Washington University in St. Louis
SCHOOL OF MEDICINE

Pulmonary AMR – Therapeutic Options & Strategies: The Old and the New

Ramsey Hachem, MD

March 28, 2017

Disclosures

- Ramsey Hachem
- I have no financial relations with any relevant commercial interests
- I will discuss the “off-label” use of multiple treatments for pulmonary AMR

Introduction

- AMR is an increasingly recognized form of lung rejection
- Most common histology is non-specific lung injury – pneumonitis, DAD
- Diagnosis requires a high index of suspicion & multidisciplinary approach
- Outcomes after AMR remain disappointing

ISHLT Consensus Definition

Table 1 Definition and Diagnostic Certainty of Clinical Pulmonary Antibody-mediated Rejection

	Allograft dysfunction	Other causes excluded	Lung histology	Lung biopsy C4d	DSA
Definite	+	+	+	+	+
Probable[a]	+	+	+	–	+
Probable	+	+	+	+	–
Probable	+	+	–	+	+
Probable	+	–	+	+	+
Possible	+	+	+	–	–
Possible	+	+	–	–	+
Possible	+	+	–	+	–
Possible	+	–	+	+	–
Possible	+	–	+	–	+
Possible	+	–	–	+	+

DSA, donor-specific antibodies; +, item present; –, item absent or missing.

[a]There is building evidence that antibody-mediated rejection can be diagnosed confidently in the absence of positive C4d staining, hence this group is recognized separately.

Definition of “Definite AMR is stringent.

4 combinations of “Probable AMR”–

Not all equal in terms of diagnostic certainty between groups of Probable/Possible

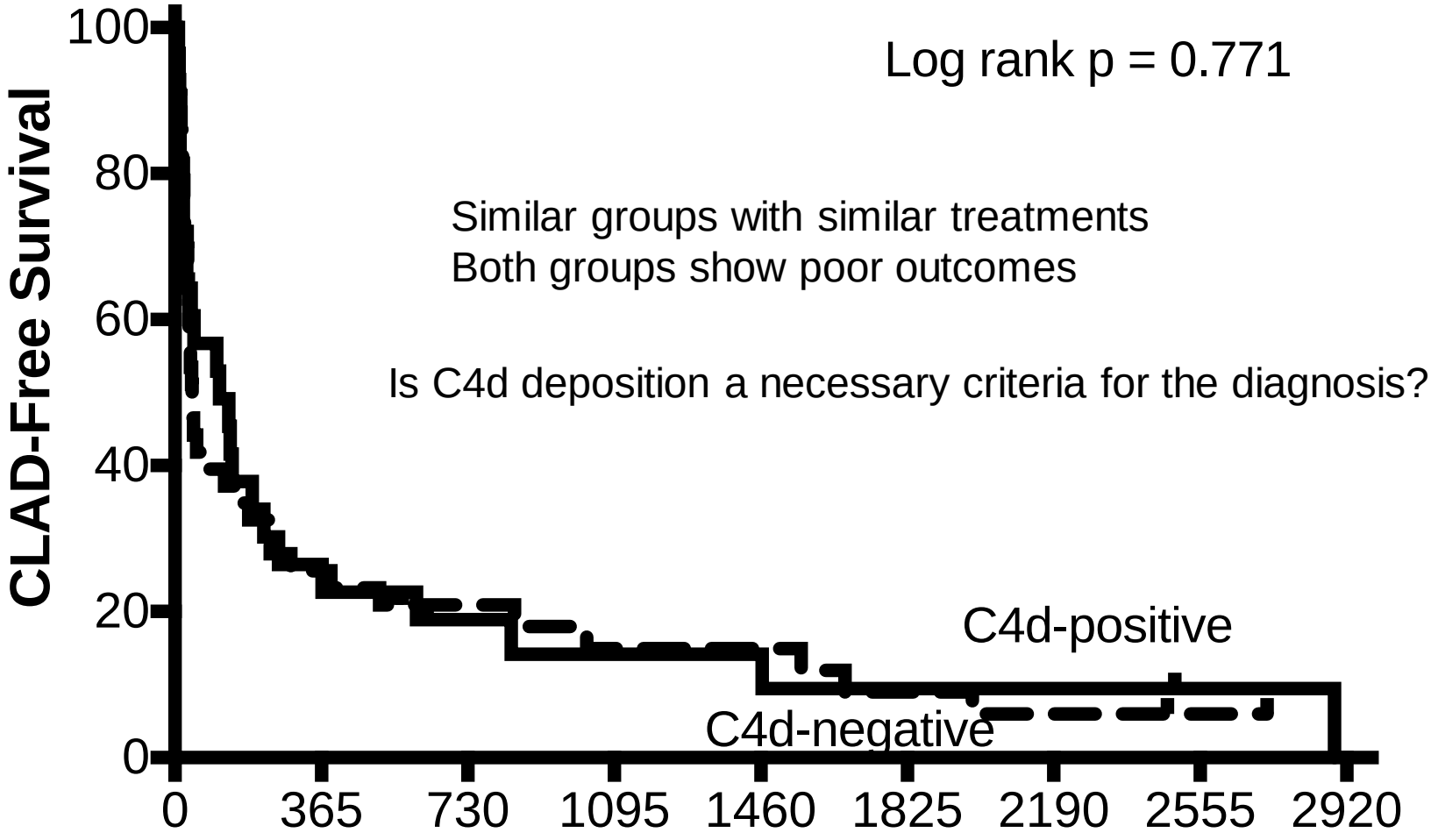
.

J Heart Lung Transplant 2016; 35: 397

Definite AMR & C4d-negative Probable AMR

Variable	C4d-positive (n = 28)	C4d-negative (n = 45)	p value
Time of onset of AMR, days	193	161	0.928
Hospitalized	23 (82%)	32 (73%)	0.359
Radiographic infiltrates	23 (82%)	36 (80%)	0.821
Mechanical ventilation	12 (43%)	16 (36%)	0.533
DSA class			0.504
Class I only	4 (14%)	3 (7%)	
Class II only	20 (71%)	33 (73%)	
Class I & II	4 (14%)	9 (20%)	
DSA to HLA-DQ	20 (71%)	36 (80%)	0.399
DSA MFI (mean ± SD)	8764 ± 4141	6839 ± 3993	0.130
C1q-positive DSA	12/12 (100%)	12/18 (67%)	0.025

CLAD-Free Survival



Log rank p = 0.771

Similar groups with similar treatments
Both groups show poor outcomes

Is C4d deposition a necessary criteria for the diagnosis?

Role of C4d in the Diagnosis

- C4d staining & interpretation problematic
  - ? Possible that these cases are false negatives
- Distinct pathways that cause AMR
  - Complement-independent pathways?
- Distinction may have therapeutic implications
  - If complement inhibitors are considered
- Further studies are necessary
  - Genomic analyses

Systemic Review
Treatment in Acute AMR in Kidney Transplantation

Reference	AMR definition	Design & intervention	Efficacy
Böhmig et al, 2007	Banff 1997	RCT; 9-14 IA	Significant benefit, rescue not effective
Bonomini et al, 1985	Vascular, steroid-resistant	RCT; 3-7 PLEX	Benefit, 7 vs. 17 at 2 wks
Blake et al, 1990	Vascular	RCT; 5 PLEX	No benefit
Kirubakaran et al, 1981	Vascular	RCT; 8 PLEX	Trend to harm
Allen et al, 1983	Vascular, steroid-resistant	RCT; 6 PLEX	No benefit

*None of these studies included IVIG/PLEX

Transplantation 2012; 94: 775
Am J Transplant 2014; 14: 255

Rituximab for Renal AMR

- 21 centers in France, RCT
  - Enrollment between 2008 – 2011
  - Rituximab vs. Placebo
    - In addition to PLEX, IVIG, CS
- 1 endpoint: graft loss or no improvement on d 12
- Additional doses of Rituximab on d 12 for insufficient efficacy

Transplantation 2016; 100: 391

Rituximab for Renal AMR

- 40 patients enrolled, 38 treated
- Placebo: n = 19, Rituximab: n = 19
- Placebo patients receiving rescue Rituximab, n = 8
- Rituximab patients receiving rescue Rituximab, n = 6
- No difference in primary endpoint
- No difference in graft loss at 1 year

Transplantation 2016; 100: 391

Principles of Treatment: Multiple interventions

- Deplete circulating DSA: does not suppress further production, may stimulate rebound
  - PLEX, immunoadsorption

- Suppress B-cells, plasma cells:
  - IVIG, Rituximab, Bortezomib, Carfilzomib
  - MMF, ATG: may be of benefit by downregulating B cell response by decreasing T-cell

- Mitigate antibody-mediated lung injury
  - Steroids, IVIG, Eculizumab

Literature on Treatment

- Imported treatment options: without appropriate clinical trials in AMR

- Dearth of data: No RCT or head-to-head comparison
- Multiple concurrent interventions

- Individualized regimens based on clinical course & response to "1st line" intervention

- Difficult to make conclusions about relative efficacy of any single intervention or regimen

- Standardizing definition of AMR is first step to allow multicenter trials or comparisons of regimens.

Treatment & Outcomes: Definite and probable AMR

- Lobo et al (CS, PLEX, RTX, IVIG, BOR):
  - 7/10 died (5 due to AMR, 2 due to sepsis after treatment)

- Otani et al (CS, PLEX, RTX, IVIG):
  - 5/9 initial clinical improvement and decreased MFI
    - 2/5 subsequent RAS & death (363, 610 d)
  - 4/9 progressive CLAD & death: no decrease in MFI
    - 2 progressive RAS & death (79, 180 d)
    - 2 progressive BOS & death (179, 288 d)

J Heart Lung Transplant 2013; 32: 70
Transpl Immunol 2014; 31: 75

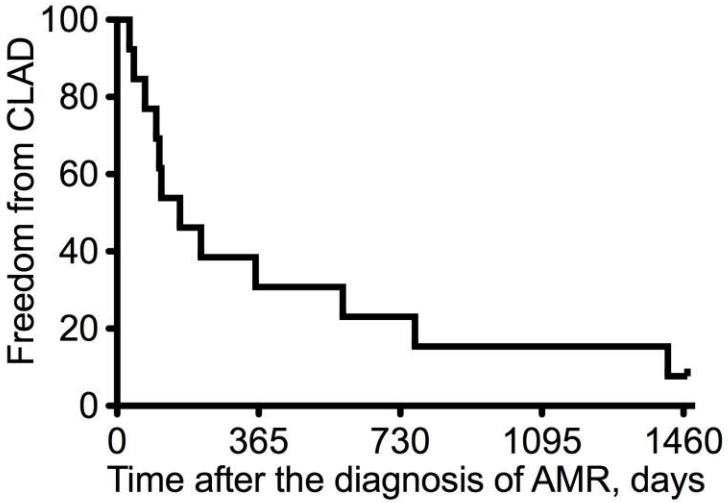
Wash U treatment approach: individualized regimen, based on severity of illness, clinical course and response to therapy. All patients met criteria for definite AMR

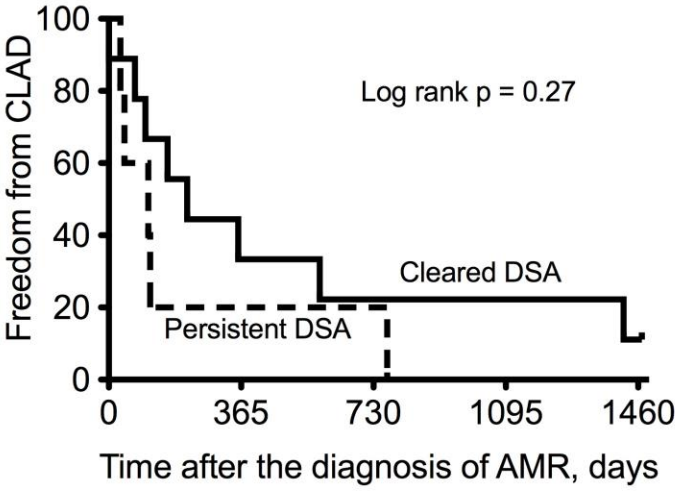
Patient	ATG	IVIg dose (number of doses)	Rituximab	Plasma exchange (number of treatments)	Bortezomib dose (number of doses)	Eculizumab	Survived to discharge
1	Yes[a]	None	—	Not done	—	—	Yes
2	—	1 g/kg (1)	375 mg/m^2	12	—	—	Yes
3	—	1 g/kg (1)	375 mg/m^2	Not done	—	—	Yes
4	—	1 g/kg (1)	375 mg/m^2	Not done	—	—	Yes
5	—	0.5 g/kg (2)	375 mg/m^2	10	—	—	No
6	—	0.5 g/kg (1)	375 mg/m^2	Not done	—	—	No
7	—	0.5 g/kg (1)	375 mg/m^2	5	—	—	Yes
8	—	0.5 g/kg (2)	375 mg/m^2	Not done	—	—	Yes
9	—	1 g/kg (1)	375 mg/m^2	Not done	—	—	Yes
10	—	0.5 g/kg (2)	375 mg/m^2	Not done	—	—	Yes
11	—	0.5 g/kg (1)	—	3	—	—	Yes
12	—	0.5 g/kg (1)	375 mg/m^2	Not done	—	—	Yes
13	—	0.5 g/kg (1)	375 mg/m^2	Not done	—	—	Yes
14	—	1 g/kg (1)	375 mg/m^2	Not done	—	—	No
15	—	0.5 g/kg (2)	—	Not done	—	—	Yes
16	—	0.5 g/kg (3)	375 mg/m^2	5	—	—	No
17	—	0.5 g/kg (1)	375 mg/m^2	Not done	—	—	Yes
18	—	1 g/kg (2)	375 mg/m^2	5	1.3 mg/m^2 (8)	—	Yes
19	—	0.5 g/kg (1)	375 mg/m^2	1	1.3 mg/m^2 (1)	—	No
20	—	0.5 g/kg(1) 1 g/kg (2)	375 mg/m^2	Not done	—	—	Yes
21	—	1 g/kg (3)	375 mg/m^2	5	1.3 mg/m^2 (4)	Yes[b]	No

J Heart Lung Transplant 2013; 32: 1034

CLAD after AMR with individualized therapy

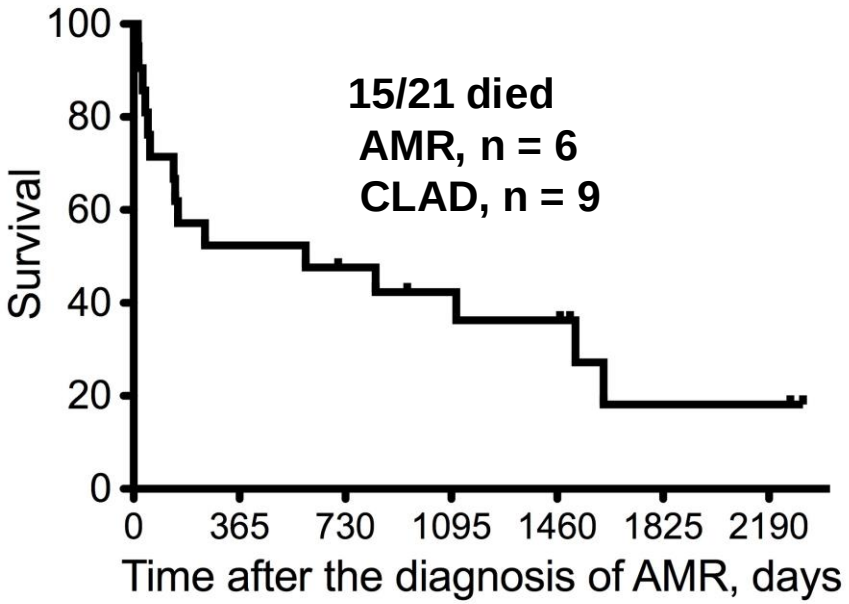
- 9/21 cleared DSA
  - All 9 who cleared DSA improved
- 15/21 initial improvement
- 6/21 died AMR
- 13/14 developed CLAD (median 114 d after AMR)

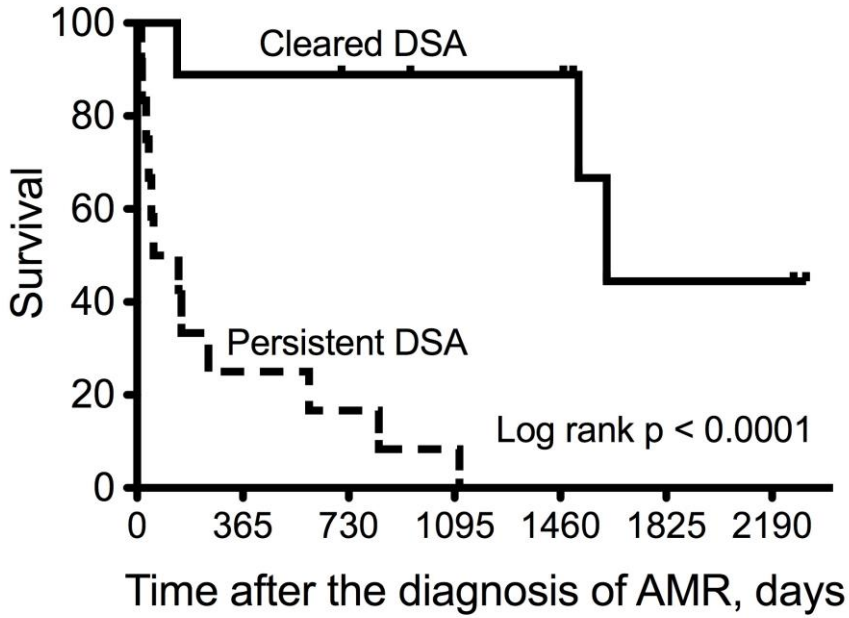




J Heart Lung Transplant 2013; 32: 1034

Survival after AMR

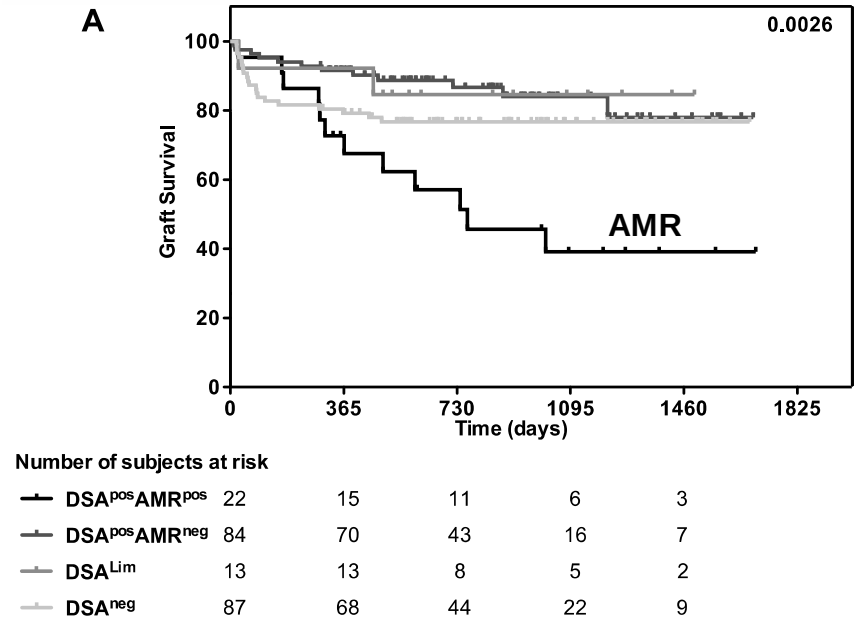


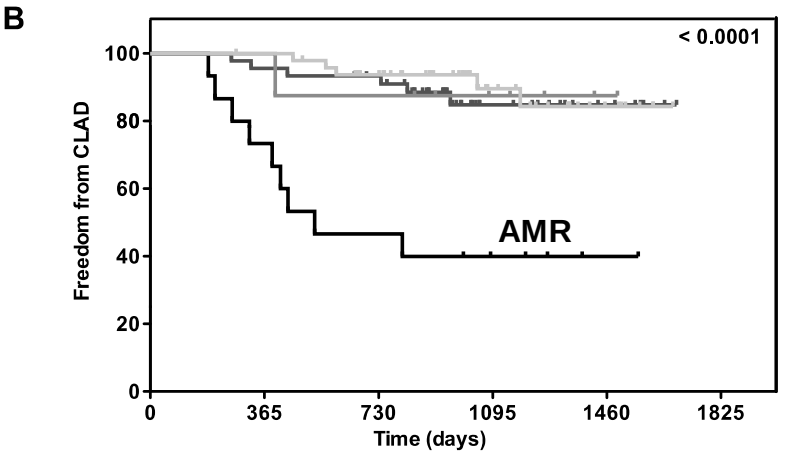


J Heart Lung Transplant 2013; 32: 1034

Treatment & Outcomes: Definite and Probable AMR

- 22 patient with definite & probable AMR
- PLEX + RTX + IVIG, n = 17
- PLEX alone, n = 3
- IVIG alone, n = 2
- DSA clearance associated with better survival
- DSA cleared in 8/10 who survived and 2/12 who died





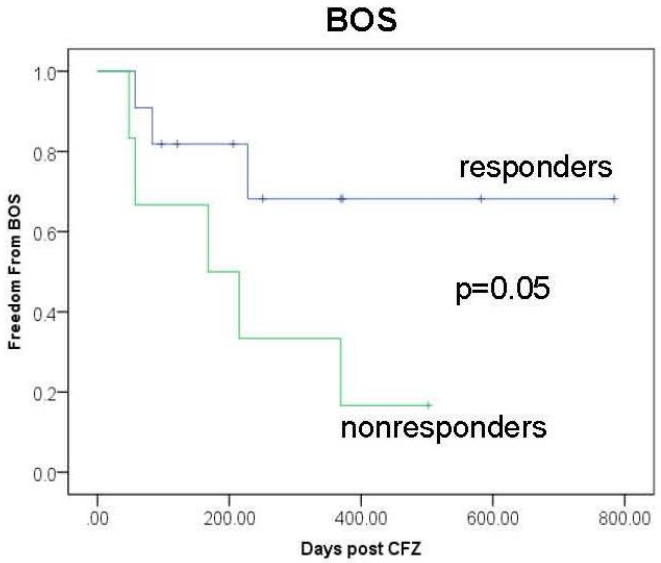
Roux , Am J Transplant 2016; 16: 1216

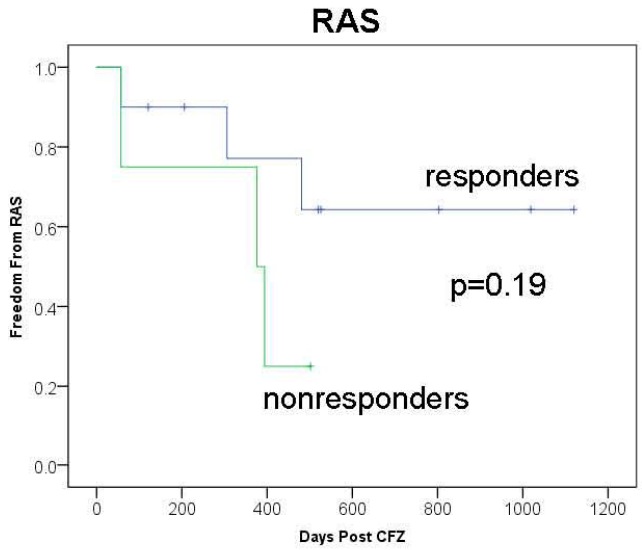
Carfilzomib: Definite, probable and possible AMR

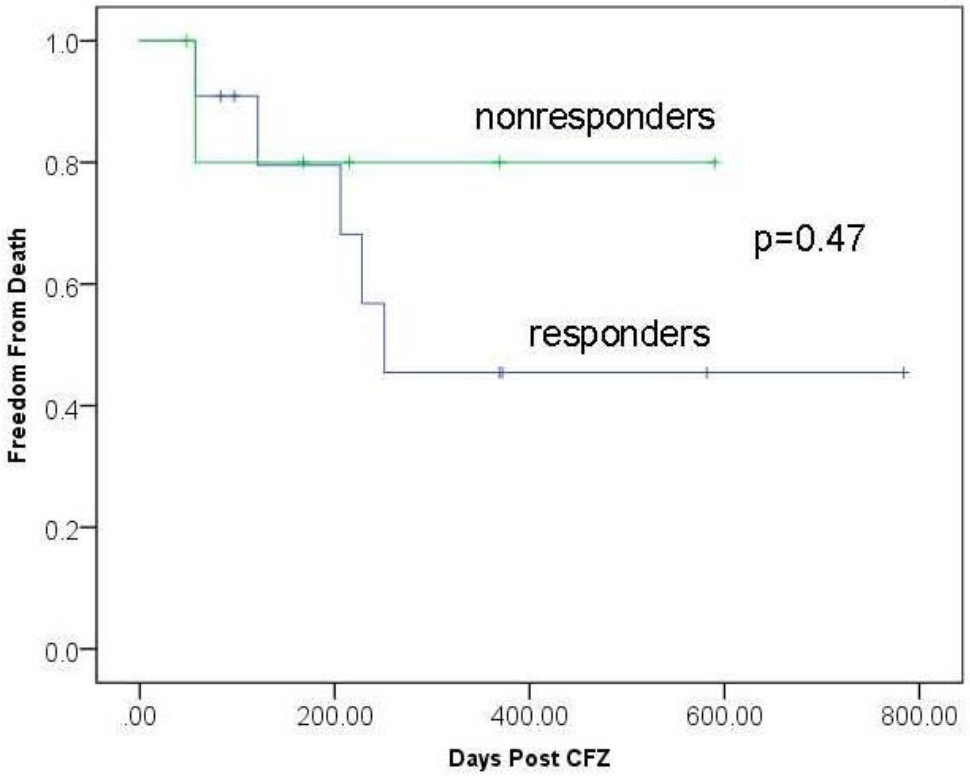
- 2nd generation proteasome inhibitor
- Binds irreversibly resulting in permanent inhibition & plasma cell apoptosis
- 14 patients with definite, probable, & possible AMR
- Carfilzomib + PLEX + IVIG
- Carfilzomib response: loss of C1q binding, n = 10

Am J Transplant 2017; In Press

Carfilzomib-based Therapy







Am J Transplant 2017; In Press

Eculizumab

- Monoclonal antibody to C5 inhibiting cleavage into C5a & C5b
- Case report of patient who could not be desensitized and developed hyperacute rejection
- Eculizumab with IVIG, Bortezomib, PLEX Rituximab
- Hyperacute rejection resolved
- Sustained clinical response 1 year after transplant
- Persistent DSA

J Heart Lung Transplant 2012; 31: 1325

Eculizumab “Resistance”

- Cases of renal AMR in spite of Eculizumab treatment
- Cases of renal AMR that don’t respond to Eculizumab
  - C4d-negative AMR
  - C1q-negative DSA
- Highlight complement-independent pathways of AMR

Transplantation 2014; 98: 1056
Am J Transplant 2011; 11: 2405

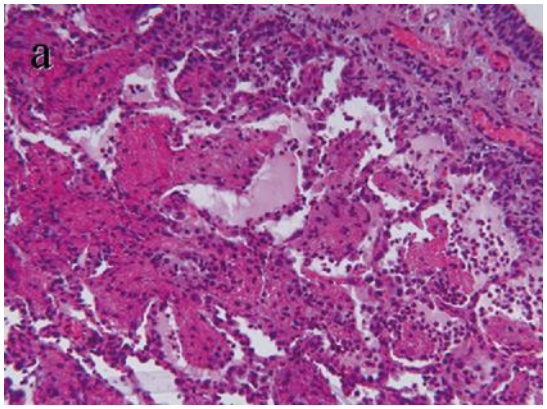
Better Diagnostics

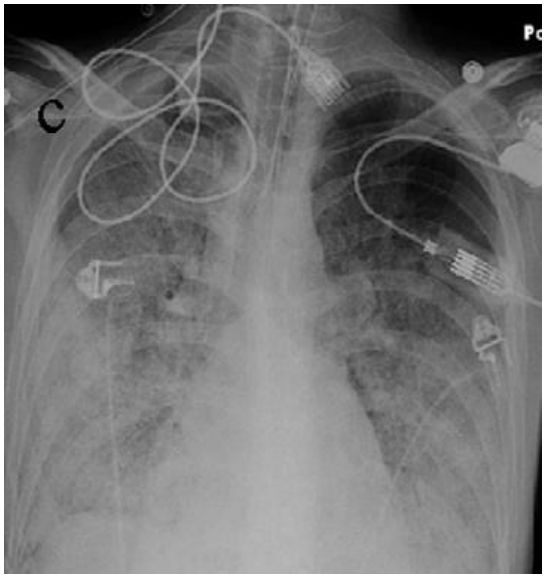
- Standardizing AMR definition is critical to ensure studies can be done.
- Current diagnostic criteria are crude: Nonspecific histologic changes, C4d issues, clinical mimics of graft dysfunction.
- Need for better precision to improve treatment decisions
- Transcriptome analysis/gene microarray
  - Effective in identifying AMR in kidney & highlighted C4d negative AMR
  - Endothelial genes, NK cells, IFN-γ
- INTERLUNG study: development of molecular microscope diagnostic report in lung

Am J Transplant 2009; 9: 2312
Am J Transplant 2013; 13: 971
Curr Opin Organ Transplant 2015; 20: 359

Exceptional Outcomes

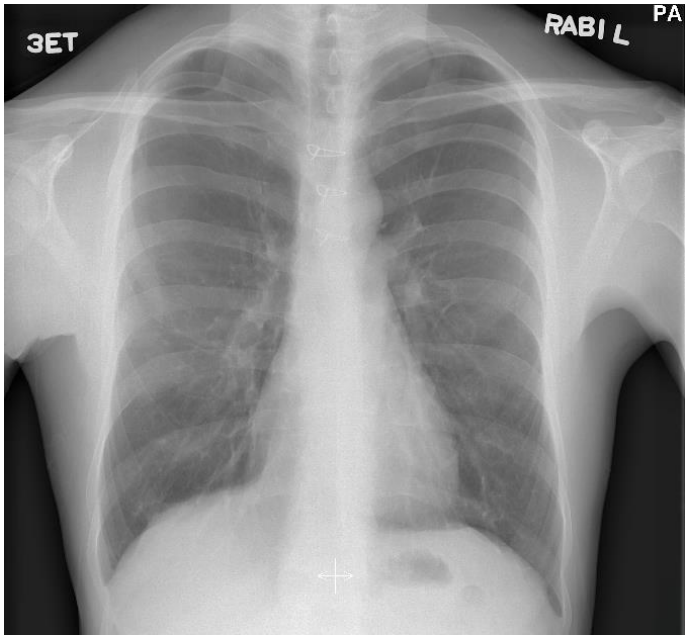
3/3/2008





Respiratory failure
Definite AMR
Treated with CS, PLEX, IVIG, RTX

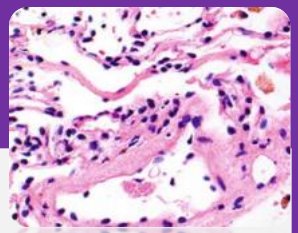
2/22/2017
FVC = 5.5 L (102%)
FEV_1 = 4.32 L (101%)



J Heart Lung Transplant 2009; 28: 96

2 Lung Transplant Recipients with + DSA

Ms. 1

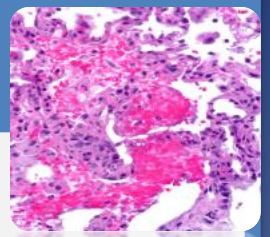


Post transplant course

- *PFTs: Progressive improvement and stabilization*
- Clinically stable, active
- Complications:
  - History of pneumonia post operatively. Resolved.
  - History of Grade 2 ACR at 6 months out. Negative C4d. Resolved. *Recent biopsy negative.*
  - *New screening DSA at 3 years: DQ5 mild, DQ 6 strong C1q negative*

Possible Subclinical AMR

Ms. 2



Post transplant course

- Did well clinically over the first year. *Progressively more dyspneic.*
- Complications:
  - *Drop in FEV1 by 18% at 20 months with continued progressive decline.*
  - *Biopsy negative for ACR or infection. + ALI, fibrin exudates, cappillaritis. Negative C4d*
  - *New DSA at 18 months : DQ7 strong, DQ 5 moderate A-2 moderate C1q negative*

Probable Clinical AMR

Question

Would you treat either of these patients for Pulmonary AMR?

1. Ms. 1
2. Ms. 2
3. Both
4. Neither

Questions regarding treatment

- **Who do we treat?**
  - Definite, probable, possible?
  - Based on risk factors of the recipient?
  - Consider adverse effects?
- **When do we treat?**
  - Asymptomatic or wait for symptoms?
  - “Prophylaxis”?
  - Only with graft dysfunction?
- **How do we treat?**
  - Do we treat all antibodies the same?
  - How many courses/cycles of treatment is appropriate
  - What therapies are best?
- **What are our goals of therapy?**
  - decreased ab titers, improved graft fxn, freedom from CLAD

Conclusions

- Insufficient evidence to guide treatment
- Optimal treatment is unknown
- AMR reversible cause of graft failure
- High incidence of subsequent CLAD
- Poor allograft survival
- Standardized definition facilitates research
- RCTs comparing existing treatments & doses