Further Reading


Sepsis, Acute Respiratory Distress Syndrome, and Glucocorticoid Resistance

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Introduction

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Glossary

**Hypoxemic respiratory failure** A life-threatening reduction in blood oxygenation requiring assisted mechanical ventilation.

**Multiple organ dysfunction** Systemic inflammation-associated impairments of vital organs: brain, lung, cardiovascular system, renal, liver, and hematopoietic system.

**Sepsis** Systemic inflammation induced by infection.

**Systemic inflammation** The release of inflammatory cytokines in the systemic circulation manifesting clinically with fever and increased heart rate, respiratory rate, and white cell blood count.

Introduction

Hundred of thousands of American are affected every year by severe sepsis (700,000) and acute respiratory distress syndrome (ARDS; 190,000) creating a significant short-term and long-term burden on public health and health-care economics. Dysregulated systemic inflammation with persistent elevation of circulating inflammatory cytokines over time is the pathogenetic mechanism for the dysfunction and failure of the vital organs, the leading cause of death in patients with sepsis and ARDS. In sepsis and ARDS, the downregulation of inflammation is *conditio sine qua non* to their resolution. An improved understanding of the cellular mechanisms that initiate, propagate, and restrict inflammation in sepsis and ARDS is essential to make advances on present treatment modalities and to develop more reliable methods of monitoring disease progression and responses to therapy.

It is now appreciated that at cellular level transcription factors nuclear factor (NF-κB), which is
activated by inflammatory signals, and the glucocorticoid receptor (GR)α, which is activated by endogenous or exogenous glucocorticoids (GCs), have diametrically opposed functions (stimulatory vs. inhibitory) in regulating inflammation. NF-κB is recognized as the principal driver of the inflammatory response, being responsible for the transcription of more than 100 genes, including tumor necrosis factor (TNF-α) and interleukin(IL-)1β (Figure 1). Once activated, NF-κB and GRα can mutually repress one another through a protein–protein interaction that prevents their DNA binding and subsequent transcriptional activity. Known interactions between NF-κB and the activated glucocorticoid receptor (GC-GRα) are depicted in Figure 1. The activation of one transcription factor in excess of the binding (inhibitory) capacity of the other shifts cellular responses toward the increased (dysregulated) or decreased (regulated) transcription of inflammatory mediators over time (Figure 2). The role of GCs in regulating inflammation during sepsis and acute respiratory distress syndrome is highlighted in Figure 1.
supplementation in patients with life-threatening systemic inflammation is undergoing a cyclical reassessment, stirred by a new understanding of the role of GCs in regulating inflammation and the positive results of recent randomized controlled studies.

**Acute Respiratory Distress Syndrome**

ARDS is a life-threatening form of hypoxic respiratory failure (mortality of 30–60%) that develops within 12–48 h of a patient’s acquiring an acute illness complicated by severe systemic inflammation. The most common condition precipitating ARDS is severe sepsis, and the mortality rate for sepsis-induced ARDS has not significantly decreased in the last 20 years. In ARDS, the evolution (regulated vs. dysregulated) of systemic inflammation in the first week of mechanical ventilation determines the physiological progression of the disease and the final outcome. Patients failing to improve in the first week of mechanical ventilation (nonimprovers) have, compared to improvers, a persistent elevation in circulating and bronchoalveolar lavage (BAL) levels of inflammatory cytokines and chemokines, markers of alveolocapillary membrane (ACM) permeability and fibrogenesis. In sepsis and ARDS, the downregulation of inflammation is essential for the restoration of homeostasis and survival.

**Systemic Inflammation-Associated Glucocorticoid Resistance**

GCs as end effectors of the hypothalamic-pituitary-adrenal (HPA) axis are the most important physiological inhibitors of inflammation, affecting hundreds of genes involved in stress-related homeostasis. However, endogenous GCs are not always effective in suppressing life-threatening systemic inflammation, and the degree of cortisolemia frequently correlates with the severity of illness and the mortality rate. Unquestionably, the elevation of GC secretion in non-survivors of sepsis and ARDS is inadequate to meet the needs of the concurrent inflammatory response and its adverse systemic effects. Its failure to suppress inflammation could be due to tissue resistance to GCs, the inadequacy of the level and duration of endogenous GC elevation to suppress a systemic inflammatory response gone awry, or both.
The concept of acquired GC resistance was first introduced by Kass and Finland in 1957. These investigators suggested that increased blood cortisol levels in nonsurvivors of sepsis might reflect a blocking of steroidal activity or transport as a consequence of the infection. In this situation, a small increase in blood levels with a low (equal to or less than physiological) dose of exogenous GCs was believed to be sufficient to facilitate the passage of steroids into host cells. GC resistance was originally described as a primary inherited familial syndrome and was recently recognized as an acquired condition. Among others, acquired immune tissue-specific GR resistance has been described in patients with asthma, acquired immunodeficiency syndrome (AIDS), severe sepsis, and sepsis-induced ARDS.

In vitro studies showed that cytokines may induce resistance to GCs by reducing GR binding affinity to cortisol and/or GC response elements (GREs). Such abnormalities of GR function were demonstrated in T cells incubated with a combination of interleukin (IL-)2 and IL-4, IL-1, IL-6, and interferon (IFN)-γ, or IL-13. GC resistance was induced in a cytokine concentration-dependent fashion and was reversed by the removal of cytokines. GR-mediated resistance in the presence of systemic inflammation was also studied in experimental models of sepsis and sepsis-induced ARDS. In a sheep model of sepsis-induced ARDS, the maximal binding capacity of GR decreased continuously after endotoxin infusion, whereas there was a marked elevation of cortisol levels. The reduced GR binding correlated negatively (r = −0.87, p < 0.01) with phospholipase A2 (PLA2) activity, a gene that is stimulated by NF-κB. In a rat model of septic shock, GR blockade by mifepristone (RU 486) exacerbated the physiological and pathological changes induced by endotoxemia. PLA2 activity in rats with 80% GR blockade was more marked than in those with 50% GR blockade. The monocytes of patients with sepsis developed near-total GC resistance in vitro when cytokines, especially IL-2, were added.

**Nuclear Factor κB and Glucocorticoid Receptor α Interaction**

New evidence indicates that a primary pathogenetic mechanism explaining GC resistance or insensitivity in patients with life-threatening systemic inflammation is the imbalance between excessive NF-κB activation by inflammatory signals and deficient GRα activation by endogenous or exogenous glucocorticoids. Using an *ex vivo* model of systemic inflammation, our group investigated 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 patients with sepsis-induced ARDS and correlated the physiological progression with laboratory findings. Exposure of naïve cells to longitudinal plasma samples 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 (*Figures 2–3*).

Plasma samples from patients with declining inflammatory cytokine levels 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 (regulated, GRα-driven response; *Figure 2*). In contrast, plasma samples from patients with sustained elevations in inflammatory cytokine levels over time 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; *Figure 3*). These findings demonstrate that insufficient GC-GRα-mediated activity is an important mechanism for early loss of autoregulation (*i.e.*, downregulation of NF-κB activity) in nonimprovers. Deficient GRα activity in naïve cells exposed to plasma from patients with dysregulated inflammation was observed despite elevated circulating cortisol and adrenocorticotropic hormone (ACTH) levels, implicating inflammatory cytokine-driven excess NF-κB activation as an important mechanism for target-organ insensitivity and/or resistance to cortisol.

Our findings are in agreement with two longitudinal studies that investigated NF-κB binding activity directly in the peripheral blood mononuclear cells of patients with sepsis or trauma. In both studies, nonsurvivors (compared to survivors) had a progressive increase in NF-κB activity over time. In one longitudinal study, nonsurvivors of septic shock had by days 2–6 a 200% increase in NF-κB activity compared to day 1. Similarly, using our *ex vivo* model we found that NF-κB binding activity on day 3 of ARDS clearly separated patients by outcome. In an immunohistochemistry analysis of lung tissue, areas with severe (vs. mild) ARDS had a higher nuclear uptake of NF-κB (13 ± 1.3 vs. 7 ± 2.9; p = 0.01) and a lower ratio of GRα : NF-κB nuclear uptake (0.5 ± 0.2 vs.1.5 ± 0.2; p = 0.007). Thus, an uninhibited increase in NF-κB activation in circulating cells over time.
appears to be a significant premortem pathogenetic component of lethal sepsis and ARDS.

**Systemic Inflammation-Induced Glucocorticoid Resistance Can Be Improved with Prolonged Glucocorticoid Supplementation**

Our findings place GC-GRα-mediated downregulation of NF-κB activity as a critical factor for the reestablishment of homeostasis during the acute, life-threatening systemic inflammation that accompanies sepsis and ARDS. A subgroup of 11 patients with dysregulated inflammation and deficient GC-GRα activity were randomized to prolonged GC supplementation initiated on ARDS day 9 ± 3. Quantitatively adequate and prolonged hormonal supplementation restored GR anti-inflammatory function, decreasing the production of inflammatory cytokines, inflammatory cytokine-driven HPA axis activity, and inflammatory cytokine-driven organ dysfunction. Normal PBL exposed to plasma samples collected during GC versus placebo treatment exhibited rapid, progressive, and significant increases in GRα-mediated activities (GRα binding to NF-κB, GRα binding to GRE DNA, stimulation of inhibitory protein IκBα, and stimulation of IL-10 transcription) and significant reductions in NF-κB χB binding and transcription of TNF-α and IL-1β. During GC treatment, the relationship between NF-κB and GC-GRα signaling pathways changed from an initial NF-κB-driven and GC-GRα-resistant state to a GC-GRα-driven and GC-GRα-sensitive one. In aggregate, the findings indicate that systemic inflammation-induced GC resistance is an acquired generalized process mediated by excess NF-κB activation and potentially reversible by increasing GC-GRα activation with quantitatively adequate and prolonged GC supplementation.

**Findings of Randomized Trials**

At present, the administration of low-dose GCs is the only treatment shown in randomized trials to have a significant positive biological and physiological effect across the longitudinal spectrum of the severity of sepsis-associated systemic inflammation: severe sepsis, septic shock, early ARDS, and unresolving ARDS.
All randomized studies showed significant physiological improvement and a reduction in the duration of stays in the intensive care unit. The overall effects on mortality are shown in Table 1.

In prolonged low-dose GC treatment, maximal benefits are obtained by (1) avoiding the premature removal of an effective drug, leading to rebound inflammation and physiological deterioration, and (2) preventing potential complications associated with GC treatment (infection surveillance and avoidance of paralysis). Uncontrolled studies have also shown a likely benefit in patients with viral pneumonia-induced ARDS, including SARS. The mortality rate in 849 cases of SARS treated with antiviral therapy and GC supplementation was only 7.7%. In hantavirus pulmonary syndrome, the mortality rate decreased from 47% in patients treated with antiviral therapy to 13% when GC supplementation was also included. The findings for severe viral pneumonia and the results of recent randomized controlled trials (RCTs) for ARDS indicate that prolonged methylprednisolone use might useful in the prevention of morbidity and mortality associated with avian influenza.

**Conclusion**

Dysregulated systemic inflammation has enormous health-care consequences. A new understanding of the cellular mechanisms responsible for inflammation-associated GC resistance provides a new rationale for investigating prolonged low-dose GC supplementation. The consistent positive results of small- to moderate-size randomized studies are very encouraging. Federal financial support is urgently needed to conduct additional RCTs investigating this inexpensive off-patent treatment in patients with life-threatening systemic inflammation.

**Acknowledgments**

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**Further Reading**


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**Table 1** Prolonged glucocorticoid treatment in sepsis and ARDS: effect on mortality

<table>
<thead>
<tr>
<th>Severity of sepsis</th>
<th>Number of RCTs</th>
<th>Number of patients (death of total)</th>
<th>Source</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Treated</td>
<td>Control</td>
<td>p value</td>
</tr>
<tr>
<td>Severe sepsis</td>
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<td>0 of 23 (0%)</td>
<td>7 of 23 (30%)</td>
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<tr>
<td>Septic shock</td>
<td>5</td>
<td>7 of 22</td>
<td>12 of 19</td>
</tr>
<tr>
<td></td>
<td>3 of 20</td>
<td>4 of 20</td>
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<tr>
<td></td>
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<td>10 of 21</td>
<td>4</td>
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<tr>
<td></td>
<td>82 of 151</td>
<td>91 of 149</td>
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<tr>
<td></td>
<td>8 of 20</td>
<td>12 of 20</td>
<td>10</td>
</tr>
<tr>
<td>Total from meta-analysis</td>
<td>106 of 236 (45%)</td>
<td>129 of 229 (56%)</td>
<td>0.01</td>
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<tr>
<td>Early ARDS</td>
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<td>50 of 63 (21%)</td>
<td>16 of 28 (43%)</td>
</tr>
<tr>
<td>Unresolving ARDS</td>
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<td>2 of 16 (12%)</td>
<td>5 of 8 (62%)</td>
</tr>
<tr>
<td></td>
<td>32 of 90 (36%)</td>
<td>31 of 90 (34%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*ARDS, acute respiratory distress; RCTs, randomized controlled trials.

*Data from:*


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**Septic Shock** See: Hypotension, Hypovolemia, and Septic Shock; Sepsis, Acute Respiratory Distress Syndrome and Glucocorticoid Resistance.