The new ARDS definitions: what does it mean?

Richard Beale

7th September 2012

METHODS

ESICM convened an international panel of experts, with representation of ATS and SCCM

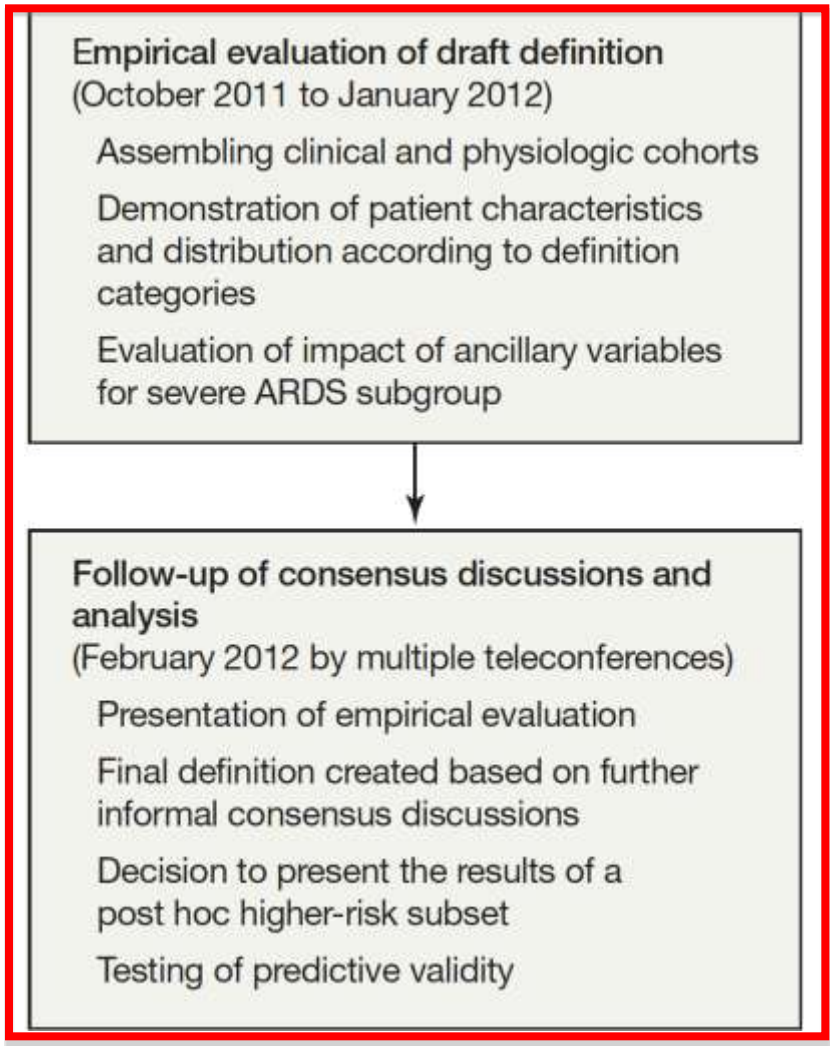
The objectives were to update the ARDS definition using a systematic analysis of:

- ***current epidemiologic evidence***
- ***physiological concepts***
- ***results of clinical trials***


Andrew
RHODES
Anders
ESTEBAN
Karen
PICKETT

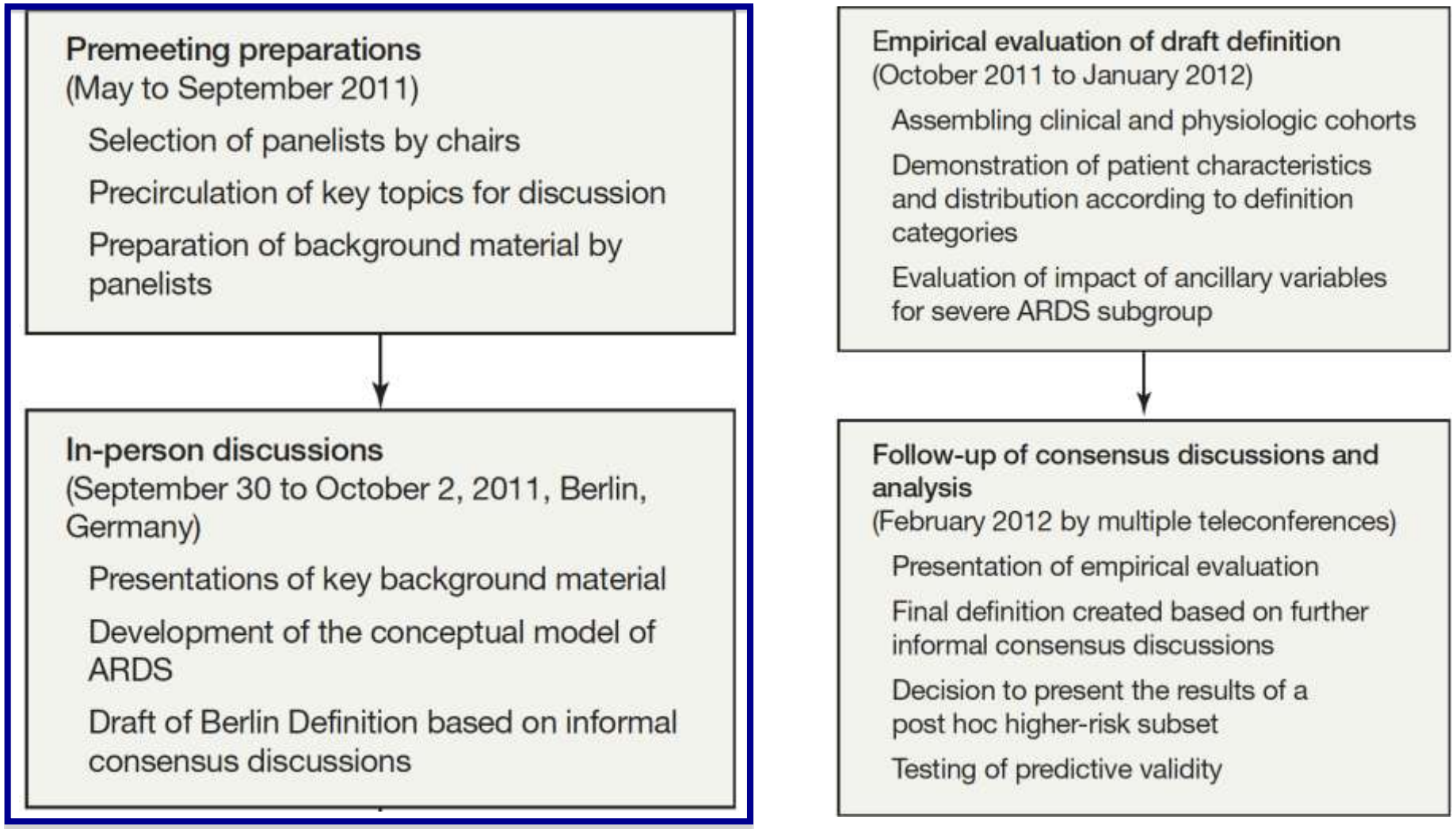
Outline of consensus process

Stage 1: Consensus process - Draft



Stage 2: Empirical evaluation of draft definition

Outline of consensus process



Stage 1: Consensus process - Draft

METHODS

All modifications were based on the principle that syndrome definitions must fulfill three criteria:

- ***feasibility***
- ***reliability***
- ***validity***

Rubenfeld:2003

FEASIBILITY

Definitions should rely on diagnostic tests that can routinely used

by CLINICIANS to identify patients for appropriate treatments and

by CLINICAL SCIENTISTS to facilitate clinical trial enrolment.

Rubenfeld:2003

RELIABILITY

…identify the same patients…

as measured by inter-observer agreement

VALIDITY

- Sensitivity and specificity in reference to a gold standard;
- However, ARDS as many syndromes in medicine does not have a gold standard as reference;
- The validity of definitions may rely on indirect techniques like face, construct, predictive, and concurrent validity

VALIDITY MEASURE	EXPLANATION	IN ARDS
FACE VALIDITY	Definition appears “on its face” to represent the disease	Patients identified by the proposed definition “feel right” to clinicians
CONTENT VALIDITY	Definition contains all of the elements relevant to the disease	Proposed diagnostic criteria contain all of the elements deemed essential to the diagnosis of ALI, usually as assessed by experts.
CRITERION VALIDITY	Definition corresponds to a gold standard	diagnostic criteria for ALI correspond to a gold standard
PREDICTIVE VALIDITY	Definition is able to predict something it theoretically should be able to predict	Diagnostic criteria predict some outcome that is unique to ALI (e.g., mortality, or response to therapy)
CONCURRENT VALIDITY	Definition is able to distinguish between groups that it theoretically should be able to distinguish between	Diagnostic criteria distinguish ALI from other forms of acute hypoxemic respiratory failure

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Face validity

Formalization in a “conceptual model” of how clinicians recognize patients with the syndrome

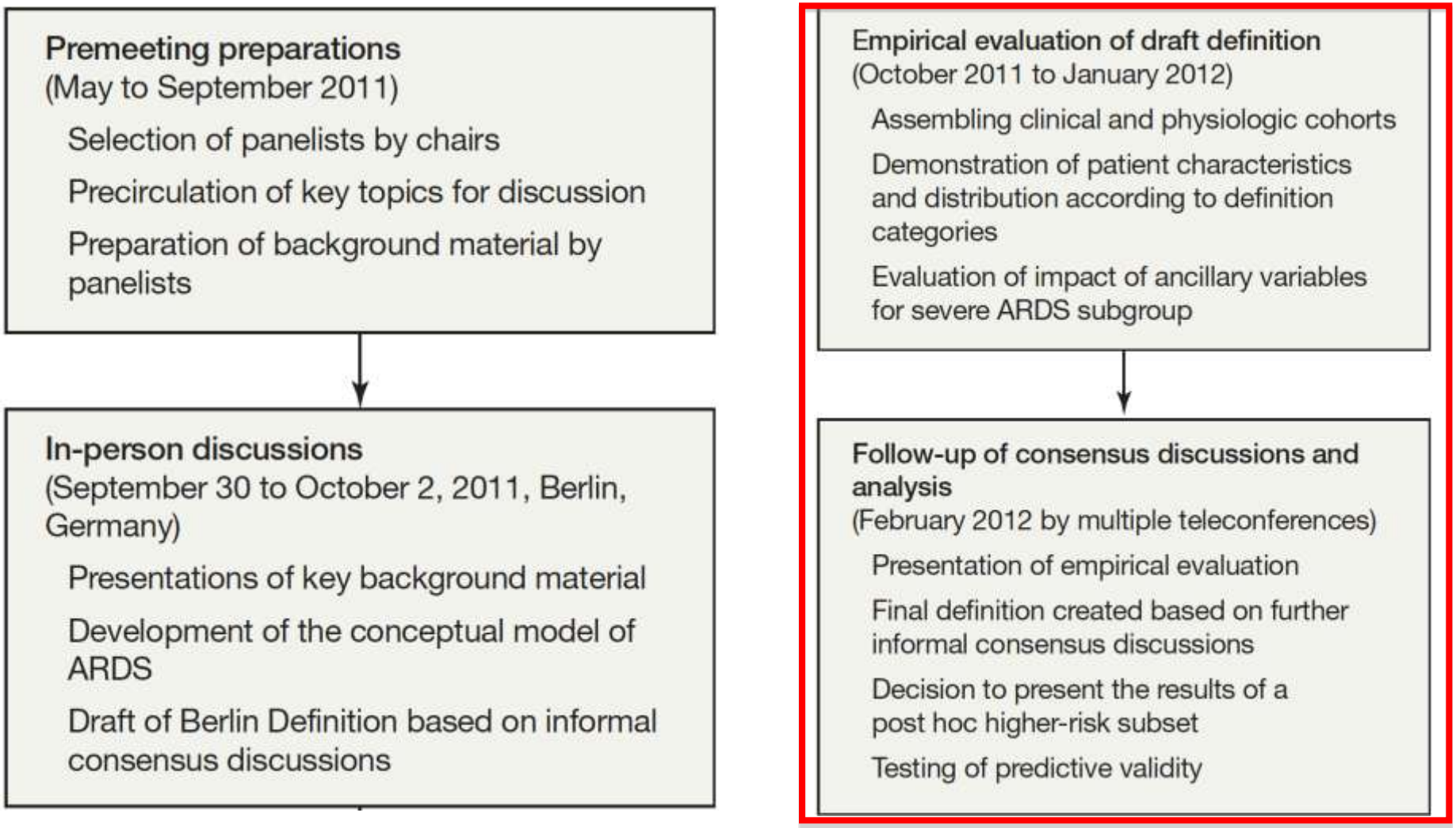
Predictive validity:

defining criteria that predict outcome (e.g., mortality, or response to therapy)

THE CONCEPTUAL MODEL OF ARDS

1. ARDS is a type of acute diffuse lung injury associated with **recognized risk factors**, characterized by inflammation leading to increased pulmonary vascular permeability and loss of aerated lung tissue.
2. The hallmarks of the **clinical syndrome** are hypoxaemia and bilateral radiographic opacities (standard chest x-ray or CT scan);
3. **Physiological** derangements include increased pulmonary venous admixture, increased physiological dead-space, decreased respiratory system compliance;
4. **Morphological hallmarks** are lung oedema, inflammation, hyaline membrane, and alveolar hemorrhage (*i.e.*, diffuse alveolar damage)

Outline of consensus process



Stage 2: Empirical evaluation of draft definition

Cohort Assembly

the panel identified studies that met the following eligibility criteria:

- large, multicenter prospective cohorts, or randomized trials,

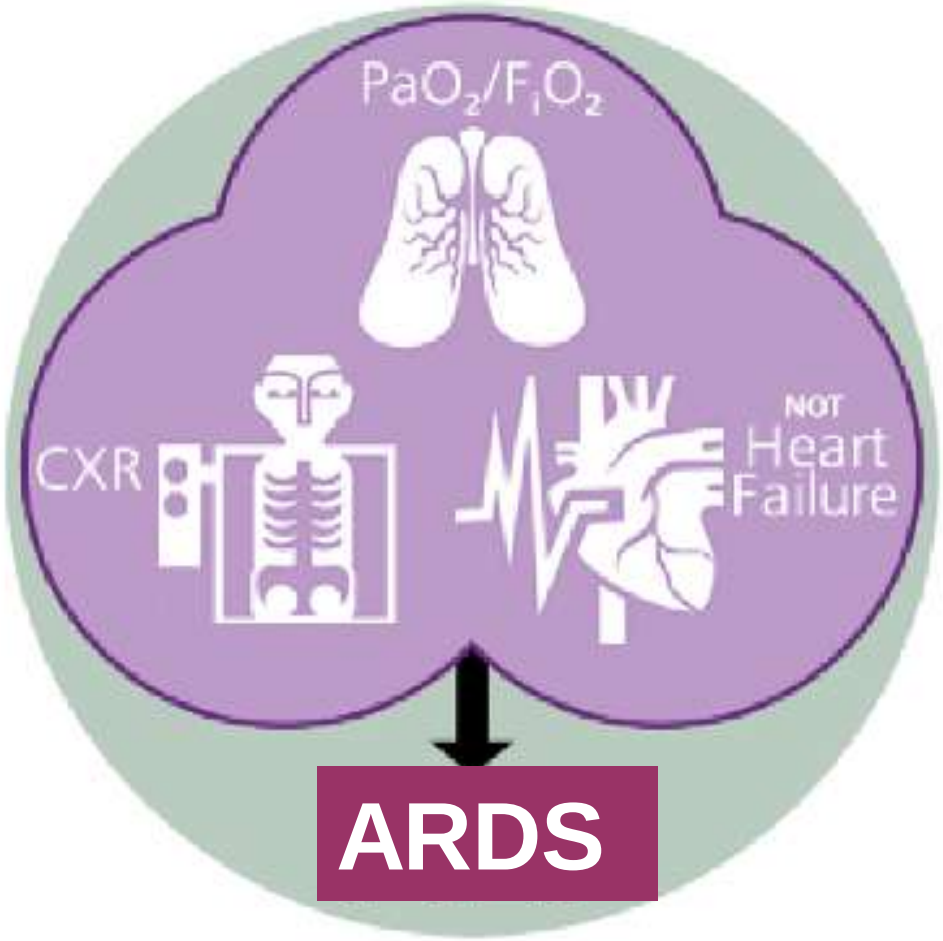
- smaller, single-center prospective studies with unique radiological or physiological data that enrolled adult patients with ALI as defined by AECC;

Variables

- Hospital or 90-day mortality;
- Ventilator- free days at 28 (composite measure of mortality and duration of mechanical ventilation);
- Duration of mechanical ventilation in survivors (indirect marker of severity of lung injury);
- Physiological data

Analytic Framework

- Determine the distribution of patient characteristics across the defined severity categories;
- Evaluate the value of proposed ancillary variables in defining the severe ARDS subgroup in the draft definition;
- Determine the predictive validity for mortality of the final Berlin Definition;
- Compare the final Berlin Definition to the AECC definition;
- In a post hoc analysis, thresholds that would identify a severe group of patients with ARDS who had more than 50% mortality and include more than 10% of the study population.


PaO_2/F_iO_2
CXR
NOT
Heart
Failure
ARDS

From: **Acute Respiratory Distress Syndrome: The Berlin Definition**
JAMA. 2012;307(23):2526-2533. doi:10.1001/jama.2012.5669

Table 1. The AECC Definition[3]—Limitations and Methods to Address These in the Berlin Definition

	AECC Definition	AECC Limitations	Addressed in Berlin Definition
Timing	Acute onset	No definition of acute[4]	Acute time frame specified
ALI category	All patients with PaO_2/FIO_2 <300 mm Hg	Misinterpreted as PaO_2/FIO_2 = 201-300, leading to confusing ALI/ARDS term	3 Mutually exclusive subgroups of ARDS by severity ALI term removed
Oxygenation	PaO_2/FIO_2 ≤300 mm Hg (regardless of PEEP)	Inconsistency of PaO_2/FIO_2 ratio due to the effect of PEEP and/or FIO_2[5-7]	Minimal PEEP level added across subgroups FIO_2 effect less relevant in severe ARDS group
Chest radiograph	Bilateral infiltrates observed on frontal chest radiograph	Poor interobserver reliability of chest radiograph interpretation[8,9]	Chest radiograph criteria clarified Example radiographs created[a]
PAWP	PAWP ≤18 mm Hg when measured or no clinical evidence of left atrial hypertension	High PAWP and ARDS may coexist[10,11] Poor interobserver reliability of PAWP and clinical assesments of left atrial hypertension[12]	PAWP requirement removed Hydrostatic edema not the primary cause of respiratory failure Clinical vignettes created[a] to help exclude hydrostatic edema
Risk factor	None	Not formally included in definition[4]	Included When none identified, need to objectively rule out hydrostatic edema

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The Berlin Definition of ARDS

From: **Acute Respiratory Distress Syndrome: The Berlin Definition**
JAMA. 2012;307(23):2526-2533. doi:10.1001/jama.2012.5669

	Acute Respiratory Distress Syndrome
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b]	
Mild	200 mm Hg < PaO_2/FIO_2 ≤ 300 mm Hg with PEEP or CPAP ≥5 cm H_2O[c]
Moderate	100 mm Hg < PaO_2/FIO_2 ≤ 200 mm Hg with PEEP ≥5 cm H_2O
Severe	PaO_2/FIO_2 ≤ 100 mm Hg with PEEP ≥5 cm H_2O

300 mmHg =	40	kPa
200 mmHg =	26.7	kPa
100 mmHg =	13.3	kPa

From: **Acute Respiratory Distress Syndrome: The Berlin Definition**
JAMA. 2012;307(23):2526-2533. doi:10.1001/jama.2012.5669

Predictive Validity of ARDS Definitions in the Clinical Database

	Modified AECC Definition[a]		Berlin Definition ARDS[a]		
	ALI Non-ARDS	ARDS	Mild	Moderate	Severe
No. (%) [95% CI] of patients	1001 (24) [23-25]	3187 (76) [75-77]	819 (22) [21-24]	1820 (50) [48-51]	1031 (28) [27-30]
Progression in 7 d from mild, No. (%) [95% CI]		336 (34) [31-37]		234 (29) [26-32]	33 (4) [3-6]
Progression in 7 d from moderate, No. (%) [95% CI]					230 (13) [11-14]
Mortality, No. (%) [95% CI][b]	263 (26) [23-29]	1173 (37) [35-38]	220 (27) [24-30]	575 (32) [29-34]	461 (45) [42-48]
Ventilator-free days, median (IQR)[b]	20 (2-25)	12 (0-22)	20 (1-25)	16 (0-23)	1 (0-20)
Duration of mechanical ventilation in survivors, median (IQR), d[b]	5 (2-10)	7 (4-14)	5 (2-11)	7 (4-14)	9 (5-17)

Abbreviations: AECC, American-European Consensus Conference; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; FIO_2, fraction of inspired oxygen; IQR, interquartile range; PaO_2, arterial partial pressure of oxygen; PEEP, positive end-expiratory pressure.

[a] The definitions are the following for ALI non-ARDS (200 mm Hg < $PaO_2/FIO_2 \leq 300$ mm Hg, regardless of PEEP), ARDS ($PaO_2/FIO_2 \leq 200$ mm Hg, regardless of PEEP), mild Berlin Definition (200 mm Hg < $PaO_2/FIO_2 \leq 300$ mm Hg with PEEP ≥5 cm H_2O), moderate Berlin Definition (100 mm Hg < $PaO_2/FIO_2 \leq 200$ mm Hg with PEEP ≥5 cm H_2O), and severe Berlin Definition ($PaO_2/FIO_2 \leq 100$ mm Hg with PEEP ≥5 cm H_2O).

[b] Comparisons of mortality, ventilator-free days, and duration of mechanical ventilation in survivors across categories of modified AECC (ALI non-ARDS and ARDS) and across categories of Berlin Definition (mild, moderate, and severe) are all statistically significant ($P < .001$).

AUROC of 0.577 vs 0.536 ; $P < .001$), with the difference in AUROC of 0.041 (95% CI, 0.030- 0.050).

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Predictive Validity of ARDS Definitions in the Physiologic Database

	Modified AECC Definition[a]		Berlin Definition ARDS[a]		
	ALI Non-ARDS	ARDS	Mild	Moderate	Severe
No. (%) [95% CI] of patients	66 (25) [19-30]	203 (75) [70-80]	66 (25) [20-30]	161 (59) [54-66]	42 (16) [11-21]
Mortality, No. (%) [95% CI][b]	13 (20) [11-31]	84 (43) [36-50]	13 (20) [11-31]	62 (41) [33-49]	22 (52) [36-68]
Ventilator-free days					
Median (IQR)	8.5 (0-23.5)	0 (0-16.0)	8.5 (0-23.5)	0 (0-16.5)	0 (0-6.5)
Missing, No.	10	26	10	25	1
Duration of mechanical ventilation in survivors, median (IQR), d	6.0 (3.3-20.8)	13.0 (5.0-25.5)	6.0 (3.3-20.8)	12.0 (5.0-19.3)	19.0 (9.0-48.0)
Lung weight, mg[c]					
Mean (SD)	1371 (360.4)	1602 (508.1)	1371 (360.4)	1556 (469.7)	1828 (630.2)
Missing, No.	16	48	16	32	16
Shunt, mean (SD), %[c,d]	21 (21)	32 (13)	21 (12)	29 (11)	40 (16)

Abbreviations: AECC, American-European Consensus Conference; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; FIO_2, fraction of inspired oxygen; IQR, interquartile range; PaO_2, arterial partial pressure of oxygen; PEEP, positive end-expiratory pressure.

[a] The definitions are the following for ALI non-ARDS (200 mm Hg $< PaO_2/FIO_2 \leq$ 300 mm Hg, regardless of PEEP), ARDS ($PaO_2/FIO_2 \leq$ 200 mm Hg, regardless of PEEP), mild Berlin Definition (200 mm Hg $< PaO_2/FIO_2 \leq$ 300 mm Hg with PEEP $\geq$5 cm H_2O), moderate Berlin Definition (100 mm Hg $< PaO_2/FIO_2 \leq$ 200 mm Hg with PEEP $\geq$5 cm H_2O), and severe Berlin Definition ($PaO_2/FIO_2 \leq$ 100 mm Hg with PEEP $\geq$5 cm H_2O).

[b] Eight patients are missing in the moderate Berlin Definition ARDS group. $P = .001$ for difference in mortality across Berlin stages of ARDS.

[c] Comparisons of lung weight and shunt across categories of modified AECC (ALI non-ARDS and ARDS) and across categories of Berlin Definition (mild, moderate, and severe) are statistically significant ($P < .001$).

[d] Only available at 1 site.

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Additional Physiological variables

- Static compliance (< 40 mL/cmH_2O);
- Plateau pressure;
- FiO_2 (> 0.7)
- PEEP (> 10 cmH_2O);
- Corrected Minute ventilation [(VtxRR)xPaO_2/40];

The value of positive end-expiratory pressure and F_{IO_2} criteria in the definition of the acute respiratory distress syndrome*

Martin Britos, MD; Elizabeth Smoot, MS; Kathleen D. Liu, MD; B. Taylor Thompson, MD; William Checkley, MD, PhD; Roy G. Brower, MD, for the National Institutes of Health Acute Respiratory Distress Syndrome Network Investigators

PaO_2/FiO_2 vs PEEP

Table 2. Mortality rates according to PaO_2/F_{IO_2} tertiles and positive end-expiratory pressure levels

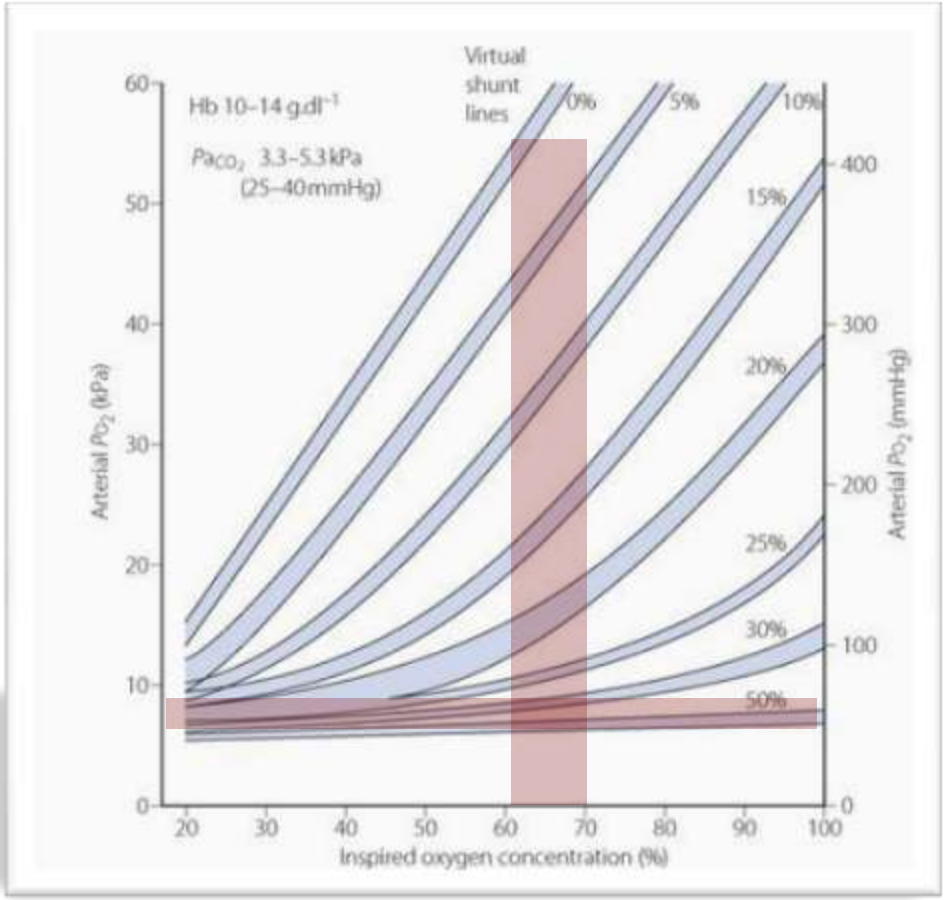
PaO_2/F_{IO_2} Tertiles	PEEP ≤5 (n = 731)	5 < PEEP ≤ 10 (n = 999)	11 ≥ PEEP (n = 582)	Total[b]
PaO_2/F_{IO_2} >175 (n = 771)	23.1 ± 5%	22.0 ± 6%	25.9 ± 18%	23.1 ± 2% ($p > .70$)
110 < PaO_2/F_{IO_2} ≤ 175 (n = 763)	31.4 ± 9%	25.4 ± 5%	28.1 ± 13%	27.8 ± 3% ($p > .37$)
PaO_2/F_{IO_2} ≤115 (n = 778)	35.7 ± 2%	35.2 ± 7%	38.2 ± 7%	36.5 ± 3% ($p > .49$)

PaO_2/FiO_2 vs FiO_2

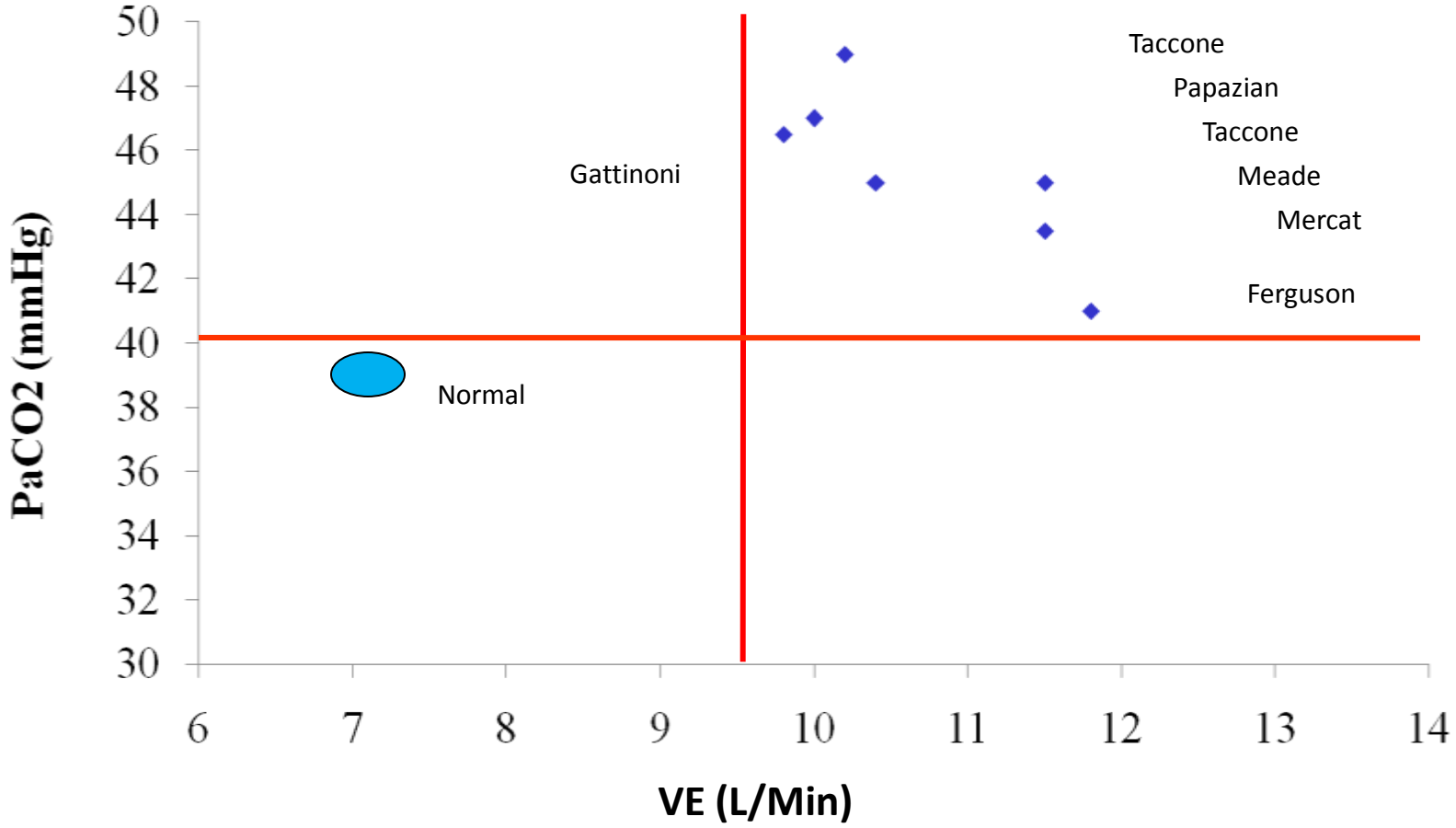
Table 3. Mortality rates according to PaO_2/F_{IO_2} tertiles and F_{IO_2} levels

PaO_2/F_{IO_2} Tertiles	F_{IO_2} ≤0.50 (n = 946)	0.50 < F_{IO_2} < 0.70 (n = 553)	0.70 ≤ F_{IO_2} (n = 819)	Total[b]
PaO_2/F_{IO_2} >175 (n = 771)	21 ± 2% (n = 593)	26 ± 4% (n = 98)	33 ± 5% (n = 84)	23 ± 2% ($p = .015$)
115 < PaO_2/F_{IO_2} ≤ 175 (n = 763)	25 ± 2% (n = 330)	26 ± 3% (n = 287)	36 ± 4% (n = 148)	28 ± 3% ($p = .016$)
PaO_2/F_{IO_2} ≤115 (n = 778)	30 ± 10% (n = 23)	28 ± 3% (168)	39 ± 2% (n = 587)	37 ± 3% ($p = .017$)

Requirement of FiO_2 > 0.7 = shunt > 30-40%

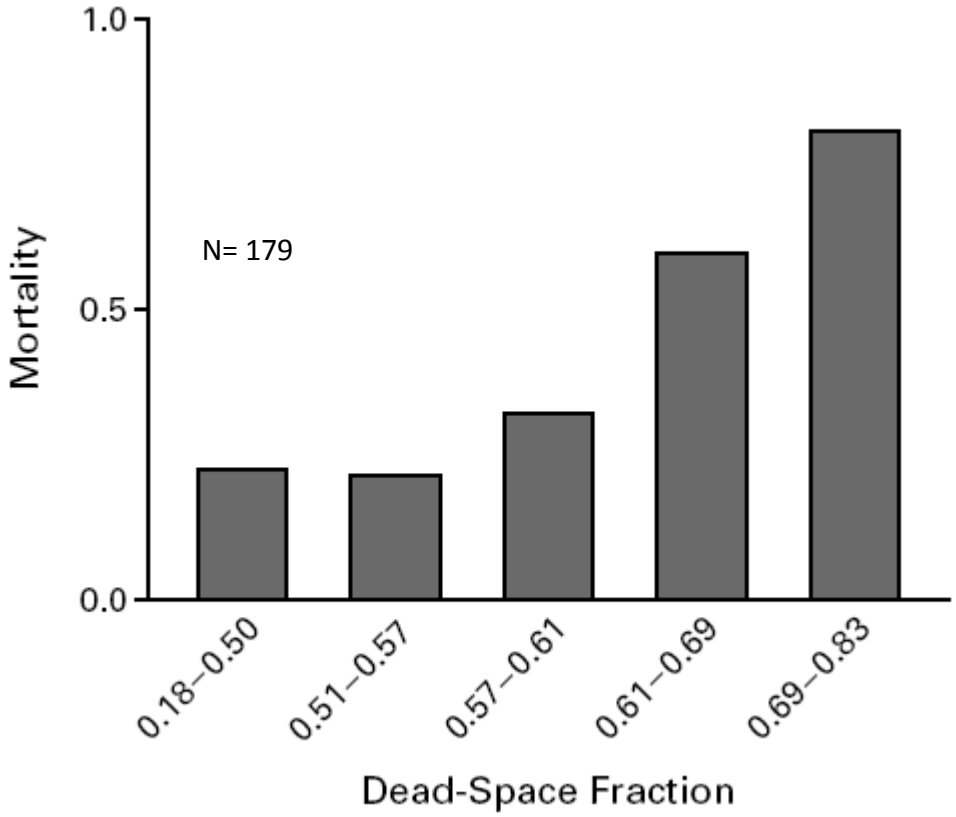


Consequences of increased dead space



PULMONARY DEAD-SPACE FRACTION AS A RISK FACTOR FOR DEATH IN THE ACUTE RESPIRATORY DISTRESS SYNDROME

THOMAS J. NUCKTON, M.D., JAMES A. ALONSO, R.R.T., RICHARD H. KALLET, R.R.T., M.S., BRIAN M. DANIEL, R.R.T., JEAN-FRANÇOIS PITTET, M.D., MARK D. EISNER, M.D., M.P.H., AND MICHAEL A. MATTHAY, M.D.



N Engl J Med, Vol. 346, No. 17 · April 25, 2002

The JAMA Network

From: **Acute Respiratory Distress Syndrome: The Berlin Definition**

JAMA. 2012;307(23):2526-2533. doi:10.1001/jama.2012.5669

Exploration of Proposed Variables to Define Severe ARDS

Severe ARDS Definition	Mild		Moderate		Severe	
	No. (%) of Patients	% Mortality (95% CI)	No. (%) of Patients	% Mortality (95% CI)	No. (%) of Patients	% Mortality (95% CI)
Consensus panel draft $PaO_2/FIO_2 \leq 100$ mm Hg + chest radiograph of 3 or 4 quadrants + PEEP ≥ 10 cm H_2O + ($C_{RS} \leq 40$ mL/cm H_2O or $\dot{V}E_{CORR} \geq 10$ L/min)	220 (22)	27 (24-30)	2344 (64)	35 (33-36)	507 (14)	45 (40-49)[b]
Consensus panel final $PaO_2/FIO_2 \leq 100$ mm Hg	220 (22)	27 (24-30)	1820 (50)	32 (29-34)	1031 (28)	45 (42-48)[b,c]

Abbreviations: ARDS, acute respiratory distress syndrome; C_{RS}, compliance of the respiratory system; FIO_2, fraction of inspired oxygen; PaO_2, arterial partial pressure of oxygen; PEEP, positive end-expiratory pressure; $\dot{V}E_{CORR}$, corrected expired volume per minute.

[a] The moderate group includes patients with $PaO_2/FIO_2 \leq 200$ mm Hg and patients with $PaO_2/FIO_2 \leq 100$ mm Hg who do not meet the additional criteria for severe ARDS in the draft definition. All patients are receiving at least 5 cm H_2O PEEP and have bilateral infiltrates on chest radiograph.

[b] $P < .001$ comparing mortality across stages of ARDS (mild, moderate, severe) for draft and final definitions.

[c] $P = .97$ comparing mortality in consensus draft severe ARDS to consensus final severe ARDS definitions.

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Exploration of Proposed Variables to Define Severe ARDS

In a *post hoc* analysis:

- PaO_2/FIO_2 of ≤100 mm Hg (13.3 kPa)
- Crs of ≤20 mL/cm H_2O
- VE_{CORR} ≥13 L/min

15% of the entire ARDS population and had a mortality of 52%(vs 37%- p<0.001).

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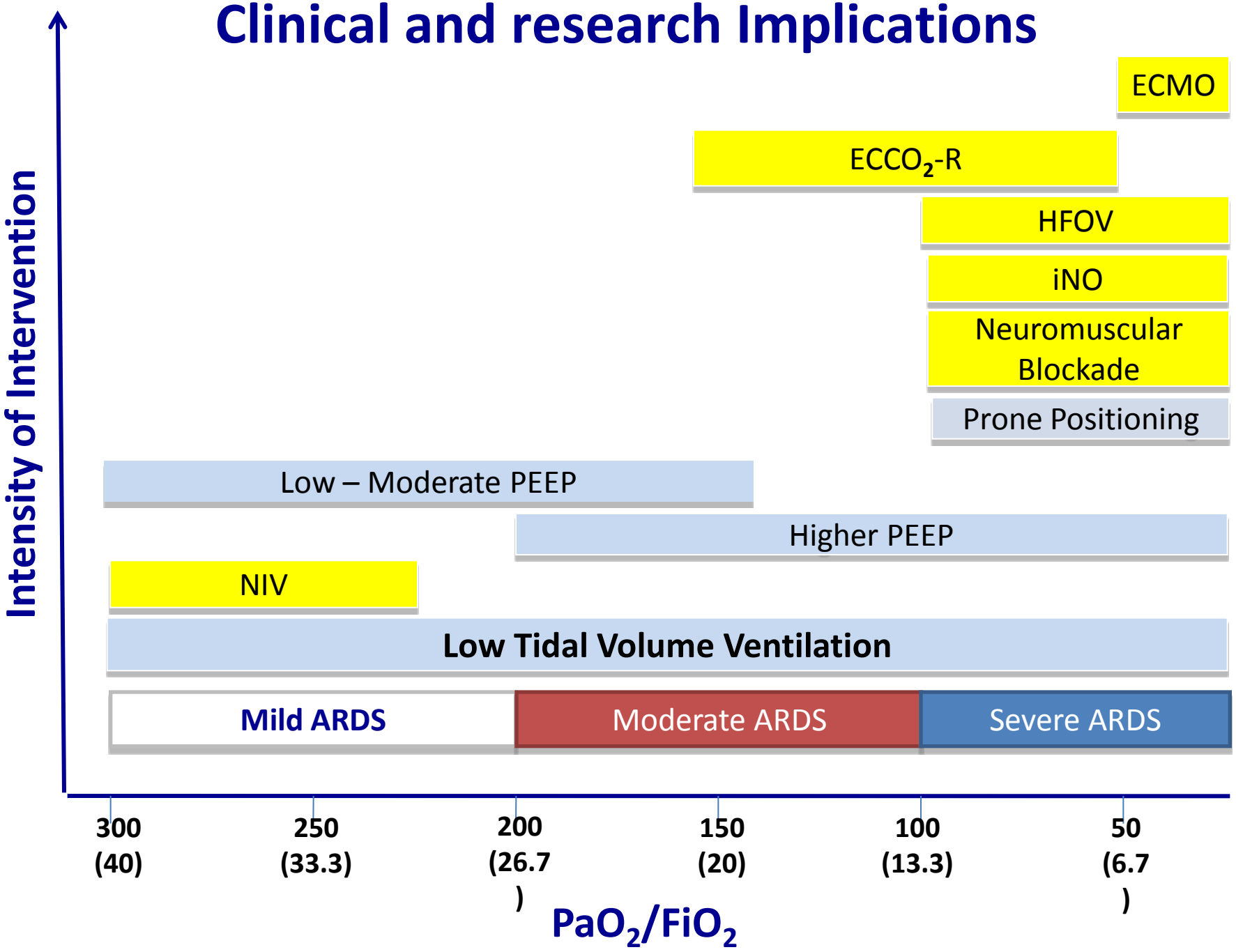
Category	Specific Criterion	Rationale for Inclusion	Reason Not Included
Oxygenation	Minimal FiO_2 requirement	• More consistency to PaO_2/FiO_2 ratio[8]	• Less feasible to mandate ventilator settings • Less relevant for $PaO_2/FiO_2 < 100$
	SpO_2/FiO_2 ratio	• Improved feasibility[9]	• Potential for misclassification of Mild as Severe ARDS[9]
	Higher PEEP requirement	• More consistency to PaO_2/FiO_2 ratio[10,11] • Improved face validity for Severe group	• Less feasible to mandate ventilator settings • Does not improve predictive validity
Imaging	Thoracic Computed Tomography (CT)	• Improved characterization of pulmonary opacities and lung volume [12]	• Infeasible to mandate based on scanner availability and/or patient safety
	Opacities in 3-4 quadrants on frontal CXR	• Improved face validity for Severe group • Associated with DAD[13]	• Poor reliability of 2 vs. 3-4 quadrants[1] • Does not improve predictive validity
	Electrical Impedance Tomography	• Improved characterization of pulmonary opacities and lung volume[14]	• Infeasible to mandate based on availability • Operating characteristics not well defined
Origin of Edema	Extravascular Lung Water	• Improved face validity • Higher values associated with mortality[15]	• Infeasible to mandate based on availability • Does not distinguish hydrostatic vs. inflammatory pulmonary edema
	Inflammatory Markers (IL-6 etc.)	• Improved face validity[16]	• Infeasible to mandate based on availability • Operating characteristics poor[16,17]
	Genetic Markers	• Improved face validity[18]	• Infeasible to mandate based on availability • Operating characteristics poor and lack of agreement on criterion standard[18]
Pulmonary Mechanics	Plateau Pressure	• Improved face validity • Higher values associated with mortality[19]	• Less feasible to mandate ventilator settings
	Dead Space	• Improved face validity • Higher values associated with mortality[20]	• Infeasible to mandate based on availability
	Respiratory System Compliance	• Improved face validity	• Does not improve predictive validity
	Minute Ventilation	• Improved face validity	• Does not improve predictive validity
Pathology	DAD on Lung Biopsy	• Confirmed pathological diagnosis[21,22]	• Infeasible to mandate lung biopsy

Clinical and research Implications



Conclusions

- This updated and revised Berlin Definition for ARDS addresses a number of the limitations of the AECC definition.
- Combining consensus discussions with empirical evaluation
- Investigators may choose to design future trials using 1 or more of the ARDS subgroups as a base study population

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eTable 3. Patient Demographics at Baseline in the Clinical Database

		All Patients*	ARDSNet	ICAP	ANZICS	KCLIP†
Hospitals		-	10-23	4	21 ICUs	21
Years enrolled		-	1996-2005	2004-2007	1999	1999-2000
Study design		-	Clinical trial	Academic centers cohort	Population cohort	Population cohort
N (%)		4188	2324 (55%)	397 (9%)	132 (3%)	1335 (32%)
N (%) evaluable by Berlin Definition		3670	2288 (62%)	391 (11%)	110 (3%)	881 (24%)
Age (years)	Mean	54.5	50.7	53.5	61.1	60.6
	Std	17.4	16.6	15.4	18.8	17.4
Gender	Male	2404 (57%)	1300 (56%)	208 (52%)	92 (70%)	804 (60%)
Primary Risk Factor	Pulmonary Sepsis	1470 (35%)	670 (29%)	184 (46%)	52 (39%)	564 (42%)
	Other Sepsis	1428 (34%)	833 (36%)	117 (30%)	44 (33%)	434 (33%)
	Trauma	302 (7%)	201 (9%)	3 (1%)	18 (14%)	80 (6%)
	Other/None	988 (24%)	620 (27%)	93 (23%)	18 (14%)	257 (19%)
Mortality	Dead	1436 (34%)	701 (30%)	195 (49%)	45 (34%)	495 (37%)
PaO_2/FiO_2 ratio	Mean	150	143	136	172	165
	Std	65.1	57.9	64.5	65.0	73.6
$PaO_2/FiO_2 \leq 200$ N (%)		3187 (76%)	1912 (82%)	324 (82%)	85 (64%)	866 (65%)
CXR with ≥ 3 quadrants	N (%)	3063 (73%)	2192 (94%)	348 (88%)	74 (56%)	449 (34%)
PEEP (cm H2O)	Mean	8.1	9.2	8.5	6.3	5.8
	Std	4.1	4.0	4.2	2.8	3.5
	Missing	338 (8%)	6 (0.3%)	1 (0.3%)	4 (3%)	327 (24%)
$V_{E,CORR}$ (L/min)	Mean	11.8	11.9	13.1	10.4	11.3
	Std	4.4	4.2	5.6	4.7	4.2
	Missing	307 (7%)	129 (6%)	7 (2%)	5 (4%)	166 (12%)
Crs (ml/cm H_2O)	Mean	34.0	33.1	31.2	39.8	37.0
	Std	13.9	13.8	13.8	14.8	13.8
	Missing (%)	1571 (38%)	683 (29%)	116 (29%)	96 (73%)	676 (51%)

* 334 patients excluded from original cohorts because onset PaO_2/FiO_2 or CXR not available
† KCLIP cohort reflects all patients regardless of FiO2

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eTable 4. Patient Demographics at Baseline in the Physiologic Database

		All Patients	Milan	Monza	Turin
N (%)*		269	113 (42%)	96 (36%)	60 (22%)
Age	Mean	59.9	57.6	61.8	61.1
	Std	16.1	16.9	16.7	13.2
Gender	Male	114 (66%)	77 (68%)	-	37 (62%)
	Missing	96	0	96	0
Primary Risk Factor	Pulmonary Sepsis	130 (48%)	41 (36%)	56 (58%)	33 (55%)
	Other Sepsis	70 (26%)	28 (25%)	22 (23%)	20 (33%)
	Trauma	23 (9%)	10 (9%)	7 (7%)	6 (10%)
	Other/None	41 (15%)	29 (26%)	11 (12%)	1 (2%)
	Missing	5 (2%)	5 (4%)	0 (0%)	0 (0%)
Mortality	Dead	97 (37%)	36 (34%)	32 (33%)	29 (50%)
	95% CI	31% - 43%	25% - 43%	24% - 44%	36% - 63%
	Missing	8	6	0	2
PaO_2/FiO_2	Mean	162	176	153	148
	Std	57.1	56.2	61.9	44.2
$PaO_2/FiO_2 \leq 200$ N (%)		203 (76%)	77 (68%)	73 (76%)	53 (88%)
PEEP (cm H2O)	Mean	11.5	10.4	11.7	13.0
	Std	3.4	2.5	3.8	3.6
	Missing	0	0	0	0
$V_{E,CORR}$ (L/min)	Mean	12.2	10.4	12.0	16.4
	Std	4.7	3.6	4.3	5.1
	Missing	10	0	1	9
Crs (ml/cm H_2O)	Mean	38.0	43.4	36.8	30.5
	Std	15.2	15.0	16.4	8.8
	Missing (%)	15	11	2	2

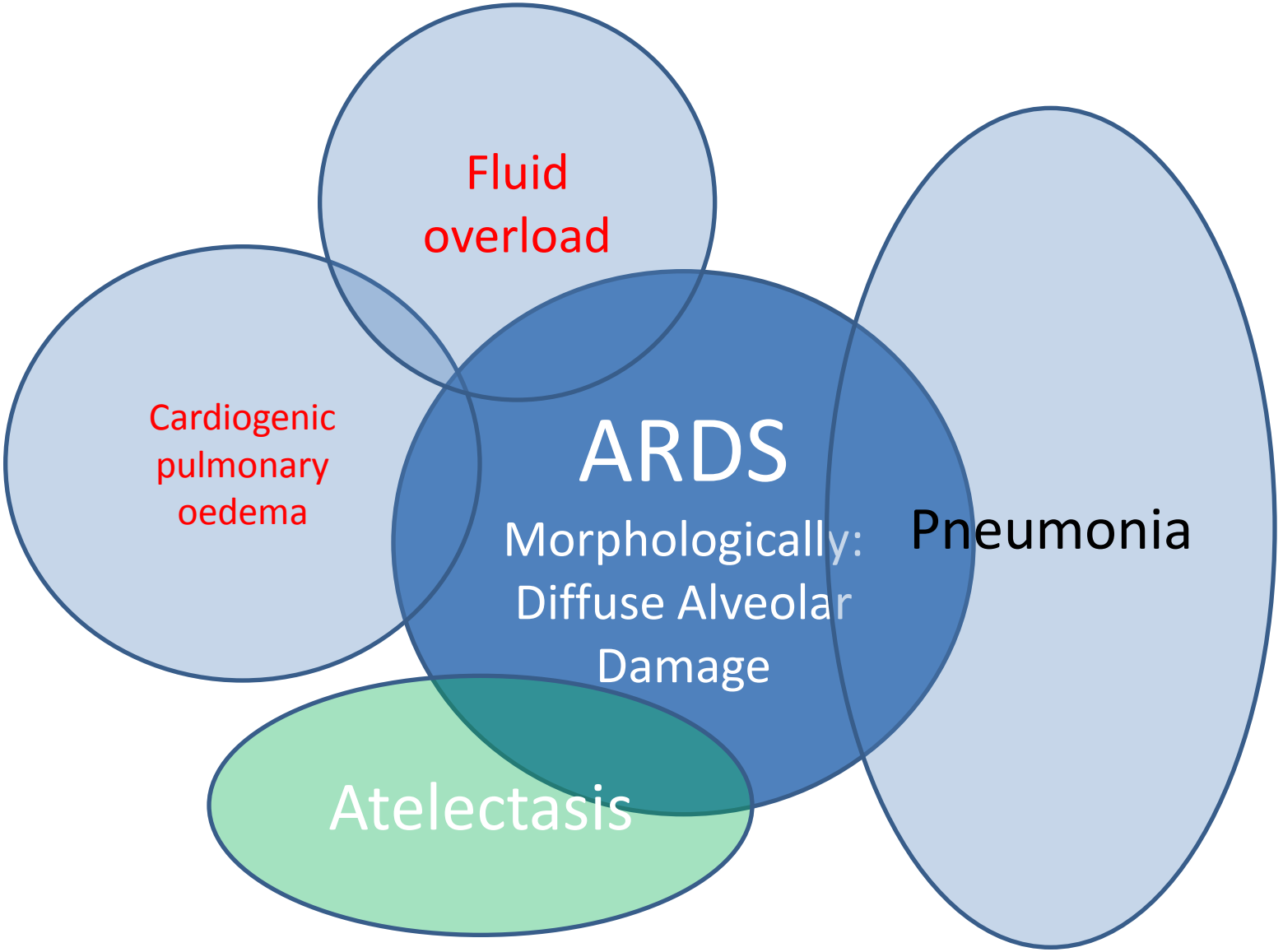
*9 patients excluded from original cohorts because onset PaO_2/FiO_2 or CXR not available

1. Why (re)-define ARDS?
2. The “BERLIN definition” of ARDS
3. Validation and prognostic implications

Why (Re)-define ARDS

- Absence of a gold standard
- Recognition depends upon a reliable definition
- Essential for :
  - institution of a standardized ‘best-evidence’ treatment
  - identification of subgroups of patients who may benefit from specific adjunctive interventions;
  - prognostication and resource allocation
  - Research – (consistent patient phenotype into clinical trials)

ARDS is an overlap Syndrome



Pathophysiology of ARDS

1. Oxygenation defect
2. Poor CO_2 elimination
3. Reduced lung volumes and compliance

American-European Consensus Conference (AECC) - 1994

	Timing	Oxygenation (PaO_2/FiO_2)	Chest Radiograph	Pulmonary Artery Wedge pressure
ALI	Acute onset	≤ 300 mmHg (40 kPa) (regardless of PEEP)	Bilateral infiltrates	≤18 mmHg/no evidence of left atrial hypertension
ARDS	Acute onset	≤ 200 mmHg (26 kPa) regardless of PEEP	Bilateral infiltrates	≤ 18 mmHg or no evidence of left atrial hypertension

From: **Acute Respiratory Distress Syndrome: The Berlin Definition**
JAMA. 2012;307(23):2526-2533. doi:10.1001/jama.2012.5669

Table 1. The AECC Definition[3]—Limitations and Methods to Address These in the Berlin Definition

	AECC Definition	AECC Limitations
Timing	Acute onset	No definition of acute[4]
ALI category	All patients with PaO_2/FIO_2 <300 mm Hg	Misinterpreted as PaO_2/FIO_2 = 201-300, leading to confusing ALI/ARDS term
Oxygenation	PaO_2/FIO_2 ≤300 mm Hg (regardless of PEEP)	Inconsistency of PaO_2/FIO_2 ratio due to the effect of PEEP and/or FIO_2[5-7]
Chest radiograph	Bilateral infiltrates observed on frontal chest radiograph	Poor interobserver reliability of chest radiograph interpretation[8,9]
PAWP	PAWP ≤18 mm Hg when measured or no clinical evidence of left atrial hypertension	High PAWP and ARDS may coexist[10,11] Poor interobserver reliability of PAWP and clinical assesments of left atrial hypertension[12]
Risk factor	None	Not formally included in definition[4]

Criticisms of AECC: *Hypoxaemia*

PaO_2/FiO_2 is not constant across a range of FiO_2 and may vary in response to ventilator settings, particularly PEEP

Gowda 1997, Ferguson 2004, Villar 1999, Villar 2007

Factors that affect PaO_2/FiO_2 *vs* FiO_2

- Cardiac output
- A-V O_2 Difference
- Distribution of blood flow to different V/Q regions
  - Low V/Q
  - Shunt
- Oxygen consumption
- Hb concentration

Effect of Intrapulmonary Shunt (S) and artero-venous O_2 Difference (AVD) on PaO_2/FiO_2

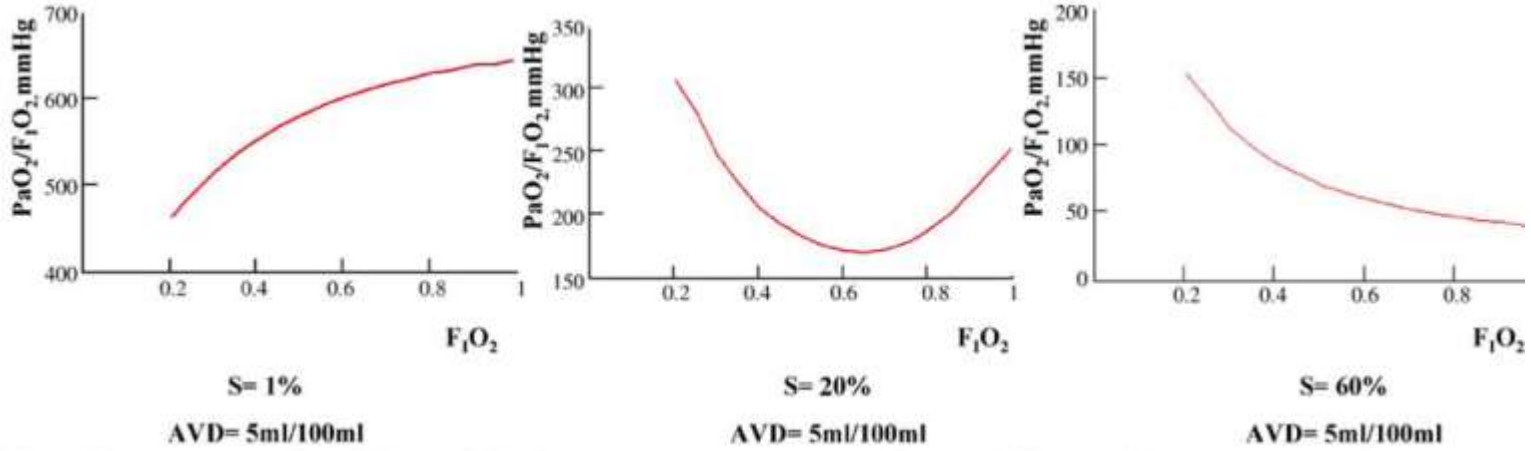
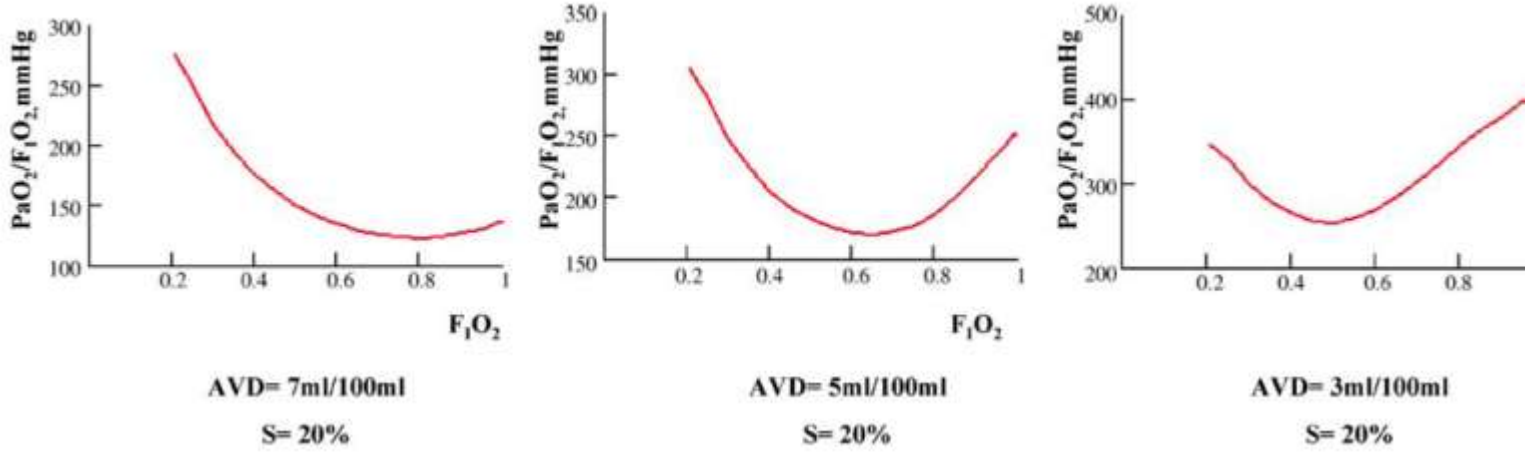


Fig. 1 Relation between PaO_2/FIO_2 and FIO_2 for a constant arterio-venous difference (*AVD*) and different shunt levels (*S*)



Intensive Care Med (2003) 29:1936–1942
DOI 10.1007/s00134-003-1943-4

ORIGINAL

Elisa Estenssoro
Arnaldo Dubin
Enrique Laffaire
Héctor S Canales
Gabriela Sáenz
Miriam Moseinco
Pierina Bachetti

Impact of positive end-expiratory pressure on the definition of acute respiratory distress syndrome

Intensive Care Med (2004) 30:1111–1116
DOI 10.1007/s00134-004-2163-2

ORIGINAL

Niall D. Ferguson
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Thomas E. Stewart

Screening of ARDS patients using standardized ventilator settings: influence on enrollment in a clinical trial

An Early PEEP/FI_{O_2} Trial Identifies Different Degrees of Lung Injury in Patients with Acute Respiratory Distress Syndrome

Jesús Villar[1], Lina Pérez-Méndez[1,2], José López[3], Javier Belda[4], Jesús Blanco[5], Iñaki Saralegui[6], Fernando Suárez-Sipmann[7], Julia López[8], Santiago Lubillo[1,9], and Robert M. Kacmarek[10], on behalf of the HELP Network*

An Early PEEP/FI_{O_2} Trial Identifies Different Degrees of Lung Injury in Patients with Acute Respiratory Distress Syndrome

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- 170 patients with ARDS by AECC criteria
- 24 hrs of standardized ventilator settings (FiO_2 0.5 and PEEP ≥ 10)

ARDS (P/F < 200)	58 %	→ 45%	Mortality
ALI (P/F 201-300)	32%	→ 20%	
ARF (P/F > 300)	9%	→ 6%	

AJRCCM 2007

Intensive Care Med (2003) 29:1936–1942
DOI 10.1007/s00134-003-1943-4

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Impact of positive end-expiratory pressure on the definition of acute respiratory distress syndrome

- 48 patients with ARDS diagnosis by AECC criteria with PEEP = 0 cm H_2O
- After 6 hrs of PEEP (mean 11.5 cm H_2O) 52% had P/F > 200 mmHg
- After 24 hrs of PEEP (mean 12.8 cm H_2O) 62% had P/F > 200 mm Hg
- Mortality 61% vs 53%

The value of positive end-expiratory pressure and F_{IO_2} criteria in the definition of the acute respiratory distress syndrome*

Martin Britos, MD; Elizabeth Smoot, MS; Kathleen D. Liu, MD; B. Taylor Thompson, MD; William Checkley, MD, PhD; Roy G. Brower, MD, for the National Institutes of Health Acute Respiratory Distress Syndrome Network Investigators

PaO_2/FiO_2 vs PEEP

Table 2. Mortality rates according to PaO_2/F_{IO_2} tertiles and positive end-expiratory pressure levels

PaO_2/F_{IO_2} Tertiles	PEEP ≤5 (n = 731)	5 < PEEP ≤ 10 (n = 999)	11 ≥ PEEP (n = 582)	Total[b]
PaO_2/F_{IO_2} >175 (n = 771)	23.1 ± 5%	22.0 ± 6%	25.9 ± 18%	23.1 ± 2% ($p > .70$)
110 < PaO_2/F_{IO_2} ≤ 175 (n = 763)	31.4 ± 9%	25.4 ± 5%	28.1 ± 13%	27.8 ± 3% ($p > .37$)
PaO_2/F_{IO_2} ≤115 (n = 778)	35.7 ± 2%	35.2 ± 7%	38.2 ± 7%	36.5 ± 3% ($p > .49$)

PaO_2/FiO_2 vs FiO_2

Table 3. Mortality rates according to PaO_2/F_{IO_2} tertiles and F_{IO_2} levels

PaO_2/F_{IO_2} Tertiles	F_{IO_2} ≤0.50 (n = 946)	0.50 < F_{IO_2} < 0.70 (n = 553)	0.70 ≤ F_{IO_2} (n = 819)	Total[b]
PaO_2/F_{IO_2} >175 (n = 771)	21 ± 2% (n = 593)	26 ± 4% (n = 98)	33 ± 5% (n = 84)	23 ± 2% ($p = .015$)
115 < PaO_2/F_{IO_2} ≤ 175 (n = 763)	25 ± 2% (n = 330)	26 ± 3% (n = 287)	36 ± 4% (n = 148)	28 ± 3% ($p = .016$)
PaO_2/F_{IO_2} ≤115 (n = 778)	30 ± 10% (n = 23)	28 ± 3% (168)	39 ± 2% (n = 587)	37 ± 3% ($p = .017$)

AECC

PaO_2/FiO_2 without PEEP or FiO_2 criteria

Heterogeneous patient population

- Different lung injury severities → different mortality rates
- Difficult to compare results of different studies
- Potential to dilute effect of a new intervention
- Potential to confound results of trials

Criticisms of AECC: *Chest X-ray*

Inter-observer reliability is only moderate even when applied by experts

Rubenfeld 1999, Meade 2000

Interobserver Variability in Applying a Radiographic Definition for ARDS*

Gordon D. Rubenfeld, MD, MSc; Ellen Caldwell, MS; John Granton, MD, FCCP; Leonard D. Hudson, MD, FCCP; and Michael A. Matthay, MD, FCCP†

FIGURE 4. Chest radiograph with 52% agreement. The majority of interpretation was consistent with ALI-ARDS. Readers commented on mild interstitial infiltrates.

(CHEST 1999; 116:1347–1353)

Inter-observer variability in diagnosing ARDS was only moderate (K=0.55)

Interobserver Variation in Interpreting Chest Radiographs for the Diagnosis of Acute Respiratory Distress Syndrome

MAUREEN O. MEADE, RICHARD J. COOK, GORDON H. GUYATT, RYAN GROLL, JOHN R. KACHURA, MICHEL BEDARD, DEBORAH J. COOK, ARTHUR S. SLUTSKY, and THOMAS E. STEWART

To measure the reliability of chest radiographic diagnosis of acute respiratory distress syndrome (ARDS) we conducted an observer agreement study in which two of eight intensivists and a radiologist, blinded to one another's interpretation, reviewed 778 radiographs from 99 critically ill patients. One intensivist and a radiologist participated in pilot training. Raters made a global rating of the presence of ARDS on the basis of diffuse bilateral infiltrates. We assessed interobserver agreement in a pairwise fashion. For rater pairings in which one rater had not participated in the consensus process we found moderate levels of raw (0.68 to 0.80), chance-corrected (κ 0.38 to 0.55), and chance-independent (Φ 0.53 to 0.75) agreement. The pair of raters who participated in consensus training achieved excellent to almost perfect raw (0.88 to 0.94), chance-corrected (κ 0.72 to 0.88), and chance-independent (Φ 0.74 to 0.89) agreement. We conclude that intensivists without formal consensus training can achieve moderate levels of agreement. Consensus training is necessary to achieve the substantial or almost perfect levels of agreement optimal for the conduct of clinical trials. **Meade MO, Cook RJ, Guyatt GH, Groll R, Kachura JR, Bedard M, Cook DJ, Slutsky AS, Stewart TE. Interobserver variation in interpreting chest radiographs for the diagnosis of acute respiratory distress syndrome.**

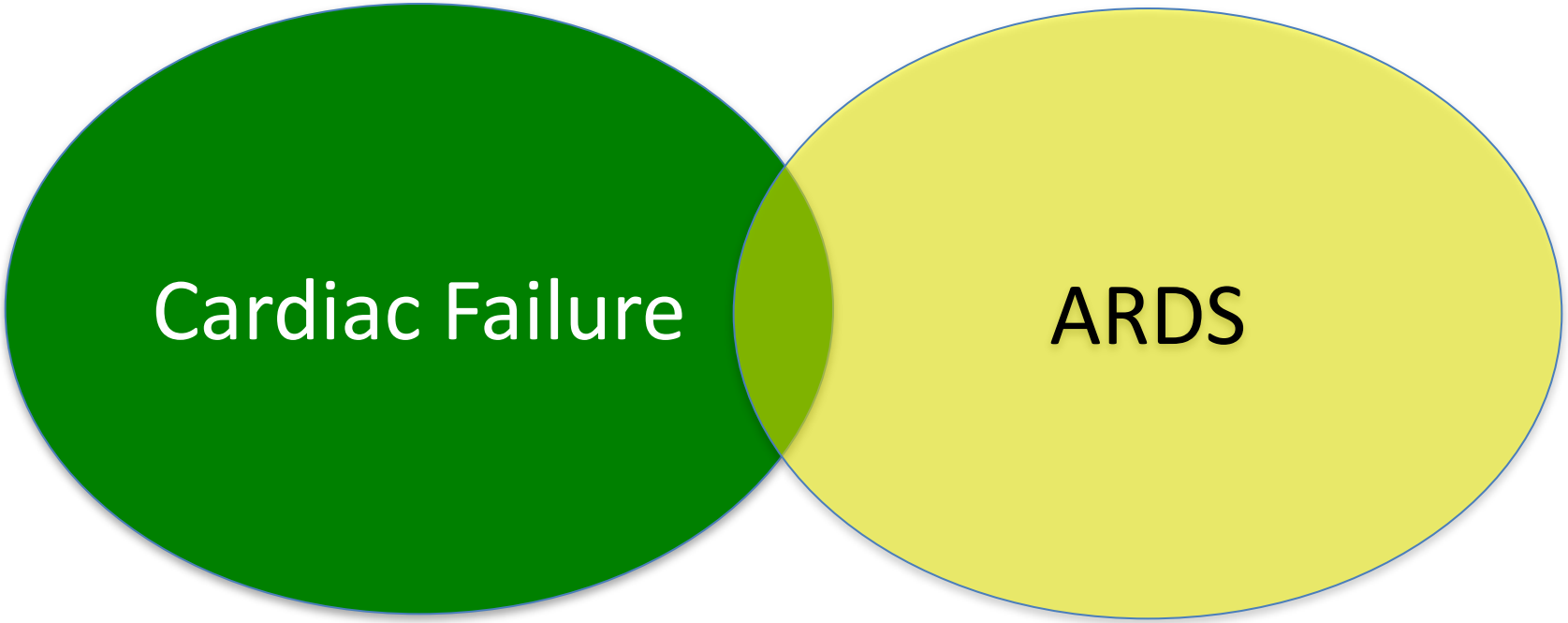
AM J RESPIR CRIT CARE MED 2000;161:85–90.

Criticisms of AECC: Wedge Pressure

Patients with ARDS may have an elevated PAWP(when measured); often because of transmitted airway pressures and/or vigorous fluid resuscitation

Ferguson 2002, ARDSNet 2006

ARDS and cardiac failure can co-exist



Report of the American-European consensus conference on ARDS: definitions, mechanisms, relevant outcomes and clinical trial coordination

G.R. Bernard, A. Artigas, K.L. Brigham, J. Carlet, K. Falke, L. Hudson, M. Lamy, J.R. LeGall, A. Morris, R. Spragg, The Consensus Committee

[syndrome]… that cannot be explained by, but may co-exist with, left atrial or pulmonary capillary hypertension.

ICM 1994

A. Rhodes
R. P. Moreno
B. Metnitz
H. Hochrieser
P. Bauer
Philipp Metnitz

Epidemiology and outcome following post-surgical admission to critical care

	All patients	Medical patients	Surgical patients	P^a
Number of patients (%)	171,009 (100)	82,505 (48.2)	88,504 (51.8)	
Patients per ICU ± SD	2,311 ± 1,716	1,115 ± 1,534	1,196 ± 1,327	
Age (years) ± SD	63.2 ± 17.1	62.5 ± 17.8	63.9 ± 16.4	<0.0001
Sex, male (%)	58.0	59.3	56.7	<0.0001
Co-morbid diseases				
None (%)	61.6	60.4	62.8	<0.0001
Chronic renal insufficiency (%)	6.6	7.5	5.8	<0.0001
Chronic respiratory insufficiency (%)	7.9	9.1	6.7	<0.0001
Chronic cardiac failure (NYHA IV) (%)	13.1	14.6	11.8	<0.0001
Malignant non-metastatic process (%)	6.4	2.8	9.8	<0.0001

13.1% of patients are presenting to ICU with NYHA IV

Intensive Care Med (2002) 28:1073–1077
DOI 10.1007/s00134-002-1354-y

ORIGINAL

Niall D. Ferguson
Maureen O. Meade
David C. Hallett
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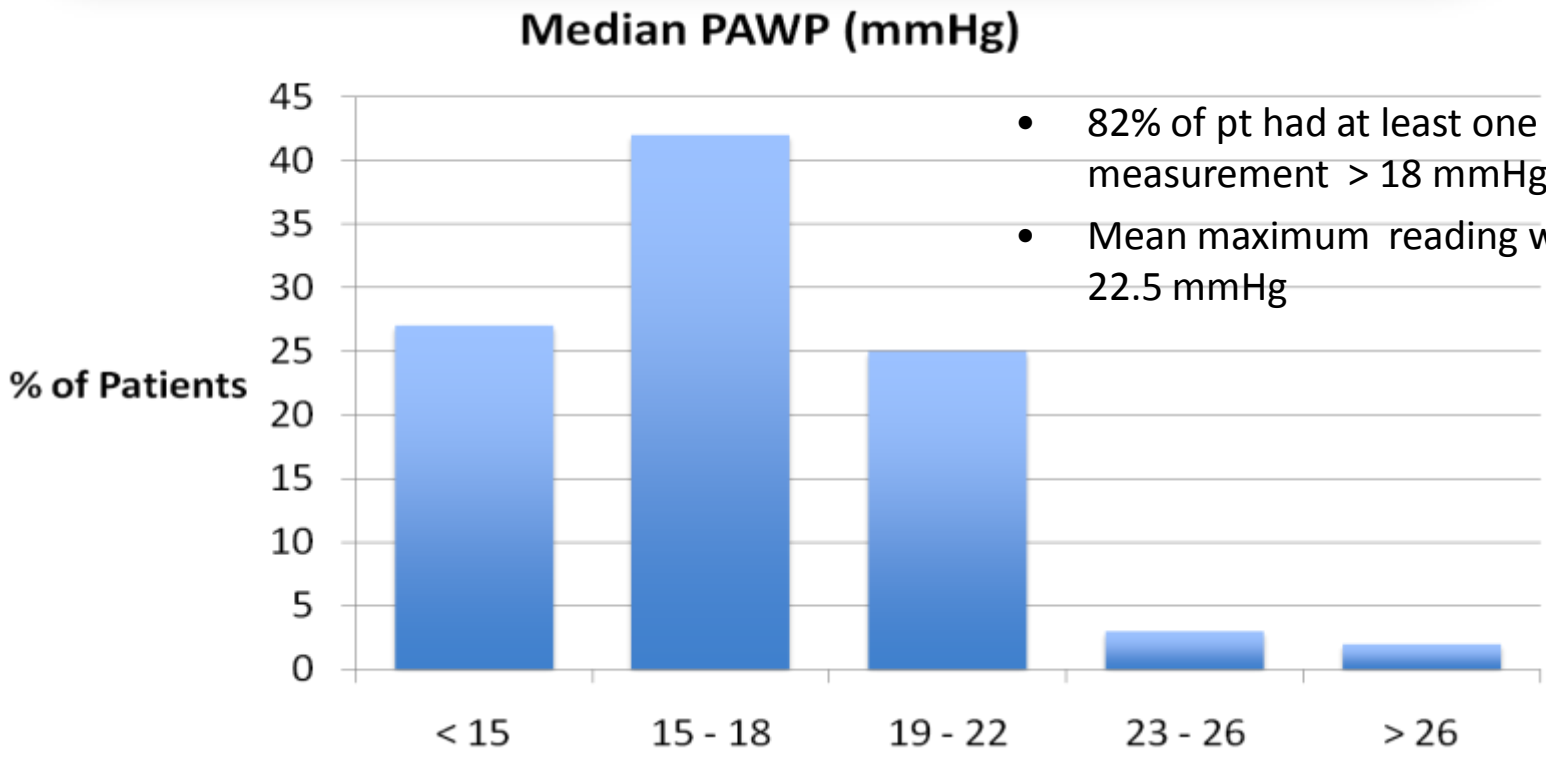
High values of the pulmonary artery wedge pressure in patients with acute lung injury and acute respiratory distress syndrome



- 82% of pt had at least one PAOP measurement > 18 mmHg
- Mean maximum reading was 22.5 mmHg

…therefore

- Cardiac failure is relatively common in ICU patients
- Cardiac failure and ARDS can co-exist
- PAOP is nowadays rarely measured.

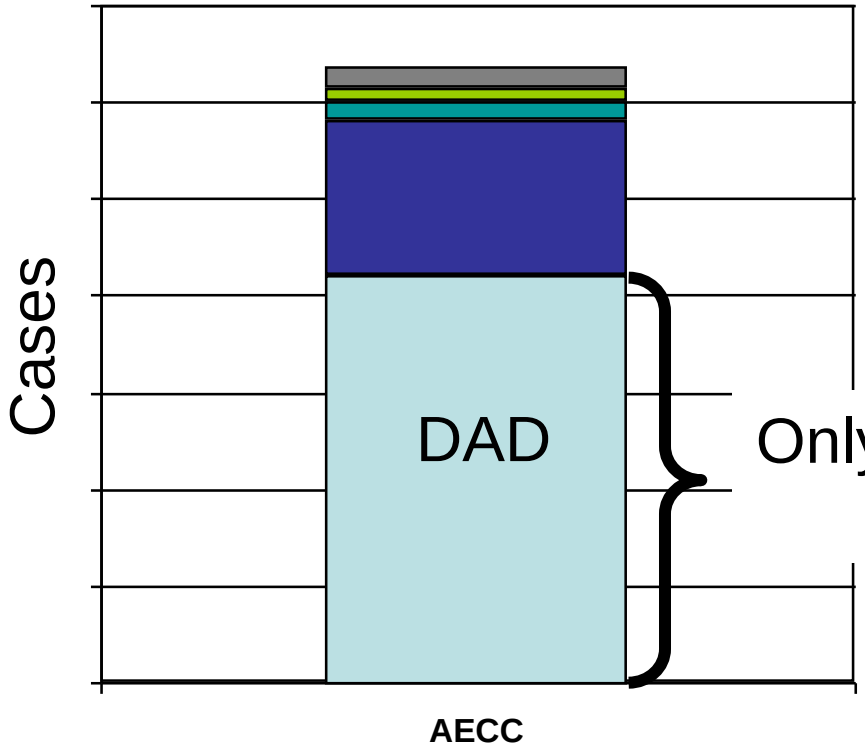
Criticisms of AECC: Sensitivity & Specificity

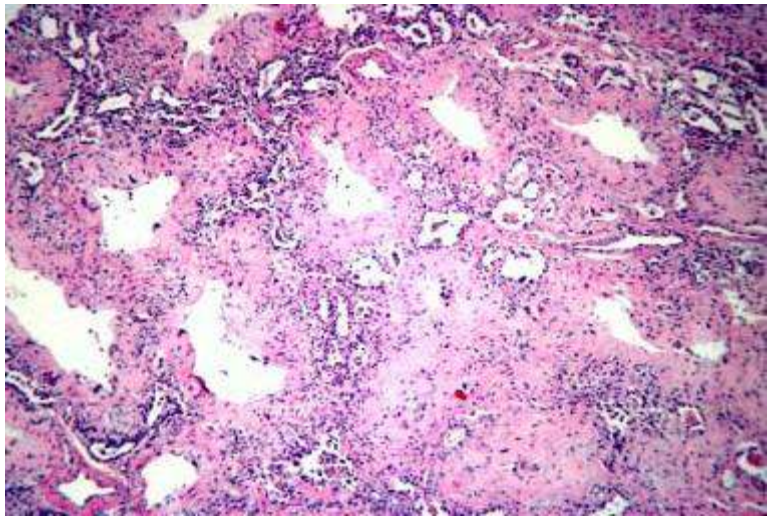
When AECC criteria are compared with DAD:
sensitivity is 84% specificity is 51%

Esteban 2004, Ferguson:2005

AECC definition – *Criterion validity*

What is the gold standard for ARDS?





Only 75% of AECC cases of ARDS show DAD

Esteban, et al *Ann Intern Med.* 2004;141:440-445