

Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial



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Summary

Background There is no proven specific pharmacological treatment for patients with the acute respiratory distress syndrome (ARDS). The efficacy of corticosteroids in ARDS remains controversial. We aimed to assess the effects of dexamethasone in ARDS, which might change pulmonary and systemic inflammation and result in a decrease in duration of mechanical ventilation and mortality.

Methods We did a multicentre, randomised controlled trial in a network of 17 intensive care units (ICUs) in teaching hospitals across Spain in patients with established moderate-to-severe ARDS (defined by a ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen of 200 mm Hg or less assessed with a positive end-expiratory pressure of 10 cm H₂O or more and FiO₂ of 0.5 or more at 24 h after ARDS onset). Patients with brain death, terminal-stage disease, or receiving corticosteroids or immunosuppressive drugs were excluded. Eligible patients were randomly assigned based on balanced treatment assignments with a computerised randomisation allocation sequence using blocks of 10 opaque, sealed envelopes to receive immediate treatment with dexamethasone or continued routine intensive care (control group). Patients in the dexamethasone group received an intravenous dose of 20 mg once daily from day 1 to day 5, which was reduced to 10 mg once daily from day 6 to day 10. Patients in both groups were ventilated with lung-protective mechanical ventilation. Allocation concealment was maintained at all sites during the trial. Primary outcome was the number of ventilator-free days at 28 days, defined as the number of days alive and free from mechanical ventilation from day of randomisation to day 28. Secondary outcome was all-cause mortality 60 days after randomisation. All analyses were done according to the intention-to-treat principle. This study is registered with ClinicalTrials.gov, NCT01731795.

Findings Between March 28, 2013, and Dec 31, 2018, we enrolled 277 patients and randomly assigned 139 patients to the dexamethasone group and 138 to the control group. The trial was stopped by the data safety monitoring board due to low enrolment rate after enrolling more than 88% (277/314) of the planned sample size. The mean number of ventilator-free days was higher in the dexamethasone group than in the control group (between-group difference 4.8 days [95% CI 2.57 to 7.03]; $p < 0.0001$). At 60 days, 29 (21%) patients in the dexamethasone group and 50 (36%) patients in the control group had died (between-group difference -15.3% [-25.9 to -4.9]; $p = 0.0047$). The proportion of adverse events did not differ significantly between the dexamethasone group and control group. The most common adverse events were hyperglycaemia in the ICU (105 [76%] patients in the dexamethasone group *vs* 97 [70%] patients in the control group), new infections in the ICU (eg, pneumonia or sepsis; 33 [24%] *vs* 35 [25%]), and barotrauma (14 [10%] *vs* 10 [7%]).

Interpretation Early administration of dexamethasone could reduce duration of mechanical ventilation and overall mortality in patients with established moderate-to-severe ARDS.

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Introduction

Acute respiratory distress syndrome (ARDS) is an intense inflammatory process of the lungs in response to acute pulmonary and systemic insults. Clinically, this heterogeneous syndrome is characterised by acute hypoxaemic respiratory failure and bilateral pulmonary infiltrates on chest x-ray.¹ Lung-protective mechanical ventilation using a tidal volume of 4–8 mL/kg predicted bodyweight and limiting end-inspiratory plateau pressure

below 30 cm H₂O is the standard method for ventilating patients' lungs with ARDS.²

There are no proven effective, specific pharmacological therapies for ARDS based on the results of randomised clinical trials. Several drugs, including nitric oxide, heparin, active protein C, ketoconazole, ibuprofen, and antioxidants have been investigated, but none have been shown to improve patient outcome.³ There has been great interest in the role of corticosteroids to attenuate the

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Research in context

Evidence before this study

There is no proven specific pharmacological treatment for patients with the acute respiratory distress syndrome (ARDS). A meta-analysis of nine small randomised clinical trials investigating prolonged corticosteroid (methylprednisolone or hydrocortisone) treatment in early and late ARDS reported, with consistency, a significant reduction in markers of inflammation, improvement in gas exchange, reduction of duration of mechanical ventilation, and reduction in length of stay in the intensive care unit. However, the aggregate data of these randomised trials provided insufficient evidence for a mortality benefit. A large confirmatory trial was needed. We searched the PubMed and Web of Science databases for all randomised trials describing the effects of dexamethasone as adjunctive therapy for mechanically ventilated patients with the ARDS. We used the search terms “acute respiratory distress syndrome”, OR “adult respiratory distress syndrome”, OR “acute lung injury”, OR “ARDS” AND “dexamethasone” OR “randomized” OR “randomized controlled trial” OR “clinical trials” OR “trials”. We also added “humans” and “NOT infant” for a second search field. No language restrictions were applied. The last search was done

in April 23, 2019. No published trials with dexamethasone in ARDS were identified.

Added value of this study

To our knowledge, this is the first randomised clinical trial testing the efficacy of dexamethasone in patients with established ARDS. Our study shows that starting treatment with intravenous dexamethasone at 24 h of ARDS onset for a maximum of 10 days, or until mechanical ventilation and extubation (if occurring before day 10 after randomisation) is not needed, is associated with a substantial reduction in duration of mechanical ventilation and all-cause 60-day mortality in patients with established moderate-to-severe ARDS ventilated with lung-protective mechanical ventilation.

Implications of all the available evidence

Despite the substantial heterogeneity of clinical conditions associated with ARDS in our study, our findings support the notion that early therapy with dexamethasone could change the systemic immune responses and thereby could reduce the duration of mechanical ventilation and the overall mortality in patients with established moderate-to-severe ARDS.

pulmonary and systemic damage in patients with ARDS because of their potent anti-inflammatory and antifibrotic properties.⁴ Different regimens of corticosteroids have been tested in ARDS with inconclusive results.^{5–8} Recent guidelines by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine have made a conditional recommendation for glucocorticoids based on evidence of moderate quality from a meta-analysis of nine randomised controlled trials in patients with ARDS.⁹ Despite no conclusive results, it remains clinically and biologically plausible that corticosteroids might benefit patients with ARDS in the early phase of their disease process, a situation that has not been evaluated in most randomised controlled trials. Paradoxically, these hormones are given to patients with septic shock and pneumonia, both causes of ARDS.^{7,10} Of note, most randomised controlled trials testing the efficacy of corticosteroids in ARDS were done in ventilated patients using non-protective mechanical ventilation. It remains uncertain whether corticosteroids in established ARDS, when combined with lung-protective mechanical ventilation, offers a survival benefit.

Dexamethasone has never been evaluated in a randomised controlled trial in patients with ARDS, despite it having potent anti-inflammatory and weak mineralocorticoid effects compared with other corticoids.¹⁰ Dexamethasone is 20–30 times more potent than the naturally occurring hormone cortisol, and 4–5 times more potent than prednisone.⁴ Dexamethasone has pharmacological effects that are long lasting, allowing for a regimen of one dose per day.¹⁰ The benefits of the addition of dexamethasone to supportive treatment are unknown in

patients with ARDS. We postulated that early adjunctive treatment with intravenous dexamethasone in patients with established moderate-to-severe ARDS might attenuate the pulmonary and systemic inflammatory responses, and thereby might decrease both duration of mechanical ventilation and all-cause mortality.

Methods

Study design and patients

This trial was an investigator-initiated, multicentre, randomised controlled trial done in a network of 17 intensive care units (ICUs) in teaching hospitals across Spain (appendix p 4). Eligible patients were aged 18 years or older; intubated and mechanically ventilated; had acute onset of ARDS, as defined by the American-European Consensus Conference criteria for ARDS,¹¹ or by the Berlin criteria as moderate-to-severe ARDS,¹² which includes having an initiating clinical condition (eg, pneumonia, aspiration, inhalation injury, sepsis, trauma, or acute pancreatitis) within 1 week of the known clinical insult, or new or worsening respiratory symptoms; bilateral pulmonary infiltrates on chest imaging (x-ray or CT scan); absence of left atrial hypertension, pulmonary capillary wedge pressure of less than 18 mm Hg, or no clinical signs of left heart failure; and hypoxaemia, as defined by a ratio between partial pressure of oxygen in arterial blood and fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) of 200 mm Hg or less on positive end-expiratory pressure (PEEP) of 5 cm H_2O or more, regardless of FiO_2 . Exclusion criteria were pregnancy or active lactation, brain death, terminal-stage cancer or other disease, a decision to do-not-resuscitate,

treatment with corticosteroids or immunosuppressive drugs, enrollment in another experimental treatment protocol, severe chronic obstructive pulmonary disease, or congestive heart failure.

We defined onset of ARDS as the day and time in which the patient first met moderate-to-severe ARDS criteria. We used an enrichment strategy at 24 h after ARDS onset to decrease heterogeneity and to restrict enrolment to screened patients at higher risk of death, thereby allowing use of mortality as an endpoint.¹³ Prognostic enrichment strategies can preclude some concerns regarding reported low overall mortality rates.¹⁴ Recent ARDS trials restricted enrolment to patients with PaO₂/FiO₂ of less than 150 mm Hg,^{15,16} resulting in baseline mortality nearly doubling from the randomised controlled trials enrolling patients with ARDS who had a PaO₂/FiO₂ of 300 mm Hg or less. In our trial, we identified patients with established ARDS by a two-step process: we made mandatory the standardisation of measuring PaO₂/FiO₂ at 24 h after ARDS onset using a standardised ventilatory setting^{17,18} on PEEP of 10 cm H₂O or higher and FiO₂ of 0.5 or higher (appendix p 8) because the cutoff value of PaO₂/FiO₂ is an important determinant for ARDS stratification, and oxygenation improves in many patients with ARDS after meeting initial inclusion criteria; only patients with a PaO₂/FiO₂ of 200 mm Hg or less under these ventilatory settings were eligible for randomisation. Thus, we only enrolled patients considered to have established ARDS who met the Berlin criteria for moderate-to-severe ARDS under a standardised ventilatory setting.

The trial was designed in accordance with the Declaration of Helsinki.¹⁹ The trial protocol and statistical analysis plan were published previously¹⁷ and are available in the appendix p 7. The protocol for this study was approved by the referral Ethics Committee (Hospital Clínico Universitario, Valencia, Spain). We obtained ethical approval and negotiated contracts from all participating hospitals, when required, before study initiation. Immediately after we assessed patients as fulfilling the criteria for established ARDS, patient representatives provided written informed consent for inclusion of patients in the study. A data and safety monitoring board oversaw conduct of the trial, while remaining masked to the outcomes of interest and recommended to continue the trial after doing an interim analysis with data from the first 157 randomly assigned patients.

Randomisation and masking

Patients were randomly assigned to receive conventional treatment (ie, continued routine intensive care; control group) or conventional treatment plus intravenous dexamethasone. Randomisation was based on balanced treatment assignments and stratified for centres using blocks of ten opaque, prenumbered, sealed envelopes

sent to each participating ICU, according to a computer-generated random-number table. The computer-generated allocation sequence was done by a statistician who was involved in the rest of the trial. Although the leading investigator in each centre was the only person responsible for enrolling patients and had access to the randomisation envelopes, the management and treatment of randomly assigned patients were provided by 400 local staff (physicians and nurses) not involved in the study. Patients, investigators, and attending clinicians were never informed about the sequence of the code of the envelopes and the number of patients in each treatment group from those blocks. When a patient was randomly assigned, the site investigator immediately reported the envelope number and treatment group to the trial data manager for confirmation. Subsequent blocks of envelopes were sent to participating ICUs with high enrolment rates. As we restricted access to unmasked data to the database manager, we are confident that allocation concealment was maintained at all sites during the entire trial.

Although dexamethasone was not administered in a masked manner, the risk of assessment bias is very low because one of the outcomes of interest (mortality) is objective, and investigators completing the statistical analysis and long-term (60-days) outcome assessment were masked collectively to the study group (appendix p 9). According to the ethical principles for medical research of the Declaration of Helsinki,¹⁹ the use of no placebo (no intervention) is acceptable when no proven intervention exists and when the patients who receive a placebo could be subjected to additional risks (eg, intravenous catheter-associated infections and interaction with other medications). The Spanish Agency of Drugs and Medical Devices and the referral Ethics Committee did not mandate a blinded design nor the administration of a placebo.

Procedures

Patients assigned to the dexamethasone group received the first dose immediately after being randomly assigned (no later than 30 h after ARDS onset). Patients in the dexamethasone group received an intravenous dose of 20 mg once daily from day 1 to day 5, which was reduced to 10 mg once daily from day 6 to day 10. We selected these doses and time of treatment by quadrupling the dose by Meijvis and colleagues¹⁰ the first 5 days and then doubling the dose used by Meijvis and colleagues¹⁰ because patients in our trial were sicker than the patients in the Meijvis trial¹⁰ who had community-acquired pneumonia, and we used half of the dose used of that in the study of Azoulay and colleagues who enrolled patients with cancer in whom they added very high doses of dexamethasone to chemotherapy until neutropenia occurred.²⁰ Treatment with dexamethasone was maintained for a maximum of 10 days after randomisation or until extubation (if occurring before day 10). If the patient

was extubated before day 10, the last dose of dexamethasone was always administered beforehand. Because clinicians were aware of the group assignments in the trial, a patient in the control group with a non-resolving ARDS due to a corticosteroid-sensitive lung condition could receive corticosteroids.²¹

Supportive management of patients enrolled in the trial was not strictly controlled. However, in both treatment groups, physicians were repeatedly asked to follow recommendations for usual critical care management, including antibiotic therapy and haemodynamic support, aimed at maintaining optimal conditions. For ventilatory management, physicians followed recommendations for lung-protective mechanical ventilation in both treatment groups. Patients were ventilated with a tidal volume of 4–8 mL/kg predicted bodyweight, with a plateau pressure of less than 30 cm H₂O, to a respiratory rate that maintained PaCO₂ between 35 and 50 mm Hg (permissive hypercapnia was allowed to target tidal volume), and with PEEP and FiO₂ combinations according to the PEEP–FiO₂ table of the ARDSnet protocol,² ensuring that among the PEEP and FiO₂ combinations, clinicians should use the PEEP levels that allowed the reduction of FiO₂ to the lowest level for maintaining a PaO₂ of more than 60 mm Hg or an SpO₂ of more than 90%. Neuromuscular blocking drugs, sedation, prone positioning, and recruitment manoeuvres were allowed at the discretion of the attending physician. Weaning off mechanical ventilation started when the attending physician considered it clinically appropriate. In both groups, patients were assessed daily for readiness using a spontaneous breathing trial based on the ARDSnet protocol² (appendix p 9). If the patient passed the trial, a decision for extubation was taken, unless there was a specific reason not to extubate.

Data from lung mechanics (eg, tidal volume, respiratory rate, plateau pressure, and PEEP), gas-exchange (eg, FiO₂, PaO₂, PaO₂/FiO₂, PaCO₂, and pH), and haemodynamics (eg, heart rate, blood pressure, and need for vasoactive drugs) were collected on days 0, 1, 3, 6, and 10, and every 7 days, including the last day of mechanical ventilation. We recorded routine biochemistry and haematological tests; the frequency of complications, such as barotrauma, pneumonia, and sepsis; the acute physiology and chronic health evaluation II score on days 0 and 1; and the sequential organ failure assessment score²² on days 0, 1, 3, 6, and the last day of mechanical ventilation. We monitored duration of mechanical ventilation and ICU and hospital mortality. Patients were followed up for 60 days after enrolment.

Outcomes

The primary outcome was the number of ventilator-free days at 28 days after randomisation. Similarly to what has been recently recommended,¹⁴ we made the following considerations for calculating number of ventilator-free days: successful liberation from mechanical ventilation

should last more than 48 h without reintubation in patients who have survived 28 days after randomisation (extubation was counted from the last successful attempt in patients who have survived 28 days since randomisation) and for patients ventilated for 28 days or more or who died before 28 days (irrespective of intubation status), the number of ventilator-free days was recorded at zero.

The secondary outcome was death from any cause 60 days after randomisation. Site investigators were contacted regularly by the data manager for reporting patient status at day 60, irrespective of whether the patient remained in the same hospital, in another health-care facility, or discharged home. If patients were discharged alive from hospital before day 60, clinical status information at 60 days was obtained from the electronic clinical record. The Public Health Care System in Spain provides information about the clinical status of any patient through the electronic clinical record system that exists in any public hospital, city, province, or region. In the few cases in which no information was obtained from the electronic clinical record (eg, the patient was not in contact with the outpatient clinic or home-care professionals), the local investigator contacted the patient or relatives by telephone to ensure the status of the patient at day 60. Additionally, lead investigators in each site confirmed the recorded 60-day mortality at the time of data analysis (appendix p 10).

Statistical analysis

We estimated the sample size on the assumption that dexamethasone could increase the number of ventilation-free days by 2 days or more or would reduce overall 60-day mortality by 15% or more. We did a power analysis according to Schoenfeld and colleagues²³ and combined both endpoints for estimating sample size, as reported in our protocol.¹⁷ Our baseline reference was 9 days for number of ventilation-free days and 48% for 60-day mortality, based on clinical judgement and several studies.^{18,23–26} We used a Markov chain simulator model for estimating the distributions of both groups.¹⁷ For sample size calculations, we used the expected distribution, the estimated SD for the mean number of ventilation-free days, and the expected 60-day mortality for each treatment group (appendix p 11). We examined various group-size scenarios, with cohort sizes between 294 and 314 patients, to detect differences with a power of 80% and a type I error of 5%. A maximum population size of 314 patients (157 in each group) satisfied all scenarios. We analysed only patients who were enrolled and randomly assigned to receive treatment. The trial design allowed one interim analysis for efficacy and futility when 50% of the planned number of patients had been randomly assigned and followed up to day 60 after randomisation. A data and safety monitoring board reviewed the results of this interim analysis (details regarding stopping rules are provided in our protocol¹⁷ and in the appendix p 12).

We report mean and SD, median and IQR, frequency and percentages, depending on the nature and distribution of variables. We compared continuous variables with the Student's *t* test. We compared categorical variables using Fisher's exact test. Primary and secondary outcomes are reported with between-group observed differences and 95% CIs. Kaplan-Meier survival curves for each group until day 60 after randomisation were compared with a log-rank test. Frequency of adverse events and complications were compared with the χ^2 test. All analyses were done according to the intention-to-treat principle, without adjustment for multiple comparisons. Two-sided *p* values of less than 0.05 were considered to indicate statistical significance. All analyses were done using R software (version 3.5.2). This study is registered with ClinicalTrials.gov, number NCT01731795.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between March 28, 2013, to Dec 31, 2018, we enrolled 277 patients and randomly assigned 139 patients to the dexamethasone group and 138 patients to the control group (figure 1). The trial was stopped following recommendations by the data and safety monitoring board due to low enrolment numbers (appendix p 14), after enrolling more than 88% (277/314) of the planned sample size (appendix p 11). Patients were most commonly excluded at the time of ARDS diagnosis due to receiving corticosteroids or immunosuppressors and before randomisation due to improvement of PaO₂/FiO₂ above 200 mm Hg at 24 h after ARDS diagnosis (figure 1). Median enrolment across the 17 participating sites was 11 (IQR 5–23) patients. Baseline characteristics of enrolled patients at ARDS onset and at the time of randomisation did not differ between the treatment groups (table 1; appendix p 14). Main causes of ARDS were pneumonia (147 [53%] of 277 patients) and sepsis (67 [24%]). During the 10-day course of treatment with dexamethasone, the median number of days patients received treatment was 10 (IQR 6–10). No patient in either group required readmission into the ICU after being discharged from ICU within the 60-days after randomisation.

For the primary outcome, patients in the dexamethasone group had a greater mean number of ventilator-free days than did patients in the control group (mean 12.3 [SD 9.9] vs 7.5 [9.0] days; between-groups difference 4.8 days [95% CI 2.57–7.03]; *p*<0.0001; table 2). Within the 28-day period after randomisation, 19 patients (12 [8.6%] in the dexamethasone group vs seven [5.1%] in the control group) developed extubation failure and were reintubated or reconnected to

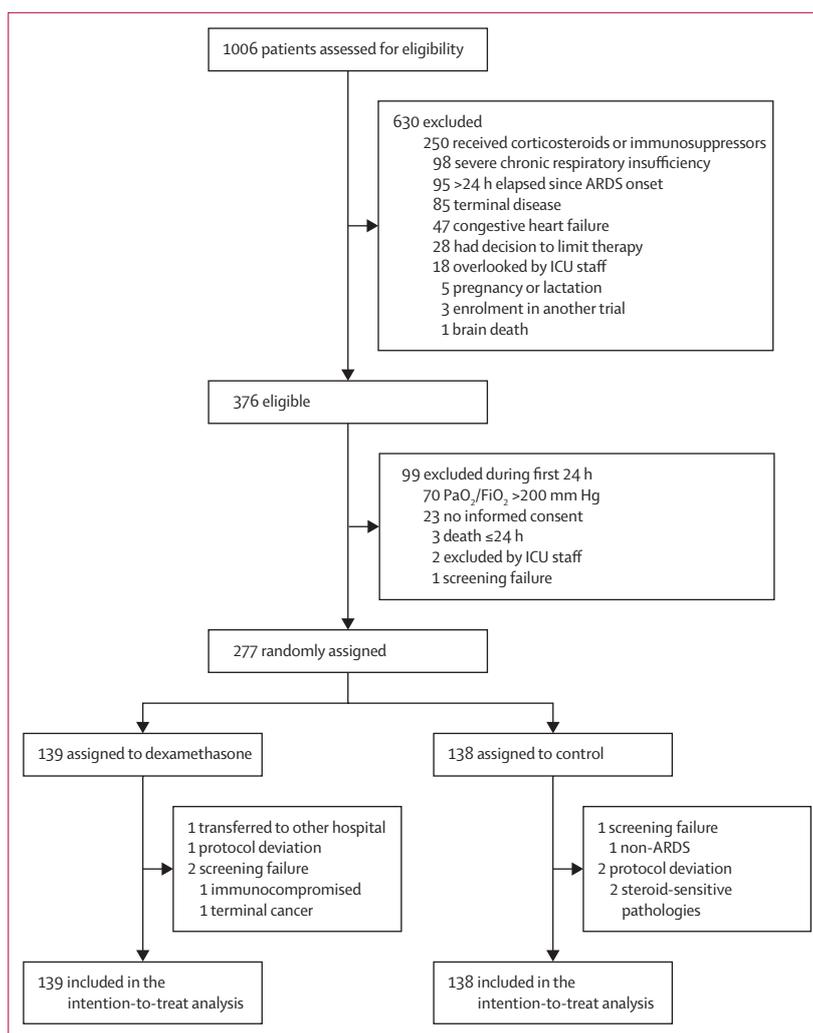


Figure 1: Trial profile

ARDS=acute respiratory distress syndrome. ICU=intensive care unit. PaO₂/FiO₂=the ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen.

mechanical ventilation (in case they had a tracheotomy). There is no evidence that weaning in the dexamethasone group was done more quickly than in the control group and therefore had no effect on the number ventilator-free days. Mean duration of mechanical ventilation (20 [SD 12] days in the control group vs 24 [9] days in the dexamethasone group) and number of deaths [three (25%) of 12 vs two (29%) of seven] were similar in both treatment groups in those 19 patients with extubation failure. We do not have any evidence from our trial that removal of dexamethasone after extubation had any influence in the clinical deterioration of patients with or without extubation failure. There were no differences in ICU mortality between patients receiving dexamethasone for 1 week or less after randomisation (ten [18%] of 55 patients) and those receiving dexamethasone up to a maximum of 10 days after randomization (16 [19%] of 84 patients).

	Dexamethasone group (n=139)	Control group (n=138)
Age, years	56 (14)	58 (15)
Sex		
Female	43 (31%)	43 (31%)
Male	96 (69%)	95 (69%)
Sequential Organ Failure Assessment score*	8.7 (3.1)	8.6 (3.2)
Time from intubation to randomisation, days	2.1 (2.6)	2.1 (2.6)
Time from ARDS diagnosis to randomisation, days	1.0 (0.1)	1.0 (0.2)
Cause of ARDS		
Pneumonia	75 (54%)	72 (52%)
Sepsis	33 (24%)	34 (25%)
Aspiration	18 (13%)	15 (11%)
Trauma	11 (8%)	10 (7%)
Others	2 (1%)	7 (5%)
Degree of lung severity, number of patients		
Moderate (100 < PaO ₂ /FiO ₂ ≤ 200)	118	121
Severe (PaO ₂ /FiO ₂ ≤ 100)	21	17
PaO ₂ /FiO ₂ , mm Hg	142.4 (37.3)	143.5 (33.4)
Tidal volume, mL per predicted bodyweight	6.9 (0.7)	6.9 (0.8)
Respiratory rate, breaths per min	23 (5)	23 (5)
FiO ₂	0.64 (0.16)	0.64 (0.15)
Positive end-expiratory pressure, cm H ₂ O	12.6 (2.7)	12.5 (2.6)
Inspiratory plateau pressure, cm H ₂ O†	26.4 (4.1)	26.1 (4.2)
PaCO ₂ , mm Hg	47.9 (10.2)	47.8 (9.3)
Arterial pH	7.34 (0.09)	7.35 (0.08)

Data are n (%), mean (SD), unless otherwise stated. ARDS=acute respiratory distress syndrome. PaO₂/FiO₂=ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen. PaCO₂=partial pressure of arterial carbon dioxide. *Ranges from 0 to 24 points, with higher scores indicating greater organ dysfunction.²² †The inspiratory plateau pressure was assessed in 138 patients in the dexamethasone group and 134 in the control group.

Table 1: Characteristics of the patients at randomisation

	Dexamethasone group (n=139)	Control group (n=138)	Between-group difference (95% CI)	p value
Ventilator-free days at 28 days	12.3 (9.9)	7.5 (9.0)	4.8 (2.57 to 7.03)	<0.0001
All-cause mortality at day 60	29 (21%)	50 (36%)	-15.3% (-25.9 to -4.9)	0.0047
ICU mortality	26 (19%)	43 (31%)	-12.5% (-22.4 to -2.3)	0.0166
Hospital mortality	33 (24%)	50 (36%)	-12.5% (-22.9 to -1.7)	0.0235
Actual duration of mechanical ventilation in ICU survivors, days	14.2 (13.2)	19.5 (13.2)	-5.3 (-8.4 to -2.2)	0.0009
Actual duration of mechanical ventilation in survivors at day 60, days	14.3 (13.3)	20.2 (14.0)	-5.9 (-9.1 to -2.7)	0.0004
Adverse events and complications*				
Hyperglycaemia in ICU	105 (76%)	97 (70%)	5.2% (-5.2 to 15.6)	0.33
New infections in ICU	33 (24%)	35 (25%)	1.6% (-8.5 to 11.7)	0.75
Barotrauma	14 (10%)	10 (7%)	2.8% (-4.0 to 9.8)	0.41

Data are n (%) or mean (SD). ICU=intensive care unit. *Data included the period from randomisation to day 10 (for hyperglycaemia) and from randomisation to ICU discharge (for new infections and barotrauma).

Table 2: Outcomes, adverse events, and complications

For the secondary outcome, at 60 days after randomisation, 29 (21%) patients allocated to the dexamethasone group and 50 (36%) patients allocated to the control

group had died (table 2; figure 2), meaning that one death in the 60-day period was avoided for every seven patients treated. Most patient deaths in both groups occurred in the ICU (table 2). Number of patients randomly assigned and number of deaths by sites are reported in appendix p 14. Of note, when grouping centres by the total number of randomly assigned patients (<10, 10–25, >25 patients), the number of total deaths at 60-days in each of those three categories was always lower in the dexamethasone group than in the control group (appendix p 15).

Actual duration of mechanical ventilation in ICU survivors was shorter in the dexamethasone group than in the control group (table 2). The distribution of patients receiving continuous infusion of neuromuscular blocking drugs or recruitment manoeuvres within the first 10 days of ARDS were similar between both groups (81 [58%] of 139 patients in the dexamethasone group vs 82 [59%] of 138 patients in the control group and 90 [65%] vs 92 [67%], respectively; appendix p 15). The use of neuromuscular blocking drugs ranged from 16 (47%) of 34 patients enrolled in 2018 to 36 (67%) of 54 patients enrolled in 2015, with no significant difference seen during this study time (p=0.16). Of note, patients in the dexamethasone group required less prone ventilation than did patients in the control group for maintaining oxygenation objectives (28 [20%] of 139 patients vs 42 [30%] of 138 patients; between-group difference 10.3% [95% CI 4–20; p=0.0492]). Also, 14 patients were treated with extracorporeal lung support for non-resolving hypoxaemia in several participating centres with expertise in extracorporeal support (five [3.6%] in the dexamethasone group and nine [6.5%] in the control group). Because extracorporeal lung support was not available in all centres, we assessed the effects of extracorporeal support on the 60-day mortality under two possible scenarios: considering all extracorporeal-assisted patients as deaths in either group, or excluding all extracorporeal-assisted patients in both groups. Both scenarios showed that dexamethasone increased survival (p=0.0087 for the first scenario and p=0.0169 for the second scenario).

Patients in the dexamethasone group had a lower sepsis-related organ failure assessment (SOFA) score as early as day 3 of initiating treatment and a higher PaO₂/FiO₂ at day 6 than did patients in the control group (table 3). The mean number of extrapulmonary organ system failures varied after randomisation for both groups and between groups. According to our protocol, the main adverse events recorded in this trial were hyperglycaemia (blood glucose >180 mg/dL) and new infections (eg, pneumonia or sepsis) after randomisation. The occurrence of hyperglycaemia within the first 10 days of randomisation was similar in both groups (table 2). Dexamethasone did not increase the type and rate of infectious complications during the ICU stay (table 2; appendix p 16).

The prevalence of pneumothorax was similarly distributed in both groups (14 [10%] of 139 patients in the dexamethasone groups vs ten [7.3%] of 138 patients in the control group; $p=0.41$; appendix p 16).

Discussion

To our knowledge, this is the first randomised trial testing the efficacy of dexamethasone in patients with ARDS and investigating prolonged corticosteroid treatment in patients with ARDS receiving lung-protective mechanical ventilation. In patients with established moderate-to-severe ARDS administered intravenous dexamethasone, we observed a reduction in the number ventilator-free days of more than 4 days and a 15% increase in the 60-day survival compared with patients in the control group.

We acknowledge that the observed treatment effect was larger than expected. However, these findings support our hypothesis that early therapy with dexamethasone could change the systemic immune responses and thereby could reduce the duration of mechanical ventilation and overall mortality. Surprisingly, the difference in the number of ventilator-free days between groups and number of patients needed to treat to prevent one death are similar to the results reported in a meta-analysis of nine randomised controlled trials of 816 patients given corticosteroids.⁹ Although we did not measure biomarkers of inflammation before and after start of treatment, as done in other studies,^{6,10} our results could have clinical and biological plausibility because the tested intervention affected both the number of ventilator-free days and overall survival in the same direction.¹⁴ In our study, the use of number of ventilator-free days as a primary outcome is more defensible because in addition to reducing mortality, dexamethasone also reduced actual duration of mechanical ventilation in survivors. This could be clinically relevant, not only for the statistical performance of ventilator-free days (ie, to the efficiency of this composite), but also for the acceptance of our trial results. In the trial by Steinberg and colleagues,⁶ methylprednisolone resulted in identical 60-day mortality (primary outcome), but more ventilator-free days at 28 days. The rate of reintubation in our trial was very low (7%). It is estimated that the rate of reintubation after extubation failure for all indications is approximately 20%.²⁷

Our findings suggest that the mechanism by which dexamethasone reduces the duration of mechanical

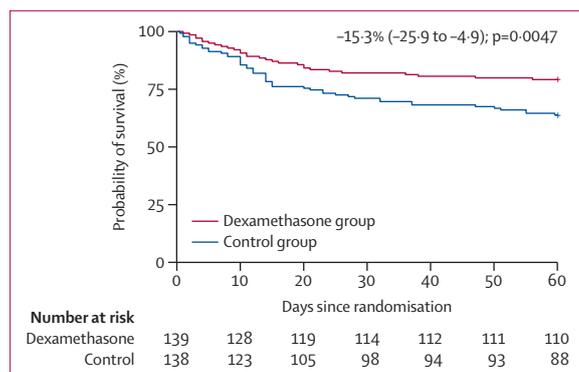


Figure 2: Kaplan-Meier survival estimates during the first 60 days of trial

	Day 0		Day 3		Day 6		Day 10	
	Control (n=138)	Dexamethasone (n=139)	Control (n=134)	Dexamethasone (n=136)	Control (n=114)	Dexamethasone (n=114)	Control (n=98)	Dexamethasone (n=70)
Sequential Organ Failure Assessment* score	8.6 (3.2)	8.7 (3.1)	8.0 (3.7)	6.6 (3.5)	6.7 (3.5)	5.2 (3.3)	Not recorded	Not recorded
Extrapulmonary organ failures	1.5 (1.0)	1.5 (1.0)	1.4 (1.1)	1.1 (1.0)	1.0 (1.1)	0.7 (0.9)	Not recorded	Not recorded
Tidal volume, mL/kg per predicted bodyweight	6.9 (0.8)	6.9 (0.7)	6.8 (1.0)	6.8 (1.3)	6.8 (1.3)	7.2 (1.5)	6.7 (1.4)	6.9 (1.3)
Respiratory rate, breaths per min	23 (5)	23 (5)	22 (5)	21 (6)	22 (5)	20 (6)	21 (6)	18 (5)
Plateau pressure, cm H ₂ O	26.1 (4.2)	26.4 (4.1)	23.7 (5.1)	22.1 (4.8)	23.7 (5.5)	20.4 (4.5)	23.3 (6.5)	20.2 (4.4)
Positive end-expiratory pressure, cm H ₂ O	12.5 (2.6)	12.6 (2.7)	12.6 (2.8)	12.0 (3.0)	11.2 (3.4)	10.7 (3.1)	10.9 (3.6)	9.4 (3.6)
FiO ₂	0.64 (0.15)	0.64 (0.16)	0.54 (0.13)	0.52 (0.13)	0.54 (0.14)	0.49 (0.15)	0.51 (0.16)	0.48 (0.13)
PaO ₂ /FiO ₂ , mm Hg	143.5 (33.4)	142.4 (37.3)	198.8 (67.9)	208.5 (70.4)	192.0 (78.6)	218.9 (85.1)	205.1 (87.0)	229.1 (80.2)
PaCO ₂ , mm Hg	47.8 (9.3)	47.9 (10.2)	46.7 (10.2)	43.5 (8.3)	46.8 (10.3)	40.6 (7.2)	46.9 (11.7)	41.0 (9.1)
pH	7.35 (0.08)	7.34 (0.09)	7.40 (0.08)	7.42 (0.06)	7.42 (0.08)	7.45 (0.06)	7.42 (0.09)	7.44 (0.07)
Glycaemia, mg/dL	156.4 (43.5)	177.6 (49.7)	158.3 (40.7)	180.6 (44.4)	157.4 (41.2)	166.6 (46.3)	148.0 (45.1)	156.2 (40.9)

Data are mean (SD). ARDS=acute respiratory distress syndrome. *Measured in six organ systems (respiratory, cardiovascular, haematological, liver, kidney, and nervous), with each organ scored from 0 to 4, resulting in an aggregated score ranging from 0 to 24, with higher scores indicating greater dysfunction.²² In some cells, the denominator differs from the stated patient population because data were not always available for the whole population.

Table 3: Data from the first 10 days after randomisation in 277 patients with established moderate-to-severe ARDS

ventilation could benefit survival. The mechanisms of action of dexamethasone are similar to other exogenous corticosteroids. In ARDS, down-regulation of pulmonary and systemic inflammation is essential to restoring homeostasis.²⁸ Prolonged glucocorticoid therapy has been associated with substantial improvement in indices of alveolar–capillary membrane permeability and mediators of inflammation and tissue repair.²⁹ In our trial, the efficiency of dexamethasone is supported by the fact that the number of ICU deaths from multiple system organ failures were half of those in the control group (12 [9%] of 139 deaths in the dexamethasone group vs 23 [17%] of 138 deaths in the control group; $p=0.0483$; appendix p 14), in line with a reduction of SOFA score in the dexamethasone group. Of note, the presence of two patients in the control group (figure 1) who received corticosteroids and survived for having a non-resolving ARDS due to a corticosteroid-sensitive lung pathology,³⁰ represents a bias against the dexamethasone group in the intention-to-treat analysis. The observed overall mortality in the control group was lower than the mortality figure used for estimating the sample size of the trial. It is plausible that the avoidance of high tidal volume and high plateau pressures and the use of moderate-to-high PEEP could explain, in part, some of the discrepancy between the expected mortality of 48% and the observed mortality of 36%.

Corticosteroids are the most broadly used medications in ARDS since its first clinical description.^{31,32} Despite the guidelines by the 2017 Corticosteroid Task Force of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine,⁹ corticosteroid therapy is not widely accepted because most trials were small and done before the implementation of lung-protective mechanical ventilation, and a large confirmatory randomised controlled trial in early ARDS was missing. However, corticosteroids are also recommended for patients with pneumonia,³³ meningitis,³⁴ and septic shock,⁹ all of which are causes of ARDS. In our trial, more than 75% of patients had ARDS associated with pneumonia or sepsis. There are substantial differences between our study and other randomised controlled trials evaluating corticosteroids in ARDS. First, trials published before 2005 tested the use of corticosteroids in patients under non-protective mechanical ventilation.⁹ Second, none of previous randomised controlled trials used the same timing, dosage, and type of corticosteroids. Our therapeutic regime is dose-equivalent to that by Meduri and colleagues⁸ with methylprednisolone in early ARDS. Third, none of previous trials evaluated the efficacy of dexamethasone in ARDS. Fourth, none of the randomised controlled trials with more than 60 patients with ARDS were associated with a significant reduction in hospital mortality.^{9,35}

The main adverse effect of corticosteroid therapy seems to be hyperglycaemia. However, with the dose and period of treatment used in this trial, the occurrence of dexamethasone-induced hyperglycaemia was similar to

the prevalence of hyperglycaemia in the acute phases of critical illness,³⁶ as observed in the control group of our trial.

This study has several strengths. First, it is the largest randomised controlled trial done to date testing the efficacy of corticosteroids in moderate-to-severe ARDS patients ventilated with lung-protective mechanical ventilation. Our trial enrolled 277 patients with established moderate-to-severe ARDS from 17 hospitals (although only 12 of those hospitals remained active) during a 70-month period. By contrast, Steinberg and colleagues⁶ enrolled 180 patients with persistent ARDS from 25 hospitals during a 76-month period. Second, because we used dexamethasone, which has a long biological half-life of 36–54 h,³⁷ the pharmacological effects can be expected from day 1 to day 12 and beyond during a 10-day treatment regimen.¹⁰ Third, patients in our trial were different from those in other trials because of the inclusion criteria we used, the etiology of ARDS, the time for enrollment, and our ventilatory management.^{5–8} None of the trials consistently reassessed patients on standardised ventilatory settings after 24 h of routine ICU treatment to ensure that only patients with established ARDS were randomised. Our assessment at 24 h was a prognostic enrichment strategy^{13,18} that allowed selection of high-risk patients for enrolment and reduced the sample size needed to examine mortality as an outcome. Failure to initiate repair of tissue damage at 24–48 h of ARDS could result in self-perpetuating inflammation with subsequent loss of organ function and a higher number of deaths.³⁸

We acknowledge several limitations of our study. First, the results cannot be generalised to all patients with ARDS. Regardless of the number of patients enrolled in a randomised controlled trial, the enrolled number represents only a small proportion of patients requiring treatment. The strict inclusion and exclusion criteria exclude the very patients whom clinicians are obligated to treat. We enrolled 27% of eligible patients and excluded patients with major pre-existing comorbidities. As part of our protocol, we excluded patients with corticosteroid-sensitive pathologies who would be expected to have a higher likelihood of benefiting from steroids. Second, we acknowledge that variability in the way in which patients were treated in participating centres could add some uncertainty to the results. However, because the patients assigned to dexamethasone also received the same protocol care as the control group, we believe that we have minimised many potential sources of bias: selection bias (there were no differences between baseline characteristics of the groups that are compared); performance bias (there were no systematic differences between groups in the reported care that was provided); detection bias (there were no systematic differences between groups in how outcomes were determined); attrition bias (there were no reported systematic differences between groups in withdrawals from the study), and

reporting bias (there were no systematic differences between reported and unreported findings). Third, although any care effect would be difficult to estimate separately from the general protocol effect, we do not think that in our trial there were changes in patient or clinician behaviour as a result of being involved in the trial. The Declaration of Helsinki demands that clinicians do their best for each individual patient in their care. Fourth, enrolment into the trial was stopped after 88% of the calculated sample size was achieved. Our data and the safety monitoring board provided advice to stop the trial (appendix p 13). The number of individuals we enrolled dropped sharply after 2017. Although there are possible reasons that could explain this low enrolment scenario (appendix p 17), none of the speculations support any intentionality in selecting patients in our trial. Although our trial did not reach the final planned size of 314 patients, we are well aware that in many circumstances randomised controlled trials of critical illnesses have been stopped early after an interim analysis showed that the results touched the beneficial boundaries, despite the trial not reaching the planned population size.^{2,26,39} Fifth, we cannot conclude whether administration of dexamethasone for a longer period of time or at a different dosage would have different effects. However, in other positive randomised controlled trials of dexamethasone to treat other illnesses, patients were given lower doses for shorter periods.^{10,34} Last, although the absence of masking could have influenced short-term assessment of dexamethasone effects, the risk of bias is low because the statistical analysis and long-term endpoint (60-days) assessment were masked collectively to study arm and to participating hospitals. There is a long history of unmasked randomised controlled trials that evaluate different drugs in several disease processes,^{40–43} including the ROSE trial in patients with moderate-to-severe ARDS.¹⁶ Paradoxically, all randomised controlled trials evaluating the effectiveness of procedural interventions in ARDS have been unmasked.^{15,44–47} Of note, the only two randomised controlled trials in ARDS reporting survival benefits were unmasked.^{2,15} Procedural interventions are delivered by physicians who need to develop technical proficiency, a process that occurs over time; therefore, insufficient experience in complex techniques is associated with a high number of severe complications.⁴⁸ By contrast, most ICU drugs (such as dexamethasone) have no such learning curves and are administered by ICU nurses and not by physicians.

In summary, our findings suggest that the early administration of dexamethasone could reduce duration of mechanical ventilation and overall mortality in patients with established moderate-to-severe ARDS.

Contributors

JV contributed to the initial study concept and design. JV, JB, and JMA obtained funding for the study. JV, CF, DM, AA, TM, JAS, GA, FA, RR, JB, EG-H, CM-R, FJD-D, JF, LC, AT, JMA, RLF, and JMG-M contributed to the final study design, participated in its coordination, and drafted the first manuscript. CF, DM, AA, TM, JAS, GA, LAC, FA, EG-H, CM-R,

FJD-D, PS-G, RR, JB, JF, LC, AT, and JMA enrolled patients into the trial and participated in the data collection, data analysis, and the final draft of the manuscript. JV, RLF, and JMG-M are responsible for data analysis. JV, RLF, and JMG-M had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

Declaration of interests

JV received grant support from Maquet. All other authors declare no competing interests.

Data sharing

All data needed to evaluate the conclusions in this Article are present and tabulated in the main text or the appendix. This article is the result of an original randomised controlled trial in patients with established moderate-to-severe ARDS. For individual de-identified raw data that underlie the results reported in this article, please contact the corresponding author.

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References

- Villar J, Slutsky AS. GOLDEN anniversary of the acute respiratory distress syndrome: still much work to do! *Curr Opin Crit Care* 2017; **23**: 4–9.
- Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; **342**: 1301–08.
- Boyle AJ, Mac Sweeney R, McAuley DF. Pharmacological treatments in ARDS; a state-of-the-art update. *BMC Med* 2013; **11**: 166.
- Rhen T, Cidlowski JA. Anti-inflammatory action of glucocorticoids—new mechanisms for old drugs. *N Engl J Med* 2005; **353**: 1711–23.
- Meduri GU, Headley AS, Golden E, et al. Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 1998; **280**: 159–65.
- Steinberg KP, Hudson LD, Goodman RB, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med* 2006; **354**: 1671–84.
- Annane D, Sébille V, Bellissant E. Effect of low doses of corticosteroids in septic shock patients with or without early acute respiratory distress syndrome. *Crit Care Med* 2006; **34**: 22–30.
- Meduri GU, Golden E, Freire AX, et al. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. *Chest* 2007; **131**: 954–63.
- Annane D, Pastores SM, Rochweg B, et al. Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Crit Care Med* 2017; **45**: 2078–88.
- Meijvis SC, Hardeman H, Remmelts HH, et al. Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: a randomised, double-blind, placebo-controlled trial. *Lancet* 2011; **377**: 2023–30.
- Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; **149**: 818–24.
- Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012; **307**: 2526–33.

- 13 US Department of Health and Human Services from the Food and Drug Administration. Enrichment strategies for clinical trials to support determination of effectiveness of human drugs and biological products. Guidance for industry. March 2019. <https://www.fda.gov/media/121320/download> (accessed May 8, 2019).
- 14 Yehya N, Harhay MO, Curley MAQ, Schoenfeld DA, Reeder RW. Re-appraisal of ventilator-free days in critical care research. *Am J Respir Crit Care Med* 2019; **200**: 828–36.
- 15 Guérin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013; **368**: 2159–68.
- 16 The National Heart, Lung, and Blood Institute PETAL Clinical Trials Network. Early neuromuscular blockade in the acute respiratory distress syndrome. *N Engl J Med* 2019; **380**: 1997–2008.
- 17 Villar J, Belda J, Añón JM, et al. Evaluating the efficacy of dexamethasone in the treatment of patients with persistent acute respiratory distress syndrome: study protocol for a randomized controlled trial. *Trials* 2016; **17**: 342.
- 18 Villar J, Pérez-Méndez L, López J, et al. An early PEEP/FIO₂ trial identifies different degrees of lung injury in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2007; **176**: 795–804.
- 19 World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013; **310**: 2191–94.
- 20 Azoulay É, Canet E, Raffoux E, et al. Dexamethasone in patients with acute lung injury from acute monocytic leukaemia. *Eur Respir J* 2012; **39**: 648–53.
- 21 Papazian L, Doddoli C, Chetaille B, et al. A contributive result of open-lung biopsy improves survival in acute respiratory distress syndrome patients. *Crit Care Med* 2007; **35**: 755–62.
- 22 Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European society of intensive care medicine. *Intensive Care Med* 1996; **22**: 707–10.
- 23 Schoenfeld DA, Bernard GR. Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. *Crit Care Med* 2002; **30**: 1772–77.
- 24 Villar J, Blanco J, Añón JM, et al. The ALIEN study: incidence and outcome of acute respiratory distress syndrome in the era of lung protective ventilation. *Intensive Care Med* 2011; **37**: 1932–41.
- 25 Brun-Buisson C, Minelli C, Bertolini G, et al. Epidemiology and outcome of acute lung injury in European intensive care units. Results from the ALIVE study. *Intensive Care Med* 2004; **30**: 51–61.
- 26 Talmor D, Sarge T, Malhotra A, et al. Mechanical ventilation guided by esophageal pressure in acute lung injury. *N Engl J Med* 2008; **359**: 2095–104.
- 27 Kacmarek RM. Noninvasive respiratory support for post-extubation respiratory failure. *Respir Care* 2019; **64**: 658–78.
- 28 Annane D, Pastores SM, Arlt W, et al. Critical illness-related corticosteroid insufficiency (CIRCI): a narrative review from a multispecialty task force of the society of critical care medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM). *Crit Care Med* 2017; **45**: 2089–98.
- 29 Meduri GU, Annane D, Chrousos GP, Marik PE, Sinclair SE. Activation and regulation of systemic inflammation in ARDS: rationale for prolonged glucocorticoid therapy. *Chest* 2009; **136**: 1631–43.
- 30 Gerard L, Bidoul T, Castanares-Zapatero D, et al. Open lung biopsy in nonresolving acute respiratory distress syndrome commonly identifies corticosteroid-sensitive pathologies, associated with better outcomes. *Crit Care Med* 2018; **46**: 907–14.
- 31 Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet* 1967; **2**: 319–23.
- 32 Ashbaugh DG, Maier RV. Idiopathic pulmonary fibrosis in adult respiratory distress syndrome. Diagnosis and treatment. *Arch Surg* 1985; **120**: 530–35.
- 33 Pastores SM, Annane D, Rochweg B. Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part II): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Intensive Care Med* 2018; **44**: 474–77.
- 34 Brouwer MC, McIntyre P, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. *Cochrane Database Syst Rev* 2013; **6**: CD004405.
- 35 Meduri GU, Siemieniuk RAC, Ness RA, Seyler SJ. Prolonged low-dose methylprednisolone treatment is highly effective in reducing duration of mechanical ventilation and mortality in patients with ARDS. *J Intensive Care* 2018; **6**: 53.
- 36 Maerz LL, Akhtar S. Perioperative glycemic management in 2011: paradigm shifts. *Curr Opin Crit Care* 2011; **17**: 370–75.
- 37 Melby JC. Clinical pharmacology of systemic corticosteroids. *Annu Rev Pharmacol Toxicol* 1977; **17**: 511–27.
- 38 Burnham EL, Janssen WJ, Riches DW, Moss M, Downey GP. The fibroproliferative response in acute respiratory distress syndrome: mechanisms and clinical significance. *Eur Respir J* 2014; **43**: 276–85.
- 39 Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; **344**: 699–709.
- 40 McKeever T, Mortimer K, Wilson A, et al. Quadrupling inhaled glucocorticoid dose to abort asthma exacerbations. *N Engl J Med* 2018; **378**: 902–10.
- 41 Zeuzem S, Dusheiko GM, Salupere R, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. *N Engl J Med* 2014; **370**: 1993–2001.
- 42 Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med* 2013; **368**: 138–48.
- 43 McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med* 2012; **366**: 1770–81.
- 44 Combes A, Hajage D, Capellier G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med* 2018; **378**: 1965–75.
- 45 Girardis M, Busani S, Damiani E, et al. Effect of conservative vs. conventional oxygen therapy on mortality among patients in an intensive care unit. The oxygen-ICU randomized clinical trial. *JAMA* 2016; **316**: 1583–89.
- 46 National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. *JAMA* 2012; **307**: 795–803.
- 47 Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med* 1999; **340**: 409–17.
- 48 Wallis CJD, Detsky AS, Fan E. Establishing the effectiveness of procedural interventions: the limited role of randomized trials. *JAMA* 2018; **320**: 2421–22.