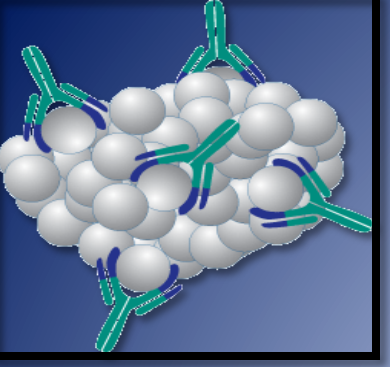
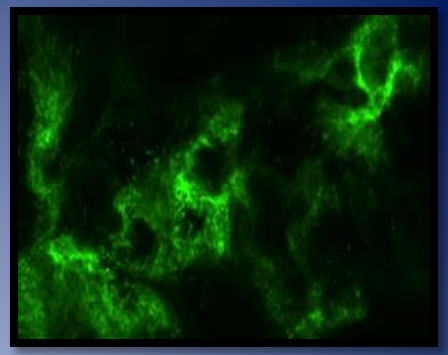
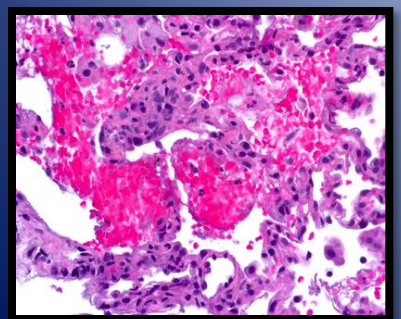


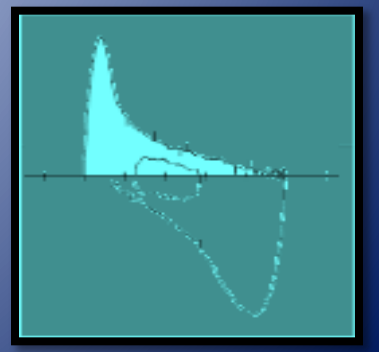


The multidisciplinary approach to AMR in lung transplantation:

Reaching a consensus

Deborah Jo Levine
Professor of Medicine
University of Texas





Disclosures

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

2 Lung Transplant Recipients

Ms. 1

Age: 62 years

History:

- COPD
- 4 years post bilateral lung transplant
- CMV mismatch
- No PGD
- PRA: 10%/No DSA

Ms. 2

Age: 62 years

History:

- COPD
- 2 years post bilateral lung transplant
- CMV mismatch
- No PGD
- PRA: 0%/No DSA

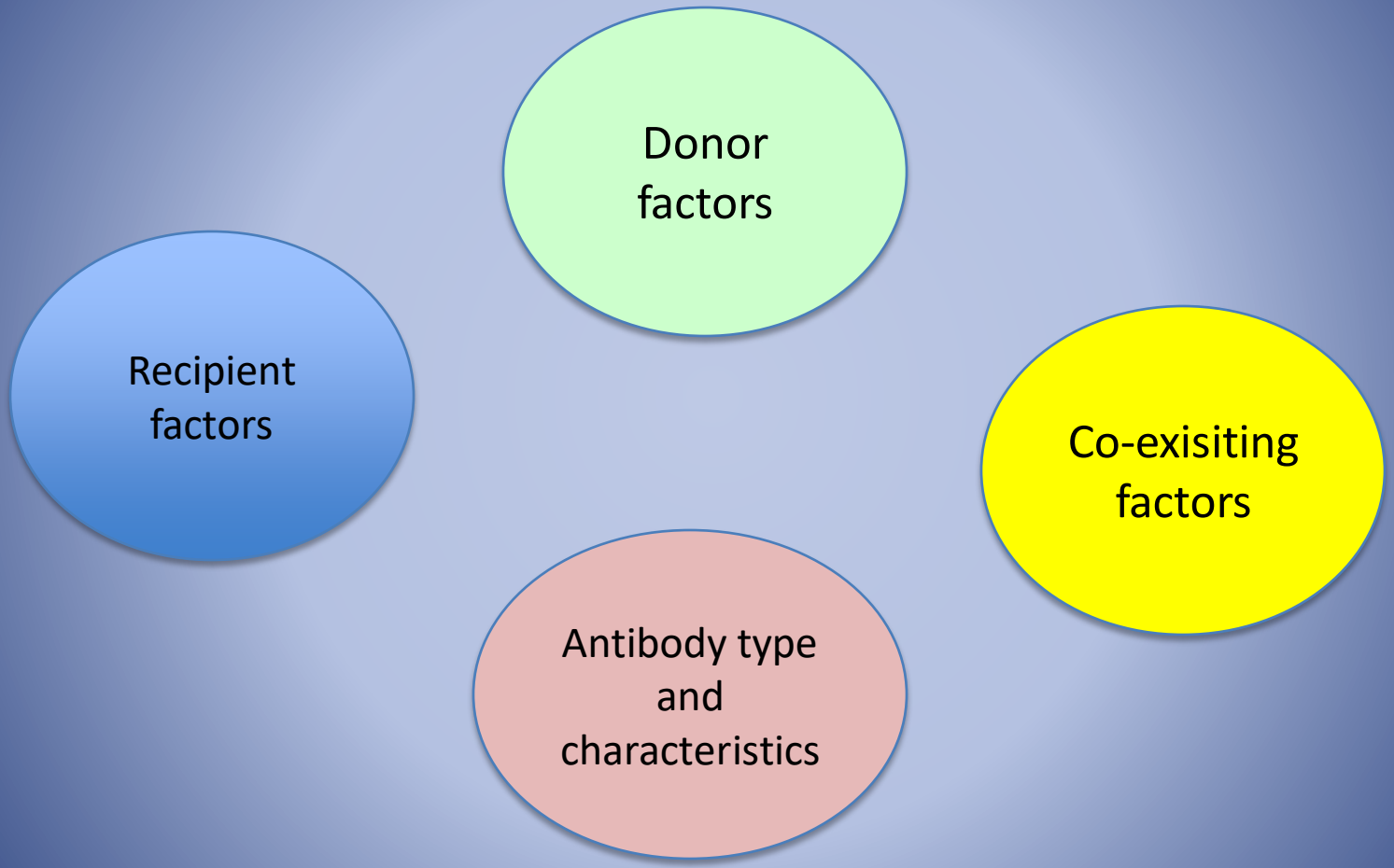
Question

- Do either or both of these patients have AMR?

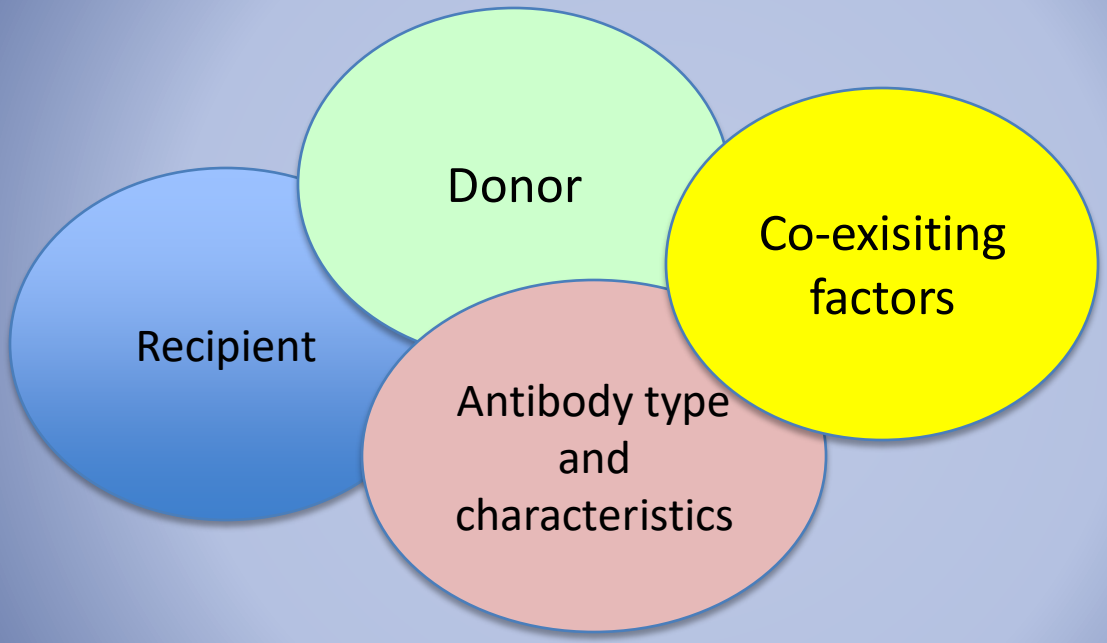
1. Neither
2. Ms. 1
3. Ms. 2
4. Both

In your experience, what is the definition of pulmonary AMR?

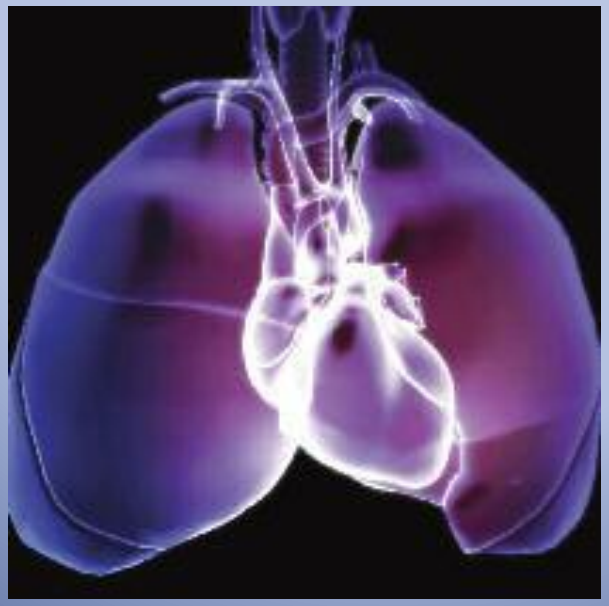
Why are these two patients with DSA experiencing such a dramatically different clinical course ?



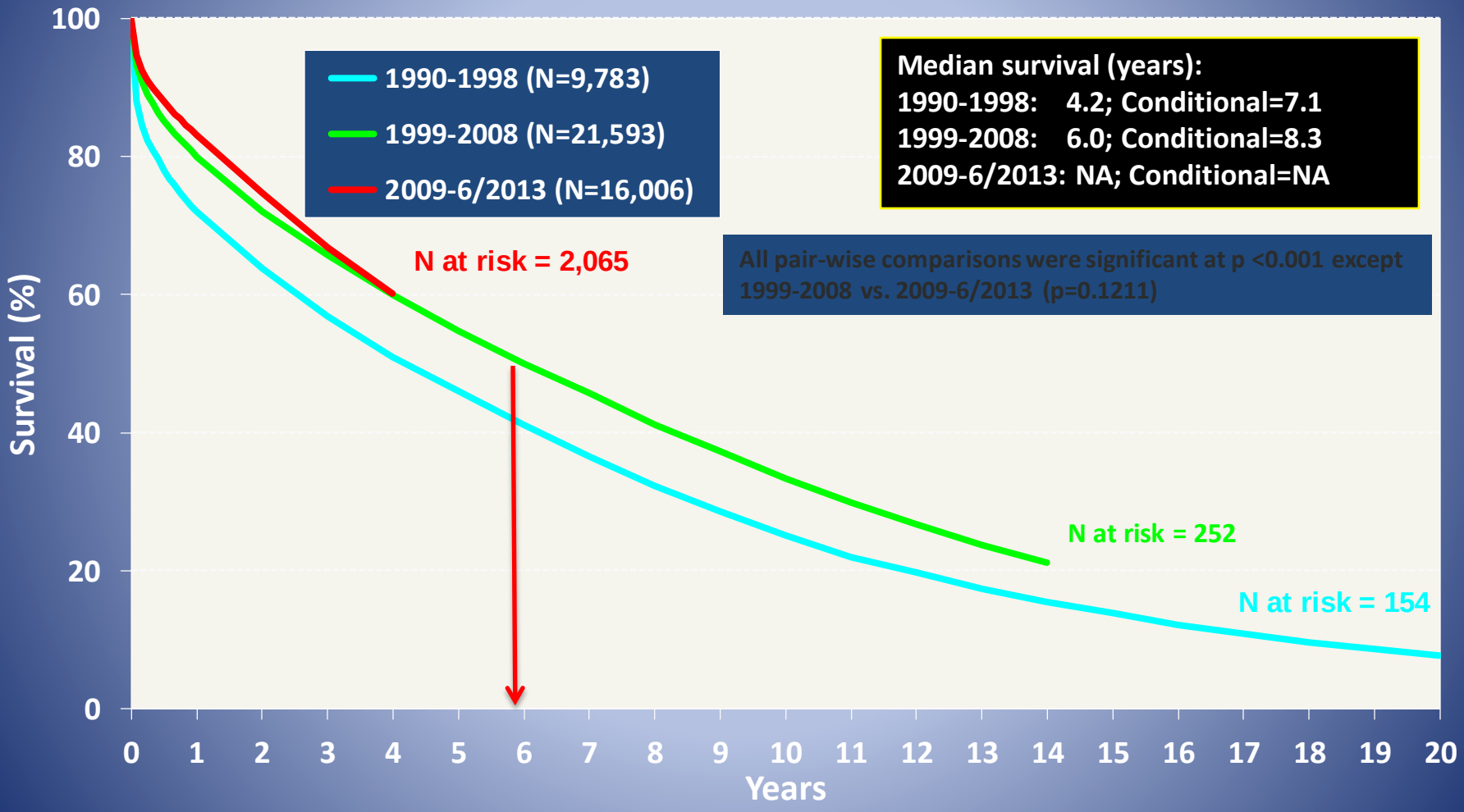
Multifactorial?



Lung Transplantation (LT) continues to be the best therapy for end-stage lung disease for which other medical or surgical therapy is not available.



Adult Lung Transplants
Survival by Era
(Transplants: January 1990 – June 2013)



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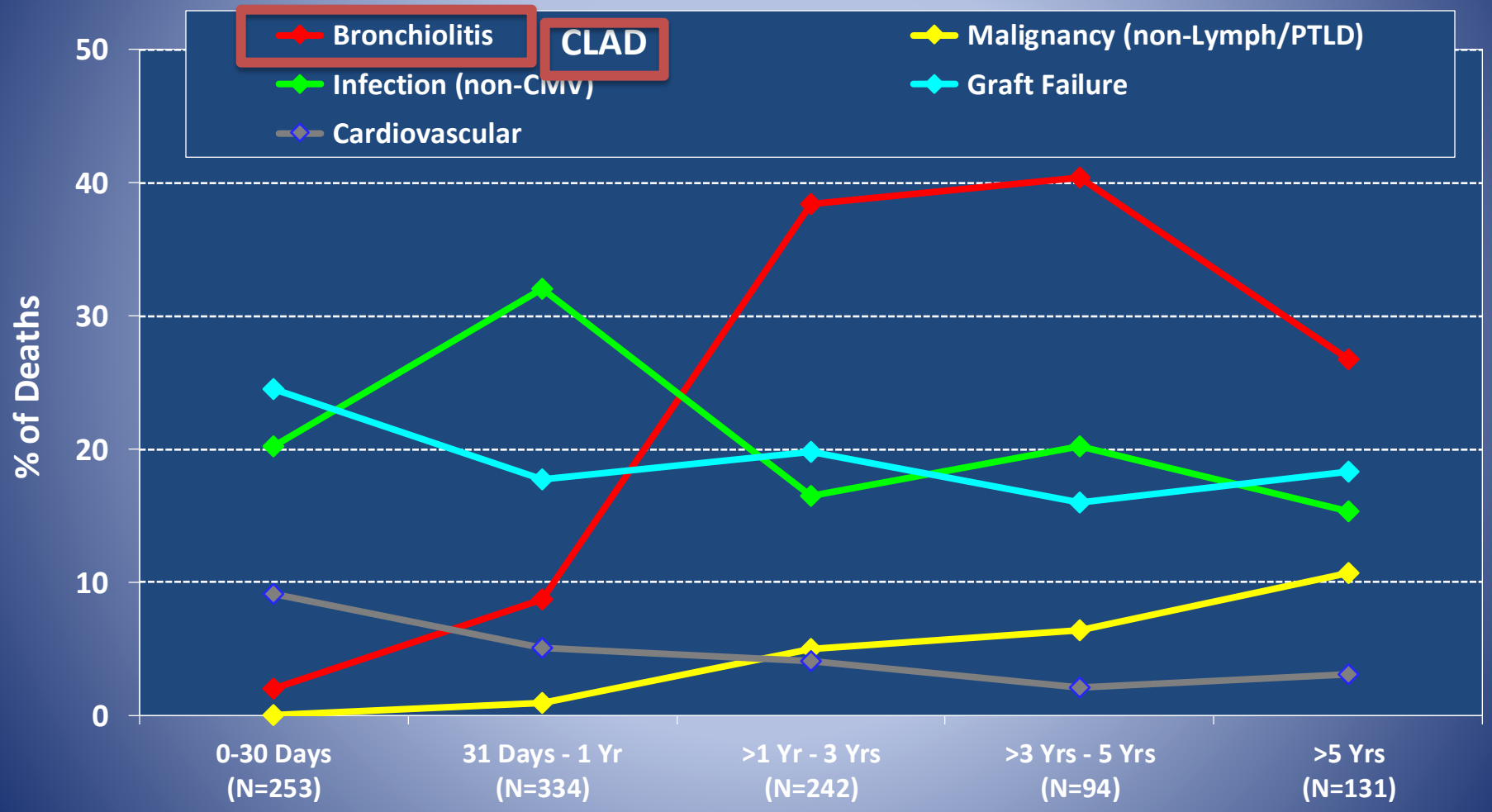
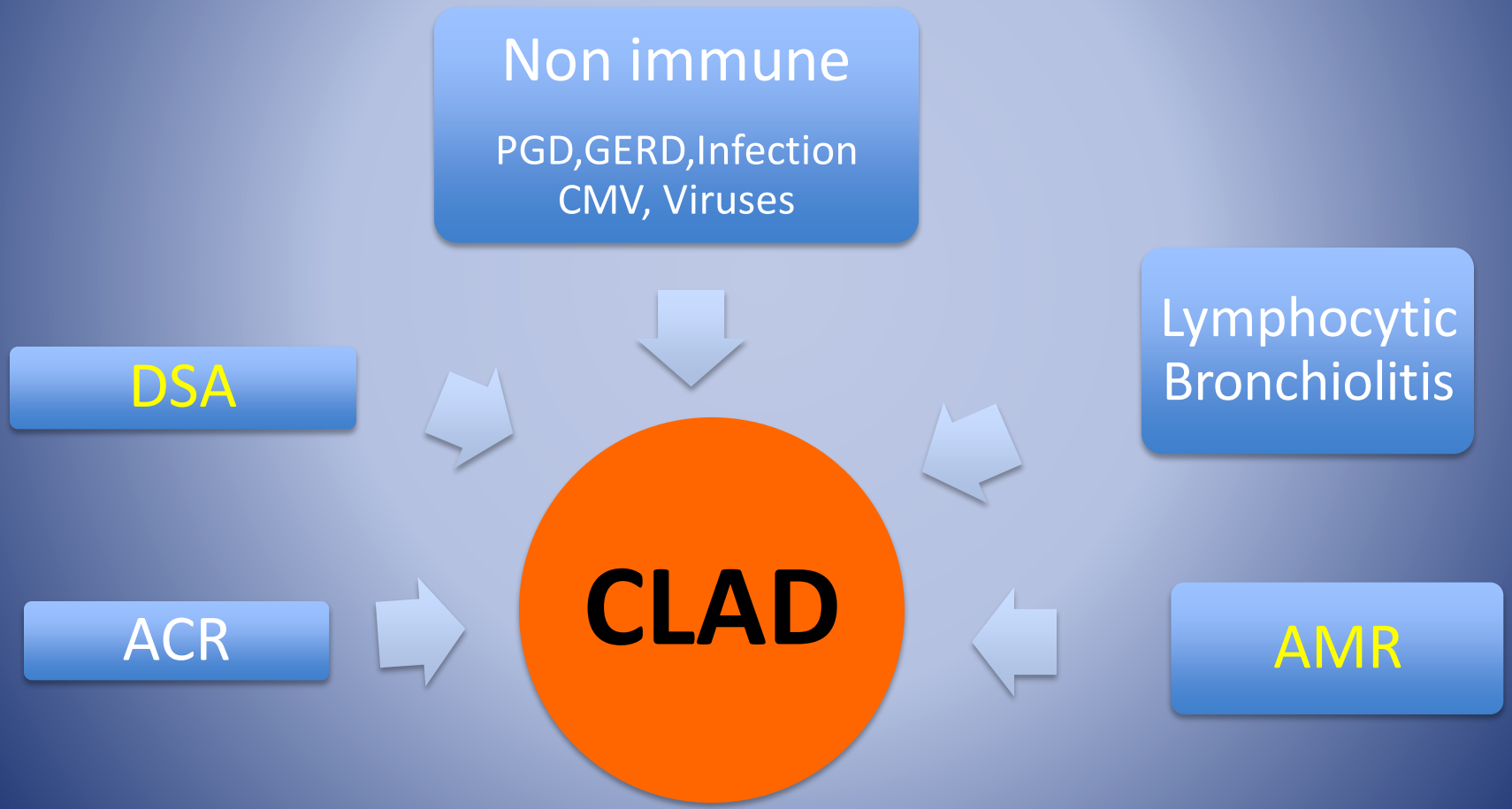
Adult Lung Transplants
Relative Incidence of Leading Causes of Death
(Deaths: January 1990 – June 2014)

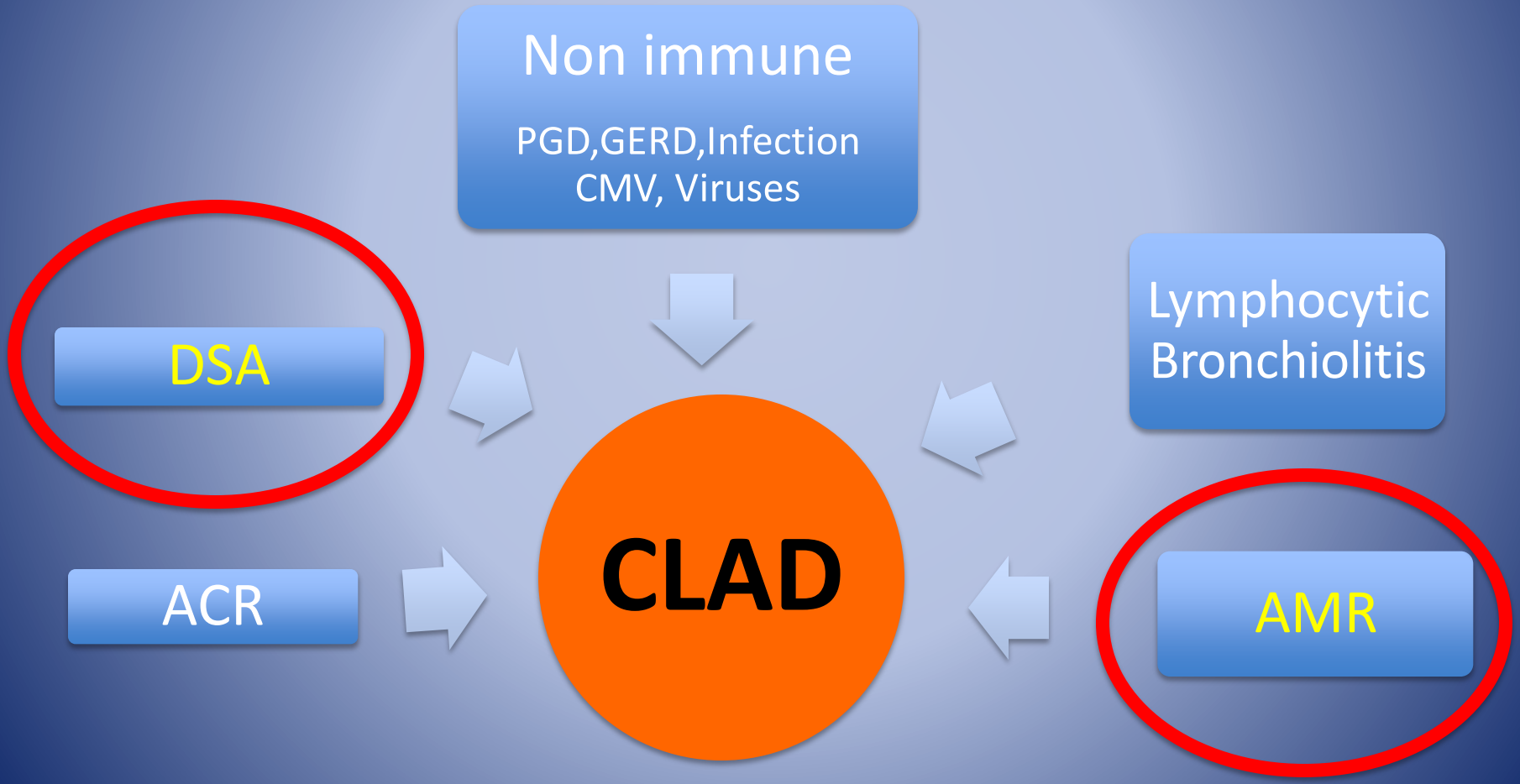


ISHLT • INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION
2015
JHLT. 2015 Oct; 34(10): 1264-1277

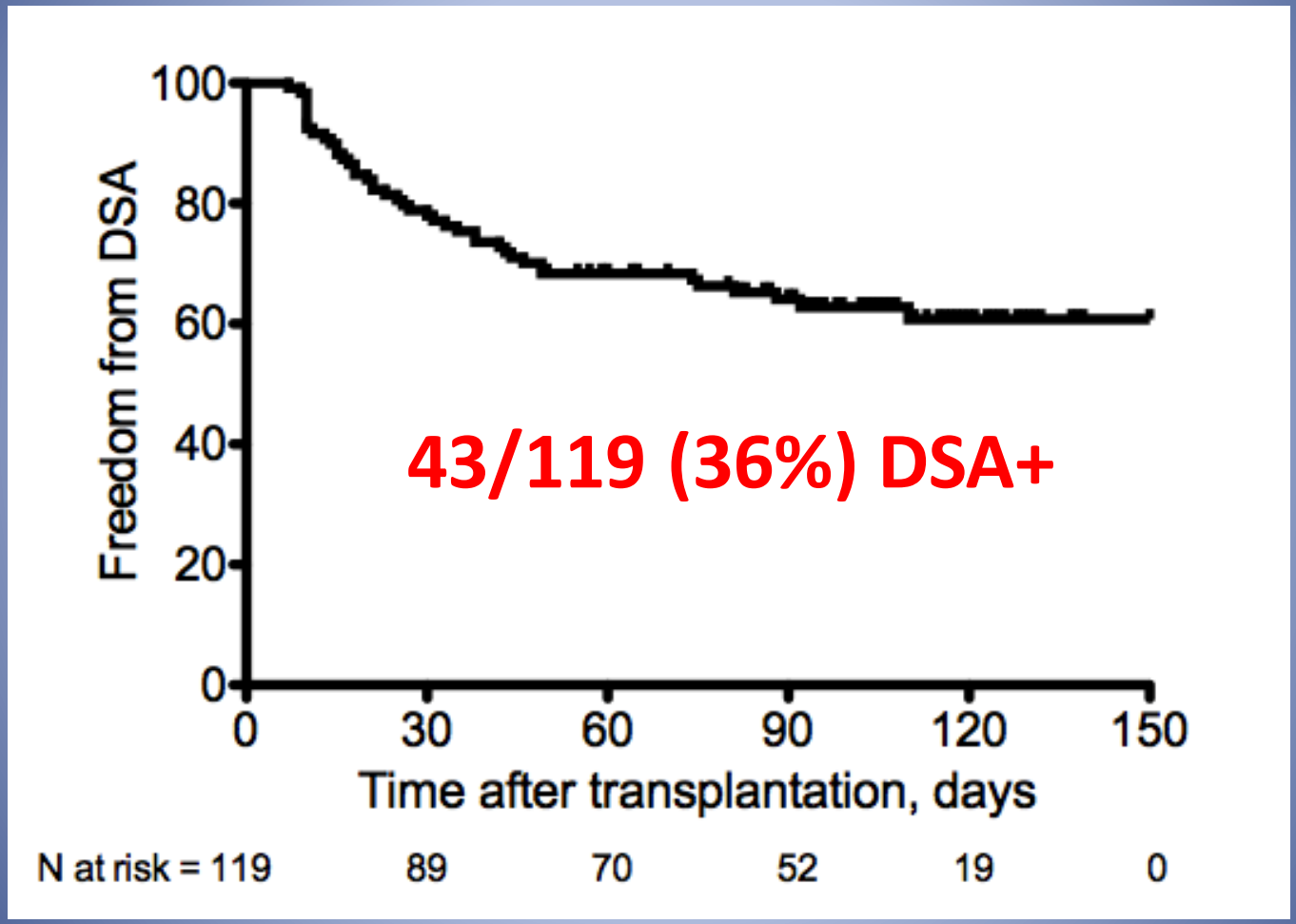
Risk Factors of Chronic Lung Allograft Dysfunction (CLAD)



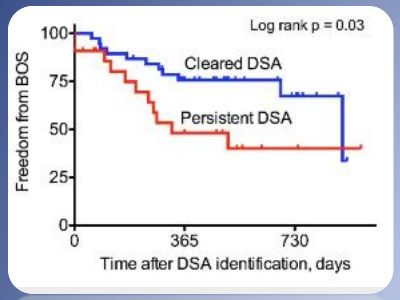
Risk Factors of Chronic Lung Allograft Dysfunction (CLAD)

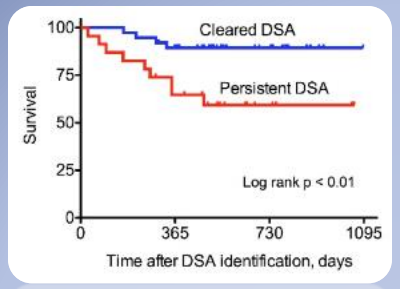


Incidence of DSA – HALT Study

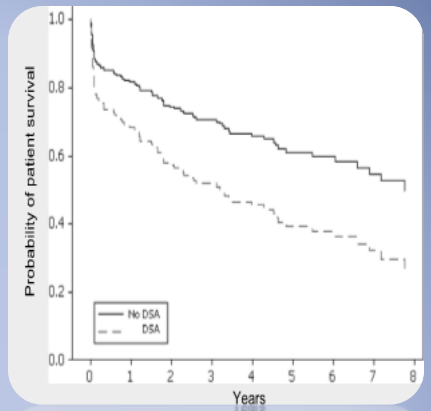


Impact of DSA on short and long-term outcomes

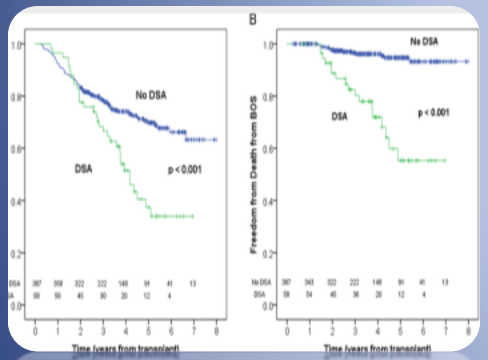




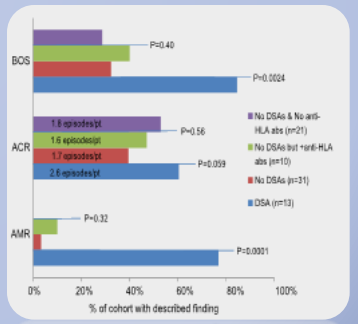
Hachem JHLT 2010; 29: 973



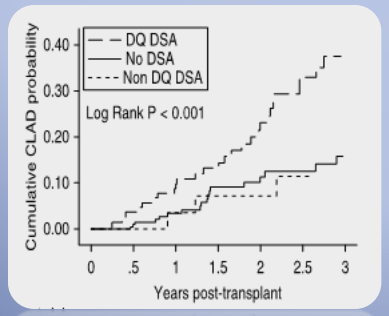
Safavi JHLT 2014;33:1273–1281



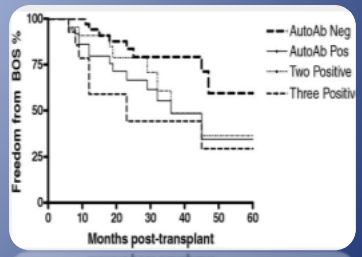
Morrel JHLT 33, No 12, December 2014



Lobo 2013 JHLT 32: 70



Tinkanen AJRCCM 2016 194L 5



Barhat Ann Thorac Surg 2010

Impact of AMR on short and long-term outcomes?

- Issues in understanding outcomes:
  - Until 2016, there was no standard criteria that all centers could use to compare their experience with AMR.
  - No specific clinical or pathological characteristics have been identified
  - Centers treating AMR without criteria/guidelines

American Journal of Transplantation 2003; 3: 708–714
Blackwell Munksgaard

ISSN 1600-6135

Antibody-Mediated Rejection Criteria – an Addition to the Banff '97 Classification of Renal Allograft Rejection

Table 2: Banff 97 diagnostic categories for renal allograft biopsies – update

1. Normal, see Definitions
2. Antibody-mediated rejection

   Rejection due, at least in part, to documented anti-donor antibody ('suspicious for' if antibody not demonstrated); may coincide with categories 3, 4 and 5

   Type (Grade)

   I. ATN-like – C4d +, minimal inflammation

   II. Capillary- margination and/or thromboses, C4d +

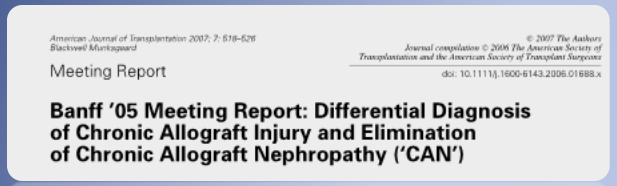
   III. Arterial – v3, C4d +
3. Borderline changes: 'Suspicious' for acute cellular rejection

   This category is used when no intimal arteritis is present, but there are foci of mild tubulitis (1–4 mononuclear cells/tubular cross-section) and at least i1; may coincide with categories 2 and 5
4. Acute/active cellular rejection

   T-cell-mediated rejection; may coincide with categories 2 and 5

   Type (Grade) Histopathological findings

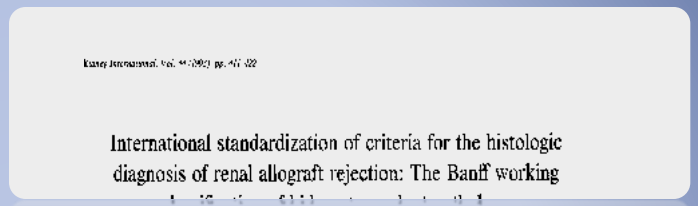
Banff established…and re-established criteria for AMR…


American Journal of Transplantation 2007; 7: 518–526
Blackwell Munksgaard

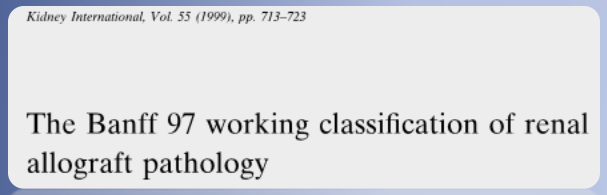
doi: 10.1111/j.1600-6143.2006.01688.x

Meeting Report

Banff '05 Meeting Report: Differential Diagnosis of Chronic Allograft Injury and Elimination of Chronic Allograft Nephropathy ('CAN')



International standardization of criteria for the histologic diagnosis of renal allograft rejection: The Banff working


Kidney International, Vol. 55 (1999), pp. 713–723

The Banff 97 working classification of renal allograft pathology


American Journal of Transplantation 2004; 4: 1562–1566
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2004.00585.x

Meeting Report

Banff 2003 Meeting Report: New Diagnostic Insights and Standards


American Journal of Transplantation 2012; 12: 563–570
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2011.03926.x

Meeting Report

Banff 2011 Meeting Report: New Concepts in Antibody-Mediated Rejection


American Journal of Transplantation 2010; 10: 464–471
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2009.02987.x

Meeting Report

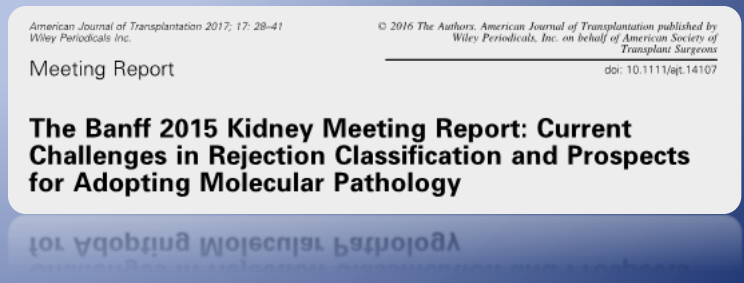
Banff '09 Meeting Report: Antibody Mediated Graft Deterioration and Implementation of Banff Working Groups


American Journal of Transplantation 2014; 14: 272–283
Wiley Periodicals Inc.

doi: 10.1111/ajt.12590

Meeting Report

Banff 2013 Meeting Report: Inclusion of C4d-Negative Antibody-Mediated Rejection and Antibody-Associated Arterial Lesions


American Journal of Transplantation 2017; 17: 28–41
Wiley Periodicals Inc.

doi: 10.1111/ajt.14107

Meeting Report

The Banff 2015 Kidney Meeting Report: Current Challenges in Rejection Classification and Prospects for Adopting Molecular Pathology

National Conference to Assess AMR in SOT:

Devoted little to AMR in the lung allograft

Stage of humoral rejection	Circulating antibody[b]	Lung biopsy specimen	Graft dysfunction
I: Latent	Yes	Normal	No
II: Silent	Yes	C4d	No
III: Subclinical	Yes	C4d + tissue pathology	No
IV: Clinical	Yes	C4d + tissue pathology	Yes

"it has been *difficult to identify features* distinguishing the clinical syndrome of primary graft failure from AMR/hyperacute rejection versus endotoxemia and severe ischemia/reperfusion injury."

Am J Transplant 2004;4:1033-41.

Revision of the 1996 Working Formulation for the Standardization of Nomenclature in the Diagnosis of Lung Rejection

Susan Stewart, FRCPath, Michael C. Fishbein, MD, Gregory I. Snell, MD, Gerald J. Berry, MD, Annette Boehler, MD, Margaret M. Burke, FRCPath, Alan Glanville, MD, F. Kate Gould, FRCPath, Cynthia Magro, MD, Charles C. Marboe, MD, Keith D. McNeil, FRACP, Elaine F. Reed, PhD, Nancy L. Reinsmoen, PhD, John P. Scott, MD, Sean M. Studer, MD, Henry D. Tazelaar, MD, John L. Wallwork, FRCS, Glen Westall, MD, Martin R. Zamora, MD, Adriana Zeevi, PhD, and Samuel A. Yousem, MD

The Journal of Heart and Lung Transplantation
December 2007

No consensus on diagnostic features of AMR

Stewart, JHLT 2007

The challenges of defining pulmonary AMR:

- Challenge to the immunologists:
  - Antibody assessment varies significantly between centers.
  - Standardization of quantifying measures (ie: MFI vs. titer, etc)
  - Serum specific issues: inhibition, saturation

- Challenge to clinicians:
  - No specific features in clinical presentation unique to AMR
    - Mimics of AMR: ACR, CLAD, infection, GERD
  - Monitoring (surveillance) schedule
  - Prevention and intervention

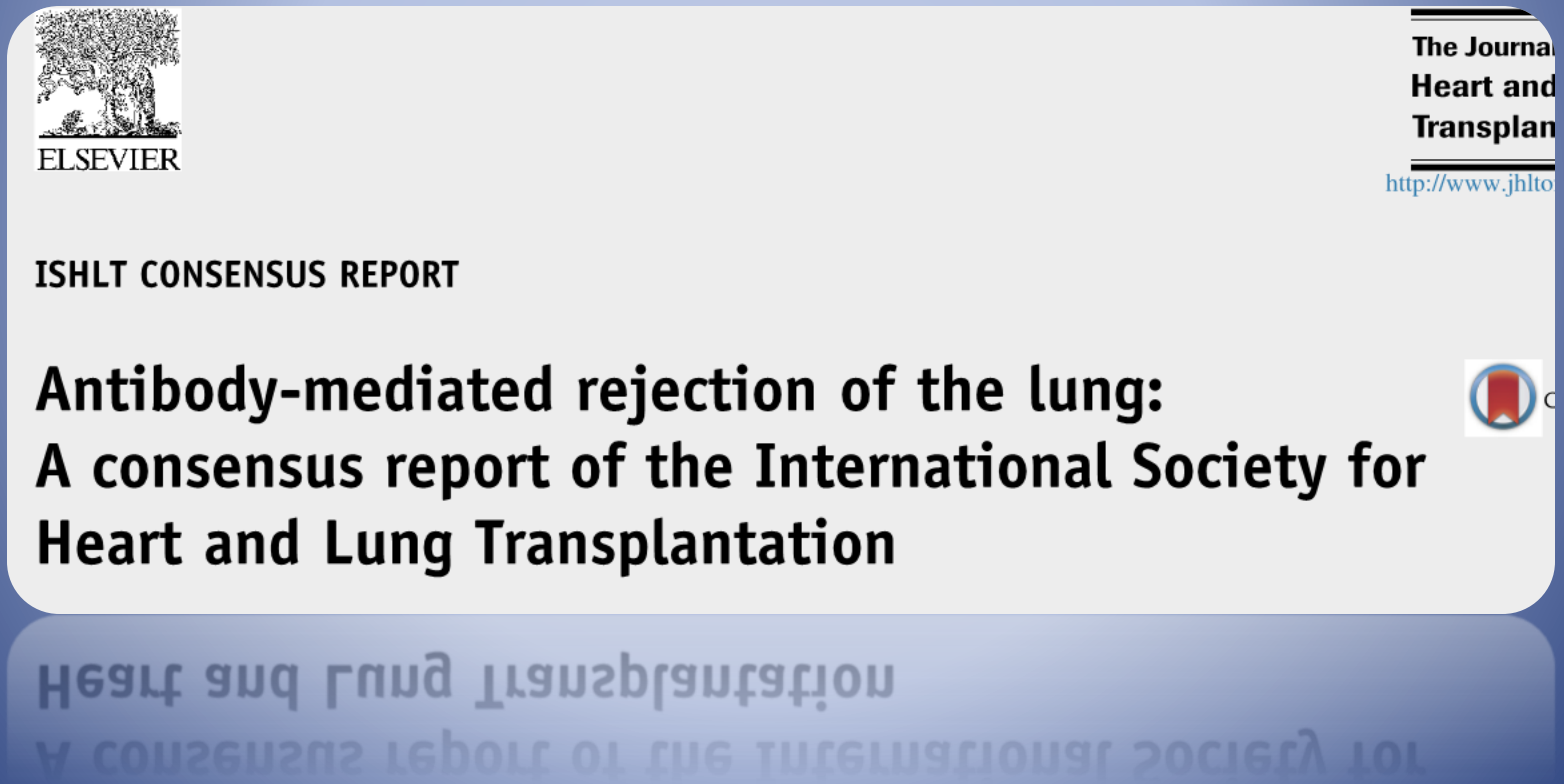
- Challenge to pathologists:
  - Histology: Non-specific findings: infection, ACR, PGD, ALI, CLAD
  - C4D with poor reproducibility, difficult to interpret.

ISHLT Pulmonary AMR Working Group Consensus

- Create a working definition of pulmonary AMR
- Crucial for evaluation, management and research
- A living document created to be updated
- A dynamic yardstick against we can start from and measure progress based on data collected going forward

Antibody mediated rejection (AMR)

ISHLT convened a working group to develop a standardized definition for pulmonary AMR.



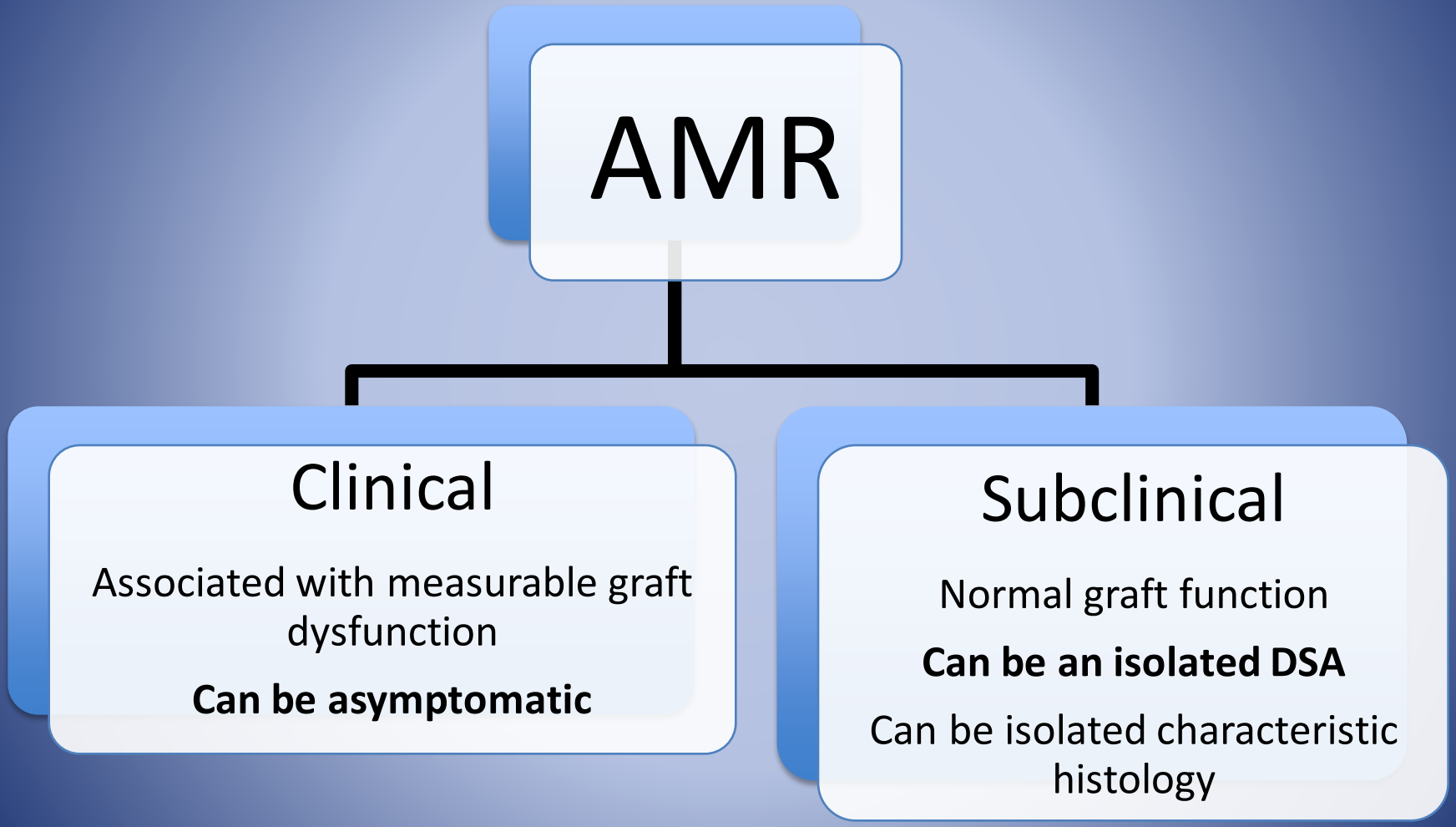
Consensus report now…
Practice guidelines later…

Characteristics	Clinical Consensus Statement	Clinical Practice Guidelines
Recommendations based on:	Expert opinion Best available evidence (ie: single center studies)	Systematic reviews and controlled trials

Diagnostic features of Pulmonary AMR

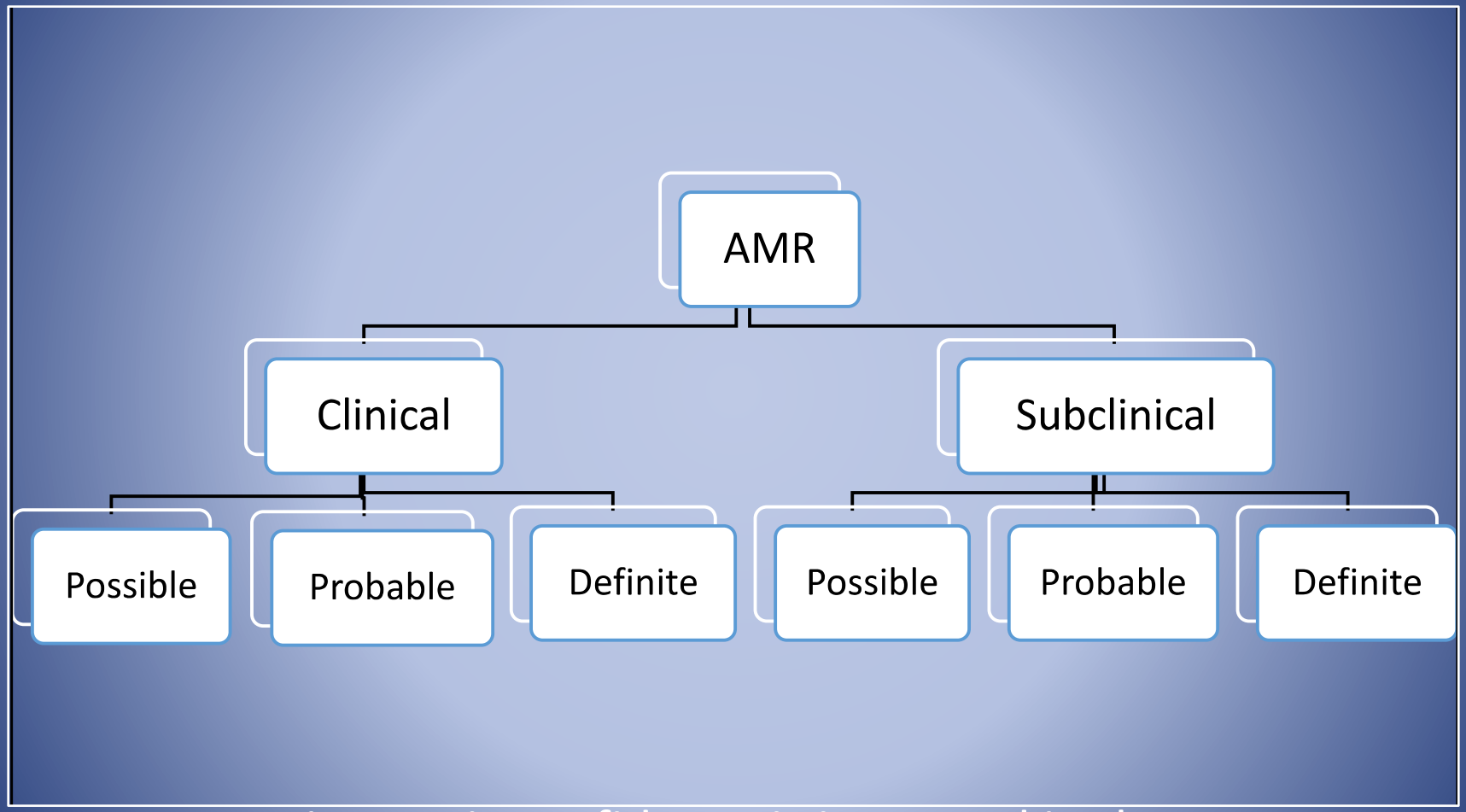
- Circulating donor specific antibody (DSA)
- Allograft dysfunction
- Histologic features of AMR
- Positive C4d Staining
- Exclusion of other causes of allograft dysfunction

ISHLT Working Group Definition of Pulmonary AMR



Degree of Certainty:

Depends on the demonstration of whether multiple criteria are present or absent.



Diagnostic confidence is increased in the presence of more positive criteria

Levine D , Glanville A, et al JHLT 2016: 35:397

Definite Clinical AMR:

All criteria are present and other possible causes are excluded

	Allograft dysfunction	Exclusion of other causes	Lung Histology	Lung Biopsy C4d	DSA
Definite	+	+	+	+	+
Probable	+	+	+	-	+
Probable	+	+	+	+	-
Probable	+	+	-	+	+
Probable	+	-	+	+	+
Possible	+	+	+	-	-
Possible	+	+	-	-	+
Possible	+	+	-	+	-
Possible	+	-	+	+	-
Possible	+	-	+	-	+
Possible	+	-	-	+	+

Levine et al JHLT 2016: 35:397

Probable clinical AMR: Lacks one criterion

	Allograft dysfunction	Exclusion of other causes	Lung Histology	Lung Biopsy C4d	DSA
Definite	+	+	+	+	+
Probable	+	+	+	-	+
Probable	+	+	+	+	-
Probable	+	+	-	+	+
Probable	+	-	+	+	+
Possible	+	+	+	-	-
Possible	+	+	-	-	+
Possible	+	+	-	+	-
Possible	+	-	+	+	-
Possible	+	-	+	-	+
Possible	+	-	-	+	+

Levine D et al JHLT 2016: 35:397

Possible clinical AMR: Lacks two criteria

	Allograft dysfunction	Exclusion of other causes	Lung Histology	Lung Biopsy C4d	DSA
Definite	+	+	+	+	+
Probable	+	+	+	-	+
Probable	+	+	+	+	-
Probable	+	+	-	+	+
Probable	+	-	+	+	+
Possible	+	+	+	-	-
Possible	+	+	-	-	+
Possible	+	+	-	+	-
Possible	+	-	+	+	-
Possible	+	-	+	-	+
Possible	+	-	-	+	+

Levine D, et al JHLT 2016: 35:397

Definite subclinical AMR

	Lung Histology	C4D staining	DSA
Definite	+	+	+
Probable	+	-	+
Probable	-	+	+
Probable	+	+	-
Possible	+	-	-
Possible	-	+	-
Possible	-	-	+

Levine et al JHLT 2016: 35:397

Probable subclinical AMR

	Lung Histology	C4D staining	DSA
Definite	+	+	+
Probable	+	-	+
Probable	-	+	+
Probable	+	+	-
Possible	+	-	-
Possible	-	+	-
Possible	-	-	+

Possible subclinical AMR

	Lung Histology	C4D staining	DSA
Definite	+	+	+
Probable	+	-	+
Probable	-	+	+
Probable	+	+	-
Possible	+	-	-
Possible	-	+	-
Possible	-	-	+

Pulmonary AMR consensus criteria: A few key points:

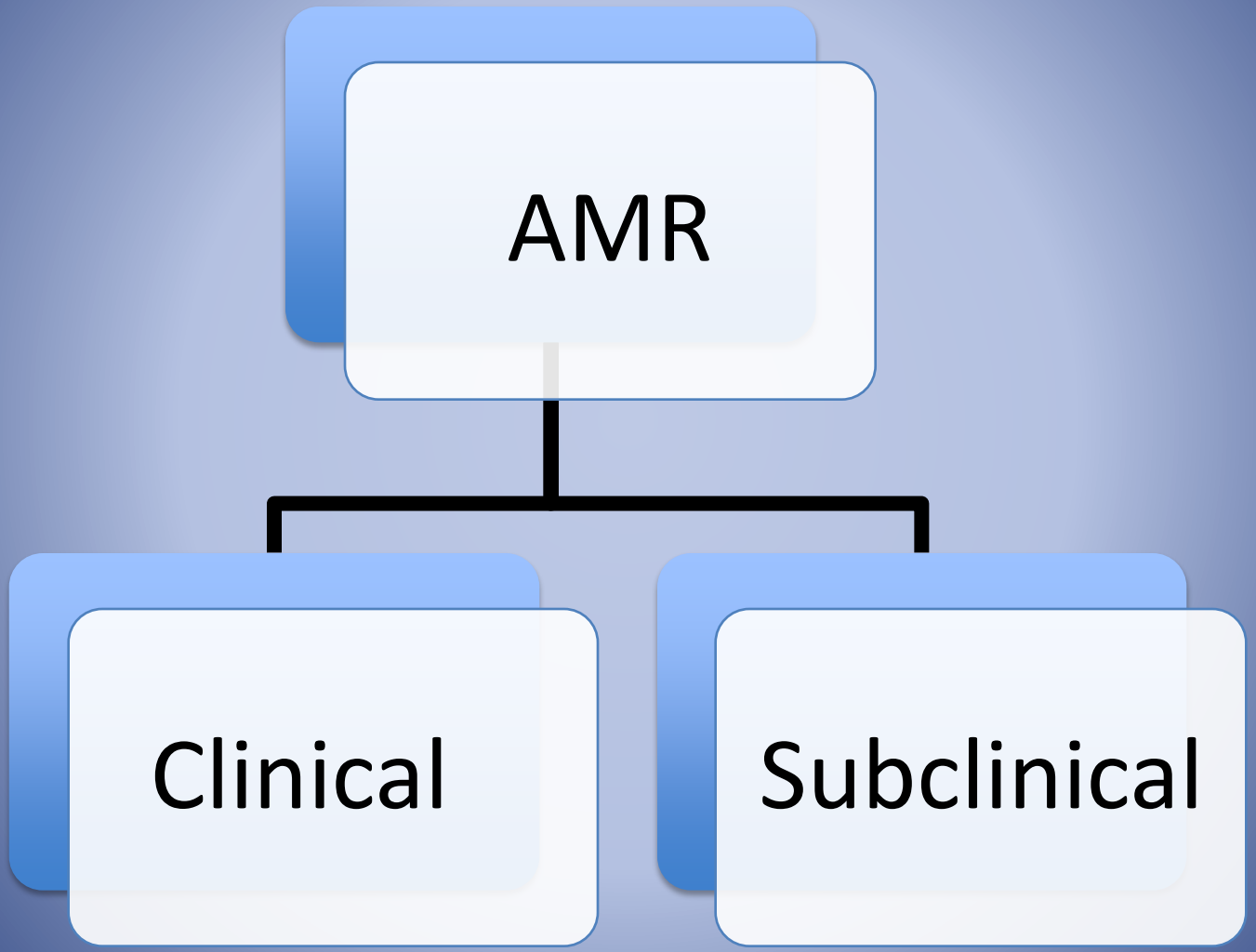
- "Definite" AMR is stringent:
  - all 4 criteria +exclusion of other causes.

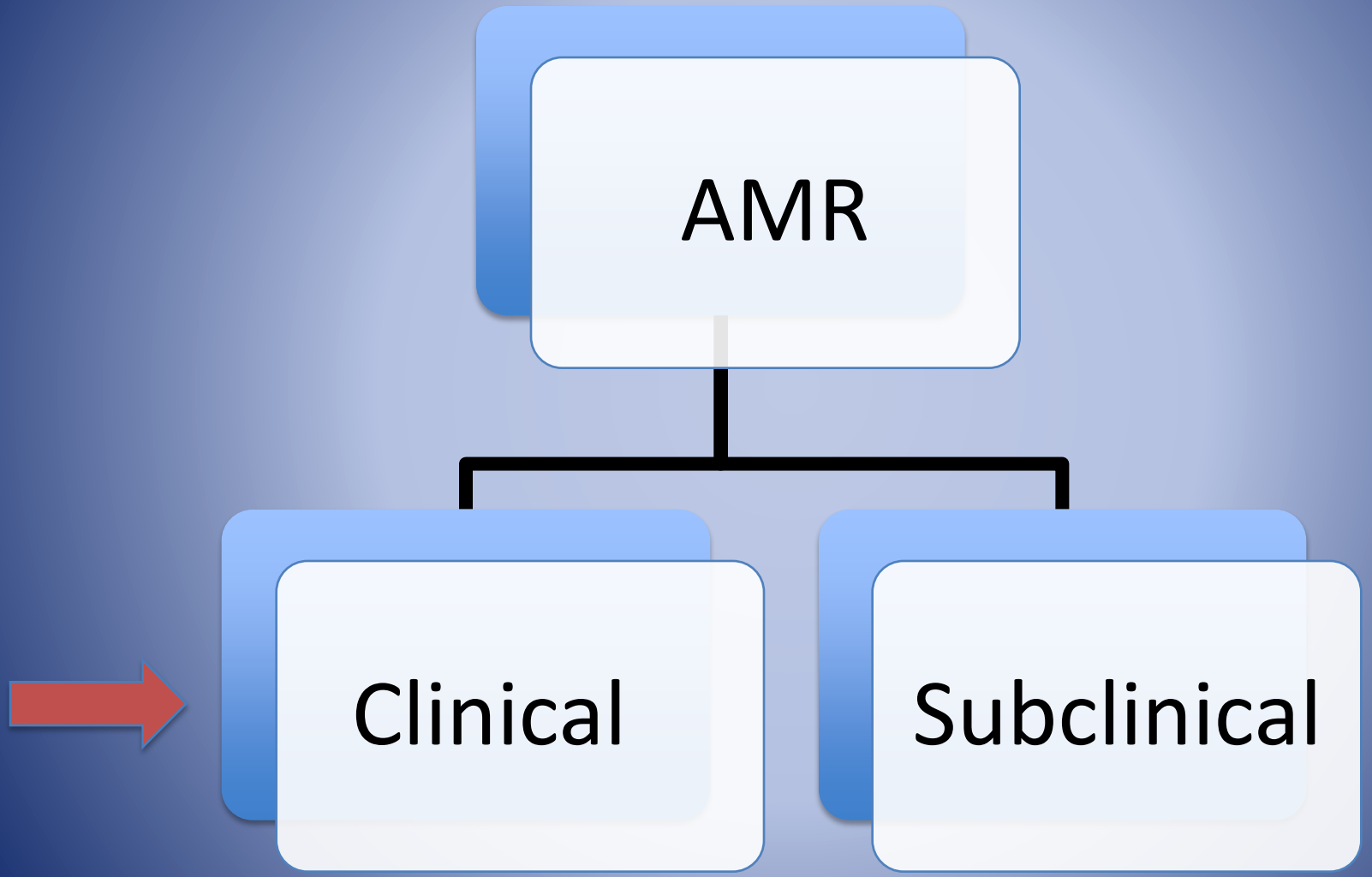
- Probable AMR:
  - 4 combinations that are likely not equal in weight.
  - There is a different diagnostic certainty between these probable groups.

Probable clinical AMR: Lacks one criterion

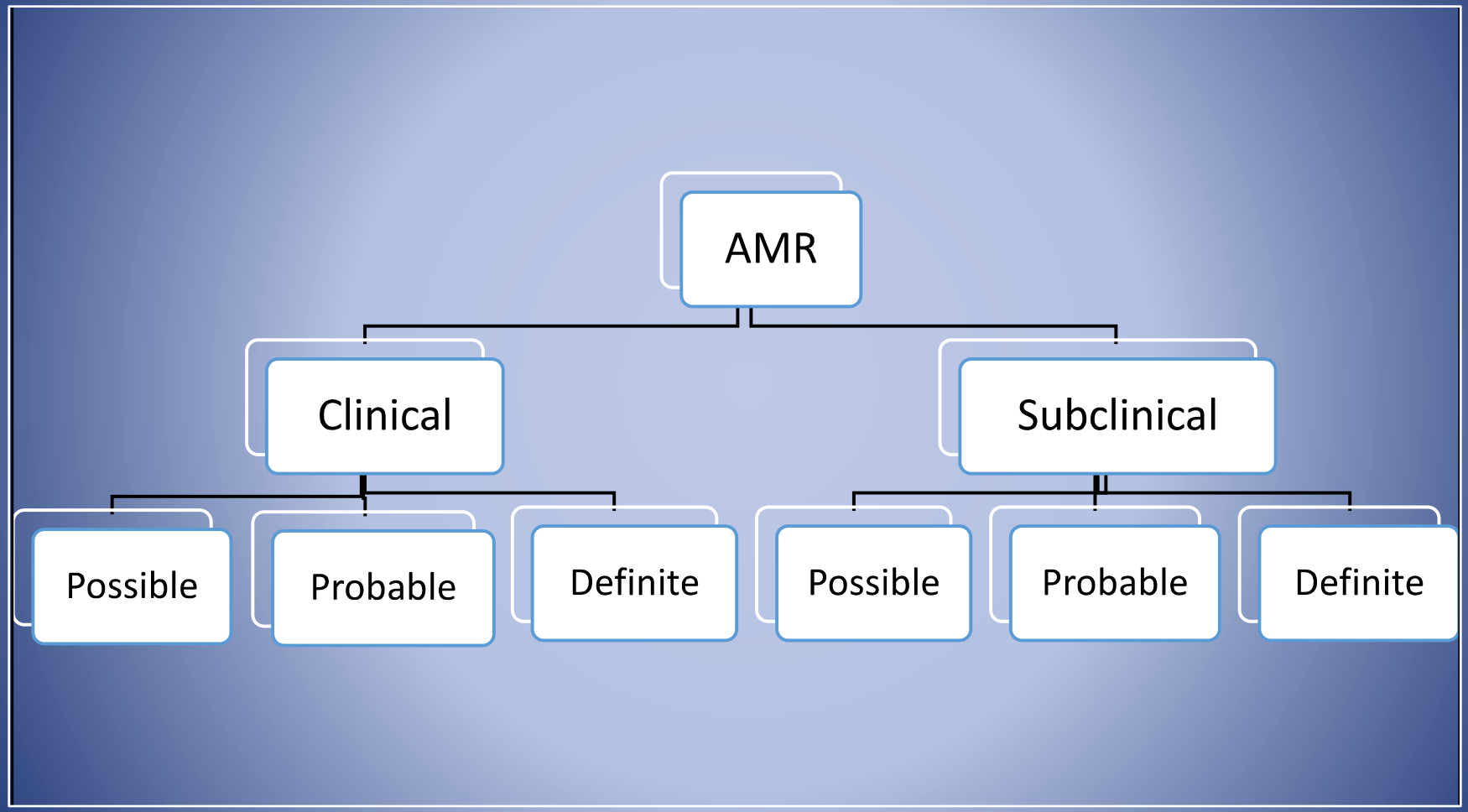
	Allograft dysfunction	Exclusion of other causes	Lung Histology	Lung Biopsy C4d	DSA
Definite	+	+	+	+	+
Probable	+	+	+	-	+
Probable	+	+	+	+	-
Probable	+	+	-	+	+
Probable	+	-	+	+	+
Possible	+	+	+	-	-
Possible	+	+	-	-	+
Possible	+	+	-	+	-
Possible	+	-	+	+	-
Possible	+	-	+	-	+
Possible	+	-	-	+	+

Levine D et al JHLT 2016: 35:397


AMR
Clinical
Subclinical

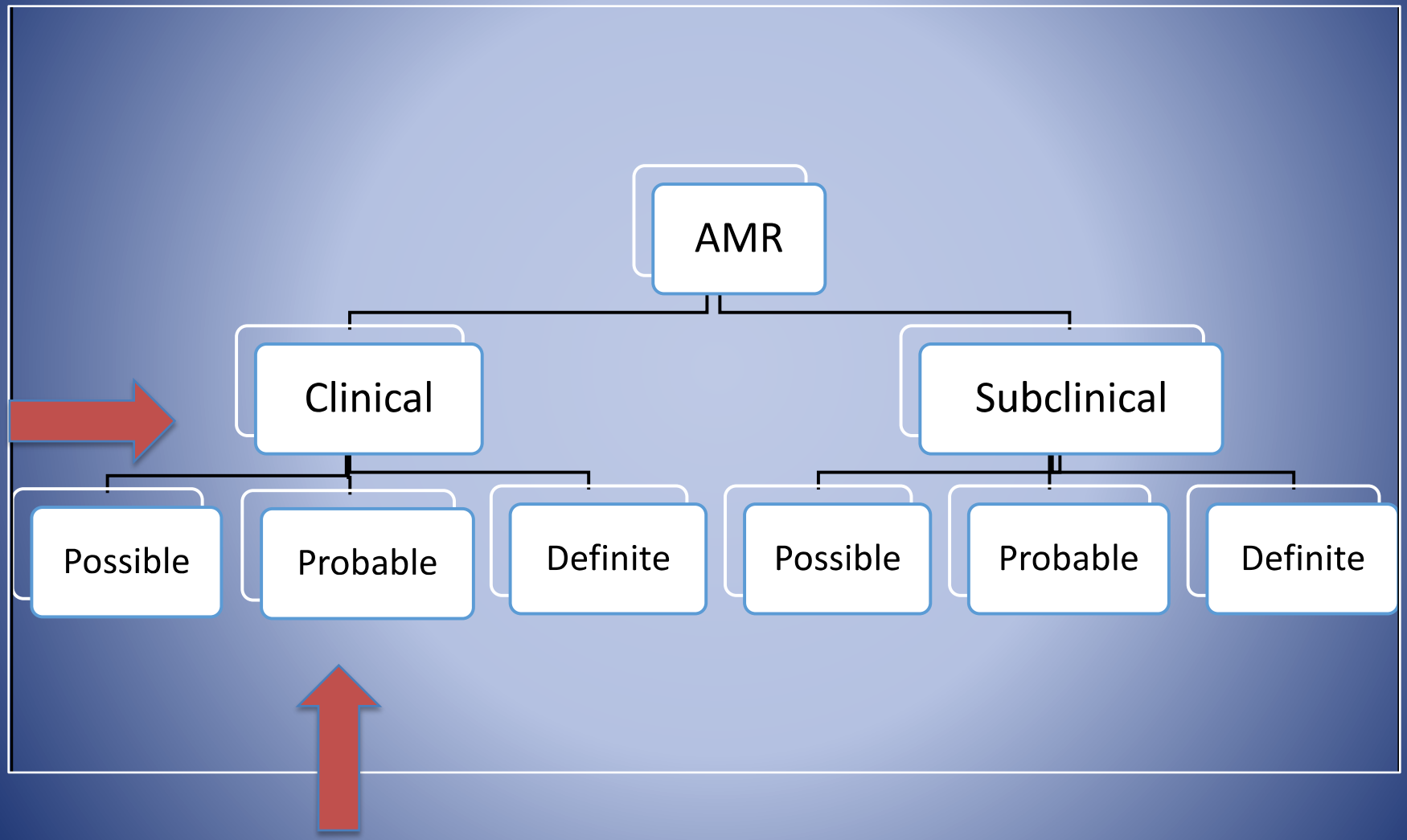

AMR
Clinical
Subclinical

Pulmonary AMR Classification

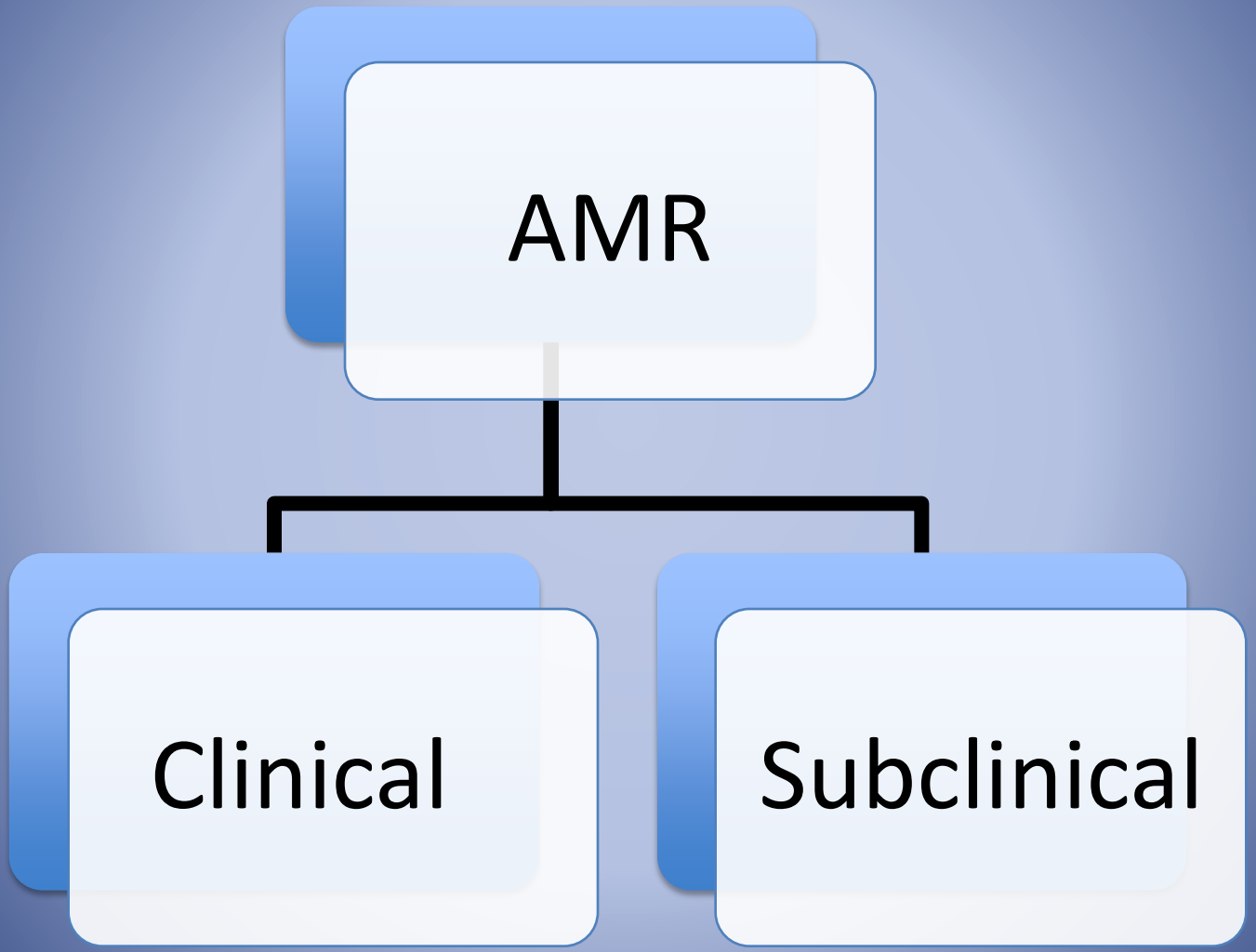


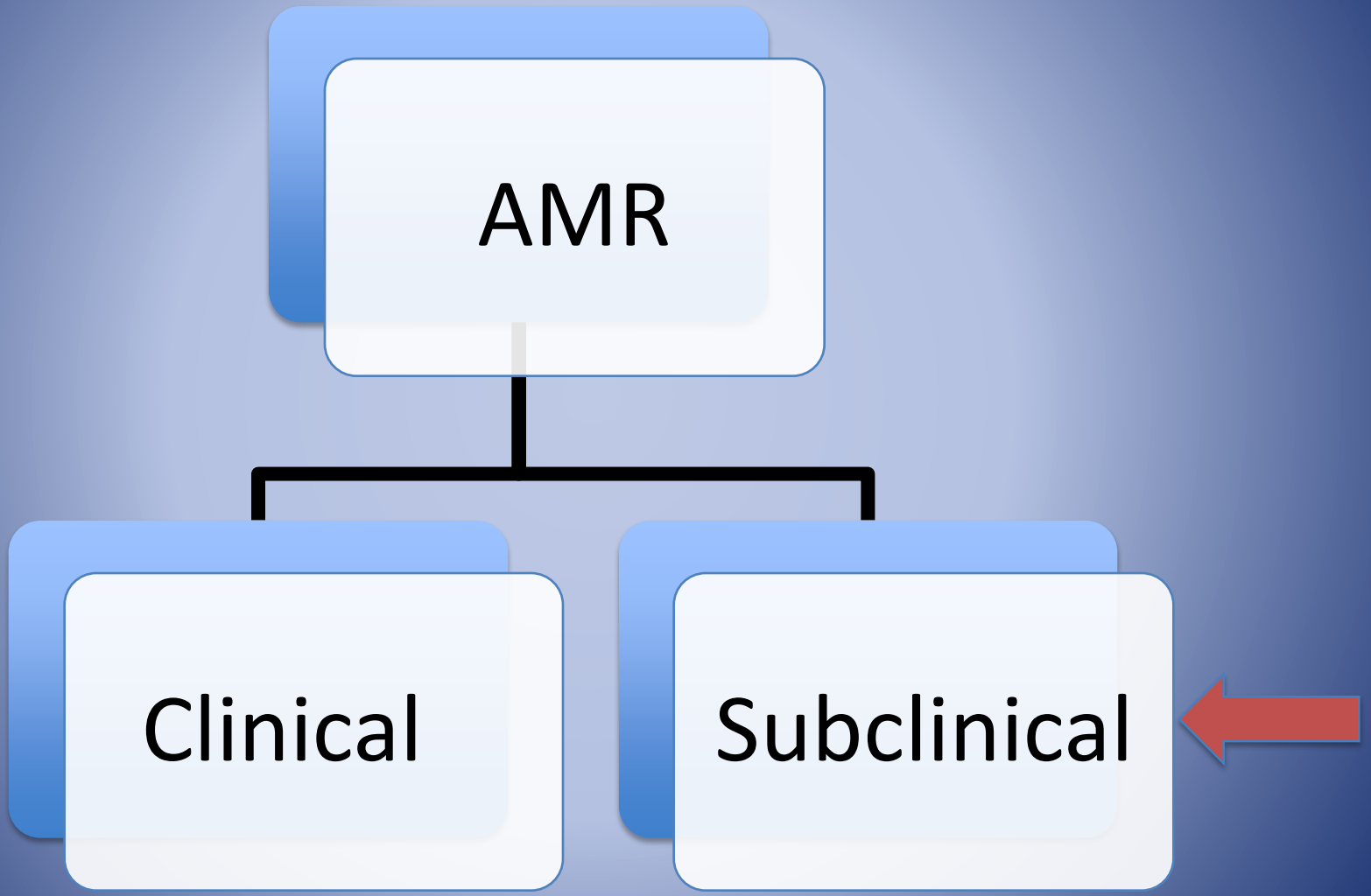
Levine D , Glanville A, et al JHLT 2016: 35:397

Pulmonary AMR Classification

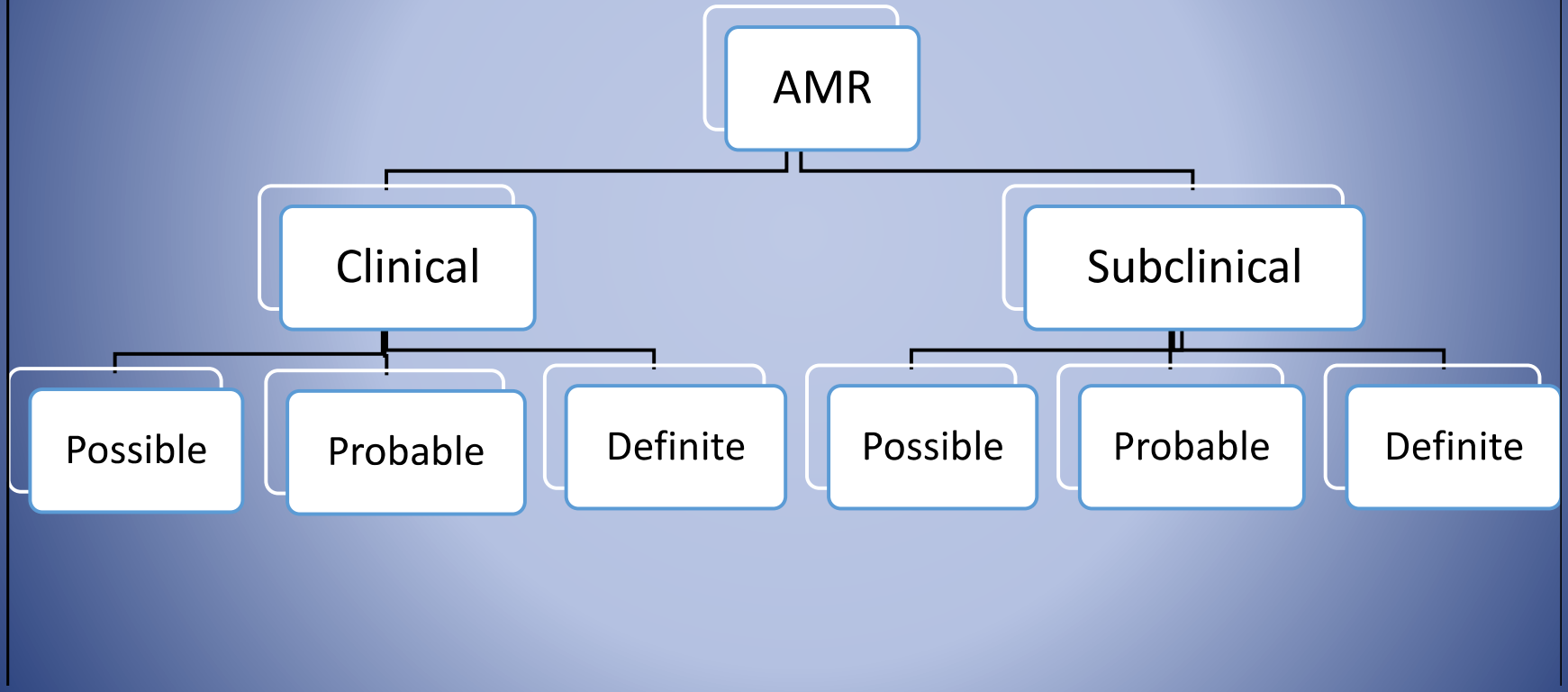


Levine D , Glanville A, et al JHLT 2016: 35:397

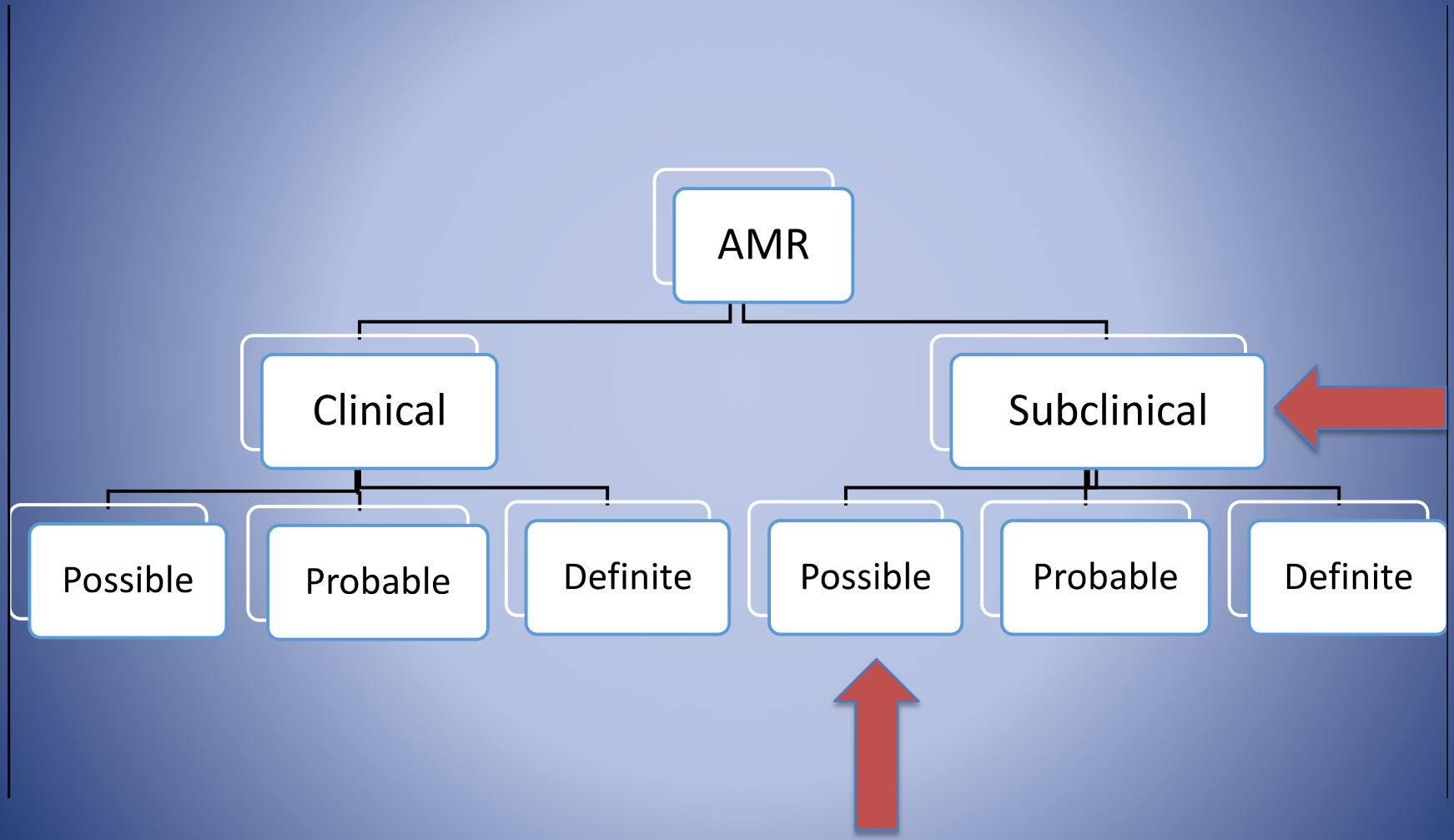

AMR
Clinical
Subclinical


AMR
Clinical
Subclinical

Pulmonary AMR Classification



Pulmonary AMR Classification



*"When there is an isolated finding of **DSA without other manifestations of AMR** such as histology, C4d staining or allograft dysfunction, **heightened surveillance for allograft dysfunction is warranted**."*

	Lung Histology	C4D staining	DSA
Definite	+	+	+
Probable	+	-	+
Probable	-	+	+
Probable	+	+	-
Possible	+	-	-
Possible	-	+	-
Possible	-	-	+

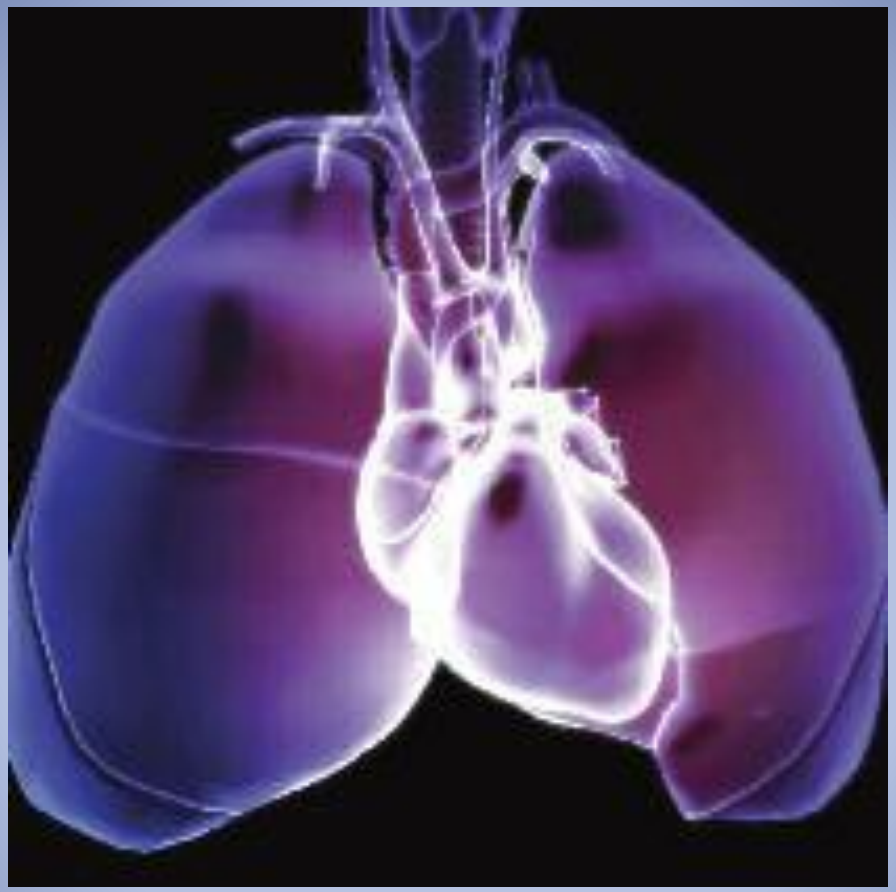
Consensus conclusions and limitations

- Definitions are dynamic and will allow modifications as new insights emerge.
- Limitations:
  - Criteria based on limited data in literature
  - All centers may not be able to evaluate all criteria
  - HLA techniques are not standardized between labs
  - Concurrence of histopathology and C4d is limited
  - Severity and phenotypes of AMR not yet defined

Where to go from here?

- Validation and modification of consensus criteria based on recent literature and collective experience.
- Develop unified surveillance strategy for monitoring.
- Consider molecular techniques in the assessment
- Characteristics of different phenotypes of AMR.
- Goals of therapy to determine who and when to treat.
- Determine appropriate response to therapy.

Do we have consensus on this consensus?



Thank you!