Literature review to follow by March 2022

Recommendations

Grading of Recommendations

These guidelines represent consensus opinion from experts in the field of transplantation in the United Kingdom and represent a snapshot of evidence available at the time of writing. It is recognised that some recommendations are made even when the evidence is weak. It is felt that this is helpful to clinicians in daily practice.

In these guidelines the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system has been used to rate the strength of evidence and the strength of recommendations (Atkins D et al 2004). The approach used in producing the present guidelines is consistent with that adopted by Kidney Disease Improving Global Outcomes (KDIGO) (Uhlig K et al 2006). Explicit recommendations are made on the basis of the trade-offs between the benefits on one hand, and the risks, burden, and costs on the other.

For each recommendation the quality of evidence has been graded as A (high), B (moderate), C (low), or D (very low):

Grade A evidence means high quality evidence that comes from consistent results from well performed randomised controlled trials, or overwhelming evidence of another sort (such as well-executed observational studies with very strong effects).

Grade B evidence means moderate quality evidence from randomised trials that suffer from serious flaws in conduct, consistency, indirectness, imprecise estimates, reporting bias, or some combination of these limitations, or from other study designs with special strength.

Grade C evidence means low quality evidence from observational evidence, or from controlled trials with several very serious limitations.

Grade D evidence is based only on case studies or expert opinion.

For each recommendation, the strength of recommendation has been indicated as one of:

Level 1 (we recommend)

Level 2 (we suggest)

Not graded (where there is not enough evidence to allow formal grading)

A Level 1 recommendation is a strong recommendation to do (or not to do) something where the benefits clearly outweigh the risks (or vice versa) for most, if not all patients.

A Level 2 recommendation is a weaker recommendation, where the risks and benefits are more closely balanced or are more uncertain.

Recommendations

1. We recommend that during transplant assessment patients are screened for the presence of IgG HLA-specific antibodies using blood samples obtained on at least two separate occasions, preferably no less than one day apart. (Grade 1B)

2. We recommend that during transplant assessment patients are HLA typed (at HLA-A, -B, -C, DRB1/3/4/5, -DQB1) using molecular methods (Grade 1B).

3. We suggest that, when preparing to activate a patient on the transplant waiting list, if IgG HLA specific antibodies are detected in the patient serum, the patient should be discussed with the relevant clinician responsible for patient care in conjunction with the H & I laboratory to determine if/which HLA specificities should be recorded as unacceptable antigens (UA) with NHSBT-ODT (Grade 2D).

   Which specificities to list as UA will depend on factors including but not limited to the patient's overall level of sensitisation (expressed as calculated reaction frequency (%cRF)), clinical urgency and whether a liver is included in the allograft (broadly following the stratification outlined as below). (Grade 2D)

   Bowel with other organs including liver: the transplanted liver is resilient to all but the highest levels of donor HLA class I specific antibodies (i.e. those likely to result in a positive CDC crossmatch) and concomitant transplantation of the liver together with other organs confers a degree of protection from acute antibody mediated rejection (AMR). HLA class I antibodies should generally **not** be included in the contraindicated list of specificities however all HLA class II antibodies should be considered and discussed with the clinical team.

   Bowel with other organs excluding a liver: 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 with a lower immunological risk. Where bowel is transplanted in the absence of a liver, antibodies against all HLA loci 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.

4. We recommend that, upon activation onto the transplant waiting list, samples for antibody screening should be obtained at least every 3 months (Grade 1B)

5. We recommend that samples should be taken for antibody screening at 2 and 4 weeks following a sensitising event (e.g. blood transfusion). If the patient is having ongoing transfusion support we recommend that the laboratory agrees a pragmatic approach to testing with the clinical team (Grade 1B)

6. We recommend that for, HLA specific antibody screening, laboratories use technologies that allow for the detection and characterisation of IgG HLA specific antibodies in serum. A common technology in current use is the luminex assay. (Grade 1B)

7. We suggest that laboratories have policies in place that include the ability to offer a 24/7 365 day on call service to provide an individualised immunological risk

assessment for a given donor and recipient pair. We suggest the following principles apply (Grade 2C):

a. The transplant unit must be able to confirm that no potential sensitising event has occurred since the last sample tested for IgG HLA specific antibodies. Otherwise we suggest that prospective antibody characterisation is undertaken using a day of transplant serum sample.

b. Patients with a current (within 3 months) negative HLA antibody test can be transplanted without prospective testing where there is sufficient confidence to predict a negative virtual crossmatch.

c. Patients with fully defined antibodies can be transplanted with a pre-transplant virtual crossmatch.

d. We recommend that patients without fully defined alloantibodies and/or where uncertainty of the prediction of a negative virtual crossmatch exists, should have prospective antibody characterisation using a day of transplant serum sample.

e. For patients with pre-transplant donor specific antibodies (DSA) these should be reported to the clinical team. The clinical risk of undertaking transplantation should be assessed together with the risk of delaying transplantation and the likelihood of identifying an alternative suitable donor. We suggest that the overall degree of sensitisation should be reported as %cRF to aid in this assessment.

The following stratification according to organ type should be applied:

Bowel with other organs including liver: the transplanted liver is resilient to all but the highest levels of donor HLA class I specific antibodies (i.e. those likely to result in a positive CDC crossmatch) and concomitant transplantation of the liver together with other organs confers a degree of protection from acute antibody mediated rejection (AMR). HLA class I antibodies should generally **not** be included in the contraindicated list of specificities however all HLA class II antibodies should be considered and discussed with the clinical team.

Bowel with other organs excluding a liver: 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 with a lower immunological risk. Where bowel is transplanted in the absence of a liver, antibodies against all HLA loci 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.

8. We suggest that, in the post-transplant period, testing for donor specific antibodies is performed at regular intervals (1, 3, 6, 9 and 12 months) and when there are clinical concerns of graft function (Grade 2D).