

CONSENSUS STATEMENT

SUMMARY OF THE INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION CONSENSUS CONFERENCE ON EMERGING UNDERSTANDING OF ANTIBODIES AND ANTIBODY-MEDIATED REJECTION IN HEART TRANSPLANTATION



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The understanding of circulating antibodies and their relationship to antibody-mediated rejection (AMR) has yet to be fully elucidated in heart transplantation. Circulating antibodies are important in both pretransplant and post-transplant. In the pretransplant period, the more antibodies detected in a patient awaiting heart transplantation often significantly reduces the chance of obtaining a compatible donor heart. In the post-transplant period, de novo antibody development against the donor

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heart remains a challenge to manage. In both pre- and post-transplant scenarios, it is not known what approach is optimal for treating these patients with circulating antibodies. To address these unmet needs, a consensus conference was organized on April 18, 2023, endorsed by the International Society for Heart and Lung Transplantation. The conference represented a collaborative multidisciplinary effort by experts in cardiothoracic transplantation from across the world to understand and discuss the optimum approach and treatment of circulating antibodies and AMR in heart transplant candidates and recipients. The conference served as a forum to better understand antibodies and AMR and their impact on transplant patients. The nature of this consensus is to prepare a platform and pave the way for further detailed studies. The findings and consensus statements are hereby presented.

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KEYWORDS:

heart transplantation; antibodies; biomarkers; antibody-mediated rejection; clinical outcomes

1. BACKGROUND

The number of sensitized patients awaiting heart transplantation has been rising in recent years, largely due to the increasing use of mechanical circulatory support (MCS) devices and the growing number of candidates with prior sensitizing events such as blood transfusions, pregnancies, organ transplants, homografts, or underlying congenital heart disease.^{1,2} Heart transplant patients developing antihuman leukocyte antigen (HLA) antibodies have been shown to have a longer wait time for heart transplantation, and subsequently are at risk for waitlist morbidity/mortality.¹ Moreover, the detection of post-transplant circulating antibodies is frequently correlated to biopsy-proven antibody-mediated rejection (AMR).³ Post-transplant survival may also be affected, with these patients often demonstrating a higher risk of post-transplant allograft failure and mortality.^{4,5} The management of detected antibodies before and after transplantation and its accompanying clinical findings remains variable and based on limited objective data. This problem affects adults and children requiring heart transplantation.

Sponsored jointly by the International Society for Heart and Lung Transplantation (ISHLT) and the California Heart Center Foundation, the Consensus Conference on the Emerging Understanding of Antibodies in Heart Transplantation was designed to provide a forum for an in-depth discussion among the leading experts in the field, to evaluate evolving science in this area ([Supplementary Materials I-IV](#)), as part of an update to previously held ISHLT Consensus Conferences on Sensitized Patients Awaiting Heart Transplant (2008),⁶ Antibody Mediated Rejection in Heart Transplantation (2010),⁷ Management of Antibodies in Heart Transplantation (2016).¹

This recent consensus conference took place on April 18, 2023, in Denver, CO, and included 52 US and 23 international multidisciplinary experts in cardiac transplantation and transplant immunology ([Appendix](#)). The objectives were

- To apprise the heart transplant community on the current understanding of the role of HLA, non-HLA, ABO antibodies, and biopsy-proven AMR in heart transplantation.
- To discuss risk factors for the development of antibodies and strategies for risk stratification.
- To identify effective modes of therapy to treat the sensitized and highly sensitized patient before, during, and after transplant.
- To explore a framework and criteria (sensitization threshold) for potential higher-status listing or priority access to compatible donors for highly sensitized patients awaiting heart transplantation.

After didactic sessions, the participants were divided into 3 breakout groups to discuss current issues in circulating antibodies and AMR in heart transplantation, as well as unmet needs. There were 7 questions that arose from 5 pre-meeting conference calls for the breakout groups to consider ([Supplementary Materials II and IV](#)). This summary of the Antibodies and AMR Consensus Conference reflects the current state of antibodies and AMR in heart transplantation and hopefully will serve as a platform for further understanding, clarification, and treatment options for patients experiencing these complications.

2. REVIEW OF THE COMMUNITY SURVEY OF HEART TRANSPLANT PROGRAMS

Before the consensus conference, a web-based survey of 86 transplant programs around the world was conducted. This survey aimed to assess the opinions of a broad group of stakeholders about their ideas on antibodies and AMR in heart transplantation, including detection/attributes of antibodies, understanding of clinical impact, and management of these complications. The survey results are summarized in [Table 1](#), and complete

Table 1 Findings of the Pre-meeting Survey Conducted Among 86 Transplant Programs Around the World

Considerations	Findings
Pretransplant considerations	- Type of antibody assays used in the center: undiluted Luminex assay (100%), dilutions (50%), and C1q (36%) [86 responses]. - In patients with significant circulating antibodies, transplantation decision is based on virtual crossmatch (84%), prospective flow cytometry crossmatch (46%), and prospective CDC crossmatch (35%) [85 responses]. 75% use an antibody threshold of 5,000 MFI or less to designate avoids [84 responses]. 36% of respondents had a different approach to avoiding class I vs class II anti-HLA antibodies [85 responses]. 46% monitor antibodies pretransplant every 3 months [84 responses]. 69% would desensitize patients preheart transplant [84 responses]. - When deciding to initiate desensitization therapy, participants would use calculated PRA and general PRA in 66% and 16% of the centers, respectively [79 responses]. 33% will desensitize for cPRA between 50% and 80%, and 33% will desensitize for cPRA greater than 80% [82 responses]. 16% of respondents had a different approach for desensitization treatment in class I vs II anti-HLA antibodies [79 responses]. - Common pretransplant desensitization therapies included plasmapheresis/immunoadsorption (87%), IVIG (79%), rituximab (74%), and bortezomib (45%) [77 responses]. 81% treat sensitized patients with special treatments perioperatively [84 responses]. - Common perioperative desensitization therapies included antithymocyte globulin (76%), plasmapheresis/immunoadsorption (61.5%), and IVIG (49%) [78 responses]. - Antithymocyte globulin (71%), plasmapheresis (53%), and IVIG (44%) were selected as first-line peritransplant desensitization treatments [75 responses]. 34% would never perform a prospective crossmatch if virtual is negative, 22% would do for PRA between 25% and 80%, and 9% for PRA greater than 80% [85 responses]. 65% would decline donor heart if prospective crossmatch is positive (no differences were recorded between flow cytometry crossmatch or CDC crossmatch) [68 responses].
Post-transplant considerations	88% of respondents routinely monitored antibodies post-transplantation [86 responses]. - Over 74% will monitor post-transplant antibodies at months 1, 3, 6, and 12 in the first year [82 responses]. - After the first year, antibodies are routinely checked on an annual basis in 44% [86 responses]. - If DSA is positive, 28% of the participants would routinely assess complement fixing via C1Q assay [86 responses]. 50% will perform a heart biopsy for detected DSA if there is cardiac dysfunction [84 responses]. - More than 52% will treat DSA if there is cardiac dysfunction, AMR 1 or greater on heart biopsy [85 responses]. - Common treatments for post-transplant DSA include plasmapheresis/immunoadsorption (86%), IVIG (84%), rituximab (69%), and augmented corticosteroids (58%) [86 responses]. - Plasmapheresis/immunoadsorption (67%), IVIG (66%), and augmented corticosteroids (47%) were selected as first-line treatments for detected DSA post-transplant [83 responses]. 16% of respondents had a different treatment approach for detected DSA class I vs II anti-HLA antibodies post-transplant [85 responses]. 34% of respondents had a different treatment approach for early (< 1 year post-transplant) vs late (> 1 year post-transplant) DSA [86 responses]. 64% state that non-HLA antibodies are of no significant concern [86 responses]. - The most commonly monitored non-HLA antibodies post-transplant were anti-AT1R (55%), anti-major histocompatibility complex class I chain-related A (35%), and anti-endothelial cell antibodies (25%) [40 responses].

Abbreviations: AMR, antibody-mediated rejection; AT1R-Ab, angiotensin II type 1 receptor antibody; CDC, complement-dependent cytotoxicity crossmatch; cPRA, calculated panel-reactive antibodies; DSA, donor-specific antibody; HLA, human leukocyte antigen; IVIG, intravenous immunoglobulin; MFI, mean fluorescence intensity; PRA, panel-reactive antibodies.

survey questions and results are included in [Supplementary Material V](#). Responses to select questions are listed below:

- When asked about the type of HLA antibody assays used in the transplant center, respondents selected undiluted Luminex assay (100%), serum dilutions (50%), and C1q (36%) [86 responses].
- In patients with significant circulating antibodies, respondents would base the transplantation decision on virtual crossmatch (VXM) (84%), prospective flow cytometry crossmatch (46%), and prospective complement-dependent cytotoxicity (CDC) crossmatch (35%) [85 responses].
- Seventy-five percent of the respondents selected an antibody threshold of 5,000 MFI or less to designate avoids [84 responses].
- Regarding pretransplant desensitization, 33% will desensitize for calculated panel-reactive antibodies (cPRA) between 50% and 80%, and 33% will desensitize for cPRA greater than 80% [82 responses].
- Common pretransplant desensitization therapies included plasmapheresis/immunoadsorption (87%), intravenous immunoglobulin (IVIg) (79%), rituximab (74%), and bortezomib (45%) [77 responses].
- Regarding post-transplant donor-specific antibody (DSA) monitoring, over 74% would monitor post-transplant antibodies at months 1, 3, 6, and 12 in the first year [82 responses], while after the first year, antibodies are routinely checked annually in 44% of the centers [86 responses].
- Common treatments for post-transplant DSA included plasmapheresis/immunoadsorption (86%), IVIg (84%), rituximab (69%), and augmented corticosteroids (58%) [86 responses].
- Sixty-four percent of the respondents stated that non-HLA antibodies are of no significant concern [86 responses].

3. FINDINGS

3.1. Question 1. What determines antibody avoids for a virtual crossmatch?

3.1.1. Background

The idea of placing antigens as avoids for donor heart allocation is to avoid crossing donor-specific HLA antibodies and hence reduce the risk of hyperacute and acute rejection.^{1,8} Luminex single antigen bead (SAB) testing has increased the sensitivity and specificity of accurately identifying HLA antibodies in support of all organ transplantation. However, the output of the assay, using mean fluorescence intensity (MFI) units, is only semiquantitative.^{1,8} Therefore, the ability to use MFI values to compare different assays, to accurately guide clinical practice, or to be used as an end-point measure in clinical trials is limited. Serum dilutions, performed at critical timepoints, are optimal for measuring antibody levels that extend beyond the Luminex linear range and for comparing the efficacy of antibody depletion therapies for desensitization or AMR treatment post-transplant.⁹ It is center-specific whether to use MFI or what MFI level to use as the threshold for determining the relevance of an antibody and the corresponding antigen to avoid when crossmatching. To facilitate organ acquisition, the VXM is typically conducted as a “first-pass” crossmatch.⁸ The VXM does not require viable donor cells but relies on the donor’s complete HLA typing (including HLA-A, B, C, DRB1, DRB3/4/5, DQA1, DQB1, DPA1, DPB1 loci) and current antibody assessment of the recipient detected by Luminex SABs.¹⁰ VXM has a negative predictive value (prediction of negative crossmatch) of 92% and a positive predictive value (forecast of positive crossmatch) of 79%.⁹ Currently, there is no agreed-upon standard on which specific antibodies should be avoided vs crossed. The cutoff point to determine antibody avoids may differ depending on the center infrastructure, expertise, available treatments, and demographics of the patient population. HLA expression on the surface of cells may impact risk assessments (HLA-A, -B, -DR > HLA-C, -DQ, and DP) and influence MFI correlations with crossmatch positivity. In general, for a single antibody, flow cytometry and CDC crossmatch will be negative at an MFI of less than 2,000 and potentially positive at an MFI greater than 4,000. Antibodies (corresponding antigens) with an MFI threshold > 2,000 may be listed as unacceptable by a conservative center, whereas less conservative centers may employ a greater antibody MFI threshold, such as > 7,000, to list an antibody as unacceptable, thereby expanding the donor pool for that patient.^{8,11,12} In this scenario, it is likely that lower-level DSA (MFI < 7,000) might be crossed. However, it has been reported that crossing lower-level DSA does not appear to compromise outcomes for heart transplant recipients, and it may be a feasible way of enhancing a sensitized patient’s chances of finding a suitable donor.¹³ In addition, the biological significance of the antibody (e.g., complement-fixing capacity) should be considered. To minimize the number of antigens avoided and thus enlarge the donor pool for highly sensitized patients, a program may choose to avoid only

antibodies that are positive at $\geq 1:8$ dilution or positive on C1q or C3d testing.^{14,15} In these cases, higher level DSAs may be crossed, which may require customized perioperative immunosuppression such as complement inhibition therapies.¹⁶

3.1.2. Breakout group discussion

It was discussed that undiluted antibody MFI binding levels are currently used to risk-stratify detected antibodies, and the following MFI risk levels were suggested: low risk $< 5,000$ MFI, moderate risk $5,000$ to $8,000$ MFI, and high risk $> 8,000$ MFI. Some participants noted that MFI binding alone may not be sufficient to assess risk for outcome in heart transplantation. The attributes of antibodies, such as the detection of antibodies in the dilution assay and/or the ability to bind complement, are essential adjuncts for risk assessment. However, not all transplant programs perform these assays. When assessing risk in crossing DSA, one should also consider patient characteristics such as older age, frailty, urgency waitlist status, comorbidities, transplant center support (e.g., expertise in managing antibodies), and infrastructure (e.g., HLA laboratory capabilities). It was mentioned that different criteria in different countries should be organized to pave the way for the definition of appropriate guidelines. It was also emphasized that a call to the general transplant community to maintain a standardized MFI threshold for circulating antibodies should be considered.

3.1.3. Consensus statements

#1. Stratify antibody risk by MFI in the undiluted assay:

- Low risk $< 5,000$ MFI
- Moderate risk $5,000$ to $8,000$ MFI
- High risk $> 8,000$ MFI

#2. Other factors to stratify antibody risk may include the patient's antibody attributes (HLA-locus, strength in dilution assay, and/or complement-binding assay) and clinical factors such as urgency waitlist status, frailty, other patient comorbidities, and center support (e.g., expertise in managing antibodies), and infrastructure (e.g., HLA laboratory capabilities).

3.2. Question 2. Who and when to desensitize in patients awaiting heart transplant? Dependent on cPRA?

3.2.1. Background

Panel-reactive antibody (PRA) screening to detect HLA antibodies (sensitization) is an important part of the evaluation for potential heart transplant recipients. cPRA is a standardized computed way to estimate percentage of donors with high-risk antigens for a given recipient in their regional donor population. Clinicians should strive to minimize the cPRA by selecting a high MFI antibody threshold (avoid fewer antibodies), which broadens the donor pool for those highly sensitized patients. The question of when to treat these sensitized patients has not been established, as no randomized trials have been performed. Many centers will consider desensitization when the cPRA is between 50% and 80% (which means that 50%-80% of potential donors in the community are not compatible with that recipient). At this cPRA range of 50% to 80%, the donor pool is significantly narrowed, which has been associated with longer wait time and potentially increased waitlist morbidity/mortality.^{8,17} For patients with cPRA $> 80\%$, beneficial desensitization may be difficult to achieve and is therefore left to the discretion of the individual program. Another critical factor to account for is racial disparities. Sensitization is more common among Black heart transplant candidates, and these patients are at higher risk for the development of post-transplant de novo DSA (dnDSA) and treated AMR.¹⁸⁻²⁰

Among risk factors for sensitization is the presence of ventricular assist devices (VAD).^{8,11} In a recent large single-center study, sensitized MCS patients were compared with sensitized non-MCS patients and nonsensitized patients in regard to postheart transplant outcomes.²¹ Compared to nonsensitized patients, sensitized MCS patients showed comparable rates of primary graft dysfunction, 1-year survival, and 1-year freedom from AMR. However, sensitized MCS patients, compared to sensitized non-MCS patients, showed significantly greater 1-year freedom from AMR (95.3% vs 85.7%, $p = 0.02$) and an earlier decline in PRA levels ($p < 0.01$) in the first year after transplant. Desensitization therapy effectively reduced the levels of PRA in both sensitized MCS patients and sensitized non-MCS patients. The authors concluded that sensitized MCS patients showed significantly lower rates of AMR and an earlier decline in PRA levels following heart transplant than sensitized non-MCS patients. It was suggested that removal of MCS device at the time of transplantation might underlie these observations.²¹ On

another note, the type of VAD may affect outcomes after a heart transplant. The HeartMate III device has been reported to be associated with a lower risk of developing HLA sensitization than the HeartMate II device.²²

Conventional desensitization therapies include targeting antibodies by removal (plasmapheresis), inactivation (IVIg), or targeting cells producing antibodies with agents such as anti-CD20 monoclonal antibodies (rituximab, obinutuzumab) and proteasome inhibitors (bortezomib, carfilzomib).²³⁻²⁵ In addition, a few emerging therapies are being investigated, including anti-CD38 (daratumumab), IL-6 inhibitors (tocilizumab), costimulation blockers (Belatacept), C1-esterase inhibitors, and IgG-degrading enzyme of *Streptococcus pyogenes*. Many of these therapies remain experimental or supported by limited evidence, such as small case series or observations in kidney recipients and are still pending supporting data on their efficacy in heart transplant recipients.²³⁻²⁵ Current conventional regimens include a combination of therapies, including rituximab/IVIg and bortezomib/plasmapheresis, among others.²³⁻⁵ Approaches using perioperative plasmapheresis and IVIg have demonstrated acceptable rates of post-transplant acute rejection and survival.²³ In a study of sensitized heart transplant candidates who were treated with a combination of plasmapheresis/IVIg/rituximab, mean PRA was reduced by more than 50%, allowing successful heart transplantation, with similar 5-year survival compared to nonsensitized heart transplant candidates.²⁶ In another study of sensitized heart transplant candidates ($n = 25$) treated with plasmapheresis/IVIg/bortezomib, 76% of patients underwent transplantation following desensitization. In addition, treatment resulted in an observed decrease in median cPRA for class I (90%-74%, $p = 0.004$) but not class II (74.5%-75.5%, $p = 0.3$).²⁷ Sriwattanakomen et al recently reported that a carfilzomib-based desensitization approach in sensitized heart transplant candidates reduced the level of HLA antibodies and complement-binding in some but not all patients. Among those patients who were successfully transplanted, outcomes were favorable at 3 years.²⁸ Importantly, physicians should be aware that treatment response during desensitization may vary across a wide range of HLA antibody titers and underlying sensitizing events.

3.2.2. Breakout group discussion

The question as to when to desensitize patients awaiting heart transplant remains unsettled. There are multiple variables affecting this decision, including patient clinical status (such as comorbidities and urgent status listing), antibody attributes, treatment toxicity, and transplant center support/infrastructure. Many discussants mentioned they would consider desensitizing if cPRA is $> 50\%$, but the ultimate decision depends on patient/antibody characteristics and center support/infrastructure, as noted. While many conference participants showed interest in referring highly sensitized patients to experienced centers, others preferred to wait for an acceptable match. The participants also discussed alternatives to desensitization therapy, such as whom not to desensitize, the use of mitigation strategies (crossing lower-level DSA) to avoid adverse effects of desensitization treatment, and the futility of therapy, such as in broadly and highly sensitized patients. Discussants mentioned that most would not treat sensitized VAD patients due to infection risk. Plasmapheresis/immunoabsorption, IVIg, and rituximab were among the common treatment options, and reduction in cPRA was considered a successful response to desensitization therapy by the vast majority of centers. Additionally, more than 80% of participants felt that equity of access (based on where they live) is another critical variable to desensitization therapy, as less-populated areas have fewer donors for a potential compatible match. It was also mentioned that patients' perspectives, as well as the transplant team's perspective, are important factors to consider for desensitization therapy. Harmonization of the patient, the transplant cardiologist and surgeon, and HLA laboratory to understand the goal of desensitization and transplant is crucial.

Table 2 illustrates various center-specific management approaches for selected case studies of pre- and post-transplant sensitization, which were discussed during the consensus conference. This table demonstrates that even experienced centers may have different protocols to treat sensitized patients.

3.2.3. Consensus statements

#3. Consider desensitizing if cPRA is $> 50\%$, depending on patient/antibody characteristics and center support/infrastructure.

#4. The goal of pretransplant desensitization therapy is to lower the cPRA to broaden the donor pool and minimize the risk of post-transplant AMR.

#5. Commonly utilized desensitization treatments include combinations of the following: plasmapheresis/immunoabsorption, IVIg, rituximab, and/or bortezomib.

Table 2 Center-Specific Management Approaches for Selected Case Studies of Detected Antibodies Pre- and Post-Transplant Discussed at the Consensus Conference

Clinical scenario cases	Case #1	Case #2	Case #3	Case #4	Case #5
	Pretransplant single Ab high MFI with C1q+ binding Ab	Pretransplant broadly sensitized, with only single C1q binding Ab	Pretransplant broadly sensitized with no Abs in the dilution assay	Post-transplant low-level de novo DSA	Post-transplant C1q+ DSA
Case and Ab profile	– 70 years/M, Status 6 – SAB: class I (0%), class II (59%) - MFI: >17,000: DR53 – Dilution: class II (50%) - MFI: 13,000–15,000: DR53 – C1q: class II (50%) - MFI: 2,500–5,000: DR53	– 68 years/F, Status 4, LVAD – SAB: class I (81%), class II (0%) - MFI: 17,500: A2 857 - MFI: 15,000–17,500: A69 B58 - MFI: 13,750–15,000: A68 - MFI: 8,750–10,000: B51 - MFI: 7,500–8,750: B35 B53 - MFI: 6,250–7,500: B78 - MFI: 5,000–5,250: B75 - MFI: 3,750–5,000: B77 B71B49 – Dilution: class I (54%) - MFI: 12,500–13,750: A2 - MFI: 5,000–6,250: B57 - MFI: 3,750–5,000: B58 – C1q: class I (48%) - MFI: >17,500: A2	– 52 years/F, Status 2 – SAB: class I: MFI: 2,500–3,750: B46 Cw8 Cw9 Cw10 Cw12 - Class II: MFI: 7,501–8,750: DQ7 DQ9 - MFI: 6,250–7,500: DQ6 DQ8 - MFI: 5,000–6,250: DR13 DR14 DR15 DR16 DQ4 DQ5 - MFI: 3,750–5,000: DR1 DR4 DR8 DR11 DR12 DR17 DR18 DR52 - MFI: 2,500–3,750: DR9 DR10 DR51 DR103 – Dilution: class I (0%), class II (0%)	– 64 years/M - asymptomatic, normal graft function - dnDSA 5 years postheart transplant – SAB: class I (0%), class II (38%) - MFI: 3,751–5,000: DQ8 - MFI: 2,500–3,750: DQ9 DQ7	– 38 years/F - Redo heart transplant + kidney transplant, asymptomatic, normal graft function – C1q+ DSA (3.5 years postheart transplant). - MFI: >17,000: DR53
Vanderbilt University Medical Center-USA	– Avoid DR53 – No need for desensitization	– PLEX/IVIIG/bortezomib – Avoid A2	– PLEX/IVIIG/bortezomib – No avoids	– Repeat DSA – EMBx if persistent or rising DSA – Transition to mTor-I	– PLEX/IVIIG, rituximab. – Transition to mTor-I
University Medical Center Hamburg-Eppendorf-Germany	– Avoid DR53 – No need for desensitization	– Avoid MFI > 5,000 – Perioperative PLEX	– Perioperative PLEX	– EMBx, treat for AMR if +ve, if -ve, enhance IS^a – Check dd-cfDNA%	– Enhance IS^a – IgM-IgG + Tocilizumab followed by extracorporeal photopheresis
Cedars-Sinai Medical Center-USA	– Avoid DR53 – No need for desensitization	– Avoid A2 only – Prospective crossmatch – Perioperative Eculizumab if crossing 1 strong DSA	– No avoids – Prospective CDC XM if crossing > 2 moderate DSA	– Switch MMF to PSI; monitor q6 months	– Surrogate donor-specific CDC XM. – If +ve, then - - IVIIG/rituximab – If refractory, then - Tocilizumab x 6 months

Continued

Table 2 Center-Specific Management Approaches for Selected Case Studies of Detected Antibodies Pre- and Post-Transplant Discussed at the Consensus Conference

University of North Carolina-USA	– Avoid DR53 – No need for desensitization	– Avoid A2, B57 – Start mycophenolate mofetil	– No need for desensitization – No avoids	– Check dd-cfDNA% – Repeat DSA – No treatments	– Kidney biopsy if abnormal renal function – Repeat DSA – EMBx: if abnormal repeat DSA/echocardiography
St Vincent's Hospital Sydney-Australia	– Avoid DR53 – No need for desensitization	– Ab tracking (if Ab developed post-LVAD) – Avoid A2 – Early postoperative PLEX/IVIg	– No need for desensitization – No avoids	– cMRI and EMBx – Increase IS	– cMRI, EMBx, and MMDx – Increase IS – Monitor closely for symptoms
Monroe Carell Jr. Children's Hospital at Vanderbilt-USA	– Avoid DR53 – No need for desensitization	– IVIG/rituximab – Avoid A2 and antibodies with MFI > 10,000	– Remove antibodies at bypass and await results of CDC XM and FCXM – If moderate or strongly +ve, continue post-op PLEX, IVIG, Rituximab, ATG	– Repeat DSA – Standard EMBx protocol – No treatment needed	– Heart and kidney biopsy – IVIG/rituximab

Abbreviations: Ab, antibody; AMR, antibody-mediated rejection; ATG, antithymocyte globulin; CDC, complement-dependent cytotoxicity; cMRI, cardiac magnetic resonance imaging; dd-cfDNA, donor-derived cell-free deoxyribonucleic acid; dnDSA, de novo donor-specific antibodies; DSA, donor-specific antibody; EMBx, endomyocardial biopsy; FCXM, flow cytometric; IS, immunosuppression; IVIG, intravenous immunoglobulin; LVAD, left ventricular assist device; MFI, mean fluorescence intensity; MMDx, Molecular Microscope Diagnostic System; MMF, mycophenolate mofetil; mToR-I, mammalian target of rapamycin inhibitors; PLEX, plasma exchange; SAB, single antigen beads; XM, crossmatch.

^aChange calcineurin inhibitors from cyclosporine A to tacrolimus or increase tacrolimus levels to 8-10 ng/ml; if chronic kidney disease (glomerular filtration rate > 40 ml/min/1.73 m²), add everolimus for the NOCTET regimen.

3.3. Question 3. Are antibody treatment approaches in pediatric patients different from adults? And what are the considerations in ABO-incompatible transplant?

3.3.1. Background

In recent years, preheart transplant sensitization has been increasingly encountered among pediatric heart transplant recipients. A number of risk factors that increase the risk of sensitization in this population have been identified, including non-White race, having a congenital etiology, pretransplant surgeries (particularly those including exposure to homograft tissue), urgent status, MCS, and blood/platelet transfusions.²⁹ Furthermore, the improved survival of pediatric patients with congenital heart disease and transplantation after completion of palliative procedures have led to a higher risk of pretransplant sensitization.³⁰ It has been suggested that preoperative treatment of allograft tissue used in congenital heart surgeries could prevent profound sensitization in patients requiring subsequent heart transplantation.³¹ Similar to adults, higher levels of pretransplant sensitization and developing dnDSA post-transplant in pediatric heart transplant recipients have been associated with adverse immune complications.²⁹ A recent study of the Pediatric Heart Transplant Society Registry database for the years 2010-2021, including 3,914 patients, revealed in multivariable analyses a shorter time to first rejection in patients with positive crossmatch compared to those with negative crossmatch.³² However, no differences were recorded in 10-year survival in the 2 groups. The authors also identified having congenital heart disease, being on extracorporeal membrane oxygenation at the time of transplant, and PRA > 50% at listing as significant risk factors for decreased graft survival.³² However, in the Clinical Trials in Organ Transplant-04 (CTOTC-04), Webber et al reported that highly sensitized and nonsensitized pediatric heart transplant recipients had similar 1-year survival.³³ Regarding newly developed DSA in pediatric heart transplant recipients, 1-year outcomes of the CTOTC-04 study have shown that one-third of the patients developed newly detected DSA. These patients had significantly higher rates of acute cellular rejection but not AMR, with no significant differences in 1-year graft or patient survival, as compared to patients who did not develop these antibodies.³⁴ In the CTOTC-09 follow-up study, it was found that sensitization status and development of first-year newly detected DSA were not associated with worse allograft function or inferior survival at 3 years; however, in children with DSA > 4,000 MFI, hemodynamically compromising rejection and AMR were significantly more frequent and lower survival over 5 years approached significance ($p = 0.058$).³⁵ Considering the above, clinicians should consider risks and benefits when listing and accepting organs for sensitized pediatric candidates.³⁶

Multiple factors distinguish pediatrics from adult heart transplant patients, which may influence the manifestations of the immune responses. For instance, HLA antibodies may be high in the first 12 to 18 months after birth, as HLA antibodies can be passively acquired maternally via the placenta. Moreover, in pediatric patients with Fontan surgery, protein-losing enteropathy can result in protein loss, and HLA antibodies may be falsely low.³⁷ For highly sensitized pediatric patients, commonly used therapeutics in adults are utilized with favorable outcomes with moderately intensified immunosuppression.^{33,34} Utilization of plasmapheresis/immunoadsorption in the pediatric population remains limited due to challenges of low blood volume, vascular access limitations, side effects, as well as patient compliance.³⁸ Angiotensin II type 1 receptor antibody (AT1R-Ab) is a non-HLA antibody that has been associated with poor clinical outcomes in adult kidney transplant recipients. There is now limited evidence to suggest that AT1R-Ab may be a significant part of the immunologic milieu impacting pediatric organ transplant outcomes and that differences in this phenomenon may exist between pediatric and adult patients.³⁹

ABO-incompatible transplants have helped expand the donor pool for infants and have been demonstrated to be safe with comparable long-term survival to ABO-compatible transplants.^{40,41} Furthermore, it was found that infants undergoing ABO-incompatible transplants demonstrate appropriate immune responses to non-self ABH (polysaccharides that define blood type) while maintaining tolerance to the allograft ABH.⁴⁰ It has also been observed that postheart transplant, these recipients were less likely to develop dnDSA (particularly class II) or acute rejection.^{42,43} Of note, ABO antibody detection methods remain variable and further work is warranted to illuminate the biological and clinical impact of ABO antibodies on various isotypes, IgG subclasses, and subtype-specificities.

3.3.2. Breakout group discussion

Participants expressed the need for different and probably age-specific approaches when managing sensitized pediatric candidates. They highlighted that sensitization in candidates with congenital heart disease remains a critical issue. The participants noted that the majority of the centers do not pre-treat homograft materials in patients undergoing congenital defect repair, which might explain the potential sensitization state in these patients who might require subsequent heart transplantation. While some centers would cross DSA with 2,000 to 5,000 MFI in pediatric heart

transplant candidates, others would be more conservative due to concerns that crossing DSA could eventually damage the heart graft. For patients undergoing ABO-incompatible transplantation, participants identified an unmet need for precision in defining ABO-related histocompatibility between donor and recipient to enable clinicians to carefully analyze risk and benefit while expanding this platform to children and select adults. Available data remain limited, and clinical trials are needed to enrich our understanding and provide guidance in these areas of pediatric heart transplantation.

3.3.3. Consensus statements

#6. There is a need for precision in defining ABO-related histocompatibility between donor and recipient to enable clinicians to carefully analyze risk and benefit while expanding this platform from infants to older children and select adults.

#7. HLA-DSA before and after heart transplantation are of clinical relevance in pediatric patients similar to adults; however, the extent, impact, and approach may be different, especially given similar early outcomes for sensitized patients and patients with a positive crossmatch.

3.4. Question 4. What considerations do you have in donor selection for sensitized patients?

3.4.1. Background

The presence of HLA antibodies in heart transplant candidates imposes substantial limitations on the donor pool and can significantly increase waiting time.⁸ Patients exhibiting positive transplantation crossmatch to donor HLA are at high risk for rejection and mortality.⁸ Successful heart transplantation requires multidisciplinary collaboration between the clinical transplant team and the institutional immunogenetics and histocompatibility laboratory.⁴⁴ The Sensitization in Transplantation Assessment of Risk (STAR) Working Group recommended comprehensive HLA typing, including information regarding all major HLA loci: HLA-A, -B, -C, -DRB1, -DRB3/4/5, -DQA1/DQB1, and -DPA1/DPB1 for both the organ donor and recipient.⁴⁵ HLA antibodies should be identified and compared against the donor HLA before acceptance for organ transplant. The VXM is recommended to avoid a positive crossmatch. If the VXM cannot be performed or in the event of recent sensitization, a prospective crossmatch is recommended.⁸ A prospective crossmatch can be performed by 2 cell-based methods: a CDC crossmatch assay and a flow cytometric crossmatch assay. Solid-phase immunoassays (SPIs) using flow cytometry assays have much greater sensitivity in detecting donor-specific HLA antibodies; however, only the CDC crossmatch detects the killing of cells.^{8,44} A majority of programs will not accept a donor having a prospective positive flow cytometry crossmatch. It has been suggested to perform a prospective CDC crossmatch when crossing moderate-high binding DSA (defined as MFI > 5,000).⁴⁶ Programs crossing high-binding DSA have utilized novel immunosuppression protocols (complement blockade therapy) as long as a prospective CDC crossmatch is negative.¹⁶

Lastly, due to the restricted number of organ procurement organizations that can perform a prospective crossmatch required for these highly sensitized patients, donor pool expansion may be constrained.

Before transplant, in an effort to minimize the list of unacceptable antigens in highly sensitized patients, some programs may order a surrogate CDC or flow cytometric crossmatch to better assess the ability of DSA to cause harm. This crossmatch uses volunteer donor cells expressing select HLA antigens (specific for the detected antibody) with the addition of the patient's sera. If this surrogate CDC crossmatch is negative for cell killing or the flow cytometric crossmatch is moderate or less in strength, then this antibody is not avoided.^{1,47}

3.4.2. Breakout group discussion

The participants highlighted that the VXM is being performed in most centers and discussed several essential considerations for conducting and interpreting findings of VXM HLA testing, including the availability of full donor HLA, the date of the sample, and recent sensitization events. The participants agreed that the VXM might not be applicable to every patient. In patients with complicated interpretations of HLA antibodies (especially those with multiple lower-level DSAs), a physical prospective crossmatch is warranted; however, it was mentioned that CDC crossmatch cannot be mandated as this testing is not readily available in all HLA laboratories. Participants suggested that a surrogate crossmatch could be done in some cases and felt surrogate flow crossmatch is as useful as a surrogate CDC crossmatch to determine whether to avoid an antibody (corresponding antigen). When crossing DSA, the participants outlined several considerations, including patient characteristics (urgency, extracorporeal membrane oxygenation support, bleeding, etc.), as well as MFI threshold level to avoid antibodies,

antibody attributes such as complement binding, and antibody class (the majority would worry about class II > class I).

3.4.3. Consensus statements

#8. VXM might not be applicable to patients with complicated interpretations of HLA antibodies (e.g., multiple lower-level DSAs); thus, a prospective crossmatch may be warranted.

#9. Crossing DSA in experienced centers may be considered for sensitized patients but should take into account patient characteristics, antibody attributes, and their biological significance.

3.5. Question 5. Do you use a customized perioperative and maintenance immunosuppression protocol for sensitized patients?

3.5.1. Background

For high-urgency highly sensitized waitlisted patients for heart transplantation, there may be little time to pursue desensitization therapy, which may take weeks to provide a benefit. For these patients, crossing DSA at the time of transplant may be necessary. Furthermore, according to a recent study by Patel et al, using eculizumab (a complement inhibitor) perioperatively in patients with persistently elevated PRA and high-preformed (MFI > 10,000) DSA may serve as a potential therapy with favorable outcomes at 1 year.¹⁶ In that study, 20 patients with median cPRA of 95% (90%-97%) and preformed DSA who had a negative prospective CDC crossmatch were administered 9 infusions of eculizumab during the first 2 months post-transplant. Retrospective B cell and T cell flow crossmatches were positive in 14 and 11 patients, respectively. Survival at 1 year was 90%, with no deaths resulting from AMR. Comparing treated patients to matched control patients, there was a significant reduction in the risk of biopsy-proven AMR in patients treated with eculizumab (hazard ratio = 0.36, 95% confidence interval [0.14-0.95], $p = 0.032$). The authors support the prophylactic use of complement inhibition for heart transplant patients at very high immunological risk. In another study, 19 highly sensitized patients were treated with a protocol combining tocilizumab intraoperatively, plasma exchange, and rituximab, followed by a 6-month course of IgGAM. At 1 year, the desensitization group had comparable survival rates to controls with negative crossmatch (94.7% vs 81.4, $p > 0.05$).⁴⁸ When employing desensitization strategies, the degree of sensitization, urgency of the transplant, and anticipated duration of therapy should be considered to help decide on the most appropriate approach.^{24,25} In addition, limited data are available on the efficacy of adjunctive peritransplant induction therapies in highly sensitized patients, with the most commonly used therapies being antithymocyte globulin (ATG) and basiliximab.

Regarding post-transplant management, there are no established guidelines providing customized post-transplant surveillance or immunosuppression approaches for sensitized patients who have been successfully transplanted while crossing DSA. Nevertheless, some measures might be undertaken in experienced centers treating these patients. At the Cedars-Sinai Medical Center, sensitized patients who cross DSA < 10,000 MFI in the undiluted assay are administered ATG induction followed by IVIG 1 gm/kg daily $\times$ 2 days. (When crossing DSA > 10,000 MFI, complement inhibition therapy is administered as previously noted.) Prednisone 5 mg daily is usually maintained indefinitely, and patients are transitioned from mycophenolate mofetil to a proliferation signal inhibitor at 6 to 12 months post-transplant.^{24,49} In addition, in the Cedars-Sinai protocol, sensitized patients are often kept to biopsy-only surveillance rather than the use of noninvasive diagnostic testing such as donor-derived cell-free DNA (dd-cfDNA) surveillance which is usually considered for nonsensitized patients.

3.5.2. Breakout group discussion

Participants expressed that they would treat sensitized patients perioperatively if crossing DSA. The majority would administer IVIG and plasmapheresis. Some would consider adding induction therapy (ATG or basiliximab). The participants indicated that they would use standard maintenance immunosuppression in these patients and would modify treatments based on the patient's clinical presentation. The majority reported that they would follow ISHLT guidelines for post-transplant antibody monitoring protocol. In cases of crossing DSA or if the patient's immunosuppression was reduced (infection and cancer), they would monitor for rejection more frequently. Some of the participants would wean steroids in sensitized patients with well-functioning grafts while maintaining steroids was recommended if crossing DSA. It was discussed that further studies are warranted to investigate prednisone weaning in sensitized patients.

3.5.3. Consensus statements

#10. Induction therapy (ATG or basiliximab) may be considered peritransplant for sensitized patients.

#11. If crossing DSA at the time of heart transplant, induction therapy or IVIG/plasmapheresis are common therapies.

#12. In experienced centers, the addition of complement blockade given perioperatively in highly sensitized patients may be considered when crossing DSA with high MFI level ($> 10,000$ MFI).

3.6. Question 6. What are the treatment considerations for DSA detected post-heart transplant?

3.6.1. Background

Post-heart transplant dnDSA is observed in up to 30% of the patients.⁵⁰ Both preformed and dnDSAs have been linked to poor outcomes, including AMR, cardiac allograft vasculopathy, and graft loss.^{50,51} The ISHLT guidelines recommend that DSA testing be performed at 1, 3, 6, and 12 months postoperatively and annually thereafter, while in sensitized patients, more frequent monitoring is recommended.⁵² In contrast to the relevance of clinical presentation to DSA management, there is no consensus on the management of DSA in asymptomatic patients.⁵² When detecting dnDSA, a careful evaluation of the graft function is warranted, and a biopsy should be performed in case of high-risk features. However, only 54% of the patients with dnDSA will develop biopsy-detected AMR, and management of dnDSA in the setting of negative biopsy with stable graft function continues to impose a clinical dilemma.⁸

Nonetheless, unrecognized subclinical AMR has been observed in previous biopsies of patients with failing heart allografts. In patients presenting with graft dysfunction, DSA testing should be performed, and it was previously suggested that DSA should be treated in the setting of graft dysfunction or restrictive cardiac physiology.^{1,53} When managing patients with DSA post-transplant, several variables could determine DSA clinical relevance to risk stratifications and post-transplant outcomes, which might help guide enhanced immunosuppression or more frequent monitoring. DSA characteristics such as DSA that remain at higher dilutions, complement binding antibodies, dnDSA (vs preformed antibodies), late rising DSA (vs early), persistently elevated DSA (vs transient), dnDSA developing against HLA-DQ antigens (vs non-HLA-DQ antigens) have been associated with adverse outcomes.^{1,54-57} In addition, it was found that the synergy of both elevated dnDSA and non-HLA (AT1R-ab) antibodies results in an increased risk of rejection as compared to elevated levels of either antibody.⁵⁸ However, current evidence on non-HLA antibodies remains limited, with no well-determined thresholds for positivity.⁵⁹ There is a growing understanding of the non-HLA antibody targets. Recently, Gates et al identified a total of 155 non-HLA antibodies in AMR patients, with responses toward 43 high-prevalence antigens found in $\geq 50\%$ of patients.⁶⁰ Longitudinal sera from a multicenter cohort of adult cardiac allograft recipients (samples: $n = 477$ no rejection; $n = 69$ rejection) identified 18 non-HLA antibodies associated with rejection ($p < 0.1$) including 4 newly identified non-HLA antigenic targets (DEXI, EMCN, LPHN1, and SSB).⁶¹ However, an independent causal role of non-HLA antibodies in contributing to graft injury is yet to be fully determined.

Novel molecular technologies are being evaluated to monitor for subclinical allograft injury such as dd-cfDNA, which has demonstrated good performance in the detection of rejection and resulted in earlier rejection detection as opposed to biopsy-based monitoring.⁶² Another promising non-invasive biomarker for the diagnosis of acute rejection is circulating microRNAs. Shah et al recently identified 17 microRNAs that can discriminate AMR and formulated a score for AMR (0-100). A score ≥ 65 can identify AMR with 82% sensitivity, 84% specificity, and 97% negative predictive value.⁶³ While these blood-based molecular profiling diagnostics could minimize surveillance biopsies, tissue diagnosis remains crucial in the setting of suspected rejection.^{64,65} Molecular profiling studies of the biopsies may also help delineate mechanisms of allograft injury, rejection, and relevance of DSA to these complications.^{64,65} The Molecular Microscope Diagnostic System (MMDx) utilizes machine learning-derived algorithms to estimate the probability of rejection using microarrays to determine messenger RNA gene expression patterns, which could significantly enhance diagnostic precision among transplant recipients.⁶⁶ Alam et al recently evaluated whether MMDx performs in agreement with dd-cfDNA and traditional biopsy and found a degree of agreement between the simultaneous use of each modality. However, significant systematic differences

were observed in classifying rejection, which altered treatment decisions and led to the treatment of rejection despite the findings of a negative traditional biopsy.⁶⁶

In an effort to minimize the number of routine endomyocardial biopsies performed, tailoring the biopsy protocol to the predicted risk of AMR has been suggested. According to a recent study involving large, international, and highly phenotyped cohorts of heart transplant recipients, factors such as time post-transplant, pretransplant sensitization, circulating DSA, graft dysfunction, and prior history of definite AMR independently predicted the risk of AMR.³

3.6.2. Breakout group discussion

Participants unanimously agreed that DSAs are clinically relevant biomarkers post-heart transplantation. However, asymptomatic DSA alone does not constitute an indication for treatment and should be interpreted in the context of other clinical manifestations, imaging findings, DSA characteristics, biopsy-proven AMR, and molecular testing. Some considered that rising trends in the DSA's MFI (2-fold increase), particularly early after transplant, might warrant more attention, while constantly low MFI-DSA might not be clinically significant. For preformed DSA that persists after transplant, participants indicated that they would monitor more frequently, consider increased immunosuppression, and delay steroid weaning. For dnDSA beyond the first year, most participants said they would increase immunosuppression. Participants outlined the need for standardized definitions for rising levels of DSA (actual levels, timing, and persistency). There was general agreement that endomyocardial biopsy is not mandated in patients with isolated post-transplant DSA. It was felt that treatment of DSA is warranted if there is evidence of graft dysfunction, biopsy-proven pAMR ≥ 2 , or high dd-cfDNA. In the case of pAMR 1, participants would evaluate for other clinical/biomarker evidence of allograft injury. The participants mentioned that access to MMDx is very limited. In regard to non-HLA antibodies, the participants acknowledged the limited evidence available, but did not discount that non-HLA antibodies could be potential contributors to graft injury, especially when DSAs are negative. The participants expressed concerns regarding the feasibility of non-HLA testing and emphasized the need to establish causation and defined thresholds.

3.6.3. Consensus statements

#13. Several variables should be considered to treat patients with post-transplant DSA, including cardiac dysfunction by imaging, abnormal hemodynamics, an increasing MFI trend in DSA, the presence of early DSA, antibody attributes (C1q+ binding, detection of DSA in dilution assay), biopsy-proven pAMR ≥ 2 , and abnormal molecular findings (dd-cfDNA and/or the MMDx) as available.

#14. Endomyocardial biopsy is not mandated in patients with asymptomatic post-transplant DSA, but should be performed when DSA are associated with signs of clinical or subclinical graft dysfunction, or graft injury.

#15. The clinical utility of treating asymptomatic post-transplant DSA remains unclear.

#16. Testing and treatment of non-HLA antibodies have not been recommended until a causal role in graft injury and defined thresholds are established.

3.7. Question 7. What are the future considerations in antibody management?

3.7.1. Background

Prioritizing sensitized patients on the waiting list continues to impose a treatment dilemma. While peri-transplant antibody risk mitigation and/or removal strategies approaches may temporize the situation, these therapies are less likely to modulate the underlying immune response and, therefore, may not potentially improve post-transplant outcomes.²³ In the United States, and in contrast to other organs (lung and kidney), cPRA is not currently used in heart allocation policy.⁶⁷ This could be in part due to a lack of evidence and standardized definitions for a cPRA threshold to determine highly sensitized heart transplant candidates. The need for standardized DSA risk assessments as proposed in this document and when a prospective crossmatch in highly sensitized individuals is indicated are other important areas for further investigation, especially in those patients where crossing preformed DSA in the VXM.^{24,46}

The use of HLA matching algorithms and HLA epitope/eplet mismatch scores to predict dnDSA development and adverse clinical outcomes have been promising. HLA epitope mismatch score may predict a

higher risk of dnDSA development.^{54,68,69} High-risk HLA-DQ epitopes have been identified in patients with persistent dnDSA and have also been associated with AMR.⁵⁴ Higher levels of eplet mismatches such as HLA-A and -B, HLA-DR, and HLA-DPB1, among others, have been linked to worse outcomes, including AMR and graft loss.⁷⁰⁻⁷² Incorporating HLA epitope/eplet mismatch scores in current allocation systems could potentially help enhance donor selection and improve clinical outcomes.⁶⁹ However, the absence and cost of high-resolution HLA typing data, variability in the definition and calculation of eplet mismatching algorithms, and the paucity of large clinical studies to optimize HLA molecular mismatch algorithms continue to hamper the development of a priority policy.¹

Moreover, given the clinical relevance of DSA to allograft prognosis and risk stratification, post-transplant DSA should be considered as an end-point in future clinical trials.⁶⁹ Finally, establishing regional centers to manage sensitized patients may provide patients in small centers with access to advanced therapeutic and diagnostic modalities. This could further enhance short- and long-term outcomes in this challenging population.

3.7.2. Breakout group discussion

All the participants agreed that sensitization should be factored into allocation and highlighted the need to identify a universal threshold of cPRA for highly sensitized patients and to standardize HLA reporting. Opinions were evenly divided in regard to the inadequacy of VXM and the need to perform prospective crossmatch in highly sensitized patients. Participants felt that the evidence surrounding epitope or eplet matching remains limited. Most discussants did not support DSA as a primary outcome for clinical trials; some suggested including DSA as a secondary end-point. Most participants viewed establishing regional centers to manage sensitized patients as an opportunity to mitigate current care gaps and standardize protocols and thresholds at the regional level. Still, long-term follow-up and insurance coverage might hinder these efforts. Participants agreed that this suggestion should be passed to the ISHLT to define standards for regional centers. All participants emphasized the need for further research, and perhaps randomized clinical trials, to enrich our understanding of DSA and novel molecular diagnostics, which could also pave the way for future work on updating the diagnostic criteria for AMR.

3.7.3. Consensus statements

- #17. Sensitization should be factored into donor heart allocation policy.
- #18. Standardization of HLA laboratory assays and reporting is needed.

4. SUMMARY

The main theme in this consensus document was to adopt a holistic approach and risk-stratify patients when managing antibodies and AMR. The consensus conference participants identified cut-offs to risk stratify and manage pretransplant-detected antibodies and underlined antibodies' attributes as essential adjuncts for risk assessment tools. Special donor considerations and the need to perform a physical prospective crossmatch were discussed. The participants also highlighted unmet needs in pediatric and ABO-incompatible heart transplantation. Discussants delved into current desensitization approaches, perioperative management, post-transplant antibody monitoring, and maintenance immunosuppression therapy strategies in highly sensitized patients. For post-transplant DSA, participants elaborated on the clinical relevance of DSA including trending characteristics, clinical manifestations, imaging findings, and molecular profiling. Future considerations for organ allocation policies, standardization of HLA reporting, and incorporating DSA in clinical trial end-points were also discussed. We hope the results of this consensus conference will provide a more standardized pathway for evaluating patients for heart transplantation and post-transplant monitoring and pave the way for future studies. The consensus conference statements are summarized in [Table 3](#).

This paper is dedicated to the memory of Jignesh Patel MD, PhD

Table 3 Summary of the Consensus Conference Statements

- #1. Stratify antibody risk by mean fluorescence intensity (MFI) in the undiluted assay:
 - Low risk < 5,000 MFI
 - Moderate risk 5,000-8,000 MFI
 - High risk > 8,000 MFI
- #2. Other factors to stratify antibody risk may include the patient's antibody attributes (HLA-locus, strength in dilution assay and/or complement-binding assay) and clinical factors such as urgency waitlist status, frailty, other patient comorbidities, and center support (e.g., expertise in managing antibodies), and infrastructure (e.g., HLA laboratory capabilities).
- #3. Consider desensitizing if cPRA is > 50%, depending on patient/antibody characteristics and center support/infrastructure.
- #4. The goal of pretransplant desensitization therapy is to lower the cPRA to broaden the donor pool and minimize the risk of post-transplant AMR.
- #5. Commonly utilized desensitization treatments include combinations of the following: plasmapheresis/immunoadsorption, IVIG, rituximab, and/or bortezomib.
- #6. There is a need for precision in defining ABO-related histocompatibility between donor and recipient to enable clinicians to carefully analyze risk and benefit while expanding this platform from infants to older children and select adults.
- #7. HLA-DSA before and after heart transplantation are of clinical relevance in pediatric patients similar to adults; however, the extent, impact, and approach may be different, especially given similar early outcomes for sensitized patients and patients with a positive crossmatch.
- #8. Virtual crossmatch might not be applicable to patients with complicated interpretations of HLA antibodies (e.g., multiple lower-level DSAs); thus, a prospective crossmatch may be warranted.
- #9. Crossing DSA in experienced centers may be considered for sensitized patients but should take into account patient characteristics, antibody attributes, and their biological significance.
- #10. Induction therapy (ATG or basiliximab) may be considered peritransplant for sensitized patients.
- #11. If crossing DSA at the time of heart transplant, induction therapy or IVIG/plasmapheresis are common therapies.
- #12. In experienced centers, the addition of complement blockade given perioperatively in highly sensitized patients may be considered when crossing DSA with high MFI level (> 10,000 MFI).
- #13. Several variables should be considered to treat patients with post-transplant DSA, including cardiac dysfunction by imaging, abnormal hemodynamics, an increasing MFI trend in DSA, the presence of early DSA, antibody attributes (C1q+ binding, detection of DSA in dilution assay), biopsy-proven pAMR ≥ 2 , and abnormal molecular findings (dd-cfDNA and/or the MMDx) as available.
- #14. Endomyocardial biopsy is not mandated in patients with asymptomatic post-transplant DSA, but should be performed when DSA are associated with signs of clinical or subclinical graft dysfunction, or graft injury.
- #15. The clinical utility of treating asymptomatic post-transplant DSA remains unclear.
- #16. Testing and treatment of non-HLA antibodies have not been recommended until a causal role in graft injury and defined thresholds are established.
- #17. Sensitization should be factored into donor heart allocation policy.
- #18. Standardization of HLA laboratory assays and reporting is needed.

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APPENDIX

Participants in the consensus conference and pre-meeting calls

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.healun.2025.02.1690](https://doi.org/10.1016/j.healun.2025.02.1690).

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