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Corticosteroids in Late Adult Respiratory Distress Syndrome – Towards a Better Use

Adult respiratory distress syndrome (ARDS) is a very severe form of lung injury, which occurs associated with a variety of pulmonary and extrapulmonary pathologies [1]. The response of the lung to injury is stereotyped and mainly results from the disruption of the alveolar-capillary unit. However, in the diffuse alveolar damage which characterizes the disease, sequential phases that correlate with the clinical evolution of the disease can be identified [2].

The *exudative* phase, in which oedema and haemorrhage occur in alveoli, develops within approximately 1 week after the onset of respiratory failure. In this early phase, the distinctive features of ARDS are hyaline membranes which derive from the leakage of plasma proteins through the damaged endothelium-epithelial barrier into the alveolar space. The second or *fibroproliferative* phase derives from the organization of intra-alveolar and interstitial exudates and takes place between the first and the third weeks after injury. Now fibroblasts and myofibroblasts proliferate and migrate through the alveolar basement membrane into the alveolar exudate. Within the alveolar wall, fibroblasts also cause alveolar septal *fibrosis*. Finally, in the last phases of ARDS, pulmonary vessels are extensively remodelled, and both chronic interstitial emphysema and pulmonary hypertension can develop. The term 'late ARDS' refers to its clinical stage in which the lungs attempt to repair the initial and persistent injury to the respiratory unit. The histologic correspondent is termed 'fibroproliferative phase' because it can lead to extensive fibrosis [3].

Mortality associated with ARDS can be as high as 50–70%. The two major causes of death in patients with late ARDS (>3 days), which are frequently unrecognized be-

fore death, are *sepsis* related to nosocomial pneumonia and pulmonary *fibrosis*. Sepsis has been claimed to be responsible for both endothelial-alveolar damage and multiple organ failure. However, uncontrolled activation of mediators of inflammation has also been described in the so-called sepsis syndrome, in which the clinical features of sepsis are present, but no focus of infection can be demonstrated [4]. In order to better understand the evolution of oedema and haemorrhage into interstitial fibrosis, several interleukins (IL-1, IL-6, IL-8) and TNF have been studied. In addition, locally produced cytokines are probably also responsible for chemotaxis and activation of lung fibroblasts and thus facilitate the development of fibrosis [5].

From the clinical point of view, it is always difficult to differentiate sepsis from the fibroproliferative evolution of the disease. Patients in the fibroproliferative phase of ARDS can have fever, leucocytosis, new or worsening localized infiltrates on a chest roentgenogram, purulent tracheal secretions and marked uptake of gallium in the lungs without any identifiable infection. Bronchoscopy with collection and analysis of distal airway secretions excludes bacterial pneumonia, even in patients with clinical findings suggesting bronchial infection. In these cases, open lung biopsy or transbronchial biopsy indicate the presence of an inflammatory process [4, 6].

From the therapeutic point of view, a precise diagnosis is important because, while sepsis must be treated with adequate antibiotic therapy, the fibroproliferative phase may be responsive to steroid treatment and reversible [7, 8]. Prospective clinical studies have shown that short courses (<48 h) of high-dose corticosteroids are not beneficial when they have been administered at the onset of

ARDS [9, 10]. In contrast, a beneficial effect has been described when corticosteroids were given in late ARDS. Three small, uncontrolled studies provide evidence that sustained courses of high-dose steroids given to uninfected patients in the later stages shorten the clinical course of the disease, with few steroid-related complications [4, 7, 8].

The study of *Keel et al.* [11] in this issue of *Respiration* reconsiders the importance of treatment in established fibroproliferative ARDS and poses the question whether corticosteroids, added to supportive therapy, can decrease the high mortality rate due to the disease. In a retrospective study, the authors analysed 31 nontrauma ARDS patients who had been on mechanical ventilation for at least 7 days. Thirteen patients received corticosteroids at a dosage equivalent to 100–250 mg methylprednisolone at the discretion of the attending physicians. Supportive care was identical in the treated and non-treated patient subgroups. However, the selection of patients was arbitrary, since 3 of the 4 physicians decided to treat their patients on the basis of the already published preliminary data, whereas the other 4 physicians judged the risks of potential infections as being too high. Mortality in the treatment group was 38% (5/13) as opposed to 67% (12/

18) in the untreated group. It is noteworthy that there was a significant improvement in the $\text{PaO}_2/\text{FiO}_2$ ratio from a median of -26 to $+5$ mm Hg measured in a 48-hour period before and after corticosteroid treatment. In addition, no significant complications attributable to corticosteroid treatment were found.

The value of the study by *Keel et al.* [11] is that it is the first comparative analysis of two well-matched ARDS patient populations that suggests the benefits of corticosteroids in established ARDS. The paper validates the results of Meduri et al. [4, 12, 13], who obtained a favourable response to a sustained course of corticosteroids administered as rescue treatment in patients who failed to improve their lung function after prolonged mechanical ventilation. Of course, in the evolution of ARDS, the magnitude of the initial inflammatory response is important. Similarly, the intensity and duration of inflammation at the initiation of corticosteroid treatment is an important factor in determining the response to anti-inflammatory therapy. These considerations have led the authors – and we agree with them – to propose prospective clinical trials, using well-selected and large patient populations, to better define the appropriate use of corticosteroids in ARDS.

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