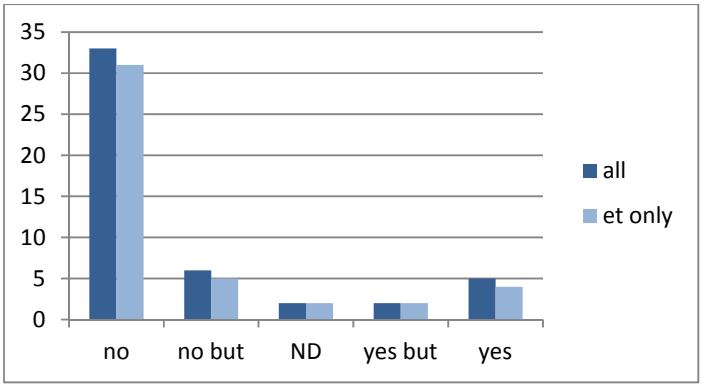
# Summary of results of the Patient Based Cases 2018

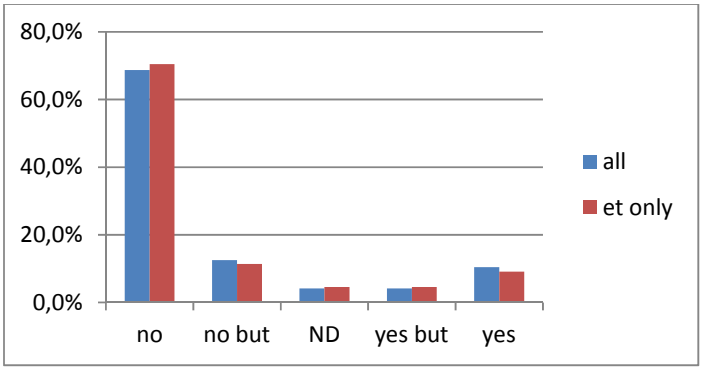
## Patient based case 2018-01

Male recipient, 60 years old
In the AM program since 6 months, blood group B pos
**HLA-type:**
A1, A19, A29, B8, B40, B60, Bw6, Cw3, Cw10, Cw7, DR3, DR17, DR52, DQ2
**HLA-type of previous transplant**
(November 2016, failed after two days; permanent non-function):
A1, A2, B7, B8, Bw6, Cw7, DR2, DR15, DR3, DR17, DR51, DR52, DQ1, DQ6, DQ2
**Current antibody information:**
CDC: A2, A28, Luminex, see histograms/excel file.
Acceptable Antigens: A74, B50, B61, B41, B48, B72
**Other relevant information:**
Autologous status: DNeg, chance for a donor (in AM program): 0.160 and vPRA: 99%
**Donor blood group:** B pos
**Donor HLA type:**
A1, A33, A19, B8, B50, B21, Bw6, Cw6, Cw7, DR17, DR3, DR52, DQ2

**Decisions overview:**
44 ET affiliated centers and 4 other centers gave their opinion on this case.

No
No but — Only under special conditions
ND — Decision cannot be made, because it depends on extra information that was not available in the case.
Yes but When additional measurements are taken
Yes



**Motivation**

**Decision is No/ No but:**

- Positive (spleen) cross match (in recipient center) is contra indication
- Positive spleen cross matched probably caused by DP/DQA antibodies (against donor)
- Reactivity might be explained by A33 antibody, epitope 76VDT
- A33 is no acceptable mismatch
- High grade sensitization against Class II including DP(epitope DEAV)
- No repeat mismatch
- Blood group identical
- DR/DQ matched
- Low chance for an organ
- Good chance to receive a better match within the AM program
- When different sera are used in donor and recipient center, immunization could have taken place between the bleeding dates
- Transplantation history with failure after two days indicates high risk
- Donor lab interpreted PBL results as false negative
- Auto cross match is negative

**Decision is ND:**

- Positive cross match can be due to bad quality of spleen cells
- Mismatch B50 is acceptable antigen
- Mismatches Cw6 and A33 no CDC and no/weak luminex antibodies
- No repeat mismatches
- Good HLA match, DR/DQ matched organ
- Immunizing event between bleeding dates of serum donor and recipient center
- False positivity of cross match can be due to use of drugs as IFNG and Rituximab

**Decision is Yes/Yes but:**

- CDC cross match on PBL negative, cross match on spleen reflects B cell cross match
- Positive spleen cross matched is caused by DP Abs/ weak anti A33/ B cell reactivity with auto or non-HLA antibodies
- Anti A33 MFI low (<3000 MFI); non cytotoxic
- No DSA for A33, B50, Cw6
- No CDC antibodies against donor
- 3 mismatches in Class I typing, DR/DQ match,
- no detectable DP antibodies, Class II cytotoxicity can be excluded.
- Patient in AM program, low chance
- Need for antibody reduction in recipient and appropriate immunosuppression

**Additional information needed:**

- Separated T and B cells cross matches (mentioned by 17 centers)
- DP and/or DQA typing of recipient and/or donor (13 centers)
- Did donor and recipient center use the same serum/sera for the cross matches (e.g. fresh serum, historical sera) (7 centers)
- Positivity score of cross matches (2 centers)
- Why is A33 no acceptable Ag, why are there so few acceptable antigens (2 centers)
- Immunization history, retest luminex after EDTA treatment, SPA results in peak serum, inclusion of DP in AM program (1 center).

**Comment on cross matches on spleen vs PBL**

- Higher percentage of B-cells in spleen in comparison to PBLs (25 centers)
- Spleen cells are show higher class II expression (10 centers)
- Positive spleen cross matched can be explained by the presence of Class II/DP antibodies (12 centers)
- Positive spleen cross matched can be explained by the presence of non HLA or auto antibodies (4 centers)
- Aberrant results because of use of different sera by donor and recipient center (4 centers)
- False positivity of cross match on spleen because of poor quality of spleen cells (7 centers)
- False positivity of cross match on spleen because of use of certain drugs (4 centers)

## Patient Based Case 2018-02

Definition of Unacceptable Antigens (UAG) for 4 different recipients on base of Luminex SA results
For 4 different patients a short description is given, including age, gender, HLA-type, if known immunizing events and Luminex SA results (both histogram and Excel file).

**21 centers described (part of) their center policies, as categorized below:**

**MFI Cut-off values**

- Antibodies with MFI <1000 clinically irrelevant
- inclusion of all repeated mismatches, with MFI >3000
- MFI>3000 and plausible specificities (known immunizing events)
- in presence of Class I and II Antigens, all antibodies with MFI >3000 UAG, other UAG: MFI >5000
- Antibodies with MFI >5000 clinically relevant, MFI 100-5000 in case of repeated mismatches
- Antibodies with MFI >10,000 UAG (independent of immunization history)
- specificities with MFI <10000 after plausibility check

**CDC results**
CDC results in addition are necessary

**Repeated Mismatches**
Mismatched Antigens from previous transplantations should also be considered UAG (even if no antibodies are detected)
repeat mismatches are acceptable when no HLA antibodies are detected with this specificity by Luminex in historical sera and last two current sera
repeat mismatches only in conjunction with corresponding antibodies are UAG
all A-B-DR mismatches are UAG, unless PRA is too high, then mismatches with MFI <1000 are excluded

**Epitopes**
high titre Cw: MFI>15000 and mismatched antigen: at least slightly positive in luminex/CREG
use epitope study to evaluate risks for positive antigen Ag with MFI <1500

**Organ in situ**
when previous kidney is still in situ, mismatches are UAG

**Cross Match**
cross match in case of organ offer

**Other**
assignment of UAG based on at least 2 samples
perform immunoadsorption in case of DSA with MFI between 2000 and 10000
luminex results are not considered, though DSA are reported to the clinician and taken along in the decision

**Comments categorized per recipient**

**Recipient A**
**AM (program) (4)**
Summarized: Propose this recipient for the AM program
**Immunizing Events (2)**
Summarized: ask for earlier pregnancies, children's Ag, transplantectomy
**Unacceptable Antigens (12)**
Summarized: Unacceptable Antigens defined based on luminex results, and/or detected DSA, and/or epitope cross reactivity, and/or German recommendations. DR4, DR7, DR9 are unacceptable because of the unacceptable antigenDR53. Cut off values: 3000, 10000 (Class I)
**Other (5)**
Summarized: This is a high risk patient; recommended additional typing for DP of the donor; possible risk antigens (DQ7, DQ9, DR9, DR14DR53, B7, B57)

**Recipient B**
**Origin of Antibodies (3)**
Summarized: Suspected natural antibodies, origin of antibodies unclear
**DQ1 antibodies (8)**
Summarized: DQ5, DQ6 are (possibly) unacceptable or risk antigens
**No Unacceptable Antigens (10)**
Summarized: No unacceptable antigens can be defined.
**Other (5)**
Summarized: Perform (additional) B cell cross match; patient is young and needs optimal matched transplant; when class I data are available revise unacceptable antigens;

**Recipient C**
**Repeated mismatches (4)**
Summarized: Immunization related to first donor, repeat mismatches give increased risk to graft loss; also repeat mismatches with low MFI included.
**MFI cut off values (4)**
Summarized: mentioned cut off values (MFI): 3000, 1000 (because of low positive control), 2000.
**Other (5)**
Summarized: Risk antigens/unacceptable antigens: HLA-A1; B51,62, Cw4,9;DR1; DQ5,6; A23, A24, A25, A32, B71, B72, B50, B53, B56, B57, B78, B58, B13. No information about transplantectomy, revise unacceptable antigens when Class I date are available.

**Recipient D**
**Bw6 Antigens (as unacceptable antigens) (12)**
Summarized: All Bw6 associated antigens are unacceptable antigens; risk factors for antibody mediated rejection; caused by pregnancy or blood transfusion?
**AM (program) (2)**
When highly immunized (confirmed by CDC); when immunization by blood transfusion is relevant, treat as AM patient or propose for AM program.
**Class II (7)**
Class II difficult to interpret due to DQA/DPA abs; high background; while unspecific/natural antibodies (irrelevant). Repeat with different sample or diluted sample. Suggested unacceptable antigens: DR4, DR 10, DR16, DQ8
level of DP antibodies could result in positive B cel flow cross match
**No UAG (6)**

No current (class II) unacceptable antigens (test second serum sample, and include CDC). B27 is not an unacceptable antigen; not enough information to define unacceptable antigens.

**Additional testing (8)**

Summary: The following additional tests are suggested: CDC/Class I tests (if positive redefine unacceptable antigens); B-cell cross match; luminex single antigen Class II (possible a-specific reaction DR4, DR16); test new serum; additional typing for DP of donor (to enable monitoring of DP antibodies)

**Immunizing events (3)**

Summary: Pregnancies, typing of children/husband. Child/husband antigens are unacceptable when MFI>3000.

**Other (3)**

Bw4 immunization (patient's own B27 is unacceptable); Strong immunization, plausibility check is difficult

Unacceptable antigens: all positive reactions with MFI>5000 (recipient without previous transplant)

**Defined Unacceptable Antigens per recipient (50 centers)**

**Recipient A**

| ≥ 75% consensus | | | ≥ 50% consensus | |
|---|---|---|---|---|
| A66(10) | 50 | | Cw18 | 35 |
| DQ7(3) | 50 | | A43 | 34 |
| DQ9(3) | 49 | | A68(28) | 34 |
| B41 | 48 | | A69(28) | 34 |
| A25(10) | 46 | | A33(19) | 31 |
| Cw17 | 46 | | Cw6 | 30 |
| A26(10) | 45 | | B49(21) | 29 |
| A34(10) | 44 | | B62(15) | 28 |
| DR53 | 43 | | B72(70) | 28 |
| DQ8(3) | 41 | | Cw5 | 27 |
| | | | A11 | 25 |

**Recipient B**

No consensus on UAG

About half of the centers defines DQ5 and DQ6 as unacceptable.

| | |
|---|---|
| DQ5(1) | 26/50 |
| DQ6(1) | 23/50 |

**Recipient C**

Note that one center did not define any unacceptable antigens

| ≥ 75% consensus | | | ≥ 50% consensus | |
|---|---|---|---|---|
| B62(15) | 49 | | B75(15) | 32 |
| B51(5) | 48 | | B52(5) | 31 |
| A1 | 40 | | B77(15) | 29 |
| B63(15) | 40 | | B76(15) | 27 |

**Recipient D**

Please note that 10/50 centers did not define unacceptable antigens

| ≥ 75% consensus | | | | | | | | | | | ≥ 50% consensus | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| B18 | 40 | B39(16) | 39 | B50(21) | 38 | B45(12) | 37 | B42 | 36 | | DR16(2) | 22 |
| B62(15) | 40 | B41 | 39 | B67 | 38 | B64(14) | 37 | B54(22) | 36 | | B27/B2708 | 29 |
| B71(70) | 40 | B60(40) | 39 | B75(15) | 38 | B65(14) | 37 | B55(22) | 36 | | | |
| | | B61(40) | 39 | B76(15) | 38 | B7 | 37 | B56(22) | 36 | | | |
| | | B72(70) | 39 | B8 | 38 | | | B81 | 36 | | | |
| | | B78 | 39 | | | | | B82 | 36 | | | |

**Patient Based Case 2018-03**

**Recipient age at time of organ offer:** 27
**Recipient gender:** female
**Recipient blood group:** A Pos
**Recipient HLA type:** A3, A11, B5, B51, B35, Bw4, Bw6, Cw4, Cw15, DR6, DR14, DR10, DR52, DQ1, DQ5

**HLA-type of previous transplant**
(transplanted early 2006; fail date and reason unknown; back on wait list early 2012)
A3, A11, B5, B51, B18, Bw4, Bw6, Cw5, Cw15, DR4, DR6, DR14, DR6, DR52, DR53, DQ1, DQ5, DQ3, DQ8

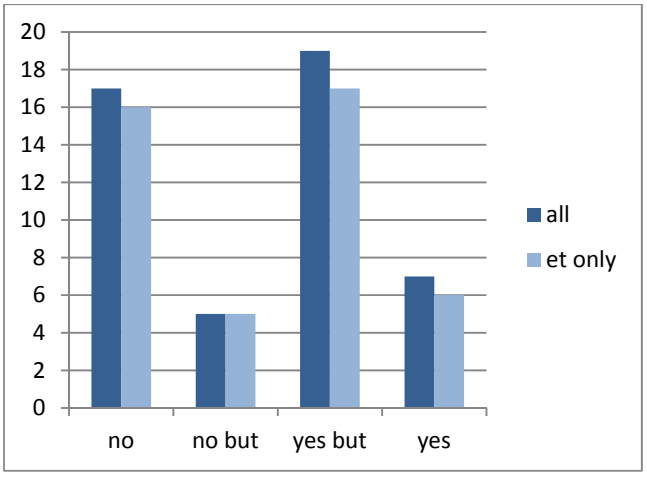
**Current antibody information:**
Antibody specificities found in CDC: DR4, DR53, DQ3, DQ7, DQ9
Antibodies found with other techniques:
No Class I antibodies detected in Luminex
Class II antibodies found in Luminex: histograms and raw data of current serum are attached.

**Other relevant information:**
Recent PRA: 46% (CDC)
Highest PRA: 84%
Autologous status: Negative

**Donor information:** Deceased (DCD)
**Donor blood group:** A Pos
**Donor HLA type:** A2, A11, B12, B44, B35, Bw4, Bw6, Cw4, Cw5, DR1, DR2, DR15, DR51, DQ1, DQ5, DQ6,
Crossmatch with unseparated cells (blood) without and with DTT: Negative

**Decisions overview:**
44 ET affiliated centers and 4 other centers gave their opinion on this case.

No
No but Only under special conditions
Yes but When additional measurements are taken
Yes



**Motivation (per decision)**

**Decision is no**

- presence of DQ6 DSA (unacceptable antigen), epitope shared with DQ8 (1st donor) (25)
- 1-1-2 mismatch (9)
- Cw5 is repeat mismatch (unacceptable antigen/could be boosted after transplantation/no antibodies detectable) (5)
- because of young age and future need of more organs be very careful in selecting donors (6)
- history of previous transplantation (likely to have more antibodies against new mismatch antigen) (3)
- B-cell cross match not available/ negative unseparated cell cross match does not guarantee protection against rejection (3)
- variety of Class II antibodies (either cytotoxic or with MFI>5000) (3)
- no repeat mismatch A, B, DR (1)
- no uncommon HLA type (1)

**Decision is no but**

- ABO identical (2)
- CDC cross match negative (2)
- does not meet minimal match criteria (2)
- DQ6 antibodies, MFI 3000-8000, associated with increased risk; according to German Guidelines Unacceptable antigen (8)
- no current CDC reactive DSA (2)
- no repeat mismatch A, B, DR (1)
- patient is waiting for 6 years (1)
- repeat mismatch Cw5, but no CDC antibodies against Cw5 (2)

**Decision is yes but**

- CDC cross match negative (8)
- with negative B cell cross match no contraindication (4)
- repeat mismatch Cw5, no antibodies detectable (previous transplant still in situ?) (6)
- DQ6 antibodies, presensitization against potential donor DQ6, effect on long term outcome? (17**)**
- immunized against all DQ except own DQ5, DQ6 can be detected with quite high MFI values in current serum (2)
- No DR match, only acceptable for high quality organs, only accept good match (including DQ1) (2)
- Chance of finding a homozygous DQ5 is low, and thus move on with (high risk) transplantation (3)
- increased immunological risk (3)
- young patient, probably will be in need of another kidney later (2)
- HLA-Class I and II antibodies found in screening (1)

**Decision is yes**

- CDC cross match is negative (4)
- Cw5 repeated mismatch, no clear immunization, negative in luminex (can be accepted) (4)

- DQ6 antibodies found in luminex cannot be explained by immunization history and are not found in CDC (10)
- low chance in ETKAS (1,68%) for blood group compatible organ when all DQ were unacceptable antigen (1)
- Class II antibodies (directed against former transplantation) not directed against current donor (3)
- the age of the recipient, and quality of life after transplantation would support acceptance(1)

**Recommendations**

**Extra (B-Cell) cross matching (24 centers)**

In summary: Perform B-cell/or separated cell cross matches/ cross matches on spleen/ cross matches with additional peak sera and proceed when cross match is negative

**Immunosuppression (8 centers)**

In summary: adapt (intensify) immunosuppressive protocol/ give induction therapy

**Plasmapheresis (5 centers)**

In summary: plasma plasmapheresis before transplantation (to remove DSA DQ6)

**Monitoring (5 centers)**

In summary: Close monitoring (screening follow up) of patient after transplantation

**Wait (3 centers)**

In summary: Await a better offer (DR matched, DQ5 homozygous donor) in case there is no urgent need for transplantation.

**AM (2 centers)**

In summary: register for AM program /STAMP/ LAMP

**Extra testing/information (6 centers)**

In summary: perform C1q/C3d on fresh sample/ to clarify DQ6 antibodies. Ask for pregnancies/type partner and children. Include specificities of historical sera. Consider clinical circumstances

**Other (3 centers)**

In summary: Communicate increased immunological risk to clinicians; register DQ6 as unacceptable antigen; living related transplantation.