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K Atabai, M A Matthay

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An understanding of the epidemiology of ALI/ARDS and the effects of treatment have been hampered by the lack of a uniform definition of the syndrome. Various definitions have been proposed, and these are reviewed with particular attention to how changes in definition have affected our understanding of the natural history and treatment options for the condition.

The acute respiratory distress syndrome (ARDS) is a common clinical disorder characterised by injury to the alveolar epithelial and endothelial barriers of the lung, acute inflammation, and protein rich pulmonary oedema leading to acute respiratory failure. Since its first description by Ashbaugh *et al*,¹ a considerable volume of both basic and clinical research has led to a more sophisticated appreciation of the pathogenesis and pathophysiology of the syndrome.² However, our understanding of the epidemiology and effects of treatments have been hampered by the lack of uniform definitions. Several attempts have been made to provide workable definitions that would be useful in both clinical management and research. The purpose of this article is to review the definitions and epidemiology of ARDS, with particular attention to how changes in defining the syndrome have affected our understanding of the natural history and treatment options.

DEFINITIONS

Basic definition

In 1967 Ashbaugh and colleagues described a clinical syndrome of tachypnoea, hypoxaemia resistant to supplemental oxygen, diffuse alveolar infiltrates, and decreased pulmonary compliance in 12 patients who required positive pressure mechanical ventilation. The onset of the syndrome was acute, typically within hours of the inciting clinical disorder. The majority of patients did not have a history of pulmonary disease. Adequate oxygenation required the use of continuous positive pressure with end expiratory pressures (PEEP) of 5–10 cm H₂O. The earliest radiographic findings were patchy infiltrates indistinguishable from cardiogenic pulmonary oedema that usually became confluent with progressive clinical deterioration. Lung compliance was substantially decreased. Gross lung specimens resembled hepatic tissue with large airways being free from obstruction. Histological examination revealed hyaline membranes in the alveoli

with microscopic atelectasis and intra-alveolar haemorrhage similar to the infant respiratory distress syndrome.¹

In a subsequent paper Petty and Ashbaugh refined and elaborated on what they coined the “adult respiratory distress syndrome”.³ In a review of 40 cases the mechanism of lung injury was either direct (chest trauma, aspiration) or indirect (pancreatitis, sepsis) and, in some cases, was attributed to mechanical ventilation. Despite the heterogeneity of inciting events, the physiological and pathological response of the lung was uniform. The use of PEEP was critical in maintaining acceptable oxygen saturation by reducing the right to left intrapulmonary shunt and increasing the functional residual capacity. Recovery from lung injury could be rapid and complete or could progress to interstitial fibrosis and progressive respiratory failure. Fatalities were primarily due to septic complications.³

Expanded definition

Over the next two decades the basic definition was thought by many experts to be a hindrance to understanding the syndrome. The definition was not sufficiently specific, was open to varying interpretations, and did not require the clinical aetiology of the syndrome to be specified. Investigators used different criteria to enrol patients in clinical studies making comparison of results across trials difficult. In 1988 Murray and colleagues proposed an expanded definition of ARDS intended to describe whether the syndrome was in an acute or chronic phase, the physiological severity of pulmonary injury, and the primary clinical disorder associated with the development of lung injury (table 1).⁴ The first part of the definition addressed the clinical course separating acute from chronic cases; patients with a prolonged course (chronic) were presumably more likely to develop pulmonary fibrosis and to have poor outcomes. The second part, the lung injury score (LIS), quantified the severity of lung injury from the degree of arterial hypoxaemia, the level of PEEP, the respiratory compliance, and the radiographic abnormalities (table 2). Finally, the cause or associated medical condition

See end of article for authors' affiliations

Correspondence to: Dr M A Matthay, Cardiovascular Research Institute, University of California, 505 Parnassus Avenue, San Francisco, CA 94143-0130, USA; mmatt@itsa.ucsf.edu

Abbreviations: ALI, acute lung injury; ARDS, acute respiratory distress syndrome; PEEP, positive end expiratory pressure; PaO₂, arterial oxygen tension; FiO₂, fractional inspired oxygen; PAO₂, alveolar oxygen tension; LIS, lung injury score; PAOP, pulmonary artery occlusion pressure.

Table 1 Three part expanded definition of clinical acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) proposed by Murray and colleagues⁴

Part 1	Acute or chronic, depending on course
Part 2	Severity of physiological lung injury as determined by the lung injury score (see table 2)
Part 3	Lung injury caused by or associated with known risk factor for ARDS such as sepsis, pneumonia, aspiration, or major trauma

Table 2 Calculation of the lung injury score⁴

	Score
Chest radiograph	
No alveolar consolidation	0
Alveolar consolidation confined to 1 quadrant	1
Alveolar consolidation confined to 2 quadrants	2
Alveolar consolidation confined to 3 quadrants	3
Alveolar consolidation confined to 4 quadrants	4
Hypoxaemia score	
$\text{PaO}_2/\text{FiO}_2 \geq 300$	0
$\text{PaO}_2/\text{FiO}_2$ 225–299	1
$\text{PaO}_2/\text{FiO}_2$ 175–224	2
$\text{PaO}_2/\text{FiO}_2$ 100–174	3
$\text{PaO}_2/\text{FiO}_2 < 100$	4
PEEP score (when mechanically ventilated)	
≤ 5 cm H_2O	0
6–8 cm H_2O	1
9–11 cm H_2O	2
12–14 cm H_2O	3
≥ 15 cm H_2O	4
Respiratory system compliance score (when available)	
≥ 80 ml/cm H_2O	0
60–79 ml/cm H_2O	1
40–59 ml/cm H_2O	2
20–39 ml/cm H_2O	3
≤ 19 ml/cm H_2O	4
The score is calculated by adding the sum of each component and dividing by the number of components used.	
No lung injury	0
Mild to moderate lung injury	0.1–2.5
Severe lung injury (ARDS)	> 2.5

was to be specified.⁴ This proposal was accompanied by an editorial by Petty endorsing the new definition.

The expanded definition had several advantages. By describing whether patients had an acute course with rapid resolution or a more chronic course, the definition differentiated between the rapidly resolving course typical of ARDS secondary to drug overdoses or pulmonary contusion and the complicated and protracted course of many patients with severe pneumonia or sepsis syndrome. The LIS quantified the severity of lung injury separating patients with severe lung injury (LIS > 2.5) from those with mild lung injury (LIS $< 2.5 \rightarrow 0.1$). Most importantly, the identification of the cause or associated medical condition addressed the aetiology of lung injury. As the authors argued, grouping all causes of ARDS under an umbrella classification potentially prevented the discovery of beneficial treatments aimed at a particular cause.⁴

NAECC definition

In 1994 the North American-European Consensus Conference (NAECC) on ARDS proposed a revised definition for acute lung injury (ALI) and ARDS (table 3).⁵ The panel recognised that accurate estimates of the incidence and outcomes of ARDS were hindered by the lack of a simple uniform definition, especially one that could be used to enrol patients

Table 3 1994 consensus conference definition of acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS)

Onset	● Acute and persistent
Oxygenation criteria	● $\text{PaO}_2/\text{FiO}_2 \leq 300$ for ALI ● $\text{PaO}_2/\text{FiO}_2 \leq 200$ for ARDS
Exclusion criteria	● $\text{PAOP} \geq 18$ mm Hg ● Clinical evidence of left atrial hypertension
Radiographic criteria	● Bilateral opacities consistent with pulmonary oedema

in clinical studies. The panel changed “adult” back to “acute respiratory distress syndrome”, recognising that the syndrome was not limited to adults (the original Ashbaugh report included one 11 year old patient). Mechanical ventilation was not a requirement, although it was anticipated that most clinical trials would only enrol intubated patients. In order to exclude chronic lung disease, the definition required an acute onset of respiratory failure.

The physiological severity of lung injury was addressed by using the term ALI to refer to patients with a $\text{PaO}_2/\text{FiO}_2$ ratio of < 300 and ARDS in those with a $\text{PaO}_2/\text{FiO}_2$ ratio of < 200 . Although this was an arbitrary separation of the clinical spectrum of lung injury, previous studies had suggested that these cut off values were reasonable.⁶ The more liberal oxygenation criteria might allow clinical trials to capture patients with lung injury earlier in their course and perhaps facilitate identification of risk factors important in predicting outcomes.⁶ In contrast to the definition of Murray *et al*, the NAECC definition did not incorporate the level of PEEP. There was considerable debate on this issue but it was decided that, for the sake of simplicity, the level of PEEP should not be used to make the diagnosis of ALI or ARDS.

The NAECC definition included exclusion criteria for patients with cardiogenic pulmonary oedema. The pulmonary artery occlusion pressure (PAOP), if measured, should be < 18 mm Hg and there should be no clinical evidence of left atrial hypertension, although left atrial hypertension might occasionally coexist with ARDS. In each case it would be up to the clinician to assess whether the clinical, radiographic, or physiological abnormalities could be explained primarily by left atrial hypertension. The radiographic criteria for the diagnosis of ALI/ARDS were simplified to the presence of bilateral opacities consistent with pulmonary oedema. There was no quantification of the radiological abnormalities nor was there an effort to separate ALI from ARDS by radiographic findings.

The NAECC definition, as with previous attempts, had limitations (table 4). The definition was descriptive and did not address the cause of lung injury. Although it stipulated an acute onset, it did not provide guidelines on how to define acute. Most importantly, the radiological criteria were not sufficiently specific. In a recent study 21 critical care specialists, including seven members of the ARDS Network group of investigators, were asked to evaluate 28 chest radiographs of patients with a $\text{PaO}_2/\text{FiO}_2$ ratio of < 300 and to decide if they would qualify for the 1994 definition of ALI.⁷ The interobserver statistical agreement was moderate, with substantially worse agreement when analysis was limited to digital radiographs. A similar study showed excellent agreement between one intensive care specialist and a radiologist in diagnosing ALI only after the two had undergone a period of training during which diagnostic discrepancies were discussed and guidelines for interpreting ambiguous radiographs were established.⁸

The NAECC definition does not account for the level of PEEP used, which affects the $\text{PaO}_2/\text{FiO}_2$ ratio. However, there is no simple solution to this issue because the level of PEEP, as

Table 4 Strengths and limitations of the different definitions of ARDS

Definition	Strengths	Limitations
Petty and Ashbaugh (1971) ³	<ul style="list-style-type: none"> Detailed clinical description of the hallmarks of ARDS which remains relevant today 	<ul style="list-style-type: none"> No formal criteria for identification of patients
Murray <i>et al</i> (1988) ⁴	<ul style="list-style-type: none"> Three part definition evaluates chronicity, severity, and cause of lung injury 	<ul style="list-style-type: none"> Lung injury score has not been predictive of mortality No formal criteria to exclude cardiogenic pulmonary oedema Cause of lung injury not required
North American-European Consensus Conference (1994) ⁵	<ul style="list-style-type: none"> Simple criteria which are easy to apply in the clinical setting Disease spectrum recognised by separation of ARDS from ALI 	<ul style="list-style-type: none"> Radiographic criteria not sufficiently specific

well as other ventilator settings, would have to be stipulated in advance before the diagnosis could be made.

Relationship between definitions

Several studies have examined the relationship between the definition of ARDS proposed by Murray *et al* and that of the NA ECC. A prospective trial using strict diagnostic criteria for ARDS as the gold standard evaluated the diagnostic accuracy of the LIS, the NA ECC definition, and a modified LIS in identifying patients with ARDS.⁹ The modified LIS consisted of two components: a $\text{PaO}_2/\text{FiO}_2$ of ≤ 174 (corresponding to grade 3 or higher LIS (table 2)) and bilateral infiltrates on a chest radiograph. The following diagnostic criteria for ARDS served as the gold standard: concomitant presence of respiratory failure requiring mechanical ventilation; bilateral pulmonary infiltrates; $\text{PaO}_2/\text{PAO}_2 < 0.2$; $\text{PAOP} < 18$ mm Hg; and static respiratory system compliance < 50 ml/cm H_2O . One hundred and twenty three patients with at least one of seven "at risk" diagnoses were followed prospectively for the development of ARDS. The diagnostic accuracy in the "at risk" population (true positive + true negative/total number of patients) was 90% for the LIS definition and 97% for both the modified LIS and the NA ECC definitions ($p=0.03$). The authors concluded that the three scoring systems identified similar populations when applied to patients with clearly defined at risk diagnoses.

A more recent study assessed the agreement between the definitions of Murray *et al* and the NA ECC in diagnosing ARDS in a prospective trial of 118 patients comparing ventilation strategies.¹⁰ The incidence using the LIS was 62% while that using the NA ECC definition was 55%. Statistical agreement between the two definitions was moderate and improved when analysis was limited to patients who had undergone compliance measurements (65%). A more liberal $\text{PaO}_2/\text{FiO}_2$ ratio decreased agreement, as did increasing the LIS threshold diagnostic of ARDS to 3 or decreasing it to 2. Omitting data on oxygenation, chest radiography, PAOP , PEEP , or respiratory compliance either decreased agreement or left it unchanged. While agreement between the definitions was only moderate, there was no difference in mortality between the two groups of patients identified. The authors concluded that, for investigative purposes, the two criteria could be used interchangeably.

Significance of definitions in clinical trials

The NA ECC updated its recommendations in 1998.^{11, 12} Although no formal changes were made, the Committee emphasised the importance of addressing epidemiological and aetiological differences between patients when designing clinical trials. Several prospective studies had identified risk factors present at the onset of lung injury that predicted poorer outcomes¹³⁻¹⁶; clinical trial organisers would need to ensure an equal distribution of these risk factors in their experimental and control arms. They also encouraged further

research focused on identifying markers predictive of progression to or poor outcomes from lung injury.¹¹ Previous definitions had relied on abnormalities of lung physiology to grade injury^{1, 3-5}; however, neither the initial LIS nor the initial $\text{PaO}_2/\text{FiO}_2$ ratio was predictive of mortality in clinical trials.^{13, 14, 16, 17} Some biological markers, on the other hand, had already been proved to be useful in identifying patients at risk for poor outcomes. For example, raised levels of procollagen III peptide in early bronchoalveolar lavage and pulmonary oedema fluid samples predicted a protracted clinical course with progression to pulmonary fibrosis in patients with ALI/ARDS,^{18, 19} and increased levels of von Willebrand factor antigen in plasma predicted the development of lung injury in patients with non-pulmonary sepsis syndrome.²⁰ Also, a recent study reported that higher levels of von Willebrand factor antigens in the plasma of ALI/ARDS patients independently predicted mortality early in the clinical course.²¹

The importance of standard definitions and a mechanistic approach to enrolling patients in clinical trials are apparent in the results of two recent randomised multicentre trials. The first, conducted by the ARDS Network, evaluated the benefits of a low tidal volume strategy of mechanical ventilation and found an absolute reduction in the primary outcome of death prior to hospital discharge of 9% using lower tidal volumes (22% relative reduction in mortality).²² Patients were enrolled using the 1994 definition and the benefit of a protective ventilation strategy was maintained in all subsets of patients with ALI/ARDS.²³ This was the first large trial to show the benefit of any intervention in ALI/ARDS.^{2, 24}

The importance of identifying the mechanism of lung injury is borne out by a recent trial of recombinant human activated protein C in severe sepsis.²⁵ A 96 hour infusion of protein C resulted in an absolute reduction in mortality of 6.1% (20% relative reduction) in a large international multicentre trial; 54% of the 1690 patients had a pulmonary source of sepsis and 75% required mechanical ventilation on entry into the study. Although the study did not report the number of patients who met the criteria for ALI/ARDS, it is likely that most did since ARDS is the most common cause of respiratory failure in sepsis and sepsis is the most common predisposing factor for the development of ARDS.^{2, 26} Based on this study, it is likely that a trial of protein C in patients with lung injury due to sepsis will show a treatment benefit while the same trial in patients with ARDS due to trauma or fat emboli may not. As more is learned about the epidemiology and pathophysiology of ARDS, identifying the cause of injury in designing treatment trials will become increasingly critical.

EPIDEMIOLOGY

Incidence

The incidence of ALI and ARDS has been difficult to establish. Most studies were conducted before the NA ECC definition was proposed and used different criteria to enrol patients.

Table 5 Annual incidence of the acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) in different clinical studies

Study	Criteria used to diagnose ALI/ARDS	Incidence (cases/100 000 population/year)	Study limitations
NHLI task force ²⁷		75	<ul style="list-style-type: none"> Broad definition of respiratory distress syndrome including patients with volume overload
Canary Islands ³¹	$\text{PaO}_2/\text{FiO}_2 < 110$ $\text{PaO}_2/\text{FiO}_2 < 150$	1.5 3.5	<ul style="list-style-type: none"> Mean age of study population was 32 Non-urban setting
Utah ³⁰	$\text{PaO}_2/\text{FiO}_2 < 110$	4.8–8.3	<ul style="list-style-type: none"> Incomplete sampling of hospitals Use of ICD-9 codes to diagnose ARDS
Berlin ²⁸	Lung injury score > 2.5 Lung injury score > 1.75 – < 2.5	3.0 17.1	<ul style="list-style-type: none"> 2 month study may miss seasonal variation in incidence of ALI/ARDS No correction for migration in and out of study population
Scandinavia ²⁹	$\text{PaO}_2/\text{FiO}_2 < 300$ $\text{PaO}_2/\text{FiO}_2 < 200$ Lung injury score > 2.5	13.5 17.9 7.6	<ul style="list-style-type: none"> 2 month study may miss seasonal variation in incidence of ALI/ARDS No correction for migration in and out of study population

Defining the population at risk in a given study has been equally problematic. Accurate measurement of disease incidence requires knowledge of the number of people with the disease within a defined population at risk for developing it. Prospective trials must account for the catchment area of the hospitals studied; each hospital's catchment area may overlap with that of several other hospitals.

In 1972 the National Heart and Lung Institute task force estimated an incidence of 75 cases of ARDS per 100 000 population per year.²⁷ Several subsequent studies have estimated a much lower annual incidence of 1.5–13.5 cases per 100 000 population (table 5).^{28–32} There are several reasons why the number of cases may have been overestimated. The task force predated the widespread acceptance of the definition of ARDS and used a broad definition of lung injury that included conditions such as renal failure and volume overload. In addition, the population at risk was not clearly defined.^{33–34} A three year study conducted in the Canary Islands was unique in that all patients requiring mechanical ventilation were cared for at one hospital.²⁹ Using a $\text{PaO}_2/\text{FiO}_2$ ratio of < 110 to define ARDS, the population incidence was 1.5 cases per 100 000 population. A $\text{PaO}_2/\text{FiO}_2$ cut off of < 150 resulted in an incidence of 3.5 cases per 100 000 population. Although the study strictly defined the population at risk, extrapolation of incidence data from this young population (average age 32) to an urban setting is questionable. A prospective three year study in Utah using a $\text{PaO}_2/\text{PAO}_2$ ratio of < 0.2 (corresponding to a $\text{PaO}_2/\text{FiO}_2$ ratio of < 110) to define ARDS estimated an annual incidence of 4.8–8.3 cases per 100 000 population. The authors recorded all cases of ARDS in six Utah hospitals and estimated the number of cases in the remaining 34 acute care hospitals using ICD-9 codes.³⁰ Although the investigators made corrections for the population migrating in and out of Utah as well as for visitors developing ARDS, the incomplete sampling of hospitals and the use of ICD-9 codes weakened the study. Also, the incidence of alcohol and tobacco use is probably much less in Utah than in other states. A 2 month prospective study in Berlin found an annual incidence of 3 cases per 100 000 population using the expanded definition proposed by Murray *et al.*²⁸ The population of Berlin was the study population and 97% of all intensive care units were surveyed. No corrections were made for migration in and out of the catchment area. Finally, a prospective 2 month study in Sweden, Denmark, and Iceland using the NAEECC definition found an annual incidence of ARDS and of ALI of 13.5 per 100 000 and 17.9 cases per 100 000, respectively.²⁹ The annual incidence of ARDS using the LIS was 7.6 cases per 100 000 population.

Table 6 Clinical disorders associated with the development of ALI/ARDS

Direct	Indirect
Common <ul style="list-style-type: none"> Aspiration pneumonia Pneumonia Less common <ul style="list-style-type: none"> Inhalation injury Pulmonary contusion Fat emboli Near drowning Reperfusion injury 	Common <ul style="list-style-type: none"> Sepsis Severe trauma with prolonged hypotension and/or multiple fractures Multiple transfusions of blood products Less common <ul style="list-style-type: none"> Acute pancreatitis Cardiopulmonary bypass Drug overdose Disseminated intravascular coagulation Burns Head injury

Interestingly, only 71 of 110 patients who met the criteria for ARDS using the LIS also met the criteria using a $\text{PaO}_2/\text{FiO}_2$ ratio of < 200 .

The true incidence of ALI/ARDS is currently unknown, but may not be as high as the 1972 NIH estimate nor as low as estimates made in the Canary Islands or Berlin. A definitive study using the NAEECC definition has been completed at the University of Washington and preliminary results suggest that the original NIH estimate may have been reasonable.³³

Incidence of ARDS in patients with known risk factors

Lung injury can be caused by direct or indirect mechanisms (table 6). Identifying risk factors for the development of ALI/ARDS is particularly important in evaluating treatments that may prevent progression to lung injury in high risk populations. Three prospective studies from the early 1980s evaluated the incidence of ARDS in patients with known risk factors.^{35–37} In each study investigators followed patients with respiratory failure and clinical conditions thought to predispose to ARDS for the development of the syndrome. All three used stricter $\text{PaO}_2/\text{FiO}_2$ ratios to diagnose ARDS than the NAEECC definition.

In the first of two studies from Seattle, 136 patients with one or more risk factors were followed for the development of ARDS defined by a $\text{PaO}_2/\text{FiO}_2$ ratio of < 150 .³⁷ The risk factors

were sepsis syndrome, aspiration of gastric contents, pulmonary contusion, multiple transfusions, near drowning, pancreatitis, multiple major fractures, and prolonged hypotension not due to sepsis or cardiogenic shock. Multiple major fractures were defined as either fractures of two or more major long bones, an unstable pelvic fracture, or one major long bone fracture and a major pelvic fracture. Multiple transfusions were defined as infusion of 10 or more units of packed red blood cells or whole blood within a 12 hour period. Although 34% of the patients identified developed ARDS, the majority of patients who developed ARDS during the study time frame were missed. Of the patients captured by the study, those with sepsis and aspiration pneumonia had the highest risk of developing ARDS (38% and 30% risk, respectively), followed by patients receiving multiple blood transfusions and pulmonary contusions (24% and 17% risk, respectively). Patients with more than one risk factor were at increased risk for developing the syndrome. Of the patients who developed ARDS, 76% had done so within 2–24 hours of the inciting event and 93% by 72 hours.

The second study from Seattle defined ARDS as a P_{aO_2}/F_{iO_2} ratio of <150 or <200 in patients on PEEP and captured 80% of patients who developed ARDS during the study.³⁶ Sepsis syndrome was again associated with the highest incidence of ARDS (41%), followed by multiple transfusions (36%), aspiration pneumonia (22%), and pulmonary contusion (22%). Interestingly, massive transfusions were equally likely to cause ARDS in medical patients as in patients with trauma.

A study from Denver identified risk factors as cardiopulmonary bypass, burn, bacteraemia, hypertransfusion, fracture, pneumonia requiring care in the intensive care unit (ICU), aspiration, and disseminated intravascular coagulation (DIC).³⁵ ARDS was diagnosed in patients with a P_{aO_2}/P_{aO_2} ratio of <0.2 , $PAOP <12$ mm Hg, and a static pulmonary compliance of <50 ml/cm H_2O . Aspiration pneumonia was associated with a 35% incidence of developing ARDS, followed by DIC (22%), and pneumonia requiring ICU care (12%). The study missed 22% of patients who developed ARDS, most of whom had presumed sepsis. Bacteraemia, defined as two positive blood cultures, was associated with a 3.8% risk of ARDS.

The data from these prospective and other studies⁶ identify sepsis as the most common risk factor for developing ARDS, followed by aspiration pneumonia, pneumonia, trauma, and multiple transfusions. The relative incidence of ALI/ARDS with each risk factor will depend on the exact definitions used; for example, if patients with pneumonia and sepsis syndrome are classified as pneumonia, then the incidence with pneumonia will be greater. Overall, approximately 20–40% of patients with well established risk factors and respiratory failure develop ARDS,^{9 15 35 36} and the more risk factors in any individual, the greater the likelihood of developing the syndrome.^{15 35 36 38} As with most of the epidemiological data currently available, these numbers may change as newer studies use the NAEECC criteria to define ALI/ARDS.

In addition to the risk factors discussed above, recent reports have identified additional conditions that influence the susceptibility of individuals to developing lung injury. In a prospective study of 351 patients the incidence of ARDS with one of seven known “at risk” diagnoses was compared in patients with and without a history of chronic alcohol abuse.¹⁵ Experimental data demonstrating the activating effect of alcohol on neutrophil adherence, chemotaxis, and phagocytosis³⁹ led investigators to speculate that patients who chronically abuse alcohol would be at a higher risk for developing ARDS. The incidence of ARDS was 43% in patients with a history of chronic alcohol abuse compared with 22% in the control group. Patients with higher APACHE II scores at the time of the “at risk” diagnosis also had a significantly higher incidence of ARDS. Both the history of chronic alcohol abuse and the APACHE II score remained significant with multivariate analysis.

Table 7 Risk factors predictive of increased mortality in multivariate analysis of patients with ALI/ARDS

Risk factor	Study
Liver dysfunction/cirrhosis	Doyle <i>et al</i> ¹³ Zilberberg <i>et al</i> ¹⁶ Monchi <i>et al</i> ⁴⁴ Lühr <i>et al</i> ²⁹ Roupie <i>et al</i> ⁴⁵
Sepsis	Doyle <i>et al</i> ¹³ Zilberberg <i>et al</i> ¹⁶ Monchi <i>et al</i> ⁴⁴
Non-pulmonary organ dysfunction	Doyle <i>et al</i> ¹³ Monchi <i>et al</i> ⁴⁴
Age	Zilberberg <i>et al</i> ¹⁶ Lühr <i>et al</i> ²⁹
Organ transplantation	Zilberberg <i>et al</i> ¹⁶
HIV infection	Zilberberg <i>et al</i> ¹⁶
Active malignancy	Zilberberg <i>et al</i> ¹⁶
Length of mechanical ventilation prior to ARDS	Monchi <i>et al</i> ⁴⁴
Oxygenation index (mean airway pressure $\times F_{iO_2} \times 100/P_{aO_2}$)	Monchi <i>et al</i> ⁴⁴
Mechanism of lung injury	Monchi <i>et al</i> ⁴⁴
Right ventricular dysfunction	Monchi <i>et al</i> ⁴⁴
$P_{aO_2}/F_{iO_2} <100$	Lühr <i>et al</i> ²⁹
Chronic alcoholism	Moss <i>et al</i> ¹⁵

The same investigators hypothesised that patients with diabetes mellitus may be protected from ARDS due to the impaired neutrophil function associated with hyperglycaemia. In a study of 113 patients with septic shock, the incidence of ARDS was 25% in diabetic and 47% in non-diabetic patients.⁴⁰ After multivariate analysis adjusting for age, a history of cirrhosis, and source of infection, the difference in incidence remained significant. Mortality was not significantly different in the two groups. This was the first study to identify a risk factor that decreased the risk of developing ARDS.⁴¹

Clinical risk factors predictive of a poor outcome

Several prospective trials using the NAEECC definition have identified risk factors that are independent predictors of mortality (table 7).^{13 14 16 29} Each study enrolled a slightly different study population which may contribute to differences in risk factors identified. In a prospective trial of 123 medical and surgical (not trauma) patients with lung injury, liver dysfunction, sepsis and non-pulmonary organ system dysfunction during the period between hospitalisation and admission to the ICU were associated with significantly increased mortality.¹³ A study of 107 medical intensive care patients with lung injury found sepsis, cirrhosis, organ transplantation, HIV infection, active cancer, and age above 65 years to be independent predictors of mortality.¹⁶ A French study of 259 patients with ARDS in a medical ICU found cirrhosis, sepsis, the duration of mechanical ventilation prior to ARDS, oxygenation index (mean airway pressure $\times F_{iO_2} \times 100/P_{aO_2}$), the mechanism of lung injury, and the occurrence of right ventricular dysfunction to be independent predictors of death.¹⁴ A Scandinavian study of 132 intensive care patients in three countries (including medical, surgical and neurological patients) found chronic liver disease, a P_{aO_2}/F_{iO_2} ratio of <100 , and age to be independent predictors of death.²⁹

In most studies the initial oxygenation abnormality defined by the P_{aO_2}/F_{iO_2} ratio did not predict mortality unless it was grossly abnormal.^{6 13 14 16 17 29 42} Similarly, the initial severity of lung injury defined by the LIS has not predicted mortality,^{13 16} although in one study the LIS measured after 4 days predicted a complicated clinical course.⁴³

Although identification of independent predictors of mortality using multivariate analysis in any single study depends on which risk factors are evaluated, cumulative data convincingly show that patients with ALI/ARDS and sepsis, liver disease, non-pulmonary organ dysfunction, or advanced age have higher mortality rates.^{6 13 14 16 29 43-7} Equal distribution of these risk factors among experimental and control groups is essential when enrolling patients in clinical trials.

CONCLUSIONS

The understanding of ARDS and its definition continues to evolve as we learn more about its epidemiology and pathophysiology. The first two decades of research after Ashbaugh and Petty's classic articles describing ARDS were hampered by the lack of uniform definitions. The expanded definition of ARDS proposed by Murray and colleagues in 1988 incorporating the chronicity, severity, and cause of lung injury represented a turning point towards a more quantitative approach. The NAEC 1994 definition simplified the diagnostic criteria proposed by Murray and colleagues by eliminating the level of PEEP from the oxygenation criteria and the measurement of respiratory compliance, and reducing the chest radiographic inclusion criteria to the presence of bilateral opacities consistent with pulmonary oedema. As with the definition of Murray *et al*, the NAEC definition graded lung injury by defining different oxygenation criteria for ALI and ARDS. In the past decade the application of these two definitions has led to substantial progress in the understanding of the natural history of lung injury. Although the two criteria define overlapping populations with a similar prognosis, it is not clear whether conclusions generated using one definition can be extrapolated to populations defined by the other. It is hoped that future trials will use the NAEC definition exclusively.

Several aspects of the definition of ALI/ARDS need further refinement. Although initial oxygenation indices have little prognostic value, the more liberal oxygenation criteria describing ALI appear to identify patients with similar baseline characteristics and prognosis at an earlier stage of the illness. If there is no prognostic or epidemiological difference between ALI and ARDS patients, then the two categories should be combined. On the other hand, in certain subsets such as trauma, patients with ALI may have better a prognosis than those with ARDS. While the radiographic criteria of the NAEC definition are easy to apply, recent data suggest that there is significant interobserver variability. Although a more standardised approach is desirable, complex schemas quantifying the severity of infiltrates in different quadrants have no prognostic value. It therefore appears that an approach that combines the simplicity of the NAEC definition with more standardised and specific criteria would be ideal.

The risk of an individual developing lung injury and its prognosis will be more predictable as more accurate physiological markers are identified. Interestingly, a recent large prospective clinical study of 179 patients has found that a markedly raised dead space fraction (0.58) occurs early in the course of ARDS and is independently associated with mortality.⁴⁸ As the pathogenesis and epidemiology of lung injury are elucidated, treatment may be individualised around the mechanism of injury and the clinical characteristics of each patient.

Authors' affiliations

K Atabai, M A Matthay, Cardiovascular Research Institute and Departments of Medicine and Anesthesia, University of California, San Francisco, USA
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