

Living Donor Liver Transplantation Across The ABO Blood Type Barrier

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		Recipient			
		O	A	B	AB
Donor	O	Compatible	Incompatible	Incompatible	Incompatible
	A	Incompatible	Compatible	Incompatible	Incompatible
	B	Incompatible	Incompatible	Compatible	Incompatible
	AB	Incompatible	Incompatible	Incompatible	Compatible

Liver transplantation across ABO blood groups

Robert D. Gordon, M.D., Shunzaburo Iwatsuki, M.D., Carlos O. Esquivel, M.D., Ph.D., Andreas Tzakis, M.D., Satoru Todo, M.D., and Thomas E. Starzl, M.D., Ph.D.,
Pittsburgh, Pa.

Six hundred seventy-one first, second, and third orthotopic liver allografts in 520 patients were reviewed to determine the effect of donor-recipient mismatches or incompatibilities for the ABO blood groups on graft survival. A significant advantage for ABO donor-recipient identity was found, especially in adults and for first grafts. However, a surprisingly large number of ABO incompatible grafts were successful. We recommend that nonidentical or incompatible grafts be limited to patients such as small children for whom the supply of available donors is severely limited or for patients in urgent need of transplantation or retransplantation.

From the Department of Surgery, University Health Center of Pittsburgh, University of Pittsburgh, and the Veterans Administration Medical Center, Pittsburgh, Pa.

Surgery 1986;100:342-348

Blood Type Incompatible Liver Transplantation

- Cadaveric Liver Transplantation

CONTRAINDICATION

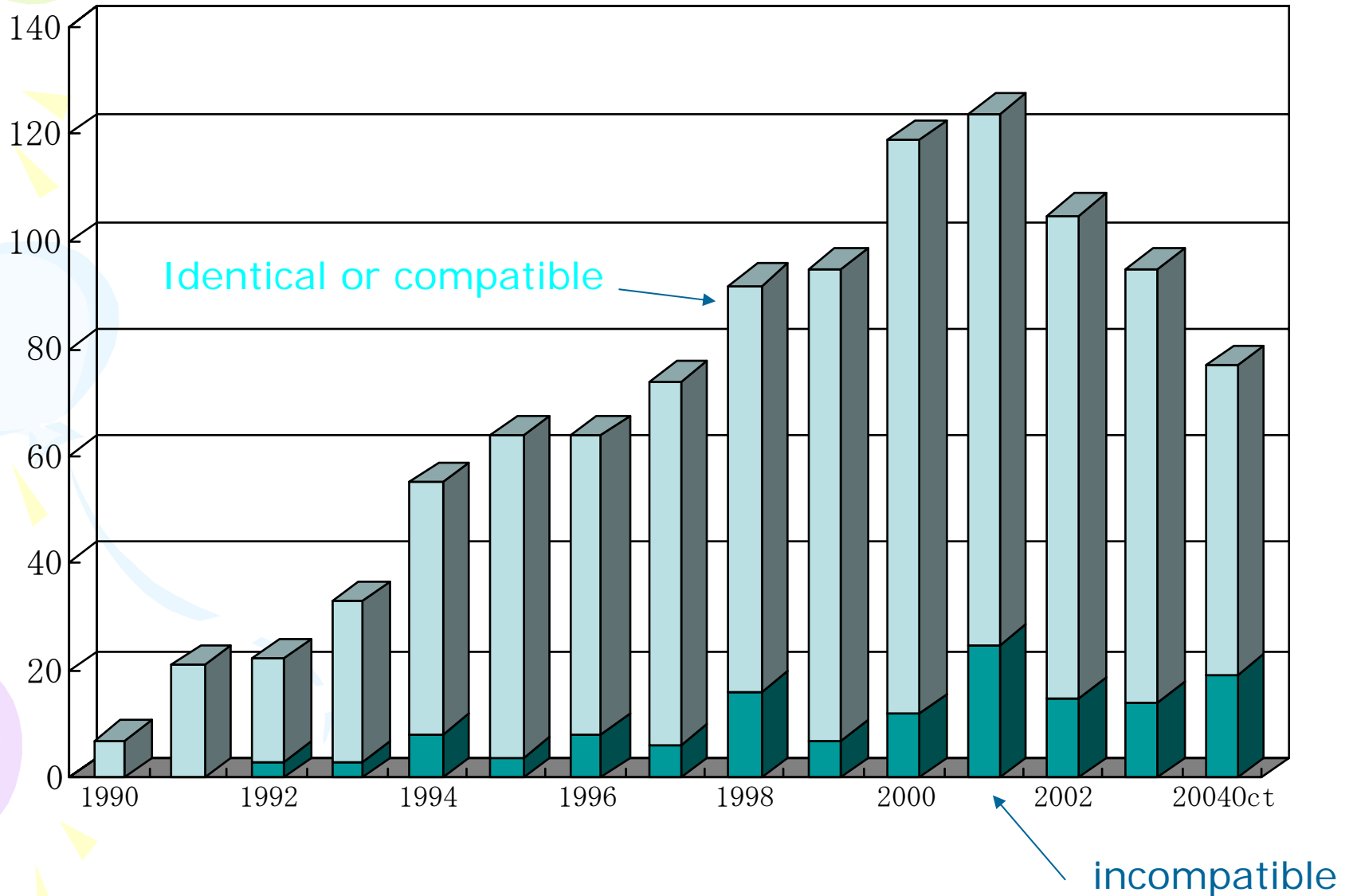
or only in an emergent situation

- Living Donor Liver Transplantation

Donor selection is highly limited.

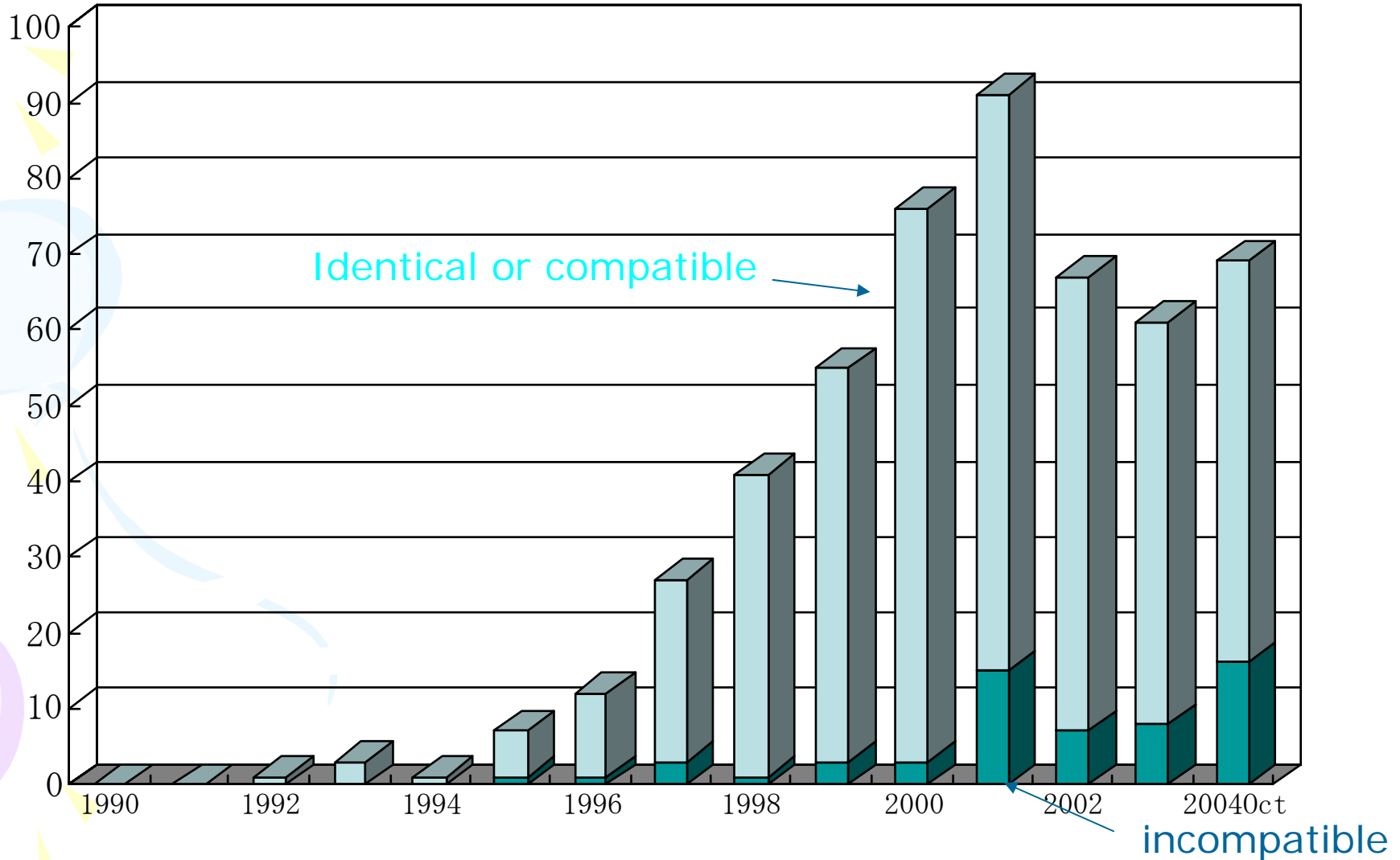
→ When the only available graft is ABO *incompatible*

Annual number of LDLT in Kyoto



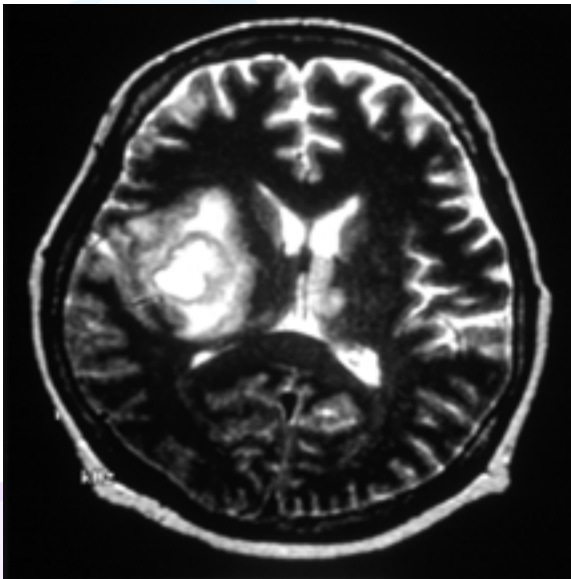
Annual number of LDLT in Kyoto

Older than 15 years old



Cause of Death in ABO-I Liver Transplantation

Infection



Hepatic necrosis



Intrahepatic biliary complication

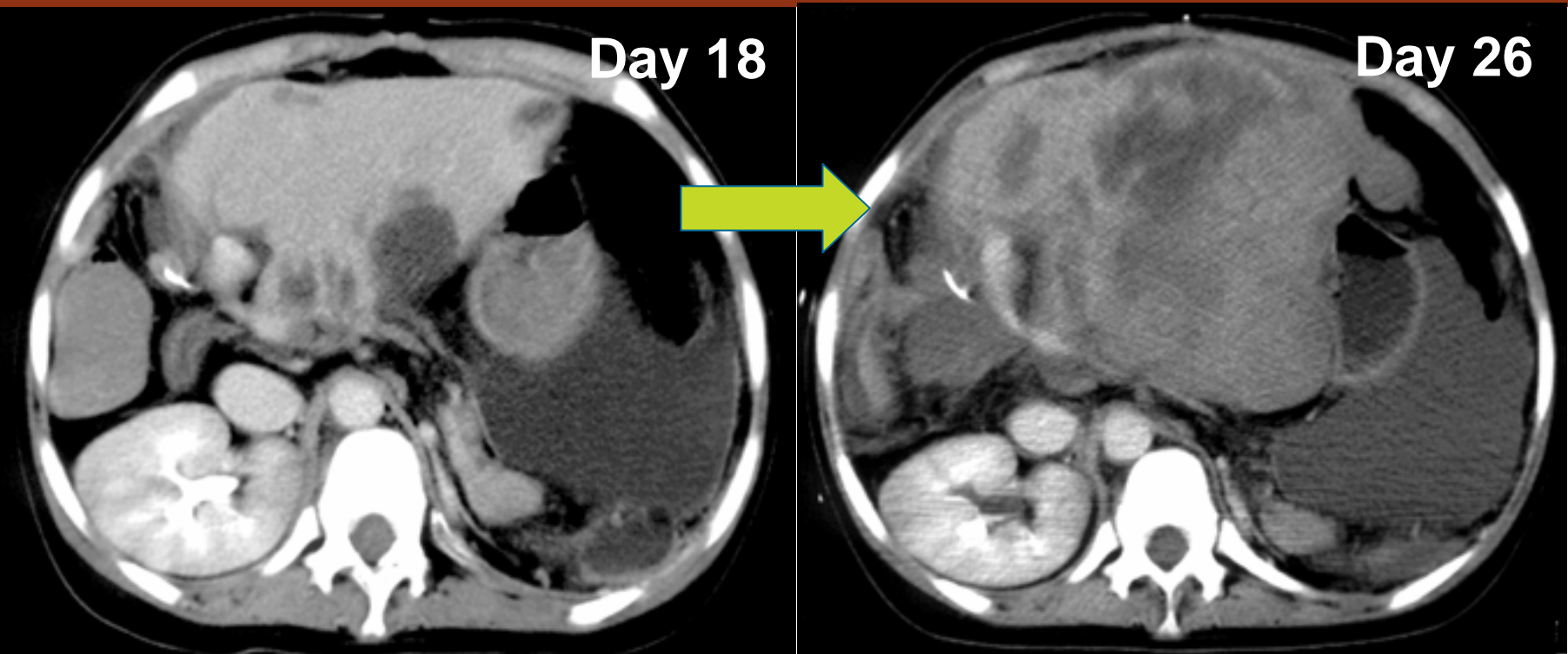


over
immunosuppression

humoral rejection

ABO-related rejection

Hepatic Necrosis



Onset: 1-3 weeks

Fever

Increase in antibody titers

Decrease in platelet counts

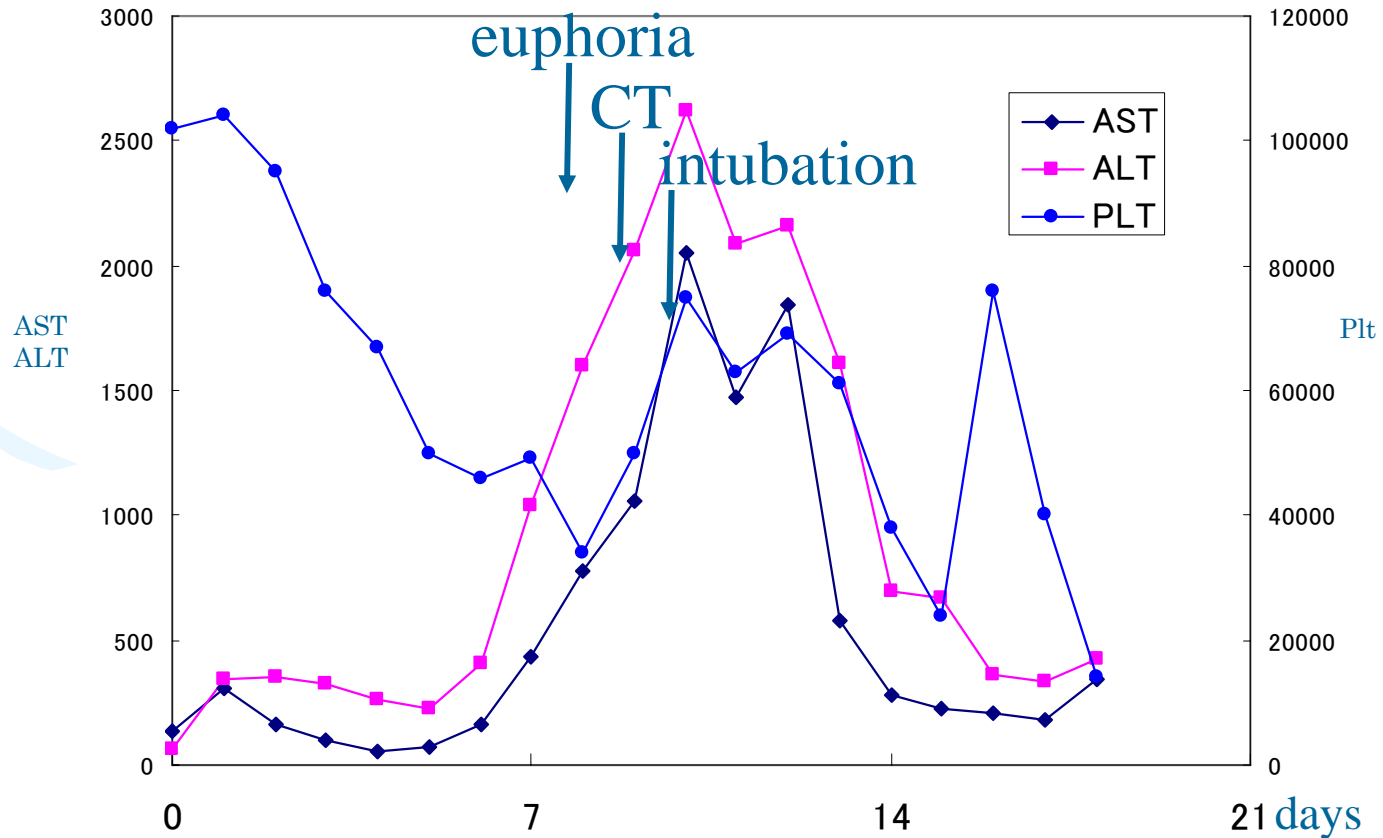
Increase in transaminase levels

Rapid development in the whole graft
Hepatic failure

Hepatic Necrosis

AB(+) \rightarrow O(+),PBC

	PE									
antiA IgG	256	8	16	128	512	512	512	256	256	256
antiA IgM	64	2	4	128	256	512	512	256	256	128
anti B IgG	2048	128	8	128	128	64	64	64	32	16
anti B IgM	32	2	4	64	64	32	32	8	4	2



ABO-related rejection

Intrahepatic Bile Duct Lesion

Clinical picture

Clinical onset:
1-3 months after LTx

Sclerosis or mixture of
stenosis and dilatation,
similar to PSC

Repeated cholangitis
leading to graft failure



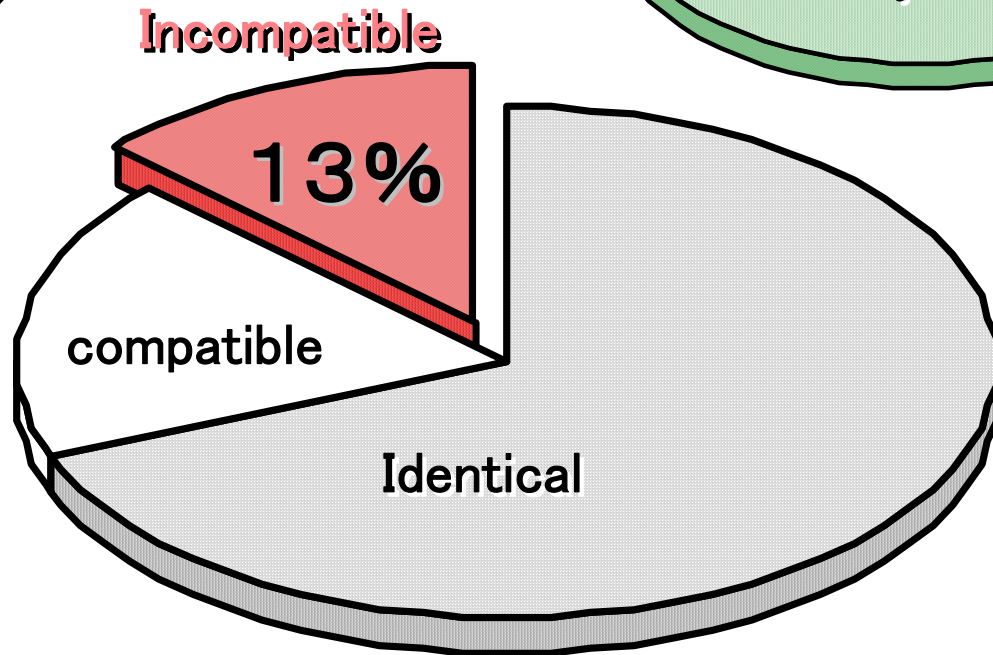
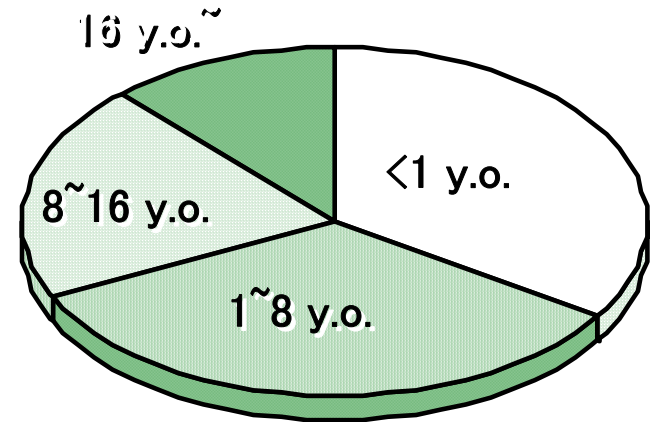
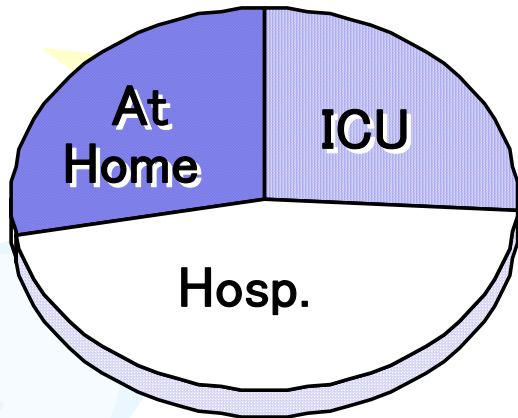
LONG TERM FOLLOW-UP OF ABO-INCOMPATIBLE LIVING-DONOR LIVER TRANSPLANTATION: RELATION BETWEEN OUTCOME AND AGE OF RECIPIENTS

Egawa et al.

Transplantation 2004; 77: 403

- June 1990 - February 2000
- 66 patients (13% in 523 patients)
- 10 months to 55 years old (median 2 years)

Patients



Strategy

Patients and
complication

Base: tacrolimus & steroid
plasma pheresis, blood exchange

Older children

OKT3 (#25 – #56)

IHBC →

splenectomy (#111 –)

hepatic necrosis →

AZA (#175–)

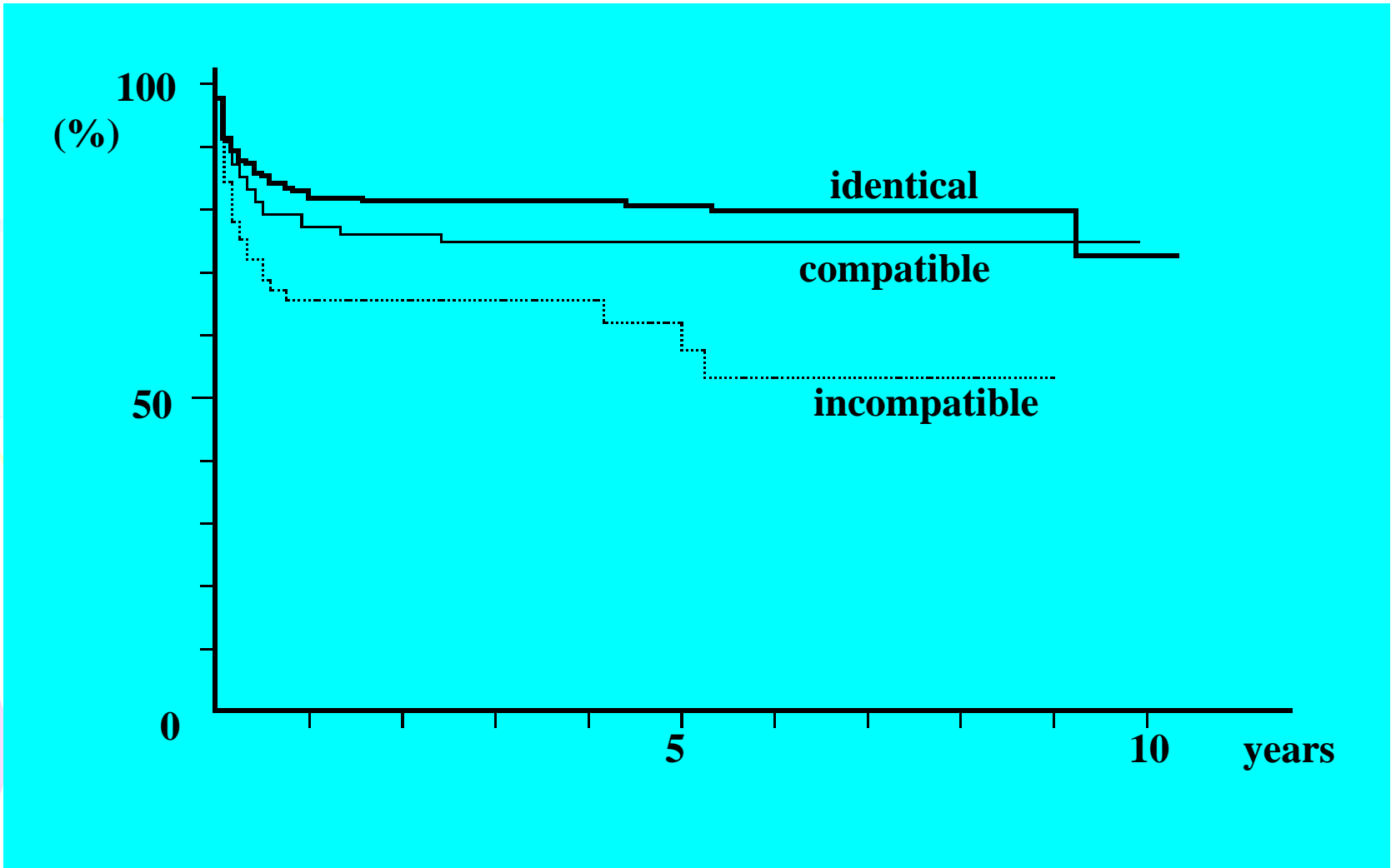
Adult

weekly pulse (#266 –

cyclophosphamide (#306 –)

Until 2000

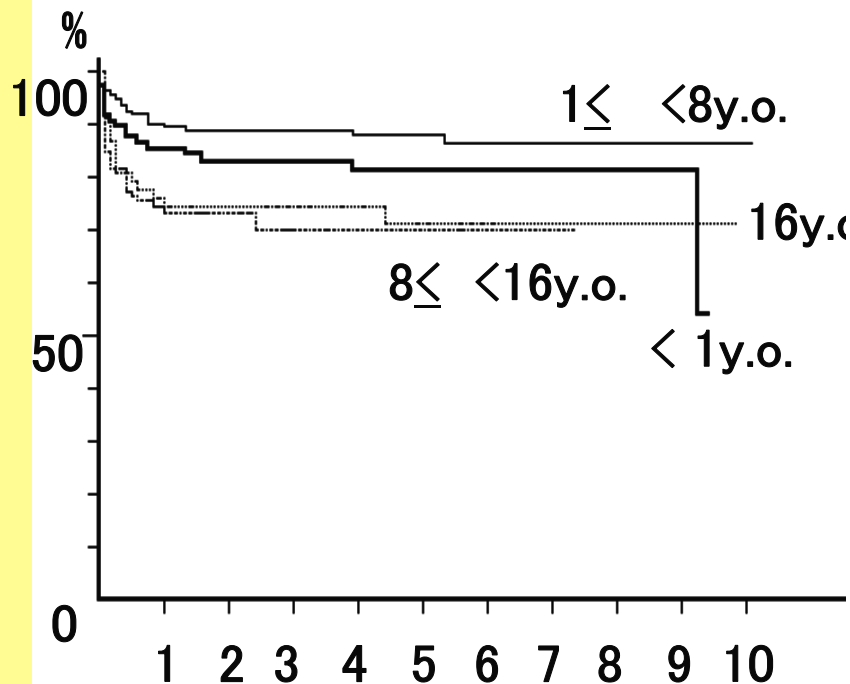
Compatibility and Survival



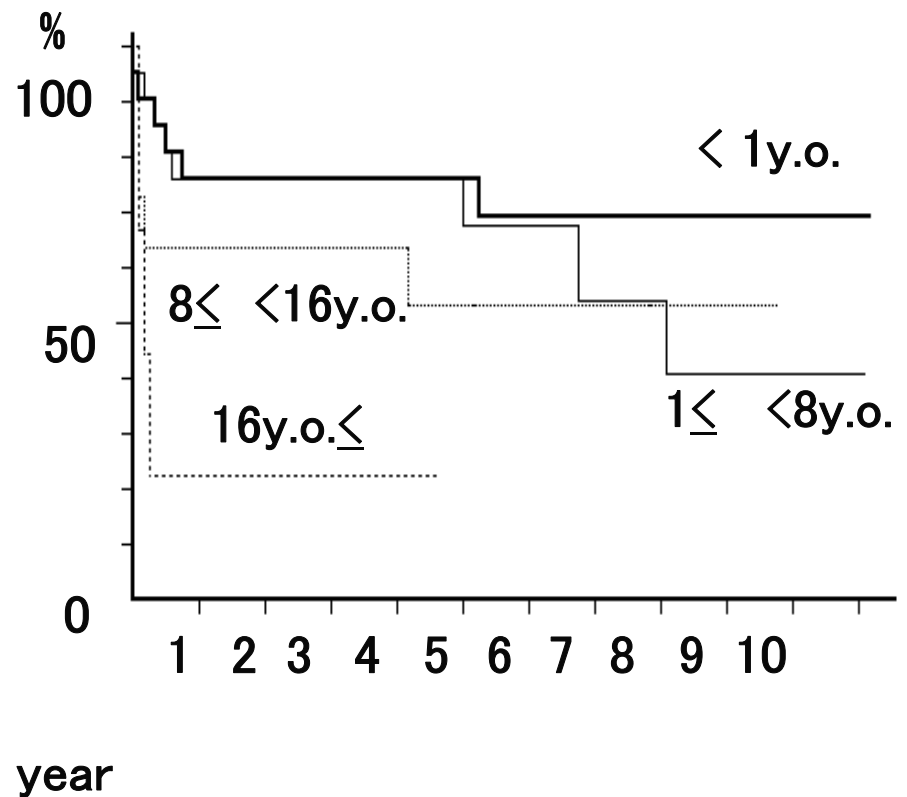
ABO Compatibility and Age —Survival after LDLT

~2000

Identical & Compatible



Incompatible



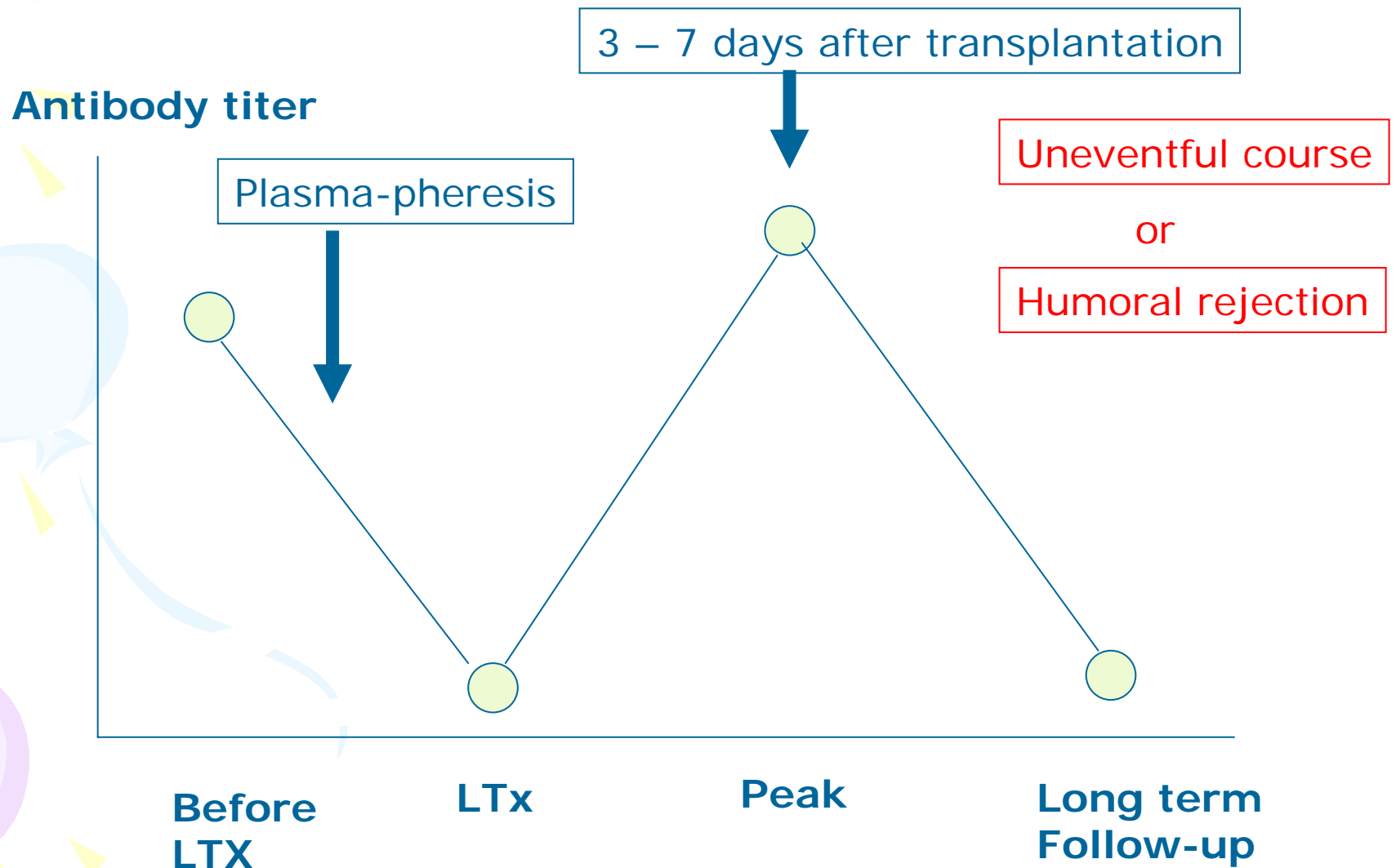
Age and complications

Age	Patients group				
	Necrosis	IHBC	Normal	Other death	Total
<1 y.o.	0	0	15	6	21
1 y.o. ≤ <8 y.o.	0	8	11	6	25
8 y.o. ≤ <16 y.o.	3	2	5	1	11
16y.o. ≤	2	2	1	4	9
Total	5	12	32	17	66

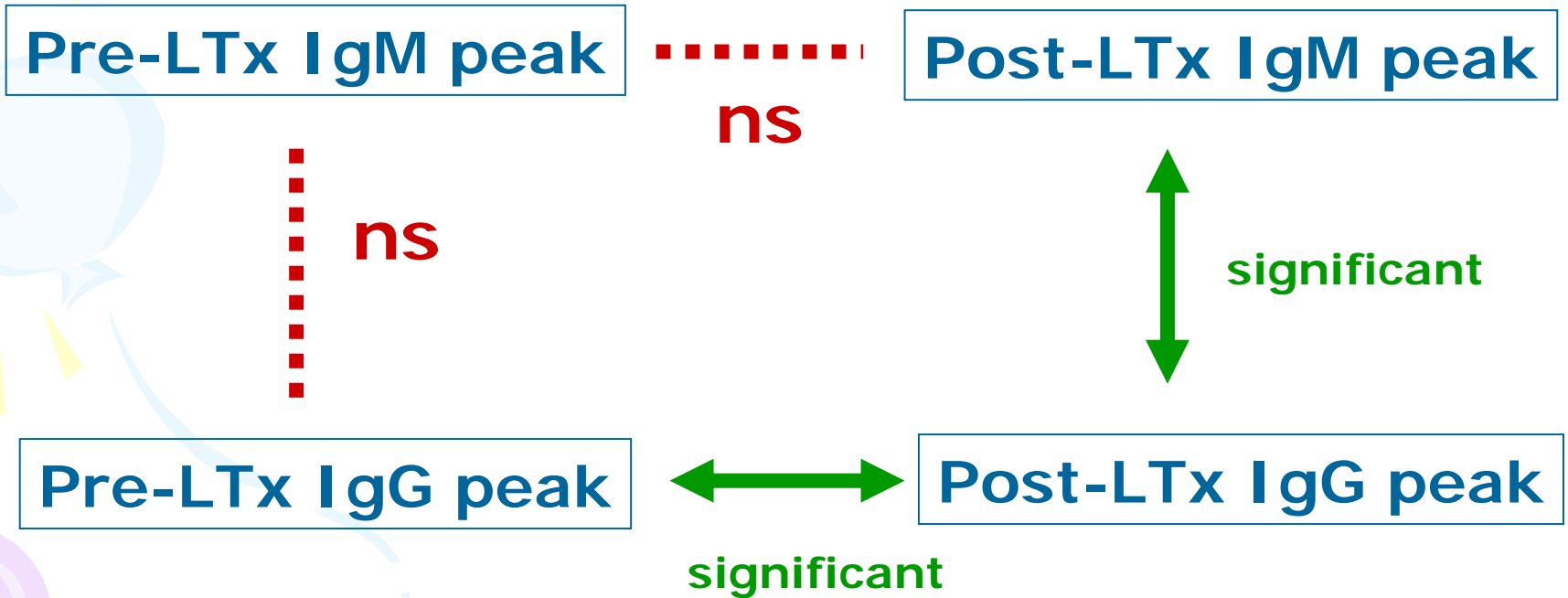
p<0.01: chi-square test

Two patients surviving shorter than 1 week were not included in this analysis.

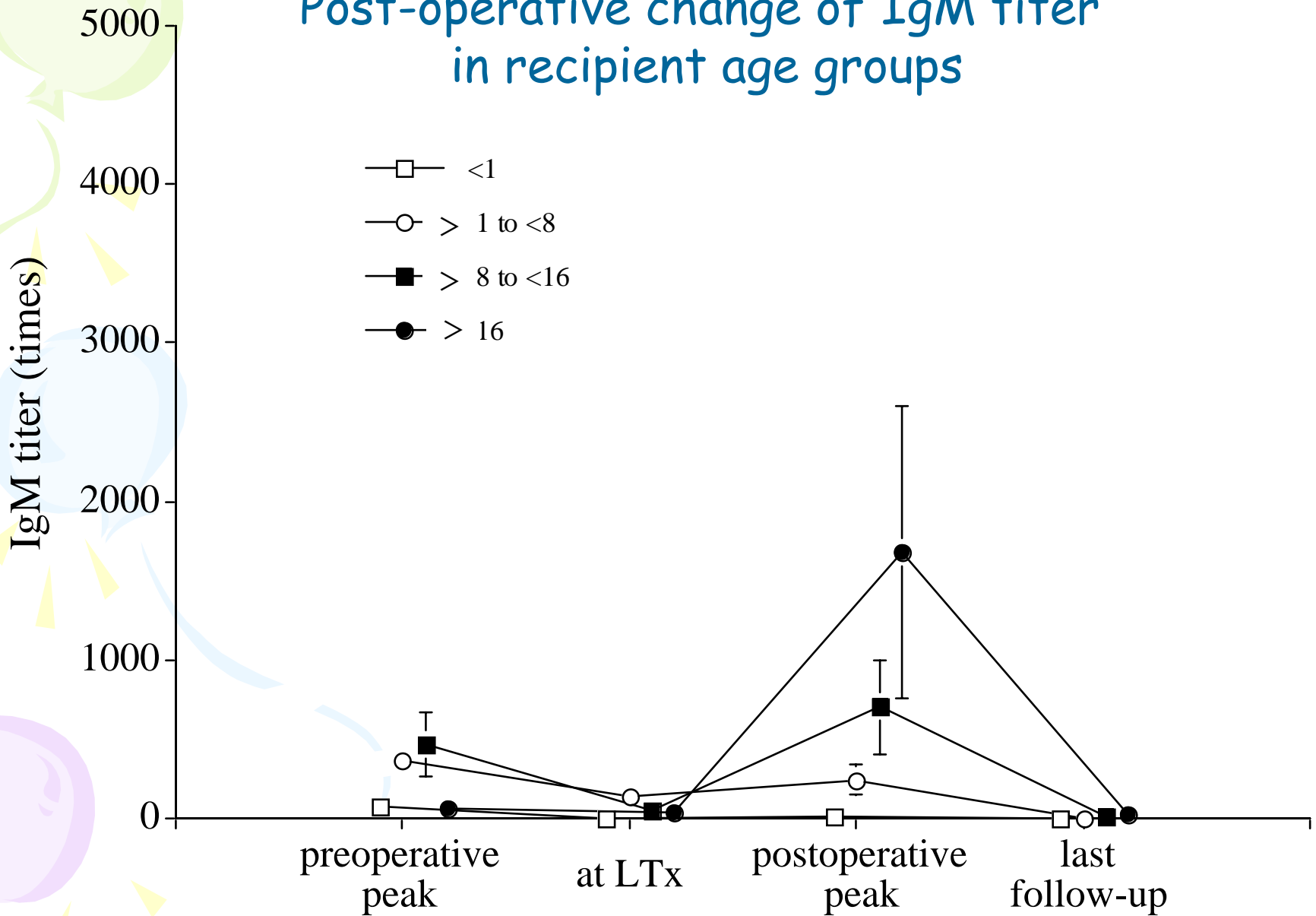
Change of antibody titer



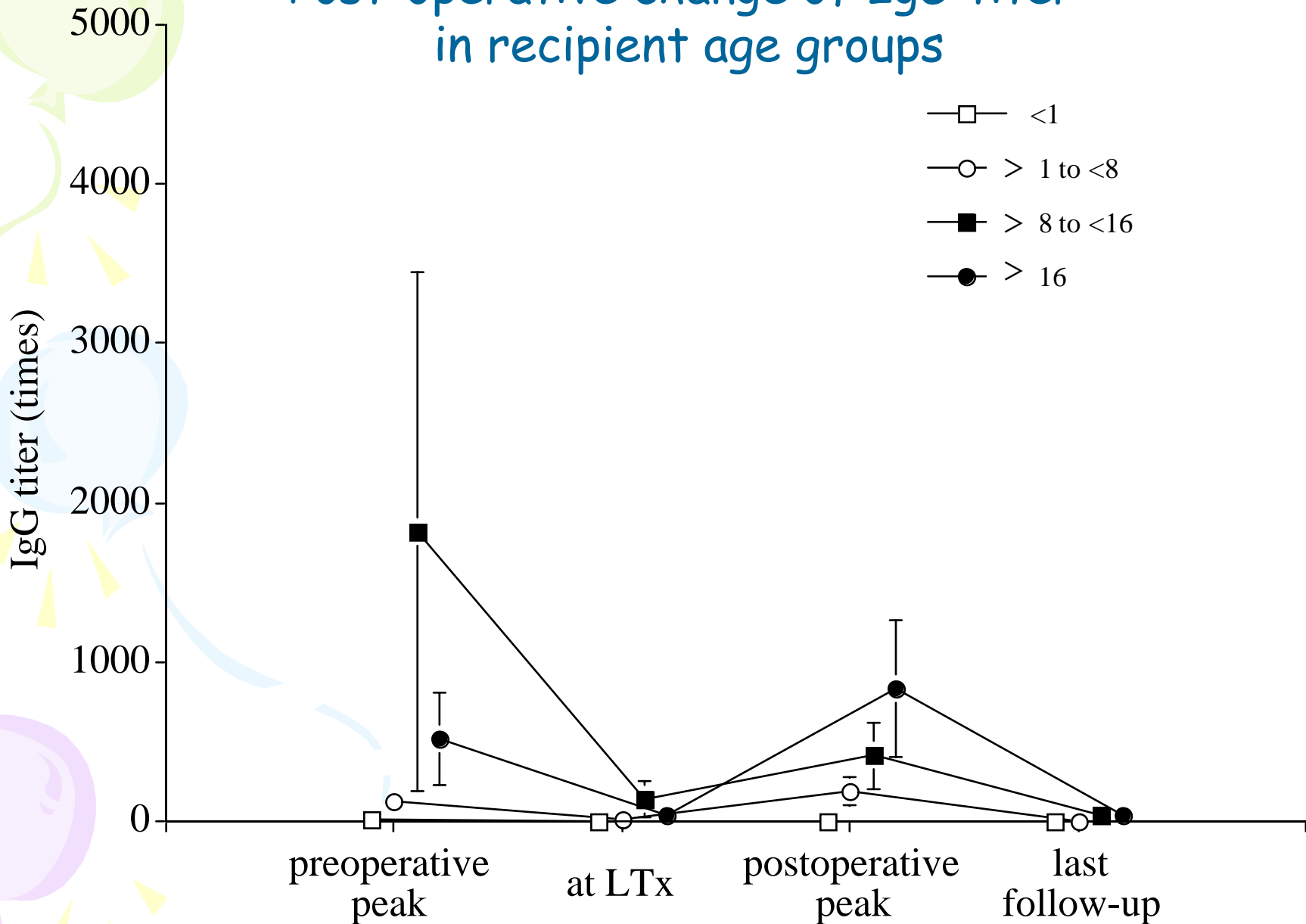
Correlation between pre & post LTx - IgM, IgG peaks



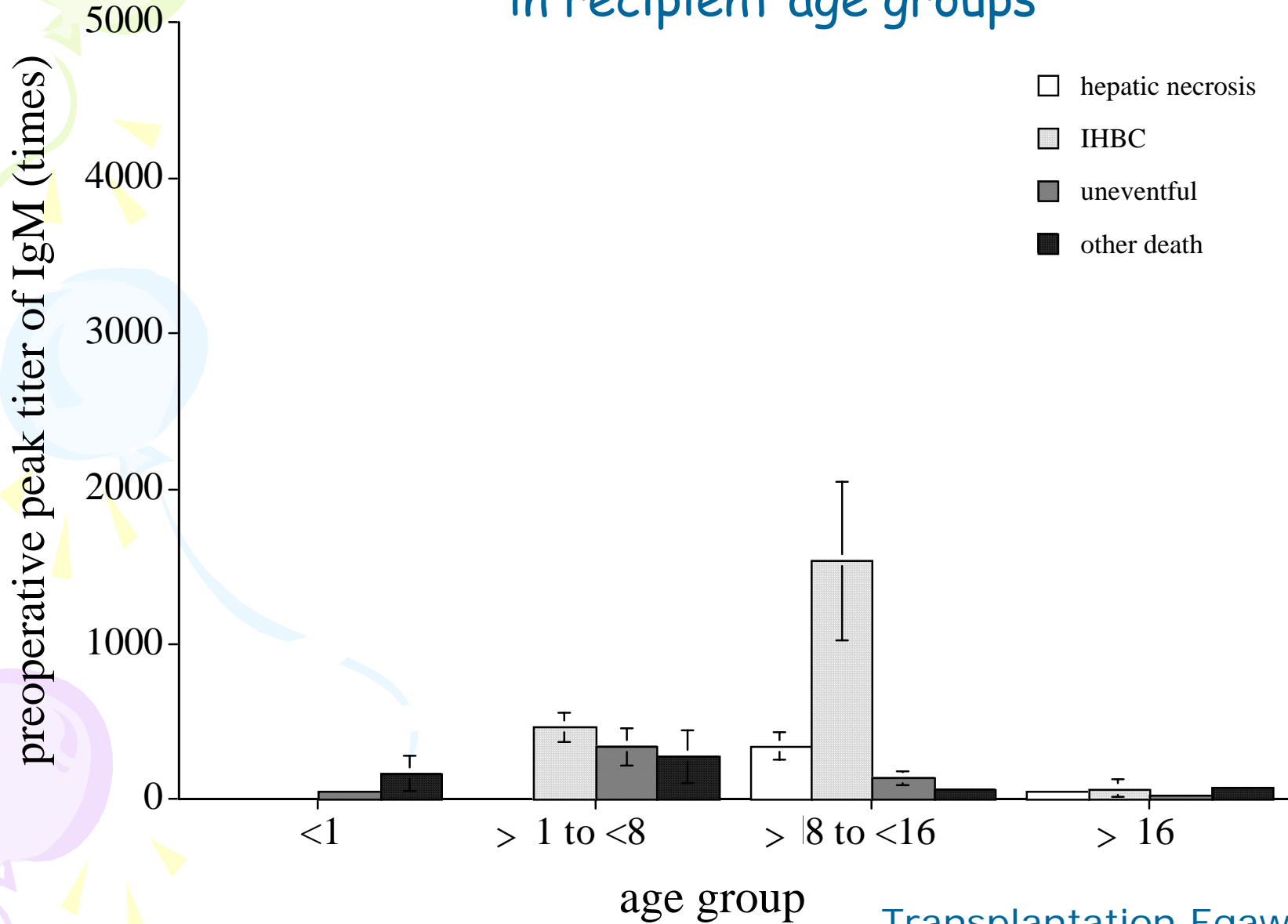
Post-operative change of IgM titer in recipient age groups



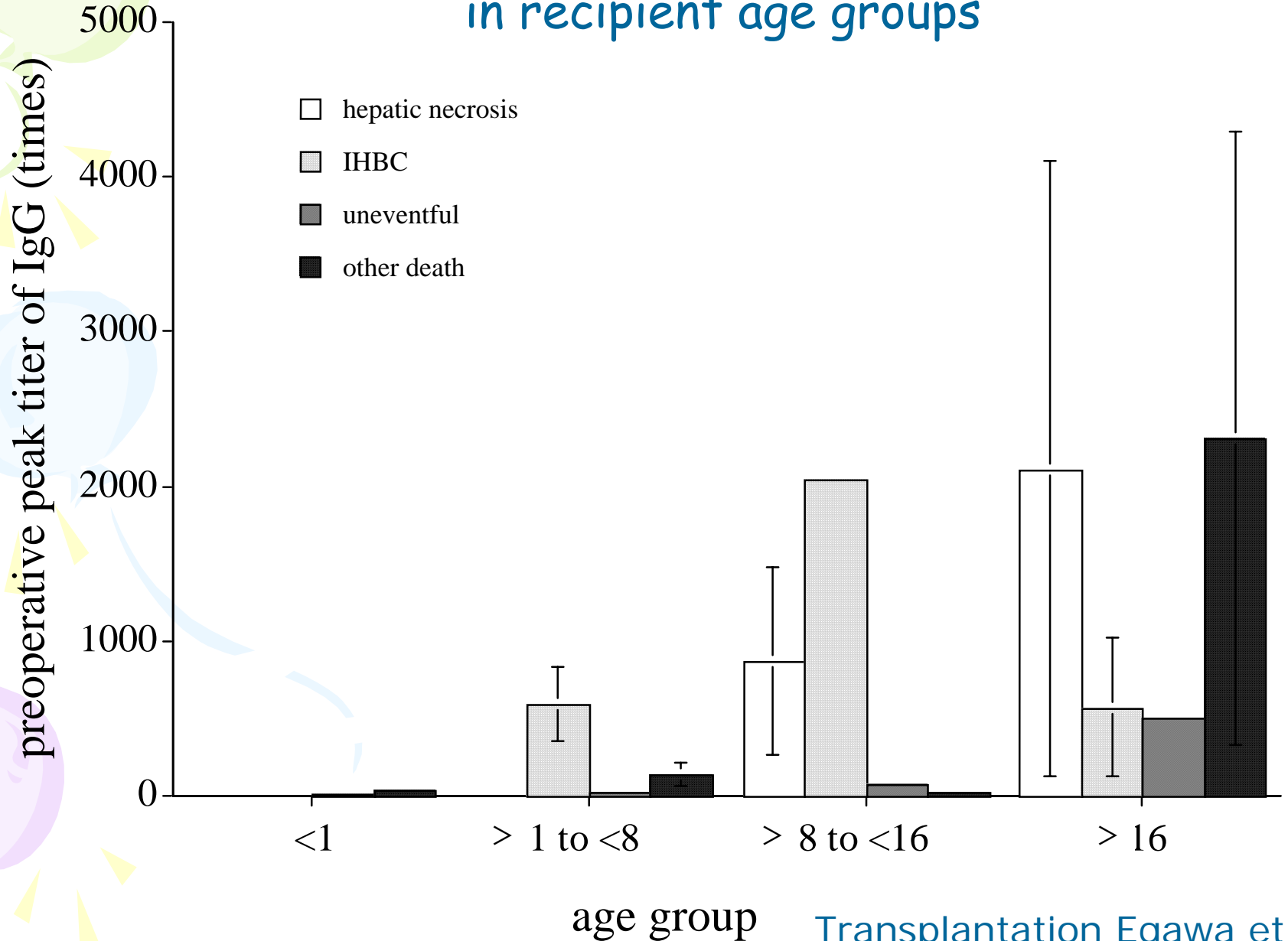
Post-operative change of IgG titer in recipient age groups



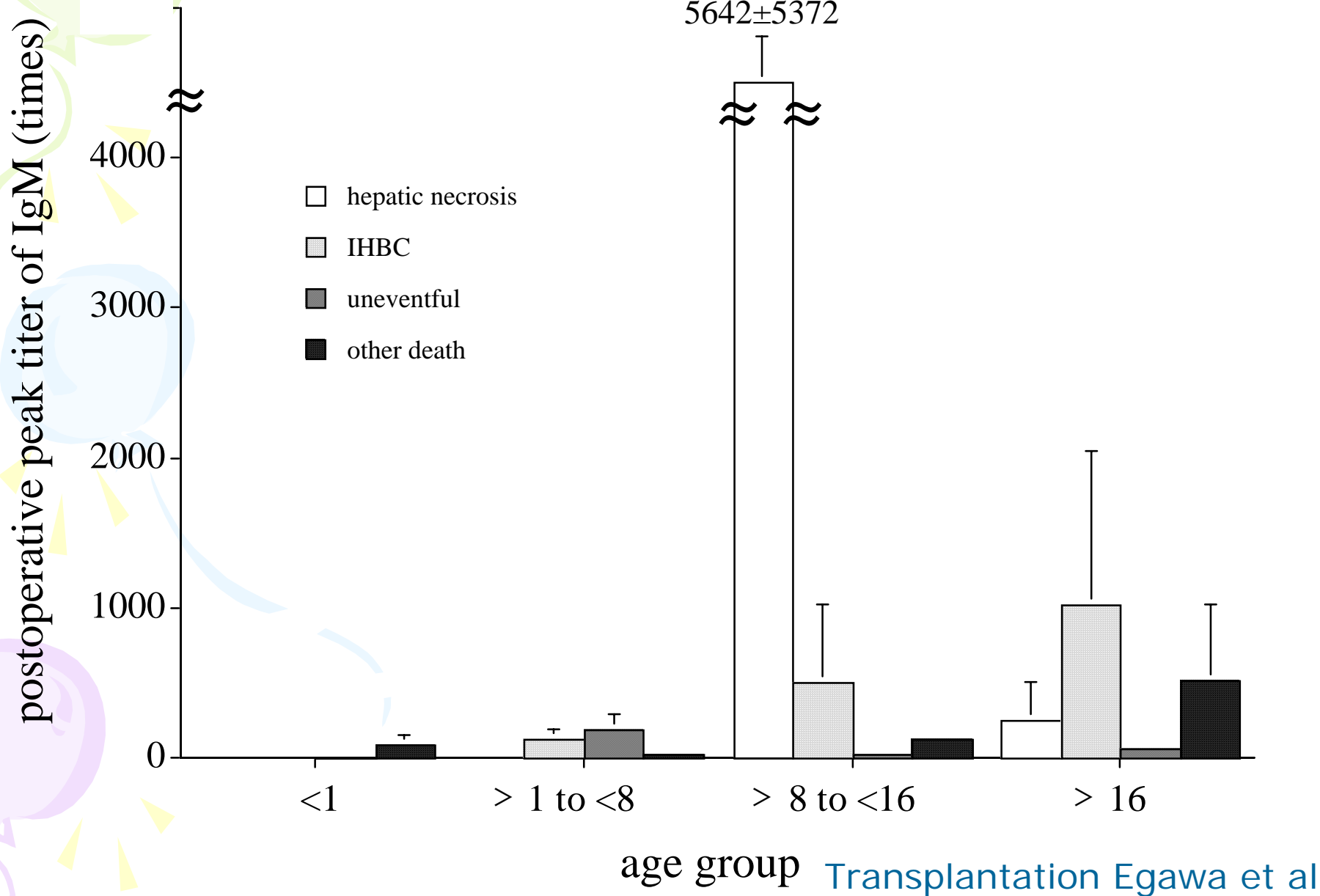
Preoperative peak IgM titer and postoperative course in recipient age groups



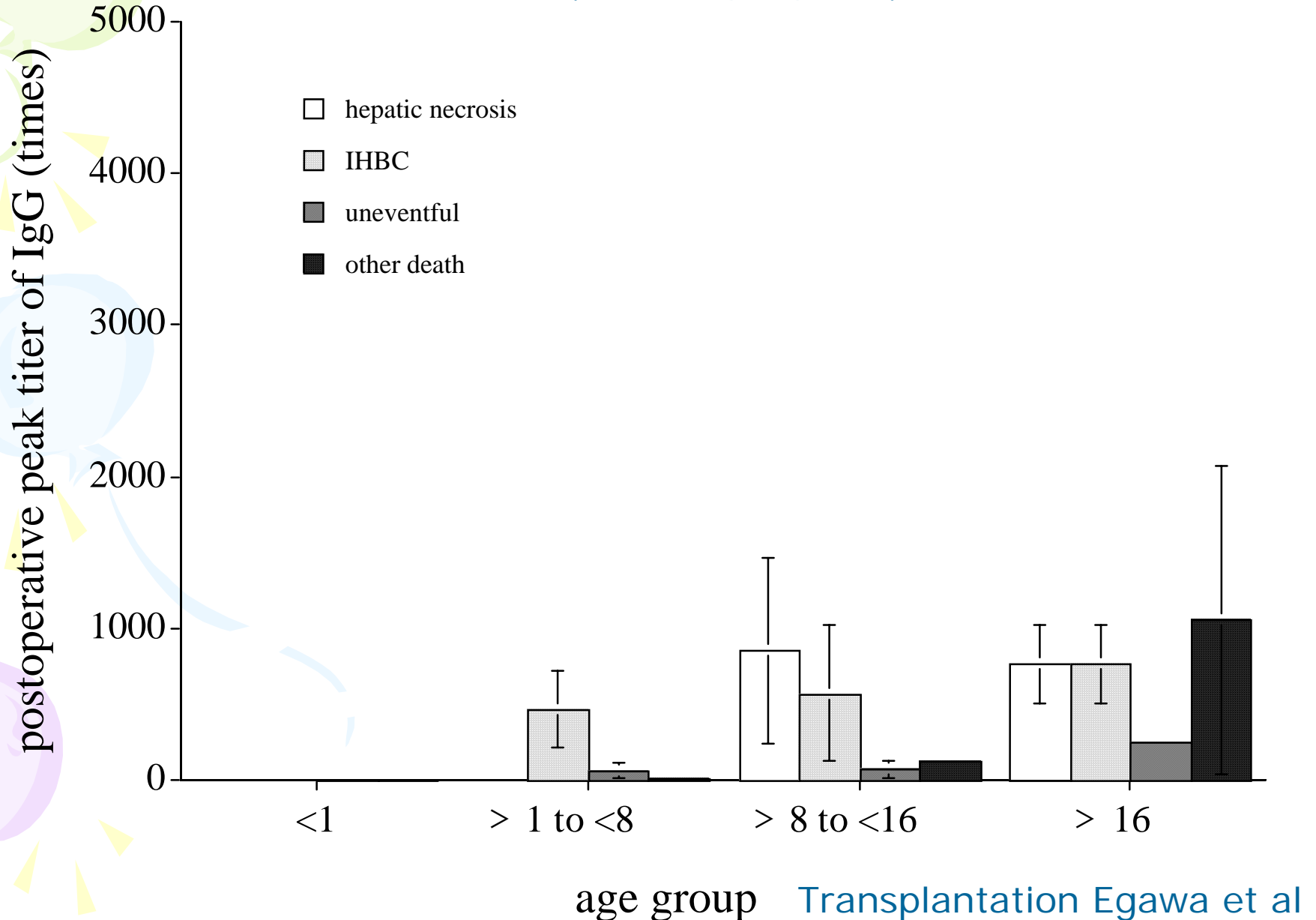
Preoperative peak IgG titer and postoperative course in recipient age groups



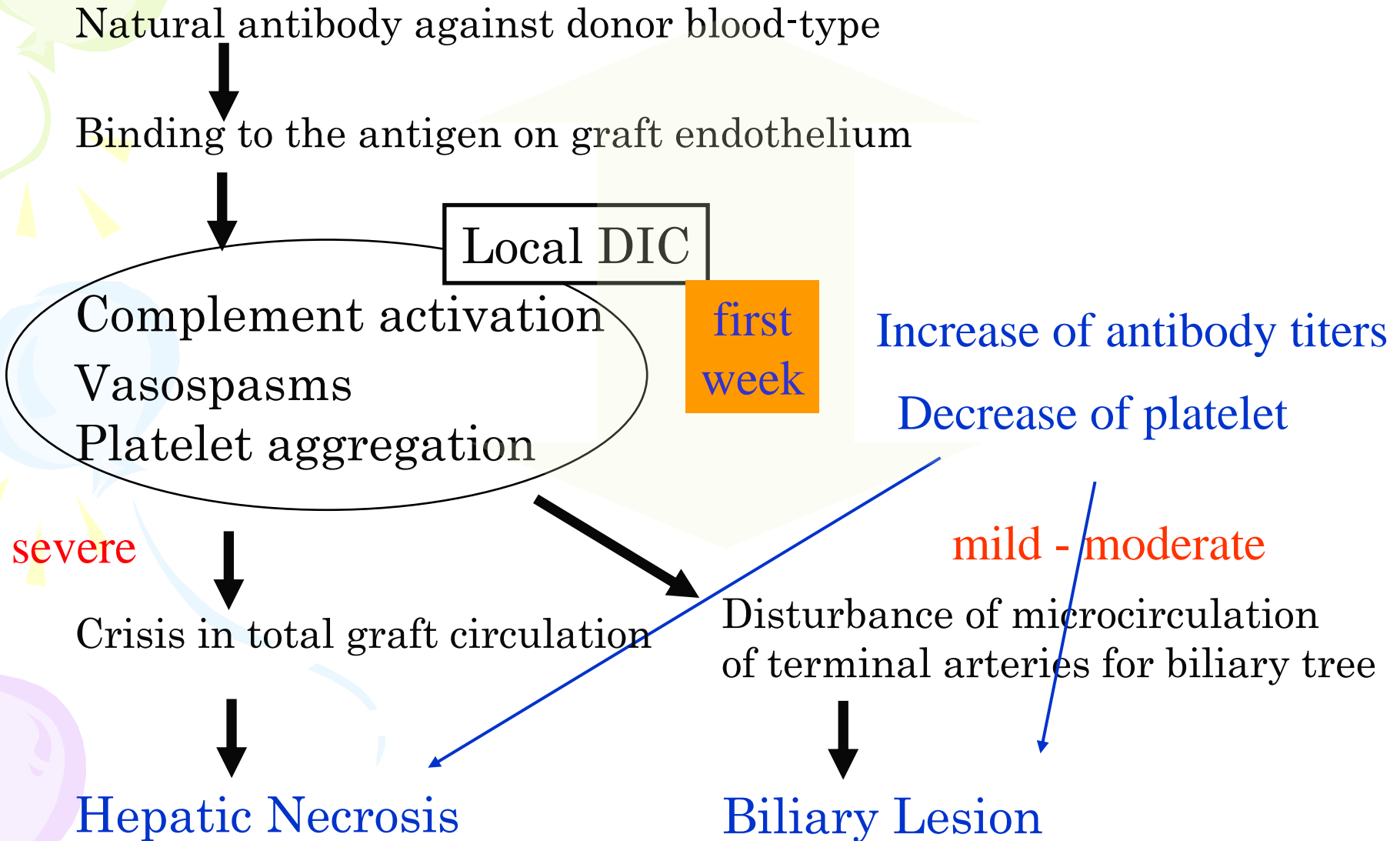
Postoperative peak IgM titer and postoperative course in recipient age groups

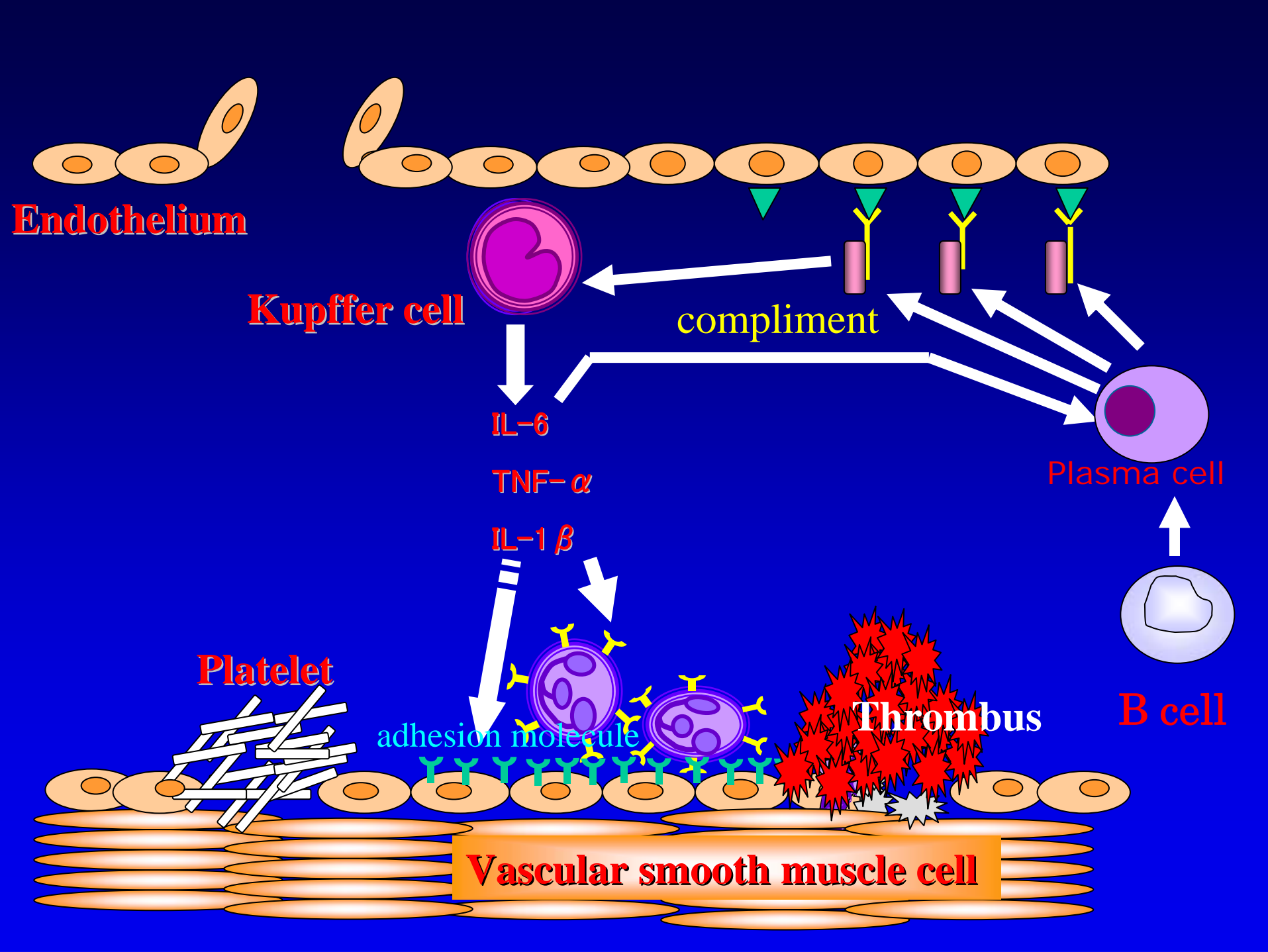


Postoperative peak IgG titer and postoperative course in recipient age groups

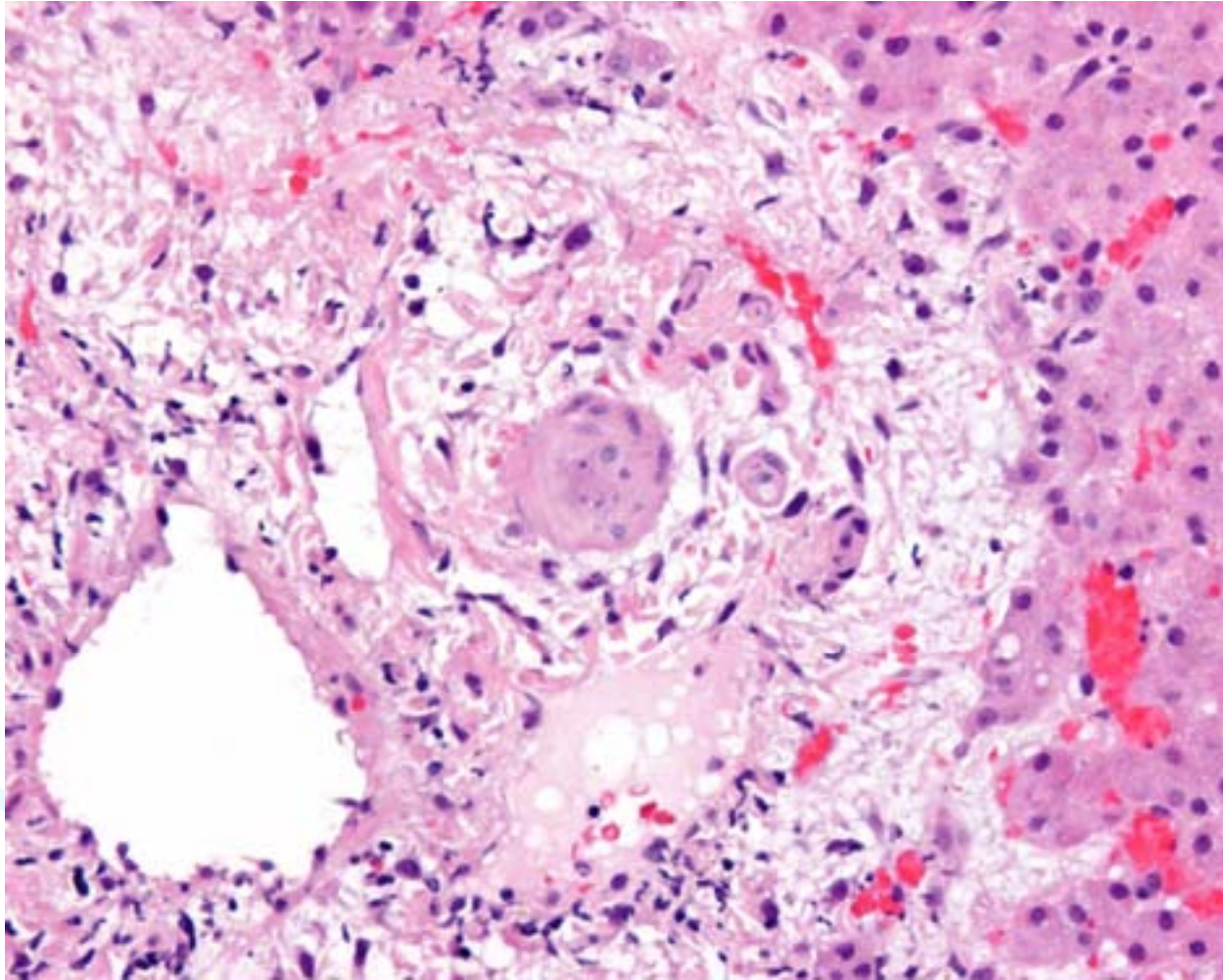


Pathology of ABO-related rejection



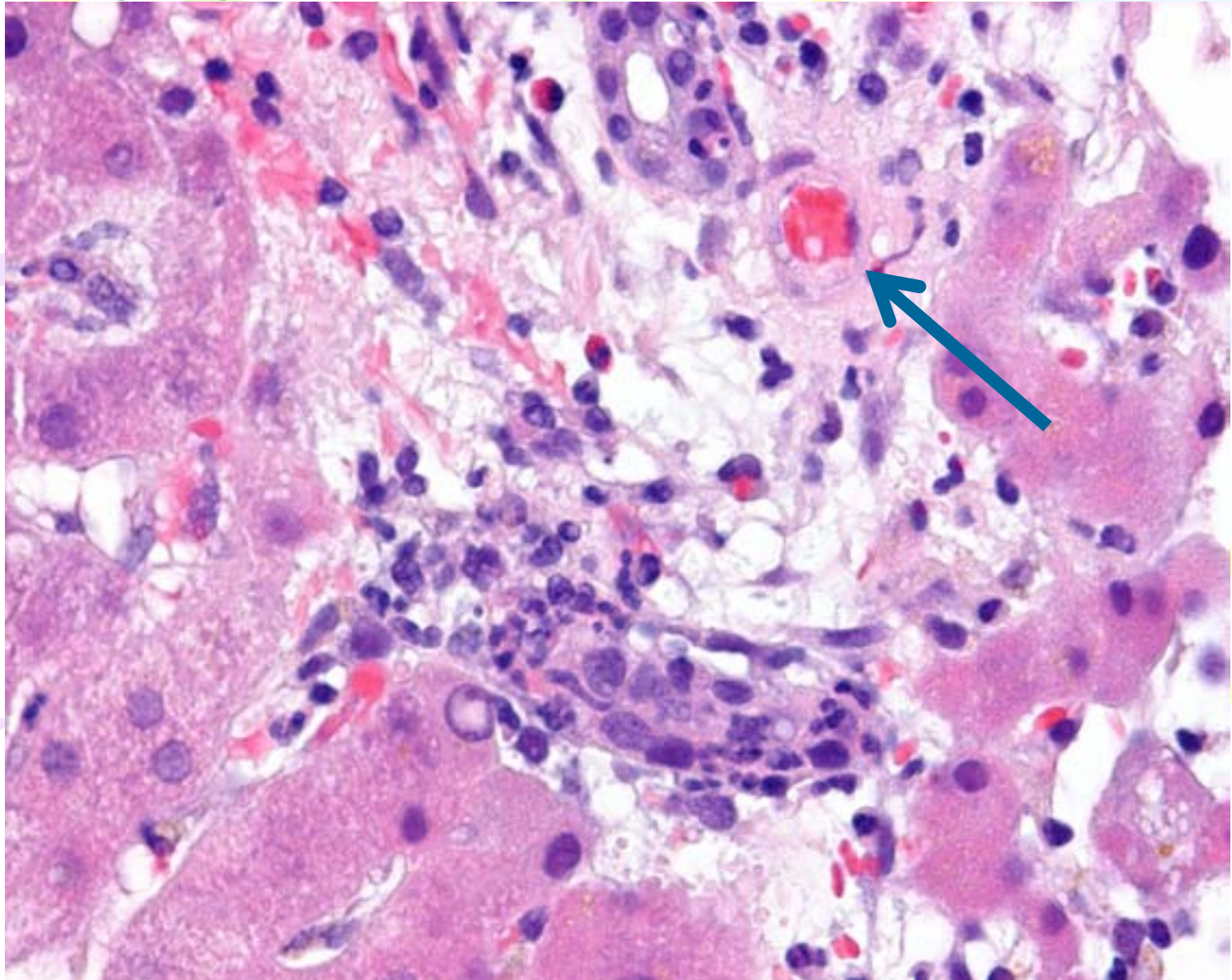


Periportal Edema and Necrosis (PEN)



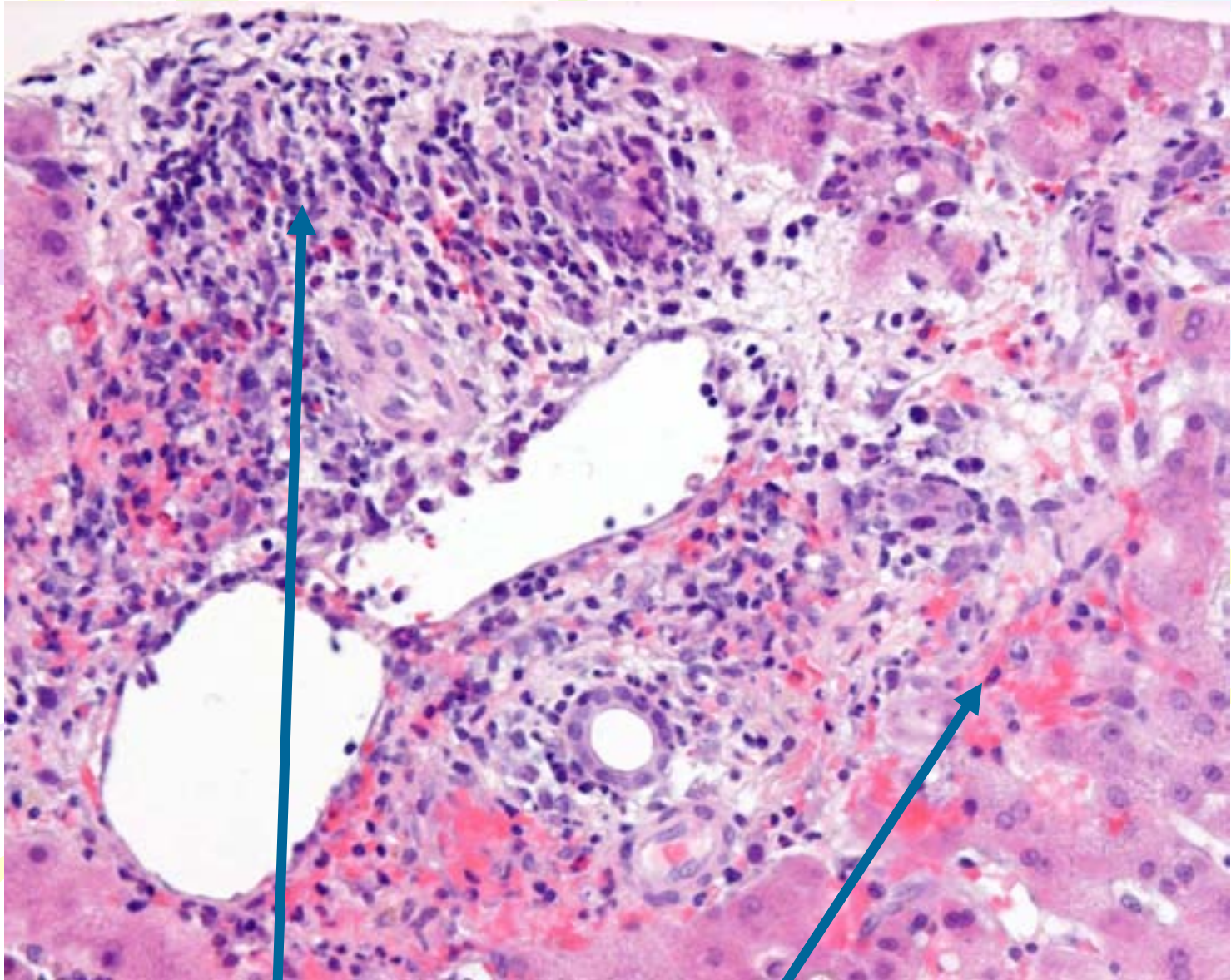
Haga et al
Liver Transplantation 2004;6:16-27

periportal edema and necrosis (PEN)



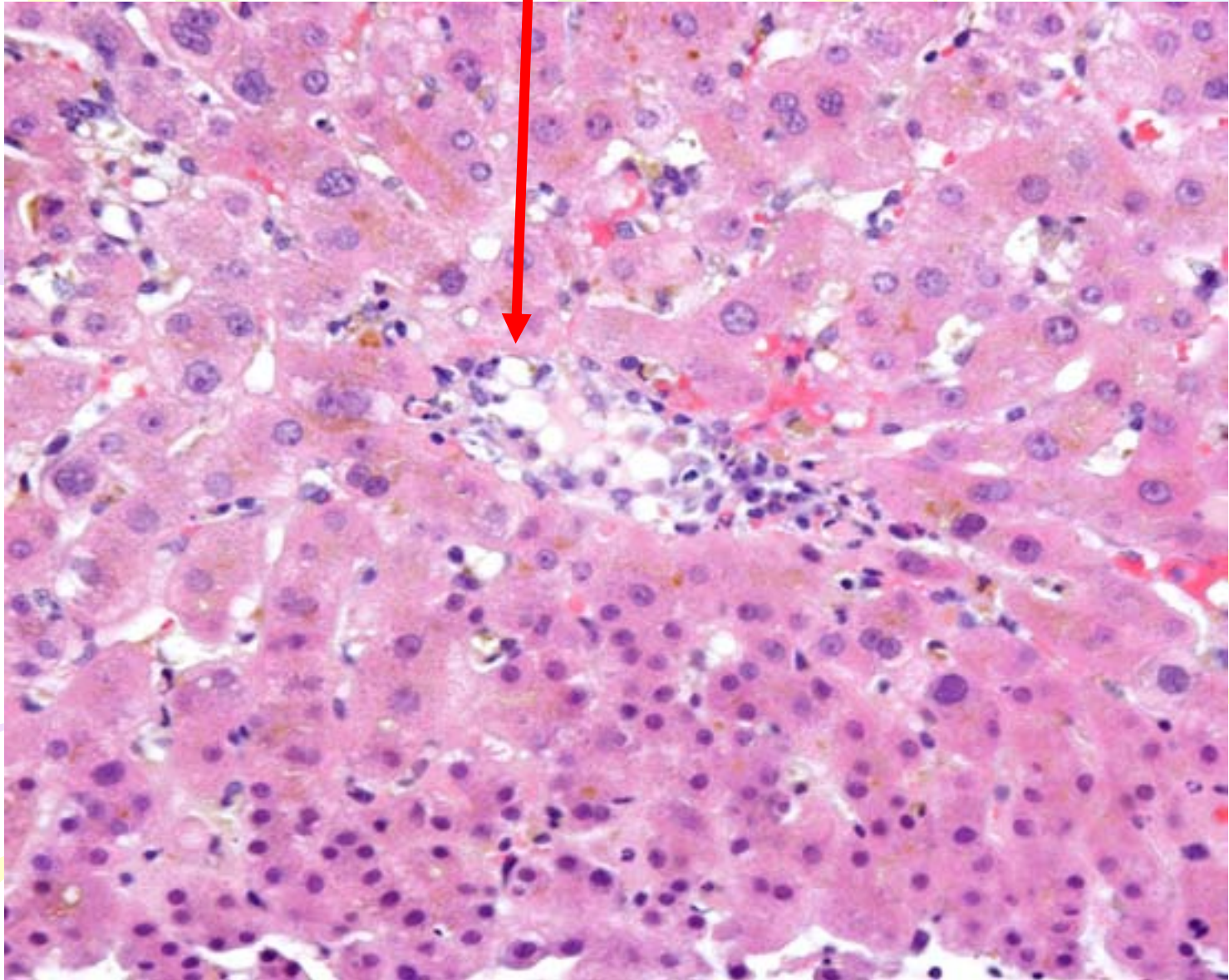
thrombus in the arteriole

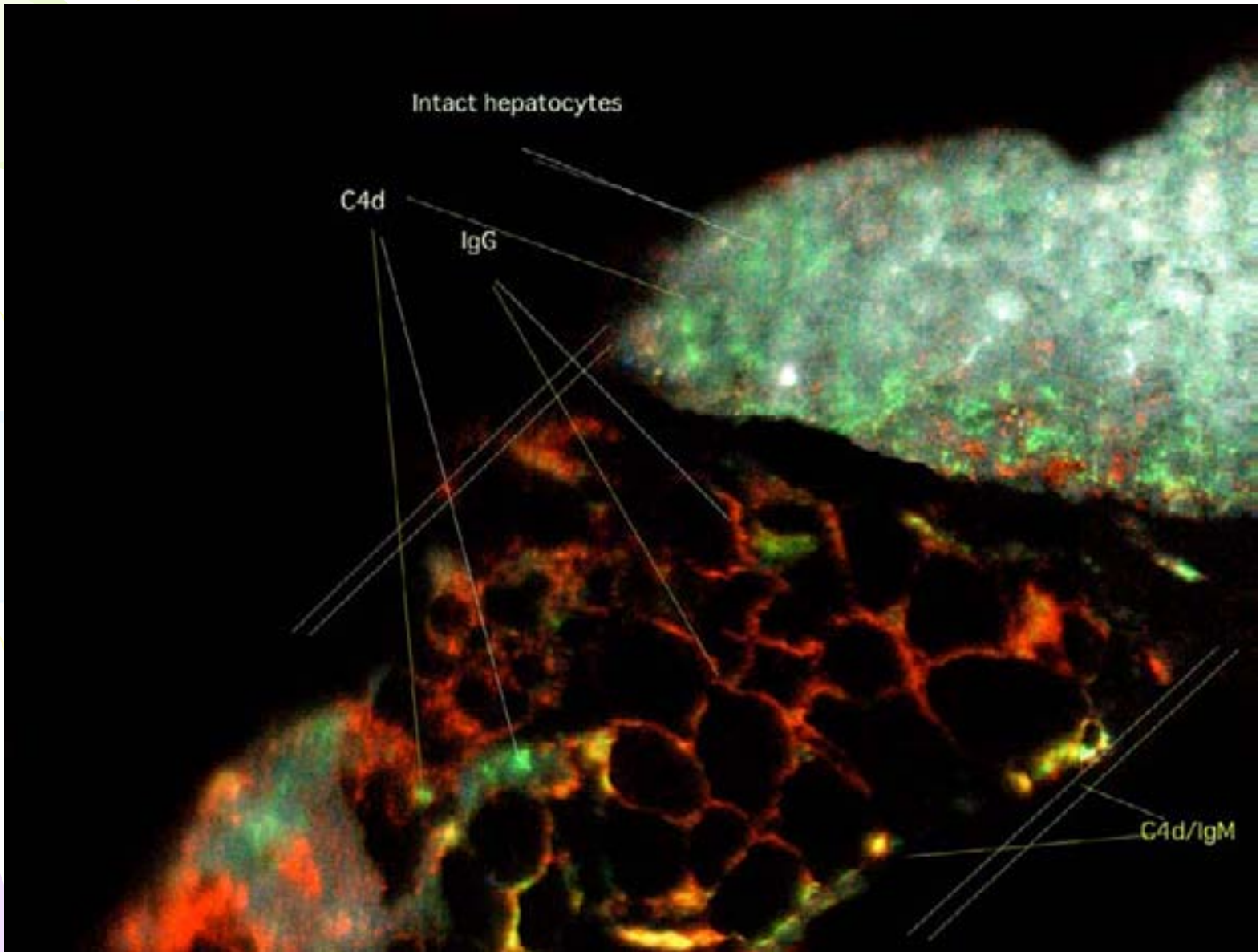
PEN with cellular rejection



lymphocytic infiltration, periportal hemorrhage

centrilobular endothelialitis, without necrosis





C4d – IgG/IgM in a hepatic necrosis case



Tactics

- Decrease antibody titer
- Decrease antigen-antibody-compliment reaction
- Decrease endothelium injury
- Decrease thrombus
- Improve microcirculation

Portal Infusion Therapy

Keio Protocol

INTRAPORTAL INFUSION THERAPY AS A NOVEL APPROACH TO ADULT ABO-INCOMPATIBLE LIVER TRANSPLANTATION¹

MINORU TANABE,^{2,3} MOTOHIDE SHIMAZU,²
GO WAKABAYASHI, KEN HOSHINO, SHIGEYUKI KAWACHI, TOMOHISA KADOMURA, HIROAKI SEKI,
YASUhide MORIKAWA, AND MASAKI KITAJIMA

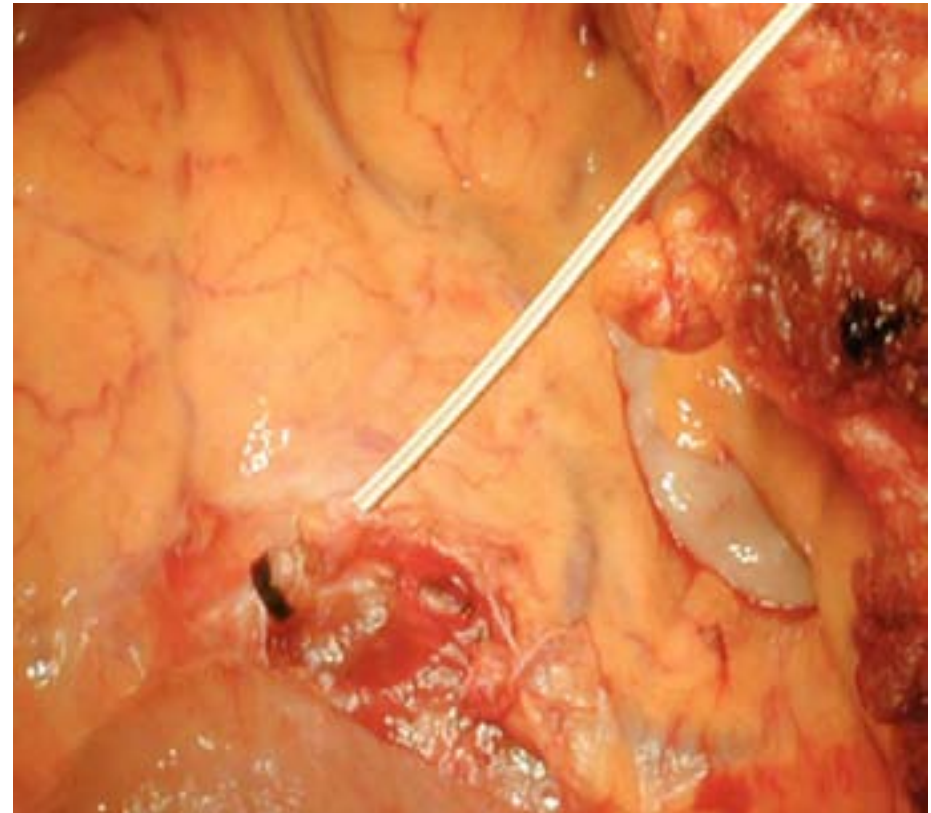
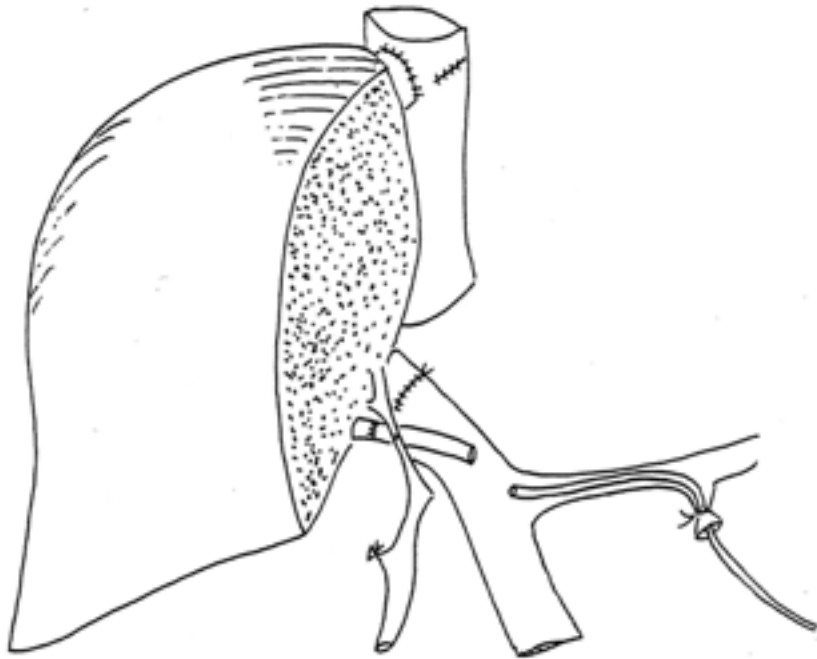
Department of Surgery, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo, 160-8582, Japan

Transplantation, June 27, 2002. Vol.73, No.12

Two successful cases with intraportal
infusion therapy for ABO incompatible liver
transplantation

PGE1, Steroids, and Gabexate Mesilate

Portal Infusion Catheter



Portal Infusion Protocol

Pre	Plasma Exchange (anti A IgM, anti B IgM < 8)		
Ope.	LTx & Splenectomy		
Post	Portal Infusion		
	Methylprednisolone	125mg/day,	~1w
		50mg/day,	~2w
	Prostaglandine E1	0.01 γ ,	~3w
	Gabexate Mesilate	1000mg/day,	~3w
	General Immunosuppression		
	Cyclophosphamide	2mg/kg/day, ~2w(iv), ~4w(oral)	
	Tacrolimus		
	Methylprednisolone		

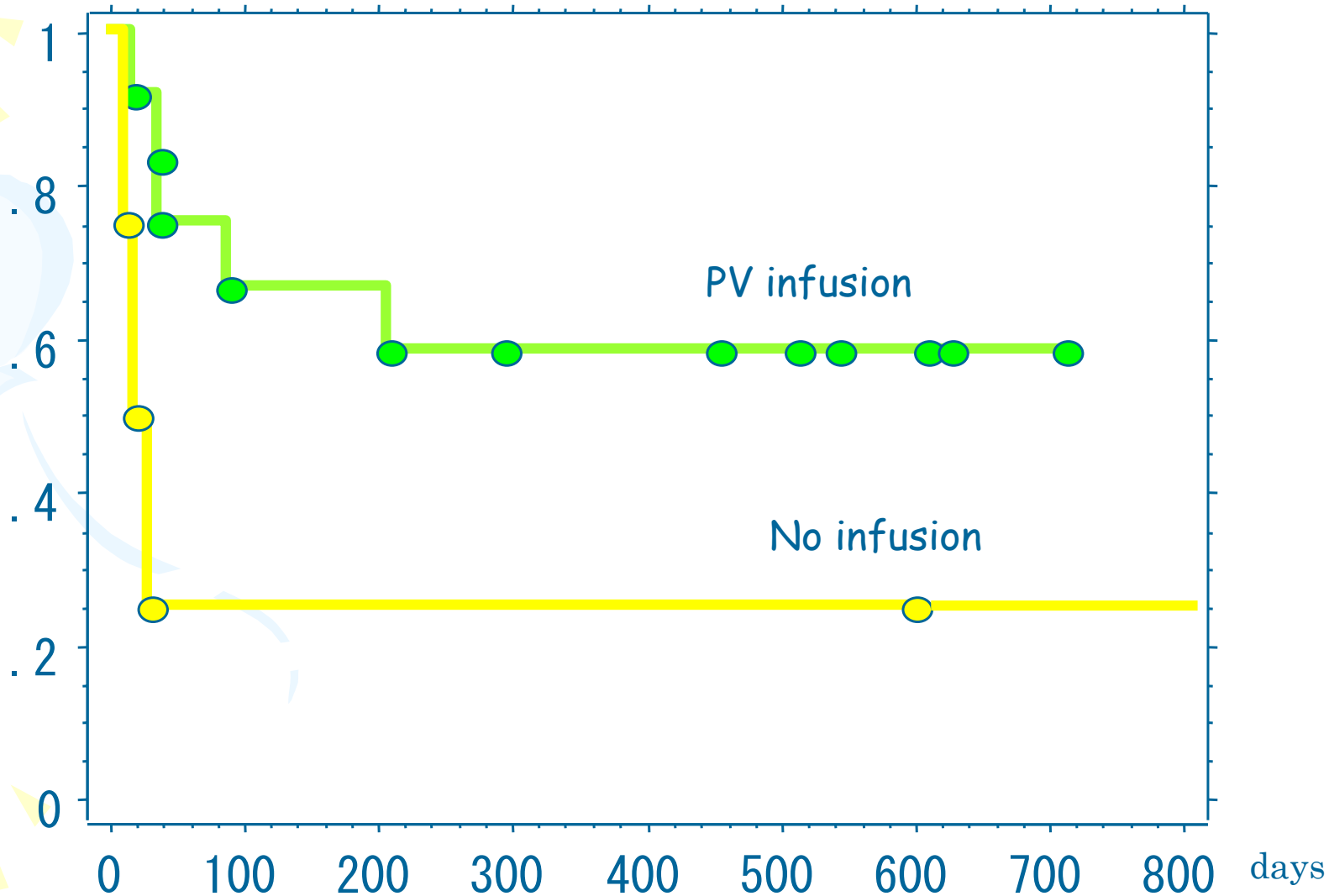
Portal Infusion Protocol

Kyoto experience: 17 patients \geq 14 y.o.

Case	Original Disease	BloodType Donor Recipient	Outcome	Follow-up	Hepatic Necrosis	Biliary Lesion	Infection
610	HCV,LC	A O	alive	897days	(-)	(-)	CMV
639	HBV,LC,HCC	B A	alive	813	(-)	(-)	CMV
98	BA,ReLTx	A O	alive	794	(-)	(-)	Abscess, CMV
651	AIH	A O	dead	(37)	(-)	(-)	Pneumonia,CMV
666	PSC	A O	alive	729	(-)	(-)	CMV
675	HCV,LC,HCC	A O	alive	701	(-)	(-)	Sepsis
676	HCV,LC	B O	alive	699	(-)	(+)	Sepsis,CMV
691	HBV,LC,HCC	AB B	dead	(38)	(-)	(-)	Sepsis,CMV
693	HCV,LC	A O	alive	640	(-)	(-)	CMV
698	BA	B O	dead	(89)	(+)HAT	(-)	Sepsis,CMV
707	PBC	AB O	dead	(18)	(+) severe	(-)	
703	ReLTx	A O	dead	(13)	(-)	(-)	Sepsis,CMV
733	PBC	B O	dead	(208)	(-)	(+)	Sepsis,CMV
741	BA	B O	alive	479	(+) mild	(-)	CMV
779	BA	A O	alive	352	(-)	(-)	
239	ReLTx	AB A	alive	342	(-)	(-)	CMV
848	HCV,LC,HCC	B O	alive	80	(-)	(-)	CMV

Patient Survival of adult ABO-I LDLT

Actuarial Patient Survival Rate



Prostaglandin E1

● *Vasodilatation*

● *Inhibition of platelet aggregation*

● *Inhibition of proinflammatory cytokine production*

Prostaglandin E1 reduces myocardial reperfusion injury by inhibiting proinflammatory cytokines production during cardiac surgery.

Kawamura T, et al. Crit Care Med. 2000 Jul;28(7):2201-8.

The modulatory effects of prostaglandin-E on cytokine production by human peripheral blood mononuclear cells are independent of the prostaglandin subtype.

Dooper MM, et al. Immunology. 2002 Sep;107(1):152-9.

● *Angiogenesis*

Clinical and experimental evidence of prostaglandin E1-induced angiogenesis in the myocardium of patients with ischemic heart disease.

Mehrabi MR, et al. Cardiovasc Res 2002 Nov;56(2):214-24

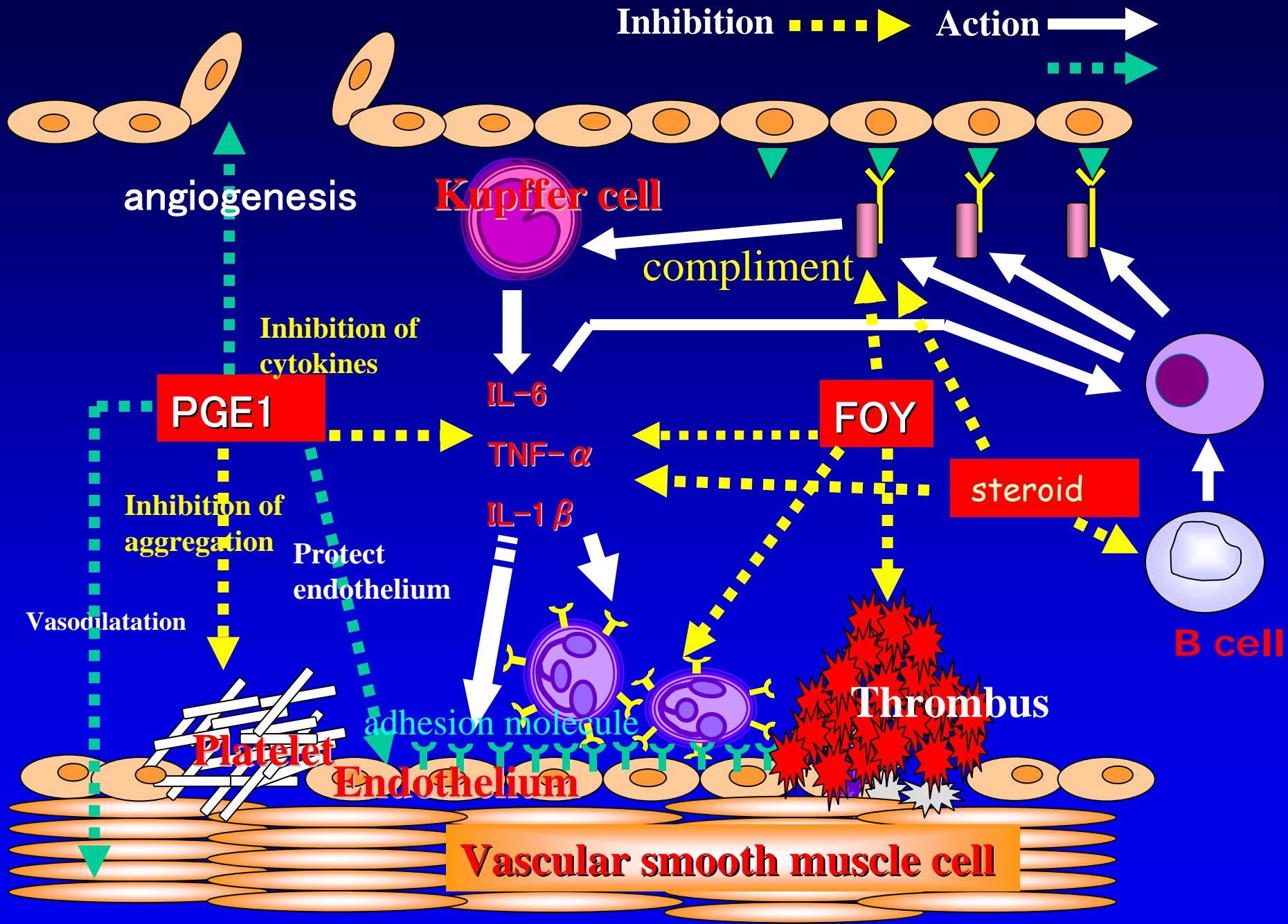
● *Immune modulation*

A new view of prostaglandin E regulation of the immune response.

Phipps RP, et al. Immunol Today 1991 Oct;12(10):349-52

Effects of prostaglandin E1 on the production of IgM and IgG class anti-dsDNA antibodies in NZB/W F1 mice.

Yoshikawa T, et al. J Rheumatol. 1993 Oct;20(10):1701-6.



Hepatic necrosis under PV infusion

Case 707 AB (+) to O(+), PBC

preope.

antiA IgG	256
antiA IgM	64
anti B IgG	2048
anti B IgM	32

9POD

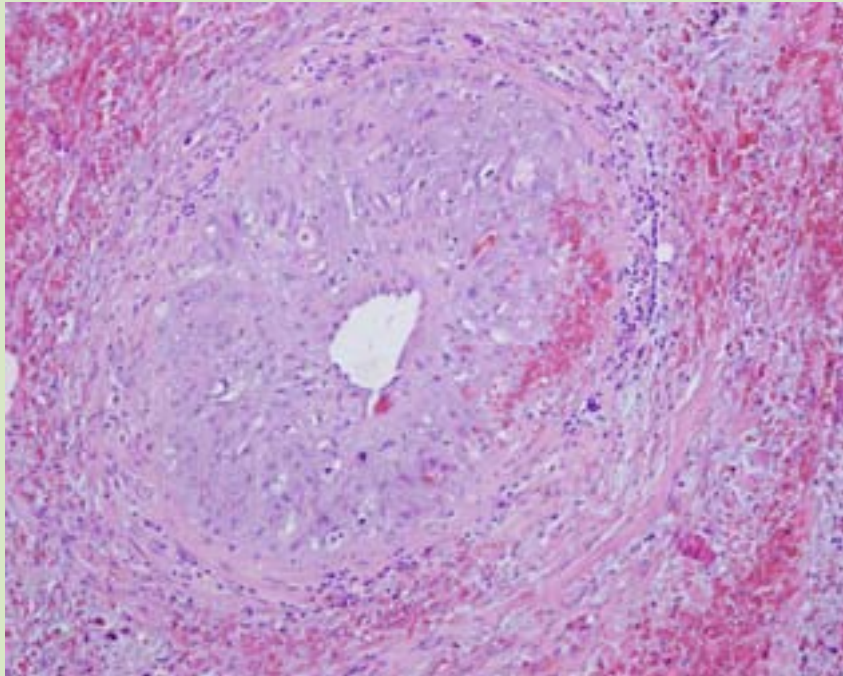
Encephalopathy
gradeII

antiA IgG	512
IgM	512
anti B IgG	64
IgM	32



ABO-related rejection

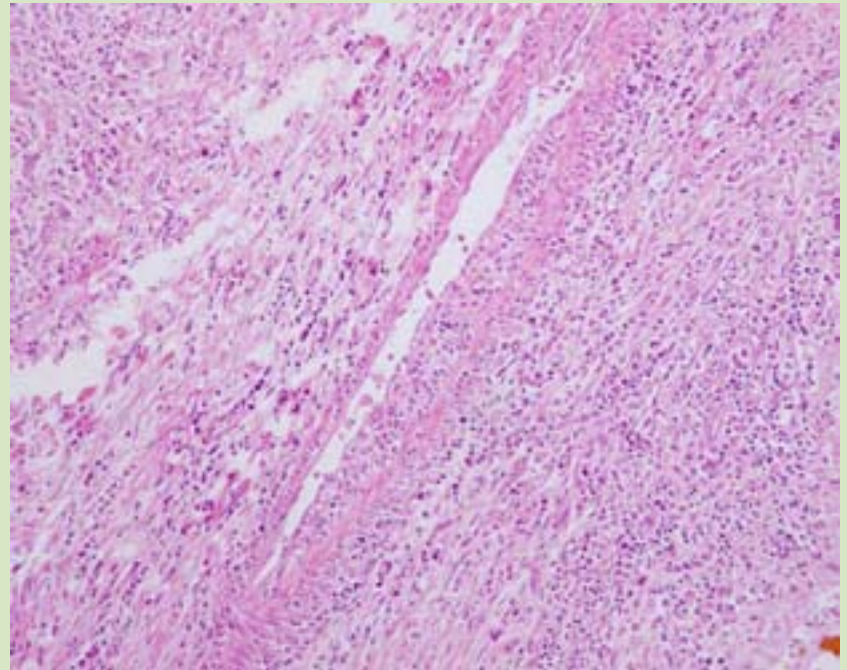
Intimal hypertrophy
of hepatic artery



Hepatic necrosis
(explant)

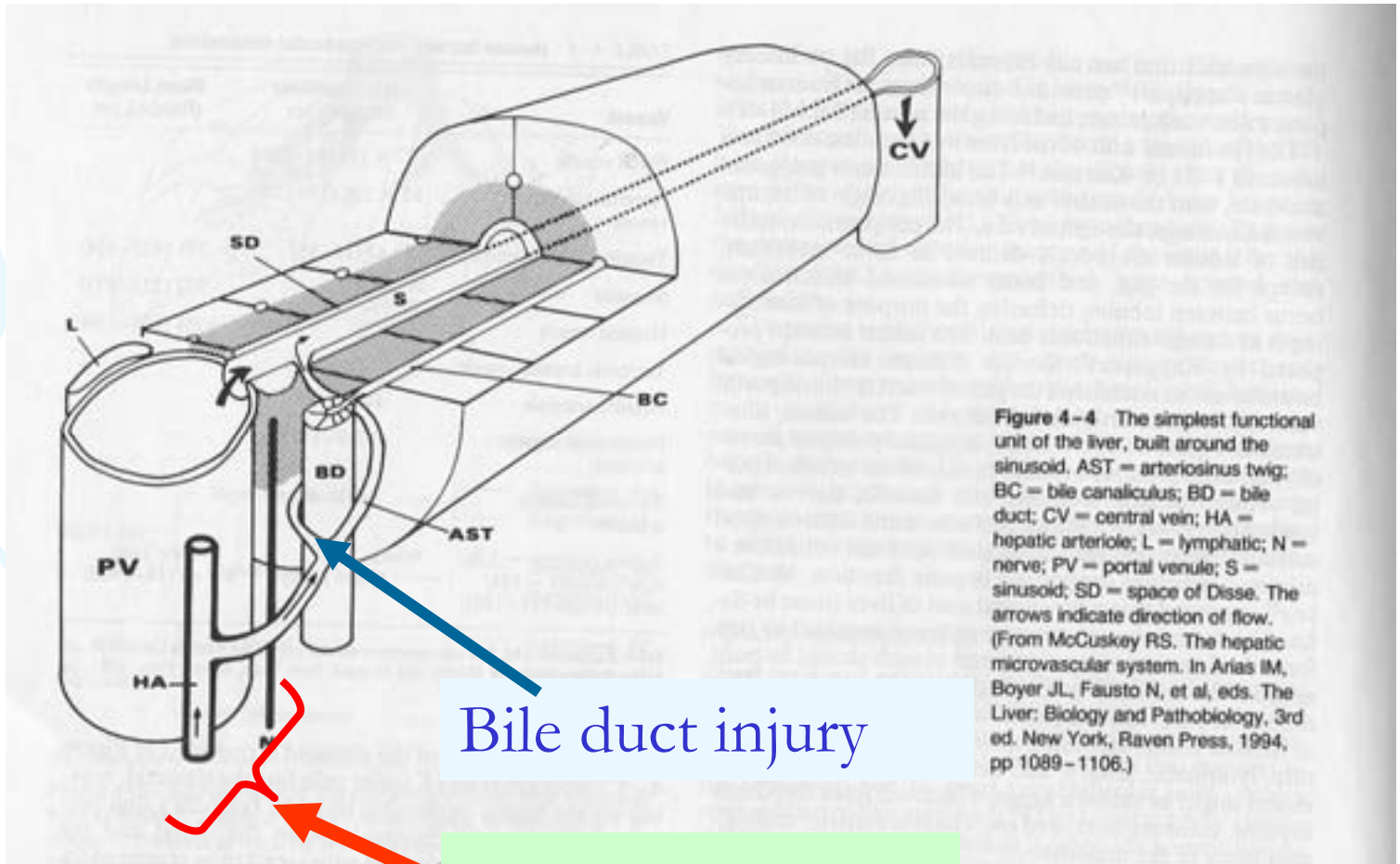
Vasculopathy

Inflammation
of hepatic artery



Intra-hepatic Biliary Complication
(explant)

Significance of HA circulation in ABO-I related complication



Bile duct injury

Liver necrosis

Sclerosing hepatic artery after ABO-I liver transplantaion





Hepatic Arterial Infusion Protocol

For ABO Incompatible LDLT

Portal infusion therapy is not enough for controlling ABO-related rejection.

Severe attack of hepatic necrosis in one case despite the use of portal infusion therapy



Hepatic arterial infusion therapy is more directly effective in preventing the arteriole injury by ABO incompatibility!

Kyoto protocol

PV + HA Infusion Protocol

Pre	Plasma Exchange (anti A IgM, anti B IgM < 8)		
Ope.	LTx & Splenectomy		
Post	Portal Infusion		
	Methylprednisolone	125mg/day,	~1w
		50mg/day,	~2w
	Prostaglandine E1	0.01 γ ,	~3w
	Gabexate Mesilate	1000mg/day,	~3w
	General Immunosuppression		
	Cyclophosphamide	2mg/kg/day, ~2w(iv), ~4w(oral)	
	Tacrolimus		
	Methylprednisolone		

Hepatic artery infusion

Placement of Hepatic Artery Catheter

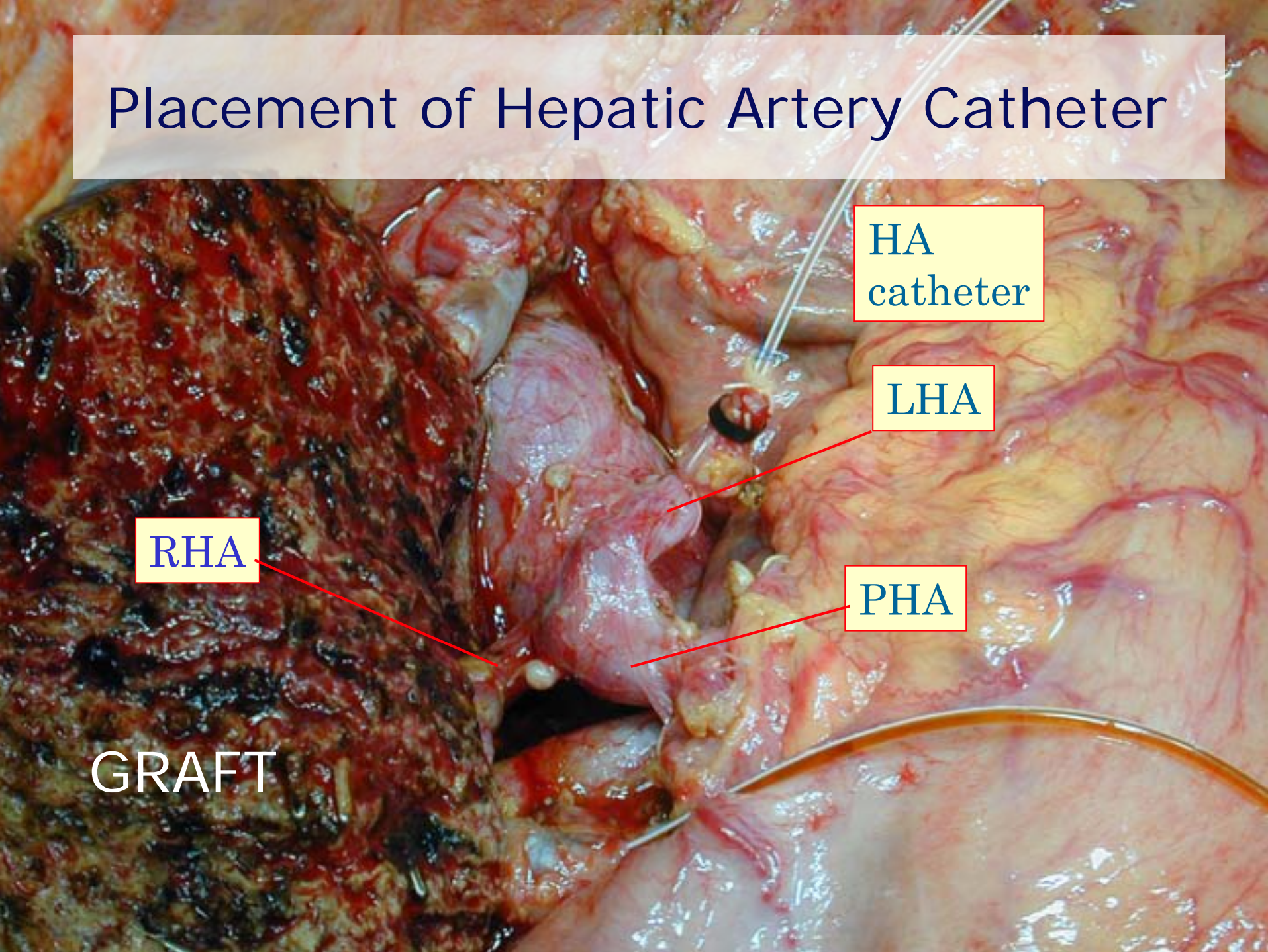
HA
catheter

LHA

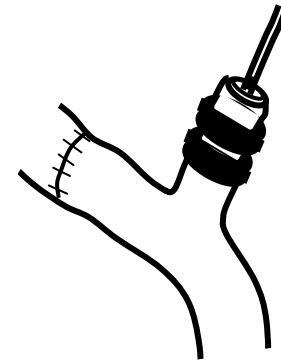
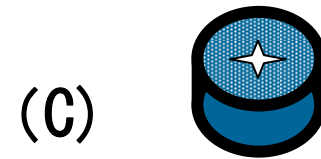
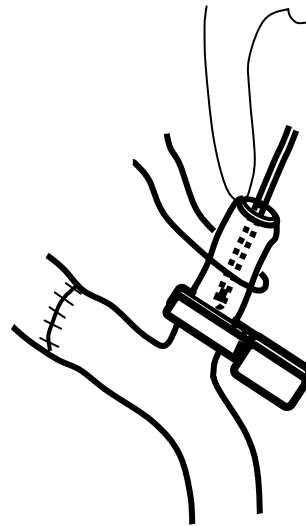
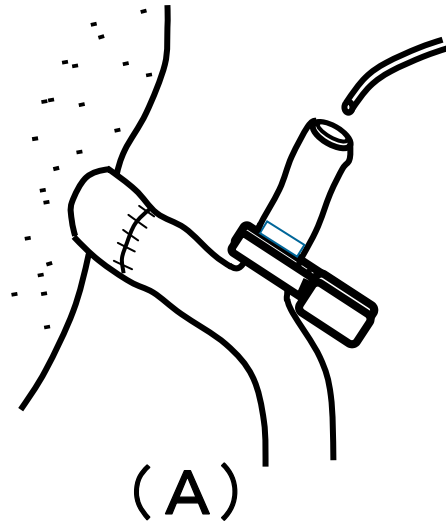
RHA

PHA

GRAFT



Placement of Hepatic Artery Catheter



(D)

No biliary lesion !

PV+HA Infusion Protocol

9 patients

Case	Original Disease	Blood Type Donor Recipient	Outcome	Follow-up	Hepatic Necrosis	Biliary Lesion	Infection
728	HCV,LC,HCC	A O	dead	(44) days	(+) moderate	(-)	Sepsis,CMV
731	HCV,LC	A O	alive	519	(-)	(-)	CMV
738	BA,HCV,HCC	A B	alive	500	(-)	(-)	
797	HCV,LC,HCC	A O	alive	281	(-)	(-)	
134	ReLTx	AB A	alive	272	(+) mild	(-)	CMV
799	PBC	AB B	alive	269	(-)	(-)	CMV
817	PBC	B O	alive	199	(+) HAT	(-)	Sepsis,CMV
820	PBC	A O	alive	185	(+) mild	(-)	CMV
836	HCC,LC,HCV	A O	alive	122	(-)	(-)	CMV

PGE1,steroids(Hepatic artery infusion), Gabexate Mesilate (Portal infusion)

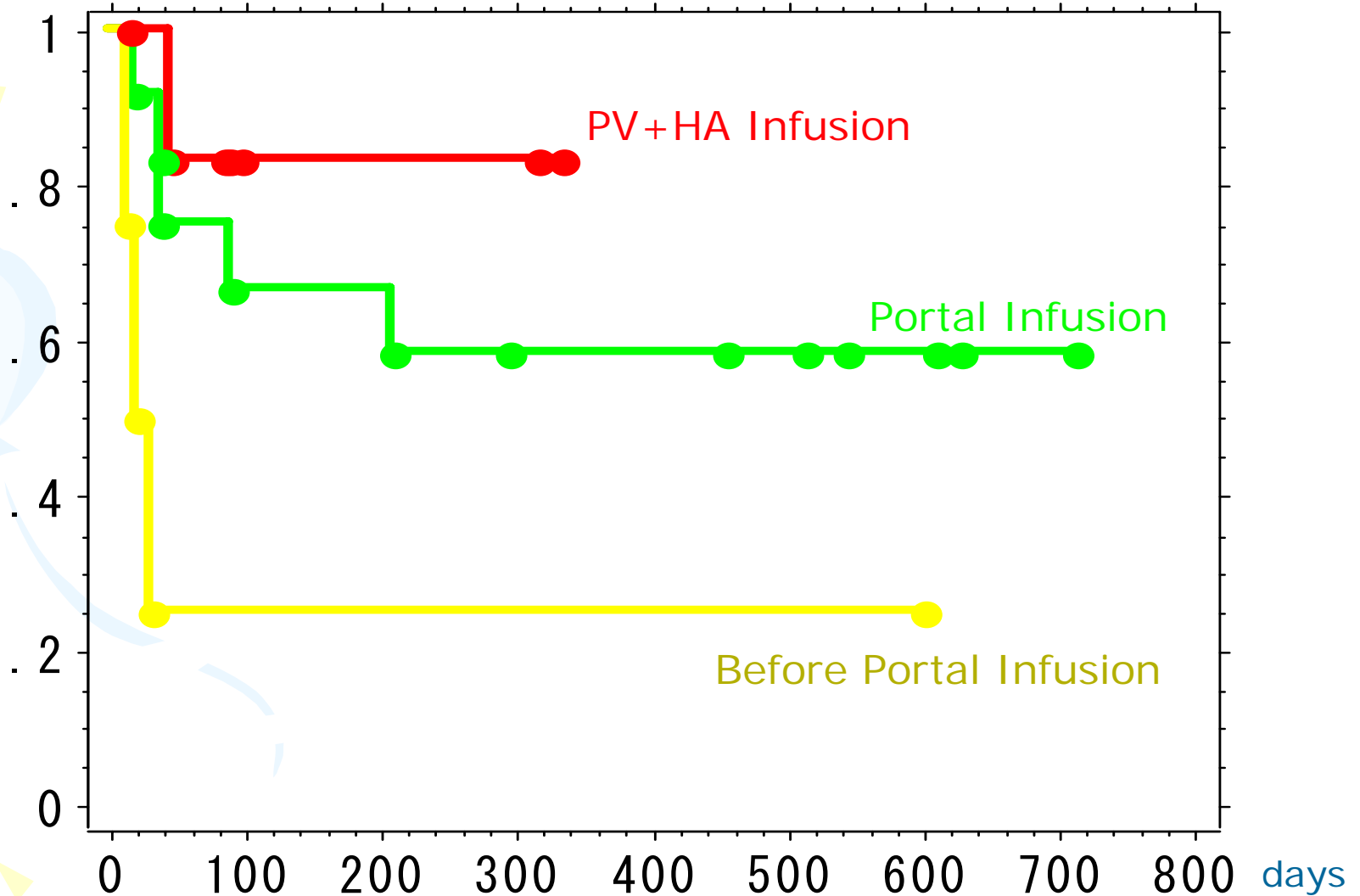
#728,731,738,797,134,799,817

PGE1,steroids (Hepatic artery infusion), No portal infusion

#820,836:

Patient Survival of adult ABO-I LDLT

Actuarial Patient Survival Rate



Problems to be solved
Over-immunosuppression

High incidence of CMV infection

14/17 82.4%

portal infusion

7/9 77.8%

hepatic artery infusion

- General immunosuppression should be weakened?
- Tailored for the risk?

Catheter related complication

Hepatic Arterial Thrombosis

Hepatic arterial & portal catheter infusion therapy:
1/9 (11.1%)

portal infusion therapy : 1/17
identical/compatible transplantation : 4/350
using right lobe

- Catheter-related ? :
 - material
 - strong anticoagulant treatments
 - position of the catheter tip
- Endothelial injury associated with ABO incompatibility ?

Catheter related complication

Portal thrombosis

9 patients developed portal thrombosis in 26 patients with portal infusion.

Portal infusion therapy: 4/17

Hepatic arterial & portal infusion therapy: 5/9

Total: 35%

portal catheter

splenectomy

thrombocytosis

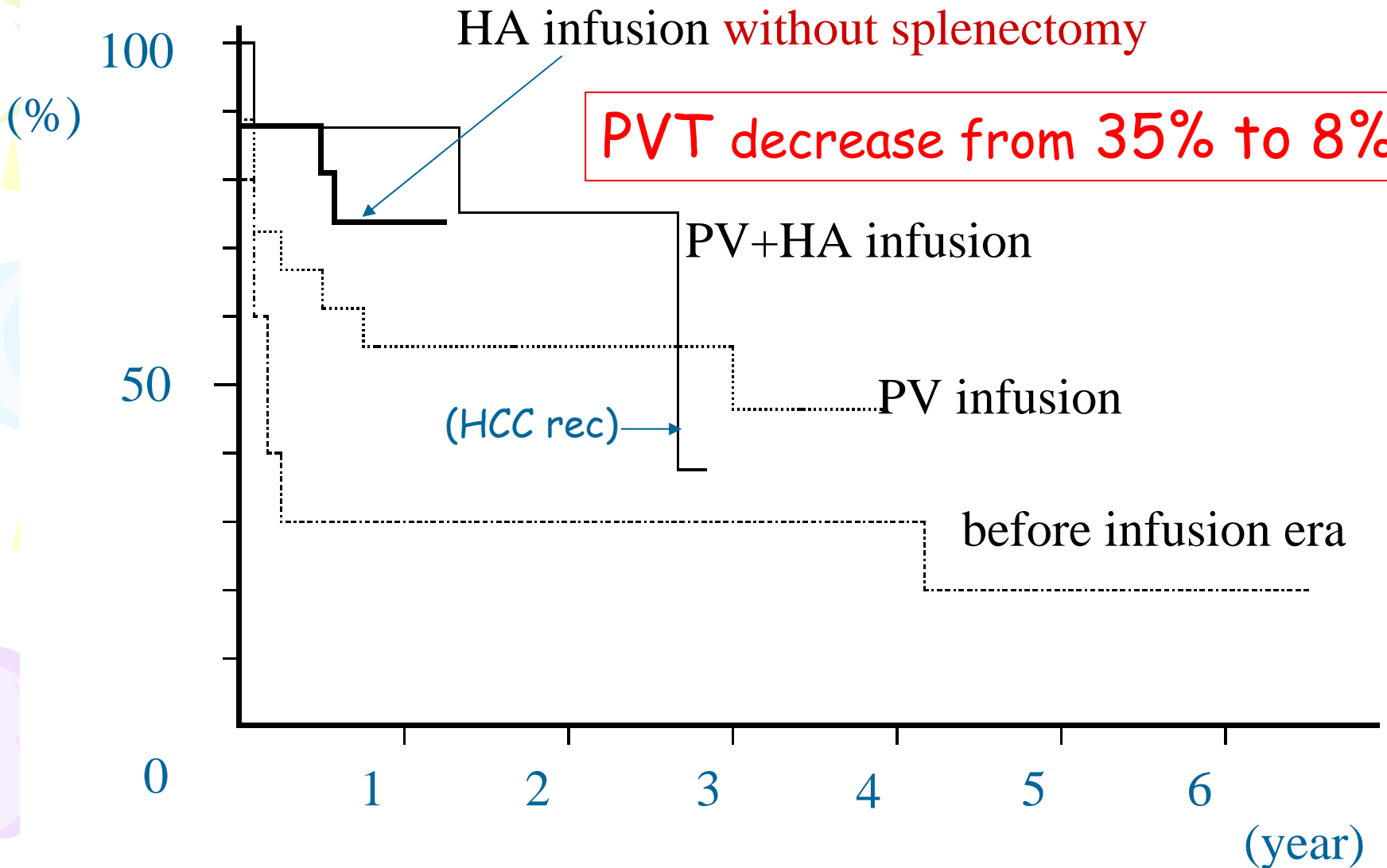
lack of splenic venous return

Portal thrombosis

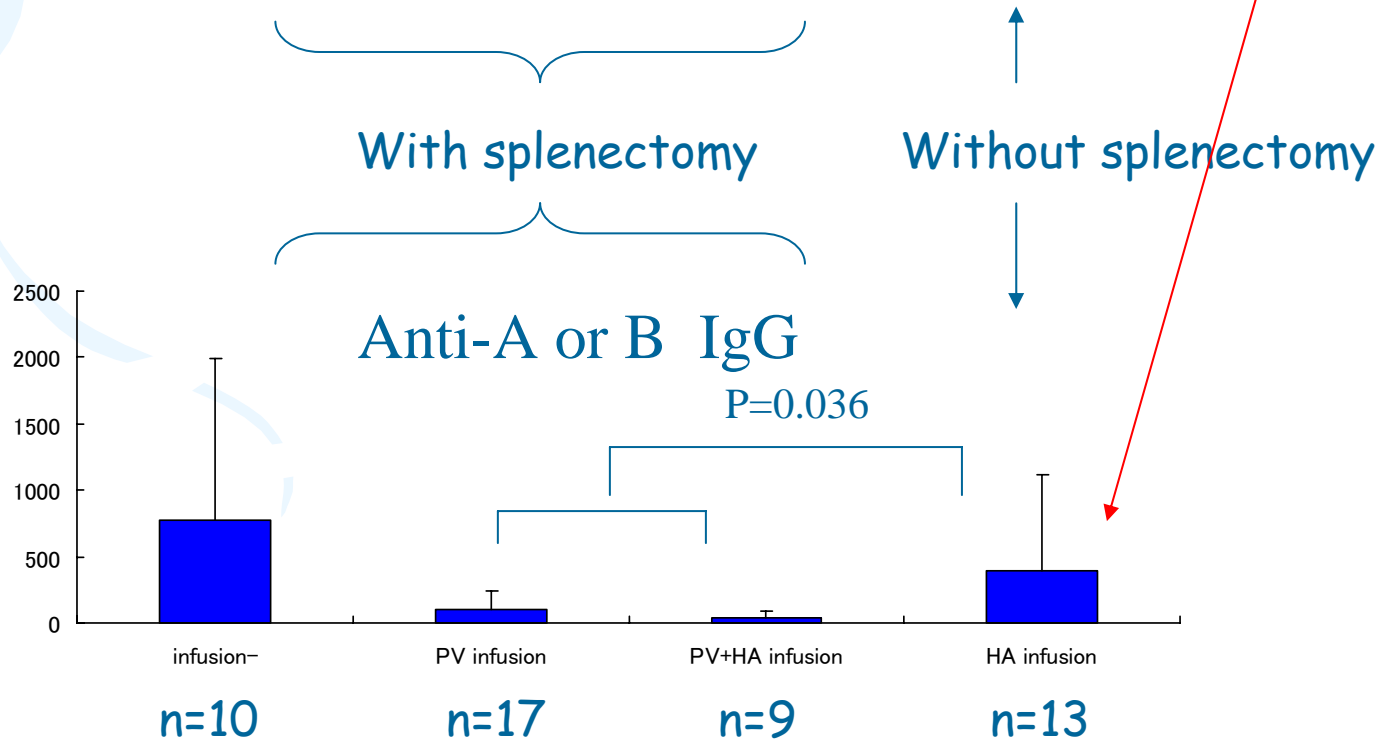
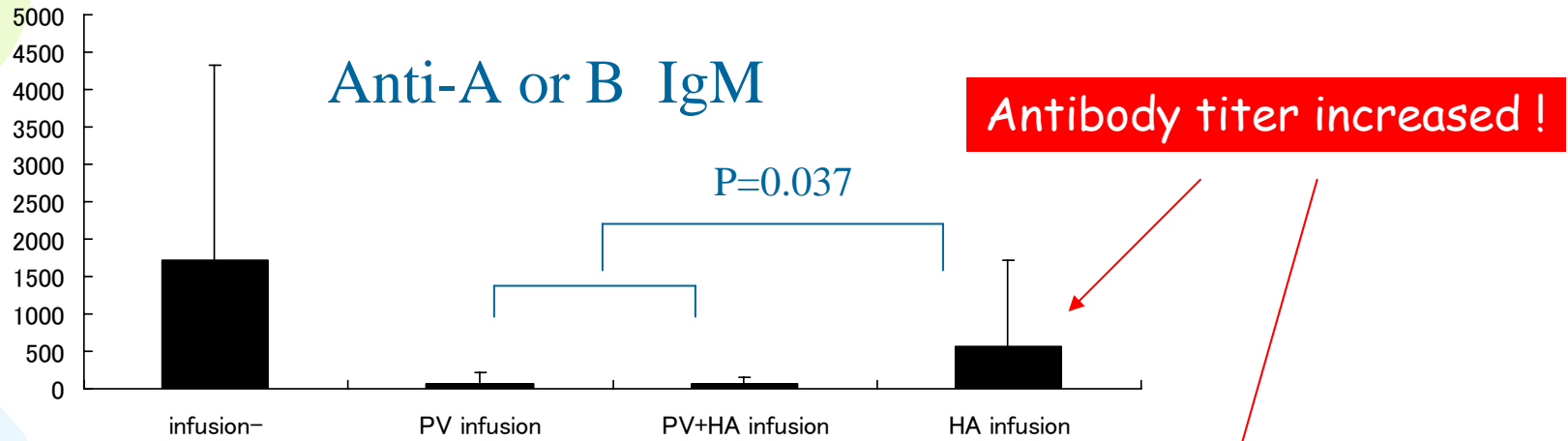
Next strategy

Hepatic arterial infusion therapy
without portal catheter
without splenectomy

Patient Survival of adult ABO-I LDLT



Effect on splenectomy on Post-transplant peak titer



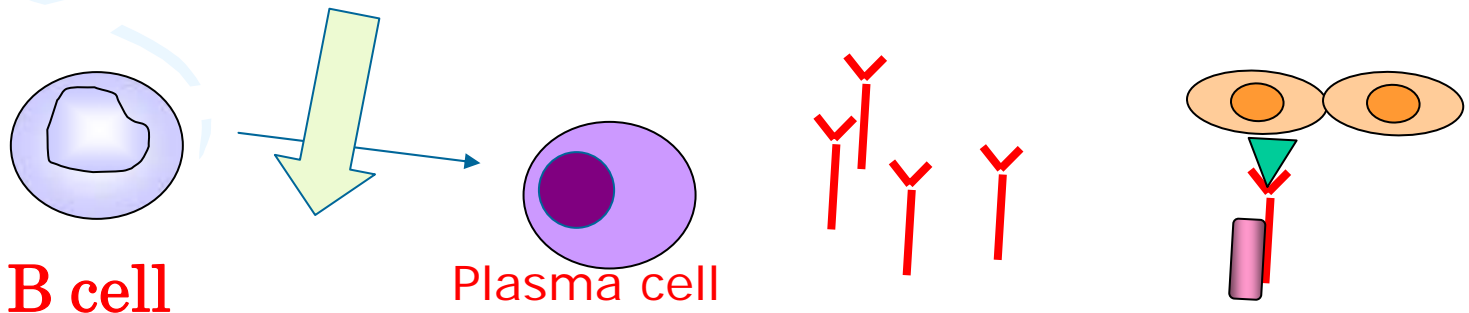
Tactics: decrease Ab titer

- Splenectomy

- Possible permanent immuno-deficiency
- Cause of portal thrombus

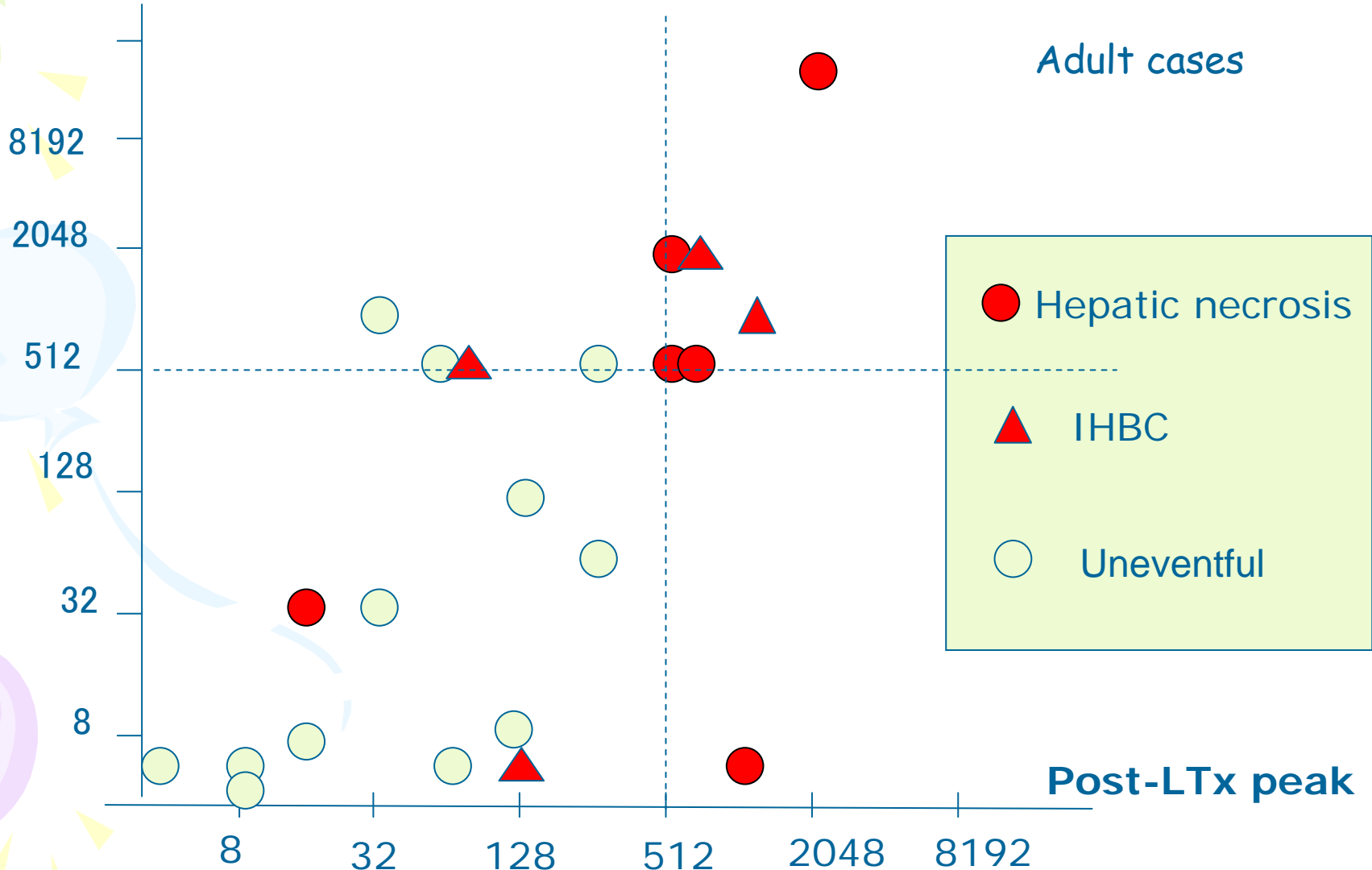


B cell deletion by Rituximab instead splenectomy



Correlation between Pre-LTx IgG peak & Post-LTx IgG peak Incompatible related complication

Pre-LTx peak



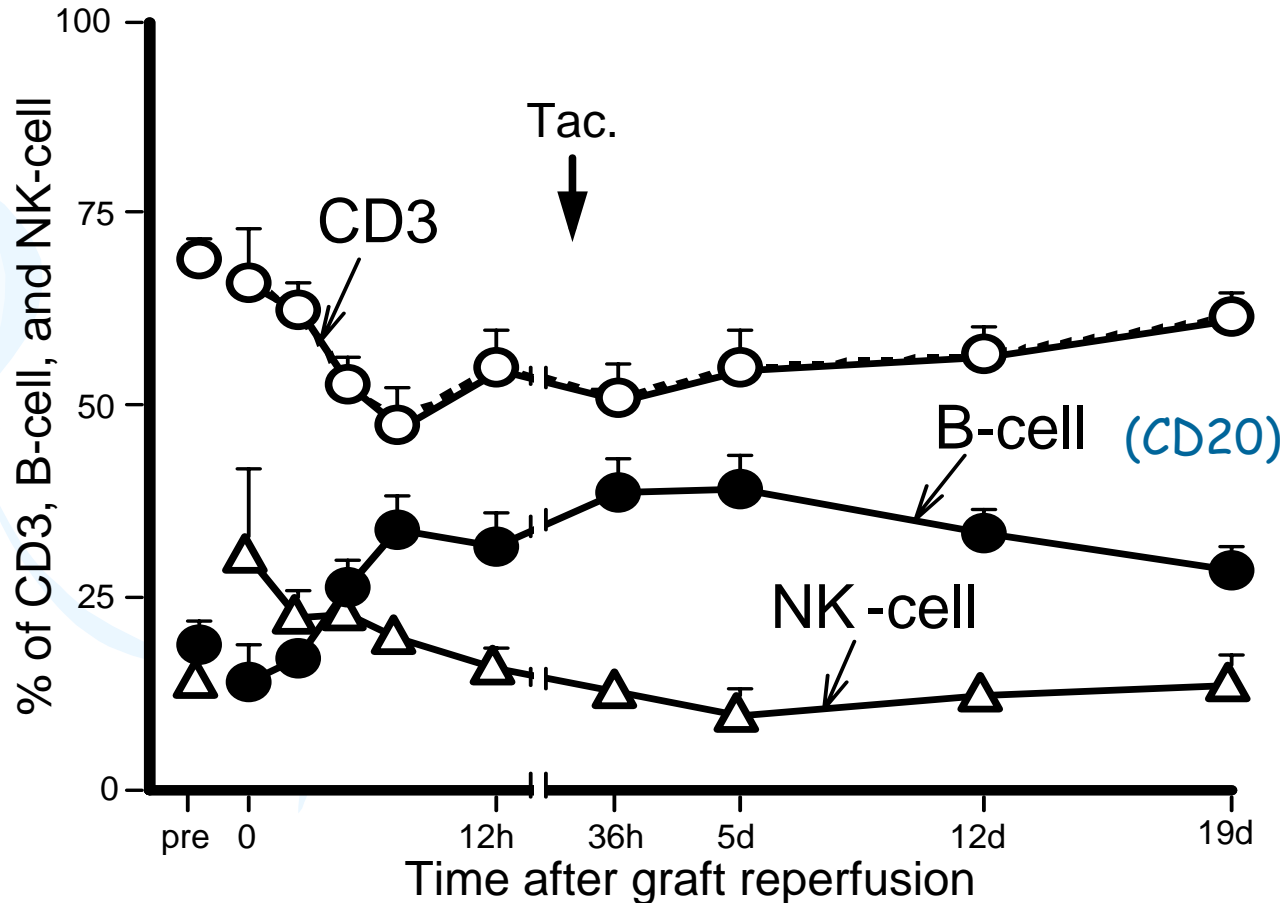
Adult cases

- Hepatic necrosis
- ▲ IHBC
- Uneventful

Post-LTx peak

Change of lymphocyte population

Adults (n=15)



IgG peak & CD20 peak after ABO-I LTx with HA infusion

IgG titer

2048

512

128

32

8

● Hepatic necrosis

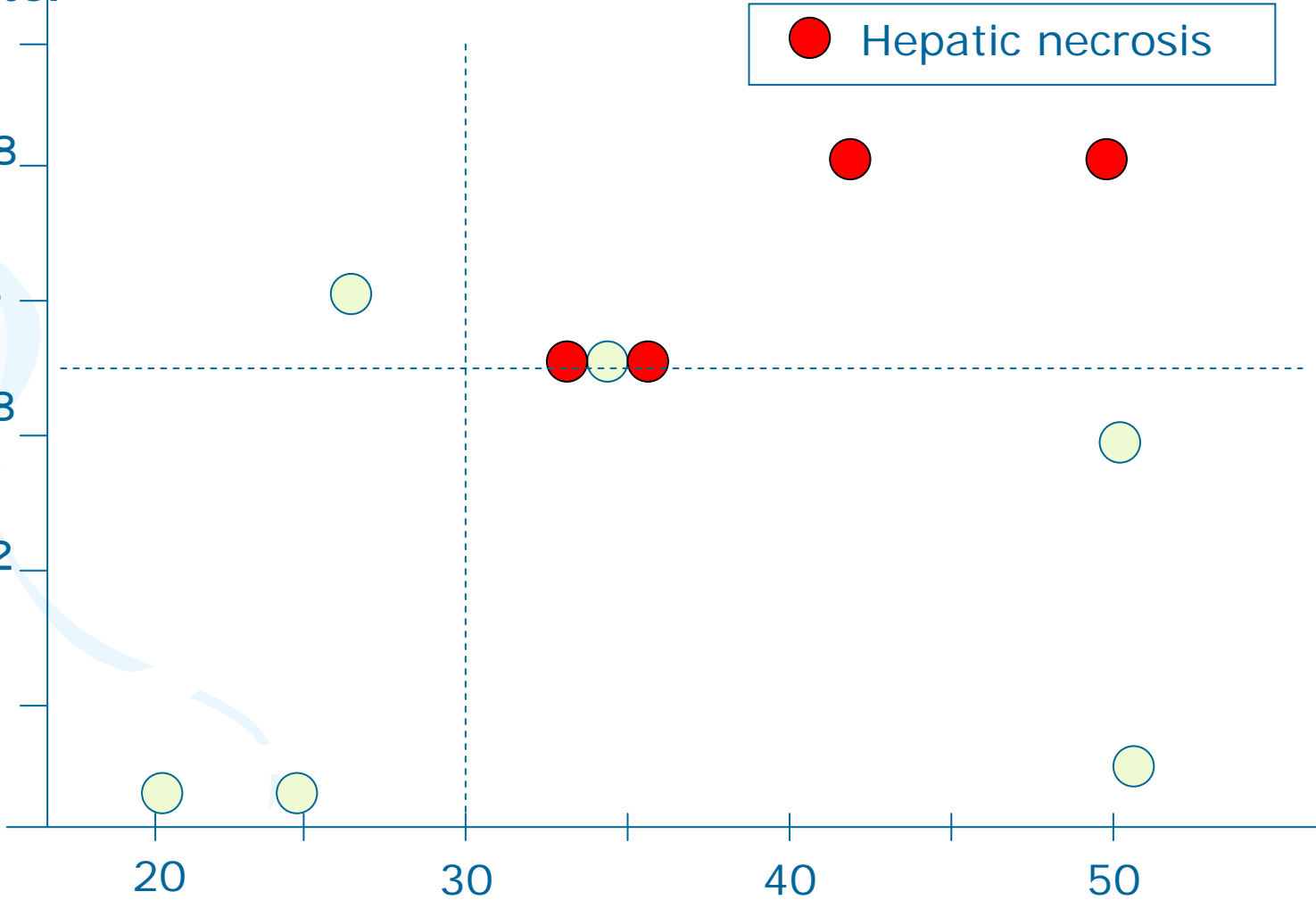
20

30

40

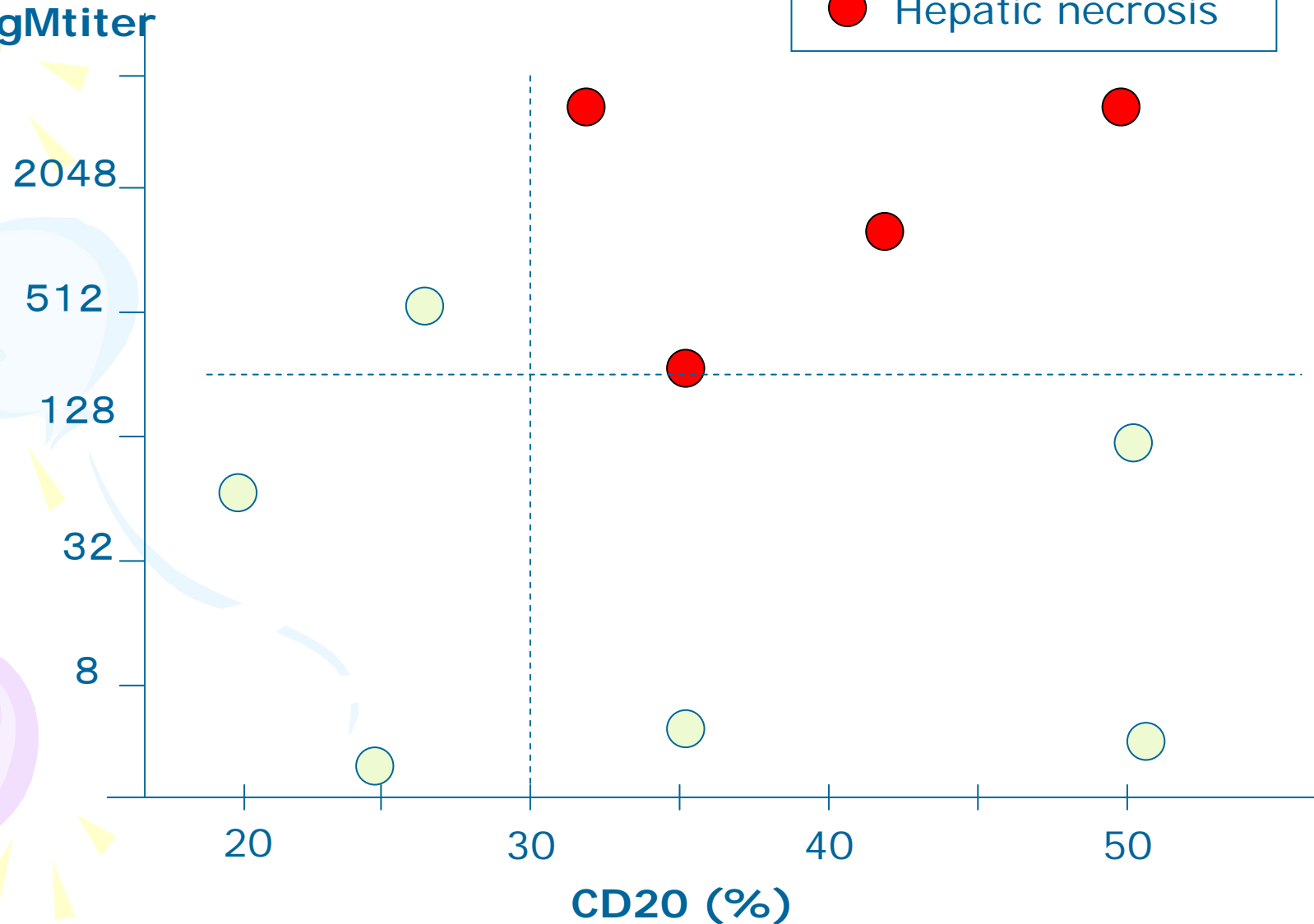
50

CD20 (%)

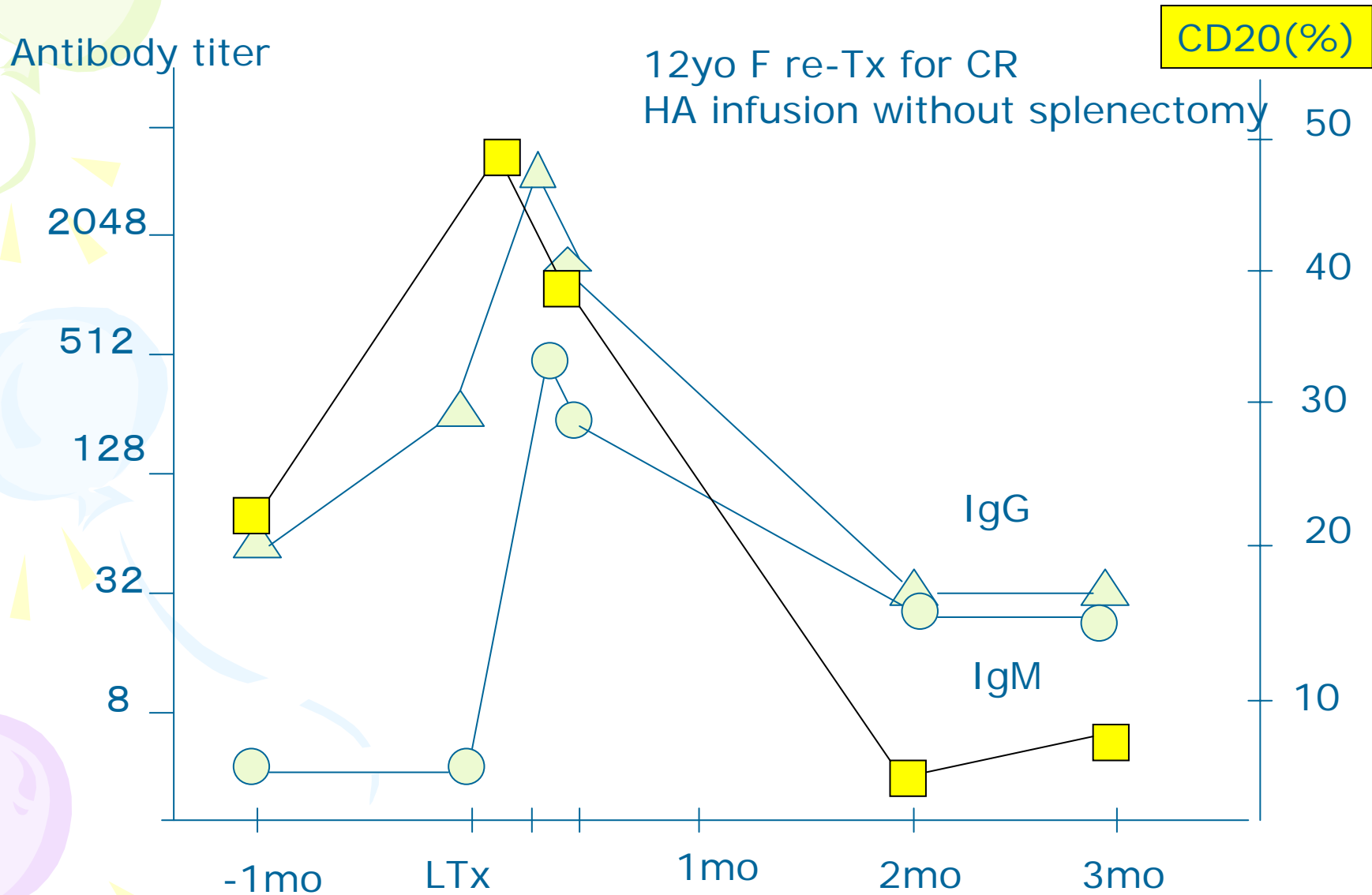


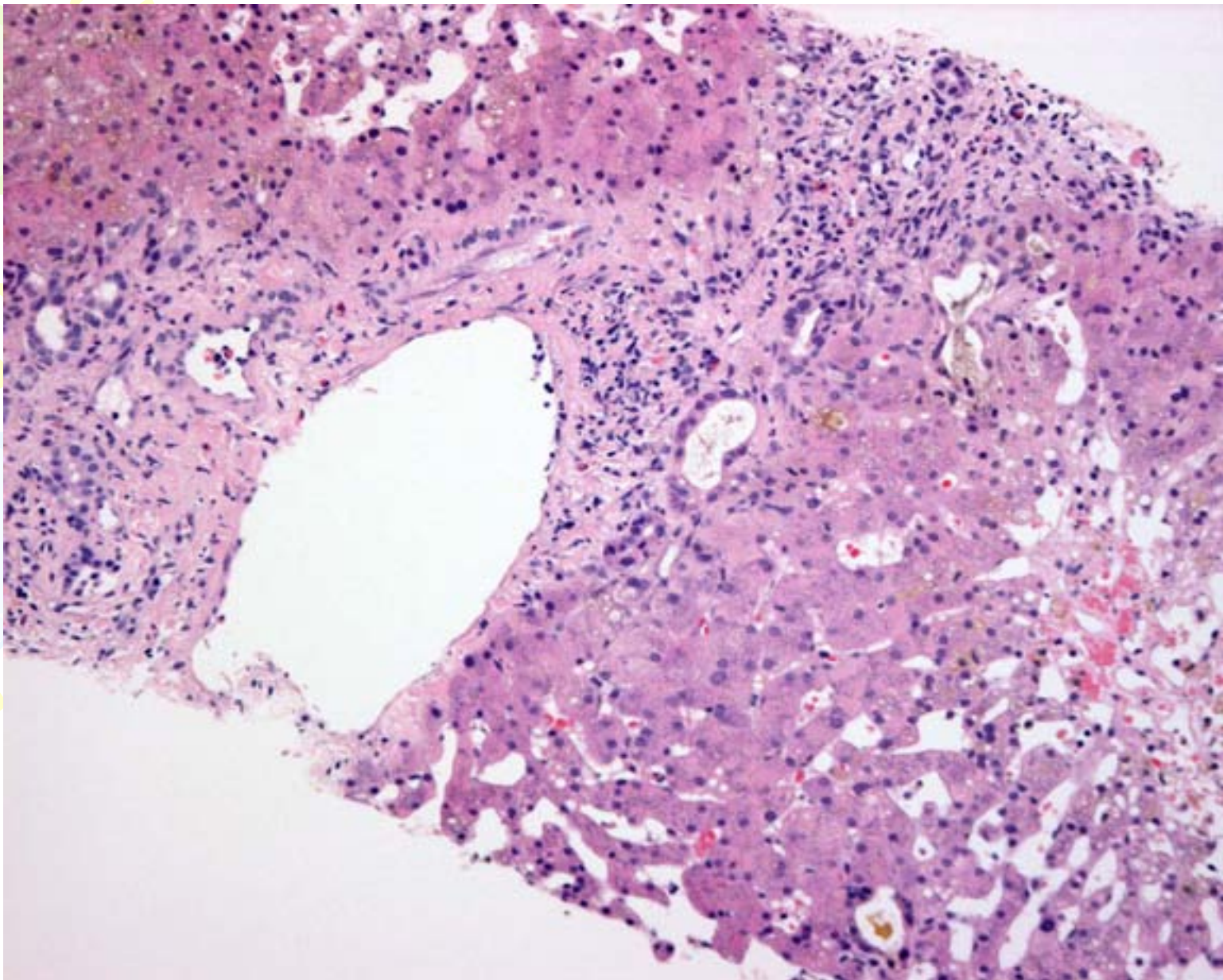
IgM peak & CD20 peak after ABO-I LTx with HA infusion

IgMtiter

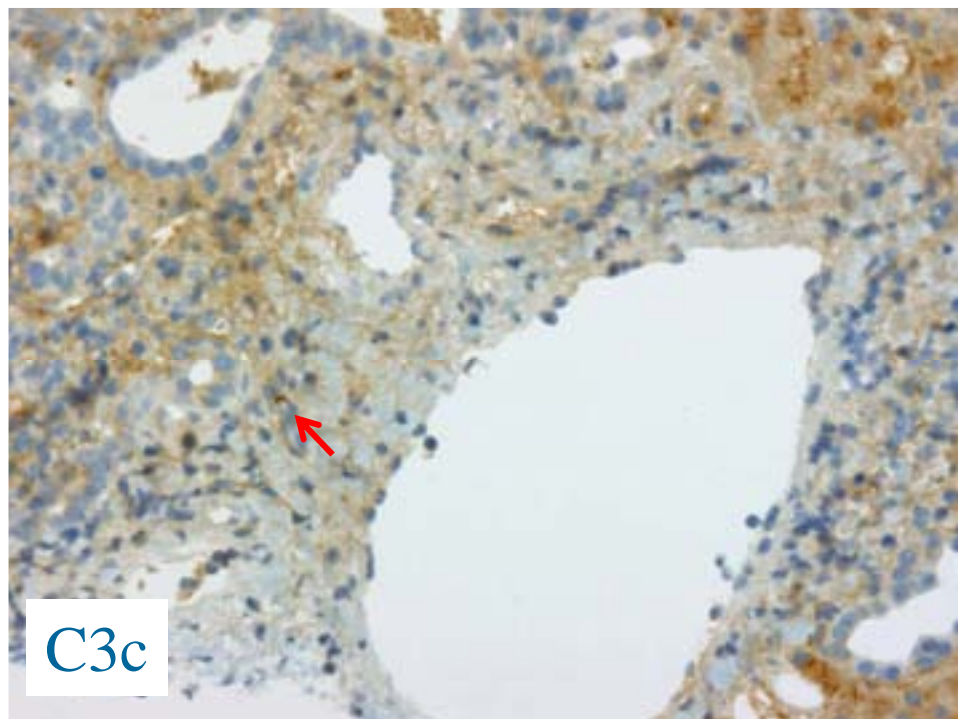
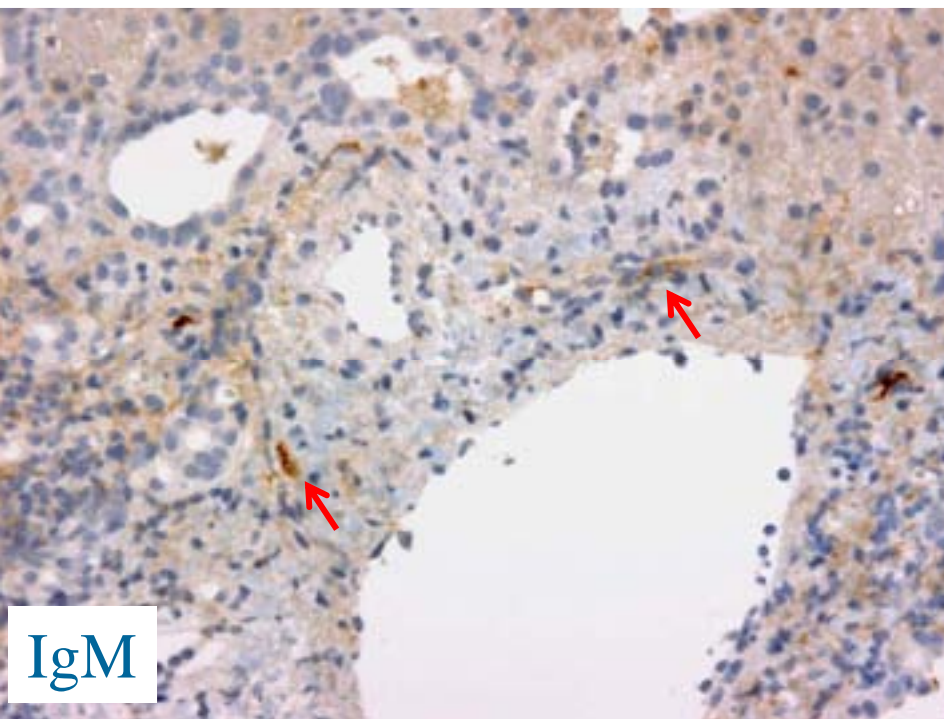
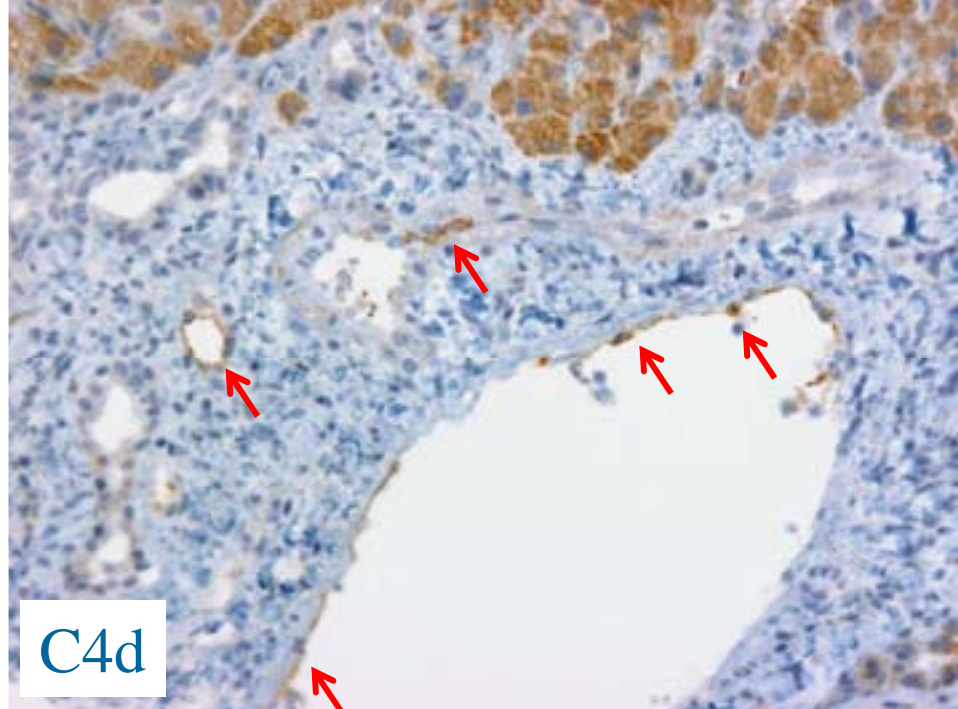
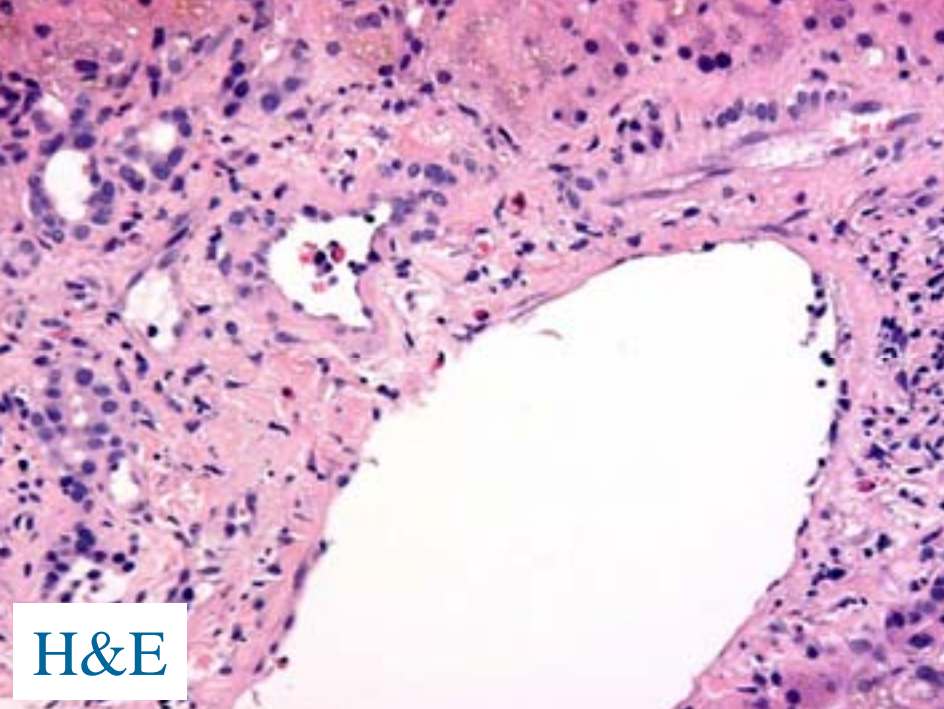


Change of CD20 and antibody titer





Day 26 (2004.1.23) Cholangitis-like ductular reaction with cholestasis and centrilobular necrosis (late phase of humoral rejection)

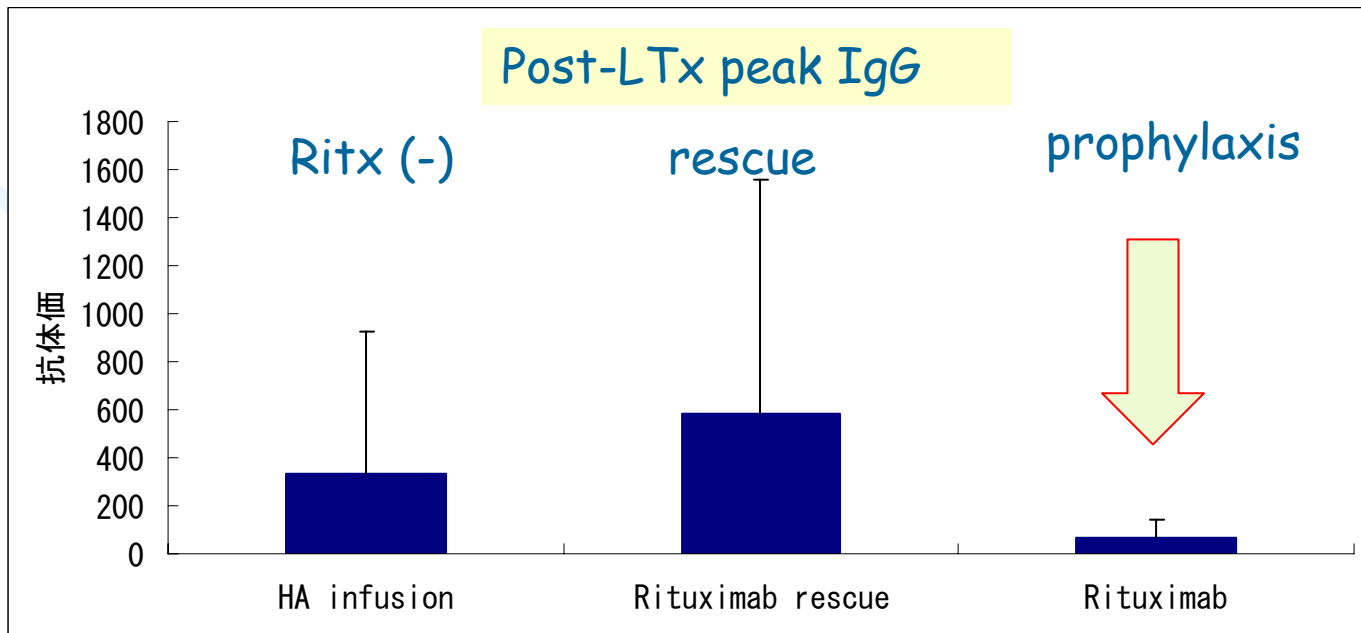
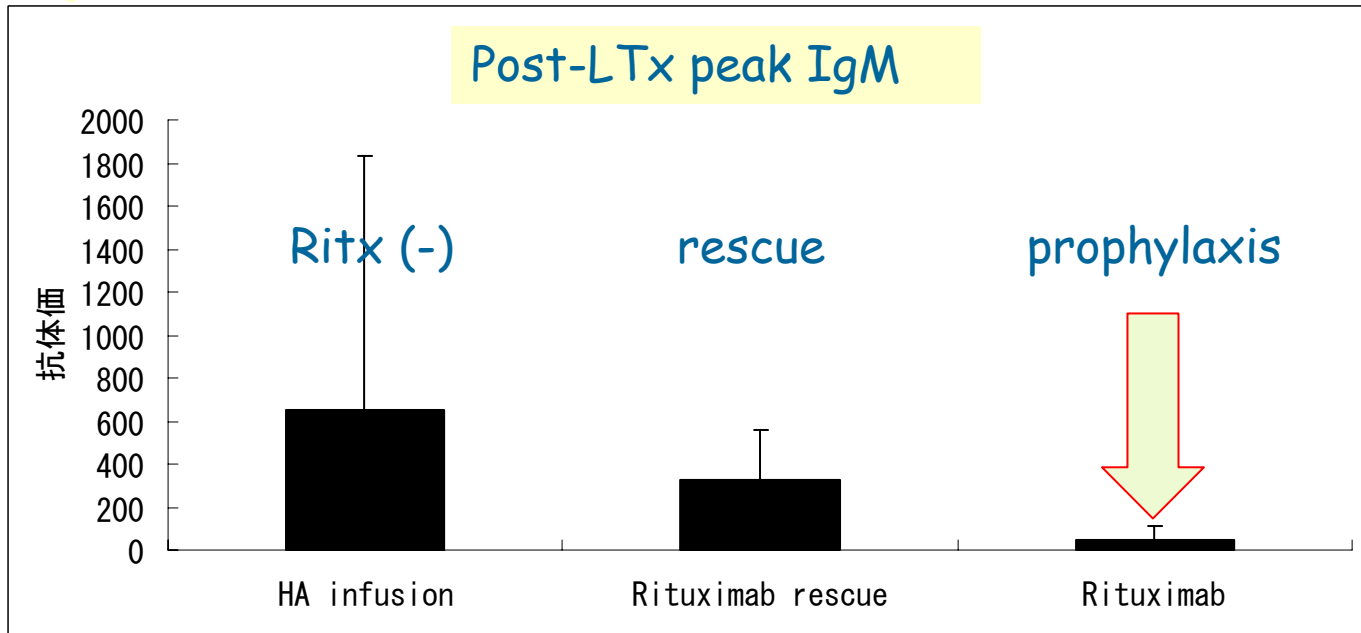




Application of Rituximab

1. Rescue therapy for elevated antibody after LTx (n=4)
2. Prophylaxis before LTx (n=6)

All cases: HA infusion without splenectomy



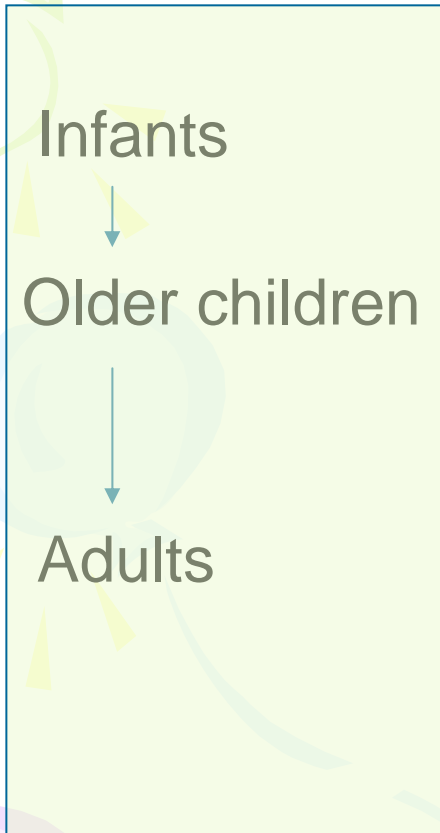
6 cases with Rituximab Prophylaxis

Case	name	sex	age	day of Ritux	pre-ope IgM	pre-ope IgG	post-ope IgM	post-ope IgG	PEN	result
1	S.M	f	29	-2	128	256	512	256	y	D(peritonitis)
2	I.Y.	f	65	-6	64	1	4	1	n	alive
3	M.Y.	f	58	-15	128	2048	64	128	n	alive
4	N.T.	f	38	-3	512	1024	32	128	y	D(pneumonia)
5	H.K.	m	57	-2	1024	64	128	32	n	alive
6	S.H.	f	61	-4	64	256	1	2	n	alive

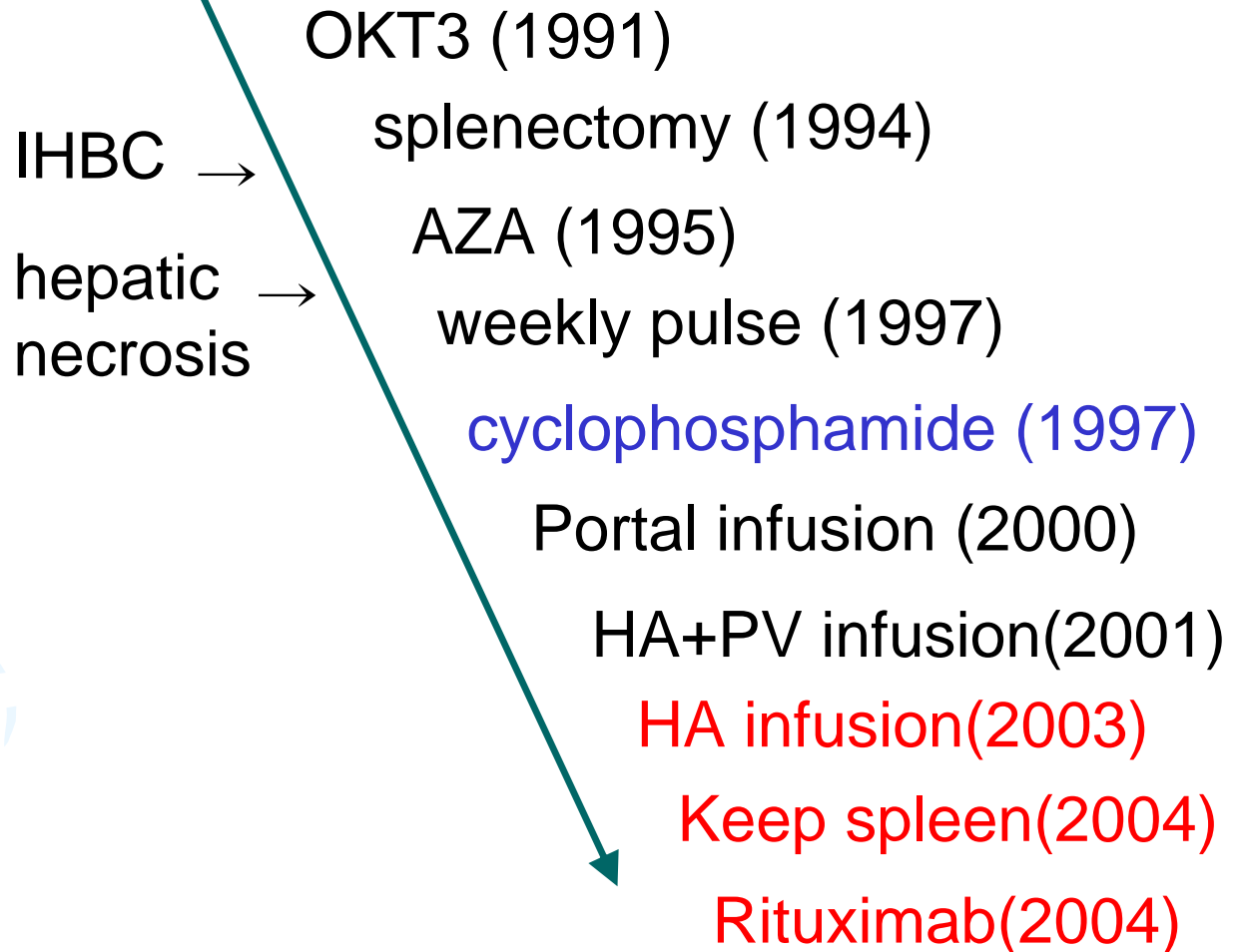
Results

	HA infusion Rituximab (-)	HA infusion Rituximab rescue	HA infusion Rituximab prophylaxis
Pathological humoral rejection	3 / 13	2 / 4	2 / 6
Total necrosis	0 / 13	2 / 4 (1:without Bx)	0 / 6
Intrahepatic biliary complication	0 / 13	0 / 4	0 / 6
death	2 / 13 peritonitis HA aneurysm	2 / 4 hepatic necrosis hepatic necrosis	2 / 6 peritonitis pneumonia

Strategy for the Blood Type Barrier in Kyoto



Base: tacrolimus & steroid
plasma pheresis, blood exchange

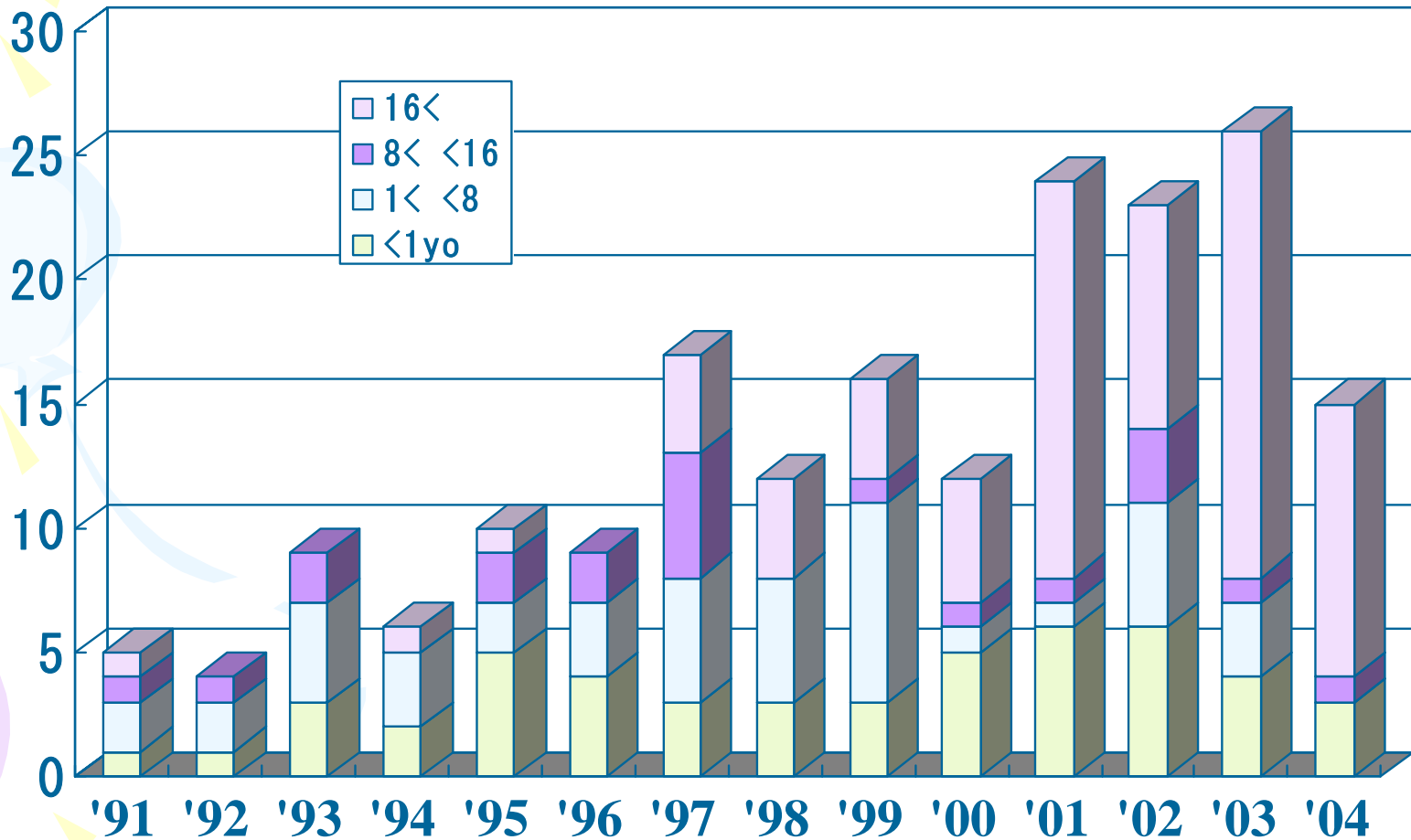




Japanese Registry of ABO incompatible Liver Transplantation 2004

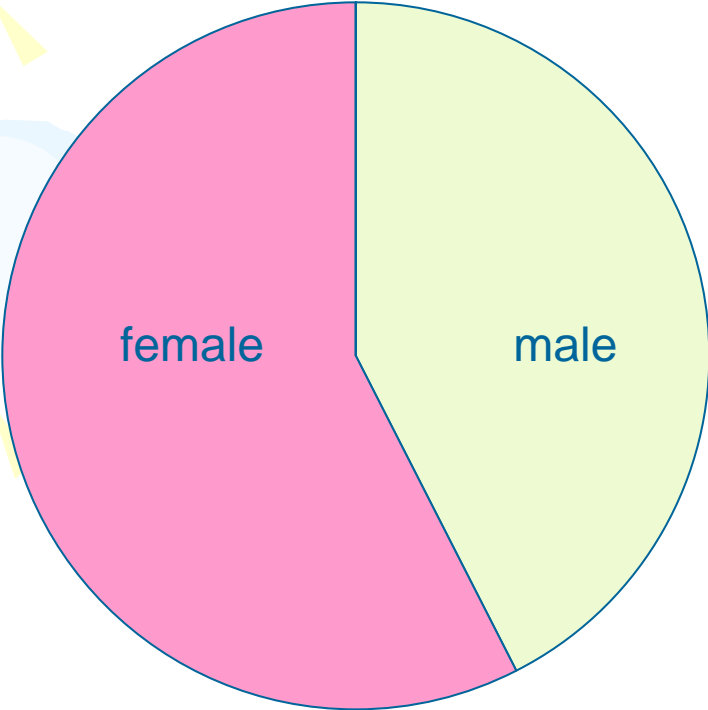
- **194 patients in 31 centers**
- **All living donor liver transplantation**

ABO-I LDLT in Japan

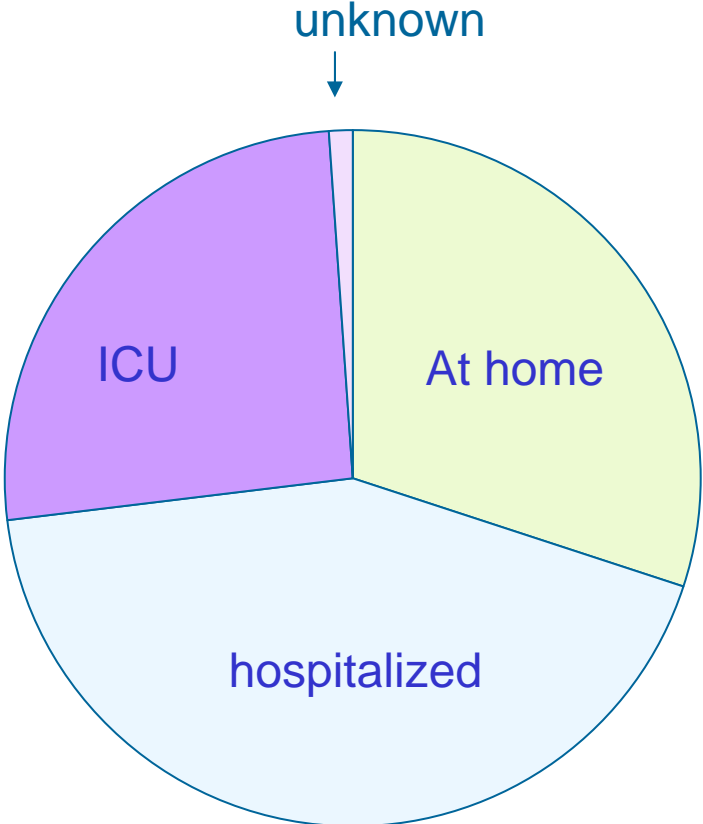


(until March/31)

Recipient

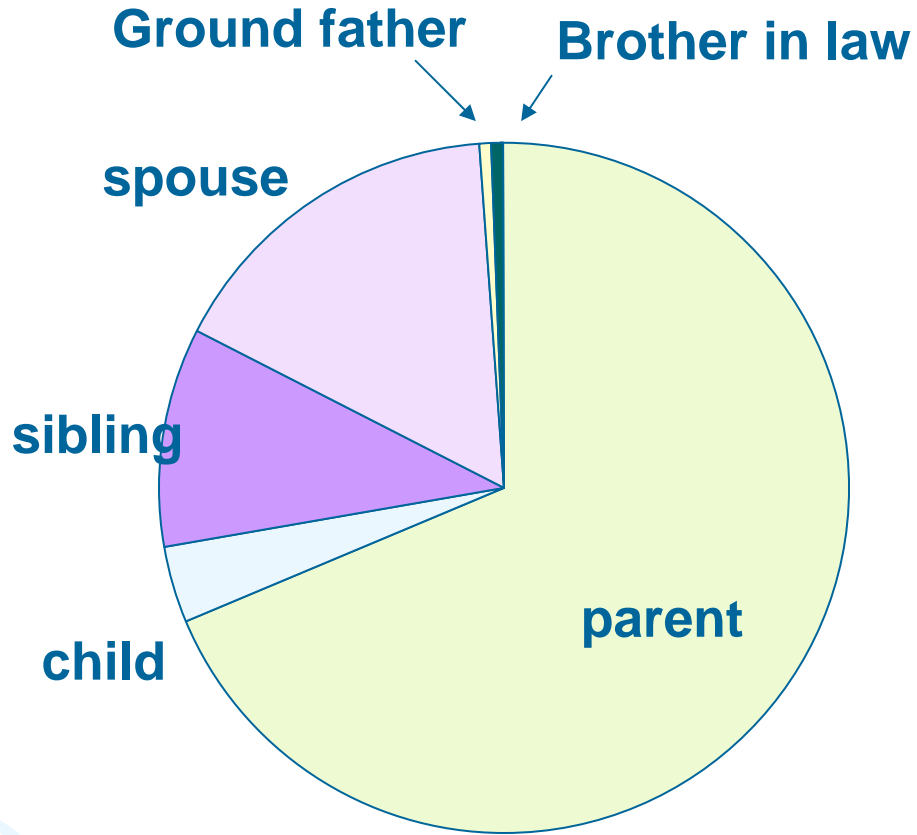


Gender



Preoperative status

Japanese Registry 2004



Donor

Indications



Infusion therapy

Catheter	patient #	Spleen kept
PV	29	1
PV+HA	15	4
HA	24	18

Age of children with a HA catheter
0,5,8,10,10,14,14,14 y.o.

HA Catheter related Complications

- Bleeding
- HAT
- Dislocation
- Bile anastomosis injury by pulling HA catheter

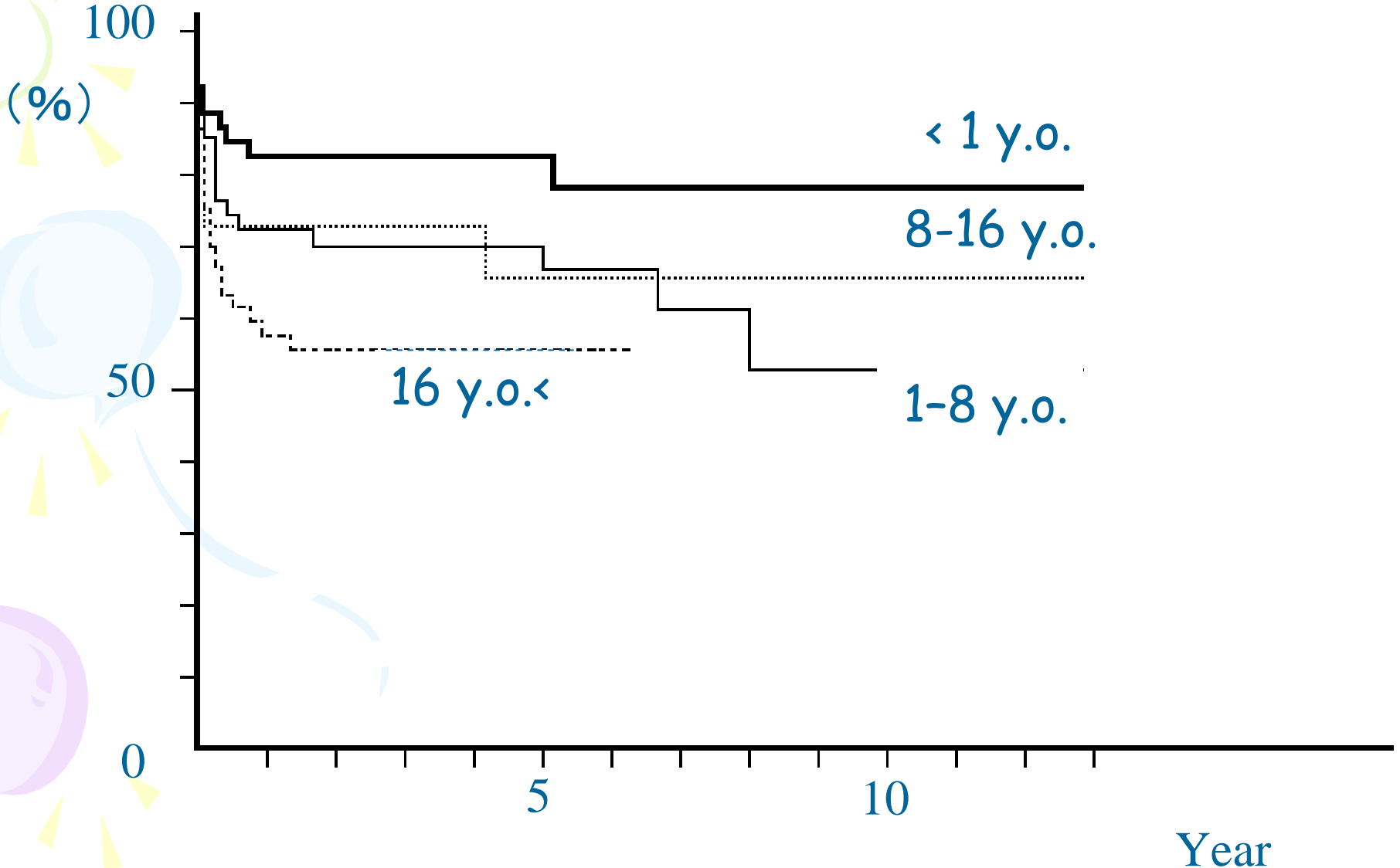
Humoral rejections

- Intrahepatic biliary complication 17
 - death 7
 - infection 5
 - esophageal varices 1
 - pulmonary hypertension 1
- Hepatic necrosis 23
 - death 17
 - graft failure 16
 - infection 1

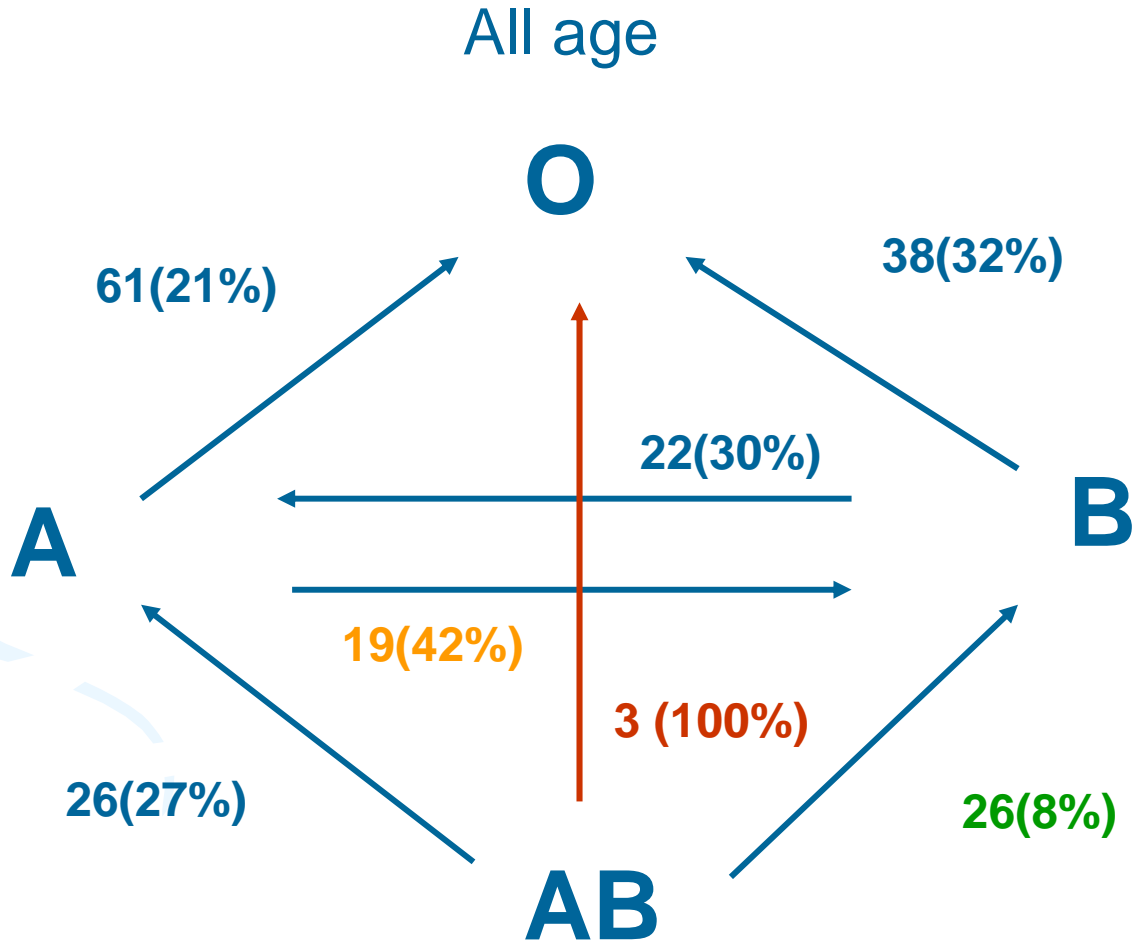
Patients began to survive necrosis in “infusion era”.

Japanese Registry 2004

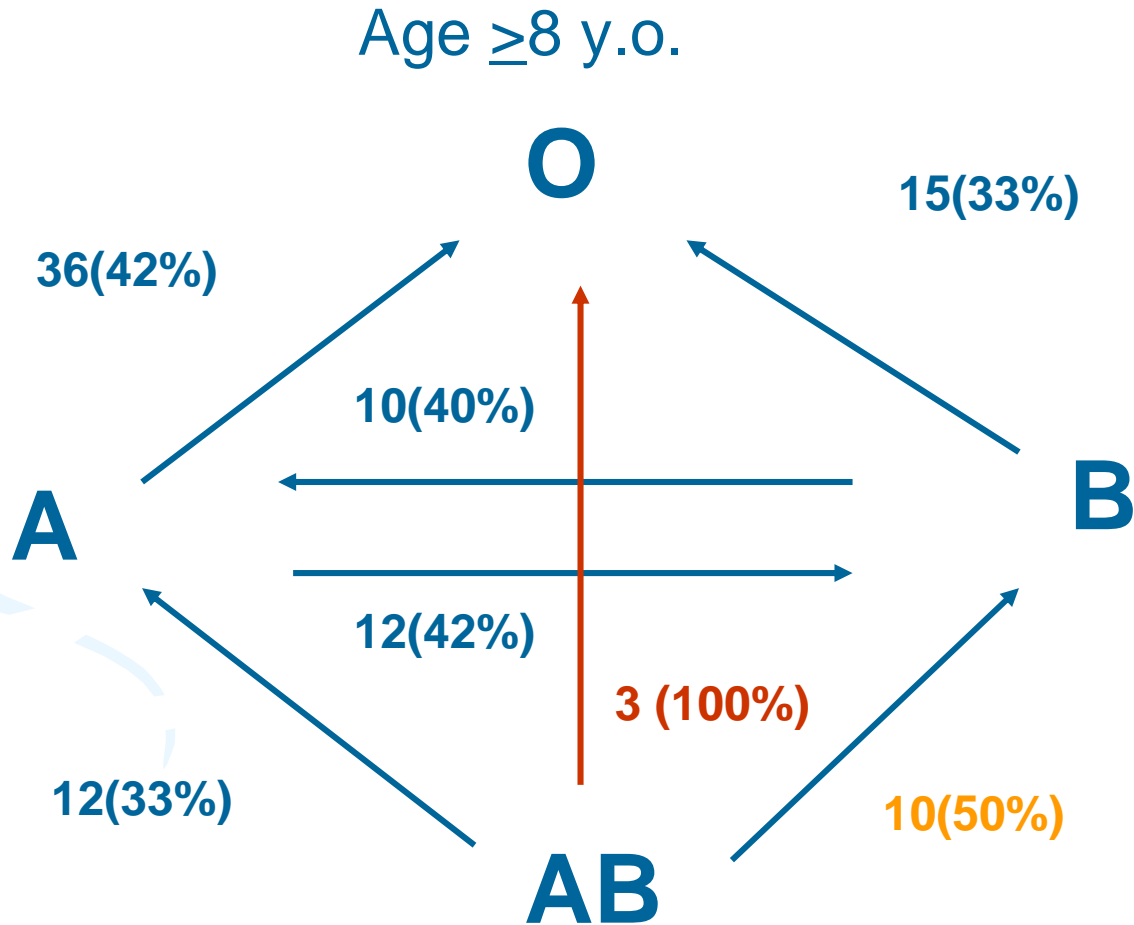
Survival of ABO-I LTx Patients



Blood Type Combination and Mortality



Blood Type Combination and Mortality



Causes of Death



What is next?

Introducing accommodation

by

Inactivating blood type antigens

by

Modulating glycosyltransferase