Prednisone as Adjunctive Therapy in the Management of Pulmonary Tuberculosis*  
Report of 12 Cases and Review of the Literature  

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A retrospective chart review was conducted over a 5-year period (1988 to 1993) in a tertiary inpatient care center on the effects of the addition of prednisone to the treatment regimens of 12 patients with pulmonary tuberculosis who continued to spike high temperatures and lose weight while showing bacteriologic response to effective antituberculosis therapy. After exclusion of other causes of fever, all patients were treated with 20 to 60 mg of prednisone daily until normalization of temperature and clinical improvement. Analyzed data included twice weekly sputum bacillary count, temperature record every 4 h, weekly patient weight, serum albumin level, liver function tests, and chest roentgenogram. The patients continued to spike temperatures of 38.3°C to 40.5°C (mean ± SD=39.6°C ± 0.6°C) even after 18 to 53 days (mean ± SD=33.9 ± 9.8 days) of antituberculosis therapy. Within 24 h after the addition of oral prednisone, temperature decreased in all 12 patients from a daily highest spike mean of 39.6°C ± 0.6°C (SD) to 38.1°C ± 0.6°C (SD) (p=0.0022). The duration of required prednisone therapy was 20.1 ± 9 days (mean ± SD). During this period patients’ appetites improved, and their weight increased from a mean (±SD) of 53.6 ± 5.7 kg to 58.1 ± 6.4 kg (p=0.0022). The serum albumin level increased from a mean (±SD) of 2.51 ± 0.4 g/dL to 3.21 ± 0.4 g/dL (p=0.0033). All the patients also showed clinical evidence of a decrease in toxic reactions associated with tuberculosis. There were no side effects from the addition of prednisone. This study shows the need for randomized controlled clinical trials to clarify the role of prednisone as adjunctive therapy in the management of pulmonary tuberculosis.

(CHEST 1995; 107:1621-30)

ACTH=adrenocorticotropic hormone; AFB=acid-fast bacilli; Cipro=ciprofloxacin; CM=capreomycin; EMB=ethambutol; ENL=erythema nodosum leprosum; INH=isoniazid; PBMC=peripheral blood mononuclear cells; PZA=pyrazinamide; Rif=rifampin; SM=streptomycin; TB=tuberculosis; TNF=tumor necrosis factor

Key words: albumin; fever; prednisone; tuberculosis; weight

Patients with pulmonary tuberculosis (TB) usually present with constitutional symptoms such as fever, weight loss, anorexia, and night sweats. Following antituberculosis therapy, the course of fever varies from 1 to 2 weeks.持久性发热可能需要超过2周的时间才能由于出现肺结核而被控制住，此外，可能因肺部或肺外细菌性感染，血症，3 nosocomial infections, occult malignant tumors, or drug hypersensitivity reactions.1,4 It has been postulated that the release of endogenous pyrogens by monocytes and antigen-stimulated release of lymphokines from specifically sensitized lymphocytes could cause the persistent fever associated with pulmonary TB itself.4 Mycobacterial antigens could also induce tumor necrosis factor (TNF) release from macrophages and peripheral blood mononuclear cells.5 TNF is one of the important mediators detected during the course of human septicemia6 and, therefore, may be responsible for persistent fever, weight loss, and necrosis of lesions.5

Two recent review articles stated that adjunct therapy with corticosteroids has some value in the management of persistent fever in particular forms of TB.7-8 The benefit of using corticosteroids as adjunct therapy with antituberculosis drugs is not clear.8-10 In the case of adrenal suppression, it is used without reservation. Studies in the 1950s and 1960s11-20 showed that the addition of prednisone or adrenocorticotropic hormone (ACTH) to antituberculosis chemotherapy benefited patients with flagrant active disease, in terms of more rapid radiographic and clinical improvement, greater elimination of cavities, and fewer respiratory sequelae and relapses of the disease. A decrease in toxic reactions, normalization of body temperature, and the control of weight loss, with improvement in other constitutional symptoms, were also observed. Radiographic resolution was appreciable in patients who received

*From the Division of Pulmonary Diseases and Critical Care Medicine, Cook County Hospital, Chicago. This study was presented in part May 20, 1992, at the 1992 International Conference of the American Thoracic Society, Miami Beach, Fla.  
Manuscript received July 27, 1994; revision accepted October 5.  
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prednisone along with chemotherapy; in addition, faster elimination of tubercle bacilli was observed.

During the era of more effective antituberculous drugs, especially rifampicin, the interest in the use of corticosteroids decreased. Currently, because of their anti-inflammatory properties, corticosteroids are used as adjunct therapy for the hypersensitivity reactions that occur with antituberculous drugs. The official statement of the American Thoracic Society regarding the treatment of TB proposes an adjunctive role of corticosteroids only in the management of some forms of extrapulmonary TB such as meningitis and pericarditis.

Over the last decade, it has been our clinical experience that, despite a documented decrease in the sputum bacillary count during the initial treatment, some patients' conditions failed to improve symptomatically and they continued to have toxic reactions, exhibiting high fever, progressive weight loss, anorexia, and an inability to thrive. The contrast between the favorable sputum response and the overall toxic picture suggests that the fever and its attendant consequences may be due to the release of tubercle protein from a large amount of destroyed tubercle bacilli. We found that, under these circumstances, a course of corticosteroid therapy may be beneficial and, most importantly, safe. To further confirm our clinical observation, we conducted a 5-year retrospective chart review for all of the patients with TB admitted to our hospital with the purpose of assessing the role of prednisone as adjunctive therapy in the management of pulmonary TB.

METHODS

The Pulmonary Medicine Division's office files of all the patients with TB who were admitted between January 1, 1989, and December 31, 1993, to our 900-bed inner-city teaching hospital were reviewed (n=1,809). A detailed hospital record review was done if a patient received prednisone in addition to antituberculosis therapy for the purpose of controlling persistent fever and weight loss. Of the 1,809 hospital admissions, 1 patient received prednisone in addition to antituberculosis therapy regimens in 1989, 6 in 1990, 2 in 1991, 1 in 1992, and 2 in 1993, resulting in a total of 12 patients for final analysis. The indication for the addition of prednisone was made by the TB ward attending physician using the following criteria: a persistent high-grade fever (temperature $\geq 38.3^\circ C$) or persistent weight loss ($\geq 2.25$ kg/wk) despite bacteriologic and radiologic improvement of TB after 3 to 4 weeks of chemotherapy, which included isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), ethambutol (EMB), or streptomycin (SM). In some cases, additional drugs such as ciprofloxacin (Cipro) and/or capreomycin (CM) were given. We reviewed patient demographics and follow-up chest radiographs, which were done weekly to detect any new infiltrates or evidence of worsening of TB. Furthermore, we reviewed the following data: twice-weekly sputum bacillary count, temperature record every 4 h, weekly patient weight, weekly nutritional assessment, including serum albumin level, and serial liver function test results.

In our hospital's laboratory, the methods for selective staining of mycobacteria are the fluorochrome procedure using auramine and rhodamine stains with further confirmation of all positive smears by Ziehl-Neelsen stain. The following quantitative acid-fast bacilli (AFB) count representing a simplification of the proposed Centers for Disease Control methodology was applied in reporting the estimate of the number of AFB observed in 1, 10, or 100 oil immersion fields.

No. of AFB Seen  Report
None                  No AFB observed
1-9/100 fields        1+
1-9/10 fields         2+
1-9/field             3+
$>9$/field           4+

The follow-up sputum smears were defined as significantly decreased if the bacillary count dropped by two grades; for example, from $>9$ per field to 1 to 9 per 10 fields or from 1 to 9 per field to 1 to 9 per 100 fields.

To rule out other causes of fever, serial blood cultures, sputum, and urine cultures, and, when appropriate, a total body gallium -67 scintigraphy seeking occult abscesses were performed. Treatment with antituberculosis drugs was withheld for up to 48 h and temperature response was monitored. A screening for occult malignant disease was also performed. A trial of intravenous broad-spectrum antibiotic therapy was administered for 3 to 4 days. In patients with positive HIV serologic test results, careful evaluation was performed to rule out other opportunistic infections. After TB itself was deemed to be the probable cause of continued fever spikes, the patients were given 40 mg of oral prednisone as a single daily dose along with the antituberculosis drugs. If there was no response, the dose was increased to 50 mg twice a day. As there was no clinical suspicion of adrenal insufficiency in this group of patients, we did not measure the baseline serum cortisol level.

After the addition of prednisone, temperature response (every 4 h), signs, and/or symptoms of systemic toxic reactions (general responsiveness, appetite, night sweats, low blood pressure, tachycardia), weekly weight, and nutritional status (using serum albumin as the marker) were monitored. The major concern of adding steroid therapy was possible dissemination of TB. This potential complication was monitored by close attention to a patient's general status, sputum bacillary count, and chest radiograph. Other potential side effects of steroid therapy such as diabetes, opportunistic infections, adrenal suppression, etc, were also closely monitored. In those patients with history of TB, the last drug susceptibility result available and the patient's history of compliance to therapy were used in selecting the current chemotherapy regimen. When new drugs were believed to be indicated for these patients, a minimum of two drugs were added at a time. For all patients with newly diagnosed conditions, chemotherapy consisting of a minimum of four drugs was started pending the availability of susceptibility reports. In most patients with newly diagnosed conditions, drug susceptibility studies were available only after the initiation of corticosteroid therapy; therefore, they were only used to confirm the impression indicated by the rapid decrease in bacillary count. Guidelines used to taper off and cease the prednisone dose were as follows: (1) lack of fever with temperature exceeding $37.2^\circ C$ for 48 h, (2) evidence of weight gain of more than 1.8 kg, or (3) improvement in appetite and general well-being. Patients were discharged from the hospital and followed up in our pulmonary clinic after their sputum smears were negative for tubercle bacilli; their medical and socioeconomic problems also were addressed.

Statistical Analysis

Our data were collected in paired fashion with each patient serving as his/her own control. Nonparametric methods were
applied for statistical analysis because of the small sample size (n=12). The Wilcoxon matched-pairs signed-ranks test was performed to test the paired differences between before-and-after steroid drug administration (temperature differences, albumin level, and weight changes). Friedman two-way analysis of variance (ANOVA) was used to compare the three related data (patient’s weight at hospital admission, before using steroids, and at hospital discharge).

RESULTS

Table 1 lists the characteristics and clinical profiles of the study subjects. Eleven men and one woman were studied. Their ages ranged from 20 to 54 years (mean ± SD=38.4 ± 10.9 years, median=38 years). Eleven patients suffered from far-advanced cavitary pulmonary TB and their sputum smears/cultures were positive for *Mycobacterium tuberculosis*; one patient had miliary TB (bronchoscopic washing smear/culture confirmed). Six patients were alcohol abusers and three patients admitted to intravenous drug use. Seven patients underwent HIV serologic tests; one had a positive test. The susceptibility studies of TB organisms isolated in all 12 patients showed no resistance to commonly tested antituberculous drugs (INH, RIF, SM, and EMB).

Five patients had a history of TB and were noncompliant during their prior therapy, three of them had at least one prior cycle of therapy for TB, one had two cycles of therapy, and one had seven prior hospital admissions for TB within 1 year. The prior chemotherapy regimen, the drug therapy started at the time of hospital admission, and the subsequent modification of chemotherapy regimen are shown in Table 2.

The initial sputum bacillary count for each of the 11 patients with cavitary pulmonary TB was 3+ organisms; the bronchial washing bacillary count of the patient with miliary TB was 1+ organism. The anti-tuberculosis therapy regimen consisted of a four- or five-drug combination as listed in Table 1; therapy was initiated on the day of hospital admission in seven patients, on the second day in four patients, and on the fifth day in one patient. After 16 to 38 days (mean ± SD=27.56 ± 8 days) of therapy, the bacillary count had decreased by two points in the 11 patients with cavitary pulmonary TB. Despite the decrease in sputum bacillary count, all patients continued to

### Table 1—Characteristics and Clinical Profiles of the Study Subjects*

<table>
<thead>
<tr>
<th>Patient No./ Age, yr/Sex</th>
<th>Risk Factor Other Illness</th>
<th>Chest Radiograph</th>
<th>HIV Serology</th>
<th>TB Drugs†</th>
<th>Steroid Dose, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/43/M</td>
<td>CRF, alcohol abuse</td>
<td>Miliary TB</td>
<td>Negative</td>
<td>INH, RIF, PZA, SM</td>
<td>40 qam</td>
</tr>
<tr>
<td>2/54/M</td>
<td>Retreatment</td>
<td>Bilateral cavities</td>
<td>Not known</td>
<td>INH, RIF, EMB, SM, PZA</td>
<td>40 qam</td>
</tr>
<tr>
<td>5/31/M</td>
<td>Schizophrenia treatment</td>
<td>Left lung cavities</td>
<td>Negative</td>
<td>INH, RIF, PZA, SM, EMB</td>
<td>40 qam</td>
</tr>
<tr>
<td>4/44/M</td>
<td>Alcohol abuse</td>
<td>Left lung cavities</td>
<td>Not known</td>
<td>INH, RIF, PZA, SM</td>
<td>40 qam</td>
</tr>
<tr>
<td>5/21/F</td>
<td>None</td>
<td>Bilateral cavities</td>
<td>Negative</td>
<td>INH, RIF, PZA, SM, EMB</td>
<td>30 qam</td>
</tr>
<tr>
<td>6/39/M</td>
<td>Alcohol abuse</td>
<td>Bilateral cavities</td>
<td>Not known</td>
<td>INH, RIF, PZA, SM, Cipro</td>
<td>10 bid</td>
</tr>
<tr>
<td>7/37/M</td>
<td>IVDA</td>
<td>Bilateral cavities</td>
<td>Positive</td>
<td>INH, RIF, PZA, EMB</td>
<td>30 qam</td>
</tr>
<tr>
<td>9/20/M</td>
<td>IVDA</td>
<td>Bilateral cavities</td>
<td>Negative</td>
<td>INH, RIF, PZA, EMB, CM</td>
<td>20 bid to 30 bid</td>
</tr>
<tr>
<td>10/54/M</td>
<td>Alcohol abuse treatment</td>
<td>Bilateral cavities</td>
<td>Negative</td>
<td>INH, RIF, PZA, Cipro</td>
<td>40 qam</td>
</tr>
<tr>
<td>11/46/M</td>
<td>Alcohol abuse treatment</td>
<td>Bilateral cavities</td>
<td>Refused</td>
<td>INH, RIF, PZA, EMB, SM</td>
<td>40 qam</td>
</tr>
<tr>
<td>12/35/M</td>
<td>Alcohol abuse</td>
<td>Bilateral cavities</td>
<td>Negative</td>
<td>INH, RIF, PZA, EMB, Cipro</td>
<td>40 qam</td>
</tr>
</tbody>
</table>

*CRF=chronic renal failure; IVDA=intravenous drug abuse; qam=every morning; bid=twice daily. Patients 2, 8, 11, and 12: TB culture and susceptibility results were available prior to addition of prednisone.
†All of the study subjects were African-American.
‡Tuberculosis culture isolates of all patients were susceptible to INH, RIF, SM, and EMB (done routinely only for these four drugs in our reference laboratory).

### Table 2—Chemotherapy Information for Patients With History of Tuberculosis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Prior Regimen</th>
<th>Drug Stated on This Hospital Admission</th>
<th>Subsequent Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>INH, RIF, PZA</td>
<td>INH, RIF, PZA, EMB, SM</td>
<td>Completed therapy with INH, RIF, EMB</td>
</tr>
<tr>
<td>3</td>
<td>Unknown, treated elsewhere</td>
<td>INH, RIF, PZA, EMB</td>
<td>INH, RIF, PZA</td>
</tr>
<tr>
<td>8</td>
<td>INH, RIF</td>
<td>INH, RIF, PZA, SM, EMB (refused to continue with SM)</td>
<td>INH, RIF, PZA, EMB</td>
</tr>
<tr>
<td>10</td>
<td>Unknown treated 1971</td>
<td>INH, RIF, PZA, EMB</td>
<td>INH, RIF</td>
</tr>
<tr>
<td>11</td>
<td>INH, RIF, PZA, EMB (multiple hospital admissions, almost monthly due to social problems)</td>
<td>INH, RIF, PZA, EMB, SM</td>
<td>INH, RIF, PZA, EMB daily supervised therapy then INH, RIF, biweekly by directly observed therapy</td>
</tr>
</tbody>
</table>
have spike temperature ranging from 38.3°C to 40.5°C (mean ± SD=39.6°C±0.6°C, median=39.6°C), which did not respond to conventional antipyretics. All patients received nutritional support by enteral or parenteral hyperalimentation. Nine patients continued to lose weight. The mean (± SD) hospital admission weight for all of the 12 patients was 55.4±5.1 kg (median=54.5 kg), which dropped to a mean (± SD) of 53.6±5.7 kg (median=53.5 kg) the day prior to administration of prednisone.

The administration of prednisone was initiated from 18 to 53 days (mean ± SD=33.9±9.8 days, median=34 days) after admission to the hospital. In three out of the five retreatment patients and in one of the seven patients with newly diagnosed conditions, drug susceptibility reports were available prior to the addition of prednisone. In the absence of drug susceptibility results, a decrease in sputum bacillary count by two grades on three consecutive sputum samples was used to indicate that the organisms were susceptible to the drug regimen of that patient. The fever declined dramatically after prednisone was added to the drug regimen (Fig 1), with a mean temperature decreasing within 24 h of the initiation of prednisone therapy from a spike mean (±SD) of 39.6°C±0.6°C to 38.1°C±0.6°C (Z=3.0594, p=0.0022). The temperature continued to decrease but less impressively in the form of low-grade fever and finally normalized at the time the corticosteroid therapy was discontinued. The total mean (±SD) duration of steroid therapy was 20.1±9 days (range, 4 to 35 days, median=20.5 days).

All of the study subjects had gained weight, ranging from 0.9 to 11.25 kg (mean ± SD=4.5±3.24 kg, median=3.825 kg). The average weight of all the study subjects before the addition of prednisone was 53.6±5.67 kg (SD) (median=53.5 kg), which had increased to 58.1±6.435 kg (SD) (median=57.8 kg) at the time of hospital discharge. Figure 2 shows the weight changes from the day of hospital admission, to the day before steroids drugs were administered, to the day of hospital discharge. Friedman two-way ANOVA test was statistically significantly different for these three related data (X2=13.04, p=0.0015). A patient’s weight had significantly increased on the day of hospital discharge compared with his/her weight the day before administration of prednisone (Z=3.0594, p=0.0022). However, no difference was noted between a patient’s weight at hospital admission and the day before administration of prednisone (Z=1.5559, p=0.1197).

The serum albumin level increased significantly, from an average of 2.51±0.4 (SD) g/dL to 3.21±0.4 (SD) g/dL. Figure 3 displays the serum albumin level changes after the addition of prednisone. Serum albumin levels between the time of hospital admission to the time of hospital discharge were statistically significant (Z=2.9341, p=0.0033). No complications were
attributable to prednisone for any of the 12 study subjects. The average duration of therapy with the addition of prednisone was 20.1 ± 9 (SD) days (median = 20.5 days). The total length of hospital stay was 49.3 ± 15 (mean ± SD) days, which is substantially paradoxically longer than the average hospital stay.

**DISCUSSION**

This study demonstrates that a selected group of patients with advanced or far-advanced cavitary pulmonary TB showed bacteriologic improvement with modern chemotherapy, yet their conditions failed to improve clinically and they continued to have high fever spikes, continued to have toxic reactions, lost weight, and failed to thrive. They all benefited from the addition of prednisone to their drug regimens, and within 24 h, a significant drop in fever resulted. Within 3 weeks, the patients had gained a significant amount of body weight, their serum albumin levels had improved, and the systemic toxic reactions were resolved. Most of the patients responded to a single 40-mg dose per day of prednisone (n = 7); some required 30 mg twice a day (n = 2). One patient required 10 mg twice a day, and two patients required 30 mg once a day (Table 1).

To support our clinical findings, we did a thorough literature review. Table 3 outlines the published clinical trials related to the adjunctive role of corticosteroids in the treatment of TB. Reports in the 1950s and 1960s described a beneficial role for corticosteroids when combined with antituberculosis chemotherapy to which tuberculosis organisms were sensitive. Most of these studies were well-designed, randomized controlled trials; three of them were double-blind placebo-controlled trials. In these studies, corticosteroid therapy was initiated and continued from 5 weeks to 3 months. Patients who received corticosteroids showed more rapid subjective improvement and a faster decline in temperature and erythrocyte sedimentation rate. Radiologically, exudative lesions cleared more rapidly, but there was no difference in the rate of cavity closure. The effects on sputum conversion, radiologic improvement, and pulmonary function improvement, however, were not consistent. Consequently, the role of the routine use of corticosteroids in the management of pulmonary TB remained controversial. For ethical reasons, there was strong support for corticosteroid use in desperately ill patients with pulmonary TB who were at risk of dying early, before chemotherapy had its full effect.

The most recent clinical trial was a study of short-course chemotherapy in India in which prednisone was given in the initial 8 weeks along with INH, rifampicin, SM, and PZA. Prednisone did not influence the speed of sputum conversion, the response to chemotherapy, the rate of disappearance of cavities, or the rate of bacteriologic relapse in patients with drug-susceptible organisms or in patients showing resistance to a single drug. Among patients with strains resistant to more than one drug, the group receiving prednisone had an unfavorable response. The authors concluded that there was no role for steroids in short-course antituberculosis chemotherapy. It must be noted, however, that the daily dose of prednisone used in this study was only 20 mg (Table 3).

A favorable report was mentioned in a 1988 case report of an HIV-infected patient with disseminated TB accompanied by hectic fever and weight loss despite effective quadruple chemotherapy; there was response to the addition of corticosteroids. A 1991 editorial on corticosteroids and TB recommended the addition of corticosteroids to antituberculosis treatment in the management of systemic symptoms and in moribund patients. A 1993 review article summarized the role of corticosteroids in the management of pleuropulmonary disease as “appropriate in patients with severe systemic toxicity, persistent pleuritic pain, or slow resolution of effusions.”

In pleural disease, corticosteroids decrease the systemic and local symptoms related to tuberculoprotein, limit the organization of pleural exudates and subsequent fibrosis, and reduce the chest wall deformity and
### Table 3—Outline of Clinical Trials Using Steroid Drugs With Chemotherapy in Pulmonary Tuberculosis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Hypotheses Tested</th>
<th>Control Group Medications*</th>
<th>Treatment Group Medications*</th>
<th>Results</th>
<th>Side Effects*</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Almuner††</td>
<td>Randomized controlled trial</td>
<td>Steroid decrease TB patients’ mortality</td>
<td>INH, SM, Penicillin 500,000 unit IM, bid (n=13)</td>
<td>INH, SM Cortisone 2,100 mg in 15 days (n=14)</td>
<td>Control group: 9 died &lt;30 d 1 died on 75th d 1 died on 50th d</td>
<td>Not stated</td>
</tr>
<tr>
<td>Weinstein and Koler‡‡ (1959)</td>
<td>Randomized double-blind placebo-controlled trial</td>
<td>Efficacy and safety of using steroids</td>
<td>INH, aminosalicylic acid or one of its salts + placebo (n=49)</td>
<td>Same chemotherapy as control + prednisolone 30 mg for 10 d 40 mg for 10 d 10 mg for 40 d 5 mg for 4 d 2.5 mg for 4 d (n=51)</td>
<td>Treatment group: 3 patients died (2 treatment group, 1 control group). steroid-treated patients showed ↓ ESR, ↓ WBC ↑ weight, and fast sputum conversion/↑ x-ray clearing/cavity than control group; Steroid can be used for selected patients with TB</td>
<td>No specific detrimental effects from steroid therapy</td>
</tr>
<tr>
<td>Horne†§  (1960)</td>
<td>Randomized controlled trial</td>
<td>Prednisolone hastens the rate of improvement</td>
<td>INH, SM, PAS (n=91)</td>
<td>ACTH gel 30 U IM on two successive days every fortnight (n=87)</td>
<td>Rapid clinical/radiographic improvement and sputum conversion in the prednisolone group</td>
<td>Control group: vestibular disturbance (n=5) hypersensitivity reaction (n=4)</td>
</tr>
<tr>
<td>Angel et al†‖  (1961)</td>
<td>Randomized controlled trial</td>
<td>Efficacy and safety of using corticotropin</td>
<td>INH, SM, PAS (n=50)</td>
<td>IMMEDIATE AND PRONOUNCED clinical improvement in corticotropin group (eg, ↓ fever, ↑ weight) radiologic results same; rapid sputum conversion in control group</td>
<td></td>
<td>Sepsis, venous thrombosis, and mental changes appeared equally in the 2 groups; control group had a much higher hypersensitivity reaction Corticotropin group: 40% of the patients had moon face, 6 patients developed diabetes mellitus, 2 patients had elevated diastolic blood pressure that fell after reduction of corticotropin dosage, 5 patients had severe withdrawal symptoms (eg, lassitude, loss of appetite)</td>
</tr>
</tbody>
</table>

*IM=intramuscular; bid=twice daily; PAS=para-aminosalicylic acid.  
(continued)
<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Hypotheses Tested</th>
<th>Control Group Medications*</th>
<th>Treatment Group Medications*</th>
<th>Results</th>
<th>Side Effects*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marcus et al\textsuperscript{12} (1962)</td>
<td>Randomized controlled trial</td>
<td>Healing of pulmonary TB different if prednisone added with anti-TB drugs</td>
<td>INH, PAS, SM (n=51)</td>
<td>INH, PAS, SM</td>
<td>Steroid group showed more rapid clinical improvement, more clearing of chest radiograph at 2 wk, but no significant difference on radiographs between two groups at the end of 6 mo; pulmonary function abnormalities same in both groups</td>
<td>Control group: rash due to SM (n=2); GI disturbances due to PAS (n=2); Treatment group: diabetes (n=1), moon face (n=1), SM-associated vertigo (n=1)</td>
</tr>
<tr>
<td>British Tuberculosis Association\textsuperscript{16} (1961)</td>
<td>Randomized controlled trial</td>
<td>Efficacy and safety of using corticotropin and prednisone</td>
<td>INH, SM, PAS (n=119)</td>
<td>INH, SM, PAS</td>
<td>Both ACTH and prednisone groups had rapid improvement in clinical condition (weight, ESR and temperature) and less residual radiographic abnormalities; prednisone more effective than ACTH</td>
<td>31 patients had severe hypersensitive reactions to chemotherapy (control group n=16, ACTH group n=7 and prednisone group n=9); 15 ACTH group patients and 7 prednisone group patients had side effects from hormone therapy</td>
</tr>
<tr>
<td>British Tuberculosis Association\textsuperscript{17} (1963)</td>
<td>Same trial (2nd yr follow-up)</td>
<td>Radiographic advantage from steroid therapy would be maintained</td>
<td>INH, SM, PAS (n=75)</td>
<td>INH, PAS, plus steroids ACTH group n=75; prednisone group (n=57)</td>
<td>2 deaths (1 ACTH, 1 prednisone) radiographic advantage from steroid therapy was maintained during the 2nd year</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>US Public Health Service Tuberculosis Therapy Trial\textsuperscript{18} (1965)</td>
<td>Multicenter randomized double-blind placebo-controlled trial (25 hospitals)</td>
<td>Steroid therapy hastens resolution of the pulmonary process and reduces toxicity to antimicrobial drugs</td>
<td>Group 1: SM, PZA, INH, PAS + placebo (n=274) Group 2: INH, PAS + placebo (n=202)</td>
<td>Group 1: SM, PZA, INH, PAS Group 2:INH, PAS Group 1+5 wk prednisolone (n=268) Group 2+5 wk prednison (n=265) Group 1+9 wk prednison (n=268) Group 2+9 wk prednison (n=267) (prednisolone dosage: 20 mg daily for 3 d 15 mg daily for 4 d 10 mg daily maintenance)</td>
<td>4 patients died of TB (2 in placebo group, 2 of those receiving prednisolone for 9 wk) Addition of prednisolone had no effect on speed of clearing of infiltrates in whites but was speedier in blacks; no evidence that prednisolone reduced the toxic reactions from anti-TB drugs; longer than 5 wk course of steroid therapy not expected to produce additional benefit</td>
<td>Six patients had hepatitis in INH-PAS group (1 in 5 wk, 3 in 9 wk, 2 in placebo group); 3 patients had severe reaction in treatment groups and discontinued from trial (1 placebo, 2 prednisolone)</td>
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*IM=intramuscular; bid=twice daily; PAS=para-aminosalicylic acid.

(continued)
scoliosis that may develop in children.26 Corticosteroids reduce the fatality rate and the frequency of neurologic sequelae among patients with tuberculous meningitis.27,28 They have been used to decrease local pressure effects that are secondary to enlarged intrathoracic tuberculous lymph nodes, especially in children,29 and have a role in the management of tuberculous pericarditis, reducing the risk of adhesions and subsequent constrictive pericarditis.30 In patients with tuberculous constrictive pericarditis, corticosteroids caused more rapid normalization of tachycardia and jugular venous pressure but did not decrease the number of deaths or the need for pericardiectomy.31 The addition of corticosteroids was reported to be beneficial in seriously ill patients with upper respiratory tract TB and painful laryngeal ulcers and laryngitis threatening the airway patency as well as in pharyngitis or disease of the oral cavity leading to difficulty in eating or swallowing medication.32

The precise mechanism for our patients’ febrile course is unclear. Endogenous pyrogens may be released from monocytes, which are activated by lymphokines released by specifically sensitized lymphocytes.4 Two major components of the mycobacterial cell walls, lipoarabinomannan (LAM) and cell wall core, are both potent triggers of TNF release from activated macrophages and monocytes.5 TNF-α provides protection against TB by enhancing the myco-

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<td>Johnson et al29 (1965)</td>
<td>Randomized double-blind placebo-controlled trial</td>
<td>Benefit and safety of steroid therapy</td>
<td>INH, PAS + placebo (n=50)</td>
<td>30% control group patients showed progression of TB at first 4 wk, no disease progression in treatment group, no difference on weight gain between 2 groups. Treatment groups had much more rapid radiographic, symptomatic (cough, spoutum, fever) improvement, and anemia correction, on 5-yr follow-up treatment group had fewer respiratory sequelae or relapses of TB.</td>
<td>15% steroid group patients showed moon face, none of the patients in the placebo group, steroid group had more hypersensitivity reactions but not significantly different from placebo.</td>
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<td>Malik and Martin20 (1969)</td>
<td>Nonrandomized controlled trial</td>
<td>Steroid drugs help early reversal of the TB infection that could alter the restrictive obstructive defects</td>
<td>Standard anti-TB drugs (n=59)</td>
<td>Standard anti-TB drugs, prednisone 40 mg every other day for 6 wk then 25 mg every day until 6 mo (n=59)</td>
<td>Radiographic regression was greater in treatment group; frequency of abnormal vital capacities was same in two groups, as well as the mean vital capacity; diffuse obstructive pulmonary syndrome was same in both groups, no difference in weight gain (1 patient died in control group). Prednisolone did not influence the speed of sputum conversion, prednisolone group patients with ≥2 drugs resistance had lower response to chemotherapy, therefore, steroids did not have benefit in short-course chemotherapy.</td>
<td>9 patients did not complete steroid regimen (2 hyperglycemia, 1 peptic ulcer, 4 psychosis, 1 skeletal fracture, 1 TB of spine).</td>
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<tr>
<td>Indian Council of Medical Research23 (1985)</td>
<td>Randomized controlled trial</td>
<td>The role of steroids on short-course anti-TB chemotherapy</td>
<td>R/5 regimens: INH, RIF, PZA, SM, daily for 2 mo then INH, PZA, SM twice a week for 3 mo (n=129)</td>
<td>Half of the patients in each regimens were given prednisolone 30 mg daily for 8 wk.</td>
<td>24% patient who had RIF and 46% non-RIF group complained of arthralgia; 17 patients had hepatitis (12 R/5 and R/7, 5 Z/7).</td>
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*IM=intramuscular; bid=twice daily; PAS=para-aminosalicylic acid.
bactericidal activity of mononuclear phagocytes; local elevation of TNF concentrations, occurring in response to mycobacterial wall components, contributes to the pathologic signs and symptoms of TB like fever, weight loss, activation of T cells, and stimulation of collagenase production by fibroblasts. Patients with TB may produce more TNF, which is associated with production of fever, necrosis of lesions and weight loss, than others. In an in vitro study to investigate the production of TNF and prostaglandin E2 (PGE2) by peripheral blood mononuclear cells (PBMC), Cadranel et al. found that PBMC from patients with TB with high-grade fever and cachexia generated more TNF than the PBMC from the control subjects. In patients being treated for septic shock, endotoxin release can be related to the administration of antibiotics, and the rate of endotoxin release varies with the antibiotic used. Thus, a similar mechanism could explain the high fever, weight loss, and toxic reactions seen in our patients who received tuberculocidal drugs. Further studies with serial measurement of TNF, PGE2, and other mediators of inflammation in our patient population might help to clarify this better.

The therapeutic benefit of glucocorticoids appears to derive chiefly from their suppression of immunologic and inflammatory responses. Corticosteroids are used as antipyretic agents in bacterial infections in conjunction with antibiotics to manage the hypersensitivity reactions that occur with antituberculosis drugs. They also decrease the release of TNF by alveolar macrophages. Pentoxifylline and thalidomide are the two other drugs known to inhibit TNF-α production. Thalidomide inhibits TNF-α production by enhancing the degradation of TNF-α mRNA; it is the drug of choice for the treatment of erythema nodosum leprosum (ENL), an acute inflammatory complication occurring in 30% of patients with lepromatous leprosy, usually associated with the initiation of multidrug therapy. The fever, anorexia, and arthralgia associated with ENL respond promptly to the addition of thalidomide. Selective inhibition of TNF-α by thalidomide without reduction of humoral or cellular immunity of patients makes this the drug of choice in the management of ENL. Such a drug, which would promptly reduce the toxic symptoms seen among our patient group but without inhibition of the patient's cellular or humoral immunity, would be better than prednisone. This is especially true in patients with AIDS in whom the intact cellular immune system is crucial. We are not aware of any clinical trials on the use of thalidomide or pentoxifylline for the management of inflammatory toxic reactions in patients with TB. Further studies are required.

Decreasing the systemic toxic reactions of our patients with prednisone improved the appetite and promoted weight gain, while the appetite stimulants and anabolic steroids would be safer than prednisone to use in patients with TB; their benefit in our study group patients is unknown. In most patients, daily administration of prednisone is sufficient; twice daily corticosteroids may suppress a fever more effectively because prednisone has a short plasma half-life of 2 to 3.5 h. Furthermore, rifampicin can decrease the half-life of prednisone by its effect on liver enzyme induction. Doubling the dose of prednisone is recommended in patients receiving rifampicin and prednisone simultaneously. Three of our patients did not respond to once-a-day prednisone but showed a response to a twice-daily dose. The approximate duration of the need for prednisone appears to be 4 to 6 weeks depending on the system involved.

The total in-hospital days for our patient group was substantially longer than is normal for patients with TB generally, primarily due to the various diagnostic workup required to rule out other causes of fever and weight loss, and also due to the nature of their far-advanced cavitary pulmonary TB. With the availability of faster drug susceptibility studies using a specific radiometric method (Bactec, Becton-Dickinson Diagnostic Instrument Systems, Sparks, MD), we will be able to initiate the addition of corticosteroids much earlier in the course of therapy, which will benefit the patients and decrease hospital stays.

**Conclusion**

We identified a subset of patients with advanced pulmonary TB who had persistently high fever and progressive weight loss even though their sputum bacillary count decreased rapidly with effective tuberculocidal drugs. Both fever and nutritional status responded favorably to the addition of prednisone along with the antituberculosis regimen. Patients who did not respond to once-daily prednisone responded well to twice-daily. No adverse effects related to prednisone were observed.

We are gratified by the results of this study, but recognize the limitations associated with our retrospective study of only 12 cases; there is need for randomized controlled clinical trials. Also, the patient population we studied came from a homogeneous, low socioeconomic urban minority group, one with the highest incidence of TB in our society. The favorable results from our study might not be reproducible in other segments of the US population. We emphasize that prior to adding prednisone to a patient's antituberculosis chemotherapy regimen, physicians should ascertain a demonstrable bacteriologic response to chemotherapy by sputum studies and should exclude other causes of fever by meticulous and thorough evaluation.
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