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

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

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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; I², 43%) and for those treated before day 14 (RR, 0.71; 95% CI, 0.59 to 0.85; p < 0.001; I², 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...
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), (2) acute-phase reaction; (3) sickness syndrome (including sickness behavior); (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. 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). Excessive release of inflammatory mediators into the circulation induces tissue changes in vital organs leading to multiple-organ dysfunction syndrome (MODS).

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, is beneficial, excessive or persistent systemic inflammation incites tissue destruction and disease progression. 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. Improved understanding of the critical role played by the neuroendocrine response in critical illness and the cellular mechanisms that initiate, propagate, and limit inflammation 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

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

*Initially, polymorph nuclear cells; later, monocytes.
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. 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 lobe (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.

Although the term “syndrome” was applied in its original description, ARDS meets all the constitutive elements of a disease process. 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.

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 PaO2/FIO2 ratio, the quasistatic lung compliance, and the degree of infiltration seen on a chest radiograph (1 point per quadrant of chest radiograph involved).

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 and persistent elevation in circulating and BAL fluid levels of inflammatory cytokines and chemokines, markers of ACM permeability and fibrogenesis. Systemic hypercytokinemia produces fever (systemic inflammatory response syndrome) in the absence of infections and creates an environment favoring bacterial growth and the development of nosocomial infections (Fig 1).

Systemic hypercytokinemia is also involved in the pathogenesis of the morbidity that is frequently encountered in patients with sepsis and ARDS, including hyperglycemia, short-term and long-term neurologic dysfunction (delirium), neuromuscular weakness, and posttraumatic stress disorder, and sudden cardiac events in those persons with underlying atherosclerosis (Fig 1).

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). In unresolving ARDS, lobules with exudation 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 and persistent elevation in circulating and BAL fluid levels of inflammatory cytokines and chemokines, markers of ACM permeability and fibrogenesis. Systemic hypercytokinemia produces fever (systemic inflammatory response syndrome) in the absence of infections and creates an environment favoring bacterial growth and the development of nosocomial infections (Fig 1). Systemic hypercytokinemia is also involved in the pathogenesis of the morbidity that is frequently encountered in patients with sepsis and ARDS, including hyperglycemia, short-term and long-term neurologic dysfunction (delirium), neuromuscular weakness, and posttraumatic stress disorder, and sudden cardiac events in those persons with underlying atherosclerosis (Fig 1).

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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. 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,26 neuromuscular weakness,39 and posttraumatic stress disorder40), and sudden cardiac events in those with underlying atherosclerosis.41

**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 axis53,54 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-
sponses toward increased (dysregulated) or decreased (regulated) transcription of inflammatory mediators over time. 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 study7 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.60-62 In vitro studies60-62 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
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.\(^6^3\)

The above findings are in agreement with two longitudinal studies\(^5^6,5^7\) that investigated NF-κB binding activity directly in the peripheral blood mononuclear cells of patients with sepsis or trauma (reviewed in Meduri and Yates\(^6^4\)). In both studies,\(^5^6,5^7\) nonsurvivors, contrary to survivors, had a progressive 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 activity 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,\(^6^5\) 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.\(^6^4\) Normal blood leukocytes exposed to plasma samples collected during GC vs placebo treatment exhibited...
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 IkBα, 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. A PGCT-induced increase in GC receptor nuclear translocation was also reported in polymorphonuclear leukocytes of patients with sepsis.

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 1 and III, and increases in IL-10 and anti-inflammatory cytokines 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 1 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). 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 and extrapulmonary organ dysfunction scores and (2) indexes of ACM permeability. 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. Experimental evidence supporting the use of PGCT in ALI-ARDS patients has been reviewed.

PGCT IN ALI-ARDS: REVIEW OF THE LITERATURE

Eight controlled studies (five randomized and three concurrent case-controlled) have evaluated the effectiveness of PGCT in patients with early ALI-ARDS (n = 314) and late ARDS (n = 314) and were the subject of two recent metaanalyses. 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 was associated with significant improvement in PaO2/FIO2 ratios, a significant reduction in multiple organ dysfunction score, duration of mechanical ventilation, and ICU length of stay (all p < 0.05). These findings 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.

Four of the five randomized trials 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, 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;...
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 (12.1 vs 10.1 days, respectively; p = 0.007).79 or conservative strategy of fluid management (14.6 vs 12.0 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 trials10,70,82,83 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-
ratory failure requiring mechanical ventilation (42% vs 100%, respectively; \( p = 0.02 \)) or progression to unresolving ARDS (8% vs 36%, respectively; \( p = 0.002 \)).

Treatment decisions involve a tradeoff between benefits and risks, as well as costs. 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. In more recent years, however, substantial evidence has accumulated 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 investigating a time-limited (24 to 48 h), massive, daily dose of GCs (methylprednisolone, up to 120 mg/kg/d), the newer trials have not reported an increased rate of nosocomial infections. Moreover, new cumulative evidence 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 and provides an environment less favorable to the intracellular and extracellular growth of bacteria.

In the reviewed studies, 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 found no association between GC treatment and electrophysiologically or clinically proven neuromuscular dysfunction. Given that neuromuscular dysfunction is an independent predictor of prolonged weaning and ARDS randomized trials have consistently reported a sizable and significant reduction in the duration of mechanical ventilation, 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 anti-inflammatory 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) makes this treatment globally and equitably available. All but three controlled studies showed a reduction in ICU or hospital mortality, and, in one retrospective subgroup analysis, mortality benefits were limited to those with relative adrenal insufficiency. The ARDS Network trial 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, however, had large differences in baseline characteristics, and the mortality difference lost significance when the analysis was adjusted for these imbalances.

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,
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. For this reason, a recent consensus statement recom- mended the early initiation of PGCT in patients with early severe ARDS (PaO2/FiO2 ratio < 200 with PEEP of 10 cm H2O). 1B) for improvement in patient-centered outcome 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 with low-dose methylprednisolone (1 mg/kg/d) in patients with early severe ARDS should

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

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

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 = PaO2/FiO2 ratio < 200 with PEEP of 10 cm H2O; 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.

RecommeNDAtions for TrEatMeNT and FuTuRe reSeArCh

The results of one randomized trial 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. If treatment is initiated after day 14, there is no evidence of either benefit or harm. The treatment response should be monitored with daily measurement of LIS, MODS score, and CRP level. 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. The following two medications should be avoided at all costs: neuromuscular blocking agents to minimize the risk of neuromuscular weakness; and etomidate, which causes the suppression of cortisol synthesis. 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 systemic diagnostic protocol 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, 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 PaO2/FiO2 ratio) associated with rebound inflammation (increased serum CRP concentration) after the completion of PGCT may require the reinstitution of treatment. 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 systemic diagnostic protocol 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, 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 PaO2/FiO2 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 with low-dose methylprednisolone (1 mg/kg/d) in patients with early severe ARDS should

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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 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.

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

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