Introduction

No pharmacological treatment has been found effective in the reduction of mortality in acute lung injury (ALI) or its more severe form, acute respiratory distress syndrome (ARDS) [1]. The initial phase of ALI is characterized by the overwhelming activation of a complex network of proinflammatory pathways and mediators. To control this reaction with an anti-inflammatory drug has been a tempting idea [2]. However, attempts to blunt or prevent this inflammatory process by cortico-steroids have led to disappointing results. In several studies, the aim of short-term therapy with massive doses of glucocorticoid has been to achieve disease resolution in the early phase of inflammatory reaction [3]. Meta-analyses of these studies regarding the use of prophylactic or early high-dose corticosteroid therapy in the treatment of patients with sepsis, patients at risk of developing ARDS, or patients in the early phase of ARDS, suggest that the use of steroids may even be harmful [4, 5]. The most likely reason for the failure of these older glucocorticoid trials has been speculated to

Abstract  Objective: To investigate the effect of steroid treatment in the late phase of primary acute lung injury (ALI) with special emphasis on pneumococcal pneumonia. Design: Retrospective study. Setting: Multidisciplinary intensive care unit (ICU) in a university hospital. Patients: Of 31 patients with primary ALI requiring mechanical ventilation for more than 10 days, 16 were treated with methylprednisolone and 15 served as controls. Measurements and results: Steroid and control groups were comparable regarding demographic data, APACHE II score, Multiple Organ Dysfunction Score (MODS), and PaO₂/FiO₂-ratio on admission to ICU. The mean start of steroid therapy was 9.7 days after establishment of respiratory failure, and values for control patients were registered on day 10. The PaO₂/FiO₂ ratio improved significantly within 3 days after the start of steroid therapy, and MODS and C-reactive protein decreased concurrently. No differences in mortality, in length of ICU stay, or in length of mechanical ventilation were detectable. In a subgroup analysis, for patients with Streptococcus pneumoniae pneumonia, beneficial change in physiological variables was evident. Conclusions: In patients with primary ALI, steroid therapy, started 10 days after the start of mechanical ventilation, improves gas exchange and is associated with a decrease in multiorgan dysfunction.

Key words  ALI · ARDS · Pneumococcal pneumonia · Corticosteroids · Methylprednisolone · Fibroproliferation
be the short duration of treatment in patients with persistent exaggerated inflammation [3].

After the early phase of an inflammatory reaction, which is characterized by an increase in alveolo-endothelial permeability, there is considerable heterogeneity in the subsequent clinical course of patients with ALI. Some patients recover rapidly, while others develop progressive ALI leading to a sustained inflammatory response and unresolved lung injury [1]. In these patients an exaggerated and protracted host defence response results in a fibroproliferative response in the lungs, associated with obliteration of alveoli by proliferating myofibroblasts and collagen deposits [1, 2]. Attenuation of this reaction by sustained treatment with corticosteroids has been reported to be beneficial in several retrospective series [6, 7, 8, 9, 10, 11, 12] and in one prospective study [13].

Late steroid therapy has been used in the ICU of our institution according to our protocol as an empirical treatment for unresolved ALI. In the present study, we retrospectively analyzed the effects of late steroid therapy on the severity of respiratory failure, multiorgan dysfunction and the degree of acute phase reaction, and on the outcome of patients with primary ALI, with special attention to ALI caused by Streptococcus pneumoniae.

**Material and methods**

**Patients**

The medical records of all mechanically ventilated patients treated in our 10-bed medical-surgical intensive care unit (ICU) during 1994–1998 were retrospectively evaluated. Criteria for inclusion in the study were: (1) mechanical ventilation for acute respiratory failure for more than 10 days; and (2) pulmonary, infectious etiology of ALI. Exclusion criteria were: (1) prior corticosteroid treatment for more than 10 days; and (2) pulmonary, infectious etiology of ALI of the 31 patients is presented in Table 1. On admission and at the start of steroid therapy or day 10, both groups were comparable, and all patients fulfilled consistent approach has been developed. The decision regarding corticosteroid treatment was based on the consultation of an infectious diseases specialist and the individual evaluation of the patient. Patients with consistently high levels of CRP as a sign of sustained inflammation, with progressive respiratory failure despite adequate antimicrobial treatment, and with no evidence of untreated infection, have been considered candidates for corticosteroid therapy. Very labile diabetes or gastrointestinal bleeding were contraindications for corticosteroids. Before the start of corticosteroid treatment, patients underwent BAL to produce samples for bacterial culture, and a computed tomography (CT) of the chest to exclude pleural empyema or lung abscesses. As corticosteroid treatment, intravenous methylprednisolone (Solu-Medrol, Pharmacia & Upjohn, Stockholm, Sweden) was initiated at a dose of 80 mg in the morning and 40 mg in the evening in order to simulate circadian variation of the natural hypothalamic-pituitary-adrenal axis. Based on clinical response, the dose was gradually tapered off.

**General care**

General care of patients with ALI consisted of invasive hemodynamic monitoring, including a pulmonary artery catheter, routine ulcer prophylaxis, thromboprophylaxis with low molecular weight heparin, and early enteral nutrition. The ventilatory support was managed by limiting static inspiratory airway pressure under 35 cmH2O and by selecting PEEP-level on a clinical basis. Pressure controlled ventilatory mode and active use of prone position ventilation was part of the ventilatory strategy. Infection surveillance was performed twice a week. Bronchial aspirates were obtained with blind suction or with a bronchoscope if a chest x-ray showed new infiltrate. Urine and wounds were also cultured twice a week. Selective decontamination of the digestive tract, or extracorporeal membrane oxygenation or inhaled nitric oxide were not used. During the study period, no major changes occurred in our treatment protocols.

**Statistical analysis**

All data were expressed as means with standard deviation. Continuous non-paired variables were tested with the Mann-Whitney independent rank sum test and categorical data with the Fisher (2-tail) exact test. A probability level of less than 0.05 was considered significant.

**Results**

The demographic data, underlying conditions and etiology of ALI of the 31 patients is presented in Table 1. On admission and at the start of steroid therapy or day 10, both groups were comparable, and all patients fulfilled