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Pre-Admission Oral Corticosteroids are Associated with Reduced Risk of Acute Respiratory Distress Syndrome in Critically Ill Adults with Sepsis

Andrew C. McKown, MD[1], **Erin M. McGuinn, MD**[2], **Lorraine B. Ware, MD**[1,3,4], **Li Wang, MS**[5], **David R. Janz, MD, MSc**[6], **Todd W. Rice, MD, MSc**[1], and **Matthew W. Semler, MD, MSc**[1]

[1]Division of Allergy, Pulmonary, and Critical Care Medicine, Vanderbilt University School of Medicine, Nashville, TN

[2]Division of Cardiology, University of Colorado Medical Center, Denver, CO

[3]Department of Medicine, Vanderbilt University Medical Center, Nashville, TN

[4]Department of Pathology, Microbiology and Immunology, Vanderbilt University School of Medicine, Nashville, TN

[5]Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN

[6]Section of Pulmonary/Critical Care & Allergy/Immunology, Louisiana State University School of Medicine, New Orleans, LA

Abstract

Objective—To determine the association between pre-admission oral corticosteroid receipt and the development of acute respiratory distress syndrome in critically ill patients with sepsis.

Design—Retrospective observational study.

Patients—A total of 1,080 critically ill patients with sepsis in an academic tertiary care hospital.

Interventions—None.

Measurements and Main Results—The unadjusted incidence of ARDS within 96 hours of ICU admission was 35% among patients who had received oral corticosteroids compared with 42% among those who had not (p=0.107). In a multivariable analysis controlling for pre-specified confounders, pre-admission oral corticosteroids were associated with a lower incidence of ARDS in the 96 hours after ICU admission (OR 0.53, 95% CI 0.33 – 0.84, p=0.008), a finding that persisted in multiple sensitivity analyses. The median daily dose of oral corticosteroids among the 165 patients receiving oral corticosteroids, in prednisone equivalents, was 10 mg [IQR 5 – 30 mg]. Higher doses of pre-admission oral corticosteroids were associated with a lower incidence of

Corresponding Author: Andrew C. McKown, 1161 21st Ave S., T-1218 MCN, Nashville, TN 37232-2650, andrew.c.mckown@vanderbilt.edu.

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ARDS (OR for 30 mg of prednisone compared with 5 mg 0.53, 95% CI 0.32 – 0.86). In multivariable analyses, pre-admission oral corticosteroids were not associated with in-hospital mortality (OR 1.41, 95% CI 0.87 – 2.28, p=0.164), ICU length of stay (OR 0.90, 95% CI 0.63 - 1.30, p=0.585), or ventilator-free days (OR 1.06, 95% CI 0.71 – 1.57, p=0.783).

Conclusions—Among ICU patients with sepsis, pre-admission oral corticosteroids were independently associated with a lower incidence of early ARDS.

Keywords

Acute lung injury; Acute Respiratory Distress Syndrome; Sepsis; Corticosteroids

Introduction

Acute respiratory distress syndrome (ARDS) is a common and life-threatening disorder of inflammatory lung injury responsible for 10% of all intensive care unit (ICU) admissions and a mortality rate of nearly 40% (1). The protein-rich, alveolar edema that characterizes ARDS results from neutrophil- and cytokine-mediated endothelial and alveolar epithelial injury, often as a consequence of severe pneumonia or systemic inflammation from extra-pulmonary infection (2). Plasma inflammatory cytokine levels are associated with higher mortality in ARDS (after accounting for the tidal volume and severity of illness), with the highest levels of inflammatory cytokines found in sepsis-associated ARDS (3). Although the complex sequence of pathogen and host interactions leading from infection to life-threatening lung injury remains incompletely understood, the challenge of treating established ARDS has yielded a growing emphasis on its prevention among at-risk patients (4, 5).

Endogenous and exogenous corticosteroids interact with glucocorticoid receptor-α to counter pro-inflammatory effects of transcription factor NF-κB (6), making corticosteroids a potentially attractive anti-inflammatory therapy for prevention or treatment of ARDS. Since the initial description of ARDS in 1967 (7), the potential role for corticosteroids in modulating the inflammation underlying ARDS has been of intense interest. Methylprednisolone has been evaluated for ARDS treatment in a few modern trials (8–10), and a recent patient-level meta-analysis concluded that initiation of corticosteroid treatment within 72 hours of ARDS onset was associated with improved outcomes (11). The small number of prior studies that examined the relationship between pre-admission corticosteroid use (before the onset of inflammation) and subsequent ARDS development have not found a clear relationship between inhaled or oral corticosteroids and risk of ARDS (12, 13).

To address the gap in the literature surrounding pre-admission corticosteroid use and ARDS, we conducted a retrospective cohort study examining the relationship between pre-admission oral corticosteroids and development of ARDS in critically ill patients with sepsis. We hypothesized that, among critically ill adults with sepsis, pre-admission receipt of oral corticosteroids would be associated with a lower incidence of ARDS.

Materials and Methods

Patients

The study population consisted of 1080 consecutive patients enrolled in the Validating Acute Lung Injury Markers for Diagnosis (VALID) study between January 2006 and September 2013 who met the 2001 consensus definition for sepsis (14) at enrollment. As previously described (15–19), VALID is a prospective cohort study approved by the Vanderbilt institutional review board in which patients 18 years or older admitted to the medical, surgical, trauma, or cardiovascular intensive care units (ICU) at Vanderbilt University Hospital are enrolled on the morning of ICU day 2. Exclusion criteria include declination to give consent, ICU admission for greater than 48 hours, impending ICU discharge, severe chronic lung disease, uncomplicated overdose, and post-operative status or absence of mechanical ventilation among cardiovascular ICU patients. For all VALID participants, the presence or absence of sepsis is prospectively determined by a trained study nurse based on presence of suspected or documented infection plus two or more systemic inflammatory response syndrome criteria. Severe sepsis is defined as patients who meet criteria for sepsis with evidence of end-organ dysfunction.

Data Collection and Definition of Exposure

For each of the 1080 patients with sepsis at the time of study enrollment, a complete list of medications at the time of presentation to the hospital was retrospectively determined by manual review of pharmacy records, inpatient and outpatient provider notes and orders, and patient or provider communications contained within the electronic medical record. For patients whose pre-admission medication list included ongoing receipt of any oral or inhaled corticosteroid, the dose, duration, and indication were recorded. Patients without oral corticosteroids on their pre-admission medication list were not considered to have received pre-admission oral corticosteroids, even if they had been prescribed oral corticosteroids in the past or were prescribed oral corticosteroids after admission.

Endpoints

The primary outcome was the presence of acute lung injury (ALI) within 96 hours of ICU admission. The presence or absence of ALI is prospectively adjudicated for all patients in the VALID cohort by two-physician consensus review of chest radiographs and clinical data using the American-European Consensus Conference definition (20). In keeping with the newer Berlin definition of ARDS, which encompasses the AECC definition of ALI (21), we refer to the outcome as “ARDS” going forward. Secondary outcomes included in-hospital mortality, ventilator-free days (VFDs), and ICU length of stay.

Statistical Analyses

Continuous data are presented as median and interquartile range and compared using the Wilcoxon rank-sum test. Categorical data are presented as frequency and proportion and compared using Pearson's Chi-square test or Fisher's exact test, as appropriate.

The characteristics of patients who did and did not receive pre-admission oral corticosteroids were compared in univariate analysis. The relationship between receipt of pre-admission

oral corticosteroids and the primary outcome of ARDS within 96 hours of ICU admission was examined using multivariable logistic regression adjusting for the following pre-specified variables: age, gender, smoking status, diabetes mellitus, alcohol use, diagnosis of leukemia or lymphoma, history of hematopoietic stem cell transplant, history of solid organ transplant, malignant solid tumor, Acute Physiology and Chronic Health Evaluation (APACHE) II score, vasopressor receipt on the day of enrollment, pulmonary origin of sepsis, medical versus non-medical ICU, and pre-admission receipt of a T-cell inhibitor medication. A number of sensitivity analyses were also undertaken evaluating the association between pre-admission oral corticosteroids and the development of ARDS including: 1) defining the outcome of ARDS more restrictively by requiring patients to meet AECC criteria for ALI and be mechanically ventilated, 2) accounting for pre-admission inhaled corticosteroid use in the model, 3) excluding the 375 patients with malignancies, hematopoietic stem cell transplant, or solid organ transplant, 4) excluding the 45 patients with a primary risk factor of trauma, 5) limiting the outcome to patients who met ARDS criteria on two consecutive days within the 96 hours after ICU admission, 6) using a combined endpoint of death or ARDS, and 7) assessing for interaction of pre-hospital corticosteroid use and pulmonary vs. non-pulmonary site of infection. Additionally, a model was fit with death as a competing risk to development of ARDS. Secondary analyses examined the relationship between pre-admission oral corticosteroid receipt and (A) in-hospital mortality using logistic regression, (B) VFDs and ICU length of stay using proportional odds logistic regression to account for non-parametric distribution, and (C) ARDS diagnosis in logistic regression modeling steroid dose as a restricted cubic spline. In all regression analyses, age and APACHE II score were modeled as continuous variables using restricted cubic splines, and all other covariates were considered categorical. Statistical analyses were performed using IBM SPSS Statistics (version 23.0, Armonk, NY) and open source R statistical software (version 3.2.2, Vienna, Austria).

Results

Of 2966 patients in the VALID cohort, 1080 met criteria for sepsis at the time of enrollment, of whom 165 had received oral corticosteroids prior to admission (Figure 1). Baseline characteristics of patients who had received pre-admission corticosteroids are compared to those who had not in Table 1. Patients who had received pre-admission oral corticosteroids were more likely to be female (53% vs 44%, p=0.019), have a hematologic malignancy (24% vs 10%, p<0.001) or a history of hematopoietic stem cell transplant (6% vs 2%, p=0.008), have a history of solid organ transplant (33% vs 2%, p<0.001), and be receiving pre-admission T-cell inhibitors (51% vs 4%, p<0.001), inhaled corticosteroids (11% vs 5%, p=0.001), and antibacterials (48% vs 21%, p<0.001). They were less likely to have ongoing alcohol (4% vs 16%, p<0.001) or tobacco use (15% vs 35%, p<0.001), be receiving mechanical ventilation (51% vs 62% p=0.008), or be admitted to a non-medical ICU (9% vs 25%, p<0.001).

The most common indication for pre-admission oral corticosteroid use was history of solid organ transplant (33%), followed by hematologic malignancy with or without hematopoietic stem cell transplant (21%), and autoimmune disease (24%) (Table 1). The median daily dose of oral corticosteroids, in prednisone equivalents, was 10 mg [IQR 5 – 30 mg].

The incidence of ARDS within 96 hours of ICU admission was 35% among patients receiving pre-admission oral corticosteroids compared with 42% among those who were not (*p*=0.107). Before adjusting for potential confounders, ICU length of stay among patients receiving pre-admission oral corticosteroids was shorter, (median and inter-quartile range, 5 days [3-10] vs 6 days [3-11], *p*=0.047), and in-hospital mortality was higher (31% vs 22%, *p*=0.018).

In multivariable analysis controlling for pre-specified confounders, pre-admission oral corticosteroids were associated with a lower incidence of ARDS in the 96 hours after ICU admission (OR 0.53, 95% CI 0.33 – 0.84, *p*=0.008) (Table 2 and Figure 2). In multiple sensitivity analyses as detailed in the methods section, pre-admission corticosteroids were consistently significantly associated with a lower rate of ARDS with a similar point estimate for the odds ratio, including when patients with malignancy, hematopoietic stem cell transplant, or solid organ transplant were excluded from the analysis (OR 0.44, 95% CI 0.21 – 0.94, *p*=0.034) (see supplemental e-Figure 1 and supplemental e-Tables 1-5). Additionally, pre-admission corticosteroids were associated with a reduction in the composite endpoint of ARDS or death within 96 hours of ICU admission (OR 0.62, 95% CI 0.39 – 0.98, *p*=0.040), and in a model treating the development of ARDS and death as competing risks, receipt of pre-admission corticosteroids continued to be associated with a reduced risk of ARDS development (HR 0.69, 95% CI 0.52 – 0.91, *p*=0.008) (see supplemental e-Figure 1 and supplemental e-Tables 6 and 7). Pulmonary vs non-pulmonary source of sepsis did not modify the effect of pre-admission corticosteroid receipt on the development of ARDS (*p* value for the interaction =0.916). Higher doses of pre-admission oral corticosteroids were associated with a lower incidence of ARDS (odds ratio of ARDS for patients on 30 mg of prednisone to patients on 5 mg 0.53, 95% CI 0.32 – 0.86) (Figure 3 and supplemental e-Table 8). In multivariable analysis controlling for pre-specified confounders, pre-admission oral corticosteroids were not associated with incidence of in-hospital mortality (OR 1.41, 95% CI 0.87 – 2.28, *p*=0.164), ICU length of stay (OR 0.90, 95% CI 0.63 - 1.30, *p*=0.585), or ventilator free days (OR 1.06, 95% CI 0.71 – 1.57, *p*=0.783) (Figure 2 and supplemental e-Tables 9-11).

Discussion

In our study of over 1,000 septic ICU patients, pre-admission oral corticosteroids were associated with a lower incidence of ARDS. Corticosteroids were not associated with hospital mortality or other clinical outcomes. With a growing emphasis on prevention of ARDS, our study raises the question of whether modest doses of oral corticosteroids given at the onset of inflammatory insult might mitigate progression from sepsis to ARDS.

Corticosteroids for the treatment of ARDS have been advocated based on experimental and clinical randomized studies showing that exogenous corticosteroids, in comparison to placebo, significantly reduce systemic and pulmonary inflammation by increasing glucocorticoid receptor-α number and function leading to reduction in NF-κB DNA-binding and transcription of inflammatory cytokines (6). A recent patient-level meta-analysis suggested lower mortality, earlier resolution of inflammation, and earlier achievement of unassisted breathing with early corticosteroid therapy in ARDS (11). A logical extension of

this line of investigation is whether early corticosteroid administration in at risk patients might prevent ARDS.

Recent studies have shown favorable outcomes for the use of early corticosteroids in community-acquired pneumonia. A 2015 trial by Blum et al randomizing hospitalized patients with community acquired pneumonia to 50 mg of prednisone or placebo daily found corticosteroids led to earlier clinical stability, but the study population was not sufficiently ill to address the question of ARDS prevention (22). A study by Torres et al of placebo versus methylprednisolone 0.5 mg/kg every 12 hours for 5 days in patients with severe community-acquired pneumonia enrolled a sicker population and found that corticosteroids decreased radiographic progression, suggesting a potential impact on ARDS development (23). A recent trial-level meta-analysis found corticosteroid use among patients with severe pneumonia to be associated with reduced progression to ARDS, receipt of mechanical ventilation, and mortality (24). Another meta-analysis of corticosteroids for *Pneumocystis* pneumonia in HIV also showed a mortality benefit (25).

To our knowledge, the current study is only the second to examine the role of pre-admission oral corticosteroids and ARDS development. The first, a retrospective cohort study by Karnatovskaia et al, enrolled adult inpatients with a diverse set of risk factors for ARDS including sepsis, pancreatitis, trauma, or high-risk surgery, excluding patients on inhaled corticosteroids or with ARDS at the time of admission (13). They observed no difference in the in-hospital development of ARDS between patients with and without pre-admission oral corticosteroids. There are important differences between our study and the study by Karnatovskaia et al that may explain the discrepancy in findings. First, we restricted our cohort to critically ill patients with sepsis as a risk factor for ARDS, generating a more homogeneous patient group with a much higher baseline severity of illness (median APACHE II score of 27 vs 9) and higher overall rate of ARDS (41% vs 7%). Second, because we studied oral corticosteroid exposure that predated the acute illness requiring hospitalization, we included patients who met the ARDS outcome at the time of admission. Pre-admission corticosteroids might be expected to influence the risk of ARDS development early in the time course when risk for ARDS is highest (26), so an effect of corticosteroids on ARDS development might have been missed by excluding patients with ARDS at enrollment in the study by Karnatovskaia et al.

Our study also contributes to the literature by examining the association between the daily dose of pre-admission corticosteroids and likelihood of ARDS development. We observed a non-linear relationship between oral prednisone dose equivalents and ARDS risk which might be consistent with a dose-response effect at lower doses and a plateauing of effect when approaching total daily dose of 50 mg of oral prednisone equivalents (Figure 3). This raises the question whether doses of oral corticosteroids up to 50 mg daily of prednisone could provide a favorable risk-benefit profile for ARDS prevention in patients with sepsis without exposing them to the risks associated with higher doses. One might wonder whether other immune-modulating drugs would similarly reduce the risk of developing ARDS, although we did not find an association between T-cell inhibitory medications and development of ARDS in our cohort.

In addition to oral corticosteroids, inhaled formulation corticosteroids have been posited as a potential tool for ARDS prevention. Festic et al performed a retrospective cohort study out of the same population as the Karnatovskaia et al study examining the association of pre-admission ICS and ARDS development and found no association in adjusted analyses (12). In contrast, the prospective, randomized LIPS-B study of ICS combined with long-acting beta agonist therapy found a potentially large treatment benefit for ARDS, but the study was small with marked differences in baseline illness (27). In our investigation, incorporation of pre-admission ICS into the model did not influence the association of pre-admission oral corticosteroid use with developing ARDS (supplemental e-Figure 1).

Compared with a typical retrospective design, our study is strengthened by the use of a prospectively collected cohort including prospective identification of sepsis as a risk factor and two-physician adjudication of the ARDS diagnosis, both without knowledge of whether prehospital steroids had been received. In addition, we evaluated the development of ARDS from ICU admission up to ICU day four, which encompasses the time period during which at-risk patients most frequently develop ARDS (26). Our study has some limitations. Although multivariable regression may partially correct for baseline differences in risk between groups, unmeasured variables may confound the identified association, particularly given the large baseline imbalances with regard to hematopoietic malignancy and solid organ transplantation. We performed a secondary analysis excluding the patients with malignancy, solid organ transplant, or hematopoietic stem cell transplant, and the multivariate analysis remained significantly in favor of pre-admission oral corticosteroids, suggesting that the data applies to the cohort as whole rather being a consequence of including immunosuppressed patients.

Furthermore, the retrospective medication review can only identify patients known to have corticosteroids on their pre-admission medication list—compliance with medication by patients at home and duration of corticosteroid use is unknown. Although best efforts are made by clinicians to correctly identify the pre-admission medications for patients, their accuracy may be less than perfect. Attempting to mitigate this limitation, we utilized all available data including the formal pre-admission medication list in the electronic chart, the History and Physical completed by the admitting physician(s) and other documentation around the time of admission including recent clinical encounters. Some may criticize the use of the AECC definition of ARDS for the primary outcome, but the definition was current at the time of cohort creation, and patients may have ARDS in the absence of mechanical ventilation (19, 28–30). Moreover, to better conform with the Berlin criteria for ARDS, we performed a sensitivity analysis with the outcome of ARDS requiring mechanical ventilation, and the results remained unchanged (OR 0.47, 95% CI 0.22-0.75, p=0.004), (supplemental e-Figure 1 and supplemental e-Table 1).

While the potential for prevention of ARDS with corticosteroids is an important finding, it is worth noting that the development of ARDS is not itself a patient-centered outcome. Indeed, in this study we did not identify an increase in ventilator-free days, reduction in ICU length of stay, or reduction in in-hospital mortality. As previously suggested, any prospective trial for the prevention of ARDS should include meaningful patient-centered outcomes (31).

Conclusion

Among septic ICU patients, pre-admission oral corticosteroids were associated with a lower incidence of ARDS during the first four ICU days. Prospective studies of early administration of low-dose corticosteroids for the prevention of ARDS in high risk populations should be considered.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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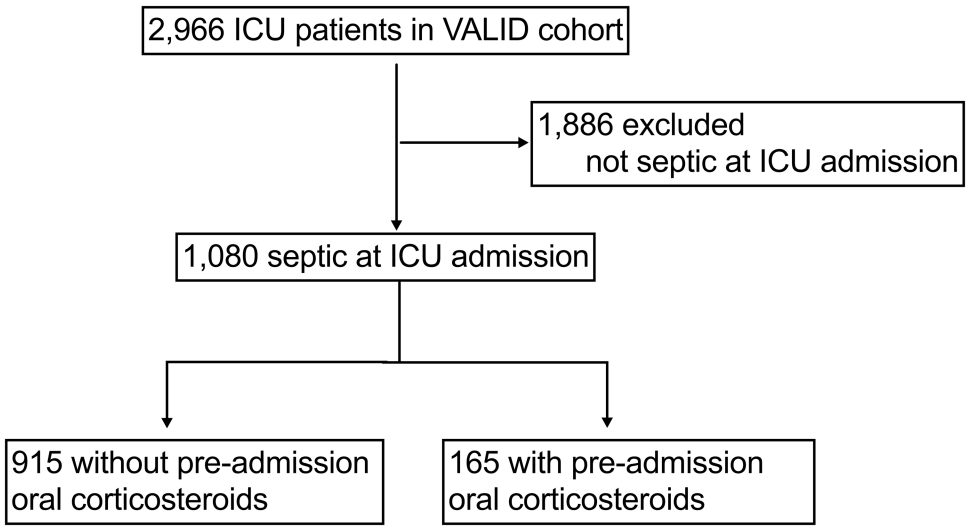

Figure 1. Enrollment, Derivation of Study Cohort, and Analysis

Of 2,966 ICU patients in the VALID cohort at the time of analysis, 1,886 were excluded for not having sepsis at ICU admission. Of the remaining 1,080 patients with sepsis, all patients were included in the analysis. 165 patients received oral corticosteroids prior to hospital admission, and 915 patients did not.

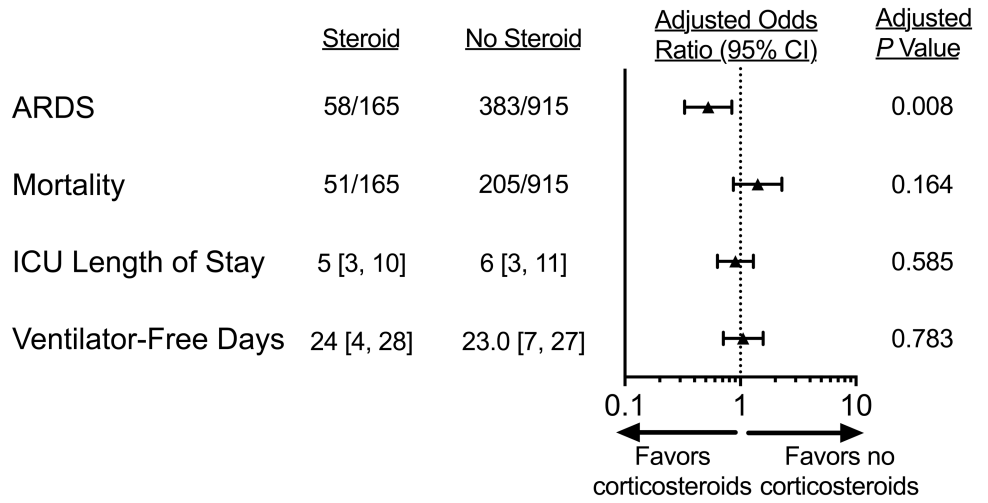

Figure 2. Outcomes by Exposure to Pre-Admission Corticosteroid Receipt

The data are presented as number of patients with the outcome of interest over the number exposed for the primary outcome of ARDS and secondary outcome of mortality. Secondary outcomes of ICU length-of-stay and Ventilator-Free Days are presented as medians [inter-quartile range]. Horizontal bars represent the 95% confidence interval of the adjusted odds ratios. The odds ratios are adjusted for age, gender, smoking status, diabetes mellitus, alcohol use, diagnosis of leukemia or lymphoma, history of hematopoietic stem cell transplant, history of solid organ transplant, malignant solid tumor, Acute Physiology and Chronic Health Evaluation (APACHE) II score, vasopressor receipt on the day of enrollment, pulmonary origin of sepsis, medical versus non-medical ICU, and pre-admission receipt of a T-cell inhibitor medication.

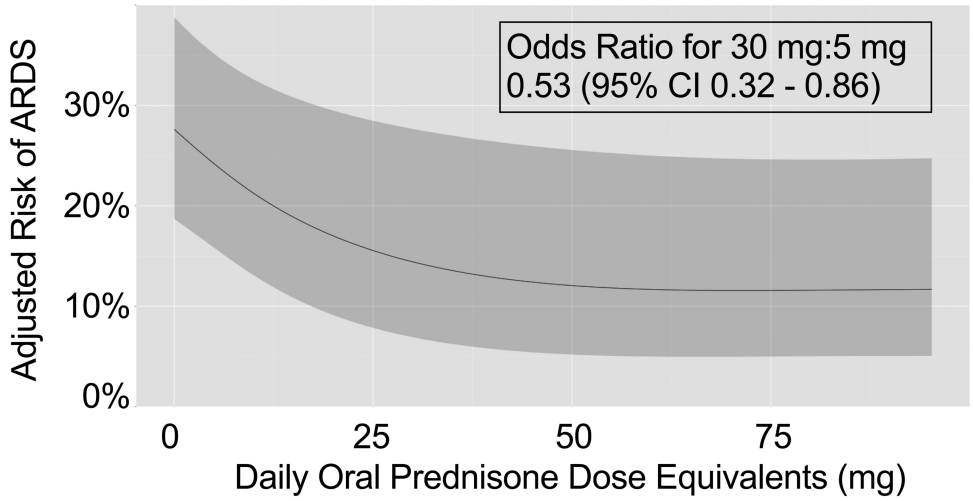

Figure 3. Adjusted Risk of Acute Respiratory Distress Syndrome by Daily Oral Prednisone Dose Equivalents

Partial effects plot of total daily oral prednisone daily dose equivalents on the risk of ARDS within the 96 hours after ICU admission in the multivariable model. Oral prednisone dose equivalents are modeled as a restricted cubic spline with three knots. The risk is adjusted for age, gender, smoking status, diabetes mellitus, alcohol use, diagnosis of leukemia or lymphoma, history of hematopoietic stem cell transplant, history of solid organ transplant, malignant solid tumor, Acute Physiology and Chronic Health Evaluation (APACHE) II score, vasopressor receipt on the day of enrollment, pulmonary origin of sepsis, medical versus non-medical ICU, and pre-admission receipt of a T-cell inhibitor medication.

Table 1
Patient Characteristics by Pre-Admission Corticosteroid Receipt

	No Steroids	Steroids	*P*
Patient Characteristics	**(n = 915)**	**(n = 165)**	
Age, years	57 [46-67]	57 [44-65]	0.173
APACHE II	27 [21-33]	29 [23-34]	0.137
Men	517 (56%)	77 (47%)	0.019
Caucasian	767 (84%)	138 (84%)	0.952
Weight, kg	78.0 [65.0-98.0]	77.0 [64.8-97.2]	0.934
Mechanical Ventilation	567 (62%)	84 (51%)	0.008
Severe Sepsis	879 (96%)	157 (95%)	0.585
Vasopressors	429 (47%)	73 (44%)	0.531
Source of Sepsis			
Pulmonary	441 (48%)	84 (51%)	0.521
Abdominal	128 (14%)	16 (10%)	0.135
Urinary, No. (%)	104 (11%)	21 (13%)	0.615
Other	448 (49%)	90 (54%)	0.187
Medical Intensive Care Unit	688 (75%)	150 (91%)	<0.001
Chronic Illnesses			
Former Smoker	260 (28%)	64 (39%)	0.010
Current Smoker	319 (35%)	25 (15%)	<0.001
Alcohol Abuse	142 (16%)	7 (4%)	<0.001
Diabetes	275 (30%)	52 (32%)	0.707
HIV or AIDS	44 (5%)	7 (4%)	0.752
Cirrhosis	76 (8%)	8 (5%)	0.127
Solid Tumor	161 (18%)	28 (17%)	0.846
Leukemia or Lymphoma	91 (10%)	40 (24%)	<0.001
Hematopoietic Stem Cell Transplant	19 (2%)	10 (6%)	0.008
Solid Organ Transplant	19 (2%)	55 (33%)	<0.001
Pre-Hospital Medications			
T-Cell Inhibitors	33 (4%)	84 (51%)	<0.001
Chemotherapy	2 (0%)	1 (1%)	0.392
Molecular Medicine	4 (0%)	6 (4%)	0.001
Inhaled Corticosteroids	42 (5%)	18 (11%)	0.001
Antibiotics	190 (21%)	79 (48%)	<0.001
Antivirals	67 (7%)	35 (21%)	<0.001
Antifungals	42 (5%)	24 (15%)	<0.001
Indication for Pre-hospital Corticosteroids			
Transplant	NA	55 (33%)	
Autoimmune Disease	NA	39 (24%)	

	No Steroids	Steroids	*P*
Patient Characteristics	**(n = 915)**	**(n = 165)**	
Hematologic Malignancy	NA	34 (21%)	
Hypothalamus-Pituitary-Gonadal Axis Disorder	NA	11 (7%)	
Solid Tumor Malignancy	NA	6 (4%)	
Other	NA	19 (12%)	

Data are presented as median [25th percentile – 75th percentile] or number (percentage). APACHE II is Acute Physiology and Chronic Health Evaluation II – ranging from 0 to 71 with higher scores indicating higher severity of illness. *P*-value is for the between-groups comparison by Wilcoxon rank-sum test for continuous data or Pearson's Chi-square test or Fisher's Exact test for categorical data, as appropriate. Source of sepsis sums to greater than 100 percent, as patients may have had more than one source of sepsis.

Table 2

Logistic Regression Model for Acute Respiratory Distress Syndrome.

Characteristic	Odds Ratio	95% Confidence Interval	*P*
Pre-Admission Oral Corticosteroids	0.526	0.329 - 0.843	0.008
Age (years)	0.513	0.349 - 0.756	0.001
APACHE II Score	1.420	0.97 - 2.079	<0.001
Female Gender	1.220	0.932 - 1.597	0.149
Current Smoker	1.102	0.813 - 1.493	0.533
Diabetes	0.938	0.697 - 1.263	0.673
Alcohol Abuse	1.378	0.928 - 2.049	0.112
Leukemia or Lymphoma	1.847	1.168 - 2.919	0.009
Hematopoietic Stem Cell Transplant	1.384	0.577 - 3.32	0.467
Solid Organ Transplant	1.043	0.508 - 2.14	0.909
Solid Tumor	1.145	0.804 - 1.632	0.453
Vasopressor	1.274	0.962 - 1.688	0.091
Pulmonary Source of Sepsis	3.665	2.776 - 4.838	<0.001
Medical ICU	0.734	0.526 - 1.024	0.069
T-cell Inhibitor Medication	1.521	0.824 - 2.808	0.180

The odds ratios presented for categorical variables are for the presence of the variable compared with itsabsence. The odds ratios for continuous variables are the 75^{th} percentile compared with the 25^{th} percentile.