Imlifidase - ‘Making the impossible possible’

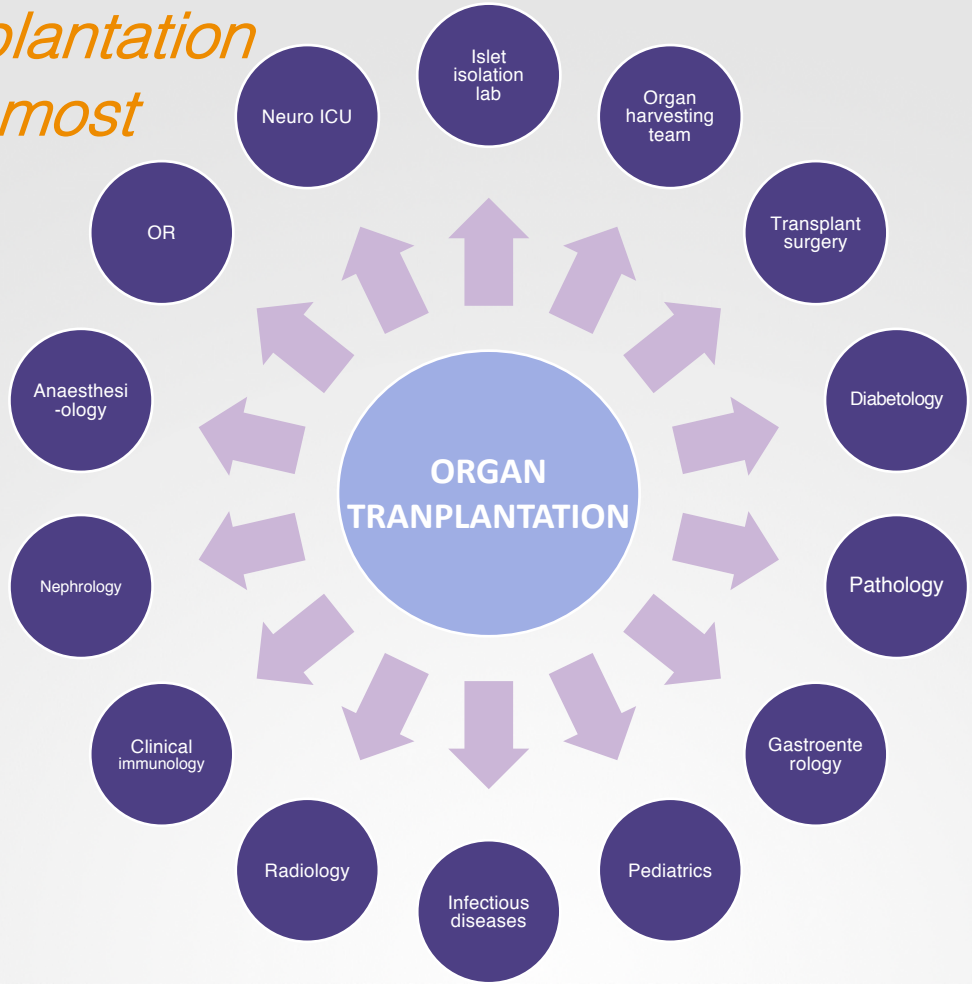
- kidney transplantation in highly sensitized patients

Dr. Tomas Lorant,

Transplant Surgeon & Senior Medical Director

Hansa Biopharma

Organ transplantation is one of the most complex procedures in medicine for several reasons…



Number of patients on the waiting list for a kidney transplant

UNOS

>100,000
(2018/19)

Eurotransplant
Scanditransplant
France Transplant
NHSBT
Etc.

>50,000
(2018/19)

ANZDATA

>1,500
(2018)

KOTRY

>2,000
(2018)

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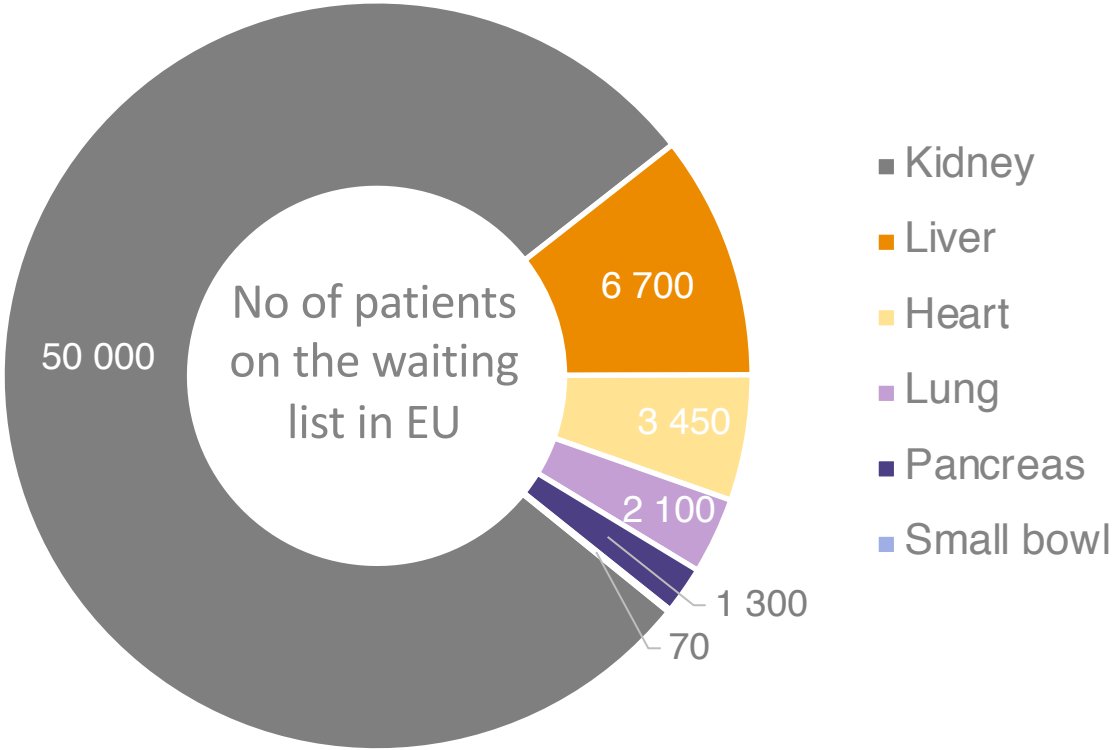
Waiting list in Europe across organ transplantations

- Nearly 4 out 5 waiting for a transplant are kidney patients

"Considering the high mortality rate of patients on dialysis, special strategies are required to enhance transplantation of long waiting highly sensitized patients"

Eurostam Final Report Summary 2016



Date 10.06.2018

https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/ev_20121009_facts_figures.pdf

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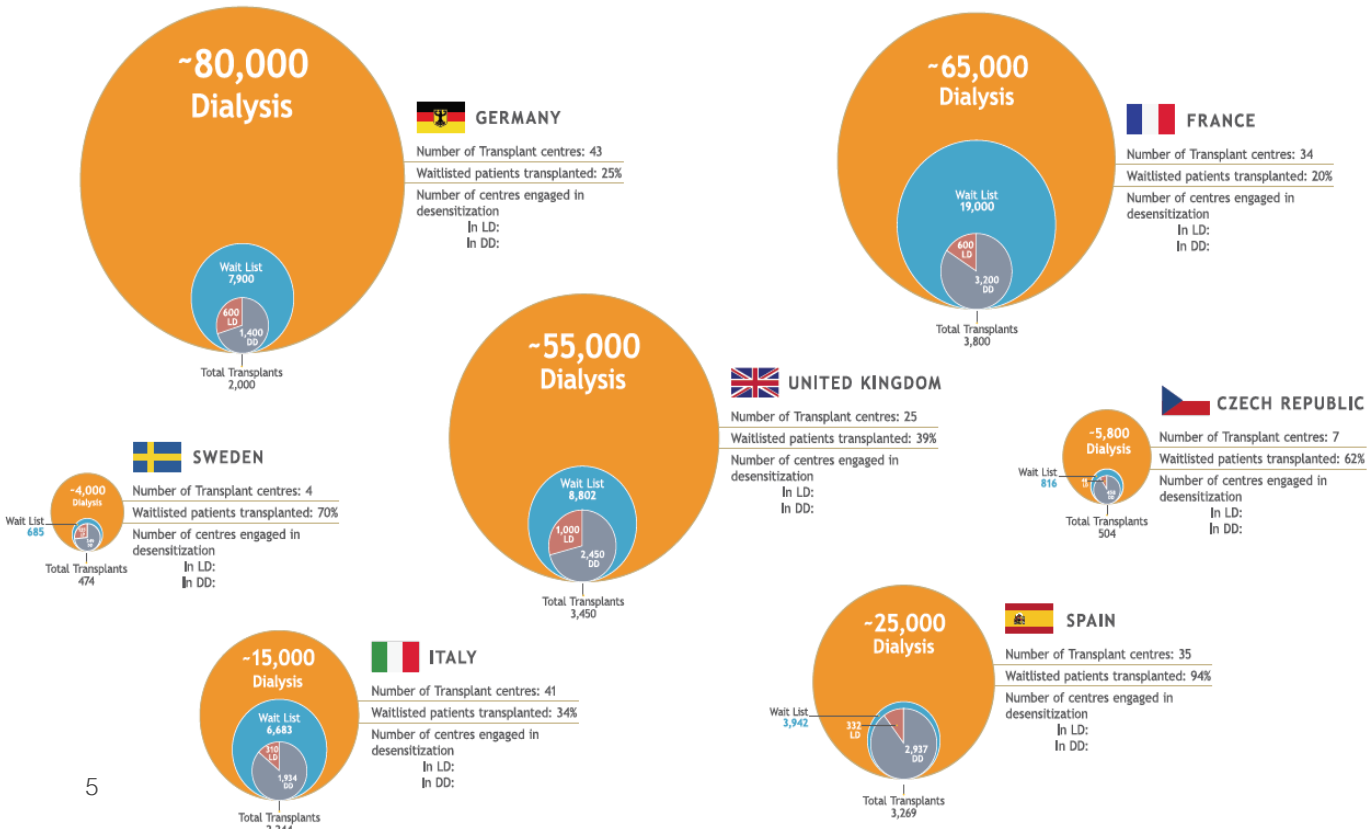
2017 Kidney Transplant Statistics



”For a significant proportion (about 35%) of the highly sensitized patients in the acceptable mismatch program no compatible donor can be found within the Eurotransplant area."

Eurostam: Final Report Summary 2016

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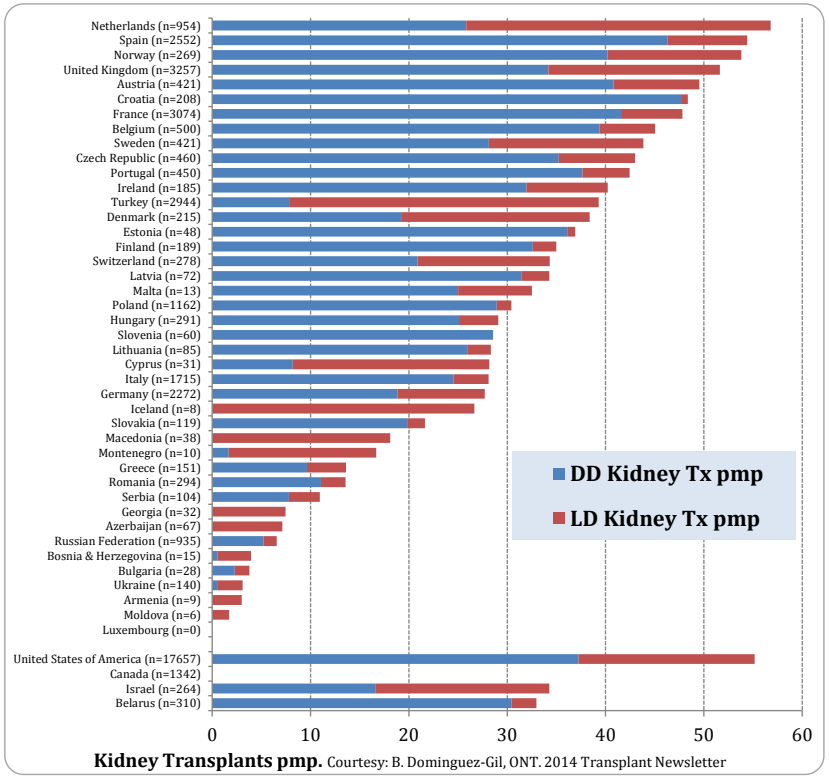
Current Status in Europe
Kidney transplantations

2013 kidney transplants per million population, Council of Europe members & observers



Kidney Transplants pmp. Courtesy: B. Dominguez-Gil, ONT. 2014 Transplant Newsletter

DD: deceased donation

LD: Living donation

→ 24,082 kidney transplants for these 42 **CoE members** (30 % from living donors)

CoE observers

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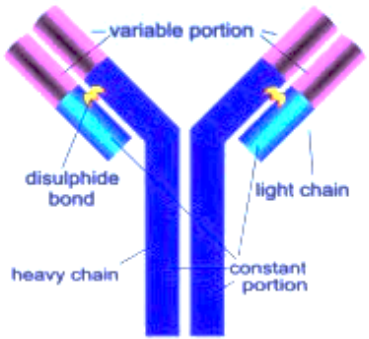
Highly sensitized patients
Characteristics

Preformed immune response to an organ donor



Donor specific antibodies (DSA)

Sensitized patients in Europe

Presence of DSA with positive cross match is a contraindication to transplantation

At least 30% of all patients waiting for a kidney are sensitized

About 15% are highly sensitized (>80% cPRA)

(8% cPRA 98-100%)

Clinical indication for kidney transplantation

Chronic kidney disease (CKD stage 5)

can develop from a number of disease stages incl:

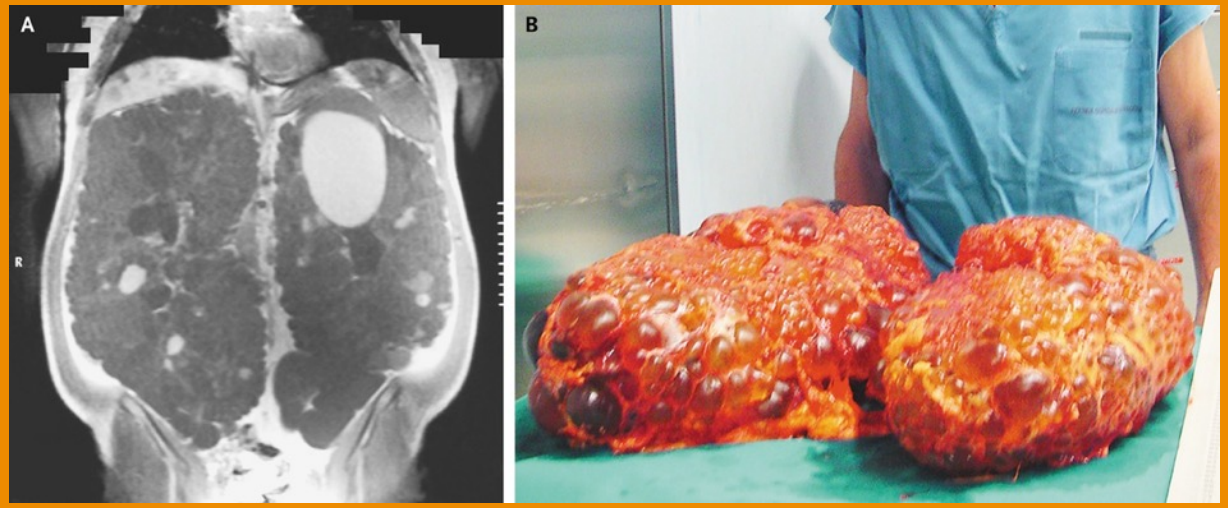
- Diabetic nephropathy
- Polycystic kidney disease
- Chronic glomerulonephritis
- Autoimmune diseases

Individuals with CKD stage 5

require renal replacement therapy

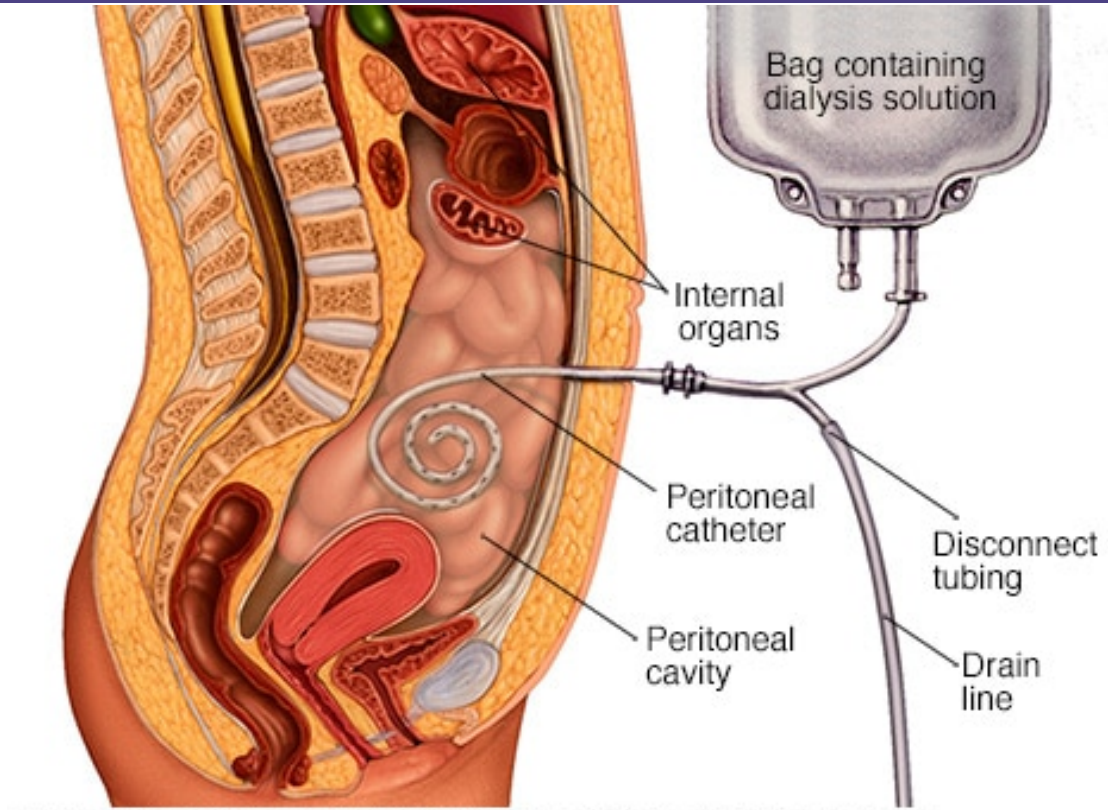
- Dialysis
- Transplantation

Polycystic kidney disease



New England Journal of Medicine 2010; 363:71

Peritoneal dialysis



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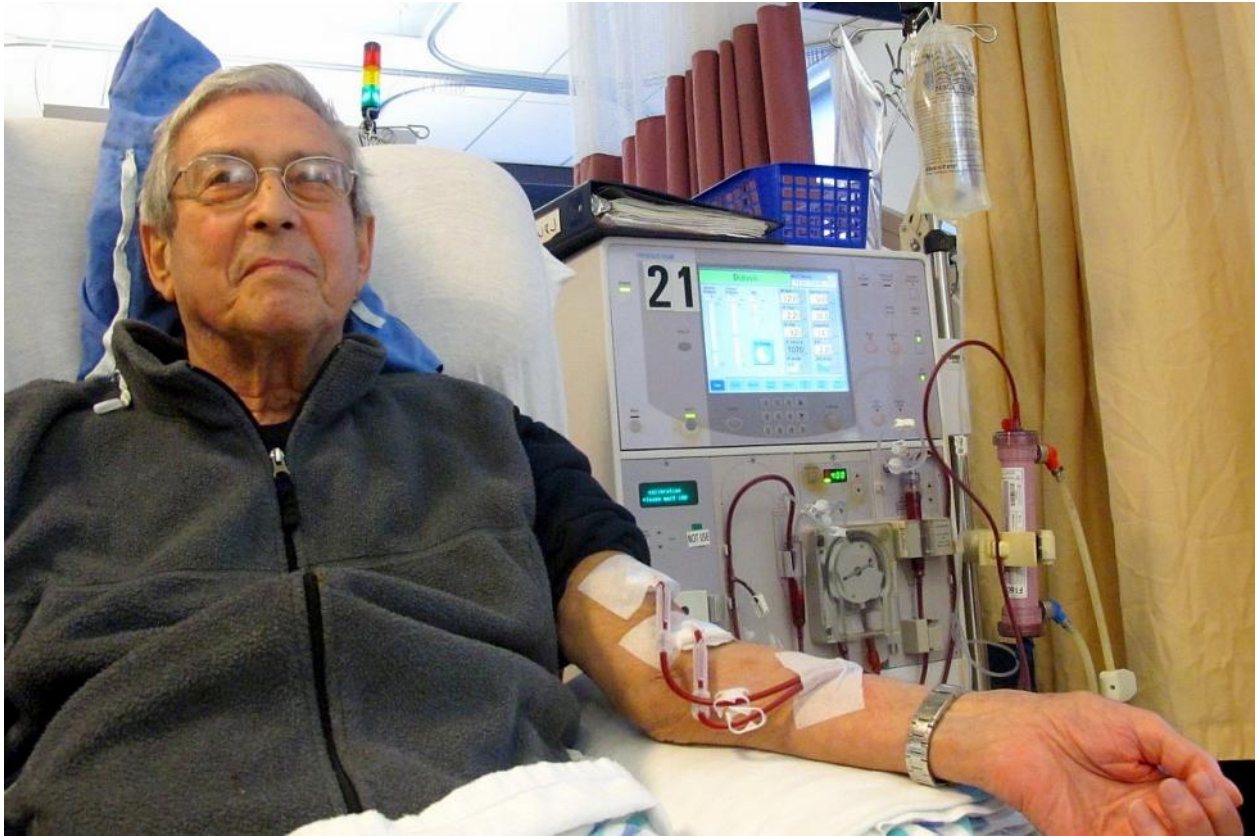
Haemodialysis



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Kidney transplantation is in most cases transplantation of a *single* kidney

CTS COLLABORATIVE TRANSPLANT STUDY

KIDNEY TRANSPLANT

Legend of Grades:

A = excellent graft function, minimal immunosuppression (serum creatinine < 130 µmol/L)
B = good graft function (serum creatinine 130 - 259 µmol/L)
C = mediocre graft function (serum creatinine 260 - 400 µmol/L)
D = poor graft function, but no chronic dialysis (serum creatinine > 400 µmol/L)

Rules for exchange of kidneys from deceased donor within the Scandiatransplant cooperation

Scandiatransplant

1. Patient with STAMP-status that are ABO compatible with donor and where all donor HLA-A, -B, -C -DRB1, -DQB1, -DPB1 antigens are either shared with the recipient or are among those defined as acceptable.
2. Highly immunized (PRA ≥ 80%) patients who are HLA-A, -B, -DRB1 compatible with donor D
3. Immunized patients (PRA ≥ 10% but below 80%) who are HLA-A, -B, -DRB1 compatible with donor.
4. If organ donor is <50 years of age, at least one kidney is offered to recipient <16 years of age (counted from time of registration), if there is HLA-DRB1 compatibility and in addition not more than 2 HLA-A, B mismatches.
5. Patients who are HLA-A, -B, -DRB1 compatible with donor unless the proposed recipient is > 30 years older than the donor.

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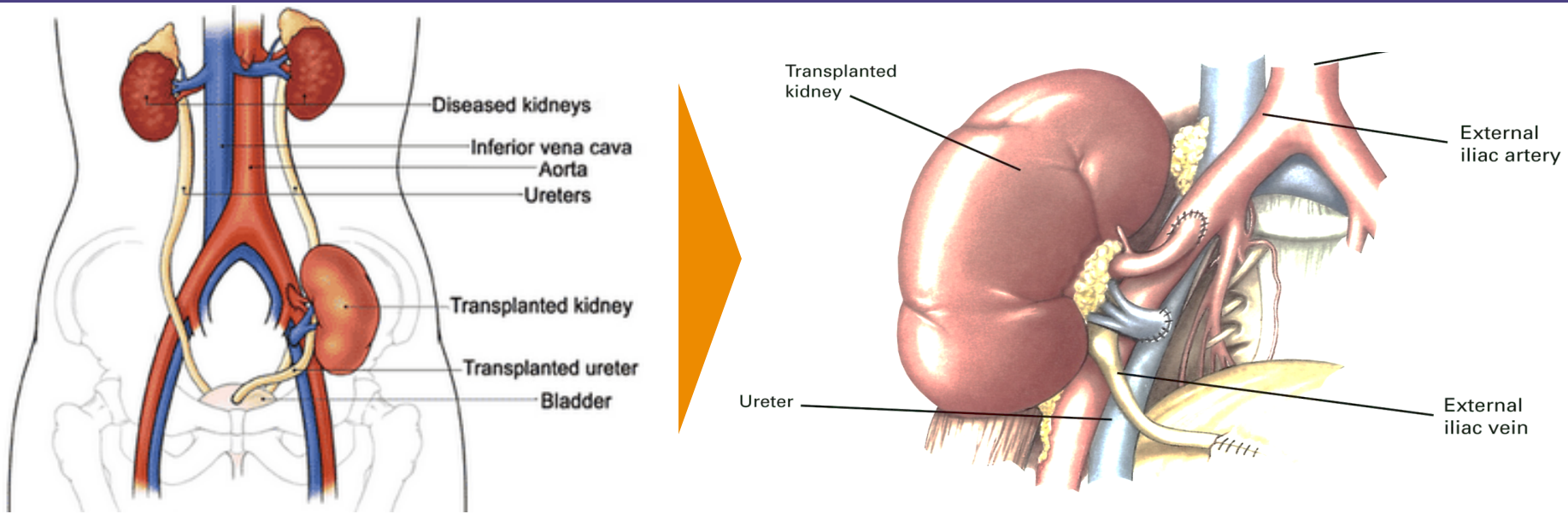
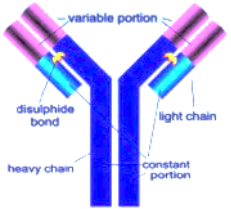
Kidney transplant



Highly sensitized patients
Characteristics

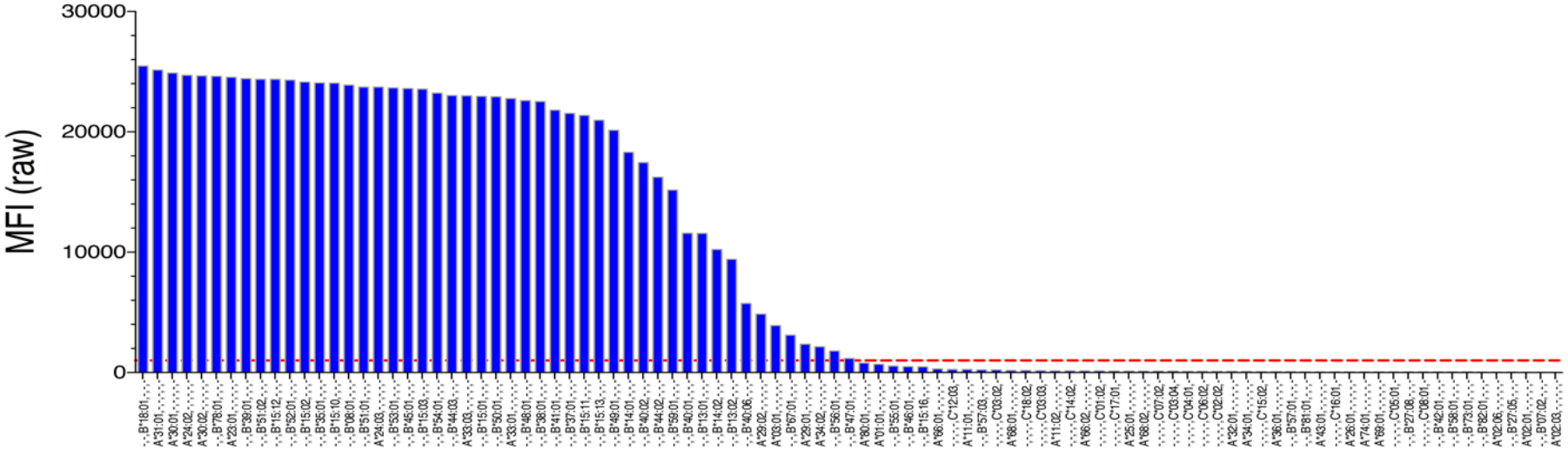
Preformed immune response to an organ donor



Donor specific antibodies (DSA) can be identified by routine laboratory tests

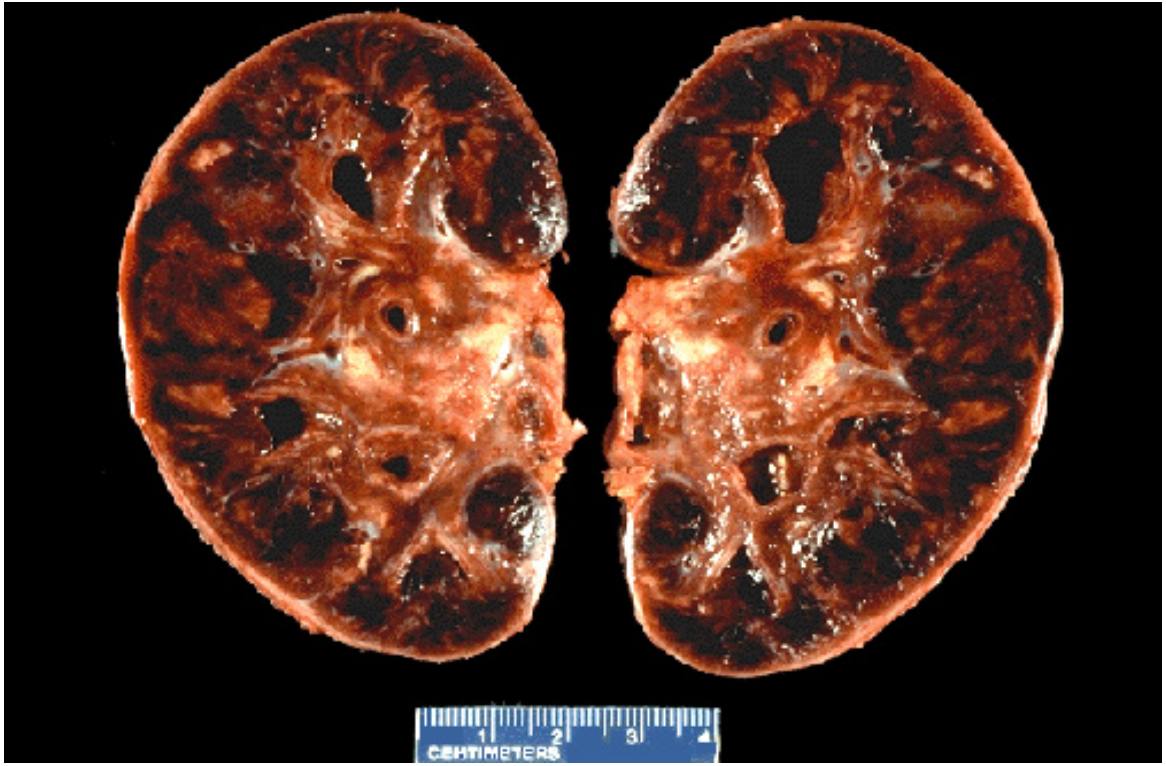
Detect the presence of antibodies tohistocompatibility molecules (HLA) expressed by a potential kidney donor

Antibody profile in highly sensitized patient



Hyperacute rejection

– Presence of preformed antidonor specific antibodies



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Highly sensitized patients
Characteristics

Preformed immune response to an organ donor

Donor specific antibodies can be identified by a routine laboratory tests

Crossmatch

All recipients are crossmatched with any potential donor before transplantation to ensure that hyperacute rejection is avoided

Detect the presence of antibodies to histocompatibility molecules (HLA) expressed by a potential kidney donor

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Currently available options for kidney transplant patients

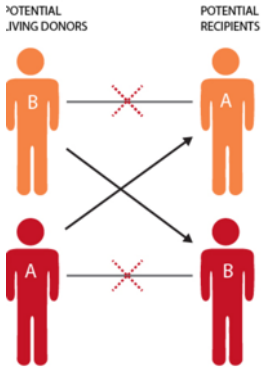
Deceased donor organ allocation (prioritized)

Gives higher priority to donor-recipient pairs with acceptable HLA mismatches

Kidney allocation system (KAS)

Acceptable Mismatch Programs (Eurostam, STAMP etc)

Kidney Exchange Programs



Institutional protocols for desensitization

Plasma exchange
Rituximab
Bortezomib
Eculizumab
IvIg
Corticosteroids and/or
Splenectomy
(all unapproved)

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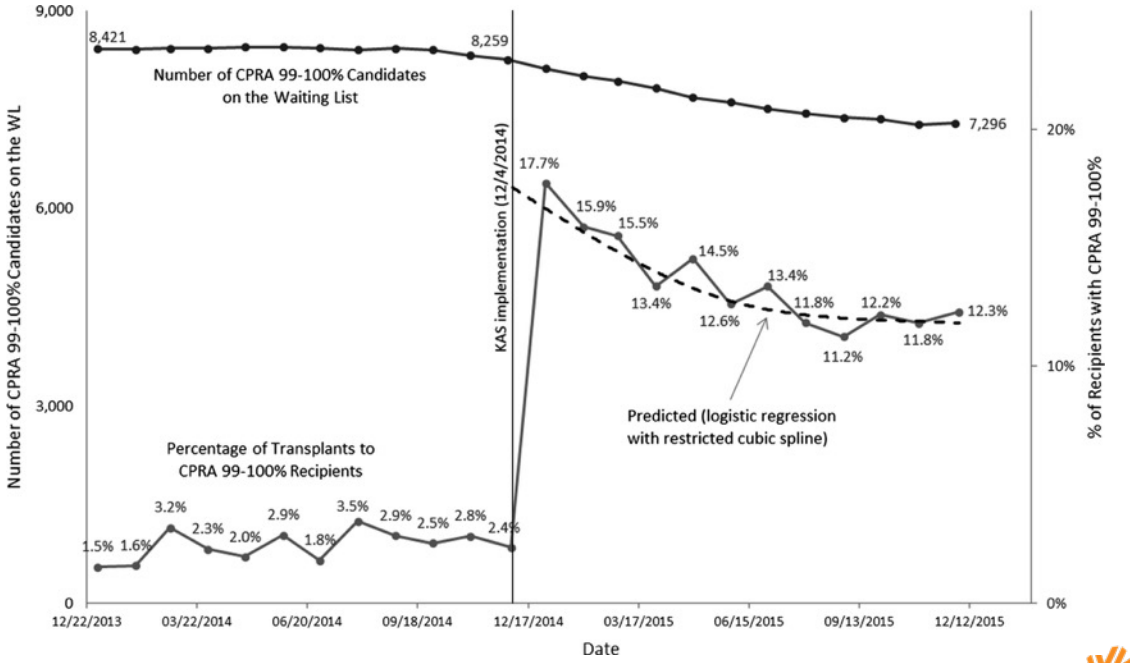
High unmet medical need for patients on the kidney transplant waiting list with very high levels of sensitization (cPRA >99%)

Only 8% of patients on the US waiting list with cPRA >99% currently receive a transplant through KAS…



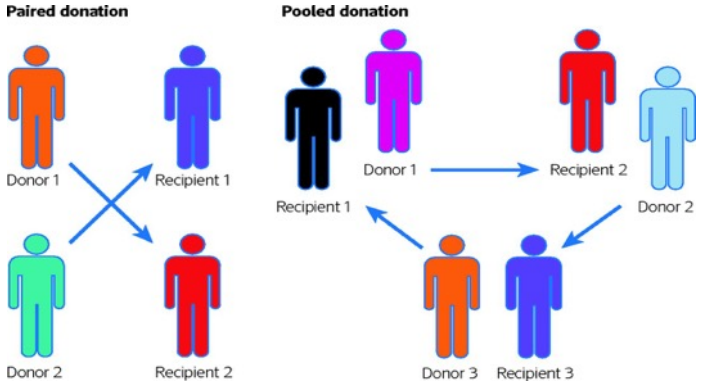
Stewart et al, 2016 AJT 16:1834-47 – Analysis of UNOS data post the introduction of KAS

Increasing number of patients worldwide with the highest levels of sensitisation are waiting on dialysis >6 years

Current treatment options for highly sensitized patients with an identified potential living donor

1. **Living donor HLA compatible transplant**

2. **Living donor paired exchange programme**

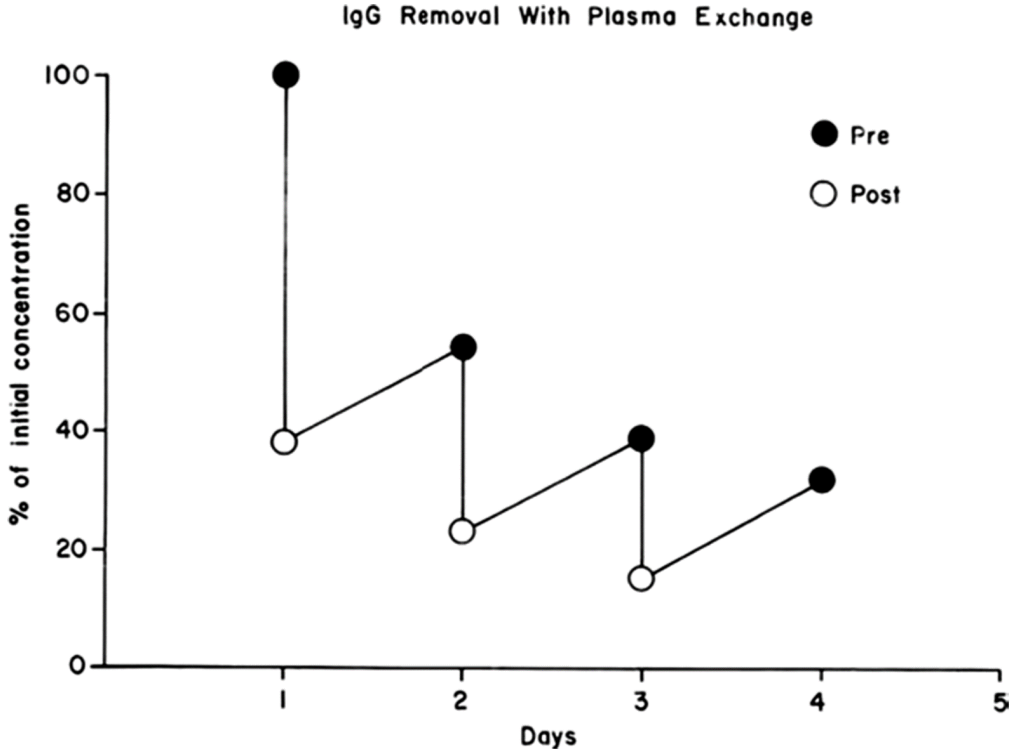


A very large pool of potential donors and recipients is required

In the USA 870 paired exchange transplants were performed in 2018 <4%

3. **Desensitisation removal of DSA**

Effect of plasma exchange on total IgG level



A.A. Kaplan, A Practical Guide to Therapeutic Plasma Exchange

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Desensitization current treatment options

Multiple rounds of plasma exchange and IVIG infusions are required to reduce the level of DSA below acceptable threshold for transplantation

Effective for patients with

- Low level of sensitisation <50% cPRA
- HLA incompatible living donor

Ineffective for patients with

- High levels of sensitisation >95% cPRA
- No living donor

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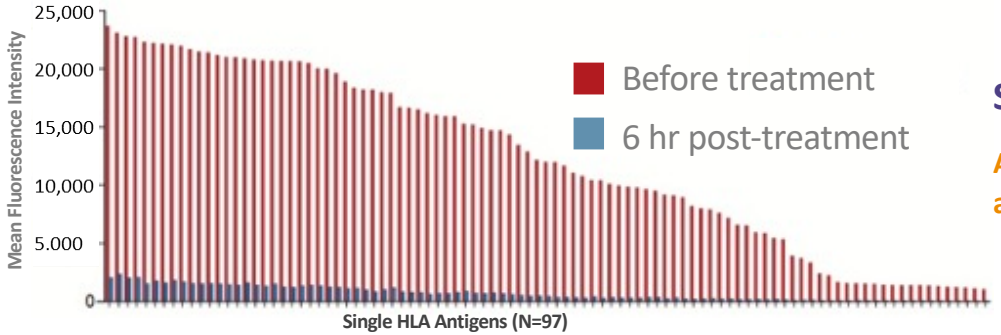
Imlifidase inactivates human IgG eliminating donor specific antibodies in highly sensitised patients

HLA antibody levels and C1q-binding HLA Antibodies After Imlifidase

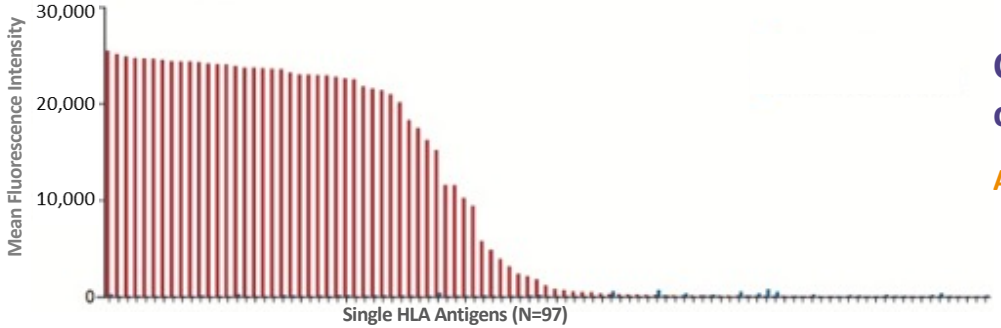
HLA-antibody levels before and 6 hr after treatment[a,b]



Significant reductions by 6 hours

Assessed with Luminex class I HLA antibody LABScreen single-antigen assay

C1q-binding HLA-Antibody levels before and 1 hr after treatment[a]



Complete/near-complete elimination of C1q binding by 1 hour

Assessed by C1qScreen single-antigen assay

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Successful kidney transplant and patient survival at 6 months in imlifidase-treated Patients

No significant difference in graft survival between XM-negative and XM-positive groups (P=0.4571)

	All patients (n=46)	XM-negative (n=7)	XM-positive (n=39)
6-month Graft Survival	**93.5%**	**100%**	**92%**
6-month Patient Survival	**100%**	**100%**	**100%**

Imlifidase has the potential to significantly reduce the waiting time for a transplant for highly sensitised patients

2 ½ Years

Calculated Reaction Frequency	Number of patients registered	Waiting time (days) Median	95% CI
0-84%	7917	963	942 - 984
85-94%	344	1577	1487 - 1667
95-99%	377	2138	1870 – 2406
100%	164	2424	2072 – 2776
TOTAL	**8802**	**1016**	**995 - 1037**

6 ½ Years

NHS Blood and Transplant

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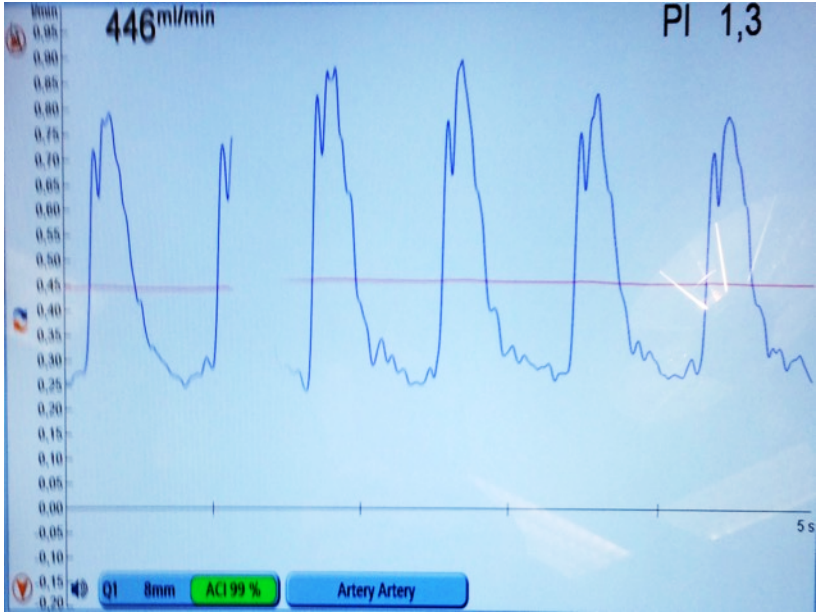
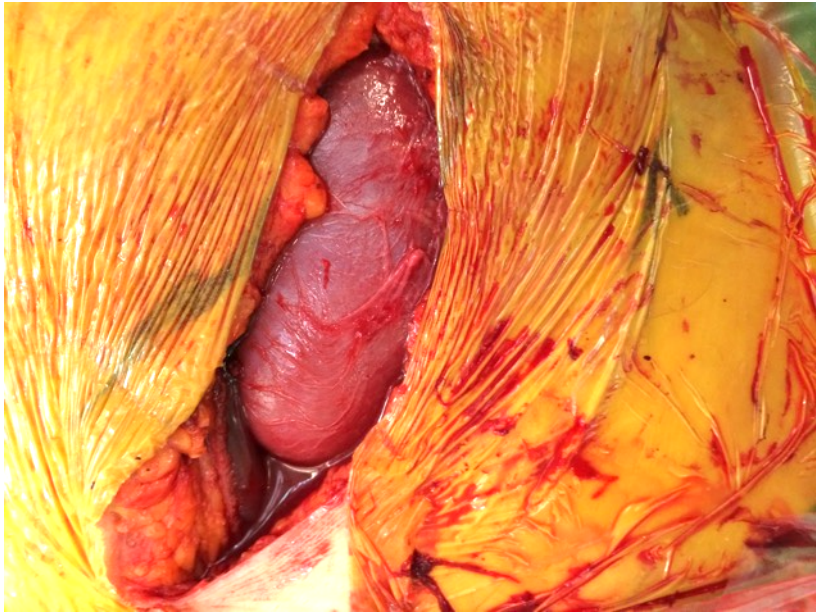
First patient ever being treated with imlifidase prior to HLAi kidney transplant





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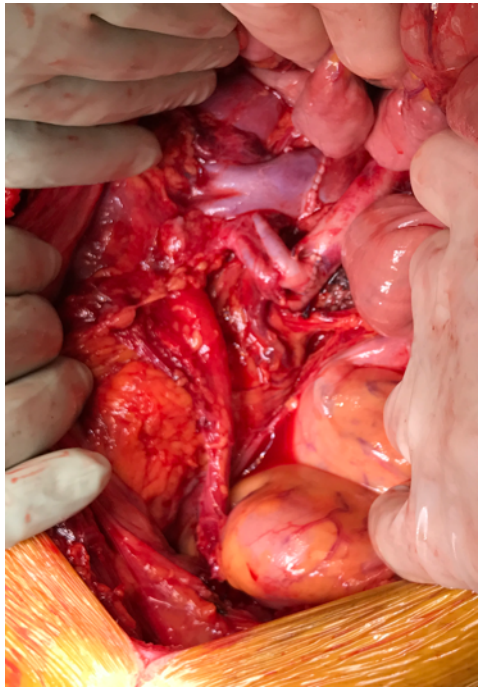
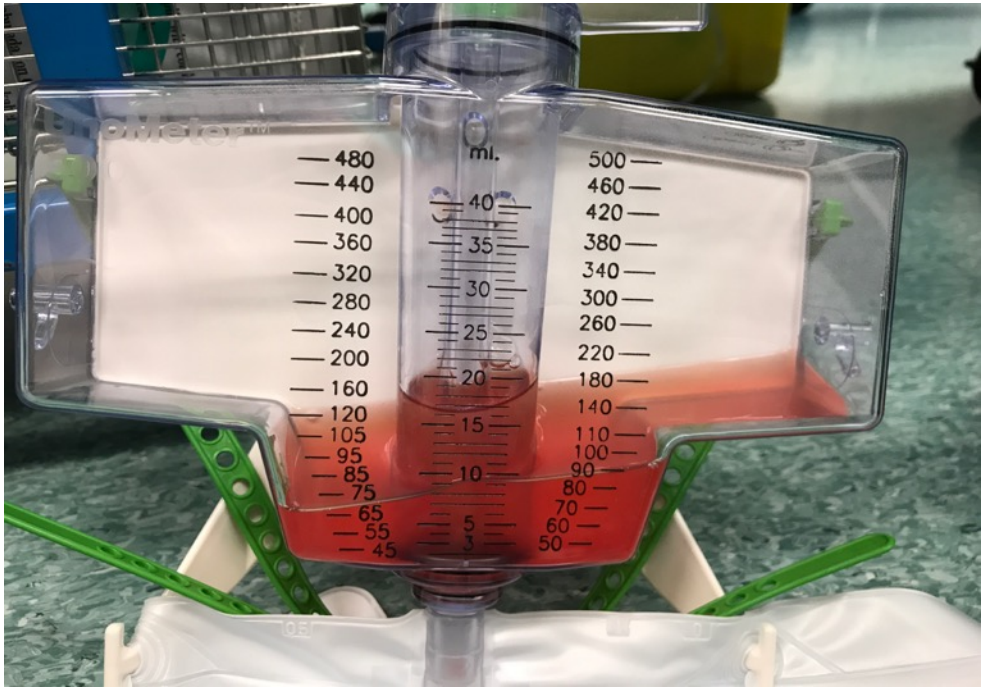
Transplant teams do complicated things to help people





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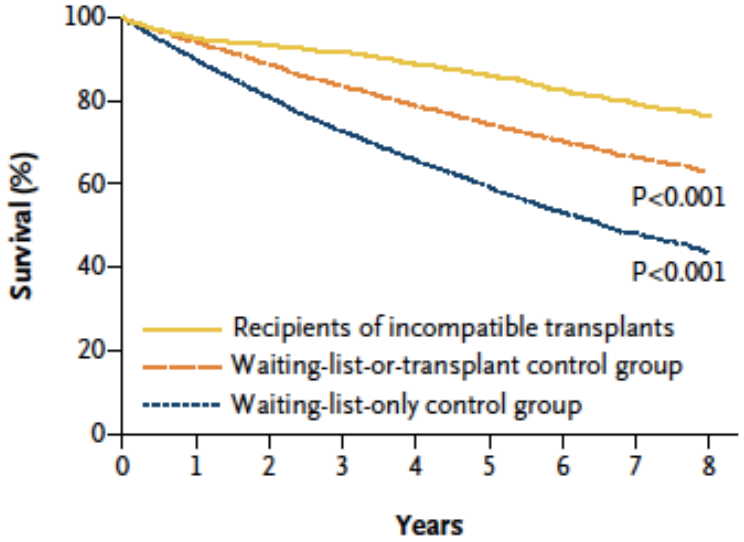
HLA-incompatible LD kidney transplantation increases patient survival



No. at Risk					
Recipients of incompatible transplants	1025	958	832	584	327
Waiting-list-or-transplant control group	5125	4546	3673	2493	1414
Waiting-list-only control group	5125	4141	3024	1810	916

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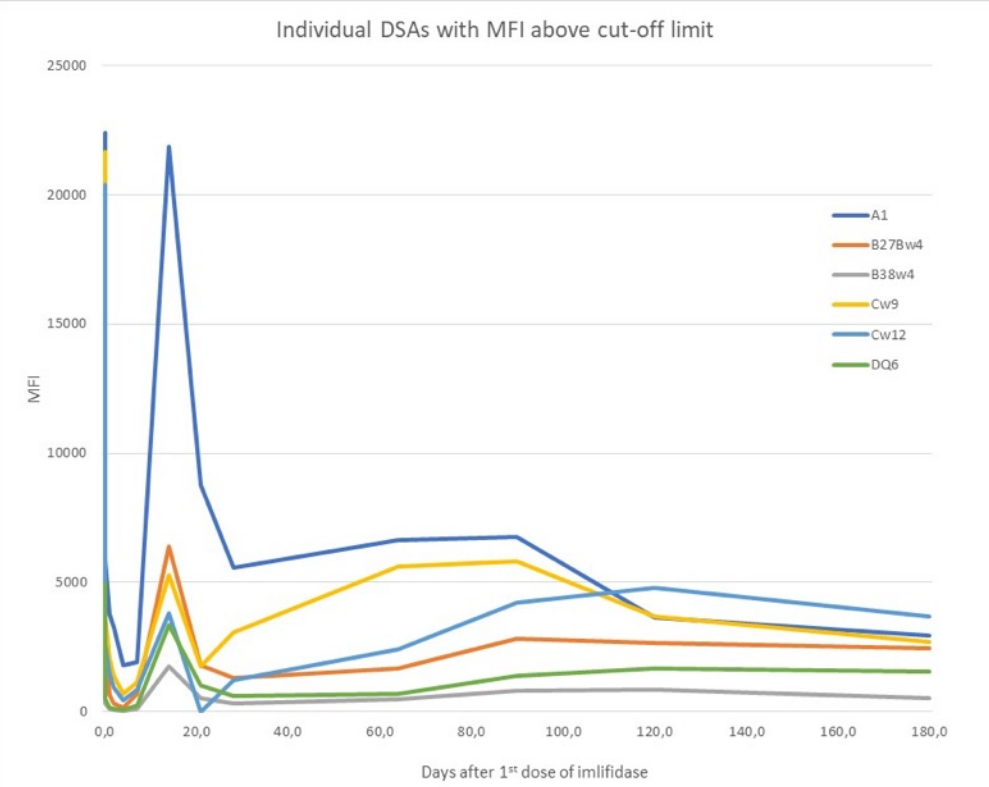
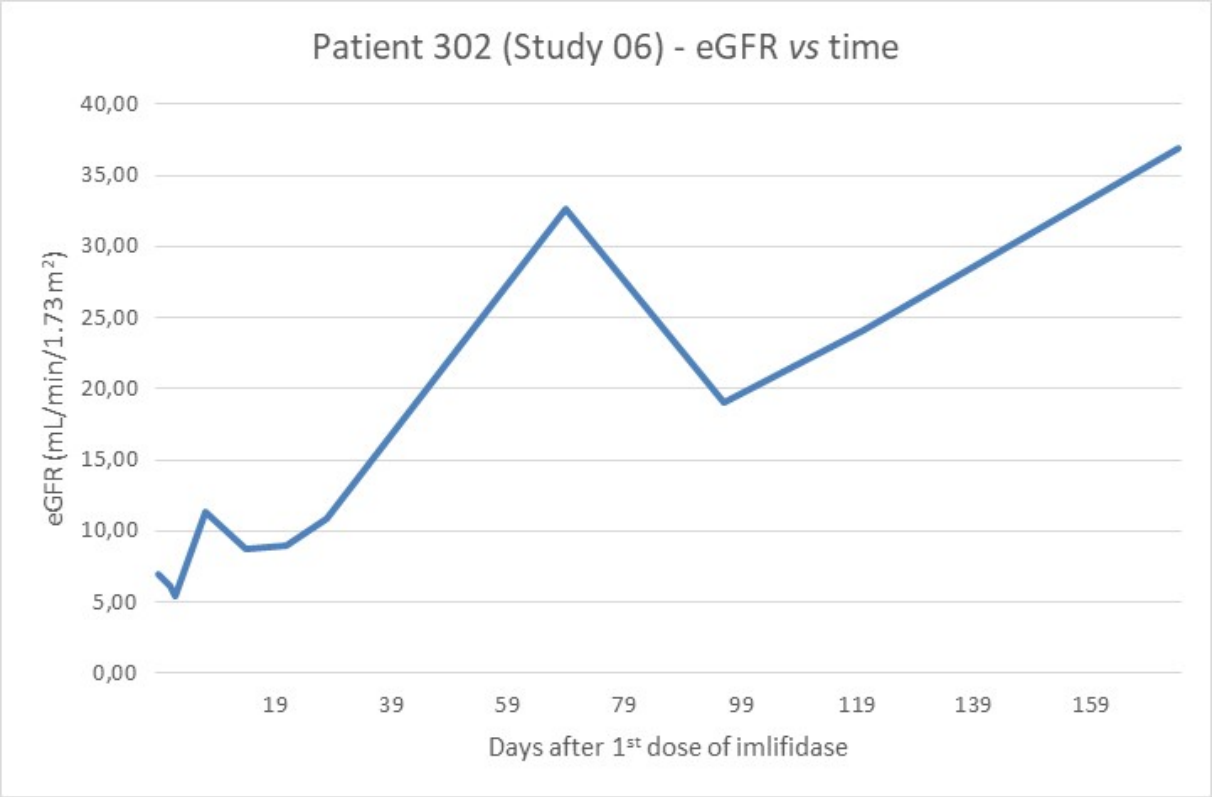
DSAs in an imlifidase treated patient



eGFR over time despite AMR episode

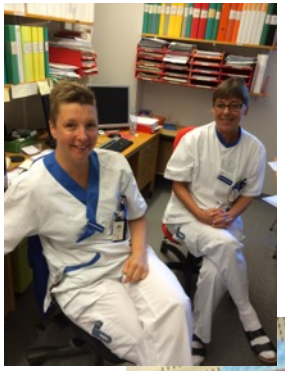
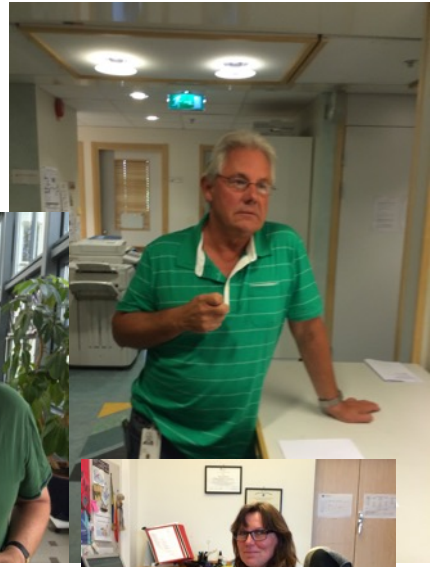
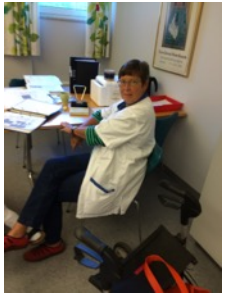
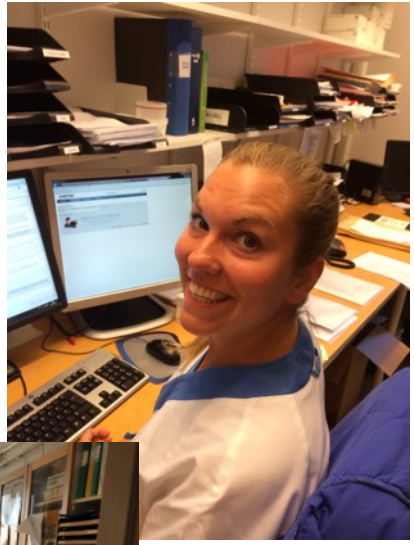


Imlifidase makes successful kidney transplantation possible for highly sensitized patients

“IdeS (imlifidase) is the most promising thing that has happened to the transplantation field these latest 15 years…”

Dr Robert Montgomery
New York University

Transplantation is teamwork and leadership!



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