

**Expanding options for sensitized and ABO disadvantaged transplant candidates:
desensitization, non-directed donation and paired kidney exchange**

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Disclosures

NO CONFLICTS OF INTEREST

I WILL BE DISCUSSING off-label uses of medical procedures and pharmaceuticals:

- Apheresis (Plasmapheresis)
- IVIG (Various companies)
- Rituximab (Rituxan, Genentech)
- Eculizumab (Soliris, Alexion)
- Bortezomib (Velcade, Millenium)

Objectives

1. Review options for management of ESRD:
understand the benefits of kidney transplantation
Barriers to transplantation
Dialysis vs transplant
2. Review transplant options for the patient with ESRD who have incompatible living donor candidates
Paired kidney exchange
Altruistic Donor Chains
ABO incompatible (ABOI) transplants
HLA Crossmatch positive (XM) transplants
3. Review protocols and outcomes for highly sensitized transplant and ABOI candidates
High PRA with crossmatch positivity (XM+)
ABOI transplants

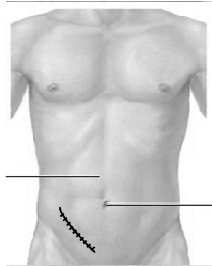
Waiting List as of January 20, 2011

All organs	112,637
Kidney	90,621
Liver	16,081
Pancreas	1,318
Kidney-pancreas	2,128
Heart	3,124
Lung	1,678
Heart-lung	61
Intestine	275

<http://optn.transplant.hrsa.gov/latestData/rptData.asp>

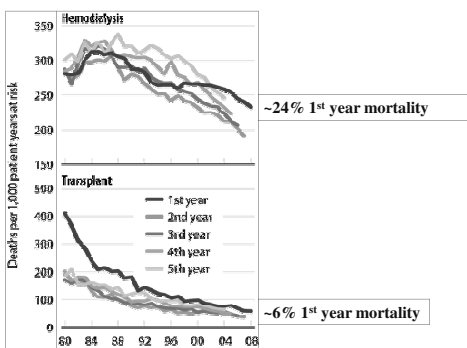
Ways to manage 'end stage' renal failure

- Dialysis
 - Hemodialysis
 - Peritoneal Dialysis
- Renal transplant
 - Deceased donor
 - Living donor
 - related or unrelated

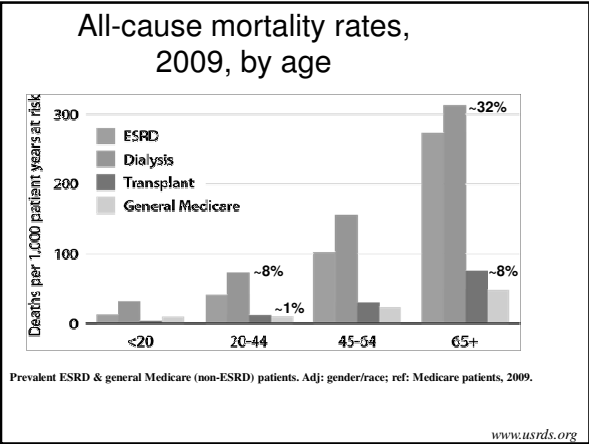


2-4 hrs per session; 3-6 x/wk
 Immunosuppressive medications
 Diet and fluid restrictions
 No donor fluid restrictions

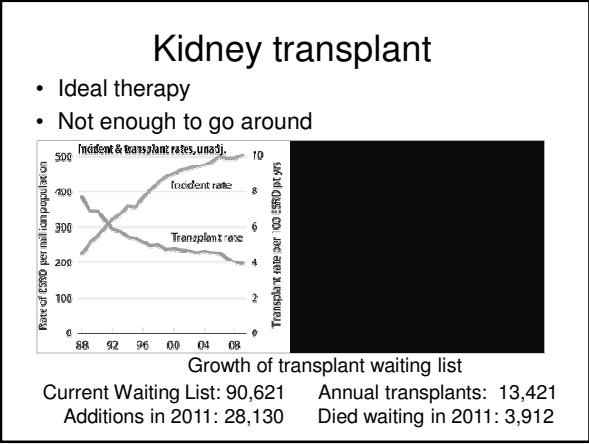
Mortality rates, by form of treatment



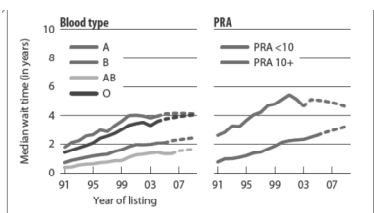
USRDS ADR 2011 Fig 5.1 (vol 2)
www.usrds.org



- ### Advantages of a renal transplant
- Health care perspective
 - Improved survival
 - Better quality of life
 - Less expensive
 - Return to productivity
 - Patients' perspective:
 - More freedom
 - More energy
 - Fewer restrictions on diet and fluid intake



Observed & projected median wait times,
overall & by race, blood type, & PRA



PRA = panel reactive antibodies which measures anti-HLA antibodies

Waiting time longer for blood group B and O and high PRA

www.usrzds.org

Kidney candidates with incompatible donors

~ 6,000 patients on deceased donor waitlist who have a willing but incompatible living donor

~ 3,500 new waitlist patients each year with either ABO- or HLA-incompatible donor

- Options:**
1. Desensitization (ABO)
 2. Desensitization (HLA)
 3. Kidney paired donation

ABO Incompatibility

Based on blood group frequencies in the USA there is a 35% chance that any 2 individuals will be ABO incompatible (ABOI).

Examples of ABO incompatibility

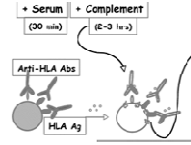
Donor	Recipient
A or B or AB blood group	O (Anti-A and Anti-B ab)
A blood group	B (Anti-A ab)
B blood group	A (Anti-B ab)

ABO incompatibility comes from naturally occurring antibodies.

HLA Incompatibility

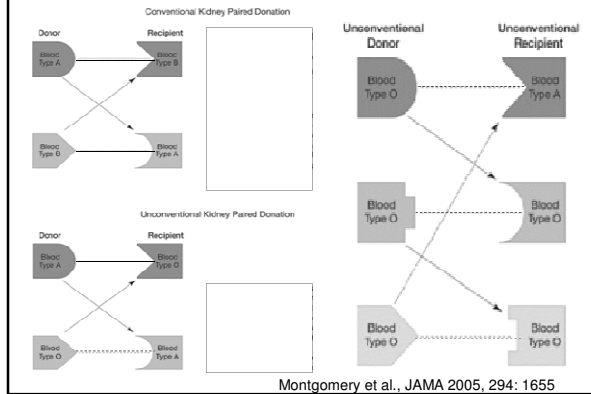
Anti-HLA antibodies are acquired as a result of previous transplants, pregnancies or blood transfusions

Anti-HLA abs can be detected by a crossmatch (XM) of donor lymphocytes with recipient serum



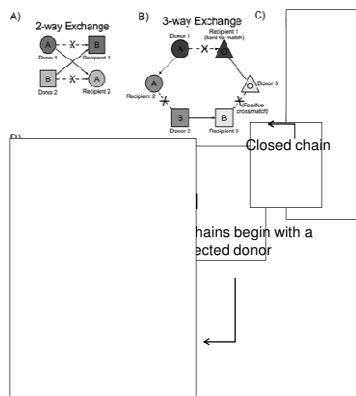
Transplantation across a +XM can result in hyperacute rejection or acute humoral rejection

Kidney Paired Donation (KPD)



Expanding options with exchanges and chains

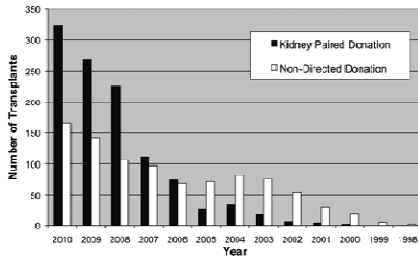
- 2 and 3-way exchanges
- Non-directed (living) donor (NDD)
- Domino paired donation (DPD)
- Never ending altruistic donor chains (NEAD)
- Bridge donor



Wallis et al., NDT 2011, doi:10.1093/ndt/gfr155

Status of KPD and NDD

KPD and NDD Transplants in U.S. 1998 - 2010



Wallis et al., NDT 2011, doi:10.1093/ndt/gfr155

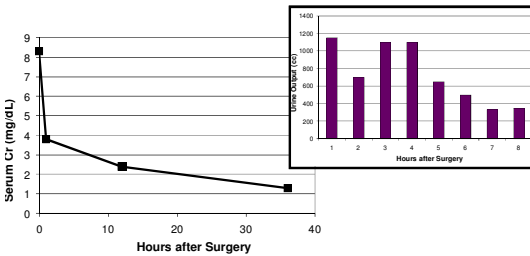
How does donor kidney get to recipient in KPD?

Options when matched donor and recipient are at different centers

1. Recipient travels to donor center
taxing for the recipient
2. Donor travels to recipient center
inconvenience for donor
has to be away from intended recipient
3. Donor kidney removed and shipped to recipient center
requires coordination of transportation

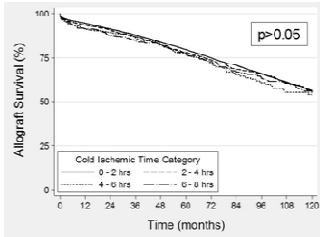
KPD Expansion: Shipping Kidneys

■ Proof of principle. Organ transport from San Francisco (CPMC) to Baltimore (JHU)



KPD Expansion: Shipping Kidneys

- No difference in DGF, rejection, or graft survival with 10 years of follow-up



Time	HR	p-value
0-2h	(ref)	(ref)
2-4h	1.09	0.12
4-6h	1.13	0.33
6-8h	1.05	0.69

Options for recipients

- With incompatible living donors
 - Kidney paired donation to find a compatible donor (preferred)
 - ABO or HLA desensitization to allow transplantation with incompatible living donor to proceed
- With no living donors
 - HLA desensitization to increase access to deceased donor organs

Desensitization therapies

Antibody-Depleting Therapies

1. Removal of antibodies

Plasmapheresis: removes circulating HLA and ABO antibodies

2. Inhibition of antibody production:

a. **Anti-CD20 antibody** – Rituximab (Rituxan)

depletes peripheral B cells

b. **Bortezomib** (Velcade)

proteasomal inhibitor which induces apoptosis of plasma cells

c. **Splenectomy** – removal of a significant fraction of B cells and plasma cells – thus reducing antibody production

3. Unknown mechanism

IVIg infusion:

binds to and neutralizes circulating deleterious antibodies (anti-IgG IgG aka anti-idiotypic)

inhibition of complement activation

inhibition of effector function (macrophages, neutrophils, NK cells) by binding to Fcγ receptors

inhibition of B cell CD19 and induction of B cell apoptosis

Induction of anti-inflammatory cytokines

Desensitization for ABO Incompatibility

Starting isoagglutinin AHG titer	Pretransplant PP/IVIg treatments	Posttransplant PP/IVIg treatments
<16	2	2
16–32	3	2–3
64	4	3
128	5–6	4
256	7–8	4
512	9–10	5
>512	>10	6

PP, plasmapheresis; AHG, anti-human globulin.

Early protocols included splenectomy or rituximab

Montgomery Transplantation 2009

ABOi Outcomes

ABOi cohort (N=60) ^a		
Years posttransplant	Graft survival ^a (%)	Patient survival ^b (%)
1 yr	98.3	96.3
3 yr	92.9	96.3
5 yr	88.7	89.4

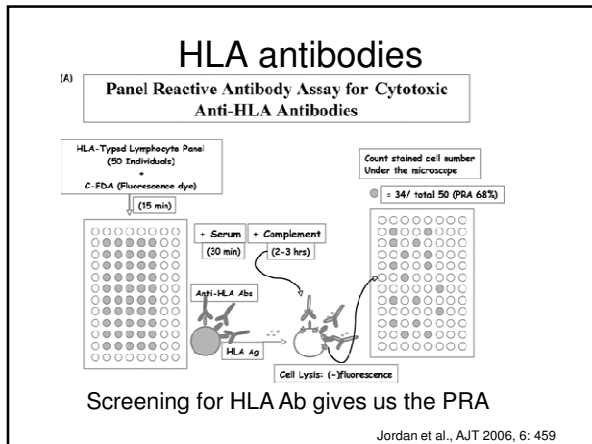
^a Reported survival was determined using Kaplan-Meier estimation.

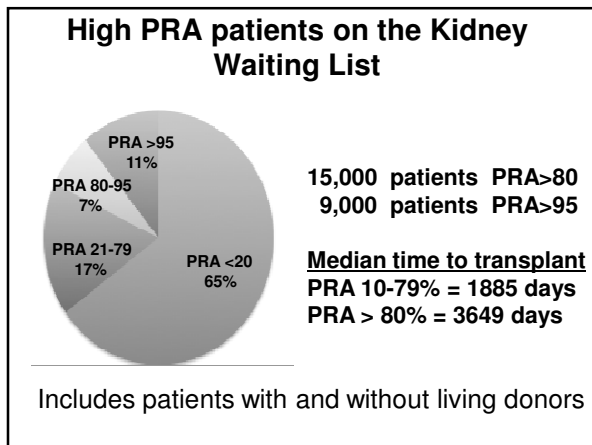
^b Death-censored graft survival: 4 graft losses occurred in the first era cohort and were secondary to non-compliance (n=1), recurrent disease (n=2), and thrombotic microangiopathy (n=1).

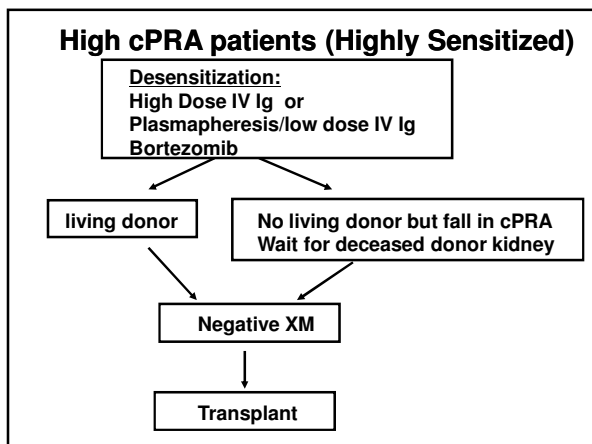
^c All 3 patients died with a functioning graft; 3 patient deaths were secondary to West Nile virus, sudden cardiac death, and metastatic liver cancer.

- Includes ABOi/+XM;
- ABOi only (N=46) 1 yr graft survival 100%; 1 yr pt 97.8%

Montgomery Transplantation 2009

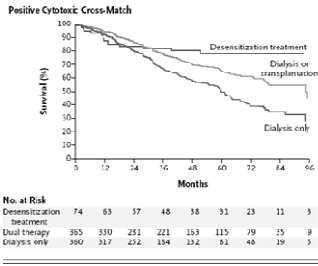






Plasmapheresis/low dose IVIG

With HLA incompatible living donors (crossmatch +ve or DSA)
 Alternate day apheresis followed by IV Ig (100mg/kg)
 Apheresis continued post transplant
 (215 patients –210 transplanted; 74 began with CDC +ve XM)



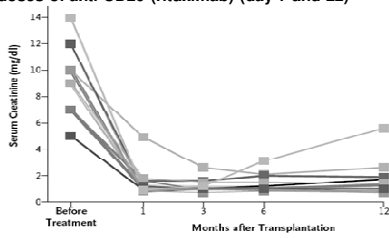
5 yr patient survival
 80.6 (Desensitization)
 vs
 51.5 (dialysis only)

Montgomery, RA; NEJM 2011, 365:318-26

Cedar Sinai Protocol: High-Dose IVIg

Applicable to patients with and without living donors

- 2 monthly doses of 2 g/kg IV Ig (day 0 and day 30)
- 2 doses of anti-CD20 (rituximab) (day 7 and 22)

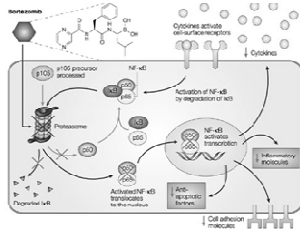


- Significant reduction in PRA
- Higher transplant rate (16/20 patients transplanted)
 (1 yr patient and graft survival of 100% and 94%)

Vo et al, NEJM, 2008, 359:242

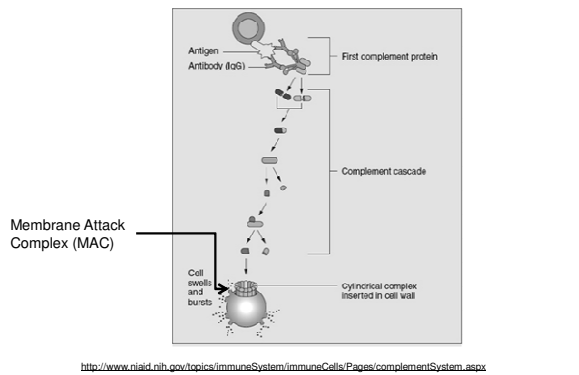
Newer agents

- Bortezomib inhibits plasma cell function
 (approved for multiple myeloma and mantle cell lymphoma)
 - used to desensitize prior to kidney transplantation
 - 1.3 mg/m² per dose on day 1,4,8 and 11
 - Used to treat AMR following transplantation
 - Efficacy unknown



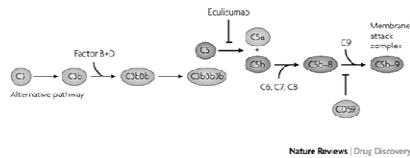
Nature reviews drug discovery 2003

The importance of complement



Newer agents - II

- Eculizumab, terminal complement (C5) inhibitor (approved for PNH and aHUS)
- Inflammation and injury with AMR is mediated via complement



Eculizumab

With HLA incompatible living donors
(flow crossmatch > 300 and <450)

- Apheresis till flow crossmatch < 300
- Apheresis continued in some post transplant
- 26 patients transplanted
- Incidence of AMR: 7.7%
- Graft survival at 1 year: 100%

American Journal of Transplantation 2011; 11: 2405-2413

Current challenges with transplants in the highly sensitized

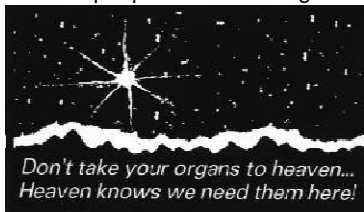
- Long waiting times
- Success with desensitization variable (neg XM)
- High rates of acute humoral rejection post transplant
12-41% (especially if XM remains positive)
- Treatment of acute humoral rejection
 - Plasmapheresis
 - IVIg
 - thymoglobulin (anti-T cell ab)
 - rituximab (anti-B cell ab)
 - bortezomib (anti-plasma cell ab)
 - eculizumab (anti-complement C5 ab)
- 2 and 5 year graft survival lower

Conclusions

- There are a large number of patients with an incompatible donor (~3,500 each year)
- Clinical outcomes from ABOI transplants and are excellent and those with high PRA and +XM transplants are improving with current desensitization protocols
- Kidney Paired Donation offers a novel solution for patients with willing but incompatible donors

The facts (2011)

- Each day last year
 - 77 people were added to the kidney waiting list
 - 37 people received a kidney transplant
 - 11 people on the waiting list died



Questions



"I'm afraid the shark got your arms and legs. It's probably not a good time, but your brother's here. He needs a kidney."
