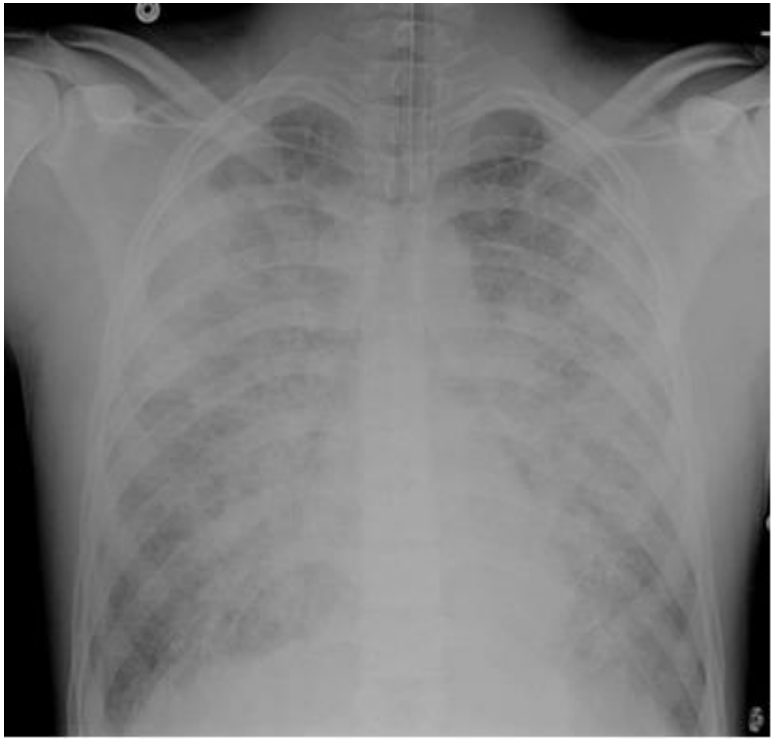
Acute Respiratory Distress Syndrome (ARDS) – An Update



Prof. A.S.M. Areef Ahsan

FCPS(Medicine)

MD(Critical Care Medicine)

MD (Chest)

Head, Dept. of Critical Care Medicine

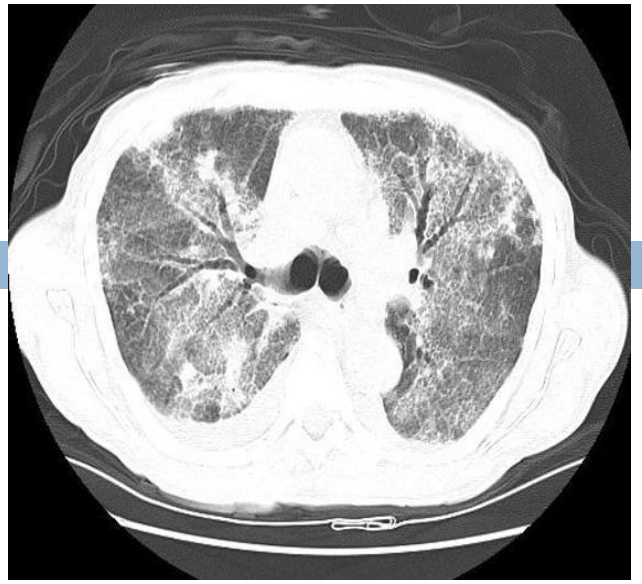
BIRDEM General Hospital

INTRODUCTION —

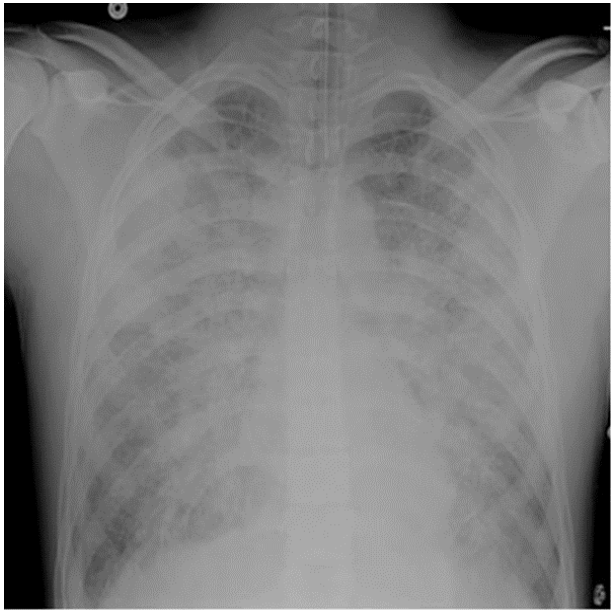
- ARDS is a distinct type of hypoxemic respiratory failure characterized by acute abnormality of both lungs.
- It was first recognized during the 1960s.
- Military clinicians working in surgical hospitals in Vietnam called it shock lung, while civilian clinicians referred to it as **adult** respiratory distress syndrome.
- The current term is acute respiratory distress syndrome (ARDS).
- In 1994, American-European Consensus Conference (AECC) defined ARDS as an acute condition characterized by bilateral pulmonary infiltrates and severe hypoxemia in the absence of evidence for cardiogenic pulmonary edema.
- The Berlin Definition of ARDS (published in 2012) has replaced the American-European Consensus Conference's definition of ARDS (published in 1994)

Berlin definition —

Respiratory symptoms must have begun within one week of a known clinical insult, or the patient must have new or worsening symptoms during the past week.



Bilateral opacities consistent with pulmonary edema must be present on a chest radiograph or computed tomographic (CT) scan. These opacities must not be fully explained by pleural effusions, lobar collapse, lung collapse, or pulmonary nodules.



The patient's respiratory failure must not be fully explained by cardiac failure or fluid overload. An objective assessment (eg, echocardiography) to exclude hydrostatic pulmonary edema is required if no risk factors for ARDS are present.

Berlin definition —

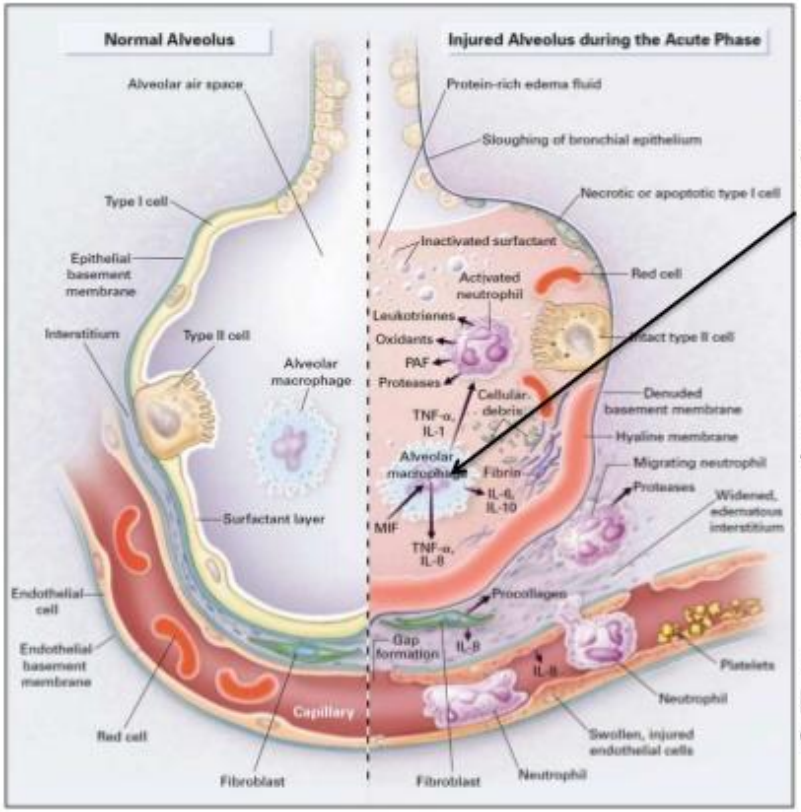
- Severity assessed by ratio of arterial oxygen tension to fraction of inspired oxygen (PaO_2/FiO_2). The severity of the hypoxemia defines the severity of the ARDS:
- •Mild ARDS – The PaO_2/FiO_2 is >200 mmHg, but ≤300 mmHg, on ventilator settings that include positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) ≥5 cm H_2O.
- •Moderate ARDS – The PaO_2/FiO_2 is >100 mmHg, but ≤200 mmHg, on ventilator settings that include PEEP ≥5 cm H_2O.
- •Severe ARDS – The PaO_2/FiO_2 is ≤100 mmHg on ventilators setting that include PEEP ≥5 cm H_2O.

- PaO_2/FiO_2

- SpO_2/FiO_2

SpO_2/FiO_2 ratio of 315 correspond to a PaO_2/FiO_2 ratio of 300

Pathophysiology of ARDS-



Pathophysiology during exudative phase

Direct or indirect injury to the alveolus causes alveolar macrophages to release pro-inflammatory cytokines

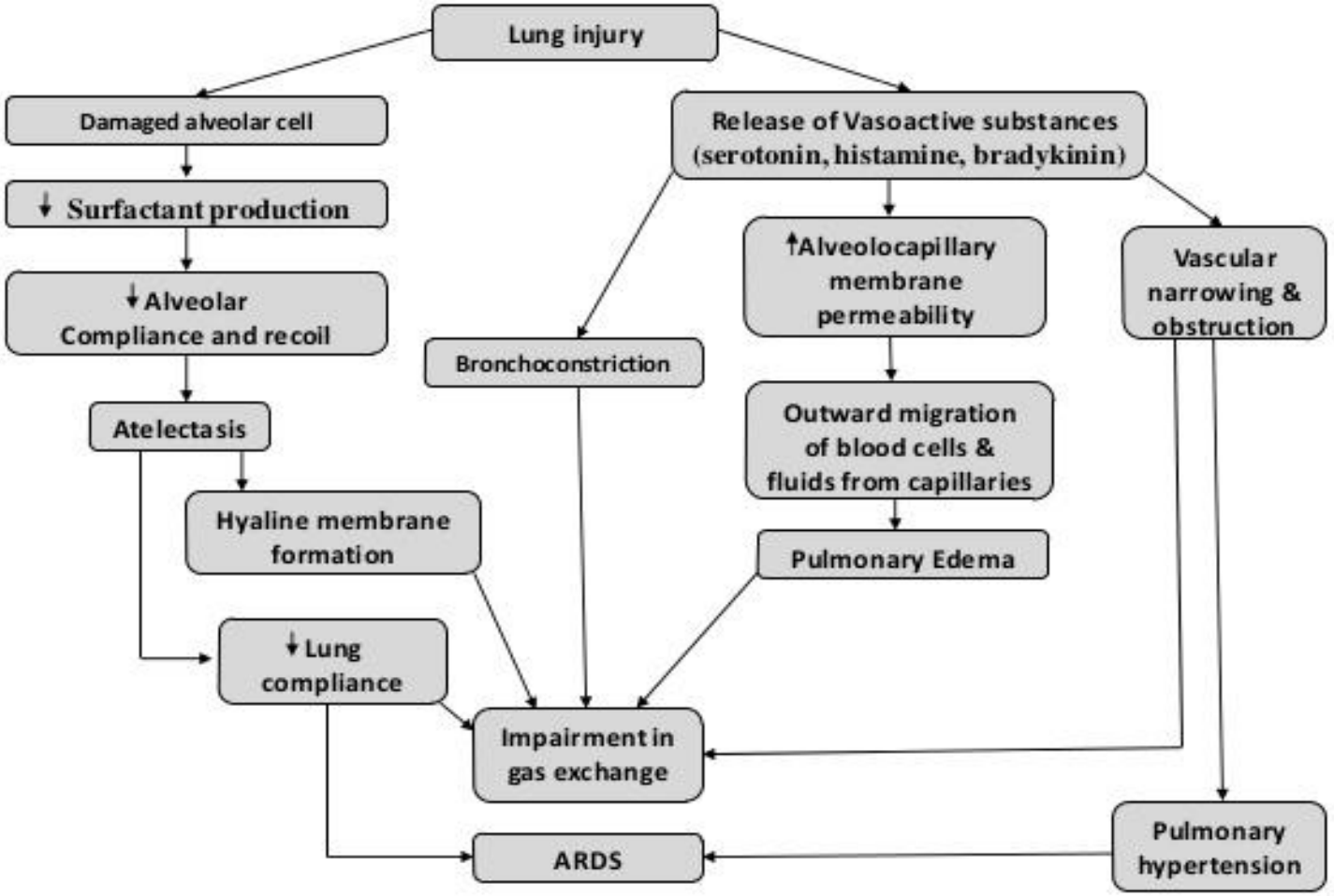
↓

Cytokines attract neutrophils into the alveolus and interstitum, where they damage the alveolar-capillary membrane (ACM).

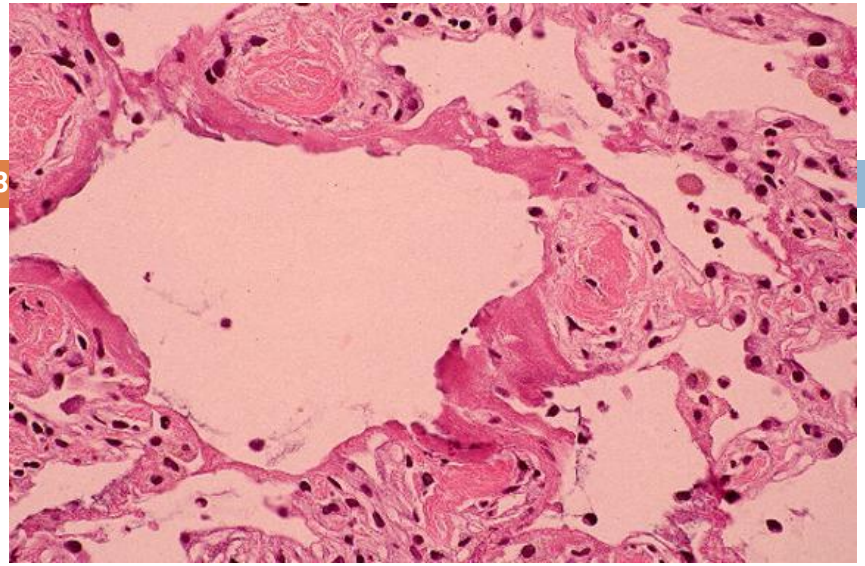
↓

. ACM integrity is lost, interstitial and alveolus fills with proteinaceous fluid, surfactant can no longer support alveolus

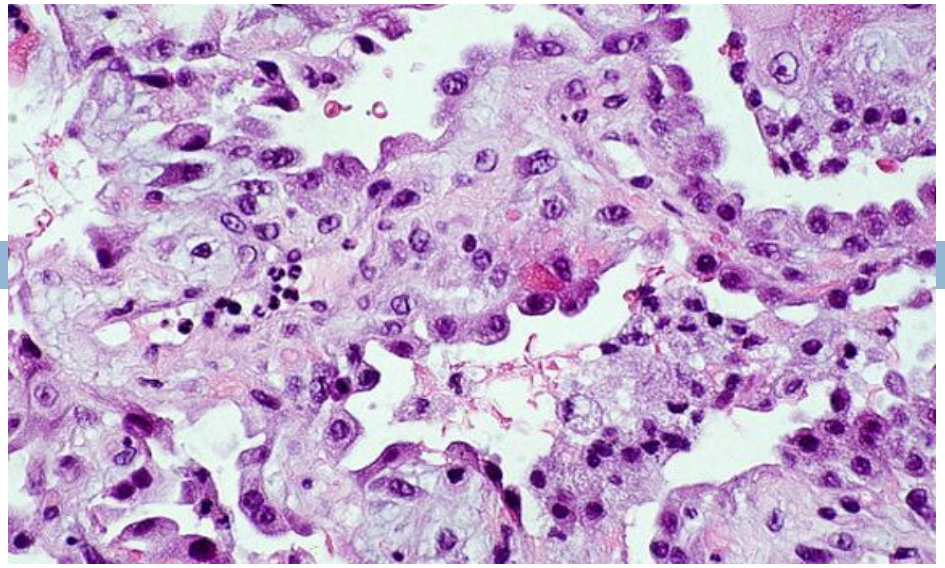
SCHEMATIC REPRESENTATION OF PATHOPHYSIOLOGY OF ARDS



PATHOLOGIC STAGES —

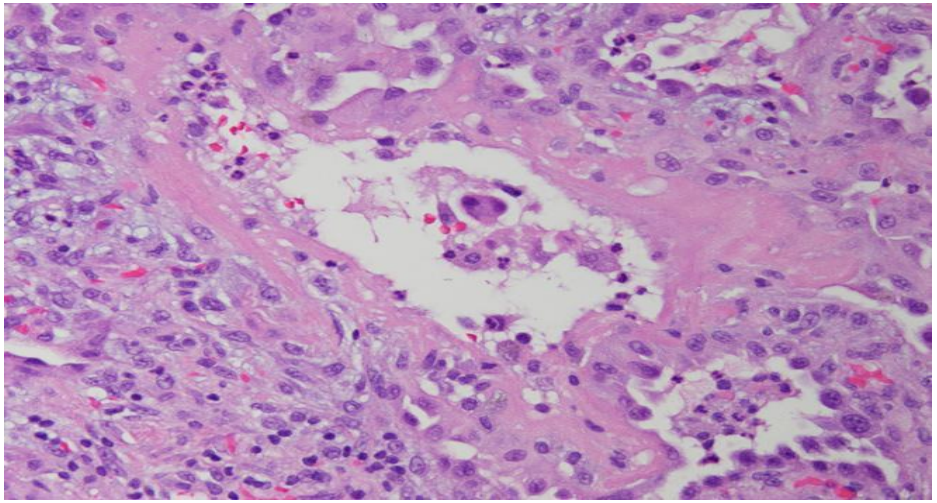


The initial stage is the exudative stage, characterized by diffuse alveolar damage.

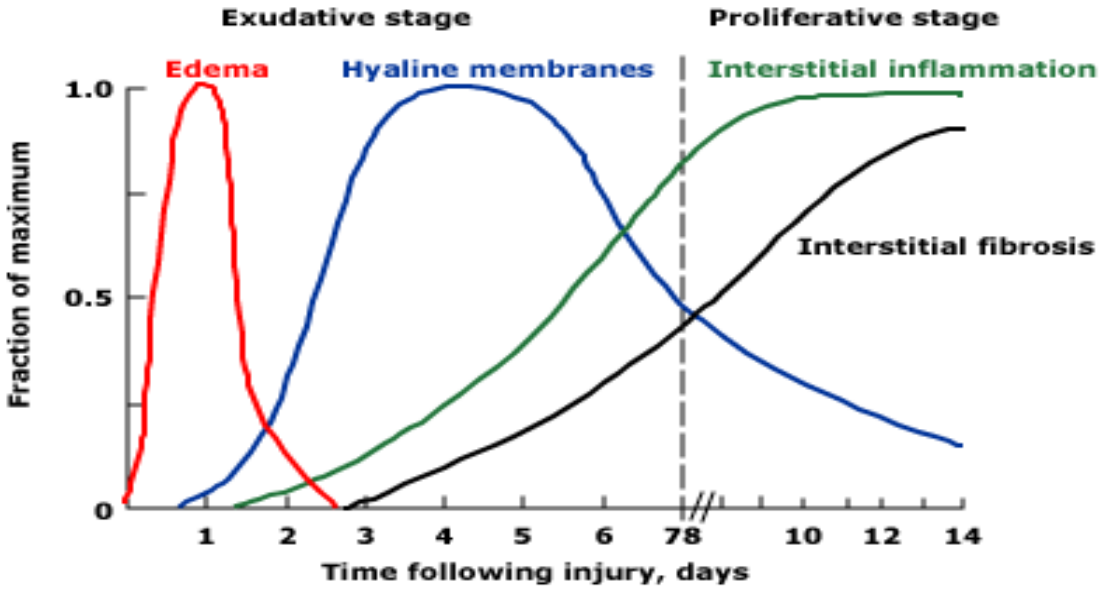


Proliferative stage is characterized by resolution of pulmonary edema, proliferation of type II alveolar cells, squamous metaplasia, interstitial infiltration by myofibroblasts, and early deposition of collagen.

Some patients progress to a fibrotic stage, characterized by obliteration of normal lung architecture, diffuse fibrosis, and cyst formation.



Time course of acute respiratory distress syndrome (ARDS)



Schematic representation of the time course of the acute respiratory distress syndrome (ARDS). During the early (or exudative) phase, the lesion is characterized by high permeability pulmonary edema followed by the formation of hyaline membranes. After seven to ten days, a proliferative phase may develop, with marked interstitial inflammation, fibrosis, and disordered healing.

List of conditions associated with acute respiratory distress syndrome (ARDS)

Sepsis	Following upper airway obstruction
Aspiration	Following bone marrow transplantation
Infectious pneumonia	Drug reaction
Severe trauma	Venous air embolism
Surface burns	Amniotic fluid embolism
Multiple blood transfusions	Neurogenic pulmonary edema
Leukoagglutin reactions	Acute eosinophilic pneumonia
Pancreatitis	Bronchiolitis obliterans organizing pneumonia (BOOP)
Drug overdose	Miliary tuberculosis
Near drowning	
Smoke inhalation	
Cardiopulmonary bypass	
Pulmonary contusion	
Multiple fractures	

Approximately 20% of patients with ARDS have no identified risk factor

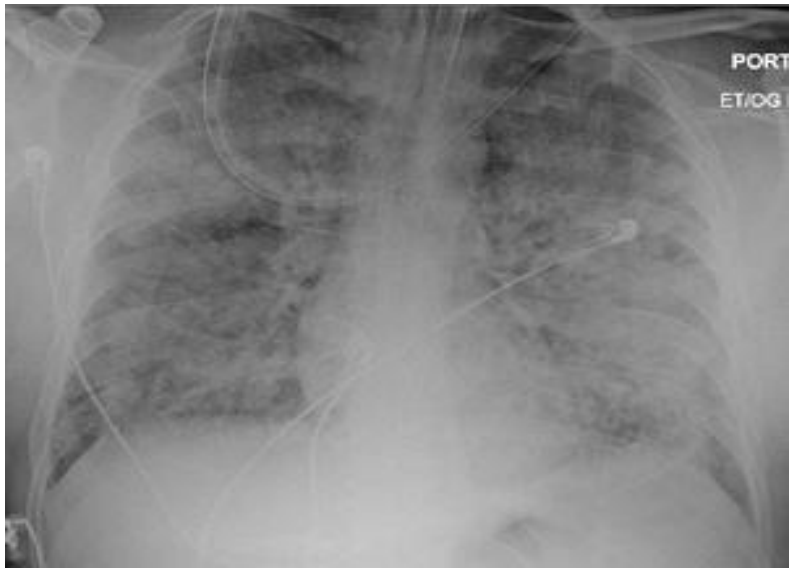
Clinical features-

❑Clinical features of ARDS usually appear within 6 to 72 hours of an inciting event and worsen rapidly

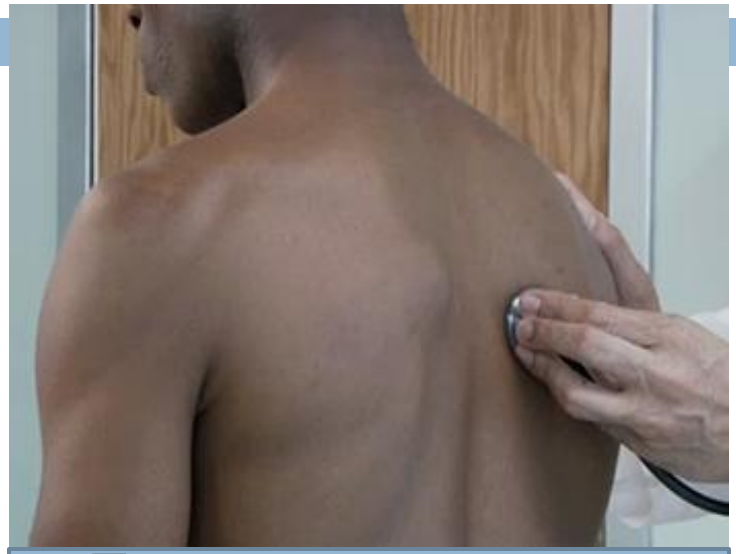
❑Acute dyspnea and hypoxemia

❑ Pts are critically ill, often with multisystem organ failure

❑Symptoms of underlying cause



Physical examination



❑ Tachypnea, tachycardia

❑ Evidence of dyspnea

❑ Evidence of hypoxia

❑ Lungs - bilateral rales

Rales may not be present despite widespread involvement.

❑ Features of underlying cause

DIFFERENTIAL DIAGNOSIS — Acute hypoxemic respiratory failure with bilateral alveolar infiltrates

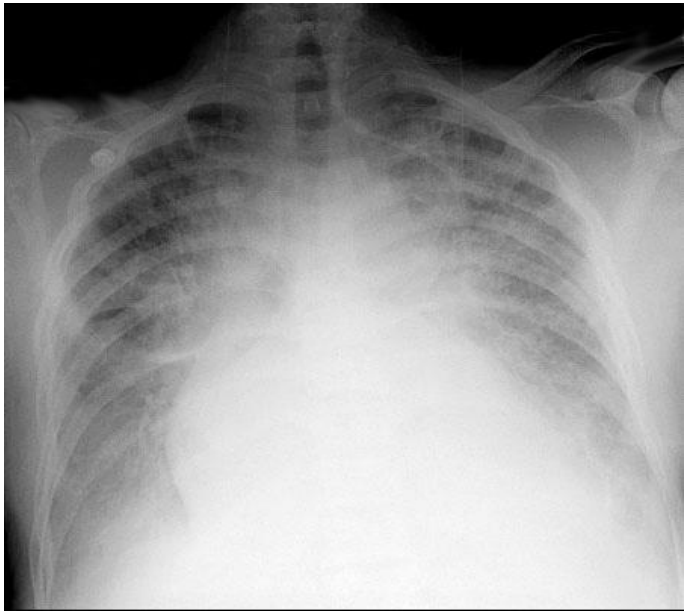
- Cardiogenic pulmonary edema
- An acute exacerbation of idiopathic pulmonary fibrosis or other chronic interstitial lung diseases
- Diffuse alveolar hemorrhage
- Idiopathic acute eosinophilic pneumonia (IAEP)
- Cryptogenic organizing pneumonia (COP)
- Acute interstitial pneumonia (Hamman-Rich syndrome)
- Cancer can disseminate through the lungs so rapidly that the ensuing respiratory failure may be mistaken for ARDS.

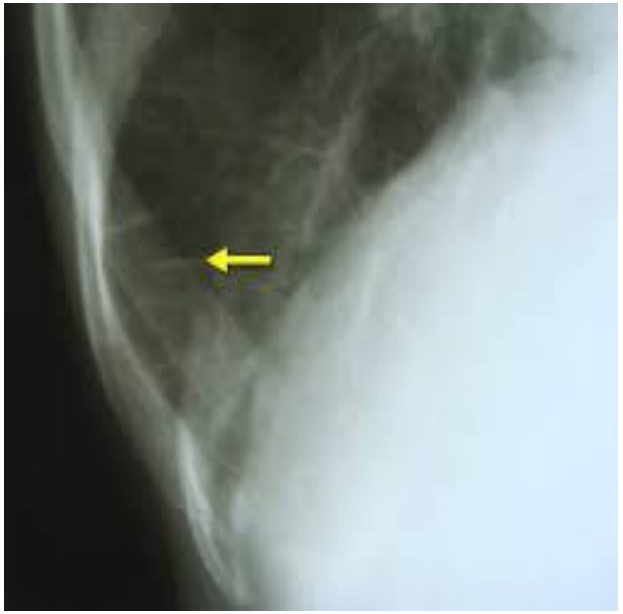
DIAGNOSTIC EVALUATION —

- The diagnostic evaluation is aimed at identifying specific causes of ARDS that are amenable to treatment and excluding other conditions that also present with acute hypoxemia, bilateral alveolar infiltrates,

Exclude cardiogenic pulmonary edema

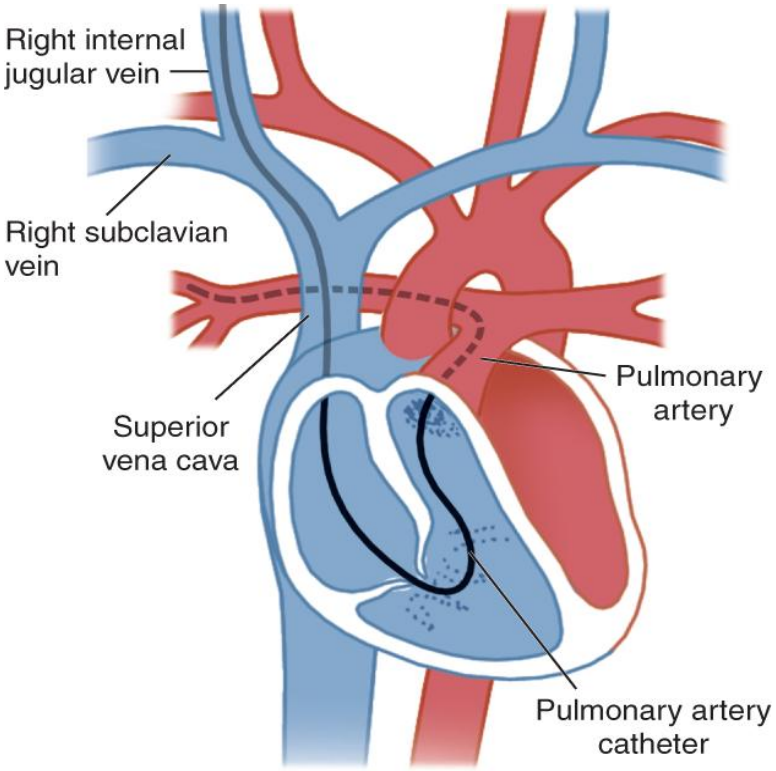
S3 or S4 gallop, new or changed murmur)





Additional diagnostic tests-

Brain natriuretic peptide (BNP) – A plasma BNP level below 100 pg/mL



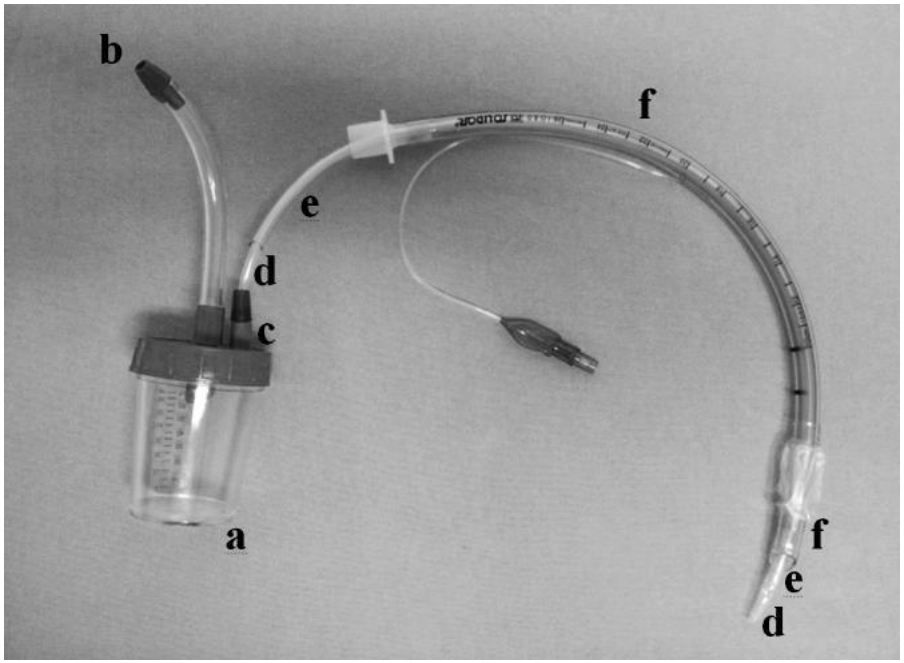
Source: Reichman EF: *Emergency Medicine Procedures, Second Edition:* www.accessemergencymedicine.com

- Severe aortic or mitral valve dysfunction,
- Severe diastolic dysfunction,
- or a severely reduced left ventricular ejection fraction

favors cardiogenic pulmonary edema,

Additional diagnostic testing-

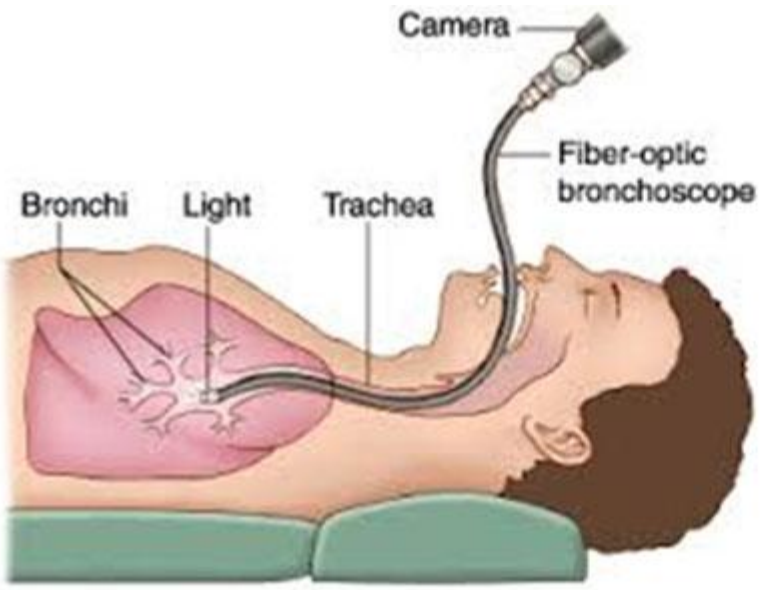
(Noninvasive respiratory sampling) –



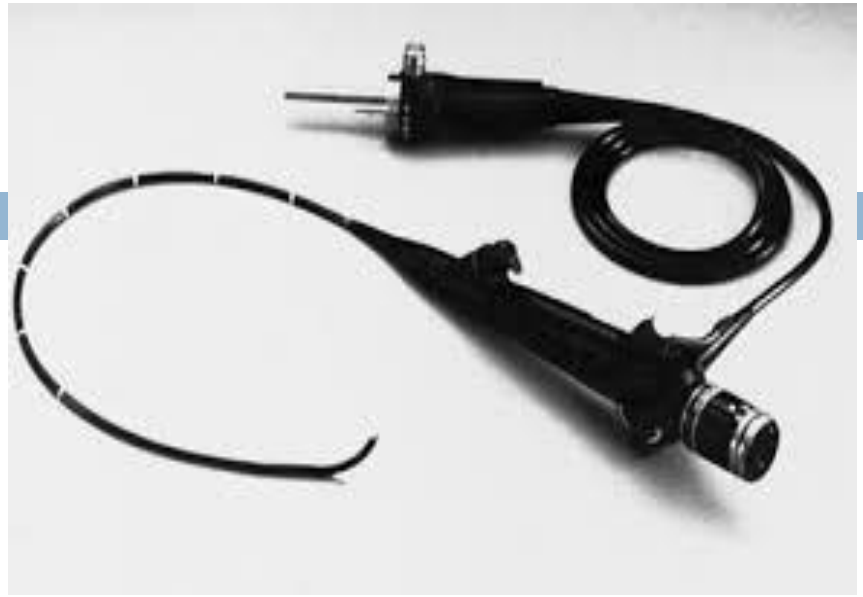
tracheobronchial aspiration

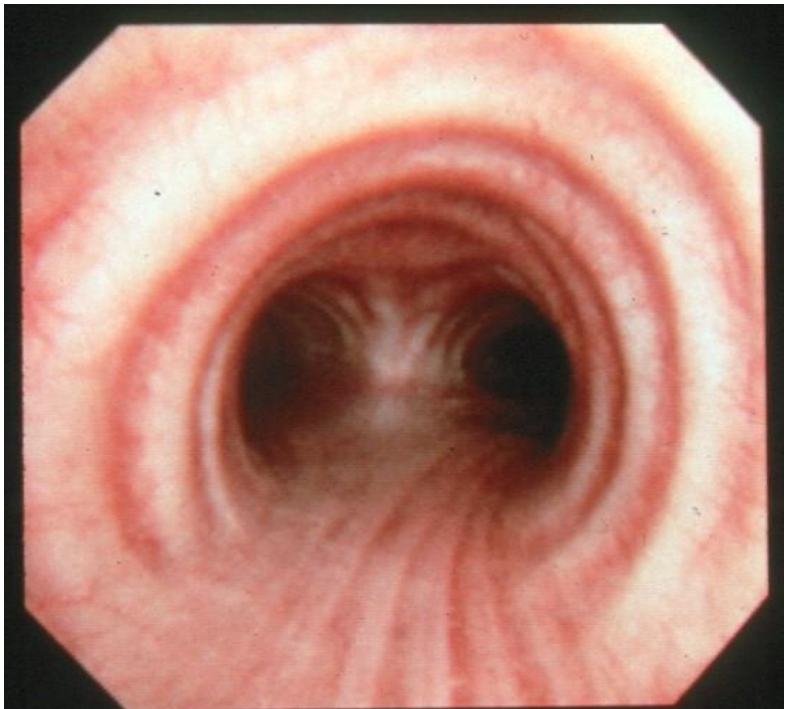
mini-bronchoalveolar lavage (mini-BAL)

Additional diagnostic testing-



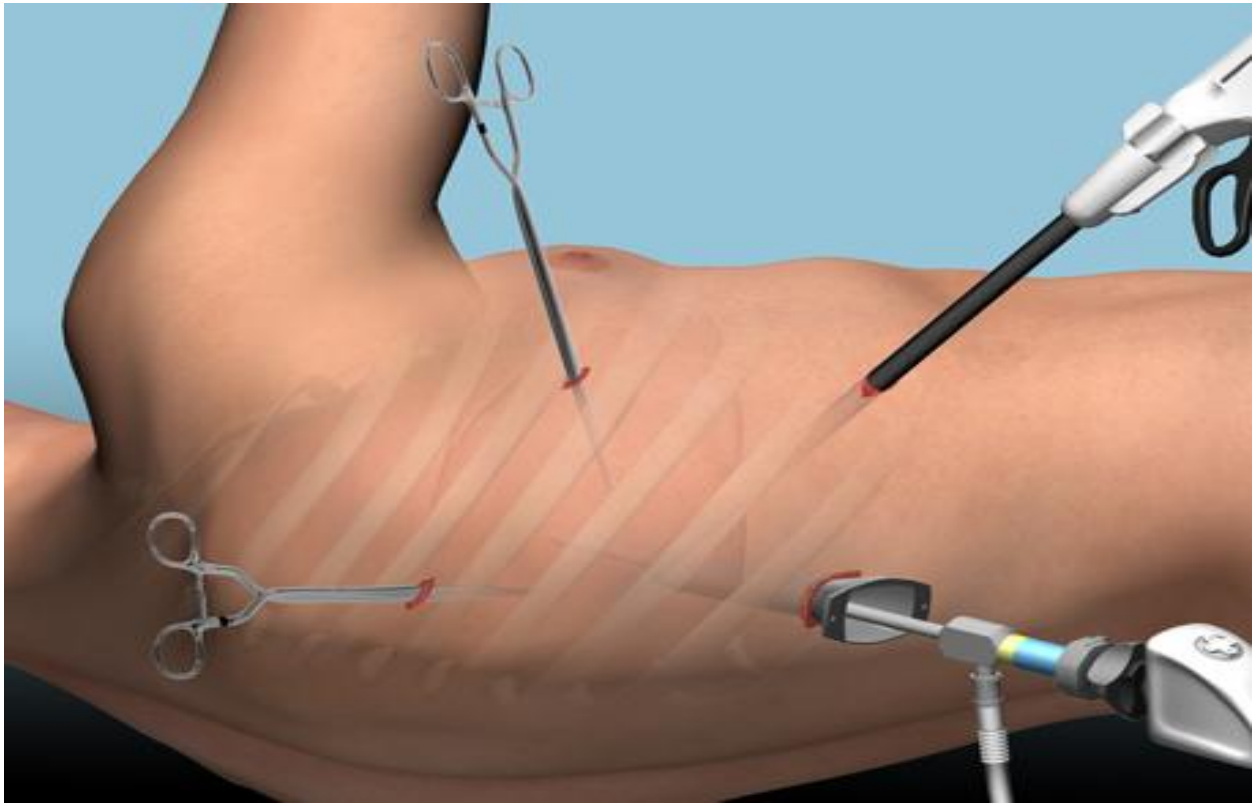
Additional diagnostic testing-





Flexible bronchoscopy

Additional diagnostic testing-

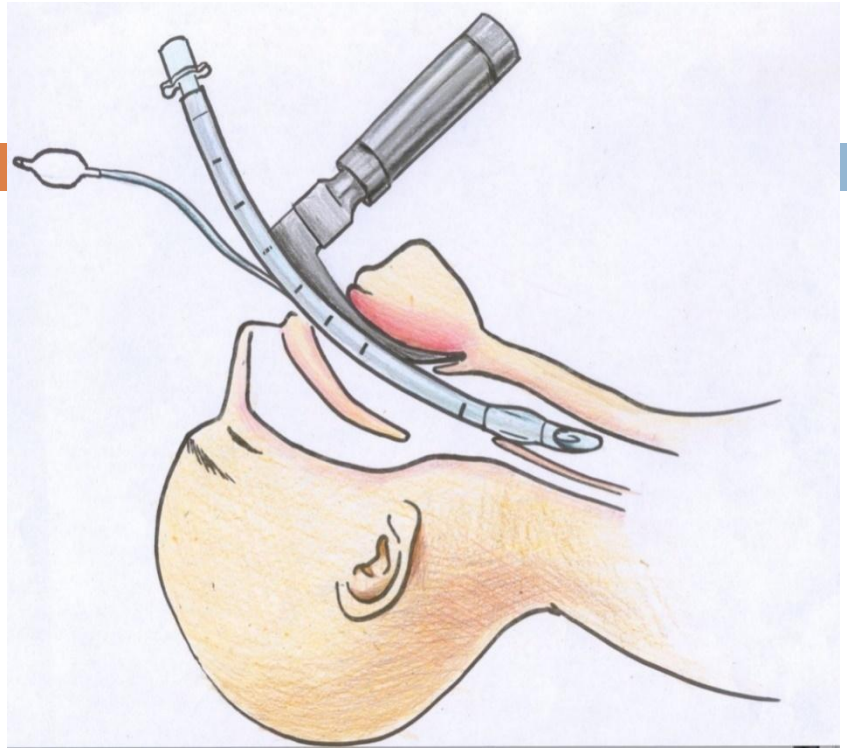


Lung biopsy

Management Headlines-

- Correction of hypoxia
- Supportive care
- No specific therapy for ARDS
- No drug has proved beneficial in management of acute respiratory distress syndrome (ARDS)
- Treatment of the underlying condition is essential

Correction of Hypoxia-



Almost all patients require intubation and mechanical ventilation. During the peri-intubation period, 95 to 100 percent oxygen should be given to ensure an adequate SaO_2

Mechanical ventilatory strategies-

- Low tidal volume ventilation (LTVV) is also referred to as lung protective ventilation.
- High positive end-expiratory pressure (high PEEP)
- Tidal volume (4 to 8 mL/kg predicted body weight

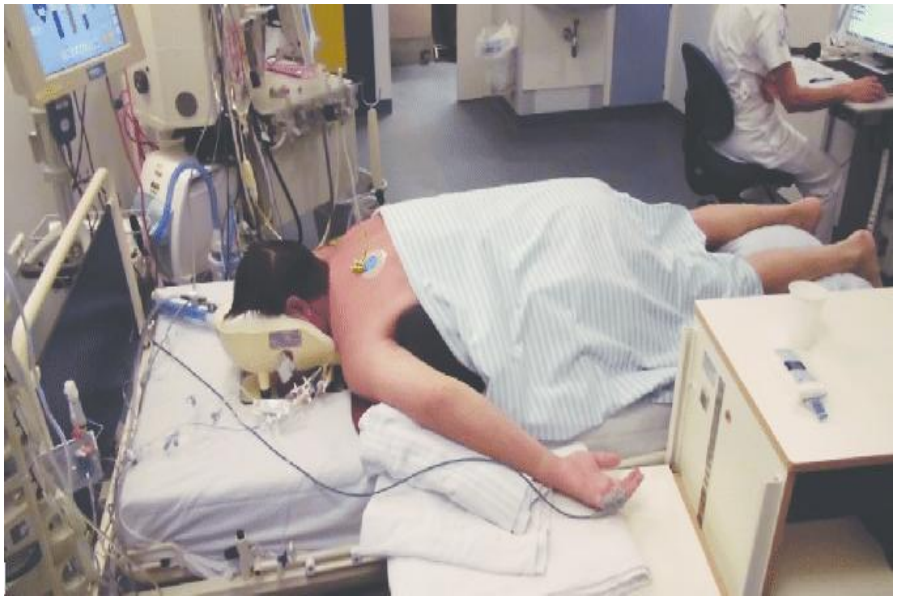
TERGET/Goal

- PaO_2 of 55 to 80 mmHg or SaO_2 88 to 95 percent
- Inspiratory plateau airway pressure ≤30 cm H_2O
- Reduce the fraction of inspired oxygen (FiO_2) to less than 65% within the first 24-48 hours

LTVV causes respiratory acidosis in some patients. This is called **Permissive hypercapnia**

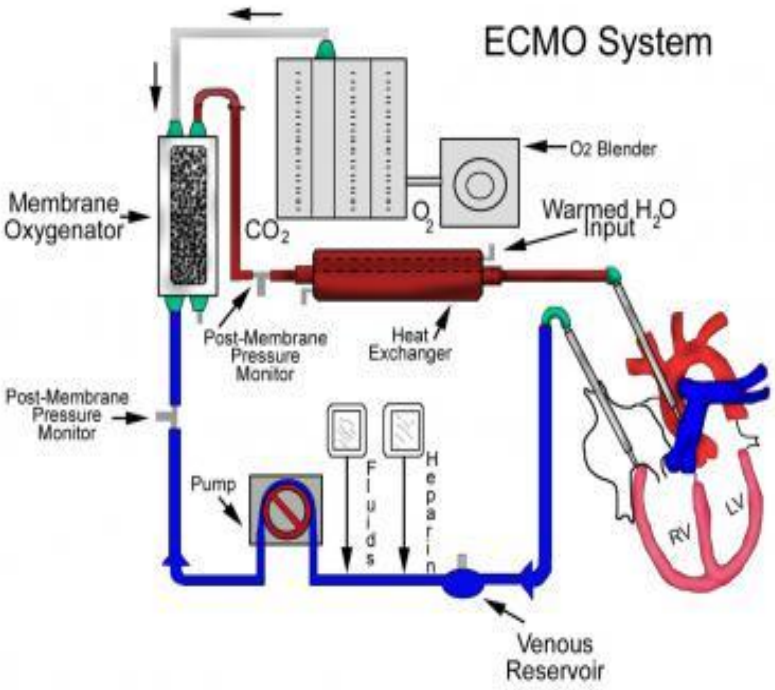
Refractory hypoxemia-

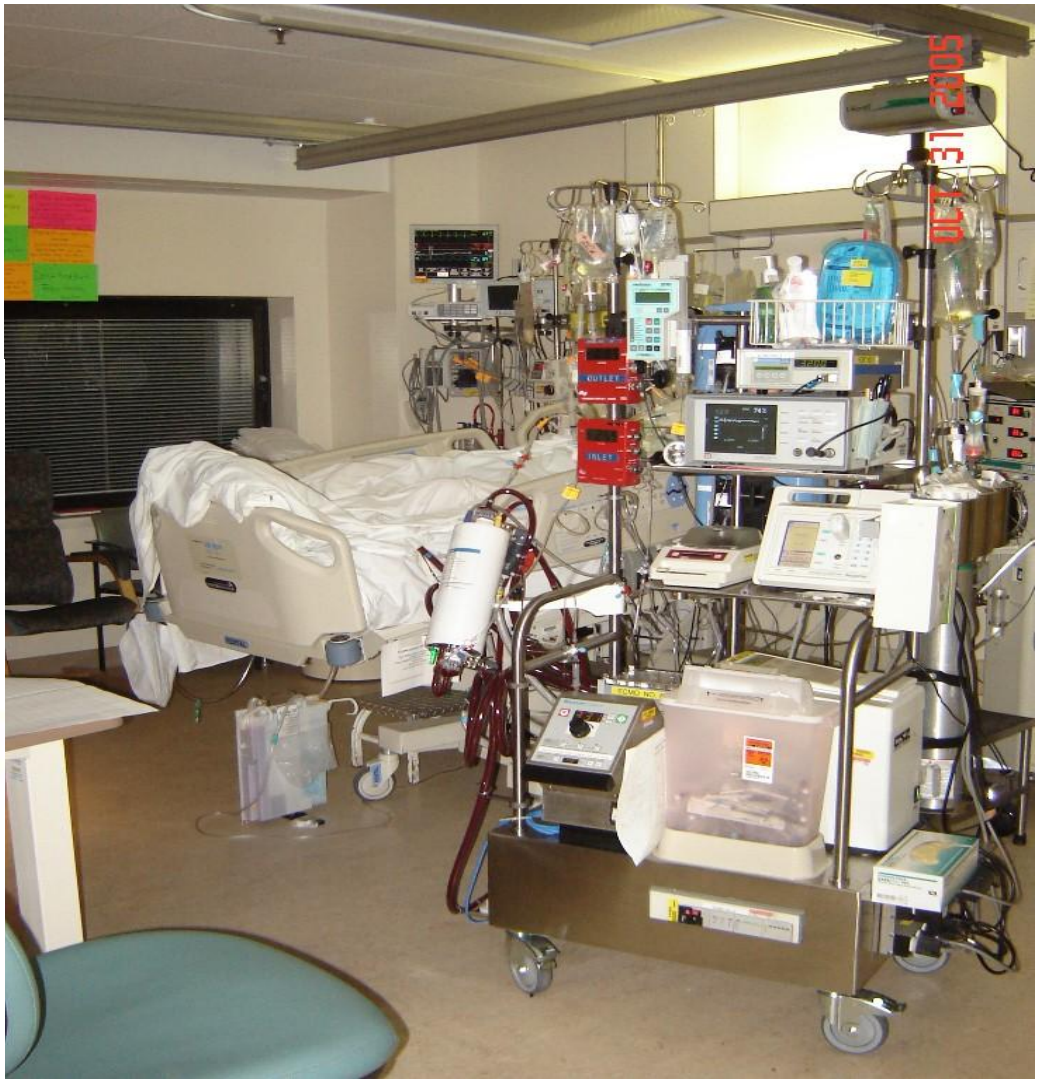
- Inverse ratio ventilation
- Pressure-controlled ventilation
- High-frequency ventilation
- **Prone positioning**



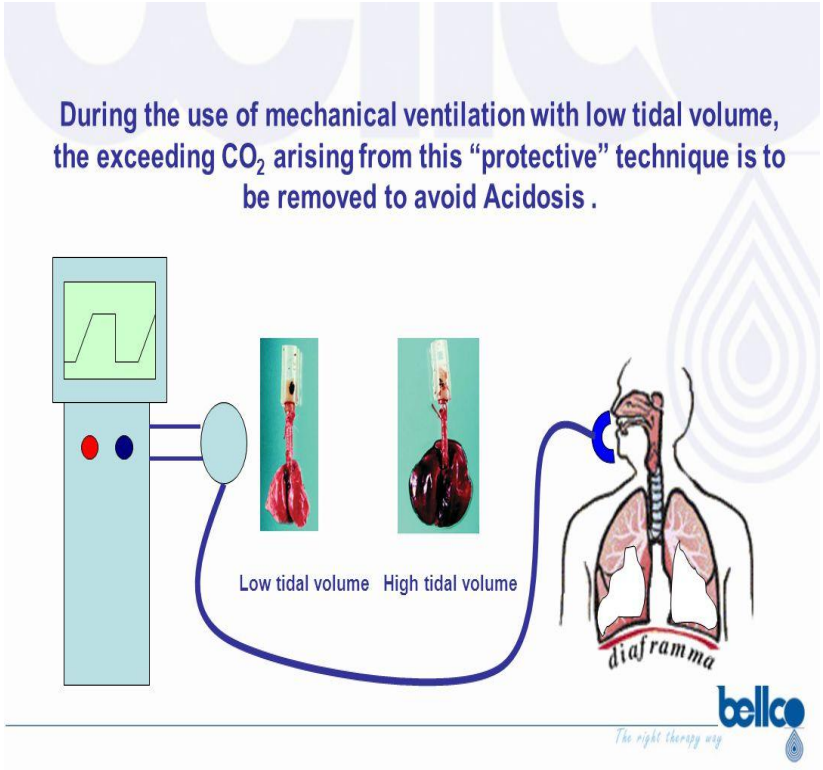
Refractory hypoxemia-

- **Extracorporeal membrane oxygenation (ECMO)**



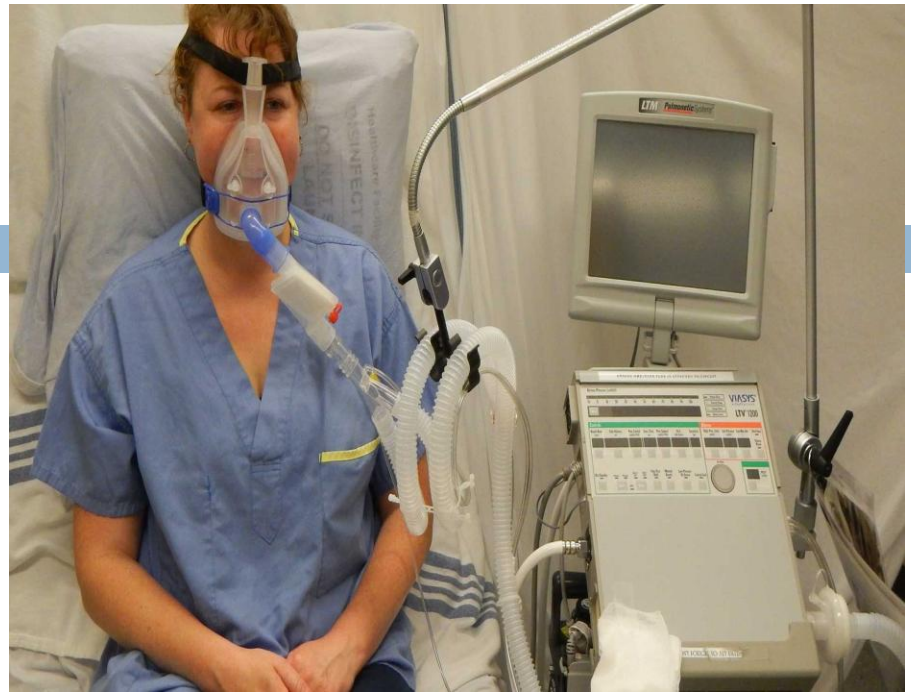


Extra Corporeal CO2 Removal (ECCO2R)



Noninvasive ventilation-

- Noninvasive ventilation (NIV) may be reserved for the occasional patient with ARDS-
- Who is hemodynamically stable.
- Does not need immediate intubation.
- Has no contraindications to its use.



Fluid management-

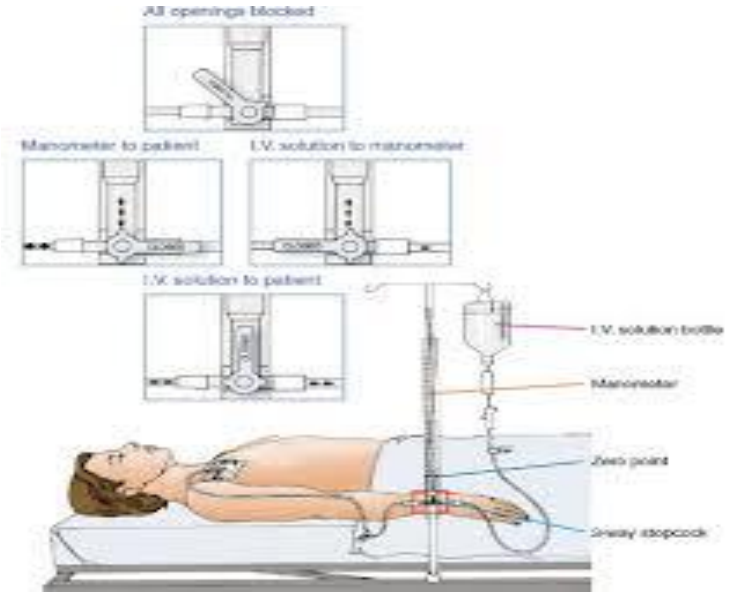
- A conservative strategy of fluid management in patients with ARDS, as long as hypotension and organ hypoperfusion can be avoided.

Target :

- Central venous pressure of <4 mmHg
- Or a pulmonary artery occlusion pressure <8 mmHg

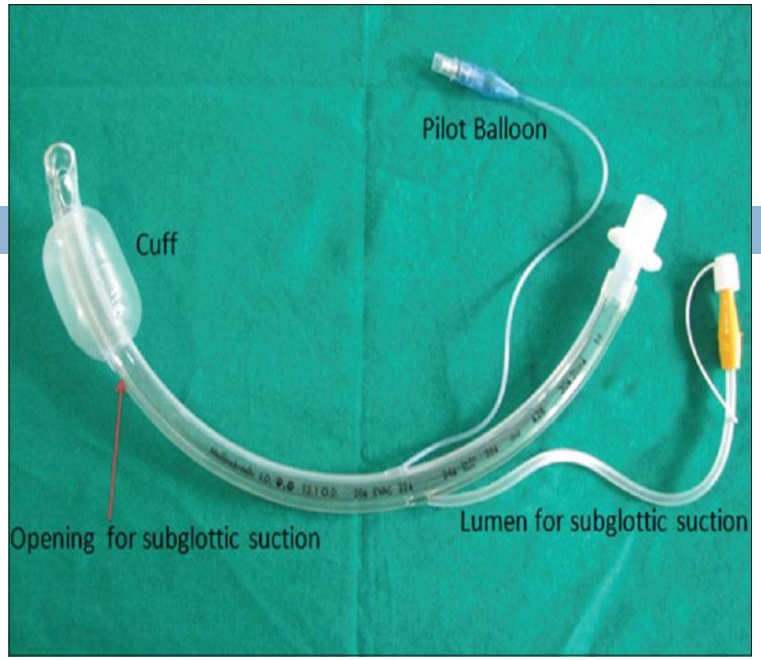
Data suggests that combination therapy with **albumin solution and furosemide** may improve fluid balance, oxygenation, and hemodynamics.

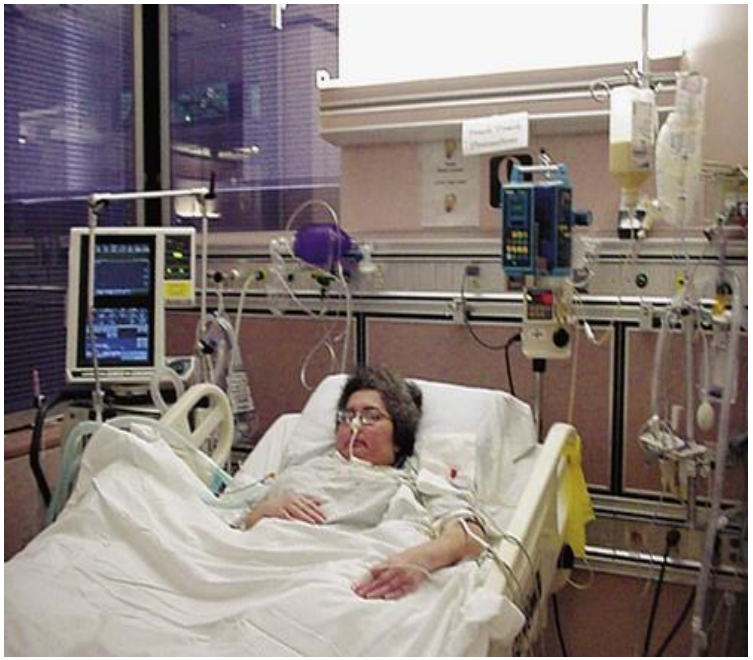
Hemodynamic monitoring-



Supportive care-

- Intelligent use of sedatives and neuromuscular blockade
- Nutritional support
- Control of blood glucose
- Deep venous thrombosis (DVT) prophylaxis
- Stress ulcer prophylaxis
- Early mobilization
- Strategies to prevent ventilator-induced pneumonia such as elevation of the head of the bed and use of a subglottic suction device





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Am J Respir Crit Care Med. 1998 May;157(5 Pt 1):1372-80.

Inhaled nitric oxide versus conventional therapy: effect on oxygenation in ARDS.

Michael JR[1], Barton RG, Saffle JR, Mone M, Markewitz BA, Hillier K, Elstad MR, Campbell EJ, Troyer BE, Whatley RE, Liou TG, Samuelson WM, Carveth HJ, Hinson DM, Morris SE, Davis BL, Day RW.

Author information

Abstract

A randomized, controlled clinical trial was performed with patients with acute respiratory distress syndrome (ARDS) to compare the effect of conventional therapy or inhaled nitric oxide (iNO) on oxygenation. Patients were randomized to either conventional therapy or conventional therapy plus iNO for 72 h. We tested the following hypotheses: (1) that iNO would improve oxygenation during the 72 h after randomization, as compared with conventional therapy; and (2) that iNO would increase the likelihood that patients would improve to the extent that the FI(O2) could be decreased by > or = 0.15 within 72 h after randomization. There were two major findings. First, That iNO as compared with conventional therapy increased Pa(O2)/FI(O2) at 1 h, 12 h, and possibly 24 h. Beyond 24 h, the two groups had an equivalent improvement in Pa(O2)/FI(O2). Second, that patients treated with iNO therapy were no more likely to improve so that they could be managed with a persistent decrease in FI(O2) > or = 0.15 during the 72 h following randomization (11 of 20 patients with iNO versus 9 of 20 patients with conventional therapy, p = 0.55). In patients with severe ARDS, our results indicate that iNO does not lead to a sustained improvement in oxygenation as compared with conventional therapy.

Comment in

Is nitric oxide inhalation a "cosmetic" therapy in acute respiratory distress syndrome? [Am J Respir Crit Care Med. 1998]

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Cochrane Database Syst Rev. 2016 Jun 27;(6):CD002787. doi: 10.1002/14651858.CD002787.pub3.

Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults.

Gebistorf F[1], Karam O, Wetterslev J, Afshari A.

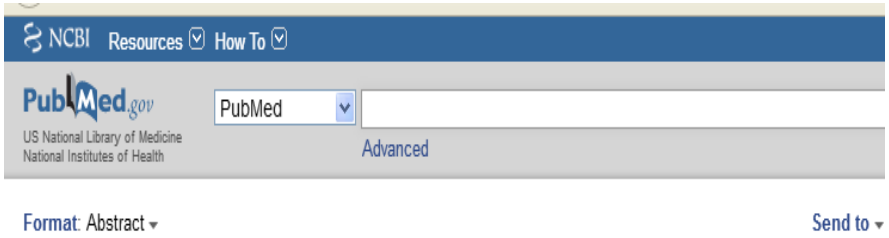
Author information

Abstract

BACKGROUND: Acute hypoxaemic respiratory failure (AHRF) and mostly acute respiratory distress syndrome (ARDS) are critical conditions. AHRF results from several systemic conditions and is associated with high mortality and morbidity in individuals of all ages. Inhaled nitric oxide (INO) has been used to improve oxygenation, but its role remains controversial. This Cochrane review was originally published in 2003, and has been updated in 2010 and 2016.

OBJECTIVES: The primary objective was to examine the effects of administration of inhaled nitric oxide on mortality in adults and children with ARDS. Secondary objectives were to examine secondary outcomes such as pulmonary bleeding events, duration of mechanical ventilation, length of stay, etc. We conducted subgroup and sensitivity analyses, examined the role of bias and applied trial sequential analyses (TSAs) to examine the level of evidence.

SEARCH METHODS: In this update, we searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2015 Issue 11); MEDLINE (Ovid SP, to 18 November 2015), EMBASE (Ovid SP, to 18 November 2015), CAB, BIOSIS and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). We handsearched the reference lists of the newest reviews and cross-checked them with our search of MEDLINE. We contacted the main authors of included studies to request any missed, unreported or ongoing studies. The search was run from inception until 18 November 2015.



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Respirology. 2016 Aug;21(6):1026-33. doi: 10.1111/resp.12820. Epub 2016 May 24.

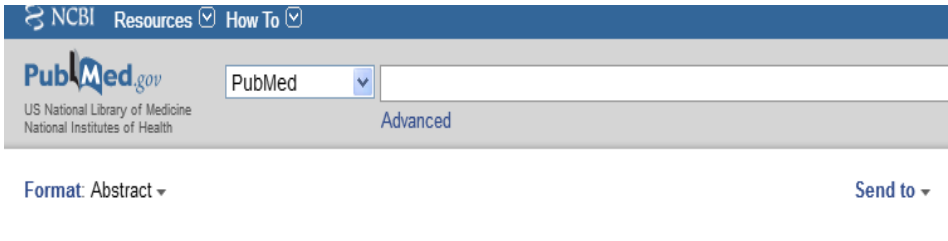
Statins for the prevention and treatment of acute lung injury and acute respiratory distress syndrome: A systematic review and meta-analysis.

Xiong B[1], Wang C[1], Tan J[1], Cao Y[1], Zou Y[1], Yao Y[1], Qian J[1], Rong S[1], Huang Y[1], Huang J[1].

Author information

Abstract

The purpose of this meta-analysis was to assess whether statins could reduce the morbidity of acute lung injury and acute respiratory distress syndrome (ALI/ARDS) in high-risk patients and improve the clinical outcomes of patients with ALI/ARDS. Studies were obtained from PubMed, Medline, Embase and Cochrane Central Register of Controlled Trials. Randomized controlled trials (RCTs) and cohort studies, which reported morbidity, mortality, ventilator-free days, length of stay in intensive care unit and hospital or oxygenation index, were included in our meta-analysis. Risk ratio (RR) and weighted mean difference (WMD) were calculated using fixed or random effect model. A total of 13 studies covering 12 145 patients were included. Both the only RCT (P = 0.10) and cohort studies (RR, 1.02; 95% CI, 0.67 to 1.55; P = 0.94) showed that statin therapy did not lower the morbidity of ALI/ARDS in high-risk patients. The mortality of ALI/ARDS patients was less likely to be improved by statins (RCT, RR, 1.00; 95% CI, 0.84 to 1.20; P = 0.97; cohort studies, RR, 1.04; 95% CI, 0.85 to 1.27; P = 0.72). Moreover, no significant difference was observed in ventilator-free days, length of stay in intensive care unit as well as hospital and oxygenation index. This meta-analysis suggests that statins neither provide benefit for lowering the morbidity of ALI/ARDS in high-risk patients nor improve the clinical outcomes of ALI/ARDS patients. Hence, it may not be appropriate to advocate statin use for the prevention and treatment of ALI/ARDS.



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Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2017 Jan;29(1):51-56. doi: 10.3760/cma.j.issn.2095-4352.2017.01.011.

[Statin in the treatment of ALI/ARDS: a systematic review and Meta-analysis based on international databases].

[Article in Chinese]

Chen M[1], Lu J, Chen Q, Cheng L, Geng Y, Jiang H, Wang X.

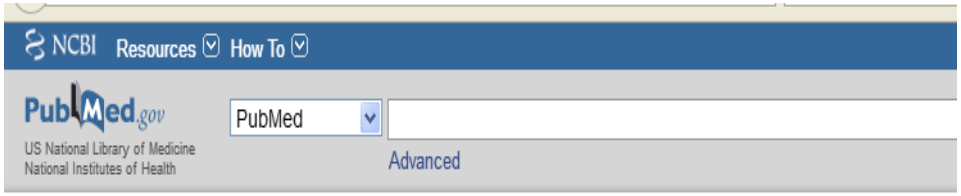
Author information

Abstract

OBJECTIVE: To confirm the effects of statin therapy on mortality of patients with acute lung injury/acute respiratory distress syndrome (ALI/ARDS).

METHODS: PubMed/Medline, Embase, Web of Science and Cochrane Central Register of Controlled Trials were searched for articles using the terms "acute lung injury", "ALI", "acute respiratory distress syndrome", "ARDS", "statin", "simvastatin" and "rosuvastatin" updated to November 17, 2015. Randomized controlled trial (RCT) or observational cohort studies investigating the effects of statin therapy on mortality in patients with ALI or ARDS were all identified, without date or language restriction. The control group was given conventional treatment, while the experimental group was treated with statins additionally. The primary outcome was in-hospital mortality. Meanwhile, ventilator-free day, intensive care unit (ICU)-free day, ICU length of stay (LOS) and ICU mortality were also analyzed. RevMan 5.2 and STATA 13 software were used for systematic review and Meta analysis, and funnel plot was used to analyze the publication bias.

RESULTS: A total of five trials including three randomized controlled trials and two observational studies were included. Among 1 636 patients enrolled in the study, there were 739 patients in experimental group, and 897 in control group. It was shown by Meta analysis that there was no significant difference in in-hospital mortality between experimental group and control group [relative risk (RR) = 0.96, 95% confidence interval (95%CI) =



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Pulm Pharmacol Ther. 2016 Aug;39:85-91. doi: 10.1016/j.pupt.2016.06.010. Epub 2016 Jun 29.

Impact of statins on ALI/ARDS: A meta-analysis.

Gao XQ[1], Li YF[2], Jiang ZL[1].

Author information

Abstract

BACKGROUND: Statins may be beneficial in treating acute lung injury (ALI) or acute respiratory distress syndrome (ARDS), but their application remains controversial.

OBJECTIVES: This meta-analysis of published studies investigated their potential benefit in ALI/ARDS treatment.

METHODS: PubMed, EMBASE, Google Scholar and Cochrane databases were searched and all randomized controlled trials (RCT) and cohort studies with head-to-head comparison between statin and standard care were included.

RESULTS: Three RCTs and six cohort studies were included. Overall, statins treatment had no significant effect on mortality compared with placebo (RCTs: OR = 0.99, 95% CI = 0.72, 1.37; cohorts: OR = 0.99, 95% CI = 0.71, 1.37). In addition, ventilator-free days were comparable between the two groups (RCTs: SMD = 0.08, 95% CI = -0.03, 0.19; cohorts: SMD = 0.06, 95% CI = -0.17, 0.29). The one-way sensitivity analysis confirmed the stability of results.

CONCLUSION: The results did not show that statins had effects on mortality and ventilator-free days among ALI/ARDS patients. However, this meta-analysis is limited by the number of RCTs included.

Crit Care Med. Author manuscript; available in PMC 2014 Mar 3.
Published in final edited form as:
Crit Care Med. 2012 May; 40(5): 1470–1477.
doi: 10.1097/CCM.0b013e3182416d7a
PMCID: PMC3939937
NIHMSID: NIHMS440119

Statin therapy as prevention against development of acute respiratory distress syndrome: An observational study*

Ednan K. Bajwa, MD, MPH, Cindy K. Malhotra, PharmD, B. Taylor Thompson, MD, David C. Christiani, MD, MPH, and Michelle N. Gong, MD, MS

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Abstract

Go to:

Objectives

The 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors ("statins") have anti-inflammatory properties and are associated with improved outcomes in critically ill patients. We investigated whether previous statin therapy affects outcomes in patients at risk for acute respiratory distress syndrome.

Crit Care. 2012; 16(6): 238.
Published online 2012 Nov 22. doi: 10.1186/cc11512
PMCID: PMC3672556

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]

Author information ▶ Copyright and License information ▶

Abstract

Go to:

Acute lung injury and acute respiratory distress syndrome (ARDS) are characterised by severe hypoxemic respiratory failure and poor lung compliance. Despite advances in clinical management, morbidity and mortality remains high. Supportive measures including protective lung ventilation confer a survival advantage in patients with ARDS, but management is otherwise limited by the lack of effective pharmacological therapies. Surfactant dysfunction with quantitative and qualitative abnormalities of both phospholipids and proteins are characteristic of patients with ARDS. Exogenous surfactant replacement in animal models of ARDS and neonatal respiratory distress syndrome shows consistent improvements in gas exchange and survival. However, whilst some adult studies have shown improved oxygenation,

Crit Care Clin. Author manuscript; available in PMC 2012 Jul 1.
Published in final edited form as:
Crit Care Clin. 2011 Jul 1; 27(3): 525–559.
doi: 10.1016/j.ccc.2011.04.005
PMCID: PMC3153076
NIHMSID: NIHMS292566

Surfactant Therapy of ALI and ARDS

K Raghavendran,[1] D Willson,[2] and RH Notter[3]

Author information ▶ Copyright and License information ▶

Abstract

Go to:

This article examines exogenous lung surfactant replacement therapy and its utility in mitigating clinical acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS). Biophysical research has documented that lung surfactant dysfunction can be reversed or mitigated by increasing surfactant concentration, and multiple studies in animals with ALI/ARDS have shown that respiratory function and pulmonary mechanics *in vivo* can be

Crit Care. 2006; 10(2): R41.
Published online 2006 Mar 8. doi: 10.1186/cc4851

PMCID: PMC1550886

Exogenous pulmonary surfactant for the treatment of adult patients with acute respiratory distress syndrome: results of a meta-analysis

Warren J Davidson,[1] Del Dorscheid,[1,2] Roger Spragg,[3] Michael Schulzer,[1] Edwin Mak,[1] and Najib T Ayas[1,2,4]

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Abstract

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Introduction

The purpose of this study was to perform a systematic review and meta-analysis of exogenous surfactant administration to assess whether this therapy may be useful in adult patients with

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Ann Pharmacother. 1995 Jul-Aug;29(7-8):784-6.

Ketoconazole to prevent acute respiratory distress syndrome in critically ill patients.

Frazee LA[1], Neidig JA.

Author information

Abstract

Ketoconazole appears to be an effective prophylactic measure in surgical patients at risk of developing ARDS. The beneficial effects may be caused by thromboxane synthetase inhibition because thromboxane B2 concentrations were decreased by ketoconazole in both studies. Two studies were unable to demonstrate a beneficial effect with the selective thromboxane synthetase inhibitor dazoxiben. Both studies consisted of a small number of subjects with already established ARDS, not prophylaxis in patients at risk of ARDS. Although the effects of ketoconazole on mortality in patients at risk of ARDS are conflicting, there may be reduced mortality in patients with sepsis. Several issues must be considered before ketoconazole is used in this setting. First, the studies to date have excluded patients at risk of hepatotoxicity, which is probably wise considering the potential hepatotoxicity with ketoconazole and the unknown benefit/risk ratio in these patients. Also, therapies that reduce gastric acidity should be avoided to ensure bioavailability. If ketoconazole is administered through a jejunostomy tube, it probably should be given with a dilute acid to enhance absorption. Furthermore, ketoconazole is a known inhibitor of the cytochrome P450 system, which results in a number of drug interactions. If ketoconazole is used, the patient's current drug therapy should be reviewed for potential interacting drugs. In light of the current studies, ketoconazole may be considered for surgical patients at risk of developing ARDS (especially patients with sepsis) with the previously noted considerations. Future research should seek to confirm ketoconazole's role for the prevention of ARDS in all critically ill patients. Additional studies also should clarify the role of various

https://www.ncbi.nlm.nih.gov/pubmed/8520099# hysiology and therapy of ARDS.

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Crit Care Med. 1993 Nov;21(11):1635-42.

A double-blind, prospective, randomized trial of ketoconazole, a thromboxane synthetase inhibitor, in the prophylaxis of the adult respiratory distress syndrome.

Yu M[1], Tomasa G.

Author information

Abstract

OBJECTIVE: To determine if ketoconazole, a thromboxane A2 synthetase inhibitor, given within the first 24 hrs after diagnosis and arrival in the intensive care unit (ICU) would decrease the frequency of adult respiratory distress syndrome in the septic patient population.

DESIGN: Prospective, randomized, double-blind, placebo-controlled study.

SETTING: Twelve-bed, surgical ICU in a university-affiliated hospital.

PATIENTS: Fifty-four consecutive patients admitted to the surgical ICU with the diagnosis of sepsis composed the study sample. Sepsis was defined as including two or more of the following signs in a patient with a systolic blood pressure of < 80 mm Hg or a systemic vascular resistance of < 800 dyne.sec/cm5: a) temperature > or = 39 degrees C or < or = 35 degrees C; b) white blood cell count of > 12,000 leukocytes, or < or = 4000 leukocytes/microL, or > or = 20% immature cells; c) positive blood culture; d) known or strongly suspected source of infection from which a known pathogen was cultured.

INTERVENTIONS: Patients were randomized to receive either ketoconazole (400 mg) or placebo in a double-blind fashion as early as possible and in < 24 hrs after surgical ICU admission or after the diagnosis of sepsis was established.

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JAMA. 2000 Apr 19;283(15):1995-2002.

Ketoconazole for early treatment of acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. The ARDS Network.

[No authors listed]

Erratum in
JAMA 2200 Nov 22-29;284(20):2597.
JAMA 2000 Nov 15;284(19):2450.
JAMA 2001 Oct 3;286(13):1578.

Abstract

CONTEXT: Three clinical studies have suggested that ketoconazole, a synthetic imidazole with anti-inflammatory activity, may prevent the development of acute respiratory distress syndrome (ARDS) in critically ill patients. However, the use of ketoconazole as treatment for acute lung injury (ALI) and ARDS has not been previously studied.

OBJECTIVE: To test the efficacy of ketoconazole in reducing mortality and morbidity in patients with ALI or ARDS.

DESIGN: Randomized, double-blind, placebo-controlled trial conducted from March 1996 to January 1997.

SETTING: Twenty-four hospitals associated with 10 network centers in the United States, constituting the ARDS Network.

PATIENTS: A total of 234 patients with ALI or ARDS.

INTERVENTION: Patients were randomly assigned to receive ketoconazole, 400 mg/d (n = 117), or placebo (n = 117), initiated within 36 hours of fulfilling study entry criteria and given enterally for up to 21 days.

MAIN OUTCOME MEASURES: Primary outcome measures were the proportion of patients alive with unassisted

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Crit Care. 2015 Oct 23;19:374. doi: 10.1186/s13054-015-1091-6.

Aspirin as a potential treatment in sepsis or acute respiratory distress syndrome.

Toner P[1], McAuley DF[2,3], Shyamsundar M[2,3].

Author information

Abstract

Sepsis is a common condition that is associated with significant morbidity, mortality and health-care cost. Pulmonary and non-pulmonary sepsis are common causes of the acute respiratory distress syndrome (ARDS). The mortality from ARDS remains high despite protective lung ventilation, and currently there are no specific pharmacotherapies to treat sepsis or ARDS. Sepsis and ARDS are characterised by activation of the inflammatory cascade. Although there is much focus on the study of the dysregulated inflammation and its suppression, the associated activation of the haemostatic system has been largely ignored until recently. There has been extensive interest in the role that platelet activation can have in the inflammatory response through induction, aggregation and activation of leucocytes and other platelets. Aspirin can modulate multiple pathogenic mechanisms implicated in the development of multiple organ dysfunction in sepsis and ARDS. This review will discuss the role of the platelet, the mechanisms of action of aspirin in sepsis and ARDS, and aspirin as a potential therapy in treating sepsis and ARDS.

TRIAL REGISTRATION: ClinicalTrials.gov NCT01659307 NCT02326350.

PMID: 26494395 PMCID: PMC4619098 DOI: 10.1186/s13054-015-1091-6

Chest. 2012 May;141(5):1153-1159. doi: 10.1378/chest.11-1908. Epub 2011 Nov 23.

Macrolide antibiotics and survival in patients with acute lung injury.

Walkey AJ[1], Wiener RS[2].

Author information

Abstract

BACKGROUND: Animal models suggest that immunomodulatory properties of macrolide antibiotics have therapeutic value for patients with acute lung injury (ALI). We investigated the association between receipt of macrolide antibiotics and clinical outcomes in patients with ALI.

METHODS: Secondary analysis of multicenter, randomized controlled trial data from the Acute Respiratory Distress Syndrome Network Lisofylline and Respiratory Management of Acute Lung Injury Trial, which collected detailed data regarding antibiotic use among participants with ALI.

RESULTS: Forty-seven of 235 participants (20%) received a macrolide antibiotic within 24 h of trial enrollment. Among patients who received a macrolide, erythromycin was the most common (57%), followed by azithromycin (40%). The median duration of macrolide use after study enrollment was 4 days (interquartile range, 2-8 days). Eleven of the 47 (23%) patients who received macrolides died, compared with 67 of the 188 (36%) who did not receive a macrolide (P = .11). Participants administered macrolides were more likely to have pneumonia as an ALI risk factor, were less likely to have nonpulmonary sepsis or to be randomized to low tidal volume ventilation, and had a shorter length of stay prior to trial enrollment. After adjusting for potentially confounding covariates, use of macrolide was associated with lower 180-day mortality (hazard ratio [HR], 0.46; 95% CI, 0.23-0.92; P = .028) and shorter time to successful discontinuation of mechanical ventilation (HR, 1.93; 95% CI, 1.18-3.17; P = .009). In contrast, fluoroquinolone (n = 90) and cephalosporin antibiotics (n = 93) were not associated with improved outcomes.

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Arch Surg. 1999 Oct;134(10):1049-54.

Role of granulocyte-macrophage colony-stimulating factor and its receptor in the genesis of acute respiratory distress syndrome through an effect on neutrophil apoptosis.

Goodman ER[1], Stricker P, Velavicius M, Fonseca R, Kleinstein E, Lavery R, Deitch EA, Hauser CJ, Simms HH.

Author information

Abstract

HYPOTHESIS: That granulocyte-macrophage colony-stimulating factor (GM-CSF) and its receptor modulate the suppression of apoptosis (Ao) of normal neutrophils incubated in the plasma of patients with postraumatic acute respiratory distress syndrome (ARDS).

DESIGN: Experimental study using cultured human neutrophils.

SETTING: University hospital, level I trauma center.

PARTICIPANTS: Plasma was obtained from 14 patients with early, fulminant posttraumatic ARDS (mean Injury Severity Score, 22). All samples were drawn within 24 hours after injury. Plasma was also taken from up to 21 healthy control subjects. These volunteers were also used as sources of polymorphonuclear leukocytes (PMNs).

MAIN OUTCOME MEASURES: (1) Effect of early, fulminant ARDS and normal plasma on spontaneous Ao and GM-CSF receptor expression in PMNs in vitro. (2) Effect of ligation of either GM-CSF or its receptor with a neutralizing monoclonal antibody (mAb) on PMN Ao in ARDS and normal plasma. (3) Correlation of extracellular GM-CSF concentration with rate of PMN Ao. (4) Levels of GM-CSF in ARDS and normal plasma and in culture supernatant of normal PMNs incubated in early, fulminant ARDS and normal plasma.

RESULTS: Plasma from patients with ARDS enhanced PMN viability at 24 hours (data are given as mean +/- SEM)

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American Journal of Respiratory and Critical Care Medicine

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Inhaled Granulocyte/Macrophage Colony-Stimulating Factor as Treatment of Pneumonia-associated Acute Respiratory Distress Syndrome

Susanne Herold[1], Katrin Hoegner[1], István Vadász[1], Tobias Gessler[1], Jochen Wilhelm[1], Konstantin Mayer[1], Rory E. Morty[1,2], Hans-Dieter Walmrath[1], Werner Seeger[1], and Juergen Lohmeyer[1]

+ Author Affiliations

https://doi.org/10.1164/rccm.201311-2041LE PubMed: 24579839

Comments

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To the Editor:

Granulocyte/macrophage colony-stimulating factor (GM-CSF) is a myeloid growth factor, which induces proliferation and differentiation of macrophages and dendritic cells.

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Anesthesiology. Author manuscript; available in PMC 2016 Feb 1.
PMCID: PMC4301977
Published in final edited form as:
Anesthesiology. 2015 Feb; 122(2): 238–240.
NIHMSID: NIHMS642494
doi: 10.1097/ALN.0000000000000546

Mesenchymal Stem Cell Therapy for Acute Respiratory Distress Syndrome: A Light at the End of the Tunnel?

Optimizing Therapeutic Potential of Human Mesenchymal Stromal Cells to Enhance Repair following Ventilator Induced Lung Injury in the Rat

Mairead Hayes, M.B., Claire Masterson, Ph.D., James Devaney, Ph.D., Frank Barry, Ph.D., Steve Elliman, Ph.D., Timothy O'Brien, M.D., Ph.D., Daniel O' Toole, Ph.D., Gerard F. Curley, M.B., Ph.D., John G. Laffey, M.D., M.A., Jae-Woo Lee, M.D.,[1] Patricia R.M. Rocco, M.D., Ph.D.,[2] and Paolo Pelosi, M.D.[3]

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Curr Opin Crit Care. 2016 Feb;22(1):14-20. doi: 10.1097/MCC.0000000000000276.

Stem cell therapy for acute respiratory distress syndrome: a promising future?

Horie S[1], Masterson C, Devaney J, Laffey JG.

Author information

Abstract

PURPOSE OF REVIEW: Acute respiratory distress syndrome (ARDS) is a devastating disease process with a 40% mortality rate, and for which there is no therapy. Stem cells are an exciting potential therapy for ARDS, and are currently the subject of intensive ongoing research efforts. We review data concerning the therapeutic promise of cell-based therapies for ARDS.

RECENT FINDINGS: Recent experimental studies suggest that cell-based therapies, particularly mesenchymal stem/stromal cells (MSCs), endothelial progenitor cells, and embryonic or induced pluripotent stem cells all offer considerable promise for ARDS. Of these cell types, mesenchymal stromal cells offer the greatest potential for allogeneic therapy, given the large body of preclinical data supporting their use, and the advanced state of our understanding of their diverse mechanisms of action. Although other stem cells such as EPCs also have therapeutic potential, greater barriers exist, particularly the requirement for autologous EPC therapy. Other stem cells, such as ESCs and iPSCs, are at an earlier stage in the translational process, but offer the hope of directly replacing injured lung tissue. Ultimately, lung-derived stem cells may offer the greatest hope for lung diseases, given their homeostatic role in replacing and repairing damaged native lung tissues.MSCs are currently in early phase clinical trials, the results of which will be of critical importance to subsequent translational efforts for MSCs in ARDS. A number of translational challenges exist, including minimizing variability in cell batches, developing standard tests for cell potency, and producing large amounts of clinical-grade cells for use in patients.

SUMMARY: Cell-based therapies, particularly MSCs, offer considerable promise for the treatment of ARDS.

Role of Steroid-

Clin Chest Med. 2014 Dec; 35(4): 781–795.
Published online 2014 Sep 24. doi: 10.1016/j.ccm.2014.08.014

Should we ever give steroids to ARDS patients?

Catherine L. Hough, MD, MSc

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Abstract

Go to:

The development and severity of ARDS are closely related to dysregulated inflammation, and the duration of ARDS and eventual outcomes are related to persistent inflammation and abnormal fibroproliferation. Corticosteroids are potent modulators of inflammation and inhibitors of fibrosis that have been used since the description of the acute respiratory distress syndrome in attempts to improve outcomes. Randomized controlled trials of steroids for ARDS have answered some, but not all, questions regarding efficacy for prevention and treatment. First, there is no evidence that corticosteroids prevent the development of ARDS among patients at risk. Second, high dose and short course treatment with steroids does not improve the outcomes of patients with ARDS. And third, while there is compelling data that low dose and prolonged treatment with steroids improves pulmonary physiology in patients with ARDS, additional studies are needed to recommend treatment with steroids for ARDS.

Keywords: ARDS, corticosteroids, prevention, treatment, outcomes

Crit Care Med. 2009 May;37(5):1594-603. doi: 10.1097/CCM.0b013e31819fb507.

Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: a systematic review and meta-analysis.

Tang BM[1], Craig JC, Eslick GD, Seppelt I, McLean AS.

Author information

Abstract

OBJECTIVE: Controversy remains as to whether low-dose corticosteroids can reduce the mortality and morbidity of acute lung injury (ALI) or the acute respiratory distress syndrome (ARDS) without increasing the risk of adverse reactions. We aimed to evaluate all studies investigating prolonged corticosteroids in low-to-moderate dose in ALI or ARDS.

DATA SOURCES: MEDLINE, EMBASE, Current Content, and Cochrane Central Register of Controlled Trials, and bibliographies of retrieved articles.

STUDY SELECTION: Randomized controlled trials (RCTs) and observational studies reported in any language that used 0.5-2.5 mg.kg.d of methylprednisolone or equivalent to treat ALI/ARDS.

DATA EXTRACTION: Data were extracted independently by two reviewers and included study design, patient characteristics, interventions, and mortality and morbidity outcomes.

DATA SYNTHESIS: Both cohort studies (five studies, n = 307) and RCTs (four trials, n = 341) showed a similar trend toward mortality reduction (RCTs relative risk 0.51, 95% CI 0.24-1.09; p = 0.08; cohort studies relative risk 0.66, 95% CI 0.43-1.02; p = 0.06). The overall relative risk was 0.62 (95% CI 0.43-0.91; p = 0.01). There was also improvement in length of ventilation-free days, length of intensive care unit stay, Multiple Organ Dysfunction

Role of Steroid-

Official publication of Indian Chest Society
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Lung India. 2011 Apr-Jun; 28(2): 114–119. PMCID: PMC3109833
doi: 10.4103/0970-2113.80324

Corticosteroids and ARDS: A review of treatment and prevention evidence

G.C. Khilnani and Vijay Hadda

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Abstract

Go to:

To systematically review the role of corticosteroids in prevention of acute respiratory distress syndrome (ARDS) in high-risk patients, and in treatment of established ARDS. Primary articles were identified by English-language Pubmed/MEDLINE, Cochrane central register of controlled trials, and Cochrane systemic review database search (1960–June 2009) using the MeSH headings: ARDS, adult respiratory distress syndrome, ARDS, corticosteroids, and methylprednisolone (MP). The identified studies were reviewed and information regarding role of corticosteroids in prevention and treatment of ARDS was evaluated. Nine trials have evaluated the role of corticosteroid drugs in management of ARDS at various stages. Of the 9, 4 trials evaluated role of corticosteroids in prevention of ARDS, while other 5 trials were focused on treatment after variable periods of onset of ARDS. Trials with preventive corticosteroids, mostly using high doses of MP, showed negative results with patients in

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BMJ. 2008 May 3;336(7651):1006-9. doi: 10.1136/bmj.39537.939039.BE. Epub 2008 Apr 23.

Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: meta-analysis.

Peter JV[1], John P, Graham PL, Moran JL, George IA, Bersten A.

Author information

Abstract

OBJECTIVE: To systematically review the efficacy of steroids in the prevention of acute respiratory distress syndrome (ARDS) in critically ill adults, and treatment for established ARDS.

DATA SOURCES: Search of randomised controlled trials (1966-April 2007) of PubMed, Cochrane central register of controlled trials, Cochrane database of systematic reviews, American College of Physicians Journal Club, health technology assessment database, and database of abstracts of reviews of effects.

DATA EXTRACTION: Two investigators independently assessed trials for inclusion and extracted data into standardised forms; differences were resolved by consensus.

DATA SYNTHESIS: Steroid efficacy was assessed through a Bayesian hierarchical model for comparing the odds of developing ARDS and mortality (both expressed as odds ratio with 95% credible interval) and duration of ventilator free days, assessed as mean difference. Bayesian outcome probabilities were calculated as the probability that the odds ratio would be > or =1 or the probability that the mean difference would be > or =0. Nine randomised trials using variable dose and duration of steroids were identified. Preventive steroids (four studies) were associated with a trend to increase both the odds of patients developing ARDS (odds ratio 1.55, 95% credible interval 0.58 to 4.05; P(odds ratio > or =1)=86.6%), and the risk of mortality in those who subsequently developed ARDS (three studies, odds ratio 1.52, 95% credible interval 0.30 to 5.94; P(odds ratio > or =1)=72.8%). Steroid administration after onset of ARDS (five studies) was associated with a trend towards

Role of Steroid-

Intensive Care Med (2016) 42:931–933
DOI 10.1007/s00134-015-4135-0

EDITORIAL

Shailesh Bihari
Michael Bailey
Andrew D. Bersten

Steroids in ARDS: to be or not to be

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S. Bihari · A. D. Bersten (✉)
Department of Critical Care Medicine, Flinders University, Bedford Park, SA, Australia
e-mail: andrew.bersten@flinders.edu.au
Tel.: +61-8-82044247

S. Bihari · A. D. Bersten
Department of Intensive Care Medicine, Flinders Medical Centre, Bedford Park, SA, Australia

M. Bailey
Department of Epidemiology and Preventive Medicine, Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, Australia

reporting no benefit from the routine use of methylprednisolone in patients with ARDS, the LaSRS investigators found that the use of methylprednisolone was associated with an increased risk of neuromuscular complications and that initiation of methylprednisolone treatment more than 2 weeks after the onset of ARDS led to an increase in the risk of death despite improved early cardiopulmonary physiology [4]. This discrepancy demands some consideration.

Meta-analysis offers some advantages over a single high-quality RCT, as the greater number of patients enrolled in the former, as well as the range of differing populations, circumstances and settings, facilitates generalisability. However, studies in critical care settings are particularly challenging due to the heterogeneity of both the cohort and the treatments, which can lead to misleading conclusions [6]. While this is minimised in IPDMA [7], which is considered the gold standard for meta-analysis [8], and therefore is the focus of our attention here, both the quality of the individual studies included in the IPDMA and of the analysis itself need to be considered.

Role of Steroid-

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Corticosteroids in ARDS

N Engl J Med 2006; 355:316-319 | July 20, 2006 | DOI: 10.1056/NEJMc066215

To the Editor:

The controlled trial of the use of corticosteroids in the acute respiratory distress syndrome (ARDS) by the National Heart, Lung, and Blood Institute (NHLBI) ARDS Clinical Trials Network (April 20 issue)[1] has limitations that affect the interpretability of the results. First, since only 180 of 3464 eligible patients (5 percent) were enrolled, the study population was not representative of those typically seen in clinical practice. Second, recent data demonstrate that patients with ARDS have excessive activation of nuclear factor-κB, with excessive production of proinflammatory cytokines.[2] This imbalance between the proinflammatory and antiinflammatory responses is present from the outset of this disorder, and it is therefore counterintuitive to delay treatment with corticosteroids until

Role of Steroid-

- Benefits remain uncertain.
- Corticosteroids may be considered in first 14 days as a form of rescue therapy that may improve oxygenation and hemodynamics but does not change mortality.
- But administering glucocorticoids two weeks or later after the onset of ARDS may be harmful.

Prognosis-

- MORTALITY — ranging from 26 to 58 percent.
- The underlying cause of the ARDS is the most common cause of death among patients who die early.
- In contrast, nosocomial pneumonia and sepsis are the most common causes of death among patients who die later in their clinical course.
- Patients uncommonly die from respiratory failure.

Predictors of increased mortality-

Positive fluid balance

Hypercapnea

Are there any preventive measures ?

- No drug has proved beneficial in the prevention of acute respiratory distress syndrome (ARDS).
- Early administration of corticosteroids to septic patients does not prevent the development of ARDS.
- Because aspiration pneumonitis is a risk factor for ARDS, taking appropriate measures to prevent aspiration (eg, elevating the head of the bed and evaluating swallowing mechanics before feeding high-risk patients).

Conclusion--

- Patients with ARDS are critically ill and often have multiorgan failure
- No drug has proven beneficial in the prevention or management of ARDS
- Further clinical trials are needed to find out a new pharmacological agent which can alter the natural history of this syndrome.

THANK YOU