Acute respiratory distress syndrome (ARDS) is an acute severe lung disease commonly encountered in intensive care units (ICU). It can be caused by several triggers, including pneumonia or trauma. It is characterised by widespread injury of the alveolar–capillary membrane, resulting in protein-rich noncardiogenic pulmonary oedema (fluid accumulation in the lungs) and acute respiratory failure (ARF). ARDS results in severe hypoxaemia, which is refractory to oxygen treatment and requires assisted ventilation. It shares some of the features of infant respiratory distress syndrome (IRDS), which results from insufficient production of surfactant that normally lines the alveoli and reduces the surface tension of the alveolar lining fluid, preventing the collapse of the airspace. In contrast to ARDS, IRDS can be treated successfully using surfactant. ARF, a term sometimes used synonymously with ARDS, is far broader and comprises respiratory failure resulting from many other conditions: for example, chronic obstructive pulmonary disease (COPD). The term ‘acute lung injury’ (ALI) was previously used to characterise a milder form of ARDS, but it is no longer recommended for use.

ARDS was first described in 1967 in patients with refractory cyanosis due to respiratory failure that necessitated mechanical ventilation. However, the criteria for defining the syndrome were not generally...
Despite a variety of triggers, the resulting acute respiratory distress syndrome, in its later stages, shows a uniform clinical and pathological pattern agreed until the American–European Consensus Conference (AECC) in 1994. This definition specified an acute onset, refractory hypoxaemia and radiographic evidence of bilateral pulmonary shadowing due to increased permeability of the alveolar–capillary membrane, with the exclusion of left ventricular failure as the cause (table 1). A cardiogenic cause of pulmonary oedema was to be excluded by pulmonary artery catheterisation showing a pulmonary artery occlusion pressure (PAOP) of less than 18 mmHg or by clinical evidence of left atrial hypertension as a sign of left heart failure. The severity of the condition was defined by the ratio of the arterial oxygen tension ($P_{aO_2}$ measured in mmHg) to the inspiratory oxygen fraction ($F_{IO_2}$; where room air is 0.21 and pure oxygen is 1.0).

This definition was superseded by the Berlin definition of 2012, which refined the AECC criteria. The onset of ARDS is now fixed as being within 7 days of an insult or of new or worsening respiratory symptoms. While bilateral radiographic ‘opacities’ are still necessary, other causes, such as effusions, nodules, and partial or complete collapse of a lobe or lung should be excluded. The exclusion of cardiac failure or fluid overload is stressed but the methods of exclusion now emphasise echocardiography, which can replace pulmonary artery catheterisation, mirroring actual clinical practice. For a clearer definition, a minimum positive end-expiratory pressure (PEEP) has been introduced and the name ALI has been omitted and replaced by grading of ARDS as mild ($P_{aO_2}/F_{IO_2}$ of more than 200 mmHg but not more than 300 mmHg), moderate ($P_{aO_2}/F_{IO_2}$ of more than 100 mmHg but not more than 200 mmHg) or severe ($P_{aO_2}/F_{IO_2}$ of not more than 100 mmHg).

**Pathogenesis**

ARDS can be initiated by various distinct conditions that lead to a common pathophysiological pathway. The triggering events are grouped into two classes: direct ‘pulmonary’ and indirect ‘extrapulmonary’ conditions. The direct causes include various conditions that injure the lung parenchyma, including pneumonia, pulmonary contusion due to trauma, aspiration and inhalation, or ingestion of toxic agents (table 2). The most frequent indirect insult is sepsis syndrome (a common and highly lethal cause of ARDS), but this group also includes acute pancreatitis, overdose of certain drugs [opiates or thiazides], disseminated intravascular coagulation, and multiple blood product transfusions (hypertransfusion). Despite the variety of triggers, the resulting ARDS, in its later stages, shows a uniform clinical
and pathological pattern, even though the pathophysiological routes and mechanisms may differ depending on the event that injures the lungs.

The acute phase of ARDS is characterised by injury to the alveolar–capillary barrier, with disruption leading to increased permeability ('leakiness'). Leukocytes accumulate in the pulmonary capillaries and invade the airspaces. The consequences include inflammatory vasoconstriction (in contrast to inflammation-induced vasodilatation in the systemic circulation), reduced compliance (greater 'stiffness') of the lungs and atelectasis (collapse of alveoli rendering them airless) due to loss of the surfactant that lines and normally stabilises alveoli, reducing surface tension of the alveolar lining fluid. The consequent respiratory failure is aggravated by severe ventilation/perfusion mismatching, with some perfused alveoli no longer receiving any ventilation ('shunt'), while others are ventilated but not perfused ('dead space').

Histopathologically, three phases are recognised during the evolution of ARDS: 1) an exudative early phase which results from diffuse alveolar damage and endothelial injury; 2) a proliferative phase which ensues about 7–14 days after the injury, incorporating repair of the damaged alveolar structure and re-establishment of the barrier function, together with proliferation of fibroblasts; 3) a fibrotic phase with chronic inflammation and fibrosis of the alveoli, which follows in some patients.

<table>
<thead>
<tr>
<th>AECC definition 1994</th>
<th>Berlin definition 2012</th>
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<tbody>
<tr>
<td>Acute onset</td>
<td>Onset within 1 week of a known clinical insult or new or worsening respiratory symptoms</td>
</tr>
<tr>
<td>Bilateral infiltrates observed on frontal chest radiograph</td>
<td>Bilateral opacities – not fully explained by effusions, lobar/lung collapse or nodules</td>
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<tr>
<td>PAOP less than 18 mmHg [if measured] or no clinical evidence of increased left atrial pressure</td>
<td>Respiratory failure not fully explained by cardiac failure or fluid overload. Objective assessment (e.g., echocardiography) required to exclude hydrostatic oedema if no risk factor present</td>
</tr>
<tr>
<td>ALI: ( P_{aO2}/F_{IO2} &lt; 300 ) mmHg</td>
<td>All grades with a PEEP or CPAP of ≥5 cmH₂O</td>
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<tr>
<td>ARDS: ( P_{aO2}/F_{IO2} &lt; 200 ) mmHg</td>
<td>Mild ARDS: 200 mmHg &lt; ( P_{aO2}/F_{IO2} &lt; 300 ) mmHg</td>
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<tr>
<td></td>
<td>Moderate ARDS: 100 mmHg &lt; ( P_{aO2}/F_{IO2} &lt; 200 ) mmHg</td>
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<td></td>
<td>Severe ARDS: ( P_{aO2}/F_{IO2} &lt; 100 ) mmHg</td>
</tr>
<tr>
<td>No risk factor included</td>
<td>If no risk factor present, need to objectively rule out hydrostatic oedema</td>
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Table 1 – Comparison of the American-European Consensus Conference (AECC) and Berlin definitions of acute respiratory distress syndrome (ARDS). PAOP: pulmonary artery occlusion pressure; ALI: acute lung injury; \( P_{aO2} \): arterial oxygen tension; \( F_{IO2} \): inspiratory oxygen fraction; PEEP: positive end-expiratory pressure; CPAP: continuous positive airway pressure.
Reports of the incidence of ARDS in its different grades of severity vary, to some extent due to the lack of precision in the earlier AECC definition. Incidence estimates range 10–58 cases per 100 000 people, depending on geographical location and on the reporting system used. Using data from a prospective multicentre European cohort study that included 6522 patients treated in ICU, the proportion with ALI and ARDS averaged 7.1% of all patients admitted to critical care. This rose to 12.5% when only patients treated for more than 24 hours in ICU were included. Another study reported that patients with ALI represented 4.5% of all those receiving ventilation at the time of admission to intensive care.

In a recent database analysis from a single ICU treating both surgical and medical patients, a decrease in the prevalence of ARDS was reported: when comparing the periods January 1993–February 1996 and January 2006–April 2009, the authors found a prevalence of 2.5% in the first period and 1.7% in the second period. While the length of stay of survivors in the ICU decreased significantly in the second period, from an average of 17 to 13 days, no significant change in mortality was reported. The mortality rates of 52% and 46% in the first and second periods, respectively, are comparable to the actual mortality seen in routine clinical intensive care. However, studies from ARDSnet, an American network that focuses on ARDS, report a decreasing mortality rate over time. In a study reported in 2000, the network found a significantly lower mortality (31% compared with 39.8%) where a ‘protective ventilation’ (i.e. small tidal volume) approach was used compared with conventional mechanical ventilation. In more recent studies, mortality rates close to 20% have been reported. The latter results, however, probably represent the mortality rates of selected patients included in trials, whereas general surveys or databank analyses of mortality in unselected patients range between 27–45%, or even up to 70%, depending on the severity of disease and comorbidity. The most common cause of death is multi-organ failure, and this has not changed over time. The first 7–10 days seem to be the most relevant for determining the ultimate prognosis of ARDS patients. Within this timespan, about 50% of patients are either successfully weaned from the ventilator or have succumbed to the disease. Young patients with ARDS following trauma seem to fare best, with lung function recovering over 6–12 months. Mild abnormalities of respiratory function (obstructive or restrictive spirometric abnormalities or impaired diffusing capacity) may persist in a proportion
Within the first 7–10 days, about 50% of patients are either successfully weaned from the ventilator or have succumbed to the disease.

Overall, the mortality of patients suffering from ARDS remains unacceptably high despite our extensive knowledge of the pathophysiology of the lung injury and the various multicentre studies of treatment reported to date.

**Treatment options**

**Mechanical ventilation**

Mechanical ventilation is a major component of the treatment of ARDS as it keeps the patient alive and ensures gas exchange despite compromised and injured lungs. Historically, the therapeutic goal was to achieve almost normal blood gas levels, even if this meant using very high tidal volumes during mechanical ventilation. However, mechanical ventilation itself also has the potential to injure the lungs, as implied by the term ‘ventilator-induced lung injury’. The optimal strategy of ventilation is therefore under constant review. In a landmark study by ARDSnet, a strategy of ‘protective ventilation’ using a low tidal volume (6 mL per kg predicted bodyweight) compared with a traditional high tidal volume (12 mL per kg predicted bodyweight) was successful in significantly reducing mortality from 39.8% to 31%. However, since this trial was reported more than 10 years ago, no further change in ventilation strategy has been shown in a multicentre trial to result in lower mortality. Different strategies in the amount of PEEP applied have shown no clear-cut effects on survival. It remains to be determined whether strategies of ultra-protective ventilation (tidal volumes less than 6 mL per kg predicted bodyweight) or high-frequency oscillation ventilation (HFOV) may prove advantageous. This is important, as overdistension of the lung by excessive tidal volumes may be responsible for both inducing and perpetuating lung injury.

**Fluid management**

The optimal strategy for supplying fluids to the patient with ARDS remains a controversial management issue. Fluid restriction may benefit gas exchange by reducing alveolar oedema, but this must be weighed against the concept that more liberal fluid management improves cardiac output, protects renal function and increases the delivery of oxygen to vital organs. The ARDSnet studies reported a shorter period of ventilation and better oxygenation, but no increase in survival, using a complex algorithm that aimed simultaneously to protect renal function and to secure circulatory function, while employing a policy of restrictive fluid management.
These goals may remain difficult to achieve, since, for example, in the early phase of the sepsis syndrome (which may lead to ARDS) a more liberal fluid strategy has proved successful in reducing mortality.

**Pharmacological treatment**

So far, no pharmacological therapy has been successful in improving the survival of patients with ARDS. Despite numerous strategies appearing to be successful in experimental studies and smaller trials, none has been shown to be successful in multicentre trials. Given the unacceptably high mortality and prevalence of ARDS among critically ill patients, there is an urgent need for a successful pharmacological treatment strategy.

The lung offers the unique possibility of treatment via both the vascular bed (intravascular injection) and via the airways (inhalational approach). Again, several apparently highly successful strategies in experimental studies and smaller clinical trials have not resulted in improved survival of real-world treated patients. Inhalation of gaseous nitric oxide, which was predicted to redirect the blood flow from injured to better ventilated areas of the lung, has been unsuccessful in general ARDS patients and remains only a last-resort option. Supplying surfactant, which, in healthy lungs, maintains the patency of the alveoli and which is destroyed by lung injury, is successful in IRDS but has not improved survival in adults. Despite these frustrating results, treatment of injured lungs via the airways remains a valuable potential approach in further research efforts.

**Extracorporeal lung support strategies**

The technique of extracorporeal membrane oxygenation (ECMO) allows complete artificial oxygenation of, and removal of carbon dioxide from, the blood by use of a membrane-oxygenator, a pump and two large-bore cannulae. The techniques have been refined in recent years and three different approaches now allow: 1) carbon dioxide removal driven by blood pressure without a pump (extracorporeal lung assist); 2) a step-up solution using the same technique with a pump; and 3) full ECMO. Experience from the most recent influenza epidemic demonstrated successful ECMO treatment of younger patients in special centres. The large CESAR (Conventional Ventilation or ECMO for Severe Adult Respiratory failure) trial for the first time showed a survival benefit when treating patients with severe ARDS in a, special centre using ECMO compared with standard treatment. Due to inherent design limitations, however, the results of this trial have not been accepted unequivocally but, at least in experienced centres, ECMO therapy may be considered as a valuable treatment option in severe cases. As to the other two above options for extracorporeal lung support, data showing their effectiveness are available but results from larger trials concerning survival, for example, are lacking.

**Other supportive measures**

Further supportive measures have been evaluated for the treatment of ARDS patients. One option is turning the patient on his stomach while he is being ventilated (prone position). This has attracted considerable interest but has not produced unequivocal results in large studies. It seems to be an option for severely ill patients when they are treated for prolonged periods. In experienced centres, it is a valuable option for maintaining oxygenation. Nutritional approaches have shown promising results in several studies but recent trials have not reproduced the favourable results.
As there are no effective pharmacological therapies available, the need for translational research in ARDS is obvious. Research strategies are necessary to understand and manipulate the molecular mechanisms that lead to loss of alveolar–capillary barrier function and oedema formation. Furthermore, newer aims include strategies to repair and regenerate the injured barrier, including new cell-therapeutic approaches. Controlling epigenetic mechanisms and new inhalational approaches, including advanced aerosol techniques and nano-particles, are also attractive prospects.

Clinical research should include strategies to improve the treatment of ARDS patients in relation to ventilatory techniques, extracorporeal devices, and supportive measures. However, such studies need to be carried out on a multicentre basis in order to have the necessary statistical power for adequate evaluation of survival benefit.

**Future developments**

**Further reading**

**Definition and diagnosis**

**Pathogenesis**

**Incidence and outcome**


### Treatment options