CHEST®

Official publication of the American College of Chest Physicians

Activation and Regulation of Systemic Inflammation in ARDS : Rationale for Prolonged Glucocorticoid Therapy

G. Umberto Meduri, Djillali Annane, George P. Chrousos, Paul E. Marik and Scott E. Sinclair

Chest 2009;136;1631-1643; Prepublished online October 3, 2009;
DOI 10.1378/chest.08-2408

ISSN:0012-3692

CHEST Special Feature

Activation and Regulation of Systemic Inflammation in ARDS

Rationale for Prolonged Glucocorticoid Therapy

G. Umberto Meduri, MD, FCCP; Djillali Annane, MD, PhD; George P. Chrousos, MD; Paul E. Marik, MD, FCCP; and Scott E. Sinclair, MD, FCCP

Experimental and clinical evidence has demonstrated a strong cause-and-effect relationship between persistence vs reduction in systemic inflammation and progression (unresolving) vs resolution (resolving) of ARDS. In this review, the cellular mechanisms involved in activating and regulating inflammation are contrasted between patients with resolving and unresolving ARDS. At the cellular level, patients with unresolving ARDS have deficient glucocorticoid (GC)-mediated down-regulation of inflammatory cytokine and chemokine transcription despite elevated levels of circulating cortisol, a condition defined as *systemic inflammation-associated acquired GC resistance*. These patients, contrary to those with resolving ARDS, have persistent elevation in levels of both systemic and BAL fluid inflammatory cytokines and chemokines, markers of alveolar-capillary membrane permeability and fibrogenesis. At the tissue level, the continued production of inflammatory mediators leads to tissue injury, intravascular and extravascular coagulation, and the proliferation of mesenchymal cells, all resulting in maladaptive lung repair and progression of extrapulmonary organ dysfunction. In ARDS, down-regulation of systemic inflammation is essential to restoring homeostasis, decreasing morbidity, and improving survival. Prolonged low-to-moderate dose GC therapy promotes the down-regulation of inflammatory cytokine transcription at the cellular level. Eight controlled studies have consistently reported a significant reduction in markers of systemic inflammation, pulmonary and extrapulmonary organ dysfunction scores, duration of mechanical ventilation, and ICU length of stay. In the aggregate (n = 628), reduction in mortality was substantial for all patients (relative risk [RR], 0.75; 95% CI, 0.63 to 0.89; $p < 0.001$; I^2, 43%) and for those treated before day 14 (RR, 0.71; 95% CI, 0.59 to 0.85; $p < 0.001$; I^2, 40%). ***(CHEST 2009; 136:1631–1643)***

Abbreviations: ACM = alveolar-capillary membrane; ACTH = adrenocorticotropic hormone; ALI = acute lung injury; GC = glucocorticoid; GC-GRα = glucocorticoid-activated-glucocorticoid receptor α complex; GRα = glucocorticoid receptor α; HDR = host defense response; HPA = hypothalamic-pituitary-adrenal; IL = interleukin; LIS = lung injury score; MODS = multiple-organ dysfunction syndrome; NF = nuclear factor; PBL = peripheral blood leukocyte; PEEP = positive end-expiratory pressure; PGCT = prolonged glucocorticoid treatment; RR = relative risk; TNF = tumor necrosis factor

In this review, we examine the cellular mechanisms involved in activating and regulating inflammation to provide a pathophysiologic rationale for low-to-moderate dose prolonged glucocorticoid treatment (PGCT) in patients with acute lung injury (ALI) and ARDS. Current understanding places dysregulated systemic inflammation, with its persistent elevation of circulating inflammatory cytokines and chemokines over time, as the central pathogenetic process for the dysfunction and failure of vital organs, the leading cause of short-term and long-term morbidity and mortality in patients with ARDS.[1–10] Longitudinal measurements of inflammatory cytokine levels have shown that systemic and pulmonary inflammation persists for several weeks and extends well beyond the clinical resolution of respiratory failure and extubation.[1,7,9,11–15] A strong cause-and-effect relationship between persistence vs reduction in systemic inflammation and progression vs resolution of ARDS was provided by comparing longitudinal intracellular and extracellular measurements of inflammation in improvers vs nonimprovers before

and after blind randomization to PGCT vs placebo.[7,9,13–15] These findings demonstrate the following: (1) down-regulation of systemic inflammation is strongly associated with restoration of homeostasis, reduction in morbidity, and improved survival; and (2) the glucocorticoid (GC)-activated GC receptor is a major regulator of inflammation the antiinflammatory activity of which can be significantly enhanced with prolonged GC administration.

For the purpose of this review, we conducted an electronic search through Medline for the period 1966 to October 2008. The search was restricted to studies in adults and used the search terms "ARDS," "adult respiratory distress syndrome," "acute respiratory distress syndrome," "noncardiogenic pulmonary edema," "respiratory insufficiency," "respiratory failure," "acute lung injury" AND "inflammation," "cytokines," "chemokines," "nuclear factor-kB," "glucocorticoid receptor," "sepsis," and "systemic inflammatory response." The search for controlled trials investigating PGCT in ALI-ARDS was previously described.[16,17]

Systemic Inflammation and Tissue Host Defense Response

Systemic inflammation is a highly organized response to infectious and noninfectious threats to homeostasis that includes the activation of at least the following five major programs: (1) tissue host defense response (HDR),[18]; (2) acute-phase reaction; (3) sickness syndrome (including sickness behavior)[19]; (4) pain program mediated by the afferent sensory and autonomic systems; and (5) the stress program mediated by the hypothalamic-pituitary-adrenal (HPA) axis and the locus ceruleus-norepinephrine/sympathetic nervous system.[20] The main effectors of systemic inflammation are inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6; chemokines and other mediators of inflammation; the acute-phase reactants, mostly of hepatic origin, such as C-reactive protein (CRP), fibrinogen, and plasminogen activator inhibitor-1; and the effectors of the sensory afferent system, such as substance P, and of the stress system, such as hypothalamic corticotropin-releasing hormone and vasopressin, cortisol, the catecholamines norepinephrine and epinephrine, and peripheral neuronal corticotropin-releasing hormone (reviewed in Elenkov et al[20]). Excessive release of inflammatory mediators into the circulation induces tissue changes in vital organs leading to multiple-organ dysfunction syndrome (MODS).[21,22]

The HDR is a tissue-protective reaction that serves to destroy, dilute, or contain injurious agents and to repair any resulting damage. The HDR consists of an integrated network of three simultaneously activated pathways (Table 1) [inflammation, coagulation, and tissue repair], which account for the histologic and physiologic changes observed with progression or resolution of ARDS and MODS. Whereas appropriately regulated inflammation, tailored to stimulus and time,[20] is beneficial, excessive or persistent systemic inflammation incites tissue destruction and disease progression.[23] It is the lack of regulation (dysregulated systemic inflammation) of this vital response that is central to the pathogenesis of organ dysfunction in patients with sepsis and ARDS.[24,25] Improved understanding of the critical role played by the neuroendocrine response in critical illness and the cellular mechanisms that initiate, propagate, and limit inflammation[26] have provided a new understanding of the role that endogenous and exogenous GCs play in acute life-threatening systemic inflammation.

Table 1—*Components of the Tissue HDR*

Inflammation	Coagulation	Tissue Repair
Vasodilatation and stasis	Activation of coagulation	Angiogenesis
Increased expression of adhesion molecules	Inhibition of fibrinolysis	Epithelial growth
Increased permeability of the microvasculature with exudative edema	Intravascular clotting	Fibroblast migration and proliferation
Leukocyte extravasation*	Extravascular fibrin deposition	Deposition of extracellular matrix and remodeling
Release of leukocyte products potentially causing tissue damage		

*Initially, polymorph nuclear cells; later, monocytes.

Manuscript received October 6, 2008; revision accepted May 12, 2009.
Affiliations: From the Department of Medicine (Drs. Meduri and Sinclair), Division of Pulmonary, Critical Care, and Sleep Medicine, University of Tennessee Health Science Center, Memphis, TN; Memphis VA Medical Center (Drs. Meduri and Sinclair), Memphis, TN; Université de Versailles SQY (Univer-Sud Paris) [Dr. Annane], Garches, France; Athens University Medical School (Dr. Chrousos), Athens, Greece; and East Virginia Medical School (Dr. Marik), Norfolk, VA.
Correspondence to: G. Umberto Meduri, MD, FCCP, University of Tennessee Health Science Center and Memphis VA Medical Center, Division of Pulmonary, Critical Care, and Sleep Medicine, 956 Court Ave, Room E222B, Memphis, TN 38163; e-mail: umeduri@utmem.edu

DOI: 10.1378/chest.08-2408

Progression of ARDS: Resolving vs Unresolving

ARDS is a disease of multifactorial etiology that is characterized by a specific morphologic lesion termed *diffuse alveolar damage*.[27] ARDS develops rapidly, in most patients within 12 to 48 h of exposure to infectious or noninfectious insults that can affect the lung directly (via the alveolar compartment) or indirectly (via the vascular compartment).[28] At presentation, (early) ARDS manifests with severe, diffuse, and spatially inhomogeneous HDR of the pulmonary lobules, leading to a breakdown in the barrier integrity and gas exchange function of the lung. Every anatomical component of the pulmonary lobule (epithelium, endothelium, and interstitium) is involved, including the respiratory bronchioles, alveolar ducts, and alveoli, as well as arteries and veins. Diffuse injury to the alveolar-capillary membrane (ACM) causes edema of the airspaces and interstitium with a protein-rich neutrophilic exudate, resulting in severe gas exchange and lung compliance abnormalities.[29] Although the term "syndrome" was applied in its original description,[30] ARDS meets all the constitutive elements of a disease process.[31] Translational clinical research has constructed, through a holistic level of inquiry, a pathophysiologic model of ARDS that fits pathogenesis (biology) with morphologic (pathology) and clinical (physiology) findings observed during the longitudinal course of the disease.[31]

The lung injury score (LIS) quantifies the impaired respiratory physiology in ARDS patients through the use of a 4-point score that is based on the level of positive end-expiratory pressure (PEEP), the Pao_2/Fio_2 ratio, the quasistatic lung compliance, and the degree of infiltration seen on a chest radiograph (1 point per quadrant of chest radiograph involved).[32] Based on simple physiologic criteria, the evolution of ARDS can be divided into resolving and unresolving based on achieving a 1-point reduction in LIS by day 7 (Table 2). Even though, at the onset of ARDS, the two groups may appear similar, daily measurement of LIS, MODS score, and CRP levels allow early identification of nonimprovers. Patients whose LIS fails to improve in the first week of receiving mechanical ventilation (*ie*, unresolving ARDS) have significantly higher levels of inflammatory cytokines at the onset of the disease,[1,7] and persistent elevation in circulating and BAL fluid levels of inflammatory cytokines[1–8,10,11] and chemokines,[9] markers of ACM permeability[11,33,34] and fibrogenesis.[13] Systemic hypercytokinemia produces fever (systemic inflammatory response syndrome) in the absence of infections[6,35,36] and creates an environment favoring bacterial growth and the development of nosocomial infections (Fig 1).[6,37] Systemic hypercytokinemia is also involved in the pathogenesis of the morbidity that is frequently encountered in patients with sepsis and ARDS, including hyperglycemia,[38] short-term and long-term neurologic dysfunction (delirium,[39] neuromuscular weakness,[39] and posttraumatic stress disorder[40]), and sudden cardiac events in those persons with underlying atherosclerosis (Fig 1).[41]

At the tissue level, persistent production of inflammatory mediators sustains inflammation with resulting tissue injury, intravascular and extravascular coagulation (exudation) in previously spared lobules, and proliferation of mesenchymal cells (fibroproliferation) with deposition of extracellular matrix in previously affected lobules (intraalveolar, interstitial, and endovascular), resulting in maladaptive lung repair evolving ultimately into fibrosis (Fig 2).[18] In unresolving ARDS, lobules with exudation can be seen adjacent to lobules with fibroproliferation[42] and have been described in detail.[43] Persistent endothelial and epithelial injury leads to protracted vascular permeability (capillary leak) in the lung and systemically. Intravascular coagulation and fibroprolifera-

Table 2—*Progression of ARDS*

Variables	Resolving	Unresolving
Onset of ARDS		
Systemic inflammation*	Moderate	Exaggerated
HPA axis response†	Adequate	Inadequate
Over time		
Systemic inflammation	Regulated	Dysregulated
Cellular activation/regulation of inflammation‡	GRα-driven	NF-κB-driven
Inflammation, markers§	Decreasing	Persistent elevation
ACM permeability, markers	Decreasing	Persistent elevation
Fibrogenesis, markers	Decreasing	Increasing
Lung repair (histology)	Adaptive	Maladaptive
Reduction in LIS	≥ 1 point by day 7	< 1 point by day 7
ICU mortality	Low	High

*In one study, one receiver operating curve analysis revealed that at the onset of ARDS, plasma levels of IL-1β (Endogen; Boston, MA), TNF-α, IL-6, (Genzyme; Cambridge, MA), and IL-8 (R & D Systems; Minneapolis, MN) > 400 pg/mL were prognostic of death. When IL-1β levels on day 1 of ARDS were categorized as either > 400 pg/mL or < 400 pg/mL, high values of IL-1β were prognostic of death (RR, 3.75; 95% CI, 1.08 to 13.07) and independent of the presence of sepsis or shock, acute physiology and chronic health evaluation (APACHE) II score, cause of ARDS, and MODS score. For IL-1 β, nonsurvivors exhibited consistently elevated values over time, while values for survivors decreased markedly during the first week.

†Cortisol/ACTH ratio, 15.

‡Inflammation: systemic (effects of longitudinal plasma samples on normal PBLs) and pulmonary (tissue immunohistochemistry in unresolving ARDS).

§Plasma and BAL fluid.

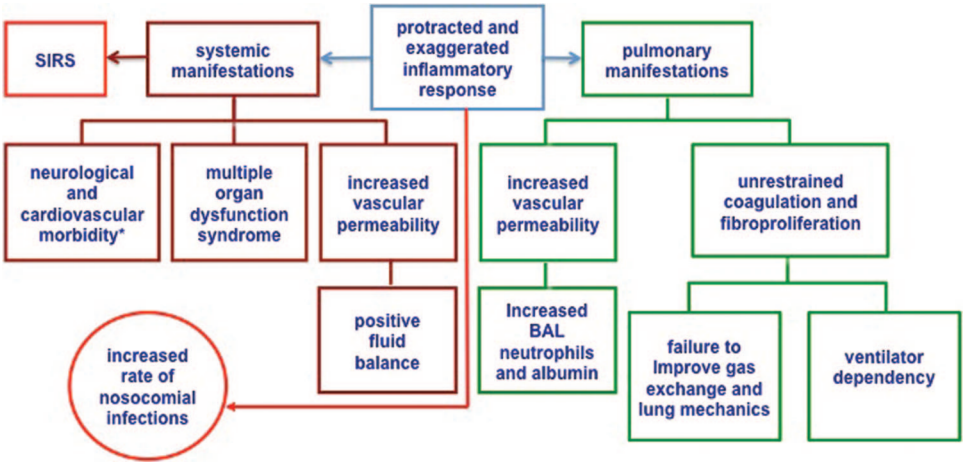

FIGURE 1. Pathophysiologic manifestations of dysregulated systemic inflammation in ARDS. Dysregulated systemic inflammation leads to changes at the pulmonary and systemic levels.[18] In the lungs, persistent elevation of inflammatory mediators sustains inflammation with resulting tissue injury, ACM permeability, intravascular and extravascular coagulation in previously spared lobules, and proliferation of mesenchymal cells with deposition of extracellular matrix in previously affected lobules, resulting in maladaptive lung repair. This manifests clinically with a failure to improve gas exchange and lung mechanics, and persistent BAL fluid neutrophilia. Systemic manifestations include (1) systemic inflammatory response syndrome in the absence of infection, (2) progression of MODS, (3) positive fluid balance, and (4) increased rate of nosocomial infections. Additional morbidity attributed to elevated cytokinemia includes hyperglycemia,[38] short-term and long-term neurologic dysfunction (delirium,[39] neuromuscular weakness,[39] and posttraumatic stress disorder[40]), and sudden cardiac events in those with underlying atherosclerosis.[41]

tion decrease the available pulmonary vascular bed, while intraalveolar fibrin deposition promotes cell-matrix organization by fibroproliferation.[44] Figure 1 displays the pathophysiologic manifestations of dysregulated systemic inflammation in ARDS. Predictors of poor outcome in ARDS, as reported in the literature, are clinical expressions of persistent and exaggerated (dysregulated) systemic inflammation.[18]

Cellular Regulation of Inflammation: Interaction Between Activated Nuclear Factor-κB and GC Receptor α

The body needs mechanisms to keep acute inflammation in check,[25] and the GC-activated GC receptor α (GRα) complex (GC-GRα) is the most important physiologic inhibitor of inflammation,[26] affecting thousands of genes involved in stress-related homeostasis with more transactivation than transrepression.[45,46] It is now appreciated that the ubiquitously present cytoplasmic transcription factors nuclear factor (NF)-κB, activated by inflammatory signals, and GRα, activated by endogenous or exogenous GCs, have diametrically opposed functions that counteract each other in regulating the transcription of inflammatory genes.[47,48] NF-κB is recognized as the principal driver of the inflammatory response and is responsible for the transcription of > 100 genes, including TNF-α, IL-1β, and IL-6.[49] NF-κB activation is central to the pathogenesis of sepsis, lung inflammation, and ALI.[50,51] At the molecular level, GCs also have very rapid (within minutes) nongenomic effects via interaction with membrane sites or the release of chaperone proteins from the GC receptor. These effects include mainly a modulation of cellular responses with decreases in cell adhesion and phosphotyrosine kinases, and an increase in annexin 1 externalization.[52]

The adrenal gland does not store cortisol; increased secretion occurs from increased synthesis under adrenocorticotropic hormone (ACTH) control. During systemic inflammation, peripherally generated TNF-α and IL-1β stimulate the HPA axis[53,54] to limit the inflammatory response through the synthesis of cortisol.[55] Cortisol, which is secreted into the systemic circulation, readily penetrates cell membranes and exerts its antiinflammatory effects by activating cytoplasmic GRα. Once activated, NF-κB and GRα can mutually repress each other through a protein-protein interaction that prevents their binding to and proper interaction with promoter and/or enhancer DNA and the subsequent regulation of transcriptional activity. The activation of one transcription factor in excess of the binding (inhibitory) capacity of the other shifts cellular re-

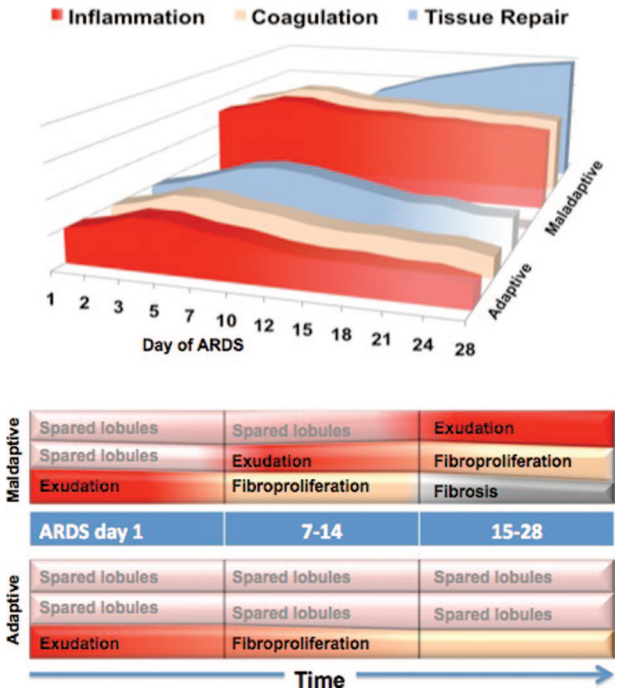

FIGURE 2. Evolution of ARDS: adaptive vs maladaptive response. *Top*: progression of the HDR in patients with adaptive and maladaptive lung repair. In the first group, the HDR is initially less severe and diminishes over time, allowing for the restoration of anatomy and function. In the second group, the HDR is initially more severe and continues unrestrained over time, leading to continuing inflammatory insults and amplification of intravascular and extravascular coagulation and fibroproliferation, resulting in maladaptive lung repair. Maladaptive lung repair manifests clinically with persistent hypoxemia, failure to improve lung mechanics, and prolonged mechanical ventilation. *Bottom*: in patients with adaptive response, with progressive reduction in NF-κB-driven TNF-α and IL-1β levels over time, previously spared lobules are not subjected to new insults, while previously affected lobules undergo an adaptive repair leading to the restoration of anatomy and function. In patients with maladaptive response who have persistent elevation in NF-κB-driven TNF-α and IL-1β levels over time, previously spared lobules are subjected to new insults, while previously affected lobules undergo a maladaptive repair (unrestrained coagulation and fibroproliferation), leading to fibrosis.

sponses toward increased (dysregulated) or decreased (regulated) transcription of inflammatory mediators over time.[15] In sepsis and ARDS, the effect of endogenous cortisol on target tissue is blunted at least partly as a result of decreased GR-mediated activity, allowing an uninhibited increase of NF-κB activation in immune cells over time and, hence, leading to an impaired down-regulation of systemic inflammation.[7,56,57]

Interaction Between Activated NF-κB and GRα in ARDS

Using an *ex vivo* model of systemic inflammation, a 2005 study[7] investigated the intracellular upstream and downstream events associated with DNA binding of NF-κB and GRα in naïve peripheral blood leukocytes (PBLs) stimulated with longitudinal plasma specimens obtained from 28 ARDS patients (with ARDS caused by sepsis in most patients). Intracellular and extracellular laboratory findings were correlated with physiologic progression (resolving vs unresolving) of ARDS in the first week of mechanical ventilation and after blind randomization to PGCT vs placebo on mean (± SD) day 9 ± 3 of ARDS (described in the next section).[7,15] The exposure of naïve cells to longitudinal plasma samples from the patients led to divergent directions in NF-κB and GRα activation that reflected the severity of systemic inflammation (defined by plasma TNF-α and IL-1β levels). The activation of one transcription factor in excess of the other shifted cellular responses toward decreased (GRα-driven) or increased (NF-κB-driven) transcription of inflammatory mediators over time.[7]

Plasma samples from patients with declining inflammatory cytokine levels (regulated systemic inflammation) over time elicited a progressive increase in all measured aspects of GC-GRα-mediated activity ($p = 0.0001$), and a corresponding reduction in NF-κB nuclear binding ($p = 0.0001$) and transcription of TNF-α and IL-1β.[7] In contrast, plasma samples from patients with sustained elevations in inflammatory cytokine levels elicited only modest longitudinal increases in GC-GRα-mediated activity ($p = 0.04$) and a progressive increase in NF-κB nuclear binding over time ($p = 0.0001$) that was most striking in nonsurvivors (dysregulated, NF-κB-driven response).[7] These findings demonstrate that insufficient GC-GRα-mediated activity is an important mechanism for the early loss of homeostatic autoregulation (*ie*, the down-regulation of NF-κB activation). The divergent directions in NF-κB and GRα activation (Fig 3, *left*) in patients with regulated vs dysregulated systemic inflammation places insufficient GC-GRα-mediated activity as an early crucial event leading to unchecked NF-κB activation.[7] Deficient GRα activity in naïve cells exposed to plasma from patients with dysregulated inflammation was observed despite elevated levels of circulating cortisol and ACTH, implicating inflammatory cytokine-driven excess NF-κB activation as an important mechanism for target organ insensitivity (resistance) to cortisol.[7] The concept of inflammation-associated intracellular GC resistance in patients with sepsis and ALI is supported by *in vitro* and animal studies.[58,59] *In vitro* studies[60–62] have shown that cytokines may induce, in a dose-dependent fashion, resistance to GCs by reducing GRα binding affinity to cortisol and/or DNA GC response elements. Because GC resistance is most frequently observed

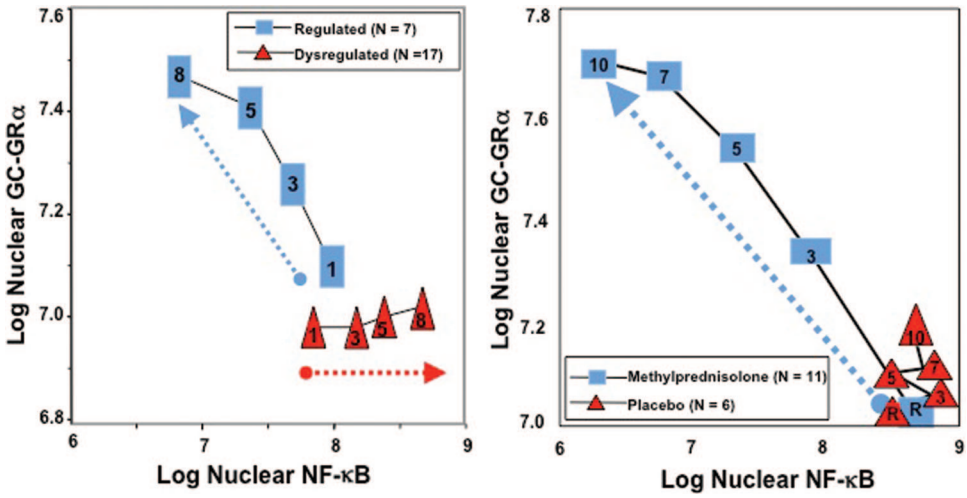

FIGURE 3. Longitudinal relation on natural logarithmic scales between mean levels of nuclear NF-κB and nuclear GRα: resolving vs unresolving ARDS (*left*) and after randomization to methylprednisolone vs placebo (*right*). The data are from Meduri and colleagues.[7,15] *Left*: plasma samples from patients with sustained elevation in cytokine levels over time (triangles) elicited only a modest longitudinal increase in GC-GRα-mediated activity ($p = 0.04$) and a progressive significant ($p = 0.0001$) increase in NF-κB nuclear binding over time (dysregulated, NF-κB-driven response). In contrast, in patients with regulated inflammation (squares), an inverse relation was observed between these two transcription factors, with the longitudinal direction of the interaction shifting to the left (decreased NF-κB) and upward (increased GC-GRα). The first interaction is defined as being driven by NF-κB (a progressive increase in NF-κB-DNA binding and transcription of TNF-α and IL-1β) and the second interaction as being driven by the GRα response (progressive increase in GRα-DNA binding, transcription of IL-10, and repression of TNF-α and IL-1β). *Right*: longitudinal relation on natural logarithmic scales between mean levels of nuclear NF-κB and nuclear GRα observed by exposing naïve PBL to plasma samples collected at randomization (R), and after 3, 5, 7, and 10 days in the methylprednisolone (squares) and placebo (triangles) groups. With methylprednisolone, contrary to placebo, the intracellular relation between the NF-κB and GRα signaling pathways changed from an initial NF-κB-driven and GR-resistant state to a GRα-driven and GR-sensitive one. It is important to compare the two figures to appreciate how methylprednisolone supplementation restored the equilibrium between the activation and suppression of inflammation that is distinctive of a regulated inflammatory response.

in patients with excessive inflammation, it remains unclear whether it is a primary phenomenon and/or whether the antiinflammatory capacity of GCs is simply overwhelmed by an excessive synthesis of proinflammatory cytokines.[63]

The above findings are in agreement with two longitudinal studies[56,57] that investigated NF-κB binding activity directly in the peripheral blood mononuclear cells of patients with sepsis or trauma (reviewed in Meduri and Yates[64]). In both studies,[56,57] nonsurvivors, contrary to survivors, had a progressive increase in NF-κB activity over time. In one longitudinal study,[57] nonsurvivors of septic shock had, by day 2 to 6, a 200% increase in NF-κB activity from day 1. Similarly, in the above-referenced study,[7] NF-κB binding activity on day 3 of ARDS clearly separated patients by outcome, providing an argument for the early initiation of PGCT. The degree of NF-κB and GRα activation also affects the histologic progression of ARDS. In immunohistochemical analysis of lung tissue, lobules with histologically severe vs mild fibroproliferation had higher mean nuclear uptake of NF-κB (13 ± 1.3 vs 7 ± 2.9, respectively; $p = 0.01$) and a lower GRα/NF-κB ratio nuclear uptake (0.5 ± 0.2 vs 1.5 ± 0.2, respectively; $p = 0.007$).[7] Thus, measurements in circulating and tissue cells have established the following: (1) that an increase in NF-κB activation over time is a significant premortem pathogenetic component of lethal sepsis and ARDS; and (2) that an increase in GC-GRα-mediated activity is required for NF-κB down-regulation.

PATHOPHYSIOLOGY OF ARDS AND THE EFFECT OF GC TREATMENT

In a randomized trial,[65] longitudinal measurements of biomarkers provided compelling evidence that prolonged methylprednisolone treatment modifies, at the cellular level, the core pathogenetic mechanism (systemic inflammation-acquired GC resistance) of ARDS, and positively affects the biology, histology, and physiology of the disease process.[64] Normal blood leukocytes exposed to plasma samples collected during GC vs placebo treatment exhibited

Table 3—*Prolonged GC Treatment in ALI-ARDS Patients*

Study/Year	Type of Study	Patients, No.	Initial Daily Dose*	Duration, d	Taper (Duration, d)
Early ALI-ARDS	3/3 RCTs	314	40–80 mg	7–21	1/3 Yes
Confalonieri et al[70]/2005	RCT	46	48 mg	7	No
Annane et al[71]/2006	RCT	177	40 mg	7	No
Meduri et al[10]/2007	RCT	91	1 mg/kg	Up to 21†	Yes (7)
Late ARDS	2/5 RCTs	314	100–250 mg	7–27	5/5 Yes
Meduri et al[65]/1998	RCT	24	2 mg/kg	Up to 21†	Yes (11)
Keel et al[67]/1998	Case control	31	100–250 mg	8	Yes (NA)
Varpula et al[68]/2000	Case control	31	120 mg	Up to 27	Yes (NA)
Huh et al[69]/2002	Case control	48	2 mg/kg	Up to 21†	Yes (11)
Steinberg et al[72]/2006	RCT	180	2 mg/kg	Up to 21†	Yes (3–4)

NA = not available; RCT = randomized controlled trial.

*Methylprednisolone equivalent.

†Treatment was continued at full dose for 14 days followed by a lower dosage for 7 days before final tapering. In two trials,[10,15] if the patient was extubated before day 14, the treatment protocol was advanced to day 15. In one trial,[23] treatment was rapidly tapered (0.5 to 1.5 days) 48 h after extubation.

rapid, progressive, significant increases in GC-GRα-mediated activities (GRα binding to NF-κB, GRα binding to GC response element on DNA, stimulation of inhibitory protein IκBα, and stimulation of IL-10 transcription), and significant reductions in NF-κB–κb-DNA binding (Fig 3, *right*) and the transcription of TNF-α and IL-1β.[15] A PGCT-induced increase in GC receptor nuclear translocation was also reported in polymorphonuclear leukocytes of patients with sepsis.[66] In ARDS patients, methylprednisolone treatment, contrary to placebo, led to a rapid and sustained reduction in mean plasma and BAL fluid levels of TNF-α, IL-1β, IL-6, IL-8, soluble intercellular adhesion molecule-1, IL-1 receptor antagonist, soluble TNF receptor 1 and 2, and procollagen amino terminal propeptide type I and III, and increases in IL-10 and anti-inflammatory-to-pro-inflammatory cytokine ratios (IL-1 receptor antagonist/IL-1β, IL-10/TNF-α, and IL-10/IL-1β ratios).[9,13–15] During PGCT, the reduction in inflammation-coagulation-fibroproliferation at the tissue level (Fig 1) was associated with a parallel improvement in the following: (1) pulmonary organ dysfunction scores[10,65,67–72] and extrapulmonary organ dysfunction scores[10,65,68–70,72]; and (2) indexes of ACM permeability.[12,72] Importantly, the extent of biological improvement in markers of systemic and pulmonary inflammation demonstrated during prolonged methylprednisolone administration is superior (qualitatively and quantitatively) to any other investigated intervention in ARDS patients.[64] Experimental evidence supporting the use of PGCT in ALI-ARDS patients has been reviewed.[73]

PGCT in ALI-ARDS: Review of the Literature

Eight controlled studies (five randomized[10,65,70–72] and three concurrent case-controlled[67–69]) have evaluated the effectiveness of PGCT in patients with early ALI-ARDS ($n = 314$)[10,70,71] and late ARDS ($n = 314$)[65,67–69,72] and were the subject of two recent metaanalyses.[16,17] Table 3 shows dosages and durations of treatment, while Table 4 shows mortality and important patient-centered outcome variables. These trials consistently reported that treatment-induced reduction in markers of systemic inflammation[10,65,67–72] was associated with significant improvement in Pao_2/Fio_2 ratios,[10,65,67–72] a significant reduction in multiple organ dysfunction score,[10,65,68–70,72] duration of mechanical ventilation,[10,65,70–72] and ICU length of stay (all $p < 0.05$).[10,65,70,72] These findings[10,65,67–72] provide additional support for a causal relationship between reductions in systemic inflammation and resolution of ARDS that is further reinforced by experimental and clinical data showing that rebound inflammation following the early removal of GC treatment leads to the recrudescence of ARDS that improves with the reinstitution of treatment.[13,67,74–78]

Four of the five randomized trials[10,65,70,72] provided Kaplan-Meier curves for the continuation of mechanical ventilation; each showed a twofold or greater rate of extubation in the first 5 to 7 days of treatment. In the ARDS Network trial,[72] the treated group had, before the discontinuation of treatment, a noteworthy reduction of 9.5 days in the mean (± SD) duration of mechanical ventilation (14.1 ± 1.7 days vs 23.6 ± 2.9 days, respectively; $p = 0.006$) and more patients discharged from the hospital to home after initial weaning from mechanical ventilation (62% vs 49%, respectively; $p = 0.006$). As shown in Figure 4, an analysis of randomized trials showed a sizable increase in the number of mechanical ventilation-free days (weighted mean difference, 6.58 days; 95% CI, 2.93 days to 10.23 days;

Table 4—*Prolonged GC Treatment in ALI-ARDS Patients*

Study/Year	Hospital Mortality* for Treatment Initiated, %		Reduction in Inflammation	Improvement in PaO_2/FIO_2 Ratio	Reduction in MV Duration	Reduction in ICU Stay	Rate of Infection†
	At Any Time	Before Day 14					
Early ALI-ARDS (≤ 3 d)	40 vs 60	40 vs 60	3 of 3	3 of 3	3 of 3	2 of 2	0.30 vs 0.39
Confalonieri et al[70]/2005‡	0.0 vs 30	0.0 vs 30	Yes	Yes	Yes	Yes	0 vs 0.17
Annane et al[71]/2006	64 vs 73	64 vs 73	Yes	Yes	Yes	NR	0.14 vs 0.13
Meduri et al[10]/2007‡	24 vs 43	24 vs 43	Yes	Yes	Yes	Yes	0.63 vs 1.43
Late ARDS (≥ 5 d)	28 vs 43	26 vs 45	5 of 5	5 of 5	2 of 3	2 of 3	0.43 vs 0.51
Meduri et al[65]/1998	12 vs 62	13 vs 57	Yes	Yes	Yes	Yes	1.50 vs 1.25
Keel et al[67]/1998	38 vs 67	NA	Yes	Yes	NR	NR	0 vs NR
Varpula et al[68]/2000	19 vs 20 (30 d)	19 vs 20 (30 d)	Yes	Yes	No	No	0.56 vs 0.33
Huh et al[69]/2002	43 vs 74	43 vs 74	Yes	Yes	NR	NR	NR
Steinberg et al[72]/2006	29 vs 29 (60 d)	27 vs 36 (60 d)	Yes	Yes	Yes	Yes	0.31 vs 0.47
Early and late ARDS	35 vs 51	35 vs 54	8 of 8	8 of 8	5 of 6	4 of 5	0.36 vs 0.44

See Table 3 for expansion of abbreviations.

*Mortality is reported as hospital mortality unless specified otherwise in parenthesis.

†Values are given as No. of infections divided by No. of patients.

‡In two positive trials,[10,70] improvement in lung function (PaO_2/FIO_2 ratio or LIS) was the primary outcome variable.

$p < 0.001$) and ICU-free days to day 28 (weighted mean difference, 7.02 days; 95% CI, 3.20 days to 10.85 days; $p < 0.001$) that was threefold greater than the one reported with low-tidal volume ventilation (12 ± 11 days vs 10 ± 11 days, respectively; $p = 0.007$)[79] or conservative strategy of fluid management (14.6 ± 0.5 days vs 12.1 ± 0.5 days, respectively; $p < 0.001$).[80] The reductions in duration of mechanical ventilation and ICU length of stay are associated with a substantial reduction in health-care expenditures.[81] Controlled trials[10,70,82,83] have also prospectively evaluated the impact of the early initiation of GC treatment on preventing progression of the temporal continuum of systemic inflammation in patients with, or at risk for, ARDS. A prospective controlled study (n = 72) found that the intraoperative IV administration of 250 mg of methylprednisolone just before pulmonary artery ligation during pneumonectomy reduces the incidence of postsurgical ARDS (0% vs 13.5%, respectively; $p < 0.05$) and duration of hospital stay (6.1 days vs 11.9 days, respectively; $p = 0.02$).[82] Early treatment with hydrocortisone in patients with severe community-acquired pneumonia prevented progression to septic shock (0% vs 43%, respectively; $p = 0.001$) and ARDS (0% vs 17%, respectively; $p = 0.11$)[70]; in patients with early ARDS, prolonged methylprednisolone treatment prevented progression to respi-

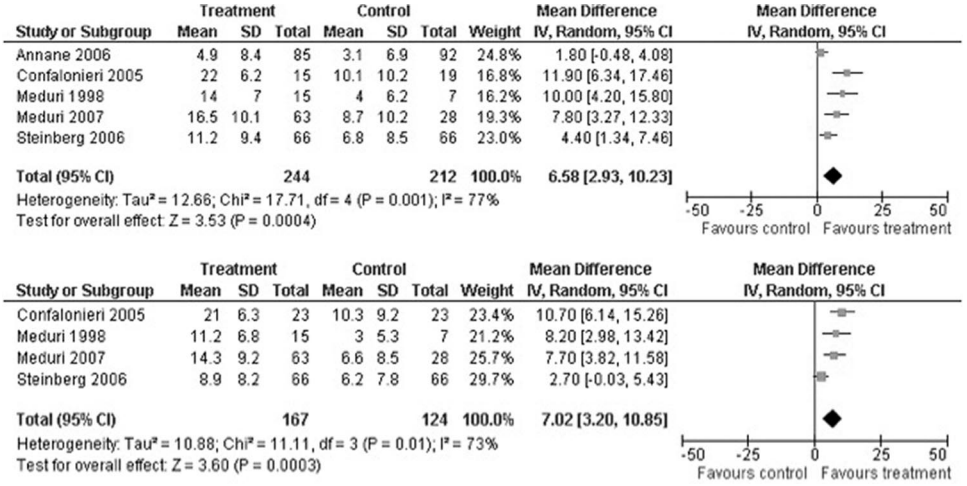

FIGURE 4. Effects of PGCT on mechanical ventilation-free days (*top*) and ICU-free days (*bottom*) to day 28.

ratory failure requiring mechanical ventilation (42% vs 100%, respectively; p = 0.02)[83] or progression to unresolving ARDS (8% vs 36%, respectively; p = 0.002).[10]

Treatment decisions involve a tradeoff between benefits and risks, as well as costs.[84] Side effects attributed to steroid treatment, such as an increased risk of infection and neuromuscular dysfunction, have partly tempered enthusiasm for their broader use in patients with sepsis and ARDS.[85] In more recent years, however, substantial evidence has accumulated[6,37,39] showing that systemic inflammation is also implicated in the pathogenesis of these complications (Fig 2), suggesting that treatment-induced down-regulation of systemic inflammation could theoretically prevent, or partly offset, their development and/or progression. As shown in Table 4, GC treatment was not associated with an increased rate of nosocomial infection. Contrary to older studies[86,87] investigating a time-limited (24 to 48 h), massive, daily dose of GCs (methylprednisolone, up to 120 mg/kg/d), the newer trials[17] have not reported an increased rate of nosocomial infections. Moreover, new cumulative evidence[37,88] indicates that, in patients with ARDS and severe sepsis, the down-regulation of life-threatening systemic inflammation with prolonged low-to-moderate-dose GC treatment improves innate immunity[89,90] and provides an environment less favorable to the intracellular and extracellular growth of bacteria.[91,92]

In the reviewed studies,[17] the incidence of neuromuscular weakness was similar in the corticosteroid-treated group and the control group (17% vs 18%, respectively). In agreement, two recent publications[93,94] found no association between PGCT and electrophysiologically or clinically proven neuromuscular dysfunction. Given that neuromuscular dysfunction is an independent predictor of prolonged weaning[95] and ARDS randomized trials have consistently reported a sizable and significant reduction in the duration of mechanical ventilation,[10,65,70–72] clinically relevant neuromuscular dysfunction caused by GC or GC-induced hyperglycemia is unlikely. The aggregate of these consistently reproducible findings shows that desirable effects (Table 4) clearly outweigh undesirable effects and provide a strong (grade 1B) level of evidence that the sustained antiinflammatory effect achieved during PGCT accelerates the resolution of ARDS, leading to earlier removal of the patient from mechanical ventilation. Importantly, the low cost of off-patent methylprednisolone (in the United States, the cost is approximately $240 for 28 days of IV therapy[10]) makes this treatment globally and equitably available. All but three controlled studies[67,68,72] showed a reduction in ICU or hospital mortality, and, in one retrospective subgroup analysis,[71] mortality benefits were limited to those with relative adrenal insufficiency. The ARDS Network trial[72] reported that treated patients had a lower mortality rate (27% vs 36%, respectively; p = 0.14) when randomized before day 14 of ARDS and an increased mortality rate when randomized after day 14 of ARDS (8% vs 35%, respectively; p = 0.01). The latter subgroup (n = 48), however, had large differences in baseline characteristics, and the mortality difference lost significance (p = 0.57) when the analysis was adjusted for these imbalances.[96]

As a result of the marked differences in study design and patient characteristics, the limited size of the studies (< 200 patients), the cumulative mortality summary of these studies should be interpreted with some caution. Nevertheless, in the aggregate (n = 628), absolute and relative reductions in mortality rate were substantial for all patients (16% and 31%, respectively) and for those treated before day 14 (19% and 35%, respectively). As shown in Figure 5, GC treatment was associated with a marked reduction in the risk of death for all patients (relative risk [RR], 0.75; 95% CI, 0.63 to 0.89; p < 0.001; I^2, 43%) and for those treated before day 14 (RR, 0.71; 95% CI, 0.59 to 0.85; p < 0.001; I^2, 40%). However,

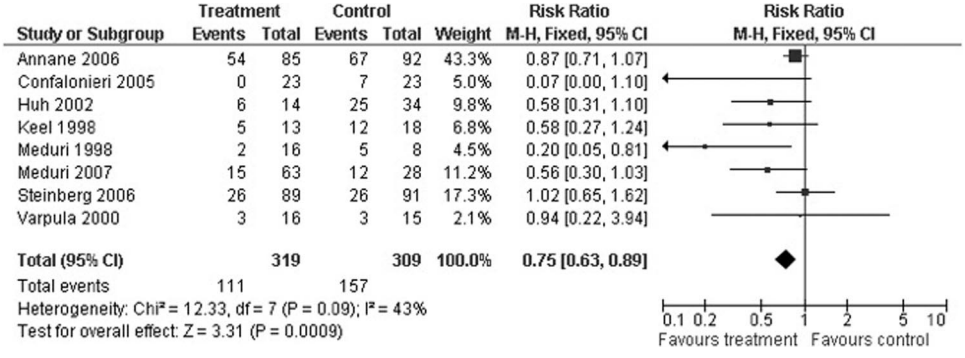

FIGURE 5. Effects of PGCT on survival of ARDS patients.

Table 5—*Methylprednisolone Treatment of Early Severe ARDS and Late Unresolving ARDS*

Time	Administration Form	Dosage
Early severe ARDS		
Loading	Bolus over 30 min	1 mg/kg
Days 1 to 14*†‡	Infusion at 10 mL/h	1 mg/kg/d
Days 15 to 21*‡	Infusion at 10 mL/h	0.5 mg/kg/d
Days 22 to 25*‡	Infusion at 10 mL/h	0.25 mg/kg/d
Days 26 to 28*‡	Infusion at 10 mL/h	0.125 mg/kg/d
Unresolving ARDS		
Loading	Bolus over 30 min	2 mg/kg
Days 1 to 14*†‡	Infusion at 10 mL/h	2 mg/kg/d
Days 15 to 21*‡	Infusion at 10 mL/h	1 mg/kg/d
Days 22 to 25*‡	Infusion at 10 mL/h	0.5 mg/kg/d
Days 26 to 28*‡	Infusion at 10 mL/h	0.25 mg/kg/d
Days 29 to 28*‡	Bolus over 30 min	0.125 mg/kg/d

The dosage is adjusted to body weight and rounded up to the nearest 10 mg (*ie*, 77 mg rounded up to 80 mg). The infusion is obtained by adding the daily dosage to 240 mL of normal saline solution. Early severe ARDS = Pao_2/Fio_2 ratio < 200 with PEEP of 10 cm H_2O; Unresolving ARDS = < 1-point reduction in LIS by day 7 of ARDS.

*Five days after the patient is able to ingest medications, methylprednisolone is administered per os in one single daily equivalent dose. Enteral absorption of methylprednisolone is compromised for days after extubation. Prednisone (available in 1-mg, 5-mg, 10-mg, and 20-mg strengths) can be used in place of methylprednisolone.

†If between days 1 and 14 the patient is extubated, the patient is advanced to day 15 of drug therapy and tapered according to schedule.

‡When patients leave the ICU, if they are still not tolerating enteral intake for at least 5 days, they should be given the dosage specified, but divided into two doses and given every 12 h IV push until they can tolerate the ingestion of medications by mouth.

there was a moderate degree of heterogeneity across the studies, namely, different timing for initiation, different doses, different duration of treatment, and different study design. Subgroup and metaregression analyses, however, showed that heterogeneity had minimal effect on treatment efficacy.[17] For this reason, a recent consensus statement[52] recommended the early initiation of PGCT in patients with severe ARDS (Pao_2/Fio_2 ratio < 200 with PEEP of 10 cm H_2O) and before day 14 for patients with unresolving ARDS (Table 5), grading the evidence for a survival benefit as weak (grade 2b).

Recommendations for Treatment and Future Research

The results of one randomized trial[10] in patients with early severe ARDS have indicated that methylprednisolone, 1 mg/kg/d, given as an infusion and tapered over 4 weeks is associated with a favorable risk-benefit profile when secondary preventive measures are implemented. For patients with unresolving ARDS, beneficial effects were shown for treatment (methylprednisolone, 2 mg/kg/d) initiated before day 14 of ARDS and continued for at least 2 weeks following extubation.[65,72] If treatment is initiated after day 14, there is no evidence of either benefit or harm.[16,96] The treatment response should be monitored with daily measurement of LIS, MODS score, and CRP level.[10,70]

We believe that secondary prevention is important to minimize serious complications associated with, or masked by, PGCT. GC treatment should be administered as a continuous infusion (while the patient is in the ICU) to minimize glycemic variations.[97,98] The following two medications should be avoided at all costs: neuromuscular blocking agents to minimize the risk of neuromuscular weakness[99]; and etomidate, which causes the suppression of cortisol synthesis.[100] GC treatment blunts the febrile response; therefore, infection surveillance is essential to identify early and to treat nosocomial infections. Secondary prevention includes surveillance bronchoscopic or nonbronchoscopic BAL fluid sampling at 5- to 7-day intervals in intubated patients (without contraindication) and a systematic diagnostic protocol[101] if the following conditions develop: (1) a change in temperature (fever or hypothermia); (2) an increase in immature neutrophil count; (3) an unexplained increase in minute ventilation (≥ 30%); (4) an unexplained increase in MODS score; (5) worsening metabolic acidosis; or (6) an unexplained increase in CRP level. Underscoring its clinical relevance, in a randomized trial,[10] infection surveillance identified 56% of nosocomial infections in patients without fever. Finally, a slow GC dosage reduction (9 to 12 days) after a complete course allows the recovery of GC receptor numbers and the HPA axis, thereby reducing the risk of rebound inflammation. Laboratory evidence of physiologic deterioration (*ie*, worsening Pao_2/Fio_2 ratio) associated with rebound inflammation (increased serum CRP concentration) after the completion of PGCT may require the reinstitution of treatment.

To conclude, we have provided considerable evidence for a cause-and-effect relationship between persistence vs reduction in systemic inflammation and progression vs resolution of ARDS. In ARDS patients, GC receptor-mediated down-regulation of systemic inflammation is essential to restore homeostasis, decrease morbidity, and improve survival, and can be significantly enhanced with prolonged low-to-moderate-dose GC treatment. The findings of controlled trials provide strong evidence (grade 1B) for improvement in patient-centered outcome (sizable reduction in duration of mechanical ventilation and ICU length of stay) and weak evidence (grade 2B) for a survival benefit. The findings reported[10] with low-dose methylprednisolone (1 mg/kg/d) in patients with early severe ARDS should

be replicated in a larger trial of patients with ALI-ARDS. The new trial should have mortality as the primary end point, avoid internal crossover, and incorporate secondary prevention measures. Similarly, the findings of a preliminary trial[70] investigating PGCT in severe CAP (the leading cause of ARDS) should be replicated in a large multicenter study. In the best interest of the public, we strongly urge governmental support for the conduct of these multicenter trials.

Acknowledgments

Financial/nonfinancial disclosures: The authors have reported to the ACCP that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Other contributions: We are grateful to Dr. David Armbruster for critical review of the manuscript.

References

1 Meduri GU, Headley S, Kohler G, et al. Persistent elevation of inflammatory cytokines predicts a poor outcome in ARDS. Plasma IL-1 β and IL-6 levels are consistent and efficient predictors of outcome over time. Chest 1995; 107:1062–1073

2 Roumen RM, Hendriks T, van der Ven-Jongekrijg J, et al. Cytokine patterns in patients after major vascular surgery, hemorrhagic shock, and severe blunt trauma. Relation with subsequent adult respiratory distress syndrome and multiple organ failure. Ann Surg 1993; 218:769–776

3 Romaschin AD, DeMajo WC, Winton T, et al. Systemic phospholipase A2 and cachectin levels in adult respiratory distress syndrome and multiple-organ failure. Clin Biochem 1992; 25:55–60

4 Groeneveld AB, Raijmakers PG, Hack CE, et al. Interleukin 8-related neutrophil elastase and the severity of the adult respiratory distress syndrome. Cytokine 1995; 7:746–752

5 Baughman RP, Gunther KL, Rashkin MC, et al. Changes in the inflammatory response of the lung during acute respiratory distress syndrome: prognostic indicators. Am J Respir Crit Care Med 1996; 154:76–81

6 Headley AS, Tolley E, Meduri GU. Infections and the inflammatory response in acute respiratory distress syndrome. Chest 1997; 111:1306–1321

7 Meduri GU, Muthiah MP, Carratu P, et al. Nuclear factor-κB- and glucocorticoid receptor α-mediated mechanisms in the regulation of systemic and pulmonary inflammation during sepsis and acute respiratory distress syndrome: evidence for inflammation-induced target tissue resistance to glucocorticoids. Neuroimmunomodulation 2005; 12:321–338

8 Parsons PE, Eisner MD, Thompson BT, et al. Lower tidal volume ventilation and plasma cytokine markers of inflammation in patients with acute lung injury. Crit Care Med 2005; 33:1–6

9 Sinclair S, Bijoy J, Golden E, et al. Interleukin-8 and soluble intercellular adhesion molecule-1 during acute respiratory distress syndrome and in response to prolonged methylprednisolone treatment. Minerva Pneumol 2006; 45:93–104

10 Meduri GU, Golden E, Freire AX, et al. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. Chest 2007; 131:954–963

11 Meduri GU, Kohler G, Headley S, et al. Inflammatory cytokines in the BAL of patients with ARDS: persistent elevation over time predicts poor outcome. Chest 1995; 108:1303–1314

12 Meduri GU, Headley S, Tolley E, et al. Plasma and BAL cytokine response to corticosteroid rescue treatment in late ARDS. Chest 1995; 108:1315–1325

13 Meduri GU, Tolley EA, Chinn A, et al. Procollagen types I and III aminoterminal propeptide levels during acute respiratory distress syndrome and in response to methylprednisolone treatment. Am J Respir Crit Care Med 1998; 158:1432–1441

14 Headley AS, Meduri GU, Tolley E, et al. Infections, SIRS, and CARS during ARDS and in response to prolonged glucocorticoid treatment [abstract]. Am J Respir Crit Care Med 2000; 161:A378

15 Meduri GU, Tolley EA, Chrousos GP, et al. Prolonged methylprednisolone treatment suppresses systemic inflammation in patients with unresolving acute respiratory distress syndrome: evidence for inadequate endogenous glucocorticoid secretion and inflammation-induced immune cell resistance to glucocorticoids. Am J Respir Crit Care Med 2002; 165:983–991

16 Meduri GU, Marik PE, Chrousos GP, et al. Steroid treatment in ARDS: a critical appraisal of the ARDS network trial and the recent literature. Intensive Care Med 2008; 34:61–69

17 Tang B, Craig J, Eslick G, et al. Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: a systematic review and meta-analysis. Crit Care Med; 2009; 37:1594–1603

18 Meduri GU. The role of the host defence response in the progression and outcome of ARDS: pathophysiological correlations and response to glucocorticoid treatment. Eur Respir J 1996; 9:2650–2670

19 Dantzer R, Kelley KW. Twenty years of research on cytokine-induced sickness behavior. Brain Behav Immun 2007; 21:153–160

20 Elenkov IJ, Iezzoni DG, Daly A, et al. Cytokine dysregulation, inflammation and well-being. Neuroimmunomodulation 2005; 12:255–269

21 Imai Y, Parodo J, Kajikawa O, et al. Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome. JAMA 2003; 289:2104–2112

22 Ranieri VM, Giunta F, Suter PM, et al. Mechanical ventilation as a mediator of multisystem organ failure in acute respiratory distress syndrome. JAMA 2000; 284:43–44

23 Suffredini AF, Fantuzzi G, Badolato R, et al. New insights into the biology of the acute phase response. J Clin Immunol 1999; 19:203–214

24 Englert JA, Fink MP. The multiple organ dysfunction syndrome and late-phase mortality in sepsis. Curr Infect Dis Rep 2005; 7:335–341

25 Mizgerd JP. Acute lower respiratory tract infection. N Engl J Med 2008; 358:716–727

26 Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids: new mechanisms for old drugs. N Engl J Med 2005; 353:1711–1723

27 Katzenstein AL, Bloor CM, Leibow AA. Diffuse alveolar damage: the role of oxygen, shock, and related factors; a review. Am J Pathol 1976; 85:209–228

28 Hudson LD, Milberg JA, Anardi D, et al. Clinical risks for development of the acute respiratory distress syndrome. Am J Respir Crit Care Med 1995; 151:293–301

29 Steinberg KP, Hudson LD. Acute lung injury and acute respiratory distress syndrome: the clinical syndrome. Clin Chest Med 2000; 21:401–417, vii

30 Ashbaugh DG, Bigelow DB, Petty TL, et al. Acute respiratory distress in adults. Lancet 1967; 2:319–323
31 Cotran RS, Kumar V, Robbins SL. Cellular injury and cellular death. In: Cotran RS, Kumar V, Robbins SL, eds. Pathologic basis of disease. Philadelphia, PA: WB Saunders, 1994; 1–34
32 Murray JF, Matthay MA, Luce JM, et al. An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 1988; 138:720–723
33 Steinberg KP, Milberg JA, Martin TR, et al. Evolution of bronchoalveolar cell populations in the adult respiratory distress syndrome. Am J Respir Crit Care Med 1994; 150:113–122
34 Gunther K, Baughman RP, Rashkin M, et al. Bronchoalveolar lavage results in patients with sepsis-induced adult respiratory distress syndrome: evaluation of mortality and inflammatory response [abstract]. Am Rev Respir Dis 1993; 147:A346
35 Andrews CP, Coalson JJ, Smith JD, et al. Diagnosis of nosocomial bacterial pneumonia in acute, diffuse lung injury. Chest 1981; 80:254–258
36 Meduri GU, Belenchia JM, Estes RJ, et al. Fibroproliferative phase of ARDS: clinical findings and effects of corticosteroids. Chest 1991; 100:943–952
37 Meduri GU. Clinical review: a paradigm shift; the bidirectional effect of inflammation on bacterial growth—clinical implications for patients with acute respiratory distress syndrome. Crit Care 2002; 6:24–29
38 Raghavan M, Marik PE. Stress hyperglycemia and adrenal insufficiency in the critically ill. Semin Respir Crit Care Med 2006; 27:274–285
39 Pustavoitau A, Stevens RD. Mechanisms of neurologic failure in critical illness. Crit Care Clin 2008; 24:1–24, vii
40 von Kanel R, Hepp U, Kraemer B, et al. Evidence for low-grade systemic proinflammatory activity in patients with posttraumatic stress disorder. J Psychiatr Res 2007; 41:744–752
41 El Gamal A, Aleech Y, Umberger R, et al. Sudden cardiac arrest is a leading cause of death in patients with ASCVD admitted to the ICU with acute systemic inflammation. Chest 2008; 134:e587
42 Bachofen A, Weibel ER. Alterations of the gas exchange apparatus in adult respiratory insufficiency associated with septicemia. Am Rev Respir Dis 1977; 116:589–615
43 Meduri GU, Eltorky M, Winer-Muram HT. The fibroproliferative phase of late adult respiratory distress syndrome. Semin Respir Infect 1995; 10:154–175
44 Cordier J-F, Peyrol S, Loire R. Bronchiolitis obliterans organizing pneumonia as a model of inflammatory lung disease. In: Epler GR, ed. Diseases of the bronchioles. New York, NY: Raven Press, 1994; 313–345
45 Galon J, Franchimont D, Hiroi N, et al. Gene profiling reveals unknown enhancing and suppressive actions of glucocorticoids on immune cells. FASEB J 2002; 16:61–71
46 Ehrchen J, Steinmuller L, Barczyk K, et al. Glucocorticoids induce differentiation of a specifically activated, anti-inflammatory subtype of human monocytes. Blood 2007; 109:1265–1274
47 Mastorakos G, Bamberger C, Chrousos GP. Neuroendocrine regulation of the immune process. In: Plotnikoff NP, Faith RE, Murgo AJ, et al, eds. Cytokines: stress and immunity. Boca Raton, FL: CRC Press, 1999; 17–37
48 Barnes PJ, Adcock IM. Glucocorticoids receptors. In: Crystal RG, West JB, Weibel ER, et al, eds. The lung scientific foundations. Philadelphia, PA: Lippincott-Raven, 1997; 37–55
49 Baeuerle PA, Baltimore D. Activation of DNA-binding activity in an apparently cytoplasmic precursor of the NF-κB transcription factor. Cell 1988; 53:211–217
50 Fan J, Ye RD, Malik AB. Transcriptional mechanisms of acute lung injury. Am J Physiol Lung Cell Mol Physiol 2001; 281:L1037–L1050
51 Liu SF, Malik AB. NF-κB activation as a pathological mechanism of septic shock and inflammation. Am J Physiol Lung Cell Mol Physiol 2006; 290:L622–L645
52 Marik PE, Pastores S, Annane D, et al. Clinical practice guidelines for the diagnosis and management of corticosteroid insufficiency in critical illness: recommendations of an international task force. Crit Care Med 2008; 36:1937–1949
53 Hermus AR, Sweep CG. Cytokines and the hypothalamic-pituitary-adrenal axis. J Steroid Biochem Mol Biol 1990; 37:867–871
54 Perlstein RS, Whitnall MH, Abrams JS, et al. Synergistic roles of interleukin-6, interleukin-1, and tumor necrosis factor in the adrenocorticotropin response to bacterial lipopolysaccharide *in vivo*. Endocrinology 1993; 132:946–952
55 Munck A, Guyre PM, Holbrook NJ. Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. Endocr Rev 1984; 5:25–44
56 Bohrer H, Qiu F, Zimmermann T, et al. Role of NF κB in the mortality of sepsis. J Clin Invest 1997; 100:972–985
57 Paterson RL, Galley HF, Dhillon JK, et al. Increased nuclear factor κB activation in critically ill patients who die. Crit Care Med 2000; 28:1047–1051
58 Meduri GU. An historical review of glucocorticoid treatment in sepsis: disease pathophysiology and the design of treatment investigation. Sepsis 1999; 3:21–38
59 Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids for treating severe sepsis and septic shock. Cochrane Database Syst Rev (database online). Issue 1, 2004
60 Almawi WY, Lipman ML, Stevens AC, et al. Abrogation of glucocorticoid-mediated inhibition of T cell proliferation by the synergistic action of IL-1, IL-6, and IFN-γ. J Immunol 1991; 146:3523–3527
61 Kam JC, Szefler SJ, Surs W, et al. Combination IL-2 and IL-4 reduces glucocorticoid receptor-binding affinity and T cell response to glucocorticoids. J Immunol 1993; 151:3460–3466
62 Spahn JD, Szefler SJ, Surs W, et al. A novel action of IL-13: induction of diminished monocyte glucocorticoid receptor-binding affinity. J Immunol 1996; 157:2654–2659
63 Farrell RJ, Kelleher D. Glucocorticoid resistance in inflammatory bowel disease. J Endocrinol 2003; 178:339–346
64 Meduri GU, Yates CR. Systemic inflammation-associated glucocorticoid resistance and outcome of ARDS. Ann N Y Acad Sci 2004; 1024:24–53
65 Meduri GU, Headley S, Golden E, et al. Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial. JAMA 1998; 280:159–165
66 Nakamori Y, Ogura H, Koh T, et al. The balance between expression of intranuclear NF-κB and glucocorticoid receptor in polymorphonuclear leukocytes in SIRS patients. J Trauma 2005; 59:308–314
67 Keel JB, Hauser M, Stocker R, et al. Established acute respiratory distress syndrome: benefit of corticosteroid rescue therapy. Respiration 1998; 65:258–264
68 Varpula T, Pettila V, Rintala E, et al. Late steroid therapy in primary acute lung injury. Intensive Care Med 2000; 26:526–531
69 Huh J, Lim C, Jegal Y, et al. The effect of steroid therapy in patients with late ARDS. Tuberc Respir Dis 2002; 52:376–384

70 Confalonieri M, Urbino R, Potena A, et al. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. Am J Respir Crit Care Med 2005; 171:242–248
71 Annane D, Sebille 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
72 Steinberg KP, Hudson LD, Goodman RB, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med 2006; 354:1671–1684
73 Fernandes AB, Zin WA, Rocco PR. Corticosteroids in acute respiratory distress syndrome. Braz J Med Biol Res 2005; 38:147–159
74 Hesterberg TW, Last JA. Ozone-induced acute pulmonary fibrosis in rats: prevention of increased rates of collagen synthesis by methylprednisolone. Am Rev Respir Dis 1981; 123:47–52
75 Hakkinen PJ, Schmoyer RL, Witschi HP. Potentiation of butylated-hydroxytoluene-induced acute lung damage by oxygen: effects of prednisolone and indomethacin. Am Rev Respir Dis 1983; 128:648–651
76 Kehrer JP, Klein-Szanto AJ, Sorensen EM, et al. Enhanced acute lung damage following corticosteroid treatment. Am Rev Respir Dis 1984; 130:256–261
77 Ashbaugh DG, Maier RV. Idiopathic pulmonary fibrosis in adult respiratory distress syndrome: diagnosis and treatment. Arch Surg 1985; 120:530–535
78 Hooper RG, Kearl RA. Established ARDS treated with a sustained course of adrenocortical steroids. Chest 1990; 97:138–143
79 Brower G, Matthay M. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome: the Acute Respiratory Distress Syndrome Network. N Engl J Med 2000; 342:1301–1308
80 Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 2006; 354:2564–2575
81 Umberger R, Headley AS, Waters T, et al. Cost-effectiveness of methylprednisolone treatent (MPT) in unreolving ARDS (U-ARDS) [abstract]. Am J Respir Crit Care Med 2002; 165:A22
82 Cerfolio RJ, Bryant AS, Thurber JS, et al. Intraoperative solumedrol helps prevent postpneumonectomy pulmonary edema. Ann Thorac Surg 2003; 76:1029–1033
83 Lee HS, Lee JM, Kim MS, et al. Low-dose steroid therapy at an early phase of postoperative acute respiratory distress syndrome. Ann Thorac Surg 2005; 79:405–410
84 Guyatt G, Gutterman D, Baumann MH, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians task force. Chest 2006; 129:174–181
85 Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Med 2008; 34:17–60
86 Weigelt JA, Norcross JF, Borman KR, et al. Early steroid therapy for respiratory failure. Arch Surg 1985; 120:536–540
87 Bernard GR, Luce JM, Sprung CL, et al. High-dose corticosteroids in patients with the adult respiratory distress syndrome. N Engl J Med 1987; 317:1565–1570
88 Meduri G, Marik P, Annane D. Prolonged glucocorticoid treatment in ARDS: evidence supporting effectiveness and safety. Crit Care Med 2009; 37:1800–1803
89 Keh DBT, Weber-Cartens S, Schulz C, et al. Immunologic and hemodynamic effects of "low-dose" hydrocortisone in septic shock: a double-blind, randomized, placebo-controlled, crossover study. Am J Respir Crit Care Med 2003; 167:512–520
90 Kaufmann I, Briegel J, Schliephake F, et al. Stress doses of hydrocortisone in septic shock: beneficial effects on opsonization-dependent neutrophil functions. Intensive Care Med 2008; 34:344–349
91 Meduri GU, Kanangat S, Bronze MS, et al. Effects of methylprednisolone on intracellular bacterial growth. Clin Diagn Lab Immunol 2001; 8:1156–1163
92 Sibila O, Luna C, Agustí C, et al. Effects of glucocorticoids in ventilated piglets with severe pneumonia. Eur Respir J 2008; 32:1037–1046
93 Stevens RD, Dowdy DW, Michaels RK, et al. Neuromuscular dysfunction acquired in critical illness: a systematic review. Intensive Care Med 2007; 33:1876–1891
94 Hough CL, Steinberg KP, Taylor Thompson B, et al. Intensive care unit-acquired neuromyopathy and corticosteroids in survivors of persistent ARDS. Intensive Care Med 2009; 35:63–68
95 De Jonghe B, Bastuji-Garin S, Sharshar T, et al. Does ICU-acquired paresis lengthen weaning from mechanical ventilation? Intensive Care Med 2004; 30:1117–1121
96 Thompson BT, Ancukiewicz M, Hudson LD, et al. Steroid treatment for persistent ARDS: a word of caution. Crit Care 2007; 11:425
97 Weber-Carstens S, Keh D. Bolus or continuous hydrocortisone: that is the question. Crit Care 2007; 11:113
98 Loisa P, Parviainen I, Tenhunen J, et al. Effect of mode of hydrocortisone administration on glycemic control in patients with septic shock: a prospective randomized trial. Crit Care 2007; 11:R21
99 Leatherman JW, Fluegel WL, David WS, et al. Muscle weakness in mechanically ventilated patients with severe asthma. Am J Respir Crit Care Med 1996; 153:1686–1690
100 Ledingham IM, Watt I. Influence of sedation on mortality in critically ill multiple trauma patients. Lancet 1983; 1:1270
101 Meduri GU, Mauldin GL, Wunderink RG, et al. Causes of fever and pulmonary densities in patients with clinical manifestations of ventilator-associated pneumonia. Chest 1994; 106:221–235