 DOI: 10.1007/s00508-016-1046-1]

56 **Loreno M**, Boccagni P, Rigotti P, Naccarato R, Burra P. Combined liver-kidney transplantation in a 15-year-old boy with alpha1-antitrypsin deficiency. *J Hepatol* 2002; **36**: 565-568 [PMID: 11943431 DOI: 10.1016/s0168-8278(02)00012-0]

57 **Benedetti E**, Pirenne J, Troppmann C, Hakim N, Moon C, Gruessner RW, Sharp H, Matas AJ, Payne WD, Najarian JS. Combined liver and kidney transplantation. *Transpl Int* 1996; **9**: 486-491 [PMID: 8875792 DOI: 10.1007/BF00336827]

58 **Elzouki AN**, Lindgren S, Nilsson S, Veress B, Eriksson S. Severe alpha1-antitrypsin deficiency (PiZ homozygosity) with membranoproliferative glomerulonephritis and nephrotic syndrome, reversible after orthotopic liver transplantation. *J Hepatol* 1997; **26**: 1403-1407 [PMID: 9210630 DOI: 10.1016/s0168-8278(97)80478-3]

59 **Grenda R**, Kaliciński P. Combined and sequential liver-kidney transplantation in children. *Pediatr Nephrol* 2018; **33**: 2227-2237 [PMID: 29322327 DOI: 10.1007/s00467-017-3880-4]

60 **Saeedi R**, Li M, Frohlich J. A review on lecithin:cholesterol acyltransferase deficiency. *Clin Biochem* 2015; **48**: 472-475 [PMID: 25172171 DOI: 10.1016/j.clinbiochem.2014.08.014]

61 **Strøm EH**, Sund S, Reier-Nilsen M, Dørje C, Leren TP. Lecithin: Cholesterol Acyltransferase (LCAT) Deficiency: renal lesions with early graft recurrence. *Ultrastruct Pathol* 2011; **35**: 139-145 [PMID: 21323422 DOI: 10.3109/01913123.2010.551578]

62 **Althaf MM**, Almana H, Abdelfadiel A, Amer SM, Al-Hussain TO. Familial lecithin-cholesterol acyltransferase (LCAT) deficiency; a differential of proteinuria. *J Nephropathol* 2015; **4**: 25-28 [PMID: 25657982 DOI: 10.12860/jnp.2015.05]

63 **Anastasopoulou C**. Lecithin-cholesterol acyltransferase (LCAT) deficiency. 2019. [Cited May 10, 2020] Available from: https://emedicine.medscape.com/article/122958-overview

64 **Panescu V**, Grignon Y, Hestin D, Rostoker G, Frimat L, Renoult E, Gamberoni J, Grignon G, Kessler M. Recurrence of lecithin cholesterol acyltransferase deficiency after kidney transplantation. *Nephrol Dial Transplant* 1997; **12**: 2430-2432 [PMID: 9394340 DOI: 10.1093/ndt/12.11.2430]

65 **Horina JH**, Wirnsberger G, Horn S, Roob JM, Ratschek M, Holzer H, Pogglitsch H, Krejs GJ. Long-term follow-up of a patient with lecithin cholesterol acyltransferase deficiency syndrome after kidney transplantation. *Transplantation* 1993; **56**: 233-236 [PMID: 8333054 DOI: 10.1097/00007890-199307000-00047]

66 **Stoynovska BB**. Successful renal transplantation in a patient with familial lecithin:cholesterol acyltransferase deficiency. *Transpl Int* 1992; **5**: 187 [PMID: 1514967 DOI: 10.1007/bf00336608]

67 **Ahmad SB**, Miller M, Hanish S, Bartlett ST, Hutson W, Barth RN, LaMattina JC. Sequential kidney-liver transplantation from the same living donor for lecithin cholesterol acyl transferase deficiency. *Clin*

Transplant 2016; **30**: 1370-1374 [PMID: 27490864 DOI: 10.1111/ctr.12826]
68 **Chen MA**, Weinstein DA. Glycogen storage diseases: Diagnosis, treatment and outcome. *Transl Sci Rare Dis* 2016; **1**: 45–72 [DOI: 10.3233/TRD-160006]
69 **Bali DS**, Chen YT, Austin S, Goldstein JL. Glycogen Storage Disease Type I. Last Aug 2016 [Cited May 7, 2020] GeneReviews® [Internet] Available from: https://www.ncbi.nlm.nih.gov/books/NBK1312/
70 **Rake JP**, Visser G, Labrune P, Leonard JV, Ullrich K, Smit GP. Glycogen storage disease type I: diagnosis, management, clinical course and outcome. *Eur J Pediatr* 2002; **161** Suppl 1: S20-S34 [PMID: 12373567 DOI: 10.1007/s00431-002-0999-4]
71 **Kishnani PS**, Austin SL, Abdenur JE, Arn P, Bali DS, Boney A, Chung WK, Dagli AI, Dale D, Koeberl D, Somers MJ, Wechsler SB, Weinstein DA, Wolfsdorf JI, Watson MS; American College of Medical Genetics and Genomics. Diagnosis and management of glycogen storage disease type I: a practice guideline of the American College of Medical Genetics and Genomics. *Genet Med* 2014; **16**: e1 [PMID: 25356975 DOI: 10.1038/gim.2014.128]
72 **Arion WJ**, Lange AJ, Walls HE, Ballas LM. Evidence for the participation of independent translocation for phosphate and glucose 6-phosphate in the microsomal glucose-6-phosphatase system. *J Biol Chem* 1980; **255**: 10396-10406 [PMID: 6253473]
73 **Froissart R**, Piraud M, Boudjemline AM, Vianey-Saban C, Petit F, Hubert-Buron A, Eberschweiler PT, Gajdos V, Labrune P. Glucose-6-phosphatase deficiency. *Orphanet J Rare Dis* 2011; **6**: 27 [PMID: 21599942 DOI: 10.1186/1750-1172-6-27]
74 **Visser G**, Rake JP, Fernandes J, Labrune P, Leonard JV, Moses S, Ullrich K, Smit GP. Neutropenia, neutrophil dysfunction, and inflammatory bowel disease in glycogen storage disease type Ib: results of the European Study on Glycogen Storage Disease type I. *J Pediatr* 2000; **137**: 187-191 [PMID: 10931410 DOI: 10.1067/mpd.2000.105232]
75 **Calderaro J**, Labrune P, Morcrette G, Rebouissou S, Franco D, Prévot S, Quaglia A, Bedossa P, Libbrecht L, Terracciano L, Smit GP, Bioulac-Sage P, Zucman-Rossi J. Molecular characterization of hepatocellular adenomas developed in patients with glycogen storage disease type I. *J Hepatol* 2013; **58**: 350-357 [PMID: 23046672 DOI: 10.1016/j.jhep.2012.09.030]
76 **Chava SP**, Singh B, Zaman MB, Rela M, Heaton ND. Current indications for combined liver and kidney transplantation in adults. *Transplant Rev (Orlando)* 2009; **23**: 111-119 [PMID: 19298942 DOI: 10.1016/j.trre.2009.01.005]
77 **Faivre L**, Houssin D, Valayer J, Brouard J, Hadchouel M, Bernard O. Long-term outcome of liver transplantation in patients with glycogen storage disease type Ia. *J Inherit Metab Dis* 1999; **22**: 723-732 [PMID: 10472532 DOI: 10.1023/a:1005544117285]
78 **Poe R**, Snover DC. Adenomas in glycogen storage disease type 1. *Am J Surg Pathol* 1988; **12**: 477-483 [PMID: 2454037 DOI: 10.1097/00000478-198806000-00008]
79 **Marega A**, Fregonese C, Tulissi P, Vallone C, Gropuzzo M, Toniutto PL, Baccarani U, Bresadola F, Toso F, Montanaro D. Preemptive liver-kidney transplantation in von Gierke disease: a case report. *Transplant Proc* 2011; **43**: 1196-1197 [PMID: 21620087 DOI: 10.1016/j.transproceed.2011.03.003]
80 **Maya Aparicio AC**, Bernal Bellido C, Tinoco González J, Garcia Ruíz S, Aguilar Romero L, Marín Gómez LM, Suárez Artacho G, Alamo Martínez JM, Serrano Díez-Canedo J, Padillo Ruíz FJ, Gomez Bravo MA. Fifteen years of follow-up of a liver transplant recipient with glycogen storage disease type Ia (Von Gierke disease). *Transplant Proc* 2013; **45**: 3668-3669 [PMID: 24314991 DOI: 10.1016/j.transproceed.2013.10.033]
81 **Panaro F**, Andorno E, Basile G, Morelli N, Bottino G, Fontana I, Bertocchi M, DiDomenico S, Miggino M, Saltalamacchia L, Ghinolfi D, Bonifazio L, Jarzembowski TM, Valente U. Simultaneous liver-kidney transplantation for glycogen storage disease type IA (von Gierke's disease). *Transplant Proc* 2004; **36**: 1483-1484 [PMID: 15251364 DOI: 10.1016/j.transproceed.2004.05.070]
82 **Labrune P**, Trioche P, Duvaltier I, Chevalier P, Odièvre M. Hepatocellular adenomas in glycogen storage disease type I and III: a series of 43 patients and review of the literature. *J Pediatr Gastroenterol Nutr* 1997; **24**: 276-279 [PMID: 9138172 DOI: 10.1097/00005176-199703000-00008]
83 **Demirci G**, Becker T, Nyibata M, Lueck R, Bektas H, Lehner F, Tusch G, Strassburg C, Schwarz A, Klempnauer J, Nashan B. Results of combined and sequential liver-kidney transplantation. *Liver Transpl* 2003; **9**: 1067-1078 [PMID: 14526402 DOI: 10.1053/jlts.2003.50210]
84 **Alfano G**, Fontana F, Francesca D, Assirati G, Magistri P, Tarantino G, Ballarin R, Rossi G, Franceschini E, Codeluppi M, Guaraldi G, Mussini C, Di Benedetto F, Cappelli G. Gastric Mucormycosis in a Liver and Kidney Transplant Recipient: Case Report and Concise Review of Literature. *Transplant Proc* 2018; **50**: 905-909 [PMID: 29573830 DOI: 10.1016/j.transproceed.2017.11.036]
85 **Belingheri M**, Ghio L, Sala A, Menni F, Trespidi L, Ferraresso M, Berardinelli L, Rossi G, Edefonti A, Parini R. Combined liver-kidney transplantation in glycogen storage disease Ia: a case beyond the guidelines. *Liver Transpl* 2007; **13**: 762-764 [PMID: 17457869 DOI: 10.1002/Lt.21147]
86 **Lee PJ**, Muiesan P, Heaton N. Successful pregnancy after combined renal-hepatic transplantation in glycogen storage disease type Ia. *J Inherit Metab Dis* 2004; **27**: 537-538 [PMID: 15334735 DOI: 10.1023/b:boli.0000037397.39725.57]
87 **Stokman M**, Lilien M, Knoers N. Nephronophthisis. Jun 2016. [Cited May 7, 2020] GeneReviews® [Internet] Available from: https://www.ncbi.nlm.nih.gov/books/NBK368475/
88 **Srivastava S**, Molinari E, Raman S, Sayer JA. Many Genes-One Disease? *Front Pediatr* 2017; **5**: 287 [PMID: 29379777 DOI: 10.3389/fped.2017.00287]
89 **Luo F**, Tao YH. Nephronophthisis: A review of genotype-phenotype correlation. *Nephrology (Carlton)* 2018; **23**: 904-911 [PMID: 29717526 DOI: 10.1111/nep.13393]
90 **Zhang H**, Luo J, Liu L, Li J, Fu Q, Chen W, Yang S, Shang W, Wang H, Deng R, Sun L, Zhu X, Wang C. Transplantation for infantile nephronophthisis with loss-of-function mutation in NPHP3: Lesson from a case. *Pediatr Transplant* 2018: e13233 [PMID: 29869359 DOI: 10.1111/petr.13233]
91 **Udagawa T**, Kamei K, Ogura M, Tsutsumi A, Noda S, Kasahara M, Fukuda A, Sakamoto S, Shigeta S,

Tanaka H, Kuroda T, Matsuoka K, Nakazawa A, Nagai T, Uemura O, Ito S. Sequential liver-kidney transplantation in a boy with congenital hepatic fibrosis and nephronophthisis from a living donor. *Pediatr Transplant* 2012; **16**: E275-E280 [PMID: 22129440 DOI: 10.1111/j.1399-3046.2011.01611.x]

92 **Goldenberg NA**, Manco-Johnson MJ. Protein C deficiency. *Haemophilia* 2008; **14**: 1214-1221 [PMID: 19141162 DOI: 10.1111/j.1365-2516.2008.01838.x]

93 **Monagle K**, Ignjatovic V, Hardikar W, Newall F, Monagle P. Long-term follow-up of homozygote protein C deficiency after multimodal therapy. *J Pediatr Hematol Oncol* 2014; **36**: e452-e455 [PMID: 24136027 DOI: 10.1097/MPH.0000000000000032]

94 **Boucher AA**, Luchtman-Jones L, Nathan JD, Palumbo JS. Successful liver transplantation for homozygous protein C deficiency with a type II mutation using a heterozygous living related donor. *Am J Hematol* 2018; **93**: 462-466 [PMID: 29218739 DOI: 10.1002/ajh.24998]

95 **Angelis M**, Pegelow CH, Khan FA, Verzaro R, Tzakis AG. En bloc heterotopic auxiliary liver and bilateral renal transplant in a patient with homozygous protein C deficiency. *J Pediatr* 2001; **138**: 120-122 [PMID: 11148525 DOI: 10.1067/mpd.2001.109199]

96 **Casella JF**, Lewis JH, Bontempo FA, Zitelli BJ, Markel H, Starzl TE. Successful treatment of homozygous protein C deficiency by hepatic transplantation. *Lancet* 1988; **1**: 435-438 [PMID: 2893866 DOI: 10.1016/s0140-6736(88)91231-7]

97 **Lee MJ**, Kim KM, Kim JS, Kim YJ, Lee YJ, Ghim TT. Long-term survival of a child with homozygous protein C deficiency successfully treated with living donor liver transplantation. *Pediatr Transplant* 2009; **13**: 251-254 [PMID: 18482214 DOI: 10.1111/j.1399-3046.2008.00972.x]

98 **Puy H**, Gouya L, Deybach JC. Porphyrias. *Lancet* 2010; **375**: 924-937 [PMID: 20226990 DOI: 10.1016/S0140-6736(09)61925-5]

99 **Ramanujam VS**, Anderson KE. Porphyria Diagnostics-Part 1: A Brief Overview of the Porphyrias. *Curr Protoc Hum Genet* 2015; **86**: 17.20.1-17.20.26 [PMID: 26132003 DOI: 10.1002/0471142905.hg1720s86]

100 **Fontanellas A**, Ávila MA, Berraondo P. Emerging therapies for acute intermittent porphyria. *Expert Rev Mol Med* 2016; **18**: e17 [PMID: 27804912 DOI: 10.1017/erm.2016.18]

101 **Harper P**, Sardh E. Management of acute intermittent porphyria. *Expert Opinion Orphan Drugs* 2014; **2**: 349-368 [DOI: 10.1517/21678707.2014.891456]

102 **Sardh E**, Wahlin S, Björnstedt M, Harper P, Andersson DE. High risk of primary liver cancer in a cohort of 179 patients with Acute Hepatic Porphyria. *J Inherit Metab Dis* 2013; **36**: 1063-1071 [PMID: 23344888 DOI: 10.1007/s10545-012-9576-9]

103 **Singal AK**, Parker C, Bowden C, Thapar M, Liu L, McGuire BM. Liver transplantation in the management of porphyria. *Hepatology* 2014; **60**: 1082-1089 [PMID: 24700519 DOI: 10.1002/hep.27086]

104 **Ajayi T**, Ward R, Summers B, Byrns J, Kappus M, Choi S, Wilder J. Pathophysiology, pharmacology and treatment of acute intermittent porphyria: a patient case description and recommendations from the current literature. *J Explor Res Pharmacol* 2017; **2**: 49-53 [DOI: 10.14218/JERP.2016.00022]

105 **Dowman JK**, Gunson BK, Mirza DF, Bramhall SR, Badminton MN, Newsome PN; UK Liver Selection and Allocation Working Party. Liver transplantation for acute intermittent porphyria is complicated by a high rate of hepatic artery thrombosis. *Liver Transpl* 2012; **18**: 195-200 [PMID: 21618697 DOI: 10.1002/Lt.22345]

106 **Turton-Weeks S**, Barone GW, Gurley BJ, Ketel BL, Lightfoot ML, Abul-Ezz SR, Anderson KE. Pretransplant evaluation of a patient with acute intermittent porphyria. *Prog Transplant* 2001; **11**: 214-216 [PMID: 11949465 DOI: 10.7182/prtr.11.3.61965k72uq73v0vx]

107 **Nunez DJ**, Williams PF, Herrick AL, Evans DB, McColl KE. Renal transplantation for chronic renal failure in acute porphyria. *Nephrol Dial Transplant* 1987; **2**: 271-274 [PMID: 3118271 DOI: 10.1093/oxfordjournals.ndt.a091556]

108 **Warholm C**, Wilczek H. Renal transplantation in a case of acute intermittent porphyria. *J Clin Pharmacol* 2003; **43**: 1158-1160 [PMID: 14517198 DOI: 10.1177/0091270003257223]

109 **Wahlin S**, Harper P, Sardh E, Andersson C, Andersson DE, Ericzon BG. Combined liver and kidney transplantation in acute intermittent porphyria. *Transpl Int* 2010; **23**: e18-e21 [PMID: 20028496 DOI: 10.1111/j.1432-2277.2009.01035.x]

110 **Bylesjö I**, Wikberg A, Andersson C. Clinical aspects of acute intermittent porphyria in northern Sweden: a population-based study. *Scand J Clin Lab Invest* 2009; **69**: 612-618 [PMID: 19401933 DOI: 10.1080/00365510902935979]

111 **Manoli I**, Sloan JL, Venditti CP. Isolated Methylmalonic Acidemia. 2016 Dec 1 [Cited May 7, 2020] GeneReviews® [Internet] Available from: https://www.ncbi.nlm.nih.gov/books/NBK1231/

112 **Dionisi-Vici C**, Deodato F, Röschinger W, Rhead W, Wilcken B. 'Classical' organic acidurias, propionic aciduria, methylmalonic aciduria and isovaleric aciduria: long-term outcome and effects of expanded newborn screening using tandem mass spectrometry. *J Inherit Metab Dis* 2006; **29**: 383-389 [PMID: 16763906 DOI: 10.1007/s10545-006-0278-z]

113 **Uhlén M**, Fagerberg L, Hallström BM, Lindskog C, Oksvold P, Mardinoglu A, Sivertsson Å, Kampf C, Sjöstedt E, Asplund A, Olsson I, Edlund K, Lundberg E, Navani S, Szigyarto CA, Odeberg J, Djureinovic D, Takanen JO, Hober S, Alm T, Edqvist PH, Berling H, Tegel H, Mulder J, Rockberg J, Nilsson P, Schwenk JM, Hamsten M, von Feilitzen K, Forsberg M, Persson L, Johansson F, Zwahlen M, von Heijne G, Nielsen J, Pontén F. Proteomics. *Science* 2015; **347**: 1260419 [PMID: 25613900 DOI: 10.1126/science.1260419]

114 **Nagarajan S**, Enns GM, Millan MT, Winter S, Sarwal MM. Management of methylmalonic acidaemia by combined liver-kidney transplantation. *J Inherit Metab Dis* 2005; **28**: 517-524 [PMID: 15902554 DOI: 10.1007/s10545-005-0517-8]

115 **Baumgartner MR**, Hörster F, Dionisi-Vici C, Haliloglu G, Karall D, Chapman KA, Huemer M, Hochuli M, Assoun M, Ballhausen D, Burlina A, Fowler B, Grünert SC, Grünewald S, Honzik T, Merinero B, Pérez-Cerdá C, Scholl-Bürgi S, Skovby F, Wijburg F, MacDonald A, Martinelli D, Sass JO, Valayannopoulos V, Chakrapani A. Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia. *Orphanet J Rare Dis* 2014; **9**: 130 [PMID: 25205257 DOI:

10.1186/s13023-014-0130-8]
116 **Vernon HJ**, Sperati CJ, King JD, Poretti A, Miller NR, Sloan JL, Cameron AM, Myers D, Venditti CP, Valle D. A detailed analysis of methylmalonic acid kinetics during hemodialysis and after combined liver/kidney transplantation in a patient with mut (0) methylmalonic acidemia. *J Inherit Metab Dis* 2014; **37**: 899-907 [PMID: 24961826 DOI: 10.1007/s10545-014-9730-7]
117 **Sloan JL**, Manoli I, Venditti CP. Liver or combined liver-kidney transplantation for patients with isolated methylmalonic acidemia: who and when? *J Pediatr* 2015; **166**: 1346-1350 [PMID: 25882873 DOI: 10.1016/j.jpeds.2015.03.026]
118 **van 't Hoff WG**, Dixon M, Taylor J, Mistry P, Rolles K, Rees L, Leonard JV. Combined liver-kidney transplantation in methylmalonic acidemia. *J Pediatr* 1998; **132**: 1043-1044 [PMID: 9627602 DOI: 10.1016/s0022-3476(98)70407-x]
119 **Jiang YZ**, Sun LY. The Value of Liver Transplantation for Methylmalonic Acidemia. *Front Pediatr* 2019; **7**: 87 [PMID: 30949461 DOI: 10.3389/fped.2019.00087]
120 **Levitsky J**, Feng S. Tolerance in clinical liver transplantation. *Hum Immunol* 2018; **79**: 283-287 [PMID: 29054397 DOI: 10.1016/j.humimm.2017.10.007]
121 **Mc Guire PJ**, Lim-Melia E, Diaz GA, Raymond K, Larkin A, Wasserstein MP, Sansaricq C. Combined liver-kidney transplant for the management of methylmalonic aciduria: a case report and review of the literature. *Mol Genet Metab* 2008; **93**: 22-29 [PMID: 17964841 DOI: 10.1016/j.ymgme.2007.08.119]
122 **Molema F**, Williams M, Langendonk J, Darwish-Murad S, van de Wetering J, Jacobs E, Onkenhout W, Brusse E, van der Eerden A, Wagenmakers M. Neurotoxicity including posterior reversible encephalopathy syndrome after initiation of calcineurin inhibitors in transplanted methylmalonic acidemia patients: Two case reports and review of the literature. *JIMD Rep* 2020; **51**: 89-104 [PMID: 32071844 DOI: 10.1002/jmd2.12088]
123 **Pillai NR**, Stroup BM, Poliner A, Rossetti L, Rawls B, Shayota BJ, Soler-Alfonso C, Tunuguntala HP, Goss J, Craigen W, Scaglia F, Sutton VR, Himes RW, Burrage LC. Liver transplantation in propionic and methylmalonic acidemia: A single center study with literature review. *Mol Genet Metab* 2019; **128**: 431-443 [PMID: 31757659 DOI: 10.1016/j.ymgme.2019.11.001]
124 **Niemi AK**, Kim IK, Krueger CE, Cowan TM, Baugh N, Farrell R, Bonham CA, Concepcion W, Esquivel CO, Enns GM. Treatment of methylmalonic acidemia by liver or combined liver-kidney transplantation. *J Pediatr* 2015; **166**: 1455-61.e1 [PMID: 25771389 DOI: 10.1016/j.jpeds.2015.01.051]
125 **Brassier A**, Krug P, Lacaille F, Pontoizeau C, Krid S, Sissaoui S, Servais A, Arnoux JB, Legendre C, Charbit M, Scemla A, Francoz C, Benoist JF, Schiff M, Mochel F, Touati G, Broué P, Cano A, Tardieu M, Querciagrossa S, Grévent D, Boyer O, Dupic L, Oualha M, Girard M, Aigrain Y, Debray D, Capito C, Ottolenghi C, Salomon R, Chardot C, de Lonlay P. Long-term outcome of methylmalonic aciduria after kidney, liver, or combined liver-kidney transplantation: The French experience. *J Inherit Metab Dis* 2020; **43**: 234-243 [PMID: 31525265 DOI: 10.1002/jimd.12174]
126 **Kayler LK**, Merion RM, Lee S, Sung RS, Punch JD, Rudich SM, Turcotte JG, Campbell DA Jr, Holmes R, Magee JC. Long-term survival after liver transplantation in children with metabolic disorders. *Pediatr Transplant* 2002; **6**: 295-300 [PMID: 12234269 DOI: 10.1034/j.1399-3046.2002.02009.x]
127 **Chan R**, Mascarenhas L, Boles RG, Kerkar N, Genyk Y, Venkatramani R. Hepatoblastoma in a patient with methylmalonic aciduria. *Am J Med Genet A* 2015; **167A**: 635-638 [PMID: 25691417 DOI: 10.1002/ajmg.a.36925]
128 **Critelli K**, McKiernan P, Vockley J, Mazariegos G, Squires RH, Soltys K, Squires JE. Liver Transplantation for Propionic Acidemia and Methylmalonic Acidemia: Perioperative Management and Clinical Outcomes. *Liver Transpl* 2018; **24**: 1260-1270 [PMID: 30080956 DOI: 10.1002/Lt.25304]
129 **Overton DA**, Shen CF. Comparison of four-drug discriminations in training compartments with four identical levers *vs* four different responses manipulanda. *Pharmacol Biochem Behav* 1988; **30**: 879-888 [PMID: 3227036 DOI: 10.1007/s12325-020-01305-1]
130 **van't Hoff W**, McKiernan PJ, Surtees RA, Leonard JV. Liver transplantation for methylmalonic acidaemia. *Eur J Pediatr* 1999; **158** Suppl 2: S70-S74 [PMID: 10603103 DOI: 10.1007/pl00014326]
131 **Giussani A**, Ardissino G, Belingheri M, Dilena R, Raiteri M, Pasciucco A, Colico C, Beretta C. Posterior reversible encephalopathy syndrome after kidney transplantation in pediatric recipients: Two cases. *Pediatr Transplant* 2016; **20**: 68-71 [PMID: 26607205 DOI: 10.1111/petr.12640]
132 **Corno V**, Lucianetti A, Stroppa P, Pinelli D, Gotti E, Bravi M, Rota G, Locatelli G, Codazzi D, Remuzzi G, Colledan M. Pediatric liver-kidney transplantation: a single center experience [abstract]. *Transpl Int* 2011; **24**: 318 (Abstract nr P-370)
133 **Taner T**, Heimbach JK, Rosen CB, Nyberg SL, Park WD, Stegall MD. Decreased chronic cellular and antibody-mediated injury in the kidney following simultaneous liver-kidney transplantation. *Kidney Int* 2016; **89**: 909-917 [PMID: 26924059 DOI: 10.1016/j.kint.2015.10.016]
134 **O'Leary JG**, Gebel HM, Ruiz R, Bray RA, Marr JD, Zhou XJ, Shiller SM, Susskind BM, Kirk AD, Klintmalm GB. Class II alloantibody and mortality in simultaneous liver-kidney transplantation. *Am J Transplant* 2013; **13**: 954-960 [PMID: 23433356 DOI: 10.1111/ajt.12147]
135 **Vandevoorde K**, Ducreux S, Bosch A, Guillaud O, Hervieu V, Chambon-Augoyard C, Poinsot D, André P, Scoazec JY, Robinson P, Boillot O, Dubois V, Dumortier J. Prevalence, Risk Factors, and Impact of Donor-Specific Alloantibodies After Adult Liver Transplantation. *Liver Transpl* 2018; **24**: 1091-1100 [PMID: 29665189 DOI: 10.1002/Lt.25177]
136 **Loupy A**, Lefaucheur C. Antibody-Mediated Rejection of Solid-Organ Allografts. *N Engl J Med* 2018; **379**: 1150-1160 [PMID: 30231232 DOI: 10.1056/NEJMra1802677]
137 **Paterno F**, Girnita A, Brailey P, Witte D, Wang J, Cuffy MC, Diwan T, Tremblay S, Revollo JY, Alloway RR, Schoech MR, Anwar N, Shah SA, Woodle SE. Successful Simultaneous Liver-Kidney Transplantation in the Presence of Multiple High-Titered Class I and II Antidonor HLA Antibodies. *Transplant Direct* 2016; **2**: e121 [PMID: 27990486 DOI: 10.1097/TXD.0000000000000633]
138 **Bunnapradist S**, Abdalla B, Reddy U. Evaluation of Adult Kidney Transplant Candidates. In: Danovitch

GM. Handbook of Kidney Transplantation. 6th edition. Wolters Kluwer, 2017: 207-239

139 **Korbitz PM**, Gallagher JP, Samant H, Singh S, Jophlin L, Ingviya T, Manatsathit W. Performance of echocardiography for detection of portopulmonary hypertension among liver transplant candidates: Meta-analysis. *Clin Transplant* 2020; e13995 [PMID: 32485008 DOI: 10.1111/ctr.13995]

140 **Lai JC**, Sonnenday CJ, Tapper EB, Duarte-Rojo A, Dunn MA, Bernal W, Carey EJ, Dasarathy S, Kamath BM, Kappus MR, Montano-Loza AJ, Nagai S, Tandon P. Frailty in liver transplantation: An expert opinion statement from the American Society of Transplantation Liver and Intestinal Community of Practice. *Am J Transplant* 2019; **19**: 1896-1906 [PMID: 30980701 DOI: 10.1111/ajt.15392]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com