Hardikar Winita (Orcid ID: 0009-0007-3615-2187)

Current status and future directions of liver transplantation for metabolic liver disease in children

Background

Orthotopic liver transplantation (OLT) in the care of children with inborn errors of metabolism (IEM) is well established. Metabolic conditions represent the second most common indication for paediatric liver transplantation in most centres worldwide, behind biliary atresia. IEM comprise 18% of paediatric transplantations in European countries (1), 15% in Australia and New Zealand (2), and up to 30% in the United States of America (USA) (3).

OLT offers cure of disease when a metabolic defect is confined to the liver. In disorders with extra-hepatic involvement and no "functional cure", liver transplantation may still be transformative on a patient's quality of life, reducing the risk of neurological damage resultant from metabolic crises. Some metabolic diseases involve progressive liver parenchymal damage, although this is not usually the primary indication for transplant. Necessity of early OLT referral is increasingly recognised in some severe defects. This is balanced with operative challenges seen in younger infants, and longer wait times to find suitable size donors (4). An increasing number of transplant referrals for children with IEM has contributed to strain on graft access in many parts of the world. With larger recipient pools, pragmatic evaluation of IEM referrals is essential. This is important in cases where progression of extra-hepatic disease is anticipated post OLT, and/or long-term outcome is expected to be poor. Liver transplantation scoring systems, such as the Paediatric End Stage Liver Disease (PELD) and Model for End Stage Liver Disease (MELD), may not accurately prioritise need in these patients compared to the remaining pool. Various strategies are utilised across the world to manage these challenges.

In centres with limited deceased donor pools, high rates of living donor liver transplantation (LDLD) may be utilised in children with inborn errors of metabolism requiring transplantation. Benefits of this approach include semi-elective capacity of scheduling and multi-disciplinary planning, and ensuring patients are metabolically fit and optimised at the time of transplant. Heterozygous status of a parental donor does not appear to affect outcome in most metabolic diseases post transplantation (5, 6). Exceptions to this include maple syrup urine disease and maternal carriers of x-linked ornithine transcarbamylase deficiency, although cases of adequate outcomes have been described (7, 8). Other approaches to waitlist management of metabolic disease include special categories (9) or additional transplant waiting list points (10).

Transplantation is ideally avoided in children during active metabolic crises. Transplantation in children with defects lacking parenchymal liver disease may be more straightforward in a technical sense. However, absence of cirrhosis and premorbid portal hypertension and portosystemic collaterals may contribute to poorer tolerance of caval and portal vein clamping. This may result in bowel wall oedema and increased post-operative vascular sequelae, such as hepatic artery thrombosis (6, 11, 12). Higher rates of late biliary complications and chronic rejection may also be seen (3, 13). Surgical team experience is known to be an important prognostic factor in children undergoing liver transplantation (14, 15). Care of children with inborn errors of metabolism undergoing OLT is further optimised

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/petr.14625

with multi-disciplinary design of a patient's individualised peri and postoperative protocol, with input from metabolic and specialists relevant to a child's extra-hepatic comorbidities (16, 17).

Outcomes post OLT for inborn errors of metabolism are generally excellent, with a 1 year survival of 97% in a large registry in USA (6). Previous post-transplant estimates predict long-term survival at over 80% at 10 years (3, 12, 18). However this benefit must be balanced with consideration of a composite risk of morbidity, and commitment to a lifetime of post-transplant chronic disease management. Decision to proceed with liver transplantation is highly individualised based on the child's dynamic risk-benefit profile, their family unit, and their treating multidisciplinary team (16, 19). Also to be considered is the chance of future treatments, such as gene therapies, emerging in the medium term.

In this review we will describe some of the most common metabolic defects for which liver transplantation is undertaken reflecting recent updates on pre and post-transplant management.

METABOLIC DEFECT CONFINED LARGELY TO LIVER

Associated structural liver disease

Tyrosinemia type 1

Hereditary tyrosinemia results from deficiency of fumarylacetoacetate hydrolase, the final step in the tyrosine catabolism,. This results in accumulation of toxic intermediate metabolites, including succinylacetone, in liver and other tissues. Severe progressive liver failure and renal dysfunction in infancy are common, however growth restriction, chronic liver disease, rickets and hepatocellular carcinoma (HCC) can manifest later in childhood. OLT offers lifetime cure of the defect and improved quality of life, but is rarely required in recent times following the transformative use of nitisinone (NTBC) in patients with tyrosinaemia type 1 (20). Combined with phenylalanine and tyrosine restricted diet, early NTBC can restore normal liver and renal function and prevent associated porphyria episodes, and may abate risk of HCC (20, 21). Liver transplantation may still be necessary in presentations with acute liver failure, if no improvement of coagulopathy or jaundice is seen with NTBC therapy, or in suspected or confirmed HCC (22, 23). Persistent renal production of succinylacetone post OLT is not believed to be pathogenic (24). NTBC is not routinely recommended post OLT.

No structural liver disease

Urea cycle disordersUrea cycle disorders represent the most common group of metabolic liver disease referred for paediatric liver transplantation in many centres (2, 3, 12, 25). The urea cycle is responsible for detoxification of nitrogenous waste products from protein catabolism in periportal hepatocytes. Ornithine transcarbamylase deficiency (OTCD) accounts for more than half of UCD, with other inherited defects shown in Table 1 (26).

Table 1: Urea Cycle Disorders

Defects within urea cycle (and associated urea cycle disorder)
Enzyme defects

- N-acetylglutamate synthase deficiency (NAGS deficiency)
- Carbamolyphosphate synthetase 1 deficiency (CPS1 deficiency)
- Ornithine transcarbamylase deficiency (OTC deficiency)
- Argininosuccinic synthase [ASS] deficiency ("Citrullinemia type 1")
- Argininosuccinate lyase [ASL] deficiency ("Argininosuccinic aciduria")
- Arginase deficiency [ARG1] ("Arginaemia")

Amino acid transporter defects

- Mitochondrial orthinine translocase deficiency [ORNT1] ("Hyperornithinemia-hyperammonemia-homocitrullinuria [HHH] syndrome)
- Citrin deficiency

Clinical manifestations include encephalopathy from hyperammonaemia, and both acute and chronic liver dysfunction. Severity of hyperammonaemia on presentation, and during subsequent metabolic crises contribute to neurological injury and a varied degree of long-term disability (27). Additional metabolic toxins, such as argininosuccinate, may also play a role in neurological dysfunction in distal enzyme defects where alternative nitrogenous waste excretion mechanisms are intact (28, 29). Outcomes do not necessarily differ between proximal mitochondrial (eg CPS1D, OTCD) and cytostolic distal defects (ASS, ASL) in this setting (28, 30).

Severe defects with complete enzyme loss present in the neonatal period any may include OTCD, CPS1, citrullinaemia type 1 and arginoionosuccinic aciduria. Severe neonatal encephalopathy with ammonia levels >360umol/L is recognised to be associated with a poor neurological prognosis long-term (31). However children presenting later, with milder defects and often partial enzyme function also have a long-term risk of neurodisability (28).

Orthotopic liver transplantation (OLT) results in functional cure of UCD, preventing further neurological injury from hyperammonaemia and improved quality of life (17, 30). High post-transplant survival rates of over 95% at 1 year have been described (32). Timing and decision for OLT for children with UCDs should be considered based on severity of disease and family preference (19). Early OLT between 3 to 12 months in severe, neonatal presentations of UCD is increasingly recognised to be necessary in preventing future irreversible neurological injury (32-34). In this group, OLT at less than 1 year may achieve improved, or even partial recovery of previous neurological insult without increased in morbidity or mortality from transplant (35, 36). Later onset, milder UCD phenotypes refractory to standard medical therapies may be considered for OLT acknowledging cognitive risks with long transplant waiting times (34).

Although low-protein diet may be liberalised in most post OLT, medical therapies may still be required in children with some UCD. For example, defective intestinal citrulline production is uncorrected post OLT in CPS and OTC, and affected children may require supplementation (32). Similarly arginine supplementation may be needed in some ASD and ASL patients post OLT with deficiency in extra-hepatic tissues (29, 37, 38).

Role of OLT is more complex in argininosuccinic acidura (ASL), a UCD which also exhibits extra-hepatic expression in brain and kidney tissue, with a variable phenotype depending on arginosuccinate lysase activity (37-39). Children with ASL may be considered for OLT in the setting of medically refractory hyperammonaemia, or progressive chronic liver disease (37). Neurocognitive stabilisation has been described post OLT in ASL (29, 37, 38). Given hyperammonaemia is not the only proposed mechanism of neurological injury in ASL, the significance of low arginine, and persistently high citrulline and argininosuccinic acid (including in cerebrospinal fluid) post OLT remains unknown (30, 37, 38).

OLT in disorders related to amino acid transporter defects is less clear. Citrin deficiency presents with a neonatal intrahepatic cholestasis in childhood. Spontaneous clinical remission is often seen by 12 months of age (40), although infants requiring OLT in the setting of hepatic dysfunction have been described (41, 42). The value of OLT to prevent progression to adult citrullinemia type 2 has not been clarified. Patients affected by HHH syndrome may exhibit years of clinical stability with medical approaches and a normal life span (43, 44). The utility of OLT in this setting is not well understood, with a single case of OLT undertaken in a child with HHH syndrome, in the setting of poor metabolic control (43).

Primary hyperoxaluria type 1

Primary hyperoxaluria is caused by an inborn error of metabolism causing aberrant glyoxylate metabolism, and enhanced hepatic oxalate production (45). Net oxalate excess results in nephrocalcinosis, with up to 50% reaching end-stage renal disease in childhood years (45). If glomerular filtration rate drops to less than 40ml/minute/1.73m^2, systemic oxalosis ensues contributing to morbidity from cardiac, vascular, bone marrow, musculoskeletal and ocular tissue oxalate accumulation.

Liver transplantation in primary hyperoxaluria type 1, is curative of the primary defect and spares future morbidity from systemic oxalosis. Pre-emptive OLT has been undertaken when early but progressive renal disease is present, acknowledging possibility of renal transplantation being required later in life (46-48). Combined liver-renal transplantation is considered in affected children with severe or established renal failure (49). However increased peri and postoperative risks from systemic oxalosis disease, and recurrence of renal oxalosis in a grafted kidney clearing mobilised oxalate post-transplant may be associated (50). A staged approach to arrest hepatic oxalate production may be used in severe ESRD, small infants with severe renal or systemic disease, or in the circumstance of limited timely graft availability (49).

A promising RNA interference therapy, lumasiran, may abate or delay need for transplantation in primary hyperoxaluria in future. This targets glycolate oxidase, the enzyme involved in oxalate production, and was approved by the USA FDA in 2020 (51). Clinical trials have demonstrated more than 50% decrease in urinary oxalate with lumasiran used in affected children (52, 53). Study of other further experimental therapies is underway.

Crigler-Najjar Syndrome

Crigler-Najjar syndrome (CNS) is a rare disease resulting from partial (type 2) or complete (type 1) loss of uridine 5'-diphosphate glucuronyltransferase activity. This results in a severe

unconjugated hyperbilirubinaemia which, particularly in type 1 CNS, can lead to kernicterus and neurological injury in up to 40% (63). Liver transplantation is currently the only viable cure for CNS1, and 10 year post transplantation survival rate of 96% has been described in a small cohort of children (63).

EXTRA-HEPATIC METABOLIC LIVER DISEASE

Associated structural liver disease

Mitochondrial disorders

Mitochondrial disorders are rare conditions of abnormal mitochondrial structure or function,resulting from mutations in genes encoded by nuclear or mitochondrial DNA (64). Disrupted electron transport (respiratory chain) or other mitochondrial pathways manifest as heterogenous, multi-system phenotypes. Organs with high aerobic energy requirements and a density of mitochondria are commonly involved; including brain, liver, skeletal muscle, gastrointestinal tract and bone marrow (64). Disorders with primary dysfunction of hepatocyte mitochondria, resulting in hepatocyte injury and liver failure, are termed mitochondrial hepatopathies (64, 65).

Liver transplantation for treatment of mitochondrial hepatopathies remains controversial. Traditionally, these disorders have been considered a transplantation contraindication, given multi-system involvement with poor outcomes that outweigh any post-transplant benefits (66). This can result in clinical conundrums in paediatric acute liver failure, when transplant-related decisions may be required for a child prior to a mitochondrial hepatopathy diagnosis being made (67, 68). If an index of suspicion for mitochondrial disease exists in this setting, rapid but thorough genetic, clinical and imaging evaluation should be undertaken [Figure 1] (3).

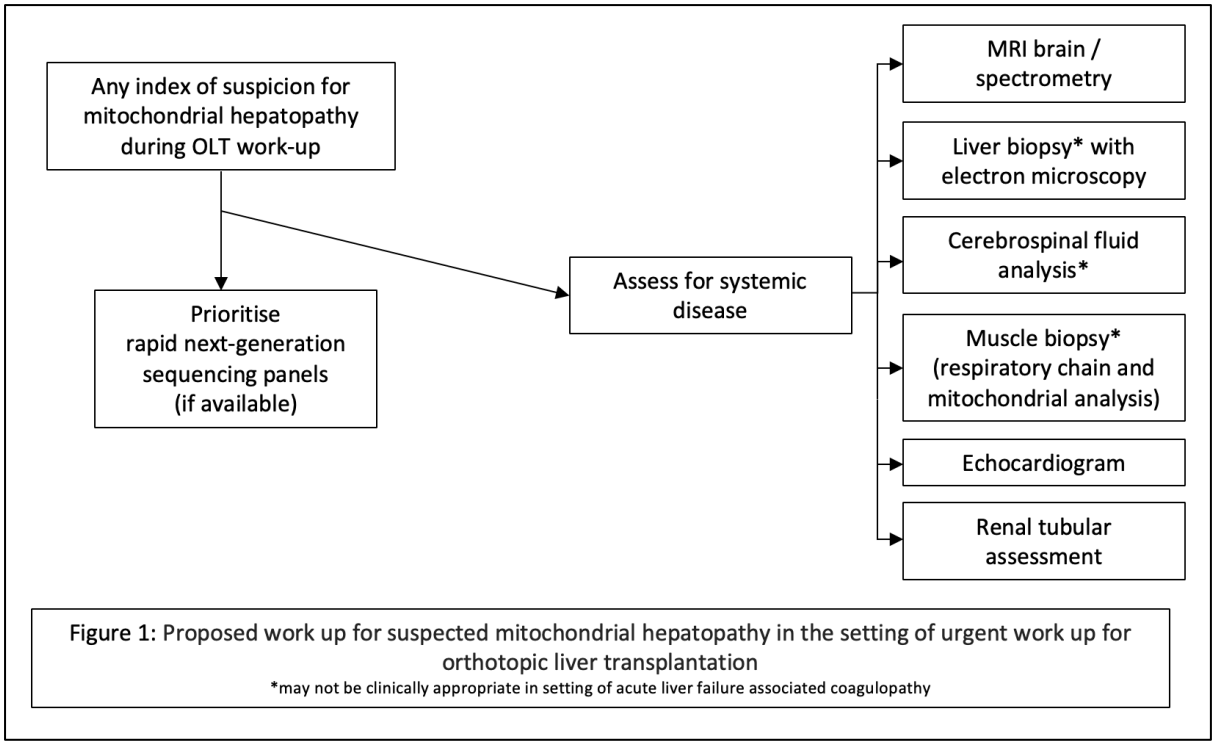

Figure 1: Proposed work up for suspected mitochondrial hepatopathy in the setting of urgent work up for orthotopic liver transplantation

*may not be clinically appropriate in setting of acute liver failure associated coagulopathy

Predominantly single-centre experiences of OLT for mitochondrial disorders have described positive outcomes in very select settings and patient groups. It is proposed that patients with primary hepatopathies or single-gene defects without neurological involvement, may experience improved disease trajectory post transplantation, however more data is required. is the major caveat to this approach is that extra-hepatic disease may not become apparent until after transplant, causing subsequent morbidity and mortality mitigating any post-transplant benefits (66, 69). This raises ethical issues in the setting of scarce organ availability, if post-transplant survival is only 50% across case series (3, 64, 65).

Mitochondrial DNA depletion syndromes (MDS), caused by POLG or other mutations, present with early, acute liver disease and are generally associated with poor prognosis and progressive neurological worsening (64, 65, 74). Increased reports of OLT experience in patients with MDS as a result of MPV17, DGUOK and TRMU mutations have been described in recent years, with both positive and poor outcomes (Table 2). However overall survival in this group post OLT Is proposed to be 41.7% (75).

Table 2: OLT in Mitochondrial DNA depletion syndromes

Mitochondrial hepatopathy	Reported survival outcomes in case series
DGUOK (deoxyguanosine kinase deficiency)	• 0/3 children survived post OLT (76) • 2014- 2/2 children survived post OLT at 5 years (77) • 0/3 children survived post OLT (75) • 1/2 children survived at 3 years post OLT (mild neurological impairment in survivors) (78)
MPV17 (mitochondrial inner membrane protein 17)	• 3/6 children survived post OLT at 2 years (minimal neurological deficits in survivors) (68) • 9/20 children survived post OLT (follow up time frame variable). Possible role of milder mutation phenotypes in survivors (75) • 7/9 children survived post OLT at median follow up 17 months (79)
TRMU (transient infantile liver failure)	• 2/2 children survived post OLT at 5 year follow up. 1 with no neurological involvement and 1 with minor deficits (68)

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) results from a single gene defect encoding thymidine phosphorylase production in the liver, causing dysfunctional mitochondrial DNA replication (70). Manifestations include gastrointestinal disease (often chronic pseudo-obstruction) and neurological dysfunction. Haemopoietic stem cell transplantation has been effective in achieving some functional recovery, but is

associated with high mortality. Case- reports of experience with liver transplantation in MNGIE suggest rapid biochemical and clinical improvement in some children, implying a select group without significant neurological compromise may benefit (71, 72). Positive post OLT outcomes have also been described in ethylmalonic encephalopathy, suggesting a role for this approach early in infancy prior to evolution of irreversible neurological damage (73).

Ongoing experimental efforts to explore novel therapies, including gene therapy, may be key in future care of monogenic mitochondrial hepatopathies (80). These may enable OLT to be a more viable option in future practice.

Glycogen storage disease

Glycogen storage diseases (GSDs) are inborn errors of carbohydrate metabolism resulting in abnormal storage of glycogen in liver, muscle and/or other tissues. Glycogen storage disease type 1a and 1b (GSD 1a and G1b) are caused by defects in the glucose-6-transporter and glucose-6-phophatase complex (81). In addition to fasting intolerance and liver disease; hyperuricaemia and progressive renal dysfunction are prominent (81). Liver nodules, including hepatic adenomas and focal nodular hyperplasia may develop, and are vulnerable to malignant transformation later in life (82, 83). GSD type 1b is further associated with neutropaenia, neutrophil dysfunction and an inflammatory bowel disease like phenotype (81, 84). Liver transplantation may be considered in GSDI patients with multifocal liver lesions, poor metabolic control or to prevent long-term complications (3, 82, 85). OLT corrects liver disease and metabolic dysfunction, with good patient and graft survival (3, 85-88). However extrahepatic disease remains uninterrupted post OLT. Progressive renal dysfunction can be seen, likely in part exacerbated by transplant related immunosuppression (81, 84). This may be less significant in children with a history of good metabolic control prior to transplant (89). Hyperuricaemia may also persist (88). Pre-emptive combined liver and renal transplant has been performed in the setting of pre transplant renal disease (90). Neutropaenia and gastrointestinal disease in GSD1b persists post OLT but is generally described to be milder (82, 84, 91). Although sustained metabolic improvement has been described in a case post hepatocyte transplant in GSD1a (92) therapeutic effects have generally been short-lived in this setting (81, 93, 94).

Glycogen storage disease type III is caused by a debrancher enzyme deficiency, resulting in accumulation of glycogen with short outer chains in liver and muscle tissue and fasting intolerance (95). In contrast, deficiency of branching enzyme in glycogen storage disease type IV results in unbranched glycogen with long outer chains accumulating in tissue (84, 96). Liver dysfunction including evolution to cirrhosis, cardiac and neuromuscular effects can be seen in both disorders. GSDIV has a widely variable phenotype across neuromuscular forms, progressive and non-progressive hepatic subtypes (91, 96). Genotype-phenotype correlation remains unclear (82). Careful selection of liver transplantation candidates is necessary given possible life-limiting extrahepatic manifestations, and acknowledgement that cardiomyopathy and myopathy may still evolve over time post OLT (84, 91, 96). Transplantation for progressive liver disease in GSD VI and IX is rarely needed (97).

No structural liver disease

Organic acidaemias (inc MSUD)

Organic acidaemias (OA) are inborn errors of metabolism resulting in increased urinary organic acid excretion and multi-system accumulation of toxic intermediary metabolites (98, 99). OA commonly present in infancy with encephalopathy after an initial asymptomatic period (98, 100). Other forms may present later in childhood with developmental delay or learning difficulties, psychiatric symptoms, ataxia or recurrent ketosis. Metabolic crises may be induced by catabolic states, such as in prolonged fasting and during intercurrent illnesses (99).

OLT is an established treatment consideration in children with the most common organic acidaemias. However this approach does not result offer complete metabolic cure, with persistence of the OA defect expressed in extra-hepatic tissues (17). OLT may however stabilise metabolically fragile patients, offering increased quality of life over a longer lifespan and net decreased health care costs (98, 101). As such decision for OLT needs to be individualised, as patients remain at risk of transplant-related morbidity and mortality and progression of defect related sequelae (17). OLT is most often indicated in affected children who experience metabolic decompensations despite medical therapy (17). Growth restriction or marked impairment of quality of life are also recognised indications (66). Optimisation of renal, cardiac and neurological OA comorbidities prior to transplant is essential. Well-designed fasting and procedural protocols should be adopted in the pre and perioperative liver transplantation period to prevent intra-procedural decompensation, and use of renal sparing immunosuppression protocols (16, 102). Perioperative vascular and long-term graft complications may be more common in this group (11, 17, 98). However long-term survival is generally favourable at over 80% (17, 98, 103).

In methylmalonic acidaemia (MMA) specifically, hyperammonaemic crises and progressive renal disease are seen, with established kidney disease often seen by late childhood. Basal ganglia infarctions are associated (104). Neutropaenia is seen in 30% (105). Post OLT, frequency of metabolic crises may reduce, with improvement in quality of life. However, continued need for dietary restriction and progression of renal and neurological disease is possible (17). Stroke post OLT is possible (106). Liver transplantation is ideally performed prior to renal impairment (eg glomerular filtration rate >50ml/min/m3), to avoid a need for combined renal and liver grafts. Patients with moderate kidney disease in MMA may benefit from combined transplantation, rather than renal transplantation in isolation, however further data is required (104, 107).

Propionic acidaemia (PA) is associated with cognitive impairment from metabolic accumulation events, neutropaenia, pancreatitis and cardiomyopathy / prolonged QT (104, 105). Renal impairment may be less prominent than seen in MMA. OLT for PA essentially eliminates risk of metabolic crises, and unlike in MMA; liberalisation of dietary protein restriction is more commonly achievable post-operatively (11, 103). Stabilised or reversal of cardiomyopathy post OLT has been described (11, 108), however persistent arrythmias including prolonged QT and risk of cerebrovascular accident should be assumed (17). Neutropaenia tends to persist post OLT, requiring monitoring and follow-up (105).

Classical maple syrup urine disease (MSUD) is a severe OA resulting in intolerance of branched chain amino acids, from mitochondrial deficiency of branched-chain keto acid

dehydrogenase enzyme complex (BCKDH). Despite aggressive dietary approaches, labile and often unpredictable metabolic crises may still ensue, and neurotoxic accumulation can result in life-threatening cerebral oedema and cumulative neurological damage (109). Children highly vulnerable to metabolic decompensation, particularly those with MSUD intolerant of <15-30mh/kg/day leucine, should be considered for OLT (66, 110, 111). OLT eliminates need for dietary restriction and metabolic decompensation risk, however many affected children have established neurodisability heading into transplant (111, 112). Living related donors with heterozygous MSUD mutations should be avoided (7). Explanted livers of patients affected by MSUD can be safely tolerated in non-MSUD patients due to presence of functional BCKDH in non-hepatic tissues (113-116).

FUTURE DIRECTIONS

Domino transplantation

Use of explanted liver for another recipient unaffected by the donor condition, is referred to as domino transplantation. Although this strategy could mitigate effect of transplantation for IEM on transplant donor pools, its feasibility is limited to well-resourced centres given the logistics, planning and parallel operating required. Use of domino transplantation should be limited to conditions where a defect is not anticipated to be expressed in recipients. MSUD is an established indication in children, with good long term outcomes and no additional operative risks described (114, 117). In recipients receiving a donor explanted liver from an individual with MSUD, subclinical decreased leucine oxidation is reported without development of MSUD clinical phenotype post-transplant (114). Although domino transplantation has been tried using explanted livers from patients with other metabolic conditions, including methylmalonic acidaemia and familial hypercholesterolaemia (118); there is insufficient evidence on safety and long-term outcomes.

Auxilary transplantation

Auxiliary transplantation involves part of a donor graft being placed alongside remaining native liver in vivo. This may be considered in children with no primary liver disease as part of their IEM, when partial enzyme correction is anticipated. Historically the premise of auxiliary transplantation in children with inherited metabolic conditions was as a bridge to future gene therapies (119). In this circumstance, withdrawal of immunosuppression is known to result in involution of donor liver portion and regeneration of native hepatocytes without sequelae. Patient (90%) and graft (70%) 5 year survival was similar to a traditional orthotopic approach in a retrospective series of children with metabolic liver disease (18). Given technical surgical complexity, challenges in approach to immunosuppression and monitoring function of the partial graft, balanced and careful selection of recipients suitable for auxiliary transplantation is necessary. An established indication for auxiliary transplantation has been Crigler-Najjar syndrome type 1 (120, 121). In this setting, less than 12% enzyme correction is sufficient to clear hyperbilirubinaemia resultant from defective uridine diphosphate glucoronosyl transferase in hepatocytes (122). Auxiliary transplantation in patients affected by urea cycle defects and in propionic acidaemia has been described, but remains controversial (119, 123, 124).

Domino auxiliary partial orthotopic liver transplantation

Cross-domino auxiliary transplant, in which liver segments are effectively exchanged between children with different metabolic conditions, remains theoretical (119). The explanted liver of a child affected by propionic acidaemia (receiving living related donor organ) has been used as an auxiliary graft in a child with Crigler-Najjar, with effective clearance of hyperbilirubinaemia and no manifestations of PA seen in the recipient (125). This may only be feasible in larger, well-resourced centres with a larger number of patients with non-cirrhotic metabolic liver disease awaiting liver transplant (126). Long-term safety of an implanted graft with a metabolic defect needs to be considered.

Hepatocyte transplantation

Hepatocyte transplantation involves injection of viable hepatocytes from a donor (deceased, living, or preserved) into a patient, where they may become functional on uptake in recipient liver tissue (127, 128). Theoretically this method, first described in humans in 1992 (129), could offer minimally invasive alternate to orthotopic liver transplantation. However the vast majority of children with metabolic liver disease have required liver transplantation within months of this approach (130). In some settings, this could be useful in children with severe defects as a bridge to OLT in the future. Hepatocytes have low proliferative capabilities in vitro, and despite experimental pre-conditioning approaches to enhance liver proliferation, including radiation, partial hepatic resection and portal vein embolization; effects are often short-lived (131, 132). Other challenges include poor cryopreservation and donor availability. Immunosuppression and detection of cellular rejection contributing to allogenic hepatocyte demise is a further challenge (131, 133). Alginate encapsulation of hepatocytes, facilitating a semipermeable barrier to transplanted cells, may be a promising method to avoid immune activation and rejection (130, 134).

Hepatocyte stem cell transplantation & gene therapies

Hepatocyte stem cell techniques are emerging. Spada et al recently described the use of human liver stem-like cells injected in the first month of life in an infant with arginosuccinic aciduria and two infants affected by methylmalonic aciduria (135). Marked metabolic stability compared to age-matched affected infants without adverse effects or need for immunosuppression was described, before eventual need for OLT. Ethical issues may be prohibitive for the use of embryonic stem cells which have the greatest differentiation potential. Induced pluripotent stem cells (iPSCs), mature cells reprogrammed into an embryonic state, carry similar ethical concerns with additional oncogenic safety risks (136). Mesenchymal stromal cells (MSC), a subtype of adult fibroblast-like cells originating from bone marrow, synovial membrane, adipose, heart, cartilage, liver, Wharton jelly of umbilical cord and placenta are an increasing area of interest (130). They too have a high proliferative capacity, exhibit anti-fibrotic properties, immunomodulatory effects on both innate and adaptive immunity, and (incomplete) hepatocyte-like differentiation potential (130, 136). Clinical trials involving use of MSC targeting a range of adult immune-mediated or fibroinflammatory diseases continue to progress. Autologous transplantation of MSC or iPSCs could offer an exciting approach for inherited metabolic disease in the future.

The arrival of gene therapies has been long-awaited in many inherited paediatric metabolic conditions. However application of many of these emerging therapies remains in animal model experimental settings; including viral and nonviral vectors, and gene editing technologies. Adenovirus-associated viral vectors are one of the more common approaches

being explored, offering potential liver specificity, low pathogenicity, lack of integration into host genome and relatively mild immune response. As successfully established in primary oxalosis, other promising new treatment approaches may target RNA interface (137). Inherited metabolic liver disease with hepatic and extra-hepatic involvement may pose a significant challenge to cure, in theory requiring systemic or multiple gene therapy approaches.

Conclusion

Liver transplantation remains a profoundly impactful treatment option in children with both severe life-threatening metabolic conditions, but also in improving quality of life and enabling long-term neurodevelopmental protection in others. Increased multi-disciplinary experience in transplantation of children with IEM has resulted in excellent long-term outcomes. Each patient requires an individualised assessment, a strong multidisciplinary approach and an open mind to emerging evidence-based treatments.

Data statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study

References

1. Baumann U, Karam V, Adam R, Fondevila C, Dhawan A, Sokal E, et al. Prognosis of Children Undergoing Liver Transplantation: A 30-Year European Study. Pediatrics. 2022;150(4).
2. Stormon MO, Hardikar W, Evans HM, Hodgkinson P. Paediatric liver transplantation in Australia and New Zealand: 1985-2018. J Paediatr Child Health. 2020;56(11):1739-46.
3. Mazariegos G, Shneider B, Burton B, Fox IJ, Hadzic N, Kishnani P, et al. Liver transplantation for pediatric metabolic disease. Mol Genet Metab. 2014;111(4):418-27.
4. Gelas T, McKiernan PJ, Kelly DA, Mayer DA, Mirza DF, Sharif K. ABO-incompatible pediatric liver transplantation in very small recipients: Birmingham's experience. Pediatr Transplant. 2011;15(7):706-11.
5. Morioka D, Kasahara M, Takada Y, Corrales JP, Yoshizawa A, Sakamoto S, et al. Living donor liver transplantation for pediatric patients with inheritable metabolic disorders. Am J Transplant. 2005;5(11):2754-63.
6. McKiernan PJ, Ganoza A, Squires JE, Squires RH, Vockley J, Mazariegos G, et al. Evolving Trends in Liver Transplant for Metabolic Liver Disease in the United States. Liver Transpl. 2019;25(6):911-21.
7. Al-Shamsi A, Baker A, Dhawan A, Hertecant J. Acute Metabolic Crises in Maple Syrup Urine Disease After Liver Transplantation from a Related Heterozygous Living Donor. JIMD Rep. 2016;30:59-62.
8. Tannuri AC, Gibelli NE, Ricardi LR, Santos MM, Maksoud-Filho JG, Pinho-Apezzato ML, et al. Living related donor liver transplantation in children. Transplant Proc. 2011;43(1):161-4.
9. Zealand TTSoAaN. Clinical Guidelines for Organ Transplantation from Deceased Donors. Version 1.10- October 2022. 2022.
10. Latt NL, Niazi M, Pyrsopoulos NT. Liver transplant allocation policies and outcomes in United States: A comprehensive review. World J Methodol. 2022;12(1):32-42.
11. Charbit-Henrion F, Lacaille F, McKiernan P, Girard M, de Lonlay P, Valayannopoulos V, et al. Early and late complications after liver transplantation for propionic acidemia in children: a two centers study. Am J Transplant. 2015;15(3):786-91.
12. Arnon R, Kerkar N, Davis MK, Anand R, Yin W, González-Peralta RP. Liver transplantation in children with metabolic diseases: the studies of pediatric liver transplantation experience. Pediatr Transplant. 2010;14(6):796-805.
13. Ng VL, Fecteau A, Shepherd R, Magee J, Bucuvalas J, Alonso E, et al. Outcomes of 5-year survivors of pediatric liver transplantation: report on 461 children from a north american multicenter registry. Pediatrics. 2008;122(6):e1128-35.
14. Edwards EB, Roberts JP, McBride MA, Schulak JA, Hunsicker LG. The effect of the volume of procedures at transplantation centers on mortality after liver transplantation. N Engl J Med. 1999;341(27):2049-53.
15. Rana A, Pallister Z, Halazun K, Cotton R, Guiteau J, Nalty CC, et al. Pediatric Liver Transplant Center Volume and the Likelihood of Transplantation. Pediatrics. 2015;136(1):e99-e107.
16. Chakrapani A, Stojanovic J, Vara R, De Nictolis F, Spada M, Dionisi-Vici C. Safety, efficacy, and timing of transplantation(s) in propionic and methylmalonic aciduria. J Inherit Metab Dis. 2023;46(3):466-81.

17. Yap S, Vara R, Morais A. Post-transplantation Outcomes in Patients with PA or MMA: A Review of the Literature. Adv Ther. 2020;37(5):1866-96.
18. Sze YK, Dhawan A, Taylor RM, Bansal S, Mieli-Vergani G, Rela M, et al. Pediatric liver transplantation for metabolic liver disease: experience at King's College Hospital. Transplantation. 2009;87(1):87-93.
19. Gerstein MT, Markus AR, Gianattasio KZ, Le Mons C, Bartos J, Stevens DM, et al. Choosing between medical management and liver transplant in urea cycle disorders: A conceptual framework for parental treatment decision-making in rare disease. J Inherit Metab Dis. 2020;43(3):438-58.
20. Bartlett DC, Lloyd C, McKiernan PJ, Newsome PN. Early nitisinone treatment reduces the need for liver transplantation in children with tyrosinaemia type 1 and improves post-transplant renal function. J Inherit Metab Dis. 2014;37(5):745-52.
21. Larochelle J, Alvarez F, Bussières JF, Chevalier I, Dallaire L, Dubois J, et al. Effect of nitisinone (NTBC) treatment on the clinical course of hepatorenal tyrosinemia in Québec. Mol Genet Metab. 2012;107(1-2):49-54.
22. Mohan N, McKiernan P, Preece MA, Green A, Buckels J, Mayer AD, et al. Indications and outcome of liver transplantation in tyrosinaemia type 1. Eur J Pediatr. 1999;158 Suppl 2:S49-54.
23. Mayorandan S, Meyer U, Gokcay G, Segarra NG, de Baulny HO, van Spronsen F, et al. Cross-sectional study of 168 patients with hepatorenal tyrosinaemia and implications for clinical practice. Orphanet J Rare Dis. 2014;9:107.
24. Bartlett DC, Preece MA, Holme E, Lloyd C, Newsome PN, McKiernan PJ. Plasma succinylacetone is persistently raised after liver transplantation in tyrosinaemia type 1. J Inherit Metab Dis. 2013;36(1):15-20.
25. Registry AaNZLaIT. ANZLITR 33rd Annual Report 2021. Melbourne, Australia; 2022 October 2022.
26. Batshaw ML, Tuchman M, Summar M, Seminara J. A longitudinal study of urea cycle disorders. Mol Genet Metab. 2014;113(1-2):127-30.
27. Buerger C, Garbade SF, Dietrich Alber F, Waisbren SE, McCarter R, Kölker S, et al. Impairment of cognitive function in ornithine transcarbamylase deficiency is global rather than domain-specific and is associated with disease onset, sex, maximum ammonium, and number of hyperammonemic events. J Inherit Metab Dis. 2019;42(2):243-53.
28. Ah Mew N, Krivitzky L, McCarter R, Batshaw M, Tuchman M. Clinical outcomes of neonatal onset proximal versus distal urea cycle disorders do not differ. J Pediatr. 2013;162(2):324-9.e1.
29. Newnham T, Hardikar W, Allen K, Wellard RM, Hamilton C, Angus P, et al. Liver transplantation for argininosuccinic aciduria: clinical, biochemical, and metabolic outcome. Liver Transpl. 2008;14(1):41-5.
30. Posset R, Gropman AL, Nagamani SCS, Burrage LC, Bedoyan JK, Wong D, et al. Impact of Diagnosis and Therapy on Cognitive Function in Urea Cycle Disorders. Ann Neurol. 2019;86(1):116-28.
31. Kido J, Matsumoto S, Häberle J, Nakajima Y, Wada Y, Mochizuki N, et al. Long-term outcome of urea cycle disorders: Report from a nationwide study in Japan. J Inherit Metab Dis. 2021;44(4):826-37.
32. Häberle J, Burlina A, Chakrapani A, Dixon M, Karall D, Lindner M, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders: First revision. J Inherit Metab Dis. 2019;42(6):1192-230.

33. Kido J, Matsumoto S, Mitsubuchi H, Endo F, Nakamura K. Early liver transplantation in neonatal-onset and moderate urea cycle disorders may lead to normal neurodevelopment. Metab Brain Dis. 2018;33(5):1517-23.
34. Ziogas IA, Wu WK, Matsuoka LK, Pai AK, Hafberg ET, Gillis LA, et al. Liver Transplantation in Children with Urea Cycle Disorders: The Importance of Minimizing Waiting Time. Liver Transpl. 2021;27(12):1799-810.
35. McBride KL, Miller G, Carter S, Karpen S, Goss J, Lee B. Developmental outcomes with early orthotopic liver transplantation for infants with neonatal-onset urea cycle defects and a female patient with late-onset ornithine transcarbamylase deficiency. Pediatrics. 2004;114(4):e523-6.
36. Campeau PM, Pivalizza PJ, Miller G, McBride K, Karpen S, Goss J, et al. Early orthotopic liver transplantation in urea cycle defects: follow up of a developmental outcome study. Mol Genet Metab. 2010;100 Suppl 1(Suppl 1):S84-7.
37. Marble M, McGoey RR, Mannick E, Keats B, Ng SS, Deputy S, et al. Living related liver transplant in a patient with argininosuccinic aciduria and cirrhosis: metabolic follow-up. J Pediatr Gastroenterol Nutr. 2008;46(4):453-6.
38. Baruteau J, Diez-Fernandez C, Lerner S, Ranucci G, Gissen P, Dionisi-Vici C, et al. Argininosuccinic aciduria: Recent pathophysiological insights and therapeutic prospects. J Inherit Metab Dis. 2019;42(6):1147-61.
39. Zielonka M, Garbade SF, Gleich F, Okun JG, Nagamani SCS, Gropman AL, et al. From genotype to phenotype: Early prediction of disease severity in argininosuccinic aciduria. Hum Mutat. 2020;41(5):946-60.
40. Okano Y, Ohura T, Sakamoto O, Inui A. Current treatment for citrin deficiency during NICCD and adaptation/compensation stages: Strategy to prevent CTLN2. Mol Genet Metab. 2019;127(3):175-83.
41. Tamamori A, Okano Y, Ozaki H, Fujimoto A, Kajiwara M, Fukuda K, et al. Neonatal intrahepatic cholestasis caused by citrin deficiency: severe hepatic dysfunction in an infant requiring liver transplantation. Eur J Pediatr. 2002;161(11):609-13.
42. Shigeta T, Kasahara M, Kimura T, Fukuda A, Sasaki K, Arai K, et al. Liver transplantation for an infant with neonatal intrahepatic cholestasis caused by citrin deficiency using heterozygote living donor. Pediatr Transplant. 2010;14(7):E86-8.
43. De Bruyne P, Verloo P, Van Hove JLK, de Hemptinne B, Vande Velde S, Van Winckel M, et al. Successful liver transplantation in hyperornithinemia-hyperammonemia-homocitrullinuria syndrome: Case report. Pediatr Transplant. 2021;25(6):e13943.
44. Martinelli D, Diodato D, Ponzi E, Monné M, Boenzi S, Bertini E, et al. The hyperornithinemia-hyperammonemia-homocitrullinuria syndrome. Orphanet J Rare Dis. 2015;10:29.
45. Cochat P, Rumsby G. Primary hyperoxaluria. N Engl J Med. 2013;369(7):649-58.
46. Perera MT, Sharif K, Lloyd C, Foster K, Hulton SA, Mirza DF, et al. Pre-emptive liver transplantation for primary hyperoxaluria (PH-I) arrests long-term renal function deterioration. Nephrol Dial Transplant. 2011;26(1):354-9.
47. Kemper MJ. The role of preemptive liver transplantation in primary hyperoxaluria type 1. Urol Res. 2005;33(5):376-9.
48. Galanti M, Contreras A. Excellent renal function and reversal of nephrocalcinosis 8 years after isolated liver transplantation in an infant with primary hyperoxaluria type 1. Pediatr Nephrol. 2010;25(11):2359-62.

49. Metry EL, van Dijk LMM, Peters-Sengers H, Oosterveld MJS, Groothoff JW, Ploeg RJ, et al. Transplantation outcomes in patients with primary hyperoxaluria: a systematic review. Pediatr Nephrol. 2021;36(8):2217-26.
50. Perera MT, McKiernan PJ, Sharif K, Milford DV, Lloyd C, Mayer DA, et al. Renal function recovery in children undergoing combined liver kidney transplants. Transplantation. 2009;87(10):1584-9.
51. Jaklevic MC. First Drug Approved for Rare Genetic Disorder Affecting Kidneys. Jama. 2021;325(3):214.
52. Sas DJ, Magen D, Hayes W, Shasha-Lavsky H, Michael M, Schulte I, et al. Phase 3 trial of lumasiran for primary hyperoxaluria type 1: A new RNAi therapeutic in infants and young children. Genet Med. 2022;24(3):654-62.
53. Garrelfs SF, Frishberg Y, Hulton SA, Koren MJ, O'Riordan WD, Cochat P, et al. Lumasiran, an RNAi Therapeutic for Primary Hyperoxaluria Type 1. N Engl J Med. 2021;384(13):1216-26.
54. Blau N, van Spronsen FJ, Levy HL. Phenylketonuria. Lancet. 2010;376(9750):1417-27.
55. Bernegger C, Blau N. High frequency of tetrahydrobiopterin-responsiveness among hyperphenylalaninemias: a study of 1,919 patients observed from 1988 to 2002. Mol Genet Metab. 2002;77(4):304-13.
56. Burton BK, Adams DJ, Grange DK, Malone JI, Jurecki E, Bausell H, et al. Tetrahydrobiopterin therapy for phenylketonuria in infants and young children. J Pediatr. 2011;158(3):410-5.
57. Levy HL, Milanowski A, Chakrapani A, Cleary M, Lee P, Trefz FK, et al. Efficacy of sapropterin dihydrochloride (tetrahydrobiopterin, 6R-BH4) for reduction of phenylalanine concentration in patients with phenylketonuria: a phase III randomised placebo-controlled study. Lancet. 2007;370(9586):504-10.
58. Muntau AC, Adams DJ, Bélanger-Quintana A, Bushueva TV, Cerone R, Chien YH, et al. International best practice for the evaluation of responsiveness to sapropterin dihydrochloride in patients with phenylketonuria. Mol Genet Metab. 2019;127(1):1-11.
59. Qi Y, Patel G, Henshaw J, Gupta S, Olbertz J, Larimore K, et al. Pharmacokinetic, pharmacodynamic, and immunogenic rationale for optimal dosing of pegvaliase, a PEGylated bacterial enzyme, in adult patients with phenylketonuria. Clin Transl Sci. 2021;14(5):1894-905.
60. Harding CO. Prospects for Cell-Directed Curative Therapy of Phenylketonuria (PKU). Mol Front J. 2019;3(2):110-21.
61. Kaiser RA, Weber ND, Trigueros-Motos L, Allen KL, Martinez M, Cao W, et al. Use of an adeno-associated virus serotype Anc80 to provide durable cure of phenylketonuria in a mouse model. J Inherit Metab Dis. 2021;44(6):1369-81.
62. Vajro P, Striscìuglio P, Houssin D, Huault G, Laurent J, Alvarez F, et al. Correction of phenylketonuria after liver transplantation in a child with cirrhosis. N Engl J Med. 1993;329(5):363.
63. Dhawan A, Lawlor MW, Mazariegos GV, McKiernan P, Squires JE, Strauss KA, et al. Disease burden of Crigler-Najjar syndrome: Systematic review and future perspectives. J Gastroenterol Hepatol. 2020;35(4):530-43.
64. Lee WS, Sokol RJ. Mitochondrial hepatopathies: advances in genetics, therapeutic approaches, and outcomes. J Pediatr. 2013;163(4):942-8.
65. Ayers M, Horslen SP, Gómez AM, Squires JE. Mitochondrial Hepatopathy. Clin Liver Dis. 2022;26(3):421-38.

66. Squires RH, Ng V, Romero R, Ekong U, Hardikar W, Emre S, et al. Evaluation of the pediatric patient for liver transplantation: 2014 practice guideline by the American Association for the Study of Liver Diseases, American Society of Transplantation and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr. 2014;59(1):112-31.
67. McKiernan P, Ball S, Santra S, Foster K, Fratter C, Poulton J, et al. Incidence of Primary Mitochondrial Disease in Children Younger Than 2 Years Presenting With Acute Liver Failure. J Pediatr Gastroenterol Nutr. 2016;63(6):592-7.
68. Uchida H, Sakamoto S, Shimizu S, Yanagi Y, Fukuda A, Horikawa R, et al. Outcomes of liver transplantation for mitochondrial respiratory chain disorder in children. Pediatr Transplant. 2021;25(8):e14091.
69. Sokal EM, Sokol R, Cormier V, Lacaille F, McKiernan P, Van Spronsen FJ, et al. Liver transplantation in mitochondrial respiratory chain disorders. Eur J Pediatr. 1999;158 Suppl 2:S81-4.
70. Hirano M, Carelli V, De Giorgio R, Pironi L, Accarino A, Cenacchi G, et al. Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE): Position paper on diagnosis, prognosis, and treatment by the MNGIE International Network. J Inherit Metab Dis. 2021;44(2):376-87.
71. De Giorgio R, Pironi L, Rinaldi R, Boschetti E, Caporali L, Capristo M, et al. Liver transplantation for mitochondrial neurogastrointestinal encephalomyopathy. Ann Neurol. 2016;80(3):448-55.
72. D'Angelo R, Rinaldi R, Carelli V, Boschetti E, Caporali L, Capristo M, et al. ITA-MNGIE: an Italian regional and national survey for mitochondrial neuro-gastro-intestinal encephalomyopathy. Neurol Sci. 2016;37(7):1149-51.
73. Olivieri G, Martinelli D, Longo D, Grimaldi C, Liccardo D, Di Meo I, et al. Ethylmalonic encephalopathy and liver transplantation: long-term outcome of the first treated patient. Orphanet J Rare Dis. 2021;16(1):229.
74. Vu TH, Tanji K, Holve SA, Bonilla E, Sokol RJ, Snyder RD, et al. Navajo neurohepatopathy: a mitochondrial DNA depletion syndrome? Hepatology. 2001;34(1):116-20.
75. Shimura M, Kuranobu N, Ogawa-Tominaga M, Akiyama N, Sugiyama Y, Ebihara T, et al. Clinical and molecular basis of hepatocerebral mitochondrial DNA depletion syndrome in Japan: evaluation of outcomes after liver transplantation. Orphanet J Rare Dis. 2020;15(1):169.
76. Dimmock DP, Zhang Q, Dionisi-Vici C, Carrozzo R, Shieh J, Tang LY, et al. Clinical and molecular features of mitochondrial DNA depletion due to mutations in deoxyguanosine kinase. Hum Mutat. 2008;29(2):330-1.
77. Grabhorn E, Tsiakas K, Herden U, Fischer L, Freisinger P, Marquardt T, et al. Long-term outcomes after liver transplantation for deoxyguanosine kinase deficiency: a single-center experience and a review of the literature. Liver Transpl. 2014;20(4):464-72.
78. Jankowska I, Czubkowski P, Rokicki D, Lipiński P, Piekutowska-Abramczuk D, Ciara E, et al. Acute liver failure due to DGUOK deficiency-is liver transplantation justified? Clin Res Hepatol Gastroenterol. 2021;45(1):101408.
79. Sasaki K, Sakamoto S, Uchida H, Narumoto S, Shigeta T, Fukuda A, et al. Liver Transplantation for Mitochondrial Respiratory Chain Disorder: A Single-Center Experience and Excellent Marker of Differential Diagnosis. Transplant Proc. 2017;49(5):1097-102.

80. Alharbi H, Priestley JRC, Wilkins BJ, Ganetzky RD. Mitochondrial Hepatopathies. Clin Liver Dis (Hoboken). 2021;18(5):243-50.
81. Boers SJ, Visser G, Smit PG, Fuchs SA. Liver transplantation in glycogen storage disease type I. Orphanet J Rare Dis. 2014;9:47.
82. Kishnani PS, Austin SL, Abdenur JE, Arn P, Bali DS, Boney A, et al. 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(11):e1.
83. Manzia TM, Angelico R, Toti L, Cillis A, Ciano P, Orlando G, et al. Glycogen storage disease type Ia and VI associated with hepatocellular carcinoma: two case reports. Transplant Proc. 2011;43(4):1181-3.
84. Matern D, Starzl TE, Arnaout W, Barnard J, Bynon JS, Dhawan A, et al. Liver transplantation for glycogen storage disease types I, III, and IV. Eur J Pediatr. 1999;158 Suppl 2(Suppl 2):S43-8.
85. Shimizu S, Sakamoto S, Horikawa R, Fukuda A, Uchida H, Takeda M, et al. Longterm Outcomes of Living Donor Liver Transplantation for Glycogen Storage Disease Type 1b. Liver Transpl. 2020;26(1):57-67.
86. Squires JE. When Considering Liver Transplant for Children with Glycogen Storage Disease 1b. Liver Transpl. 2020;26(1):12-3.
87. Maheshwari A, Rankin R, Segev DL, Thuluvath PJ. Outcomes of liver transplantation for glycogen storage disease: a matched-control study and a review of literature. Clin Transplant. 2012;26(3):432-6.
88. Yuen WY, Quak SH, Aw MM, Karthik SV. Long-term outcome after liver transplantation in children with type 1 glycogen storage disease. Pediatr Transplant. 2021;25(2):e13872.
89. Chan YC, Liu KM, Chen CL, Ong AD, Lin CC, Yong CC, et al. Modifiable factors affecting renal preservation in type I glycogen storage disease after liver transplantation: a single-center propensity-match cohort study. Orphanet J Rare Dis. 2021;16(1):423.
90. Marega A, Fregonese C, Tulissi P, Vallone C, Gropuzzo M, Toniutto PL, et al. Preemptive liver-kidney transplantation in von Gierke disease: a case report. Transplant Proc. 2011;43(4):1196-7.
91. Liu M, Sun LY. Liver Transplantation for Glycogen Storage Disease Type IV. Front Pediatr. 2021;9:633822.
92. Ribes-Koninckx C, Ibars EP, Calzado Agrasot M, Bonora-Centelles A, Miquel BP, Vila Carbó JJ, et al. Clinical outcome of hepatocyte transplantation in four pediatric patients with inherited metabolic diseases. Cell Transplant. 2012;21(10):2267-82.
93. Muraca M, Gerunda G, Neri D, Vilei MT, Granato A, Feltracco P, et al. Hepatocyte transplantation as a treatment for glycogen storage disease type 1a. Lancet. 2002;359(9303):317-8.
94. Dhawan A, Mitry RR, Hughes RD. Hepatocyte transplantation for liver-based metabolic disorders. J Inherit Metab Dis. 2006;29(2-3):431-5.
95. Kishnani PS, Austin SL, Arn P, Bali DS, Boney A, Case LE, et al. Glycogen storage disease type III diagnosis and management guidelines. Genet Med. 2010;12(7):446-63.
96. Massese M, Tagliaferri F, Dionisi-Vici C, Maiorana A. Glycogen storage diseases with liver involvement: a literature review of GSD type 0, IV, VI, IX and XI. Orphanet J Rare Dis. 2022;17(1):241.
97. Kishnani PS, Goldstein J, Austin SL, Arn P, Bachrach B, Bali DS, et al. Diagnosis and management of glycogen storage diseases type VI and IX: a clinical practice resource of the

American College of Medical Genetics and Genomics (ACMG). Genet Med. 2019;21(4):772-89.
98. Critelli K, McKiernan P, Vockley J, Mazariegos G, Squires RH, Soltys K, et al. Liver Transplantation for Propionic Acidemia and Methylmalonic Acidemia: Perioperative Management and Clinical Outcomes. Liver Transpl. 2018;24(9):1260-70.
99. Forny P, Hörster F, Ballhausen D, Chakrapani A, Chapman KA, Dionisi-Vici C, et al. Guidelines for the diagnosis and management of methylmalonic acidaemia and propionic acidaemia: First revision. J Inherit Metab Dis. 2021;44(3):566-92.
100. Spada M, Calvo PL, Brunati A, Peruzzi L, Dell'Olio D, Romagnoli R, et al. Early Liver Transplantation for Neonatal-Onset Methylmalonic Acidemia. Pediatrics. 2015;136(1):e252-6.
101. Li M, Dick A, Montenovo M, Horslen S, Hansen R. Cost-effectiveness of liver transplantation in methylmalonic and propionic acidemias. Liver Transpl. 2015;21(9):1208-18.
102. Molema F, Martinelli D, Hörster F, Kölker S, Tangeraas T, de Koning B, et al. Liver and/or kidney transplantation in amino and organic acid-related inborn errors of metabolism: An overview on European data. J Inherit Metab Dis. 2021;44(3):593-605.
103. Zhou GP, Jiang YZ, Wu SS, Kong YY, Sun LY, Zhu ZJ. Liver Transplantation for Propionic Acidemia: Evidence From a Systematic Review and Meta-analysis. Transplantation. 2021;105(10):2272-82.
104. Baumgartner MR, Hörster F, Dionisi-Vici C, Haliloglu G, Karall D, Chapman KA, et al. Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia. Orphanet J Rare Dis. 2014;9:130.
105. Grünert SC, Müllerleile S, De Silva L, Barth M, Walter M, Walter K, et al. Propionic acidemia: clinical course and outcome in 55 pediatric and adolescent patients. Orphanet J Rare Dis. 2013;8:6.
106. Chakrapani A, Sivakumar P, McKiernan PJ, Leonard JV. Metabolic stroke in methylmalonic acidemia five years after liver transplantation. J Pediatr. 2002;140(2):261-3.
107. Dello Strologo L, Spada M, Vici CD, Atti MCD, Rheault M, Bjerre AK, et al. Renal outcome and plasma methylmalonic acid levels after isolated or combined liver or kidney transplantation in patients with methylmalonic acidemia: A multicenter analysis. Mol Genet Metab. 2022;137(3):265-72.
108. Romano S, Valayannopoulos V, Touati G, Jais JP, Rabier D, de Keyzer Y, et al. Cardiomyopathies in propionic aciduria are reversible after liver transplantation. J Pediatr. 2010;156(1):128-34.
109. Kenneson A, Osara Y, Pringle T, Youngborg L, Singh RH. Natural history of children and adults with maple syrup urine disease in the NBS-MSUD Connect registry. Mol Genet Metab Rep. 2018;15:22-7.
110. Strauss KA, Mazariegos GV, Sindhi R, Squires R, Finegold DN, Vockley G, et al. Elective liver transplantation for the treatment of classical maple syrup urine disease. Am J Transplant. 2006;6(3):557-64.
111. Mazariegos GV, Morton DH, Sindhi R, Soltys K, Nayyar N, Bond G, et al. Liver transplantation for classical maple syrup urine disease: long-term follow-up in 37 patients and comparative United Network for Organ Sharing experience. J Pediatr. 2012;160(1):116-21.e1.

112. Díaz VM, Camarena C, de la Vega Á, Martínez-Pardo M, Díaz C, López M, et al. Liver transplantation for classical maple syrup urine disease: long-term follow-up. J Pediatr Gastroenterol Nutr. 2014;59(5):636-9.
113. Badell IR, Hanish SI, Hughes CB, Hewitt WR, Chung RT, Spivey JR, et al. Domino liver transplantation in maple syrup urine disease: a case report and review of the literature. Transplant Proc. 2013;45(2):806-9.
114. Khanna A, Hart M, Nyhan WL, Hassanein T, Panyard-Davis J, Barshop BA. Domino liver transplantation in maple syrup urine disease. Liver Transpl. 2006;12(5):876-82.
115. Barshop BA, Khanna A. Domino hepatic transplantation in maple syrup urine disease. N Engl J Med. 2005;353(22):2410-1.
116. Raghu VK, Dobrowolski SF, Sindhi R, Strauss KA, Mazariegos GV, Vockley J, et al. Domino liver transplant from a donor with maple syrup urine disease into a recipient with phenylketonuria. Mol Genet Metab Rep. 2022;31:100866.
117. Celik N, Kelly B, Soltys K, Squires JE, Vockley J, Shellmer DA, et al. Technique and outcome of domino liver transplantation from patients with maple syrup urine disease: Expanding the donor pool for live donor liver transplantation. Clin Transplant. 2019;33(11):e13721.
118. Khanna A, Gish R, Winter SC, Nyhan WL, Barshop BA. Successful Domino Liver Transplantation from a Patient with Methylmalonic Acidemia. JIMD Rep. 2016;25:87-94.
119. Reddy MS, Rajalingam R, Rela M. Revisiting APOLT for Metabolic Liver Disease: A New Look at an Old Idea. Transplantation. 2017;101(2):260-6.
120. Whitington PF, Emond JC, Heffron T, Thistlethwaite JR. Orthotopic auxiliary liver transplantation for Crigler-Najjar syndrome type 1. Lancet. 1993;342(8874):779-80.
121. Rela M, Muiesan P, Vilca-Melendez H, Dhawan A, Baker A, Mieli-Vergani G, et al. Auxiliary partial orthotopic liver transplantation for Crigler-Najjar syndrome type I. Ann Surg. 1999;229(4):565-9.
122. Asonuma K, Gilbert JC, Stein JE, Takeda T, Vacanti JP. Quantitation of transplanted hepatic mass necessary to cure the Gunn rat model of hyperbilirubinemia. J Pediatr Surg. 1992;27(3):298-301.
123. Rela M, Battula N, Madanur M, Mieli-Vergani G, Dhawan A, Champion M, et al. Auxiliary liver transplantation for propionic acidemia: a 10-year follow-up. Am J Transplant. 2007;7(9):2200-3.
124. Morioka D, Kasahara M, Takada Y, Shirouzu Y, Taira K, Sakamoto S, et al. Current role of liver transplantation for the treatment of urea cycle disorders: a review of the worldwide English literature and 13 cases at Kyoto University. Liver Transpl. 2005;11(11):1332-42.
125. Govil S, Shanmugam NP, Reddy MS, Narasimhan G, Rela M. A metabolic chimera: Two defective genotypes make a normal phenotype. Liver Transpl. 2015;21(11):1453-4.
126. D'Antiga L, Colledan M. Surgical gene therapy by domino auxiliary liver transplantation. Liver Transpl. 2015;21(11):1338-9.
127. Soltys KA, Soto-Gutiérrez A, Nagaya M, Baskin KM, Deutsch M, Ito R, et al. Barriers to the successful treatment of liver disease by hepatocyte transplantation. J Hepatol. 2010;53(4):769-74.
128. Squires JE, Soltys KA, McKiernan P, Squires RH, Strom SC, Fox IJ, et al. Clinical Hepatocyte Transplantation: What Is Next? Curr Transplant Rep. 2017;4(4):280-9.
129. Mito M, Kusano M, Kawaura Y. Hepatocyte transplantation in man. Transplant Proc. 1992;24(6):3052-3.

130. Vimalesvaran S, Nulty J, Dhawan A. Cellular Therapies in Pediatric Liver Diseases. Cells. 2022;11(16).
131. Soltys KA, Setoyama K, Tafaleng EN, Soto Gutiérrez A, Fong J, Fukumitsu K, et al. Host conditioning and rejection monitoring in hepatocyte transplantation in humans. J Hepatol. 2017;66(5):987-1000.
132. Puppi J, Strom SC, Hughes RD, Bansal S, Castell JV, Dagher I, et al. Improving the techniques for human hepatocyte transplantation: report from a consensus meeting in London. Cell Transplant. 2012;21(1):1-10.
133. Allen KJ, Mifsud NA, Williamson R, Bertolino P, Hardikar W. Cell-mediated rejection results in allograft loss after liver cell transplantation. Liver Transpl. 2008;14(5):688-94.
134. Mitry RR, Jitraruch S, Iansante V, Dhawan A. Alginate Encapsulation of Human Hepatocytes and Assessment of Microbeads. Methods Mol Biol. 2017;1506:273-81.
135. Spada M, Porta F, Righi D, Gazzera C, Tandoi F, Ferrero I, et al. Intrahepatic Administration of Human Liver Stem Cells in Infants with Inherited Neonatal-Onset Hyperammonemia: A Phase I Study. Stem Cell Rev Rep. 2020;16(1):186-97.
136. Iansante V, Mitry RR, Filippi C, Fitzpatrick E, Dhawan A. Human hepatocyte transplantation for liver disease: current status and future perspectives. Pediatr Res. 2018;83(1-2):232-40.
137. An D, Schneller JL, Frassetto A, Liang S, Zhu X, Park JS, et al. Systemic Messenger RNA Therapy as a Treatment for Methylmalonic Acidemia. Cell Rep. 2017;21(12):3548-58.

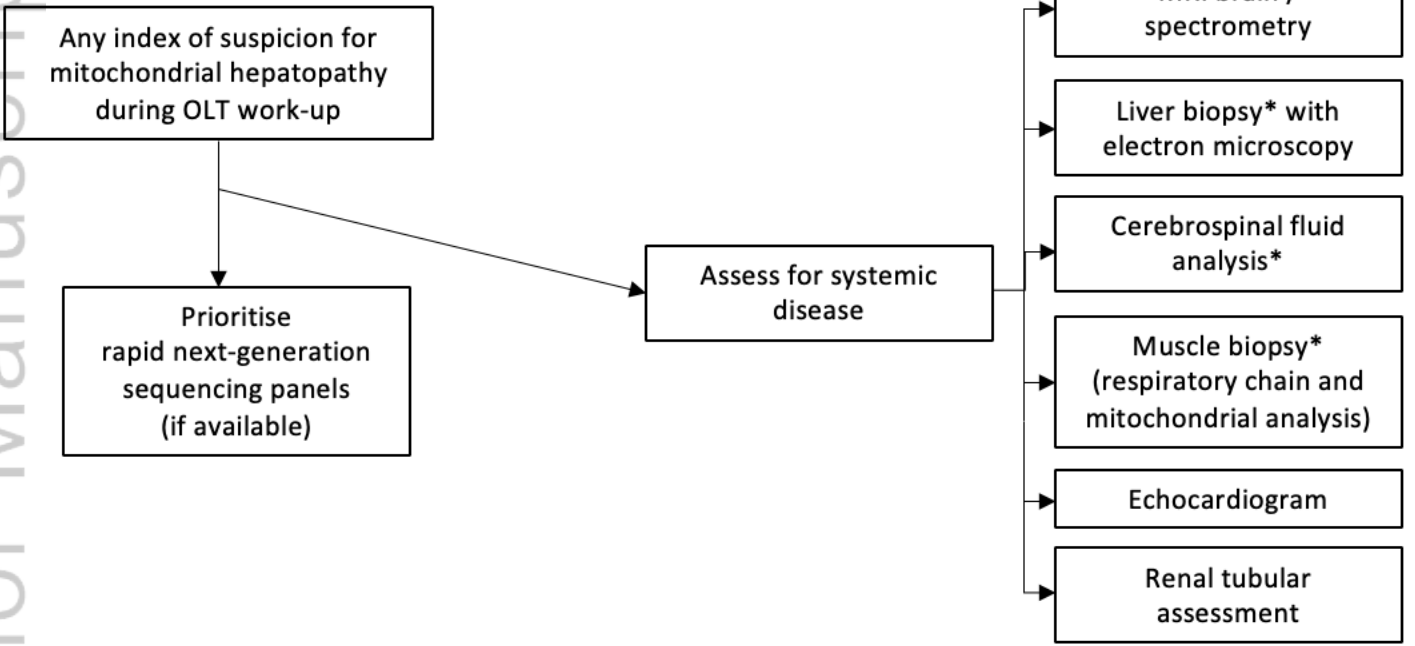

Figure 1: Proposed work up for suspected mitochondrial hepatopathy in the setting of urgent work up for orthotopic liver transplantation

*may not be clinically appropriate in setting of acute liver failure associated coagulopathy