Complement activation and corticosteroid therapy in the development of the adult respiratory distress syndrome.

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Complement Activation and Corticosteroid Therapy in the Development of the Adult Respiratory Distress Syndrome*


Fifty-nine patients in septic shock were observed for the development of the adult respiratory distress syndrome (ARDS) prior to and after receiving either 30 mg/kg methylprednisolone sodium succinate, 6 mg/kg dexamethasone sodium phosphate or no steroid. Serum levels of C3, C4 and Factor B allowed classification of 42 patients by activation of complement pathways. Despite a trend toward patients with severe septic shock who activate the alternative pathway being protected from the development of ARDS, complement pathway determination did not allow prediction of the development of ARDS and steroid pretreatment did not influence complement levels or prevent ARDS.

Patients with sepsis have a high incidence of developing the adult respiratory distress syndrome (ARDS), a condition associated with a high mortality. The availability of laboratory markers for patients at risk for ARDS would be both of prognostic value and helpful in the assessment of various early therapeutic interventions. While the causes of ARDS may be multifactorial, complement activation has been proposed to be involved in the development of both septic shock and ARDS. Furthermore, the possibility exists that corticosteroid administration might prevent ARDS by interfering with complement activation. In fact, corticosteroids have been recommended by some for patients with ARDS. The purpose of this present study was to evaluate complement activation in patients with septic shock as a marker for the development of ARDS. In addition, we sought to determine if the administration of corticosteroids to patients in septic shock would influence complement levels and the subsequent development of ARDS.

Methods and Materials

Patients with septic shock at the University of Miami Affiliated Hospitals, including the Veterans Administration Medical Center and Jackson Memorial Hospital Center (between August 1979 and February 1982) were selected for study. Fifty-nine patients in septic shock were observed for ARDS and sera from 42 patients were assayed for levels of complement components.

Study Entry Criteria

Patients were considered to be in septic shock if they met the following four criteria: (1) systolic blood pressure either less than 90 mm Hg or 50 mm Hg less than a previously determined systolic pressure in a hypertensive patient; (2) signs of decreased organ perfusion as evidenced by an altered mental status and/or oliguria (less than 20 ml/hr); (3) continued hypotension or requirement for vasopressors despite an intravenous infusion of at least 500 ml of 0.9 percent NaCl; and (4) bacteremia or an identified source of infection. Bacteremia was defined as a positive blood culture for microorganisms. Patients had an identified source of infection when a body fluid (urine, sputum, cerebrospinal fluid, etc) containing white blood cells and bacteria was believed to be responsible for the patient's clinical condition. For every patient enrolled in the study, approximately three to four patients were evaluated and excluded because intravenous fluids reversed the shock state. All patients with hypotension possibly secondary to hemorrhage, acute myocardial infarction, cardiopulmonary arrest, or acute pulmonary aspiration were excluded from the study. Patients were graded for severity of shock and underlying disease as previously described. The patients were further characterized by the presence of positive blood cultures for Gram-positive organisms, Gram-negative organisms or for no growth.

Patients were enrolled at the time they met the study criteria for septic shock whether or not the culture results were available. Patients were admitted to the Medical Intensive Care Unit as expeditiously as possible for treatment of their septic shock. Patients were supported with antibiotics, fluid resuscitation with crystalloid and/or colloid solutions, vasopressors, and other measures as clinically indicated. Patients were randomized to receive either methylprednisolone sodium succinate 30 mg/kg intravenously over 10 to 15 minutes, dexamethasone sodium phosphate 6 mg/kg as a 10 to 15 minute intravenous infusion, or no steroid therapy, the control group. If shock persisted, the same dose was repeated in four hours.

Patients were considered to have ARDS when they met the following three criteria: (1) diffuse bilateral pulmonary infiltrates; (2) hypoxemia with a partial pressure of oxygen/fractional inspired oxygen concentration (PaO2/FIO2) ratio <150; and (3) a pulmonary artery wedge pressure <15 mmHg. Patients were categorized as having ARDS before or at the time of study drug administration (group 1), after study drug administration (group 2), or not developing ARDS (group 3).

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Adult Respiratory Distress Syndrome (Schein et al)
Serum Complement Determination

Blood was drawn from an indwelling arterial or central venous catheter. Serum levels of C3, C4 and factor B were determined in samples collected immediately prior to the study drug administration. The C3 and C4 were also measured in samples collected 1.5 and 24 hours after drug infusion. Sera were separated by centrifugation and stored in small aliquots at -70°C within 30 to 45 minutes of drawing. Immediately after thawing the sera, the levels of C3 and C4 were determined by functional hemolytic assays.10 Factor B was quantified by radial immunodiffusion.11 Serum levels of C3 and C4 were also determined in a group of 100 normal subjects composed of attending and resident physicians, laboratory personnel, and patients visiting their physicians for routine care.

Values of 19,200 to 76,700 CHU/ml for C3, 304,800 to 819,200 CHU/ml for C4, and 12 to 30 mg/dl for factor B were considered normal. The classic pathway was considered activated if C3 and C4 were decreased in titer compared to normal values and factor B concentrations were normal, or if the C4 titers were decreased and C3 and factor B levels were normal. The alternative pathway was considered activated if C4 levels were normal and either C3 and/or factor B levels were decreased. If C3, C4, and factor B levels were decreased, both pathways were considered activated, whereas if C3, C4 and factor B levels were normal, the complement system was not considered activated.12

Statistical Methods

Data are expressed as mean ± standard error of the mean (SEM). The chi square or Fisher's exact test were used as tests of frequency and analysis of variance used for tests of means. Statistical significance was defined as p<0.05. The present study was approved by the Veterans Administration and University of Miami Human Studies Research Committees.

RESULTS

Fifty-nine patients in septic shock were studied. The mean age was 54±2 years. Patients received a mean of 2,509±345 ml of isotonic saline over 5.7±1.2 hours prior to study drug infusion. The mean dosage of dopamine at the time of the study drug administration was 21±3 μg/kg/min. The time from onset of shock to study drug administration was 17.5±5.4 hours. There were no significant differences in age, dose of vasopressor, time from shock to study drug, severity of shock, severity of underlying disease, or presence or type of organism cultured from the blood between the patient groups with and without ARDS or between those patients receiving corticosteroids or in the control group. Seventeen patients (29 percent) developed ARDS prior to study drug administration (group 1), ten (17 percent) developed ARDS 65±20 hours after the study drug infusion (group 2), and 32 (54 percent) did not develop ARDS (group 3).

Relation of Complement Activation to ARDS

Complement levels were obtained in 42 of 59 patients. Seventeen patients were excluded because of insufficient sample collection or inadequate sample preparation. Timing of the samples was indexed to the administration of study drugs, that is, after the failure of volume infusions to reverse shock and the initiation

Table 1—Complement Values

<table>
<thead>
<tr>
<th>Group</th>
<th>C3 (CHu/ml)</th>
<th>C4 (CHu/ml)</th>
<th>Factor B (ng/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11,146±2,317</td>
<td>315,514±2,111</td>
<td>15.7±1.6</td>
</tr>
<tr>
<td>2</td>
<td>12,900±2,786</td>
<td>114,578±34,972</td>
<td>16.5±2.0</td>
</tr>
<tr>
<td>3</td>
<td>16.4±2.4</td>
<td>22.4±2.2</td>
<td>16.2±2.0</td>
</tr>
</tbody>
</table>

*No significant differences between groups.

Effect of Corticosteroids on Development of ARDS

Corticosteroids did not affect the development of ARDS. Four (25 percent) of 16 methylprednisolone-treated patients, three (23 percent) of 13 dexamethasone-treated patients, and two (15 percent) of 13 control patients developed ARDS. In addition, there were no changes in the baseline and posttreatment C3 and C4 levels in the methylprednisolone, dexamethasone, or control groups (Table 3).

DISCUSSION

The present study examined the utility of complement activation as a marker for the subsequent develop-

Table 2—Complement Pathway Activation

<table>
<thead>
<tr>
<th>Group</th>
<th>Classical</th>
<th>Alternative</th>
<th>Both</th>
<th>Neither</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>0</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>6</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

*No significant differences between groups.
opment of ARDS in a subgroup of patients at high risk and also the effects of high dose corticosteroids in preventing ARDS.

Experimental work with animals has suggested a role for complement activation in the production of acute lung injury. Thus, infusions of purified C5a or activated complement, \(^{9,13,16}\) cobra venom factor, \(^{7,17}\) or zymosan\(^{18,19}\) all have produced lung injury characterized by combinations of hypoxemia, pulmonary hypertension, edema, intrapulmonary aggregation of neutrophils, and increased protein in lung lymph. Noteworthy is that many of these studies involved primary activation of the alternative complement pathway and that most\(^{9,17,18,19}\) show that activated complement alone is not sufficient to produce lung injury but that polymorphonuclear white cells (PMN) and possibly other factors are necessary.\(^{20,21}\)

Clinical studies, thus far, have been less clear as to the relevance of serum complement levels. Hammer-schmidt et al\(^ {22}\) found that in 31 of 33 patients who ultimately developed ARDS, C5a assays became positive, whereas in those patients who did not develop ARDS, only five of 28 had positive assays. Differences were significant with or without septic patients included. However, any positive assay within 72 hours preceding the diagnosis of ARDS was considered to be a positive result and C5a activity was inferred by the ability of patients' plasma to aggregate neutrophils. Duchateau et al\(^ {25}\) studied 50 patients of whom 35 developed ARDS. They found that C5a activity was present in 81 percent of patients developing ARDS but also was present in patients at risk who did not develop ARDS. Weinberg et al\(^ {26}\) found that in 40 patients, C5a des arg and C3a des arg could not be used to predict the development of respiratory failure. Studies employing bronchoalveolar lavage have shown transient increases in hemolytic levels of C3 and C5\(^ {24}\) and increases in proteolytic activity.\(^ {20,26}\) In the present study, we were able to define no consistent correlation between either the absolute values of C3, C4, and factor B or pathway activation and the subsequent development of ARDS. When patients who were already in ARDS or later developed ARDS were compared with those patients never developing respiratory failure, patients were significantly less likely to show activation of the alternative pathway than the classic pathway alone or both pathways. These findings suggest that complement activation is important in ARDS but give no support to the use of these measurements as clinically valuable predictors. Activation of the alternative pathway in septic shock may provide some protection from the development of ARDS. Our results may have been effected by several factors. Septic shock alone may produce activation of either or both pathways,\(^ {14,17,20}\) thus obscuring a particular pattern of activation in this subgroup of patients. Serial sampling of blood might have produced different results. Finally, the possibility of complement activation despite normal serum complement levels should be considered since static measurements of serum levels may underestimate the turnover of complement factors.

The role of corticosteroids in the prevention and treatment of ARDS is controversial. The aggregation of PMNs by complement has been proposed as an initiating factor in lung injury.\(^ {9,22}\) Corticosteroids have been shown to limit the activation of complement in models of the alternative\(^ {7}\) and classic pathways.\(^ {6}\) Steroids are believed to inhibit the activation of complement and prevent PMN aggregation.\(^ {4}\) Steroid pretreatment using a rhesus monkey model, however, failed to show an inhibitory effect on degranulation or aggregation of PMNs.\(^ {20}\) Additional roles for corticosteroids in preventing pulmonary hypoxic vasoconstriction,\(^ {30}\) blunting changes in capillary permeability,\(^ {32,33}\) and reducing total lung water\(^ {34}\) have been suggested. There have been few relevant clinical studies. Sladen\(^ {35}\) found increased PaO\(_2\) after corticosteroid therapy in patients with "shock lung." Patients with lung contusions were found to have decreased systemic and pulmonary vascular resistances with no change in oxygen delivery or consumption following treatment with methylprednisolone.\(^ {35}\) Lucas and Ledgerwood\(^ {36}\) found increased central venous pressure and diminished PaO\(_2\) in corticosteroid treated patients at risk for ARDS because of massive transfusion. Sibbald et al\(^ {37}\) noted that corticosteroids decreased the increased permeability in ARDS when given early in the course of the syndrome. Weigelt et al\(^ {38}\) found no decrease in the development of ARDS in high risk surgical patients already intubated.

Our experience with medical patients in severe late

### Table 3—Corticosteroid Effect on Complement

<table>
<thead>
<tr>
<th></th>
<th>PRE 1-hour</th>
<th>24 Hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3 (M)*</td>
<td>13,308 ± 2,565</td>
<td>13,067 ± 2,463</td>
</tr>
<tr>
<td>(CH₅₀ U/ml)</td>
<td>12,854 ± 2,340</td>
<td>12,854 ± 2,289</td>
</tr>
<tr>
<td></td>
<td>11,343 ± 4,208</td>
<td>6,943 ± 2,532</td>
</tr>
<tr>
<td>C4 (M)</td>
<td>110,392 ± 25,528</td>
<td>109,792 ± 25,615</td>
</tr>
<tr>
<td>(CH₅₀ U/ml)</td>
<td>168,746 ± 18,861</td>
<td>146,277 ± 21,370</td>
</tr>
<tr>
<td></td>
<td>106,457 ± 39,943</td>
<td>106,457 ± 39,531</td>
</tr>
</tbody>
</table>

* M is methylprednisolone sodium succinate; D, dexamethasone sodium phosphate, and C, control subject.
† No significant differences between pre- and post-treatment values.
septic shock has shown no benefit to the use of steroids in decreasing the incidence of ARDS. Interestingly, while septic shock may be a risk factor for the development of ARDS, 27 (63 percent) patients who developed ARDS already met criteria for ARDS prior to resuscitation from shock. This indicates that using shock for a marker of ARDS in the subgroup of septic patients does not allow for early therapeutic intervention in a significant portion of those patients. Nine patients went on to develop ARDS over a time period allowing for potential preventive therapy. Among these patients, we found no evidence for the benefit of corticosteroids in the prevention of ARDS. This result may be related to the small number of patients, but is consistent with the data of Weigelt et al. in surgical patients. Although it is not quite appropriate to make assessments of the statistical power of a study after the fact, the observations of this study may be used to determine the sample sizes that would be required if similar studies were planned. Thus, taking group 3 C3 and C4 values as 15,500 CH20 U/ml and 159,000 CH20 U/ml, respectively, a total of 65 patients in each group would have an 80 percent chance (at alpha = 0.05) of detecting a true difference with respect to groups 1 and 2 as large as that shown in this study. The possibility that corticosteroid therapy might actually increase the development of ARDS might be raised. Taking the rate of the development of ARDS which was 15 percent in the control group, as the target variable, a total of 134 patients would be needed in each group for a statistical power of 80 percent if the rate of ARDS increased to 30 percent with corticosteroid therapy. A very much larger clinical trial might therefore provide statistically superior results of dubious clinical significance. Rather than indicating too small sample sizes, the lack of steroid effect on complement levels and the development of ARDS may indicate that patients were treated too late in the course of their disease to see any benefit. If complement activation is one of the initiating factors in the development of ARDS, it probably occurs early in or preceding the shock state rendering corticosteroids inadequate to reverse the process once septic shock is clinically recognized.

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REFERENCES

Call for Abstracts, 12th International Conference on Lung Sounds

The 12th International Conference on Lung Sounds will be held in Paris, France, September 16-18. Abstracts of papers for presentation should not exceed 200 words and should be submitted by July 1. Notification of acceptance will be sent by July 15. Abstracts may relate to any aspect of lung sounds; examples are studies of mechanisms of production, clinical implications, physiologic correlations, methods for recording, analysis or representation. Abstracts and inquiries should be addressed to Dr. Robert G. Loudon, University of Cincinnati Medical Center, Pulmonary Disease Division, 231 Bethesda Avenue, Cincinnati 45267-0564 (513:872-4831).

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