

21 questions and formulates 21 recommendations on the following domains: (1) definition; (2) phenotyping, and respiratory support strategies including (3) high-flow nasal cannula oxygen (HFNO); (4) non-invasive ventilation (NIV); (5) tidal volume setting; (6) positive end-expiratory pressure (PEEP) and recruitment maneuvers (RM); (7) prone positioning; (8) neuromuscular blockade, and (9) extracorporeal life support (ECLS). In addition, the CPG includes expert opinion on clinical practice and identifies the areas of future research.

Keywords: Acute hypoxemic respiratory failure, Acute respiratory distress syndrome, Mechanical ventilation, Extracorporeal membrane oxygenation, Prone position, Non-invasive ventilation, Prognosis, Practice guidelines

Introduction

Acute respiratory distress syndrome (ARDS) is the term applied to a spectrum of conditions with different etiologies which share common clinical-pathological characteristics including: (1) increased permeability of the alveolo-capillary membrane, resulting in inflammatory edema; (2) increased non-aerated lung tissue resulting in higher lung elastance (lower compliance); and (3) increased venous admixture and dead space, which result in hypoxemia and hypercapnia [1]. Over the last 55 years, ARDS definitions have focused primarily on the syndrome's radiological appearance and on the severity of the oxygenation defect (e.g., $\text{PaO}_2/\text{FiO}_2$ ratio), which reflect both the original description of the syndrome [2] and its conceptual understanding [1]. The current definition, the definition of Berlin [3], implies that at time of diagnosis the patient receives at least 5 cmH_2O of positive end-expiratory pressure (PEEP). Formally, patients not receiving positive pressure can thus not be considered as suffering from ARDS. Nevertheless, a lot of patients with AHRE, especially when due to bacterial or viral pneumonia or in case of septic shock, have the same disease and are thus also considered in this guideline.

ARDS accounts for ~10% of admissions to intensive care unit (ICU) and 23% of ventilated patients, with mortality up to 45% in the severe category [4]. The recognition that patients with ARDS are susceptible to additional lung injury induced by mechanical ventilation (ventilator-induced lung injury, VILI) [5] has led to lung-protective strategies designed to reduce total stress (transpulmonary pressure) and strain (the ratio between tidal volume and functional residual capacity) on the aerated lung tissue [6]. These strategies include lower tidal volume and plateau pressure to protect the 'baby lung' [7]; the use of PEEP and lung recruitment maneuvers (RM) to reduce the amount of non-aerated lung; and ventilation in prone position to increase lung homogeneity, improve ventilation/perfusion ratio and lung/chest wall shape matching, reduce stress and strain, and decrease the risk of VILI [8]. Ventilation in the prone position improves outcomes in patients with moderate-to-severe ARDS [9, 10].

Concomitantly, clinicians and investigators alike have sought to avoid invasive ventilation altogether for

patients with early acute hypoxemic respiratory failure (AHRE) using non-invasive respiratory support modalities (e.g., non-invasive ventilation, high-flow nasal oxygen). These therapies seek to improve oxygenation and unload respiratory muscles, thereby reducing inspiratory effort and the risk of patient-self-inflicted lung injury (P-SILI) [11], and allow time for the underlying disease to be treated without the need for sedation and tracheal intubation. For patients with more severe disease, VILI [5] can be theoretically reduced with extracorporeal support techniques which allow partial or total oxygenation and/or carbon dioxide removal and a significant reduction in ventilator mechanical power [12].

The aim of these guidelines is to review and summarize the literature published since the last clinical practice guideline (CPG) of the European Society of Intensive Care Medicine (ESICM) [13] across different aspects of ARDS and AHRE, including ARDS due to coronavirus disease 2019 (COVID-19) in ICU. The scope of this CPG is limited to adult patients and to non-pharmacological respiratory support strategies (except for neuromuscular blockers, which are adjuncts to mechanical ventilation). The document combines a methodologically rigorous evaluation of clinical studies with expert opinion on the respiratory management of patients. This work did not include a cost-effectiveness analysis.

Methods

Topic and panel composition

These guidelines were formulated by an international panel of experts on behalf of the ESICM and address three broad topics within ARDS: (1) definition; (2) phenotyping, and (3) respiratory support strategies. The ESICM Executive Committee selected these three topic areas and nominated three chairpersons (CC, LC, GG) and one methodologist (DP), who arranged the guidelines into nine domains of investigations: (1) definition; (2) phenotyping; (3) high-flow nasal cannula oxygen (HFNO); (4) non-invasive ventilation (NIV); (5) tidal volume setting; (6) PEEP and lung RM; (7) prone positioning; (8) neuromuscular blockade, and (9) extracorporeal life support (ECLS). Each domain was assigned to a group of experts within the panel, and each domain was