

NHS BLOOD AND TRANSPLANT BOWEL ADVISORY GROUP

HLA specific antibodies in bowel transplantation: Standardisation of testing, reporting and crossmatch protocols in the UK.

General Considerations

1. Antibody levels can increase or decrease which means that the donor-specific antibody (DSA) risk level could change over time. For a transient diminishing antibody known to be stimulated by transfusion only, risk stratification should be based on the latest sample tested.
2. A DSA negative case does not indicate no risk of antibody mediated rejection. Rather, this should imply a standard or baseline known immunological risk level.
3. There is no evidence to suggest that adult and paediatric patients should be treated differently, therefore this document relates to all patients.
4. Different risk stratification should be applied depending on the organs transplanted:
 - i) Bowel alone: consider all DSA. The risks of transplanting against a known DSA should be balanced against the risks from not transplanting.
 - ii) Bowel with other organs including liver: the transplanted liver is resilient to all but the highest levels of donor HLA class I specific antibodies and concomitant transplantation of the liver together with other organs confers a degree of protection from acute AMR. HLA class I antibodies should not be included in the contraindicated list of specificities, all Class II antibodies should be considered and discussed with the clinical team.
 - iii) Bowel with other organs, excluding a liver- apply the same risk stratification that applies to the other organs transplanted. The risks of transplanting against a known DSA should be balanced against the risks of not transplanting and the likelihood of the patient receiving an alternative donor offer with a lower immunological risk.
5. Where bowel is transplanted in the absence of a liver, antibodies against all HLA loci (A, B, C, DRB1, DRB3, DRB4, DRB5, DQA1, DQB1, DPA1 and DPB1) should be considered equally. Antibodies to different specificities may differ in pathogenicity, but there are insufficient peer-reviewed studies to define the magnitude of such differences.
6. This information informs the surgeon in assessing the risk of proceeding to transplant in a particular donor recipient combination, but the decision to proceed, or not, to transplant will be made by the surgeon in the context of all risk factors together with the probability of achieving alternative transplant options within a clinically acceptable timeframe.

Consensus protocols:

HLA specific antibody testing protocol

1. Best practice is for two independent samples to be tested before listing. Any HLA specific antibody positive results must be tested for specificity by Luminex single antigen beads. Where a first sample has a positive screen result the second sample can be tested directly for specificity.
2. Discrepant results with the same test (e.g. between successive samples) must be investigated by testing a further sample.

3. In exceptional circumstances of clinical urgency, transplantation may proceed after a single pre-transplant result subject to the transplant centre taking responsibility for deviation from protocol and a written and retained concession document.
4. Samples should be sent from patients on the waiting list for antibody testing at regular intervals; at least one sample every three months. For sensitised patients monthly samples are recommended to ensure a current sample is available at the time of transplant offer.
5. Best practice is for further samples to be obtained for antibody testing after all known potential allosensitisation events. The timing and frequency of these samples should be agreed following advice from the H&I laboratory as each case arises.
6. Where patients are transferred between transplant units the local H&I laboratory should be informed so that historical antibody details (and archived serum samples) can be requested from the referring unit's H&I laboratory.

Reporting protocol

1. Antibodies resembling HLA specificities but considered to be due to non-allogeneic stimulation (e.g. infection) or characteristic of a known false-positive reaction pattern can be excluded from being reported.
2. All HLA positive antibody specificities must be reported.
3. The overall degree of sensitisation should be reported as cRF% (calculated reaction frequency) using the ODT cRF tool.
4. Each positive HLA specificity should be assigned an immunological risk based on its MFI level. For patients with pre-transplant DSA the clinical risk of undertaking antibody incompatible transplantation should be assessed together with the risk of delaying transplantation and the likelihood of identifying an alternative suitable donor.
5. Risk Stratification, (consensus view)
 - i. No detectable donor HLA specific antibody. Standard risk.
 - ii MFI <2,000. Minimum risk of hyperacute rejection due to low level donor HLA specific antibodies, but greater than standard risk of rejection
 - iii MFI 2,000 - 8,000. Flow Cytometric donor crossmatch likely to be positive, conferring an intermediate risk of humoral rejection.
 - iv MFI > 8,000. Lymphocytotoxic donor crossmatch (CDC) likely to be positive, conferring a high risk of humoral rejection.
6. The overall cRF% should be reported together with reduced values following the removal of unacceptable specificities identified for each successive risk level, as appropriate.
7. When a donor becomes available for a sensitised patient it is possible that if the donor HLA type carries two or more mismatched antigens to which the patient is sensitised then the cumulative MFI could raise the risk level. Where a donor is homozygous for a mismatch the corresponding MFI will be doubled.

Crossmatch protocol

1. The transplant unit must be able to confirm that no potential sensitising event has occurred since the last sample tested for HLA antibodies. Otherwise a prospective lymphocyte crossmatch using fresh serum sample may be indicated. Omission of a prospective pre-transplant donor lymphocyte crossmatch in patients with recent allosensitisation events

must be subject to a documented risk assessment. Sensitising events include transfusion with blood products, infection, transplant and pregnancy.

2. Patients with a current negative HLA antibody test can be transplanted without a prospective pre-transplant crossmatch when there is sufficient confidence to predict a negative (virtual) donor lymphocyte crossmatch caused by donor (HLA) specific antibodies. A retrospective lymphocyte crossmatch should be performed with a time of transplant serum sample.
3. Patients with fully defined antibodies can be transplanted with a pre-transplant virtual crossmatch and a retrospective lymphocyte crossmatch (which must include a time of transplant serum sample from the patient).
4. Patients without fully defined alloantibodies must have a prospective pre-transplant donor lymphocyte crossmatch test.
5. All virtual crossmatch tests must be assessed and reported by an appropriately qualified HPC registered H&I Scientist.

Post-transplant antibody monitoring protocol

1. All patients should be tested for HLA specific antibodies at one, 3, 6 and 12 months and annually thereafter.
2. All incidents of suspected or diagnosed rejection should be accompanied by an HLA antibody test to determine the involvement of donor HLA-specific antibodies in the rejection episode. Further testing will depend on the course of the rejection.

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