

Approaches to Prevent and Manage Antibody Development

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Disclosure

- Employed by Hansa Biopharma AB as the Scientific Affairs Director
- Off-label usage of medications will be discussed in this presentation

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Learning Objectives

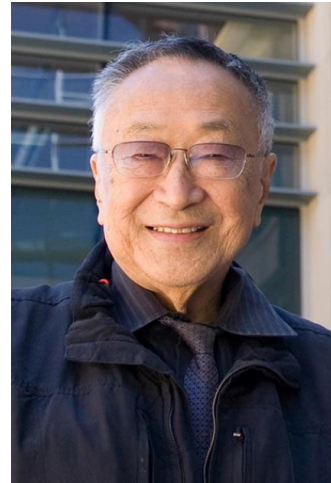
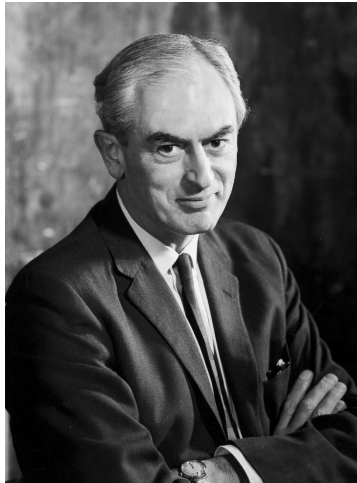
- Distinguish the role of patient characteristics, and pharmacotherapy on immunologic risk
- Differentiate current evidence-based desensitization regimens with a focus on optimal patient selection
- Compare methods of pharmacologic immunosuppression management of failed allografts
- Assess current interventions for immunologic event monitoring

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Immunologic Risk

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Cellular Theory vs Humoral Theory



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The Humoral Theory of Transplantation

- Antibodies cause the rejection of allografts
- Three main steps – 40 to 50 years apart
 - Dye Exclusion test (1910-1950s)
 - Detection of cytotoxic antibodies
 - Microlymphocyte cytotoxicity test (1960-2000s)
 - 0.001 of reagents and lymphocytes = one lambda
 - Human leukocyte antigen (HLA)
 - Hyperacute rejection described
 - Single antigen bead test (1980-present day)
 - (SAB, Luminex)
 - Antibodies emerge first → allograft rejection (acute/chronic)

Terasaki PI. Transplantation 2012;93:751-756.

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Present Day

Consensus Guidelines on the Testing and Clinical Management Issues Associated With HLA and Non-HLA Antibodies in Transplantation

Methods for antibody screening and cross-matching in solid organ transplantation

| Method | Pretransplantation Screening | Pretransplantation XM | Comment | Basic information pretransplant | Posttransplantation | Comment |
|------------------|------------------------------|-----------------------|--|---------------------------------|---------------------|--|
| CDC/CDC modified | +++ | +++ | Prevention of HAR or early AMR | + | -/+ | Donor cells required |
| FC/FC modified | +++ | +++ | Prevention of HAR or early AMR | + | + | Donor cells required |
| ELISA generic | +++ | - | Detection of HLA antibodies | + | -/+ | Useful only if patient nonsensitized |
| ELISA specific | +++ | - | Specification of HLA antibodies | (Only if patient sensitized) | ++ | Low level of sensitivity |
| LUM generic | +++ | - | Detection of HLA antibodies | + | -/+ | Detection of antibody breath and level |
| LUM phenotype | +++ | - | Specification of HLA antibodies | + | ++ | Low level of sensitivity |
| LUM SAB | +++ | | Comprehensive specification HLA antibodies | + | +++ | Comprehensive locus/allele specification |

AMR, antibody-mediated rejection; CDC, complement-dependent cytotoxicity; ELISA, enzyme-linked immunosorbent assay; FC, flow cytometry; HAR, hyperacute rejection; HLA, human leukocyte antigen; LUM, Luminex-based immunoassays (generic, phenotype, single-antigen beads [SAB]); XM, crossmatch

Modified in accordance with Tait BD, et al. Transplantation. 2013 Jan 15;95(1):19-47.

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Present Day

Consensus Guidelines on the Testing and Clinical Management Issues Associated With HLA and Non-HLA Antibodies in Transplantation

Methods for antibody screening and cross-matching for each type of organ transplant

| Organ/single or combined | Pretransplantation screening | Generic methods | Extended Methods (SPI-SAB) | XM | Comment |
|---------------------------------|------------------------------|-----------------|-----------------------------|-------------------------|--------------------------------|
| Kidney | +++ | SPI±CDC/FC | (All patients) ^a | CDC/FC/vXM ^a | Prevention of HAR or early AMR |
| Heart | +++ | SPI±CDC/FC | All patients | CDC/FC/vXM ^a | Prevention of HAR or early AMR |
| Lung | | SPI±CDC/FC | All patients | CDC/FC/vXM ^a | Prevention of HAR or early AMR |
| Liver | | SPI±CDC/FC | All patients | CDC/FC/vXM ^a | AMR |
| Pancreas ^b /(islets) | | SPI±CDC/FC | All patients | CDC/FC/vXM ^a | Prevention of HAR or early AMR |
| Intestinal | | SPI±CDC/FC | All patients | CDC/FC/vXM | Prevention of HAR or early AMR |

^a Depending on local/national/organ exchange organization policy

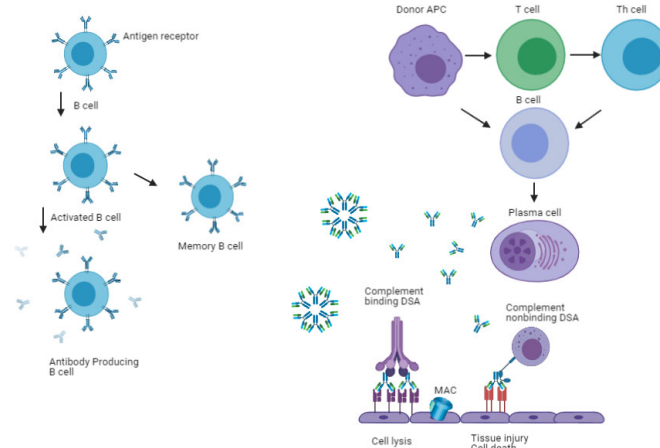
^b Pancreatic islet cells can be transplanted with a positive XM

AMR, antibody-mediated rejection; CDC, complement-dependent cytotoxicity; ELISA, enzyme-linked immunosorbent assay; FC, flow cytometry; HAR, hyperacute rejection; SPI, solid-phase immunoassay; vXM, virtual crossmatch; XM, crossmatch

Modified in accordance with Tait BD, et al. Transplantation. 2013 Jan 15;95(1):19-47.

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Donor Specific Antibody Formation



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Modified in accordance with Zhang R. Clin J Am Soc Nephrol. 2018;13:182-192.

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DSA Characteristics

Comparison of the dominant characteristics of classes I and II donor-specific antibodies

| | Class I DSA | Class II DSA |
|-----------------------------|---------------------|--------------------------------|
| HLA | | |
| Antigens | A, B, and C | DR, DQ, and DP |
| Epitopes location | α -chain | α - and β -chains |
| Expression | All nucleated cells | Antigen-presenting cells |
| Preformed DSA | | |
| Important | Very | Less |
| Positive crossmatch | T cells | B cells |
| Transplant decision | No transplant | Permissible |
| <i>De novo</i> DSA | | |
| Detection | Sooner | Later |
| IgG subclasses | IgG1, IgG3 | IgG2, IgG4 |
| Complement binding | Strong | Weak/no |
| Frequency | Fewer | Common, especially DQ |
| Antibody-mediated rejection | | |
| Phenotypes | Acute | Chronic, subclinical |
| Presentation | Early | Later |
| Graft dysfunction | Rapidly | Slowly |
| C4d deposit | Positive | Negative |
| Treatment | More responsive | Less responsive |
| Graft loss | Early | Later |

Modified in accordance with Zhang R. Clin J Am Soc Nephrol. 2018;13:182-192.

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Pre-Formed vs De Novo DSA

- Pre-Formed
- De Novo
 - HLA mismatch
 - Class II DQ
 - Immunosuppression
 - Inadequate
 - Medication Non-Adherence
 - Graft Inflammation
 - Viral
 - Cellular rejection
 - Ischemia

Zhang R. Clin J Am Soc Nephrol. 2018;13:182-192.

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Risk Factors For Antibody Development

- Race
- Age
- Sex
- Previous transplantation
- Pregnancy
- Blood transfusion
- Ventricular assist devices

Sensitization in Transplantation: Assessment of Risk (STAR) 2017 Working Group Meeting Report

- An accurate patient history must be obtained and shared with the histocompatibility laboratory, on an ongoing basis [1A]. Specifically, the clinical program needs to document:
 - I. HLA sensitizing events:
 - Pregnancies
 - Transfusions
 - Previous transplant
 - Implants (VADs, homografts, etc.)
 - II. Inflammatory events that may boost pre-existing alloimmune memory
 - Major surgeries
 - Major infections
 - Recent vaccinations
- Only patients without HLA sensitizing events may be considered immunologically low risk for alloimmune memory [EO]. All other patients should be categorized as having latent potential or active potential for an alloimmune memory response.
- The patient's alloimmune status should be used for risk stratification and informing frequency of pre- and post-transplant testing [EO].
- The patient's immunization to alloantigens is dynamic. Re-evaluation of this status is required pre- and post-transplantation to assess whether management and monitoring protocols should be adjusted [EO].

Modified in accordance with Tambur AR, et al. Am J Transplant. 2018 Jul;18:1604-1614. Lawrence C, et al. Transplantation 2013;95:341-6.; Askar M, et al. J Heart Lung Transplant. 2013;32:1241-1248.

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Question 1: A 46-year-old female with a history of previous simultaneous kidney/pancreas transplant for type 1 diabetes mellitus 10 years ago, para 3 gravida 2, has recently returned to dialysis after allograft explantation due to bleeding. Laboratory values are Na⁺ 130, K⁺ 5.2, Cl⁻ 100, CO₂ 18, BUN 30, SCr 2.8, Hgb/Hct 8/32 and her current cPRA is 0%. Which statement best describes her immunologic risk as it pertains to her candidacy for a re-transplant?

- A. She is low immunologic risk as her cPRA is 0% and the allografts have been removed
- B. She is high immunologic risk as she has a history of multiple sensitizing events which may elicit a latent alloimmune memory response
- C. She is high immunologic risk as she is currently on dialysis
- D. She is low immunologic risk as her current cPRA indicates that she is no longer at risk of active alloimmune memory response

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Key Takeaways

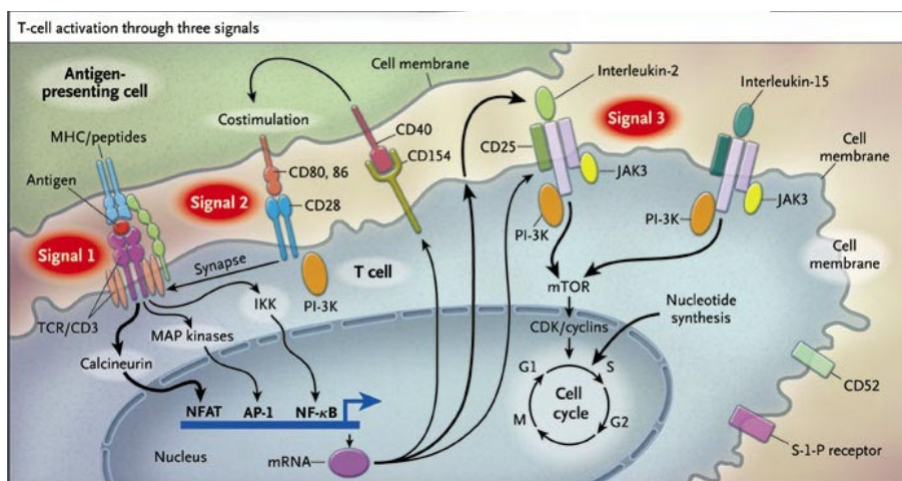
1. The presence of donor specific antibody, whether pre-formed or de novo is a significant predictor of graft dysfunction and graft loss
2. Class I DSA are usually detected sooner after transplant and are associated with acute AMR and early graft loss
3. Class II DSA usually appear later, tend to be persistent, and are associated with cAMR and TG
4. Sensitization by exposure to human tissue or VAD has a significant impact on the development of DSA compared to age, race, or sex

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Role of Maintenance Immunosuppressive Regimens in Preventing Antibody Formation

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Immunosuppression in Transplantation



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Induction Agents

- rATG
 - *In vitro* = Naïve, activated B cells, bone marrow resident plasma cells
 - *In vivo*?
- Alemtuzumab
 - Initial depletion → repopulation →
 - Increase in naïve and transitional B cells, decrease in memory B cells
- Basiliximab
 - B cells expressing CD25
 - IL-2 role in differentiation of activated B cells toward plasma cells *in vitro*
- High Dose Corticosteroids
 - Apoptosis
 - Differentiation of activated B cells toward plasma cells *in vitro*

Thaunat O, et al. J Am Soc Nephrol. 2016;27:1890-1900.

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Maintenance Immunosuppression

- Triple IS Therapy
 - Antiproliferative
 - CNI
 - Corticosteroids
- Co-Stimulation Blockade
 - Belatacept
- mTORi
 - Sirolimus
 - Everolimus

Thaunat O, et al. J Am Soc Nephrol. 2016;27:1890-1900.; Halloran PF. N Engl J Med. 2004; 351:2715-2729.

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De Novo DSA in BENEFIT and BENEFIT EXT

| BENEFIT | | | |
|-------------------|-----------------------|-----------------------|-------------|
| dnDSA specificity | Belatacept MI (n=219) | Belatacept LI (n=226) | CsA (n=215) |
| Total, n | 3 | 8 | 26 |
| Class I, n | 0 | 4 | 5 |
| Class II, n | 3 | 4 | 15 |
| Class I and II, n | 0 | 0 | 6 |

| BENEFIT-EXT | | | |
|-------------------|-----------------------|-----------------------|-------------|
| dnDSA specificity | Belatacept MI (n=183) | Belatacept LI (n=174) | CsA (n=179) |
| Total, n | 7 | 2 | 20 |
| Class I, n | 4 | 2 | 13 |
| Class II, n | 2 | 0 | 4 |
| Class I and II, n | 1 | 0 | 3 |

Modified in accordance with Bray RA, et al. Am J Transplant. 2018;18:1783-1789.

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Pre-existing DSA in BENEFIT and BENEFIT EXT

| BENEFIT | | | |
|----------------------------------|---------------------|----------------------|---------------------|
| | Belatacept MI | Belatacept LI | CsA |
| % (n) | 4.6 (10/219) | 4.9 (11/226) | 6.3 (14/221) |
| Average Baseline MFI (range) | 10,689 (199-24,000) | 9,806 (2,400-19,000) | 7014 (1,166-23,000) |
| Kaplan Meier Death or Graft Loss | 10.0% | 31.8% | 29.1% |
| Kaplan Meier Acute Rejection | 20% | 18.2% | 10% |

| BENEFIT-EXT | | | |
|----------------------------------|---------------------|--------------------|----------------------|
| | Belatacept MI | Belatacept LI | CsA |
| % (n) | 6 (11/184) | 5.7 (10/175) | 9.2 (17/184) |
| Average Baseline MFI (range) | 4,454 (1900-15,000) | 5,495 (900-15,000) | 6,204 (1,000-18,000) |
| Kaplan Meier Death or Graft Loss | 41.8% | 46.7% | 27.4% |
| Kaplan Meier Acute Rejection | 25% | 40% | 19.1% |

Bray RA, et al. Am J Transplant. 2018;18:1774-1782.

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ZEUS and De Novo DSA

| Cox proportional hazard modeling for risk for dnDSA formation and AMR | | | | | | |
|---|------|---------------------|-------|-------|-----------------------|-------|
| De novo DSA formation | | Univariate analyses | | | Multivariate analyses | |
| Covariates* | HR | 95% CI | p | HR | 95% CI | P |
| Time on dialysis (>24 vs. ≤ 24 months) | 0.43 | 0.18-1.02 | 0.047 | - | - | - |
| Donor type (living vs. deceased) | 2.39 | 1.01-5.65 | 0.040 | 2.39 | 1.01-5.66 | 0.048 |
| Number of mismatches (4-6 vs. 0-3) | 3.13 | 1.32-7.44 | 0.006 | 3.26 | 1.37-7.75 | 0.008 |
| Regimen (everolimus vs. cyclosporine) | 2.43 | 0.98-6.04 | 0.048 | 2.67 | 1.07-6.66 | 0.035 |
| Treated AR during the first year (yes vs. no) | 3.11 | 1.03-9.39 | 0.034 | - | - | - |
| Antibody-mediated rejection | | | | | | |
| Renal disease (GN vs. other) | 2.42 | 0.63-9.35 | 0.187 | - | - | - |
| Recipient age (>55 vs. ≤ 55 years) | 0.03 | 0.00-6.20 | 0.024 | - | - | - |
| Gender (female vs. male) | 0.34 | 0.07-1.61 | 0.153 | - | - | - |
| Donor type (living vs. deceased) | 3.80 | 1.07-13.53 | 0.027 | 5.78 | 1.44-23.16 | 0.013 |
| Number of mismatches (4-6 vs. 0-3) | 3.84 | 1.11-13.30 | 0.022 | 5.10 | 1.39-18.72 | 0.014 |
| Regimen (everolimus vs. cyclosporine) | 4.53 | 0.96-21.38 | 0.036 | 5.35 | 1.11-25.70 | 0.036 |
| Treated AR during the first year (yes vs. no) | 8.46 | 2.33-30.75 | 0.000 | 10.22 | 2.56-40.87 | 0.001 |

Modified in accordance with Liefeldt L, et al. Am J Transplant. 2012; 12: 1192-119.

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CONCEPT and DSA

Baseline characteristics of the ITT population in the postconcept study

| ITT population (n=162) | | SRL+MMF group (n=77) | CsA+MMF group (n=85) |
|-----------------------------------|-----------|----------------------|----------------------|
| Recipient characteristics | | | |
| - Age (years) | Mean ± SD | 47 (±11.9) | 47.7 (±10.5) |
| - Gender, male (%) | | 71.4 | 72.9 |
| - BMI (kg/m ²) | | 24.1 (±3.3) | 25.2 (±4.3) |
| - Initial nephropathy (%) | | | |
| Polycystic kidney | | 27.3 | 16.5 |
| Glomerulopathy | | 16.9 | 31.8 |
| Heredity nephropathy | | 9.1 | 5.9 |
| Interstitial nephritis | | 5.2 | 7.1 |
| Uropathy | | 3.9 | 2.4 |
| Hypertensive nephropathy | | 2.6 | 5.9 |
| Pyelonephritis | | 1.3 | 0.0 |
| Insulin dependent diabetes | | 1.3 | 4.7 |
| Other | | 32.5 | 25.9 |
| Donor Characteristics | | | |
| - Age (years) | Mean ± SD | 43.6 (±14.0) | 44.3 (±13.2) |
| - Gender, male (%) | | 58.4 | 71.8 |
| - Cause of death (%) | | | |
| Stroke | | 50.7 | 44.7 |
| Brain trauma | | 24.7 | 21.2 |
| Other | | 24.7 | 34.1 |
| Transplant Characteristics | | | |
| - Cold ischemia time (h) | Mean ± SD | 18.4 (±5.9) | 18.3 (±6.1) |
| - Panel reactive antibodies, >0% | | 1.3 | 0.0 |
| - Delayed graft function (%) | | 10.4 | 14.3 |
| - Slow graft function (%) | | 23.4 | 25.0 |

- Sirolimus = 12%
- CSA control = 21%
- P=0.24

Modified in accordance with Lebranchu Y, et al. Am J Transplant. 2011;11:1665-75.

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Everolimus and DSA in Kidney and Liver Transplants

Outcome of kidney function and immunological parameters in the everolimus and control groups

| | Everolimus Group (n=61) | | | Control Group (n=61) | | |
|---------------------------|-------------------------|----------------|---------|----------------------|----------------|---------|
| | Baseline | Last Follow-up | P-value | Baseline | Last Follow-up | P-value |
| CsA/Tac/Belatacept | 41/91/1 | - | - | 31/30/0 | 23/38/0 | NS |
| Anti-metabolite | 1 | 93% | NS | 0 | 0 | NS |
| Steroids | 87% | 75% | NS | 97% | 95% | NS |
| Creatinine level (μM) | 97% | 141 ± | NS | 77% | 72% | NS |
| aMDRD GFR (ml/min) | 135 ± | 54 | NS | 133 ± | 131 ± | NS |
| Anti-HLA | 37 | 56 ± 22 | NS | 51 | 45 | NS |
| Anti-HLA A/B antibodies | 54 ± 18 | 26% | NS | 65.7 ± | 62 ± 24 | NS |
| Anti-HLA DR/DQ antibodies | 14.75% | 18% | 0.07 | 25 | 18% | NS |
| Anti-HLA DR/DQ antibodies | 11.5% | 16% | 0.03 | 6.5% | 10% | NS |
| DSA | 5% | 9.8% | | 5% | 10% | |
| DSA | 0% | | | 0% | 5% | |

The Patients' characteristics

| Variable | Results (n=56) |
|---|-----------------|
| Age at transplantation (yr) | 51 ± 13 |
| Sex: male/female | 46 (82)/10 (18) |
| Initial liver disease (%) | |
| - Alcohol related liver disease | 22 (39.5) |
| - Viral infection | 14 (25) |
| - Cancer | 13 (23) |
| - Other | 7 (12.5) |
| HLA mismatches | |
| - Class I | 3.2 ± 0.8 |
| - Class II | 3.4 ± 0.9 |
| - Class I and Class II | 6.6 ± 1.2 |
| Time between liver tx & conversion to mTORi (months)[min-max] | 34 (1-206) |
| IS before mTORi | |
| CNI | 54 (98) |
| - Cyclosporine A | 6 (14) |
| - Tacrolimus | 48 (84) |
| Mycophenolic acid (MPA) | 38 (68) |
| Steroids | 53 (98) |
| IS therapy after switch (%) | |
| mTORi + MPA +steroids | 29 (52) |
| mTORi + MPA | 8 (14) |
| mTORi + steroids | 16 (29) |
| mTORi only | 3(5) |

mTORi = 3/47 (6.5%)
CNI = 17/184 (9%)
P=n.s.

Modified in accordance with Kamar N, et al. Clin Transplant. 2013;27:455-462; Del Bello A, et al. J Hepatol. 2014;61:963-5.

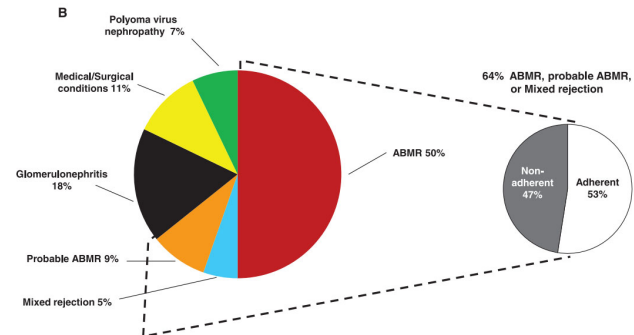
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Medication Non-Adherence and De Novo DSA

A

| Histological diagnosis | n | Attributed causes of allograft failure | | | | | | | Non-adherence |
|-----------------------------|-----------|--|---------------|-----------------|---------------------------|--------------------|----------------|--------------|---------------|
| | | Antibody-mediated rejection | Probable ABMR | Mixed rejection | Polyoma virus nephropathy | Glomerulonephritis | Medical causes | Missing data | |
| Antibody-mediated rejection | 28 | 28 | — | — | — | — | 2 | — | 11 |
| Probable ABMR | 2 | — | 2 | — | — | — | — | — | 1 |
| Mixed rejection | 6 | 2 | — | 3 | — | — | 1 | — | 2 |
| T cell-mediated rejection | 1 | — | 1 | — | — | — | — | — | 1 |
| Borderline | 1 | — | 1 | — | — | — | — | — | 1 |
| Polyoma virus nephropathy | 1 | — | — | — | 1 | — | — | — | 0 |
| Glomerulonephritis | 12 | — | 1 | — | — | 9 | 2 | — | 2 |
| No major abnormalities | 3 | — | — | — | — | — | 1 | 2 | 1 |
| Atrophy-fibrosis | 3 | — | — | — | — | 1 | — | 2 | 0 |
| Other | 3 | — | — | — | 3* | — | — | — | 0 |
| Total | 60 | 28 | 5 | 3 | 4 | 10 | 6 | 4 | 19 |

* Patients whose biopsies showed histologic changes highly suggestive of polyoma virus nephropathy, although the IC/in situ hybridization was reported either inconclusive (n=1) or negative (n=2)



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Medication Non-Adherence and De Novo DSA

| Variable | Univariate HR | p | Stepwise model HR | p |
|--|-----------------|-------|-------------------|---------|
| Age of Recipient | 1.0 (1.0, 1.0) | 0.45 | | |
| Race | 0.9 (0.4, 2.0) | 0.86 | | |
| Deceased donor | 0.9 (0.4, 1.9) | 0.79 | | |
| Steroid containing IS | 1.8 (0.7, 4.9) | 0.22 | | |
| History of nonadherence | 3.2 (1.5, 7.0) | 0.002 | 6.5 (2.6, 15.9) | <0.0001 |
| Prior kidney transplant | 0.8 (0.3, 2.1) | 0.60 | | |
| Viral infection requiring IS reduction | 2.1 (0.9, 4.6) | 0.07 | 5.3 (2.1, 13.5) | 0.0004 |
| BK nephropathy prior to DSA | 1.2 (0.4, 4.1) | 0.75 | | |
| C1q (MFI>1000) | 5.9 (2.3, 15.6) | 0 | 3.8 (1.5, 9.3) | 0.0039 |
| IgG3 (MFI>1000) | 3.2 (1.5, 7.0) | 0.002 | | |
| IgG4 (MFI>1000) | 2.1 (0.8, 5.7) | 0.14 | | |
| Dominant MFI (Log) | 1.4 (0.46, 4) | 0.57 | | |
| Number of DSA specificities | 1.1 (0.9, 1.3) | 0.35 | | |
| Anti-class I DSA only | 0.7 (0.2, 2.1) | 0.52 | | |
| Anti-class II DSA only | 0.7 (0.3, 1.5) | 0.36 | | |
| Both anti-class I and II DSA | 2.0 (0.9, 4.3) | 0.10 | | |
| Center | | | | |
| Center B | - | | | |
| Center A | 1.1 (0.4, 2.8) | 0.86 | | |
| Center C | 0.6 (0.2, 1.4) | 0.22 | | |
| Time to dnDSA (years post-transplant) | 1.2 (1.1, 1.3) | 0.004 | 1.2 (1.0, 1.3) | 0.01 |
| C-stat | NA | NA | 0.80 | |

The interaction term between C1q and IgG subclasses was nonsignificant P>0.05

Modified in accordance with Schinstock CA, et al. Transplant International. 2019;32:502-515.

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Question 2: A 68-year-old male with a history of deceased donor kidney transplant secondary to type 2 diabetes mellitus 6 months ago presents alone to your post-transplant clinic for follow-up. He has recently been diagnosed with dementia and admits that he does not remember if he has taken his medications on any given day. Per his chart, he has significant variation in his tacrolimus troughs, which have ranged between 2.8-15.1 mg/dL within the last 2 months. His serum creatinine nadir was 0.8 mg/dL 3 days after transplant and is 1.3 mg/dL today. His biopsy did not indicate a rejection process and his DSA test is pending. Which is the best immunosuppression change for this patient?

- A. Change tacrolimus IR to tacrolimus ER
- B. Change tacrolimus IR to everolimus
- C. **Change tacrolimus IR to belatacept after confirming that patient is EBV seropositive**
- D. Change tacrolimus to cyclosporine

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Key Takeaways

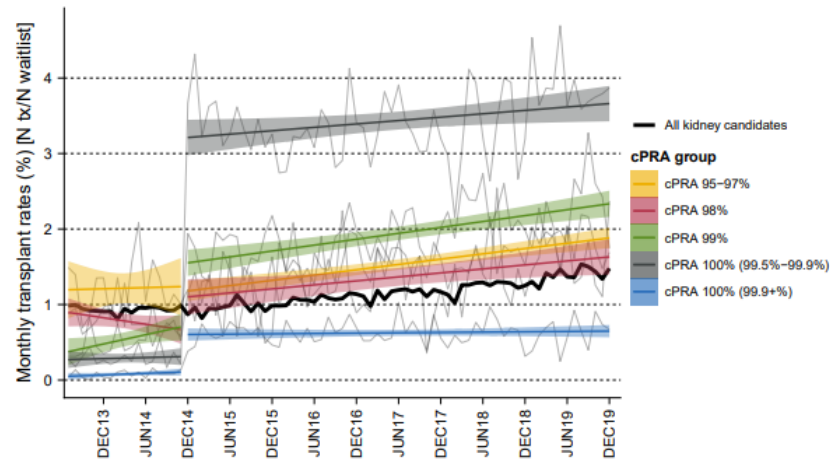
1. Induction agent selection may prevent some formation of antibodies but is fleeting compared to the burden of maintenance immunosuppression
2. Maintenance immunosuppression suppresses the formation of antibody mainly through T cell mediated effects rather than direct effects on B cell formation and activity
3. Non-calcineurin inhibitor based immunosuppressive regimens have variable affect on mitigating antibody formation with the most benefit seen with belatacept
4. Medication non-adherence is perhaps the most critical factor in the development of de novo DSA after transplantation

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Evidence Based Regimens for Desensitization

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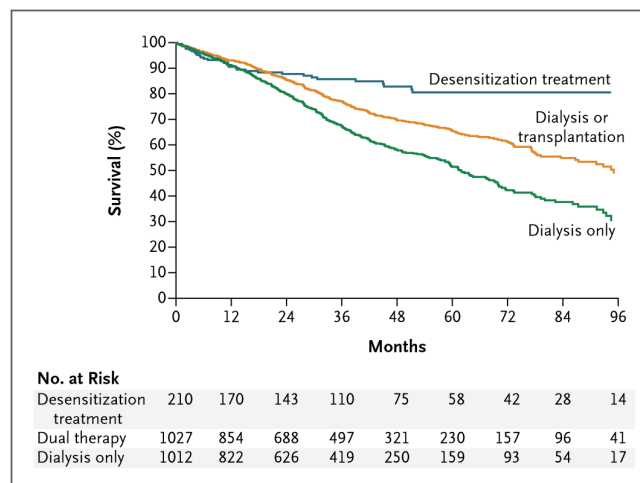
Highly Sensitized Kidney Transplant Candidates



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Desensitization and Overall Survival



P<0.001)

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Desensitization Strategies

Tools Available to Desensitize HLA-Incompatible Kidney Transplant Candidates

| Apheresis | Immunosuppressants |
|--|---|
| Plasmapheresis <ul style="list-style-type: none"> - Inexpensive - Efficient if DSA MFI < 9,000 - Many repeated sessions - Depletion of Ig/clotting factors | IVIg IVIg + Rituximab Rituximab Bortezomib Tacrolimus + mycophenolic acid Eculizumab IdeS |
| Double filtration plasmapheresis <ul style="list-style-type: none"> - Inexpensive - Efficient if DSA MFI < 12,000 - Many repeated sessions - Depletion of Ig/clotting factors | |
| Semi-specific immunoadsorption <ul style="list-style-type: none"> - Expensive - Columns adsorbing only Ig - Many repeated sessions - Reusable columns - Efficient if DSA MFI < 15,000 - Depletion only of Ig | |

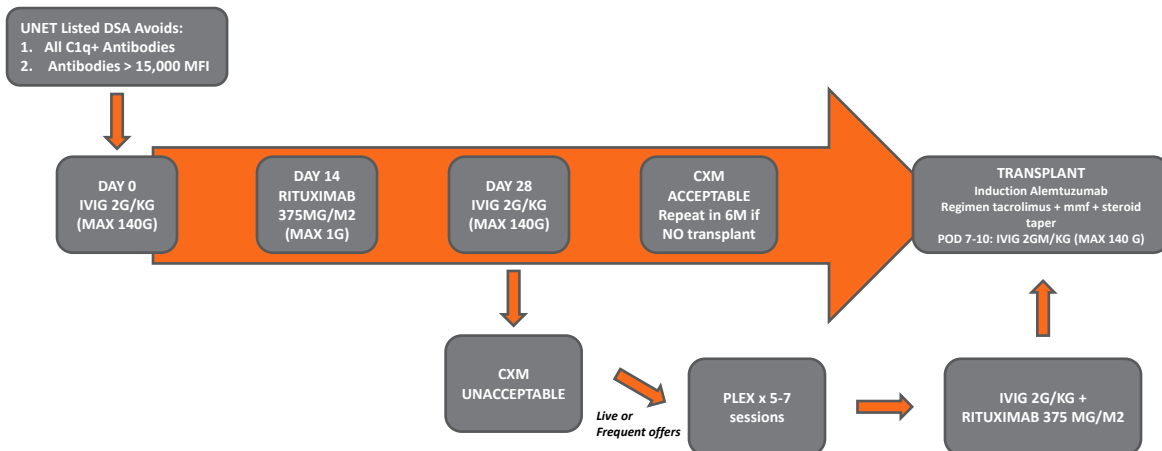
Treatment Options for Sensitized Patients Awaiting Heart Transplantation

| Treatment Options |
|---|
| Removal of Antibodies: <ul style="list-style-type: none"> - Plasmapheresis or immunoadsorption |
| Intravenous immunoglobulin: <ul style="list-style-type: none"> - Is thought to work in multiple ways, including Fc-receptor blockade, complement inhibition, downregulation of β receptors, neutralizing circulating antibody and cytokines |
| Immunosuppressive agents: <ul style="list-style-type: none"> - Corticosteroids - Rituximab (anti-CD20), depletes B-cells - Bortezomib (proteasome inhibitor), depletes plasma cells - Alemtuzumab (anti-CD52), partly depletes T- and B-cells - Eculizumab (C5 inhibitor), blocks antibody-mediated complement activation - Anti-thymocyte globulin (depletes thymic cells: T-cells and T-precursor cells, and partly B-cells) - Cyclophosphamide (cytostatic, rarely used) |
| Other modalities: <ul style="list-style-type: none"> - Photopheresis - Total lymphoid irradiation (rarely used) |

Modified in accordance with Malvezzi P, et al. Exp Clin Transplant. 2018;16:367-375.; Kobashigawa J, et al. J Heart Lung Transplant. 2018;37:537-547.

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Example Desensitization Protocol



Modified in accordance with Vo AA, et al. Transplantation. 2019;103: 2666–2674.

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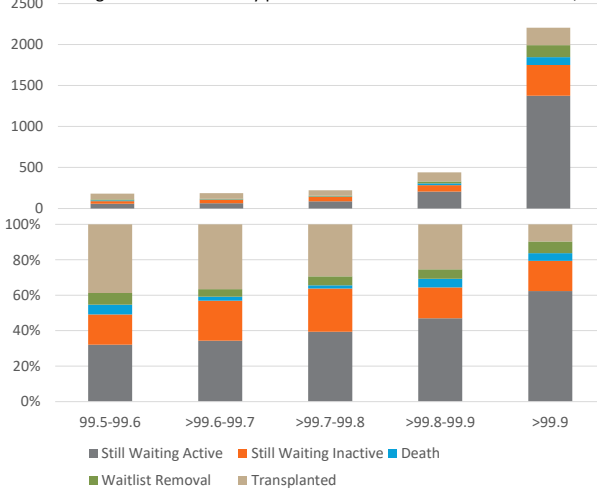
Patient Selection Considerations

- Time on dialysis
- Co-morbidities
- Frailty
- Quality of offered organ
- Ability to withstand post-transplant complications
 - Added immunosuppression/side effects
 - PNF
 - DSA rebound/AMR

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Patient Selection: KAS vs KPD

Change in status over a 1-y period for 100% CPRA active as of June 1, 2016



All transplants performed from June 1, 2016 – June 1, 2017 (n=11,129)

| CPRA group | <80% (n=9355) | ≥ 80% (n=1774) All (n=1774) | 80%-89% (n=377) | 90%-98% (n=607) | 99% (n=262) | 100% (n=528) |
|------------------------------|------------------|--------------------------------------|--------------------|--------------------|----------------|-----------------|
| Deceased donor n (%) | 6647 (71.1) | 1640 (92.4) | 326 (86.5) | 552 (90.9) | 249 (95) | 513 (97.2) |
| All living donor n (%) | 2500 (26.7) | 116 (6.5) | 35 (9.2) | 55 (9.1) | 13 (5.0) | 13 (2.5) |
| Living related n (%) | 1002 (37.0) | 36 (31.0) | 13 (37.1) | 15 (27.3) | 2 (15.4) | 6 (46.2) |
| Living unrelated n (%) | 1144 (42.2) | 29 (25) | 11 (31.4) | 16 (29.0) | 2 (15.4) | 0 (0) |
| Kidney paired donation n (%) | 354 (14.2) | 57 (49.1) | 21 (60.0) | 20 (36.4) | 9 (69.2) | 7 (53.8) |
| Unknown n (%) | 208 (2.2) | 12 (0.7) | 6 (1.6) | 4 (0.7) | 0 (0%) | 2 (0.4) |

Modified in accordance with Schinstock CA, et al. Clin Transplant. 2019;33:e13751.

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Patient Selection: Relative Intensity Scale

| DSA-RIS | |
|-----------|-------------------------------|
| 0 points | No DSA |
| 2 points | Weak DSA MFI <5,000 |
| 5 points | Moderate DSA MFI 5,000-10,000 |
| 10 points | Strong DSA MFI <10,000 |

Characteristics of ABMR in patients with or without graft loss

| Characteristic | No graft loss (n=27) | Graft loss (n=18) | P |
|-----------------------|----------------------|-------------------|-------|
| C4d+/C4d- | 17 (63%)/10 (37%) | 16 (89%)/2 (11%) | 0.086 |
| TMA+ | 2 (7%) | 6 (33%) | 0.045 |
| TMA+/Eculizumab+ | 2/2 (100%) | 0/6 (0%) | 0.036 |
| DSA RIS at Transplant | 19.9 ± 17 | 22 ± 17 | 0.43 |
| DSA RIS at ABMR | 14.5 ± 11.5 | 16.6 ± 12.1 | 0.75 |
| DSA RIS 1 M post-ABMR | 10.1 ± 6.5 | 9.7 ± 8.1 | 0.87 |

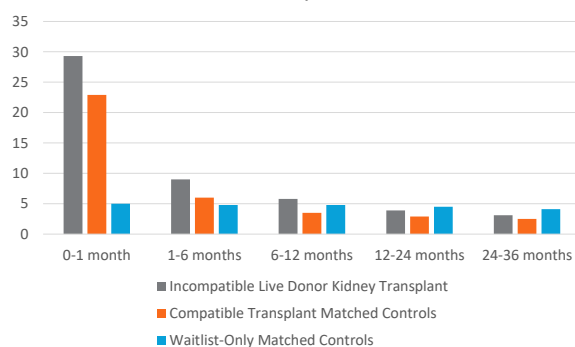
TMA, thrombotic microangiopathy; ABMR, antibody mediated rejection

Modified in accordance with Vo AA, et al. Transplantation. 2015;99: 1423-1430.

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Post-Incompatible Transplant Readmission

Incidence of Readmission per 1000 Patient
Days



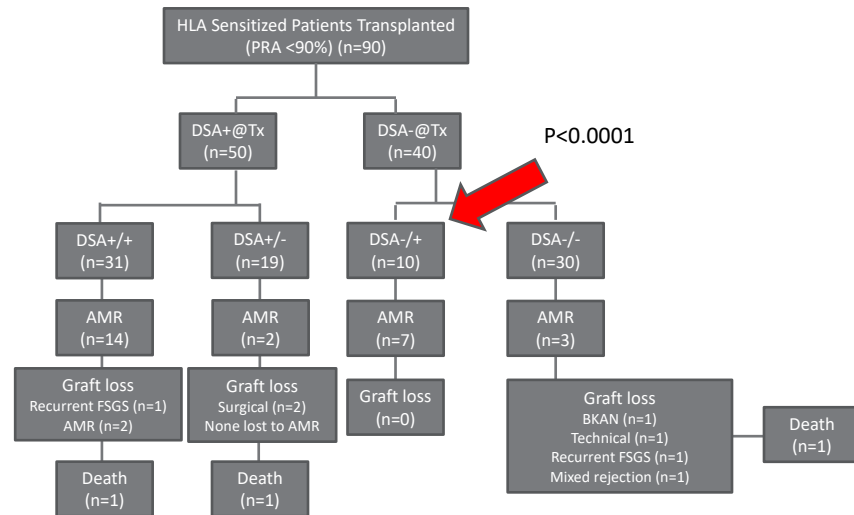
Relative risk of readmission

| Time post-kidney transplant discharge/matching | Relative risk of readmission – ILDKT vs compatible transplant matched controls | P-value | Relative risk of readmission – ILDKT vs waitlist-only matched controls | P-value |
|--|--|---------|--|---------|
| 1 month | 1.28 (1.13-1.46) | <.001 | 5.86 (4.96-6.92) | <.001 |
| 1-6 months | 1.51 (1.36-1.68) | <.001 | 1.89 (1.69-2.10) | <.001 |
| 6-12 months | 1.67 (1.49-1.87) | <.001 | 1.22 (1.09-1.36) | <.001 |
| 12-24 months | 1.37 (1.23-1.52) | <.001 | 0.85 (0.77-0.95) | .002 |
| 24-36 months | 1.24 (1.10-1.40) | <.001 | 0.74 (0.66-0.84) | <.001 |

Modified in accordance with Orandi BJ, et al. Am J Transplant. 2018;18:650-658.

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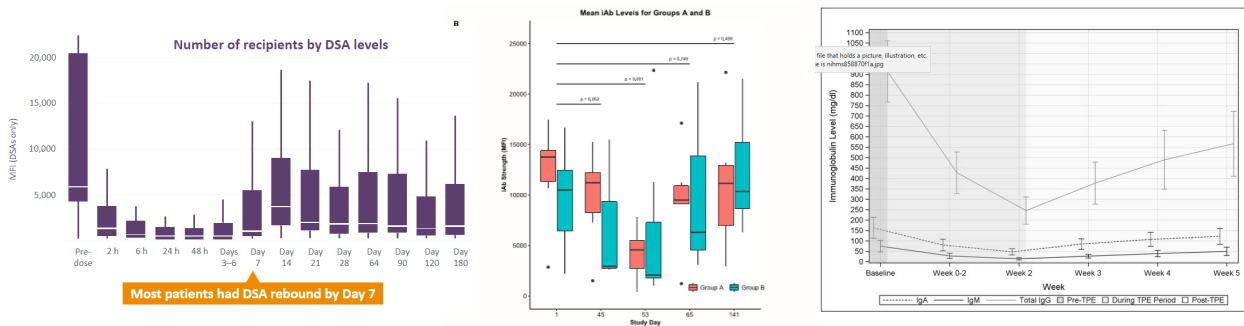
Post-transplant DSA and AMR



Vo AA, et al. Transplantation. 2019;103: 2666–2674.

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Post-Desensitization DSA Rebound



Reprinted with permission in accordance with Jordan SC, et al. Transplantation. 2020. doi: 10.1097/TP.0000000000003496; Tremblay S, et al. Am J Transplant. 2020;20:411-421.; Guptill JT, et al. Autoimmunity. 2016;49:472-479.

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Question 3: A 66 year-old-female with ESRD from IgA nephropathy and a cPRA of 100% comes to your transplant clinic to discuss her transplantation options. She has a living donor who is incompatible and has been on the waiting list for 10 years. Her highest Class I MFI is 8,000 and Class II MFI is >20,000. Which is the best desensitization regimen for this patient?

- A. Eculizumab, plasmapheresis, splenectomy
- B. Plasmapheresis, belatacept
- C. Low dose intravenous immune globulin
- D. High dose intravenous immune globulin, plasmapheresis, and rituximab

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Question 4: The same patient asks you about what to expect if she decides to pursue desensitization. Which of the following statements is correct?

- A. Desensitization may reduce her waiting time for a transplant but may result in increased risk of post-transplant complications such as antibody-mediated rejection
- B. Desensitization will result in complete and permanent removal of her antibodies leading to a successful transplantation
- C. Desensitization utilizes medications with very little risk or side effects
- D. Desensitization is highly unlikely to be successful in recipients of living donor kidneys and the subsequent outcomes would not outweigh the benefit

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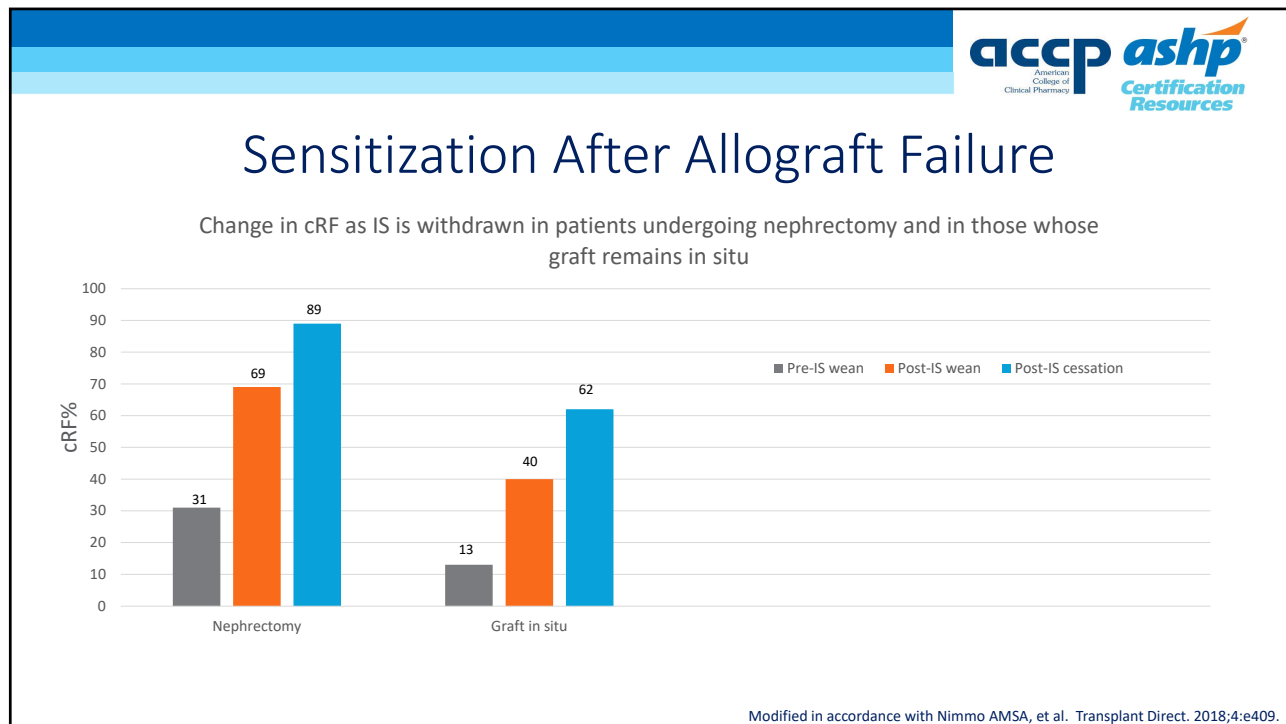
Key Takeaways

1. Strategies such as living donor paired kidney donation and changes to the kidney allocation system have increased access to transplantation for highly sensitized patients
2. Patients who are the most highly sensitized (cPRA ~100%) continue to have prolonged waiting times for a compatible transplant
3. Desensitization strategies are multifactorial and take into account patient and donor characteristics. To date, there is no one standard of practice to address the variable immunologic risks of each patient
4. Patient selection and “readiness” is key for manageable post-transplant outcomes in patients who have received an incompatible transplant

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Methods to Wean Immunosuppression After Graft Failure

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accp ashp
American College of Clinical Pharmacy Certification Resources

Sensitization After Allograft Failure

Patient demographics in graft nephrectomy and GIS groups

| | Graft Nephrectomy (n=24) | Failed GIS (n=17) | P |
|--|--------------------------|-------------------|------|
| Sex, % (n) male | 58% (14) | 71% (12) | 0.36 |
| Age: median (IQR), y | 47 (38-51) | 51 (27-60) | 0.37 |
| Donor type (n) | | | |
| - Live donor | 6 | 5 | |
| - DBD | 17 | 11 | |
| - DCD | 1 | 1 | |
| Delayed graft function, % (n) | 29% (7) | 18% (3) | 0.48 |
| Transplant to graft function, median (IQR), mo | 58 (8-108) | 141 (70-249) | 0.01 |
| Graft failure to nephrectomy, median (IQR), d | 384 (95-453) | N/A | N/A |
| Relisted for transplant, % (n) | 92% (22) | 94% (16) | 1.0 |

Modified in accordance with Nimmo AMSA, et al. Transplant Direct. 2018;4:e409.

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Management of IS After Graft Failure

Management of Immunosuppression

We recommend that:

- Consideration be given to the relative risk of maintaining recipient immunosuppression after return to dialysis and relisting for a repeat kidney transplant, the clinical benefit of immunosuppressive drug tapering or withdrawal, and the risk of de novo allosensitization that may preclude options for future kidney transplantation. This is particularly relevant for pediatric recipients and young adults who are likely to require retransplantation within their lifetime. (1D)
- All immunosuppression apart from steroids be stopped immediately after transplant nephrectomy, with subsequent gradual withdrawal of steroids. (1D)
- In the event of severe acute rejection after withdrawal of immunosuppression, we recommend that steroid therapy be restarted, followed by transplant nephrectomy when acute inflammation has settled. (1D)
- For patients relisted for transplantation, that the clinical team notify the histocompatibility laboratory of significant changes in immunosuppression and that additional serum samples be obtained for human leukocyte antigen specific antibody screening 4 weeks after any such changes. (1C)

We suggest that:

- Immunosuppressive therapy be continued to avoid immunologic sensitization if a living kidney donor is available and there is the prospect of retransplantation preemptively or within 1 year of starting dialysis. (2C)
- Immunosuppressive treatment be withdrawn after graft failure when there are immunosuppression-related complications such as skin cancer and an anticipated delay in retransplantation. (2C)

We suggest that:

- Widely accepted indications for graft nephrectomy include:) localizing symptoms (pain, infection, bleeding) that are resistant to medical therapy in a failed graft;) to create space for retransplantation;) to enable complete withdrawal of immunosuppression;) risk of graft rupture;) graft malignancy;) refractory anaemia with raised C-reactive protein (Not graded).
- We suggest that: & In the absence of prospective data, decisions on whether to remove a failed or failing graft be made on perceived benefits and risks and on a case-by-case basis. (2B)

Modified in accordance with Andrews PA, et al. Transplantation. 2014;98:1130-1133.

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Question 5: A 24-year-old female with lupus nephritis who received a deceased donor kidney 7 years ago has been admitted to your service with acute abdominal pain over the allograft site, hematuria, a serum creatinine of 10 mg/dL and a K of 8.2 mmol/L. The patient is diagnosed with acute on chronic rejection secondary to medication non-adherence (> 6 weeks; tacrolimus, mycophenolate mofetil and prednisone) and is started on dialysis. She is blood group type O and her cPRA is now 100%. The transplant team asks your advice regarding immunosuppression management in this patient who has not responded to standard AMR treatment. Which is the best initial strategy?

- Discontinue all immunosuppression as the patient is young and you would like to avoid increasing her risk of infection and malignancy from overexposure
- Resume all previous doses of immunosuppression as her chances of retransplantation with a deceased donor are imminent
- Resume all previous doses of immunosuppression as you would like to avoid the risk of de novo allosensitization
- Resume corticosteroids, followed by transplant nephrectomy when acute inflammation has settled

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- C. Resume all previous doses of immunosuppression as you would like to avoid the risk of de novo allosensitization
- D. **Resume corticosteroids, followed by transplant nephrectomy when acute inflammation has settled**

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Question 6: A 41-year-old male patient with a preemptive living donor kidney transplant for polycystic kidney disease 6 years ago has come to your clinic for evaluation of fistula placement in anticipation of initiating dialysis. His graft failure is attributed to BK nephropathy. He is currently on tacrolimus extended release 5 mg daily (trough levels 3-5 ng/mL), mycophenolate sodium 540 mg BID and prednisone 5 mg daily. He would like to remove his failed kidney transplant as it was from his ex-wife and he no longer "wants it." Which statement reflects this patient's risk of HLA sensitization in regards to nephrectomy?

- A. Patients undergoing allograft nephrectomy will only have an increase in Class II DSA
- B. The percentage of patients with DSA decreased after nephrectomy
- C. Patients undergoing nephrectomy and stopping immunosuppression have higher DSA levels than those stopping immunosuppression without nephrectomy
- D. A decrease in calculated reaction frequency (cRF) was seen after nephrectomy

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Key Takeaways

1. Most transplant recipients are off immunosuppression by 12 months after allograft failure
2. The decision to wean or cessation of immunosuppression should be balanced between the long-term risks of systemic immunosuppression versus post-failure allosensitization and the likelihood of retransplantation
3. Graft nephrectomy in the absence of overt clinical need remains controversial as removal of the graft may precipitate allosensitization

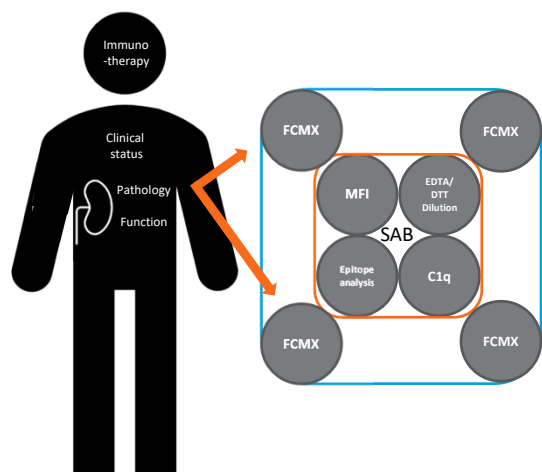
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Immunologic Event Monitoring



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Could We? Should We? Why?



- Prospective
 - Timing within the first year of transplant
 - Timing beyond
- For Cause
 - Immunosuppression changes
 - Immunostimulating events
 - Viral infection
 - Other
 - Scheduled decreases in immunosuppression
 - 3, 5, 12 months post-transplant, etc
 - Changes in allograft function
 - Acute injury
 - Chronic injury

Modified in accordance with Ma J, et al. Adv Chronic Kidney Dis. 2016;23(5):317-325.

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Rationale for DSA Monitoring

Emerging Criteria for Evaluation of a Screening Program

- (1) The screening program should respond to a recognized need.
- (2) The objectives of screening should be defined at the outset.
- (3) There should be a defined target population.
- (4) There should be scientific evidence of screening program effectiveness.
- (5) The program should integrate education, testing, clinical services, and program management.
- (6) There should be quality assurance, with mechanisms to minimize potential risks of screening.
- (7) The program should ensure informed choice, confidentiality, and respect for autonomy.
- (8) The program should promote equity and access to screening for the entire target population.
- (9) Program evaluation should be planned from the outset.
- (10) The overall benefits of screening should outweigh the harm.

Adapted from Andermann et al.

Posttransplantation Group

A need is recognized for the following:

19. Serial screening of serum to determine timing of onset of de novo DSA before onset of graft dysfunction.
20. Protocol biopsies at first appearance of de novo DSA to document pathologic correlation.
21. Assessment of DSA for complement fixing activity and correlation with clinical events (e.g., DSA C1q binding and IgG subclass specificity of DSA).
22. Clinical trials that include serial DSA monitoring posttreatment and posttreatment biopsies to correlate DSA levels with histologic response to therapy and long-term outcome.
23. Clinical trials to prevent production of DSA.

Ma J, et al. Adv Chronic Kidney Dis. 2016;23(5):317-325.; Tait BD, et al. Transplantation. 2013 Jan 15;95(1):19-47.

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Prospective DSA Monitoring

DSA risk classification strategy

| | HLA Category |
|----------|---|
| High | <ul style="list-style-type: none"> Crossmatch positive and DSA Crossmatch borderline (positive or negative) and DSA Crossmatch negative and DSA CPRA > 80% (removed Sept 2014) |
| Moderate | <ul style="list-style-type: none"> Crossmatch positive with no DSA |
| | <ul style="list-style-type: none"> DGF (added Sept 2014) Child to mother transplant Prior transplant failure due to rejection CPRA 20-80% (removed Sept 2014) |
| Low | <ul style="list-style-type: none"> All patients not meeting the above criteria |

Antibody testing schedule

| Testing frequency | Early phase | Week 2 | Month 1 | Month 2 | Month 3 | Month 6 | Month 9 | Month 12 | Long Term |
|-------------------|---------------------------------|-----------|--------------------------------|-----------|--------------------------------|---------|---------|--------------------------------|---------------------------------|
| High | DSA 48-72 hours post-transplant | DSA | DSA and protocol kidney biopsy | DSA | DSA and protocol kidney biopsy | DSA | DSA | DSA and protocol kidney biopsy | DSA every 6 months or for cause |
| Moderate | For cause | For cause | DSA | DSA | DSA and protocol kidney biopsy | DSA | | DSA and protocol kidney biopsy | Annual DSA or for cause |
| Low | For cause | For cause | For cause | For cause | DSA and protocol kidney biopsy | DSA | | DSA and protocol kidney biopsy | Annual DSA or for cause |

Modified in accordance with Gilbert A, et al. Clin Transpl. 2016;32:93-101.

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Outcomes But At What Cost?

| | Historic Cohort 6/1/07-12/31/10 | Current Cohort 4/1/12-4/1/16 | P value |
|-----------------------------------|------------------------------------|---------------------------------|---------|
| Number of patients | 266 | 614 | - |
| Number tested for DSA, n(%) | 97 (36.5) | 587 (95.6) | - |
| Number with de novo DSA, n(%) | 66 (24.8) | 108 (17.6) | 0.016 |
| % of tested who were positive | 68.0% | 18.4% | - |
| Mean/median time to DSA (days) | 248 | 147 | 0.02 |
| AMR rates, n (%) | | | |
| Acute AMR | 12 (4.5) | 7 (1.1) | 0.0037 |
| Chronic AMR | 11 (4.1) | 1 (0.2) | <0.0001 |
| Total AMR | 23 (8.6) | 8 (1.3) | <0.0001 |
| ACR rates, n (%) | | | |
| 1A or 1B | 26 (9.8) | 89 (14.5) | - |
| 2A or 2B | 11 (4.1) | 18 (2.9) | - |
| 3 | 0 | 0 | - |
| Total | 34 (12.8) | 112 (18.2) | 0.049 |
| Average time to ACR (days) | 184 | 228 | - |
| Graft losses/death, n (%) | 12 (4.5) | 50 (8.1) | 0.062 |
| Average time to graft loss (days) | 317 | 253 | - |

Modified in accordance with Gilbert A, et al. Clin Transpl. 2016;32:93-101.

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Question 7: Which of the following patients would most benefit from routine DSA monitoring?

- A. A patient who converted from one generic tacrolimus formulation to another with subsequent TDM within goal levels
- B. A patient who received an HLA-incompatible transplant after receiving desensitization treatment
- C. A patient who had prolonged delayed graft function after transplantation, who is stable one year out from transplant
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Question 8: You have a new transplant attending who has just joined your transplant program. During a quality assurance/performance improvement meeting, she notes that she would like to decrease the incidence of AMR within the first year post-transplant within the program and would like to implement routine DSA monitoring. Which strategy would most likely help the program achieve its QAPI goal while maintaining cost-effectiveness?

- A. Monitor all patients monthly and treat any DSA with an MFI above the detected threshold
- B. Monitor all patients who have high inpatient variability in tacrolimus levels as flagged by the electronic health record with treatment of DSA according to protocol
- C. Monitor patients and treat according to individual physician clinical decision making
- D. Monitor all patients quarterly and only treat DSA once a diagnosis of AMR is confirmed with biopsy

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Key Takeaways

1. DSA monitoring represents a “snapshot” in time and should be combined with clinical presentation when determining significance
2. Routine monitoring of post-transplant DSA may detect the emergence of AMR and clinical changes sooner than for cause monitoring
3. There are clearly a subset of patients who require more frequent DSA monitoring such as patients who are highly sensitized, those who have changes to immunosuppression, and those with sensitizing events

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Approaches to Prevent and Manage Antibody Development

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