Current strategies to kidney allocation

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From organ sharing to organ allocation optimization

Center or Patient based approach?

**Center based approach or so-called “local” priority**
- Intuitive, natural, practical way to deal with organ allocation
- It preserves individual medical decision
- Links the level of transplantation activity to the level of dead donors procurement in a given area
  - Inequity in access to transplantation between patients from the same country
- Deals with too few prevalent patients on the waiting list a given day
  - Non-optimal graft and patient survival because of bad recipient-donor age or HLA matching

**Patient based approach**
- To use organs with the highest possible relevance
- To allocate vital organs “just in time”
- To optimize donor-recipient matching on multivariate criteria
- Based on a scoring function taking into account multiple allocation criteria
- Implies acceptance of a supra-center computerized decision rule
- Has to be supported by a powerful Information System
- Requires to deal with logistical issues related to the transportation of organs

Patients with the highest score will receive the kidney
Which criteria for a fair kidney allocation?

- Transplant access rate
- HLA matching
- Dialysis time
- Waiting time
- Level of sensitization
- Pediatric specificities
- Geographic level
- Age matching

Equity?

Efficiency?
Waiting time? An increasing proportion of preemptive transplant recipients

- No guidelines for the timing of registration during CKD progression

- Mean eGFR: 9.2 in 1995 to 13.8 ml/min/1.73m² in 2009 (P < 0.001)

- eGFR >15 ml/min/1.73m²: 9% in 1995 to 35% in 2009

UNOS database. 1995-2009, end point 31/12/2007, Deceased and living donors; 1st adult KTR
Absence of benefit to a too early transplantation

May subject patients to premature operative and immunosuppressive risk and waste the native kidney function of recipients

*Propensity score-adjusted.


No improvement of graft survival after preemptive KTR with lower pretransplant eGFR

Akkina, AJT 2008

“No relationship between pre-Tx eGFR and 6-month eGFR, suggesting that post-Tx renal function is independent of the level of pre-Tx renal function. These data suggest that preemptive kidney transplantation should be delayed as long as possible”

Ishani, AJKD, 2003
But a real negative impact of time dialysis on graft survival and patient survival!

“ESRD time is arguably the strongest independent modifiable risk factor for renal transplant outcomes”.


“The duration of ESRD was a significant risk for recipient death (HR 1.04 per year, p<0.001)”

USRDS database. 1990-1999, only primary kidney transplantation
In France, Waiting Time and Dialysis time as equity criteria

\[
\text{Score}_{\text{H\Delta age}} [0 - 1050] = 100 \times f_1(DD) + 200 \times f_2(DA, Dial)
\]

Dialysis time (DIAL) from the date of dialysis start

Waiting time from the date of registration according to dialysis (DA,Dial)
Why to optimize HLA matching?

- To improve graft survival
- To decrease the risk of allosensitization
  - Following failure of a first renal TR
  - Incrementally with the number of mismatches at all HLA A,B,DR,DQ loci
  - For all recipients?

"better HLA matching is associated not only with better graft survival, but also with the administration of lower dosages of immunosuppressive agents, a lower incidence of side-effects of immunosuppression such as non-Hodgkin lymphoma, hip fractures, and death from infection"
HLA matching: a solution to preserve immunological capital

**Impact of donor mismatches at individual HLA-A, -B, -C, -DR, and -DQ loci on the development of HLA-specific antibodies in patients listed for repeat renal transplantation**

Kosmoliaptsis, Kidney International 2014

**Table 2 | Influence of HLA mismatches on the likelihood of developing HLA-specific allosensitization after re-listing for repeat transplantation**

<table>
<thead>
<tr>
<th>HLA Loci</th>
<th>Likelihood of developing sensitization to individual HLA loci per mismatch</th>
<th>Likelihood of increasing cRF for individual HLA loci per mismatch</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR (95% CI)</td>
<td>P-value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>HLA-A</td>
<td>3.2 (2.0, 4.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HLA-B</td>
<td>3.4 (2.2, 4.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HLA-C</td>
<td>2.5 (1.5, 3.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HLA-DRB1</td>
<td>3.5 (2.3, 5.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HLA-DRB3/4/5</td>
<td>3.9 (2.4, 7.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HLA-DQ</td>
<td>3.0 (2.0, 4.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**A Lifetime Versus a Graft Life Approach Redefines the Importance of HLA Matching in Kidney Transplant Patients**

Meier-Kriesche, Transplantation 2009

“negative impact from poor HLA matching of their first kidney transplant... particularly important in patients with a long life expectancy because of the high likelihood of needing a second transplant during their lifetime”

**The Impact of Human Leukocyte Antigen Mismatching on Sensitization Rates and Subsequent Retransplantation After First Graft Failure in Pediatric Renal Transplant Recipients**

Gralla J et al, Transplantation 2013,
How to optimize immunological matching

\[ + \left[ 100 \times f_3(AB) + 400 \times f_4(\text{DR}) + 100 \times f_4(\text{DQ}) + 150 \times f_7(\text{FAGN}) \right] \]

The young recipients obtain the maximum of points for HLA matching (class II especially)

It is decreasing as from 45 years, and no more taken into account beyond 75 years.

\[ x \, f_5(\text{AgeR, 45, 75}) \]
Age matching

Données UNOS, Kasiske, JASN, 2002

Meier-Kriesche, AJT, 2005

- Relative risk of graft loss (with death censure) regarding donor-recipient age combination
- Cox model
- Referent risk factor: R=D= age 18-29 y

- By excluding transplantation of younger kidneys to older recipients
- The overall projected improvement in graft survival: 3 years per transplant.
- Significant increase of the overall graft life, by a total 27 500 graft years, between 1990 and 2002

Figure 5: Projected graft years saved with allocation amendment.
To optimize donor-recipient matching on multivariate criteria

- Age matching is a major allocation criteria
  - More efficient to allocate old grafts to older recipients who have shorter life expectancies and who need less nephronic mass
  - Not as a “cut-point” but redistribution of grafts towards recipients with same age or slightly younger.

- Eurotransplant Senior Program (ESP)
  - Availability of elderly donors doubled
  - Waiting time for ESP patients decreased
  - Local allocation led to shorter cold ischemia time and less DGF
  - Graft and patient survival were not negatively affected by the ESP allocation
How to define and measure sensitization?

**Complement dependent cytotoxicity**

<table>
<thead>
<tr>
<th>Donor</th>
<th>Recipient sera</th>
<th>+ C'</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor 3</td>
<td></td>
<td></td>
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<tr>
<td>Donor 4</td>
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<td></td>
</tr>
<tr>
<td>Donor 5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor 6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PRA: 30/100 = 33%

**Solid-phase assays**

- HLA Ab anti-A2 from patient’s serum
- PE anti-IgG
- Purified Ag HLA (Molecule HLA A2)

**Date**
- 24/2/09

**T**
- 12/40

**B**
- 2/10

**Specificity**
- Anti-A2

(agence de la Biomédecine)
The solid-phase techniques:

- Accurate definition of a patient sensitization profile
  - More (too?) sensitive, rapid and reproducible
    - (…but MFI variation !!) inter and intra laboratories
    - Reed AJT 2013

- Exclusively HLA class I or class II Ag
  - Exclude non HLA Ag recognition

- Tracks of HLA Ab deleterious to the graft not revealed by cells phase assay

- Permits precise identification of the unacceptable HLA Ags even in broadly sensitized patients

- More unacceptable HLA Ags are identified, leading to exclude more potential donors

- cPRA (2009)
Match donor potentiel : extra points for patients with a low Transplant accessibility

Match Donor Potentiel :
Number of donors matching recipient blood group, retrieved during the 5 past years in France, without unacceptable HLA antigen, and with less than 3 HLA A, B and DR mismatches
cPRA and national priorities

If cPRA ≥ 85% → National priority:

% of actual kidney donors (retrieved for at least one kidney grafted) over the previous 5 years within France

Matched for blood group

With 1 or more of the unacceptable HLA Ag

Since 1996

H3 program
If ≤ 1 HLA A B DR mismatch
National priority if $\leq 1$ HLA A B DR MM with the donor
Election promise !!
**Acceptable mismatch program (April 2005)**

- **Objective**: to increase the number of HLA compatible donors without increasing the immunological risk of graft failure and without increasing the cold ischemia time.

- **How**: By authorizing more than 1 mismatch under conditions that each mismatch corresponds to an acceptable Ag according to the national recommendations.

- An Ag is considered as permissible when the highest bead bearing this Ag presents a normalized MFI <500 on historic and current sera (Single Ag assay exclusively).

**Donor HLA typing**
- HLA A2, A29, B7, B44, DR4, DR17, DQ2, DQ4

**Recipient HLA typing**
- HLA A2, A3, B51, B7, DR4, DR13, DQ2, DQ6
  - A24, A25, A29, A31, B8, B44, B35, B61, DR17, DQ4

**Concept of virtual CXM**
- No DSA HLA A B DR DQ
- Peak and current sera
- Without taking into account Ab anti DP or CW
HAP results: graft survival

- An improved access to transplantation for hyper-immunized patients
  - 2 years access: from 42 to 51 %, in France in the same period.
  - Increase proportionally with the rate of recipients included in this program
- Efficient only on a large pool of donors (national priority)
- Good 2-years (86%) and 5-years graft survival
- Can we improve the acceptable mismatch concept
  - Better selection of eligible patients?
  - How to determine more accurately HLA Ab specificities with clinical relevance?
  - Problem of HLA DQ barriers and its effects on cPRA calculations

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>1 months</th>
<th>1 year</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non immunized</td>
<td>13050</td>
<td>96,2%</td>
<td>92,3%</td>
<td>79,2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[95,9% - 96,5%]</td>
<td>[91,8% - 92,7%]</td>
<td>[78,4% - 80,0%]</td>
</tr>
<tr>
<td>number at risk*</td>
<td></td>
<td>12379</td>
<td>11308</td>
<td>4337</td>
</tr>
<tr>
<td>Hyperimmunized exclude HAP</td>
<td>552</td>
<td>95,9%</td>
<td>90,9%</td>
<td>71,2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[93,8% - 97,3%]</td>
<td>[88,2% - 93,1%]</td>
<td>[65,5% - 76,1%]</td>
</tr>
<tr>
<td>number at risk*</td>
<td></td>
<td>509</td>
<td>439</td>
<td>122</td>
</tr>
<tr>
<td>Hyperimmunized and HAP</td>
<td>1082</td>
<td>95,9%</td>
<td>90,1%</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[94,6% - 97,0%]</td>
<td>[88,1% - 91,7%]</td>
<td></td>
</tr>
<tr>
<td>number at risk*</td>
<td></td>
<td>1006</td>
<td>841</td>
<td>117</td>
</tr>
</tbody>
</table>
Adapted from the acceptable mismatch program of Eurotransplant more than 450 Tx since May 1996

- Eurotransplant: 2% of hyper-immunized patients
- Improved access to transplantation: 17% to 60% after 2 years
- 4% of + CM
- Graft survival in « AM » patients is identical to that of non-sensitized recipients (87% at 2 years)

**FIGURE 3.** Long-term graft survival of patients transplanted via the AM program. Claas, Tx, 2009

- Only one HLA referent center for Eurotransplant (Leiden) for inclusion
- Only patients with a virtual PRA more than 85% will be included in the AM program + waiting time > 1 year
  - Serum are screened in complement-dependent cytotoxicity (CDC), including HLA repeat mismatch with a previous Tx
  - Virtual PRA is mainly based on HLA-A, -B, and –DR Ab specificities (compared to a panel of donor HLA type from Eurotransplant)
  - HLAMatchmaker is used for the identification of potential acceptable HLA mismatches
- Final CDC crossmatch will only be performed in the recipient center (mostly current serum)
For which geographical level and matrix

Changes in Geographic Disparity in Kidney Transplantation Since the Final Rule

- USA: difference between the maximum and minimum median waiting times to transplantation each year across UNOS regions

- France: Transplant access kinetic according to area of registration

Biomedecine Agency Datas
Unique registration on the national waiting list
Donor-recipient ABO blood group identity

Nationwide allocation priorities
1. High emergency
2. Hypersensitized recipients
3. Children < 18 y if donor age < 18 y

Regional priority
1. Emergency
2. Combined transplantation
3. Children (if donor age < 30 y)

Local level
Patient based Allocation system

Absence of well age-matched recipient locally

National level
- To a patient according to a score system
- Taking into account proximity
- Disappearance of geographical levels

Recipient
Allocation policy

- Requires a national waiting list: an efficient mean to support a transparent, traceable and auditable allocation system.
- Elaborated with all concerned parties:
  - Health care professionals
  - National health authority (public state agency: Agence de la biomédecine)
  - Patients and population representatives
- Applied by a public state agency, guarantee for a proper application of procedures
- An empirical compromise between equity, justice, efficacy, practicability, quality of post-transplant results and technical constraints related to organ retrieval and preservation
  - So difficult to simultaneously maximize utility, efficiency, equity and predictability
- Promoting as much as possible a patient-based allocation and not a center-based allocation system
- Remains a moving and open topic, needing periodic evaluations to exclude bias or side effects
  - Complete information for both health professionals and the general public
  - The interest of simulation tools
- Objective, official, clear, transparent and fair in order to obtain the general public trust and organ donation acceptance
gràcies per la seva atenció

La première égalité, c'est l'équité.
Victor Hugo « Les Misérables »
Les mismatch du conjoint, ceux du ou des greffon (s) antérieur(s), les anti-CW et anti-DP

<table>
<thead>
<tr>
<th>HLA type</th>
<th>PRA LCT</th>
<th>Pic cPRA ≥ 85%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current cPRA &gt; 70%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Non authorized mismatch

Acceptable mismatch

Unacceptable HLA Ag are registered on the National Transplant Database (CRISTAL)

Les mismatch du conjoint, ceux du ou des greffon (s) antérieur(s), les anti-CW et anti-DP

HAP programm : DSA antiCw and anti DP authorized

Potentiel match donor (with restriction in HLA MM (≤3 ABDR MM))