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

General Considerations

1. Antibody levels can increase or decrease which means that the DSA risk level could change over time. VAD patients are particularly prone to changing their antibody profile. For a 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 risk level.
3. There may be differences of sensitivity to alloantibody in lung and heart recipients but there are currently insufficient published studies to provide differing advice for each organ.
4. There is no evidence to suggest that adult and paediatric recipients should be treated differently.
5. Antibodies against all HLA isotypes (A, B, C, DRB1, DRB3, DRB4, DRB5, DQA1, DQB1, DPA1 and DPB1) are likely to have some bearing on transplant outcome but each HLA specificity may differ in pathogenicity, although again there are insufficient peer-reviewed studies to define the magnitude of such differences.
6. This information informs the clinical team 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 team in the context of all risk factors together with the probability of achieving alternative transplant options within a clinically acceptable timeframe.

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Consensus protocols

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Antibody testing protocol

1. Best practice is for two independent samples to be tested before listing. Any screen positive result 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 three-monthly for previously sensitised patients, and 6 monthly for patients who have consistently been negative for HLA specific antibodies.
5. Best practice is for further samples to be obtained for antibody testing after all known potentially sensitising 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 referred 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.

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Reporting protocol

1. Antibodies resembling HLA specificities but considered to be due to non-allogeneic stimulation (eg infection) or characteristic of a known false-positive reaction pattern can be excluded from being reported.
2. All true positive HLA antibody specificities must be reported.
3. The overall degree of sensitisation must be reported as cRF% (calculated reaction frequency) using the ODT cRF tool.
4. Each positive HLA specificity should be assigned a 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 a suitable alternative donor.
5. Risk Stratification
    i. No detectable HLA 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 - 5,000. Low risk of hyperacute rejection but may be increased risk of early rejection and antibody mediated graft damage. Immediate pre-transplant antibody reduction may be considered when feasible.
    iv. MFI > 5,000. Transplant veto apart from exceptional cases. Further testing such as CDC tests, or complement fixation in Luminex assays (C1q, C3d or C4d) should be considered in these cases to further refine risk profiles..
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 has two or more 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.

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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 or emergency HLA antibody screen using fresh serum sample may be indicated in all cases. Omission of a prospective crossmatch or HLA antibody test in patients with recent allosensitisation events must be subjected to a documented risk assessment.
2. Patients with a current negative HLA antibody test can be transplanted without a prospective pre-transplant crossmatch. 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.
5. All virtual crossmatch tests must be assessed and reported by an appropriately qualified HCPC registered H&I scientist.

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Post-transplant antibody monitoring protocol

1. All cases above standard risk should be tested for HLA specific antibodies at least at days 7 and 28, and 3, 6, 9 and 12 months after transplantation and then as required after discussion between clinicians and H&I lab. More frequent testing would be advised according to level of risk, other risk factors and suspicion of rejection.
2. HLA antibody testing should be undertaken when antibody mediated rejection is suspected and when patients present with episodes of rejection associated with haemodynamic compromise.. Further testing will depend on the course of the rejection episode.