Corticosteroid Use in AIDS patients with PCP
Author: Kevan Beth Meadors, MD

Article: A Controlled Trial of Early Adjunctive Treatment with Corticosteroids for *Pneumocystis carinii* Pneumonia in the Acquired Immunodeficiency Syndrome.

Pneumocystis carinii Pneumonia (PCP), or more recently known as *Pneumocystis Jirovecii* Pneumonia (PJP) due to the causative fungus, is the **most common opportunistic infection in HIV/AIDS** patients that causes extensive lung injury by attacking the interstitial, fibrous lung tissues and thickening the alveoli and septa causing hypoxia. Conversely, corticosteroids have an anti-inflammatory action. The goal of this article was to evaluate if incorporating corticosteroids into the treatment regimen of PCP could decrease the signs and symptoms of the disease, improve lung function, and increase the patients' tolerance for therapy.

Methods: This was a randomized, unblinded clinical trial. 333 patients were originally enrolled across 6 treatment centers from June of 1987 to June of 1989. Patients had to have undergone <36 hours of PCP treatment and be >18 years old. They were not included in the study if they had an intolerance to corticosteroids, were mechanically ventilated, or had a hypoxemia ratio of <75. (Hypoxemia Ratio = partial pressure of arterial oxygen divided by fraction of inspired oxygen.) This ratio can be obtained by dividing two values found on an ABG and was used as a critical value during this study. These patients were stratified into three groups based on the severity of their illness: Group 1 = mild disease = hypoxemia ratio >350; Group 2 = moderate disease = hypoxemia ratio >250 but <350; Group 3 = severe disease = hypoxemia ratio >75 but <250. Acceptable treatment regiments included PO or IV Bactrim, IV pentamidine or PO dapsone + TMP. Patients could switch between treatment regimens due to intolerance. Corticosteroids were given at 40 mg BID for 5 days, then tapered to 40 mg daily for 5 days, then 20 mg daily for the remainder of the treatment time. IV methylprednisolone was substituted if the patient was unable to tolerate PO medication. The patients were evaluated at baseline, and then subsequently at day 3, 6, 10, 14, 21 and 84, for fever (>38 C), respiratory symptoms, occurrence or progression of another disease and the negative effects of treatment. A baseline cortisol was drawn along with serial ABGs and CBCs. The primary endpoint was respiratory failure, defined as the need for mechanical ventilation, having a hypoxemia ratio of <75 and death. Secondary endpoints were both death and toxicity from therapy enough to stop treatment.

Results: 333 patients were originally enrolled, but 5 initially had respiratory failure and 77 were confirmed to be negative for PCP. Thus, 251 patients were divided into the "treatment group" and "control group". 123 patients were assigned to the treatment group and were treated with both corticosteroids and their standard treatment regimen. 128 patients were assigned to the control group and were treated with the standard treatment alone. 41 patients died during the acute episode (end of 21 days), 7 had to be intubated and 7 more had a hypoxemia ratio of <75. Of the remaining candidates, the cumulative risk of respiratory failure in the treatment group vs the control group by day 21 was 13% vs 28%, respectively. The cumulative risk of death was 9% vs 18%, and the cumulative

risk of toxicity enough to stop treatment was 22% vs 31%. By day 84, the end of the study, the cumulative risk of death of 16% vs 26%. The cumulative risks of both respiratory failure and death were significantly different between the two groups, but the risks of toxicity of treatment was not. However, patients in the TMP-SMX regimen treatment group were still more likely to complete a 14 day course of antibiotics (70% vs 54%) than their counterparts. No deaths were noted in the Group 1/Mild disease group except for one patient whose death was attributed to a Staph Aureus infection. Fever, cough and dyspnea at rest were all seen less often in the treatment group patients. Chest pain was not significantly different in the two groups. None of the symptoms measured were found more frequently in the treatment group vs the control group. There was, however, an increased incidence of reactivation of the herpesvirus (26% in the treatment group vs 15% in the control group) and an increase in oral thrush (53% vs 41%) at the end of 84 days. Other diseases showed no difference between the two groups, including CMV, Cryptococcus, Esophageal Candidiasis and Kaposi's Sarcoma. The effect on pulmonary function showed that on day 3, the hypoxemia ratio increased by 4 in the treatment group and decreased by 41 in the control group. By day 21, it had increased by 66 in the treatment vs increasing by 17 in the control group. Of note, high dose "rescue" corticosteroids were given for patients in respiratory failure at the discretion of the primary physician.

Discussion: Early corticosteroid use in PCP patients showed about a 50% reduction in the risks of both acute respiratory failure and death. Most respiratory failure cases showed early deterioration in oxygenation, which highlights the need for early treatment. The steroids did not significantly reduce treatment-limiting toxicity of therapy but showed patients taking steroids were more likely to complete their full 14 day course of treatment. No direct adverse effects of corticosteroids were seen but the increase of incidence of both herpetic lesions and oral thrush was observed. Thus, the study suggests that PCP patients with a hypoxemia ratio <350 should be treated early with prednisone or an equivalent for the best results fighting respiratory failure and death.

TAKE HOME POINT: Here in Parkland, most residents use the PAO2 and/or the A-a gradient as the decision factors for starting steroids in the emergency room. A **PAO2<70 and an A-a gradient >35** both indicate the need for steroids in HIV patients.

Reference:
Bozzette, SA, et al. A Controlled Trial of Early Adjunctive Treatment with Corticosteroids for *Pneumocystis carinii* Pneumonia in the Acquired Immunodeficiency Syndrome. New England Journal of Medicine 1990; 323: 1451-7.