Histologic Acute Graft Pyelonephritis after Renal Transplant: Risk Factors and Outcomes

Harry Ross Powers MD[1], Cherise Cortese MD[2], Mohamed Elrefaei MD PhD[2], Samir Khouzam MD[2], Hani Wadei MD[3], Zhuo Li MS[4] and Walter Hellinger MD[1]
Division of Infectious Diseases[1], Division of Laboratory Medicine and Pathology[2], Division of Transplant Medicine[3], Division of Biomedical Statistics and Informatics[4]
Mayo Clinic, Jacksonville, Florida

Mayo Clinic
4500 San Pablo Road
Jacksonville, FL 32224
Tel: 904-953-2000
Fax: 904-953-0655
Powers.harry@mayo.edu

Background

- Histological acute graft pyelonephritis (HAGPN) is an infrequently reported complication of renal transplantation[1,2,3]
- Risk factors and outcomes have not been identified.
- We previously identified 46 cases of HAGPN out of 1391 renal transplants from 2008 to 2017 giving an incidence of 5% [4]
- Indications for the biopsies that led to identification of HAGPN were: assessment of treated rejection (19, 40%), center specific kidney transplant protocol (19, 41%) and acute kidney injury (7, 15%)
- At time of HAGPN diagnosis, 46 % had negative urine cultures, and 50% had concurrent histologic rejection

Objectives

- Establish risk factors for development of HAGPN
- Evaluate outcomes of patients diagnosed with HAGPN

Methods

- Patients with HAGPN were previously identified from cohort of renal transplants from 2008 to 2017
- Of the renal transplants at MCF from 2008 to 2017 that did not develop HAGPN, 3 non-HAGPN cases were selected by a random number generator for each HAGPN case
- All patients underwent protocol renal biopsies as well as biopsies for unexplained rise in serum creatinine and to follow up treated rejection
- Patient, donor, operative, and post-transplant characteristics were obtained through review of electronic health records
- Univariable Cox regression models were used to identified significant risk factors for development of HAGPN.
- Multivariate analysis was done by creating a base model with 3 factors that were based on clinical and statistical significance. Then other risk factors for HAGPN were added one at a time
- The association of graft loss and death with HAGPN was evaluated using Cox regression model

Table 1: Association of Patient, Donor, Operative and Post-Transplant Characteristics with HAGPN in Univariable Cox Proportional-Hazards Models

Characteristics	Hazard Ratio	P-value
Age at transplant	1.01 (1.00, 1.02)	0.19
Recipient gender		
Female	1.00 (reference)	N/A
Male	1.11 (0.78, 1.57)	0.58
Etiology of ESRD		
HTN	1.00 (reference)	N/A
DM	1.53 (0.89, 2.61)	0.12
Other	1.24 (0.77, 2.00)	0.39
DM at transplant		
No	1.00 (reference)	N/A
Yes	1.52 (1.07, 2.16)	**0.020**
Transplant type		
Deceased	1.00 (reference)	N/A
Living related	0.25 (0.10, 0.62)	**0.003**
Living unrelated	0.39 (0.18, 0.84)	**0.016**
Kidney transplant number		
1	1.00 (reference)	N/A
≥2	0.83 (0.20, 3.34)	0.79
Transplant operative time (1 hour)	1.11 (1.03, 1.19)	**0.004**
Donor gender		
Female	1.00 (reference)	N/A
Male	1.07 (0.75, 1.53)	0.70
Donor age	0.99 (0.98, 1.00)	0.23
CMV match		
D-/R-	1.00 (reference)	N/A
D-/R+	1.16 (0.60, 2.26)	0.65
D+/R-	0.55 (0.27, 1.10)	0.092
D+/R+	1.02 (0.55, 1.89)	0.96
A/B/DR		
≥4	1.00 (reference)	N/A
<4	3.74 (1.19, 11.76)	**0.024**
Multi-organ transplant		
No	1.00 (reference)	N/A
Yes	0.99 (0.53, 1.83)	0.97
Induction immunosupression		
ATG	1.00 (reference)	N/A
Alemtuzumab	0.67 (0.42, 1.06)	0.087
Basiliximab	1.59 (1.05, 2.42)	**0.029**
Ureteral stent placed at transplant		
No	1.00 (reference)	N/A
Yes	0.61 (0.43, 0.88)	**0.008**
Dialysis w/in 7 days after transplant		
No	1.00 (reference)	N/A
Yes	2.10 (1.47, 3.00)	**<0.001**
Cold ischemic time (hours)	1.04 (1.02, 1.06)	**0.001**
cPRA	1.11 (0.65, 1.90)	0.70
Time-dependent covariates		
Urological malformation by day 30		
No	1.00 (reference)	N/A
Yes	5.34 (2.85, 10.02)	**<0.001**
Acute rejection after transplant		
No	1.00 (reference)	N/A
Yes	10.82 (5.66, 20.72)	**<0.001**
UTI after transplant		
No	1.00 (reference)	N/A
Yes	4.38 (2.30, 8.34)	**<0.001**
ASB after transsplant		
No	1.00 (reference)	N/A
Yes	3.39 (1.80, 6.41)	**<0.001**
UTI or ASB after transplant		
No	1.00 (reference)	N/A
Yes	6.28 (3.43, 11.50)	**<0.001**
CMV diseasee after transplant		
No	1.00 (reference)	N/A
Yes	2.55 (0.59, 11.00)	0.21

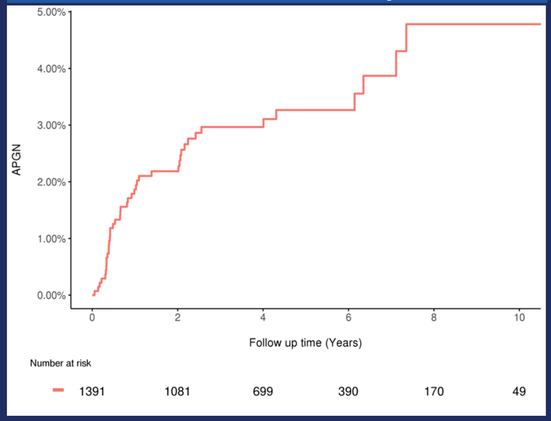
Table 2: Multivariate Models Adjusting for Urological Malformation w/in 30 days Post-transplant, Rejection after Transplant and UTI or ASB after Transplant

Characteristics	Hazard Ratio	P-value
Urological malformation	4.99 (2.40, 10.36)	**<0.001**
Acute rejection after transplant	13.14 (6.44, 26.79)	**<0.001**
UTI or ASB after transplant	3.69 (1.91, 7.14)	**<0.001**
DM at transplant	2.44 (1.29, 4.63)	**0.006**
Urological malformation by day 30 after transplant	4.56 (2.30, 9.08)	**<0.001**
Acute rejection after transplant	12.35 (6.18, 24.67)	**<0.001**
UTI or ASB after transplant	3.38 (1.77, 6.47)	**<0.001**
Transplant type		
Living related vs deceased	0.18 (0.04, 0.78)	**0.021**
Living unrelated vs deceased	0.55 (0.19, 1.58)	0.27
Urological malformation by day 30 after transplant	3.54 (1.73, 7.25)	**<0.001**
Acute rejection after transplant	11.34 (5.53, 23.23)	**<0.001**
UTI or ASB after transplant	3.77 (1.88, 7.55)	**<0.001**
Transplant operative time (1 hour)	0.99 (0.86, 1.14)	0.9
Urological malformation by day 30 after transplant	3.50 (1.78, 6.89)	**<0.001**
Acute rejection after transplant	11.77 (5.84, 23.73)	**<0.001**
UTI or ASB after transplant	3.63 (1.90, 6.97)	**<0.001**
Cold ischemic time (hours)	1.04 (1.00, 1.08)	**0.041**
Urological malformation by day 30 after transplant	3.36 (1.72, 6.58)	**<0.001**
Acute rejection after transplant	11.62 (5.77, 23.41)	**<0.001**
UTI or ASB after transplant	4.33 (2.23, 8.40)	**<0.001**
Ureteral stent placed at transplant	0.48 (0.26, 0.89)	**0.02**
Urological malformation by day 30 after transplant	3.59 (1.82, 7.10)	**<0.001**
Acute rejection after transplant	11.28 (5.59, 22.76)	**<0.001**
UTI or ASB after transplant	3.74 (1.92, 7.30)	**<0.001**
A/B/DR < 4	0.92 (0.21, 3.97)	0.91
Urological malformation by day 30 after transplant	3.88 (1.88, 8.01)	**<0.001**
Acute rejection after transplant	12.28 (6.04, 24.95)	**<0.001**
UTI or ASB after transplant	2.94 (1.43, 6.07)	**0.003**
Induction immunosupression		
Alemtuzumab vs ATG	0.71 (0.32, 1.60)	0.41
Basiliximab vs ATG	1.49 (0.74, 3.00)	0.26
Urological malformation by day 30 after transplant	5.23 (2.51, 10.91)	**<0.001**
Acute rejection after transplant	13.25 (6.36, 27.60)	**<0.001**
UTI or ASB after transplant	3.87 (1.99, 7.55)	**<0.001**
Dialysis w/in 7 days after transplant	4.07 (2.05, 8.08)	**<0.001**

Table 3: Univariable Cox Proportional-Hazards models for Death and Graft failure

	Death		Graft failure	
	HR (95% CI)	P-value	HR (95% CI)	P-value
AGPN	17.04 (7.39, 39.31)	**<0.001**	3.77 (1.73, 8.20)	**<0.001**

Figure 1: Cumulative Incidence of HAGPN in Renal Transplants



Discussion

- In univariable analysis, diabetes mellitus, HLA mismatch, transplant operative time, lack of ureteral stent placed at transplant, deceased donor transplant, cold ischemic time, basiliximab induction, delayed graft function, urologic dysfunction by day 30, bacteriuria, and acute rejection were identified as risk factors for HAGPN
- In multivariate analysis, urologic dysfunction by day 30, bacteriuria, and acute rejection remained significantly associated with HAGPN
- When adjusted for above, lack of ureteral stent placed at transplant, deceased donor transplant, cold ischemic time, and delayed graft function remained associated with HAGPN
- Adjustment of the association of HAGPN with the increased risk of graft failure and death was beyond the scope of the current investigation

Conclusion

- HAGPN is an infrequent, unanticipated complication of renal transplantation
- It identifies patients at increased risk of graft loss and death
- Optimal management strategies need to be identified
- Prevention of dysfunction of the urine collecting system and placement of ureteral stent at transplant could mitigate the development of HAGPN
- Patients with risk factors for HAGPN deserve close clinical monitoring and possibly low threshold for renal biopsy

References

1. Gregg K et al. Asymptomatic acute transplant pyelonephritis: A single-center experience. Am J Transplant 2013. 13 (5)
2. Varma P, J.A., Hooda A, Badwal S, Renal outcome in biopsy proven cases of graft pyelonephritis. Indian J Nephrol, 2014. 24(3): p. 161-165.
3. Idrees MK, S.S., Ali T, Rehman IU, Akhtar SF, Biopsy-proven acute graft pyelonephritis: A retrospective study from sindh institute of urology and transplantation. Saudi J Kidney Dis Transpl, 2020. 31(2): p. 415-422.
4. Powers et al. Retrospective Review of Biopsy Proven Acute Graft Pyelonephritis in Renal Transplant Patients. Open Forum Infectious Diseases. 2019; 6(Supplemental_2):S518