Serious Infectious Complications of Corticosteroid Therapy for COPD*

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We report seven elderly patients with COPD who developed serious infectious complications during prolonged treatment with high doses of corticosteroids. Infections included invasive pulmonary aspergillosis, Herpes simplex stomatitis and esophagitis, cytomegalovirus pneumonia, bacterial sepsis, fungemia and meningitis due to Cryptococcus neoformans. Each of the three patients who developed invasive aspergillus pneumonia died. The efficacy of prolonged therapy with high doses of corticosteroids in patients with COPD is not proven. These cases illustrate the potential for serious infections in patients with COPD treated with corticosteroids.

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The administration of corticosteroids is an accepted therapeutic modality for status asthmaticus and chronic asthma.1,2 With limited data to support their efficacy, corticosteroids are also used in outpatient and inpatient management of COPD.4-11 We report here seven patients with COPD who developed serious infections while receiving prolonged treatment with high doses of corticosteroids.

CASE REPORTS

C A S E 1

A 68-year-old man with COPD (Table 1) was receiving prednisone, 40 to 50 mg/day, for five months (Table 2) as an outpatient. He developed dysphagia and shortness of breath and was hospitalized. Pulmonary function tests were remarkable for reduced FEV↑ and FVC; the FEV↑/FVC ratio was 47 percent suggesting severe airway obstruction. The FEV↑ increased only 8 percent after administration of inhaled bronchodilators. Physical examination on admission revealed oral thrush. Potassium hydroxide smear was positive for Candida. Esophagoscopy revealed a friable ulcerated mucosa. Biopsy showed multinucleated giant cells consistent with Herpes simplex infection. Cultures grew Herpes simplex virus. The patient was treated with acyclovir, amphotericin B, acyclovir, and methylprednisolone, 20 to 40 mg per day. Fifty-four days after admission, a culture of sputum grew Aspergillus fumigatus. Over the next several days, he developed progressive bilateral pulmonary infiltrates, gastrointestinal bleeding, and intractable generalized seizures. He died 63 days after admission. Autopsy revealed bilateral necrotizing pneumonia. The left upper lobe of the lung showed extensive invasion of the vasculature by Aspergillus. In addition, cells containing inclusion bodies suggestive of cytomegalovirus were found throughout the lungs, lymph nodes, and duodenum.

C A S E 2

A 54-year-old man with insulin-dependent diabetes mellitus and COPD presented with increasing shortness of breath and hypoglycemia. His symptoms were attributed to an exacerbation of his lung disease with superimposed congestive heart failure. He was treated with aminophylline, diuretics, beta agonists, and methylprednisolone, 60 mg intravenously every six hours. Shortly after admission, he required intubation. He developed Staphylococcus aureus and Morganella morgagni sepsis three weeks after admission and was treated with oxacillin and cefotaxime. Renal failure developed and was attributed to sepsis. Methylprednisolone was continued at a dose of 50 mg/day. Over the next six weeks, he required ventilator support and intermittent hemodialysis. Cultures of blood and a femoral catheter tip culture grew Candida albicans. Treatment included vancomycin, tobramycin, amphotericin B, acyclovir, and methylprednisolone, 20 to 40 mg per day. Fifty-four days after admission, a culture of sputum grew Aspergillus fumigatus. Over the next several days, he developed progressive bilateral pulmonary infiltrates, gastrointestinal bleeding, and intractable generalized seizures. He died 63 days after admission. Autopsy revealed bilateral necrotizing pneumonia. The left upper lobe of the lung showed extensive invasion of the vasculature by Aspergillus. In addition, cells containing inclusion bodies suggestive of cytomegalovirus were found throughout the lungs, lymph nodes, and duodenum.

C A S E 3

A 90-year-old man with a history of COPD who had been treated with prednisone, 10 to 40 mg per day for more than two years, was admitted for dyspnea. Previous pulmonary function tests had demonstrated a baseline FEV↑ of 1.25 L that increased to 1.49 L after administration of bronchodilators. He was treated with aminophylline, beta-agonists, and methylprednisolone, 60 mg intravenously every six hours. His respiratory symptoms rapidly improved. Five days after admission, he complained of a painful left shoulder. Examination revealed a tender warm and erythematous shoulder with decreased range of motion. Aspiration of the joint revealed purulent material. Gram-positive cocci in clusters were seen on Gram stain and were later identified as Staphylococcus aureus. He was treated successfully with intravenous nafcillin, surgical drainage of his shoulder, and a reduction in the dose of corticosteroids.

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Table 1—Summary of Infections in Patients with COPD Treated with Prolonged High Doses of Corticosteroids

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/Sex</th>
<th>Underlying Disease</th>
<th>Infectious Complications</th>
<th>Treatment/Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68/male</td>
<td>COPD</td>
<td>Herpes simplex; esophagitis</td>
<td>Acyclovir/resolved</td>
</tr>
<tr>
<td>2</td>
<td>54/male</td>
<td>COPD, Diabetes mellitus</td>
<td>Oral candidiasis</td>
<td>Died</td>
</tr>
<tr>
<td>3</td>
<td>90/male</td>
<td>COPD</td>
<td>Pulmonary aspergillosis</td>
<td>Died</td>
</tr>
<tr>
<td>4</td>
<td>61/male</td>
<td>COPD</td>
<td>Staph aureus and Morganella sepsis</td>
<td>Nafcillin aspiration/resolved</td>
</tr>
<tr>
<td>5</td>
<td>61/male</td>
<td>COPD</td>
<td>CMV pneumonitis</td>
<td>Died</td>
</tr>
<tr>
<td>6</td>
<td>61/male</td>
<td>COPD</td>
<td>Staph aureus; septic arthritis</td>
<td>Died</td>
</tr>
<tr>
<td>7</td>
<td>80/female</td>
<td>COPD, CHF</td>
<td>Cryptococcus neoformans fungemia and meningitis</td>
<td>Amphotericin B Flucytosine/resolved</td>
</tr>
</tbody>
</table>

CHF, congestive heart failure; MI, myocardial infarction.

Case 4

A 61-year-old man with a history of Mycobacterium kansasii pneumonia and COPD was hospitalized for hemoptysis and weight loss. Pulmonary function tests one year prior to admission revealed a FEV₁ of 1.01 L and an FVC of 2.65 L. He had been treated with prednisone, 20 to 60 mg per day, for more than two years. At admission, his prednisone dose was 50 mg per day. Chest roentgenogram showed changes consistent with COPD and bilateral apical fibrosis without change from previous roentgenograms. Cultures of bronchoscopic brushings grew Aspergillus fumigatus. Sputum cultures also grew Aspergillus. There were precipitin lines to A fumigatus in his serum. The prednisone dose was gradually reduced, but was increased to 60 mg per day because of increased respiratory distress. His respiratory symptoms quickly resolved and he was discharged on 50 mg per day of prednisone. Nine days later, he was readmitted for dyspnea. He was treated with methylprednisolone, 60 mg every six hours, aminophylline, and beta-agonists. His symptoms resolved over the next few days. Sixteen days after admission, the dose of methylprednisolone was reduced to 40 mg every six hours. Two days later, a chest roentgenogram revealed a new density in the right upper lobe. Blood and sputum cultures grew Klebsiella pneumoniae, and he was treated with ampicillin and amikacin. He had a respiratory arrest and died 22 days after hospitalization. Postmortem examination revealed Klebsiella pneumoniae and invasive pulmonary aspergillosis; no acid-fast bacilli or mycobacteria were seen.

Case 5

A 61-year-old man with a history of COPD who had been treated with prednisone, 10 to 40 mg every other day for at least ten years, was hospitalized for dyspnea and cough. No infiltrates were seen on chest roentgenogram. His symptoms improved when he was treated with methylprednisolone, 60 mg every six hours, aminophylline, and beta-agonists. Eight days after admission, massive hemoptysis developed and at bronchoscopy, bleeding was observed from the posterior segment of the right upper lobe of the lung. Sputum cultures obtained at bronchoscopy grew Aspergillus fumigatus. The hemoptysis resolved. A repeat chest roentgenogram demonstrated a new lower lobe infiltrate and culture of sputum grew Enterobacter cloacae. Treatment with clindamycin and amikacin was begun. The pulmonary infiltrate enlarged. Nine days later, a repeat bronchoscopy and transbronchial biopsy were nonrevealing. Erythromycin, trimethoprim-sulfamethoxazole, and amphotericin B were empirically added to his antibiotic regimen. Open lung biopsy three weeks after admission revealed a necrotizing pneumonia with invasion of blood vessels by organisms with septate hyphae. Cultures grew Aspergillus fumigatus. The patient died 24 days after admission. Post mortem examination showed emphysema and bilateral invasive Aspergillus pneumonia.

Case 6

A 61-year-old man with a history of COPD treated intermittently with corticosteroids for over two years, cor pulmonale, and Paget's

Table 2—Summary of Corticosteroid Therapy in Patients with COPD

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Prehospitalization</th>
<th>Inpatient</th>
<th>Complication Hospital (Day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drug* Daily Dose</td>
<td>Duration</td>
<td>Drug* Daily Dose Duration (Day)</td>
</tr>
<tr>
<td>1</td>
<td>P 40-50 mg</td>
<td>5 months</td>
<td>P</td>
</tr>
<tr>
<td>2</td>
<td>None</td>
<td>. . .</td>
<td>MP</td>
</tr>
<tr>
<td>3</td>
<td>P 10-40 mg</td>
<td>&gt;2 years</td>
<td>MP</td>
</tr>
<tr>
<td>4</td>
<td>P 20-60 mg</td>
<td>&gt;2 years</td>
<td>MP</td>
</tr>
<tr>
<td>5</td>
<td>P 10-40 mg</td>
<td>10 years</td>
<td>MP</td>
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<tr>
<td>6</td>
<td>P 0-40 mg</td>
<td>2 years</td>
<td>MP</td>
</tr>
<tr>
<td>7</td>
<td>P 10-60 mg</td>
<td>2 years</td>
<td>P</td>
</tr>
<tr>
<td>8</td>
<td>None</td>
<td>. . .</td>
<td>MP</td>
</tr>
</tbody>
</table>

*P, prednisone; MP, methylprednisolone.
Complications

Corticosteroids may be effective in patients with acute exacerbations of COPD. In a double-blind randomized, placebo-controlled trial, a select group of patients with acute respiratory insufficiency were treated with methylprednisolone, 0.5 mg/kg or placebo every six hours for 72 hours. Improvement in FEV1 was significantly greater in patients receiving methylprednisolone when compared to control subjects. No changes in arterial blood gas levels were found. Further analysis of these data suggests that the benefit attributable to corticosteroids may have been the consequences of statistical artifact. To date, the results of this trial have not been independently confirmed and the efficacy of long-term steroid administration to patients with acute exacerbations of COPD has not been studied.

Corticosteroid administration can be associated with impairment of host immune responses, T-lymphocyte, macrophage, and granulocyte function can be impaired leading to increased susceptibility to infection with opportunistic pathogens. Bacterial pathogens including S aureus, Gram-negative organisms, Listeria, as well as Nocardia and M tuberculosis have caused infections in patients treated with corticosteroids. Likewise, an increased frequency of viral infections due to Herpes simplex virus, Varicella-zoster virus, and cytomegalovirus, has been observed in patients receiving corticosteroids. In addition, fungal pathogens, such as Candida, Aspergillus, Zygomycetes, Cryptococcus neoformans, as well as protozoan and helminthic pathogens such as Pneumocystis carinii, and Strongyloides stercoralis, have caused serious disease in patients treated with corticosteroids.

In clinical and experimental settings, infections are more commonly associated with higher doses and prolonged treatment with corticosteroids. The development of invasive aspergillosis in corticosteroid-treated rabbits is dose-dependent. In renal transplant patients, treatment of rejection crisis with high doses of corticosteroids (particularly prednisone doses exceeding 40 mg/day) was associated with a greater frequency of infectious complications. Similarly, the frequency of infections in patients with various arthritic disorders treated with oral corticosteroids and in asthmatics treated with inhaled corticosteroids increased with progressively higher doses. Patients receiving corticosteroids for three to four weeks or more appear to experience a higher frequency of infections than patients treated for shorter periods. Fewer infectious complications are seen in patients receiving alternate day corticosteroids.

In this study, we report seven patients with COPD...
who received prolonged courses and high doses of corticosteroids and developed serious infections during therapy. All but one patient had been receiving corticosteroids as outpatients for periods ranging from five months to greater than two years (Table 2). In the exceptional patient (patient 2), a bacterial infection was first noted after 21 days and a fungal infection was found eight weeks after treatment with high doses of corticosteroids in hospital. Thus, infectious complications were associated with long-term treatment and high doses of corticosteroids. Six patients admitted for acute exacerbations of COPD were treated with high doses of methylprednisolone for periods ranging from five to 63 days. These durations of therapy were longer than justified by available data. Furthermore, one patient (case 7) was treated with corticosteroids for presumed acute exacerbations of COPD, whereas much of her illness may have been attributable to congestive heart failure. Our observations indicate that prolonged administration of high doses of corticosteroids to the elderly patient with COPD may lead to serious infectious complications.

Because we could not accurately determine the number of outpatients with COPD receiving corticosteroids in our referral area, we could not estimate in this retrospective study the frequency of steroid-related complications in this population. Despite this limitation, our experience indicates that the infectious complications in this population can be life-threatening and are observed primarily in patients receiving prolonged courses of corticosteroids as outpatients and very high doses of corticosteroids (up to 240 mg/day methylprednisolone) as inpatients.

Identification of patients with COPD who might benefit from corticosteroid treatment has been difficult. Blood or sputum eosinophilia,6-7,41 personal or family history of atopy,42,43 length of illness, history of wheezing,44 or spirometric response to an inhaled beta-adrenergic agent6 all have been proposed as predictive of clinical response to corticosteroids. None have consistently predicted a response.6 Spirometric improvement after a trial of oral corticosteroid administration has been used to identify individuals who might benefit from therapy.4-11

We observed serious infectious complications in seven elderly patients during prolonged treatment with high doses of corticosteroids. Fungal infections were the most frequent with three cases of aspergillosis, one of cryptococcosis, and one case of candidiasis. The three patients with invasive pulmonary aspergillosis died. Other infections due to Herpes simplex, CMV, S aureus, and Gram-negative bacteria were found. These patients survived with a reduction in the dose of corticosteroids.

Some clinical trials have suggested that a short course (up to two weeks) of up to 40 mg per day of prednisone (or its equivalent) may improve air flow in only a minority of patients with stable COPD.13-14 Another study has suggested that methylprednisolone 0.5 mg/kg every six hours for 72 hours may improve air flow in the setting of acute respiratory failure.13 The benefits of treatment with higher corticosteroid doses and longer durations are unproven, and in our experience, are associated with a risk of developing life-threatening infections. Generation of criteria predictive of steroid responsiveness in COPD is essential. Until such criteria are available, spirometric response to a therapeutic trial of corticosteroids may be the most reasonable method to identify patients who might benefit from corticosteroid administration.4-11 Carefully designed trials are needed to identify the optimal dose of corticosteroids and to ascertain if their benefits outweigh their risks.

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Compton

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Coccal

Cluff

Function.

Rinehart

Blood

Neoplastic

Nocardial

Infection

23

A

Recipients:

Vogt

Therapy

Good

Kaplan

Madras

Bach

Gallis

Haggerty

1974;

1968;

593x783

19


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