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Liver transplantation for pediatric metabolic disease ☆

George Mazariegos [a,b], Benjamin Shneider [c], Barbara Burton [e], Ira J. Fox [a,b,f], Nedim Hadzic [g], Priya Kishnani [h], D. Holmes Morton [i], Sara Mcintire [j], Ronald J. Sokol [k], Marshall Summar [l], Desiree White [m], Vincent Chavanon [n], Jerry Vockley [d,o,p,*]

[a] Hillman Center for Pediatric Transplantation, Children's Hospital of Pittsburgh of UPMC, Faculty Pavilion, 4401 Penn Avenue, Pittsburgh, PA 15224, USA
[b] University of Pittsburgh School of Medicine/UPMC Department of Surgery, Thomas E. Starzl Transplantation Institute, E1540 Biomedical Science Tower (BST), 200 Lothrop Street, Pittsburgh, PA 15261, USA
[c] Division of Pediatric Gastroenterology, Hepatology and Nutrition, Children's Hospital of Pittsburgh of UPMC, Rangos Research Center, 4401 Penn Avenue, 7th Floor, Pittsburgh, PA 15224, USA
[d] Department of Pediatrics, University of Pittsburgh School of Medicine, 4401 Penn Avenue, Pittsburgh, PA, USA
[e] Department of Pediatrics, Northwestern University Feinberg School of Medicine/Ann & Robert H. Lurie Children's Hospital of Chicago, Box MC 59, 225 E Chicago Avenue, Chicago, IL 60611, USA
[f] McGowan Institute for Regenerative Medicine, University of Pittsburgh, Pittsburgh, PA, USA
[g] King's College Hospital, Paediatric Liver Center, London, UK
[h] Department of Pediatrics, Division of Medical Genetics, Duke University Medical Center, DUMC 103856, 595 Lasalle Street, GSRB 1, 4th Floor, Room 4010, Durham, NC 27710, USA
[i] Franklin and Marshall College, Clinic for Special Children, 535 Bunker Hill Road, Strasburg, PA 17579, USA
[j] Department of Pediatrics, Paul C. Gaffney Diagnostic Referral Service, University of Pittsburgh School of Medicine, Children's Hospital of Pittsburgh of UPMC, 4401 Penn Avenue, Suite Floor 3, Pittsburgh, PA 15224, USA
[k] Department of Pediatrics, University of Colorado School of Medicine and Children's Hospital Colorado, Section of Gastroenterology, Hepatology and Nutrition, 13123 E. 16th Avenue, B290, Aurora, CO 80045-7106, USA
[l] Division of Genetics and Metabolism, George Washington University, Children's National Medical Center, Center for Genetic Medicine Research (CGMR), 111 Michigan Avenue, NW, Washington, DC 20010-2970, USA
[m] Department of Psychology, Washington University, Psychology Building, Room 221, Campus Box 1125, St. Louis, MO 63130-4899, USA
[n] Division of Plastic and Reconstructive Surgery, Mount Sinai Hospital, 5 East 98th Street, 15th Floor, New York, NY 10029, USA
[o] Department of Human Genetics, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA 15261, USA
[p] Division of Medical Genetics, Children's Hospital of Pittsburgh of UPMC, Rangos Research Center, 4401 Penn Avenue, Pittsburgh, PA 15224, USA

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ABSTRACT

Liver transplantation (LTx) was initially developed as a therapy for liver diseases known to be associated with a high risk of near-term mortality but is based upon a different set of paradigms for inborn metabolic diseases. As overall outcomes for the procedure have improved, LTx has evolved into an attractive approach for a growing number of metabolic diseases in a variety of clinical situations. No longer simply life-saving, the procedure can lead to a better quality of life even if not all symptoms of the primary disorder are eliminated. Juggling the risk-benefit ratio thus has become more complicated as the list of potential disorders amenable to treatment with LTx has increased. This review summarizes presentations from a recent conference on metabolic liver transplantation held at the Children's Hospital of Pittsburgh of UPMC on the role of liver or hepatocyte transplantation in the treatment of metabolic liver disease.

1. Introduction

Liver transplantation (LTx) was initially developed as a therapy for liver diseases known to be associated with a high risk of near-term mortality. In pediatrics, a classical example is biliary atresia [1–3]. The natural history of this disorder is quite well characterized — it is one of progressive liver disease if surgical treatment by portoenterostomy is unsuccessful, where survival beyond 36 months of life is rare [3]. LTx affords long term survival in over 80% of biliary atresia patients. Therefore, risk/benefit decisions are relatively easy in this circumstance — near-universal mortality with the existing disease versus substantially less risk with transplantation. Thus, LTx is clearly an excellent therapeutic approach for biliary atresia when portoenterostomy has failed.

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* Corresponding author at: Department of Human Genetics, University of Pittsburgh Graduate School of Public Health, 4401 Penn Avenue, Suite Floor 3, Pittsburgh, PA 15224, USA.
E-mail addresses: George.Mazariegos@chp.edu (G. Mazariegos), Benjamin.Shneider@chp.edu (B. Shneider), b-burton1@northwestern.edu (B. Burton), Ira.Fox@chp.edu (I.J. Fox), nedim.hadzic@kcl.ac.uk (N. Hadzic), priya.kishnani@duke.edu (P. Kishnani), dhmorton@clinicforspecialchildren.org (D.H. Morton), mcintiresc@upmc.edu (S. Mcintire), ronald.sokol@childrenscolorado.org (R.J. Sokol), MSummar@childrensnational.org (M. Summar), dawhite@wustl.edu (D. White), vincent.chavanon@mountsinai.org (V. Chavanon), gerard.vockley@chp.edu (J. Vockley).

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LTx for inborn metabolic diseases is based upon a different set of paradigms [4]. It is of potential use for disorders in which toxic intermediary metabolites from multiple organ systems can freely interchange with other organs through the systemic circulation. In this setting, a genetically normal liver can correct metabolic balance in other organs. Initially, LTx was reserved for those disorders with essentially lethal outcomes (for example, the neonatal form of the urea cycle defect ornithine transcarbamylase deficiency) [5]. However, as risks of the procedure have decreased and post-operative outcomes have improved, LTx has evolved into an attractive approach for a growing number of metabolic diseases with considerably more complicated issues and a very distinct risk benefit profile [1,6–12]. As the collective experience with LTx has grown, the view of the procedure as life-saving vs. life-improving is evolving, blurring the line between standard medical management and a more aggressive surgical therapy [13]. The risks and benefits of LTx must be placed in the context of current and potential medical advances [4]. Genotypic and phenotypic diversity in nearly every metabolic disease complicate the ability to predict long-term outcome and response to therapy [14,15]. Ultimately, it is critical to have a relatively complete understanding of the biology of the disease to predict the potential impact of LTx on the body, especially when the enzyme in question is not hepatocyte-specific and when living donor transplantation is contemplated from an obligate heterozygote parent with reduced enzyme activity.

Children's Hospital of Pittsburgh of UPMC (CHP) organized a conference, "Challenging the Paradigms: Liver Transplantation in Metabolic Disease" (May 4, 2012, Pittsburgh, PA), that addressed the role of liver or hepatocyte transplantation in the treatment of metabolic liver disease. This manuscript reviews the information presented at that conference, including CHP's three decades of outcome data regarding pediatric LTx for a broad range of metabolic diseases.

2. Metabolic diseases cured by LTx

2.1. Maple syrup urine disease

Maple syrup urine disease (MSUD) is caused by mutations in six gene loci responsible for encoding the branched-chain alpha-ketoacid dehydrogenase (BCKDH) complex, resulting in the body's transcarbamylaseinability to fully break down the essential amino acids valine, leucine, and isoleucine. Accumulating metabolites are excreted in the urine, sweat, and ear cerumen, the latter two leading to a sweet odor resembling maple syrup. The most common treatment for MSUD is a diet restricted in the affected amino acids, along with a variety of dietary supplements [16]. However, even with aggressive treatment, patients can experience episodes of metabolic decompensation during times of illness or physiologic stress, with incumbent risk of cerebral edema.

Before 1989, mortality from cerebral edema in MSUD was high (11/20) within the Mennonite population. Moreover, 100% of the patients from this era who survived had significant mental and physical disabilities as a result of delays in diagnosis, prolonged brain leucine intoxication, essential amino acid deficiencies, and untreated cerebral edema [17]. None of these survivors were able to attend schools with their siblings and peers and many had significant neurologic sequelae, including spastic paraparesis. Between 1990 and 2012, timely diagnosis and improved local care for the ill patient has markedly improved outcomes in this population at the Clinic for Special Children in Strasburg, Pennsylvania [16,17]. None of the 70 neonates diagnosed and treated since 1990 have died of cerebral edema. Hospitalization rates decreased from seven days-per-patient/year of follow-up before 1989 to less than 0.2 days per-patient/year [16]. None of the children have cerebral palsy-like physical disabilities, all attend normal school with their peers, and recent formal studies testing IQ and adaptive measurements show scores in the normal range. Although these data suggest that classical MSUD can be medically managed to allow normal growth and development and low hospitalization rates, neurologic function may still deteriorate rapidly at any age because of metabolic intoxication provoked by common infections and injuries.

Effective chronic control of MSUD is optimized with weekly determination of plasma amino acids to monitor dietary therapy, routine childhood vaccines and seasonal flu-vaccines to prevent infections, and easy access to outpatient medical services during intercurrent illnesses [16,17]. Chronic management, including parental education, use of appropriate metabolic formulas, and formal sick day plans, is necessary for optimal outcome. Access to in-hospital services is also critical, including availability of MSUD hyper-alimentation solutions, care from physicians experienced with management of metabolic illnesses and cerebral edema, and measurement of plasma amino results in 4 h or less. This therapeutic regimen is not universally available and there are limited numbers of clinicians with detailed experience in the medical management of this rare disorder.

Based on the ongoing risk for metabolic crisis and cerebral edema despite optimal medical care, LTx becomes a viable option for treatment of classical/severe MSUD, for which it now has been demonstrated to be effective [18,19]. Relief of the burden of metabolic care improves the quality of life for patient and family regardless of a patient's current neurodevelopmental status, with relief from severe dietary protein restriction, metabolic formulas, and the threat of coma, cerebral edema, and brain injury with each intercurrent illness. The potential benefit is especially increased in patients who live at a distance from an experienced metabolic treatment center or in individuals with particularly poor metabolic control. LTx is essentially curative for the disorder; patients can immediately discontinue a protein-restricted diet and are protected from catabolic crisis. Neurological function stabilizes and the risk of strokes or death from cerebral edema is greatly reduced or eliminated. LTx, however, does not reverse existing spasticity, dystonia, or mental retardation. Unfortunately, approximately 20% of the MSUD LTx patients at CHP have had significant cognitive and physical disabilities before transplantation [19]. Analysis of cognitive and adaptive functioning in a cohort of transplanted patients thus far has demonstrated stability, but not improvement, in IQ or adaptive functioning post-transplant [20].

MSUD is a notably rare situation in which domino transplantation can be performed, with the explanted liver from an MSUD patient being used for another recipient without metabolic disease [21–23]. Just as a new liver provides metabolic protection for the rest of the body in an MSUD patient, the normal systemic metabolism of branch chain amino acids in a domino recipient can counter the effects of an MSUD liver. Normal branch chain amino acid metabolism has been documented in all domino recipients of MSUD livers thus far, with no sequelae of MSUD in any of these recipients. Reuse of the MSUD liver diminishes the impact of the original transplant on the overall pool of available transplant organs.

2.2. Urea cycle disorders

The urea cycle requires six enzymes (n-acetylglutamine synthetase [NAGS], carbamoylphosphate synthetase I [CPS1], ornithine transcarbamylase [OTC], argininosuccinate synthase [ASS], argininosuccinate lyase [ASL], and arginase [ARG1]), along with several mitochondrial transporters [24]. The fully constituted cycle is limited to the liver and removes waste nitrogen generated through protein catabolism. Urea cycle defects (UCDs) are caused by inherited deficiencies in one of the pathway's enzymes or transporters; thus a defect can lead to the development of life threatening hyperammonemia. Clinical findings include cerebral edema, seizures, coma, and death, with long-term developmental disabilities in survivors, although variability is common based on the deficient enzyme and the mutation leading to its inactivation. In general, NAGS, OTC, and CPS1 deficiencies have the most severe metabolic derangements and worst outcome with neonatal onset of hyperammonemia and death in the first year of life. Hyperammonemia may require dialysis

or hemofiltration to reduce blood ammonia levels. Medical management includes a diet restrictive of protein and use of ammonia conjugating agents, but still leaves patients at risk for episodes of hyperammonemia [25]. Loss of metabolic control is difficult to predict, is usually abrupt, and can lead to devastating consequences or death. ASS and ASL deficiencies can also present with neonatal hyperammonemia, but affected individuals are more likely to survive infancy with medical management. However, there is a growing recognition of long term intellectual deficit in these patients, including developmental delay (67% and 60%, respectively for ASS and ASL deficiency) and increased risk for hepatic tumors [26]. Developmental delay in ASS and ASL deficiencies is even more pronounced in patients with neonatal presentations, 90% and 78%, respectively.

Because of poor outcome with medical management, treatment of NAGS, CPS1, and OTC deficiencies has incorporated LTx prior to the first year of life, and as early as three months of age with medical management serving only as a bridge until transplant is possible [25]. In contrast, ASS and ASL deficiencies have continued to be primarily managed medically, but this practice is being questioned, especially in neonatal onset patients [26]. A single high risk procedure of LTx is now considered less dangerous overall in severe defects than longer term exposure and long-term risk of catastrophic decompensation [5].

The current consensus from the Urea Cycle Disorders Consortium (UCDC) on the management of patients with absent or very low enzyme function in all UCDs, excluding NAGS and arginase deficiency, is: 1) aggressive treatment and stabilization; and 2) placement on the LTx list (age varies with center but at the earliest practical) [24–26]. A European treatment guideline on the role of LTx for ASS and ASL deficiencies is less definitive [25]. Since measurement of enzyme activity for most urea cycle enzymes requires a liver biopsy, molecular testing is typically the first line test to confirm diagnosis. While genotype has a good predictive value for disease severity (especially for OTC deficiency), the correlation is not absolute; thus, neonatal presentation with severe hyperammonemia should be considered a strong indication to LTx as a therapeutic approach. It is important to note that LTx best addresses toxin clearance. Thus, while LTx essentially eliminates the risk of hyperammonemia, it may not affect other aspects of these disorders, especially neurometabolic. In addition, patients with proximal defects will still require supplementation of urea cycle intermediates even after a successful LTx, since the gut is the main exporter of citrulline and arginine. LTx for children with less severe UCDs still generates considerable controversy, as episodes of overwhelming hyperammonemia are less common in them than in patients with early onset disease. Nevertheless, milder patients are still at risk for intellectual impairment. In one study, 21% with late onset UCD showed mild intellectual disability and a 4% showed severe intellectual disability [26].

3. Metabolic diseases improved by LTx

3.1. Mitochondrial disease

Mitochondrial hepatopathies are an increasingly recognized group of diseases leading to acute liver failure, fatty liver, cirrhosis, or intermittent liver dysfunction [27,28]. Primary mitochondrial hepatopathies include disorders caused by mitochondrial DNA (mtDNA) deletions or mutations or, more commonly, by mutations in nuclear genes that encode specific respiratory chain subunits, or transcription, assembly, or translational machinery for mitochondria. Secondary mitochondrial hepatopathies may be caused by endogenous or exogenous toxins, drugs, or other genetic diseases in which mitochondrial dysfunction (e.g. fatty acid oxidation defects) plays a key role [29,30]. The hepatocerebral form of the mtDNA depletion syndrome (most commonly caused by *POLG*, *DGUOK*, *MPV17*, *SUCLG1*, and Twinkle mutations) frequently presents with acute liver failure or hepatic steatosis in early childhood with a variety or neurologic and muscular features [28]. Diagnosis is usually established following positive screening tests (elevated serum and CSF lactate and elevated serum lactate/pyruvate ratio >20–25, hyperammonemia, hypoglycemia, urine Krebs cycle intermediates, CNS imaging), by genotyping, or by analysis of affected tissues for mtDNA depletion, respiratory chain enzyme activity, or blue native gel polyacrylamide gel electrophoresis. Current medical therapies are primarily supportive with avoidance of mitochondrial toxic drugs, balanced nutritional therapy, and possible therapy with mitochondrial substrates, antioxidants, co-enzyme Q, or L-carnitine. Many of the conditions are fatal despite optimal medical management, so discussion entertaining the option of LTx ensues.

Although LTx can lead to normal hepatic function, it neither stabilizes nor normalizes mitochondrial function in extrahepatic affected tissues; thus, severe systemic manifestations of mitochondrial disease are generally considered a contraindication to LTx [31]. Certainly, in *POLG* (Alpers–Huttenlocher disease) and *MPV17* disease with pre-existing neurologic symptoms (such as Navajo neurohepatopathy), transplantation will neither improve nor prevent progression of the severe CNS involvement [32]. However, selected patients without neurologic findings may have good outcomes after LTx. Thus, patients with hepatic decompensation should rapidly undergo a thorough genetic and clinical/imaging evaluation (CNS, peripheral nervous system, heart, muscle, retina, intestine) to determine if the evidence of more extensive systemic disease precludes the option of LTx. Most recent data demonstrate about a 50% survival rate for those transplanted (in a highly selected group) [33], well below post-transplant survival in other diseases. Recently, several specific genetic causes (e.g., *TRMU* mutations) have been associated with clinical reversibility [34], making a rapid evaluation important to avoid a potentially unnecessary liver transplant. Ongoing research efforts to develop novel therapies to correct mitochondrial defects may change the outlook for these diseases and may make LTx a more viable option in the future. In this event, use of "fast track" mutational analysis for *POLG*, *MPV17*, *DGUOK* will be important in children with supportive previous medical history (developmental delay, atypical convulsions, early infantile deaths, etc.) when they present with acute liver failure.

3.2. Propionic acidemia and methylmalonic academia

Propionic acidemia (PA) and primary methylmalonic academia (MMA) are organic acidemias resulting from defective catabolism of the amino acids isoleucine, valine, methionine, and threonine due to mutations in the genes for propionyl-CoA carboxylase or methylmalonyl-CoA mutase, respectively [35,36]. MMA is additionally present in several inborn errors of cobalamin (vitamin B12) metabolism [37,38]. Severe forms typically present with severe hyperammonemia, ketoacidosis, and neurological problems, including coma very soon after birth. To minimize neurological sequelae, intensive clinical management, including aggressive treatment such as dialysis or hemofiltration, is required. Despite early diagnosis and maximal metabolic control, many patients develop considerable neurological, psychological, cardiac, and renal complications [36,39].

Tables 1 and 2 show data reported in the literature on LTx performed for PA and MMA, respectively. Clinical experience with effects of LTx on the natural history of PA and MMA is emerging but remains relatively limited due to low prevalence of these diseases [39–42]. Successful LTx appears to achieve metabolic stabilization, resulting in better quality of life, improvement of cardiac involvement, less strict dietary restrictions, and positive effects on the developmental delay. However, other consequences of the diseases can still manifest despite successful LTx, including CNS complications such as metabolic stroke and progressive renal failure, especially with the cobalamin defects. Benefits must also be weighed against the risks of long term immunosuppression. Pre-LTx considerations include optimal assessment of neurological, cardiac, and renal comorbidities, surgical aspects such as LTx timing,

Table 1
Reported Cases of Liver Transplantation for Propionic Acidemia.

No cases	Age at LTx (mo)	Gender	Tx type	Complication surgical	Complication medical	Follow up (mo)	Outcome	Reference
2	84, 108	NR	OLTx	NR	ACR (1) PTLD (1)	54	1 died 1 alive	Saudubray et al. (1999)
1	36	M	OLTx	NR	NR	3	1 died	Kayler et al. (2002)
1	14	NR	OLTx	NR	NR	NR	Alive	Kim et al. (2003)
3	7, 24, 26	F (×3)	LR-LTx	Intestinal perforation (1)	Cardiac failure (1)	median: 40	Alive (×3)	Yorifuri et al. (2004)
2	12, 24	F (×1) M (×1)	OLTx	HAT–reOLTx (1)	Cardiac failure (1)	44, 6	8 alive 4 died	Barshes et al. (2006)
1	8	F	OLTx	NR	NR	9	Alive	Manzoni et al. (2006)
1	26	F	LR-LTx	NR	NR	7	Alive	Sato et al. (2009)
5	Median: 14	M (×2) F (×3)	pALTx (1) LR-LTx (1) OLTx (3)	HAT–reOLTx (1)	Metab stroke (1) PTLD (1)	Median: 88	Alive 4 1 died since publication	Vara et al. (2011)
1	7	NR	LR-LT	NR	NR	20	Alive	Nagao et al. (2013)

NR — not reported; OLTx — orthotopic liver transplant; ACR — acute cellular rejection; PTLD — post-transplant lymphoproliferative disorder; pALTx — partial auxiliary liver transplantation; LR-LTx — living-related liver transplantation; HAT — hepatic artery thrombosis. See References [8,39–42,46,92–102].

and the use of auxiliary partial orthotopic grafts, consideration of living-related heterozygous carrier donors, and the role of novel chronic medical therapies, hepatocyte transplantation and genetic manipulation in the future [43–46]. The underlying renal involvement should warrant use of "renal-sparing" modifications to standard immunosuppression [47]. Combined liver and kidney transplant is reasonable when significant renal impairment is already present.

4. Metabolic diseases for further consideration

4.1. Glycogen storage diseases

Glycogen storage disease (GSD) types I, III, IV, VI, and IX are congenital disorders of glycogen metabolism often associated with severe liver disease [48–50]. Current interventions for the liver GSDs include dietary modifications and medical interventions such as pharmacotherapy for issues not corrected by diet. For GSD type I, nocturnal continuous enteral drip feeding to avoid fasting hypoglycemia and frequent oral uncooked corn starch intake for prolonged glucose release have significantly improved metabolic control. In some instances, there is a need for use of agents such as allopurinol for hyperuricemia, low dose ACE inhibitors for proteinuria, and GCSF for neutropenia in GSD type Ib. For patients with GSD types III, VI, and IX, a high protein diet combined with uncooked cornstarch is the mainstay of therapy. Although these interventions have successfully improved metabolic control, enhanced growth and pubertal development, and prolonged long-term survival for these disorders, long-term complications still occur. In addition, adherence to the medical regimens required for GSD treatment is burdensome and may not be maintained by all individuals, leading to significant morbidity.

Hepatocellular adenomas (HCAs) with risk for transformation to hepatocellular carcinoma (HCC) have been noted in individuals with GSD I in early adulthood [49]. Although the incidence and pathogenesis of adenoma-to-carcinoma transformation is not established, HCC in GSD I patients most often occurs within pre-existing adenomatous nodules. Liver cirrhosis has been noted in a nine-year-old boy with GSD Ib [51]. Some patients with GSD III progress to liver cirrhosis, while others develop HCC [48]. Patients with GSD IIIa can develop cardiac complications such as life threatening arrhythmias as well as a progressive myopathy. For GSD IV, the phenotype varies and some patients develop liver cirrhosis and HCC. Patients with GSD VI typically do not present with liver involvement requiring intervention beyond frequent feeding or a high carbohydrate diet, however a small subset of patients have been found to have adenomas and/or hepatocellular carcinoma [52].

As individuals with GSD are living longer, it is being recognized that despite medical treatment, long term complications make these patients candidates for LTx [48,53–57]. Overall, outcomes following LTx have been very encouraging, with improvement in biochemical and clinical parameters including glucose, cholesterol, triglycerides, neutrophils, and growth. LTx can be both preventative and curative: simultaneous liver–kidney preemptive transplantation (SLKPT) led to improvement in a patient with GSD Ia, curing both liver and kidney anomalies [58]. However, certain metabolic abnormalities such as hyperuricemia and neutropenia (the latter in GSD Ib) may persist. Long-term follow-up after LTx for GSD shows excellent graft and patient survival. While LTx corrects the primary hepatic enzyme defect, the extrahepatic manifestations of GSD often complicate post-transplantation management. In patients with GSD I, kidney disease can progress. For patients with GSD IIIa, cardiomyopathy and skeletal myopathy are not

Table 2
Reported cases of liver transplantation for methylmalonic acidemia.

No cases	Age at LTx (y)	Gender	Tx type	Complication surgical	Complication medical	Follow up (mo)	Outcome	Reference
1	13	M	LTx–K	NR	NR	16	Alive	van't Hoff et al. (1998)
2	13, 16	M (1) F(1)	LTx–K (1) pALTx (1)	HAT–reOLTx (1)	PTLD (1)	13, 47	Alive (2)	Kayler et al. (2002)
1	22	F	OLTx	NR	NR	2	Alive	Nyhan et al. (2002)
1	0.9	NR	OLTx	NR	NR	? NR	Alive	Hsui et al. (2003)
2	10, 21	M (×2)	LTx–K (2)	NR	Diabetes mellitus	60, 18	Alive (2)	Nagarajan et al. (2005)
1	0.9	F	OLTx	Bile leak	NR	12	Alive	Manzoni et al. (2006)
18	Median:19.5	M (8) F (10)	L-LTx (6) LTx–K (5)	HAT–reOLTX (2), Bile leak (1) PVT (1)	Metabolic stroke (1) Renal failure (4)	Median: 36	Alive (15) died (3)	Kasahara et al. (2006)
1	NR	NR	OLTx	NR	NR	120	Alive	Kaplan et al. (2006)
7	NR	NR	LR-LTx (7)	NR	NR	Median: 10.5	Alive (6) died (1)	Morioka et al. (2007)
3	Median: 10.8	NR	LTx–K (1)	NR	NR	43	Alive (×3)	Stevenson et al. (2009)

NR — not reported; OLTx — orthotopic liver transplant; ACR — acute cellular rejection; PTLD — post-transplant lymphoproliferative disorder; LR-LTx — living-related liver transplantation; pALTx — partial auxiliary liver transplantation; HAT —hepatic artery thrombosis; PVT — portal vein thrombosis; LTx–K — liver kidney transplantation. See References [11,103–112].

corrected by the LTx. For GSD IV, LTx is often the first line of treatment, especially for the ones that develop liver cirrhosis; however for some forms of GSD IV, extrahepatic manifestations are a part of the disease and persist. Although limited experience with hepatocyte transplantation in lieu of whole organ transplantation has been reported, several reports indicate positive outcomes [59,60]. A pediatric GSD Ia patient underwent hepatocyte transplantation and subsequently showed no additional episodes of hypoglycemia [61].

LTx should be considered for patients with GSD who have very poor metabolic control despite medical management, have multiple recurrent adenomas, progressive liver cirrhosis, and/or hepatic failure. Organ allocation is less highly prioritized than for patients with urea cycle defects, PPA, or MMA as the perceived lack of life threatening episodes places GSD patients in a lower priority class. In general, LTx has been shown to improve overall quality of life in patients with GSD and therefore should also be an option for long-term preventative care [62].

4.2. Phenylketonuria

Phenylketonuria (PKU) results from a deficiency of phenylalanine hydroxylase, the enzyme in the liver that converts phenylalanine to tyrosine. Due of this deficiency, phenylalanine (Phe) rises to toxic levels in the brain, and untreated patients typically develop intellectual disability and psychiatric problems. Universal newborn screening for PKU is now performed throughout the developed world so that treatment can be initiated and continued from the early weeks of life. This approach has been very effective in preventing intellectual disability. Nonetheless, early- and continuously-treated patients often have IQs lower than expected in comparison with family members, problems in specific aspects of cognition such as executive abilities, and a higher incidence of psychiatric problems such as depression and anxiety [63–65], all of which have been associated with poorer metabolic control. However, PKU is unlike many other metabolic disorders in that it is not associated with episodes of acute metabolic complications requiring hospitalization.

We now know that treatment for PKU should be maintained for life [66]. Current treatment primarily comprises restriction of phenylalanine intake and dietary supplementation with phenylalanine-free amino acid mixtures (medical foods, formulas) to satisfy protein requirements [67]. The PKU diet is extremely restrictive, consisting primarily of fruits, vegetables, and low protein modified food products such as bread, rice, and pasta. Not surprisingly, adherence to this diet is not ideal and becomes particularly problematic as patients enter adolescence and adulthood [68,69].

More recently, the medication sapropterin, the pharmaceutical form of the tetrahydrobiopterin cofactor of phenylalanine hydroxylase, has been shown to reduce blood Phe levels in about 50% of PKU patients tested [70]. Pegylated phenylalanine ammonia lyase (PEG-PAL), an enzyme substitution therapy, is another pharmaceutical agent that is currently in Phase III clinical trials. PEG-PAL would theoretically normalize Phe levels in any patient with PKU, but it is a foreign protein and safety data are not yet available. Finally, gene therapy for PKU is being explored in animal models [71].

One patient with PKU has received a LTx for reasons unrelated to PKU, and not surprisingly, the patient's blood Phe level normalized after transplant [72]. Nevertheless, transplantation of a whole liver for this condition is not likely to be acceptable to the majority of patients and treating physicians due to the availability of non-surgical therapeutic options. However, transplant of isolated hepatocytes and stem cells has been considered as viable alternatives [73]. Hepatocyte transplant has been performed in one patient who had poor dietary control, with temporary improvement of blood Phe levels [74]. For this therapy to be viable, issues such as optimal post-transplant immunotherapy, the risks of immunotherapy, and appropriate indications for transplant need to be considered relative to the potential for improved quality of life.

5. Hepatocyte transplantation

The use of solid organ LTx to treat liver-based metabolic disorders is limited by a severe shortage of donor organs, the risks associated with major surgery, and the low, but real, long-term risk of graft loss from rejection. Hepatocyte transplantation holds promise as an alternative to organ transplantation, and numerous animal studies indicate that transplants of isolated liver cells can correct metabolic deficiencies of the liver. Clinically, the procedure involves isolation of cells from livers rejected for solid organ transplant, which are then transplanted via the portal vascular system into the liver [75]. This procedure is far less intrusive than replacement of the liver. Since the native liver is not removed, the transplanted hepatocytes need only improve the single enzyme deficiency and need not replace all hepatic functions.

Clinical trials have demonstrated long-term safety of hepatocyte transplant, but only partial correction of metabolic disorders has been achieved [60,76–81]. Conditioning with low-dose liver-directed radiation has been shown to facilitate repopulation of the native liver by transplanted hepatocytes and completely correct animal models of hereditary metabolic deficiencies of the liver [82]. Following additional safety and efficacy studies of a radiation-based conditioning regimen in non-human primates, an FDA-approved clinical trial of hepatocyte transplantation for treatment of life-threatening metabolic liver diseases, such as Crigler–Najjar syndrome and UCDs, has begun at CHP along with a second trial for the treatment of PKU.

6. Current indications and outcomes

Inborn errors of metabolism represent approximately 15–25% of disease indications for LTx in children and have been reported to have comparable or better outcomes than transplant of patients with decompensated cirrhosis or other forms of chronic liver disease in both single and multi-center studies (Table 3) [8,13,83]. Three issues fundamentally affect decision making regarding a possible LTx. First, is there structural liver disease which carries “standard indications for transplantation” such as functional hepatic decompensation from cirrhosis, portal hypertension, or tumor risk? Second, is the metabolic defect liver-specific or expressed in other tissues? Third, what is the severity of the clinical manifestation of the metabolic defect (hyperammonemia, neurologic sequelae, uncontrollable hypoglycemia)? Relative to LTx, metabolic diseases can be broadly categorized based on the presence or absence of liver injury and the presence and mechanism of development of extrahepatic damage (Table 4) [6,8,9,11,13,31]. For example, diseases such as alpha-1-antitrypsin deficiency and Wilson disease both cause primary liver injury, but the latter also manifests with additional significant extrahepatic manifestations through intrinsic intracellular accumulation of a toxin (copper). On the other hand, diseases like Crigler–Najjar syndrome type 1 or UCDs are caused by liver specific metabolic defects, but exhibit extrahepatic sequelae due to the accumulation of extrinsic toxic metabolites. In the latter diseases, LTx replaces an otherwise healthy liver in order to cure a systemic disease [12]. The specificity of the defect and its phenotypic expression affect both urgency of the transplant, surgical options, and the possibility for a “cure.”

The efficacy of LTx for metabolic diseases has been demonstrated through single- and multi-center reviews as well as in reviews of

Table 3
Reported outcomes of pediatric liver transplantation for metabolic diseases.

Reference	Case experience	Patient survival at 5 years	Graft survival 5 years
SPLIT [13]	446	88.9%	83.8%
UNOS [9]	551	92%	

See References [8,13,83].

Table 4
Metabolic diagnoses for which liver transplant has been reported.

Conditions with liver injury	
Intrahepatic	Extrahepatic
Alpha-1-antitrypsin deficiency (*SERPINA1*) • Tyrosinemia type I • GSD Type IV (*GBE1* gene) • BSEP deficiency • MDR-3 deficiency • Primary bile acid synthesis disorders • Hepatic porphyrias o Acute intermittent porphyria o Variegate porphyria • Glycogen storage disease type Ia • Hereditary fructose intolerance • Indian childhood cirrhosis	• Wilson disease • Cystic fibrosis • FIC-1 deficiency • Glycogen storage disease types Ib, III and IV • Non-alcoholic steatohepatitis • Gaucher disease • Niemann–Pick disease • Cholesterol ester storage disease • Mitochondrial cytopathies • Cerebrotendinous xanthomatosis • Citrin deficiency • Erythropoietic porphyria
Conditions without liver injury	
Intrahepatic	Extrahepatic
• Crigler–Najjar syndrome type 1 • Primary hyperoxaluria • Urea cycle disorders • Familial hypercholesterolemia • Fatty acid oxidation defects • Coagulation defects o Hemophilia A o Factors V and VII deficiency o Proteins C and S deficiencies • Factor H deficiency • Afibrinogenemia • Amyloidosis type 1	• Citrulinemia • Cystinosis • Branched amino acids disorders (organic acidemias) o Propionic acidemia o Methylmalonic acidemia o Mevalonic acidemia o Maple syrup urine disease

See References: [6,8,9,11,13,31].

national databases, achieving a >82% survival rate at 10 years (Table 3) [8,13,83]. The single center experience at CHP in Pittsburgh is particularly instructive in that it provides longer outcomes than previous reports. The thirty year experience with LTx for a broad range of metabolic diseases at CHP is shown in Table 5. In that time, two-hundred and eighty-five children underwent pediatric LTx for metabolic indications. The mean age at transplantation was 7.6 years (16 days to 23 years). Forty-three children underwent re-LTx at a mean of 2.3 years (2 days to 18.2 years) post-transplant. Overall patient and graft survival are shown in Table 6. Historically, the majority of patient deaths and graft losses occurred within one-year of transplantation. Infection was the most common cause of death (25.4%). Chronic rejection and hepatic artery thrombosis accounted for 21.4% and 17.9% of graft loss, respectively. However, results over the last 10–13 years have demonstrated significant improvement in patient and graft survival with a sharp reduction in early death or graft loss, as well as maintenance of patient and graft survival over an extended follow-up period of greater than 10–15 years (Figs. 1 and 2). Of patients receiving transplants over the past decade at CHP, only three died (two of infection and one of suicide) and only one required retransplantation, with patient survival over the past 10 years currently at 97%.

Of particular note is the high patient and graft survival rates with diseases such as MSUD (100% patient and graft survival at five years) and UCDs (80% at 20 years). Despite overall excellent outcomes at centers experienced in pediatric LTx, a true benefit and risk assessment in the current era requires a more in depth analysis of not only late graft loss and mortality, but also complications for non-allograft related morbidities due to the consequences of immunosuppression.

Table 5
Children's Hospital of Pittsburgh of UPMC experience in pediatric liver transplantation for metabolic diseases.

Indication	Number
Alpha-1-antitrypsin deficiency	73
Maple syrup urine disease	38
Familial cholestasis	37
Wilson's disease	28
Tyrosinemia	20
Cystic fibrosis	19
Glycogen storage diseases	15
Crigler–Najjar syndrome I	15
Urea cycle disorders	14
Oxalosis	10
Histiocytosis	5
Hemochromatosis	4
Type II hyperlipidemia	2
Niemann–Pick disease	1
Neurovisceral storage disease	1
Acyl-CoA dehydrogenase deficiency	1
Indian childhood cirrhosis	1
Erythropoietic protoporphyria	1
Total	285

Table 6
Patient and graft survival (percent) of patients with metabolic diseases (with n > 10) at 1, 5, 10 and 20 years after transplantation at Children's Hospital of Pittsburgh of UPMC.

Years	Survival	
	Patient	Graft
1	87.7%	79.3%
5	84.9%	73.1%
10	80.1%	67.4%
20	70.1%	56.9%

6.1. Assessment of late graft dysfunction

Long term studies of allograft health suggest that subtle abnormalities are common in long term LTx survivors. In an analysis of 461 children evaluated at five years post-transplant, nearly 50% showed abnormal GGT levels, suggesting the possibility of late biliary complications or chronic rejection [10]. The etiology of late biliary complications may be technical in nature or related to long term ischemic changes in the allograft. Immunologic causes of altered biliary tract enzymes include late onset acute rejection or development of chronic rejection. Another concerning issue is the development of fibrotic changes of

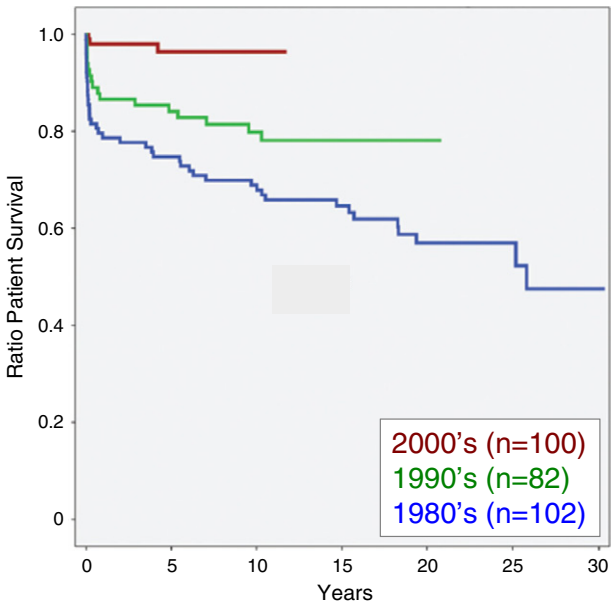

Fig. 1. LTx for metabolic disease (with n > 10) patient survival by decade (1981–2012) at Children's Hospital of Pittsburgh of UPMC. The lines differ significantly (p < 0.001).

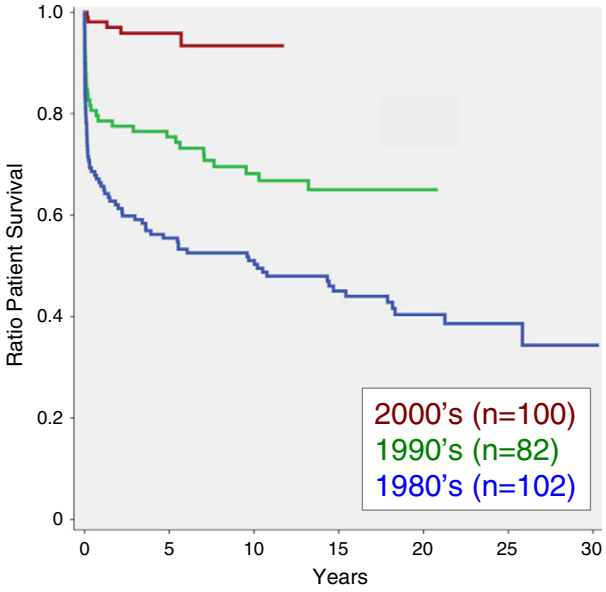

Fig. 2. LTx for metabolic disease (with n > 10) graft survival by decade (1981–2012) at Children's Hospital of Pittsburgh of UPMC. The lines differ significantly ($p < 0.001$).

immune [84] or other etiologies in long term pediatric allografts [85,86]. The published data as well as results at CHP in the past decade suggests that events leading to graft loss or death are overall rare after the one year anniversary, but longer follow-up will be needed to properly advise both patients and caregivers [87].

6.2. Non-allograft related complications

Immunosuppressant use, while enabling long term allograft maintenance, also contributes to potentially serious complications over time. Although minimal long term exposure to immunosuppression is a goal of pediatric transplantation, immune monitoring to guide immunosuppression is not routinely available clinically. As a result, optimizing immunosuppression is difficult and not well-standardized. In the Studies in Pediatric LIver Transplantation (SPLIT) database, immunosuppression varied by two to three fold at the five-year anniversary [10]. This database has systematically documented complications such as hypertension, renal insufficiency, and post-transplant malignancy in patients surviving ten years or more after pediatric transplantation [88]. Other complications include glucose intolerance, altered cholesterol metabolism, and abnormal growth and development.

Better assessment of true risks must take into account both allograft and extrahepatic complications in an attempt to document "ideal" outcomes. An example of a proposed metric is shown in Table 7 (modified from Ref. [88]) utilizing 13 clinical criteria. In the SPLIT analysis, only 32% of the 10 year survivors had data to document presence of all optimal criteria. CHP data on current metabolic survivors demonstrates excellent outcomes according to these metrics, although continued follow-up is ongoing. For example, 75% of the patients transplanted for MSUD with a greater than four-year follow-up met all 13 criteria.

Transplant for metabolic disease presents both long term advantages and challenges for patients post-transplant. Disease recurrence in the allograft is expected to be rare compared to that in children undergoing transplant for autoimmune type disease. Most patients undergoing transplant for metabolic disease are clinically stable at the time of transplant and normally would not have consequences of previous surgeries or portal hypertension, which contributes to the documented excellent perioperative survival. However, metabolic patients may be prone to extrahepatic manifestations of their underlying disease, which may be incompletely treated by the LTx. Clearly, clinical decision-making is best undertaken by a discussion of the best available long term results of transplant in the context of the metabolic patients' specific medical options and future alternatives.

7. Organ allocation issues

The shortage of available livers for transplantation is an important issue to consider with the use of LTx for metabolic disorders, as increasing the number of LTx performed for these conditions will further tax the pool of donor organs. While the use of living donors expands the liver pool, a potential complicating issue is that parents of children with metabolic disorders are likely carriers for the conditions, and there is a 2/3 chance that their siblings are carriers. Typically, carriers' livers function at half of their normal activity. The critical question then becomes whether 50% of normal activity restricted to the liver sufficient to improve metabolic control. Domino transplants could increase the pool of livers as with MSUD; however, there are a limited number of conditions in which domino transplant could work. In conditions where liver function worsens over time, domino transplants could work, but are not optimal.

Another consideration is how to account for metabolic diseases in the prioritization for available livers. In the United States, the Pediatric End Stage Liver Disease (PELD — for LTx candidates <12 years old) and Model for End Stage Liver Disease (MELD — for LTx candidates

Table 7
An example of a proposed transplantation risk metric utilizing 13 clinical criteria that takes into account both allograft and extrahepatic complications. Modified from Ref. [88].

Medical variable: result reported at 10-year visit	Patient data available, n	Patients who answered "yes" to variable as phrased, n (%)	Patients missing data, n (%)
Sustainability of allograft			
1. No retransplantation	167	147 (88%)	0
2. No chronic rejection; confirmed diagnosis previously/presently	167	152 (91%)	0
3. Serum ALT normal	166	148 (89%)	1 (1%)
4. Serum TB normal	165	161 (98%)	2 (2%)
5. Serum albumin normal	162	160 (99%)	5 (3%)
6. Serum GGT normal	149	126 (85%)	18 (11%)
Absence of immunosuppression-induced comorbid conditions			
7. No PTLD; previous diagnosis of tissue-confirmed PTLD	167	158 (94%)	0
8. No renal dysfunction; cGFR <90 mL/min/1.73 m^2	118	107 (91%)	49 (29%)
9. Acceptable linear growth; > −2 SD for healthy population	121	112 (93%)	46 (27%)
10. No diabetes	167	165 (99%)	0
Absence of need for additional medications			
11. No ongoing use of prednisone	167	135 (81%)	0
12. No use of antihypertensive agent	167	146 (87%)	0
13. No use of antiseizure medication	167	167 (100%)	0

12–17 years old) scoring systems are used to prioritize LTx patients. These scores are typically based upon biochemical parameters of advancing liver failure and portal hypertension that predict near term prognosis. In many metabolic diseases, there is no progressive liver disease and as such, the system does not adequately predict risk. Candidates with UCDs or organic acidemias are assigned a PELD or MELD score of 30, which is a fairly high prioritization. If the candidate does not receive a LTx within 30 days, they may be listed as Status 1B (Status 1B candidates are children who have chronic liver disease with severe and life-threatening complications. Status 1B is the second highest level of prioritization just behind acute liver failure [89,90] without Regional Review Board review or hospitalization). Candidates with other metabolic diseases must apply for exception PELD or MELD scores, as they typically don't have significant intrinsic liver disease [4,91]. Where should children with other metabolic disorders be placed on the waiting list? As new indications and diseases arise, how do they fit in? How should the scoring system account for diseases that are less life-threatening, but impair quality of life (mitochondrial disease, PA, MMA), since LTx would treat some symptoms but not cure the disease? Expansion of the metabolic indications for LTx requires that the issue of organ allocation be addressed.

8. Summary

LTx has been revolutionary and life-saving for disorders such as severe UCDs and MSUD. Initially viewed as a rescue procedure for such conditions, the risk of death or disability due to these inborn errors of metabolism now far outweigh the morbidity or mortality of transplant or long term sequelae related to immunosuppression. What factors play into this dramatic reversal? Of course, it is not hard to argue that increased experience with the technique over time has led to a broader pool of qualified pediatric transplant specialists, and thus improved outcome. However, equally importantly, the recognition that patients in good metabolic control have better surgical outcomes has fostered close cooperation between medical and surgical teams, and it is clear that impeccable metabolic therapy prior to transplant is vital to a good transplant program. With operative mortality now at near zero, and aggressive weaning of immunotherapy reducing risks of post-transplant infection and malignancy, there is good reason to consider a paradigm shift in the use of LTx beyond metabolic rescue. It is now increasingly incumbent on metabolic physicians and transplant surgeons to consider transplant for other than purely life-saving reasons. This conference and paper have highlighted some such uses. LTx has not completely eliminated all symptoms in patients with metabolic disease, but it has led to improved quality of life. In summary, data suggests that LTx has emerged from its position as a treatment of last resort for inborn errors of metabolism to play a more robust role in a wider variety of diagnoses. Divining the appropriate mix of disorders and conditions for transplant will be the challenge of the next decade in this field and will likely best be accomplished through close cooperation between the metabolic treatment and liver transplant teams.

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