ISHLT JOURNAL WATCH

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Edited by C Patterson, MD
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HS Kulkarni, *et al*. *Pseudomonas aeruginosa* and acute rejection independently increase the risk of donor-specific antibodies after lung transplantation.

Am J Transplant. 2019 Nov 2. doi: 10.1111/ajt.15687. [Epub ahead of print]

STUDY HIGHLIGHTS

Hypothesis: There is an association between the isolation of *Pseudomonas* aeruginosa in respiratory tract and development of DSA after lung transplantation.

Methods: Single-center retrospective cohort study of 460 primary lung transplant recipients to examine risk factors for DSA using Cox regression models. Acute cellular rejection **(ACR)**, lymphocytic bronchiolitis **(LB)** and bacterial isolation after transplantation treated as time-dependent covariates.

Results: Of 460 recipients, 205 (45%) developed DSA; the majority developed Class II DSA (n = 175, 85%), and 145 of 205 (71%) developed DSA to HLA-DQ alleles.

CENTRAL FIGURES

	Nonstratified			Stratified for CPB		
Variable	HR	95% CI	*P*	HR	95% CI	*P*
Pseudomonas isolation post-LTx[a]	1.75	1.18-2.60	.005	1.76	1.19-2.61	.005
Pretransplant CPRA	1.01	1.00-1.01	.009	1.008	1.00-1.01	.008
PGD grade 3 at any point	1.25	0.91-1.71	.176	1.173	0.85-1.62	.331
LAS	1.00	1.00-1.01	.397	1.00	0.99-1.01	.879
	Nonstratified			Stratified for CPB		
Variable	HR	95% CI	*P*	HR	95% CI	*P*
Acute rejection grade ≥ A2[a]	2.06	1.43-2.97	<.001	2.01	1.4-2.9	<.001
Pretransplant CPRA	1.01	1.00-1.01	.017	1.01	1.00-1.01	.015
PGD grade 3 at any point	1.27	0.92-1.75	.141	1.2	0.87-1.65	.276
LAS	1.00	1.00-1.01	.430	1.00	0.99-1.01	.927
	Nonstratified			Stratified for CPB		
Variable	HR	95% CI	*P*	HR	95% CI	*P*
Lymphocytic bronchiolitis Grade ≥ B1R[a]	1.72	1.18-2.51	.005	1.72	1.18-2.51	.005
Pretransplant CPRA	1.01	1.00-1.01	.012	1.01	1.00-1.01	.01
PGD grade 3 at any point	1.3	0.94-1.78	1.109	1.21	0.88-1.68	.238
LAS	1.00	1.00-1.01	.389	1.00	0.99-1.01	.876

In multivariable analyses, Pseudomonas isolation and LB, but NOT PGD or ACR, were associated with worse CLAD-free survival.

In multivariable analyses, *Pseudomonas* isolation, ACR, pre-transplant CPRA and LB, but NOT PGD, were independent risk factors for DSA.

Association between the number of positive Pseudomonas cultures and the risk of DSA.

Variable	HR	95% CI	*P*
Pseudomonas isolation post-LTx[a]	1.42	1.11-1.81	.005
PGD grade 3 at any point	1.22	0.94-1.57	.14
LAS	1.00	1.00-1.01	.41
Variable	HR	95% CI	*P*
Lymphocytic bronchiolitis, >=B1R[a]	1.29	1.02-1.62	.035
PGD grade 3 at any point	1.20	0.93-1.55	.171
LAS	1.00	1.00-1.01	.34

REVIEWER'S COMMENTS

- Study links *Pseudomonas* isolation, ACR, and LB with DSA detection after lung transplantation.
- Significant association between *Pseudomonas* isolation and the development of DSA to mismatched DQ alleles.
- Association between Pseudomonas isolation, LB and CLAD.
- Differs from published literature in suggesting PGD3, ACR, and community acquired respiratory viral infections not associated with CLAD

Limitations:

- Association ≠ causation
- Does not distinguish between *Pseudomonas* isolation/infection.
- Single center retrospective study

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LK Tague, *et al*. Lung transplant outcomes are influenced by severity of neutropenia and granulocyte colony-stimulating factor (GCSF) treatment.

Am J Transplant. 2020 Jan;20(1):250-261. doi: 10.1111/ajt.15581.

STUDY HIGHLIGHTS

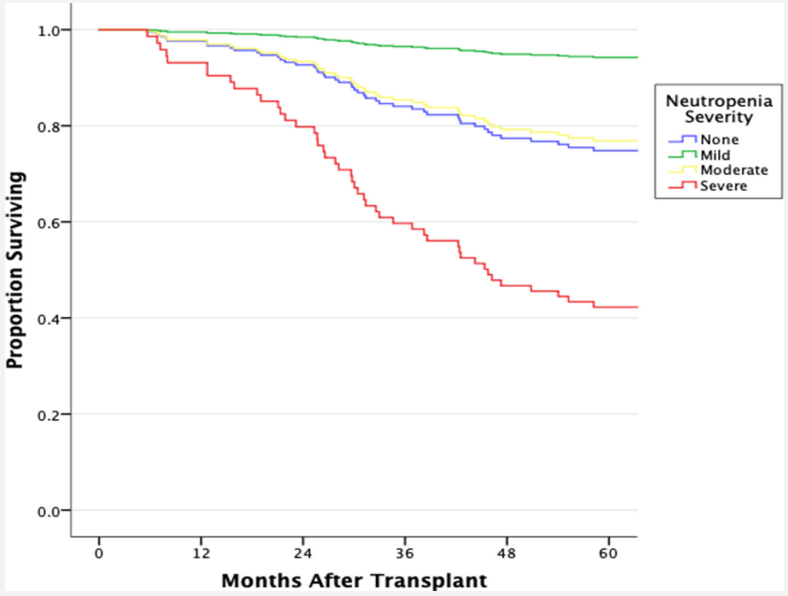
Questions: 1. Is there an association between severity of neutropenia with allograft rejection or survival? 2. How GCSF administration might influence this association?

Methods: Single-center retrospective cohort study of 228 lung transplant recipients. Neutropenia categorized as

- Mild: Absolute neutrophil count (ANC) 1000-1499
- Moderate: ANC 500-999
- Severe: ANC <500

Association of neutropenia with outcomes assessed with Cox proportional hazards regression. Association of GCSF therapy with outcomes analyzed by propensity score matching.

CENTRAL FIGURES



Severe neutropenia was associated with higher mortality.

Adjusted hazard ratio (aHR) for severe neutropenia versus…
-No neutropenia: 2.97
(95% CI 1.05-8.41, P = .040)

Mild neutropenia: 14.51
(95% CI 1.58-13.34, P = .018)

Moderate neutropenia: 3.27
(95% CI 0.89-12.01, P = .074)

Results:

- Of 228 recipients, 101 (42.1%) developed neutropenia.
- Severe neutropenia was associated with decreased survival and increased rate of infection.
- No association between neutropenia and increased risk of ACR or CLAD.
- GCSF administration was associated with a reduced risk of death in severely neutropenic patients (aHR 0.24, 95% CI 0.07-0.88, P = .031).
- There was a trend towards a higher rate of CLAD in mildly neutropenic patients treated with GCSF (aHR 3.49, 95% CI 0.93-13.04, P = .063),

REVIEWER'S COMMENTS

- Demonstrates severe neutropenia is a risk factor for death after lung transplantation and suggests GCSF administration to severely neutropenic recipients may modify this outcome.

Limitations:

- Single center retrospective study
- Small sample size with low number of patients for subgroup analysis.

Question raised:

- Is mild neutropenia protective for the graft?
- Is the treatment of mild asymptomatic neutropenia with GCSF harmful?

ISHLT JOURNAL WATCH

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M Wijesinha, *et al*. Survival Associated with Sirolimus Plus Tacrolimus Maintenance Without Induction Therapy Compared With Standard Immunosuppression After Lung Transplant.

JAMA Netw Open. 2019 Aug 2;2(8):e1910297. doi: 10.1001/jamanetworkopen.2019.10297.

STUDY HIGHLIGHTS

Objective: To compare survival between patients receiving sirolimus plus tacrolimus vs mycophenolate mofetil (MMF) plus tacrolimus.

Methods: UNOS-based cohort study of lung transplant recipients Jan 2003 - Aug 2016. Primary analyses based on patients alive and free of chronic rejection and malignant disease at 1 year in all groups. Regression models adjusted for potential confounders, including transplant center performance.

Results:
9,019 patients, median age 57, 57.6% men. When compared to MMF plus tacrolimus, sirolimus plus tacrolimus was associated with:

- **better survival** (median 8.9 vs 7.1 years)
- **lower chronic rejection incidence** (aHR, 0.75; 95% CI, 0.61-0.92; P = .005)
- **lower mortality after chronic rejection** (aHR, 0.52; 95% CI, 0.31-0.81; P = .009)

The induction-maintenance combination with the highest survival was sirolimus plus tacrolimus without induction therapy

Figure 1. Survival for Sirolimus vs Mycophenolate Mofetil (MMF) and Other Standard Therapies

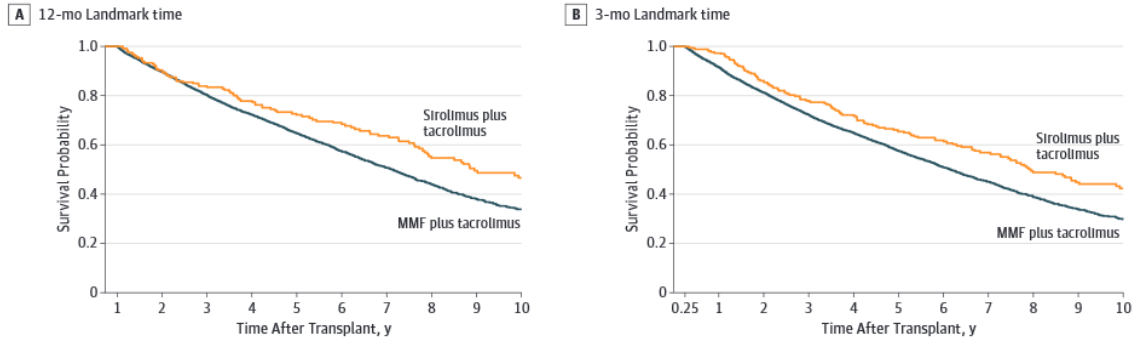
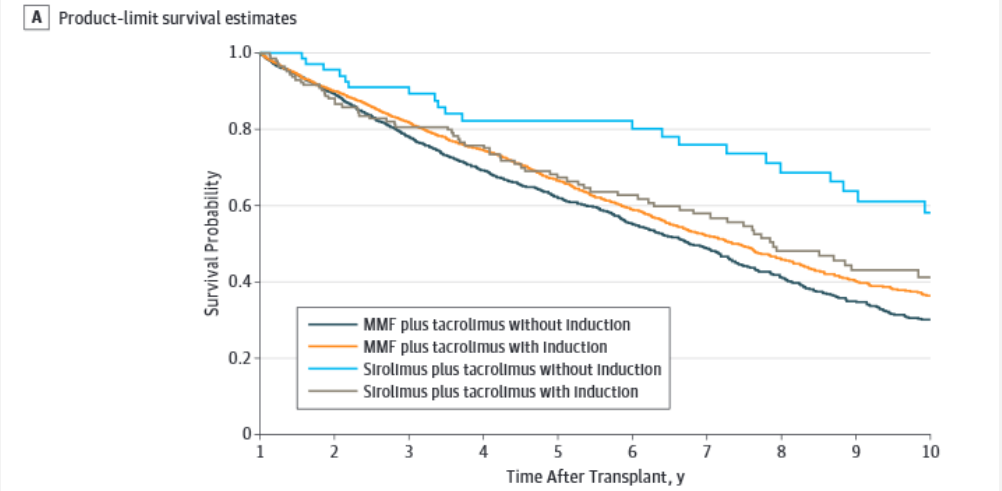


Figure 3. Survival for Sirolimus vs Mycophenolate Mofetil (MMF), With or Without Induction Therapy



REVIEWER'S COMMENTS

Strengths:

- Large number of patients
- Looks at long term survival
- Sirolimus group consisted of patients from more than 30 centers
- Adjusts for many co-variates

Limitations:

- Retrospective, non-randomized
- Some confounding is possible regarding why sirolimus was initiated at centers who contributed small numbers of patients

Questions raised:

- Is there a safe and effective immunosuppression regimen that allows avoidance of induction immunosuppression?
- What is the optimal dosing of sirolimus?
- ? Harm of MMF