

Recurrence of diseases after KTx

Prof. Dr. med. Lars Pape

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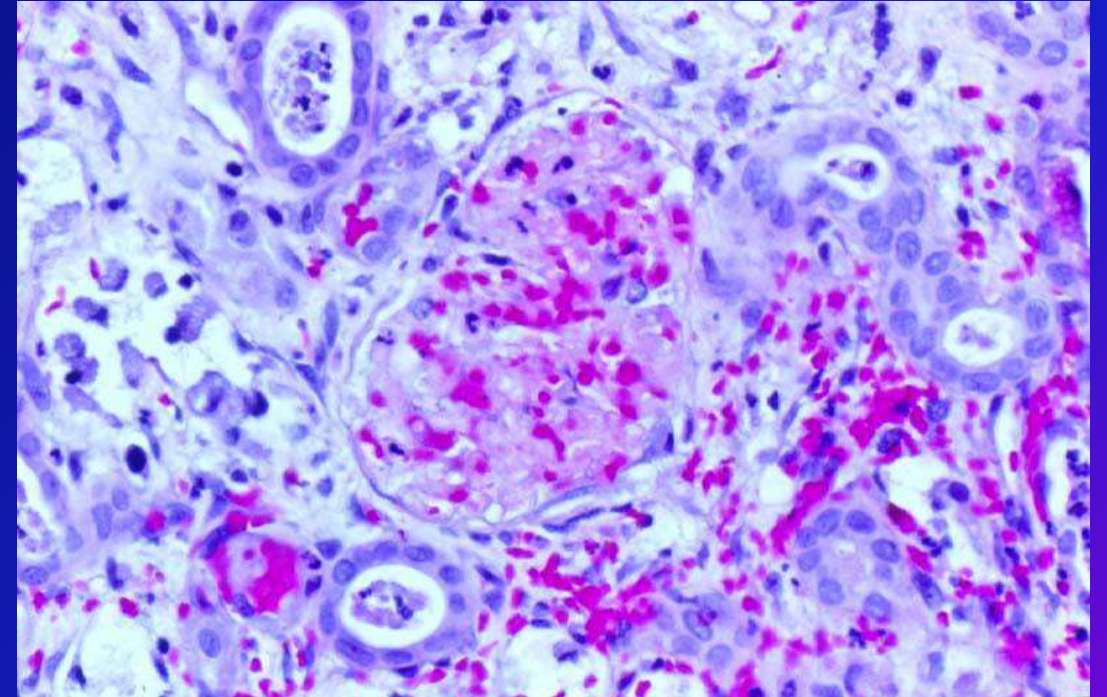
End-stage Renal Disease Transplantation

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Introduction

- 1955 Hume 8/10 hyper acute rejections with ABOi Tx



- ABOi absolute contraindication
- Cross match positive tx – Anti HLA antibodies
- Non – HLA antibodies: Anti-endothelial antibodies

Blood Group Antigens

- A, B and H antigens are blood group antigens on surfaces of different cell types – RBC, endothelial cells, kidney parenchymal cells
- Blood group O determined by Antigen H- matrix for A and B
- A transferase modifies Antigen H → Blood group A
- B transferase modifies Antigen H → Blood group B
- Blood group O no A or B transferase
- A2 subtype low A transferase activity, small amts of A antigen
- Isohemagglutinins are natural antibodies reacting against non-self ABO antigen
- Infancy contact with gut commensal bacteria

ABOi Kidney Transplant

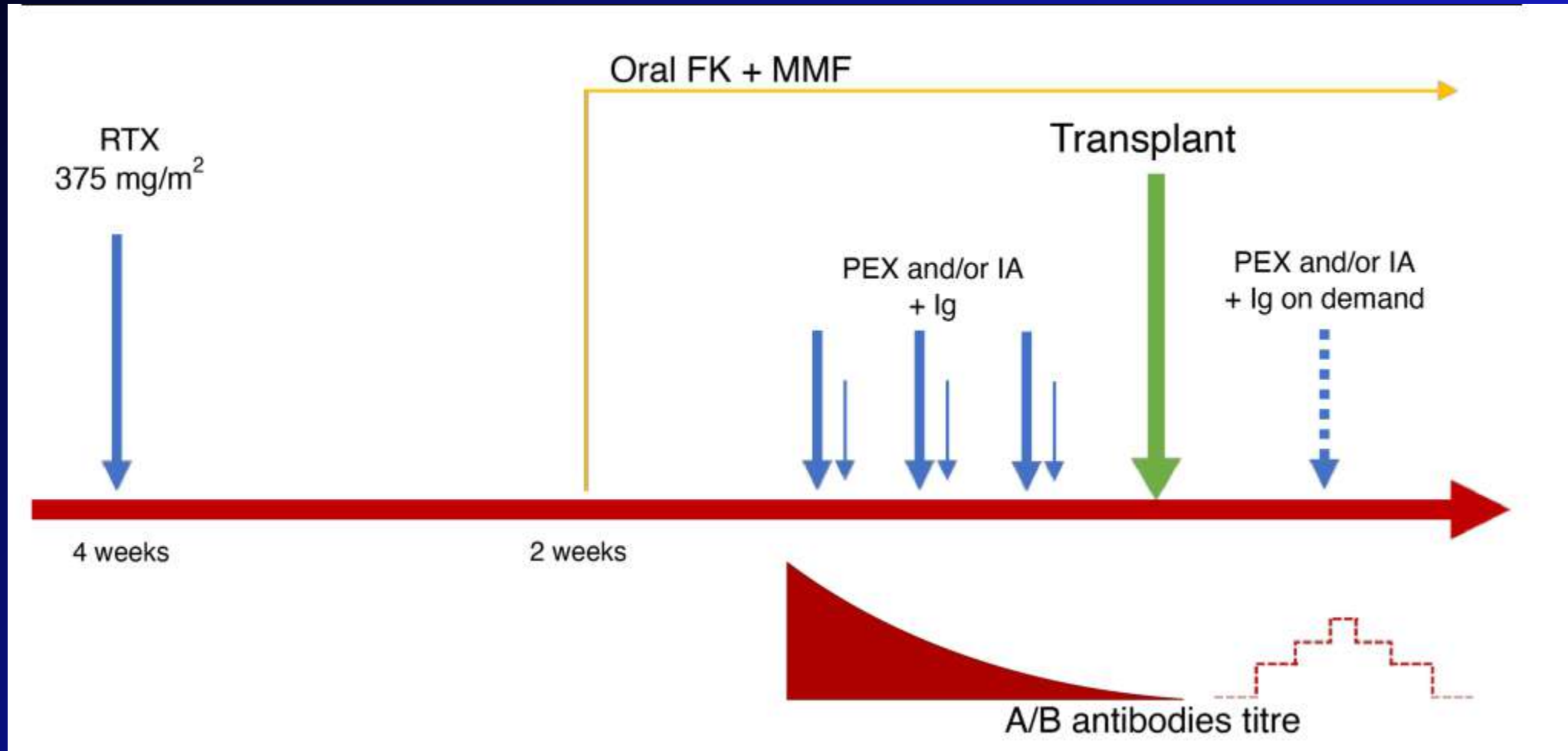
- 1987: Alexandre from Belgium 26 ABOi transplants
 - Desensitisation by PEX, splenectomy, donor thymocyte transfusion and intensified immunosuppression
 - 1 yr graft survival 75%
- Tolerance occurs
 - C4d deposition routinely occurs
 - Accommodation in the graft
 - Different from anti HLA antibodies
 - Mechanism is unclear
- ABOi Japan 1980s, US 1990s and Europe 2000s

Methods of Detection of Anti ABO Antibody

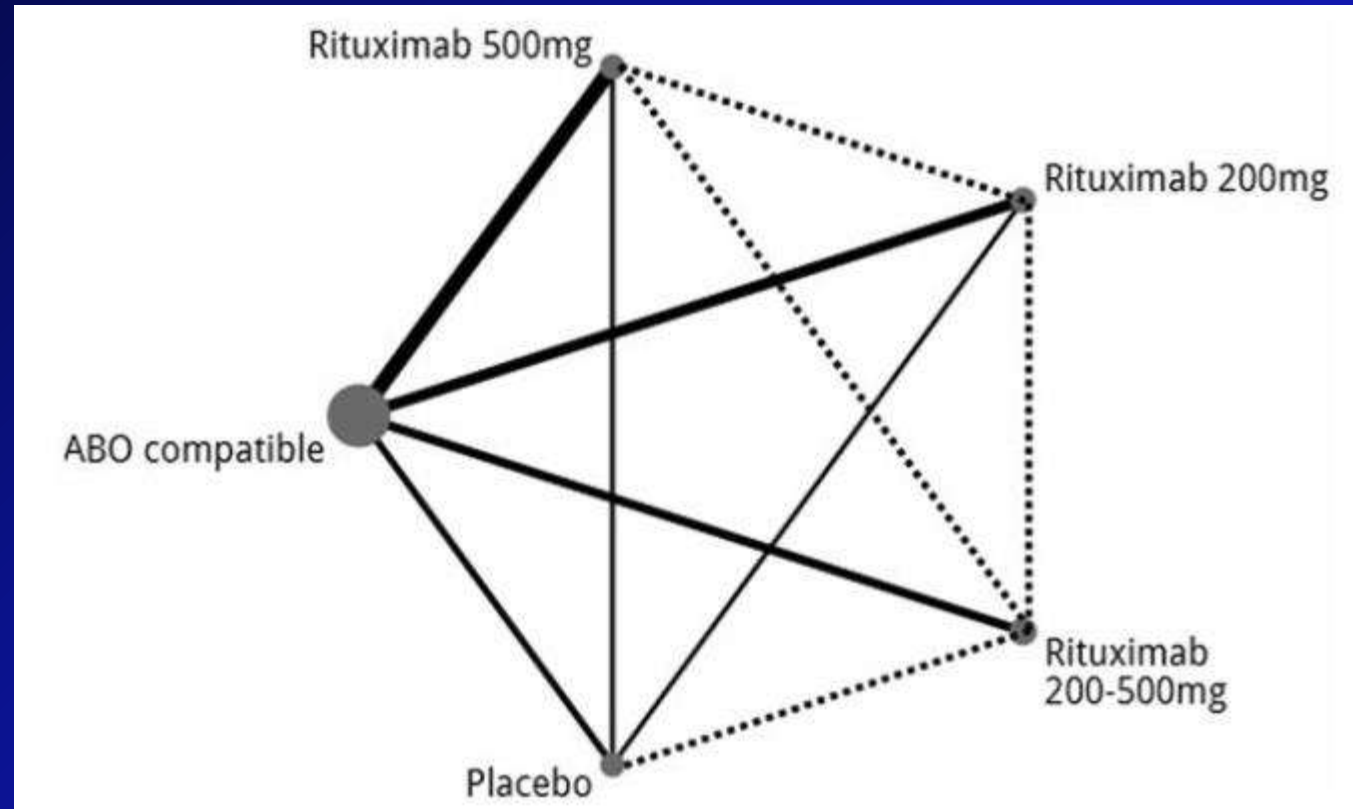
- Two methods:
 - Tube incubation
 - **Gel Column technique**
- Requires less quantity of serum
- Easy to perform
- Automation is possible
- More consistent results
- More sensitive

Principles of Desensitisation

- Anti A/B antibody removal:
 - Plasmapheresis (PEX)
 - Double filtration plasmapheresis (DFPP)
 - Immunoabsorption (IA)
- Modulation of immune system by IVIg
- Reduction of B lymphocyte by splenectomy or Rituximab
- Inhibition of complement activation by eculizumab



Effect of Rituximab dose as Induction Network Meta-Analysis



Lee HR, et al. Medicine 2021;100:10(e24853).

Effect of Rituximab dose as Induction

Network Meta-Analysis

- 21 trials; 4256 patients
- Mortality significantly higher with rituximab 500mg and 200-500 mg doses as compared to 200 mg dose OR 3.5
- BKV significantly lower in 200 mg dose
- Conclusions:
 - Low dose rituximab more efficacious than higher doses
 - Reduced infection risk

Preconditioning Therapy Meta-Analysis

- Searched database for any preconditioning regimen
- 83 studies; 4810 ABOi
- Mean follow-up 28 months
- Overall Confidence in available evidence low
- Rituximab or Immunoabsorption promising preconditioning strategies
- More RCTs required different types, dosing and frequency of preconditioning therapies

Department of Nephrology AIIMS

Protocol for ABOi Renal Transplant

Day	Date	Days	PLEX	IVIg (0.5 g/Kg) wt 60 kg	Tac (0.10 mg/kg)	MMF	Wys	Biological	Anti A Titer	Tests
-14	11.10.22	Fri						Ritux 200 mg Valgan, Septran	IgG 1: 256	CDC Neg FxCm Neg
-10	15.10.22	Tues	HD		12 mg	500 mg BD				
-9	16.10.22	Wed			12 mg	500 mg BD			Anti A	
-8	17.10.22	Thurs	PLEX		12 mg	500 mg BD				
-7	18.10.22	Fri	HD		12 mg	500 mg BD			Anti A	Tac
-6	19.10.22	Sat	PLEX	10	12 mg	500 mg BD				
-5	20.10.22	Sun	HD		12 mg	500 mg BD				
-4	21.10.22	Mon	IA	10	12 mg	500 mg BD			Anti A	
-3	22.10.22	Tues	HD		12 mg	500 mg BD			Anti A	CDC
-2	23.10.22	Wed	IA	10	12 mg	1000 mg BD				
-1	24.10.22	Thurs	±PLEX, HD		12 mg	1000 mg BD			Anti A	
0	25.11.22	Fri			12 mg	1000 mg BD		MP 500 mg		Tac, RT

MAIN BLOOD BANK. DEPT. OF TRANSFUSION MEDICINE, AIIMS, NEW DELHI
THERAPEUTIC PLASMA EXCHANGE ASSESSMENT AND REQUIREMENT FORM

History of the patient

Name - Age/Gender : Height:- Weight:-

UHID _____ Diagnosis _____ TBV: _____ PV: _____ Blood group: _____

Indication for PLEX-	AFSA-
Hemoglobin	PT
Hematocrit	APTT
Platelet count	INR
TLC	Calcium
RBC Count	Na
Total protein	K
	AST
	Urea
	Creatinine
	Serum Bilirubin
	ALP
	ALT

Requirements

1. Vascular access: DLFC (12F)
2. Consumable kit: SPECTRA OPTIA 10220
3. ACD: 2-3
4. FFP N/A (Send request for in the morning 8 a.m. of the day of the procedure)
5. Normal Saline 500 ml GLASS BOTTLES 10-12
6. 100 ml ALBUMIN (20%) 8
7. UPS FOR POWER BACK UP
8. Three way cannula - 2
9. IV set - 2
10. 10 ml syringe -10
11. 50 ml syringe- 2
12. 100 ml NS BOTTLES-2
13. Calcium Gluconate -3 VIALS
14. Heparin Injection- 5 ml / Heparin 5000IU or 25000 IU INJECTION -1 VIALS
15. Cardiac Monitor /SPO2 probe
16. Infusion pump
17. OT Sheet -2

*Kindly make sure that patient's attendant donates blood.

1. All the prerequisites (include arranging of the Aphaeresis kit ,Albumin ,FFP,ACD) should be completed before calling the blood bank at 3876
- 2.All the equipments in the ward will be managed by the bed side staff (includes vascular access management ,albumin preparation, patient vital monitoring and connection ,inlet and return connection to apheresis machine)
- 3.A Resident and Nursing officer should always be present bed side with the patient
- 4.Failure to provide bedside services in view of the patient care shall lead to delay or postponement of the procedure

Senior Resident ward

Sister in charge of ward



ALL INDIA INSTITUTE OF MEDICAL SCIENCES
Ansari Nagar, New Delhi-110029

ESTIMATE CERTIFICATE

(For Availing Financial Assistance through RAN/HMDG)

This is to certify that Mr./Mrs./Ms. _____ Age _____ Sex (M/F), UHID _____ is suffering from (complete diagnosis) _____
The patient is currently under treatment of Dr. _____ (designation),
_____ (Department) _____ The patient will be unable to afford the cost of the treatment of the
aforementioned disease.

Assistance is being sought for the following through the existing RAN packages:

S.NO.	Procedure Code (As given in the Package Master)	Name of the Procedure	Cost
1	MG072A	Hemodialysis (One)	1500/-
2	OT001B	Induction	39526/-
3	MG073A	Plasmapheresis (One)	2000/-
4	OT001A	Transplant surgery including donor nephrectomy	2,15,595/-
5	OT001D	Post-Transplant Medication – Month 1-3	50,000/-
6	OT001E	Post-Transplant Medication – Month 3-6	50,000/-
7	OT001F	Post-Transplant Medication – Month 6-12	40,000/-
		TOTAL	3,98,621

Details of medicines/consumables/procedure not available in the Package Master, i.e. in addition to the standard procedure as above but are required for treatment of patient and are as follows:

S.NO.	Detail of Medicine/Consumable/Procedure (Not mentioned/Included in package master) Procedure Code	Approximate Cost in rupees (to be mentioned as approximate cost actually limited to one month, and approximate monthly cost thereafter)
1	Hemodialysis 3 per week/six months including medications	2,50,000/-
2	Donor and recipient work-up	45,000/-
3	CMV Management Post Transplant	1,80,000/-
4	Additional Induction (Basiliximab/ATG)	1,10,000/-
5	Additional Plasmapheresis including P2 Dry Filter, Human albumin 20% and tubing	1,90,000/-
6	Immunoadsorption column	2,75,000/-
	TOTAL	10,50,000/-

TOTAL= Rs. 3,98,620/ + Rs. 10,50,000/ = 14,48,620/ (Fourteen lac, forty eight thousands and six twenty only)

Name and Signature
(Head of the Department)

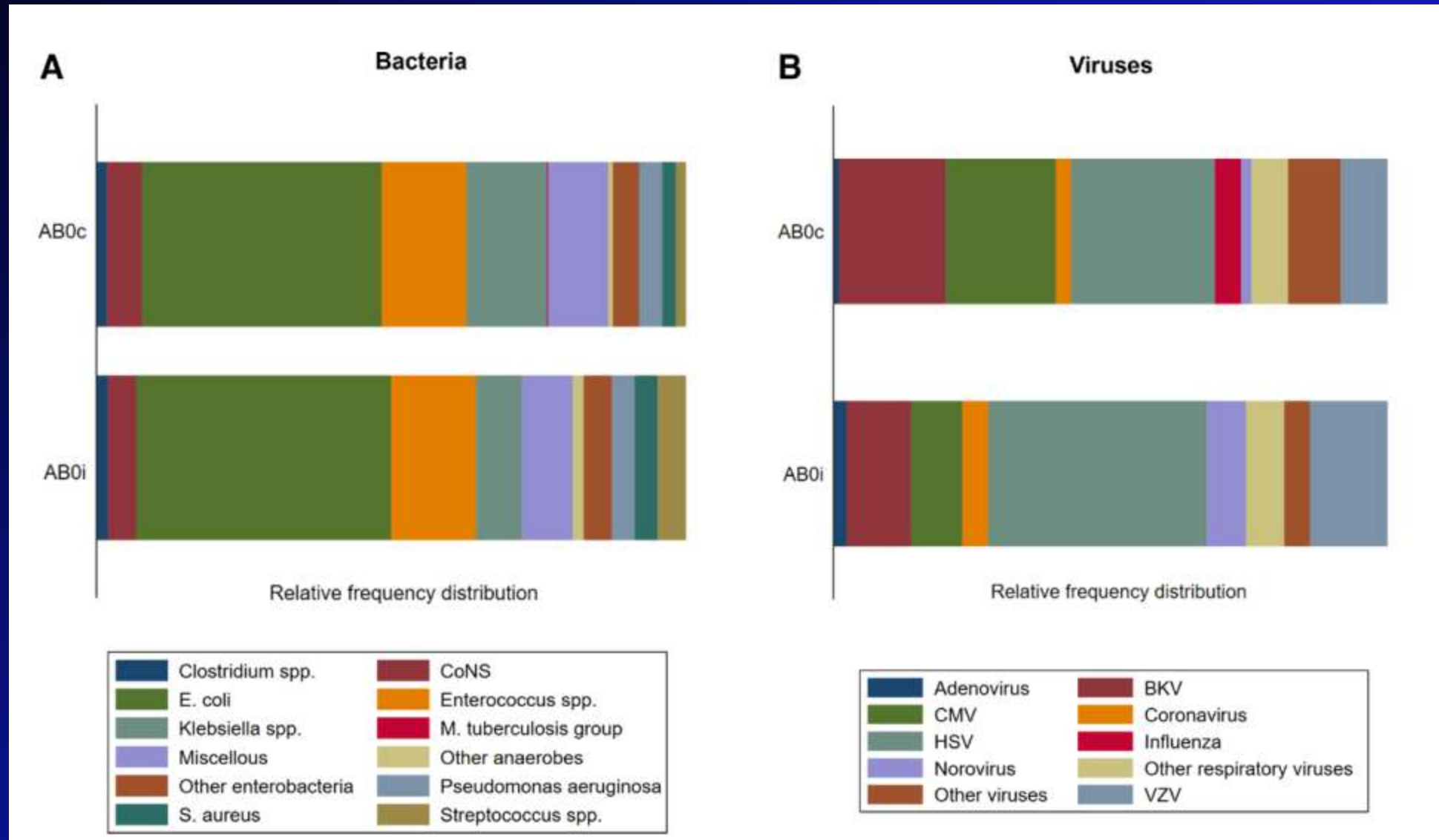
Name and Signature
(Treating Faculty)

Medical Superintendent

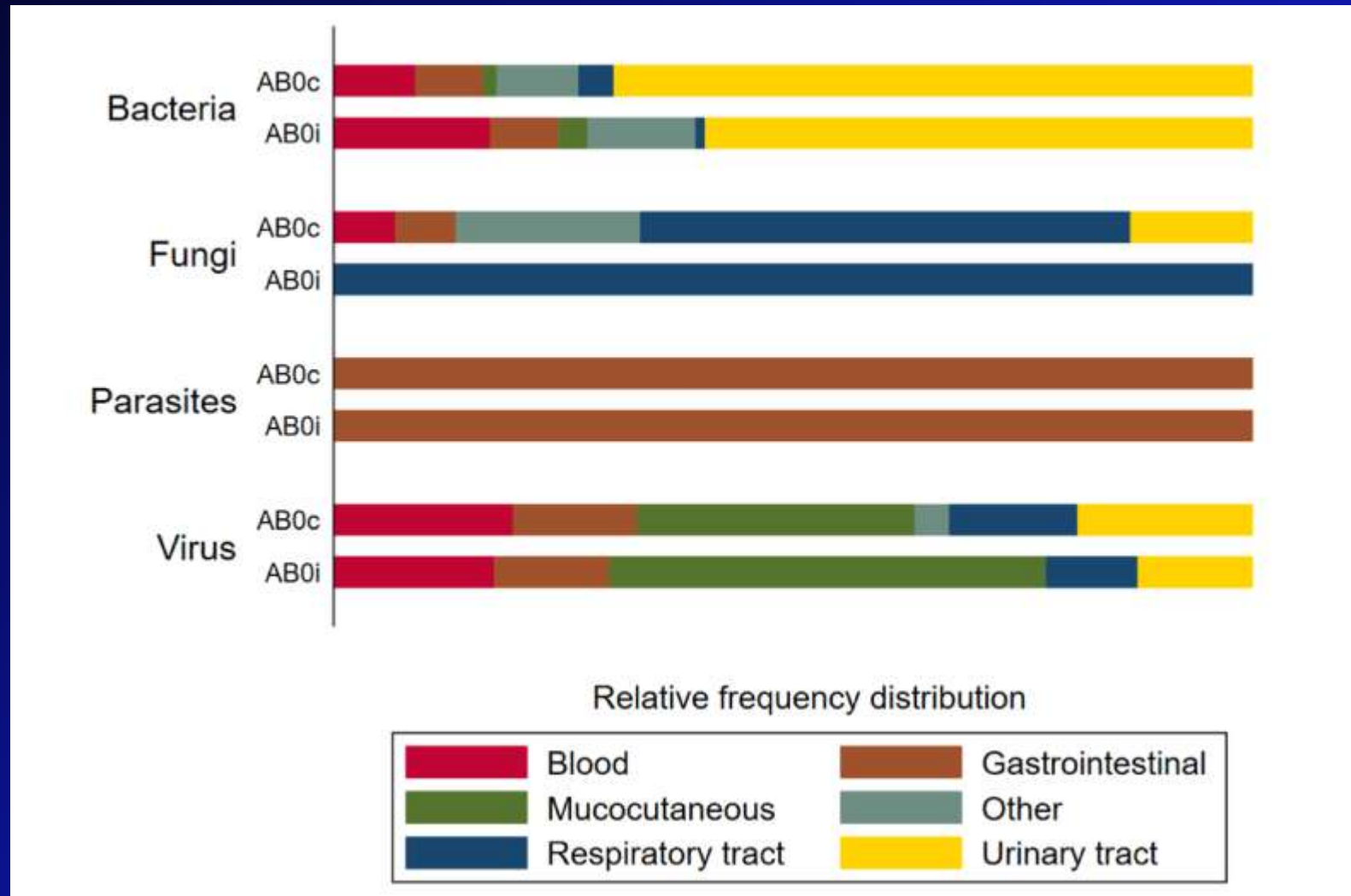
Infection Risk

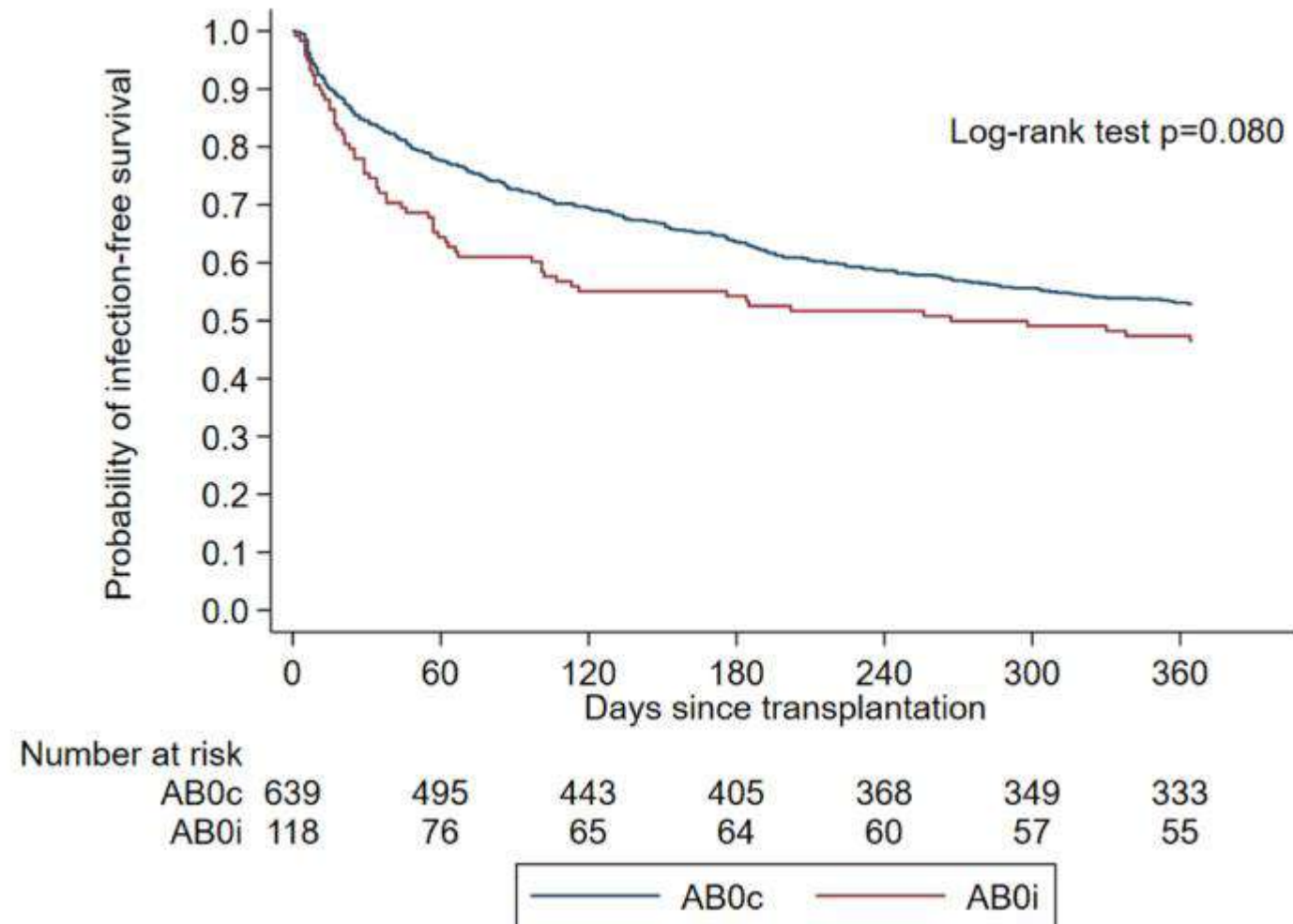
- ABOi: 118, ABO: 639
- 717 infection episodes
- Crude infection rate
 - ABOi: 1.1 episodes per patient year, ABOc: 0.94
- Spectrum of causative pathogens and anatomical sites similar
- Overall burden high, but not different

Relative Frequency Distribution of Pathogen



Relative Frequency Distribution of Anatomical Location of Infection

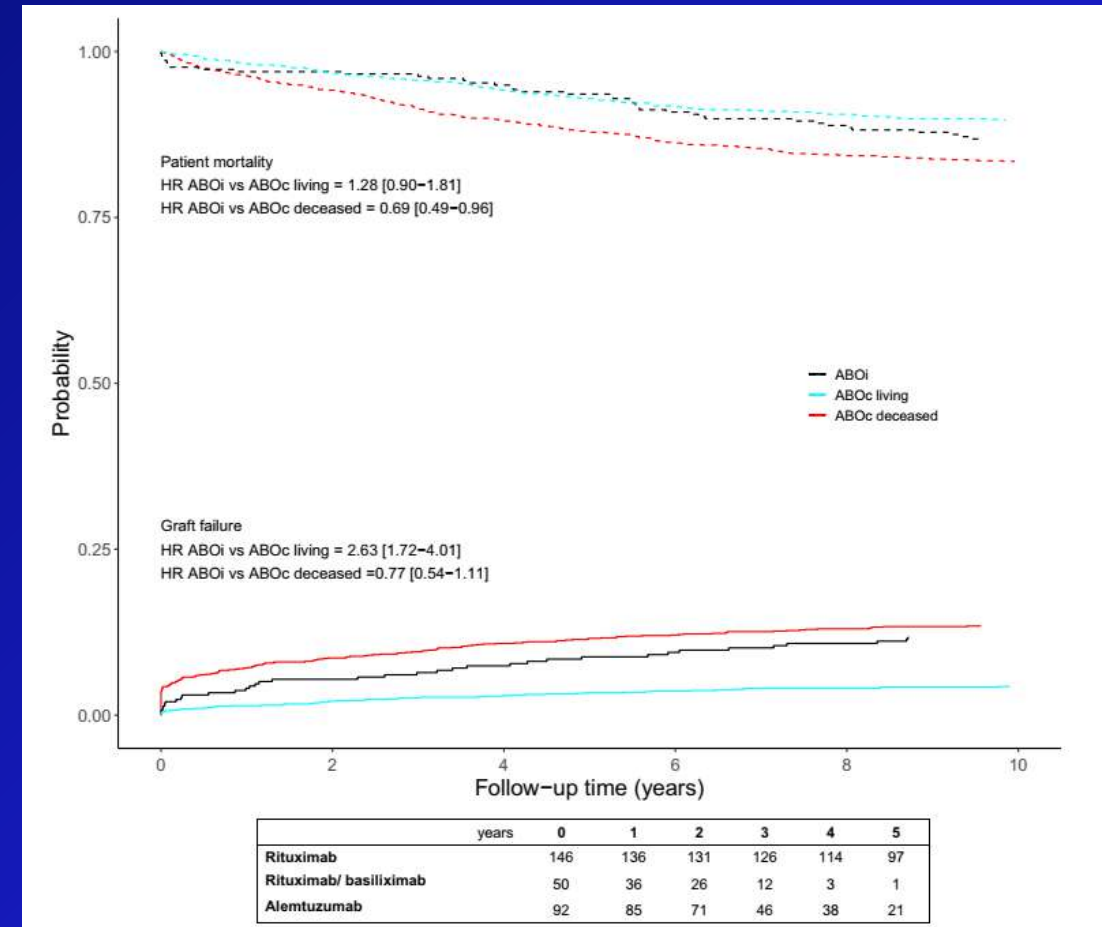




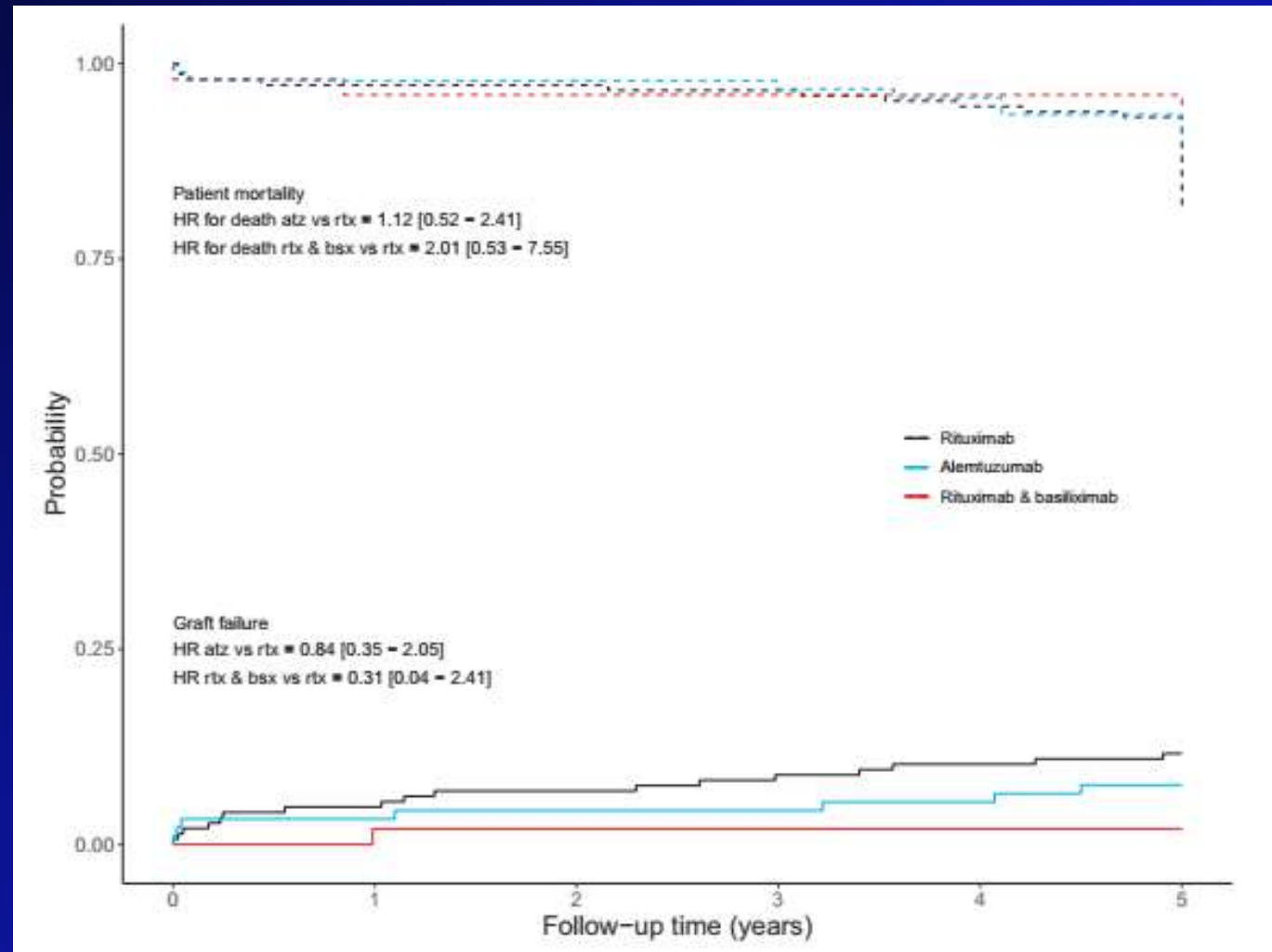
Hirzel C, et al. Transplantation 2022;106:1875.

Comparison of 3 types of Transplantations

- Netherlands Registry
- Retrospective Study 2006-2019
- ABOi: 296, ABOc: 1184 living
- ABOc: 1184 deceased
- Propensity score matching
- Patient survival better than deceased
- Non-significant from living
- Rejection and Graft failure higher than living



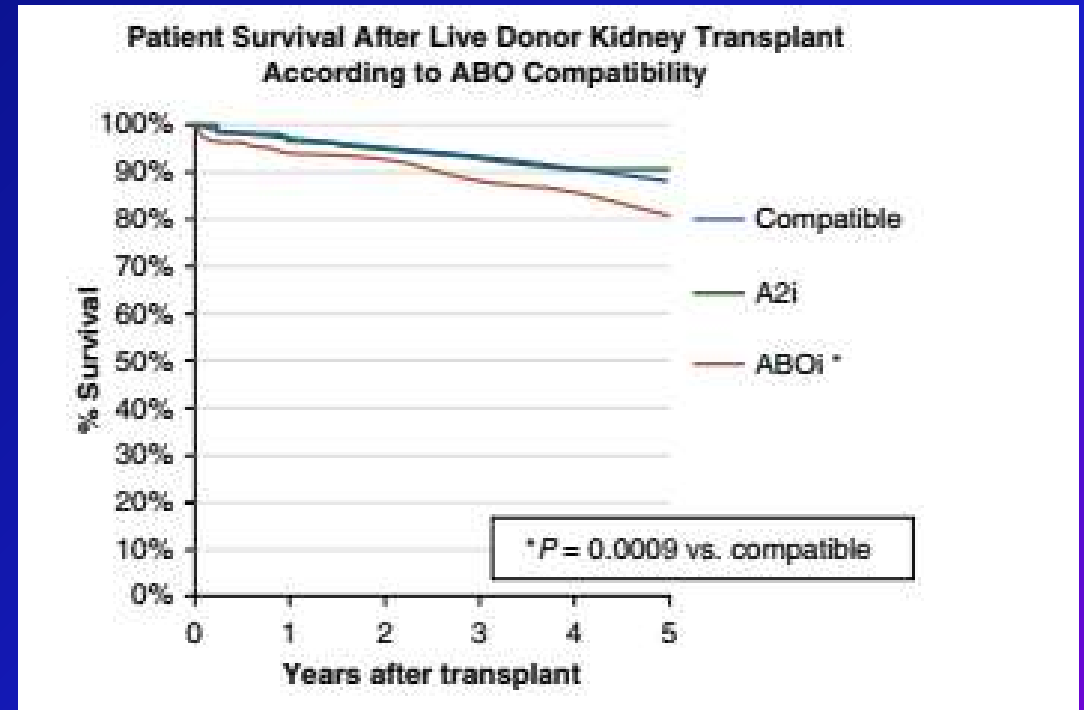
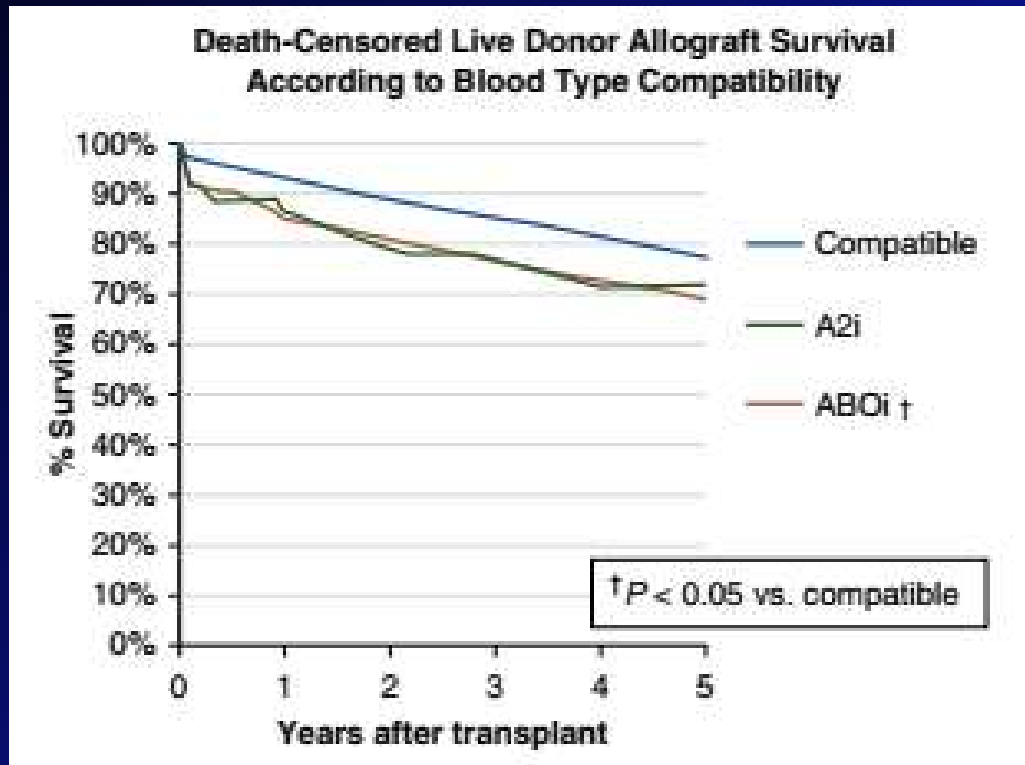
Comparison of 3 types of Induction Regimens



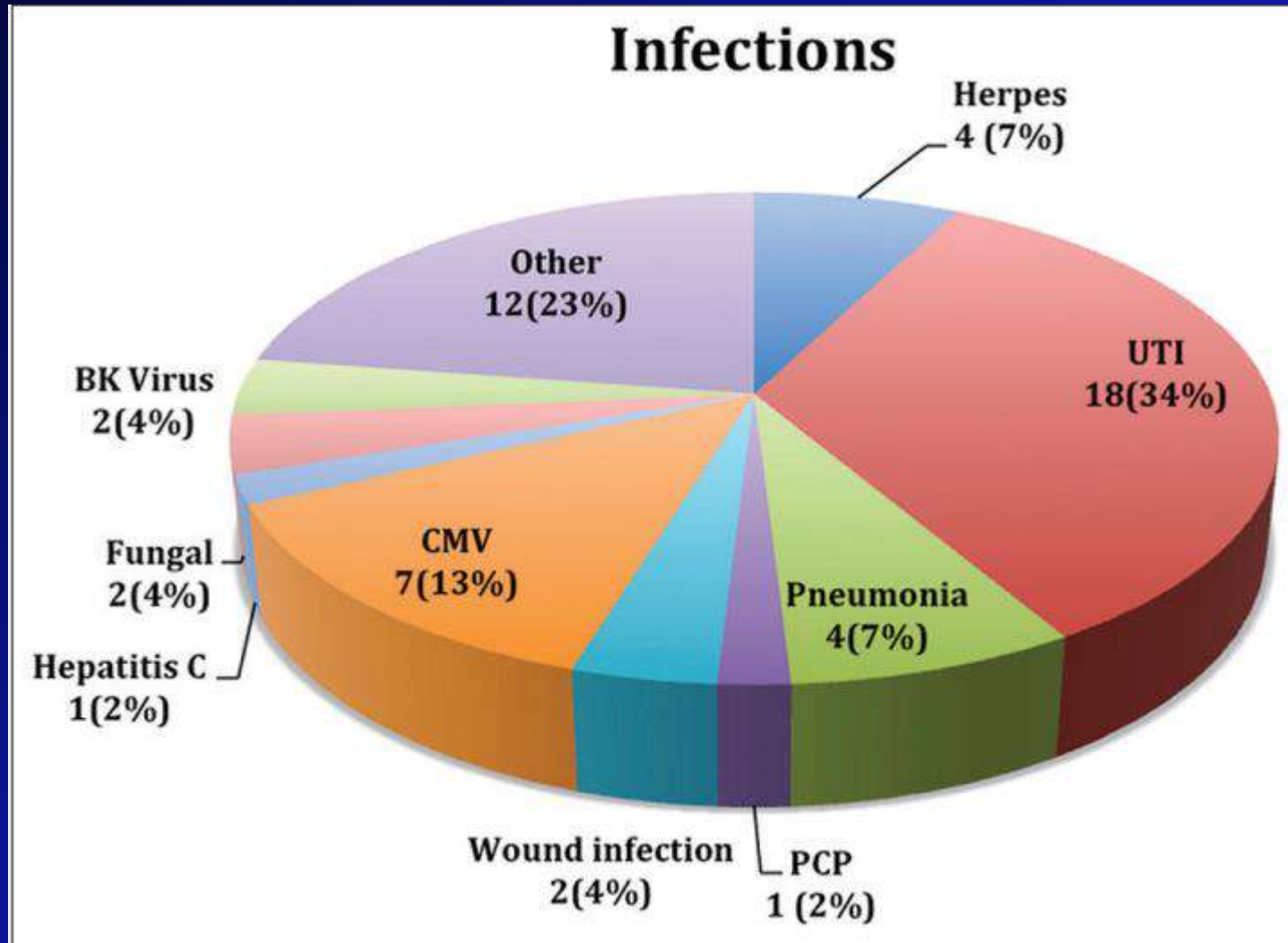
Clinical Outcomes after ABOi

Systematic Review and Meta-Analysis

- Observational Studies with ABOC control group
- Follow-up more than 1 year
- Outcome of graft / patient survival
- 1264 studies screened; 49 patient groups identified
- 7098 patients with ABOi
- Death censored graft survival lower at 1 and 3 years
- Higher 1 year mortality at 1, 3 and 5 years
- Graft losses equivalent after 5 yrs & pt survival after 8 yrs



100 cases in Medanta Hospital



Outcomes of Pediatric ABOi 2000-2015

Analysis of Japanese Kidney Transplant Registry

- 102 ABOi vs 788 ABOc
- All received Basiliximab during operation and D4
 - 10 mg body weight <35 kg & 20 mg body weight > 35 kg
- Tac dose 0.1-0.3 mg/kg adjusted to Tac levels
 - 0-3 mths: 8-12, 4-6 mths: 6-8 and > 6 mths: 3-6
- MMF: 600-1200 mg/m²
- Methylprednisolone 10-15 mg/kg iv intraop
 - 0.1-0.25 mg/kg/day 1 month
 - 0.1 0.2 mg/kg alternate days

Outcomes of Pediatric ABOi 2000-2015

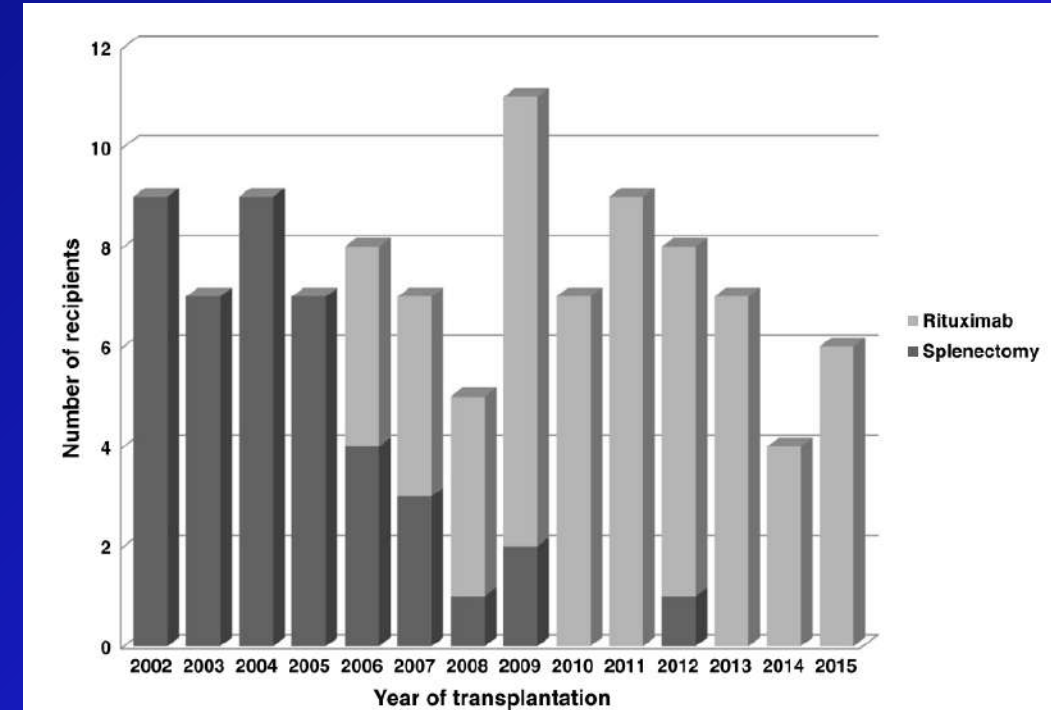
Analysis of Japanese Kidney Transplant Registry

- **ABOi preconditioning:**

- Splenectomy before 2005
- Ritux 150-375mg/m²
- MP and MMF 1-2 wks before tx.
- PEX / DFPP; IA not done in Japan
- Anti AB level <1:8 to 1:16
- No routine post-op PEX

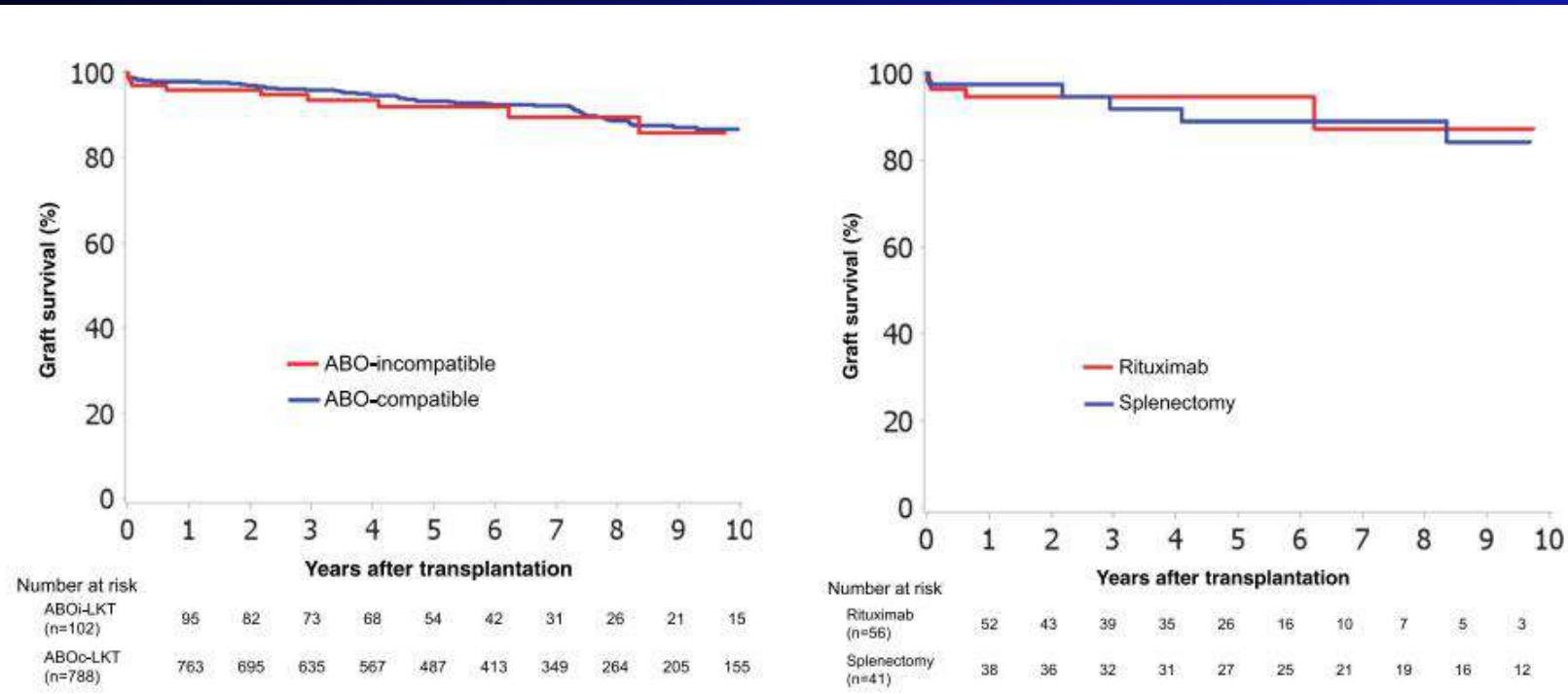
- Cotrimoxazole for 6 months

- Routine CMV monitoring & Pre-emptive therapy



Outcomes of Pediatric ABOi 2000-2015

Analysis of Japanese Kidney Transplant Registry



Graft loss: 1.58 vs 1.45 /100 pt yrs
 Death rates: 0.17 vs 0.17 /100 pt yrs

Outcomes of Pediatric ABOi 2000-2015

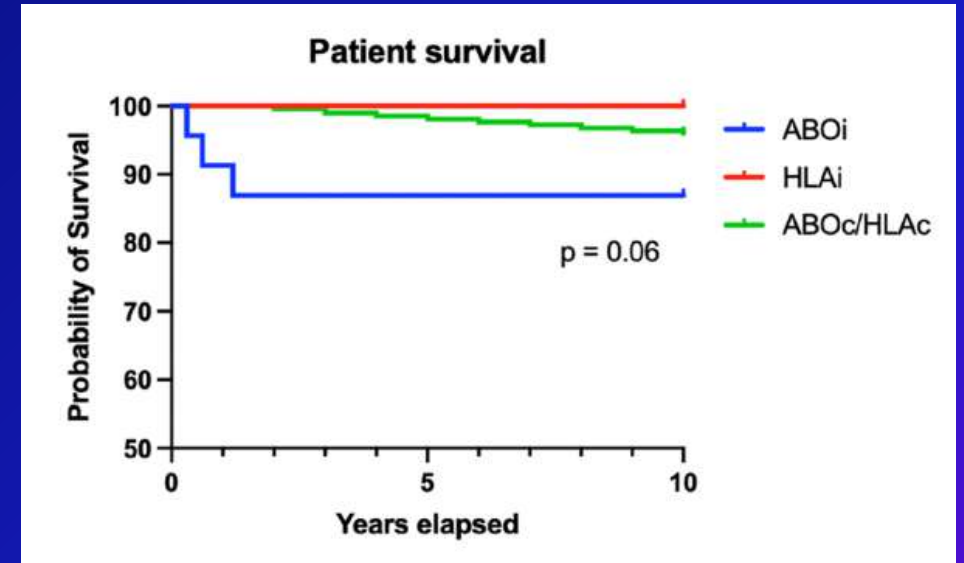
Analysis of Japanese Kidney Transplant Registry

Causes of graft loss in the study population stratified by ABO compatibility		
	ABOi-LKT	ABOc-LKT
	n = 102	n = 788
Graft loss	9 (8.8%)	74 (9.4%)
Component graft loss		
Death with functioning graft	1 (1.0%)	6 (0.8%)
Acute rejection	1 (1.0%)	5 (0.6%)
Chronic rejection	3 (2.9%)	27 (3.4%)
Recurrence of primary kidney disease	2 (2.0%)	4 (0.5%)
Nonadherence	0	13 (1.6%)
Technical and/or thrombosis	2 (2.0%)	7 (0.9%)
Other	0	11 (1.4%)
Unknown/missing	0	1 (0.1%)

Hattori M, et al. Transplantation 2018;102:1934.

UK Experience

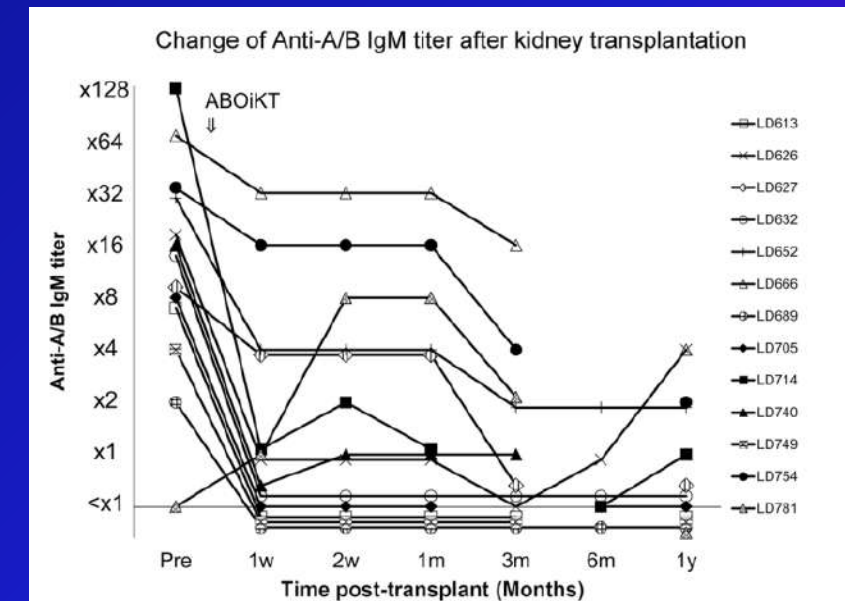
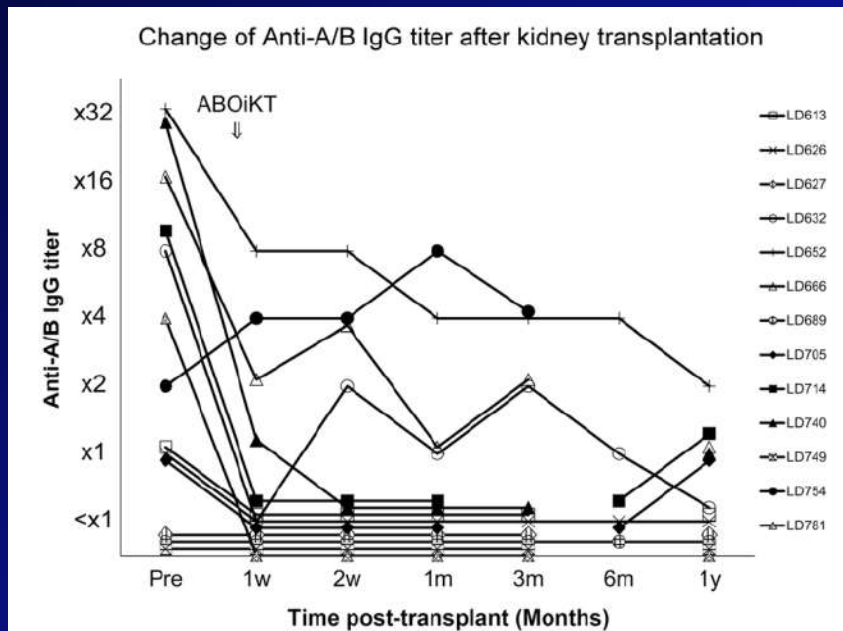
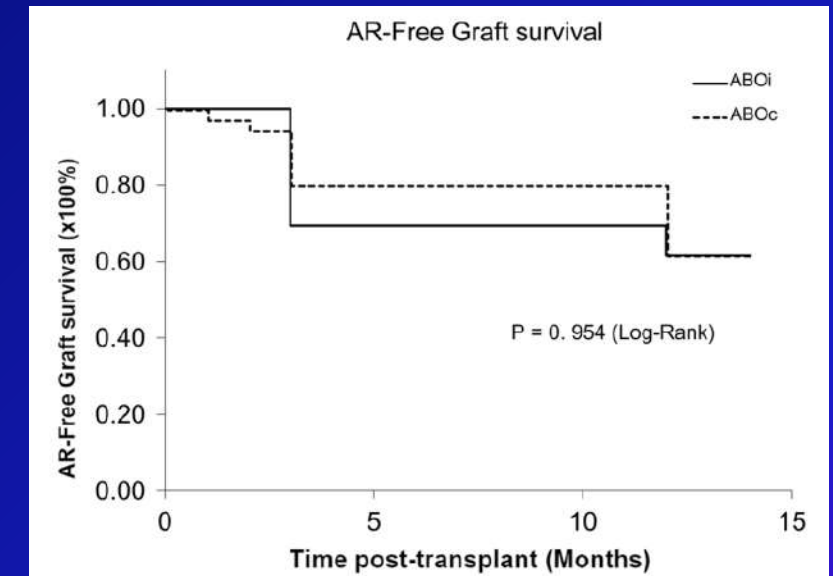
- Questionnaires to 13 UK centres
- Total 711 living
 - 23 ABOi
 - 6 HLA i
- Fu 6.8 years
- Death censored kidney survival 100% all groups



Pediatric ABOi without Antibody Removal

- Tokyo University
- 13 patients 7.4 years (3.4-15.7)
- Baseline anti A/B IgG titres < 1:64
- ABOi without antibody removal or splenectomy
- Rituximab 100 mg twice
- MMF initiated on day -10
- Protocol biopsies at 3 mths and 1 year
- Compared with 37 ABOc
- Mean fu 32 mths vs 28 mths

- eGFR No difference in both groups
- Death censored graft survival 100% ABOi vs 94.6%
- Patient survival 100% both groups



Indian Data

- Medanta group
- 3 ABOi transplants
- Pediatr Transplant 2018;22:e13138

Conclusion

- ABOi is now a clinical reality
 - Adults and pediatrics
- Comparable and acceptable results
- More research needed
 - Preconditioning regimen: method, dose

THANK YOU