Established ARDS Treated with a Sustained Course of Adrenocortical Steroids*

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Short treatment courses of ACS have been shown to be of no demonstrable value in the treatment of ARDS. We gave two patients with persistant ARDS a trial of ACS after they demonstrated pulmonary uptake of "Ga. Brief initial improvement disappeared with tapering of the ACS. A sustained course of ACS led to resolution of the ARDS in both patients. In all, ten patients with established ARDS were treated with sustained ACS over an 18-month period. The eight additional patients had uninterrupted courses of therapeutic ACS for greater than 21 days. The patients averaged 12 days of greater than 40 mg a day. At the time of treatment, all patients had established ARDS, meeting for at least 72 hours, criteria for the diagnosis of ARDS. A sustained course of ACS may be effective in the treatment of selected patients with established ARDS. Controlled studies of established ARDS are indicated to define the characteristics of these patients and their management.

ACS = adrenocortical steroids

The word, "controversy," is repeatedly used to describe the debate surrounding the use of ACS in patients suffering from ARDS. Prominent clinicians and scientists are on opposite sides of the issue quoting well-done work to support their views. Recent carefully performed studies have shown short-term, high-dose adrenocortical steroids do not improve ultimate outcome. Our experience has led us to question further the use of these agents in this complicated problem. What is the effect of a longer course of therapy? Can patient selection identify a group or subset who may respond to this therapy? What are the implications of gallium uptake by ARDS lungs for pathogenesis and therapy?

When confronted with a patient who was persistently ventilator-dependent due to ARDS, one of the authors utilized "Ga citrate scanning to identify if a potentially reversible inflammatory component existed within the diffuse pulmonary process. A surprising degree of "Ga uptake was present. Adrenocortical steroids were administered and a clinical improvement followed. Tapering of the ACS was followed by deterioration in respiratory function. Reinstitution then led to further improvement and subsequent resolution. In a second case, a similar pattern of events was observed.

These two clinical experiences stimulated us to utilize a sustained course of ACS in the treatment of patients with established ARDS, since short treatment courses have been shown to be of no demonstrable value. Our experience in an uncontrolled patient population provides suggestive evidence that a sustained course of ACS is beneficial in the treatment of established ARDS. The dosages of ACS administered; duration for which we employed them; and the patients we selected to treat all differ significantly from those utilized in studies arguing against their value. Our experience suggests a need for further controlled studies of the use of ACS in patients with established ARDS.

Patient Profiles and Clinical Techniques

Ten patients with established ARDS were cared for by the authors over an 18-month period and represent our total experience with ARDS treated with ACS since the index case (Table 1). The first two patients initially had a limited course of ACS, but subsequently completed a sustained course of greater than 21 days. Seven patients had uninterrupted courses of therapeutic ACS for greater than 21 days while one died during therapy.

We define established ARDS as ARDS where the causative process has resolved and where the ARDS has existed for greater than 72 hours' duration. At the time of diagnosis, all patients had criteria for ARDS based on accepted definitions including the following: severe impairment of oxygenation (requiring FIO2 > 0.6 for PaO2 of > 55); diffuse infiltrates on chest roentgenography; and hemodynamic stability and pulmonary capillary wedge pressure of less than 16 mm Hg by Swan-Ganz catheter measurements. All patients met these criteria for greater than 72 hours before the treatment with ACS was instituted. Patients selected for therapy were free of identifiable infections; however, hepatic or renal insufficiency did not exclude patients from consideration.

Gallium-67 citrate scans were performed at 48 hours using standard techniques in patients clinically stable enough for transport to imaging. All patients were injected prior to the initiation of ACS therapy. Intensity of uptake was quantified by two methods: computer generated ratios of background activity to the lung activity, and a visual scoring system of 0 to 3 with 0 equaling no activity and 3 as maximum uptake similar to that of the liver.

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ARS Treated with Sustained Adrenocortical Steroids (Hooper, Kearl)
Table 1—Patient Experience: Established ARDS Treated with Sustained ACS

<table>
<thead>
<tr>
<th>Case No.</th>
<th>ARDS Classification*</th>
<th>Duration of ARDS, Days</th>
<th>Total Duration</th>
<th>Dose/(Mg/Day)</th>
<th>Computer Ratio</th>
<th>Visual Score</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Isolated</td>
<td>40</td>
<td>150</td>
<td>19</td>
<td>...</td>
<td>2</td>
<td>Survived</td>
</tr>
<tr>
<td>2</td>
<td>Complicated</td>
<td>7</td>
<td>28</td>
<td>None</td>
<td>1.7</td>
<td>3</td>
<td>Died</td>
</tr>
<tr>
<td>3</td>
<td>Isolated</td>
<td>25</td>
<td>21</td>
<td>13</td>
<td>...</td>
<td>2</td>
<td>Survived</td>
</tr>
<tr>
<td>4</td>
<td>Isolated</td>
<td>7</td>
<td>28</td>
<td>3</td>
<td>...</td>
<td>3</td>
<td>Survived</td>
</tr>
<tr>
<td>5</td>
<td>Isolated</td>
<td>3</td>
<td>21</td>
<td>None</td>
<td>3.9</td>
<td>3</td>
<td>Died</td>
</tr>
<tr>
<td>6</td>
<td>Complicated</td>
<td>4</td>
<td>22</td>
<td>10</td>
<td>1.86</td>
<td>2</td>
<td>Survived</td>
</tr>
<tr>
<td>7</td>
<td>Complicated</td>
<td>5</td>
<td>37</td>
<td>12</td>
<td>7.79</td>
<td>2</td>
<td>Survived</td>
</tr>
<tr>
<td>8</td>
<td>Isolated</td>
<td>9</td>
<td>30</td>
<td>14</td>
<td>1.46</td>
<td>2</td>
<td>Survived</td>
</tr>
</tbody>
</table>

*Status at time of initiating therapy (see text and Table 2).

Case 1

A 70-year-old woman (Fig 1) suffered a cardiac arrest at the time of an outpatient cardiac catheterization for evaluation of aortic stenosis. Aortic valve replacement was performed on the ninth hospital day. Cardiac function improved rapidly after surgery to support normal hemodynamics and cardiac output. The postoperative period was complicated by multiple system disease including transient renal insufficiency, two episodes of sepsis, and persistent ARDS. The ARDS was characterized by diffuse interstitial roentgenographic abnormalities, hypoxemia, and ventilator dependence. By the 27th postoperative day (36th hospital day), ARDS was the

![Graphs](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21605/)
only major unresolved problem.

A $^{67}$Ga citrate scan was obtained to assess for the presence of an active inflammatory component, and significant $^{67}$Ga uptake was found. Based upon this finding, a therapeutic course of ACS was begun on the 39th hospital day. Within four days, the patient demonstrated significant improvement in both oxygenation and chest roentgenogram. She was also able to support her own ventilation. The ACS dosage was rapidly reduced to a maintenance level. The patient responded with a deterioration in all parameters and required the reinitiation of mechanical ventilation on the 50th hospital day. Again, the major clinical problem was respiratory insufficiency with significant oxygenation difficulties.

The dosage of ACS was increased on the 60th hospital day. Again, a positive response was seen in oxygenation, chest roentgenogram, and ventilatory assistance requirements, although the responses were slower and less dramatic. On the 96th hospital day, the patient was discharged on nocturnal oxygen and a slowly tapering dose of steroids. Three months after discharge, the patient was not receiving ACS or nocturnal oxygen and was living an active life.

CASE 2

One week following an acute myocardial infarction, a 37-year-old native American woman (Fig 2) required emergency replacement of the mitral valve for severe acute mitral regurgitation. The postoperative course was complicated by diffuse pulmonary infiltrates and prolonged ventilator dependence. By the seventh hospital day, there had been no improvement in the ARDS in spite of supportive measures. Hemodynamic measurements showed a wedge pressure of 19 mm Hg and pulmonary artery pressures of 43/29. A $^{67}$Ga citrate scan demonstrated significant pulmonary uptake of isotope at 48 hours (Fig 3). A rapidly tapering dose of ACS was given, and distinctive improvements in oxygenation and chest roentgenogram were observed. The patient was successfully weaned from mechanical ventilation and extubated. However, the patient, who had been improving daily, began to deteriorate without apparent reason.

The progressive deterioration was consistent with ARDS. Repeat pulmonary arterial catheter measurements showed a pulmonary arterial pressure of 35/20 with a wedge pressure of 15. The cardiac output was 5.9 liters. A repeat $^{67}$Ga scan demonstrated further uptake of isotope. The ACS therapy was reinstituted although heated debate regarding its value and safety occurred. Again, a pattern of improvement was recorded. Fifteen days after the reinstitution of ACS, the patient was able to obtain satisfactory oxygenation from room air. The roentgenogram cleared and the ARDS was felt to be resolved. Unexpectedly, the patient had a sudden cardiac arrest the day prior to her planned discharge and died. A postmortem examination could not be performed.

FIGURE 3. Thoracic portion of $^{67}$Ga citrate scan in patient 2 on the seventh day of ARDS. Measurements of pulmonary uptake were a computer derived ratio of 1.7 (pulmonary/background) and a visual score of 3 (maximum on 0-3 scale).

FIGURE 5. Portable chest roentgenogram of patient 3 prior to onset of adrenocortical steroid therapy taken on the 25th hospital day.
CASE 3

A 40-year-old native American woman (Fig 4) was admitted after an assault for treatment of multiple facial fractures and exposure. She was intubated upon admission for airway control but subsequently developed pneumonia and later bilateral pulmonary infiltrates. When consulted on the 24th hospital day, an author found the patient to be ventilator-dependent with hypoxic and hypercarbic respiratory failure, noncompliant lungs, and diffuse roentgenographic abnormalities (Fig 5). ACS therapy was begun. Carbon dioxide retention improved rapidly, and over the ensuing 14 days, the patient showed marked improvement in oxygenation, compliance, and on roentgenogram (Fig 6). On the 14th day of therapy, she was weaned from mechanical ventilation, and by the 18th day after initiating ACS, she was satisfactorily oxygenated on room air.

TOTAL EXPERIENCE

Ten patients have been treated with a program of sustained ACS for established ARDS including the three described above (Table 1). In all patients, the initiating event(s) had resolved prior to the use of ACS. The ARDS had been present from four to 40 days before the ACS program was initiated (average 11 days). The etiologies of ARDS in our patients were sepsis, aspiration, and trauma (one patient each); cardiopulmonary arrest (two patients); and post-pump cardiopulmonary bypass (five patients). The ACS therapy was longer than three weeks in all surviving patients and a dosage of greater than 40 mg a day was employed for an average of 12 days. Patients 3 through 10 were all treated with uninterrupted courses of ACS (Table 1). Their responses to ACS were similar to that demonstrated in patient 3 (Fig 4) except for case 6 who died. After four to seven days of therapy, significant clinical improvement in ventilatory requirements, oxygenation, and chest roentgenograms were apparent in all patients. Nine 67Ga citrate scans were performed in eight patients. Significant uptake was observed in all scans (Table 1 and Fig 3).

Two infectious complications were seen. A sternal incision infection with sternal separation occurred in patient seven. The patient survived and was discharged after open drainage, antibiotic therapy, and the placement of pectoral flaps. Patient 9 suffered empyema following a persistent bronchopleural fistula. All patients were treated with an H-2 blocker and no significant gastrointestinal bleeding was identified.

Two in-hospital deaths occurred for a 20 percent overall mortality rate (Table 2). Only one death occurred while the patients were being treated for ARDS (patient 6). This patient had suffered a cardiopulmonary arrest during alcohol withdrawal and aspirated. The ARDS developed and persisted until his death; however, improvement was noted in respiratory parameters after ACS was given. The illness was complicated by progressive liver failure and ultimately with congestive heart failure and sepsis. A second death occurred in the hospital. The patient described above in case 2 had demonstrated complete resolution of her infiltrates and satisfactory oxygenation on room air when a sudden event led to her death. An arrhythmia or pulmonary embolism was suspected but could not be confirmed.

DISCUSSION

The three patients we have presented in detail demonstrate responses of ARDS to a sustained course of ACS. In the first two patients, short ACS trials resulted in temporary, limited responses in clinical condition, oxygenation, and roentgenographic abnormalities which regressed when the dosage was reduced. Subsequently, longer therapeutic trials resulted in a resolution of these abnormalities. Prolonged unimproving cases of ARDS responded to sustained courses of ACS as in cases 1 and 3. Our experience, although limited and uncontrolled, suggests an important role for a sustained course of ACS in the treatment

Table 2—ARDS: Classification and Mortality

<table>
<thead>
<tr>
<th>Classification</th>
<th>Historic*</th>
<th>ARDS Treated with Steroids†</th>
</tr>
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<tbody>
<tr>
<td>I. Established ARDS (&gt;72 Hours)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— Initial process controlled</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. ARDS alone</td>
<td>Unknown</td>
<td>0% (0/5)</td>
</tr>
<tr>
<td>2. ARDS + additional organ dysfunction</td>
<td>Unknown</td>
<td>40% (2/5)</td>
</tr>
<tr>
<td>Totals</td>
<td>59% (22/37)</td>
<td>20% (2/10)</td>
</tr>
<tr>
<td>II. Acute ARDS (&lt;72 Hours)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— Initial process uncontrolled</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Series totals for all patients (I + II)</td>
<td>68% (32/47)</td>
<td>20% (2/10)</td>
</tr>
</tbody>
</table>

*Montgomery et al.
†Current series
of selected ARDS patients with established disease. These observations enhance our perspective and understanding of ARDS and do not conflict with other published work.

The duration of the therapeutic dosage of ACS we utilized was designed to reverse the established inflammatory process of ARDS and in our patients, ACS worked effectively to achieve that goal. Reports which do not support the use of ACS have uniformly utilized treatment protocols which employ high dosages for short durations.\(^1,^{5}\) Bernard and associates\(^1\) have clearly shown in scientifically exacting studies that the administration of ACS at a dose of 30 mg/kg over 24 hours given early in the course of ARDS has little effect on the outcome of ARDS.\(^1\) Bone and associates\(^8\) administered ACS over 24 hours, Weigelt et al\(^3\) studied ACS over 48 hours, Coffin et al\(^6\) chose to administer one dose, and others gave ACS over three days.\(^3,^5\) In an experience similar to ours, Ashbaugh and Maier\(^4\) were able to demonstrate significant benefit with the use of ACS for periods of greater than three weeks. Dosage and duration of therapy are important variables which must be considered before dismissing any therapeutic drug as ineffective.

Our patient population differs from the population of studies not supporting the use of ACS. All of our patients had survived the primary or causative process, had persistent ARDS, and were free of obvious active infectious processes. If the primary process which produced ARDS cannot be controlled, therapy directed at ARDS, even if highly effective, cannot be expected to be more than a temporizing step in the course of events. Ashbaugh and Maier\(^4\) also successfully treated ARDS with ACS in patients who had established ARDS as their primary clinical problem. However, in reports of studies which did not demonstrate benefit from high dose, short duration therapy, the duration of ARDS before treatment was brief and the state of the process which initiated the ARDS is not mentioned. By treating only patients with established ARDS, we have selected those most likely to respond.

We believe that our selection of patients with established ARDS for treatment with ACS does not provide a complete explanation for our findings. A study of the natural history of ARDS indicates progression of the primary or causative process occurs in one-fifth of all patients and results in one-third of all deaths within 72 hours.\(^9\) When this 20 percent of patients who died with ARDS within 72 hours is excluded, the remaining patients still have a 59 percent mortality (Table 2). This evidence suggests a substantial mortality for patients we have labeled as having established ARDS which is far in excess of the 20 percent we observed. Ashbaugh and Maier,\(^6\) treating established ARDS with sustained ACS, also observed a mortality rate of 20 percent. This experience and their report, both anecdotal in character, represent the only data available on patients with established ARDS treated with a sustained course of ACS.

In an effort to define our patient population, we have utilized the classification system in Table 2. The classification we propose separates patient populations based on the duration of the ARDS. We reason that by defining established ARDS as beginning at 72 hours, the causative process will have been controlled in those patients. We further divided the established ARDS group into those with isolated ARDS or complicated ARDS (additional organ dysfunction) since we reasoned mortality should be related to the complexity of the clinical problems. Five of our patients had uncomplicated ARDS which may be an explanation for our good results. Since our report is an uncontrolled experience, we used the work of Montgomery and associates\(^8\) on the natural history of ARDS for comparison. It is the only data from which mortality of patients with what we have defined as established ARDS can be calculated.

Further complicating the picture, several works which argue against the use of ACS in ARDS studied a different population of patients. They studied the treatment of conditions that are highly associated with ARDS to see if ACS would lessen the incidence or severity of the ARDS which developed in their populations.\(^3,^5\) In addition, they used high dose, short duration therapy. These works were not designed to study the treatment of ARDS, but rather the prevention or the amelioration of it. They provide evidence that short-term, high-dose treatment does not prevent ARDS or ameliorate its severity if it subsequently occurs, but they do not address the question of whether a longer therapeutic course of ACS is effective for established ARDS.

The \(^{69}\)Ga citrate lung scans we performed demonstrated significant pulmonary uptake of the isotope. The \(^{69}\)Ga uptake is an indicator of active inflammation.\(^7,^8\) Although the mechanism of gallium uptake by the lungs is not clear, leukocytes are known to concentrate the isotope and uptake is thought to be dependent upon the leukocyte mass available to bind the radioisotope.\(^11-13\) While isolated descriptions of significant \(^{69}\)Ga uptake in ARDS patients have been reported, no organized study has been published.\(^14,^15\) The finding does conform with current knowledge of pathology and pathogenesis.\(^16-20\) The magnitude of the uptake in our ARDS patients suggests an intense inflammatory response to their lung injuries. The active inflammatory condition demonstrated by \(^{69}\)Ga in our patients is additional evidence that an appropriately administered anti-inflammatory agent should, if the injurious process is controlled, benefit individuals with ARDS.
The ACS therapy is employed in a variety of disease states because of its anti-inflammatory properties. Two principles of ACS therapy learned from the treatment of inflammatory diseases should be applicable to their use in established ARDS.\(^\text{21}\) In the initiation of therapy, a satisfactory dosage at frequent enough intervals over a long enough period of time is required to achieve a suppression of inflammatory activity. And, if suppression is not achieved prior to its reduction or cessation, relapse is often observed. In many inflammatory disease states, a treatment course of weeks is required to bring the disease process under control. Before ACS is dismissed as ineffective in the treatment of established ARDS, sustained therapy should be employed.

We believe that a sustained course of ACS is effective in the treatment of selected patients with established ARDS. It has been extremely effective in this limited, uncontrolled, anecdotal experience. We believe there is a subpopulation of ARDS patients with established disease who benefit from the use of a sustained course of ACS. Controlled investigations are indicated to define this population and its appropriate treatment.

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REFERENCES