ABO INCOMPATIBLE KIDNEY TRANSPLANTATION

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29th SATS & 6th SATiBA
CONGRESS
11 – 13 November 2022
STIAS, STELLENBOSCH, CAPE TOWN

ABO INCOMPATIBLE KIDNEY TRANSPLANTATION

Conflicts

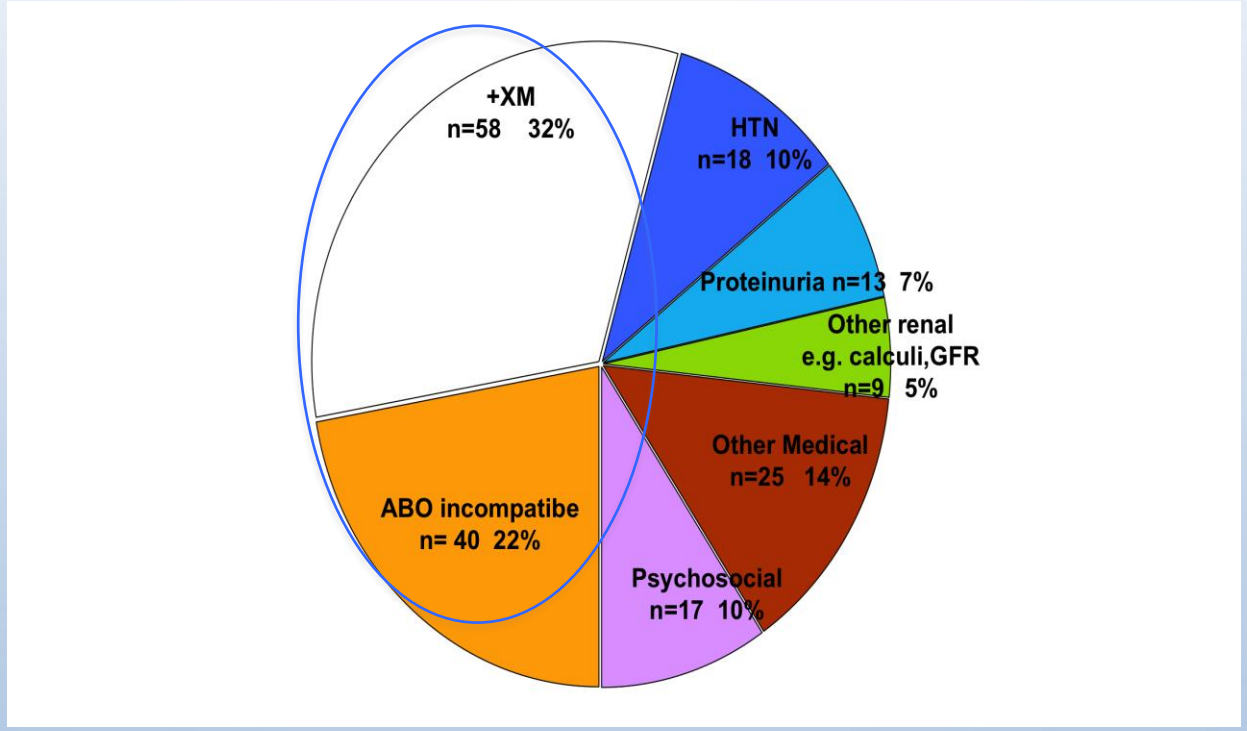
- None to declare

Objectives

1) Brief overview of Canadian National Kidney paired donation
2) ABOi living donor transplant overview
3) ABOi living donor experience at St. Michael's


ST. MICHAEL'S HOSPITAL
Patient Care Tower

Reasons for living donor exclusions n=180

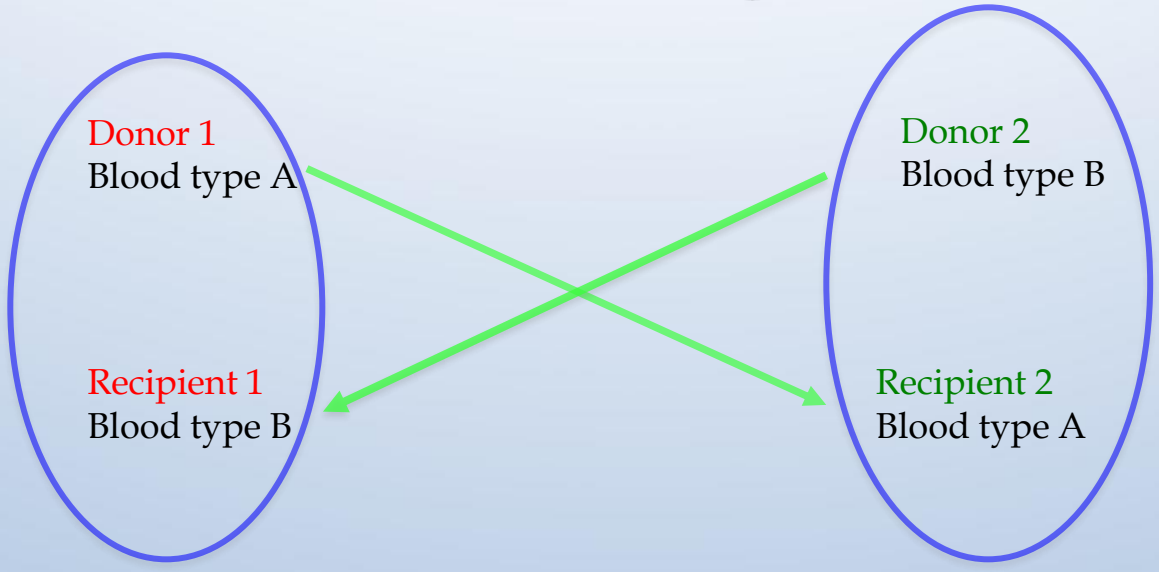


Karpinski et al. Am J Kidney Dis. 2006 Feb;47(2):317-23

Canadian Kidney Paired Donation: National System 2008-2020

Canadian Blood Services
it's in you to give

Paired Living Donor Kidney Exchange



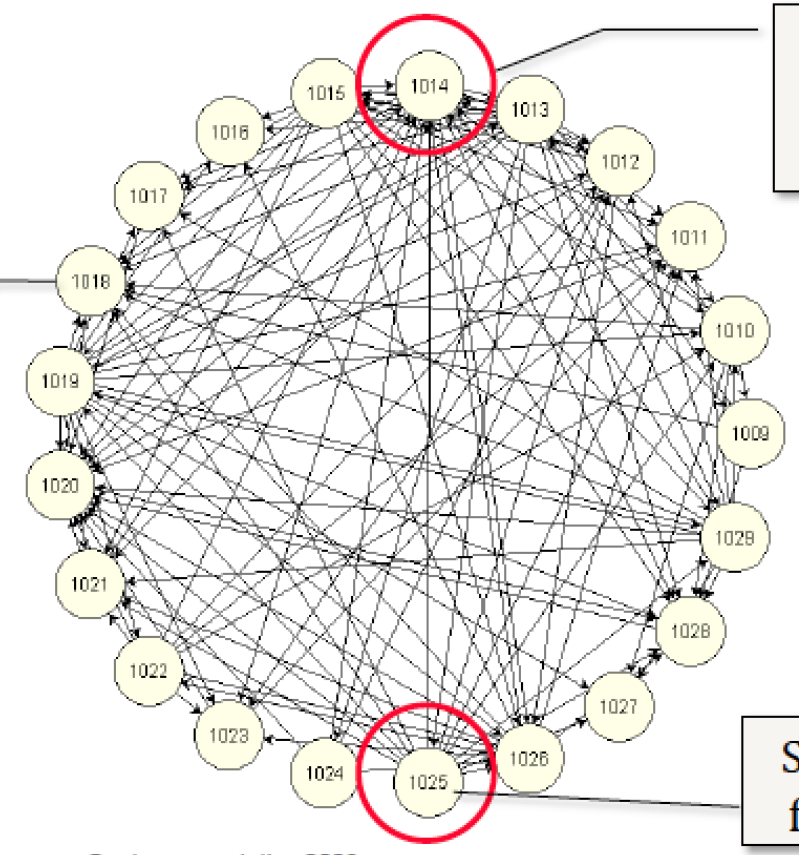
Match by high level virtual cross-match

- Lots of Background work to get all Canadian HLA labs up to speed
- All donor class l and ll HLA alleles (molecular) entered
- All recipient HLA antibodies entered
- Computer match based upon acceptable (negative) virtual cross-match
- Following match cycle all proposed matches are reviewed by HLA experts
- Final cross-matches done by flow

- ALL CANADIAN TRANSPLANT PROGRAMS PARTAKE
- 3 MATCH CYCLES ANNUALLY
- 100-130 PAIRS
- ~33% Match per cycle

Kidney Paired Donation Program

Possible Paired Exchanges



Some pairs have multiple potential matches

Registered Pair

Some pairs have only a few potential matches

Canadian Blood Services
it's in you to give

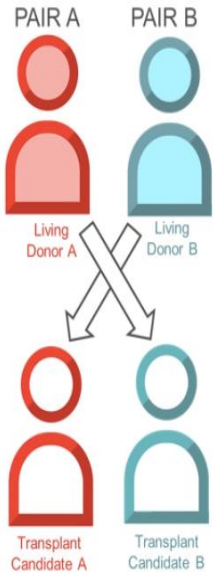
Gentry presentation 2008

Canadian Kidney Paired Donation Program To Date

Canadian Blood Services
it's in you to give

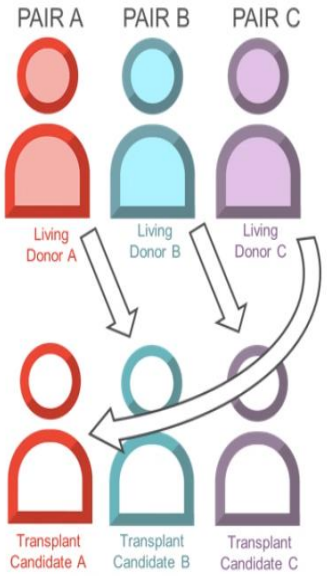
894 KPD Transplants as of April 29, 2022

76 from Paired Exchanges



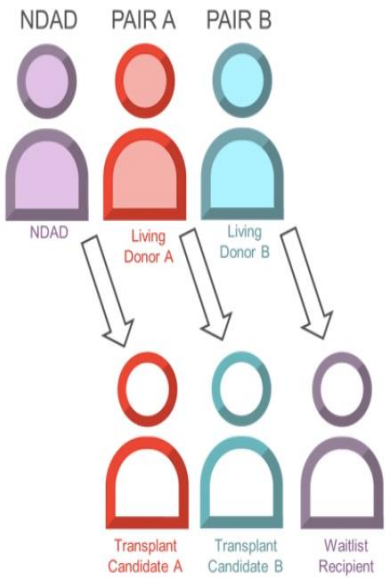
38 paired exchanges

227 from Closed Chains*



58 chains of up to six transplants each

591 from Domino Chains*



189 chains of up to six transplants each

KPD Participants:

244 NDAD Candidates

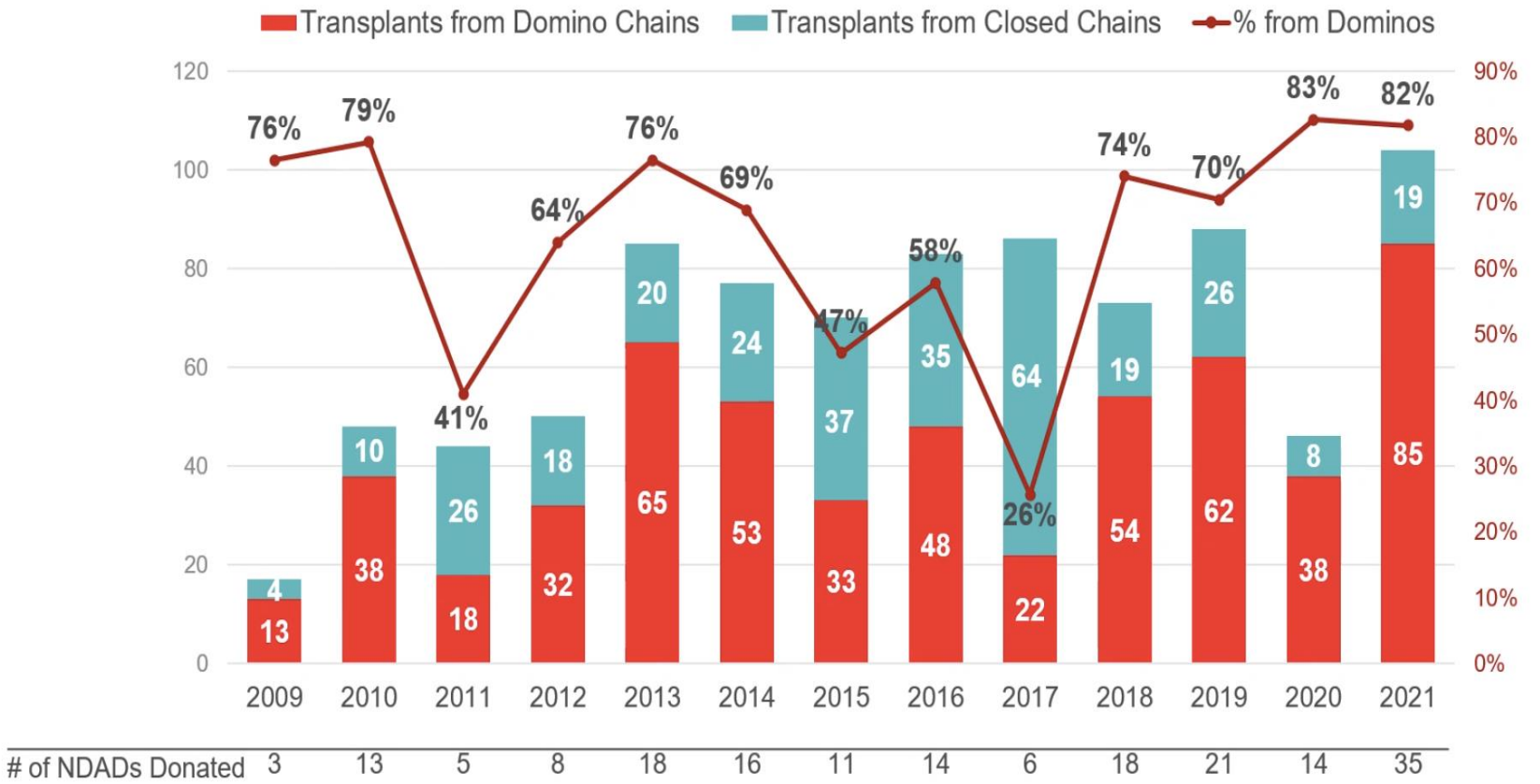
1397 Transplant Candidates

1525 Donor Candidates

Canadian Blood Services BLOOD PLASMA STEM CELLS ORGANS & TISSUES

*Closed chains are also referred to as "N-way exchanges"; domino chains are also referred to as "domino exchanges"

Power of the NDAD: Domino chains are essential



Canadian Blood Services — BLOOD PLASMA STEM CELLS ORGANS & TISSUES

NDAD: "Non-Directed Anonymous Donor"
Data as of April 25, 2022
Results Based on date of transplant/donation

ABOi kidney transplants in living donation

ABOi kidney transplant

- Has been done for many years in Japan (no Brain death laws until recently)
- Previously involved heavy IS and splenectomy
- Most centers now use combination of PLEX and IViG +/- Rituximab
- Results in long-term are comparable with compatible donation

ABOi renal transplant historical context

- First attempts in 1955. Poor success 4/10 survival
- Thiekle et at al, 1987, showed 12/20 graft survival A2 to O recipients
- Early work out of Japan included splenectomy to reduce antibody production. Tanabe et al transplantation 1998 27;65(2):224
  - 1989-1995: 67 ABOi kidney txp: Induction with ATG, PLEX or IA: and cyclosporine, azathioprine (deoxyspergualin), prednisone . All patients underwent splenectomy at time of transplant, and all received local irradiation to the allograft. Allograft survival 79% at 1 year, 73% at 8 years.
- In Japan 20-30% of living transplants are ABOi

Transplantation. 2009 Apr 27;87(8):1246-55.

ABO incompatible renal transplantation: a paradigm ready for broad implementation.

Montgomery RA, Locke JE, King KE, Segev DL, Warren DS, Kraus ES, Cooper M, Simpkins CE, Singer AL, Stewart ZA, Melancon JK, Ratner L, Zachary AA, Haas M.

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Abstract

The requirements for potent immunosuppression coupled with the formidable risk of irreversible antibody-mediated rejection (AMR) have thus far limited the expansion of ABO incompatible (ABOi) kidney transplantation. We present a retrospective review of our single-center experience with 60 consecutive ABOi kidney transplants and describe the evolution of our treatment protocol to one that consists only of a brief escalation in immunosuppression without long-term B-cell suppression from splenectomy or anti-CD20. The 1-, 3-, and 5-year graft survival rates for the cohort were 98.3%, 92.9%, and 88.7%, respectively, which is comparable with United Network for Organ Sharing data for compatible live donor transplants. No instances of hyperacute rejection were observed, and no grafts were lost secondary to AMR. In fact, fewer than 15% of the patients experienced a clinical episode of AMR, and rejections were mild. Elimination of B-cell ablative therapies did not result in an increased incidence of AMR. Excellent graft function persists with a current median creatinine clearance of 60 mL/min. The findings of this study and the relatively simple therapeutic regimen used should facilitate widespread application of ABOi kidney transplantation resulting in one of the most rapid escalations in access to organs in the modern era of kidney transplantation.

1, 3 , 5 yr graft survival 98.3%, 92.9%, 88.7%

ABOi transplants; modern era, splenectomy no longer utilized

Principles:

-Reduce antibody production

-depletion of pre-existing antibody

Plasma exchange

double-filtration plasma filtration

antigen specific immunoadsorption

-Immunomodulation

-immunosuppression

-surveillance post-transplant

Reduce antibody Production

- Rituximab: inhibits CD20
- Splenectomy

Depletion of pre-existing antibody

PLEX	Double filtration PE	Ag specific Immunoadsorption
Least cost	costly	Most costly
Readily available	Not easily available	Proprietary product
20 % reduction	20-50% reduction	>50%
Multiple sessions	Less than PLEX	Fewest sessions
Limited by antibody titres	?	Titre reduction As high as 1: 1056
Plasma or Albumin infusion Depletion of factors	Some depletion	N/A

Immunomodulation

Intravenous immunoglobulin:

-Blocks the Fc receptor on the mononuclear phagocyte, also the direct neutralization of the alloantibody. Inhibits the CD19 expression on the activated B cell, as well as that of the complement and the allo-reactive T cell.

-Effects last months, even after rebound of alloantibody

Immunosuppression

- Same immunosuppression as for ABO compatible transplants
- Often start 1 week prior to transplant
- Calcinuerin inhibitor: tacrolimus
- Steroids
- Anti-metabolite: Mycophenolate
- Induction at time of transplant: anti-CD25 or polyclonal ATG

Post-transplant surveillance

- All protocols require measurement of iso anti-body formation
- Rational: if antibody levels rise, then risk of accelerated rejection and additional desensitization required
- Variation: but usually can stop after 14 days

Why is graft protected even if iso-antibodies increase later?

- Graft accommodation
    - Detectable anti-ABO antibody in recipient, with normal graft histology and function similar to ABOc transplant
- Mechanism is unclear
- Antibody quality: Ishida et al. Transplant Int 2005;18(6) 716
- Shift from IgG1 to IgG2 isotype: Kirk et al. AJT 2007;(6):1464
- Decreased apoptosis: Park et al. AJT 2003;(8):952

ABOi protocols

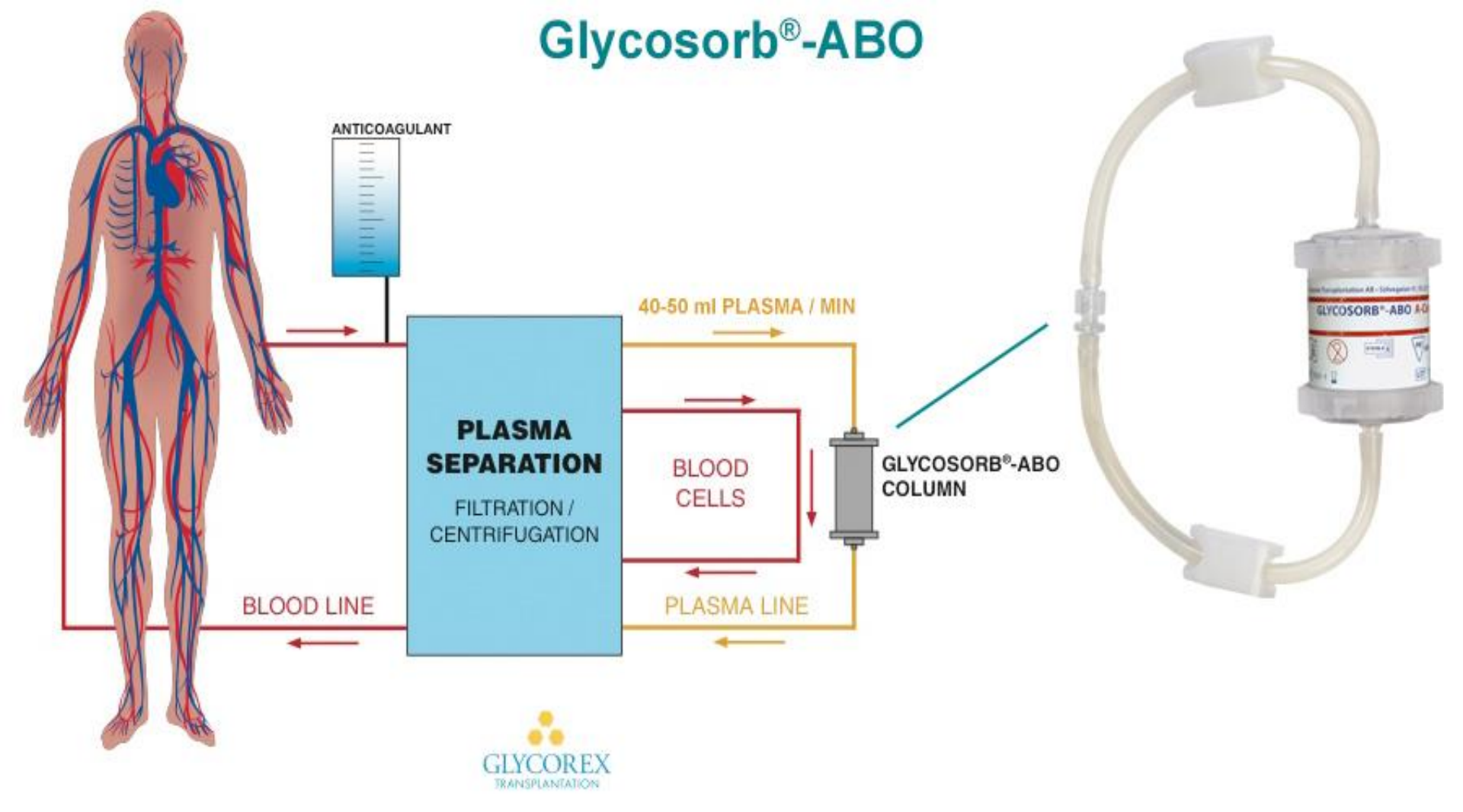
Shin et al. J transplant 2011; 2011:970421

	Pretransplant desensitization				Acceptable final titer	Posttransplant desensitization				Posttrans-plant monitoring	Splenectomy
	Ab depletion	IVIG	Rituximab	IS drug		Ab depletion	IVIG	Rituximab	IS drug		
Montgomery, 1st era (Johns Hopkins)	PP or IA	Low dose* (0.1 g/kg): CMV-IVIG	No: if high risk, single dose at POD# −1	FK/MMF: start at the beginning of PP	<1 : 16	PP or IA	Low dose (0.1 g/kg): CMV-IVIG	No	Daclizumab: initial 2 mg/kg, and then 1 mg/kr q 2 wks for 5-dose FK/MMF/MPD	Anti-ABO IgG titer: weekly for POD# 1 mon at POD# 2, 3, 6, 12 mon	No (work as rescue therapy for ABMR)
Tyden (Stockholm)	IA: at POD# −6, −5, −4, −1	Standard dose (0.5 g/kg): single dose at POD# −1	Yes (375 mg/m^2): single dose at POD# −10	FK/MMF/MPD (high dosage): start at POD# −10	<1 : 8	IA: preemptive 3 times at each 3 days	No	No	FK/MMF/MPD	Anti-ABO IgG titer	No
Genberg (Stockholm)	IA	Standard dose (0.5 g/kg): single dose at POD# −1	Yes (375 mg/m^2): single dose at POD# −30	FK/MMF/MPD (high dosage): start at POD# −10	no	IA: preemptive 3 times	Low dose (0.5 g/kg): 5 doses	No: If high B cell count, add dose	FK/MMF/MPD	B-cell count measurement at posttransplant 6 month	No
Wilpert (Germany)	IA	Standard dose (0.5 g/kg): single dose at POD# −5 ~ −1	Yes (375 mg/m^2): single dose at POD# −30	FK/MMF/MPD: start at POD# −7	≤1 : 4	IA	No	No	basiliximab FK/MMF/MPD	Anti-ABO IgG titer: ≥1 : 8 in 1st week and ≥1 : 16 in 2nd week	No

	Pretransplant desensitization				Acceptable final titer	Posttransplant desensitization				Posttrans-plant monitoring	Splenectomy
	Ab depletion	IVIG	Rituximab	IS drug		Ab depletion	IVIG	Rituximab	IS drug		
Flint (Australia)	TPE	Low dose* (0.1 g/kg): but, 0.5 g/kg at POD# −1	No	MMF: start at POD# −10	≤1 : 8	TPE	Low dose (0.1 g/kg)	No	basiliximab FK/MMF/MPD	Anti-ABO IgG titer: daily for the first 2 weeks and then, twice a week for the first 2 months	No (work as rescue therapy for ABMR)
Gloor (Mayo)	TPE	Low dose* (0.1 g/kg)	Yes (375 mg/m^2): 2 doses at the starting of PP	MMF	≤1 : 8	No	No	No	ATGAM FK/MMF/MPD		No
Oettl (Basel)	IA (daily)	Standard dose (0.5 g/kg): single doseat POD# −1	Yes (375 mg/m^2): single dose at POD# −30	FK/MMF/MPD: start at POD# −14	≤1 : 8 (IgM, IgG)	IA	No	No	basiliximab FK/MMF/MPD	Anti-AB IgM or IgG titer ≥1 : 8	No
Tanabe (Tokyo)	DFPP: start at POD# −7	No	Yes (200 mg/m^2): single dose	FK/MMF/MPD: start at POD# −7	≤1 : 32	No	No	No	basiliximab FK/MMF/MPD	No	Yes (selectively)
Montgomery, 2nd era (Johns-Hpokins)	PP	Low dose* (0.1 g/kg): CMV-IVIG	No	FK/MMF: start at the beginning of PP	≤1 : 16	PP: preemptive 2 times	Low dose (0.1 g/kg): CMV-IVIG	No	daclizumab FK/MMF/MPD	Anti-ABO IgG titer >1 : 32 (If so, protocol biopsy)	No

GLYCOSORB COLUMN

Glycosorb® ABO columns. These low molecular carbohydrate columns include A or B blood group antigens linked to a sepharose matrix that adsorbs isoglutinine both effectively and specifically.




Optia
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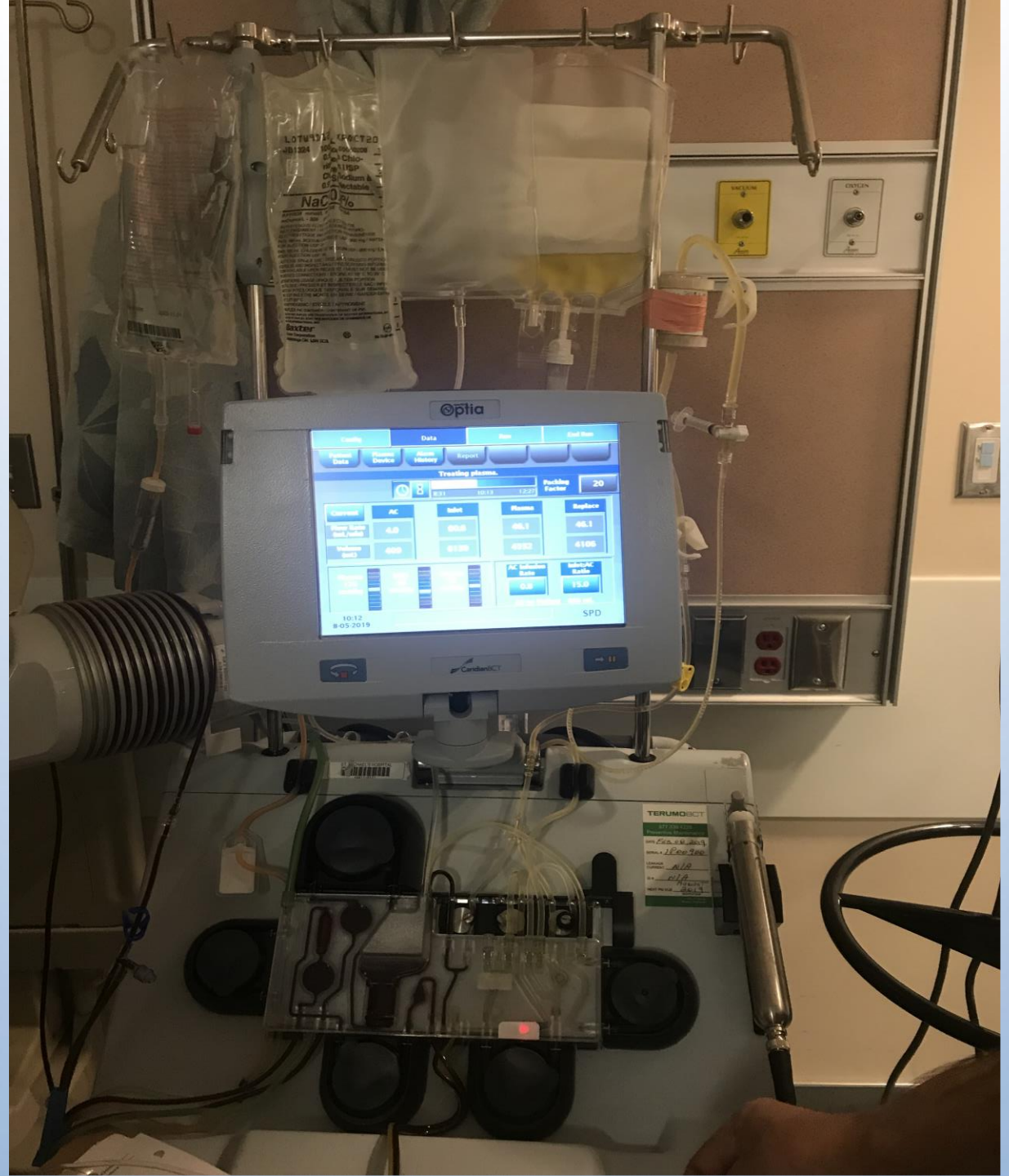
apheresis system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American Journal of Transplantation 2005; 5: 145–148
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2004.00653.x

ABO Incompatible Kidney Transplantations Without Splenectomy, Using Antigen-Specific Immunoadsorption and Rituximab

Gunnar Tydén[a,*], Gunilla Kumlien[b], Helena Genberg[a], John Sandberg[a], Torbjörn Lundgren[a] and Ingela Fehrman[c]

Introduction

Historically, ABO incompatible kidney transplantations

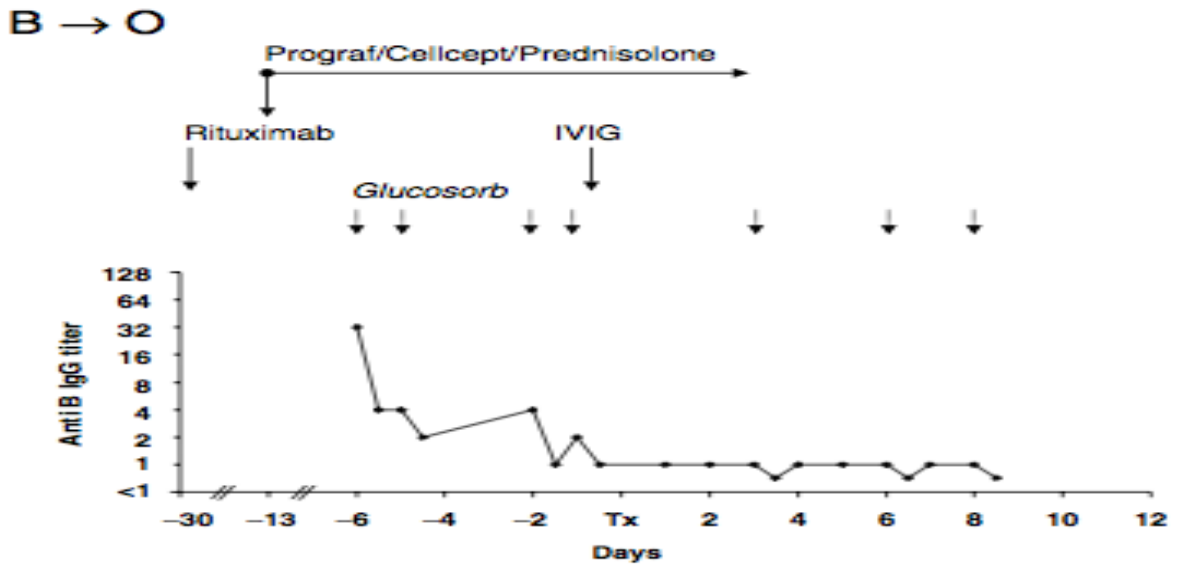


Figure 1: The effect of antigen-specific immunoadsorption (Glycosorb) on antigen titers. The timing of the different components of the immunosuppressive protocol is also shown.

St. Michael's protocol

Adapted from Tydén

- Consider: A-0, A-B, B-0, B-A, AB-A, AB-B
- Anti-donor isoagglutinin titers determined by the saline method for IgM and the indirect Coombs test for IgG. Maximum antibody titer to be accepted is 1:512

Pre-Op

- Rituximab 375 mg/m^2 IV x 1,four weeks prior to transplant
- Triple immunosuppressive regimen with Tacrolimus Extended Release (Advagraf®) 1.5 mg/kg/dy , Mycophenolate 720 mg bid, prednisone 0.5 mg/kg/dy one week prior to transplant.
- Immunoadsorption treatment to be started one week prior to transplant every other day or daily until IgG anti-A/B titers are ≤ 1:4. Typically 3-4 sessions. 2 PLASMA VOLUMES PER SESSSION
- If target not achieved, transplant to be postponed for one week and four more sessions to be performed. 2-3 plasma volumes processed per session. IgG and IgM isoagglutinin titres reduced by approximately two to three titre steps with each session
- *IVIG 0.5 grams/kg IV x 1 dose to be given the evening prior transplant (only for titres 1:128 or greater)* followed by induction : Basiliximab 20 mg IV x 1 dose POD 0 and Methylprednisolone Succinate 2 mg/kg IV x 1 dose pre-op.

Post-Op

Immunosuppresive regimen:

- Basiliximab 20 mg IV x 1 dose POD 4
- Tacrolimus Extended Release (Advagraf®) 0.1 mg/kg po daily
- Mycophenolate 720 mg bid,
- Methylprednisolone Succinate (Solumedrol®) 1 mg/kg IV q12h x 48 hrs
- Prednisone taper as per post op transplant protocol and physician discretion

Post-op

Anti- A, anti B titre monitoring:

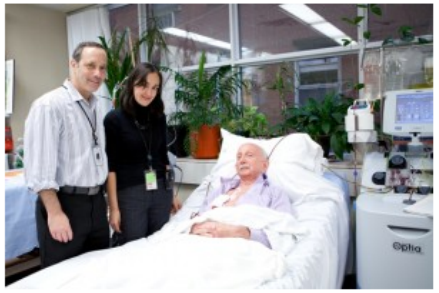
- IgG anti-A/B titers daily post operatively for the first week and on days 8, 10, 12 and 14.
- Immunoadsorption required if IgG anti-A/B titers exceed 1:8 post-operatively in the first week and 1:16 in the second week
- No further monitoring after week 2

ABO incompatible with Glcosorb
1st in North America

Patient receives kidney transplant from donor with different blood type

OCTOBER 31, 2011 11:35 AM VIEWS: 287 SHARE: TWITTER FACEBOOK

TAGS: GLYCOSORB ABO KIDNEY TRANSPLANT PLASMAPHERESIS ST. MICHAEL'S HOSPITAL



Dr. Zaltzman with patient Martin Taylor and Katerina Pavenski, director of transfusion medicine.

St. Michael's Hospital is the first in North America to have used a novel device that cleaned the blood of a kidney patient and allowed him to receive a transplant from a donor with a different blood type.

Andre Cossette, a Grade 4 teacher at Ange-Gabriel Elementary Catholic School in Mississauga, Ont., was on dialysis for three years before undergoing plasmapheresis at St. Michael's. He then received a kidney transplant from his brother, who has Type AB blood, even though Cossette has Type A blood.

Plasmapheresis separates plasma from a patient's blood, and runs it through an immunoadsorbent column containing synthetic carbohydrate beads that trap the blood group antibodies. It removes only the anti-A or anti-B antibodies, sparing the other antibodies. The washed plasma is then returned to the patient's body.

St. Michael's was the first hospital in North America to perform plasmapheresis using a device known as the Glycosorb ABO, developed by Glycorex Transplantation, a Swedish company, and approved

The First North American Experience Using Glycosorb Immunoadsorption Columns for Blood Group-Incompatible Kidney Transplantation

Can J Kidney Health Dis 2020 Oct 8 doi: 10.1177/2054358120962586.

- 24 ABOi incompatible donor recipient pairs
- 21 (87.5% male), Mean age 51 years (23-73)

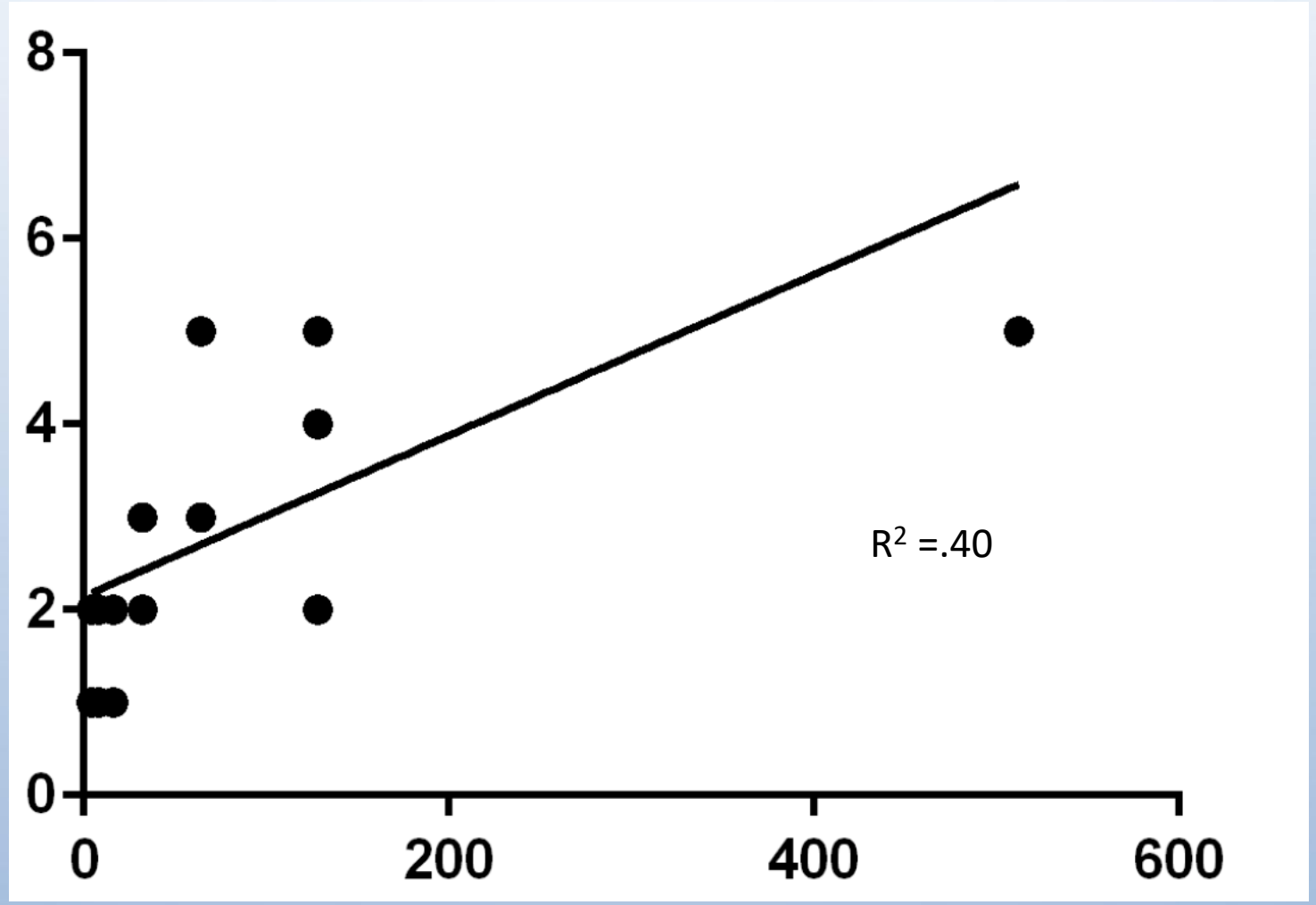
ABOI types

Don----Rec	#
A------0	10
A----- B	3
B------A	3
B------O	7
AB-----A	1
AB-----B	1

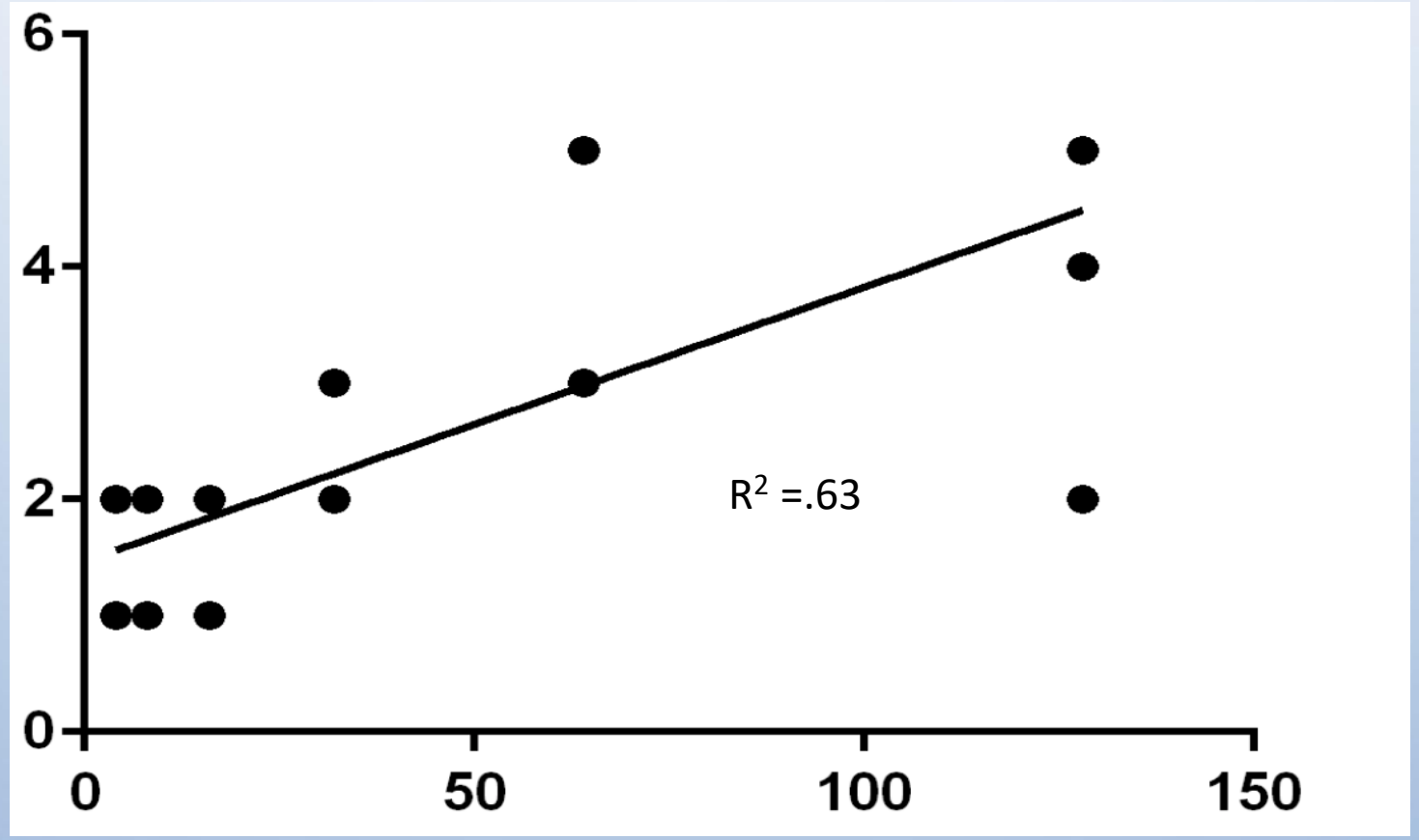
Titres and sessions

- Starting ABOi titres ranged from 1:4 to 1:512
- Pre-transplant glycosorb treatments ranged from 1-5 (mean 2.08)
- 3/25 (12 %) required one post-transplant treatment

Correlation of treatments vs Pre-Transplant ABOi titre



Correlation of treatments vs Pre-Transplant ABOi titre excluding single recipient with titre 1:512



Results 2011-2019
n=24

- 100% patient survival
- 96% graft survival- One graft loss after successful desensitization owing to technical loss
- 1 Patient discontinued glycosorb sessions
- No acute rejections
- Allograft function:

  creatinine range 51-160 umol/l (0.58-1.8 mg/dl)

  mean creatinine 85.6 umol/l (0.97 mg/dl)

Since 2019

- 24 patients from 2011-2019
- Jan 2019 - November 2022, additional 8 patients
- All successful.
- Mean # of glycosorb: 3 (2-5)
- No post-transplant treatments required
- Mean creatinine 115 umol/l (94-145)
- No rejections

Summary

- ABOi incompatible kidney transplants no longer a barrier
- Options: Kidney paired donation, desensitization
- In modern era, outcomes with direct ABOi transplant are equal to ABOc transplant
- IA commercial columns, expensive but likely most efficacious

Acknowledgements

- Galo Meliton RN-living transplant donor coordinator
- Megan Buchholz RN- Apheresis nurse
- Patti Lou Cheatley RN- Apheresis nurse
- Katerina Pavenski MD- Director Transfusion services
- kidney donors and their transplant recipients