Where are we in the management of ARDS?

Ayman El-Menyar, MD,FRCP
Director Clinical Research in Trauma & Vascular Surgery , Qatar
Associate Prof Weill Cornell Med College

ARDS

‘An acute inflammatory syndrome with
Diffuse pulmonary oedema and respiratory failure that cannot be explained by, but may co-exist with, LVF

=

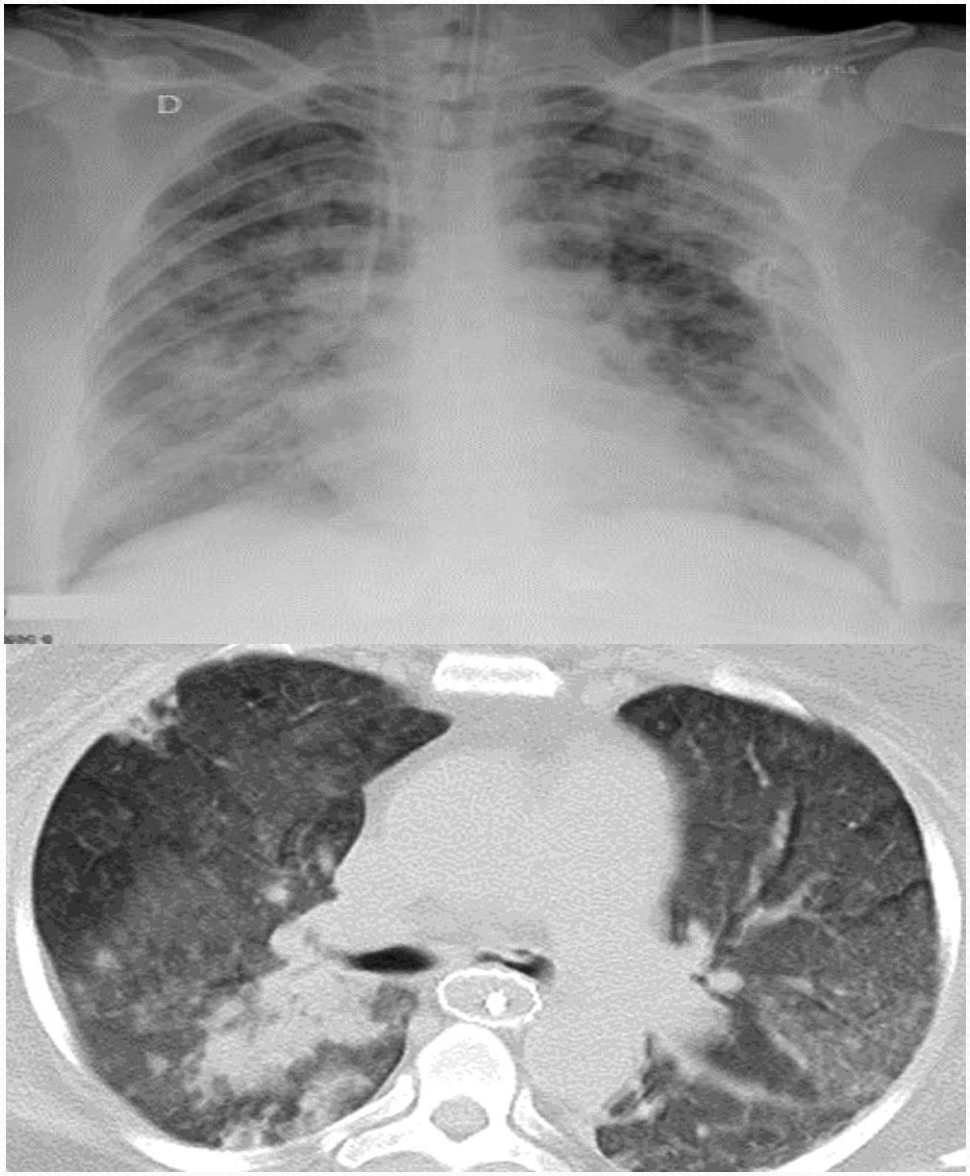
Acute onset of severe respiratory distress and cyanosis which is refractory to oxygen therapy and associated with diffuse CXR abnormality and decreased lung compliance

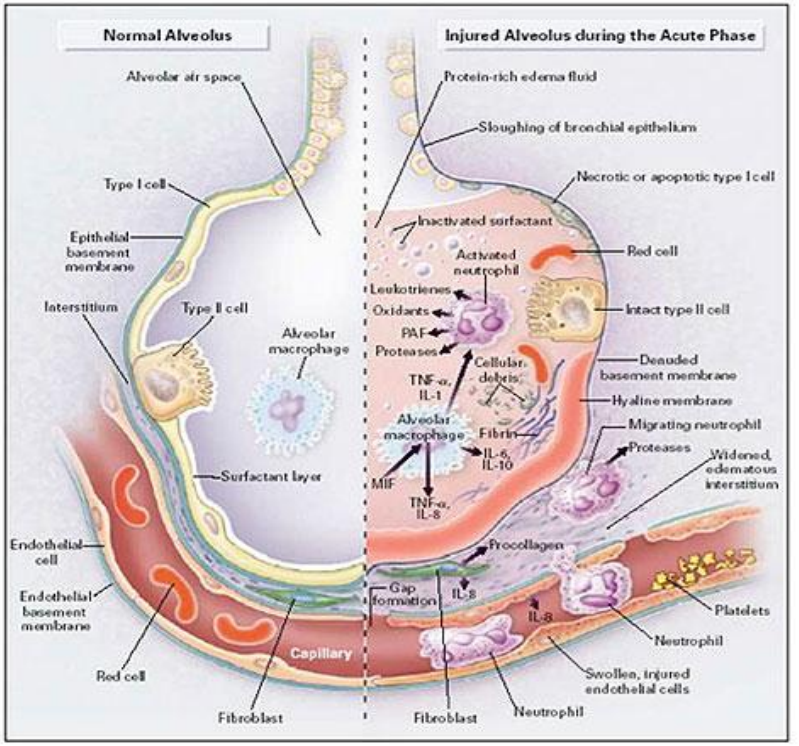
The American European Consensus Conference (AECC) definition

Pathophysiology

Acute inflammation affecting the lung's gas exchange surface, the alveolar-capillary membrane

The resulting acute inflammatory exudate inactivates surfactant leading to collapse and consolidation of distal airspaces with progressive loss of the lung's gas exchange surface area. This would be compensated for by hypoxic pulmonary vasoconstriction




Normal Alveolus
Injured Alveolus during the Acute Phase
Alveolar air space
Type I cell
Epithelial basement membrane
Interstitium
Type II cell
Alveolar macrophage
Surfactant layer
Endothelial cell
Endothelial basement membrane
Red cell
Capillary
Fibroblast
Protein-rich edema fluid
Sloughing of bronchial epithelium
Necrotic or apoptotic type I cell
Inactivated surfactant
Activated neutrophil
Red cell
Leukotrienes
Oxidants
PAF
Proteases
Intact type II cell
Cellular debris
TNF-α, IL-1
Denuded basement membrane
Hyaline membrane
Alveolar macrophage
Fibrin
Migrating neutrophil
Proteases
IL-6, IL-10
MIF
TNF-α, IL-8
Widened, edematous interstitium
Procollagen
Gap formation
IL-8
IL-8
Platelets
Neutrophil
Swollen, injured endothelial cells
Fibroblast
Neutrophil

- As a syndrome rather than a disease, there is no laboratory, imaging, or other ‘gold standard’ diagnostic investigation for ARDS.

- ARDS is caused by a huge range of conditions and as a consequence patients with ARDS are heterogeneous.

A four-point lung injury scoring system for quantifying ARDS severity based on:

1. level of PEEP,
2. ratio of the partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2)
3. dynamic lung compliance
4. degree of radiographic infiltration

Outcome

- Determined by:

1-the underlying causes of ARDS,

2-patient specific factors such as co- morbidities,

3-clinical management

4-the severity of illness

- Survivors commonly suffer from muscle weakness and neuropsychiatric problems, Fewer than 50% have returned to work 1y after leaving ICU
- The mortality rates are approximately 40%

ARDS cases at the Hamad Trauma center 2011-2018 (n=118)		
	Alive (60%)	Dead (40%)
Age	29(15-67)	30(14-91)
Males	93%	91.5%
Head	52.5%	47.5%
Chest	63%	37%
Abdomen	64%	36%
Long bone fracture	64%	36%
Spine	65%	35%
ISS	25(8-59)	30(9-75)
Sepsis	41%	38%
Pneumonia	59%	36%
Blood transfusion	90%	94%

Ten topics based on existing guideline recommendations :

- Corticosteroids
- Extra-corporeal Membrane Oxygenation (ECMO)
- Extra-corporeal Carbon Dioxide removal (ECCOR)
- Fluid Strategy
- High Frequency Oscillation (HFOV)
- Inhaled Vasodilators (iVasoD)
- Lung Protective Ventilation: Tidal Volume (Vt)
- Neuromuscular Blocking Agents (NMBA)
- Positive End-Expiratory Pressure (PEEP)
- Prone Positioning

https://www.ficm.ac.uk/news-events-education/news/guidelines-management-ards

Corticosteroids compared to placebo for Acute Respiratory Distress Syndrome

Patient or population: Adults with ARDS
Settings: Intensive Care
Intervention: Corticosteroids
Comparison: Placebo

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of evidence (GRADE)	Comments
	Control risk	Intervention risk				
	Placebo	**Corticosteroids**				
Mortality (Hospital)	**526 per 1000**	**326 per 1000** (121 to 663)	**RR 0.62** (0.23 to 1.26)	561 (5 studies)	+--- **VERY LOW** Due to serious risk of bias, serious inconsistency and serious imprecision	All studies conducted in the pre-lung protection strategy era. One study changed ventilation protocol during the study, following ARDS Net ARMA result
Mortality (Hospital or 60 day)	50% **500 per 1000**	45.5% **455 per 1000** (355 to 590)	**RR 0.91** (0.71 to 1.18)	725 (8 studies)	++-- **LOW** Due to serious inconsistency and serious imprecision	Pooled estimate from studies of both treatment and preventative steroids
Adverse Events	**350 per 1000**	**287 per 1000** (175 to 477)	**RR 0.82** (0.5 to 1.36)	494 (4 studies)	++-- **LOW** Due to serious risk of bias and serious imprecision	Composite of infection; neuromyopathy; diabetes, Gastro-intestinal bleeding and others

NS

Extra-Corporeal Membrane Oxygenation (ECMO) compared to standard care for Acute Respiratory Distress Syndrome

Patient or population: Adults with ARDS
Settings: Intensive Care
Intervention: ECMO
Comparison: Standard care

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of evidence (GRADE)	Comments
	Control risk **Usual Care**	Intervention risk **ECMO**				
Mortality (pooled)	51.7% 517 per 1000	32% **324 per 1000** (264 to 408)	**RR 0.64** (0.51 to 0.79)	505 (3 studies)	+--- **VERY LOW** Due to serious risk of bias and serious indirectness	Includes data from 2 quasi-randomised trials of patients with influenza A H1N1
Adverse Event: Bleeding	**0 per 1000**	**250 per 1000**	**RR 26.02** (3.68 to 184.16)	249 (2 studies)	+--- **VERY LOW** Due to serious risk of bias and serious indirectness	

Compared with conventional mechanical ventilation, use of venovenous ECMO in adults with severe acute respiratory distress syndrome was associated with reduced 60-day mortality. However, venovenous ECMO was also associated with a moderate risk of major bleeding (Lancet Respir Med. 2019 Feb;7(2):163-172..

Extra-Corporeal Carbon Dioxide Removal (ECCOR) compared to standard care for Acute Respiratory Distress Syndrome

Patient or population: Adults with **ARDS Settings:** Intensive Care **Intervention:** ECCOR **Comparison:** Standard Care

Outcomes	Relative effect (95% CI)	No of participants (studies)	Quality of evidence (GRADE)	Comments
Mortality (Hospital)	No MA conducted	457 (13 studies)	+--- VERY LOW Due to serious risk of bias, serious inconsistency, serious indirectness and serious imprecision	Mostly observational studies. Only 2 RCTs performed. No MA performed as variable approach to ECCOR and standard ventilator strategies. Mortality estimates presented as simple descriptions – 27 to 75% (mean 55.5%, standard deviation 47.2 to 60.3)
Adverse Events	No MA conducted	485 (13 studies)	+--- VERY LOW Due to serious risk of bias, serious inconsistency, serious indirectness and serious imprecision	0-25% incidence of arterial injury. Higher incidence of transfusion reported in 2 studies. Complications presented as aggregated simple descriptions – 0-25%

Conservative compared to liberal fluid management for Acute Respiratory Distress Syndrome

Patient or population: Adults with ARDS
Settings: Intensive Care
Intervention: Conservative fluid strategy
Comparison: Liberal fluid strategy

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of evidence (GRADE)	Comments
	Control risk	Intervention risk				
	Liberal fluid strategy	**Conservative fluid strategy**				
NS ↓ Mortality (pooled up to 60 days)	**311 per 1000**	**283 per 1000 (239 to 332)**	**RR 0.91** (0.77 to 1.07)	1206 (5 RCTs)	++-- **LOW** Due to serious indirectness and serious imprecision	Variable fluid strategies, fluid balance achieved and outcome reporting
Adverse Event: Acute kidney injury (AKI)				1000 (1 study)	+++- **MODERATE** Due to serious imprecision	Single study. There were a similar number of renal failure free days between conservative and liberal fluid management groups. In a post-hoc analysis where creatinine was adjusted for fluid balance, conservative fluid management was associated with lower incidence of AKI (58% versus 66%).
↑ Adverse Event: Renal replacement therapy (RRT)	**141 per 1000**	**100 per 1000 (70 to 139)**	**RR 0.71** (0.50 to 0.99)	1000 (1 study)	+++- **MODERATE** Due to serious imprecision	Single study

High Frequency Oscillatory Ventilation (HFOV) compared to usual care for Acute Respiratory Distress Syndrome

Patient or population: Adults with ARDS
Settings: Intensive Care
Intervention: HFOV
Comparison: Standard Care

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of evidence (GRADE)	Comments
	Control risk	Intervention risk				
	Standard Care	**HFOV**				
Mortality (ICU)	**308 per 1000**	**442 per 1000** (308 to 447)	**RR 1.22** (0.93 to 1.60)	1321 (3 studies)	+++- **MODERATE** Due to moderate inconsistency and mild indirectness	Changes in conventional ventilation strategies accounted for heterogeneity
Mortality (30 day)	**411 per 1000**	**404 per 1000** (373 to 432)	**RR 1.04** (0.83 to 1.31)	1580 (5 studies)	+++- **MODERATE** Due to moderate inconsistency	Changes in conventional ventilation strategies accounted for heterogeneity

Inhaled Vasodilators (iVasoD) compared to placebo or usual care for Acute Respiratory Distress Syndrome

Patient or population: Adults with ARDS
Settings: Intensive Care
Intervention: iVasoD, inhaled nitric oxide (iNO) for all studies
Comparison: placebo or usual care

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of evidence (GRADE)	Comments
	Control risk	Intervention risk				
	Placebo/Usual care	**iVasoD**				
Mortality (pooled)	**315 per 1000**	**346 per 1000** (296 to 406)	**RR 1.10** (0.94 to 1.29)	1142 (9 studies)	**++--** **LOW** Due to serious risk of bias and serious indirectness	Six out of 9 studies compared iNO with usual care rather than placebo Highly variable dose and duration of iNO and inclusion criteria
Adverse Event: Renal dysfunction	**124 per 1000**	**191 per 1000** (142 to 258)	**RR 1.55** (1.15 to 2.09)	919 (4 studies)	**++--** **LOW** Due to serious risk of bias and serious indirectness	Highly variable dose and duration of iNO and inclusion criteria Variable criteria used to define renal dysfunction

NS

Lower Tidal Volume compared with Higher Tidal Volume (at similar PEEP) for Acute Respiratory Distress Syndrome

Patient or population: Adults with ARDS
Settings: Intensive Care
Intervention: Lower tidal volume
Comparison: Higher, conventional tidal volume

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of evidence (GRADE)	Comments
	Control risk	Intervention risk				
	Higher tidal volume	**Lower tidal volume**				
↑ Mortality (60 Day)	**379 per 1000**	**467 per 1000** (303 to 717)	**RR 1.23** (0.8 to 1.89)	116 (1 study)	**++--** **LOW**	
Mortality (Hospital) ↓	**408 per 1000**	**338 per 1000** (290 to 400)	**RR 0.83** (0.71 to 0.98)	1033 (3 studies)	**+++-** **MODERATE** due to serious indirectness	
↑ Adverse Event: Barotrauma	**30 per 1000**	**35 per 1000** (19 to 65)	**RR 1.17** (0.63 to 2.18)	1149 (4 studies)	**+++-** **MODERATE** due to	

https://www.ficm.ac.uk/news-events-education/news/guidelines-management-ards

Lower Tidal Volume and Higher PEEP compared to Higher Tidal Volume and Lower PEEP for Acute Respiratory Distress Syndrome

Patient or population: Adults with ARDS
Settings: Intensive Care
Intervention: Lower Tidal Volume and higher PEEP (LV/PEEP)
Comparison: Higher Tidal Volume and lower PEEP (HV/PEEP)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of evidence (GRADE)	Comments
	Control risk	Intervention risk				
	Low PEEP/ HIGH TV	**High PEEP/ Low TV**				
Mortality (ICU)	**594 per 1000**	**339 per 1000** (238 to 487)	**RR 0.57** (0.4 to 0.82)	148 (2 studies)	**++--** **LOW**	ARDS Net ARMA study control group had higher TVs (11.5/12) than controls in the other 4 studies
Mortality (28 day)	**708 per 1000**	**383 per 1000** (220 to 645)	**RR 0.54** (0.31 to 0.91)	53 (1 study)	**++--** **LOW**	
Mortality (Hospital)	**609 per 1000**	**377 per 1000** (268 to 530)	**RR 0.62** (0.44 to 0.87)	148 (2 studies)	**++--** **LOW**	
Adverse Events: Nosocomial pneumonia	**458 per 1000**	**587 per 1000** (344 to 999)	**RR 1.28** (0.75 to 2.18)	53 (1 study)	**++--** **LOW**	
Adverse Events	**214 per 1000**	**165 per 1000** (105 to 261)	**RR 0.77** (0.49 to 1.22)	254 (2 studies)	**++--** **LOW**	

NS

Neuromuscular Blocking Agents (NMBAs) compared to placebo for Acute Respiratory Distress Syndrome

Patient or population: Adults with ARDS
Settings: Intensive Care
Intervention: NMBAs, cisatracurium infusion in all studies
Comparison: Placebo

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of evidence (GRADE)	Comments
	Control risk	Intervention risk				
	Placebo	**NMBAs**				
Mortality (ICU)	**447 per 1000**	**313 per 1000** (246 to 398)	**RR 0.70** (0.55 to 0.89)	431 (3 studies)	+++- **MODERATE** Due to serious risk of bias and serious indirectness	All trials studied a 48 hour infusion of cisatracurium besylate
Mortality (28 day)	**389 per 1000**	**257 per 1000** (195 to 339)	**RR 0.66** (0.50 to 0.87)	431 (3 studies)	+++- **MODERATE** Due to serious risk of bias and serious indirectness	See above
Mortality (Hospital)	**471 per 1000**	**339 per 1000** (273 to 429)	**RR 0.72** (0.58 to 0.91)	431 (3 studies)	+++- **MODERATE** Due to serious risk of bias and serious indirectness	See above truncated at 90 days
Adverse events: ICU acquired weakness	**298 per 1000**	**322 per 1000** (247 to 420)	**RR 1.08** (0.83 to 1.41)	431 (3 studies)	+--- **VERY LOW** Due to very serious risk of bias, serious inconsistency and serious indirectness	Lack of robust screening for weakness in first two RCTs. Third RCT only assessed weakness until ICU discharge. Screening methods differed greatly between RCT

NS

Higher PEEP compared to lower PEEP for Acute Respiratory Distress Syndrome

Patient or population: Adults with ARDS
Settings: Intensive Care
Intervention: Higher PEEP
Comparison: Lower PEEP

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of evidence (GRADE)	Comments
	Control risk	Intervention risk				
	Lower PEEP	**Higher PEEP**				
Mortality (Hospital)	**369 per 1000**	**332per 1000** (299 to 373)	**RR 0.90** (0.81 to 1.01)	2299 (3 studies)	**+++-** **MODERATE** due to serious inconsistency	Different strategies used to set PEEP between trials
Mortality (28 day)	**330 per 1000**	**274 per 1000** (221 to 334)	**RR 0.83** (0.67 to 1.01)	1921 (5 studies)	**++--** **LOW** due to very serious inconsistency	includes studies whose intervention compares high vs low tidal volume
Subgroup analysis patients with moderate / severe ARDS (p/F <27kPa) (Subgroup analysis) Mortality (ICU)	**561 per 1000**	**377 per 1000** (270 to 534)	**RR 0.67** (0.48 to 0.95)	205 (3 studies)	**++--** **LOW** due to very serious inconsistency	includes studies whose intervention compares high vs low tidal volume

Prone Positioning compared to standard care for Acute Respiratory Distress Syndrome

Patient or population: Adults with ARDS
Settings: Intensive Care
Intervention: Prone Positioning
Comparison: Standard Care

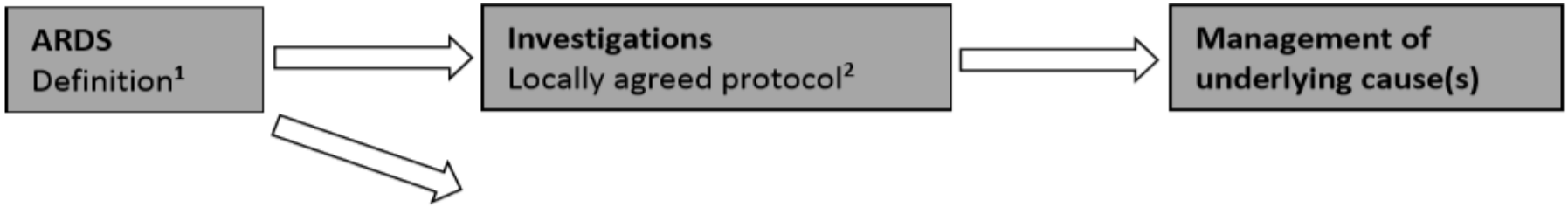
Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of evidence (GRADE)	Comments
	Control risk	Intervention risk				
	Standard Care	**Prone Positioning**				
Mortality (pooled)	**467 per 1000**	**421 per 1000** (383 to 458)	**RR 0.90** (0.82 to 0.98)	2141 (8 studies)	+--- **VERY LOW** due to serious risk of bias, very serious inconsistency and serious indirectness	Failure to blind outcome, failure of allocation concealment, and incomplete outcome data Includes sub-groups receiving additional interventions known to demonstrate a potential mortality benefit
Sub group analysis Prone positioning with lung protective ventilation Mortality	**447 per 1000**	**326 per 1000** (277 to 384)	**RR 0.73** (0.62 to 0.86)	910 (5 studies)	+++- **MODERATE** Due to serious risk of bias	Failure to blind outcome, failure of allocation concealment, and incomplete outcome data
Sub group analysis Prone positioning without lung protective ventilation Mortality	**483 per 1000**	**488 per 1000** (435 to 546)	**RR 1.01** (0.9 to 1.13)	1231 (3 studies)	+++- **MODERATE** Due to serious risk of bias	See above

NS

Table 1: Summary of the FICM/ICS Guidelines for the management of ARDS in adult patients

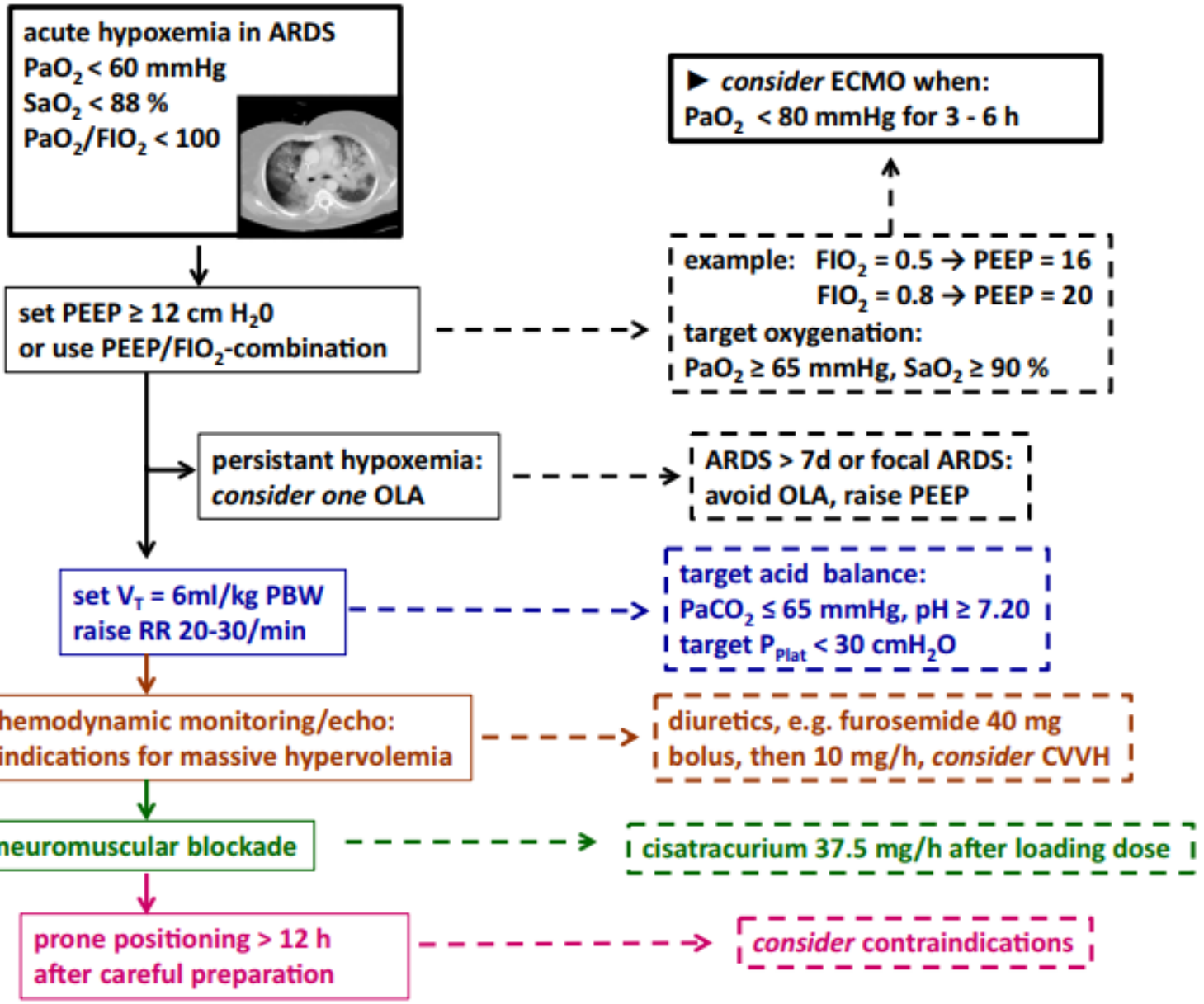
Topic	GRADE Recommendation	Conditions
Tidal Volume	Strongly in favour	Tidal volume ≤ 6 ml/Kg ideal body weight; Plateau pressure < 30cmH_2O
Prone Positioning	Strongly in favour	Proning for ≥ 12 hours per day Patients with moderate/severe ARDS (P:F ratio ≤ 20kPa)
High frequency oscillation (HFOV)	Strongly against	
Conservative Fluid Management	Weakly in favour	
Higher Peek End-Expiratory Pressure (PEEP)	Weakly in favour	Patients with moderate or severe ARDS (PF ratio ≤ 27kPa)
Neuromuscular Blocking Agents (NMBA)	Weakly in favour	Evidence for cisatracurium besylate Continuous 48-hour infusion Patients with moderate/severe ARDS (≤ 20kPa)
Extra-Corporeal Membrane Oxygenation (ECMO)	Weakly in favour	With lung-protective mechanical ventilation Patients with severe ARDS, lung injury score ≥3 or pH <7.20 due to uncompensated hypercapnoea
Inhaled Vasodilators	Weakly against	Evidence for inhaled nitric oxide
Corticosteroids	Research recommendation	
Extra-Corporeal Carbon Dioxide Removal (ECCO2R)	Research recommendation	

https://www.ficm.ac.uk/news-events-education/news/guidelines-management-ards

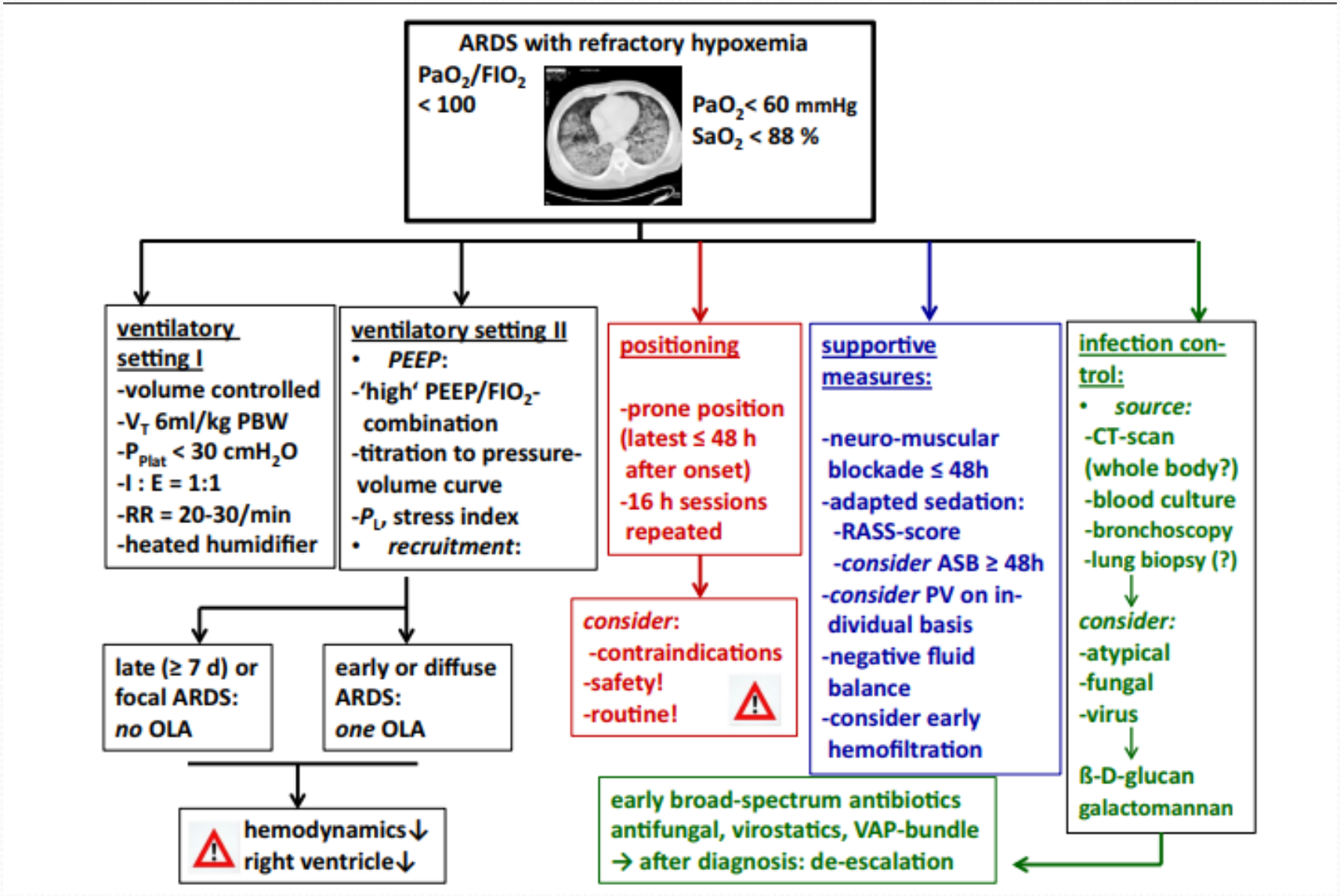


ARDS specific management		
Mild 200 mmHg < PaO_2/FIO^2 ≤ 300 MmHg with PEEP or CPAP 5 cmH_2O	**Moderate** 100 mm Hg < PaO_2/FIO_2 ≤ 200 Mm Hg with PEEP 5 cmH_2O	**Severe** PaO_2/FIO_2 < 100 mm Hg with PEEP 5 cmH_2O
Conservative fluid balance target		
Low tidal volume ventilation (≤6 ml/Kg IBW[3]; Plateau pressure <30cmH_2O)		
	Prone positioning (≥12 hr/day)	
	Neuro-muscular blockade (first 48 hour)	
	Higher PEEP[4]	
		Refer to local ECMO centre[5]
		Other measures[6]
Non ARDS-specific support		
Rehabilitation: early mobilisation, NICE CG83[7]		
Nutrition: enteral where possible, trophic feeding acceptable initially, consider naso-jejunal tube after pro-kinetics for absorption failure		
Transfusion of blood products: avoid unless absolutely indicated		
Sedation:		

https://www.ficm.ac.uk/news-events-education/news/guidelines-management-ards



Intensive Care Med (2016) 42:699–711



Intensive Care Med (2016) 42:699–711

Thanks

1	**ARDS Definition**	**Timing**	Acute: onset within a week of onset of a known insult, or new or worsening respiratory symptoms
		Respiratory failure	$PaO_2/FIO_2 \leq 300$ mmHg with PEEP (or CPAP 5 cmH_2O for mild ARDS)
		Radiology Chest radiograph or CT scan	Bilateral opacities, not fully accounted for by pleural effusions, collapse or nodules
		Origin of oedema	Not likely to be caused by left sided heart failure or fluid over-load. Echocardiography indicated to assess cardiac function and to detect right-to-left shunts
2	**Investigations**	To diagnose under-lying conditions and complications, to monitor progress and aid prognostication (see appendix B)	
3	**Ideal Body Weight (IBW)**	Male = 50 + 2.3 x ((height cm/2.54)-60) Female = 45.5 + 2.3 x ((height cm/2.54)-60)	
4	**High PEEP**	Individual titration of PEEP recommended. Mean PEEP levels in 'High PEEP' groups in randomised trials was approximately 15 cmH_2O on day 1	
5	**Referral to local ECMO Centre UK**	Potentially reversible respiratory failure Murray Lung Injury Score > 2.5 Points: 0 | 1 | 2 | 3 | 4 P/F ratio (kPa): 240 | 30-39.9 | 23.3-29.9 | 13.3-23.2 | <13.3 PEEP (cmH_2O): ≤5 | 6-8 | 9-11 | 11-14 | ≥15 Compliance (ml/cmH_2O): 280 | 60-79 | 40-59 | 20-39 | ≤19 CXR quadrants infiltrated: 0 | 1 | 2 | 3 | 4 Murray Score = Total Points / 4 PH < 7.2 FiO_2 not > 0.8 for 7 days Plateau pressure not > 30 cmH_2O for 7 days No contraindication to anticoagulation	
6	**Exceptional Measures**	Under exceptional circumstances (for example contraindication to ECMO) short term improvements in gas exchange and right ventricular function can be achieved by using recruitment manoeuvres, inhaled vasodilators (nitric oxide or nebulised prostacyclin) or high frequency oscillatory ventilation depending on local expertise and availability	
7	**NICE CG83**	https://www.nice.org.uk/guidance/cg83/evidence/full-guideline-242292349	

https://www.ficm.ac.uk/news-events-education/news/guidelines-management-ards

Table 2: The Lung Injury Prediction Score

Predisposing conditions	LIPS Score	Examples
Shock	2	(1) Patient with history of alcohol abuse with septic shock from pneumonia requiring $FIO_2 > 0.35$ Emergency room: sepsis + shock + pneumonia + alcohol abuse + $FIO_2 > 0.35$ 1 + 2 + 1.5 + 1 + 2 = 7.5 (2) Motor vehicle accident with traumatic brain injury, lung contusion, and shock requiring $FIO_2 > 0.35$ Traumatic brain injury + lung contusion + shock + $FIO_2 > 0.35$ 2 + 1.5 + 2 + 2 = 7.5 (3) Patient with history of diabetes mellitus and urosepsis with shock sepsis + shock + diabetes 1 + 2 − 1 = 2
Aspiration	2	
Sepsis	1	
Pneumonia	1.5	
High-risk surgery*		
Orthopaedic spine	1	
Acute abdomen	2	
Cardiac	2.5	
Aortic vascular	3.5	
High-risk trauma		
Traumatic brain injury	2	
Smoke inhalation	2	
Near drowning	2	
Lung contusion	1.5	
Multiple fractures	1.5	
Risk modifiers		
Alcohol abuse	1	
Obesity (BMI>30)	1	
Hypoalbuminemia	1	
Chemotherapy	1	
$FIO_2 > 0.35$ (>4 L/min)	2	
Tachypnoea (RR > 30)	1.5	
$SpO_2 < 95\%$	1	
Acidosis (pH < 7.35)	1.5	
Diabetes mellitus**	-1	

BMI = body mass index; RR = respiratory rate; SPO_2 = oxygen saturation by pulse oximetry
*Add 1.5 points in case of emergency surgery
**Only in cases of sepsis