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Acute Respiratory Distress Syndrome: The Era of Prevention

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Acute respiratory distress syndrome (ARDS) results in increased use of critical care resources and the overall associated mortality remains high. The identification of patients at risk and the implementation of preventive strategies are necessary.

Introduction

Acute respiratory distress syndrome (ARDS) is common in critically ill patients admitted to intensive care units (ICU). ARDS is characterised by acute hypoxaemia and bilateral pulmonary infiltrates and pulmonary oedema due to an increased permeability without left cardiac failure (Rubenfeld and Herridge 2007; ARDS Definition Task Force 2012).

There is an incidence of 58.7 cases per 100,000 people/year (Rubenfeld et al. 2005). Data about mortality vary widely. A systematic review, which analysed mortality from ARDS from 1994 to 2006, selected all trials that included patients based on the American-European Consensus Conference definition, and concluded that mortality decreased over the last decade, with an overall mortality of 43%, in-hospital mortality of 48.7% and ICU mortality of 44.3% (Zambon and Vincent 2008). A recent analysis reports an overall mortality of 44.3% (Phua et al. 2009). ARDS involves a high health cost and high overall mortality. Several indicators of poorer prognosis in ARDS have been identified (Ware 2005; Stapleton et al. 2005). The most important factors related to mortality are co-morbidities, age, severity (Simplified Acute Physiology Score [SAPS] II) and shock and organ failure (mortality has a direct relation with the number of organ failures and increases up to 83% with three or more organ failures). Once treatment is initiated, prognostic factors are correlated with response to treatment.

Currently there is no specific treatment for ARDS. The best care emphasises adequate and correct supportive care focused on the treatment of the underlying cause and avoiding iatrogenic complications. Mechanical ventilation remains the most important support therapy in ARDS.

Patients At Risk of Development of ARDS

ARDS is rarely present at the hospital admission; rather, it develops in a short time period from hours to days in patients with predisposing factors. Patients with risk factors at admission for ARDS develop ARDS in a median of 2 days (interquartile range 1-4) (Gajic et al. 2011). A chain reaction based on multiple hits can be involved in the pathogenesis of ARDS development and/or the progression of severity (Pavord et al. 2006). Host predisposing conditions act as a first hit in healthy lungs, where multiple hits can induce ARDS. In the absence of these predisposing

conditions, the probability that the other hits will result in ARDS is lower (de Haro et al. 2013).

Early identification of patients at risk for ARDS may represent a good opportunity for preventive strategies. Following the paradigm of early goal-directed therapy in sepsis, early identification and treatment of ARDS patients could improve surveillance.

Several predisposing factors have been ascribed to ARDS development. Hudson et al. evaluated the presence of one or more of eight clinical conditions (sepsis, aspiration, drug overdose, near drowning, pulmonary contusion, multiple transfusions, multiple fractures, cranial traumatism), determined in previous studies, in ARDS development, and they obtained a 79% sensitivity and 26% specificity (Hudson et al. 1995). Gong et al. demonstrated that a pulmonary aetiology of injury, haematologic failure, transfusion of eight or more units of concentrated red blood cells, respiratory rate > 33 rpm, haematocrit > 37.5%, arterial pH < 7.33, albumin ≤ 2.3g/dL and transfer from another hospital increase ARDS risk (Gong et al. 2005). Ferguson et al. (2007), in patients from hospital wards, determined that pulmonary risk factors had a higher rate of ARDS progression than non-pulmonary risk factors, but shock was the most potent predictor factor. Trillo-Alvarez et al. developed in 2011 a predictor index for ARDS, called the Lung Injury Prediction Score (LIPS), which identified patients at risk of ARDS before ICU admission (Trillo-Alvarez et al. 2011). Gajic et al. (2011), in a multicentre prospective observational trial, determined that ARDS development varies due to the presence of predisposing factors and that the LIPS model discriminates efficiently (AUC 0.80; CI 95%; 0.78-0.82) between those with a low risk of ARDS development and those who developed ARDS. If adjusted for severity and predisposing factors, ARDS development increases in-hospital mortality (OR 4.1; CI 95%; 2.9-5.7). A recent trial, which studied the role of potentially preventable hospital exposures in the development of ARDS, suggests that the avoidance of second hits can decrease the development of ARDS and improve safety and outcomes for critically ill patients (Ahmed et al. 2014). The hospital exposures with a strong association with development of ARDS were preventable medical and surgical adverse events, inadequate antimicrobial therapy, larger volumes of blood product and intravenous fluid administration and documented pulmonary aspiration (Ahmed et al. 2014).

Focus on Prevention

Gajic et al. (2004), in a retrospective trial, hypothesised that one of the most important risk factors for ARDS development is mechanical ventilation with high tidal volumes. They demonstrated an increase of OR 1.3 per mL above 6 mL/kg predicted body weight (PBW) (Gajic et al. 2004). In 2010 Determann et al. conducted a trial, stopped at the interim analysis, in which patients ventilated with low tidal volumes (6mL/kg PBW versus 10 mL/kg PBW) developed less ARDS (13.5% vs. 2.6%; p = 0.01) (Determann et al. 2010). This trial supports the results of previous cohort trials suggesting that mechanical ventilation with traditional tidal volumes can contribute to the development of lung injury (Wrigge et al. 2004). Martin-Loeches et al. (2013) showed that protective ventilation strategies (plateau pressure < 30 cm H2O) were associated with lower mortality in septic patients without ARDS. A recent multicentre trial demonstrated that the use of a lung-protective mechanical ventilation strategy during major abdominal surgery results in fewer pulmonary postoperative complications (Futier et al. 2013). A meta-analysis by Serpa Neto et al. (2012) showed that protective ventilation with lower tidal volume in patients without ARDS was associated with better clinical outcomes. Further prospective trials in critically ill patients are needed, but a protective mechanical ventilation strategy in patients at risk of ARDS seems to be a good prevention strategy.

Sepsis precipitates ARDS in 25% to 40% of cases, and the risk increases if a systemic inflammatory response, shock, or organ dysfunction is present. Early appropriate antibiotic therapy seems to be one of the most important preventive strategies, while there is no specific preventive treatment (Iscimen et al. 2008; Ferrer et al. 2008; Kumar et al. 2009).

Fluid balance has been identified in multiple trials as an important risk modifier in the development of ARDS. There are no specific trials evaluating a fluid strategy in patients without ARDS, but many trials support a conservative strategy in ARDS patients, with better outcomes (National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network 2006; Murphy et al. 2009). Fluid overload could be a preventable hospital exposure in patients at risk of development of ARDS.

There is an association between blood products and ARDS. This effect depends on the amount of red cell transfusions and alloimmunisation (Zilberberg et al. 2007; Gong et al. 2005; Toy et al. 2005). A policy of less transfusion is probably the best preventive strategy (Yilmaz et al. 2007).

Different pharmacologic treatments are under study, but as yet there are no results. Exposure to antiplatelet agents during the at risk period was associated with a decreased risk of ARDS (Ahmed et al. 2014), but there are no prospective trials in human patients evaluating this treatment. Other treatments, such as activated protein C, inhaled corticosteroids, statins, mesenchymal stem cells and beta-2 adrenergic agonists have been tested in experimental studies, but have yet to show promising results in human patients (Maniatis et al. 2010; Chimenti et al. 2012; Levitt and Matthay 2012).

In conclusion, preventive strategies are a new field of research aiming to avoid the progression of ARDS. Early identification of patients at risk for ARDS and the control of hospital exposures (multiple hits) seem to be the best options for prevention of the disease or to avoid ARDS progression.

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