ABO incompatible kidney transplantation from a living donor: an effort to establish a common Belgian protocol in the context of the Belgian Transplantation Society

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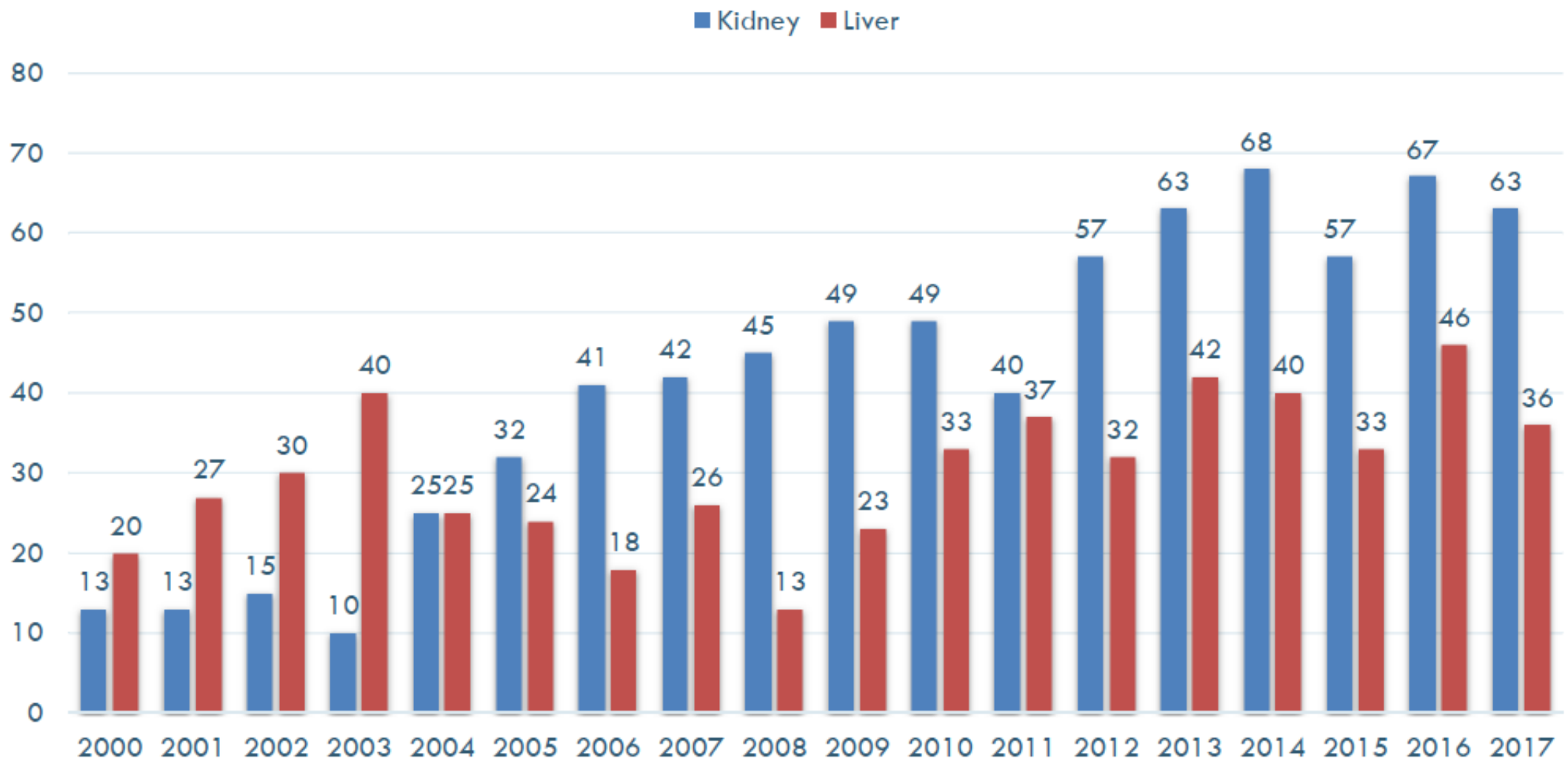
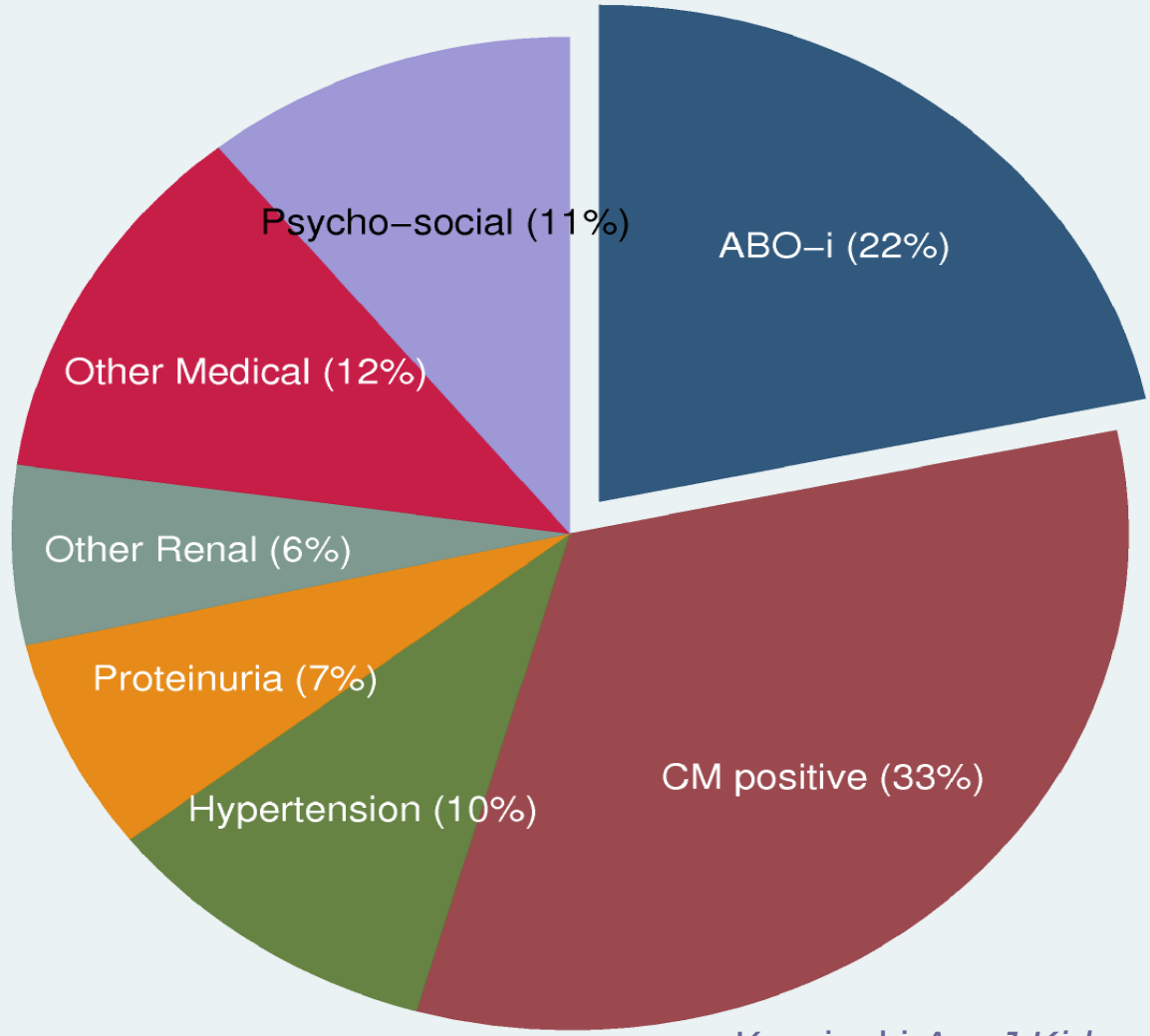
Outline of the presentation

1. Why a Belgian ABOi protocol?
2. What numbers/proportions can we expect?
3. ABOi Tx: biology and results
4. Principles of successful ABOi TP
5. The first draft of the Belgian ABOi protocol
6. Future hurdles to be tackled

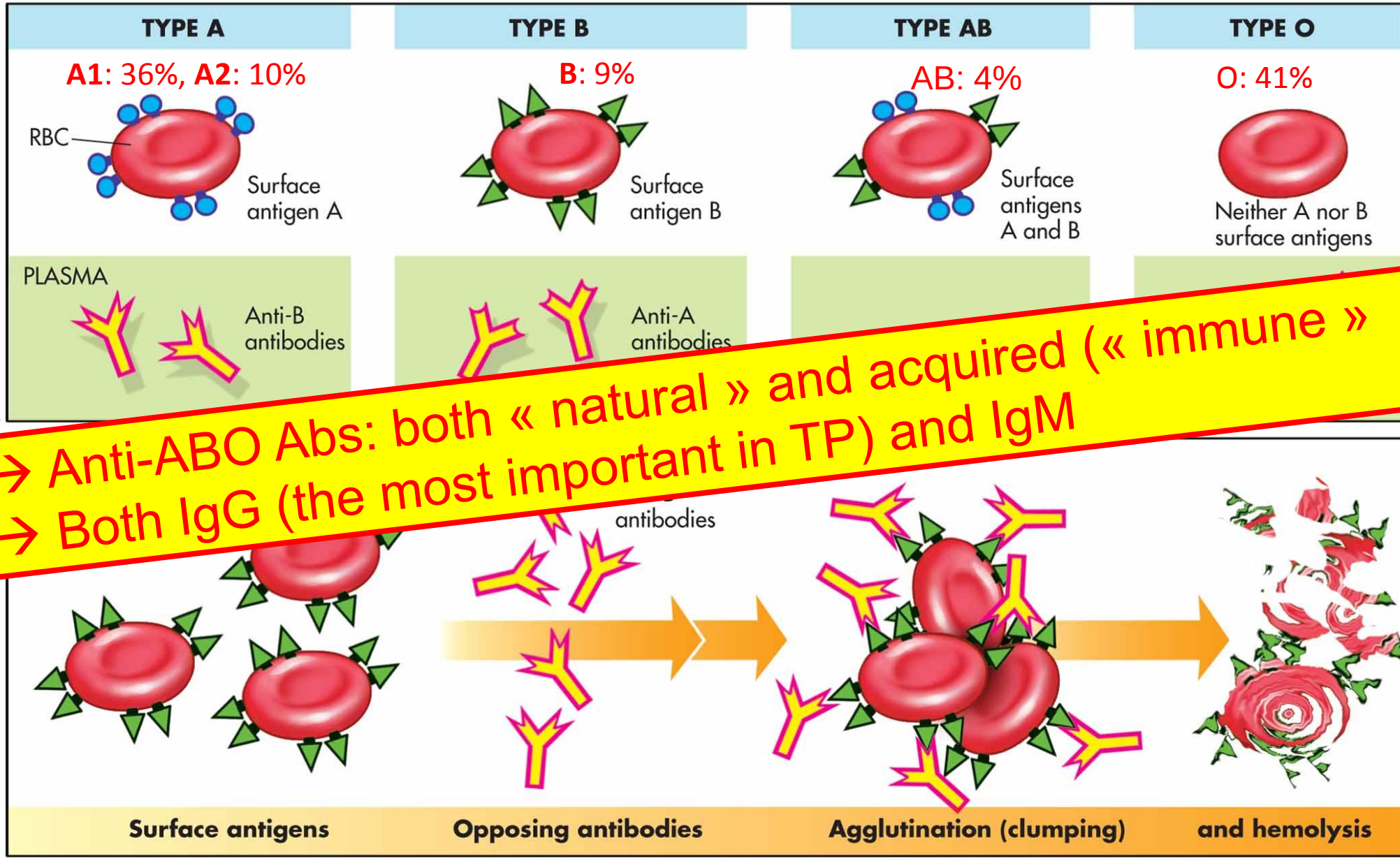
LIVING DONOR TRANSPLANTS 2017



Up to 30% of potential LD are excluded because of ABOi



Karpinski *Am J Kidney Dis* 2005; 47:317



→ Anti-ABO Abs: both « natural » and acquired (« immune »

→ Both IgG (the most important in TP) and IgM

Expression des Ag ABO dans le rein

- Artères, veines

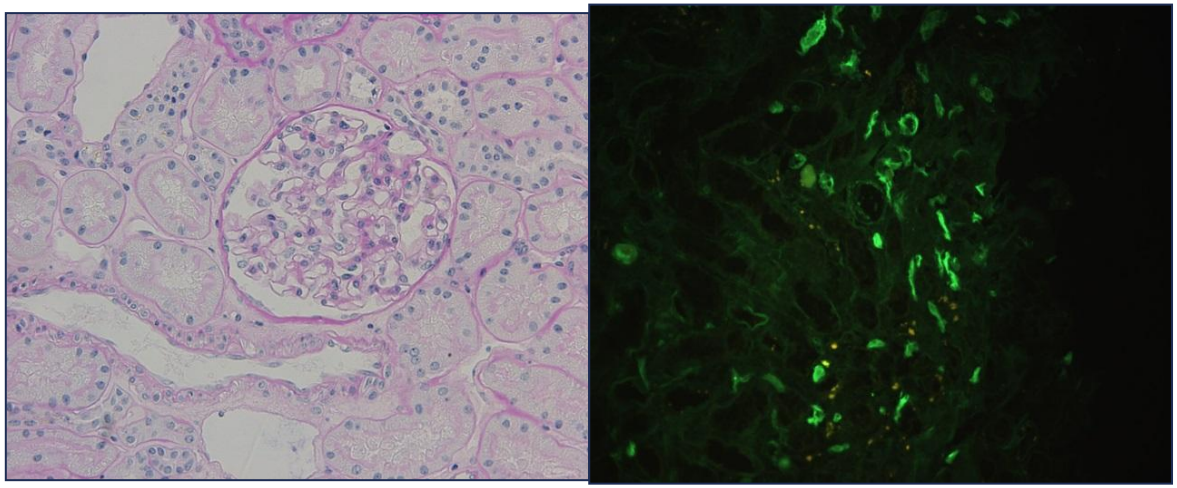
- Capillaires
  Glomérulaires

- Membranes basales
  des cellules
  épithéliales des tubes

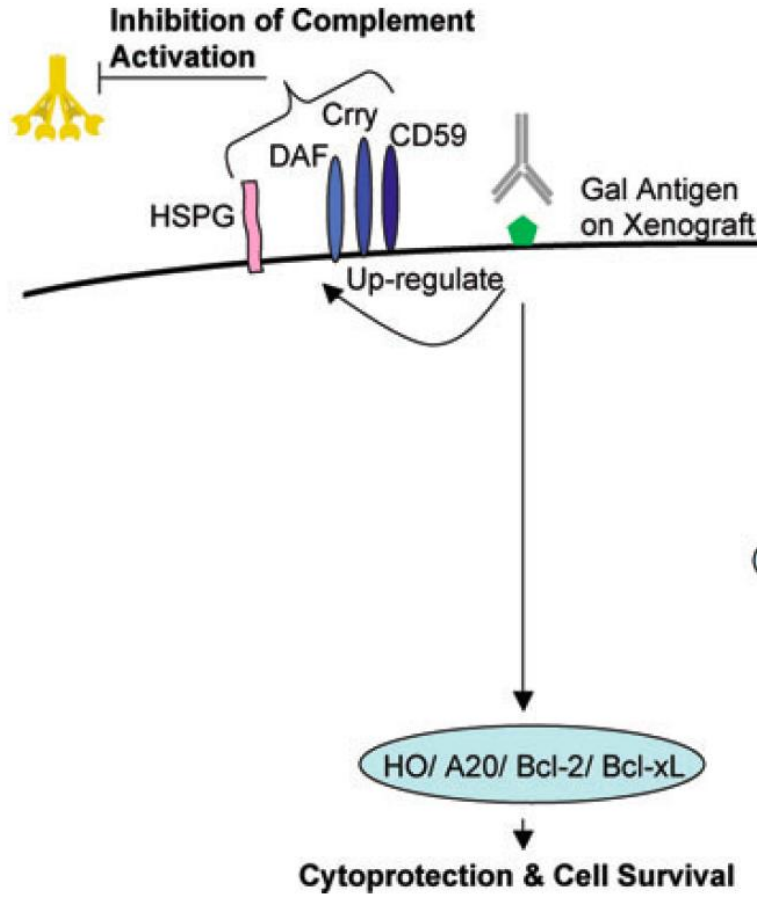
→Rejet hyperaigu humoral si transplantation en présence d'Acs anti-ABO

Accomodation: limited Ct activation without graft damage

Systematic Tx biopsy, day 21, nl Tx function, anti-A: 1/32



Light MO C4d staining



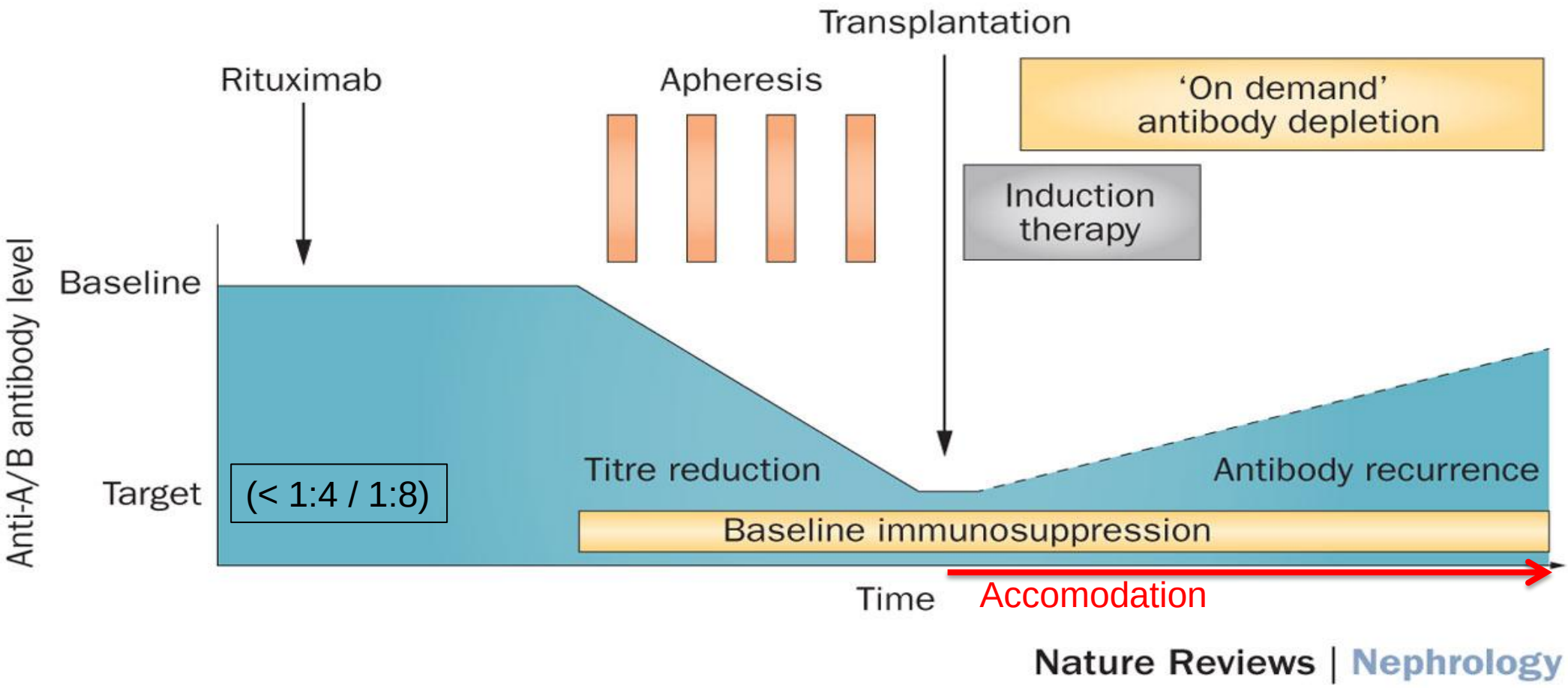
PRE-TRANSPLANT DESENSITISATION

1. ANTIBODY REMOVAL
2. ASSAY AB TITERS
3. PREVENT AB (RE)SYNTHESIS
4. IMMUNOSUPPRESSION

'APHERESE'

MANY DIFFERENT PROTOCOLS, NO SINGLE RCT!

DESENSTISATION PROTOCOL



Böhmig, G. A. *et al.* (2015) Strategies to overcome the ABO barrier in kidney transplantation
Nat. Rev. Nephrol. doi:10.1038/nrneph.2015.144

Three-Year Outcomes Following 1420 ABO-Incompatible Living-Donor Kidney Transplants Performed After ABO Antibody Reduction: Results From 101 Centers

Gerhard Opelz,[1] Christian Morath,[2] Caner Süsal,[1] Thuong Hien Tran,[1] Martin Zeier,[2] and Bernd Döhler[1]

Transplantation, 2014

>2000: Japan, Europe, US: results of ABOi kidney TP virtually as good as ABOc TP

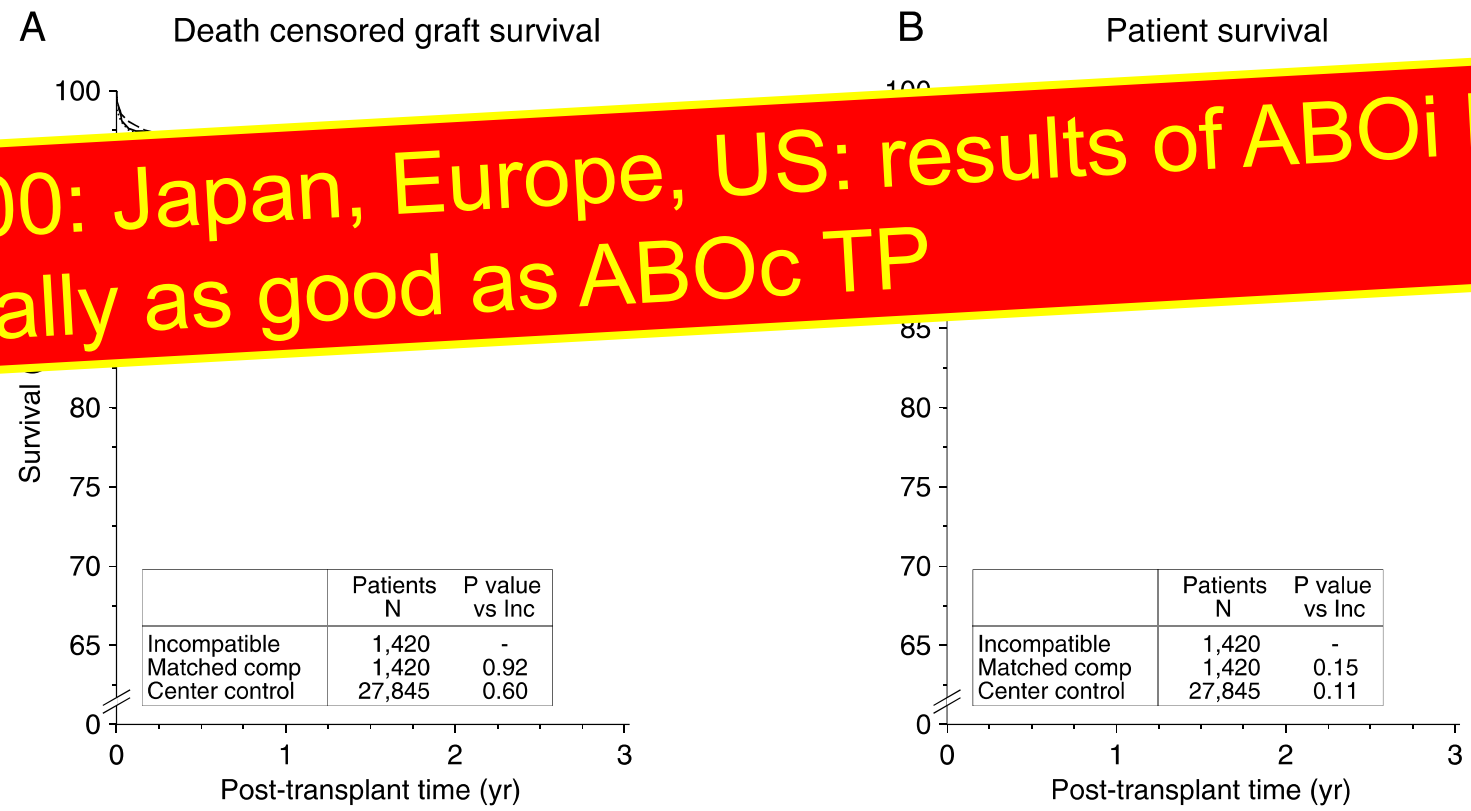


FIGURE 1. Cumulative incidence of (A) death-censored graft survival and (B) patient death in living-donor recipients of an ABO-incompatible graft, matched controls receiving an ABO-compatible graft, or all ABO-compatible transplants from centers that performed at least five ABO-incompatible grafts during the study period ('center control' group) (Kaplan-Meier estimates). *P* values according to the log-rank test.

The Belgian ABOi kidney transplantation protocol

Version 3 18/10/2018

Four meetings: 17/05/2017, 18/10/2017, 20/3/2018, 11/7/2018 (meeting with Fresenius, Miltenyi bioyech, Glycosorb)

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Alain Le Moine (ULB), Michel Mourad (UCL), Daniel Abramowicz (UZA)

1. Inclusion criterias (all)
2. LDEP (MN, LC)
3. Do we need Rituximab for ABO incompatible (ABOi) transplantation ? (ALM, DA)
4. Which apheresis technique will be used? (LC, MM)
5. What titer of anti-A/B antibodies should be achieved ? Which method should be used? (SVL, LP)
6. Immunosuppressive therapy (ALM, DA)
7. Do we need Ivig for ABOi KTR ? (ALM, DA)
8. Is there a need for post-transplant AB titers FU and systematic biopsies? (SVL, MM)
9. Database ABOi Tx (MN, LP)

Inclusion criteria

- Living donors A, B, or AB; recipient O, A, or B; HIV neg; crossmatch negative, signed informed consent.
- The working group advises inclusion of patients in need of a first transplantation, with a PRA < 30% (ET), DSA negative. However, inclusion of patients will be performed according to local practice and falls under the responsibility of the center.

Algorithm LDEP/ABOi protocol

Every living donor-recipient pair in which the transplant cannot be performed because of ABO incompatibility should be informed about the possibility to be included in:

→the nationwide LDEP program

→an ABOi protocol.

Pre-emptive indication: ABOi couples should be proposed to enroll in the LDEP program, and **wait for a match**, until dialysis is imminent (within the following three months) and an ABOi transplant can be scheduled. **The number of LDEP runs is not relevant here.**

Patients already in dialysis: ABOi couples should be proposed to enroll in the LDEP program, and **if one run is not successful, or if the run is not scheduled within a reasonable time frame (more than 2 months), the couple should be offered ABOi transplantation**

Use of Rituximab

A single dose of Rituximab (Mab-Thera) drip infusion, 375 mg/m², approximately 1 month prior to transplantation is administered.

Rituximab can be infused through a peripheral vein or through the venous line of an a-v fistula.

Start with 50mg/h, if well tolerated increase drip infusion to 100mg/h after 30 min, 200mg/h after 60 min, and 400mg/h after 90 min.

In order to avoid adverse effects, use a pre-medication with: paracetamol, 1g po, 30-60 min before infusion; diphenhydramin 25mg po, or an equally potent anti-histaminicum, 30-60 min before infusion.

How should AB blood titers be measured?

Table 3: Blood group incompatibilities and antibody titers by three methods

Donor blood group	Recipient blood group	Tube titer	Ortho titer	Diamed gel card titer
A1	O	32	16	4
A1	O	64	8	4
A1[c]	B	16	4	2
A2	O	32	4	
A2	O			
A2[b]				
				4
		16	2	1
	A	32	4	4
B	A	32	8	2
B	A	8	4	1
B	A	16	16	4
B	A	1	1	1
B[a]	A	32	16	4
A1B	A	8	2	1
A1B	A	16	8	2
A1B	A	8	2	1
A1B[d]	B	32	8	2

→Large inter-assays variations

→Need to agree between centers on the method to be used

What titer of anti-A/B abs should be achieved ? Which method should be used?

- Sample analysis at local blood bank laboratory of the Red Cross
- Measure IgG and IgM
- Column agglutination Gel cards methods (Bio Rad®, http://www.bio-rad.com
- Scheme for Ab-titer measurement
  - At referral (consider exclusion if titer > 1:1024)
  - After administration of Rituximab, before apheresis
- **Target titer before transplantation ideally ≤ 1:4 on 2 consecutive days preceeding the transplantation** (taken into account the kinetics of the antibody titer relative to apheresis).
- If not achievable within a reasonable amount of apheresis sessions (≤ 8), **a titer of 1:8 on the day of transplantation seems acceptable.**
- Before and after each aferesis treatment.
- Post-Tx, in decreasing frequency with time

Immunosuppressive protocol

- Steroids (prednisone or methylprednisolone): **At start of apheresis:** 20 mg/d po; day 0: 250 mg iv; day 1: 125 mg iv; day 2-7: 40 mg po; day 8-28: 20 mg po; day 29-60: 15 mg po; day 61-180: 10 mg; after day 180: 5 mg. **The working group does not advise steroid withdrawal, but immunosuppressive regimens belongs to center responsabilities.**
- Tacrolimus 2 x 0.10 mg/kg/d, **starting one week prior to planned transplantation.** Dose adjustment according to trough levels is suggested as follows: day –7 to 90: 8-12 ng/ml; day 91 to 365: 6-10 ng/ml; day > 365: > 5 ng/ml. (Advagraf ® can be used according to local practice)
- Mycophenolate mofetil (or equivalent doses of Myfortic): 2 x 500 mg/day, starting one week prior to planned transplantation; 2x1000 mg/day from the day of Tx until the end of month 1; then 2x750 mg/day (according to center practice).
- Simulect (basiliximab): 20 mg, day 0 and day 4. **The working group recommends caution when using a T-cell depleting agent in B-cell depleted patients.**

Do we need Ivig?

Center	Apheresis technique	Ivig use
Tokyo Women's hospital center, Japan	DFPP	No
Johns Hopkins Hospital, Baltimore, USA	Plasma exchanges (PE)	Yes
University Medical Center, Freiburg, Germany	Immunoadsorption and PE	No
Karolinska University Hospital, Sweden	Immunoadsorption	Yes
Cedars-Sinai Medical Center, LA, USA	PE	Yes

As the clinical results of these various centers are impossible to compare in detail, all claiming excellent patient and graft survival, one comes to the conclusion that **Ivig does not seem to be an obligatory component of ABOi KTR, and certainly not when immunoadsorption columns are used.**

Therefore, **we do not recommend the routine use of Ivig for ABOi KTR.**

Which apheresis technique will We use?

Number of ABOi Kidney Transplants

JAPAN (DFPP) > 2000 *(as to year 2010)*
USA (PE) > 1000 *(as to year 2011)*
Germany (IA) > 1000 *(as to year 2012)…..*

REGARDLESS OF THE TYPE OF APHERESIS

DFPP, Double-Filtration PlasmaPheresis
PE, standard Plasma Exchange
IA=ImmunoAdsorption (Selective or Non-selective)

GLYCOREX TRANSPLANTATION AB

Offer

Offer No/Customer No: 6683 20011603

Offer date: 2018-07-13

Delivery address
Universitair Ziekenhuis Antwerpen
Wilrijkstraat 10

2650 Edegem
Belgium

Invoice address
Universitair Ziekenhuis Antwerpen
Wilrijkstraat 10

2650 Edegem
Belgium

Your reference	Prof. Dr. Daniel Abramowicz	Our reference	Cecilia Höst
Your ref. No		Terms of payment	20 days net
Terms of delivery	ExWorks	Valid until	2019-07-13
Transported by	UPS	Penalty interest	18,00 %

Article No	Denomination	Quantity	Unit	Unit price	Discount	Total
7601-1 7602-1	GlycoSorb A or GlycoSorb B SINGLE USE ONLY	75	unit	4 095,00	31,5 %	210 375,00

Is there a need for post-transplant AB titers FU and systematic biopsies?

- Postoperative titers are measured daily the first 5 days, second daily until day 14, and then weekly for the first 2 months, at month 3, 6, 12 or after decline of kidney function.
- The aimed targets should be titers ≤1:16 the first week and ≤1:32 the second week (card method) **above which plasmapheresis or immunoadsorption is needed.**

- Protocol biopsies occur at the discretion of the treating physician. The histological presence of C4d without signs of rejection is common and of uncertain significance.

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The Belgian ABOi protocol: hurdles to be tackled

1. Finalize the protocol (due early 201[illegible]

Thank you for you attention !
Bedankt voor uw aandacht!
Mèrci d'vosse atincion!

[illegible]sting in June 2018)