Acute Respiratory Distress Syndrome

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Editor
Davide Chiumello
Director of Anaesthesia and Intensive Care
Services, ASST Santi Paolo e Carlo
Department of Scienze della Salute
University of Milan
Milan
Italy

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Acute Respiratory Distress Syndrome (ARDS): Definition, Incidence, and Outcome

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Rémi Coudroy, Florence Boissier, and Arnaud W. Thille

1.1 Definition of ARDS

1.1.1 From the First Clinical Description to the First Consensus Definition of ARDS

In 1967, Ashbaugh and colleagues reported for the first time the clinical and physiological characteristics in 12 patients with sudden respiratory failure that they called "acute respiratory distress syndrome" (ARDS) [1]. None of these patients had past history of cardiac or pulmonary disease, and they rapidly developed acute hypoxemia, stiff lungs, and diffuse bilateral alveolar infiltration on chest X-ray a few days later after a precipitating factor. Their outcome was dramatic as 7 of the 12 patients (58%) died. An autopsy was performed in all deceased patients, and six of them (86%) had a characteristic histological pattern of diffuse alveolar damage including hyaline membranes, edema, cell necrosis, or fibrosis [1].

In 1971, Petty and Ashbaugh described principles of management of ARDS based mainly on mechanical ventilation using high FiO_2 and positive end-expiratory pressure (PEEP) [2]. Whereas cyanosis refractory to oxygen was one of the clinical

R. Coudroy, MD • F. Boissier, MD, PhD
CHU de Poitiers, Réanimation Médicale, Poitiers, France

INSERM CIC 1402 (ALIVE Group), Université de Poitiers, Faculté de Médecine, Poitiers, France

A.W. Thille, MD, PhD (✉)
CHU de Poitiers, Réanimation Médicale, Poitiers, France

INSERM CIC 1402 (ALIVE Group), Université de Poitiers, Faculté de Médecine, Poitiers, France

Réanimation Médicale, CHU de Poitiers,
2 rue la Milétrie, 86021 Poitiers Cedex, France
e-mail: aw.thille@gmail.com

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criteria for ARDS, the authors did not specify any hypoxemia threshold. Five years later, Bone and colleagues proposed a threshold of hypoxemia below 70 mmHg despite FiO_2 of at least 0.5 and PEEP [3]. In 1982, Pepe and colleagues added to the definition the presence of new diffuse bilateral infiltrates on chest X-ray and a pulmonary wedge pressure lower than 18 mmHg, thereby excluding cardiogenic pulmonary edema [4]. In 1988, Murray and colleagues proposed the lung injury score (LIS) as a means of assessing the severity of ARDS according to the PaO_2/FiO_2 ratio, the PEEP level, respiratory system compliance, and the number of quadrants with infiltration seen on chest X-ray [5].

Since this original description, the definition of ARDS has considerably evolved over the time, but it was not until 1994 that an international American–European Consensus Conference (AECC) laid the foundations for the first clinical definition of ARDS [6]. This consensus conference aimed to bring uniformity to the definition of ARDS for research, epidemiologic studies, and individual patient care [6]. ARDS was consequently defined using the following four criteria: (1) the acute onset of hypoxemia, (2) a PaO_2 to FiO_2 ratio $\leq$200 mmHg regardless of PEEP level, (3) the presence of bilateral infiltrates on chest X-ray, and (4) pulmonary artery wedge pressure $\leq$18 mmHg or no clinical sign of left atrial hypertension [6]. Patients meeting all these criteria but having less severe hypoxemia with a PaO_2 to FiO_2 ratio between 201 and 300 mmHg were considered as having acute lung injury (ALI) and not ARDS. However, this clinical definition has been criticized on each criterion [7] leading to the establishment of a new definition in 2012, the Berlin definition [8].

1.1.2 The Current Berlin Definition

The Berlin definition aimed to provide a better clinical definition and to classify patients according to severity. An expanded rationale was then published by the expert panel to propose treatments and ventilatory management according to the degree of hypoxemia [9]. The changes proposed in the Berlin definition to address the major limitations of AECC definition are the following:

First, the "acute onset" of ARDS has been specified, and respiratory symptoms have to be present within 7 days after a clinical insult (Table 1.1). Timing accuracy enables elimination of mimickers of ARDS who develop respiratory symptoms over several weeks such as idiopathic pulmonary fibrosis, nonspecific interstitial pneumonitis, cryptogenic organizing pneumonia, granulomatosis with polyangiitis, or drug-induced lung disease [10].

Second, patients have been stratified according to their severity in terms of hypoxemia and classified as mild, moderate, and severe ARDS when PaO_2/FiO_2 ratio is between 201 and 300, between 101 and 200, and equal to or below 100 mmHg, respectively [8]. By including patients with a PaO_2/FiO_2 ratio up to 300 mmHg, the Berlin definition now encompasses the patients with mild ARDS that was formerly named acute lung injury. Oxygenation criteria were well correlated to severity with mortality of 27, 32, and 45% in mild, moderate, and severe ARDS, respectively. As a major limitation of the AECC definition was the

Table 1.1 Risk factors of acute respiratory distress syndrome adapted from [9]

Direct lung insult (pulmonary ARDS)
Pneumonia (bacterial, viral, etc.)
Aspiration of gastric content
Inhalation injury
Pulmonary contusion
Pulmonary vasculitis
Near drowning
Indirect lung injury (extrapulmonary ARDS)
Non-pulmonary sepsis
Non-cardiogenic shock
Pancreatitis
Major trauma
Multiple transfusion or transfusion-related acute lung injury
Severe burns
Drug overdose

assessment of PaO_2/FiO_2 ratio regardless of the PEEP level used, the Berlin definition stated that PaO_2/FiO_2 ratio had to be measured with a PEEP level of at least 5 cmH_2O [8].

Third, the AECC definition considered that pulmonary arterial wedge pressure should not exceed 18 mmHg in ARDS [6]. However, high values of pulmonary wedge pressure are commonly observed in patients with ARDS [11, 12], and routine use of pulmonary artery catheter is pointless for hemodynamic management [13]. Therefore, pulmonary artery wedge pressure requirement was removed from the Berlin definition, and it was stated that respiratory failure must not be fully explained by cardiac failure of fluid overload as judged by the clinician or confirmed by echocardiography, if needed, to rule out cardiogenic pulmonary edema [8].

Fourth, the Berlin definition considered radiological findings as bilateral opacities on chest X-ray but also on CT scan, which were not fully explained by effusions, lobar or lung collapse, or nodules [8].

Four ancillary variables were assessed for severe ARDS, including more extensive opacities on chest radiograph, i.e., at least three quadrants, a high PEEP level $\geq$10 cmH_2O, low respiratory system compliance $\leq$40 ml/cm H_2O, and a corrected expired volume $\geq$10 L/min. However, these criteria were not included in the Berlin definition because they did not help to discriminate patients with severe ARDS [8].

1.1.3 What Are the Limitations of the Current Definition?

The major limitation is that ARDS and its severity can be assessed on a single blood gas measurement without prior standardized ventilator settings. However, PEEP may have a major influence on oxygenation, and in the three RCTs that have compared two levels of PEEP (lower vs. higher), oxygenation was always more satisfactory in the higher-PEEP group than in the lower-PEEP group [14–16]. In a

meta-analysis including these three trials, survival was better using high PEEP than using low PEEP in patients with a PaO_2 to FiO_2 ratio ≤200 mmHg [17], and therefore, the experts have recommended the use of high PEEP levels in patients with moderate or severe ARDS [9]. After optimizing ventilator settings and by increasing the PEEP level, several studies have shown that a high proportion of patients could have their severity modified based on PaO_2/FiO_2 ratio, from severe to moderate/mild or from moderate to mild [18–20]. FiO_2 variations may also be associated with significant changes in PaO_2/FiO_2 ratio [18, 21], and it has been shown that, for the same PaO_2/FiO_2 ratio, patients ventilated with high FiO_2 had higher mortality than those ventilated with lower FiO_2 [22]. To homogenize disease severity, ventilatory settings should be optimized using low tidal volumes around 6 mL/kg of predicted body weight and high PEEP level. Likewise, the time from ventilator settings to PaO_2/FiO_2 measurement seems crucial. Indeed, Villar and colleagues reported that mortality was more reliably predicted according to the three categories of severity (mild, moderate, and severe) when PaO_2/FiO_2 ratio was measured with a PEEP level at least 10 cmH_2O and FiO_2 at least 0.5 [19, 20]. However, assessment of PaO_2/FiO_2 ratio yielded a more clinically relevant ARDS classification when measured 24 h after ARDS onset than immediately after FiO_2 and PEEP settings [19, 20]. This finding is illustrated by the inclusion criteria used in the PROSEVA trial, which found a significant reduction of mortality in patients treated with prone position for which patients with a PaO_2/FiO_2 below 150 mmHg were eligible if such a high degree of hypoxemia persisted more than 12 h after optimization of ventilator settings [23]. Therefore, standardized ventilator settings with a PEEP level of at least 10 cmH_2O and the persistence of hypoxemia may perhaps help to improve ARDS classification.

The other main limitation is the difficulty in quantifying morphological lung injury. Since it was first reported, diffuse alveolar damage (DAD) has been regarded as the morphological hallmark of the lung in ARDS [24, 25]. However, the incidence of DAD in ARDS is highly variable from one study to another and largely depends on the type of examination (autopsy vs. open lung biopsy) (Table 1.2). In a large database of clinical autopsies including 356 patients with ARDS, overall incidence of DAD was only 45% [42]. However, the incidence of DAD depended on the severity of ARDS and time from ARDS onset to pathological examination. Hyaline membranes may take 2–3 days to appear [24] and this explains why the incidence of DAD was significantly higher (56%) in patients with ARDS for more than 72 h. The proportion of patients with DAD also increased in more severe patients with an incidence of 12, 40, and 58% in mild, moderate, and severe ARDS, respectively. The incidence of DAD was as high as 69% in patients with severe ARDS after 3 days of evolution [42]. In this study, whereas almost all patients with DAD on autopsy examination met the clinical criteria of the Berlin definition for ARDS (high sensitivity), fewer than half of the patients with ARDS had DAD (low specificity). Perhaps the low specificity of the Berlin definition in DAD detection is ascribable to the presence of other processes with a similar clinical picture. Many diseases may mimic ARDS such as alveolar hemorrhage due to vasculitis, drug-induced pulmonary toxic pneumonia with a lymphocytic pattern or acute

Table 1.2 Incidence of diffuse alveolar damage (DAD) on open lung biopsy or autopsy in patients with acute respiratory distress syndrome (ARDS)

Author (year) [Ref]	*N* patients	Time from ARDS onset to examination, days	Overall incidence of DAD, *N* (%)	Mild ARDS	Moderate ARDS	Severe ARDS
Suchyta (1991) [26]	9	<14	6 (67%)	–	–	–
Warner (1988) [27]	80	6 ± 4	0 (0%)	–	–	–
Papazian (1998) [28]	36	10 (5–55)	5 (14%)	–	4/24 (17%)	1/12 (8%)
Patel (2004) [29]	57	3 (0–25)	23 (40%)	–	–	–
Esteban (2004) [30]	127	3 (1–6)	84 (66%)	–	–	–
Cho (2006) [31]	53	–	23 (43%)	–	–	–
Kao (2006) [32]	41	3 ± 2	12 (29%)	–	–	–
Lim (2007) [33]	36	4 (1–23)	0 (0%)	–	–	–
Arabi (2007) [34]	14	9 (1–30)	7 (50%)	–	–	–
Papazian (2007) [35]	100	7 (6–14)	13 (13%)	–	–	–
Baumann (2008) [36]	22	8 (2–76)	2 (9%)	0/4 (0%)	2/15 (13%)	0/3 (0%)
Lin (2009) [37]	60	8 ± 1	16 (27%)	–	–	–
De Hemptinne (2009) [38]	64	6 (0–48)	32 (50%)	–	–	–
Charbonney (2009) [39]	19	5 (2–11)	9 (47%)	–	–	–
Melo (2009) [40]	19	13	7 (37%)	–	–	–
Sarmiento (2011) [41]	49	–	31 (63%)	–	–	–
Thille (2013) [42]	356	5 (2–13)	159 (45%)	6/49 (12%)	56/141 (40%)	97/166 (58%)
Guérin (2015) [43]	83	9 (6–14)	48 (58%)	4/11 (36%)	33/56 (59%)	11/16 (69%)
Kao (2015) [44]	101	7 ± 7	57 (56%)	13/17 (77%)	32/57 (56%)	12/27 (44%)
Total	***N* = 1353**		***N* = 537 (40%)**	**23/81 (28%)**	**127/293 (43%)**	**121/224 (54%)**

eosinophilic pneumonia, organizing or diffuse interstitial pneumonia, cancer infiltration, and at times idiopathic lymphangitis [10, 45]. These ARDS without common risk factors, the so-called ARDS mimickers, represent around 7–8% of patients mechanically ventilated for ARDS and could have higher mortality than the others [45]. For such atypical ARDS cases, a complete diagnostic workup, including bronchoalveolar lavage fluid cytology and chest CT scan patterns, should be performed to identify patients who might benefit from specific therapies, including corticosteroids. A recent study suggests that the presence of DAD is associated with higher mortality as compared to patients without DAD [46]. Unfortunately, no biomarkers exist to diagnose alveolar damage.

1.2 Incidence and Outcome of ARDS

The incidence of ARDS obviously depends on the definition used and will, as expected, be higher using the Berlin definition that includes patients with a PaO_2/FiO_2 up to 300 mmHg. At the beginning of the 2000s, three studies assessed incidence and outcome of ARDS using the AECC definition [47–49]. In these studies, around 7–8% of the patients admitted in the ICU met clinical criteria for ARDS, with mortality ranging from 35 to 50% in patients with a PaO_2/FiO_2 of 200 mmHg or less.

A large international survey performed in 2014 among 459 ICUs in 50 countries and over a 4-week period screened all patients who met clinical criteria for ARDS according to the current Berlin definition [50]. Patients with ARDS represented 10.4% of all ICU admissions, a rate slightly higher than in the abovementioned studies using the previous AECC definition [47–49]. This represented at least 5 patients per bed and per year or at least 100 patients per year in a 20-bed ICU. Among all intubated patients in ICU, 23% had met clinical criteria for ARDS during their ICU stay. Among them, 30% had mild, 47% had moderate, and 23% had severe ARDS. The risk factors triggering ARDS were pneumonia in 59% of cases, aspiration in 14%, extrapulmonary sepsis in 16%, and non-cardiogenic shock in 7.5%. Whereas some patients may have several risk factors, none of the usual risk factors had been identified in around 8% of the cases (ARDS mimickers). This survey also highlighted the fact that many patients with ARDS had not been recognized by the clinician as having this disease. In mild ARDS, this was the case in around half of the patients. Clinical recognition of ARDS was better for severe ARDS but still underdiagnosed since 21% of them were not recognized. Moreover, clinician recognition of ARDS at the time of fulfillment of clinical criteria was only 34%, suggesting that diagnosis of this pathology was frequently delayed. In this survey, overall mortality was 34% in ICU and 40% in hospital [50]. In-hospital mortality was 35% for those with mild, 40% for those with moderate, and 46% for those with severe ARDS.

1.2.1 Has Mortality Decreased Over Time?

One question is whether or not mortality has declined over time. In a systematic review evaluating 89 studies published between 1984 and 2006 and focusing on ARDS, mortality seemed to have decreased from 1984 to 1993 but not from 1993 to 2006 [51]. The use of protective ventilation including low tidal volumes, high PEEP levels, and strict monitoring of plateau pressure to avoid exceeding 30 cmH_2O is the cornerstone of the current recommendation [9]. After the 2000s, several studies have demonstrated that this strategy was associated with better survival [17, 52, 53], and this change in clinical practice should have had an impact on overall mortality. After 2010, several large RCTS have *shown* a reduction in mortality, especially in ARDS patients with PaO_2/FiO_2 ratio below 150 mmHg, using neuromuscular blockers [54] or prone positioning [23]. Despite this, a recent review focusing on the more recent articles suggested that overall mortality did not seem to have changed

substantially during the last decade, with a proportion in observational studies greater than 40% in patients with moderate or severe ARDS [55], in keeping with the recent LUNG SAFE study [50].

1.2.2 How Can We Explain the Lack of Improvement in Outcome in ARDS?

The positive results reported in RCTs may not be as efficient when applied to all nonselected patients with ARDS in an ICU. It has been found that mortality in ARDS was lower in RCTs than in observational studies that are closer to real life [51]. Indeed, patients included in RCTs are expressly selected, and those with major comorbidities such as hematological malignancies, cirrhosis, and chronic cardiac or respiratory disease are usually excluded. Among the three studies having compared two levels of PEEP, only one of them has provided a flow chart study. In this study, only 22% of the patients assessed for eligibility were included and randomized (768 of 3429 patients) [15].

In a RCT, after excluding patients with exclusion criteria, a high proportion of patients potentially eligible are not enrolled. The outcome of ARDS patients enrolled in a recent RCT has been compared to that of patients who met inclusion criteria but who were not enrolled in the study due to various reasons such as no consent, physician refusal (24%), missed randomization window, etc. [56]. The patients who were included in the study had lower mortality than those who were potentially eligible but not enrolled, suggesting that enrollment in clinical trials may be associated with improved outcomes. The better outcome reported in patients included in RCTs may be due to optimal management including standardized lung protective ventilation and application of other effective therapies. Indeed, in real-life situations, as reported in the recent LUNG SAFE survey, 35% of patients with ARDS were ventilated with a tidal volume above 8 mL/kg of predicted body weight. The mean PEEP level was only 8 ± 3 cmH_2O in moderate and 10 ± 4 cmH_2O in severe ARDS. Prone positioning was used in only 16% of the patients with severe ARDS. Therefore, in 2014, patients with ARDS were receiving excessively high tidal volumes and excessively low levels of PEEP in "real life," while plateau pressure was measured in only 40% of the cases.

1.2.3 Causes of Death and Subphenotypes in Patients with ARDS

In ARDS, the main cause of death is sepsis complicated by multi-organ failure [42, 57, 58]. In a large database of patients who died of ARDS and had clinical autopsy over a 20-year period from 1990 to 2010, the pattern of death was refractory shock in more than half of the 356 patients analyzed, while refractory hypoxemia did not exceed 20% of the cases [42]. These results are in keeping with previous literature with a rate of death due to refractory hypoxemia of around 20% [57, 58]. Obviously,

death due to withdrawal of life support has increased over time [58], and in more recent studies, the vast majority of deaths among patients with ARDS were preceded by a "do not resuscitate" order [59].

Patients with trauma as cause of ARDS have better survival rates than the others [60]. However, the mortality of patients with ARDS of pulmonary origin is similar to that of patients with ARDS of extrapulmonary origin [60]. In a recent study, Calfee and colleagues identified two subphenotypes of ARDS that could have different outcomes [61]. The hyperinflammatory subphenotype was characterized by more severe inflammation with higher plasma concentrations of inflammatory biomarkers and higher prevalence of sepsis. These patients were more likely to have shock and metabolic acidosis, and they had higher mortality than the others. The use of high PEEP levels did not seem beneficial in this subset of patients, while it was beneficial in the other patients.

1.2.4 Long-Term Outcome

ARDS is characterized by specific morphological changes of the lung with an initial exudative and then a proliferative phase. The exudative phase, maximal during the first week after the onset of ARDS, is characterized by capillary congestion and intra-alveolar edema subsequently followed by alveolar type I cell necrosis. The later repair phase is characterized by intense proliferation of alveolar type II cells and interstitial fibroblasts [24, 25]. This phase can either result in normal tissue resolution or progress toward fibrosis if lung injury is persistent. Fibrosis is rare during the first week of evolution of ARDS. However, it can be observed as early as the second week of evolution, and its prevalence markedly increases beyond the third week after the onset of ARDS, especially in ARDS of pulmonary origin [62]. The patients with fibrosis have more altered lung compliance and more frequently interstitial opacities on chest X-ray [63]. After recovery, they may have more long-term residual pulmonary dysfunction than the others [64]. Patients with many radiologic reticulations on chest CT scan 6 months after hospital discharge had altered total lung capacity, forced vital capacity, and carbon monoxide diffusion capacity [65]. In this last study, a chest CT scan performed 14 days after ARDS onset could predict altered quality of life. However, ARDS survivors who have had fibrosis also had more severe disease and more prolonged duration of mechanical ventilation than the others. Moreover, restrictive pulmonary function can be due not only to pulmonary impairment but also to extrapulmonary complications, such as depression and neuromuscular weakness. Herridge and colleagues have followed ARDS survivors discharged from the hospital for 5 years [66, 67]. Among them, 89% were alive at 1 year and 68% at 5 years. They had normal lung volumes and spirometry measurements by 6 months, but carbon monoxide diffusion capacity remained low, and 6-min walk test was abnormal throughout the 12-month follow-up [66]. At 5 years, pulmonary spirometry was normal or near normal, but patients did not return to normal predicted levels of physical function with persistent exercise limitation and decreased physical quality of life [67]. The median 6-min walk distance was 281 m

at 3 months, 422 m at 1 year, and 436 m at 5 years (76% of predicted distance), and, although younger patients had a greater rate of recovery than older patients, neither group returned to normal predicted levels of physical function at 5 years. Health-related quality of life was mainly altered due to extrapulmonary complications. Actually, muscle weakness and fatigue were the main reasons for their functional limitation [66–68]. Moreover, 1 or 2 years after ARDS, the majority of survivors present with clinically significant general anxiety, depression, and posttraumatic stress disorder symptoms [69] and even sometimes psychiatric symptoms [70]

Short- and long-term quality of life is markedly altered in ARDS survivors [71] and seems more altered at 12 months than in other critically ill patients with similar severity but without ARDS during their ICU stay [72]. However, in another study, the quality of life was similar between ARDS and non-ARDS patients, and functional status at 6 months after hospitalization could be largely explained by baseline condition [73].

Conclusion

The definition of ARDS is still challenging and problematic, as is improvement of adherence to the "protective bundle" in real life. Indeed, although some RCTs have demonstrated therapeutic strategies that could improve mortality, negative outcome has hardly decreased in the last decade, and survivors still have a markedly altered quality of life.

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Pathophysiology of Acute Respiratory Distress Syndrome

2

Pedro Leme Silva and Patricia R.M. Rocco

2.1 Introduction

The acute respiratory distress syndrome (ARDS) is a form of hypoxemic respiratory failure characterized by severe inflammatory damage to the alveolar–capillary barrier. This damage can be triggered by primary injury to the epithelium (pulmonary ARDS), as in cases of pneumonia or bronchial aspiration, or to the endothelium (extrapulmonary ARDS), as in cases of nonpulmonary sepsis [37, 51, 54]. Recently, evidence has emerged showing differences in molecular phenotypes between these two etiologies [8]. In addition, patients who develop ARDS after trauma (trauma-associated lung injury) may exhibit distinct clinical features and biomarker profiles compared to other forms of ARDS [7]. Not only the distinction in severity among ARDS patients seems important, but also discrimination among different ARDS phenotypes and etiologies, i.e., whether associated to trauma, transfusion, cancer, and septic events. Novel therapies targeted specifically at these entities may benefit from this separation by pathophysiology.

2.2 Pathophysiology of Acute Respiratory Distress Syndrome: The Actors

The innate immune response plays a profound role in the pathophysiology of ARDS. Multiple immune processes involving macrophages, neutrophils, and epithelial and endothelial cells are implicated in mediating tissue injury.

P.L. Silva • P.R.M. Rocco, MD, PhD (✉)
Laboratory of Pulmonary Investigation, Carlos Chagas Filho Biophysics Institute, Federal University of Rio de Janeiro, Avenida Carlos Chagas Filho, 373, Bloco G1-014, Ilha do Fundão, 21941-902 Rio de Janeiro, Brazil
e-mail: prmrocco@gmail.com

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2.2.1 Alveolar Macrophages

Alveolar macrophages form the first line of defense against airborne particles and microorganisms and use a variety of pattern recognition mechanisms and receptors to sense and phagocytose pathogens [2]. During lung inflammation, two main states of differentiation exist, characterized by classically activated macrophages (CAMs) and alternatively activated macrophages (AAMs). CAMs display the M1 macrophage phenotype and produce high levels of proinflammatory cytokines, such as interleukin (IL)-1β, tumor necrosis factor (TNF)-α, IL-12, and inducible nitric oxide synthase (iNOS), in response to paracrine signaling from the T helper 1 (Th1) cytokine interferon (IFN)-γ and in response to autocrine signaling by IFN-β [28, 62]. AAMs display the M2 macrophage phenotype and produce the anti-inflammatory cytokines IL-10 and IL-1Ra in response to signaling from the Th2 cytokines IL-4 and IL-13. Most studies on detection of macrophage phenotype have been experimental, and, although few studies have been conducted in humans, these investigations are noteworthy. In a comparison of bronchoalveolar lavage fluid (BALF) from patients with ARDS and cardiogenic pulmonary edema, both under mechanical ventilation, and from nonventilated healthy volunteers, Rosseau et al. showed that alveolar macrophages from ARDS patients skewed toward classically activated macrophages, i.e., the M1 phenotype. Persistence of the M1 phenotype is associated with worse outcomes [52]. After exposure of healthy human subjects to intratracheal LPS, an increase was observed in total alveolar macrophages, mainly constituted of pulmonary monocyte-like cells. These cells were recruited to the alveolar space and were $CD16^{-}$, different from nonresident $CD16^{+}$ monocytes [71].

2.2.2 Neutrophils

Neutrophils are the first leukocytes to be recruited to sites of inflammation in response to chemotactic factors released by activated macrophages and pulmonary epithelial and endothelial cells [67]. It has been reported that the concentration of neutrophils in the BALF of patients with ARDS correlates with disease severity and with poor outcome [33]. It has been postulated that neutrophils are involved in endothelial–epithelial barrier disruption [16]. On the other hand, neutropenic patients can develop ARDS in the absence of invading neutrophils [44]. This illustrates the heterogeneity of ARDS, since it may involve neutrophil-dependent and neutrophil-independent processes. The chemokine IL-8, also known as CXCL8, is thought to be central to neutrophil recruitment into the lung during ARDS [68]. Important correlations have been drawn from clinical ARDS samples, including pulmonary edema aspirates and BALF, between increased IL-8 concentrations, disease severity [38], and neutrophil migration into airspaces [39]. IL-8 is considered to be the most potent neutrophil chemoattractant in BALF from ARDS patients and is the predominant neutrophilic chemokine released from LPS-stimulated human alveolar macrophages [26]. Not only isolated IL-8 but also its complexes are associated with ARDS pathophysiology. The IL-8 immune complexes are characterized by IL-8 binding to endogenous immunoglobulin G (IgG), mainly the IgG3 and

IgG4 subclasses. Elevated levels of IL-8 immune complexes have been associated with poor clinical outcome in patients with ARDS and in those at risk of developing ARDS [27]. One possible mechanism could be the decrease in neutrophil apoptosis rate, which is associated with an increase in expression of Bcl-xL and a decrease in Bak and Bax [17]. In this line, it is well established that neutrophil apoptosis is delayed in patients with ARDS [29], which may explain the perpetuation of tissue injury by the release of neutrophil products, namely, proteinase-3, cathepsin-G, and several matrix metalloproteinases (MMPs). Another mechanism of neutrophil action is the release of neutrophil extracellular traps (NETs), in a process of cell death known as NETosis [5]. NET formation involves disintegration of the nuclear membrane, chromatin condensation, and release of DNA and granule proteins into the extracellular space [6]. Although NETs have potent antimicrobial properties, they contain histones, enzymes, and peptides that are directly toxic to host cells. NETs have also been observed in sterile transfusion-related acute lung injury (TRALI) in human patients [60], and protection against TRALI has been observed to follow inhibition of extracellular histones [9]. Therefore, in a scenario of uncontrolled NET formation, their inhibition could be an attractive strategy.

2.2.3 Alveolar Epithelium

After a direct insult, the pulmonary epithelium is the primary injured structure. Epithelial damage leads to alveolar flooding [65], reduced removal of edema fluid from the alveolar space [40], decreased production and turnover of surfactant [21], and fibrosis [4]. A recent study with two distinct patient cohorts [8] found that pulmonary ARDS is characterized by more severe lung epithelial injury compared with indirect ARDS and, conversely, that indirect ARDS is characterized by more severe endothelial injury and inflammation. Among the wide range of plasma biomarkers analyzed (surfactant protein [SP]-D, IL-6, IL-8, angiopoietin [Angpt]-2, receptor of advanced glycation end products [RAGE], and von Willebrand factor [vWF]) and their respective prognostic values, the SP-D was the most reliable molecular indicator of the direct lung injury phenotype. SP-D, produced by type II epithelial and club cells, is a large hydrophilic protein that interacts with glycoconjugates and lipids through the carbohydrate recognition domain (CRD) on the surface of microorganisms, including Gram-positive and Gram-negative bacteria [22]. It can cause agglutination of bacteria, hindering their entry into host cells and dissemination, and may lead to bacterial death through permeabilization of the bacterial cell wall, increasing respiratory burst by macrophages and neutrophils and enhancing opsonization by phagocytic cells [25].

2.2.4 Alveolar Endothelium

The vascular endothelium is the first barrier encountered by fluid or inflammatory cells tracking from the vasculature to the alveoli. Endothelial barrier function is an essential and tightly regulated process that ensures proper compartmentalization of

the vascular and interstitial spaces while allowing for the diffusive exchange of small molecules and controlled trafficking of macromolecules and immune cells [36]. Failure of endothelial barrier integrity results in excessive leakage of fluid and proteins from the vasculature into the airspace. The loss of barrier integrity can be a consequence of neutrophil activity, in which they accumulate in the microcirculation of the lung, become activated, and subsequently degranulate and release several toxic mediators, including reactive oxygen species (ROS), proteases, proinflammatory cytokines, and procoagulant molecules. Injury done by neutrophils and their intracellular products may increase vascular permeability by altering focal adhesions, transmembrane integrins, and the cytoskeleton of endothelial cells. Further inflammatory mediators, despite neutrophils, can act directly on the lung capillaries, resulting in increased expression of chemokines and cell surface molecules that are important for leukocyte adhesion [35, 49]. Furthermore, injury to the endothelial barrier may be mediated by bacterial or viral products, independently of the effects of activated leukocytes. For example, toxins produced by *Pseudomonas aeruginosa* and *Staphylococcus aureus* break down the endothelial barrier as well as the epithelial barrier [12, 66]. Not only NF-κB pathway inflammatory mediators but also specific transmembrane tyrosine kinases from endothelial cells (Tie-2) play an important role in ARDS pathophysiology. Their ligands Angpt-1 and Angpt-2, with nanomolar affinity, can have opposing effects on endothelial cell function. Angpt-1 is largely synthesized and secreted by periendothelial cells and platelets, whereas Angpt-2 is synthesized in the endothelium, where preformed protein is stored for rapid release in granules called Weibel–Palade bodies [15]. The N-terminal region of Angpt-1 may even promote local adherence to the extracellular matrix [61], leading to a high tissue concentration despite low circulating levels. In sepsis, ARDS, and related conditions, circulating Angpt-1 appears to be suppressed [48]. In addition, the magnitude of Angpt-1 decline tends to be two- to threefold or less, compared with the 5- to 20-fold increase in circulating Angpt-2 observed in sepsis or ARDS. Circulating Angpt-2 concentrations have a much broader dynamic range than Angpt-1. In 2006, Parikh et al. reported 10- to 20-fold elevations of circulating Angpt-2 levels in individuals with severe sepsis at the time of ICU admission as compared with patients with uncomplicated sepsis and hospitalized healthy subjects. The authors noted that subjects with severe sepsis developed higher peak Angpt-2 concentrations than those with uncomplicated sepsis and further observed that individuals with impaired lung gas exchange had higher peak Angpt-2 values than those with normal gas exchange [69]. In single-center and multicenter cohort studies, Angpt-2 was a robust indicator of extrapulmonary ARDS [8]. The induction of Angpt-2 clearly precedes adverse outcomes, a point strongly illustrated in an emergency department-based study of 270 adults with suspected infection in whom circulating Angpt-2 measured within the first hour of hospitalization predicted inpatient mortality, with an area under the receiver operator characteristic (ROC) curve of 0.91 [10]. On comparison of several relevant biomarkers, Angpt-2 was the only one capable of predicting the severity, monitoring the course, and prognosticating the outcome of late-onset ARDS in febrile critically ill patients, irrespective of underlying risk factor [23].

2.3 Pulmonary Versus Extrapulmonary ARDS: The Myth Is a Fact

ARDS was long thought to be a uniform expression of a diffuse, overwhelming inflammatory reaction of the pulmonary parenchyma to a variety of serious underlying diseases. The most frequent causes include sepsis, severe pneumonia, peritonitis, and polytrauma. Since 1999, Gattinoni et al. have highlighted the differential responses of respiratory mechanics in ARDS of pulmonary versus extrapulmonary origin [18]. This could be associated with different underlying pathologies resulting from two different pathogenic pathways: a "direct" insult to the lung parenchyma in ARDS caused by pulmonary diseases, such as diffuse pneumonia, versus an "indirect" insult to the lung parenchyma in ARDS caused by extrapulmonary diseases, such as abdominal sepsis or pancreatitis [45]. One explanation for the differences gathered from this landmark study was that prevalent consolidation is expected in "direct" injury-type ARDS, whereas prevalent interstitial edema and alveolar collapse are seen in "indirect" injury-type ARDS [37, 51, 54]. Sixteen years on, Calfee et al. demonstrated that pulmonary ARDS is characterized by more severe lung epithelial injury compared with extrapulmonary ARDS, while extrapulmonary ARDS is characterized by more severe endothelial injury and inflammation [8]. With few exceptions, these findings were robust to adjustment for differences in severity of illness and of lung injury. These distinct molecular phenotypes of pulmonary versus extrapulmonary lung injury provide strong evidence that the heterogeneity in ARDS pathogenesis observed in experimental models [37] is relevant to human ARDS, a finding that may have important implications for clinical trials of novel therapies. As well as molecular phenotypes, pulmonary permeability also seems to differ between pulmonary and extrapulmonary ARDS. In analyses with the transpulmonary thermodilution method, patients with pulmonary ARDS exhibited a higher pulmonary vascular permeability index compared with extrapulmonary ARDS patients for the first 3 consecutive days of intensive care unit stay [42]. On the other hand, the extravascular lung water index differed only at day 3 (extrapulmonary ARDS, 14.9 ± 6.0; pulmonary ARDS, 17.6 ± 7.8, $p = 0.02$). Although this study had few patients, unbalanced allocation, and SOFA score at baseline measurements, the transpulmonary thermodilution method was able to distinguish between the ARDS etiologies through assessment of pulmonary permeability. In short, there appear to be clear differences in pathophysiology, morphological aspects, respiratory mechanics, and hemodynamic parameters between pulmonary and extrapulmonary ARDS in humans.

2.4 ARDS Phenotypes

The establishment of clear definitions of ARDS has led to significant advances in the standardization of populations in research studies; however, a number of studies have shown significant heterogeneity within the population of patients meeting consensus criteria for ARDS [13, 63]. Heterogeneity has been described on the basis of

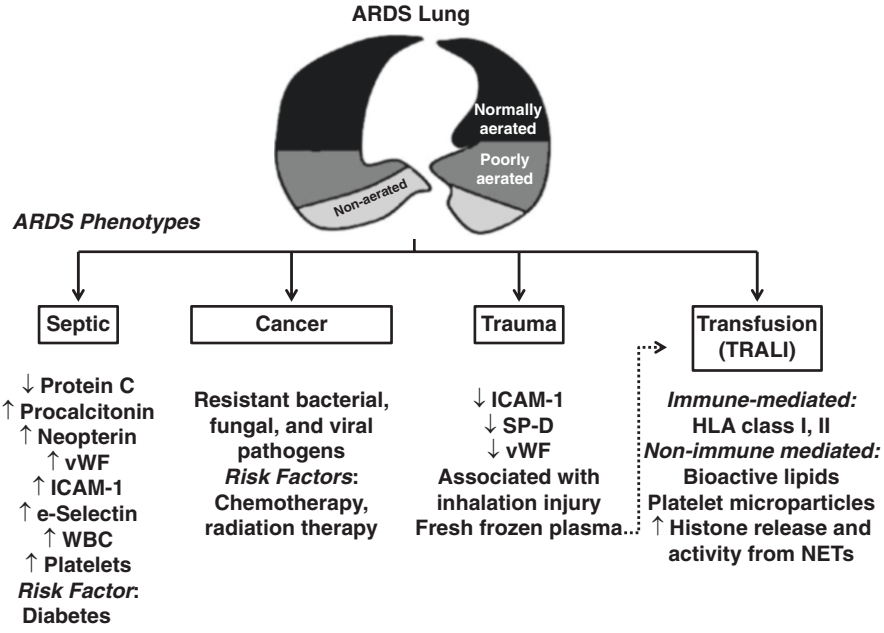

Fig. 2.1 Acute respiratory distress syndrome phenotypes related to sepsis, cancer, trauma, and transfusion. *HLA* human leukocyte antigen, *ICAM-1* intercellular adhesion molecule 1, *NET* neutrophil extracellular traps, *SP-D* surfactant protein D, *TRALI* transfusion-related acute lung injury, *vWF* von Willebrand factor, *WBC* white blood cell

predisposing insult, such as sepsis, cancer, transfusion, and trauma, or by mechanism of injury, such as direct or indirect pulmonary injury [7]. One recent example corroborating the distinction in ARDS phenotypes relates to the presence or absence of diffuse alveolar damage (DAD) on postmortem analysis. Lorente et al. [31] showed that non-survivors of ARDS have different clinical characteristics depending on the underlying histology. Patients with ARDS and DAD at postmortem had a different clinical phenotype than patients with ARDS and other histologic findings without DAD. These findings support the concept that the presence of DAD defines a specific subphenotype within patients with the clinical diagnosis of ARDS. How to detect this or other phenotypes at bedside remains unclear. Figure 2.1 provides an overview of the most common ARDS phenotypes, including expected biomarker levels, likely risk factors, and association with specific injuries.

2.4.1 Septic and Cancer Phenotypes

Studies measuring circulating biomarkers in patients with ARDS showed that protein C levels were lower in patients with sepsis-related ARDS than in those with non-sepsis-related ARDS, whereas procalcitonin, neopterin, von Willebrand factor antigen, soluble intercellular adhesion molecule 1, and soluble E-selectin levels