Clinical Conference on Management Dilemmas*

Progressive Infiltrates and Respiratory Failure

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Key words: acute interstitial pneumonitis; ARDS; barotrauma; corticosteroid therapy; Hamman-Rich syndrome; liquid ventilation; mechanical ventilation; positive end-expiratory pressure; protective ventilation; surfactant

Abbreviations: AIP = acute interstitial pneumonia; BOOP = bronchiolitis obliterans organizing pneumonia; DAD = diffuse alveolar damage; ESR = erythrocyte sedimentation rate; FiO₂ = fraction of inspired oxygen; LDH = lactate dehydrogenase; NIH = National Institutes of Health; Pplat = plateau pressure; SaO₂ = arterial oxygen saturation; VT = tidal volume

Pulmonary clinicians are often faced with management problems for which there are no answers at hand, either because there is no literature that definitely gives answers, because there are conflicting data in the literature, or because the circumstances surrounding the clinical cases are unusual enough to prevent the application of existing scientific knowledge. When faced with these problems, clinicians are forced to make decisions based on a logical extension of their scientific knowledge into uncharted clinical waters. They are forced to make judgments based on the conviction of their speculations and on prior experiences.

This case conference addresses difficult management problems without singularly correct decisions; its object is not necessarily to seek consensus. Defining the exact issues, formulating rationales for decision making, and committing to the decisions themselves are all equally important in this presentation. This is a real case in which the decisions were made by the “treating pulmonologist” or “treating intensivist” without input from the other participants. The “responses of pulmonary experts” are given only with the knowledge of the case presentation up to the moment at which each expert gave his or her decision and without the knowledge of any of the other opinions rendered. The last “commentary” opinions are given only with the knowledge of the “case presentation” and the remarks of the “treating pulmonologist (or intensivist)” but without the knowledge of any of the other opinions rendered. Although the “commentary” opinions are the last in the sequence of this presentation, they are not necessarily offered as definitive solutions to the problems posed in the case. The reader is the ultimate arbiter in this presentation of decision-making alternatives.

Case Presentation

A 49-year-old homosexual African-American man presented with new onset of exertional dyspnea for 3 months. The dyspnea had worsened over the 3 weeks prior to admission and was associated with a nonproductive cough and streaky hemoptysis. On admission, the patient appeared well nourished and in no acute distress. BP was 152/75 mm Hg, heart rate, 119 beats/min; respiratory rate, 18 breaths/min; and temperature, 97.6°F. Lung examination revealed diffuse coarse rales. Cardiac, extremity, and abdominal examinations were unremarkable. Chest radiograph...
(Fig 1) demonstrated bilateral interstitial infiltrates. Arterial blood gas on room air revealed the pH was 7.46; $\text{PaCO}_2$, 39 mm Hg; $\text{PaO}_2$, 34 mm Hg; and arterial oxygen saturation ($\text{SaO}_2$), 69%. WBC count was 13,400 cells/cm$^3$ (79% neutrophils, 2% bands); hemoglobin, 13 g/dL; hematocrit, 42%; platelet count, 348,000. Electrolytes, BUN, and creatinine were normal; lactate dehydrogenase (LDH) was 1,007 U/L (normal, 313 to 618 U/L); all other liver chemistries were normal.

The patient was treated with IV piperacillin/tazobactam, erythromycin, furosemide, and cotrimoxazole, and oral prednisone 60 mg bid. Blood and sputum cultures had no growth. A two-dimensional echocardiogram showed mild biventricular hypertrophy, right atrial enlargement, and normal systolic ventricular function. Initially, 2 L/min of oxygen via nasal cannula resulted in an $\text{SaO}_2$ of 91%; however, over the next 2 days, the respiratory rate increased to 34 breaths/min, and the $\text{SaO}_2$ fell to 84%. The fraction of inspired oxygen ($F_{\text{io}}_2$) was increased to 0.40 via mask, and $\text{SaO}_2$ improved to 93%.

The patient was transferred to the medical ICU, and on the fourth hospital day, bronchoscopy demonstrated normal bronchial mucosa, minimal secretions, and no endobronchial lesions. Stains and cultures of bronchial washings were negative for Pneumocystis, acid-fast bacilli, fungi, bacteria, and viruses. However, because of complications during the procedure, including unstable respiratory parameters, BAL and transbronchial biopsy were judged too dangerous and were not performed. The results of the HIV-1 test were negative, and cotrimoxazole and prednisone were discontinued. The erythrocyte sedimentation rate (ESR) was 78 mm/h (normal, 0 to 15 mm/h). The antinuclear antibody (ANA) titer was 1:80 with a cytoplasmic pattern; the antineutrophilic cytoplasmic antibody test was negative. Serum IgG and IgA levels were 2,598 mg/dL (normal, 564 to 1,765 mg/dL) and 616 mg/dL (normal, 85 to 385 mg/dL), respectively; serum IgM, C3, and C4 levels were normal. Antiglomerular basement membrane antibodies were not present.

Respiratory rates increased to 32 to 40 breaths/min requiring an $F_{\text{io}}_2$ of 0.60 to maintain an $\text{SaO}_2$ of >90%. The chest radiograph showed worsening infiltrates (Fig 2). On the sixth hospital day, a right-heart catheter was placed to confirm that the infiltrates were noncardiogenic in nature (see Table 1 for hemodynamic data). The patient was afebrile. The pulmonary artery catheter was removed on hospital day 8.

On the ninth hospital day, the respiratory rate rose to 60 breaths/min and the heart rate to 130 beats/min. Arterial blood gases on an $F_{\text{io}}_2$ of 0.55 were as follows: pH, 7.41; $\text{PaCO}_2$, 39 mm Hg; $\text{PaO}_2$, 54 mm Hg; and $\text{SaO}_2$, 88%. Fever developed and rose to 102°F, and the chest radiograph infiltrates were reported to have worsened. The WBC count increased from 17,000 to 27,000 cells/cm$^3$. The patient was intubated and mechanically ventilated in the assist-control mode with a tidal volume ($V_t$) of 800 mL, a rate of 12/min, and an $F_{\text{io}}_2$ of 1.00. Arterial blood gases were now a pH of 7.26; $\text{PaCO}_2$, 53 mm Hg; $\text{PaO}_2$, 76 mm Hg; and $\text{SaO}_2$, 93%. Levofloxacin was added to the other antibiotics. Blood, urine, and sputum cultures were repeated but were subsequently negative.

Several hours after the initiation of mechanical ventilation, the

<table>
<thead>
<tr>
<th>Time</th>
<th>Sam. Initial Reading</th>
<th>10PM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>96</td>
<td>118</td>
</tr>
<tr>
<td>Central venous pressure, mm Hg</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure, mm Hg</td>
<td>31</td>
<td>41</td>
</tr>
<tr>
<td>Pulmonary artery occlusion pressure, mm Hg</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Mean systemic arterial pressure, mm Hg</td>
<td>96</td>
<td>84</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>9.7</td>
<td>17.6</td>
</tr>
<tr>
<td>Cardiac index, L/min/m$^2$</td>
<td>4.7</td>
<td>8.5</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>101.0</td>
<td>149.2</td>
</tr>
<tr>
<td>Systemic vascular resistance, dyne $\cdot$ s $\cdot$ cm$^{-5}$</td>
<td>742</td>
<td>341</td>
</tr>
<tr>
<td>Pulmonary vascular resistance, dyne $\cdot$ s $\cdot$ cm$^{-5}$</td>
<td>148</td>
<td>132</td>
</tr>
</tbody>
</table>

The patient was transferred to the medical ICU, and on the fourth hospital day, bronchoscopy demonstrated normal bronchial mucosa, minimal secretions, and no endobronchial lesions. Stains and cultures of bronchial washings were negative for Pneumocystis, acid-fast bacilli, fungi, bacteria, and viruses. However, because of complications during the procedure, including unstable respiratory parameters, BAL and transbronchial biopsy were judged too dangerous and were not performed. The results of the HIV-1 test were negative, and cotrimoxazole and prednisone were discontinued. The erythrocyte sedimentation rate (ESR) was 78 mm/h (normal, 0 to 15 mm/h). The antinuclear antibody (ANA) titer was 1:80 with a cytoplasmic pattern; the antineutrophilic cytoplasmic antibody test was negative. Serum IgG and IgA levels were 2,598 mg/dL (normal, 564 to 1,765 mg/dL) and 616 mg/dL (normal, 85 to 385 mg/dL), respectively; serum IgM, C3, and C4 levels were normal. Antiglomerular basement membrane antibodies were not present.
patient’s BP fell to 89/48 mm Hg, prompting fluid administration, 5 μg/kg/min of dopamine, and 5 μg/kg/min of dobutamine. A right-heart catheter was inserted for hypotension (see Table 2 for hemodynamic data). On a Vt of 800 mL and PEEP of 14 cm H2O, the peak airway pressure was 84 cm H2O; plateau pressure was 82 cm H2O; respiratory dynamic and static compliances were 11.4 and 11.8 mL/cm H2O, respectively. Arterial blood gases were pH 7.25; PaCO2, 55 mm Hg; PaO2, 70 mm Hg; and SaO2, 90%.

**Table 2—Hemodynamics on Hospital Day 9**

<table>
<thead>
<tr>
<th>Time</th>
<th>6PM, Initial Reading (on Dopamine and Dobutamine)</th>
<th>10PM (After Increased Dopamine, IV Fluids, No Dobutamine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>134</td>
<td>113</td>
</tr>
<tr>
<td>Central venous pressure, mm Hg</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure, mm Hg</td>
<td>42</td>
<td>51</td>
</tr>
<tr>
<td>Pulmonary artery occlusion pressure, mm Hg</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>Mean systemic arterial pressure, mm Hg</td>
<td>63</td>
<td>94</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>10.0</td>
<td>6.3</td>
</tr>
<tr>
<td>Cardiac index, L/min/m²</td>
<td>4.8</td>
<td>3.0</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>74.6</td>
<td>55.8</td>
</tr>
<tr>
<td>Systemic vascular resistance, dyne ⋅ s ⋅ cm⁻⁵</td>
<td>400</td>
<td>977</td>
</tr>
<tr>
<td>Pulmonary vascular resistance, dyne ⋅ s ⋅ cm⁻⁵</td>
<td>208</td>
<td>419</td>
</tr>
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**Response of the Pulmonary Experts**

**John J. Marini, MD, FCCP, St. Paul, MN**

The accelerating course of this patient’s hypoxic respiratory failure despite therapy suggests the likelihood of either an unconsidered or discarded diagnosis, or the presence of a second process superimposed on the first. At a minimum, a missed diagnosis wastes resources, and at worst, it aggravates a potentially treatable but lethal disease. Therefore, in my view, it is imperative to establish the underlying diagnosis with reasonable certainty while initiating supportive treatment.

The condition that initiated this patient’s problems cannot be confidently established from the limited data at hand. Medical, occupational, smoking, and social histories are not available. The 3 months of exertional dyspnea prior to hospitalization, in association with reduced lung volumes, generalized infiltrates that initially predominated in the lower lung fields, and streaky hemoptyis suggest an underlying disease such as accelerated interstitial pneumonitis (Hamman-Rich syndrome), aspiration pneumonitis, embolism or thrombosis, bronchiolitis obliterans organizing pneumonia (BOOP), limited Wegener’s granulomatosis, parenchymal hemorrhage, or congestive heart failure. Elevations of LDH, ESR, serum immunoglobulins, and antinuclear antibodies are nonspecific markers of inflammation that do not give insight to the underlying pathophysiology. Although this hypertensive patient might be at risk for diastolic dysfunction, echocardiographic and pulmonary artery catheterization data argued strongly against a primary role for systolic myocardial dysfunction or for impairment of the left-sided cardiac valves. Extensive arborizing air bronchograms are evident, a radiographic sign that argues further against heart failure as the primary problem.1

The possibility of underlying immune compromise and secondary infection with Pneumocystis or another opportunistic organism was considered, but dismissed on the strength of a negative HIV-1 test and unproductive bronchial washings. A truly negative HIV-1 test makes AIDS unlikely, but not impossible, especially if the virus were acquired very recently or if the immune compromise results from an uncommon strain. We are not told the total lymphocyte count, nor the complete leukocyte differential. In view of the patient’s sexual history and elevated LDH, I would have ordered a CD4 count and a helper/suppressor ratio if the total lymphocyte count were subnormal. In an immune-compromised patient, invasive aspergillosis is a devastating disease that can present in this fashion and often eludes diagnosis.

Normal serum indicators of renal function, as well as normal hemoglobin levels and cardiac filling pressures, suggest a problem largely confined to the lungs. Pulmonary neoplasia (eg, adenocarcinoma or alveolar cell carcinoma) can present with a subacute course and extensive pulmonary infiltration without involving extrapulmonary vital organs.

It is surprising that despite extensive bibasilar infiltrates, the patient’s profound hypoxemia initially responded to modest concentrations of inspired oxygen without the need for continuous positive airway pressure. Reduced hypoxic drive to breathe and,
consequently, less work of breathing and metabolic stress, could have amplified the benefit of supplemental oxygen. Widely varying and extremely elevated values for cardiac output (up to 17 L/min), at a time when the patient did not require mechanical ventilation, suggest a hypermetabolic condition (eg, liver disease, sepsis) or the possibility of measurement error. Such artifacts may arise from tricuspid regurgitation or, more rarely, from direct transseptal flow of venous blood and thermal indicator to the left circuit under the influence of elevated pulmonary arterial pressure (an oxygen-induced reduction of pulmonary artery pressure and intracardiac shunt might help to explain the unexpectedly dramatic effect of inspired oxygen on arterial oxygenation).

How would my management have differed? Although it is always risky to conjecture from a distance, I feel certain that I would have intubated the patient, if necessary, to allow lung lavage to be conducted safely. A thin-section CT and/or spiral CT with IV contrast might also have helped to classify the nature of the pulmonary infiltrates. If these results proved nondiagnostic, I would have strongly considered a videofluoroscopic or even open biopsy to establish the diagnosis. With a reliable diagnosis established, high-dose corticosteroid therapy and/or antifungal treatments could have been undertaken or withheld with more confidence.

Whatever the underlying process, I would not have allowed airway pressures to rise as high as those described. Although a patient with a stiff chest wall may tolerate relatively high pressures without alveolar overdistention, end-inspiratory plateau pressures exceeding 35 cm H$_2$O should be applied only with caution. Laboratory experiments unequivocally demonstrate that high tidal inflation pressures cause hemorrhagic edema, disrupt functional lung units, and may predispose to bacteremia. Moreover, in clinical practice, peak airway pressures that exceed 60 cm H$_2$O are associated with a high incidence of life-threatening alveolar rupture (barotrauma). Two recent clinical studies suggest that limiting tidal alveolar pressures to values below those normally associated with total lung capacity (35 cm H$_2$O in most patients) may reduce morbidity. A multicenter trial of the low-V$_t$, pressure-limiting approach to ARDS ventilation was recently terminated after a 25% reduction in mortality was documented using this strategy. Another study placed emphasis on re-aerating collapsed lung tissue without overstretching the lung parenchyma. To achieve both objectives, high PEEP levels were used, V$_t$ was reduced, and hypercapnia was accepted as a consequence. Recruitment maneuvers (sustained applications of moderately high transpulmonary pressure) were often used to help establish airway patency.

Data from that study emphasized the central importance of maintaining adequate end-expiratory lung volume—a more important determinant of survival than “driving pressure” (a direct correlate of V$_t$). There is also a growing consensus that prone positioning, a highly effective method for recruitment, often improves oxygenation in this setting and may help avert ventilator-induced lung injury. This benefit may accrue because prone positioning sustains relatively high regional transpulmonary forces and establishes airway patency in the well-perfused dorsal areas.

In the case at hand, I would have initiated a strategy geared toward establishing and preserving patency of the open lung without exceeding plateau pressures of ~35 cm H$_2$O. I generally allow hypercapnia but keep pH > 7.20. Therefore, after intubation, completion of diagnostic bronchoscopy, and initiation of a high PEEP/low V$_t$ strategy, I would have attempted recruiting maneuvers and repeated them after prone positioning. If the biopsy did not demonstrate invasive fungi or otherwise contraindicate their use, corticosteroids may have helped this patient, perhaps at very high doses. Although the documentation for steroid use is currently limited to the important, yet unconfirmed, work of Meduri and colleagues, my own experience is in agreement that corticosteroids are indeed helpful in the later phases of ARDS.

Warren R. Summer, MD, FCCP, New Orleans, LA

This case presents with a wide range of etiologic possibilities that could be responsible for the subacute illness and acute decline. Despite a negative HIV-1 enzyme-linked immunosorbent assay, infection with human T-cell lymphotrophic virus (HTLV)-1 is still possible with resultant opportunistic infection or noninfectious lung injury (eg, lymphocytic interstitial pneumonitis, Kaposi’s sarcoma, etc). Of course, unusual presentations of common infections or diffuse alveolar damage (DAD) in an immunocompetent patient is also a possibility. The rapid decline in this patient on day 9 may be related to progression of the primary disease due to lack of appropriate therapy, discontinuation of prednisone, or a nosocomial infection. Despite a lack of evidence supporting improved outcome with invasive diagnostic interventions in groups of patients with acute lung disease, I would have attempted a repeat BAL on day 5 or even video-assisted thoracoscopic surgery with biopsy on day 6 because a specific diagnosis is likely to help direct therapy in a puzzling individual patient. However, in the ICU, we often have to focus
on a patient’s compromised cardiopulmonary status and initiate aggressive therapy with no clear diagnosis.

Optimum management of ARDS is still problematic, and the American-European Consensus Conference on ARDS has outlined several excellent goals. The findings of the recent National Institutes of Health (NIH) ARDS Network Clinical Trial has firmly demonstrated that low Vt (6 mL/kg) and presumably lung inflation below the upper inflection point of the volume-pressure curve reduces mortality by > 25%. Other experimental data and clinical trials have demonstrated benefit with PEEP at or above the lower inflection point. In this patient, a Vt of 800 mL is probably overdistending many alveolar units with potential ventilator-induced lung injury. Although we don’t know the “best” PEEP for any given individual, I take a practical approach to reach my gas exchange goals. I try to adjust PEEP according to the static volume-pressure curve characteristics. I begin ventilation with low Vt (~6 mL/kg), a PEEP of 5 cm H2O, and an FIO2 of 1.0. Then I raise the PEEP 2 to 4 cm H2O every 5 min until SaO2 exceeds 90% or until the plateau pressure (Pplat) rises to ~30 cm H2O. This usually results in recruitment of lung units without overdistention and usually allows a reduction in FIO2 to < 0.75, avoiding oxygen toxicity. When these targets have been achieved, I usually increase the PEEP by another 2 to 4 cm H2O, looking for an additional large increase in Pao2 (which would suggest that more recruitable lung is present) without exceeding a Pplat of 35 cm H2O. The usual PEEP is 14 cm H2O. A recent clinical study suggested that overdistention may be occurring in some patients at low PEEP despite an improvement in SaO2.10 However, maintaining low Vt and not allowing Pplat to exceed our target will likely prevent significant ventilator-induced lung injury. If the Pao2 is still < 55 mm Hg or if the FIO2 is > 0.75, a slight prolongation of the inspiratory time to increase mean airway pressure may further improve Pao2 into the low 60s, which would be acceptable. The Pplat of 82 cm H2O in this patient is much too high. The calculated static compliance is extremely low because he is being ventilated above his upper inflection point with excessive Vt.11 His compliance is likely to be better if Vt is only 6 mL/kg. Low Vt may compromise gas exchange; however, a slow elevation of PCO2 appears well-tolerated in most patients. Low Vt may also produce oxygenation difficulties, but these can be overcome (as mentioned above) and mortality will be reduced.

I acknowledge that sepsis is a concern in this patient, but my major concern at this juncture is not sepsis (although it is perhaps present). Rather, my greatest concern rests with the ventilator-induced elevations in intrathoracic pressure to which this patient has been subjected, and that may explain some of the more worrisome hemodynamic findings that others might attribute to sepsis. Although very stiff lungs will not always transmit ventilator-induced positive airway pressures to the pleural space (which could decrease cardiac output), the combination of high PEEP, large inflation pressures, and diuresis can result in decrements in cardiac output,12 as seen in this patient. Lung overinflation may impinge on the cardiac fossa, leading to decreased venous return, and also may promote ventricular interdependence by physiologically restricting the heart. Thus, the relatively low cardiac indexes in this patient—4.8 and 3.0 L/min/m2 (see Table 2)—probably reflect a ventilator-induced effect. However, in spite of this attenuation of cardiac index, it is still clinically acceptable at this point, and I would not try to increase venous return through fluid administration (in view of the risk of increasing lung edema and worsening gas exchange). I would rather initially treat the patient’s altered hemodynamics by manipulating the ventilator in order to reduce mean airway pressure, principally through reductions in Vt.

In summary, major attention must be paid to oxygen delivery and avoiding ventilator-induced lung injury. If hemodynamic stability cannot be achieved (mean arterial pressure in this patient was 84 mm Hg) by Vt and pleural pressure reduction, the use of norepinephrine should be instituted and treatment with dopamine and dobutamine stopped. Treatment of nosocomial infection with broad coverage for meticillin-resistant Staphylococcus aureus and Pseudomonas is also indicated on day 9. Optimizing this patient’s cardiopulmonary status may allow for further diagnostic evaluation.

**HOSPITAL COURSE**

Because of the high airway pressures, the Vt was reduced to 700 mL, the PEEP increased to 17 cm H2O, and the inspiratory:expiratory ratio was changed from 1:1.7 to 1:1. But the Pao2 fell to 51 mm Hg and the oxygen saturation to 79%. Thus, the Vt was changed back to 800 mL, and the Pao2 and oxygen saturation returned to 70 mm Hg and 90%, respectively. Open lung biopsy was considered, but the patient was believed to be too unstable to undergo the procedure.

On the 10th hospital day, subcutaneous emphysema was noted on physical examination, and the chest radiograph and CT scan showed diffuse alveolar infiltrates, extensive pneumomediastinum, pneumoperitoneum, and a small right pneumothorax (Fig 3). A right chest tube was placed. Temperature
dipped to 94.0°F, PaO₂ fell to 43 mm Hg, and creatinine rose to 2.6 mg/dL. Methylprednisolone was begun empirically, and midazolam and vecuronium infusions were discontinued. In spite of this, the patient remained comatose: he was unresponsive to stimuli and diffusely flaccid, and lacked light, corneal, and oculocephalic reflexes. On hospital day 12, arterial blood gases revealed a pH of 7.22, PaCO₂ of 44 mm Hg, PaO₂ of 59 mm Hg, an oxygen saturation of 88% on a VT of 800 mL, a respiratory rate of 22/min, an FiO₂ of 1.00, and 20 cm H₂O of PEEP. On day 15, a left chest tube was inserted for a tension pneumothorax (Fig 4). On the following day, a nuclear brain scan was performed and revealed no cerebral blood flow. The regional organ procurement organization was consulted; however, the patient was refused as an organ donor. After the family was consulted, the patient was removed from life support and died. [Editor's note: The decisions against bronchoscopic lavage, transbronchial biopsy, and open lung biopsy in this case were not made by the authors.]

Comments of the Treating Intensivist in this Case
Timothy G. Janz, MD, FCCP; Dayton, OH

The operating diagnosis of this patient was pneumonia complicated by septic shock and ARDS. The respiratory failure was particularly complicated by progressive hypoxemia, persistent hypercapnia, and excessively high airway pressures. Barotrauma and multiple organ failure complicated the ARDS.

Over the last several years, animal and human studies have documented the existence of ventilator-induced lung injury. Currently advocated “lung-protective strategies” for ventilatory management include the use of VTs of 5 to 7 mL/kg, the avoidance of peak airway pressures of >40 to 50 cm H₂O, Pplats of >30 to 35 cm H₂O, inverse ratio ventilation, permissive hypercapnia, and PEEP titrated to the inflection point on the static pressure-volume curve. Rather than constructing a pressure-volume curve, we titrated the PEEP to optimize oxygen delivery and assure adequate arterial oxygenation.
Several methods for optimizing PEEP therapy have been suggested, but none have proven to be superior to other methods.\(^8\)\(^,\)\(^16\) My major concern has generally been arterial oxygenation. At the time of this case, none of the above-mentioned “advocated approaches” to mechanical ventilation in ARDS had been conclusively shown to be superior to more conventional, volume-controlled methods, eg, VTs of 10 to 12 mL/kg. Because of the conflicting literature, my own approach has been to use a conventional method of mechanical ventilation with PEEP therapy, unless airway pressures are consistently high, eg, Pplat of > 30 to 35 cm H\(_2\)O or peak airway pressures of > 40 cm H\(_2\)O. When they are high, I prefer to use smaller VTs (eg, 6 to 8 mL/kg) and, if needed, inverse-ratio ventilation.\(^17\)

However, a recent multicenter ARDS study was prematurely stopped when patients ventilated with 6 mL/kg VTs had a 25% reduction in mortality compared with patients ventilated with 12 mL/kg VTs.\(^4\) Although the study data were not available when we managed this patient, use of smaller VTs in ARDS may prove to be superior to more conventional VTs. However, in our patient, we found that a PEEP of 17 to 20 cm H\(_2\)O accomplished our above-stated goals, with F\(_{\text{IO}}\(_2\)) ranging from 70 to 100%. Because of the very high airway pressures and eventual development of barotrauma, the level of PEEP was not increased further, and the goal of lowering the F\(_{\text{IO}}\(_2\)) was sacrificed. Although oxygen toxicity is well described in the literature, its clinical occurrence, particularly in the setting of ARDS, is uncertain.\(^18\) Because the clinical presentation of oxygen toxicity is similar to that of ARDS, its contribution to morbidity in this setting is confusing. The F\(_{\text{IO}}\(_2\)) in our patient ranged from 70 to 100% for 7 to 8 days. Despite these high F\(_{\text{IO}}\(_2\)) levels for a relatively long time, I do not think our patient developed oxygen toxicity, because his PaO\(_2\) values and chest radiograph stabilized and showed mild improvement in the days prior to his being disconnected from life support.

The initial VT of 800 mL (approximately 9.5 mL/kg) was reduced in an attempt to decrease the high airway pressures. However, as the VT was reduced, the patient became more hypoxic. Repeated attempts to lower the VT were uniformly associated with reductions in our ability to oxygenate the patient. Consequently, the VT was maintained at the initial setting of 800 mL. We tried inverse-ratio ventilation, but there was no significant improvement in either oxygenation or ventilation. Some controlled trials have shown that as many as 75% of patients with ARDS have improvement in oxygenation when moved from a supine to a prone position.\(^8\) Prone positioning was considered, but because of the technical difficulties of positioning the patient, it was abandoned. Despite the inherent technical difficulties, a trial of prone positioning might have improved gas exchange, but we did not feel this would have ultimately altered the progression of the disease or the patient’s hospital course.

Although corticosteroids have not been proven to be helpful in the early stages of ARDS,\(^19\) there is data suggesting that their use during the fibroproliferative phase of ARDS may be of benefit.\(^7\) Based on this data and the severity of the disease in this case, we empirically began corticosteroids 7 to 8 days after the onset of ARDS (hospital day 10). Unfortunately, we were unable to demonstrate any advantage with their use in this patient. I am not currently convinced that the data supports the use of corticosteroids in all or most cases of ARDS, although the rationale for their use is appealing.

**AUTOPSY**

At autopsy, the lungs were edematous and the right and left lungs weighed 1,200 and 1,000 g, respectively. The lungs were “brick red” with gross “hepatization.” Figure 5 shows a microscopic field from the patient’s lungs. The pathology report stated that on sectioning, both lungs showed diffuse hemorrhagic consolidation. The bronchi contained large amounts of bloody mucus. No thromboemboli were found. Microscopic examination revealed diffuse proliferation of fibroblasts within the alveoli and alveolar septa with fibrin lay-down. Increased numbers of type II pneumonocytes and squamous metaplastic cells were found in the alveoli. Small hemorrhages were also noted in the alveoli and interstitium with interstitial edema. Vascular intimal fibrosis was seen. “Diffuse alveolar damage” was referred to. The final bacterial, mycobacterial, and viral cultures revealed no growth. The final pathologic diagnosis was reported as “acute interstitial pneumonitis.”

**COMMENTARY**

G. Umberto Meduri, MD, FCCP, Memphis, TN

This patient presented with a 3-month history of exertional dyspnea that worsened in the 3 weeks prior to admission. Such a subacute presentation excludes ARDS, a disease characterized by acute onset (usually < 48 h) of bilateral diffuse alveolar infiltrates with severe hypoxemia, following a known precipitating event (eg, sepsis, trauma, shock, etc).\(^20\)

The patient had several factors indicating the presence of a rapidly progressive interstitial lung disease: (1) failure to resolve spontaneously over a period of 3 months with recent clinical deterioration;
(2) severe hypoxemia at rest; (3) diffuse bilateral interstitial infiltrates on chest radiograph; and (4) echocardiographic evidence of pulmonary hypertension with right atrial enlargement. The immunologic profile revealed several abnormalities (elevated ESR, ANA, serum IgG and IgA levels) usually not observed in ARDS. In the presence of a nondiagnostic incomplete bronchoscopy (no BAL or transbronchial biopsies obtained), I would have subjected the patient to open lung biopsy early in the hospital course.

The differential diagnosis included several conditions with a similar clinicoradiographic presentation, such as usual interstitial pneumonia, desquamative interstitial pneumonia, diffuse alveolar hemorrhage syndrome (history of hemoptysis), acute eosinophilic lung disease, rapidly progressive interstitial pneumonitis associated with connective tissue diseases, hypersensitivity pneumonitis, and so forth.

Recently it has been appreciated that a short course of glucocorticoids may increase proinflammatory cytokine (e.g., TNF-α) release in response to a later inflammatory signal for a period of ≥ 6 days after steroid discontinuation. Theoretically, the rapid deterioration observed in this patient in association with a new suspected infection might have been related to an amplification of the inflammatory response from prior use of a short course of glucocorticoids. Conversely, recent randomized trials indicate a beneficial response to prolonged (7 to 12 days) glucocorticoid administration in patients with septic shock.

In this patient, methylprednisolone treatment for presumed unresolved ARDS was initiated on hospital day 10 and was not associated with a physiologic improvement. This response is not surprising, as acute interstitial pneumonia (AIP) is a condition unlikely to be responsive to glucocorticoids once acute respiratory failure develops. The histologic findings of AIP resemble the organizing stage of DAD. In our institutional experience, the histologic features of AIP resemble those of ARDS patients who failed to respond to methylprednisolone treatment, and include dense acellular fibrosis, loss of alveolar architecture, and presence of arteriolar subintimal fibroproliferation. In our experience, the following variables were significantly different among responders and nonresponders: presence of preserved alveolar architecture (p = 0.045), myxoid-type alveolar and interstitial fibrosis (p = 0.045), coexistent intraluminal bronchiolar fibrosis (p = 0.0045), and absence of arteriolar subintimal fibroproliferation (p = 0.045).

I believe prolonged methylprednisolone administration in ARDS patients failing to improve in the first week of mechanical ventilation is the only treatment intervention shown to be associated with an effective and sustained biological and physiologic improvement, although it is not universally effective. Late institution (i.e., day 20 of ARDS) has been associated with a 50% failure rate. Furthermore, we have observed that morbidly obese patients frequently do not respond to treatment (unpublished data).

We have underscored the fact that during methylprednisolone treatment, infections develop in the absence of fever, and that a surveillance program is indispensable for detecting and treating infections that can otherwise be easily missed. Not uncommonly, we have observed a dampening of patient recovery in the presence of infection that is reversed following treatment of the infection.

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It should probably be said up front that it is likely that no therapeutic intervention would have had a

**Figure 5.** Top and bottom, microscopic fields from the patient’s lungs at autopsy revealing diffuse fibroblastic proliferation, fibrin lay-down, increased numbers of type II pneumocytes with metaplastic squamous cells found within alveoli, alveolar hemorrhages, alveolar and interstitial edema, and vascular intimal fibrosis.
major impact on the outcome in this case. Nevertheless, there are a number of points that are worthy of discussion. The epidemic of AIDS and our improved understanding of the manifestations of severe HIV infection have altered practice patterns significantly and largely for the better. Along these lines, the possibility of HIV-associated illness has led us to place other possible etiologies lower on the differential diagnosis. In this particular case, the probability of *Pneumocystis carinii* pneumonia or other HIV-associated diseases likely prompted a more leisurely approach to diagnosis than would otherwise have been pursued. By the fourth or possibly the fifth hospital day, in the setting of a negative HIV-1 test and negative bronchial washings, a more aggressive diagnostic approach may have been warranted. A narrow window of opportunity at this time may have allowed a thoracoscopic lung biopsy that was not possible later. Similarly, a high-resolution CT scan with thin cuts of the lung parenchyma may have provided additional diagnostic information. An early diagnosis of AIP may have prompted high-dose corticosteroid therapy and possibly cytotoxic therapy at that time. If the risks of obtaining a diagnostic tissue sample were believed to outweigh the benefits (as the clinicians in this case may have believed), I believe I would have instituted high-dose corticosteroid therapy earlier in the patient’s course. Unfortunately, only 20/20 hindsight makes this decision simple. At the bedside, it is never that straightforward. As this case illustrates, the alternative of expectant observation may be equally fraught with risk, particularly in the setting of rapidly progressive infiltrates with marked derangement of function.

Once intubated, the patient meets physiologic criteria for ARDS.27 There is no clear consensus of what defines the term *acute*, and time limits in various clinical trials vary. In this patient, although the history of dyspnea dates back 3 months, there is no information about the duration of the pulmonary infiltrates and so it is unclear if a diagnosis of ARDS is truly appropriate. At a minimum, the time course of the patient’s presentation is atypically prolonged and suggests that he may not respond or behave in ways that are the norm for ARDS. Nevertheless, there is no diagnostic test or assay that confirms or denies the presence of this syndrome, and recent lessons from the management of ARDS should apply. We know that ARDS is associated with intense inflammation in the lung and the eventual onset of a dramatic fibrotic response. A variety of therapies directed specifically at that inflammation (eg, early corticosteroid administration19) have been attempted without success. Direct instillation of pulmonary surfactant into the airways appears promising,13 but I do not believe this preliminary data is sufficient to support surfactant administration outside of controlled clinical trials. In contrast, recent information from animal studies and preliminary information from large-scale clinical trials now confirms that ventilator management can markedly influence outcome in patients with ARDS.

Substantial animal data demonstrate that positive-pressure ventilation with airway pressures as low as 30 cm H2O causes diffuse injury to the alveolar-capillary membrane.14,15 This is accompanied by influx of inflammatory cells and morphologic changes identical to those seen in patients with ARDS.28 This injury appears related to repetitive stretch of the alveolar-capillary membrane rather than pressure *per se*, as efforts to limit excursion of the lung minimize the injury. For this reason, application of PEEP in these animal models (presumably by limiting the decrease in the volume of alveoli in exhalation) protects against this injury.14 These observations lead to the obvious questions of whether these findings apply to ventilation of patients with lung injury and whether they apply to ventilator management strategies in general.

A recent NIH ARDS Network trial examined a low-volume vs a moderate-volume ventilation strategy. In this study, subjects with ARDS were randomly assigned to receive ventilation with either 6 mL/kg or 12 mL/kg VT. These volumes were calculated based on lean body weight and were closer to 5 and 11 mL/kg actual body weight in the study subjects. PEEP and *F*O₂ were adjusted based on algorithm and were comparable in both groups. Respiratory rate was adjusted to maintain minute volume at prerandomization levels. Pplat limits of 30 and 50 cm H2O were set for the small and large VT groups and algorithms were used to reduce VT if these limits were exceeded. Although pH and Pco₂ levels were comparable in the two groups, *Po₂* levels were marginally but significantly lower in the low-volume group. Despite this, the study was stopped before it reached its target patient accrual because of excess mortality in the subjects receiving larger VT (40%) compared with those receiving small VT (30%).4,20 I believe this study, together with similar results in smaller trials,5 conclusively demonstrates that ventilator strategies resulting in higher airway pressures and larger VT can damage human lungs as well as those of small or large animals. The occurrence of this survival benefit despite somewhat worse oxygenation parameters suggests that optimization of oxygenation may not be a sufficient goal for patients with ARDS and perhaps not for ventilated patients in general.

In this particular patient, I would have opted for a lung-protective strategy with initiation of low VT breaths from the outset. To achieve this, I prefer a
pressure-cycled ventilation strategy limiting the driving pressure to 20 cm H2O with an inspiratory time of 0.8 to 1.0 s, adding PEEP to a minimum of 8 to 10 cm H2O, and incrementing to achieve PaO2 of >50 mm Hg. However, acceptance of the principles of evidence-based medicine suggests that a strategy directly paralleling that used in the NIH trial may be preferable. I have not found inverse-ratio ventilation helpful except in very rare circumstances, and would not have used it here. Whether any of these approaches would have been successful in this unfortunate individual is not possible to predict.

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Acute infectious pneumonia or a pneumonia superimposed on a chronic process are appropriate considerations for a patient with 3 weeks of worsening dyspnea, cough, crackles, severe hypoxemia, and lower lung radiographic infiltrates. The fulminant course that then developed during the first 5 days of hospitalization suggests an infectious or septic-related ARDS. The findings also suggest a noninfectious catastrophic illness such as rapidly progressive BOOP or AIP. A lung biopsy would have been beneficial at this stage, especially for the discovery of an inflammatory process that could respond to corticosteroid therapy, but it was reported that the patient was too unstable.

During a recovery stage of a viral or atypical bacterial pneumonia, some patients may develop an “organizing pneumonia” process. This is an unlikely occurrence in this patient because the illness relentlessly progressed in severity and the process did not respond to corticosteroid therapy. The organizing pneumonia generally occurs during a stabilization phase and almost always responds to corticosteroid therapy. Lung tissue at autopsy, 12 days after hospitalization, indicated a diagnosis of AIP.

The clinical findings are typical of AIP. In an early report of eight patients and a later report of 29 patients, most had symptoms for <3 weeks. Many had an associated febrile or flu-like illness. The mean age was 30 years in the earlier study and 50 years in the later study. Male and female patients were equally affected. Nonproductive cough was common. Crackles were reported in 10% and hemoptysis occurred in one patient. These findings are indistinguishable from fulminant or rapidly progressive BOOP.

The chest radiograph in this patient was typical for AIP. Among a group of nine patients, the films showed bilateral airspace opacification in all of them, lower lungs in two. The chest CT scans showed ground-glass attenuation in all patients. Subpleural honeycombing was seen in three patients. Among 14 patients with AIP, the high-resolution CT scans showed increased attenuation without traction bronchiectasis in the exudative phase and increased attenuation with traction bronchiectasis and honeycombing in the fibrotic phase. Air bronchograms were prominent in this patient, suggestive of an infectious pneumonia, although this finding occurs in BOOP as well. Air bronchograms were not mentioned in the studies of the radiographic features of AIP although a case report of a 63-year-old woman with AIP indicated nodules with an air bronchiogram.

The histologic hallmark of AIP is interstitial fibrosis and edema associated with type II pneumocyte hyperplasia. There is extensive fibroblast proliferation and little collagen deposition. Findings of hyaline membranes reflect early findings in DAD. No histologic features are prognostically useful. AIP differs from BOOP because the former is associated with DAD, hyaline membranes, and interstitial fibrosis, while the latter is associated with granulation tissue organization in the bronchioles and alveoli. Corticosteroid therapy is considered the best treatment option, although most patients do not respond. The prognosis is poor. Survival rates range from a low of 14% to a high of 41%.

In summary, AIP is a distinct respiratory entity. It differs from acute eosinophilic pneumonia, fulminant BOOP, nonspecific interstitial pneumonia, desquamative interstitial pneumonia, and from usual interstitial pneumonia. Synonyms include acute diffuse interstitial fibrosis and the Hamman-Rich syndrome. Among the four patients described by Hamman and Rich, three were typical of AIP. The disorder is characterized by rapid-onset acute respiratory failure and poor response to corticosteroid therapy.

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