Corticosteroids in Acute Respiratory Distress Syndrome

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Contributor: Emmanuelle Kuperminc , Nicholas Heming , Miguel Carlos , Djillali Annane

Acute respiratory distress syndrome (ARDS) is frequently associated with sepsis. ARDS and sepsis exhibit a common pathobiology, namely excessive inflammation. Corticosteroids are powerful anti-inflammatory agents that are routinely used in septic shock and in oxygen-dependent SARS-CoV-2 related acute respiratory failure.

glucocorticoids acute respiratory distress syndrome sepsis

1. Introduction

The efficacy of corticosteroids in acute respiratory distress syndrome (ARDS) has been a subject of controversy for decades [1][2]. In animal models of ARDS, corticosteroids decreased the expression of pro-inflammatory mediators in lung tissue, including TNF-a, IL-1a, IL-1b, IL-6 and IL-12 p40, and reduces lung injury through the reduction of oxygen radicals produced by neutrophils [3][4]. Beyond their anti-inflammatory effects during the acute phase of inflammation, corticosteroids also contributed to the resolution of inflammation, trough reprogramming effects on macrophages. Corticosteroids have been administered during two distinct phases of ARDS, during the early stage of ARDS when inflammation is expected to be most important and during late phase of ARDS, when lung fibrosis predominates. The biological and pathological characteristics of these two entities differ greatly, explaining the observed conflicting results in the effects of corticosteroids in these two distinct conditions [5].

2. Corticosteroids in Early Stage Acute Respiratory Distress Syndrome

The early phase of ARDS is characterized by major alveolar inflammation. Thus, corticosteroids, potent anti-inflammatory agents, are theoretically expected to be relevant treatment for ARDS. In practice, clinical trials found variably favorable, neutral or harmful effects of corticosteroids in ARDS.

In an ancillary analysis of a RCT focused on septic shock, Annane et al., found that 7-day treatment with low dose of steroids was significantly associated with better outcomes in septic shock associated with early septic ARDS in non-responders to short cosyntropin stimulation test [6]. In a trial of 24 ARDS patients, early corticosteroid treatment (methylprednisolone 2 mg/kg/d followed by progressive dose tapering over 32 days] was associated with a significant reduction in lung injury score (LIS) ($p < 0.003$ at 5 days) [7]. Similar findings were observed in a larger cohort (LIS 69.8% in placebo group vs. 35.7% in corticosteroids group; $p = 0.02$), with methylprednisolone 1 mg/kg/d (progressively tapered off over 28 days) [8]. In an Egyptian study, early administration of hydrocortisone in

septic ARDS was associated with improved oxygenation parameters and LIS without achieving a survival benefit on day 28 [9]. Trial of short course of high dose corticosteroids (vs. placebo] found no evidence for improved 45-day mortality in adults with ARDS (60% vs. 63% p = 0.74) [10]. More recently, Villar et al., found that in ARDS, dexamethasone (20 mg IV daily between day 1 to 5, then 10 mg daily between day 6 to 10) compared to placebo, increased the number of ventilator-free days (between-group difference 4.8 days [95% CI 2.57 to 7.03]; p < 0.0001), and reduced mortality at day 60 (between-group difference −15.3% [−25.9 to −4.9]; p = 0.0047) [11].

3. Corticosteroids in Late-Stage Acute Respiratory Distress Syndrome

Late-stage ARDS is characterized histologically by ongoing inflammation with fibroproliferation, presence of hyaline membranes, and persistent diffuse alveolar damage, leading to prolonged mechanical ventilation and a higher risk of death [12]. Meduri et al., reported in 9 ARDS patients with pulmonary fibrosis, that high dose of methylprednisolone may improve the LIS [13]. Wajanaponsan et al., found that low dose methylprednisolone administered >14 days after onset of ARDS was associated with increased mortality rates at 60 and 180 days [14]. The largest multicenter placebo-controlled trial, found no evidence for difference in 60-day mortality with corticosteroids initiated for late-stage ARDS (36% vs. 27% p = 0.26) [15].

4. Dose and Type of Corticosteroid

Not all corticosteroids exhibit the same biological properties. The dose and type of corticosteroid may yield variable effects on patients' outcomes. In a trial of 304 patients with sepsis, high doses of methylprednisolone led to numerically more patients with ARDS in corticosteroids vs. placebo (32% vs. 25% p = 0.1), fewer reversions of ARDS (31% vs. 61% p = 0.015), and a higher 14-day mortality (52% vs. 22% p = 0.04) [16]. In another ARDS trial, high doses of methylprednisolone [30 mg/kg every 6 h for 1 day] did not reduce mortality (p = 0.74) or reverse ARDS (p = 0.77) [10]. In another trial in patients with ARDS and critical illness related corticosteroids insufficiency, hydrocortisone administered 3 times a day (1 mg/kg/d) for seven days increased survival rates and reduced shock rate (5/12 vs. 10/14, p < 0.05), with no significant effect on 28-day mortality [17].

5. Adverse Events

The administration of corticosteroids may be associated with adverse events. In high-quality trials and meta-analyses in sepsis and in ARDS, indicate the main adverse events associated with corticosteroids may include neuromuscular weakness, gastrointestinal bleeding, hypernatremia and hyperglycemia [18][19]. A meta-analysis of 18 trials including 2826 ARDS patients, found no evidence for increased risk of muscular weakness: RR 0.85 95% CI [0.62 to 1.18] or gastrointestinal bleeding RR 1.20 95% CI [0.43 to 3.34], but increased risk of hyperglycemia RR 1.11 95% CI [1.01 to 1.23] (**Table 1**).

Table 1. Corticosteroids for early ARDS.

Author, Reference	Type	Sample Size	Study Population	Treatment	Results
Bernard et al. [10]	RCT, multicenter	99	ARDS as Partial pressure of oxygen ≤ 70 mm Hg on > 40% oxygen, PaO_2/PAO_2 ratio < 0.3, bilateral lung infiltrates, pulmonary artery wedge pressure ≤ 18 mm Hg	MPS 30 mg/kg IV 6 hourly for 24 h vs. placebo	PEP mortality MPS 30/50 (60%); PI 31/49 (63.2) OR 0.75 [0.4 to 1.57] $p = 0.74$
Meduri et al. [7]	RCT multicenter	24	ARDS 1994 7 days of mechanical ventilation with an LIS of 2.5 or greater and less than a 1-point reduction from day 1 of ARDS, and no evidence of untreated infection.	MPS Loading dose of 2 mg/kg; then 2 mg/kg/d from day 1 to day 14, 1 mg/kg/d from day 15 to day 21, 0.5 mg/kg/d from day 22 to day 28, 0.25 mg/kg/d on days 29 and 30, 0.125 mg/kg/d on days 31 and 32. vs. placebo	PEP Lung injury and mortality day 10 MPS 1.7 [0.1]; PI 3.0 [0.2]; $p < 0.001$ SEP: *Mortality* MPS 0/16 (0%); PI 5/8 (62%) $p = 0.002$ *Mortality in hospital* MPS 2/16 (12.5%); PI 5/8 (62.5%) OR 0.41 [0.06 to 99] $p = 0.03$
Steinberg et al., ARDSnetwork, [15]	RCT Multicenter	132/180	ARDS 1994 in early and late stage At least 7 days duration ARDS; $p/F < 200$ Intubated, mechanical ventilation	MPS Loading dose of 2 mg/kg of predicted body weight followed by 0.5 mg/kg 6 hourly for 14 days; 0.5 mg/kg 12 hourly for 7 days; and then tapering of the dose.	In early ARDS (7–13 d) PEP mortality at 60 days MPS (36%); PI (27%) $p = 0.26$
Annane et al. [6]	post Hoc RCT	129/300 177 ARDS: 129 non responders, 48 responder	ARDS 1994 bilateral infiltrate on chest radiography, PaO_2/FiO_2 < 200 mm Hg and Pulmonary occlusion pressure ≤ 18 mm Hg or no clinical evidence	HSHC 50 mg IV 6 hourly and 9-alpha fludrocortisone once a day for 7 days.	PEP: mortality at 28-day In the non-responder subgroup HSHC + FC 33/62 (53%); PI

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			of left atrial hypertension		50/67 (75%) RR = 0.71; 95% CI [0.54 to 0.94] p = 0.013 OR = 0.35; 95% CI [0.15 to 0.82], p = 0.016). In the responder group No significant result HSHC + FC 16/23 (70%); PL 12/25 (48%) RR = 1.4; 95% CI [0.89 to 2.36] p = 0.130 OR = 2.29; 95% CI [0.49 to 10.64] p = 0.290
Meduri et al. [8]	RCT multicenter	91	ARDS 1994 Intubated and Mechanical ventilation ARDS ≤ 72 H of study entry	MPS Loading dose of 1 mg/kg Then 1 mg/kg/d from day 1 to day 14, 0.5 mg/kg/d from day 15 to day 21, 0.25 mg/kg/d from day 22 to day 25, 0.125 mg/kg/d from day 26 to day 28.	PEP 1-point reduction in LIS or MPS 69.8% vs. Pl 35.7%; p = 0.002 successful extubation 7-day MPS 53.9% vs. Pl 25.0%; p = 0.01
Tongyoo et al. [20]	RCT Single center	197	Severe sepsis or septic shock receiving IMV for hypoxemic respiratory failure within 12 H of study entry + ARDS 1994 then reclassified accordingly to ARDS 2012	HSHC 50 mg every 6 h or placebo	PEP 28 day all-cause mortality HSHC (22.5%) vs. Pl (27.3%) RR 0.82 [0.50 to 1.34] p = 0.51 HR 0.80, 95% CI [0.46 to 1.41]; p = 0.44

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Villar et al., DEXA-ARDS, [11]	RCT multicenter	277/314 stopped low enrollment 88%	ARDS 2012 (but PEEP ≥ 10) Moderate to severe ARDS < 24 h (but PEEP ≥ 10)	DXM IV 20 mg once daily day 1 to 5 then 10 mg once daily day 6 to 10	PEP N° ventilator-free from day of randomization to day 28 Between-group difference 4.8 days 95% CI [2.57 to 7.03]; *p* < 0.0001).
Horby et al., RECOVERY, [21]	RCT multicenter	6425	Hospitalized patients with suspected or laboratory confirmed COVID-19	DXM 6 mg (IV or orally) during 10 days vs. usual care	PEP 28 d mortality Overall: DXM 482/2104 (22.9%); PI 1110/4321 (25.7%) (age-adjusted RR 0.83; 95% CI [0.75 to 0.93]; *p* < 0.001) >sub group mechanical ventilation (1007): 29.3% vs. 41.4%; RR 0.64; 95% CI [0.51 to 0.81]
Tomazini et al., CoDEX, [22]	RCT multicenter	299/350	COVID-19 infection suspected or confirmed, receiving IMV within 48H of meeting criteria for moderate to severe ARDS 2012	DXM 20 mg daily for 5 days followed by 10 mg daily for 5 days	PEP Ventilator-free days (alive + free from IMV) DXM 6.6 95% CI [5.0 to 8.2) vs. PI 4.0 95% CI [2.9 to 5.4] difference 4.0 95% CI [2.9 to 5.4]
Dequin et al., CAPE COVID [23]	RCT multicenter	149/290	Confirmed or suspected SARS-CoV-2 + 1 severity criteria IMV (PEEP > 5 cm H_2O), *p*/F < 300 HFOT > 50% Fi, PaO_2/FiO_2 < 300 FMOT (specified charts), PSI > 130	HSHC 200 mg daily for 4 to 7 then 100 mg daily for 2 to 4 days then 50 mg daily for 2 to 3 days total 8 days	PEP: 21-day treatment failure (death or persistent dependency on mechanical ventilation or high-flow

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					oxygen therapy HSHC 42.1% vs. pl 50.7% Difference −8.6% [95.48% CI, −24.9% to 7.7%]; *p* = 0.29)
Angus et al., REMAP CAP-[24]	RCT multicenter	384	COVID-19 suspected or confirmed, severe ICU for Respiratory failure (invasive or non-invasive IMV or HFN flow rate > 30 L/m, and FI > 40% Cardiovascular failure: vaopressor/inotrope	3 randomization arms Fixed: HSHC 50 mg every 6 h daily for 7 days Shock: HSHC 50 mg/6 h for 7 days while in shock No HSHC Or 200 mg/6 h for 7 days	PEP Composite of hospital mortality and ICU organ support-free days to day 21 Fixed 0 QR, −1 to 15; OR 1.43 95% CI [0.91 to 2.27] Shock 0 IQR, –1 to 13; OR1.22 95% CI [0.76–1.94] None 0 0 (IQR, −1 to 11)
Barros et al., MetCOVID [25]	RCT single center	246	Clinical-radiological suspicion of COVID-19 Sat ≤ 94% in room air or Requiring O_2 or IMV	MPS IV 0.5 mg/kg every 12 h × 5 days	PEP pulmonary function testing at day 120 follow-up visit. (Pulmonary function and maximal respiratory pressure testing, DASI, 6MWT) FEV1 (2.6, [0.7], *p* = 0.01) and FVC (3.2, [0.8], *p* = 0.01
Dequin et al., CAPE COD, [26]	RCT multicenter	795	Severe community-acquired pneumoniae, defined by the presence of at least one of four following criteria The initiation of MV (invasive or	HSHC continuous IV 200 mg/day during the first 4 days. On day 4, regarding medical decision	PEP mortality at day 28 HSHC 25 of 400 patients 6.2%; 95% CI, [3.9 to 8.6] vs. placebo 47 of 395 patients

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			noninvasive) with a positive end-expiratory pressure level ≥ 5 cm of water The initiation of the administration of oxygen through a HFOT with a ratio of PaO_2:FiO_2 < 300, with a FiO_2 of 50% or more; For patients wearing a non-rebreathing mask, an estimated PaO_2:FiO_2 ratio < 300, or a score of more than 130 on the Pulmonary Severity Index, which classifies patients with community-acquired pneumonia into five groups according to increasing severity, with a score of more than 130 defining group V	based on predefined criteria, following administration for a total of 8 or 14 days	11.9%; 95% CI, [8.7 to 15.1] (Absolute difference, −5.6 percentage points; 95% CI, [−9.6 to −1.7]; p = 0.006).

PEEP: positive end-expiratory pressure; SEP: secondary end point; MPS: Methylprednisolone; HSHC: hemisuccinate hydrocortisone; DXM: dexamethasone ARDS: acute respiratory distress syndrome; AHRF: acute hypoxemic respiratory failure; IMV: invasive mechanical ventilation; LIS: lung injury score; HFOT = High flow oxygen therapy; FMOT: face max oxygen therapy; PaO_2/FiO_2: partial pressure of oxygen/fraction of inspired oxygen; ARDS AEEC 1994: acute syndrome, hypoxemia $PaO_2/FiO_2 < 200$, bilateral infiltrate on chest radiography, cannot be due to cardiac failure [elevated left atrial pressure] assessed by clinical examination or a PCWP ≤ 18 cm H_2O; ARDS Berlin 2012: 7 days since onset of predisposing clinical demition, bilateral opacities on X-ray or CT scan no attributed to pleural effusion, atelectasis or nodules, respiratory failure that cannot be attributed to heart failure or volume overload; PaO_2/FiO_2 with use of ≥5 cm H_2O of PEEP ([201–300 mm Hg] as mild ARDS; [101–200 mm Hg] as moderate ARDS; <100 mm Hg as severe ARDS) and perform additional studies to rule out cardiogenic oedema (echocardiography, BNP).

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