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ESPS PEER REVIEW REPORT

Name of journal: World Journal of Transplantation
ESPS manuscript NO: 10249
Title: METHODOLOGICAL ASPECTS OF ANTI-HLA ANTIBODY ANALYSIS IN SOLID ORGAN TRANSPLANTATION
Reviewer code: 00503180
Science editor: Xiu-Xia Song
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Date reviewed: 2014-04-02 21:21

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[Y] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[Y] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Existing	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] No records	
[ ] Grade D: Fair		BPG Search:	[ ] Rejection
[ ] Grade E: Poor	[ ] Grade D: Rejected	[ ] Existing	[ ] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

Dear Sir It is a nice update review. thanks osama gheith

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Name of journal: World Journal of Transplantation
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[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] Existing	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] No records	
[ ] Grade D: Fair		BPG Search:	[ ] Rejection
[ ] Grade E: Poor	[ ] Grade D: Rejected	[ ] Existing	[ ] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

It is a very good review, especially for transplant clinicians and transplant Immunologists. I'm going to allow only make 2 observations. 1. In the section on "Non-specific antibody reactivity", there are typos. 2. If possible, update references to 2014.

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[ ] Grade E: Poor		[ ] Existing	[ ] Major revision
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COMMENTS TO AUTHORS

It is kwon that Donor HLA-specific antibodies (DSAs) have been implicated in poor graft outcome and decreased survival in solid organ recipients. The development of de novo donor HLA-specific antibody can appear before the graft loss, implicating a mechanism of progressive graft injury, and the frequency and impact of these antibodies may be underestimated. More recently, antibodies to non-donor HLA-specific targets and antibodies to non-HLA-specific targets have been implicated in the graft rejection process. COMMENTS: 1) Alloimmunity and autoimmunity acting in concert and not playing independent roles in the comprehensive immune response to organ transplants. Donor-specific antibodies to HLA may inflict a tissue inflammatory response resulting in exposure of autoantigens and a subsequent loss of tolerance. The development of DSA before the development of non-HLA responses has been reported. It is interesting to consider that donor HLA-specific antibody together with Non-HLA-specific antibodies result in a lower freedom of rejection than the presence of either antibody alone. The authors should consider this aspect in their work 2) Identification of antibodies to human leukocyte antigens (HLA) by single antigen bead arrays has led to the common practice of virtual crossmatching. However, inappropriate assignment of anti-HLA specificities can lead to false-positive virtual crossmatching, resulting in the decline of potentially crossmatch-negative organ offers. In this study we describe identification of antibodies to cryptic HLA present on denatured forms of HLA on single antigen bead array and provide a reassessment of

calculated panel-reactive antibody (CPRA) based on elimination of false-positive reactions due to antibodies to cryptic HLA epitopes, to identify antibodies to cryptic HLA vs native HLA. Antibodies to cryptic HLA can be reliably identified by iBeads technology, and usually do not fix complement nor produce positive flow cytometry crossmatches. Identification and removal of antibodies to cryptic HLA from the panel of unacceptable antigens may have dramatic and meaningful effects on CPRA and virtual crossmatch strategies. The authors should include and discuss this subject. 3) As a clinical diagnostic, single antigen bead assays are widely used to screen for HLA-specific antibodies in patient sera. Such assays are very effective at determining reactivity to a given HLA allotype, but it remains difficult to determine antibody concentration or functional relevance via gradations in MFI. Several explanations might explain a lack of correlation between MFI and antibody concentration, and the auhtros should examine how changes to the antibody milieu impact correlations of MFI and IgG concentration. Interference of IgM is thought to effect SAB assay MFI values, and postulate that a lack of consistency between MFI and IgG measurement might be due to IgM and IgA multimeric alloantibodies interfering with the detection of IgG. However, the removal of multimeric antibodies by physical separation failed to align MFI values and IgG levels. These data suggest that multimeric antibodies have a modest influence on MFI values and that variables including antibody affinity and epitope specificity must also influence MFI indications of IgG concentration. The authors should include these comments and consider the studies that test purified antibodies by surface plasmon resonance may best assess the correlation of antibody affinity and diagnostic MFI. 4) In Luminex bead arrays with cross-match results, MFI measures cannot directly be converted into antibody titers as the MFI simply represents a surrogate marker for the amount of bound antibody and is affected by several factors, including antibody concentration in the serum but also density, conformation and orientation of the antigen, as well as by the antibody avidity toward the respective antigen. The authors should take into account and discuss this comment.

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ESPS PEER REVIEW REPORT

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[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[ ] Accept
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[ ] Grade E: Poor	[ ] Grade D: Rejected	[ ] Existing	[Y] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

It is well prepared manuscript. May be, the author should stress that not all antibodies are dangerous for the graft. There is a group of so called "enhancing antibodies" which protect graft and even improve graft survival (a couple of publications by French immunologist Voisin in second half of the last century). Small suggestion: - Reference 114: Personal comminication is not usually included in references. - Description of Fig. 7 in Figure legends should be more detailed (what are blue cicles, what means different colors of bars, ets..)