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Inside this issue: Update in Acute Respiratory Distress Syndrome

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Acute respiratory distress syndrome (ARDS) is a permeability pulmonary edema characterized by refractory hypoxemia together with severely decreased respiratory system compliance. The mortality rate of ARDS is still high up to now reaching higher 45% in severe cases. Although it has been passed exactly a half century since its first publication in 1967 at Lancet, the treatment options are still mainly focused on ventilator managements. This article summarizes some notable findings related with ARDS, which were recently published since 2015.

Epidemiology, Patterns of Care, and Mortality for Patients with Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries

Authors: Bellani G et al for the LUNG SAFE Investigators and the ESICM Trials Group

Reference: JAMA. 2016;315:788-800

URL: http://jama.jamanetwork.com/article.aspx?articleid=2492877

Comment: The epidemiology, recognition, management, and outcomes of patients with ARDS are limited. In the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) cohort with 29144 patients admitted to participating ICUs, 3022 (10.4%) fulfilled ARDS criteria. Of these, 2377 patients developed ARDS in the first 48 hours and managed with invasive mechanical ventilation. The period prevalence of mild ARDS was 30.0%; of moderate ARDS, 46.6%; and of severe ARDS, 23.4%. ARDS represented 0.42 cases per ICU bed over 4 weeks and represented 10.4% of ICU admissions and 23.4% of patients requiring mechanical ventilation. Less than two-thirds of patients with ARDS received a tidal volume 8 of mL/kg or less of predicted body weight. Plateau pressure was measured in 40.1%, whereas 82.6% received a positive end-expository pressure (PEEP) of less than 12 cm H_2O. Prone positioning was used in 16.3% of patients with severe ARDS. Clinician recognition of ARDS was associated with higher PEEP, greater use of neuromuscular blockade, and prone positioning. Hospital mortality was 34.9% for those with mild, 40.3% for those with moderate, and 46.1% for those with severe ARDS. This large cohort international study showed ARDS appeared to be under-recognized and undertreated and associated with a high mortality rate. At the same time, these findings indicate there is room for improvement in the management of patients with ARDS.

A Clinical Classification of the Acute Respiratory Distress Syndrome for Predicting Outcome and Guiding Medical Therapy

Authors: Villar J et al for the Acute Lung Injury: Epidemiology and Natural history (ALIEN) Network

Reference: Crit Care Med 2015;43:346–353

URL: http://ovidsp.tx.ovid.com/sp-3.20.0b/ovidweb.cgi?&S=EELJFPDODODDCMKHNCIKGHFBJGCAAA00&Link+Set=S.sh.22%7c1%7csl_10

Comment: Current in-hospital mortality of the acute respiratory distress syndrome (ARDS) is above 40%. The authors investigated whether two widely accepted cutoff values of PaO_2/FiO_2 and positive end-expiratory pressure (PEEP) would identify subsets of patients with ARDS for predicting outcome and guiding therapy. In a 16-month prospective, multicenter, observational study, the authors studied 300 consecutive ARDS patients ($PaO_2/FiO_2 \leq$ 200 mm Hg) on PEEP greater than or equal to 5 cm H_2O, and followed up until hospital discharge. Based on threshold values for PaO_2/FiO_2 (150 mm Hg) and PEEP (10 cm H_2O) at ARDS onset and at 24 hours, patients were assigned to four categories: group I ($PaO_2/FiO_2 \geq 150$ on PEEP < 10), group II ($PaO_2/FiO_2 \geq 150$ on PEEP ≥ 10), group III ($PaO_2/FiO_2 < 150$ on PEEP < 10), and group IV ($PaO_2/FiO_2 < 150$ on PEEP ≥ 10). Overall hospital mortality was 46.3%. Although at study entry, patients with PaO_2/FiO_2 less than 150 had a higher mortality than patients with a PaO_2/FiO_2 greater than or equal

to 150 ($p = 0.044$), there was minimal variability in mortality among the four groups ($p = 0.186$). However, classification of patients in each group changed markedly after 24 hours of usual care. Group categorization at 24 hours provided a strong association with in-hospital mortality ($p < 0.00001$): group I had the lowest mortality (23.1%), whereas group IV had the highest mortality (60.3%). According to the authors' findings, lung dysfunction established by a PaO_2/FiO_2 of 150 mm Hg and a PEEP of 10 cm H_2O suggested that ARDS is not a homogeneous disorder. The four subsets of ARDS as proposed by the authors need to be considered in future clinical trials.

Driving pressure and survival in the acute respiratory distress syndrome.

Authors: Amato MB et al.
Reference: N Engl J Med. 2015;372(8):747-55
URL: http://www.nejm.org/doi/full/10.1056/NEJMsa1410639

Comment: Decreasing lung stress in injured alveoli by adopting lower tidal volume, lower plateau pressure, and high PEEP is a key of lung-protective ventilation. Plateau pressure reflects the peak alveolar pressure during mechanical ventilation. This study was conducted to determine which of lung mechanics variables during mechanical ventilation was most closely related with outcome of ARDS using 9 previously reported randomized trials. The authors newly define driving pressure as a ratio of tidal volume divided by respiratory-system compliance (Crs), in which tidal volume is intrinsically normalized to functional lung size. In another word, the driving pressure is the difference between plateau pressure and PEEP. Higher Crs leads to a lower driving pressure to reach the same tidal volume, because driving pressure will depend on the functional lung volume to receive the delivered tidal volume. Because the functional lung units are markedly decreased in ARDS, the authors thought that the driving pressure would be a better predictor of outcomes in ARDS than either tidal volume determined by a predicted

body weight or static Crs or level of applied PEEP. Using a statistical tool, the authors found that the driving pressure was the most closely related ventilator variable to survival. The 1-SD increment in driving pressure was associated with increased mortality (relative risk, 1.41) even in patients receiving protective plateau pressure and tidal volume. Individual changes in tidal volume or PEEP after stratification by driving pressure were not independently associated with survival. This article shows a clinical implication of driving pressure in ARDS, suggesting a way to set ventilator support requiring well controlled prospective studies to prove. The problem is that a study design using the driving pressure as an independent variable is not easy, because the driving pressure is interrelated with other respiratory variables.

Open lung approach for the acute respiratory distress syndrome: a pilot, randomized controlled trial

Authors: Kacmareck RM et al.
Reference: Crit Care Med. 2015;44(1):32-42
URL: http://ovidsp.tx.ovid.com/sp-3.20.0b/ovidweb.cgi?&S=EELJFPDODODDCMKHNCIKGHFBJGCAAA00&Link+Set=S.sh.80%7c1%7csl_10

Comment: The beneficial effect of PEEP in ARDS has been proven since its first report in 1967. The practical problem is how to set an optimal PEEP level at an individual ARDS patient. The open lung approach is a mechanical ventilation strategy recruiting collapsed alveoli through application of high airway pressure in a brief time followed by a decremental PEEP trial to find the least PEEP necessary to maintain the lung open. The authors conducted a prospective, multicenter, pilot, randomized controlled trial in 200 ARDS patients, who were on mechanical ventilation for less than 96 hours. The recruitment maneuver (RM) was performed using pressure control ventilation to a peak pressure between 50 and 60 cm H_2O and PEEP 35-45 cm H_2O depending on patient's response. For the decremental PEEP trial, mechanical ventilation mode was volume/assist control setting 4-6 ml/kg of tidal volume, PEEP 25 cm H_2O, and ventilator rate set at the level prior to the RM. Then, PEEP was decreased in 2 cm H_2O steps until the PEEP level corresponding to the maximum compliance was identified. Following the second RM, the mode was changed to pressure assist/control, maximum compliance PEEP + 3 cm H_2O, pressure assist/control level set to establish a peak inspiratory pressure less than 30 cm H_2O, 4–8 mL/kg of tidal volume. The PEEP level was set according to the ARDS network protocol in control group. The authors found that mortality at day-60 (29% of RM group and 33% of control group, p=0.18), ICU mortality, and ventilator-free days were not statistically different. Airway driving pressure and PaO_2/FiO_2 improved significantly at 24, 48, and 72 hours in patients of RM group compared with the control group. This study shows the open lung approach can be used to decrease the driving pressure and to improve oxygenation in a short time period in ARDS patients with refractory hypoxemia.

High-Flow Oxygen through Nasal Cannula in Acute Hypoxemic Respiratory Failure

Authors: Frat J-P et al for the FLORALI Study Group and the REVA Network

Reference: N Engl J Med 2015;372:2185-96.

URL: http://www.nejm.org/doi/full/10.1056/NEJMoa1503326

Comment: High-flow nasal oxygen is an emerging method for delivering oxygen in patients with acute hypoxemic respiratory failure. The authors recruited patients
with acute hypoxemic respiratory failure (PaO_2/FiO_2 300 mmHg or less) and assigned them into high-flow oxygen group (n=106), standard group (n= 94) and noninvasive ventilation group (n= 110). The intubation rate (primary outcome) was 38% in the high-flow–oxygen group, 47% in the standard group, and 50% in the noninvasive-ventilation group (P = 0.18 for all comparisons). The mean number of ventilator-free days at day 28 was higher in the high-flow–oxygen group (24 days, vs. 22 in the standard- oxygen group and 19 in the noninvasive-ventilation group; P = 0.02 for all comparisons). The hazard ratio for death at 90 days was 2.01 (1.01 to 3.99) with standard oxygen versus high-flow oxygen (P = 0.046) and 2.50(1.31 to 4.78) with noninvasive ventilation versus high-flow oxygen (P = 0.006). This study is the first large scale multicenter randomized trial for the efficacy of high-flow oxygen therapy for acute hypoxic respiratory failure. The results suggest this new oxygen therapy may help avoid intubation in patients with hypoxemia close to the severity of ARDS.

Timing of Intubation and Clinical Outcomes in Adults With Acute Respiratory Distress Syndrome

Authors: Kangelaris KN et al.

Reference: Crit Care Med 2016;44:120–129

URL: http://ovidsp.tx.ovid.com/sp-3.20.0b/ovidweb.cgi?&S=EELJFPDODODDCMKHNCIKGHFBJGCAAA00&Link+Set=S.sh.64%7c1%7csl_10

Comment: The prevalence, clinical characteristics, and outcomes of nonintubated ARDS patients remain inadequately characterized. The database of this study was ARDS patients enrolled in a large, multi-ICU prospective cohort study. Of 457 patients with ARDS, 106 (23%) were not intubated at the time of meeting ARDS criteria. Nonintubated patients had lower morbidity and severity of illness than intubated patients; however, mortality at 60 days was the same (36%) in both groups (p = 0.91). Of the 106 nonintubated patients, 36 (34%) required intubation within the subsequent 3 days of follow-up; this late-intubation subgroup had significantly
higher 60-day mortality (56%) when compared with the both early intubation group (36%, P<0.03) and patients never requiring intubation (26%; p = 0.002). Increased mortality in the late intubation group persisted at 2-year

follow-up. A substantial proportion of ARDS were not intubated in their initial days of intensive care, and many were never intubated. Late intubation was associated with increased mortality. The authors' findings warrant the need of criteria to define ARDS prior to need for intubation in order to establish optimal strategy for those who will ultimately require intubation.

Timing of low tidal volume ventilation and intensive care unit mortality in acute respiratory distress syndrome: a prospective cohort study

Authors: Needham DM et al.
Reference: Am J Respir Crit Care Med. 2015;191(2):177-185
URL: http://www.atsjournals.org/doi/abs/10.1164/rccm.201409-1598OC?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed#.Vz0ekTWLTcc

Comment: This study was conducted to determine the effect of the timing of lower tidal volume, which is associated with mortality decrease in ARDS. To evaluate the association of ICU mortality with initial tidal volume and with tidal volume change over time, a multivariable, time-varying Cox regression analysis of a multisite, prospective study of 482 patients with ARDS was performed. Tidal volume, which was evaluated in milliliter per kilogram of predicted body weight (PBW), was measured twice daily. The authors found that an increase of 1 ml/kg PBW was associated with a 23% increase in ICU mortality risk (adjusted hazard ratio, 1.23). A 1 ml/kg PBW increase in subsequent tidal volumes compared with the initial tidal volume was associated with a 15% increase in mortality risk (adjusted hazard ratio, 1.15). Compared with a prototypical patient receiving 8 days with a tidal volume of 6 ml/kg PBW, the absolute increase in ICU mortality of receiving 10 and 8 ml/kg PBW, respectively, across all 8 days was 7.2% and 2.7%. The authors concluded timely recognition of ARDS and adherence to low tidal volume ventilation is important for reducing mortality. This study suggests that higher tidal volume even shortly after ARDS onset could lead to worse outcome. Although the results were obtained through an observational study, the importance of low tidal ventilation is reproduced through this study. Moreover clinical value of timely application and prompt stick to low tidal volume ventilation thereafter were shown at this study.

Critical care ultrasonography differentiates ARDS, pulmonary edema, and other causes in the early course of acute hypoxemic respiratory failure

Authors: Sekiguchi H et al.

Reference: Chest. 2015 Oct;148(4):912-8.

URL: http://www.sciencedirect.com/science/article/pii/S0012369215502791

Comment: This study was conducted to evaluate the diagnostic utility of combined cardiac and thoracic critical care ultrasonography (CCUS) in patients with acute hypoxemic respiratory failure (AHRF). Authors divided patients

into 3 categorized cardiogenic pulmonary edema (CPE), ARDS, and miscellaneous. One hundred thirty-four patients were enrolled Fifty-nine patients (44%) received a diagnosis of CPE; 42 (31%), ARDS; and 33 (25%), miscellaneous cause. Analysis of CCUS findings showed that a low B-line ratio (proportion of chest zones with positive B-lines relative to all zones examined) was predictive of miscellaneous cause vs CPE or ARDS (receiver operating characteristic area under the curve [AUC], 0.82; 95% CI, 0.75-0.88). For differentiation of CPE from ARDS, left-sided pleural effusion (> 20 mm), moderately or severely decreased left ventricular function, and a large inferior vena cava minimal diameter (> 23 mm) were predictive of CPE (AUC, 0.79; 95% CI, 0.70-0.87). this study shows combined cardiac and thoracic CCUS assists in early bedside differential diagnosis of ARDS, CPE, and other causes of AHRF. However this study enrolled relatively small number patients and limited diseases, so some diseases were not included in this study including interstitial lung disease and so on.

The effect of intravenous interferon-beta-1a (FP-1201) on lung CD73 expression and on acute respiratory distress syndrome mortality: an open-label study

Authors: Bellingan G et al.

Reference: Lancet Respir Med. 2014 Feb;2(2):98-107.

URL: http://www.sciencedirect.com/science/article/pii/S2213260013702595

Comment: This study was conducted to test whether interferon-beta-1a (IFN-beta-1a), which increases CD73 synthesis, can reduce vascular leakage and mortality in patients with ARDS. Because production of anti-inflammatory adenosine by ecto-5'-nucleotidase (CD73) helps maintain endothelial barrier function. IFN-beta-1a increased the number of CD73-positive vessels in lung culture by four times on day 1 (p=0·04) and by 14·3 times by day 4 (p=0·004). The optimal tolerated FP-1201 dose was 10 µg per day for 6 days. By day 28, 3 (8%) of 37 patients in the treatment cohort and 19 (32%) of 59 patients in the control cohort had died-thus, treatment with FP-1201 was associated with an 81% reduction in odds of 28-day mortality (odds ratio 0·19 [95% CI 0·03-0·72]; p=0·01).

This study shows FP-1201 up-regulates human lung CD73 expression, and is associated with a reduction in 28-day mortality in patients with ARDS and suggests that IFN-beta-1a could be the first effective, mechanistically targeted, disease-specific pharmacotherapy. However IFN-beta-1a should be proven in large, prospective randomised trials. Because during many decades we have learned blocking only one inflammatory pathway or one step in pathophysiology of ARDS was not effective in patients with ARDS through many failed trials.

The association between acute respiratory distress syndrome, delirium, and in-hospital mortality in intensive care unit patients

Authors: Hsieh SJ et al.

Reference: Am J Respir Crit Care Med. 2015 Jan 1;191(1):71-8.

URL: http://www.atsjournals.org/doi/abs/10.1164/rccm.201409-1690OC?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed&#.VzsBBa3ouHs

Comment: This study was conducted to evaluate whether ARDS is associated with a higher risk for delirium compared with respiratory failure without ARDS, and to determine the association between ARDS and in-hospital mortality after adjusting for delirium.

Of the 564 patients in our cohort, 48 had ARDS (9%). Intubated patients with ARDS had the highest prevalence of delirium compared with intubated patients without ARDS and nonintubated patients (73% vs. 52% vs. 21%, respectively; P < 0.001). After adjusting for common risk factors for delirium, ARDS was associated with a higher risk for delirium compared with mechanical ventilation without ARDS (odds ratio [OR], 6.55 [1.56-27.54]; P = 0.01 vs. OR, 1.98 [1.16-3.40]; P < 0.013); reference was nonintubated patients. Although ARDS was significantly associated with hospital mortality (OR, 10.44 [3.16-34.50]), the effect was largely reduced after adjusting for delirium and persistent coma (OR, 5.63 [1.55-20.45]).

This study shows ARDS is associated with a greater risk for ICU delirium than mechanical ventilation alone and suggest ICU delirium as a novel risk factor for poor outcomes in ARDS patients. However this study did not include many therapies affect mortality in ARDS such as NMB, prone positioning, driving pressure, pulmonary dead-space fraction, ECMO and so on. So we should think all together to considering mortality benefit. Future studies are needed to determine if prevention and reduction of delirium in ARDS patients can improve outcomes.

Vitamin D deficiency contributes directly to the acute respiratory distress syndrome (ARDS)

Authors: Dancer RCA et al.

Reference: Thorax. 2015;70:617-624

URL: http://thorax.bmj.com/content/70/7/617.long

Comments: This study was conducted to determine if ARDS is associated with vitamin D deficiency in clinical, murine model. 52 Patients with ARDS (100%) were vitamin D-deficient (plasma 25(OH)D3 <50 nmol/L). In 57 patients undergoing oesophagectomy (at risk of ARDS), preoperative median plasma levels of 25(OH)D3 were significantly lower in those patients who were ventilated with ARDS postoperatively (ARDS 16.97 nmol/L vs no ARDS

25.46 nmol/L, p=0.014). Oesophagectomy patients with severe vitamin D deficiency (plasma 25(OH)D3 <20 nmol/L) had a 37.5% risk of postoperative lung injury as opposed to a 15% risk with vitamin D levels >20 nmol/L. The odds of ARDS decreases by 17% for every 1 nmol/L decrease in 25(OH)D (OR 0.83 (95% CI 0.69 to 0.98; p=0.033)), adjusted for age, gender, diagnosis, staging and pack-years smoked. In murine model, following LPS challenge, vitamin D-deficient mice had increased evidence of alveolar epithelial damage as measured by BALF RAGE and BALF permeability index and elevated cellular inflammation and neutrophil apoptosis in BALF. These data suggest that easily treatable vitamin D deficiency may increase the risk of ARDS in patients at risk and vitamin D replacement strategy may have value as a treatment for patients at risk of ARDS. However, authors was unsure as to whether levels of 25(OH)D3 were low prior to the development of ARDS because blood from ARDS patients was obtained as soon as possible following admission to intensive care unit.

Type III procollagen is a reliable marker of ARDS-associated lung fibroproliferation

Authors: Forel JM et al

Reference: Intensive Care Med. 2015;41:1-11

URL: http://link.springer.com/article/10.1007%2Fs00134-014-3524-0

Comments: In this study, authors measured the N-terminal-peptidetype III procollagen (NT-PCP-III) in non-resolving ARDS to find a specific biomarker of post-ARDS fibroproliferation. Thirty- two patients with persistent ARDS (> 5 days) were included and 19 patients (59.4 %) presented with a histopathological diagnosis of ARDS-associated lung fibroproliferation. Serum and alveolar NT-PCP-III obtained within 1 week prior to biopsy. Using a threshold of 9 µg/L, alveolar NT-PCP-III had the highest accuracy for diagnosing fibroproliferation (sensitivity = 89.5 % and specificity = 92.3 %). Regarding the 51 patients included at day 7 in the validation cohort, the mortality rate at day 60 was increased in patients presenting an alveolar NT-PCP-III level higher than 9 µg/L (69 vs. 17 %, p < 0.001). The mean alveolar level of NT-PCP-III on day 7 was 8.1-fold higher in nonsurvivors (p = 0.03). Authors suggest alveolar PCP-III at day 7 in persistent ARDS is able to identify patients with fibroproliferation. The generalization of the findings is limited because fibrosis was rarely observed during the first week of ARDS evolution in other studies.

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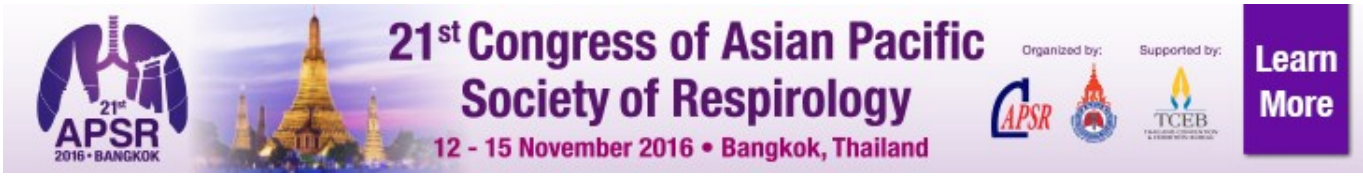

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