

Organ transplantation in individuals with urea cycle disorders and classic organic acidurias

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Introduction

The role of liver transplantation in propionic acidemia.

Quintero J¹, Molera C², Juamperez J¹, Redecillas S³, Meavilla S², Nuñez R³, García C², Del Toro M⁴, García Á⁵, Ortega J⁶, Segarra Ó³, Martín de Carpi J², Bilbao I⁷, Charco R⁷.

Living donor liver transplantation for inborn errors of metabolism – An underutilized resource in the United States

Pham TA, Enns GM, Esquivel CO. (2016) Living donor liver transplantation for inborn errors of metabolism – An underutilized resource in the United States. *Pediatr Transplant*, 20: 770–773. DOI: 10.1111/petr.12701

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Liver Transplantation for Propionic Acidemia and Methylmalonic Acidemia: Perioperative Management and Clinical Outcomes.
Critelli K¹, McKiernan P^{1,2}, Vockley J^{2,3}, Mazariegos G^{2,4}, Squires RH^{1,2}, Soltys K^{2,4}, Smith R^{2,4}

Evaluation and management of patients with propionic acidemia undergoing liver transplantation: A comprehensive review
Barshes NR, Vanatta JM, Patel AJ, Carter BA, O'Mahony CA, Karpen SJ, Goss JA. Evaluation and management of patients with propionic acidemia undergoing liver transplantation: A comprehensive review. *Pediatr Transplantation* 2006; 10: 773–781. © 2006 Blackwell Munksgaard

CASE REPORT

Reversal of cardiomyopathy in propionic acidemia after liver transplantation: a 10-year follow-up

Chiara Arrizza,^{1,2} Andrea De Gottardi,³ Ezio Foglia,⁴ Matthias Baumgartner,^{5,6} Matthias Gautschi^{1,2} and Jean-Marc Nuoffer^{1,2}

Combined liver–kidney transplant for the management of methylmalonic aciduria: A case report and review of the literature
Peter J. Mc Guire^{a,b,*}, Elizabeth Lim-Melia^{a,b}, George A. Diaz^{a,b}, Kimiyo Raymond^b, Alexandra Larkin^b, Melissa P. Wasserstein^{a,b}, Claude Sansaricq^{a,b}

Introduction

- Study initiative

- E-IMD 2017 Carlo Dionisi-Vici, Luca Dello Strologo
- MetabERN/
AOA subnetwork S. Kolker, M. Williams, Trine Tangeraas
- French group Pascale Lonlay, S. Sassaoui, Anaïs Brassier

Introduction

- The number of IMDs for which liver transplant can be used is rapidly expanding (Sirrs 2018)
- Propionic acidemia
 - Liver transplantation **is increasingly discussed** as a relevant alternative (Tuncel 2018)
 - Liver transplantation should be considered in patients with **frequent episodes of hyperammonemia, metabolic crises and acute decompensations** (Tuncel 2018)
- UCD
 - Orthotopic liver transplant is the treatment of choice for symptomatic patients with UCDs who have **not yet sustained severe neurological injury** (Haberle et al 2012)
 - Data available suggest that transplantation for this indication is less frequent performed in adults than in children for UCD (Sirrs 2018)

Introduction




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Organic acidurias in adults: late complications and management

Authors

[Authors and affiliations](#)

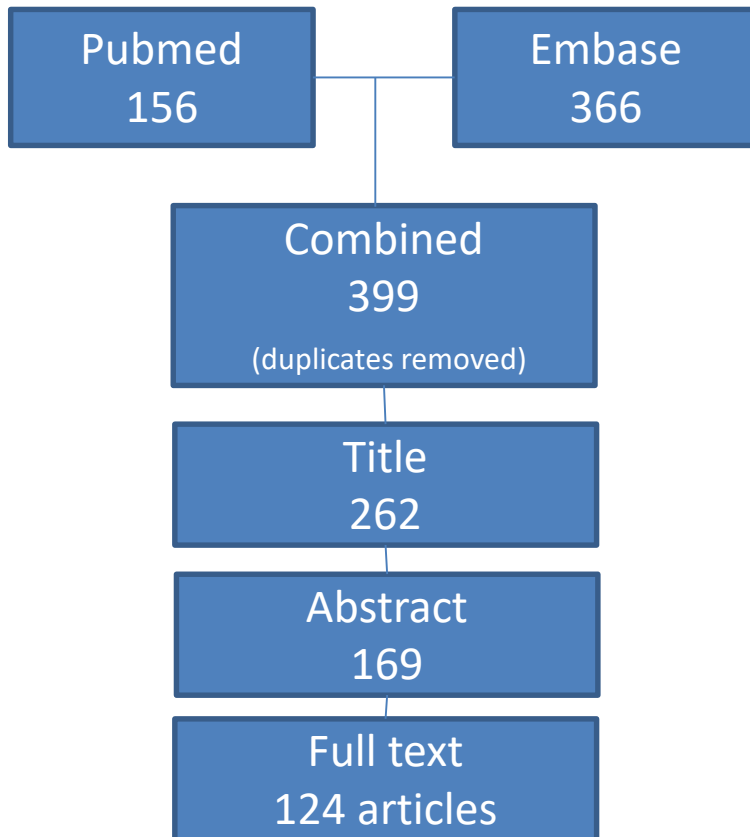
Ali Tunç Tuncel, Nikolas Boy, Marina A. Morath, Friederike Hörster, Ulrike Mütze, Stefan Kölker 

- MMA
 - More systematic studies addressing **who, when and which organs** (liver, kidney, combined liver/kidney) should be transplanted are needed.
- PA
 - Suggest that liver transplantation should be considered **earlier in life**, since younger organ recipients show better outcomes
 - Older recipients developed severe complications, such as hepatic artery thrombosis, cardiac or pulmonary insufficiency
 - Progression of **cardiomyopathy in PA may be halted or even reversed** after liver transplantation, which is unlikely to be achieved with conventional metabolic therapy

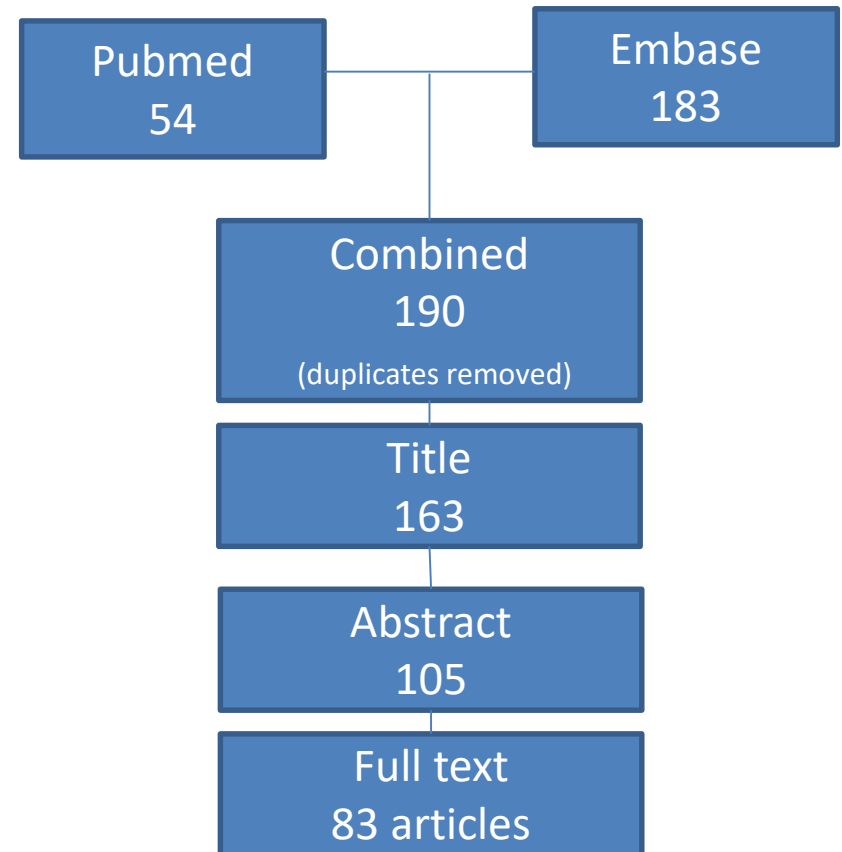
Literature search

Date search: 11-09-2018

Methylmalonic acidemia



Propionic acidemia



Literature search

- Baseline characteristics

Disease	MMA	PA
Liver transplantation	116	128
Kidney transplantation	35	2
Combined transplantation	78	None
Re-transplantation	6 (2.6%) Combined n=2 Liver n=4	10 (7.7%)
Total transplantation (n =)	235	140
Gender % female	46	50
Age transplant (median, range)	3.0y, 0.58-42.0y	3.0y, 0.6-42.0y

Literature search

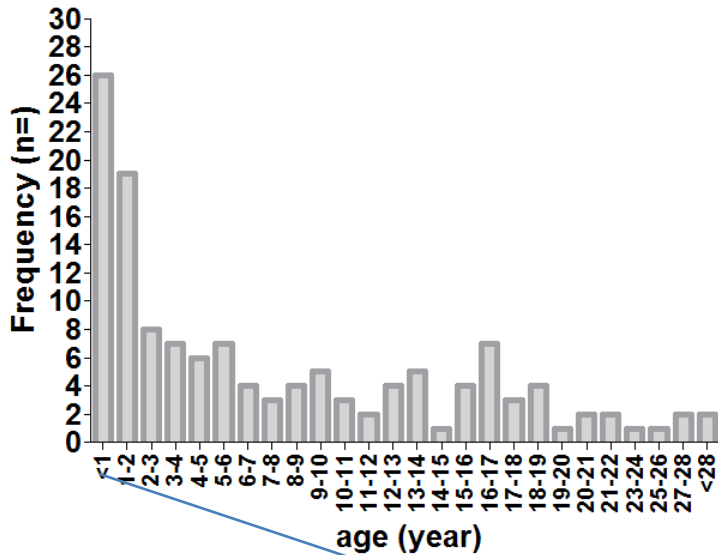
- Baseline characteristics
 - Number of patient with known outcome

Disease	MMA	PA
Total transplantation (n =)	235	140
Follow-up (n =)	161	98
Death/alive (n =)	160	88
Age transplantation (n =)	133	67
Age follow-up(n =)	82	56
Complications before Tx (n =)	79	63
Complications after Tx (n =)	89	81
Hemodialysis before Tx (n =)	42	4
Protein intake before and after Tx (n =)	59; 93	19; 38
Medication before and after Tx (n =)	54; 49	37; 32
Metabolic crisis before and after Tx (n =)	71; 61	41; 46

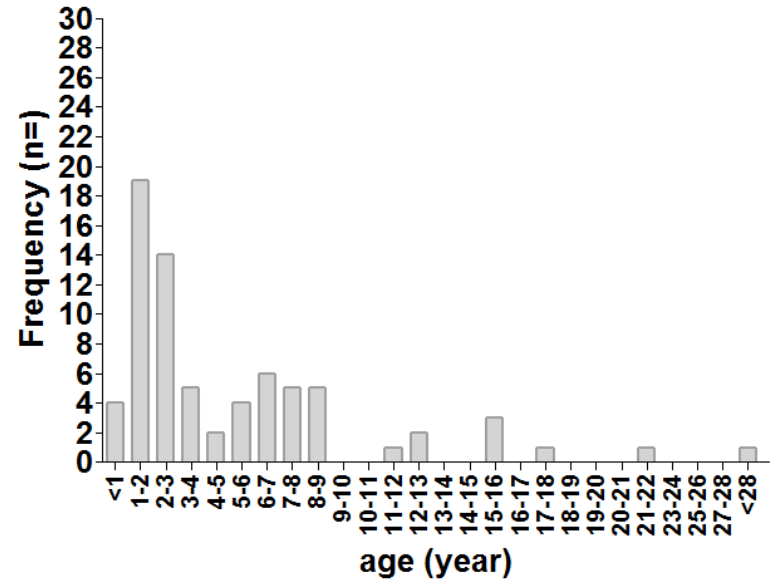
Literature search

- Baseline characteristics
 - Age at transplantation

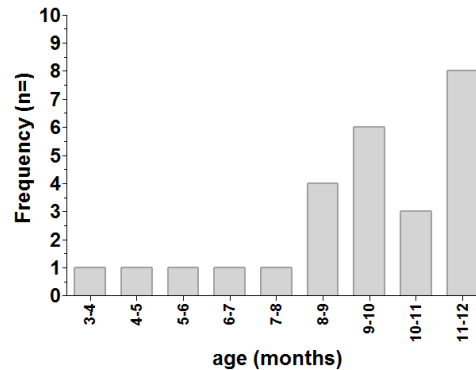
MMA



PA



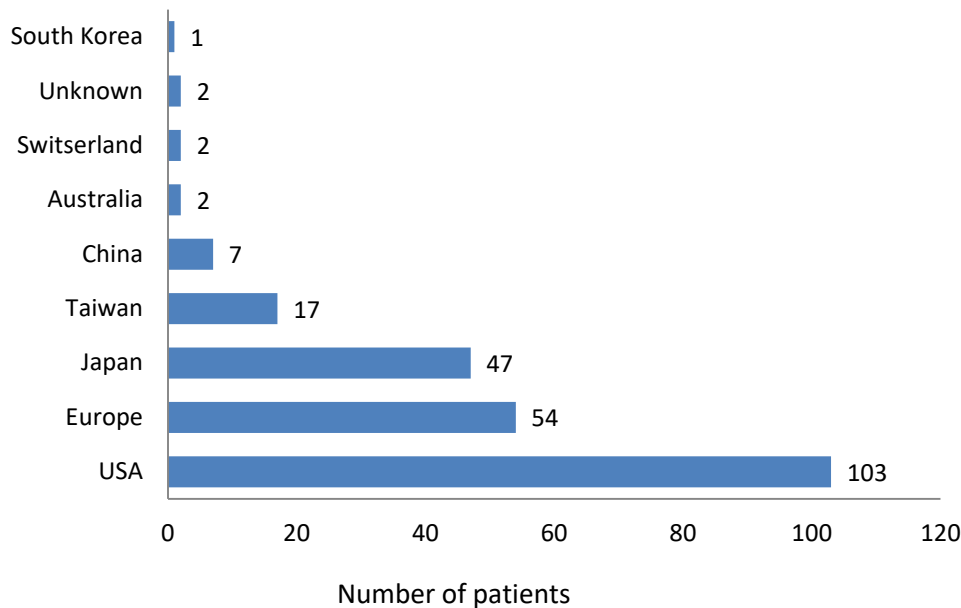
MMA



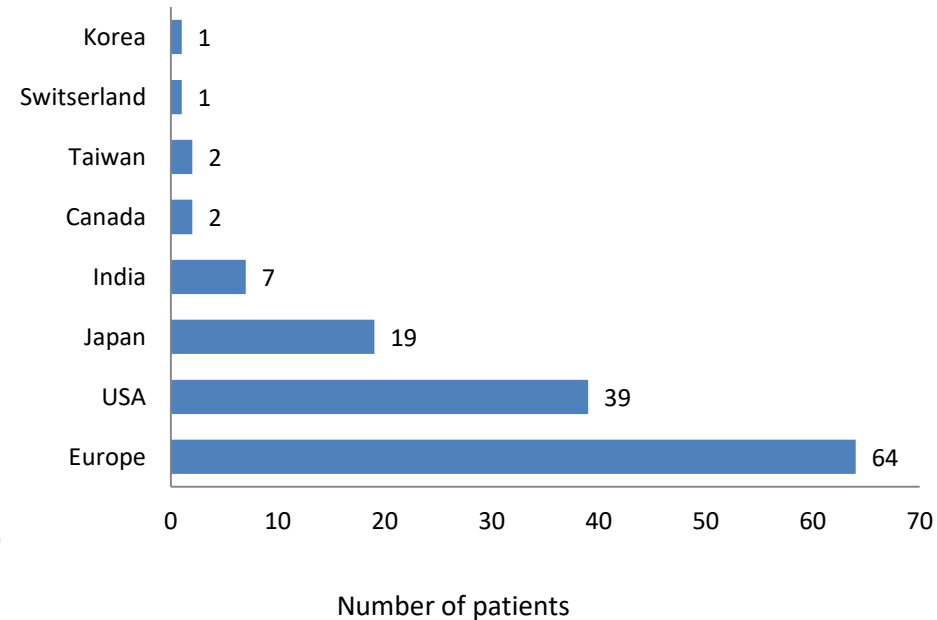
Literature search

- Baseline characteristics
 - Countries

MMA



PA



Literature search

- Criteria decision making/reason for transplantation
 - MMA

Reason for transplantation	Kidney failure	Metabolic decompensations	Liver failure	Hepatoblastoma	Developmental delay	Pre-emptive	Unfavourable course
Liver transplantation	4	7	1		1	5	1
Kidney transplantation	20				1		
Combined transplantation	29	5 (all-in combination with kidney failure)		1		1	

– PA

Reason for transplantation	Kidney failure	Metabolic decompensations	Cardiomyopathy	Developmental delay	Pre-emptive	Other
Liver transplantation		21	16	10	5	9
Kidney transplantation	2					

Literature search

- Outcome

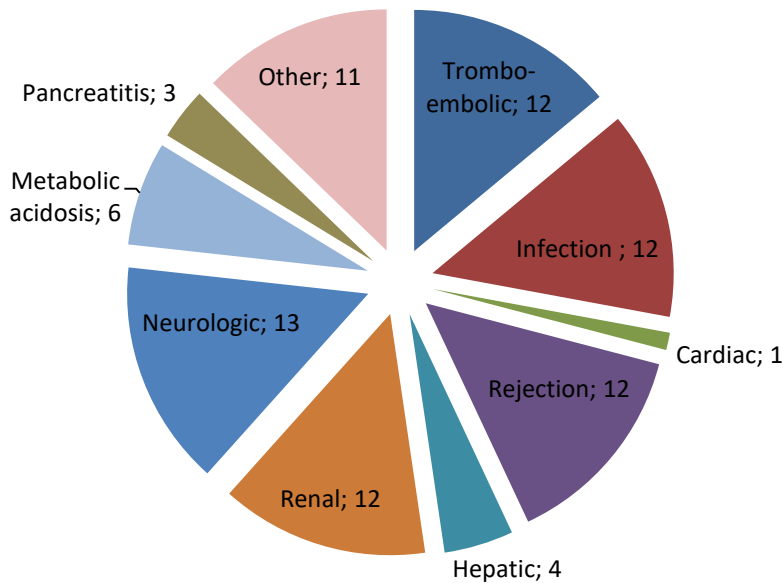
	MMA		PA	
Mortality	17/160	11%	21/88	24%
Complications	71/89	80%	60/81	74%
Follow-up duration (median, range)	3.0 year	0.04 - 14.0 year	2.0 year	0.03 - 19.8 year
Re-operation	10/161	6%	9/98	9%
Metabolic episodes per year before Tx (approximately)	3/year		6/year	
Total metabolic episodes after Tx	53x 0 episodes 5x 1 episodes 2x 2 episodes 1x 5 episodes		44x 0 episodes 2x 1 episode	

Literature search

- Outcome
 - Complications

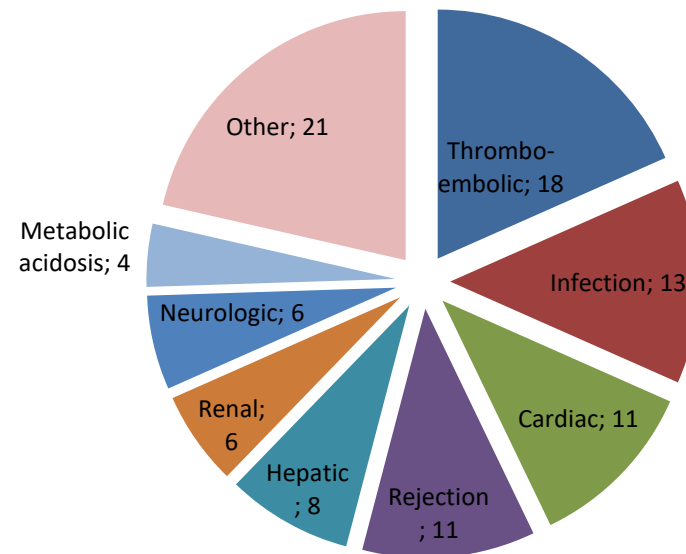
MMA (% of total)

Total follow up: 161 patients



PA (% of total)

Total follow up: 98 patients



Literature search

- Outcome
 - Complications and age at transplantation

Age transplantation		< 6 years of age	> 6 years of age
Trombo-embolic complications (n=)	MMA	10/61 (16%)	7/57 (12%)
	PA	6/48 (13%)	6/23 (26%)
Cardiac complications (%)	PA	4/48 (8%)	3/23 (13%)
Death (%)	MMA	5/49 (10%)	8/53 (15%)
	PA	9/40 (23%)	4/23 (18%)

Literature search

- Outcome
 - Reason for retransplant

	MMA		PA	
Reason for retransplant	HAT*	n=4	HAT*	n= 6
	Acute rejection	n=1	Primary non-function	n= 1
	Unknown	n=1	Chronic rejection	n= 1
			Graft failure	n= 1
			Unknown	n= 1

* Hepatic artery thrombosis

Literature search

- Outcome
 - Cause of death

	MMA		PA	
Cause of death	Infection/sepsis	n=5	Multi-organ failure (3 pt in combination with heart failure)	n = 4
	Metabolic crisis	n=3	Hepatic failure	n = 4
	Pancreatitis	n=3	PTLD ⁺	n = 2
	Heart failure	n=2	Rejection	n = 2
	Metabolic stroke	n=1	Chronic liver cirrhosis	n = 1
	ATN*	n=1	Infection	n = 1
	Hepatoblastoma	n=1	Severe cardiomyopathy	n = 1
	Unknown	n=1	Respiratory failure	n = 1
			Unknown	n = 5

*Acute tubular necrosis

+ Post transplant lymphoproliferative disorder

Literature search

- Outcome
 - Time of death after transplantation

MMA	Time after transplant	Total (n=)	Pancreatitis	Infection /sepsis	Metabolic stroke	Metabolic acidosis	Heart failure	ATN [#]	Hepatoblastoma
	<30 days	3x	1x	1x	1x				
	30 days – 1 year	3x		2x		1x			
	>1 year	7x	2x			1x	2x	1x	1x

PA	Time after transplant	Total (n=)	MOF* with heart failure	Hepatic failure	MOF* with HAT	Infection	Respiratory failure	Rejection	Chronic liver graft cirrhosis	PTLD ⁺	Unknown
	<30 days	9x	3x	3x	1x						2x
	30 days – 1 year	4x	1x			1x	1x	1x			
	>1 year	3x							1x	2x	

[#] Acute tubular necrosis

* Multi organ failure

⁺ Post transplant lymphoproliferative disorder

Literature search

- Outcome

- MMA

Europe versus USA:

- Europe more frequent single kidney

Type of transplant	Europe (n=)	USA (n=)
Liver	14 (26%)	35 (34%)
Kidney	24 (44%)	7 (7%)
Combined	16 (30%)	61 (59%)

- Europe higher mortality

Outcome	Europe (n=)	USA (n=)
Alive	26	65
Death	8 (24%)	1 (2%)

Literature search

- Outcome

- MMA:

Age at transplantation, mortality and complications

Between single liver, single kidney and combined transplantation

	Age transplantation (median, range)	Death		Complications	
Liver transplantation	1.6y, 0.3-22.0y	6/84	7%	31/42	74%
Kidney transplantation	15.5y, 3.0-43.0y	8/25	32%	17/21	81%
Combined transplantation	11.0y, 0.9-28.0y	3/51	6%	23/26	88%

Literature search

- Outcome

- MMA:

- Cause of death

- Between single liver, single kidney and combined transplantation

Type of transplant	Cause of death	
Liver transplantation	Infection	n=2
	Severe acidosis	n=2
	Multi-organ failure	n=1
	Metabolic stroke	n=1
Kidney transplantation	Pancreatitis	n=3
	Infection	n=2
	Cardiorespiratory failure	n=2
	Hepatoblastoma	n=1
Combined transplantation	Metabolic crisis	n=1
	Acute tubular necrosis	n=1
	Not reported	n=1

Literature search

- Outcome
 - MMA:
Renal function

Type of transplant	Liver	Kidney	Combined	Total
Worsening renal function	7	2	1	10
Improved Renal function	1	8	2	11
Stable Renal function	5	1	2	8

Literature search

- Outcome

- PA

- Heart function before and after transplantation

Heart function before transplant	n =	Heart function after transplant	n =	
Cardiomyopathy	16	Cardiomyopathy resolved Surgical cardiac arrest, later resolution Slight improvement Not described	6 1 1 8	
Not described	9	Heart failure Cardiorespiratory decompensation	8 1	Heart failure in 3 cause of death
Cardiomyopathy resolved at time transplant	1	Cardiomyopathy	1	

Literature search

- Conclusions

Disease	MMA		PA	
Total transplantation (n=)	235		140	
Mortality	11%		24%	
Complications	80%		74%	
Main complications (% of total patients with follow-up)	Trombo-embolic	12 %	Trombo-embolic	18 %
	Infection	12 %	Infection	13 %
	Rejection	12 %	Rejection	11 %
	Renal	12 %	Cardiac	11 %
	Neurologic	13 %	Hepatic	8 %
Outcome	Single kidney - Often improved renal function - Higher mortality (3 due to pancreatitis) than single liver or combined Single liver; often worsening of renal function		Cardiomyopathy - Resolved in n=6 - Heart failure occurred in n=8 → of which 3 died	

What remains unsolved

Despite first transplantation in 1995

Several questions remain unanswered:

- Criteria that should be used to decide to transplant
- Optimal age transplantation
- Factors predictive of post-transplant death or graft lost
- Do patients with pre-transplantation haemodialysis have better outcome
- Optimal protein intake after transplantation
- Effect discontinuation medical therapy

Study project

Drawbacks review literature

- Obtained retrospectively
- Substantial amount of data was missing
- Publication bias may also have influenced the data available for interpretation

Goal

- European database/registry including liver and/or kidney transplantation in amino acid disorders
 - With the attempt to come up with guideline recommendations

Study conditions

1. Project organization

- Project proposal by
 - E-IMD
 - AOA of MetabERN

2. Determine

- Project leaders
- Advisory board
- Steering board

3. Contact

- ERNrare liver
- CERTAIN
- ELTR
- ERN transplant child
- ERKNET

4. Define rules of agreement

5. Determined centers to be involved

All organizations involved	
MetabERN (AOA)	Amino acid and organic acids related disorders
E-IMD	
ERN rare liver	
CERTAIN	Cooperative European Paediatric Renal Transplant Initiative
ELTR	European Liver transplant registry
ERN transplant child	
ERKnet	European Reference Network for Rare Kidney Diseases
All European metabolic and transplantation centers	

Study proposal

1. Short questionnaire
2. Consensus meeting
3. More detailed survey
4. Start registry, make new guidelines, make a protocol

Study project

- Short questionnaire

1. Hospital

Doctor:.....
 Hospital:.....
 Country:.....
 City:
 Email address:.....

2. Transplantation characteristics

Year range transplantation performed:.....
 Average waiting time for transplantation:.....
 Type transplantation:
 Post-mortal donation (n=):.....
 Living related(n=):.....
 Living not related(n=):.....
 Deceased kidney (n=):.....
 Main reason to transplant:

3. Patient characteristics

Disorder	Total number of patients treated in your center (n=)	Number of patients transplanted (n=)	Age at Transplantation (...years) (respectively of all patients)	Current age (respectively of all patients)	Number of patients identified by NBS (n=)
Classic Organic Acidemias: <u>MMA</u> mut0 mut- CblB <u>PA</u> <u>IVA</u>	1. 5.	1. 5.
			2. 6.	2. 6.	
			3. 7.	3. 7.	
			4. 8.	4. 8.	
			
MSUD	1. 5.	1. 5.
			2. 6.	2. 6.	
			3. 7.	3. 7.	
			4. 8.	4. 8.	
<u>Urea Cycle Disorders:</u> CPS1-D OTC-D male OTC-D female ASS-D ASL-D ARG1-D	1. 5.	1. 5.
			2. 6.	2. 6.	
			3. 7.	3. 7.	
			4. 8.	4. 8.	
			
<u>Tyrosinemia</u>	1. 5.	1. 5.
			2. 6.	2. 6.	
			3. 7.	3. 7.	
			4. 8.	4. 8.	

*In case of Methylmalonic acidemia, please provide us the following information:

Liver (n=)	Kidney (n=)	Liver and kidney (n=)
.....

Study project

- Short questionnaire

4. Outcome

Disorder	Number patients died after transplantation	Age death (respectively of each patient (years)	Graft failure (n= in how many patients)	Rejection (n= in how many patients)	Peri/postoperative complications (n=, in how many patients)	Development after transplantation (n= in how many patients)
Classic Organic Acidemias*		1. 5. 2. 6. 3. 7. 4. 8.				Decreased: Same: Improved:
MSUD		1. 5. 2. 6. 3. 7. 4. 8.				Decreased: Same: Improved:
Urea Cycle Disorders		1. 5. 2. 6. 3. 7. 4. 8.				Decreased: Same: Improved:
Tyrosinemia		1. 5. 2. 6. 3. 7. 4. 8.				Decreased: Same: Improved:

5. Protocol

- Is there a pre-operative protocol for transplantation in IMD
 Yes
 No
- Is there a peri-operative protocol for transplantation in IMD
 Yes
 No
- Is there an post-operative protocol for transplantation in IMD
 Yes
 No
- Is there a multidisciplinary team for transplantation in IMD
 Yes
 No

6. Quality of life

- Measured

before Tx (respectively of each patient)		after Tx (respectively of each patient)	
1.	5.	1.	5.
2.	6.	2.	6.
3.	7.	3.	7.
4.	8.	4.	8.

- Not determined

7. Treatment after transplantation

Disorder	Pre-operative dietary restriction (n=)	Post-operative dietary restriction (n=)	Medication specifically for IMD before Tx (n=)	Medication specifically for IMD after Tx (n=)
Classic Organic Acidemias				
MSUD				
Urea Cycle Disorders				
Tyrosinemia				

Study project

- More detailed questionnaire

1. What is the current **frequency** of patients receiving liver and/or kidney transplantation compared to the total patient population in each metabERN center?
2. What are the **criteria used for** decision making in transplantation?
3. Can an **optimal age for** transplantation be defined by using current data on European OAD and UCD transplanted patients?
4. What is the (short term) **survival** of OAD and UCD patients following liver, kidney or combined transplantation in Europe?
5. Which **factors are predictive of post-transplant death or graft lost?**
6. What is the prevalence and incidence **of complications** in OAD and UCD patients, before and after organ transplantation?
7. In OAD, do patients receiving **pre-transplantation hemodialysis** have better outcome of transplantation and do patients receiving **combined kidney and liver transplantation have a better outcome compared to patients receiving single kidney or liver transplantation?**
8. **Diet restrictions:** Is protein tolerance increased after organ transplantation/relaxation of the diet compared to pre-transplantation and do patient still use emergency regimes and fasting restrictions?

Study project

- More detailed questionnaire

Demographics			Decision to transplant	Pre and posttransplant laboratoria characteristics	Pre and post transplant treatment	Pre and post transplant characteristics	Peri-operative protocol	Immunosuppressive protocol and intra/peri/post operative complications
Hospital	Highest ammonia concentration	Pre-operative dialysis	Reason for transplant	Was pt metabolic stable	Protein restriction	Patient measurements	Duration fasting	Medication
Disorder	Number hospital admissions	Reason dialysis	Persons involved in decision making	Liver function Kidney function	Feeding	IQ	Medication sedation	ICU stay Total hospital stay
Mutations	Current age	Response dialysis	MELD score	Free carnitine, acylcarnitines, organic s, plasma amino acids	Natural, total, liquid intake	Long-term complications	Glucose , NaCl infusion	Complications peri-op
Enzyme activity	Age transplantation	Follow-up time after transplantation	Ammonia, pH, anion gap, ketone bodies concentration onset		Emergency regimes, fasting restrictions		Medication	Complications post operative (rejection, GVHD, graft failure, death)
Gender	Date transplantation	Retransplantation	Type transplant HLA match		Dialysis			
Age of onset disease	Waiting time transplantation	Age retransplantation	Year in which retransplantation performed + waiting time		Medical treatment			

Take home

- Liver and/or kidney transplantation can improve patient outcome
 - But be aware of mortality risk and high risk of complications
- International collaboration is important