Acute lung injury and acute respiratory distress syndrome

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Key points
Acute lung injury (ALI) is a common condition that is associated with a high mortality.

Correct diagnosis of ALI is important because other causes of hypoxaemia may be more easily treated.

Identification and treatment of the underlying condition is paramount.

Management includes standard ICU supportive care and a tidal volume limited to 6 ml kg⁻¹.

A conservative fluid management strategy might have some benefits.

Acute lung injury (ALI) is a common condition that is characterized by acute severe hypoxia that is not due to left atrial hypertension. The term ALI encompasses a continuum of clinical and radiographic changes that affect the lungs with the acute respiratory distress syndrome (ARDS) representing the more severe end of this continuum. Despite advances in our understanding of the pathophysiology and management of ALI, it is still associated with a high mortality.

The aim of this review is to provide an overview of ALI and present the best available evidence for its management.

Definition and diagnosis
ALI is a condition that is diagnosed clinically and radiologically based on the presence of non-cardiogenic pulmonary oedema and respiratory failure in a critically ill patient. It was first described in 12 patients in 1967 and termed respiratory distress syndrome.

The definition in current use was described in 1994 at the American–European Consensus Conference on ARDS. The aim of the definition was to improve the diagnostic consistency of ARDS and ALI allowing comparison of data relating to epidemiological and treatment studies. The criteria for diagnosing ALI are listed in Table 1.

Strengths of these definition criteria are that they are clinically relevant and easy to use, making them ideal for use both in the clinical setting and for research purposes.

Weaknesses are that the radiological criteria are non-specific and are subject to inter-observer variability. These radiological criteria might be the only way in which ALI is distinguished from other pulmonary conditions such as pneumonia. It is therefore possible that a patient with the same condition is diagnosed with pneumonia by one clinician and with ALI (secondary to pneumonia) by another.

There is also no agreed standard ventilatory strategy for patients before meeting the criteria for hypoxaemia. It is possible, for example, to improve the $P_{aw}/F_{O_2}$ ratio of patients meeting the diagnostic criteria by increasing PEEP. In addition, patients with high atrial hypertension from other causes, for example, left ventricular failure or mitral regurgitation, are not immune from developing ALI, but it is unclear how to make the diagnosis in these cases.

Inconsistencies in the application of these criteria could explain some of the variability in the reported incidence of ALI. Universal application of the diagnostic criteria without searching for other causes of hypoxaemia may lead to over-diagnosis of the condition. It is essential to exclude conditions such as fluid overload before the diagnosis is made.

In summary, the diagnosis of ALI requires the application of the consensus criteria by a clinician who is able to take into account all the factors mentioned above.

Epidemiology
The incidence of ALI is quoted to be between 17 and 34 per 100 000 patients per year.¹ About 16% of all patients ventilated in the ICU for 24 h or more develop ALI. These patients have a high mortality. This is a reflection of the severity of the primary pathology causing ALI, other associated organ failures, and complications associated with critical illness. The extent to which ALI contributes to the mortality of patients is unknown, but most patients die due to other organ failures rather than hypoxaemia. There is some evidence, though, that mechanical ventilation might contribute to the failure of other organs as mentioned below.

Aetiology
ALI is a multifactorial disease process that occurs due to an environmental trigger on the background of a genetic predisposition. The environmental causes of ALI can be classified as direct or indirect depending on the mechanism of injury to the lung. The most common...
cause of ALI in the UK is sepsis which may be either intra- or extrapulmonary. Other important causes are listed in Table 2.

The precise genetic basis of ALI remains elusive due to several factors: the diversity of environmental stimuli involved, the complex gene–environment interaction, the heterogeneous nature of the illness itself, and the presence of varying comorbidity. Nevertheless, genomic markers have been identified that are associated with a phenotype that predisposes to ALI. Other genes have been identified which may influence the severity of the illness, providing multiple potential targets for novel therapies to be developed.

Pathophysiology

Patients with ALI and ARDS progress through a similar pathophysiological process irrespective of whether the damage is a direct effect on the alveolar epithelial cells by an external stimulus or an indirect process resulting from a more distant systemic inflammatory process mediated via cytokines.

The course of ALI can be described in three overlapping phases. The acute or exudative phase starts early, lasts for up to 7 days from onset and is characterized by the development of hypoxaemia, infiltrates on the chest radiograph, and a reduction in pulmonary compliance. These clinical changes are accompanied by leakage of protein-rich fluid in the alveoli, haemorrhage, and diffuse neutrophilic alveolar infiltrate with resultant endothelial and epithelial injury. These activated neutrophils that have been sequestered in the alveoli can be seen on microscopy of bronchoalveolar lavage fluid.

The subacute or proliferative phase of ALI can occur from day 5 onwards. It is characterized by persistent hypoxaemia, increased dead space, and reduced lung compliance. This is accompanied by interstitial fibrosis, proliferation of type 2 alveolar cells, and disruption of capillary function due to microvascular thrombus formation. In some patients, these changes resolve and clinical improvement follows whereas other patients progress into the chronic or fibrotic stage. This stage results from widespread pulmonary fibrosis and loss of the normal lung structure leading to worsening lung compliance and an increase in dead space. This manifests clinically as a reduction in carbon dioxide excretion which may be accompanied by an improvement in oxygenation. This chronic stage is not clearly defined temporally but may start as early as 14 days and last for many weeks.

The pathophysiological changes described above do not occur homogeneously in the lungs. High-resolution computed tomography (CT) of the chest demonstrates this heterogeneity of alveoli involvement.

Investigations

ALI is primarily a clinical diagnosis, although a chest X-ray (CXR) and arterial blood gas analysis are also required to make the diagnosis. Table 3 lists typical findings on CXR that may differentiate ALI from other conditions. These characteristic changes can be seen in Figure 1. It should be remembered, however, that there are no pathognomonic radiographic findings for ALI and it is often difficult to differentiate it from other conditions purely on the basis of radiographic findings.

CT of the chest may give useful information in the patient with ALI and typically demonstrates the heterogeneous nature of the consolidation seen in ALI. It is predominantly visible in dependent areas and has a patchy appearance with air bronchograms. CT may also be useful to demonstrate the sequelae of ARDS such as pneumothoraces and fibrosis. The risks of transferring a ventilated patient to the CT scanner have to be considered carefully.

Management

General care

The principles of treating ALI are providing good supportive care and maintaining oxygenation while diagnosing and treating the underlying cause. It is important to emphasize that if the patient fails to respond to therapy in the expected manner, then it should...
Mechanical ventilation

Mechanical ventilation is conventionally delivered as positive pressure ventilation with PEEP via a tracheal tube. The principle of ventilation in patients with ALI is to maintain adequate gas exchange until the cellular damage resolves without causing ventilator-induced lung injury. The latter condition encompasses the tetrad of barotrauma, volutrauma, atelectrauma, and biotrauma and poses a significant risk to all patients receiving mechanical ventilation.

The ARDSnet (National Heart, Lung, and Blood Institute’s Acute Respiratory Distress Syndrome Clinical Trials Network) tidal volume study\(^3\) showed a significant reduction in mortality by utilizing a low-volume ventilatory strategy based on predicted body weight (6 ml kg\(^{-1}\) and peak pressures <30 cm H\(_2\)O vs 12 ml kg\(^{-1}\) and peak pressures <50 cm H\(_2\)O). Traditionally, high volumes were used in an effort to normalize the patient’s arterial blood gases. These large volumes are thought to damage the remaining areas of healthy lung by over-inflation due to the relatively normal compliance of these areas compared with the segments affected by ALI. This more conservative ventilatory strategy is also associated with a significantly lower level of circulating cytokines, the cause of biotrauma, and distant organ damage.

PEEP improves oxygenation in ALI by maintaining the patency of injured alveoli and allowing an improvement in ventilation/perfusion matching and a reduction of intrapulmonary shunt. It also prevents atelectrauma caused by the repeated opening and closing of alveoli. These factors have led investigators to try to define an optimal level of PEEP in ALI/ARDS. The ARDSnet group conducted a large randomized controlled trial\(^4\) that did not demonstrate a difference in outcome between patients ventilated with a lower level of PEEP (8 cm H\(_2\)O) and those ventilated with a higher level of PEEP (14 cm H\(_2\)O). Two recent large randomized controlled trials also studied the effect of elevated levels of PEEP and failed to show any reduction in mortality.\(^5\) \(^6\)

Recruitment manoeuvres have been used for many years to improve oxygenation by opening up collapsed alveoli. Notwithstanding recent advances in the monitoring of recruitment manoeuvres using CT and electrical impedance tomography, no study has demonstrated an improvement in survival using these measures.

Despite the many different ventilator modes available, there is no evidence to date to suggest that any method improves survival, provided the above limitations to tidal volume and peak pressure are adhered to. With regard to weaning from mechanical ventilation, no method has been proven to be superior to any other.

Fluid management

Owing to the altered capillary permeability in ALI, excessive fluid administration leads to a deterioration in gas exchange. This is because excess fluid increases the capillary hydrostatic pressure, which in turn causes pulmonary oedema and worsening oxygenation and carbon dioxide elution. On the other hand, the benefits of a more liberal fluid strategy are an increase in cardiac output with a possible improvement in non-pulmonary organ perfusion.

The benefit of fluid restriction was partially demonstrated by the Fluids and Catheters Treatment Trial (FACTT) study carried out by the ARDSnet group,\(^7\) which compared a conservative (-163 ml in first 7 days) with a liberal (+6992 ml in first 7 days) fluid strategy. Patients who were in the conservative fluid group had a reduction in duration of ventilation and ICU stay, but no reduction in mortality. Notably, there was no increase in any clinically significant adverse event, including renal failure. On this basis, we would recommend a conservative fluid regime as a low-cost, low-risk intervention that could lead to improvement in clinically important outcomes.

Steroids

Steroids exert an anti-inflammatory effect by inhibiting arachidonic acid metabolism and reducing eosinophil activity. As ALI is associated with an increase in both serum and bronchoalveolar lavage levels of cytokines and chemokines, it is tempting to think that the anti-inflammatory effects of steroids would be beneficial. For this reason, their use has been investigated as a preventive measure and also a therapeutic one in all phases of the condition. A recent meta-analysis of the use of steroids in the early exudative phase of ALI confirmed that steroids confer no survival benefit.

In the subacute phase, the alveoli are infiltrated by myofibroblasts and collagen deposits. Following a study that showed a
significant reduction in this process after the administration of methylprednisolone,\textsuperscript{8} the ARDSnet group performed a large multicentre randomized controlled trial using the same trial protocol.\textsuperscript{9} This larger study failed to show a difference in hospital mortality. On the basis of these studies, the routine use of methylprednisolone is not recommended in patients with ALI.

Prone positioning

Prone positioning has been demonstrated to enhance oxygenation by improving alveolar ventilation/perfusion matching. It improves lung mechanics by increasing compliance and recruitment of atelectatic basal regions in addition to improving clearance of respiratory secretions.

By achieving the same $P_{a\text{O}_2}$ at lower airway pressures, it was postulated that prone positioning might reduce the occurrence of ventilator-induced lung injury. Despite improving the $P_{a\text{O}_2}/F_{\text{I}_2}$ ratio, reducing the incidence of ventilator-associated pneumonia, and not being associated with major adverse airway complications,\textsuperscript{10} routine prone positioning does not improve survival or reduce the duration of mechanical ventilation in patients with ALI/ARDS. On this basis, its routine use is not recommended; however, it may be a useful temporary measure in a patient who is critically hypoxic.

Other therapies

Nitric oxide

A recent systematic review of the use of iNO in ALI\textsuperscript{11} showed no improvement in clinical outcome, despite a short-lived (24–48 h) improvement in oxygenation and a reduction in pulmonary vascular resistance. On this basis, its routine use for patients with ARDS/ALI cannot be recommended.

Extracorporeal lung support

Extracorporeal membrane oxygenation (ECMO) has been suggested as a therapy for ALI/ARDS, as it allows gas exchange to continue while preventing further damage to the lung by ventilation. The recently completed Conventional ventilation vs ECMO in Severe Acute Respiratory failure (CESAR) trial suggests that the use of ECMO results in improved survival without severe disability with a number needed to treat of 6 and thus may prove to be cost-effective when compared with conventional ventilation. This study was not published in a peer-reviewed journal at the time this manuscript was written. The use of ECMO is also confined to a few specialist centres in the UK. Arteriovenous extracorporeal CO$_2$ removal (AVECCO$_2$R) has also been proposed as a rescue therapy in severe ARDS in order to treat hypercarbia. Current evidence is based on case series and results from these are promising. Uncoupling of respiratory functions allows carbon dioxide clearance while maintaining oxygenation by low-frequency positive pressure ventilation or apnoeic oxygenation, effectively preventing further ventilator-induced injury. Both ECMO and AVECCO$_2$R have interventional procedure guidance available from the National Institute for Health and Clinical Excellence.

Physiotherapy and positioning

The role of physiotherapy in ARDS is uncertain and little evidence exists concerning its use. Aims of physiotherapy in ARDS are similar to those in most ICU patients—to promote the removal of retained secretions and to encourage active and passive movements in patients who are often bed bound for a long period of time.

Methods used to achieve these aims include:

- positioning to enhance the removal of secretions and to improve gas exchange;
- percussion and vibration;
- tracheal suction;
- continuous rotational therapy.

Sitting ventilated patients up to 30$^\circ$ may reduce the risk of aspiration and subsequent ventilator-associated pneumonia and can be recommended on the basis of the available evidence.

Outcome

A large European study in 2004 demonstrated that ICU and hospital mortality associated with ALI were 45.8% and 54.7%, respectively.\textsuperscript{12} Mortality was significantly worse for patients with ARDS (ICU mortality 49.4% and hospital mortality 57.9%) compared with those who had ALI but not ARDS (ICU mortality 22.6% and hospital mortality 32.7%).

Independent factors associated with an increase in mortality include:

- advanced age;
- immunocompromise;
- high APACHE-II/SAPS-II/SOFA score;
- $\text{H}^+$ over 50 nmol litre$^{-1}$;
- early barotrauma (air leak within first 2 days).

Although respiratory function is often normal by 12 months after admission to the ICU for patients who survive ALI, long-term sequelae are common. These include neurocognitive impairment, psychological morbidity, and muscle weakness that often delay the return to a normal quality of life and sometimes lead to permanent disability.

Conclusion

ALI is a common condition in patients admitted to the ICU. Despite recent advances, ALI is still associated with significant morbidity and mortality. Basic management should include good supportive care and treatment of the underlying cause. The only specific management strategy shown to have a survival benefit is restrictive ventilation with a tidal volume of 6 ml kg$^{-1}$ and a plateau pressure of $<30$ cm H$_2$O. A conservative fluid management strategy has been shown to reduce duration of mechanical ventilation and ICU stay. Other measures may be considered in
individual cases, but there is insufficient evidence to recommend their widespread use for all patients.

References


Please see multiple choice questions 13–15