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J. Villar
L. Pérez-Méndez
R. M. Kacmarek

Current definitions of acute lung injury and the acute respiratory distress syndrome do not reflect their true severity and outcome

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Jesus Villar (✉)
Research Institute, Hospital de la Candelaria, Tenerife, Canary Islands, Spain; Samuel Lunenfeld Research Institute, Toronto, Canada;
Critical Care Medicine,
Mercer University, Macon, Ga., USA
(e-mail: jvillar@cistia.es;
Tel. + 34(922)602389;
Fax + 34(922)600562)

L. Pérez-Méndez
Department of Epidemiology,
Research Institute,
Hospital de la Candelaria, Tenerife,
Canary Islands, Spain

R.M. Kacmarek
Department of Respiratory Care,
Massachussetts General Hospital, Boston;
Department of Anesthesia,
Harvard University, Boston, Ma., USA

Mailing address:
Research Institute,
Hospital de la Candelaria,
Carretera del Rosario, s/n,
38010 Santa Cruz de Tenerife,
Canary Islands, Spain

Abstract *Background*: Despite intensive research, there are no universally accepted clinical definitions for acute lung injury (ALI) or the acute respiratory distress syndrome (ARDS). A recent joint American-European Consensus Conference on ARDS formally defined the difference between ALI and ARDS based on the degree of oxygenation impairment. However, this definition may not reflect the true prevalence, severity and prognosis of these syndromes.
Methods: During a 22-month period, 56 consecutive mechanically ventilated patients who met the American-European Consensus definition for ARDS [arterial oxygen tension/fractional inspired oxygen ($PaO_2/FIO_2 \leq 200$ mmHg regardless of the level of positive end-expiratory pressure (PEEP), bilateral pulmonary infiltrates, and no evidence of left heart failure] were admitted into the intensive care units (ICU) of the Hospital del Pino, Las Palmas, Spain, and prospectively studied. The diagnosis of ALI and ARDS was made by a PEEP-FIO_2 trial, 24 h after patients met the Consensus inclusion criteria. Patients were classified as having ALI_{-24h} if the PaO_2/FIO_2 was > 150 mmHg with PEEP = 5 cmH_2O, and $ARDS_{-24h}$ if the PaO_2/FIO_2 was ≤ 150 mmHg with PEEP ≥ 5 cmH_2O.
Results: Overall mortality was 43 % (24 of 56). However, 24 h after inclusion, PaO_2 response to PEEP 5 cmH_2O allowed the separation of our patients into two different groups: 31 patients met our ALI_{-24h} criteria (PaO_2/FIO_2 > 150 mmHg) and their mortality was 22.6 %; 25 patients met our $ARDS_{-24h}$ criteria ($PaO_2/FIO_2 \leq 150$ mmHg) and their mortality was 68 % ($p = 0.0016$). The differences in the respiratory severity index during the first 24 h of inclusion, PaO_2/FIO_2 ratio at baseline and at 24 h, maximum plateau airway pressure, maximum level of PEEP, and number of organ system failures during the ICU stay were statistically significant.
Conclusions: Since the use of PEEP in the American-European Consensus criteria for ARDS is not mandatory, that definition does not reflect the true severity of lung damage and outcome. Our data support the need for guidelines based on a specific method of evaluating oxygenation status before the American-European Consensus definition is adopted.

Key words ARDS · Acute lung injury · Sepsis · Outcome · Risk factor · Positive end-expiratory pressure · Oxygenation index · Definition

Introduction

Definitions are an essential component of medical progress, but they are not immutable and need to be refined continuously as new knowledge is accrued. In 1967, Ashbaugh et al (1) studied a cohort of 272 patients who were receiving ventilatory support and from this cohort identified 12 patients with a syndrome that was similar to the infant respiratory distress syndrome. The patients were identified as having respiratory distress with tachypnea, hypoxemia, decreased respiratory system compliance, and bilateral pulmonary infiltrates. The mortality was 58 % and at autopsy the non-survivors had heavy lungs, atelectasis, interstitial and alveolar edema, as well as hyaline membranes. Since that time, the hallmarks of the acute respiratory distress syndrome (ARDS) have included: (1) a risk factor for the development of ARDS, (2) arterial hypoxemia despite a relatively high fractional inspired oxygen (FIO_2); (3) decreased pulmonary compliance, (4) bilateral pulmonary infiltrates, and (5) all the above in a setting in which cardiogenic pulmonary edema has been ruled out.

Although there is general agreement on the criteria on which to base a definition of ARDS, the specific ranges and conditions under which to evaluate these variables vary among clinicians and researchers. Furthermore, ARDS is a syndrome that cannot be described by any single laboratory test and is not associated with or caused by any single etiology. This highlights the question of whether a universal definition of ARDS is required. In terms of prognosis of patients with ARDS, there would certainly be some utility in having a universal definition so that data in the literature could easily be interpreted for use by individual physicians. When viewed from the prospective of research into ARDS, a very strong argument can be made for a universal definition since it would help standardize experimental and clinical studies related to etiology, pathophysiology and treatment of this syndrome, as well as improve our ability to compare data among various studies and centers [2]. In an attempt to overcome some of these problems, a lung injury scoring system [3] and a recent joint American-European Consensus definition [4] have been adopted in a number of studies. However, these definitions and scoring systems have not, as yet, been validated. In this study, we hypothesize that the current American European Consensus ARDS criteria do not identify patients with similar lung injury severity and outcome.

Patients and methods

During a 22-month period, 56 consecutive mechanically ventilated patients who met the American-European Consensus definition for ARDS [arterial oxygen tension ($PaO_2/FIO_2 \leq 200$ mmHg regardless of the level of positive end-expiratory pressure (PEEP), bilateral pulmonary infiltrates visible on an anterior/posterior chest radiograph with no clinical evidence of left heart failure] were admitted into the intensive care units (ICU) of the Hospital del Pino, a teaching hospital located on the island of Gran Canaria, Spain. Some of these patients were studied as part of a prospective, multicenter, European study of the epidemiology of ARDS.

All patients admitted into the ICU with respiratory failure due to acute lung injury (ALI) were considered for this study. The term ARDS was reserved for the most severe form of ALI. Inclusion criteria for the diagnosis of ALI or ARDS were: (a) a condition known to have a clinical association for the development of ALI or ARDS; (b) bilateral pulmonary infiltrates on chest X-ray, (c) refractory arterial hypoxemia, (d) no clinical or hemodynamic (pulmonary capillary wedge pressure < 18 mmHg) evidence of left atrial hypertension. According to the American-European guidelines [4], ALI was deemed to exist when the PaO_2/FIO_2 ratio was ≤ 300 regardless of the PEEP level and ARDS when the PaO_2/FIO_2 ratio was ≤ 200 regardless of the PEEP level.

Although refractory arterial hypoxemia was defined as the presence of $PaO_2 \leq 100$ mmHg with $FIO_2 \geq 0.5$ regardless of the PEEP level, a PEEP FIO_2 trial was performed in every patient after 24 h of meeting the inclusion criteria in an attempt to define the impact of lung function improvement on ALI or ARDS outcome. After 30 min of ventilation at a tidal volume (V_T) of 10 ml/kg with a square wave inspiratory flow, FIO_2 0.5, PEEP 5 cmH_2O, and inspiratory/expiratory time ratio of 1/2, an arterial blood sample was drawn for arterial blood gas analysis. For our purposes, patients were classified as having ALI if the PaO_2/FIO_2 ratio was ≥ 150 mmHg with PEEP 5 cmH_2O (ALI_{-24h}), and ARDS if the PaO_2/FIO_2 ratio was ≤ 150 mmHg with PEEP ≥ 5 cmH_2O ($ARDS_{-24h}$) [2, 5]. We did not drop PEEP in those patients who required PEEP > 5 cmH_2O to maintain adequate gas exchange.

Data compiled from each patient included the following: (a) demographic information; b) clinical conditions associated with the development of ALI/ARDS, (c) routine laboratory measurements, (d) Simplified Acute Physiology Score (SAPS) [6], (e) number of days on mechanical ventilation, (f) number of days in the ICU, (g) pulmonary physiologic and ventilatory measurements, including arterial blood gases, level of PEEP, duration of PEEP > 10 cmH_2O, maximum plateau airway pressure, respiratory severity index [$P(A–a)O_2/PAO_2 + 0.014$ PEEP] [7], FIO_2, duration of $FIO_2 > 0.7$, (V_T), (h) cardiovascular data, (i) number of organ failures, (j) outcome. Definitions of sepsis and organ failure were those previously described by Fry et al. [8], Bell et al. [9], and Villar et al. [10]. We considered renal failure, liver failure, central nervous system failure, cardiac failure, shock, gastrointestinal failure, and disseminated intravascular coagulation as organ system failures in addition to lung failure. Any organ failure occurring during the 12-h period prior to death was considered part of the terminal event and therefore, not counted. In general, therapeutic goals were to maintain $PaO_2 > 70$ mmHg, systolic systemic blood pressures > 90 mmHg, right or left end-diastolic ventricular filling pressures between 5 and 15 mmHg, hemoglobin concentrations of 9 to 14 g/dl, and diuresis > 0.5 ml/kg per h. In addition, no patient received nitric oxide or other experimental pharmacologic intervention for either ALI and ARDS or for sepsis.

Results of the descriptive statistics are expressed as mean ± SE or median and range, as indicated. Continuous data were compared with the *t*-test. Pearson's chi-square test was used to compare frequency distributions of categorized variables between different groups. Mean values from variables without a normal distribution were analyzed using the Mann-Whitney *U* test. For these analyses we considered a difference to be statistically significant if $p < 0.05$. A comparison of survival between the groups was per-

Table 1 Clinical conditions associated with the development of the acute respiratory distress syndrome. Values are number (%)

Etiology	Total ARDS	Mortality (%)	Group 1 ($ALI_{-24\,h}$ patients)	Mortality	Group 2 ($ARDS_{-24\,h}$ patients)	Mortality
Trauma	17	5 (29.4)	13	3 (23.1)	4	2 (50)
Gastric aspiration	13	5 (38.4)	8	3 (37.5)	5	2 (40)
Sepsis	11	7 (63.6)	3	1 (33.3)	8	6 (75)
Pneumonia	9	3 (33.3)	5	–	4	3 (75)
Acute pancreatitis	4	3 (75.0)	1	–	3	3 (100)
Eclampsia	1	–	1	–	–	
Drug overdose	1	1 (100)	–	–	1	1 (100)
Total	56	24 (42.9)	31	7 (22.6)	25	17 (68)

formed using Kaplan-Meier curves and the log-rank test. All tests of statistical significance were two-sided. The statistical software SPSS was used for all statistical calculations.

Results

All assessed data from the 56 enrolled patients were documented on a specifically designed form. Clinical conditions associated with the development of ARDS are shown in Table 1. Age ranged from 17 to 76 years (mean 39 ± 16 SE). There were 39 males (70%) and 17 females (30%). As a whole, the most common predisposing factor for the development of ARDS (meeting the American-European guidelines) was trauma (30%), followed by gastric aspiration (23%), sepsis (20%), and pneumonia (16%). Overall mortality was 42.9% (24 of 56). Acute pancreatitis and sepsis were the factors associated with the highest mortality (75% and 63.6%, respectively).

Twenty-four hours after patients met the inclusion criteria, the PaO_2 in response to a PEEP-FIO_2 trial with PEEP 5 cmH_2O and FIO_2 0.5 separated this population into two different groups: 31 patients had a PaO_2/FIO_2 ratio > 150 mmHg (group 1) and 25 patients had a PaO_2/FIO_2 ratio ≤ 150 mmHg (group 2). Patients within group 1 were classified as $ALI_{-24\,h}$ and group 2 as $ARDS_{-24\,h}$ Mortality of patients in group 1 was significantly lower than in group 2 (22.6 vs 68%) ($p = 0.0016$). Trauma was significantly more common in patients within group 1 (42%) than in group 2 (16%) and sepsis was the most common cause of ARDS in group 2 (32 vs 10%) (Fig. 1).

The mean ± SE for age, SAPS, respiratory severity index, ventilatory variables and number of organ failures in each group are summarized in Table 2. The differences in the respiratory severity index during the first 24 h of inclusion, PaO_2/FIO_2 ratio at baseline and at 24 h, maximum plateau airway pressure, maximum PEEP, and number of organ system failures during the ICU stay were statistically significant. In general, patients in group 2 ($ARDS_{-24\,h}$) required higher levels of FIO_2, had a maximum inspiratory pressure above 40 cmH_2O, required higher levels of PEEP, and had three or more organ failures in addition to the lung. Figure 2 shows the survival curves for days in the ICU for the two groups of patients (log rank test, $p = 0.0259$). Most deaths occurred in the first 10 days of meeting the $ARDS_{-24\,h}$ inclusion criteria.

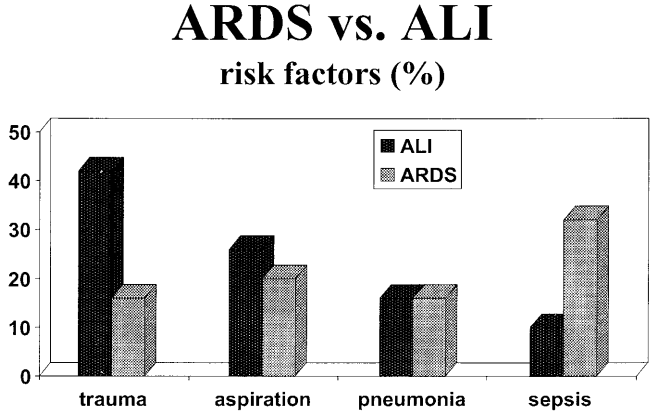

Fig. 1 Most common risk factors in 56 patients meeting the American-European Consensus Definition for ARDS. A PEEP-FIO_2 trial at 24 h of entry criteria, separated these patients in to two groups: (**a**) $ALLI_{-24\,h}$, When the PaO_2/FIO_2 ratio was above 150 mmHg, and (**b**) $aRDS_{-24\,h}$, when the PaO_2/FIO_2 ratio was below 150 mmHg

Discussion

ARDS is an important life-threatening condition that commonly affects critically ill patients. Assessing the severity of ARDS is important in determining the prognosis in any given patient and in assessing the benefit from various forms of therapy. However, despite numerous studies and clinical trials targeted to treat ARDS patients, there is a lack of demonstrable efficacy in reducing the mortality associated with the development of this syndrome. Although a number of studies have identified various factors that indicate a poor prognosis in patients with ARDS [11–13], the reported mortality data

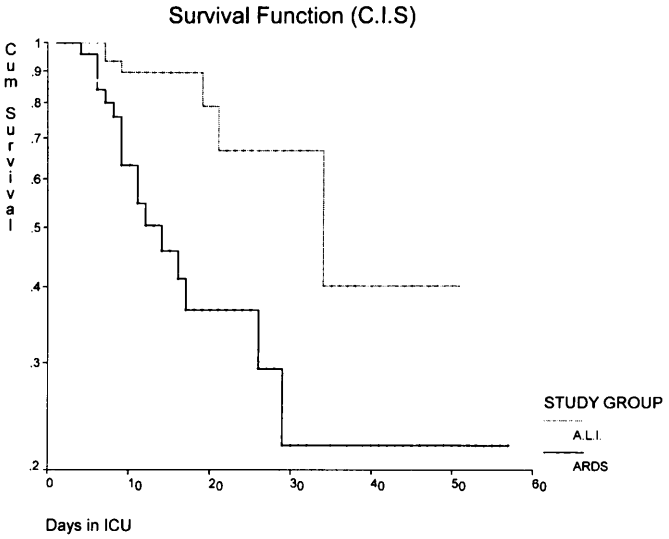

Fig. 2 Survival curves for days in the ICU for patients who fulfill the American-European Consensus Definition for ARDS after a PEEP-FIO_2 trial at 24 h of the entry criteria. The group with $ALI_{-24\,h}$ represents the patients with a PaO_2/FIO_2 ratio greater than 150 mmHg (mortality 22.6 %) and the $ARDS_{-24\,h}$ group includes patients with a PaO_2/FIO_2 below 150 mmHg (mortality 68 %) (log rank test, $p = 0.0259$)

are greatly dependent on the specific criteria used for the diagnosis of ARDS [2, 14]. In our study, we have only focused our attention on how a recent proposed definition for ARDS [4] might enhance the enrolement of inappropiate patients into clinical trials and might explain some of the disparity in death rates among published series.

In our cohort of patients, the use of the current definition of ARDS proved to be incapable of identifying a uniform group of patients, although the most common causes associated with the development of ARDS were similar to those reported in other published ARDS studies [15–17]. Surprisingly, the 43 % mortality in ARDS in our series was similar to that reported in several recent published randomized, clinical studies [18–21] evaluating ventilatory strategies. Amato et al. [18] reported a mortality of 38 % in 29 ARDS patients treated with a protective ventilation strategy, not significantly different from the 47 % mortality in 60 patients studied by Stewart et al. [19], the 47 % mortality in 54 patients studied by Brochard et al. [20], and the 46 % mortality in 26 patients studied by Brower et al. [21]. However, none of these studies used the same definition for ARDS nor evaluated the same ventilatory approaches. Only Brower et al. [21] used the Consensus Conference definition in their study. Stewart et al. [19] enrolled patients with a PaO_2/FIO_2 ratio below 250 at a PEEP of 5 cmH_2O, a less stringent criterion which may have included many patients with mild acute lung injury. Amato et al. [18] and Brochard et al. [20] included patients with a lung injury score of 2.5 or higher [3]. The lung injury score considers various pathophysiologic features but may not be specific for ARDS. Since this scoring system has not been validated, it is not clear whether patients with identical lung injury scores have similar degrees of pulmonary pathology and the same prognosis.

Our results illustrate the problems experienced when trying to compare the findings of various clinical trials since patients with very different levels of lung dysfunction and disease may have been enrolled. Since the Consensus Conference definition for ARDS does not specify a level of PEEP for the oxygenation criterion, a patient could fit the ARDS criteria when a PaO_2 is measured with zero PEEP but not when measured at a PEEP of 5 cmH_2O. Hudson et al. [15] and Doyle et al. [16] never reported the value of PEEP at the time of classification in their studies. Doyle et al. [16] found that the mortality of patients with a $PaO_2/FIO_2 < 150$ mmHg at the time of enrollment was the same as for patients with a $PaO_2/FIO_2 > 150$ mmHg (59

Table 2 Mean age, SAPS, ventilatory values, and number of organ failures between the $ALI_{-24\,h}$ and $ARDS_{-24\,h}$ groups. These groups were identified after a PEEP-FIO_2 trial at 24 h of meeting the American-European ARDS inclusion criteria. Values are mean ± SE (*RR* relative risk)

Parameter	$ALI_{-24\,h}$	$ARDS_{-24\,h}$	*p*	95 % confidence interval
No.	31	25		
Mortality (%)	22.6	68	0.0016*	RR (1.5 to 6.1)
Age (years)	37.4 ± 19.6	40.9 ± 14	0.437**	μ_d (– 5.5 to 12.6)
SAPS, 1st day	10.4 ± 3.2	11.2 ± 3.5	0.416**	μ_d (– 1.1 to 2.5)
Respiratory severity index	0.88 ± 0.08	0.93 ± 0.09	0.023**	μ_d (0.01 to 0.1)
Days on mechanical ventilation	12 ± 9	14 ± 12	0.637***	
PaO_2/FIO_2 (T0) (mm Hg)	116 ± 31	93 ± 31	0.008**	μ_d (– 40.1 to – 6.3)
PaO_2/FIO_2 (T24) (mm Hg)	233 ± 54	111 ± 26	0.0001**	μ_d (– 145 to – 98)
Maximum plateau airway pressure (cmH_2O)	38.6 ± 4.2	49 ± 7	0.0001**	μ_d (7.13 to 13.3)
Maximum PEEP (cmH_2O)	9.9 ± 3	12.2 ± 4.6	0.01***	
No. of organ failures	1.5 ± 1.5	3 ± 1.5	0.0002***	

* Chi-square; ** *t*-test; *** Mann-Whitney U test; μ_d estimation of the mean of the differences

vs 57 %). We cannot provide the values of PaO_2/FIO_2 on admission under the same level of PEEP, but in a recent analysis of 101 clinical studies on ARDS, Krafft et al. [22] from Vienna found that neither the PaO_2/FIO_2 ratio nor the lung injury score on admission was a reliable predictor of outcome. The most clinically relevant finding in our study is that a very simple, easy-to-do bedside maneuver allowed us to identify within 24 h of inclusion, based on "standard" inclusion criteria, two groups of patients with presumably the same initial pulmonary derangements but with different responses to treatment and outcome. Despite receiving identical ventilatory, hemodynamic, and general support, the degree of hypoxemia within 24 h of meeting entry criteria improved significantly in more than 50 % of our patients, and only a fifth of them died, mostly due to complications derived from their underlying disease.

Several studies have reported that differences in patient selection, severity of underlying disease, patient age, and predisposition for ARDS may in fact explain the differences in mortality in most patient series [10, 11, 14, 23–25]. In our study, none of the parameters evaluated during the first 24 h distinguished the two groups of patients, except the respiratory severity index. During the European Collaborative Study, Artigas et al. [5] partially addressed this issue in a book chapter, but the data never received peer review evaluation. Bone et al. [26] analyzed the magnitude of hypoxemia as manifested by the PaO_2/FIO_2 ratio and its early response to conventional therapy including PEEP in a group of 74 patients. In that study, the PaO_2/FIO_2 ratio at the time of diagnosis of ARDS was the same in patients who lived as in those who died (50 % mortality). However, by day 1 of conventional therapy, those patients who survived increased their PaO_2/FIO_2, whereas in non-survivors the ratio was unchanged. That finding was never tested as an independent predictor, and we could not validate it, since 32 % of our patients with refractory hypoxemia at day 1 survived.

Since the highest survival rate is found in patients with trauma-associated ARDS, and trauma was the most common etiology in our series, we reanalyzed our data excluding patients with trauma as a primary cause or risk factor for ARDS. Excluding trauma, the mortality was still significantly different between groups: 22.2 % in ALI_{-24h} (4 of 18) vs 71.4 % in $ARDS_{-24h}$ (15 of 21) ($p = 0.006$). To exclude the possibility that other etiologies or parameters could be confounding factors, we performed a multivariate analysis of predictive factors of death by using a model of logistic regression with forward stepwise conditional methods in which we included classification ALI_{-24h} or $ARDS_{-24h}$ as the main independent variable, and SAPS, sepsis, or non-sepsis as covariates. We found that none of these covariates were confounding (sepsis $p = 0.6525$; SAPS $p = 0.6910$). These results demonstrated that neither trauma, sepsis, nor SAPS modifies the probability associated with the higher mortality in the $ARDS_{-24h}$ group (68 %) compared to ALI_{-24h} (22.6 %) (relative risk 3.011; confidence interval 1.5 to 6.1, as shown in Table 2). Since the most common predisposition for ARDS is infection, we performed the same analysis with a new covariate (infectious vs non-infectious causes of ARDS) by adding the cases of ARDS associated with sepsis and pneumonia and we obtained similar results ($p = 0.8526$).

We propose that the evaluation of the oxygenation defect for those patients who fulfill the Consensus Conference ARDS criteria should be determined with a specific level of PEEP, since the level of PEEP can markedly alter the degree of hypoxemia. Considering the wide spectrum of patients developing ALI, a more precise and less ambiguous definition of ARDS is needed to insure recruitment of uniform populations of patients into clinical trials. Our data support the need for guidelines based on a specific method of evaluating oxygenation status before the American-European Consensus definitions for ALI and ARDS can be universally adopted.

References

1. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE (1967) Acute respiratory distress in adults. Lancet II:319–323
2. Villar J, Slutsky AS (1989) The incidence of the adult respiratory distress syndrome. Am Rev Respir Dis 140: 814–816
3. Murray JE, Matthay MA, Luce JM, Flick MR (1988) An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 138: 720–723
4. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, LeGall JR, Morris A, Spragg R, the Consensus Committee (1994) The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 149: 818–824
5. Artigas A, Le Gall JR, Chastang CL, Carlet J, Blanch L, Fernandez R (1991) Clinical presentation, prognostic factors, and outcome of ARDS in the European Collaborative Study. A preliminary report. In: Zapol WM, Lemaire F (eds) Adult respiratory distress syndrome, Marcel Dekker, New York pp 37–63
6. LeGall JR, Loirat P, Alperovitch A (1983) Simplified acute physiological score for intensive care patients. Lancet II:741

7. Jardin F, Prost JF, Bazin M, Dessfond P, Ozier Y, Margairez A (1982) Modalités évolutives du syndrome de détresse respiratoire aigüe de l'adulte: valeur pronostique d'un indice de gravité tiré de l'oxygenation artériele. Nouv Press Med 11: 29–33
8. Fry DE, Pearlstein L, Fulton RL, Polk HC (1980) Multiple system organ failure. The role of uncontrolled infection. Arch Surg 115: 136–140
9. Bell RC, Coalson JJ, Smith JD, Johanson WG (1983) Multiple organ system failure and infection in adult respiratory distress syndrome. Ann Intern Med 99: 293–298
10. Villar J, Manzano JJ, Blazquez MA, Quintana J, Lubillo S (1991) Multiple system organ failure in acute respiratory failure. J Crit Care 6: 75–80
11. Heuser MD, Case LD, Ettinger WH (1992) Mortality in intensive care patients with respiratory disease: is age important? Arch Intern Med 152: 1683–1688
12. Smith PEM, Gordon IJ (1986) An index to predict outcome in adult respiratory distresss syndrome. Intensive Care Med 12: 86–89
13. Fowler AA, Hamman RF, Zerbe GO, Benson KN, Hyers TM (1985) Adult respiratory distress syndrome: prognosis after onset. Am Rev Respir Dis 132: 472–478
14. Villar J, Slutsky A (1996) Is the outcome from acute respiratory distress syndrome improving? Curr Opinion Crit Care Med 2: 79–87
15. Hudson LD, Milberg JA, Anardi D, Maunder RJ (1995) Clinical risks for development of the acute respiratory distress syndrome. Am J Respir Crit Care Med 151: 293–301
16. Doyle RL, Szaflarski N, Modin GW, Wiener-Kronish JP, Matthay MA (1995) Identification of patients with acute lung injury. Predictors of mortality. Am J Respir Crit Care Med 152: 1818–1824
17. Ferring M, Vincent JL (1997) Is outcome from ARDS related to the severity of respiratory failure? Eur Respir J 10: 1297–1300
18. Amato MBP, Barbas CSV, Medeiros DM, Magaldi RB, Schettino GPP, Lorenzi-Filho G et al (1998) Effect of a protective ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 338: 347–354
19. Stewart TE, Meade MO, Cook DJ, Granton JT, Hodder RV, Lapinsky SE et al (1998) Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. N Engl J Med 338: 355–361
20. Brochard L, Roudot-Thoraval F, Roupie E, Delclaux C, Chastre J, Fernandez-Mondejar E et al (1998) Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trial Group on Tidal Reduction in ARDS. Am J Respir Crit Care Med 158: 1831–1838
21. Brower R, Shanholtz C, Shade D, Fessler H, White P, Wiener C, et al (1997) Randomized controlled trial of small tidal volume ventilation in ARDS. Am J Respir Crit Care Med 155:A93
22. Krafft P, Fridrich P, Pernerstorfer T, Fitzgerald RD, Koc D, Schneider B et al (1996) The acute respiratory distress syndrome: definitions, severity and clinical outcome. An analysis of 101 clinical investigations. Intens Care Med 22: 519–529
23. Montgomery AB, Stager MA, Carrico CJ, Hudson LD (1985) Causes of mortality in patients with adult respiratory distress syndrome. Am Rev Respir Dis 132: 485–489
24. Suchyta MR, Clemmer TP, Elliot CG, Orme JF, Weaver LK (1992) The adult respiratory distress syndrome: a report of survival and modifying factors. Chest 101: 1074–1079
25. Hyers TM (1993) Prediction of survival and mortality in patients with adult respiratory distress. New Horizons 1: 466–470
26. Bone RC, Maunder R, Slotman G, Silverman H, Hyers TM, Kerstein MD, Ursprung JJ, and the Prostaglandin E1 Study Group (1989) An early test of survival in patients with the adult respiratory distress syndrome: the PaO_2/FIO_2 ratio and its differential response to conventional therapy. Chest 96: 849–851