ARDS

Updates

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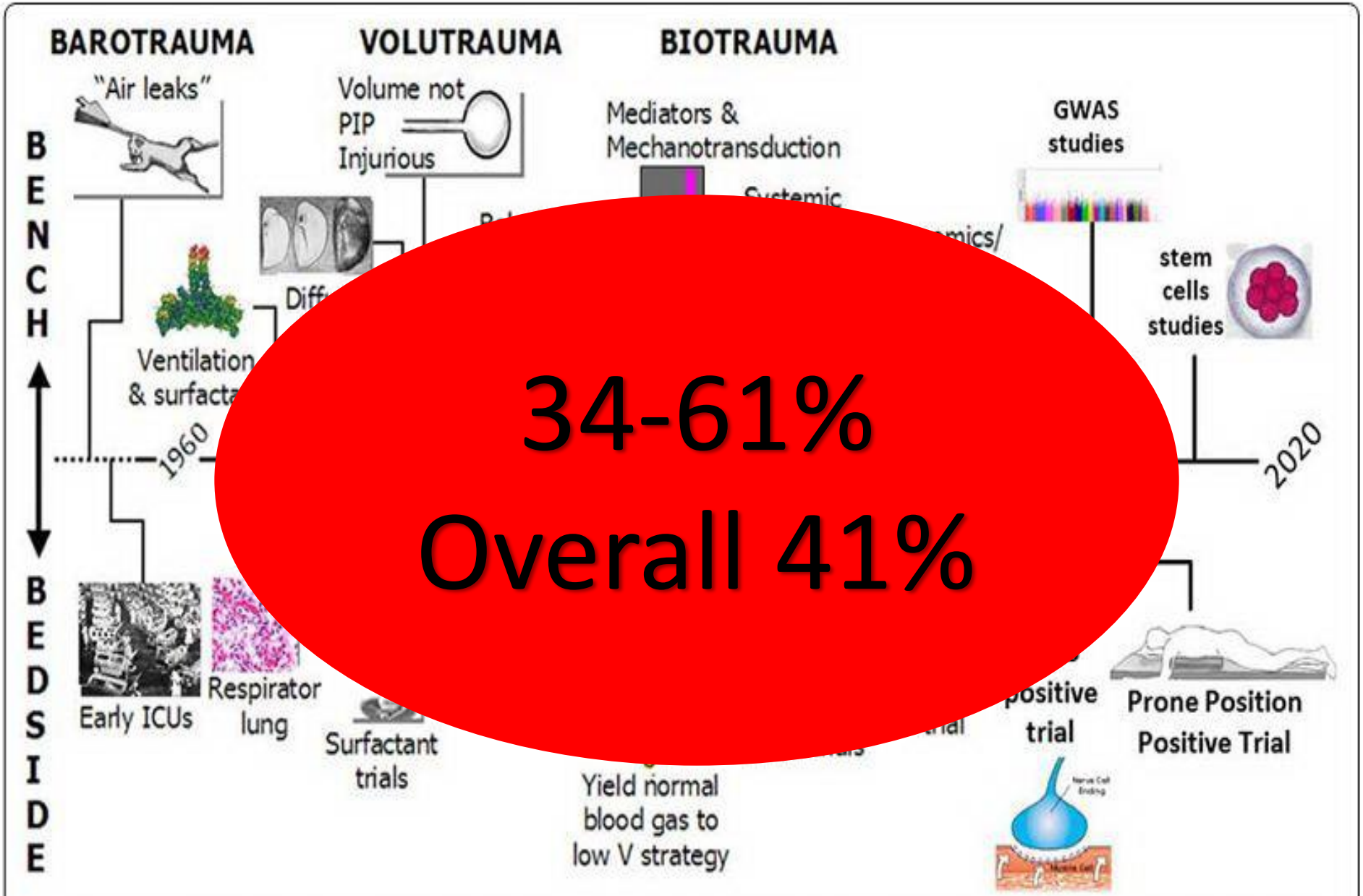


Fig. 1 Major advances related to the acute respiratory distress syndrome (ARDS) and ventilator-induced lung injury (VILI): from the bench to the bedside. *GWAS* genome-wide association studies, *ICU* intensive care unit, *NMB* neuromuscular blocking agents, *PIP* peak inspiratory pressure, *PMN* polymorphonuclear cells, *V* volume, *vent.* ventilation. (Modified from [21])

Guidelines

BMJ Open Respiratory Research

Guidelines on the management of acute respiratory distress syndrome

Mark J D Griffiths,[1] Danny Francis McAuley,[2] Gavin D Perkins,[3] Nicholas Barrett,[4] Bronagh Blackwood,[2] Andrew Boyle,[2] Nigel Chee,[5] Bronwen Connolly,[6] Paul Dark,[7] Simon Finney,[1] Aemun Salam,[1] Jonathan Silversides,[2] Nick Tarmey,[5] Matt P Wise,[8] Simon V Baudouin[9]

Intensive Care Med
https://doi.org/10.1007/s00134-023-07050-7

CONFERENCE REPORTS AND EXPERT PANEL

ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies

CORTICOSTEROIDS

Table 1 Corticosteroids compared to placebo for ARDS

Patient or population: adults with ARDS
Settings: intensive care
Intervention: corticosteroids
Comparison: placebo

Out	Illustrative comparative risks (95% CI)		Relative effect (95%	No. of participants	Quality of evidence	
	Control risk	Intervention risk				
Mor (hos						cted in ction study on ne RDS
Mor (hos day)						ıd oids
					and serious imprecision	
Adverse events	350 per 1000	287 per 1000 (175 to 477)	RR 0.82 (0.5 to 1.36)	494 (four studies)	++-- LOW Due to serious risk of bias and serious imprecision	Composite of infection; neuromyopathy; diabetes, gastrointestinal bleeding and others
Adverse event: post-ICU cognitive function	Mean—74.31	Mean—10.71 higher (5.22 higher to 16.2 higher)		100 (one study)	+--- VERY LOW Due to very serious risk of bias and serious indirectness	Assessed with: cognitive function component of QLQ-C30 Scale from: 0 to 100, with a higher score representing better cognitive function

GRADE recommendation statement

The use of corticosteroids in established ARDS should be the subject of a suitably powered, multicentre RCT with long-term follow-up (GRADE Recommendation: research recommendation).

frontiers in Medicine

ORIGINAL RESEARCH
published: 26 July 2021
doi: 10.3389/fmed.2021.678260

The Role of Glucocorticoids in the Treatment of ARDS: A Multicenter Retrospective Study Based on the eICU Collaborative Research Database

Conclusion: Rational use of GCs can reduce the ICU mortality of ARDS patients in ICU. In addition to the use of GCs treatment, clinicians should also focus on the shifting trend of PaO2/FiO2 level to provide better conditions for patients' survival.

Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017

Recommendation:

We suggest use of corticosteroids in patients with early moderate to severe ARDS (PaO_2/FiO_2 of < 200 and within 14 days of onset)
(conditional recommendation, moderate quality of evidence)

Methylprednisolone in patients with early (up to day 7 of onset; P/F of < 200) in a dose of 1 mg/kg/day and

late (after day 6 of onset) persistent ARDS in a dose of 2 mg/kg/day followed by slow tapering over 13 days).

- MP is suggested because of its greater penetration into lung tissue and longer residence time.
- MP should be weaned slowly (6–14 days) and not stopped rapidly (2–4 days) or abruptly as deterioration may occur from reconstituted inflammatory response.
- Glucocorticoid treatment blunts the febrile response; therefore, infection surveillance is recommended to ensure prompt identification and treatment of infection

Intensive Care Med (2017) 43:155–170
DOI 10.1007/s00134-016-4573-3

SYSTEMATIC REVIEW

Conservative fluid management or deresuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness: a systematic review and meta-analysis

- In adults and children with ARDS, sepsis or SIRS, a conservative or deresuscitative fluid strategy results in an increased number of VFD and a decreased ICU LOS compared with a liberal strategy or standard care.
- The effect on mortality remains uncertain.

Uhlig *et al. Critical Care* 2014, **18**:R10
http://ccforum.com/content/18/1/R10

CRITICAL CARE

RESEARCH Open Access

Albumin versus crystalloid solutions in patients with the acute respiratory distress syndrome: a systematic review and meta-analysis

Christopher Uhlig[1†], Pedro L Silva[1,2†], Stefanie Deckert[3], Jochen Schmitt[3] and Marcelo Gama de Abreu[1*]

Therapy with albumin solutions improved the early oxygenation without affecting mortality, as compared to crystalloid solutions.

There is a need for large RCTs addressing the potential benefits of albumin solutions, or even synthetic colloids, as volume expanders in ARDS patients.

Fluid Management

Table 4 Conservative compared to liberal fluid management for ARDS

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: Liberal fluid strategy	Intervention risk: Conservative fluid strategy				
Mortality (p… up to 60 da…						…id strategies, …ce achieved …ne reporting
Adverse ev… AKI						…ly. There …ilar number …ure free days between conservative and liberal fluid management groups. In a posthoc analysis where creatinine was adjusted for fluid balance, conservative fluid management was associated with lower incidence of AKI (58% vs 66%).
Adverse event: RRT	141 per 1000	100 per 1000 (70 to 139)	RR 0.71 (0.50 to 0.99)	1000 (one study)	+++- MODERATE Due to serious imprecision	Single study

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; RRT, renal replacement therapy.

Grade recommendation statement

We suggest the use of a conservative fluid strategy in patients with ARDS (GRADE recommendation: weakly in favour).

iVasoDs

Table 6 iVasoD compared to placebo or usual care for ARDS

Patient or population: adults with ARDS
Settings: intensive care
Intervention: iNO for all studies
Comparison: placebo or usual care

Outcom	Illustrative comparative risks (95% CI) Control risk	Intervention risk	Relative	No. of	Quality of	
Mortality (pooled)					of bias and serious indirectness	ies usual cebo 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 (four 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

ARDS, acute respiratory distress syndrome; iNO, iVasoD, inhaled nitric oxide; iVasoD, inhaled vasodilators.

Grade recommendation statement

We do not suggest using iNO in patients with ARDS (GRADE Recommendation: weakly against).

NMBDs

Grade recommendation statement

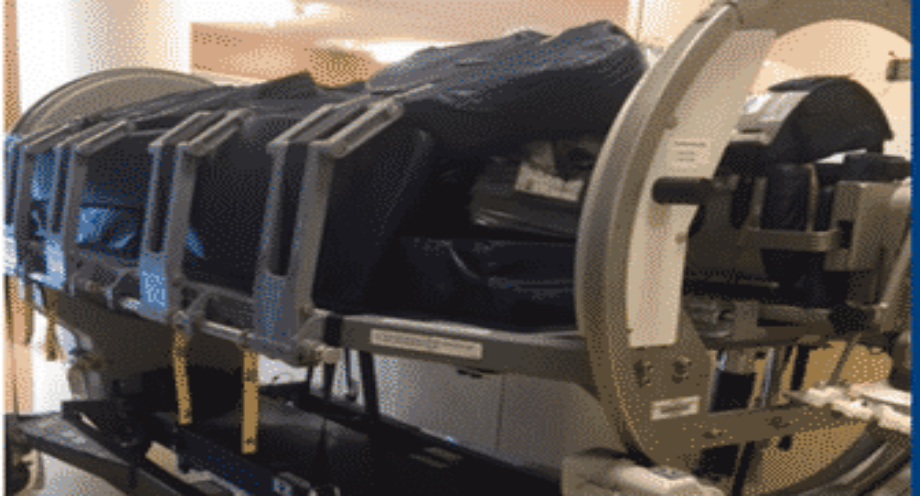
We do not suggest using NMBAs for all patients with ARDS (GRADE Recommendation: weakly against). We suggest the use of cisatracurium besylate by continuous 48 hours infusion in patients suffering early moderate/severe ARDS (P/F≤20 kPa: GRADE Recommendation: weakly in favour).

Recommendation 8.1

We **recommend against** the *routine* use of continuous infusions of NMBA to reduce mortality in patients with moderate-to-severe ARDS not due to COVID-19.
Strong recommendation, moderate level of evidence.

We are **unable to make a recommendation** for or against the *routine* use of continuous infusions of NMBA to reduce mortality in patients with moderate-to-severe ARDS due to COVID-19.
No recommendation; no evidence.

Is prone position evidence- based ?



PRONE positioning

Table 2 Contraindications to prone positioning defined in the trials

Gattinoni [55]	Guérin [48, 54]	Mancebo [56]	Taccone [57]
Cerebral edema or intracranial hypertension	ICP > 30 mmHg or CPP < 60 mmHg	Cranial trauma and/or clinical suspicion of high ICP	Intracranial hypertension
	Massive hemoptysis requiring an immediate surgical or interventional radiology procedure		
	Tracheal surgery or sternotomy during the previous 15 days except for airway access		
	Serious facial trauma or facial surgery during the previous 15 days		
	Deep venous thrombosis treated for less than 2 days		
	Cardiac pacemaker inserted in the last 2 days		
Fractures of the spine	Unstable spine, femur, or pelvic fractures	Pelvic and/or spine fractures	Spine or pelvic fracture
Severe hemodynamic instability	MAP < 65 mmHg		
	Pregnancy		
	Single anterior chest tube with air leaks		

Methods For Prone Positioning

Use of the Vollman Prone Positioner

Methods For Prone Positioning

The use of the Rotoprone Therapy System

Methods For Prone Positioning

Another method used for prone positioning is the Stryker frame

Prone P

Table 11 Prone positioning compared with standard care for ARDS

Outcomes	Illustrative comparative risks (95% CI) Control risk Standard Care	Intervention risk Prone Positioning	Relative effect (95% CI)	No. of participants (studies)	Quality of evidence (GRADE)	Comments
Mortality (pooled)	467 per 1000	421 per 1000 (383 to 458)	RR 0.90 (0.82 to 0.98)	2141 (eight 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
Subgroup 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 (five studies)	+++- MODERATE Due to serious risk of bias	Failure to blind outcome, failure of allocation concealment, and incomplete outcome data
Subgroup analysis Prone positioni without lung protective ventilation Mortality						
Subgroup analysis Prone positioni for more than 1 hours Mortality						
Subgroup analysis Prone positioni for less than 12 hours Mortality						
Adverse events (pooled)			1.2)		Due to serious risk of bias and very serious inconsistency	ıe, failure of t, and incomplete outcome data
Adverse events: cardiac events	278 per 1000	281 per 1000 (242 to 325)	RR 1.01 (0.87 to 1.17)	1599 (three studies)	+--- VERY LOW Due to serious risk of bias and very serious inconsistency	Failure to blind outcome, failure of allocation concealment, and incomplete outcome data Cohort includes subgroups receiving additional interventions known to demonstrate a potential mortality benefit for example, lung- protective ventilation
Adverse events: endotracheal tube displacement	101 per 1000	134 per 1000 (103 to 176)	RR 1.33 (1.02 to 1.74)	1597 (five studies)	++-- LOW Due to serious risk of bias and serious imprecision	See above
Adverse events: ventilator-associated pneumonia	248 per 1000	218 per 1000 (176 to 270)	RR 0.88 (0.71 to 1.09)	1007 (four studies)	++-- LOW Due to serious risk of bias and serious imprecision	See above
Adverse events: pressure sores	375 per 1000	462 per 1000 (402 to 529)	RR 1.23 (1.07 to 1.41)	1095 (two studies)	++-- LOW Due to serious risk of bias and serious imprecision	See above

Grade recommendation statement

We do not recommend the use of prone positioning for all patients with ARDS. We recommend the use of prone positioning for at least 12 hours per day in patients with moderate/severe ARDS (P/F ratio≤20 kPa: GRADE recommendation: strongly in favour).

Recommendation 7.1

We **recommend** using prone position as compared to supine position for patients with moderate-severe ARDS (defined as $PaO_2/FiO_2 < 150$ mmHg and PEEP $\geq$ 5 cmH_2O, despite optimization of ventilation settings) to reduce mortality.
Strong recommendation, high level of evidence in favor.

This recommendation applies also to ARDS from COVID-19.
Strong recommendation; moderate level of evidence in favor for indirectness.

Recommendation 7.2

We **recommend** starting prone position in patients with ARDS receiving invasive mechanical ventilation early after intubation, after a period of stabilization during which low tidal volume is applied and PEEP adjusted and at the end of which the PaO_2/FiO_2 remains < 150 mmHg; and proning should be applied for prolonged sessions (16 consecutive hours or more) to reduce mortality.
Strong recommendation; high level of evidence in favor.

This recommendation applies also to ARDS from COVID-19.
Strong recommendation; moderate level of evidence in favor for indirectness.

Recommendation 7.3

We **suggest** awake prone positioning as compared to supine positioning for non-intubated patients with COVID-19-related AHRF to reduce intubation.
Weak recommendation; low level of evidence in favor.

We are **unable to make a recommendation** for or against APP for non-intubated patients with COVID-19-related AHRF to reduce mortality.
No recommendation; moderate level of evidence of no effect.

We are **unable to make a recommendation** for or against APP for patients with AHRF not due to COVID-19.
No recommendation; no evidence.

Intensive Care Med
DOI 10.1007/s00134-017-4996-5

ORIGINAL

A prospective international observational prevalence study on prone positioning of ARDS patients: the APRONET (ARDS Prone Position Network) study

Conclusions: PP was used in 32.9% of patients with severe ARDS, and was associated with low complication rates, Significant increase in oxygenation and a significant decrease in driving pressure.

- PROSEVA study:16h/d
- LUNG SAFE: 16%
- APRONET study: (32.9 % of patients had PP(may be after LUNG SAFE study?)(overestimation of PP is the choice and the number of the ICUs included in this work.
- APRONET enrolled 141 ICUs from 20 countries (mostly European). most of the ICUs recruited were located in France, Spain and Italy which are the countries that have shown the higher interest in ARDS treatment and have published the larger studies on PP)

Ruste et al. Ann. Intensive Care (2018) 8:120
https://doi.org/10.1186/s13613-018-0464-9

Annals of Intensive Care

RESEARCH

Open Access

Hemodynamic effects of extended prone position sessions in ARDS

Conclusion: PP is associated with an increase in cardiac index in 18% to 32% of all PP sessions and a sustained increase in GEDVI reversible after return to supine position. Return from prone to supine position is associated with a slight hemodynamic impairment.


PRONE

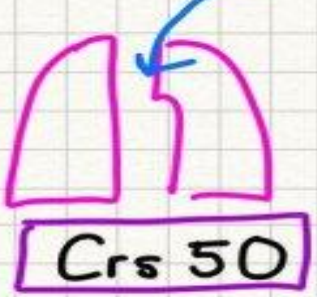
Driving Pressure

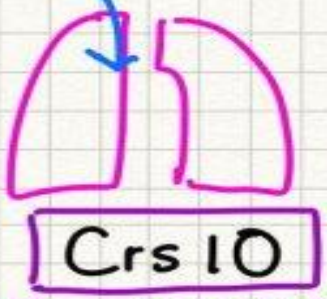
DRIVING PRESSURES → $P_{PLAT} - PEEP$ → AT THE BEDSIDE → AIM ≤ 14

DRIVING PRESSURES → ΔP

DRIVING PRESSURES → lung protection is not all about volume

400ml





ΔP MUCH GREATER

$V_T / Crs \rightarrow \Delta P$

V_T = lung size

MEDIATION ANALYSIS → SUPPORTS ΔP, rather than V_T as common factor in ↓ mortality

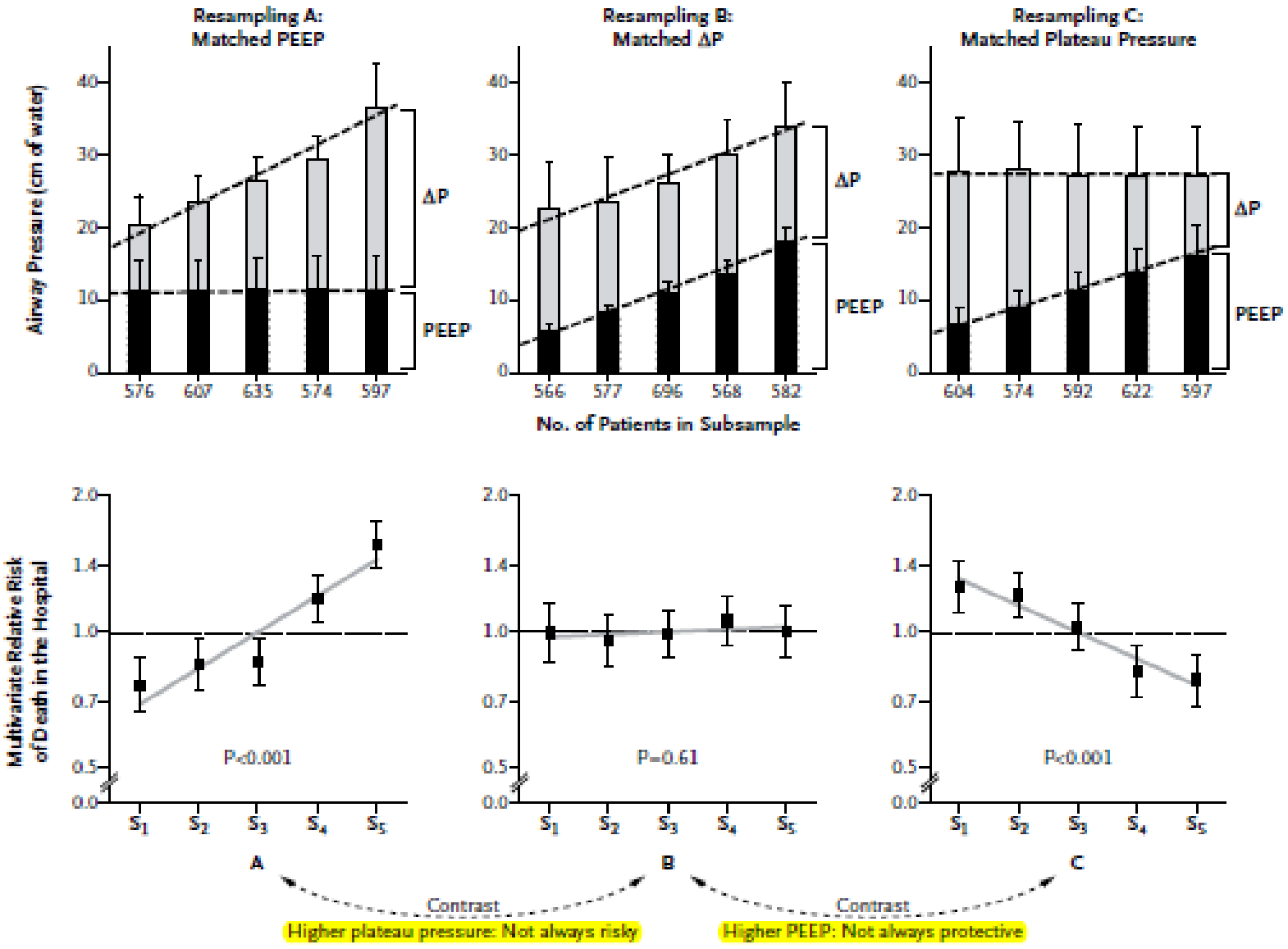
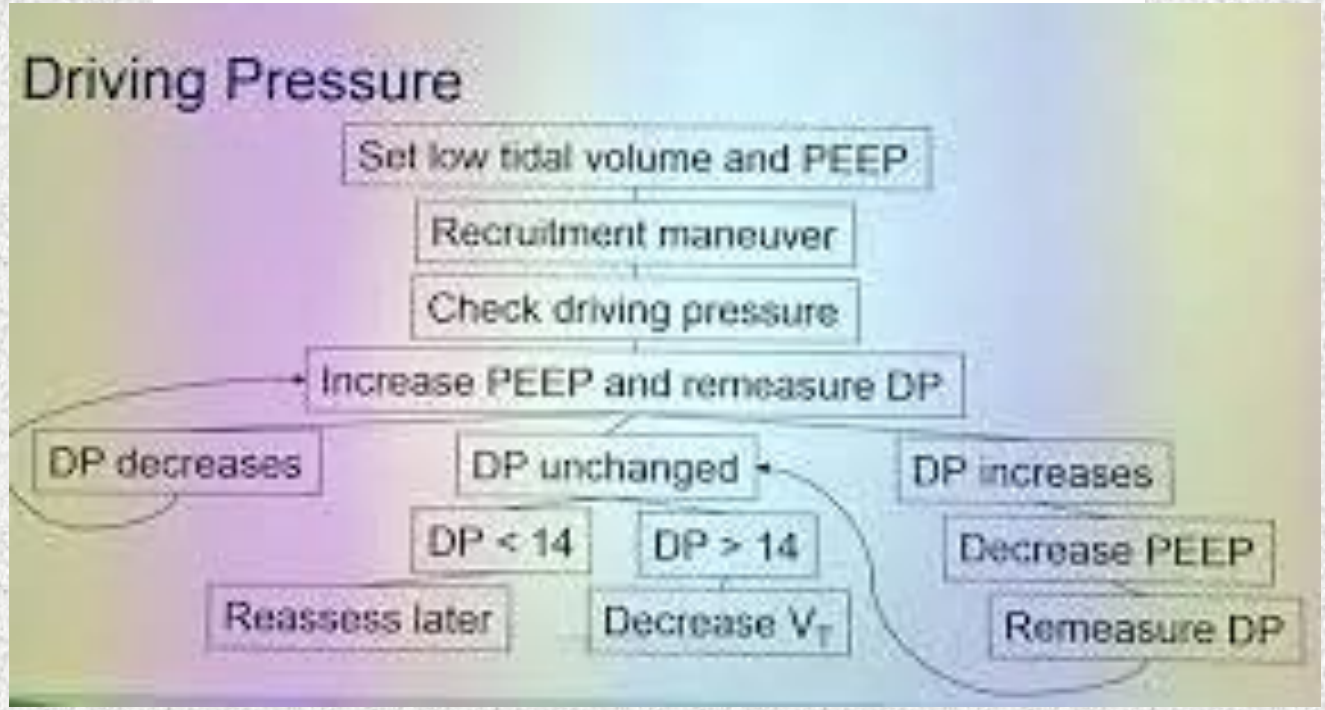


Figure 1. Relative Risk of Death in the Hospital across Relevant Subsamples after Multivariate Adjustment — Survival Effect of Ventilation Pressures.

Limiting Driving Pressure

- $\Delta P = P_{plat} - PEEP$
- Limit to < 15 cwp



Cochrane Library

Cochrane Database of Systematic Reviews

Pressure-controlled versus volume-controlled ventilation for acute respiratory failure due to acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) (Review)

Chacko B, Peter JV, Tharyan P, John G, Jeyaseelan L

Currently available data from RCTs are insufficient to confirm or refute whether PC or VC ventilation offers any advantage for people with acute respiratory failure due to ALI or ARDS.

Cochrane Database of Systematic Reviews 2015, Issue 1. Art. No.: CD008807.

Dushianthan *et al. Critical Care* 2012, **16**:238
http://ccforum.com/content/16/6/238

CRITICAL CARE

REVIEW

Clinical review: Exogenous surfactant therapy for acute lung injury/acute respiratory distress syndrome – where do we go from here?

Ahilanandan Dushianthan*[1,2], Rebecca Cusack[1], Victoria Goss[2], Anthony D Postle[2] and Mike PW Grocott[1,2]

- Refining surfactant preparations that incorporate all surfactant proteins.
- Targeting of surfactant delivery to the lobes that are most affected
- The target population needs to be characterised according to surfactant synthetic function using the best available technology, including non radioisotope labelling of surfactant precursors.

Nutrients **2015**, *7*, 5572-5585; doi:10.3390/nu7075239

OPEN ACCESS

nutrients

ISSN 2072-6643

www.mdpi.com/journal/nutrients

Article

Enteral Immunomodulatory Diet (Omega-3 Fatty Acid, γ-Linolenic Acid and Antioxidant Supplementation) for Acute Lung Injury and Acute Respiratory Distress Syndrome: An Updated Systematic Review and Meta-Analysis

Congcong Li †, Liyan Bo †, Wei Liu, Xi Lu * and Faguang Jin *

- Enteral immunomodulatory diet could not reduce the mortality of patients with ALI/ARDS and also could not extend the 28-day VFD or 28-day ICU-free days.

- Subgroup analysis showed that enteral immunomodulatory nutrition could benefit ALI/ARDS patients with high mortality, but it should be used with caution.

EXPERIMENTAL AND THERAPEUTIC MEDICINE 14: 2863-2868, 2017

Effects of N-acetylcysteine treatment in acute respiratory distress syndrome: A meta-analysis

YING ZHANG[1*], SHAOXUE DING[2*], CAIFENG LI[1], YIFENG WANG[1], ZHE CHEN[3] and ZHIQIANG WANG[1]

No severe adverse reactions were observed in the patients included.

Although the duration of ICU stay was shortened, the clinical benefits of NAC were limited for ARDS based on the present meta-analysis.

As the number of included trials and patients was small, additional trials are required to provide sufficient evidence for the efficacy of NAC in ARDS

Mansur et al. BMC Medicine (2015) 13:128
DOI 10.1186/s12916-015-0368-6

BMC Medicine

RESEARCH ARTICLE Open Access

Impact of statin therapy on mortality in patients with sepsis-associated acute respiratory distress syndrome (ARDS) depends on ARDS severity: a prospective observational cohort study

Ashham Mansur[1*], Maximilian Steinau[1], Aron Frederik Popov[2], Michael Ghadimi[3], Tim Beissbarth[4], Martin Bauer[1] and José Hinz[1]

Conclusions: This investigation suggests a beneficial effect of continuous statin therapy in patients with severe sepsis-associated ARDS and a history of prior statin therapy. Further study is warranted to elucidate this potential effect.

Neither study showed differences in the outcomes of mortality, VFD, or ICU-free days.

Results suggested an association between the use of statins and renal and hepatic injury.

It is unlikely there will be further consideration of statins in this setting

Intensive Care Med (2017) 43:663–671
DOI 10.1007/s00134-016-4649-0

SYSTEMATIC REVIEW

Statin therapy for acute respiratory distress syndrome: an individual patient data meta-analysis of randomised clinical trials

Myura Nagendran[1], Daniel F. McAuley[2], Peter S. Kruger[3,8], Laurent Papazian[4], Jonathon D. Truwit[5], John G. Laffey[6], B. Taylor Thompson[7], Mike Clarke[2] and Anthony C. Gordon[1*]

Conclusions: We found no clinical benefit from initiation of statin therapy in adult patients with ARDS, either overall or in predefined subgroups. While there was an increased incidence of raised serum creatine kinase and transaminase levels, there was no difference in serious adverse events among groups. Therefore, we do not recommend initiation of statin therapy for the treatment of ARDS.

ARDS:
Rest the lungs
or the ventilator?

Grade recommendation statement

We do not recommend the routine use of ECMO for all patients with ARDS (GRADE Recommendation: weakly against). We suggest the use of ECMO with lung-protective mechanical ventilation in selected patients with severe ARDS (GRADE Recommendation: weakly in favour).

Grade recommendation justification

The use of ECMO in selected adults suffering severe ARDS (defined as a Lung Injury Score of 3 or more or pH<7.20 due to uncompensated hypercapnoea),was given a weakly positive recommendation based on very low quality evidence. The most widely used indications

an increased risk of bleeding associated with the use of ECMO: consistent with data from the extracorporeal life support organisation (ELSO), which publishes its registry data from around 300 centres world-wide. The incidence of serious bleeding (approximately 15% overall) and intracranial haemorrhage (3.9%) associated with the use of veno-venous ECMO for respiratory failure in adult

Recommendation 9.1

We **recommend** that patients with severe ARDS not due to COVID-19 as defined by the EOLIA trial eligibility criteria, should be treated with ECMO in an ECMO center which meets defined organizational standards, adhering to a management strategy similar to that used in the EOLIA trial.
Strong recommendation, moderate level of evidence in favor

This recommendation applies also to patients with severe ARDS due to COVID-19.
Strong recommendation; low level of evidence in favor for indirectness.

Recommendation 9.2

We **recommend against** the use of $ECCO_2R$ for the treatment of ARDS not due to COVID-19 to prevent mortality outside of randomized controlled trials.
Strong recommendation, high level of evidence of no effect.

This recommendation applies also to patients with severe ARDS due to COVID-19.
Strong recommendation; moderate level of evidence of no effect for indirectness.

Table 1
ELSO guidelines for ECMO for adult respiratory failure

Indications	Risk of mortality ≥80% Pao_2/Fio_2 <100 on Fio_2 >90% Murray score 3–4 Hypercarbia with plateau pressure >30 cm H_2O Severe air leak Patient awaiting lung transplant with need for intubation immediate respiratory collapse unresponsive to optimal emergent management
Relative contraindications	Advanced age Immunosuppression Central nervous system hemorrhage Terminal malignancy Severe comorbidity Mechanical ventilation for ≥7 d

Table 2
Paris Sorbonne University hospital network criteria for ECMO cannulation for COVID-19

Indications	ARDS criteria[86,87] plus optimal ventilator management (Fio_2 of $\geq$80%, tidal volume 6 ml/kg of predicated body weight, PEEP of $\geq$10 cm H_2O) and one of the following: 1. Pao_2 to Fio_2 ratio of <50 mm Hg for >3 h 2. Pao_2 to Fio_2 ratio of <80 mm Hg for >6 h 3. Arterial blood pH of <7.25 and $Paco_2$ of $\geq$60 mm Hg for $\geq$6 h
Contraindications	Age >70 y Severe comorbidities Cardiac arrest (unless immediate cardiopulmonary resuscitation is provided and low-flow time < 15 min) Irreversible neurologic injury Mechanical ventilation for >10 d Refractory multiorgan failure Simplified Acute Physiology Score II of >90

SUPERNOVA Trial

The SUPERNOVA trial has been registered in the ClinicalTrials.Gov Protocol Registration System.

The SUPERNOVA Trial PRS account number is NCT02282657

Strategy of UltraProtective Lung Ventilation With Extracorporeal CO2 Removal for New-Onset Moderate to seVere ARDS (SUPERNOVA)

HFOV

Table 5 HFOV compared to usual care for ARDS

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	**Grade recommendation statement** We do not recommend the use of HFOV in the management of patients with ARDS (GRADE recommendation: strongly against).					nges in ventional ilation tegies unted for rogeneity
Mortality (30 day)					inconsistency and mild indirectness	nges in ventional ilation strategies accounted for heterogeneity
Adverse events: barotrauma	122 per 1000	147 per 1000 (101 to 212)	RR 1.205 (0.834 to 1.742)	752 (four studies)	++-- LOW Due to serious imprecision	Barotrauma variably defined
Adverse events: oxygen failure	102 per 1000	77 per 1000 (61 to 89)	RR 0.557 (0.351 to 0.884)	757 (three studies)	++-- LOW Due to serious imprecision	Oxygenation failure variably defined.

ARDS, acute respiratory distress syndrome; HFOV, high-frequency oscillatory ventilation.

Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials

Carolyn S Calfee, Kevin Delucchi, Polly E Parsons, B Taylor Thompson, Lorraine B Ware, Michael A Matthay, and the NHLBI ARDS Network

Summary

Background Subphenotypes have been identified within heterogeneous diseases such as asthma and breast cancer, with important therapeutic implications. We assessed whether subphenotypes exist within acute respiratory distress syndrome (ARDS), another heterogeneous disorder.

Methods We used data from two ARDS randomised controlled trials (ARMA trial and ALVEOLI trial), sponsored by the National Heart, Lung, and Blood Institute. We applied latent class modelling to identify subphenotypes using clinical and biological data. We modelled data from both studies independently. We then tested the association of subphenotypes with clinical outcomes in both cohorts and with the response to positive end-expiratory pressure (PEEP) in the ALVEOLI cohort.

Findings We analysed data for 1022 patients: 473 in the ARMA cohort and 549 in the ALVEOLI cohort. Independent latent class models indicated that a two-class (ie, two subphenotype) model was the best fit for both cohorts. In both cohorts, we identified a hyperinflammatory subphenotype (phenotype 2) that was characterised by higher plasma concentrations of inflammatory biomarkers, a higher prevalence of vasopressor use, lower serum bicarbonate concentrations, and a higher prevalence of sepsis than phenotype 1. Participants in phenotype 2 had higher mortality and fewer ventilator-free days and organ failure-free days in both cohorts than did those in phenotype 1 ($p<0\cdot007$ for all). In the ALVEOLI cohort, the effects of ventilation strategy (high PEEP *vs* low PEEP) on mortality, ventilator-free days and organ failure-free days differed by phenotype ($p=0\cdot049$ for mortality, $p=0\cdot018$ for ventilator-free days, $p=0\cdot003$ for organ-failure-free days).

Interpretation We have identified two subphenotypes within ARDS, one of which is categorised by more severe inflammation, shock, and metabolic acidosis and by worse clinical outcomes. Response to treatment in a randomised trial of PEEP strategies differed on the basis of subphenotype. Identification of ARDS subphenotypes might be useful in selecting patients for future clinical trials.

Funding National Institutes of Health.

Lancet Respir Med 2014

Published Online
May 20, 2014
http://dx.doi.org/10.1016/S2213-2600(14)70097-9

See Online/Comment
http://dx.doi.org/10.1016/S2213-2600(14)70116-X

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Hayes *et al. Critical Care* 2012, **16**:205
http://ccforum.com/content/16/2/205

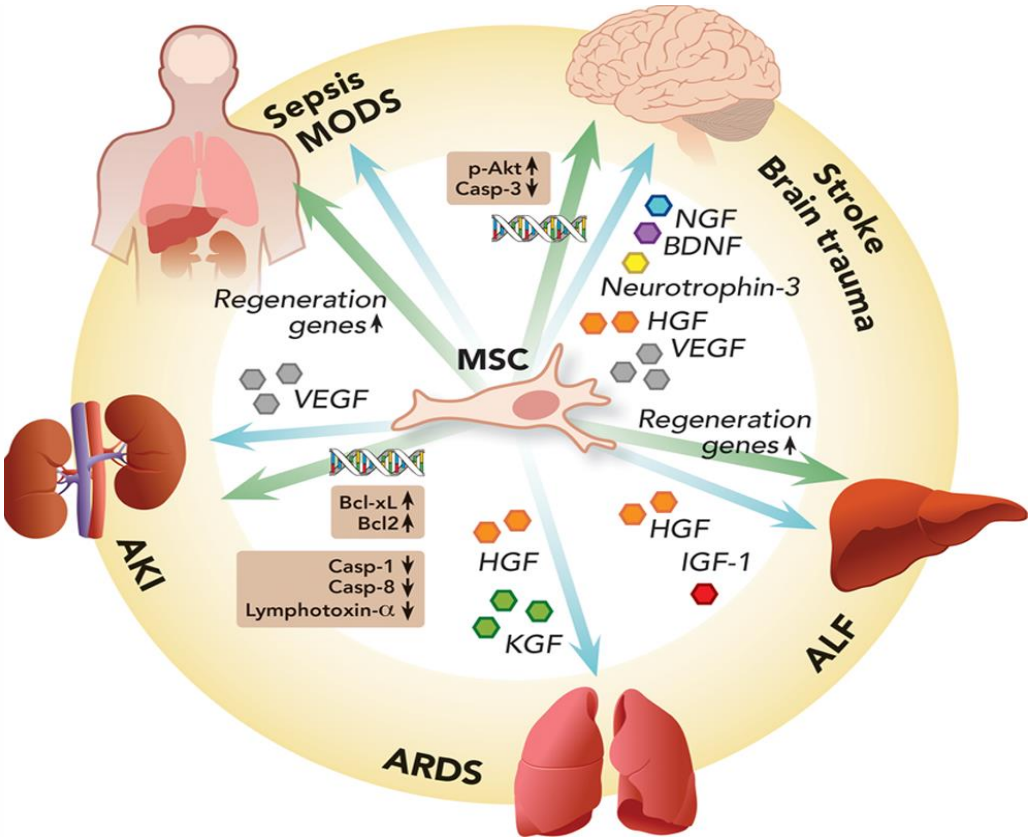
CRITICAL CARE

REVIEW

Clinical review: Stem cell therapies for acute lung injury/acute respiratory distress syndrome - hope or hype?

Mairead Hayes[1,2], Gerard Curley[1,2], Bilal Ansari[1,2] and John G Laffey[1,2,3*]

STEM CELL THERAPY



Mesenchymal stem cells: mechanisms of potential therapeutic benefit in ARDS and sepsis

James Walter, Lorraine B Ware, Michael A Matthay

- Regulation of endothelial cell permeability
- Increased alveolar fluid clearance
- Regulation of epithelial cell permeability
- Antimicrobial effect
- Antiapoptotic effect
- Antiinflammatory effects
- Paracrine mechanisms
- Extracellular vesicles
- Direct contact of cells with metastatic cell contents.

PLOS | ONE

RESEARCH ARTICLE

Efficacy of Mesenchymal Stromal Cell Therapy for Acute Lung Injury in Preclinical Animal Models: A Systematic Review

Treatment with MSCs, significantly decreased the overall death in animals with ALI.
Efficacy was maintained across different types of animal models and means of ALI induction; MSC origin, source, route of administration and preparation; and the clinical relevance of the model (timing of MSC administration, administration of fluids and or antibiotics).

The results from our meta-analysis support that MSCs substantially reduce the odds of death in animal models of ALI but important reporting elements were sub optimal and limit the strength of our conclusions.

PLOS ONE | DOI:10.1371/journal.pone.0147170 January 28, 2016

ELSEVIER

Archives of Medical Research 52 (2021) 93–101

Archives of Medical Research

EPIDEMIOLOGICAL

Mesenchymal Stem Cells Current Clinical Applications: A Systematic Review

David E. Rodríguez-Fuentes,[a] Luis E. Fernández-Garza,[b] John A. Samia-Meza,[a] Silvia A. Barrera-Barrera,[c] Arnold I. Caplan,[d] and Hugo A. Barrera-Saldaña[b]

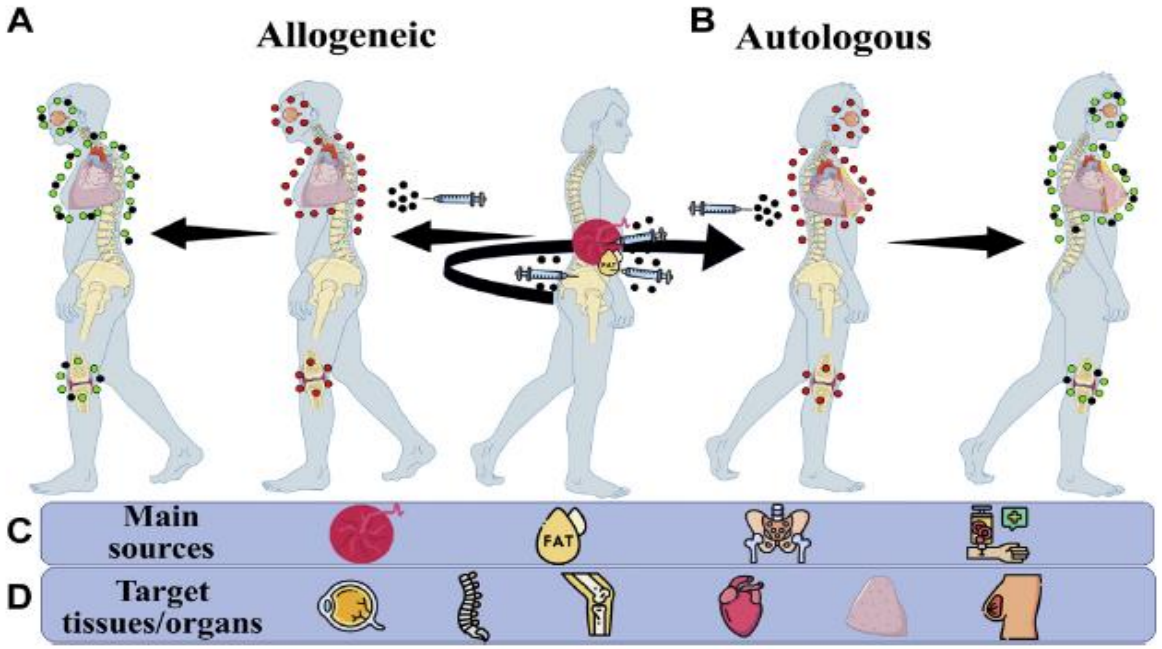


Figure 1. Treating with Medicinal Signaling Cells (MSCs). A. Therapy with allogeneic MSCs. B. Therapy with autologous MSCs. After the administration of MSCs, they migrate to the sites of inflammation and tissue damage associated with cytokine outburst, to generate a regenerative microenvironment by secreting bioactive molecules capable of stimulating local stem cells to repair injured sites. C. Main sources of MSCs: Placenta, subcutaneous adipose tissue, bone marrow, and peripheral blood. D. Target issues or organs in the reviewed clinical trials: vitreous body, spinal cord, bone marrow, cartilage, heart, lungs, and adipose tissue.

- Dose:40-100 million /infusion, Time/interval: Infusions apart 72 h

  1-10 million/kg/PBW single dose

  in 50 mL vehicle solution containing human serum Alb and heparin, infused over10 ± 5 minutes,

- Sources(Bone marrow, umbilical cord, fat)

- Route of administration

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REVIEW ARTICLE OPEN

Check for updates

Stem cell-based therapy for COVID-19 and ARDS: a systematic review

Gabriele Zanirati[1,2], Laura Provenzi[1,3], Lucas Lobraico Libermann[1,3], Sabrina Comin Bizotto[1,3], Isadora Machado Ghilardi[1,2], Daniel Rodrigo Marinowic[1,2,3], Ashok K. Shetty[4] and Jaderson Costa Da Costa[1,2,3]✉

- MSCs treatment could be considered a potential candidate for adjuvant therapy in moderate-to-severe COVID-19 cases and compassionate use.

MSC-Derived Products as Cell-Free Therapy

- Implantation time of MSC is generally too short for an effective impact and <1% of MSC survived more than a week following iv administration.
- Beneficial effects of MSC are mainly caused by their secretion of soluble paracrine factors. MSC secretom may be considered a successful approach
- (i) the uncertainty related to immunological incompatibility, tumorigenicity, emboli formation, transmission of infections and potential entry of MSC into senility
- (ii) secretome can be better assessed in terms of their safety, dose and potency
- (iii) secretome can be stored without requiring potentially toxic cryopreservative vehicles
- (iv) the use of secretome-derived products is both more cost-effective and convenient for clinical use, since the use of secretome may avoid the time and costs associated with expanding and sustaining clonal cell lines.

IVYSPRING INTERNATIONAL PUBLISHER

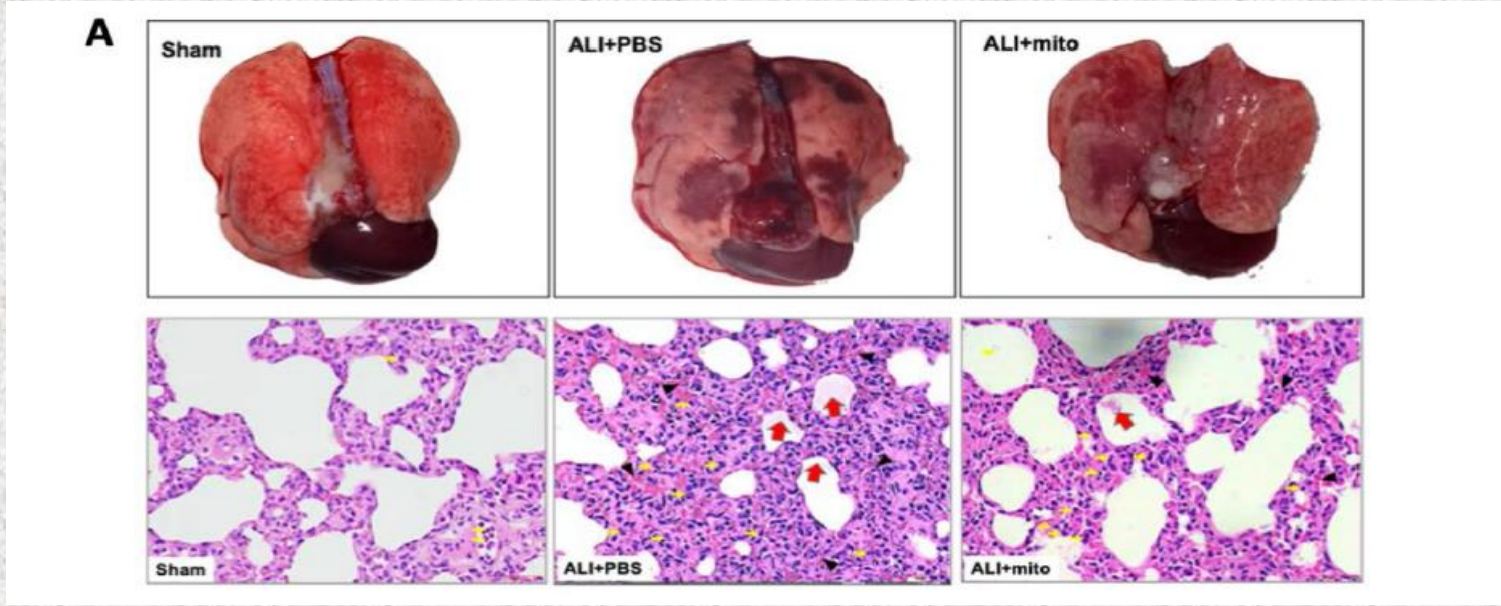
International Journal of Medical Sciences

2022; 19(6): 1036-1046. doi: 10.7150/ijms.73151

Research Paper

Viable Allogeneic Mitochondria Transplantation Improves Gas Exchange and Alveolar-Capillary Permeability in Rats with Endotoxin-Induced Acute Lung Injuries

Yu-Li Pang[1], Shi-Yuan Fang[2], Tzu-Ting Cheng[3], Chien-Chi Huang[3,4], Ming-Wei Lin[4], Chen-Fuh Lam[3,5*]✉, Kuen-Bao Chen[6*]✉



REVIEW

Acute respiratory distress syndrome: shifting the emphasis from treatment to prevention

Michelle Ng Gong[a,b] and B. Taylor Thompson[c]

- Most ARDS patients die of MODS rather than refractory hypoxemia.
- There has been a shift in emphasis at improving outcomes in ARDS to early identification of at-risk patients and early treatment and prevention in patients presenting outside of ICU like the ED.
- The outcome measure in ARDS prevention trials should encompass more patient-centered outcomes like mortality or long-term functional outcomes.

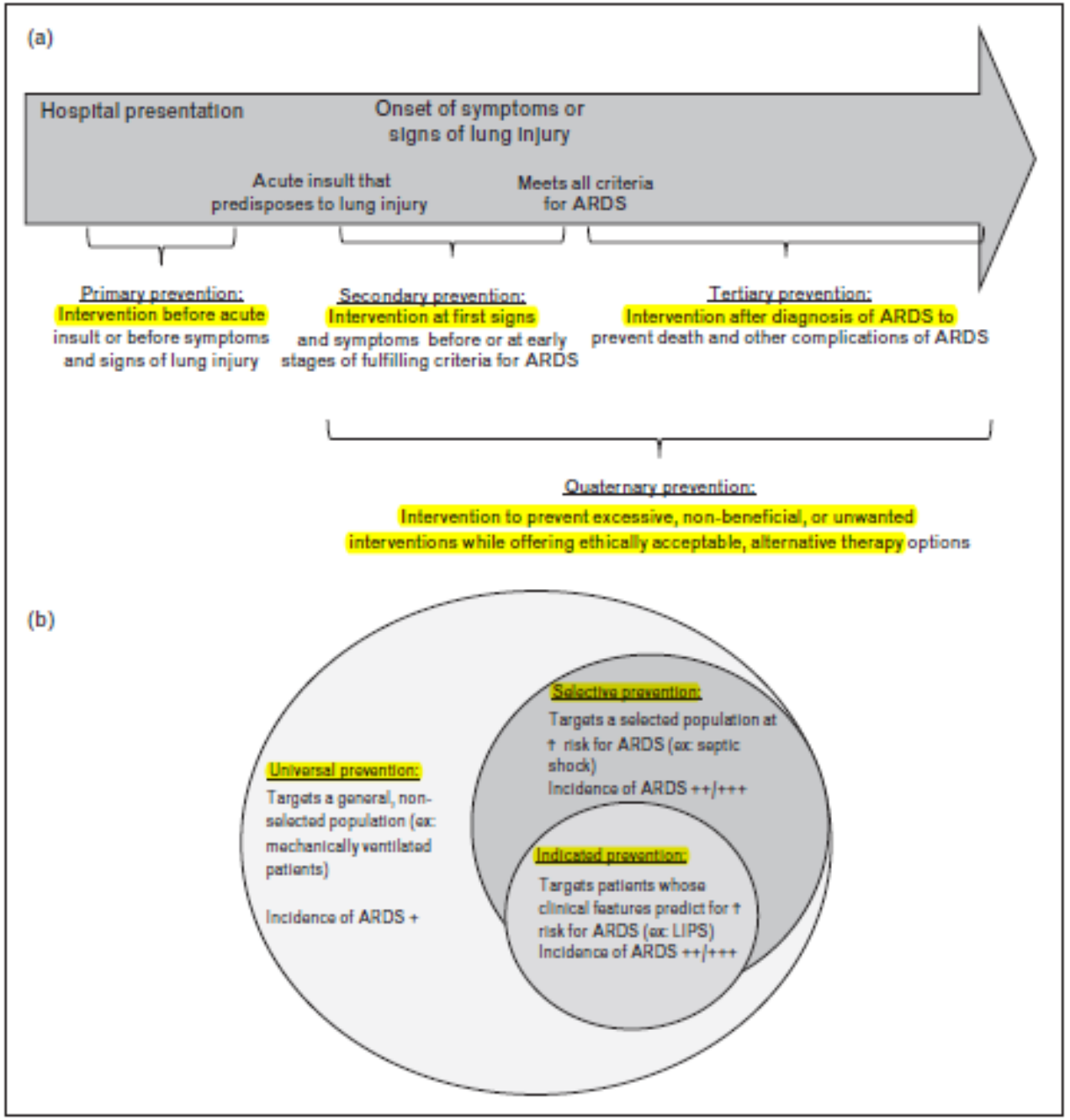
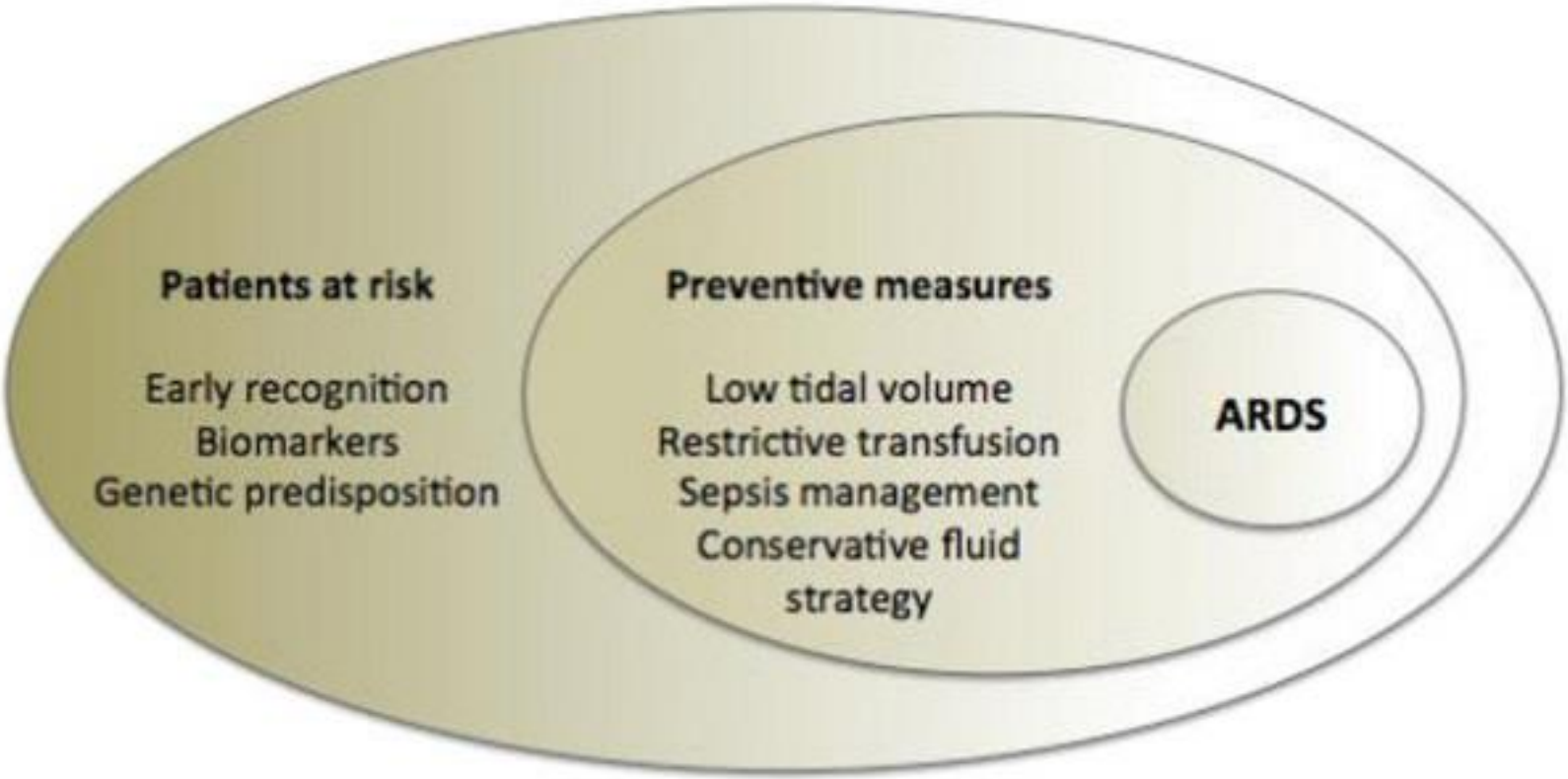
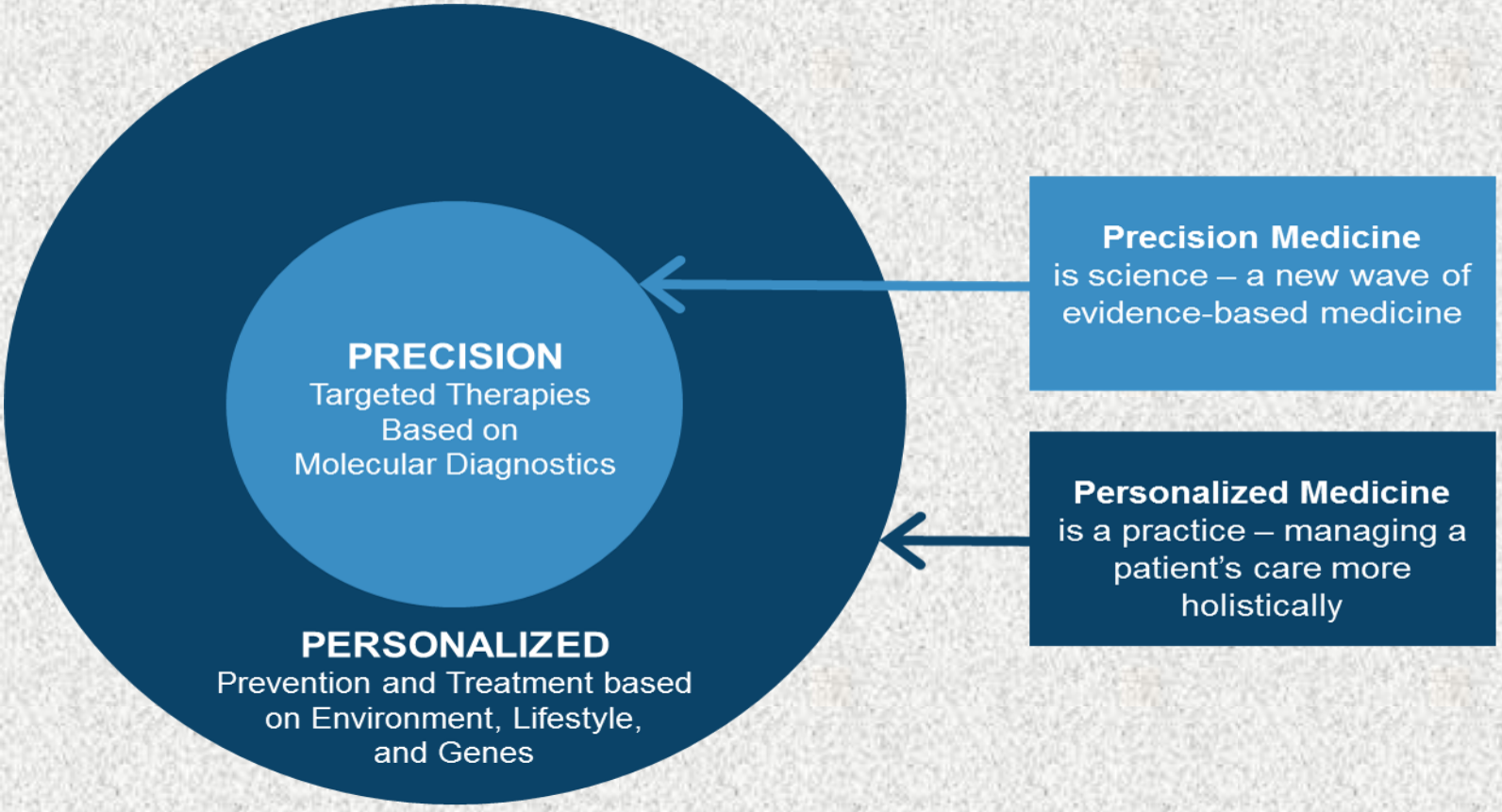


FIGURE 1. Prevention levels and strategies in the course of acute respiratory distress syndrome development and course.



Latest progress of Acute Respiratory Distress Syndrome


PERSONALIZED
PRECISION

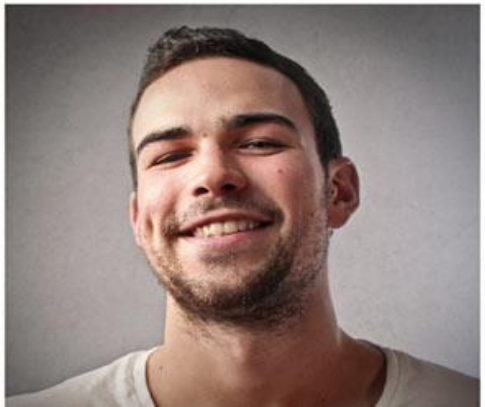

PRECISION
Targeted Therapies
Based on
Molecular Diagnostics
PERSONALIZED
Prevention and Treatment based
on Environment, Lifestyle,
and Genes
Precision Medicine
is science – a new wave of
evidence-based medicine
Personalized Medicine
is a practice – managing a
patient's care more
holistically

Medicine Today

Reactive, population-based, one-size-fits-all model of care

Personalized Medicine

Predictive, preventive, patient-centric model of care



Tobin *Critical Care* (2022) 26:392
https://doi.org/10.1186/s13054-022-04271-y

Critical Care

PERSPECTIVE Open Access

ARDS: hidden perils of an overburdened diagnosis

Martin J. Tobin*

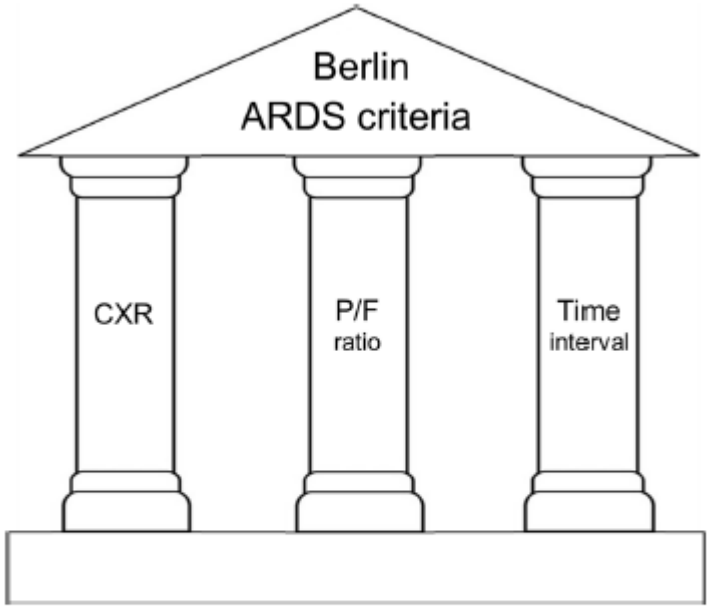


Fig. 1 The Berlin criteria for the definition of ARDS consist of three pillars, each of which is flimsy. Chest X-ray (CXR) infiltrates have a kappa interrater agreement score of 0.296. Arterial PO_2 to fractional inspired oxygen (P/F ratio), an index of patient oxygenation, is physiologically flawed and not fit for purpose. A 7-day interval

Table 1 Perils that ensue upon making a diagnosis of ARDS

Protocol mandate	Physiologic consequences	Clinical problems
Prescription of tidal volume 6 ml/kg in all patients, irrespective of plateau pressure	Severe air hunger ensues when delivered tidal volume does not match heightened stimulation of sensory receptors	Sedatives, opiates, and paralytic agents do not allay air hunger but contribute to complications
	If mechanical inspiratory time is shorter than neural inspiratory time, double triggering is inevitable	Despite adjusting a ventilator to deliver 6 ml/kg, the patient actually receives 12 ml/kg
Fixed PEEP options	Constraints imposed by use of PEEP-F_IO_2 table	If F_IO_2 is 0.60: patient got either PEEP 10 or 20 cm H_2O with no other options If F_IO_2 is 0.80: patient got either PEEP 14 or 22 cm H_2O with no other options

never
never
never
give
up

(winston churchill)

Winston Churchill


THANK YOU