



## PRACTICE

## EASILY MISSED?

# Acute respiratory distress syndrome

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A 40 year old woman presented to the emergency department with fever, dyspnoea, and coughing purulent sputum. Chest radiograph revealed bilateral infiltrates, and peripheral capillary oxygen saturation (breathing 50% oxygen) was 92%. Antibiotics and a trial of non-invasive ventilation were commenced, and the patient was admitted to a medical ward.

Twenty four hours later she had worsening dyspnoea, fatigue, and hypotension, and was transferred to the intensive care unit for vasopressor infusion and invasive ventilation. The ventilation was weaned at 3 weeks, but rehabilitation was slow. Two months later, at hospital discharge, she had residual weakness and post-traumatic stress disorder, and her return to work seemed uncertain. Case review showed exemplary management of sepsis but noted a week's delay in the diagnosis of acute respiratory distress syndrome (ARDS) because of incorrect initial interpretation of the chest radiograph—despite all criteria for ARDS being present in the emergency department. Furthermore, none of the proven strategies in ARDS were employed.

## What is ARDS?

Acute respiratory distress syndrome was first described in 1967<sup>1</sup> and has become a defining condition in critical care. It is an acute inflammatory lung injury, often caused by infection, which increases lung microvascular permeability, resulting in hypoxaemic respiratory failure. It presents with dyspnoea, predominantly in the emergency department or hospital ward,<sup>2 3</sup> and requires assisted ventilation. Around 40% of patients with ARDS will die,<sup>2</sup> and survivors experience long term sequelae. No drug treatments exist for ARDS, however good supportive management reduces harm and improves outcome. Early diagnosis—ideally before admission to intensive care—maximises benefit.<sup>4</sup> Most cases of ARDS are diagnosed in hospital, but up to one third of patients with ARDS fulfil diagnostic criteria in the emergency department.<sup>3</sup> It is helpful, therefore, for primary care clinicians to be aware of ARDS and have a low threshold for rapid referral of patients who have an

evolving illness associated with breathlessness and hypoxia to an emergency setting. Patients might also need additional support in the community with longer term complications.

## How common is it?

The incidence of ARDS is variable (7–70 per 100 000 person years),<sup>5</sup> reflecting in part the differences in recognition. The LUNG SAFE study, a prospective observational cohort study (29 000 patients in 459 intensive care units in 50 countries), allowed for retrospective diagnosis of ARDS by researchers using clinical data, independent of the treating clinicians. In that study, more than 10% of patients admitted to intensive care units—and more than 20% of those requiring invasive ventilation—had ARDS.<sup>2</sup>

## How is it diagnosed?

ARDS should be suspected in all patients presenting to primary care or the emergency department with recent onset of severe respiratory symptoms and with clinical signs of hypoxia (fig 1).

ARDS can be anticipated where a risk factor is present (eg, pneumonia, sepsis, aspiration of gastric contents, massive blood transfusion).

**Clinical features:** respiratory symptoms and signs (elevated respiratory rate, lung crackles on auscultation); clinical signs of hypoxia (central cyanosis).

**Investigations:** these clinical features mandate a chest radiograph and an arterial blood gas analysis.

The chest radiograph should show diffuse opacities over both lung fields (fig 2). The radiologic criteria from the diagnostic definition of ARDS states that the chest radiograph findings show “bilateral opacities that are not fully explained by effusions, lobar/lung collapse, or nodules.” The arterial blood

**What you need to know**

- Consider the possibility of acute respiratory distress syndrome (ARDS) in any sick patient with respiratory distress, especially in the presence of risk factors such as pneumonia, sepsis, trauma, or aspiration of gastric contents.
- Perform a radiograph of the chest and arterial blood gas sampling for all patients with acute respiratory distress to aid early recognition of ARDS.
- Timely diagnosis of ARDS facilitates implementation of simple measures that can reduce mortality, morbidity, and financial cost.

gas analysis will show low arterial oxygen tension, ie, arterial hypoxaemia. As oxygen tension is dependent on inspired oxygen concentration, the ratio of arterial oxygen tension to inspired oxygen fraction is calculated. If this ratio is less than 40 (oxygen tension measured in kPa), then the oxygenation criterion for ARDS is fulfilled.

**Diagnosis**

The diagnostic criteria for ARDS have evolved since its first description in 1967, with the most recent criteria developed by a panel of experts following a consensus conference in Berlin in 2012 (convened by the European Society of Intensive Care Medicine, with the endorsement of the American Thoracic Society and the Society of Critical Care Medicine). The diagnosis of ARDS<sup>6</sup> requires the presence of three criteria:

- Acute onset: within one week of a known clinical insult (ie, a risk factor) or of new/worsening respiratory symptoms (where insult is unknown)
- Pulmonary oedema: bilateral lung field opacities on chest imaging; oedema must not be entirely hydrostatic (ie, caused by cardiac failure or fluid overload)
- Hypoxia: ratio of arterial oxygen tension to inspired oxygen concentration <40 kPa.

Cardiogenic pulmonary oedema is the main differential diagnosis, so when there is no clear predisposing cause for ARDS, patients need to be evaluated for heart failure. As both congestive heart failure and ARDS can coexist, the diagnosis of ARDS can still be made, as long as congestive heart failure is not the sole apparent cause of the hypoxia and chest radiograph findings.

**What is the evidence that ARDS is missed?**

The LUNG SAFE study reported that 40% of cases of ARDS were not recognised at any time during a patient's stay in the intensive care unit.<sup>2</sup> Delayed diagnosis was the norm, with <30% diagnosed on the first day that criteria were present.<sup>2</sup> Although this evidence is new and compelling, the issue is not new. A decade old study of ARDS proven through autopsy noted that <50% of cases were identified in the clinical notes,<sup>7</sup> while in a 2013 study <30% of patients with all criteria for ARDS had the condition recorded in their notes.<sup>8</sup>

**Why is the diagnosis of ARDS usually missed?****Evolving illness in a complex environment**

While the individual criteria are simple, the diagnosis relies on recognising patterns in patients with evolving illness and receiving complex care. Recognition is poor where doctor and/or nurse to patient ratio is low,<sup>2</sup> and, in contrast, it is higher when attention is focused (eg, younger patients with single organ failure or more severe hypoxaemia).<sup>2</sup> The clinician might be caring for several patients with complex conditions, therefore

information overload—pervasive in intensive care units<sup>9,10</sup>—occurs, and even experienced clinicians cannot process extreme volumes of information.<sup>11</sup> Thus, recognition might be delayed or missed.

**Assumption of rarity**

ARDS is incorrectly considered to be rare, especially by clinicians less familiar with intensive care units, who might even consider it restricted to the intensive care unit. The diagnosis requires chest imaging and arterial blood gas analysis; therefore ARDS can be suspected, but generally not confirmed, in the primary care setting. If the index of suspicion is low, the diagnosis will be missed even in high risk patients, and where fewer risk factors exist, the risk of missed diagnosis is increased.<sup>2</sup>

**Misinterpretation of chest radiograph**

The utility of chest radiography in ARDS can be poor, and substantial inter-observer variation has been documented.<sup>12</sup>

**Limitations of ARDS consensus definition**

The high sensitivity and low specificity of the ARDS consensus definition (sensitivity 89% and specificity 63% compared with histologic criteria)<sup>13</sup> is problematic; it is better for screening than for diagnosis, and clinicians might therefore take “positive criteria” less seriously.

**Why does this matter?**

Delayed or failed recognition of ARDS leads to delayed or non-implementation of beneficial treatment. Under-recognition is linked to under treatment.<sup>2</sup> Fewer than 50% of those with ARDS who died had received muscle relaxation, and <20% had a trial of prone positioning: two interventions with proven survival advantage.<sup>14,15</sup> In contrast, patients in whom ARDS was recognised were more likely to receive these interventions.

Early recognition (and anticipation) in the community, in the emergency department, or on the ward, can facilitate measures that increase the odds of survival (with fewer complications). Strategies to reduce iatrogenic harm include avoidance of excess intravenous fluid,<sup>16</sup> avoidance of high tidal volume<sup>17</sup> (breath size delivered by the mechanical ventilator), or the use of prone positioning,<sup>18</sup> and transient muscle relaxation (box 1).<sup>15,19</sup> Because high tidal volume is more injurious if used earlier, this underscores the need for early recognition.<sup>4</sup> These interventions are relatively simple in an acute care setting, easy to implement, and have excellent benefit/risk profiles.

This matters to the patient because failure to recognise ARDS leads to failure to use proven treatments, and this translates into higher chances of death, and almost certainly, worse quality of life (because of cognitive impairment, muscle wasting, and functional limitation<sup>20</sup>) among those who survive. These disabilities persist, with survivors of ARDS experiencing substantial limitations in physical function five years after their critical illness.<sup>21</sup> Only 48% had returned to work at one year, which increased to 77% by the end of year 5. Over half of ARDS survivors reported at least one episode of physician diagnosed depression, post-traumatic stress disorder, or anxiety in the five years after ARDS. There was a substantial impact on the mental

**Box 1: Evidence based strategies to avoid iatrogenic harm in patients with ARDS**

- Low tidal volume ventilation: high tidal volume further injures the lung in patients with ARDS. The effect is most pronounced in the early phases of ARDS.<sup>4</sup> Reduction of tidal volume increases patient survival.<sup>17</sup>
- Judicious fluid treatment: fluid overload can worsen gas exchange. Careful fluid management, with focus on avoiding circulatory overload, increases patient survival.<sup>16</sup>
- Muscle relaxation: muscle relaxation in the early phases of moderate to severe ARDS improves survival. The mechanism of effect is unclear, but might reduce lung injury by eliminating patient dyssynchrony with ventilator.
- Prone positioning: prone positioning in the early phases of moderate to severe ARDS improves survival.<sup>18</sup> The mechanism of effect includes better lung mechanics and matching of ventilation to perfusion in the prone position.

health of other family members.<sup>21</sup> In another study, 24% of survivors of critical illness showed impairment of cognitive function at 12 months similar to that seen with mild Alzheimer's disease.<sup>22</sup> Survivors require extensive rehabilitation in the community after ARDS, and guidelines have been developed by the National Institute for Health and Care Excellence in relation to this.<sup>23</sup>

**How can we improve diagnosis of ARDS?**

Simple steps could improve recognition. Increased awareness (clinicians, patients, relatives) elevates the index of suspicion and thus the likelihood of diagnosis. In one retrospective, single centre study, introduction of an ARDS standard operating procedure increased awareness of ARDS, leading to an increased frequency of ARDS diagnosis ( $P<0.05$ ), increased application of early prone positioning ( $P<0.05$ ), and use of neuromuscular blockers ( $P<0.02$ ) in ARDS patients.<sup>24</sup> Any patient with a peripheral oxygen saturation of 95% in receipt of at least 30% oxygen would fulfil the oxygenation criteria for ARDS. As >20% of ventilated patients in intensive care units have ARDS, it should be considered in any sick patient with respiratory distress—in the community, emergency department, or hospital ward.

Given variability in interpretation of chest radiographs<sup>12</sup> and the failure of education programmes to reduce this variability,<sup>25</sup> low dose computed tomography might be preferable for ARDS diagnosis.<sup>26</sup> Detection might be further enhanced by computer aided pattern recognition, reducing information overload.<sup>27</sup>

The discovery of biomarkers might help, but, given the high sensitivity of the consensus criteria, additional markers might be superfluous for detection—but could be of great use in confirmation (ie, to reduce “false positives”).

Finally, better patient care depends on how well clinicians understand the profile of ARDS—when to suspect it, how to confirm, and how to mitigate iatrogenic injury.

**How is ARDS managed?**

Management of ARDS involves three complementary strategies.

- Measures are needed to sustain life; in particular, advanced support of oxygenation and organ function is required.
- Underlying causes must be addressed (eg, antibiotic treatment and source control for sepsis).
- Hospital acquired harm must be prevented (eg, minimising lung injury caused by mechanical ventilation, avoidance of fluid overload) (box 1).

In patients with more severe ARDS, early use of muscle relaxation<sup>15</sup> and prone positioning<sup>18</sup> can further improve outcome, and in rare cases, extracorporeal membrane oxygenation can be life saving in severely hypoxaemic cases unresponsive to conventional support.

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Specifically, JGL, CM, and BPK each made substantial contributions to the conception or design of the work; drafted the work, and revised it critically for important intellectual content; gave final approval of the version to be published, and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. JGL is responsible for the overall content as guarantor.

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### How patients were involved in the creation of this article

One of the authors (CM) is a survivor of sepsis and ARDS, and has published articles on her experience. She was consulted after the initial draft and edited the subsequent versions.

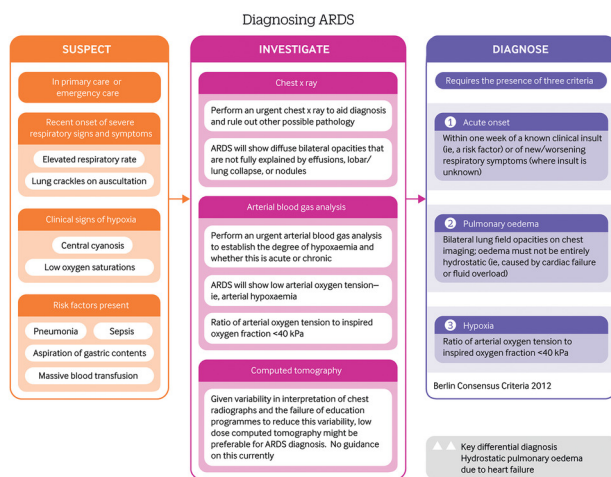
### Education into practice

- Are you aware of the diagnostic criteria for ARDS and when to have a high degree of clinical suspicion in patients presenting in primary or secondary care?
- Are you aware of the potential longer term complications for patients who develop ARDS? How might you address these in your local setting?
- What might you do differently as a result of reading this article?

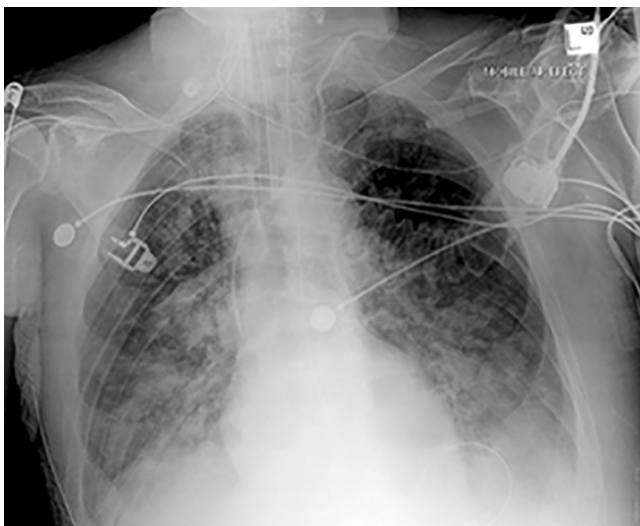
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## Figures



**Fig 1** Diagnosing acute respiratory distress syndrome



**Fig 2** Chest radiograph from a patient with acute respiratory distress syndrome, showing bilateral airspace opacities diffusely spread over both lung fields. This is a classic chest radiograph for ARDS (image provided courtesy of Prof Frank Gaillard, Radiopaedia.org, rID: 35985)