

PEDIATRIC HEPATOCYTE TRANSPLANTATION

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AIMS OF PEDIATRIC HEPATOCYTE TRANSPLANTATION:^{1,2,3}

- Improved regeneration.
- Down-regulation immune liver damage.
- Supplement hepatocyte function.
- Native liver in place.
- Less invasive procedure /Organs short supply.
- Bridge to and post LT.

Bench SIDE -> bedside^{4,5,6,7}

- >100 PTS UPTILL NOW
- 13 centres.
- (MELD)/PELD score improved from 15 to 10 within the first 18 months.
- No episodes hepatic encephalopathy.

Disease	Age	Reference	Cells
<i>Urea cycle</i>			
OTC	5 yr	Strom <i>et al.</i> [26]	1×10^9 fresh, intra-portal
OTC	Day2	Mitry <i>et al.</i> [9]	1.9×10^9 fresh / frozen
OTC	Day1	Horlsen <i>et al.</i> [6]	4×10^9 fresh
OTC	14 m	Stephenne <i>et al.</i> [27]	2.4×10^9 frozen
ASL	3 yr	Stephenne <i>et al.</i> [36]	3.4×10^9
OTC	10 wk	Meyburg <i>et al.</i> [37]	
OTC	3 y	Meyburg <i>et al.</i> [37]	3×10^9
Citrullinemia	2 y	Fisher and Strom[38]	
<i>Crigler-Najjar I</i>	10 y	Fox <i>et al.</i> [4]	6×10^9 fresh
	8 y	Darwish <i>et al.</i> [28]	7.5×10^9 fresh / frozen

<i>GSD1a</i>	47 y	Muraca <i>et al.</i> [5]	2×10^9 fresh
<i>GSD1b</i>	18 y	Lee <i>et al.</i> [34]	6×10^9 fresh / frozen
<i>Refsum</i>	4 y	Sokal <i>et al.</i> [35]	2.1×10^9 fresh/frozen
<i>Factor VII def.</i>	3 mo	Dhawan <i>et al.</i> [7, 30]	1.1×10^9 frozen
	3 y		2.2×10^9 fresh / frozen
<i>PFIC1</i>	3 mo	A. Dhawan (unpub)	3×10^9 fresh / frozen
	16 mo	Dhawan <i>et al.</i> [30]	2.3×10^8 fresh
	3 yr		3.7×10^8 fresh

Disease	no. of patients	Effect/outcome	Reference
Familial hypercholesterolaemia	5*	Some reduction in LDL in 3 patients	Grossman <i>et al.</i> (30)
Crigler–Najjar syndrome type I	1	50% reduction in serum bilirubin;	Fox <i>et al.</i> (5)
	1	40% reduction in serum bilirubin	Dhawan <i>et al.</i> (unpublished)
Urea cycle defect	1	Some clinical improvement; died after 42 days	Strom <i>et al.</i> (31)
	1	Lowered blood ammonia and increased protein tolerance	Horslen <i>et al.</i> (7)
	1	No hyperammonaemia, increased urea synthesis	Mitry <i>et al.</i> (14)
Infantile Refsum’s disease	1	Partial correction of metabolic abnormality	Sokal <i>et al.</i> (32)
Glycogen storage disease type Ia	1	No hypoglycaemia on normal diet	Muraca <i>et al.</i> (6)
Factor VII deficiency	2	80% reduction in recombinant factor VII requirement	Dhawan <i>et al.</i> (33)
PFIC2	2	No clear benefit—fibrosis already present	Dhawan <i>et al.</i> (unpublished)

SOURCE OF HEPATOCYTES:

ROUTE/ACCESS: ^{8,9,10,11,12}

Through portal vein: Gold std.

Through hepatic vein:

intrasplenic / intraperitoneal / renal capsule

NEONATES: umbilical vein

Old: surgery/IR.

middle colic vein via the inferior mesenteric vein.

Indication OF PEDIATRIC HEPTOCYTE TRANSPLANT:

- Metabolic
- ALF
- ESLD
- ACLF

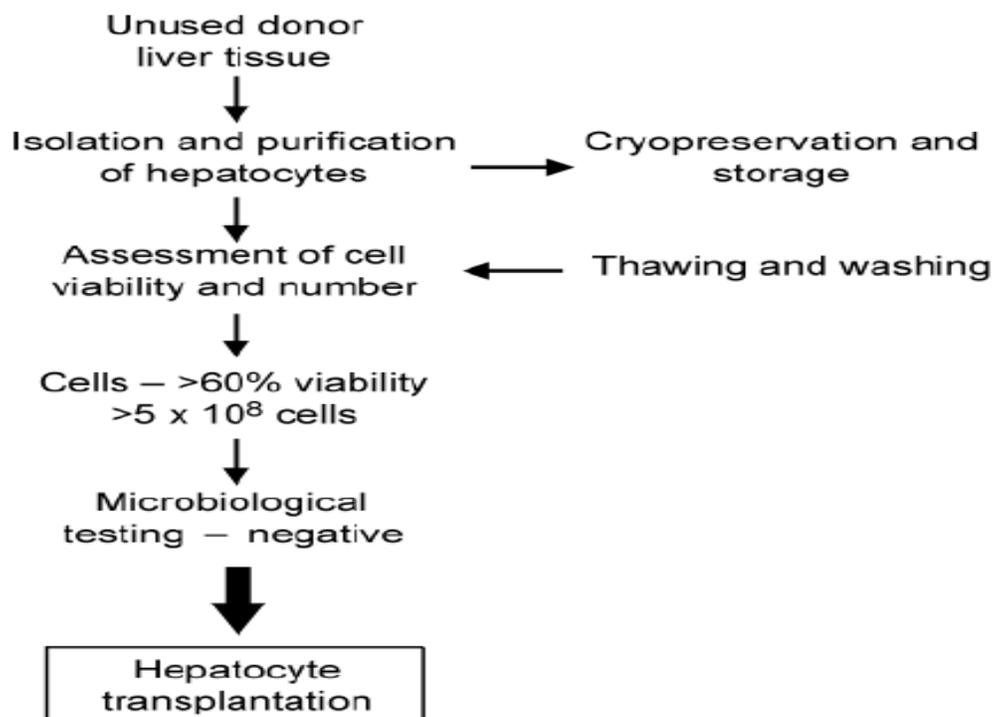
ENGRAFTMENT STRATERGIES

Temporary embolization of the portal vein:ANIMAL MODELS

Liver irradiation (25Gy): ANIMAL MODELS

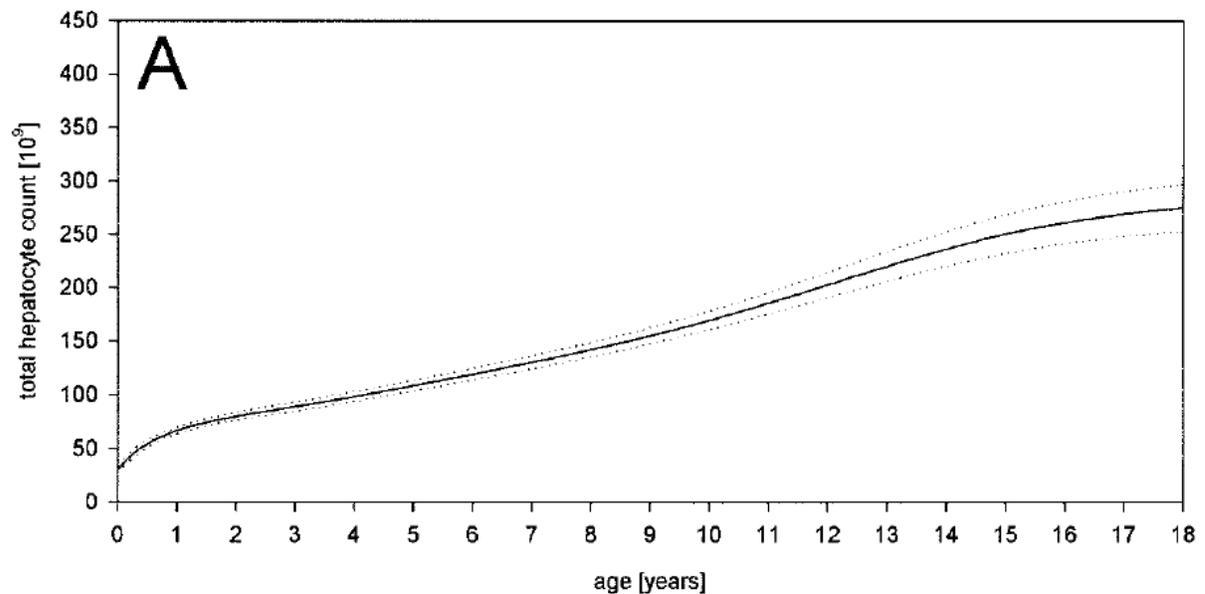
Gastroenterology 2005; 129: 1643–53.

Cell Transplantation, Vol. 20, pp. 303–311, 2011



FACTOR DETERMINING HEPATOCYTE DOSE:¹³

- reduction of the portal vein flow: PVT
- increase in portal venous pressure : PVT
- pulmonary embolism are dose dependent.
- proliferation of the engrafted cells.
- upregulation of specific enzyme activities.
- quality of donar cells.
- Catheter used.



30–100 million cells per kg weight / *N Engl J Med* 1998; 338: 1422–6.

Hepatocytes viability > 60% *J R Soc Med* 2005; 98: 341–5.

BASICS OF DOSE:^{14,15,16}

- Different presentation : different requirement.
- 100 million cells per kg body weight :can be given
- avg adult liver : $2.8 * 10^{11}$ hepatocytes.
- **<1% of liver mass @ 1 infusion.**
- amount of cells infused was 5% of normal liver mass.
- 30% of the transplanted hepatocytes engraft.
- 5% hepatocytes -→ 1.5% of permanently engrafting.
- Children : $0.2 * 10^9$ hepatocytes/kg
- Crigler-Najjar syndrome type I: 5% of enzyme activity , $0.2 * 10^9$ cells/kg,10 yr, girl.
- urea cycle disorders: 8% of enzyme activity

CONCLUSIONS:

- $0.2 * 10^9$ cells/kg. is required.
- six individual applications.
- mean vitality of 75%.
- mean cell concentration of $0.8 * 10^6$ cells/ml.
- application time <60 min.
- M(volume) of 5.5 ml/kg for the individual app.
- rates of 1 ml/min for <10 kgs.
- 2 ml/kg for 10-20 kg .
- hepatocyte Heparin suspension: 2-5 u/ml
- engraftment Time transplanted hepatocytes: 16-20 hrs.
- Application time between 2 infusion: min: 6 hrs

- LDH normalizes within 12 h and AST after 24 h., ALT ABN.....SLOWLY COME DOWN.
- Post transplant immuno-supp is required.

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