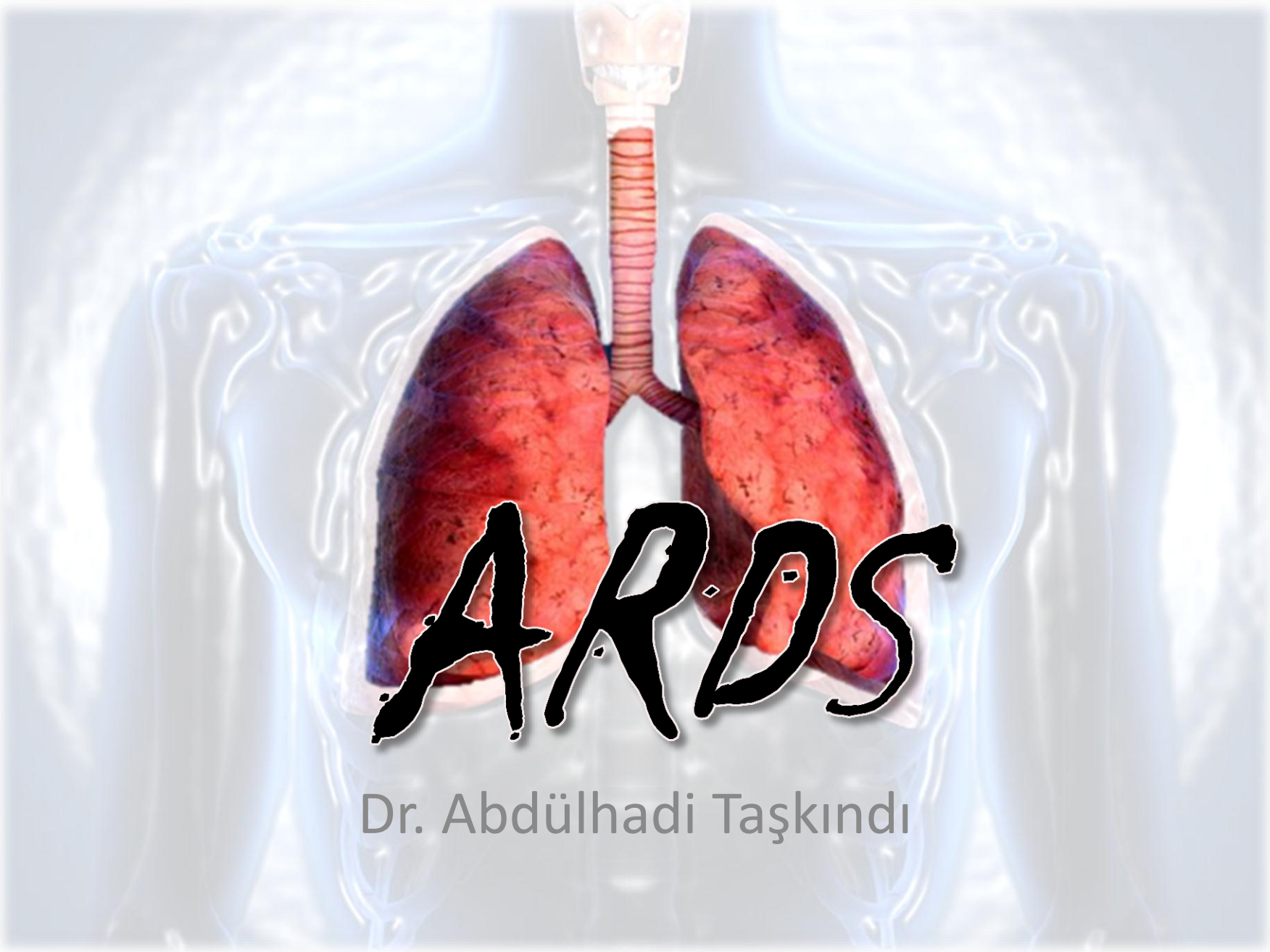


Dr. Abdülhadi Taşkındı

People feel the **PEACE**, **JOY** & the **LOVE**

What's ARDS?

- Acute respiratory distress syndrome (ARDS) is:

  A clinical syndrome of lung injury marked by **acute** onset with **hypoxemia** and bilateral radiographic **infiltrates** and **without** left atrial hypertension.

  Also called:
  - Respiratory distress syndrome
  - Adult respiratory distress syndrome
  - Acute lung injury

What's ARDS?

- **<u>The Berlin definition consists of:</u>**
  - **Onset**

    within **1 week** of a known clinical insult or new or worsening respiratory symptoms
  - **Bilateral**

    opacities not fully explained by effusions, lobar/lung collapse, or nodules on chest x-ray or CT
  - **Respiratory failure**

    not fully explained by a cardiac failure or fluid overload
  - **Impaired oxygenation** status

Limitations of Berlin definition are that patients presenting with pulmonary conditions such as multi-lobar pneumonia and pulmonary hemorrhage could meet the criteria for ARDS but the underlying treatment and pathophysiology of these conditions are quite different

What's ARDS?

- **Impaired oxygenation** status:
  - **Mild** ARDS is defined as
    - a PaO_2/FiO_2 > 200 mm Hg but ≤ 300 mm Hg with positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) ≥ 5 cm H_2O
  - **Moderate** ARDS is defined as
    - PaO_2/FiO_2 > 100 mm Hg but ≤ 200 mm Hg with PEEP ≥ 5 cm H_2O
  - **Severe** ARDS is defined as
    - PaO_2/FiO_2 ≤ 100 mm Hg with PEEP ≥ 5 cm H_2O

	PaO_2/FiO_2	PEEP/CPAP
Mild	> 200 mm Hg but ≤ 300 mm Hg	≥ 5 cm H_2O
Moderate	> 100 mm Hg but ≤ 200 mm Hg	≥ 5 cm H_2O
Severe	≤ 100 mm Hg	≥ 5 cm H_2O

Mortality

- **Varies with severity:**
  - **Mild** is associated with **27%** mortality
  - **Moderate** is associated with **32%** mortality
  - **Severe** is associated with **45%** mortality

JAMA 2012 Jun 20;307(23):2526

Etiology

Direct lung injury		Indirectly by inflammatory processes focused in other organs
• Pneumonia	Most common	• Non-Pulmonary sepsis
• Aspiration of gastric contents		• Severe trauma
• Pulmonary sepsis • Pulmonary contusion • Near-drowning • Inhalation injury • Respiratory syncytial virus • MERS-CoV	Less common	• Burns • Acute pancreatitis • Drug overdose • Transfusion related acute lung injury (TRALI)

Management

- Treat the underlying cause if it is known.
  - treatment is generally supportive in combination with aggressive management of precipitating conditions
- Mechanical ventilation
- conservative fluid management
- Corticosteroids
- extracorporeal membrane oxygenation (ECMO).
- Others

Management

- **Mechanical ventilation**
  - supports gas exchange while waiting for the illness to resolve.

Barotrauma from mechanical ventilation can contribute to lung injury.
The goal should be to: maintain adequate rather than "normal" gas exchange to minimize any lung injury.

Management

The goal should be to: maintain **adequate** rather than "normal" gas exchange to minimize any lung injury.

Management

- **Mechanical ventilation**
  - **Lower tidal volume** (≤ 7 mL/kg) associated with reduced mortality compared to tidal volume 10-15 mL/kg in patients with acute lung injury or acute respiratory distress syndrome on mechanical ventilation

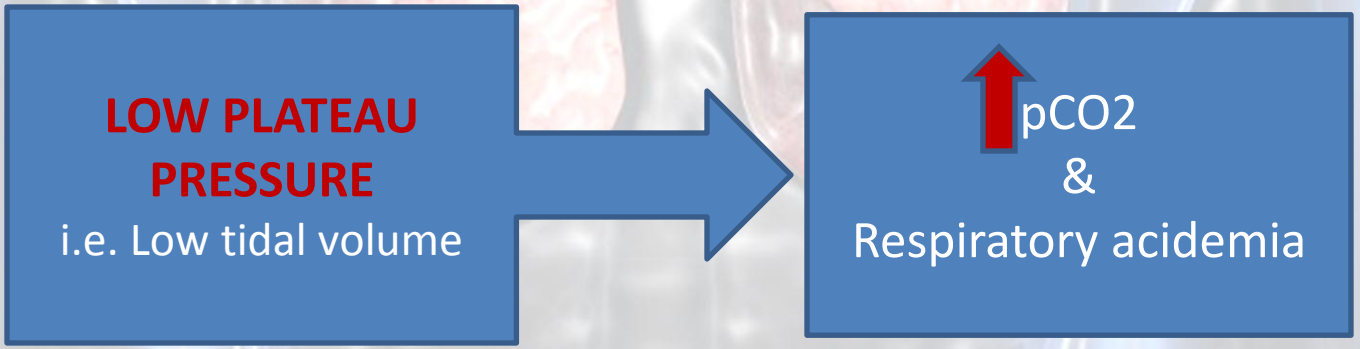
    (level 2 [mid-level] evidence)
  - **Positive end-expiratory pressure (PEEP)**
    - Higher levels of PEEP may reduce in-hospital mortality in patients with ARDS (but not in patients with ALI without ARDS)

      (level 2 [mid-level] evidence)
    - High PEEP may reduce duration of mechanical ventilation compared to low PEEP

      (level 2 [mid-level] evidence)

Management

- **<u>Permissive Hypercapnia in ARDS</u>**
  - Survival benefit from low tidal volume ventilation and low plateau pressures observed in clinical trials
    - (or if you prefer, the *harmful* effects seen from using "normal" or physiologic tidal volumes with resulting high plateau pressures).



Management

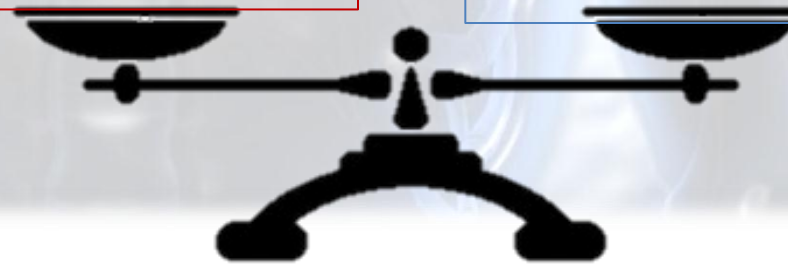
- **<u>Permissive Hypercapnia in ARDS</u>**
  - How "permissive" can one be?
  - Mechanically ventilated patients with ARDS appear to tolerate very low blood pH and very high pCO_2 without any adverse sequelae:
    - Current consensus suggests it is safe to allow pH to fall to at least 7.20.
    - The actual pCO_2 is of little importance.
    - However, it is unknown whether such correction of acidemia is helpful, harmful, or neither (good evidence is lacking for any of these hypotheses).

Management

- **Permissive Hypercapnia in ARDS**
  - Conditions in which permissive hypercapnia for ARDS could theoretically be harmful include:

1. cerebral edema,
2. mass lesions
3. seizures;
4. active coronary artery disease;
5. arrhythmias;
6. hypovolemia;
7. GI bleeding

Potential risks of hypercapnia against the risks of ARDS



Management

- **Others**

Use prone positioning for ≥ 16 hours/day early after initiation of ventilation,.	especially in patients with severe hypoxemia or tidal volumes ≤ 8 mL/kg
Consider using higher PEEP	to potentially reduce mortality and reduce the duration of mechanical ventilation.
Optimize PEEP to reduce FiO_2 to < 60%.	
The optimal ventilator settings may require heavy sedation and even neuromuscular blockade if sedation and analgesics do not achieve vent synchrony.	Use Cisatracurium (a neuromuscular blocking agent) in patients with early, severe ARDS to improve survival

- **Prone positioning**
  - improves gas exchange and has long been used as an adjunctive or salvage therapy for severe or refractory ARDS.
  - **standard of care for ARDS** after a multicenter trial published in 2013, demonstrated a dramatic near-50% relative risk reduction, and a 17% absolute risk reduction for mortality.
    - Patients were kept in prone position for 16 hours a day in that trial, which was conducted at 27 European centers.

    PROSEVA , *N Engl J Med* May 20, 2013
  - A **meta-analysis of 6 randomized trials** also concluded prone positioning saves lives in ARDS when added to a lung-protective ventilatory strategy.

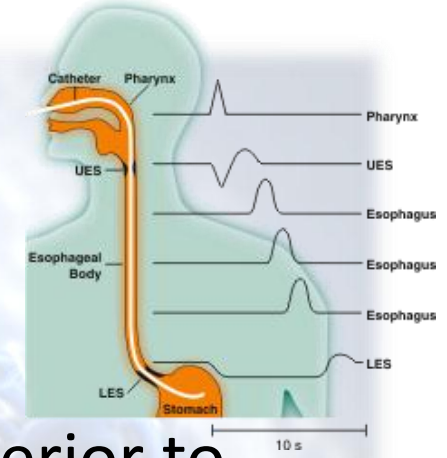
    CMAJ May 26, 2014

Management

- **General supportive measures:**
  - **Pulmonary artery catheters** do not reduce mortality or length of stay for adult patients in ICU (level 1 [likely reliable] evidence)
  - **Enteral diet supplementation** with eicosapentaenoic acid and gamma-linolenic acid (EPA/GLA) may reduce duration of mechanical ventilation in patients with ALI/ARDS

    (level 2 [mid-level] evidence)
  - **Venous thromboembolism** prophylaxis suggested with low-molecular-weight heparin or low-dose unfractionated heparin (ACCP Grade 2C), or mechanical thromboprophylaxis if heparin contraindicated (ACCP Grade 2C)

Management



- **Esophageal manometry** is considered superior to plateau pressures through its measurement of **transpulmonary pressure**, considered a more precise measure of potentially injurious pressures in the lung.
    - Because it is invasive and the probes are prone to migration, esophageal manometry is not widely used.

Crit Care Med. 2006 May; 34(5): 1389–1394

Management

- **<u>Conservative fluid management:</u>**
  - In patients with acute lung injury (ALI) to reduce the need for mechanical ventilation and shorten ICU.
  - Consider using dobutamine before vasopressor when low filling pressures cause low blood pressure

Fluid and Catheter Treatment (FACTT) trial (N Engl J Med 2006 Jun 15;354(24):2564
conservative fluid management in patients with acute lung injury (ALI) improves fluid balance, reduces need for mechanical ventilation and shortens intensive care unit (ICU) stay

Crit Care Med 2015 Feb;43(2):288
simplified conservative fluid management protocol may reduce cumulative fluid balance compared to conservative protocol without affecting mortality or number of ventilation-free days in critically ill patients with ARDS

Management

- **Corticosteroids**
  - Conflicting evidence, benefit depend on the underlying etiology. **(level 2 [mid-level] evidence)**
    - » No significant difference in mortality in patients with unselected ARDS or sepsis-related ARDS.
  - The evidence suggests increased mortality in ARDS associated with influenza.
  - The evidence suggests decreased mortality in postoperative ARDS.

Exploring the heterogeneity of effects of corticosteroids on acute respiratory distress syndrome: a systematic review and meta-analysis. Ruan SY et al. Crit Care 2014 Apr 7;18(2):R63

ECMO

- **Consider referral for extracorporeal membrane oxygenation (ECMO)**
    - Associated with improved survival compared to conventional ventilation support in patients with severe respiratory failure

(level 2 [mid-level] evidence)

ECMO

- **Extracorporeal membrane oxygenation (ECMO)**

- **To date, only two randomized clinical trials have been published, separated by 30 years.**
  1. Randomized clinical trial by **Zapol** et al published in 1979 reported an approximate 90% mortality in the control and treatment groups. These results could be considered as having arisen from the consequences of old harmful **ventilatory strategies** in both groups, the use of **inappropriate ECMO** techniques and/or the lack of **experience** of some of the participating centers.
  2. The **CESAR trial** reported in 2009 a 16% increase in long-term survival in the group of patients transferred to a center with the capacity to provide ECMO , although this result does not seem entirely attributable to the ECMO treatment, since this technique was applied to only 76% of the patients transferred. In fact, increased survival is not significant when studied only in the ECMO treated patients in this study.

ECMO

- **Extracorporeal membrane oxygenation (ECMO)**

Referral to specialized ECMO center may improve survival without severe disability compared to conventional ventilation support in patients with severe respiratory failure (level 2 [mid-level] evidence)

- comparing ECMO vs. conventional management
- 6-month survival without disability in 63% vs. 47% (p = 0.03, NNT 7)
- referral to ECMO associated with 0.03 quality-adjusted life-year gain at 6-month follow-up
- median intensive care unit (ICU) length of stay 24 days vs. 13 days
- median hospital length of stay 35 days vs. 17 day

CESAR trial (Lancet 2009 Oct 17;374(9698):1351)

ECMO

- **Extracorporeal membrane oxygenation (ECMO)**

Transfer to an ECMO center may be associated with lower hospital mortality in patients with influenza A(H1N1)-associated respiratory failure (level 2 [mid-level] evidence)

- hospital mortality among ECMO-referred patients vs. controls
- with individual matching 23.7% vs. 52.5% (relative risk [RR] 0.45, 95% CI 0.26-0.79)

JAMA 2011 Oct 19;306(15):1659

ECMO

- **Extracorporeal membrane oxygenation (ECMO)**

ECMO and conventional mechanical ventilation associated with similar mortality in patients with influenza A(H1N1)-associated ARDS (level 2 [mid-level] evidence)

Am J Respir Crit Care Med 2013 Feb 1;187(3):276

ECMO

- **Extracorporeal membrane oxygenation (ECMO)**

higher PEEP associated with decreased risk of ICU mortality in mechanically ventilated patients receiving ECMO (level 2 [mid-level] evidence)

- factors associated with increased mortality in multivariate analysis included:
  - plateau pressure > 30 cm H_2O before ECMO initiation (OR 5.18, 95% CI 1.88-14.31)
  - lower lactate levels at day 3 on ECMO (OR 4.77, 95% CI 2.12-10.73)
  - increased time between admission and ECMO initiation (OR 1.15, 95% CI 1.06-1.26)

Crit Care Med 2015 Mar;43(3):654

ECMO

- **Extracorporeal membrane oxygenation (ECMO)**

Kanji H.D., McCallum J., Norena M., et al: Early veno-venous extracorporeal membrane oxygenation is associated with lower mortality in patients who have severe hypoxemic respiratory failure: a retrospective multicenter cohort study. J Crit Care 2016; 33: pp. 169-173

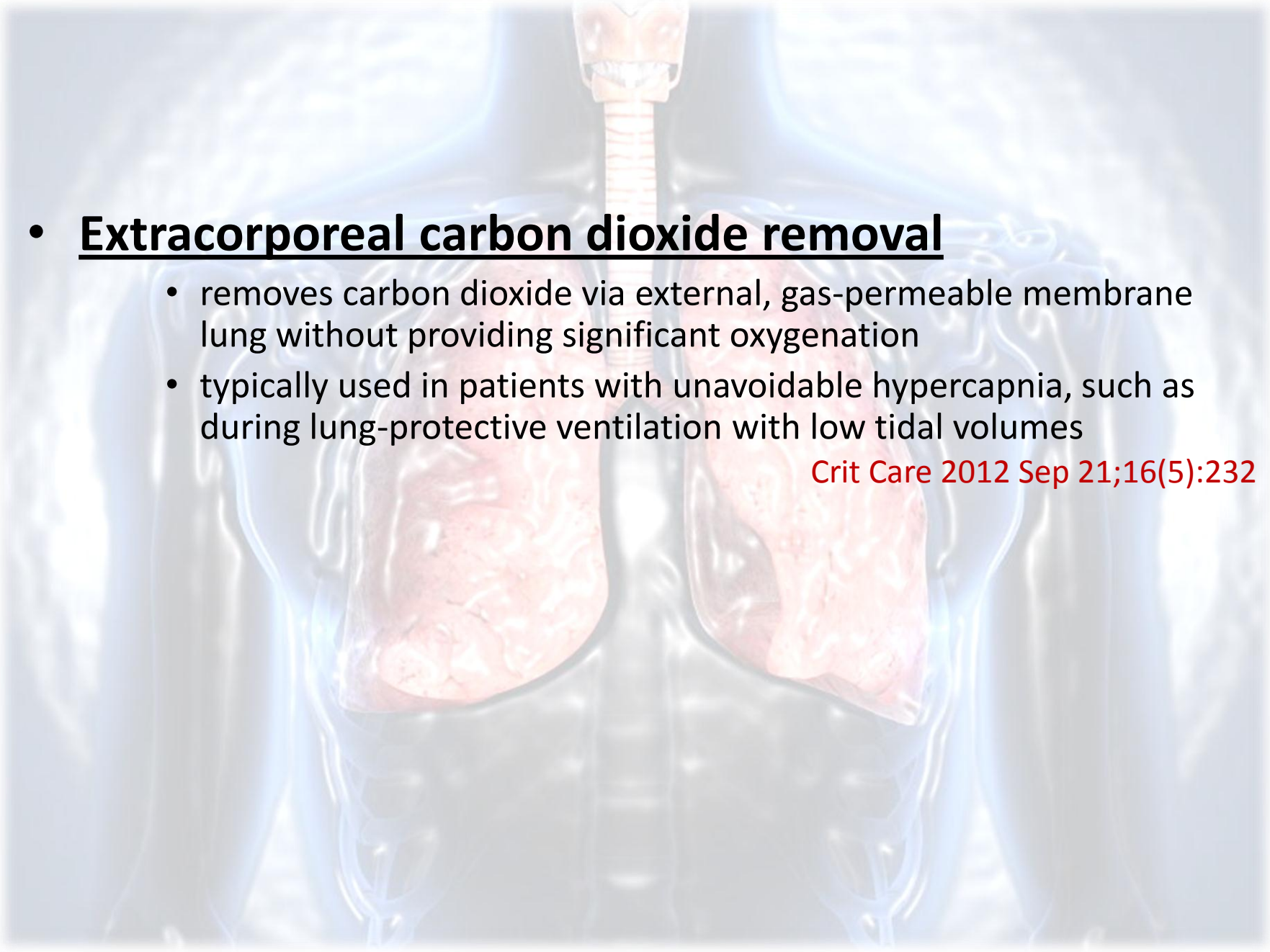
- Kanji et al have published a multi-center study that analyzed 46 patients with severe ARDS treated with ECMO within the first 3 days of mechanical ventilation compared with a control group of 298 patients treated with conventional ventilation.
  - They found that ECMO was associated with a lower mortality (OR 0.30, 95% CI 0.13–0.67), although at the expense of doubling the ICU and hospital stay.

ECMO

- **Extracorporeal membrane oxygenation (ECMO)**

Muñoz Javier, **Extracorporeal membrane oxygenation (ECMO) in adults with acute respiratory distress syndrome (ARDS)**
The Journal of Acute and Critical Care, 2017-03-01

- ECMO as a rescue therapy in adults with ARDS, although there are some risks associated with a learning curve as well as an important increase in the days of patient stay and costs.
- The results from new studies and trials are needed in order to define the real role of this technique, the type of patients that will benefit the most, as well as the best way of providing the expert assistance.
- In the meantime, the indication of ECMO therapy in adults with ARDS should be undertaken in an individualized manner, rigorously considering the benefits and harm associated for each individual patient



- **Extracorporeal carbon dioxide removal**
  - removes carbon dioxide via external, gas-permeable membrane lung without providing significant oxygenation
  - typically used in patients with unavoidable hypercapnia, such as during lung-protective ventilation with low tidal volumes

Crit Care 2012 Sep 21;16(5):232

Extracorporeal carbon dioxide removal

- **Pressure-controlled inverse ratio ventilation followed by low-frequency positive pressure ventilation-extracorporeal carbon dioxide removal may not increase survival in patients with severe ARDS (level 2 [mid-level] evidence)**

  Am J Respir Crit Care Med 1994 Feb;149

- **Extracorporeal CO_2 removal with low tidal volumes (< 6 mL/kg) reported to reduce markers of inflammation and ventilator-induced lung injury in adults with ARDS with plateau pressure of 28-30 cm H_2O on lung-protective ventilation (level 3 [lacking direct] evidence)**

  Anesthesiology 2009 Oct;111(4):826

- **Low tidal volume (3 mL/kg) with extracorporeal carbon dioxide removal may increase number of ventilator-free days in mechanically ventilated patients with ARDS and PaO_2/FiO_2 ≤ 150 (level 2 [mid-level] evidence)**

  Xtravent trial (Intensive Care Med 2013 May;39(5):847)

- **Extracorporeal carbon dioxide removal may not improve survival in patients with acute respiratory failure secondary to ARDS (level 2 [mid-level] evidence)**

  Crit Care 2014 May 15;18(3):222

Management

- **RBC transfusion associated with increased in-hospital mortality in patients with acute lung injury (ALI) (level 2 [mid-level] evidence)**

Chest 2007 Oct;132(4):1116
Crit Care Med 2009 Dec;37(12):3124

  - transfusion of any packed RBCs associated with increased risk of in-hospital mortality (odds ratio 3.12, 95% CI 1.28-7.58)
  - transfusion **after onset of ALI** associated with increased risk of in-hospital mortality (adjusted odds ratio 1.13, 95% CI 1.07-1.2)
  - transfusion before ALI onset not associated with higher risk

Gamma-linolenic acid, GLA

- GLA was supplemented enterally along with *Eicosapentaenoic acid* (fish oil), vitamin C, E, and beta-carotene in a high-fat, low carbohydrate enteral feeding.
- Patients fed this diet exhibited significantly fewer days of ventilatory support and ICU hospitalization versus control subjects fed a high-fat low carbohydrate feeding without GLA.
- The treated patients also were less likely to develop a new organ failure during ARDS.

Crit Care Med 1999;27:1409—20

Others:

Clinical utility of the neutrophil elastase inhibitor sivelestat for the treatment of acute respiratory distress syndrome.
Aikawa N, Kawasaki Y - Ther Clin Risk Manag - January 1, 2014; 10 (); 621-9

- The currently available evidence suggests that sivelestat **may show some benefit** in the treatment of acute lung injury/acute respiratory distress syndrome, although large, randomized controlled trials are needed in specific pathophysiological conditions to explore these potential benefits.

Mesenchymal Stem Cells **(MSCs) for Treatment of Acute Respiratory Distress Syndrome (ARD) in Stem Cell Transplant Patients**

Adult respiratory distress syndrome after treatment with pegylated *interferon α-2a* and ribavirin

Efficacy of continuous *haemodia-filtration* using a polymethylmethacrylate membrane haemofilter (PMMA-CHDF) in the treatment of sepsis and acute respiratory distress syndrome (ARDS)

The use of *surfactant* remains controversial.
Patients who receive surfactant have a greater improvement in gas exchange in the initial 24-hour period than patients who receive standard therapy alone; however, the use of exogenous surfactant does not improve survival

Ventilator Mode	• Volume assist/control until weaning.								
Tidal Volume (V t)	• Initial V t : 6 ml/kg predicted body weight. • Measure inspiratory plateau pressure (Pplat, 0.5 sec inspiratory pause) every 4 hours AND after each change in PEEP or V t . • If Pplat >30 cm H_2O, decrease V t to 5 or to ml/kg. • If Pplat <25 cm H_2O and V t <6 ml/kg PBW, increase V t by 1 ml/kg PBW.								
Respiratory Rate (RR)	• With initial change in V t , adjust RR to maintain minute ventilation.								
	• Make subsequent adjustments to RR to maintain pH of 7.30-7.45, but do not exceed RR = 35/min, and do not increase set rate if Pa co_2 <25 mm Hg.								
I:E Ratio	• Acceptable range = 1:1 to 1:3 (no inverse ratio).								
F io_2 , Positive End-Expiratory Pressure (PEEP), and Arterial Oxygenation	• Maintain Pa o_2 = 55-80 mm Hg or Sp o_2 = 88%-95% using the following PEEP/F io_2 combinations:								
	F io_2	0.3-0.4	0.4	0.5	0.6	0.7	0.8	0.9	1
	PEEP	5-8	8-14	8-16	10-20	10-20	14-22	16-22	18-25

From Vincent JL, Abraham E, Moore FA, et al: *Textbook of critical care* , ed 6, Philadelphia, 2011, Elsevier Saunders

Acidosis Management	1. If pH <7.30, increase RR until pH ≥7.30 or RR = 35/min. 2. If pH remains <7.30 with RR = 35, consider bicarbonate infusion. 3. If pH <7.15, V t may be increased (Pplat may exceed 30 cm H_2O).
Alkalosis Management	• If pH >7.45 and patient not triggering ventilator, decrease set RR but not below 6/min.
Fluid Management	• Once patients are out of shock, adopt a conservative fluid management strategy.
	• Use diuretics or fluids to target a central venous pressure (CVP) of <4 or a pulmonary artery occlusion pressure (PAOP) of <8.

From Vincent JL, Abraham E, Moore FA, et al: *Textbook of critical care* , ed 6, Philadelphia, 2011, Elsevier Saunders

Liberation from Mechanical Ventilation	• Daily interruption of sedation. • Daily screen for spontaneous breathing trial (SBT). • SBT when all of the following criteria are present: (a) F io $_2$ <0.40 and PEEP <8 cm H $_2$ O. (b) Not receiving neuromuscular blocking agents. (c) Patient awake and following commands. (d) Systolic arterial pressure >90 mm Hg without vasopressor support. (e) Tracheal secretions are minimal, and the patient has a good cough and gag reflex.
Spontaneous Breathing Trial	• Place patient on 5 mm Hg pressure support with 5 mm Hg PEEP *or* T-piece. • Monitor HR, RR, oxygen saturation for 30-90 minutes. • Extubate if there are no signs of distress (tachycardia, tachypnea, agitation, hypoxia, diaphoresis).

From Vincent JL, Abraham E, Moore FA, et al: *Textbook of critical care* , ed 6, Philadelphia, 2011, Elsevier Saunders

Management

- Treat the underlying cause if it is known
- Mechanical ventilation
- conservative fluid management
- Corticosteroids
- extracorporeal membrane oxygenation (ECMO)
- Others

THANK YOU